UNIVERSITÀ DEGLI STUDI
DI MILANO

FACOLTÀ DI SCIENZE MATEMATICHE, FISICHE E NATURALI
DIPARTIMENTO DI CHIMICA ORGANICA E INDUSTRIALE

CORSO DI DOTTORATO DI RICERCA IN

CHIMICA INDUSTRIALE - XXI CICLO

Chim/06

TESI DI DOTTORATO DI RICERCA

Synthesis of enantiomerically pure polyfluorobenzo[d]sultams

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ANNO ACCADEMICO 2008/2009

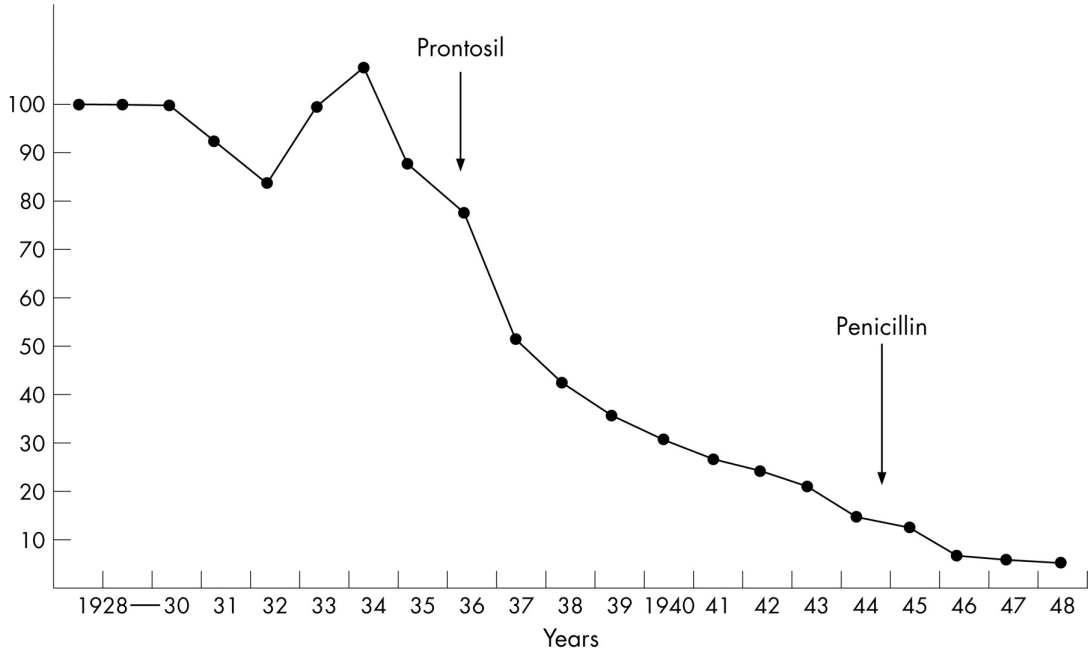
1 INTRODUCTION

Sulfonamido group, the open-chain analog and the historical "ancestor" of sultams, is a very common organic functional group; in fact it is well known for its wide range of biological activities, holding the prestigious position of being the first synthetic compounds to have had utility in human therapy. Sulfonamide drugs in fact were the first antimicrobial drugs, and paved the way for the antibiotic revolution in medicine.

The first sulfonamide synthesized was trade named *Prontosil* and was discovered by a team under the general direction of Farben executive Heinrich Hoerlein, synthesized by Bayer chemist Josef Klarer and tested under the direction of physician/researcher Gerhard Domagk, who subsequently would have received the 1939 Nobel Prize in Medicine.[1] The first official communication about the breakthrough discovery was not published until 1935,[2] more than two years after the drug was patented by Klarer and his research partner Fritz Mietzsch.

Experiments with Prontosil began in 1932 in the laboratories of Bayer AG, at that time a component of the huge German chemical trust IG Farben and showed that Prontosil was the first medicine ever discovered that could effectively treat a range of bacterial infections inside the body.[3,4] It had a strong protective action against infections caused by streptococci, including blood infections, childbed fever, and erysipelas, and a lesser effect on infections caused by other cocci.

Few people today would deny that 1936 was the turning point in the history of puerperal infection, one of the most common cause of death during childbirth, and that the arrival of Prontosil brought about the change: obviously when penicillin became available in 1945 the situation became better still, because that antibiotic is an even more potent antistreptoccal agent than the sulfonamides, but it is evident that even if penicillin had not arrived when it did, the story of streptococcal puerperal fever would not have been very different.



Graphic 2-1: Decline in puerperal sepsis mortality in England and Wales, 1928–1948. The average figure for the years 1928–30 istaken as 100 and the total for each subsequent year is expressed in terms of that.

In 1935 Tréfouël and his colleagues at the Pasteur Institute observed that Prontosil had no effect at all in the test tube, exerting its antibacterial action only in live animals; they soon surprised the scientific world by the suggestion that the red dye was probably a prodrug and that was metabolized into two pieces inside the body, to a much simpler compound, p-aminobenzene sulfonamide. The discovery helped establish the concept of "bioactivation" and dashed the German corporation's dreams of enormous profit; the active sulfanilamide had been known for many years being synthesized in 1906 and was widely used in the dye-making industry; its patent had since expired and the drug was available to anyone. These findings naturally led to a change-over in human therapy from red prontosil to the simpler and cheaper compound which we soon came to know by the name Sulfanilide, the first of the ‘‘sulfa drugs’’.

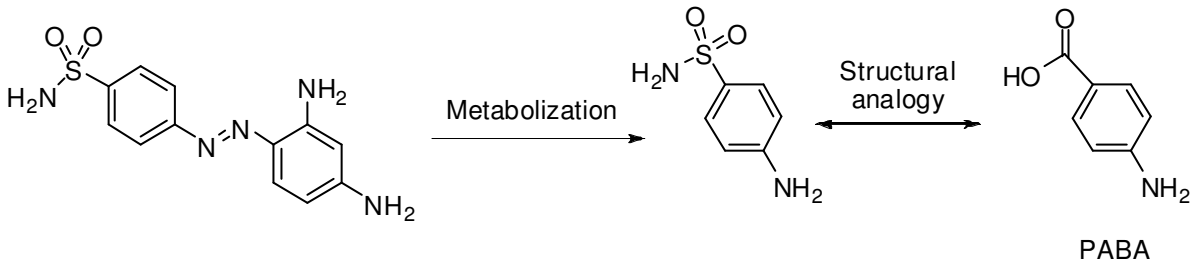


Figure 2-1

The important role of sulfonamide is due to its structural analogy to p-Aminobenzoic acid (PABA) which is needed in bacteria organisms for the synthesis of folic acid; they interfere with folate metabolism in the bacterial cell by competitively blocking the biosynthesis of tetrahydrofolate, which acts as a carrier of one-carbon fragments and is necessary for the ultimate synthesis of nucleic bases (most notably thymine, but also purine bases) but also for the synthesis of DNA, RNA and bacterial cell wall proteins. Unlike mammals, bacteria and protozoan parasites usually lack a transport system to take up preformed folic acid from their environment. Most of these organisms must synthesize folates, although some are capable of using exogenous thymidine, circumventing the need for folate metabolism.

Thus folate deficiency hinders DNA synthesis and cell division, affecting RNA transcription, and subsequent protein synthesis. Sulfonamides are capable to interfere with the metabolic processes in bacteria that require PABA in particular, having a greater affinity than p-aminobenzoic acid, they compete as a substrate of the enzyme dihydropteroate synthetase in the conversion of dihydropteroate diphosphate in dihydropteroic acid.

The result of this discovery was a sulfa craze. For several years in the late 1930s hundreds of manufacturers produced tens of thousands of tons of myriad forms of sulfa. This and nonexistent testing requirements lead to the **ELIXIR SULFANILAMIDE DISASTER** in the fall of 1937; in the same year S. E. Massengill Co., a pharmaceutical manufacturer, created a preparation of sulfanilamide using diethylene glycol as a solvent, and called the preparation "Elixir Sulfanilamide". Diethylene glycol is poisonous to humans, but the company's chief pharmacist and chemist, was not aware of this, although it was known at the time. At least 100 people were poisoned with diethylene glycol and died and this led to the passage of the Federal Food, Drug, and Cosmetic Act in 1938 but, as the first and only effective antibiotic available in the years before Penicillin, sulfa drugs continued to thrive through the early years of World

War II and they are credited with saving the lives of tens of thousands of patients. Sulfa had a central role in preventing wound infections during the war: in fact american soldiers were issued a first aid kit containing sulfa powder and were told to sprinkle it on any open wound.

Figure 2-2

Many thousands of molecules containing the sulfanilamide structure have been created since its discovery (by one account, over 5400 permutations by 1945), yielding improved formulations with greater effectiveness and less toxicity.

Sulfonamides, however, are not only used as competitive inhibitors of the enzyme dihydropteroate synthetase but they have been in clinical use for over 50 years, because of their antibacterial and antimycotic activity, for example in the treatment of many diseases like:

- pneumonia caused by *Pneumocystis Carinii*,
- drug-resistant Malaria and Toxoplasmosis,
- some sexually transmitted infections (*Trachoma, Clamydia, Chancroid*),
- in inflammatory bowel disease,
- for respiratory infections for special problems (e.g. infection with *Nocardia*),
- for acute urinary tract infection
- for infected burns.

Moreover these molecules are still widely used for conditions such as acne and urinary tract infections, and are receiving renewed interest for the treatment of infections caused by bacteria resistant to other antibiotics.

Unsaturated sulfonamides were also identified as potent, and irreversible inhibitors of cysteine proteases[5], which are essential to the life cycles of many pathogenic protozoa; preliminary

biological evaluation of some of this molecules has shown a promising pharmacological activity; this kind of structures have been studied even in relation with their ability to inhibit a series of matrix metalloproteinases, particularly gelatinase A, collagenase-3, and stromelysin-1 and for the treatment of multiple sclerosis, artherosclerotic plaque rupture, aortic aneurysm, heart failure, left ventricular dilation, restenosis, periodontal disease, or other autoimmune or inflammatory disorders dependent upon tissue invasion.[6]

For example **ACETAZOLAMIDE** (trade name Diamox) is a carbonic anhydrase inhibitor that blocks the formation of H^+ and H_2CO_3 from CO_2 and H_2O with the end result that bicarbonate is excreted in the urine. For glaucoma sufferers, the drug decreases fluid formation in the eye resulting in lower intraocular pressure. In epilepsy, its main use is in absence seizures, with some benefit in other seizure syndromes. It is also used to decrease generation of cerebrospinal fluid in benign intracranial hypertension and has shown efficacy in autosomal dominant hyperkalemic periodic paralysis. It's been demonstrated in drug trials to relieve symptoms associated with dural ectasia in indivduals with Marfan Syndrome. Off-label uses include Acetazolamide as a conjunction drug to merely assist patients with sleep apnea by lowering blood pH and encourage respiration.

FUROSEMIDE (most common trade name Lasix marketed by Sanofi-Aventis) is a loop diuretic used in the treatment of congestive heart failure and edema associated with heart failure, hepatic cirrhosis, renal impairment, nephrotic syndromeedema, hypertension, adjunct in cerebral/pulmonary edema where rapid diuresis is required (IV injection).

It is also sometimes used in the management of severe hypercalcemia in combination with adequate rehydration. Moreover it has been used to prevent thoroughbred and standardbred race horses from bleeding through the nose during races.

Along with some other diuretics, furosemide is also included on the World Anti-Doping Agency's banned drug list due to its alleged use as a masking agent for other drugs.

BUMETANIDE too (trade name Bumex, marketed by Hoffmann-La Roche) is a loop diuretic of the sulfamyl category to treat heart failure. It is often used in patients in whom high doses of Furosemide are ineffective with the main advantage consisting in Bumetanide higher bioavailability.

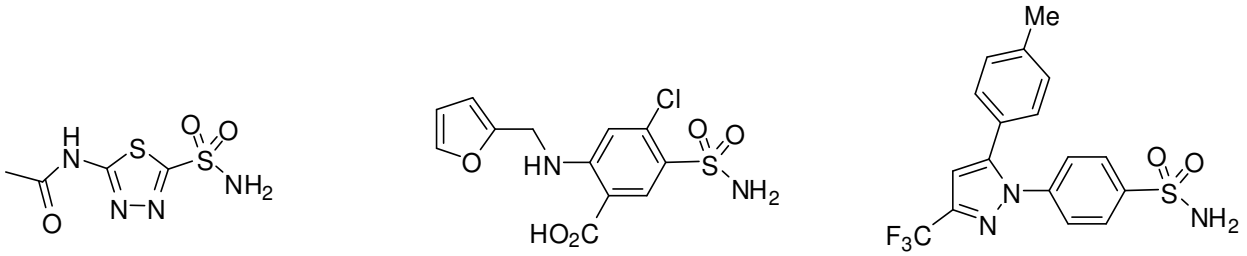


Figure 2-3

CELECOXIB (trade name Celebrex, marketed by Pfizer) is non-steroidal anti-inflammatory drug (NSAID) being a highly selective COX-2 inhibitor and primarily inhibits this isoform of cyclooxygenase (inhibition of prostaglandin production), whereas traditional NSAIDs inhibit both COX-1 and COX-2 ; it is used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms, and to reduce numbers of colon and rectum polyps in patients with familial adenomatous polyposis.

DORZOLAMIDE (trade name Trusopt) is a carbonic anhydrase inhibitor used to lower increased intraocular pressure in open-angle glaucoma and ocular hypertension. It is an anti-glaucoma agent and topically applied in the form of eye drops(dorzolamide hydrochloride ophthalmic solution). This drug has the particularity to be the first drug in human therapy (market introduction 1995) which resulted from structure-based drug design developed by University of Florida researchers.

HYDROCHLOROTHIAZIDE (trade names: Apo-Hydro, Aquazide H, Dichlotride, Hydrodiuril, HydroSaluric, Microzide, Oretic) belongs to the thiazide class of diuretics, like Furosemide and Bumetanide and acts on the kidneys to reduce sodium reabsorption in the distal convoluted tubule. This increases the osmolarity in the lumen, causing less water to be reabsorbed by the collecting ducts leading to increased urinary output.

It is effective for nephrogenic diabetes insipidus (paradoxical effect, which decreases urine formation) and is also sometimes used for hypercalciuria and Dent's Disease.

Thiazides are also used in the treatment of osteoporosis decreasing mineral bone loss by promoting calcium retention in the kidney, and by directly stimulating osteoblast differentiation and bone mineral formation.

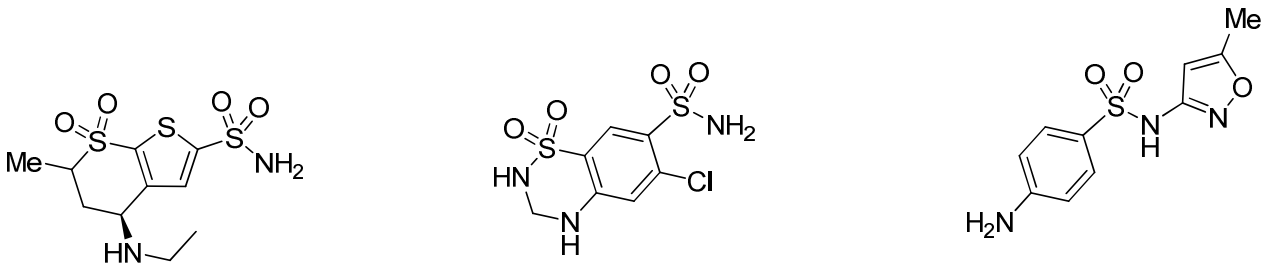


Figure 2-4

SULFAMETHOXAZOLE (trade names Bactrim, Septrin, or Septra) is a sulfonamide bacteriostatic antibiotic most often used as part of a synergistic combination with trimethoprim in a 5:1 ratio in co-trimoxazole. Its primary activity is against susceptible forms of Streptococcus, Escherichia coli, Haemophilus influenzae, and oral anaerobes.

SULTIAME is a sulfonamide and inhibitor of the enzyme carbonic anhydrase. It is used as an anticonvulsant with specific effects in benign focal epilepsies of childhood as well in West syndrome and other refractory epilepsies.

Among the huge number of therapeuthic sulfonamides we must name CHLORTALIDONE, XIPAMIDE, CLOPAMIDE, INDAPAMIDE, MEFRUSIDE, METOLAZONE, all thiazide-like diuretics, DICLOFENAMIDE and ETHOXYZOLAMIDE a sulfonamide medications that function as a carbonic anhydrase inhibitors. They are used in the treatment of glaucoma, duodenal ulcers, MAFENIDE (Sulfamylon) is a sulfonamide often used to treat severe burns, PROBENECID is used to combat influenza increasing antibiotic concentrations in serious infections while SUMATRIPTAN is a triptan drug for the treatment of migraine headaches.

Finally, one of the last applications concerns the use of a series of polyhalobenzene sulfonamides as chemotherapic drug[7], showing the ability to inhibit the growth of a variety of human tumour cell lines, like cervical adenocarcinoma or human breast tumour.

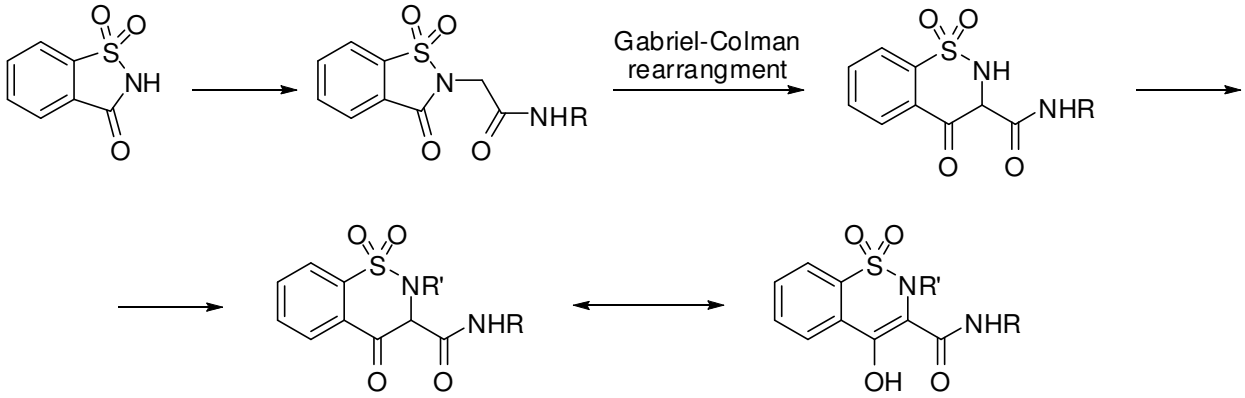
2 SULTAMS

Sultams, containing a functional group very similar to sulfonamidic, have been incorporated into a wide range of known biologically active compounds, either as a substituent group or as a replacement of another ring. Moreover, since the introduction of Oppolzer's camphorsultam, sultams have been used as an instrument to control the stereochemical course of many reactions and they rank today among the most practical chiral auxiliaries available for organic chemistry.

2.1 Sultams in medicinal chemistry

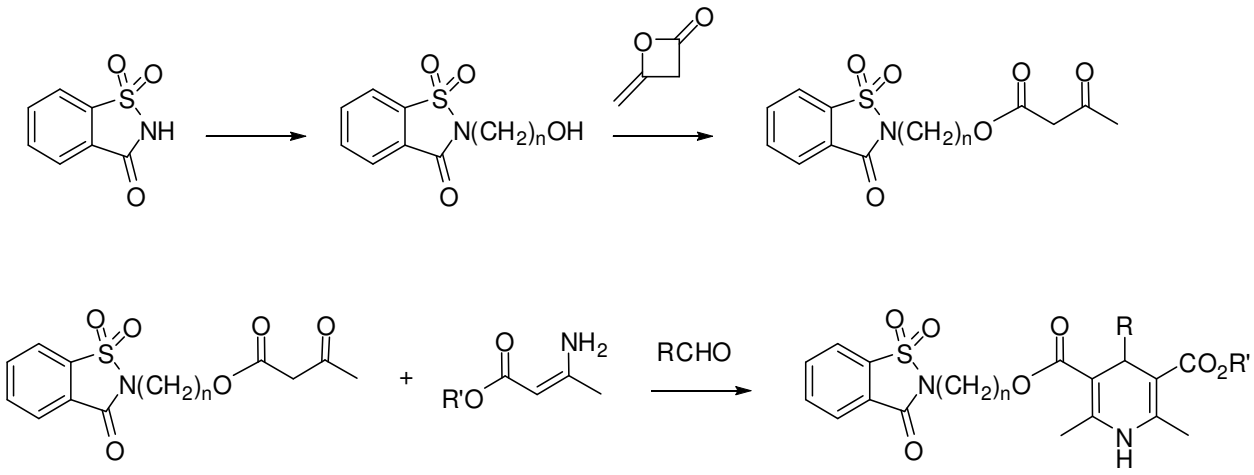
One of the first example in which a sultam ring is employed as pharmacological active compound was reported in 1971 by Lombardino[8]: in his work he investigated the anti-inflammatory activity of a series of 3-carboxamides of 2-alkyl-4-hydroxy-2H-1,2-benzothiazine 1,l-dioxide. Inspired by a work by Abe and coworkers[9], the first to apply the principle of the Gabriel-Colman rearrangement of phthalimide to the rearrangement of *N*-phenacylsaccharin, Lombardino studied a powerful procedure for isomerizing saccharin-2-acetic ester and acetamides to 4-hydroxy-2H-l,2-benzothiazine-3—esters/amides 1,1-dioxide in DMSO (Scheme

2-1) and compared their anti-inflammatory activity to that of the clinically useful drugs



Scheme 2-1

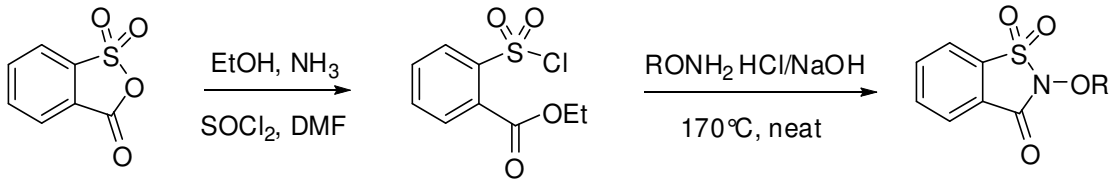
indomethacin and phenylbutazone. The good results obtained showed that most compounds were inhibitors of carrageenin-induced rat foot edema and some exceeded phenylbutazone in potency. Sunkel et coworkers[10] in 1988 reported a series of l,4-dihydropyridines bound to 1,2-benzisothiazol-3-one (Scheme 2-2). They synthesized and evaluated them for their ability to inhibit platelet aggregation induced by collagen in human platelet-rich plasma (PRP) and to protect mice against experimental thrombosis.



Scheme 2-2

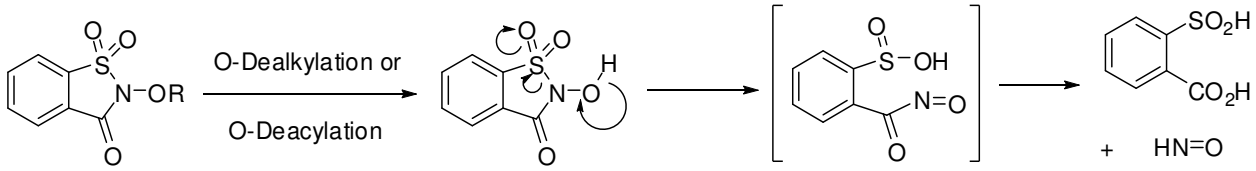
The results showed that the compounds were in vitro inhibitors of collagen-induced platelet aggregation and that most of them were also effective in reducing mortality in antithrombotic assay conducted in mouses.

In 1995 Nagasawa et Al[11]. described for the first time the synthesis of *N*-hydroxysaccharin, (Scheme 2-3) a nitroxyl prodrug, starting from *o*-sulfobenzoic anhydride the oxygenated saccharine analogue;



Scheme 2-3

this molecule, when treated with aqueous NaOH, liberates nitroxyl, a known inhibitor of aldehyde dehydrogenase (AlDH). The author makes a paragon between his new compound and Piloty's acid (benzenesulfohydroxamic acid) another well known prodrug of nitroxyl by releasing it either by the cytochrome P-450-catalyzed dealkylation of the *O*-alkyl group or by esterase-mediated deacylation of the *O*-acyl moiety (Scheme 2-4).



Scheme 2-4

Results indicated that hydroxysultam was a much more stable molecule and this was reflected in the differential inhibition of yeast AlDH by Piloty's acid and *N*-hydroxysaccharin respectively.

Always talking about saccharine-derived compounds, we must mention the 3-aryl pyrrolidine derivative showed in Figure 2-1: the development of selective and potent ligands for serotonin

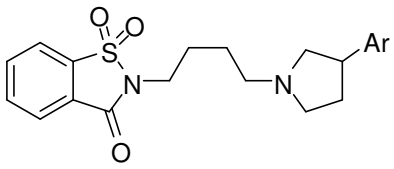
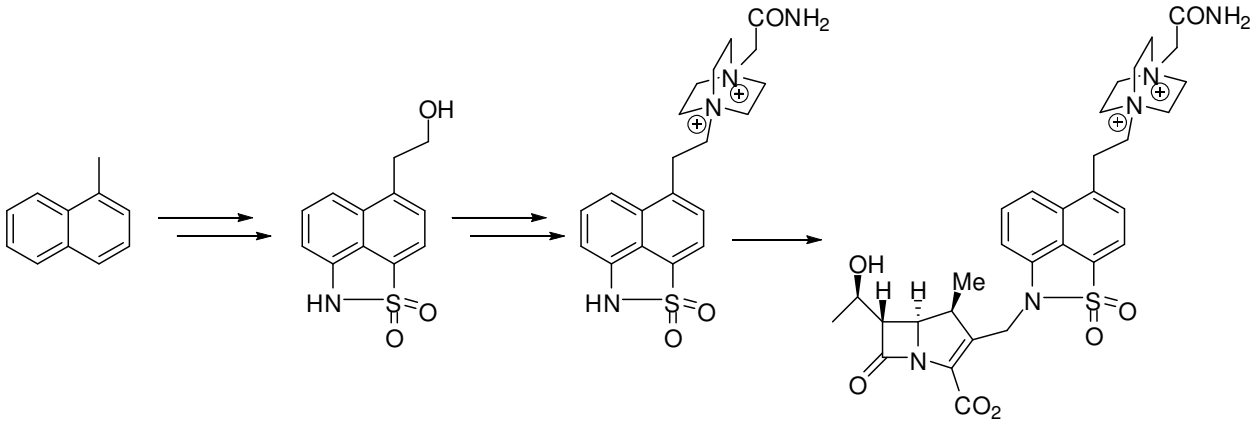


Figure 2-1

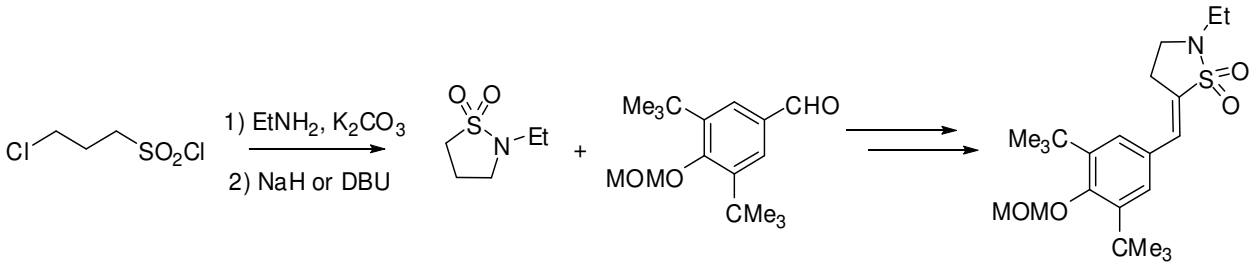
receptors has attracted a considerable interest, since they are promising drug candidates for treatment of mood and anxiety disorders. This molecule, synthesized in 1999 by Ahn et Al.[12], showed good affinity and selectivity toward serotonin 1A receptor (5-HTIA): is noteworthy notice that all the examples showed until now use as starting material the natural occurring sultam saccharine.

Much more interesting is the example reported by Miller, Humphrey and Lieberman[13] in which the synthesis of a naphthosultam based side chain of a novel anti-MRSA carbapenem, is carried out in a seven step protocol (Scheme 2-5) with an overall yield of 27%.



Scheme 2-5

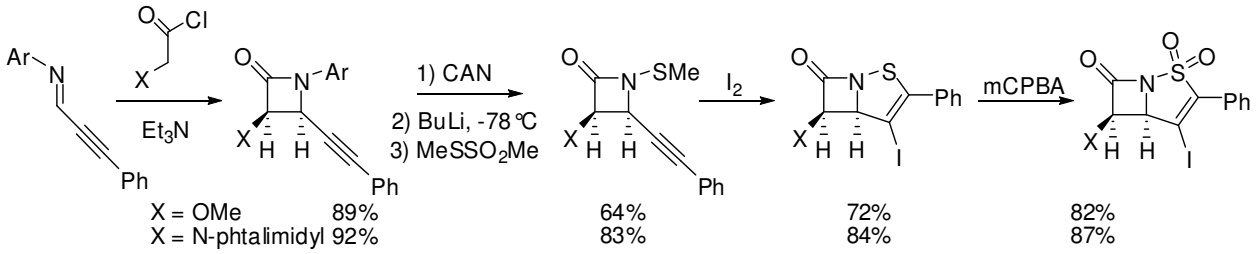
The synthesis has been reproducibly demonstrated on the multikilogram scale in high purity and has allowed the production of side chain essential for the large-scale synthesis of the novel β-lactam antibiotic. In the same year Matsumoto and coworkers[14] described the synthesis of novel γ-sultam derivatives containing the di-*tert*-butylphenol antioxidant moiety.



Scheme 2-6

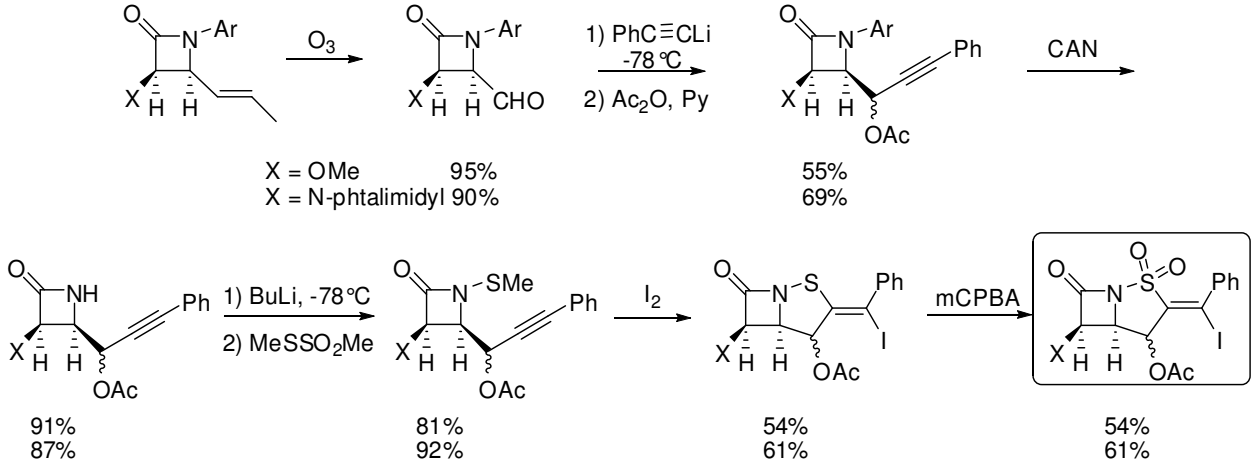
Along with this employment of sultams, bicyclic β-lactam ring systems, that are isomeric to those of the penicillin, penem, and clavulanic acid families of antibiotics, have been studied as an alternative to the well known antibiotics:

in particular penem-monobactam hybrid (Scheme 2-7)



Scheme 2-7

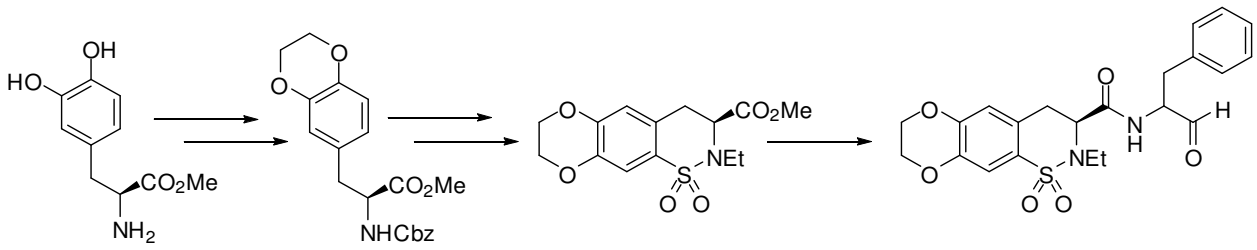
and clavulanic acid-monobactam hybrid (Scheme 2-8) have been synthesized and studied.[15]



Scheme 2-8

Among the several compounds synthesized, γ-sultam shoved in Scheme 2-6 displays multiple inhibition of cyclooxygenase (COX)-2 and 5-lipoxygenase (5-LO), as well as inflammatory cytokines interleukin (IL)-1 production (similar to tenidap) and also good selective COX-2 inhibition like celecoxib. The molecule, designated as an agent having both NSAID and cytokine modulating properties and exerteding excellent anti-inflammatory activity without any ulcerogenic effects, is now under clinical trials.

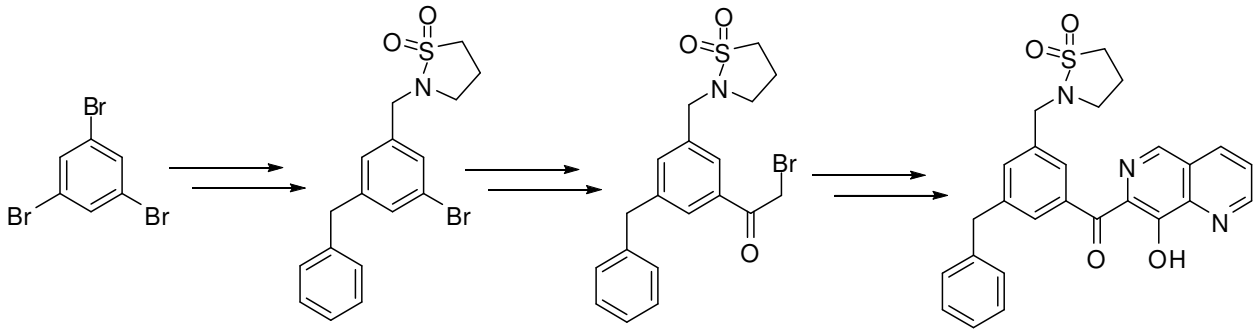
In 2001 Bihovsky and coworkers discovered a novel class of benzothiazine peptide mimetics[16] that potently and selectively inhibit calpain I. Calpains, nonlysosomal calcium-activated cysteine proteases present in most mammalian cells including neurons, have been implicated in neurodegeneration following cerebral ischemia, traumatic brain injury, spinal cord trauma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, motor neuron damage, and muscular dystrophy. Calpain I inhibitors appear to prevent some



Scheme 2-9

of the damage caused by overactivated calpain under pathophysiological conditions and are therefore being investigated as possible treatments for neurodegeneration resulting from cerebral ischemia, traumatic brain injury, or spinal cord trauma.[17] The sultams synthesized (Scheme 2-9) inhibit calpain I with a strong efficiency and ranks among the best reversible and selective inhibitors evaluated.

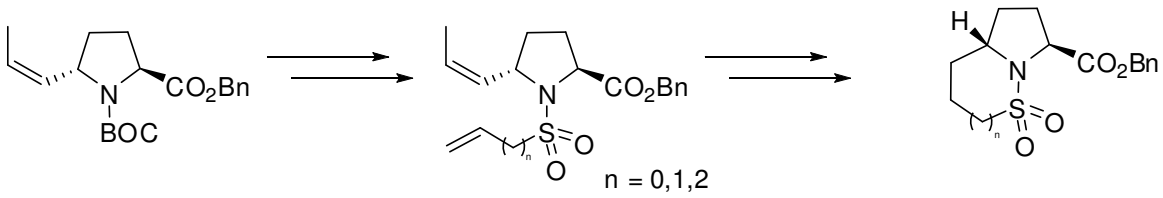
Some years later, the group of Zhuang prepared and studied the inhibition properties of a sultam-naphthyridine[18] (Scheme 2-10) of the strand transfer of the integration process catalyzed by Human immunodeficiency virus-type 1 integrase: results indicate



Scheme 2-10

very low values of IC50 with an inhibition of 95% of the spread of HIV-1 infection in cell culture. It does not exhibit cytotoxicity in cell culture showing a good pharmacokinetic profile when dosed orally to rats; moreover the antiviral activity of the sultam-naphthyridine and its effect on integration were confirmed using viruses with specific integrase mutations.

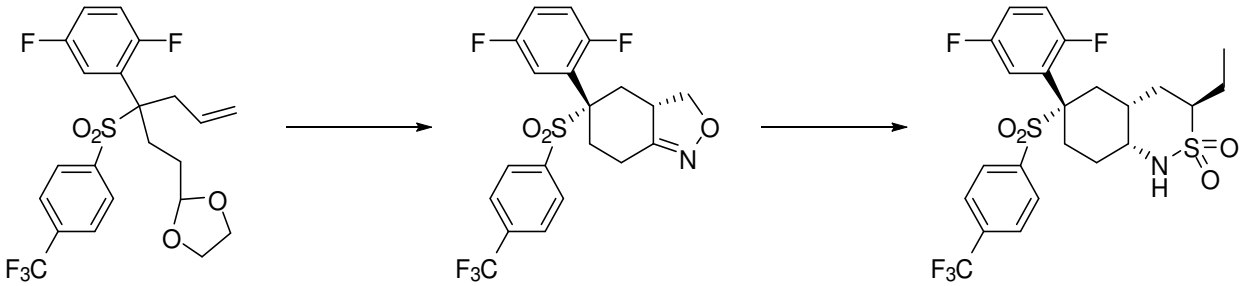
In 2003 Hanessian[19] prepared a series of bicyclic sultams as constrained proline analogues; the synthesis, performed from the known 4-cis-(2-propenyl)-*N*-Boc-L-proline benzyl ester, uses as key step a ring-closure metathesis reaction. The sultams were synthesized (Scheme 2-11) varying in the size of the second ring (5,6 and 7 members) and he studied the application to the design of potential thrombin inhibitors and its activity against the enzyme thrombin



Scheme 2-11

Human neutrophil elastase (HNE) is a serine enzyme which is one of the most destructive proteolytic enzymes, being able to catalyze the hydrolysis of the components of connective tissue. It has been implicated in the development of diseases, such as emphysema, cystic fibrosis, and rheumatoid arthritis. In a recent paper[20] is demonstrated the activity of β-sultams as serine protease inhibitor, moreover is reported the use of a 3-oxo β-sultams that, acting both as sultam that lactam, represent a novel class of inactivators of elastase which can act by either sulfonylation or acylation of the active site serine residue.

Alzheimer's disease (AD) is a progressive and chronic neurodegenerative disease that leads to loss of intellect and memory in those afflicted. AD affects around 18 million people worldwide, and with the limited therapies currently available, this represents a major unmet medical need. One of the main pathological characteristics of this disease is the production of the 40-42 amino acid amyloid-β (Aβ) peptide, in which the protease enzyme γ-secretase plays a critical role through cleavage of the β-amyloid precursor protein (βAPP). γ-Secretase, therefore, represents a potential target for AD therapeutic intervention and this theme is faced in a paper by Scott[21] in which, exploiting as the key transformation a highly diastereoselective intramolecular nitrile oxide cycloaddition, a practical asymmetric synthesis of a γ-secretase inhibitor is described (Scheme 2-12).

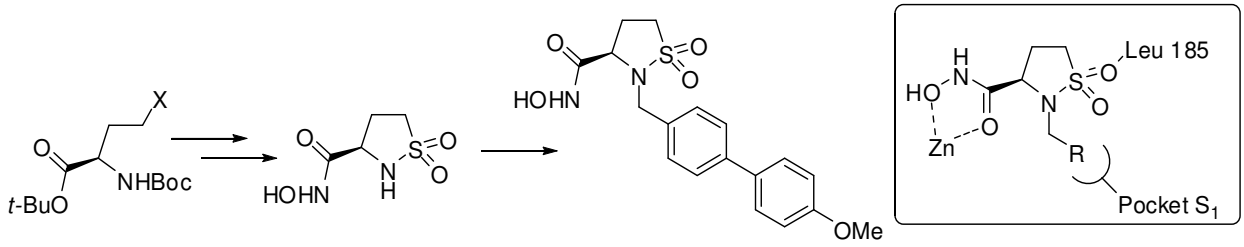


Scheme 2-12

Several recently approved biologics have revolutionized the treatment of autoimmune/inflammatory conditions, including rheumatoid arthritis (RA) and Crohn's disease. These agents work by sequestering tumor necrosis factor-α (TNF-α), which is an

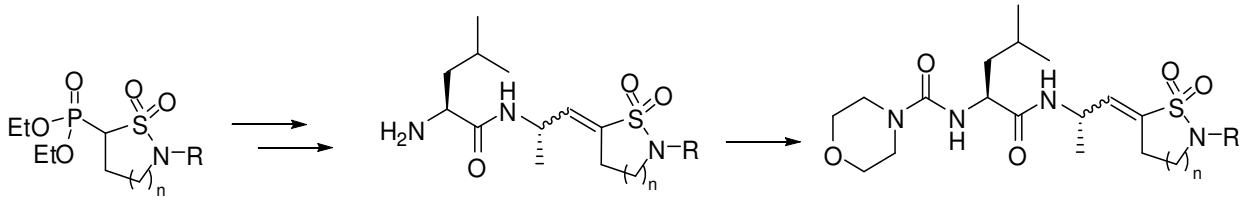
inflammatory cytokine overproduced in these diseases. There is a great deal of interest in finding a bioavailable small molecule that can mimic these marketed biologics. As a member of the ADAM (a disintegrin and metalloproteinase) family, MMPs is contained within the metzincin superfamily and it was shown that MMP inhibitors could prevent the release of TNF-α from cells through their interaction with TACE.

Hence, many groups searched for MMP inhibitors and in 2004 Cherney and coworkers[22] described a novel set of sultam hydroxamates binding the active site zinc by the classical bidentate ligation with hydroxamate; the rest of the inhibitor sulfonyl of the sultam can be positioned within the hydrogen bond distance of Leu-185 (Scheme 2-13).



Scheme 2-13

Malaria is the major life-threatening parasitic disease in tropical and sub-tropical regions. Worldwide, there are at least 300 million acute cases of malaria and more than 1 million deaths each year, mostly young children infected with Plasmodium falciparum. With the rapid spread of multidrug-resistant P. falciparum strains, the development of safe and effective antimalarials has become an important strategy towards achieving effective control of malaria. Cysteine proteases, like Falcipain-2, regulate a broad spectrum of physiological functions and. in humans, elevated levels of these enzymes can lead to disease states such as osteoporosis, rheumatoid arthritis and cancer.



Scheme 2-14

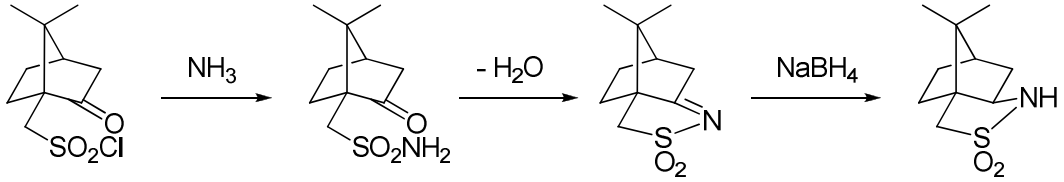
In parasites, they play a crucial role in reproductive function and metabolism as it is likely involved in the hydrolysis of haemoglobin that produces free amino acids required for parasite survival. Moreira, Iley and coworkers[23] in a 2006 paper, describe the synthesis of a dipeptide

vinyl sultams consisting in the preparation of a γ- and δ-sultam core derivatives via the Wittig–Horner reaction and then its coupling with the dipeptide moiety (Scheme 2-14). Although weakly active, vinyl sultams are selective for recombinant falcipain-2 and *Plasmodium falciparum* W2.over papain.

2.2 Sultams as chiral auxiliaries

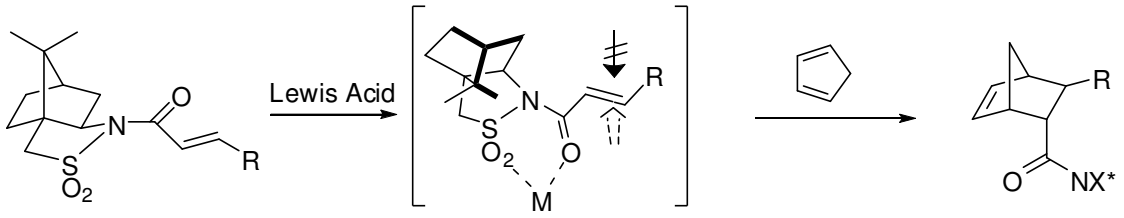
Since early '80, with the introduction of Oppolzer's camphorsultam, the use of 1,2-isothiazolidine 1,1-dioxides as an instrument to control the stereochemical course of many reactions has been widespreading more and more and they rank today among the most practical chiral auxiliaries available for organic chemistry, having important applications in asymmetric version of several reactions.

Camphorsultam, readily available from camphor sulfonyl chloride (Scheme 2-15), find for



Scheme 2-15

example application in Diels-Alder reaction and was initially conceived with the scope to electronally enhance the dienophilicity ot the *N*-enoyl derivative; indeed in the presence of $EtAlCl_2$ or $TiCl_4$, cyclopentadiene adds redily both with acryloyl and with crotonyl derivative[24]. The adducts were formed with excellent *endo*- and facial selectivities; moreover $EtAlCl_2$ promoted cycloaddition of butadiene and isoprene too (Scheme 2-16).

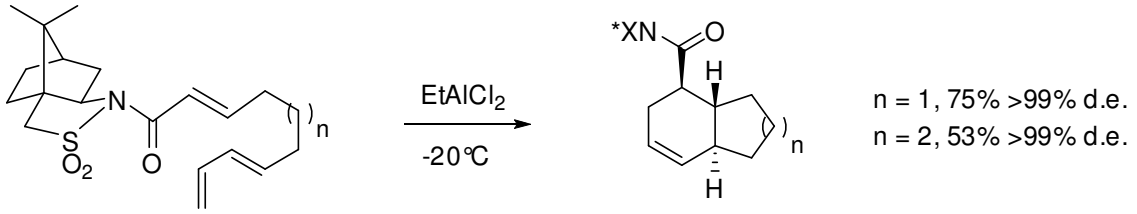


Scheme 2-16

R	Diene	Lewis Acid	T (°C)	Yield (%)	d.e. (%)
H	Cyclopentadiene	$EtAlCl_2$	-130	83	99
Me	Cyclopentadiene	$TiCl_4$,	-78	83	>99
H	1,3-butadiene	$EtAlCl_2$	-78	85	99
H	isoprene	$EtAlCl_2$	-94	68	>99

Table 2-1

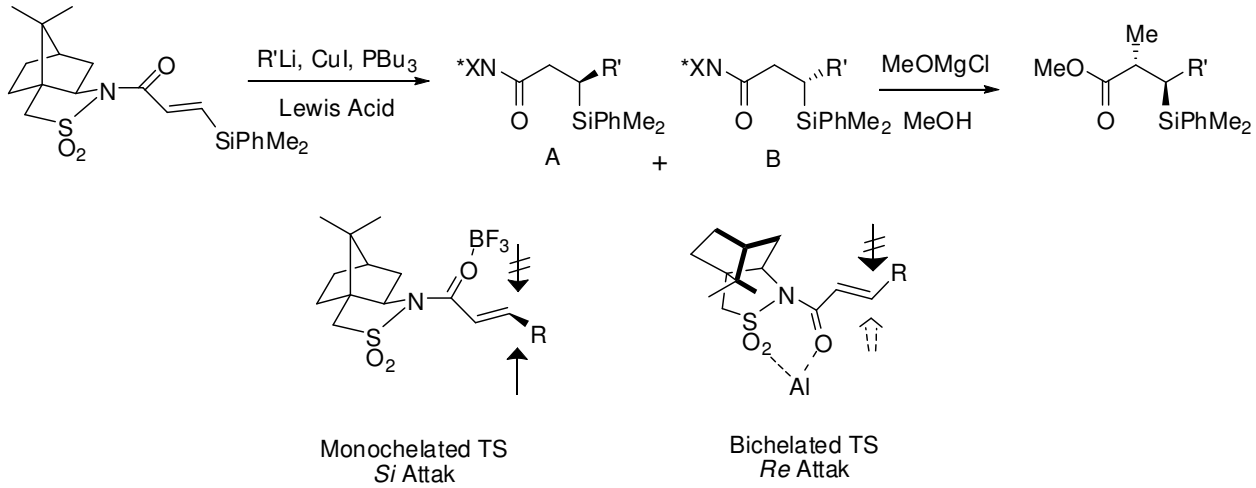
Even trienoyl sultams cyclize, on treatment with $EtAlCl_2$, with exceptional *endo*- selectivity to give bicylcic compounds each one in >99% d.e. (Scheme 2-17);



Scheme 2-17

all this results prove that reactions conducted with sultams are in great consistence with the prediction.[25]

Camphorsultams has been used too for the synthesis of β-silylcarboxyl derivatives by 1,4-addition of organocopper reagents: this useful and versatile building block has been synthesized by Oppolzer and coworkers[26] treating *N*-(β-silylenoyl) sultams with alkenyl- and alkyl-copper reagents obtaining good diasterofacial selectivities (86-96%, Scheme 2-18Table 2-2); quite interesting is the obtainment of the epimer only by changing the lewis acid:



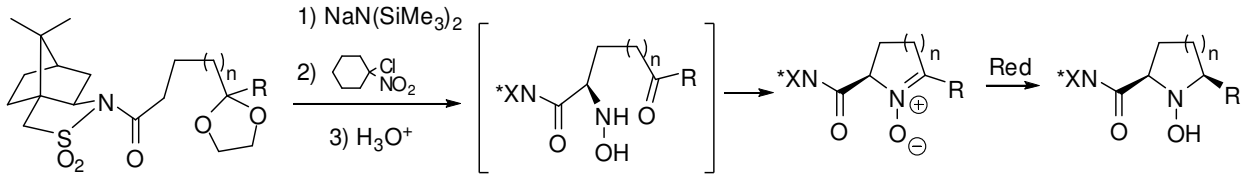
Scheme 2-18

R	Lewis Acid	Yield (%)	Ratio A/B
Vinyl	$BF_3{\cdot}OEt_2$	60	97:3
Vinyl	$EtAlCl_2$	57	2:98
(Z) Prop-1-enyl	$EtAlCl_2$	65	1:99
(Z) Prop-1-enyl	$EtAlCl_2$	67	2:98
Me	$EtAlCl_2$	61	3.3:96.7
i-Pr	$EtAlCl_2$	64	3:97
Ph	$EtAlCl_2$	86	0:100

Table 2-2

this striking difference was attribute by the authors to the mono-coordinated transition state with BF_3, with *anti* disposition of SO_2/CO groups instead of the Al-di-chelated transition state favoring reverse side attack.

Always Oppoltzer[27] proposed the use of *N*-(ε-ketoacyl) or *N*-(δ-ketoacyl) sultam acetal as the starting compound for an asymmetric electrophilic –hydroxyamination for the synthesis of *N*-hydroxy-piperidines or -pyrrolidines;



Scheme 2-19

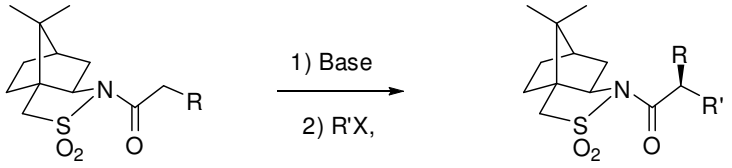
R	n	Reducing agent	Yield of nitrone (%)	Yield (%)
n-$C_{11}H_{23}$	2	H_2, Pd/C	70	90
n-C_3H_7	2	H_2, Pd/C	72	92
n-C_7H_{15}	1	$NaCNBH_3$	64	97

Table 2-3

treatment of acylsultam with sodium hexamethyldisilazide, 1-chloro-1-nitrocyclohexane and HCl furnishes the diasteromerically pure nitrone which, in turn, is reduced to the cis-2,6-disubstituted piperidine, by palladium catalyzed hydrogenation, or to the cis-2,5-disubstituted pyrrolidine by treatment with sodium cyanoborohydride. The heterocycles obtained can also undergo deoxigenative decarboxylation leaded by trapping with hydride or organometal addition[28]: this methodology allow the obtainment of important key intermediate for the synthesis natural compound as (-)-Coniine, (-)-Solenopsin A and (-)-Xenovenine.

N-enoyl camphorsultam has been employed also in oxidation reaction:[29] treatment of the over and over quoted β-substituted α,β-enoyl sultam with *N*-methyl morpholine-*N*-oxide in the presence of OsO_4 provided glycols with good diasteroselectivities (80-90%) and acceptable yields (63-79%); in addition, even the catalytic hydrogenation of β,β-disubstituted sultams[30] gave, in those days, unprecedented results with great topological control (91-98% d.e.) and excellent yields (93-99%).

Finally alkylation, one of the most simple but at the same time one of the most important methods for the asymmetric formation of carbon-carbon bond, can be carried out on acyl camphorsultam.[31]



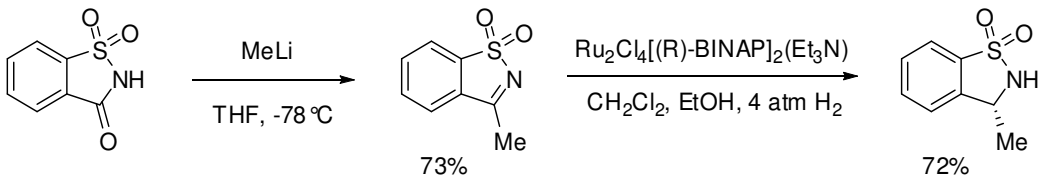
Scheme 2-20

R	R′	X	Base	Yield	d.e.
Me	$PhCH_2$	I	NaHDMS	100	96.5
Me	$Me_2C{=}CHCH_2$	Br	BuLi/10%ICA	82	98.8
Me	$HC{\equiv}CHCH_2$	Br	BuLi	82	98.3
Me	$tBuO_2CCH_2$	Br	NaHDMS	80	98.5
Me	$Me_2CH(CH_2)_3$	I	NaHDMS	89	99
OMe	$PhCH_2$	I	NaHDMS	81	99

Table 2-4

In 1990, to gain a deeper understanding and an even broader scope of the stereofacial directing bias of sultams, Oppolzer and coworkers[32] designed a related chiral sultam with the following characteristics: it is simple, but crystalline sultam containing a single stereogenic centre instead of the bornane skeleton; it does not contain any acidic proton at the carbon atom vicinal to the sulfinamido group; it allows easier NMR analysis and HPLC detection (having an aryl chromophore) of substrate and products.

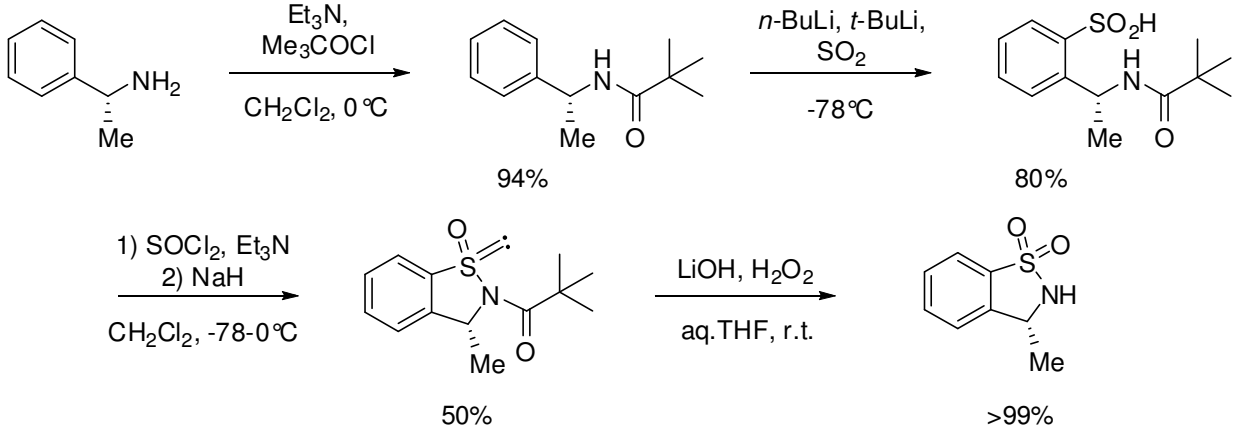
The first approach to obtain this molecule provides enantiomerically pure sultams from achiral saccharine; addition of MeLi in Et_2O to saccharine provide, after crystallization, the imine that, after asymmetric reduction, furnishes enantiomerically pure sultam



Scheme 2-21

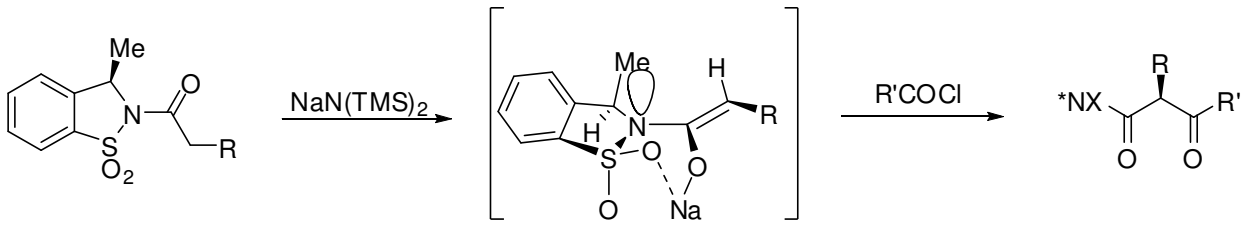
A second approach starts from α-phenethylamine and pass through its acylation with pivaloyl chloride leaded by *ortho* deprotonation using *n*-BuLi followed by *t*-BuLi and trapping of the di-

lithiated intermediate with SO_2; the so obtained sulfinic acid is converted into the sulfinyl chloride then cyclized with sodium hydride. Finally oxidation and reductive elimination of the protecting group lead to the desired product with an overall yield of 37%.



Scheme 2-22

Oppolzer initially, in order to explore the potentiality of the new saccharine-derives sultam, used the *N*-acyl benzosultam in reaction of alkylation, acylation and aldol condensation:[33] in particular *C*-acylation, accomplished by subsequent treatment with NaHDMS and a carboxyl acid chloride, afford the 1,3-dicarbonyl compound in high yield and d.e.(Scheme 2-23, Table 2-5).

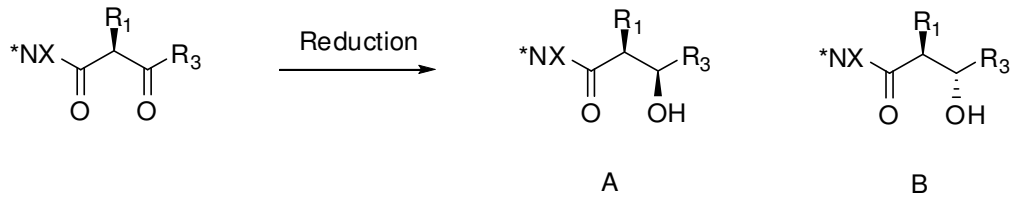


Scheme 2-23

R	R'	Yield	d.e.
Me	Ph	>99	99.4
Me	CH_2CHMe_2	>97	97
Et	Me	97.5	97.6

Table 2-5

The obtained compounds can be subjected to chelate-control reduction both with zinc borohydride, obtaining selectively the *syn*-aldol, while reduction with sodium tri-*s*-butyl borohydride afford the *anti*-aldol (Scheme 2-24, Table 2-6).

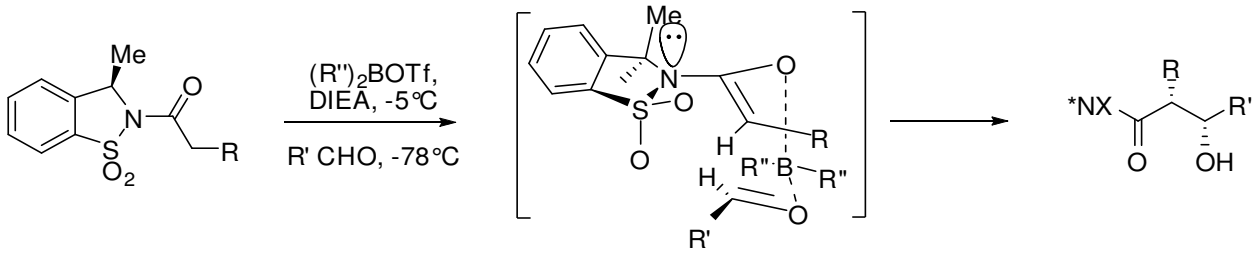


Scheme 2-24

R	R′	Reducing agent	Yield	Ratio A/B
Me	Me	$Zn(BH_4)_2$	81	91.3 : 8.7
Me	Ph	$Zn(BH_4)_2$	82	99.1 : 0.9
Me	Me	NaHB(*s*-Bu)$_3$	80	0.2 : 99.8
Me	CH_2CHMe_2	NaHB(*s*-Bu)$_3$	53	2.1 : 97.9

Table 2-6

Treatment of acyl benzosultam with dialkylboryl triflate and an aldehyde, produced the *syn*-aldols; again we observe an electrophilic attack to the opposite enolate face than observed in acylation but also in alkylation: this dichotomy is ascribed to the transition state (again involving a (Z)-enolate) in which the boron atom, being fully coordinated thus incapable of chelation with SO_2 (see Scheme 2-18), forces the enolate to adopt an electrostatically favored *N*-SO_2/CO-B *s-trans* conformation.

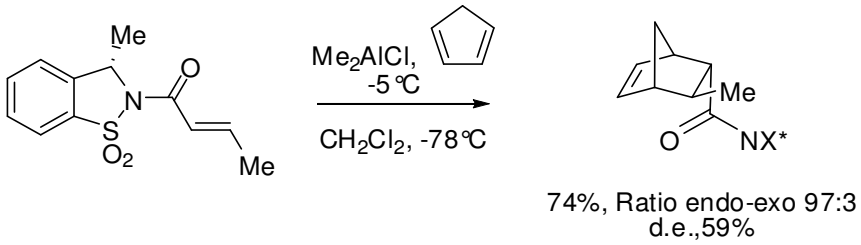


Scheme 2-25

R	R′	R″	Yield	d.e.
Me	Ph	Et	100	>99
Me	Me	Et	100	>99
Me	*i*-Pr	Et	99	>99
Me	*i*-Bu	Et	92	>99

Table 2-7

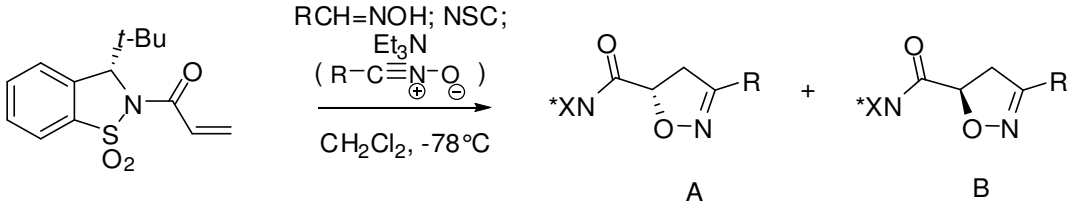
In the same year optically pure 3-methyl benzosultam has been employed also in asymmetric version of Diels-Alder cycloaddition[34]



Scheme 2-26

Oppolzer, basing on the challenging attempt made by Curran et Al.[35] who obtained good face selectivities in the addition of nitrile oxides to the *N*-acryloyl sultam, decided to investigate the reaction using the new auxiliary: unfortunately, 1,3-dipolar cycloaddition to *N*-acryloyl benzosultam proceeded with only moderate stereoface discrimination, giving products in ratio 79:21 at most; Oppolzer decided then to modify the substituent in position 3 of the benzosultam:[36] addition of *t*-BuLi to saccharine provided *t*-butyl imine that undergoes asymmetric hydrogenation only in negligible yield. On the other hand, reduction with the hydride obtained from $LiAlH_4$, *N*-Methylephedrine and 3,5-dimethylphenol afforded 3-*t*-butyl benzosultam in 81 % e.e. (then purified to the enantiomerically pure compound by fractional distillation); alternatively the racemic compound obtained by the reduction with $NaBH_4$ has been resolved by crystallization after the conversion into the *N*-camphorsulfonyl derivative.

The so obtained chiral auxiliary has been tested in the cycloaddition of various nitrile oxides to *N*-acryloyl 3-*tert*-butyl benzosultam giving dramatic increase in diasteroselectivities exerted by the sterically more demanding auxiliary, even exceeding values provided by the classical camphorsultam (Scheme 2-27, Table 2-8).

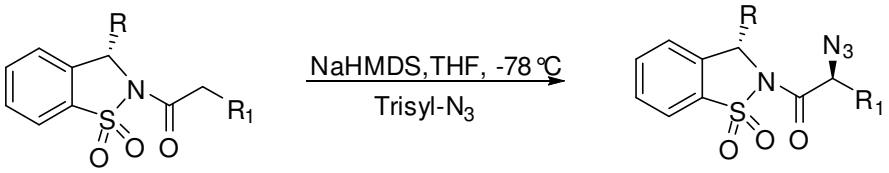


Scheme 2-27

R	Yield	Product ratio
t-Bu	87	98 : 2
Ph	77	95 : 5
Et	81	95 : 5
Me	81	96 : 4

Table 2-8

Some years later, when enantiomerically pure 3-alkyl benzosultam become more accessible,[37] with the new reductive methodology introduced by Ahn and coworkers, it has been possible to study the influence of substituent in position 3, in reaction like asymmetric azidazion.



Scheme 2-28

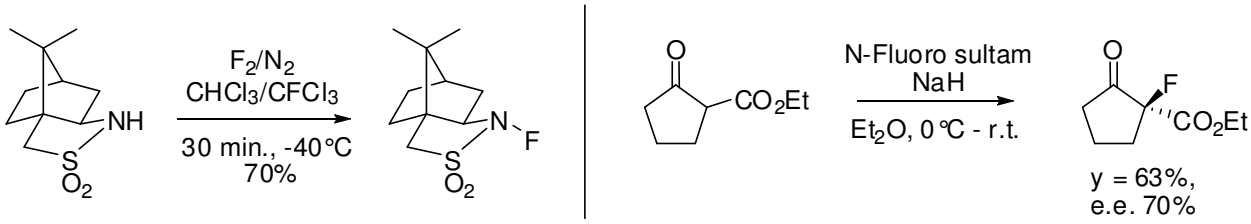
R	R′	Yield	Product ratio
Me	All	72	95 : 5
i-Pr	All	73	95 : 5
t-Bu	All	96	98 : 2
t-Bu	Bn	95	99 : 1

Table 2-9

2.3 Sultams as fluorinating agent

The introduction of fluorine substituents in strategical position of organic compound is an extremely effective tool for modifying reactivity both for biological application[38] and for analytical chemistry. Enormous effort have been made to solve the synthetic problems and to avoid the use of the potentially hazardous perchloryl fluoride or fluorooxy compounds, reagents commonly used until then. From the 80's on, new *N*-fluoro compounds have been developed as new fluorinating agents effective, for example, to fluorinate a metal enolate and to convert it into a α-fluoro carbonyl compound; among these new molecules we must mention *N*-fluoro-2-pyridone,[39] *N*-fluoro quinuclidinium fluoride,[40] *N*-fluoro sulfonamides[41] and *N*-fluoro-pyridinium triflate[42] all molecules that for the enolate approach, displayed good control of regioselectivity whereas stereoselectivity still remained an unsolved problem.

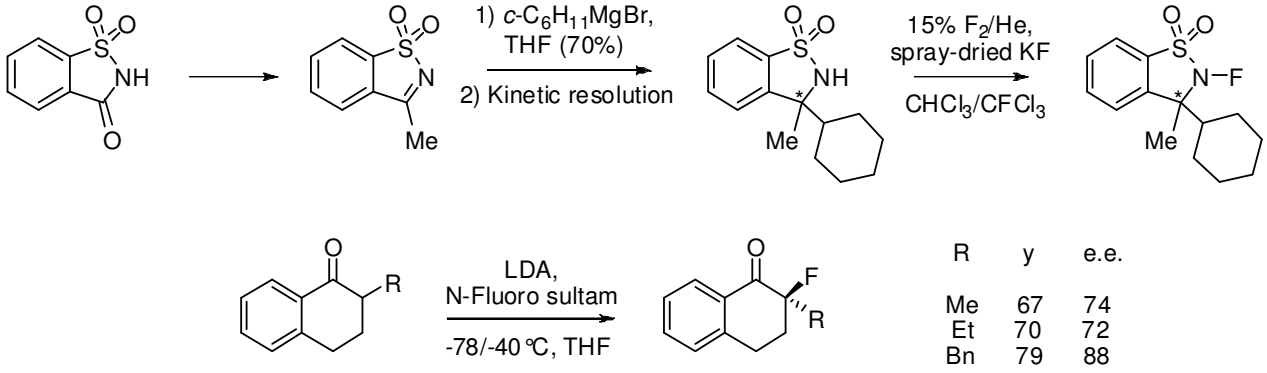
In 1988 Nang and Differding[43] described the synthesis and the application of two camphor derived *N*-fluoro sultams as the first example of enantioselective reagents; the camphorsultam, readily obtained according to Oppolzer's procedure, is fluorinated by treatment with 10% F_2/N_2 in a $CHCl_3/CFCl_3$ solution at -40°C. Their pioneering results showed both a good reactivity with various metal enolates and good enantiomeric excesses even if depending strongly on the structure of the enolate (Scheme 2-29).



Scheme 2-29

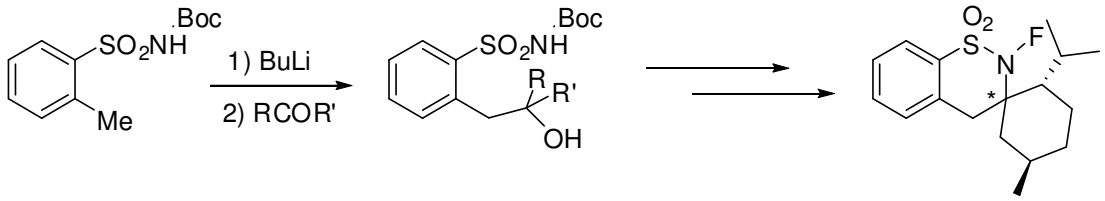
The enantioselectivity was improved by the same authors, up to 75% for the fluorination of 2-methyl-1-tetralone by the use of *N*-fluoro-3,3-dichlorocamphorsultam.[44] In a more recent paper, Takeuchi and coworkers[45] describe a simple synthesis of enantiomeric *N*-fluoro-3-cyclohexyl-3-methyl-2,3-dihydrobenzo[1,2-d]- isothiazole 1,1-dioxide, an agent that effects asymmetric fluorinations of ketone metal enolates to furnish optically active fluoroketones with enantioselectivity reaching 88% ee. The starting imine, which was prepared from saccharin by Oppolzer's method[32], was subjected to alkylation with cyclohexylmagnesium bromide to give

the 3-cyclohexyl-3-methyl benzo[*d*]sultam in 70% yield. Its optical resolution carried out by derivatization with (-)-menthoxyacetyl chloride, gave the enantiopure compound subsequently fluorinated (Scheme 2-30).



Scheme 2-30

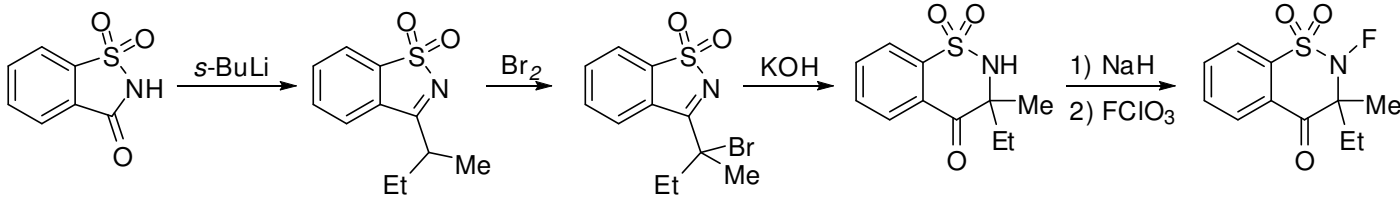
The best results, with e.e. as high as 88%, represents a significant advance in agent-controlled asymmetric fluorination. The following year, the same author proposed a novel method[46] for a facile construction of 3,3-disubstituted and 3,3-spiro 2H,4H-benzo[*e*]sultam in which *N*-Boc-*o*-toluenesulfonamide is taken as starting material. *o*-Methyl lithiation, followed by reaction with a variety of ketones, gave the corresponding carbinol sulfonamides which underwent cyclization under acidic or neutral conditions (Scheme 2-31). The resulting sultams were subjected to $FClO_3$ fluorination to give the *N*-fluorosultams which were tested for electrophilic asymmetric fluorination; results reached lower enantiomeric excesses (70%) for enantioselective fluorination of the lithium enolate of 2-methyl-1-tetralone but no kinetic resolution is required in the synthetic pathway to for the sultam construction.



Scheme 2-31

Another type of benzosultam that has been employed as a template for developing a N-F agent, is the 3,3-disubstituted 2*H*-benzo[*e*][1,2]thiazine 1,1,4-trione synthesized by Takeuchi;[47] saccharine was converted in three steps consisting in sequential alkylation with s-BuLi, bromination and ring expansion according to Abramovitch procedures. Racemic sultam in general showed good reactivity towards lithium and sodium enolates generated from

indanones, tetralones and benzosuberones to give the corresponding α-fluoro derivatives in good tields (64-100%).

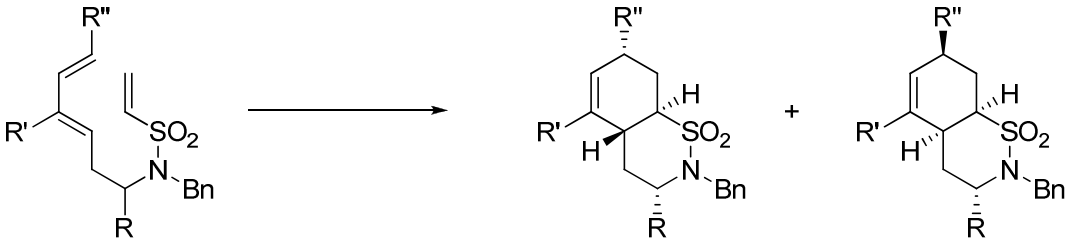


Scheme 2-32

2.4 Strategies used in sultam synthesis

Many effort are made to find new strategies for the synthesis of an important class of heterocycles like that of sultams and benzosultams; in the next pages are exposed the most significant progresses appeared in the last years.

In 2000 Metz and coworkers[48] proposed a Diels–Alder cyclization of vinylsulfonic esters and amides bearing acyclic and carbocyclic 1,3- diene moieties by application of high pressure. This methodology leads to excellent yields of sultones and sultams, respectively, at ambient temperature with modest diastereoselectivities (Table 2-10).

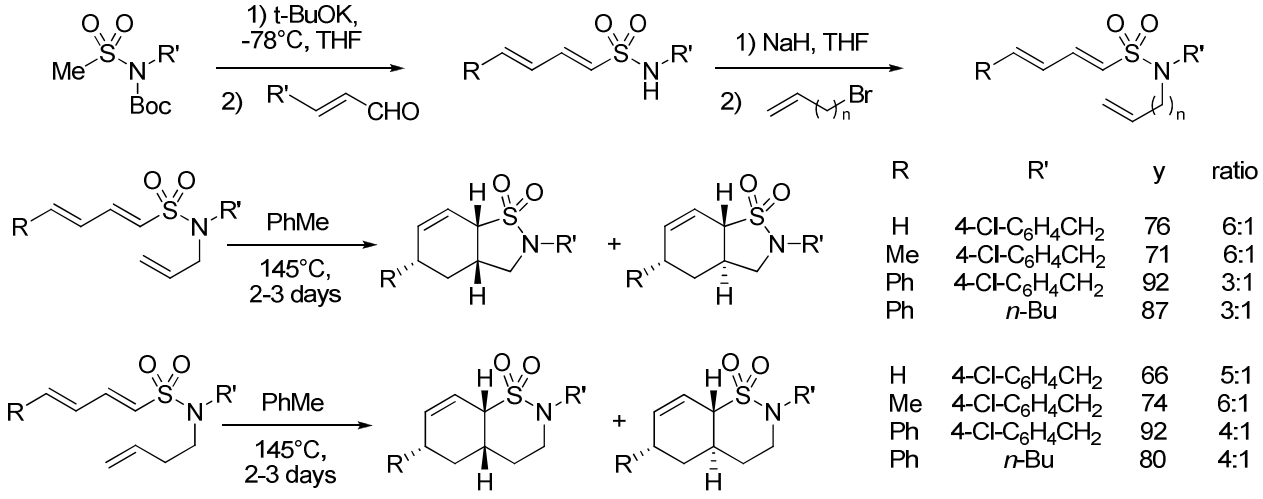


Scheme 2-33

R	R′	R″	y (%)	Ratio
H	H	H	79	1 : 1.6
H	H	H	76	1 : 1
Me	H	Me	81	1 : 1.6
Me	H	Me	61	1.6 : 1

Table 2-10

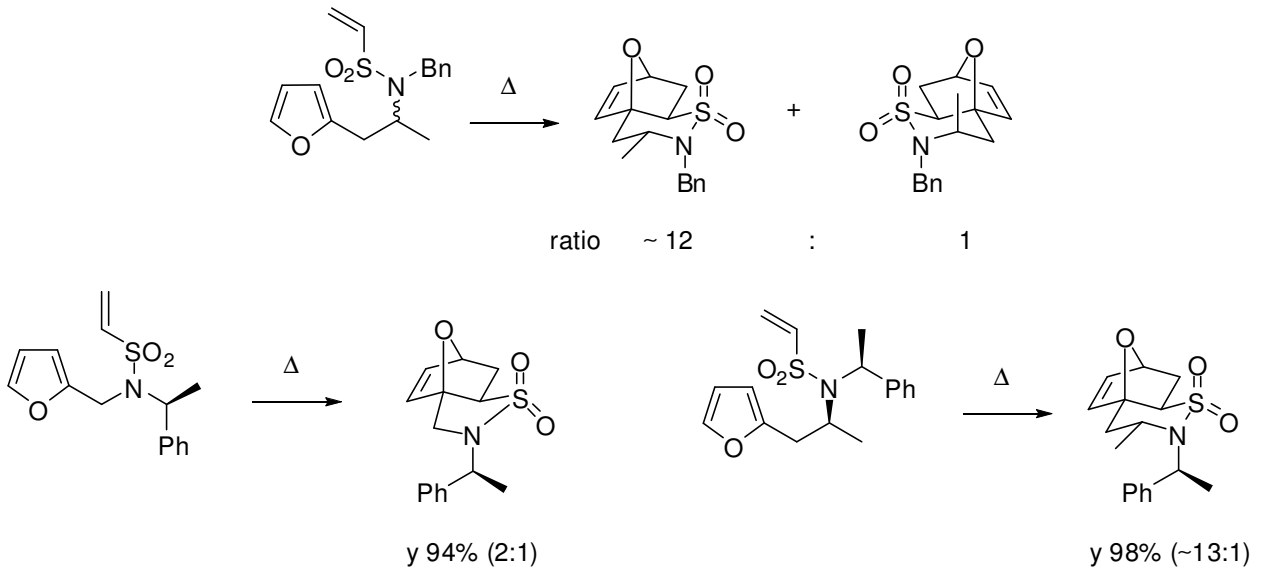
Just on the same year a similar methodology proposed by Tozer49, consisted in the synthesis of both δ- and γ-sultams (Scheme 2-34).



R	R'	y	ratio
H	4-Cl-$C_6H_4CH_2$	76	6:1
Me	4-Cl-$C_6H_4CH_2$	71	6:1
Ph	4-Cl-$C_6H_4CH_2$	92	3:1
Ph	*n*-Bu	87	3:1
H	4-Cl-$C_6H_4CH_2$	66	5:1
Me	4-Cl-$C_6H_4CH_2$	74	6:1
Ph	4-Cl-$C_6H_4CH_2$	92	4:1
Ph	*n*-Bu	80	4:1

Scheme 2-34

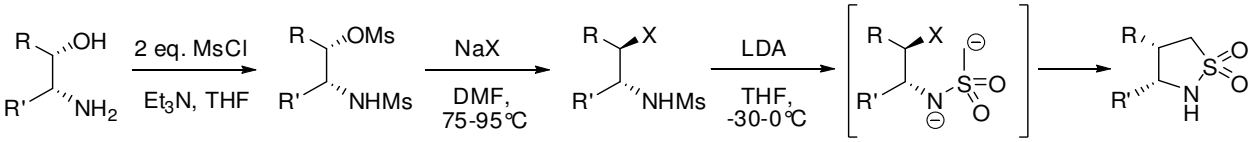
Always considering Diels-Alder cyclization as a tool to obtain sultams, we must mention reaction with purely thermal activation and under high pressure of vinylsulfonamides bearing furan moiety proposed always by Metz and coworkers[50]. This methodology allows the obtainment of δ- and γ-sultams with good diasteromeric excesses while enantiopure compounds were readily prepared by reaction of optically pure *N*-1-phenylethyl substituted vinylsulfonamides (Scheme 2-35).



Scheme 2-35

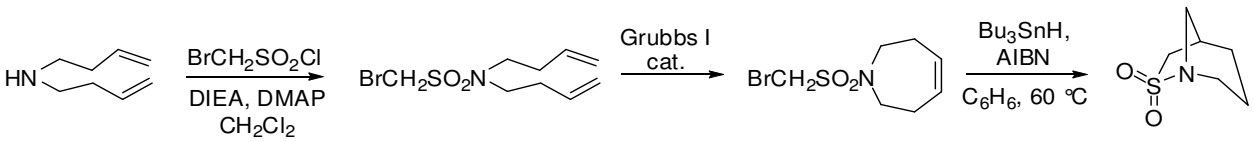
In 2003 Lee[51] exposed a practical and high yielding method for the synthesis of sultams starting from β-amino alcohols. The synthetic pathway consists in the *N,O*-bis-methanesulfonylation of amino alcohols followed by S_N2 displacement with sodium halide in DMF to give the desired

haloalkanesulfonamide; finally, the key step, the sulfonamide dianion alkylation, was applied to obtain successfully five-membered sultam synthesis (Scheme 2-36).



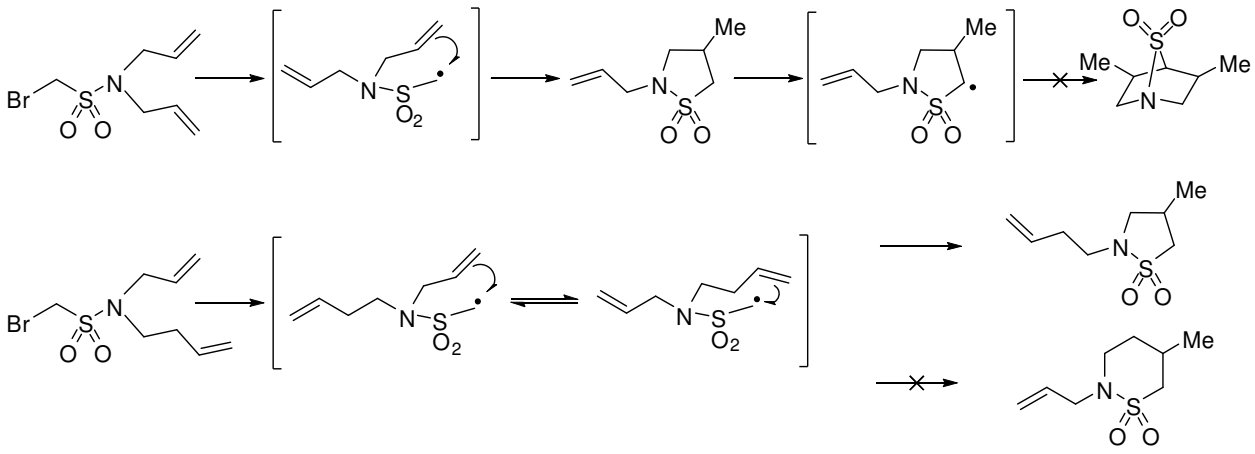
Scheme 2-36

The same idea has been resumed by Cleator et Al. using the reaction between an epoxide and a sulfonylamide to obtain in one step the desired β-amido alcohol.[52] In 1999 Paquette proposed,[53] as the first examples of bridgehead bicyclic sultams, the radical displacement reactions on halosulfonamides; despite this kind of reaction are generally not feasible for steric and stereoelectronic reasons, sulfonyl radicals are not stabilized, and they are prone to rapid intramolecular cyclization (Scheme 2-37).



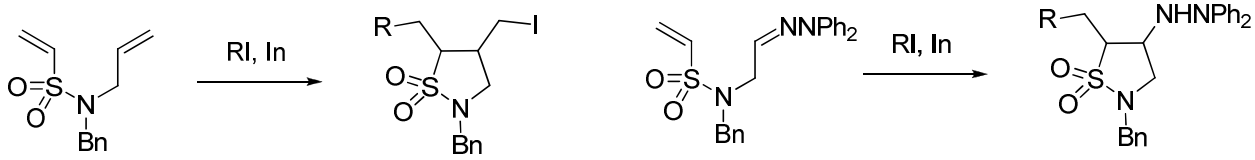
Scheme 2-37

Always in 1999 and always Paquette extended his previous work[54] demonstrating his reaction a preparatively useful route to sultams. He prepared homologous of sulfonamidyl radicals, generated by the well known reaction of halomethyl precursors with tri-*n*-butyltin hydride under AIBN catalysis. Moreover he evaluated the intramolecular cyclization capability of these highly reactive intermediates studying *exo* and *endo* transition state for the regioselectivity understandment (Scheme 2-38).



Scheme 2-38

The radical addition- cyclization-trap reaction of a substrate having a vinyl sulfonamide and an hydrazonic or olefinic moiety group was studied by Naito[55] as a potential method to obtain sultams; tandem carbon-carbon bond-forming reactions were studied in aqueous media by using indium as a single-electron-transfer radical initiator in the absence of toxic tin hydride. Therefore the radical addition-cyclization reaction gave the functionalized cyclic iodomethyl or hydrazino sultams (Scheme 2-39).



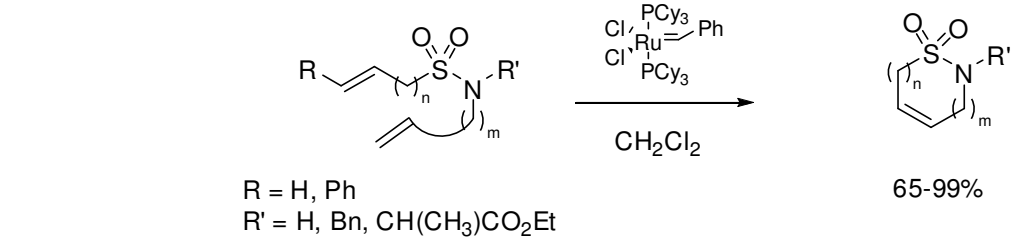
Scheme 2-39

RI	Solvent	y (%)	RI	Solvent	y (%)
i-PrI	H_2O	81	*i*-PrI	H_2O-MeOH	93
i-PrI	H_2O-CH_2Cl_2	42	*i*-PrI	H_2O-CH_2Cl_2	94
c-PentylI	H_2O	84	*c*-PentylI	H_2O-MeOH	86
t-BuI	H_2O	79	*t*-BuI	H_2O-MeOH	42

Table 2-11

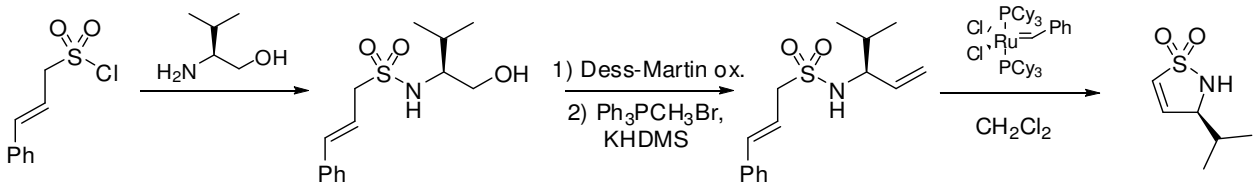
Finally, even RMC has been considered as an efficient methodology for the construction of sultamic ring: the reaction has been studied initially by Hanson and coworkers[56] taking as starting material allyl or vinylsulfonamides, easily synthesized from the styrene derived sulfonyl chloride[57] and allylsulfonyl chloride[58] This compounds were cyclized in good to

excellent yield via the ring closing methatesis with Grubbs I cat. demonstrating the feasibility of the RCM strategy en route to complex sulfonamides (Scheme 2-40).



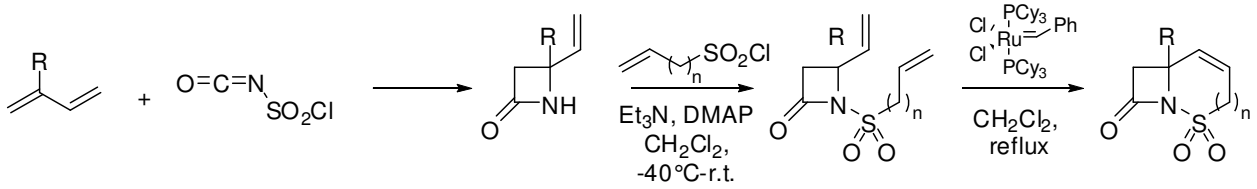
Scheme 2-40

The same author developed, some year later, a similar method in which the allyl or omo allyl amine is substituted by chiral unsaturated amines deriving from natural amino acids (Scheme 2-41).[59]



Scheme 2-41

Moreover, as in the past years were reported a range of nonconventionally fused β-lactams including the *N*-sulfonyl compounds showed in Scheme 2-7 and Scheme 2-8. Metz[60] developed β-lactams fused to a sultam from low cost, commercially available starting materials, always using ring closing metathesis as the key operation. Lactams were synthesized by cycloaddition of chlorosulfonyl isocyanate with 1,3-butadiene or isoprene and the resulting compounds were converted to *N*-sulfonyl derivatives with olefinic sulfonyl chlorides, readily derived from commercially available 2-chloroethanesulfonyl chloride or from the corresponding olefinic bromides; finally RCM strategy allowed the formation of unsaturated sultams with different ring size (from 5 to 8 members, Scheme 2-42).

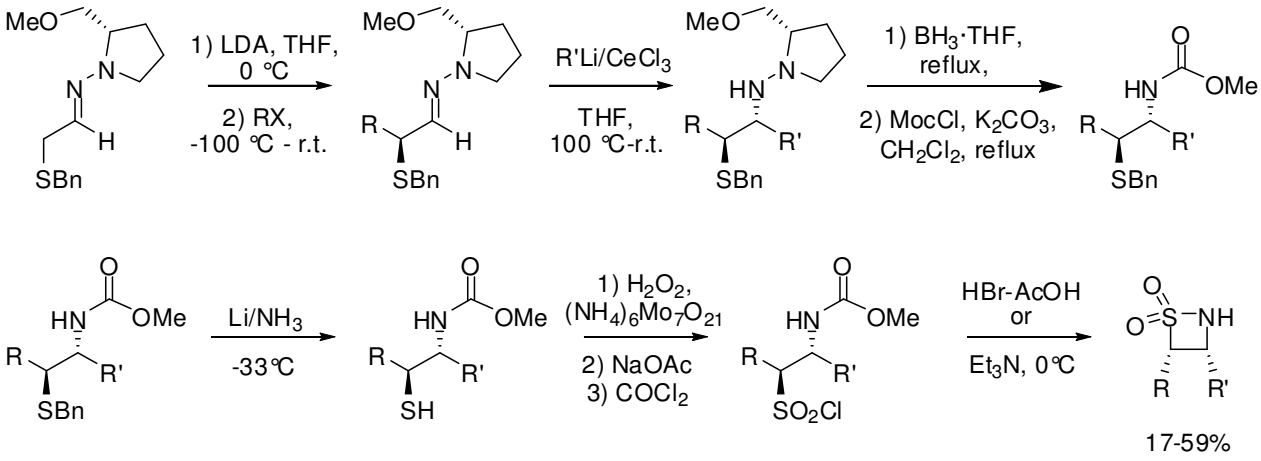


Scheme 2-42

Even β-sultams themselves can be seen as a building blocks for the synthesis of new synthetic drugs, for example corresponding to β-lactam antibiotics In general, β-sultams can be synthesised by [2+2] cycloaddition of sulfene intermediates with imines,[61] of alkenes with *N*-sulfonylamines[62] or by intramolecular cyclization.[63]

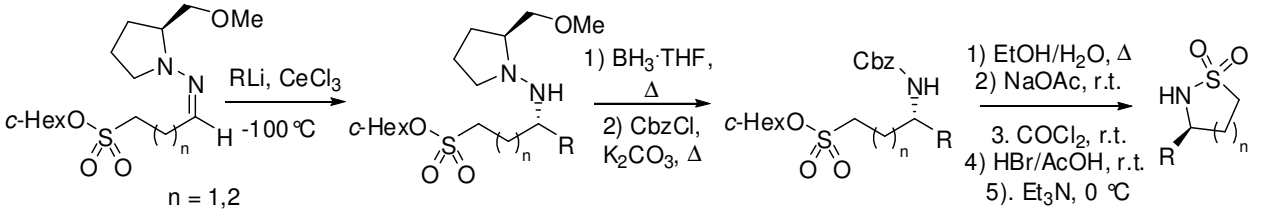
Kataoka et al., for example, described the diastereoselective [2+2] cycloaddition using mesyl chloride and chiral imines.[64] However, the adaptable substrates are not only restricted in the choice of substituents, the cycloaddition also yields unsatisfactory stereoselectivities. Another access to enantiomerically pure β-sultams is the synthesis starting from natural amino acids. Initially Otto et al. utilized cysteine derivatives[65] as precursors, but recently also embarked on other amino acids followed by introduction of the sulfur moiety.[66]

Among all these protocols, quite interesting is the asymmetric synthesis of *cis*-3,4-disubstituted β-sultams reported by Enders and Moll[67]. The protocol is based on the initial synthesis of the *anti*-1,2-benzylsulfanyl amines previously reported by the same author[68]: key steps are the diastereoselective α-alkylation of α-sulfanylated acetaldehyde-SAMP-hydrazone, reaction conducted with various electrophiles and subsequent nucleophilic 1,2-addition of organocerium compounds to the hydrazone C=N double bond. The resulting hydrazines were converted to the corresponding protected amines by reductive N–N bond cleavage-oxidation of 1,2-aminothiols with H_2O_2 and ammonium heptamolybdate. The obtained *anti*-1,2-benzylsulfanyl amines has been cleaved to the deprotected thiol and sequently oxidized; chlorination of the resulting β-amino sulfonic acids was achieved with phosgene and the β-aminosulfonyl chlorides obtained were cyclized to the title compounds under basic conditions without epimerisation and good overall yields (Scheme 2-43).



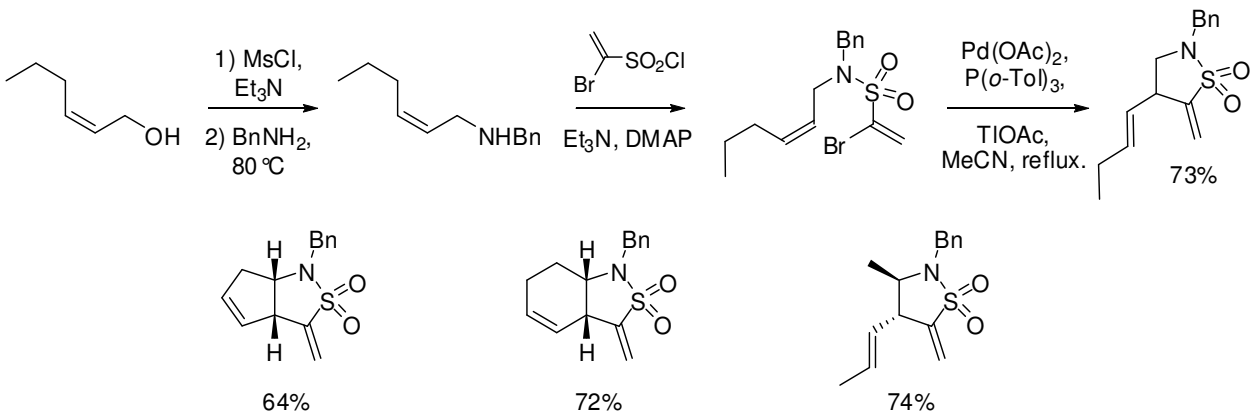
Scheme 2-43

Certainly, when is possible, the most simple way to obtain sultams is the direct formation of S-N bond: as an example we can mention the work of the above mentioned author[69] in which the synthesis of a five or six membered heterocycle is carried out with a final step consisting in a simple amidation (Scheme 2-44).



Scheme 2-44

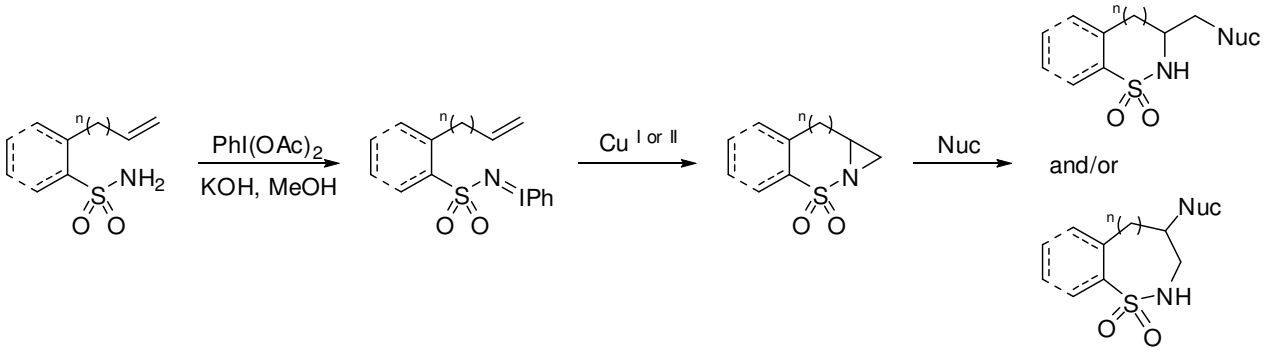
Metz again reported in 2005[70] a concise access to α-methylene-γ-sultams via the intramolecular Heck reaction of α-bromovinylsulfonamides which, in turn, are readily available from isethionic acid sodium salt by a known three-step sequence.[71] The synthesis of the sulfonamide substrates with cyclic and acyclic allyl amine moieties employed in this study is carried out as shown in Scheme 2-45 and is quite important even in the light of the structural similarity of α-Methylene-γ-sultams to α-methylene-γ-butyrolactones, which display a wide range of interesting biological activities.[72]



Scheme 2-45

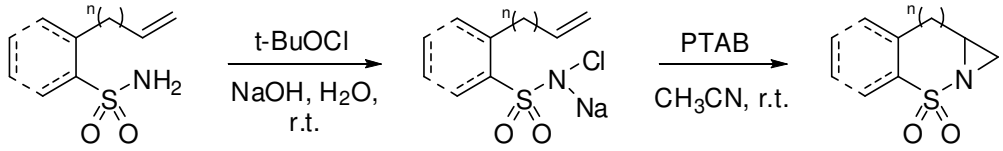
Moreover, inspired by recent work of Roush with vinylsulfonyl compounds[73], they demonstrated the reactivity of bicyclic α-Methylene-γ-sultams as potent Michael acceptors towards the sulfur nucleophiles.

Among the newest strategies, intramolecular aziridinations of unsaturated sulfonamides and metal-catalysed amidation has received much attention as a method for the sultam synthesis: for instance [*N*-(alkylsulfonyl)imino]phenyliodinanes, derived from ω-unsaturated sulfonamides, react intramolecularly in the presence of a catalytic quantity of copper (I) or (II) triflate to give bicyclic aziridines[74] of the type showed in Scheme 2-46 which, in turn, can be opened by a variety of nucleophiles.



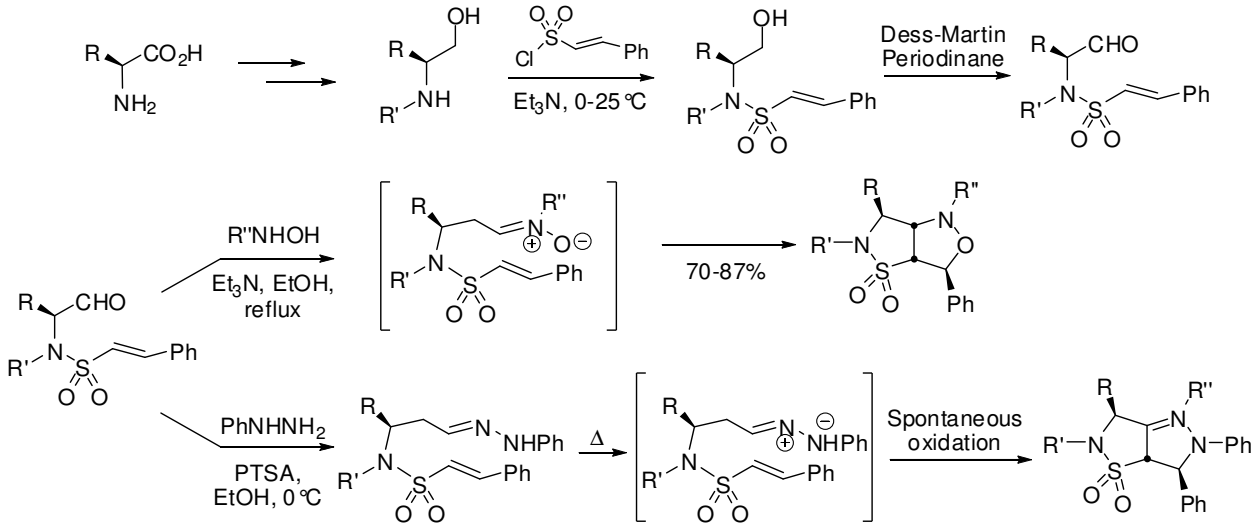
Scheme 2-46

The same authors explored too the possibility of applying an intermolecular bromine-catalyzed aziridination of olefins using *N*-chloramine salts of sulfonamides (Scheme 2-47).[75]



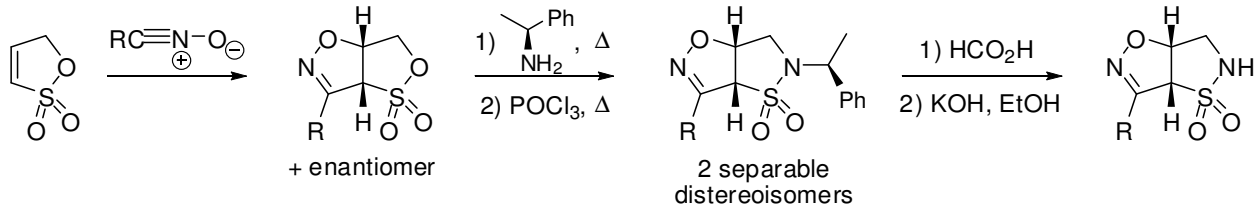
Scheme 2-47

As a proof of the versatility of the aziridination methodology, even rhodium[76] has been proven to be a valid catalys giving the corresponding sultam products in excellent yields (up to 98%) and with good to excellent conversions. The successful employ of rhodium opened the way to the an enantioselective version of this protocol[77] that is potentially useful for effecting intramolecular aziridination in a stereocontrolled manner. In 2001 Chiacchio and coworkers proposed a stereoselective sultams synthesis using intramolecular cycloaddition reaction as the key step[78]: their methodology starts form commercially available L-amino acids and leads, in few steps, to various α-sulfonamido aldehydes; their subsequent treatment with different *N*-substituted hydroxylamines furnishes the unstable nitrones which immediately underwent 1,3 dipolar cycloaddition to give the bicycle sultam-isoxazolidinic compound (Scheme 2-48). The same authors investigated too the possibility to obtain the pyrazolidinic analogue employing hydrazine derivatives instead of hydroxylamine.



Scheme 2-48

In a similar way Chan et Al.[79] proposed a trans amidation to obtain bicyclic sultam starting from the corresponding sultans which in turn are obtained via cycloaddition reaction (Scheme 2-49).



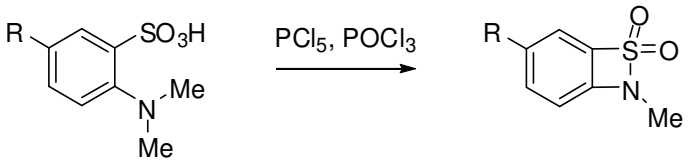
Scheme 2-49

The relative effectiveness as new chiral auxiliaries in asymmetric synthesis of these compounds was evaluated for the asymmetric Diels–Alder reactions with cyclopentadiene obtaining good chemical yield and excellent endo selectivity.

2.5 Strategies used in benzosultam synthesis

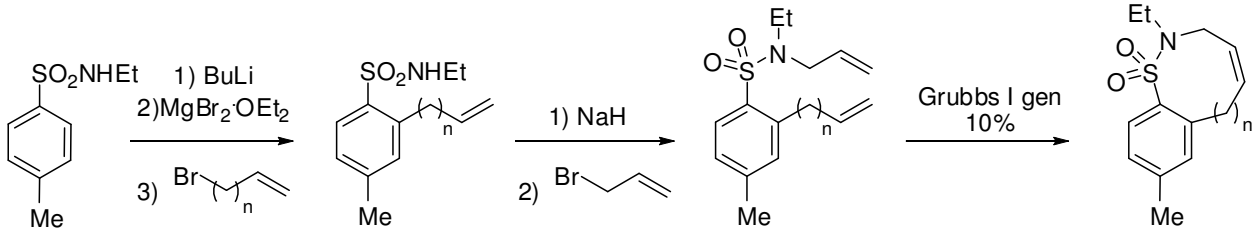
As we have seen before, also benzosultams make up an important class of molecules, both as chiral auxiliaries and for medicinal chemistry: however few examples are reported for the synthesis of these heterocylces and the following pages have the purpose to illustrate the most important improvements[80].

As regards four membered ring, Wu has reported a synthesis via demethylative cyclization:[81] when *ortho*-dimethylamino benzan sulfonic acid are heated with phosphorus oxychloride in the presence of phosphorus pentachloride , β-benzo[*c*]sultam was formed in good yield (Scheme 2-50);



Scheme 2-50

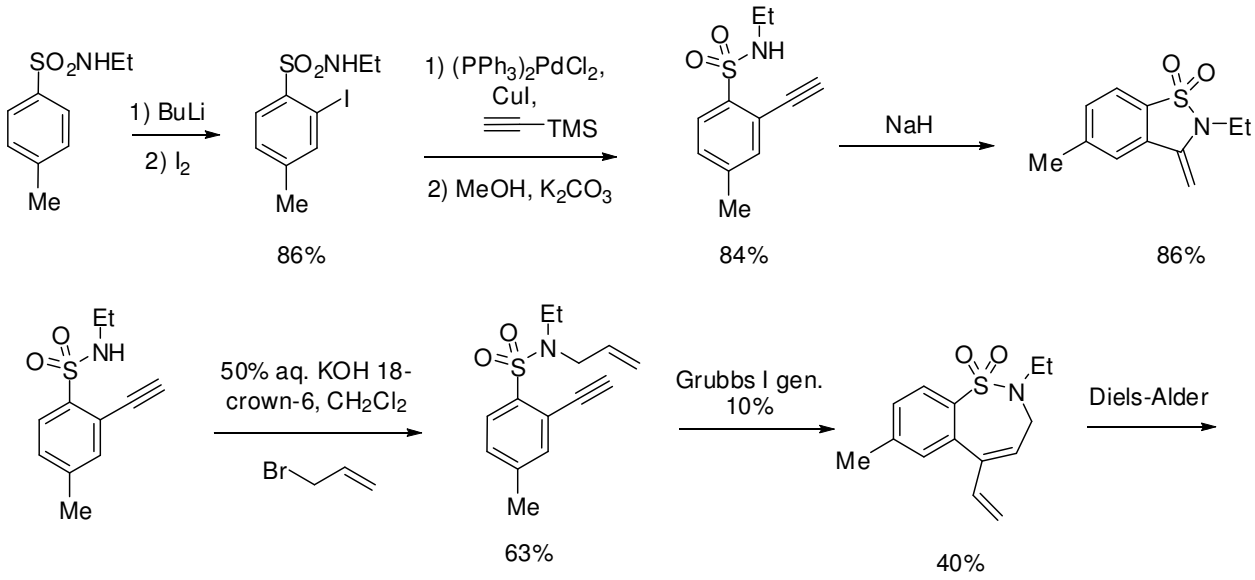
also Snieckus and coworkers[82] proposed a simple synthesis of six-and seven-membered ring by intramolecular anionic "Friedel-Crafts" cyclization of α–sulfonamido amides readily available from the condensation of amides deriving from natural α-amino acids with benzene or *p*-toluene sulfonyl chlorides; in addition, higher membered benzosultams can be approached using methodology based on the direct *ortho*-metalation (DoM) together with RCM (Scheme 2-51)



Scheme 2-51

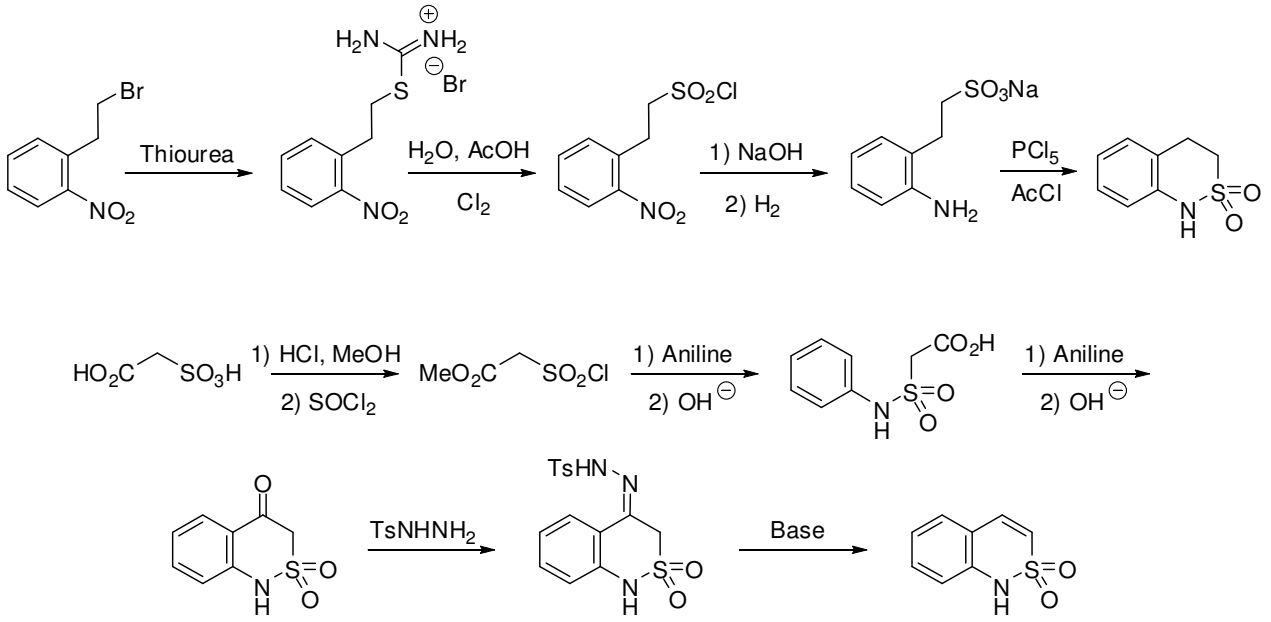
as an extention of this methodology, even ene-yne RCM has been carried out on *o*-alkynyl *N*-allyl sulfonamides with the purpose to allow further anellation via Diels-Alder reaction (Scheme 2-52).[83]

Up to today, few methods for the construction of 3,4-dihydro-2,1-benzothiazine 2,2-dioxide skeleton are known, i.e., the cyclization of 2-(*o*-aminophenyl) ethanesulfonic acid,[84] the cyclization of *N*-benzyl-*N*-methanesulfonyl(*o*-chloromethyl)aniline,[85] and the cyclization of *N*-phenylsulfamoylacetic acid and subsequent reduction of the carbonyl group;[86]



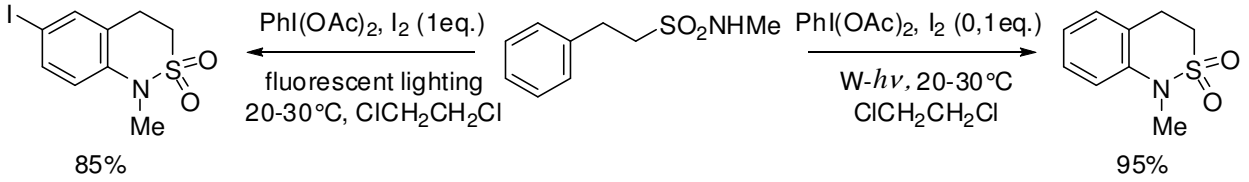
Scheme 2-52

however these obsolete methods (Scheme 2-53) require many steps, and the yields of the cyclized products are not good.



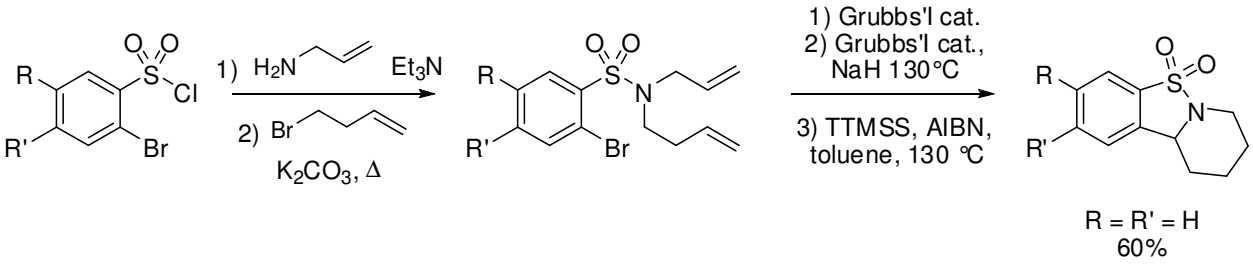
Scheme 2-53

Togo et al reported in 2000 a new preparative method[87] of 3,4-dihydro-2,1-benzothiazine 2,2-dioxides from *N*-alkyl 2-(aryl)ethanesulfonamides with (diacetoxyiodo) arenes under photochemical conditions (Scheme 2-54).



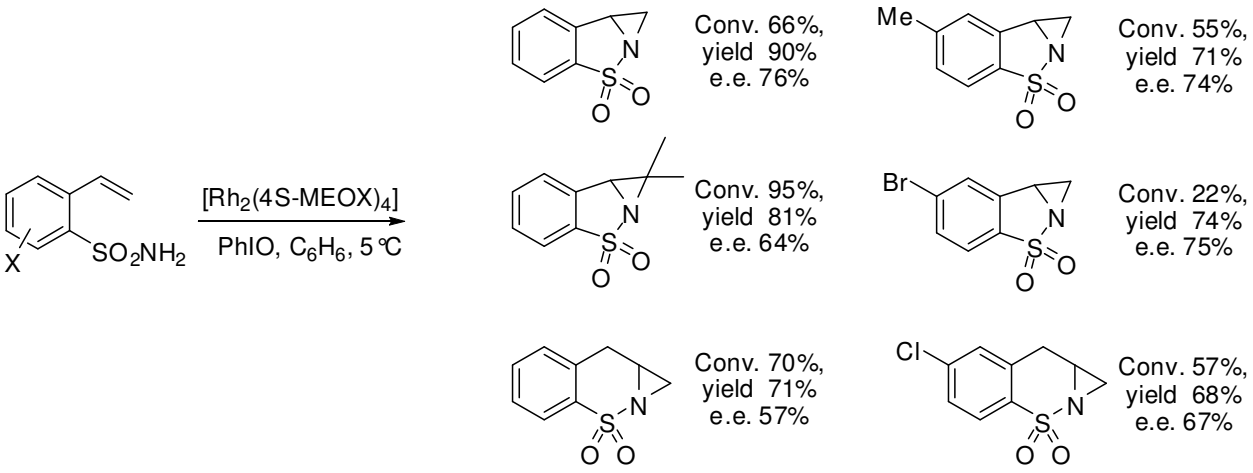
Scheme 2-54

Always in 2005 Piva et Al.[88] proposed a new one-pot procedure to prepare tri- or tetracyclic sultams starting from readily available unsaturated sulfonamides,.combining a ring-closing metathesis, an isomerization step and a radical cyclization (Scheme 2-55).



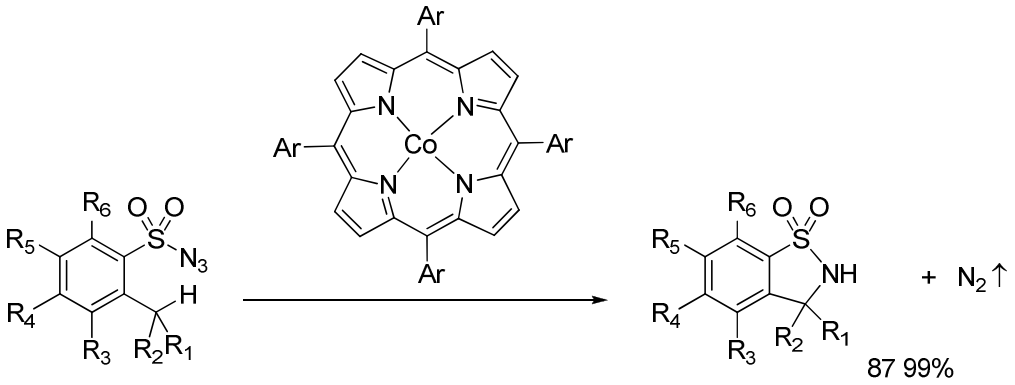
Scheme 2-55

Even the previously seen methodology of aziridination[77] has been employed for the synthesis of benzosultams, obtaining good yield and good e.e.'s accompanied with only modest conversions (Scheme 2-56).



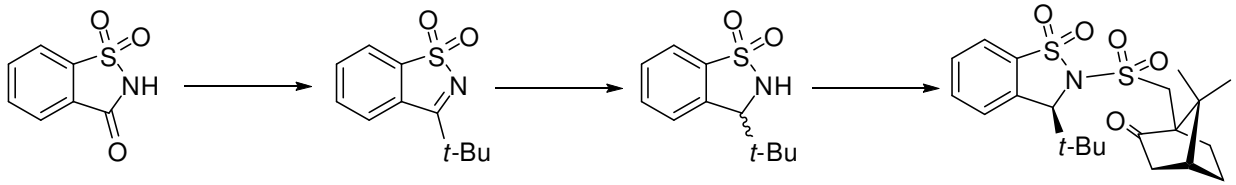
Scheme 2-56

Cobalt complexes of porphyrins are effective catalysts for intramolecular C–H amination with arylsulfonyl azides. In 2007 Zhang and coworkers[89] used a cobalt-catalyzed process for the synthesis of benzo[d]sultmas that can proceed efficiently under mild and neutral conditions in low catalyst loading without the need of other reagents or additives, generating nitrogen gas as the only byproduct. The catalytic system can be applied to primary, secondary, and tertiary C–H bonds and is suitable for a broad range of arylsulfonyl azides, leading to high-yielding syntheses of various benzosultams (Scheme 2-57).



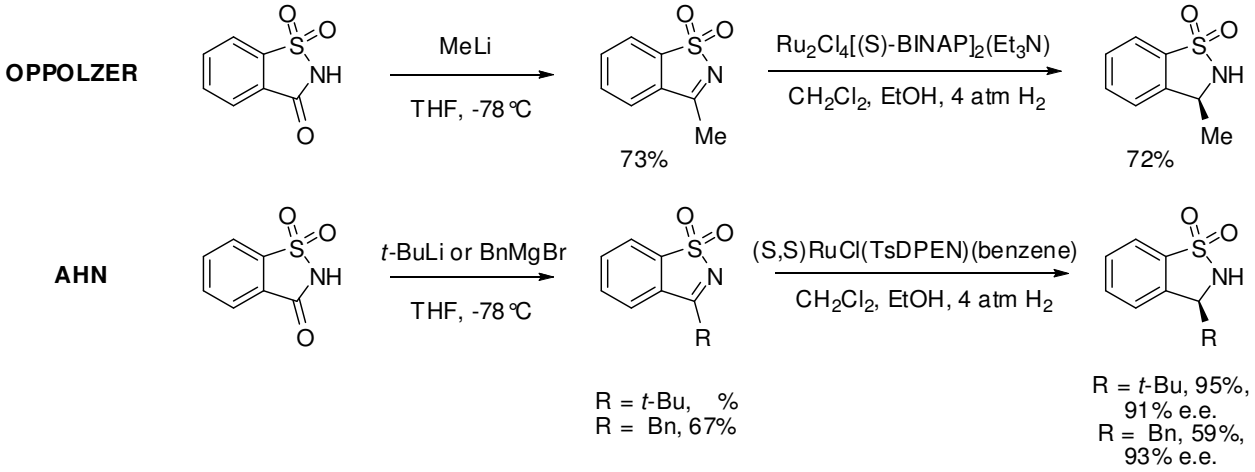
Scheme 2-57

As we have seen before, 3-substituted γ-benzo[*d*]sultams have received much attention because of their excellent stereofacial discrimination when used as chiral auxiliaries: however their usefulness has not been explored fully, probably owing to its tedious preparation involving, for example for the 3-*tert*-Butyl substituted sultam, a necessary chemical resolution of the racemic mixture via *N*-(*S*)-camphorsulfonylated compound (Scheme 2-58)



Scheme 2-58

3-alkyl γ-benzo[*d*]sultams became more accessibles in 90's, because of the development of a more efficient synthesis via the asymmetric hydrogenation of the sulfonylimine (a synthetic route just exploited by Oppolzer for R = Me, Scheme 2-59); anyway the requirement of an asymmetric reduction step made with an expansive and hazardous catalyst like Ru-BINAP, make the whole approach not much achevable especially for a large-scale synthesis.

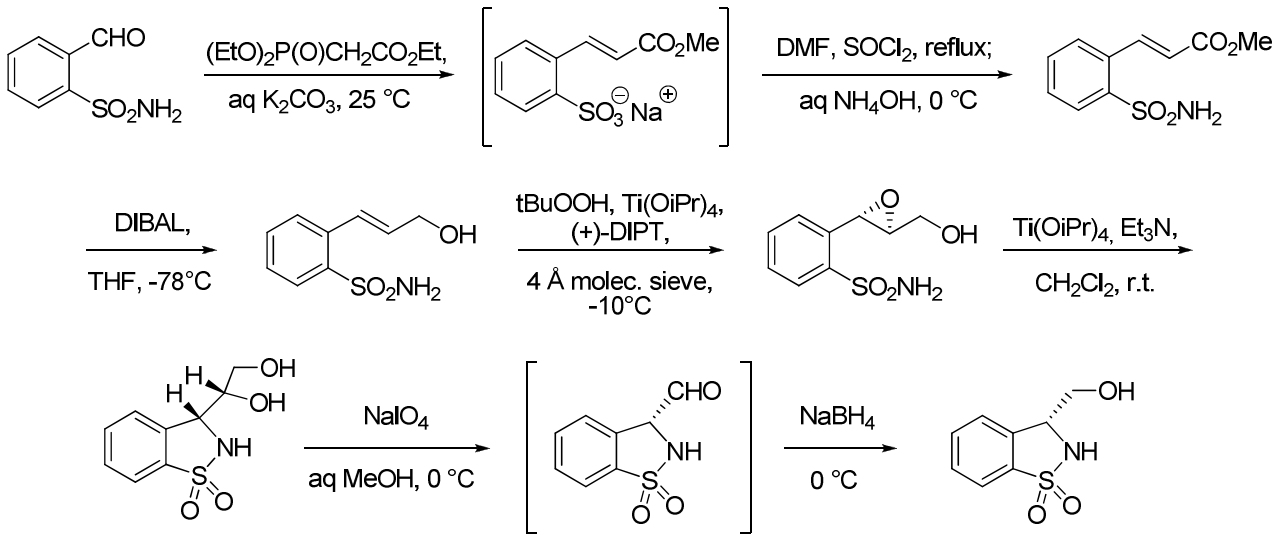


Scheme 2-59

The most important work appeared in 2000 and described for the first time the attempt of the synthesis of 3-carboxy γ-benzo[*d*]sultam;[90] although the direct nucleophilic addition approaches are useful for the synthesis of 3-alkyl- or 3-arylsubstituted derivatives, all the attempt to introduce directly a functional moiety such as cyano group were unsuccessful. To synthesize 3-carboxy analogues Ahn has studied both an asymmetric approach and a racemic synthesis followed by chemical resolution.

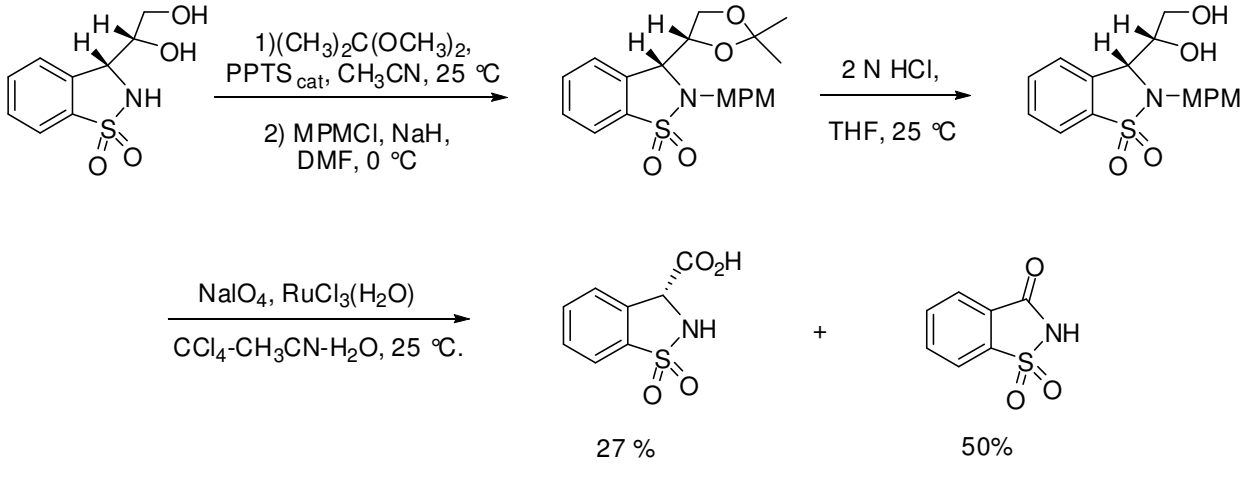
The asymmetric route use (Scheme 2-60) as starting material, sodium *o*-formylbenzenesulfonate and pass through an aqueous Wittig-Horner-Emmons reaction followed by the conversion of the resulting cinnamate derivative into a sulfonamide. Reduction of the ester group leads to the *o*-(aminosulfonyl)-trans-cinnamyl alcohol employed in the key steps, the Sharpless asymmetric epoxidation and a subsequent intramolecular epoxide opening by the sulfonamido group.

The final step, an oxidative conversion of the diol functionality into the carboxy group, was



Scheme 2-60

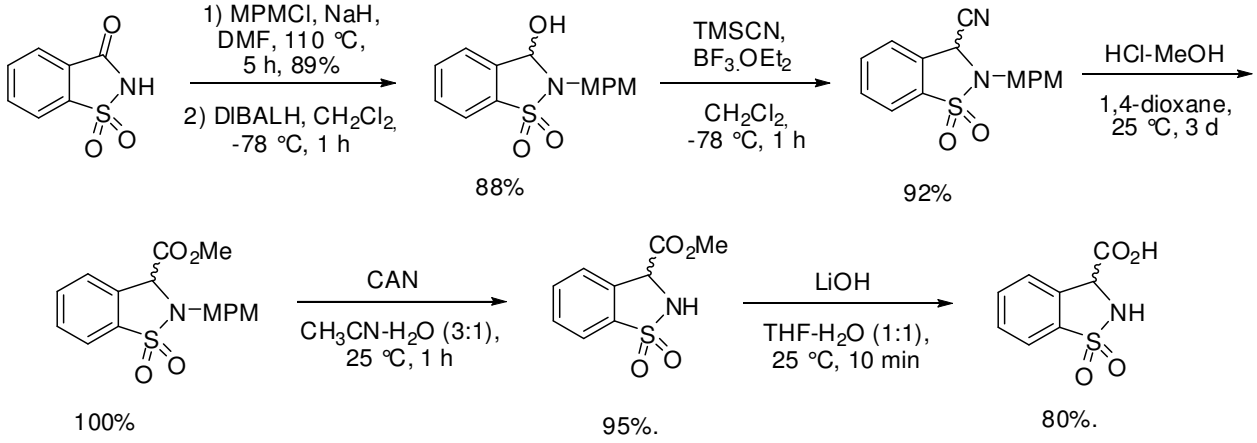
found to be difficult due to the instability of the reaction intermediate. Treatment of diol with sodium periodate produced the corresponding aldehyde, and subsequent in situ oxidation with potassium permanganate produced decomposed products instead of the desired 3-carboxysultam. Treatment with sodium periodate followed by sodium borohydride leads to the corresponding alcohol, compound impossible to oxidize with PDC, $KMnO_4$, or Ru(IV) reagents. Again when *N*-protected diol was subjected to the $RuCl_3$-$NaIO_4$ oxidation (Scheme 2-61), the



Scheme 2-61

major product was not the desired carboxylic acid but saccharine: these results indicate that 3-formylsultam and its *N*-protected derivatives have limited stability and may undergo deformylation and pushes the authors to turn their attention to a racemic route.

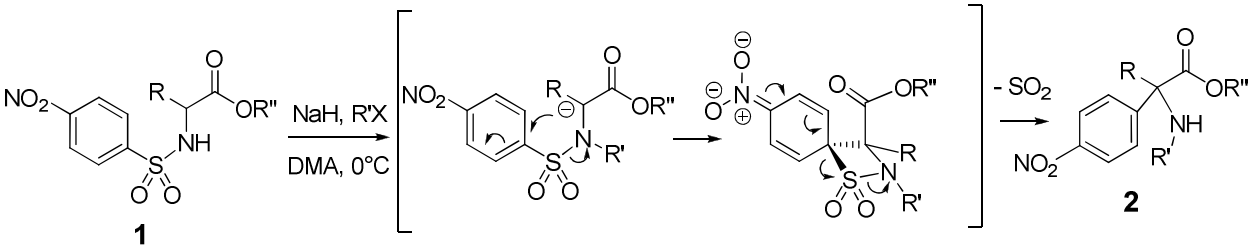
This one starts from the *N*-Protected saccharin, and proceed through conversion to the semi aminal by treatement with DIBALH and subsequent **c**onversion of the hydroxy group into the cyano group with TMSCN in the presence of $BF_3{\cdot}OEt_2$; after hydrolyzation to the corresponding methyl ester, deprotection of the MPM group and hydrolysis of the ester group, racemic 3-carboxysultam was obtained (Scheme 2-62) and the two single enantiomers were prepared by coupling with (*S*)-(-)-*α*-methylbenzylamine and chromatographic separation of the mixture of diastereomeric amide.



Scheme 2-62

3 RESULTS

Our interest in the synthesis of benzosultams starts with an observation that we made during the study of a particular class of reactions: the intramolecular degradative rearrangement of the *N*-(4-nitrobenzene)sulfonamido derivatives **1** of natural α-amino esters; we discovered that treatment of these compounds with an excess of sodium hydride, followed by addition of an alkylating agent, furnished the corresponding *N*-alkyl-α-4-nitrophenyl-α-amino esters **2** (Scheme 3-1).

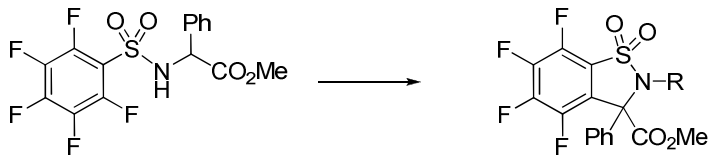


Scheme 3-1

The reaction needs a strong electron withdrawing substituent in the *para* position to the sulfonyl group, in order to stabilize the Meisenheimer intermediate, which evolves to the rearranged product, loosing sulfur dioxide. In the screening of various sulfonamido esters activated to this transposition, we tested the *N*-(pentafluorobenzene)sulfonyl derivative. In fact, we supposed that this compound, bearing the strongly electronegative five fluorine atoms, could easily give

the bicyclic Meisenheimer activated structure, through the aromatic intramolecular substitution.

Preliminary tests showed a particularly interesting behavior of **3a**: the molecule, after the initial *N*-alkylation with an alkyl halide, cyclizes by displacement of the fluorine atom in the *ortho* position to the sulfonyl group furnishing the *N*-alkyl benzo[*d*]isothiazole-1,1-dioxide (**4,** Scheme 3-2)



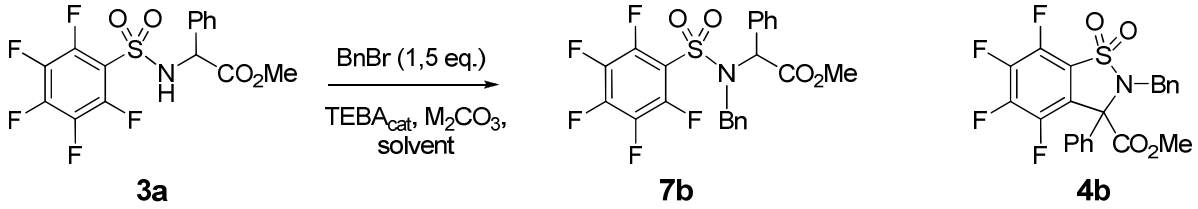
Scheme 3-2

3.1 Synthesis of Benzosultams

Sulfonamide **3a** has been prepared by condensation of the commercially available pentafluorobenzene sulfonyl chloride (**5a**) and phenylglycine methyl ester hydrochloride **6a**. The reaction, conducted at 0–25 °C, in dichloromethane with di-(*iso*-propyl)ethylamine (DIEA) as a base to neutralize the hydrogen chloride formed during the condensation, gave the desired product **3a** in good yield after crystallization of the crude (Scheme 3-3).

Scheme 3-3

Sulfonamide **3a** was the starting point for an extensive study devoted to find the best reaction conditions for the cyclization. In a preliminary step, we studied the alkylation of the open chain sulfonamide and our attention was focused on the alkylation with benzyl bromide, an activated alkylating agent. Analogously to that obtained with (4-nitrobenzene)sulfonamides, we found that solid-liquid phase transfer catalysis (SL-PTC) conditions provide great reactivity. The reaction was carried out in acetonitrile at room temperature, using a solid, anhydrous alkaline metal carbonate, in the presence of a catalytic amount of triethylbenzylammonium chloride (TEBA), as PTC agent. Results (Table 3-1) indicate good yield of the *N*-benzyl derivative **7b** together with small but indicative amounts of the cyclized product **4b** (Scheme 3-4). In the screening for the best reaction solvent, this behavior was invariable in all cases (DMF, DME), but in DMSO, in which an increased yield of the sultam **4b** (Table 3-2, entries 1-2) has been obtained at 50°C in 20h. As indicated by these preliminary data, DMSO shows the better solvent ability toward the cyclization process.



Scheme 3-4

	M_2CO_3	T[°C]	t[h]	7b (%)	4b (%)
1	Na_2CO_3	25	40	62	13
2	K_2CO_3	25	44	52	22
3	Na_2CO_3	25	20	75	15
4	Na_2CO_3	50	18	72	12
5	Cs_2CO_3	25	24	15	15
6	$CaCO_3$	25	48	33	22

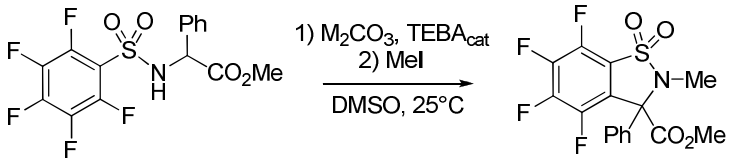
Table 3-1

Additional experiments were performed on the *N*-benzylsulfonamide **7b** cyclization, by changing reaction solvent, base, temperature and time. The most active bases were the alkaline metal carbonates (entries 1-5, 11-13) while DMSO was confirmed the most effective solvent (entries 1-2).

	Solvent	M_2CO_3	T[°C]	t[h]	4b (%)		Solvent	M_2CO_3	T[°C]	t[h]	4b (%)
1	DMSO	Na_2CO_3	25	20	32	8	DME	NaOH 50%	25	8	--
2	DMSO	K_2CO_3	25	6	45	9	DME	Na_2CO_3	0	1	--
3	DME	Na_2CO_3	25	20	27	10	DME	NaH	-20	5	10
4	DME	K_2CO_3	25	20	28	11	MeCN	Na_2CO_3	25	20	23
5	DME	$KHCO_3$	25	48	32	12	MeCN	K_2CO_3	25	20	24
6	DME	$KHCO_3$	80	20	10	13	MeCN	$Na_2CO_{3\ acq}$	25	20	26
7	DME	NaOH	25	5	--	14	DMF	$KHCO_3$	25	40	--

Table 3-2

In summary, an excess of potassium carbonate as a base in DMSO at room temperature represents the best reaction conditions. However, the non satisfactory yields achieved prompted us to change the alkylating agent, in order to reduce the steric hindrance around the nucleophilic carbon atom, and our choice fell on the smaller but, at the same time, reactive methyl iodide.

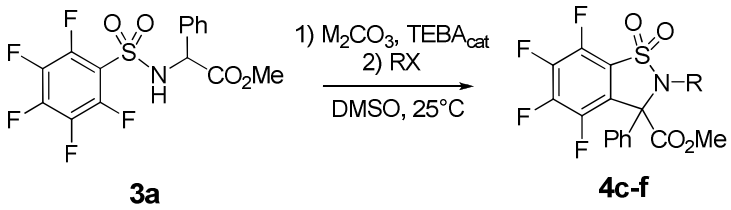


Scheme 3-5

	M_2CO_3	eq. MeI	t[h]	4a (%)
1	$KHCO_3$	1.5	48	70
2	Na_2CO_3	1.5	48	75
3	K_2CO_3	1	20	72
4	K_2CO_3	1.5	20	92

Table 3-3

The collected data, illustrated in Table 3-3, indicated that effectively the cyclization is strongly influenced by the nature of the alkylating agent: moreover, we performed several reaction by changing the alkyl halide and the results, summarized in Table 3-4, indicate good to acceptable yields of **3** with ethyl, *n*-propyl and *n*-butyl iodide, in DMSO at room temperature (entries 1-4). We observed no reaction with more crowded alkyl halides (entries 5-6), while the cyclization in other non hydrogen bonding donor (non-HBD) solvents gave comparable yields (entries 7-8). The data demonstrate also the dependence of reactivity on the increasing dimension of the alkylic substituent on the nitrogen atom.



Scheme 3-6

	RX	t[h]	Sultam (%)
1	EtI	20	**4d** 83
2	*n*-PrI	24	**4e** 51
3	*n*-BuBr	48	**4f** 37
4	*n*-BuI	48	**4fe** 61
5	*t*-BuI	72	**---**
6	BnCl	96	**---**
7	*n*-BuI	20, NMP	**4f** 62
8	*n*-BuI	48, DMPU	**4f** 58
9	BnBr	6	**4b** 45
10	AllBr	24	**4c** 46

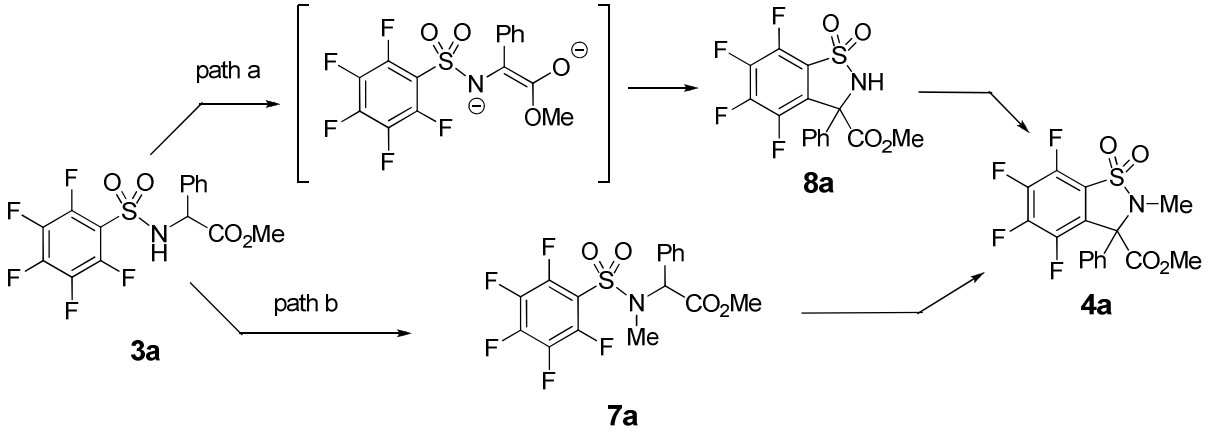
Table 3-4

The successive stage consisted in determine the mechanism for this "one-pot" reaction, since the *N*-alkylated sultam can be obtained through two different pathways (Scheme 3-7):

a) cyclization of the amidide-enolate, followed by *N*-alkylation;

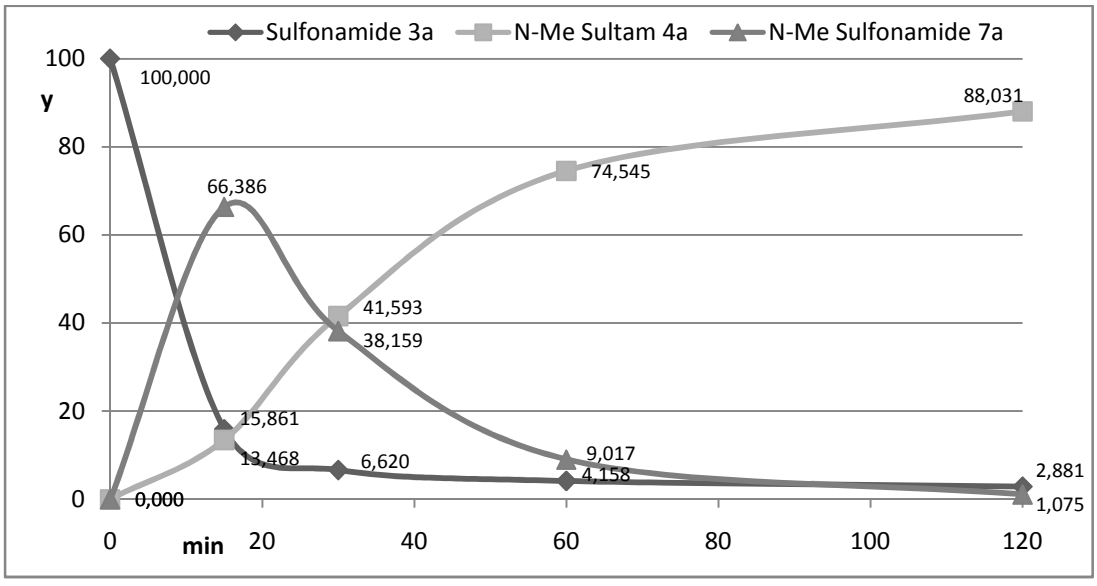
b) alkylation of the open-chain sulfonamide then cyclization.

For this purpose, we decided to investigate the formation of **4a** by mean of HPLC analysis, monitoring the amount of the starting sulfonamide **3a**, of the products **4a** and of the supposed intermediates, the *N*-alkyl sulfonamide **7a** and the non-alkylated sultam **8a**.

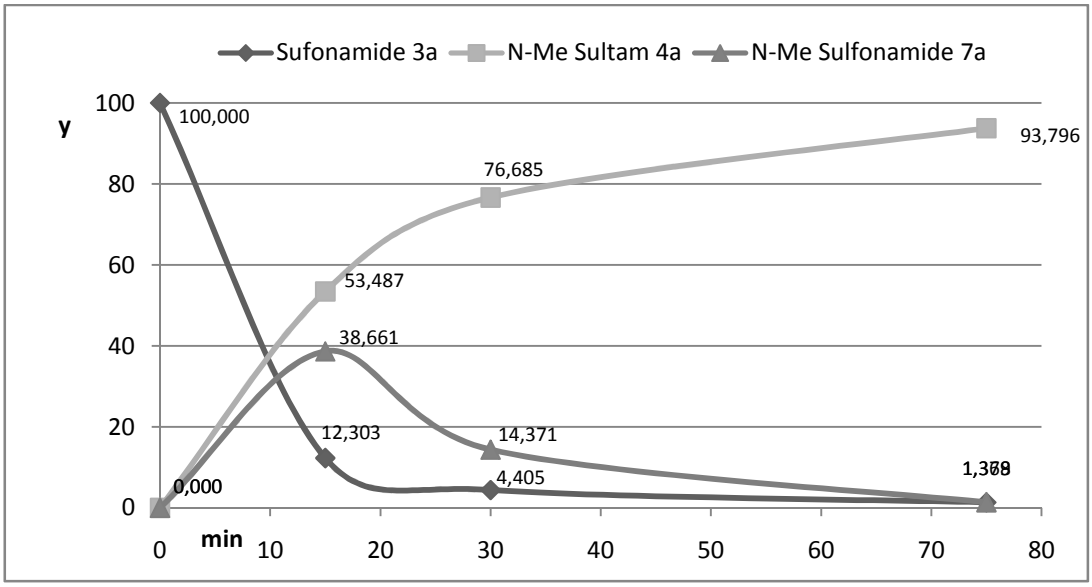


Scheme 3-7

Analysis of the reaction conducted in DMSO using potassium carbonate (Graphic 3-1) or cesium carbonate (Graphic 3-2) indicates the absence of the non-alkylated sultam and meanwhile, the process showed a typical consecutive trend, in which the *N*-methyl sulfonamide **7a** is the intermediate.

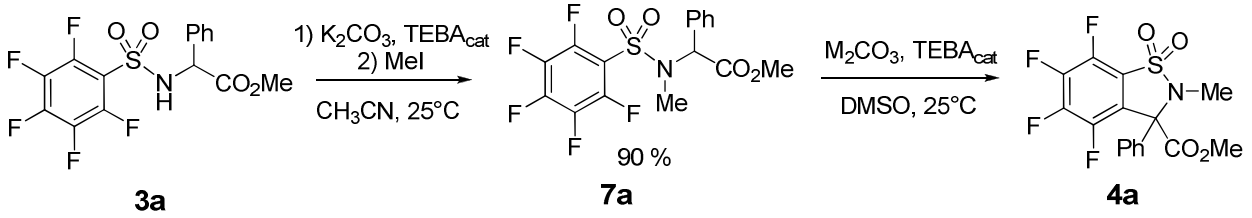


Graphic 3-1



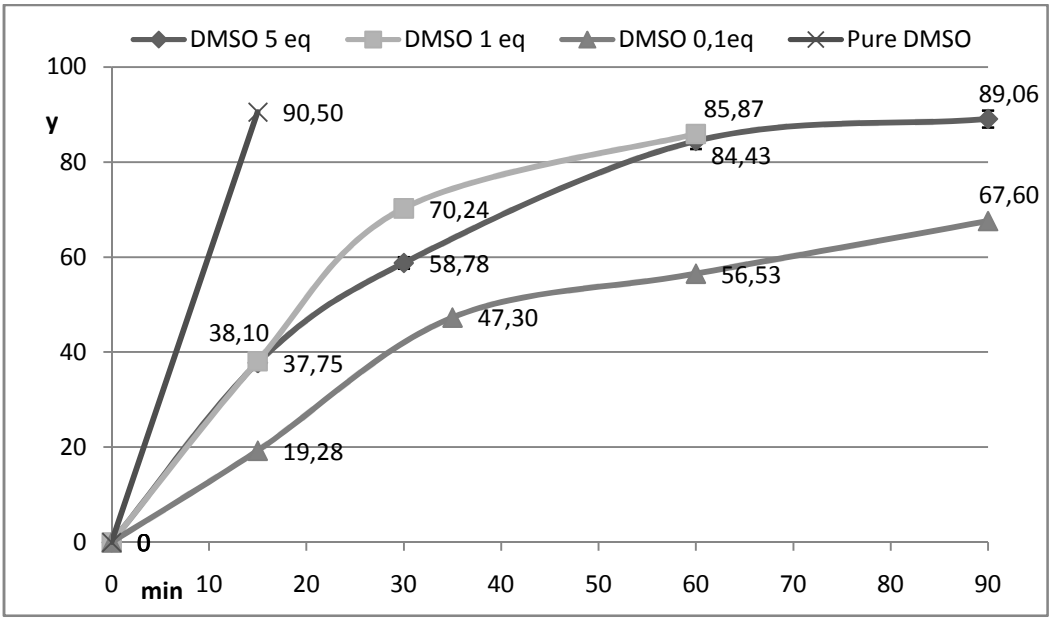
Graphic 3-2

As a confirm that the initial step of the optimized SL-PTC procedure was the nitrogen alkylation, the *N*-methyl sulfonamide **7a** was synthesized, isolated and, in a subsequent step, cyclized to **4a**. Compound **3a** was then reacted with methyl iodide in MeCN, in the presence of anhydrous K_2CO_3 and a catalytic amount (0.1 mol equiv.) of TEBA.



Scheme 3-8

The resulting *N*-methyl sulfonamide **7a** was then transformed into the corresponding *N*-methyl-tetrafluorobenzo[*d*]sultam **4a** by generating the enolate, under SL-PTC in DMSO, which rapidly cyclizes. Having determined the optimal reaction conditions and with a better comprehension of the facts, we were able to study the role of the solvent that is particularly crucial, as we have seen for the selectivity of the ring closing step. Actually, rapid conversion and high cyclization yield of sultam were reached by operating in pure DMSO (Table 3-5, entry 1) or in MeCN containing at least 1 molar equivalent of DMSO as an additive (entry 3), whereas a low **4a** yield was obtained with a catalytic amount of DMSO (entry 4), indicating the formation of an equimolar adduct sulfonamide/DMSO as the plausible activated species.

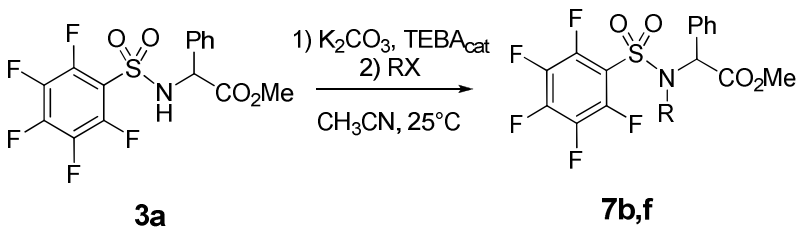


Graphic 3-3

	Solvent	DMSO	t [min]	4a (%)
1	DMSO	-	15	91
2	MeCN	5	90	89
3	MeCN	1	90	86
4	MeCN	0.1	90	68
5	MeCN	-	90	-

Table 3-5

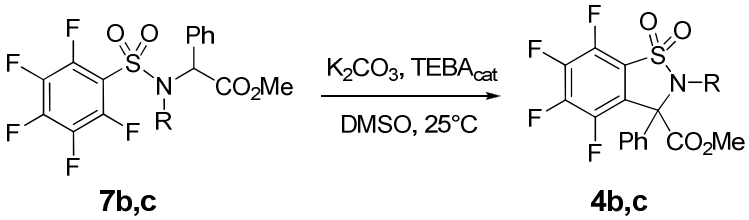
As a natural consequence, and in light of the low yields obtained in the "one-pot" cyclization-alkylation, we decided to apply this methodology to the synthesis of the bulkier *N*-allyl (**4c**) and *N*-benzyl (**4b**) sultams, but *N*-alkylation of the open-chain sulfonamide **3a** with benzyl and allyl bromide (Scheme 3-9, Table 3-6) gave low yields (45%), of the corresponding *N*-alkylsulfonamides **7b,c**, probably due to the steric hindrance around the nucleophilic center. In addition, the cyclization of these sulfonamides gave not acceptable yields of the desired compounds **4b,c** (Scheme 3-10, Table 3-7), preventing the application of this protocol to the synthesis of bulky *N*-alkyl derivatives.



Scheme 3-9

	RX	t [h]	Sulfonamide (%)
1	BnBr	20	**7b** 88
2	AllBr	40	**7c** 48

Table 3-6



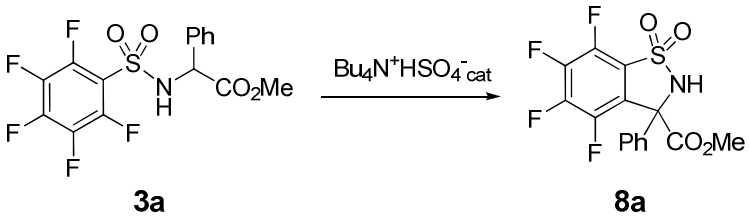
Scheme 3-10

	R	t [h]	Sultam (%)
1	Bn	12	**4b** 45
2	All	12	**4c** 61

Table 3-7

In order to solve this problem, we thought that the ring closure of the sulfonamide **3a** without the alkylating agent (Scheme 3-7, path a), would lead to the non-alkylated sultam **8a**, a much more interesting compound. This molecule, in fact, is the single scaffold which could eventually be *N*-alkylated in a subsequent step, therefore this way represents a valid alternative to the "one-pot" cyclization.

A screening of reaction conditions showed that PTC technique failed (Table 3-8, entry 1) even when drastic conditions were applied (entry 2);



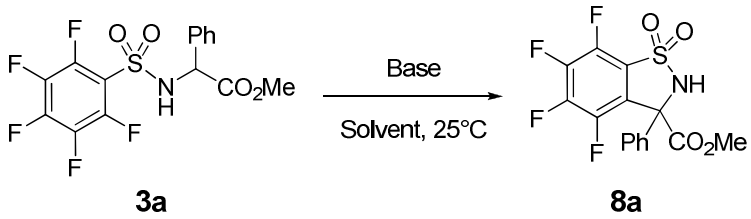
Scheme 3-11

	solvent	Base	T[°C]	t [h]	8a (%)
1	DMSO	Na_2CO_3	25	90	---
2	DMSO	Na_2CO_3	80	90	28
3	DMSO	K_2CO_3	50	90	10
4	DMSO	Cs_2CO_3	50	90	8
5	DMF	Na_2CO_3	80	60	---
6	MeCN	Na_2CO_3	80	60	---

Table 3-8

a change in the anhydrous alkaline carbonate indicates a decreasing yield along the series Na>K>Cs (entries 2-4), while any attempt to change the reaction solvent (entries 5,6) was unsuccesful.

After these negative results obtained under PTC conditions, we turned our attention to the cyclization under homogeneous conditions, considering that many organic soluble bases are well known to enolize carboxylic compounds: among the bases tested, 1,8-diazabicycloundec-7-ene (DBU) gave the best yields (Table 3-9, entries 4,5); on the other hand 1,4-diazabycyclo[2.2.2]octane (DABCO, entry 3) gave low yields, while tetramethylguanidine (TMG, entry 2) gave good yields but in very long time reaction. Moreover, the choice of the solvent is important as demonstrated by the different yields obtained passing from DMSO (entry 1) to a less polar solvent like, e.g., DME (entries 4,5).



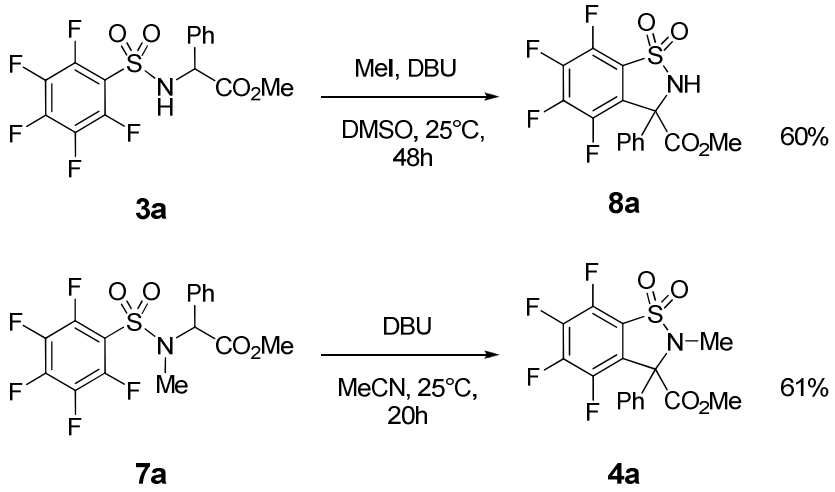
3a **8a**

Scheme 3-12

	solvent	Base	t [h]	8a (%)
1	DMSO	DBU	48	62
2	MeCN	TMG	80	96
3	MeCN	DABCO	24	54
4	DME	DBU	16	96
5	MeCN	DBU	20	98

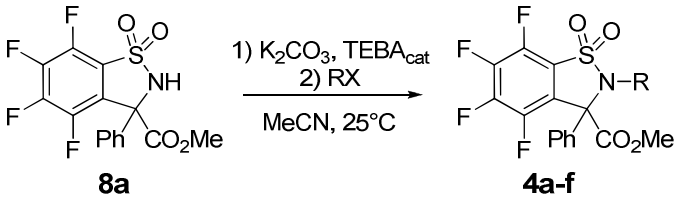
Table 3-9

The application of the homogeneous methodology to the "one-pot" synthesis of the *N*-methyl benzosultam **4a** by cyclization of the corresponding open-chain sulfonamide **3a** in the presence of excess MeI, gave only low yields of the non-alkylated benzosultam **8a.** Analogously, the cyclization of the *N*-methyl sulfonamide **7a** failed, producing the correspondent sultam **4a** only in modest yield (Scheme 3-13).



Scheme 3-13

To complete the synthetic procedure, the N-H sultam **8a** has been reacted under SL-PTC conditions with a series of alkyl halides RX (Scheme 3-14), and the desired *N*-alkyl tetrafluorobenzo sultams **4a-f** were obtained in very good overall yields (74-90%), starting from sulfonamide **3a**.



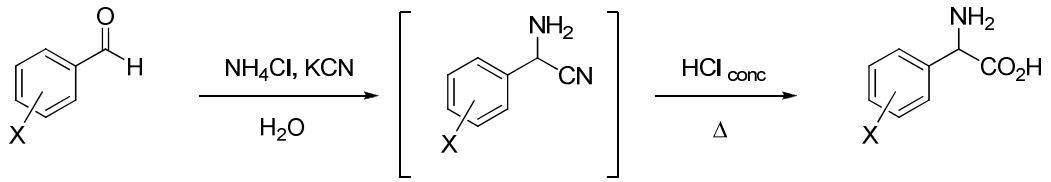
Scheme 3-14

	RX	t [h]	Sultam (%)
1	MeI	18	**4a** 99
2	EtI	48	**4d** 95
3	*n*-PrI	48	**4e** 88
4	*n*-BuI	48	**4f** 82
5	BnBr	20	**4b** 85
6	AllBr	20	**4c** 82

Table 3-10

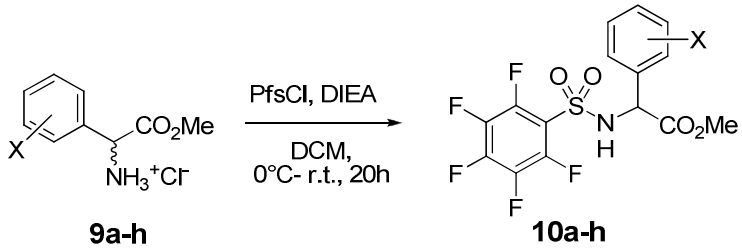
These results clearly show that homogeneous cyclization followed by nitrogen alkylation emerges as the best protocol to produce *N*-alkyl benzo[*d*]sultams, and preferred alternative to the "one-pot" cyclization, especially in the case of bulky benzyl and allyl derivatives **4b** and **4c**.

In order to check the reaction scope, we decided to synthesize several different 3-aryl substituted benzo[*d*]sultams, starting from the correspondent 2-aryl-2-aminoacetic acids. Arylglycines are both commercially available and easily obtainable by Strecker reaction on aromatic aldehydes (Scheme 3-15);



Scheme 3-15

Variously substituted arylglycines methyl ester **9a-h**, bearing both an electron withdrawing group and an electron donor group, were then synthesized and condensed with (pentafluorobenzene)sulfonyl chloride to give the corresponding sulfonamides **10a-h** (Scheme 3-16, Table 3-11).

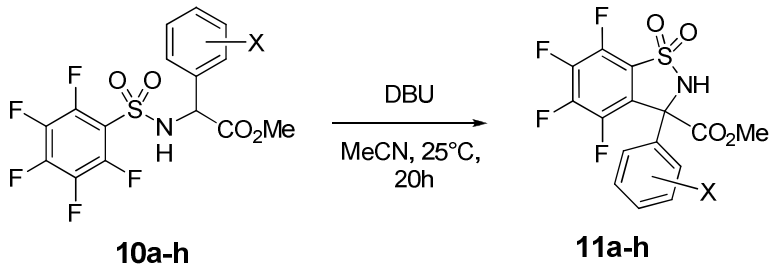


Scheme 3-16

	X	Sulfonamide (%)
1	3-F	**10a** 81
2	4-F	**10b** 80
3	4-Cl	**10c** 78
4	4-Br	**10d** 82
5	4-Me	**10e** 90
6	3-OMe	**10f** 85
7	4-OMe	**10g** 80
8	4-OBn	**10h** 83

Table 3-11

All these sulfonamides were then cyclized to the corresponding 3-aryl substituted benzo[*d*]sultams **11a-h** in good to excellent yields, or quantitative yields in the case of *m*-fluoro, *p*-fluoro, *p*-methyl, *m*-methoxy , and *p*-methoxy derivatives (Scheme 3-17, Table 3-12).

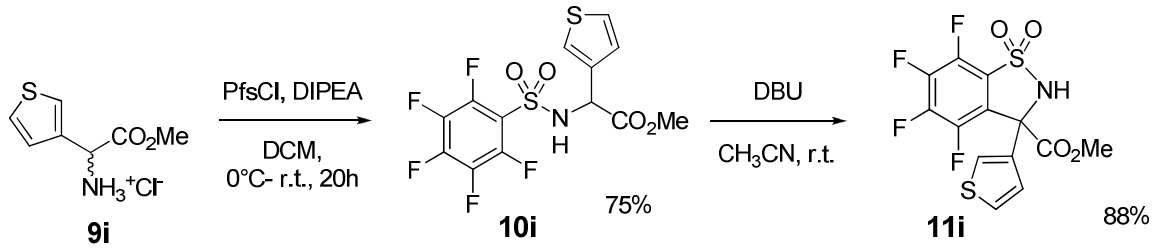


Scheme 3-17

	X	Sultam (%)
1	3-F	**11a** 98
2	4-F	**11b** 98
3	4-Cl	**11c** 97
4	4-Br	**11d** 93
5	4-Me	**11e** 99
6	3-OMe	**11f** 98
7	4-OMe	**11g** 98
8	4-OBn	**11h** 81

Table 3-12

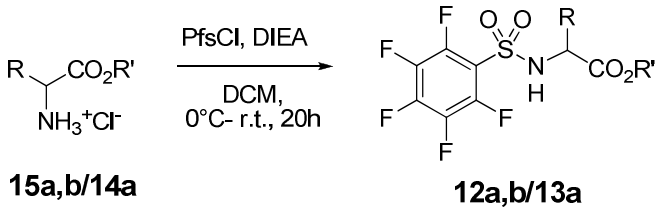
With this methodology[91], even heterocyclic derivatives can be synthesized, as demonstrated by the cyclization of the 3-thyenyl derivative **10i** (Scheme 3-18), which in turn has been obtained from 3-thienylglycine methyl ester **9i**.



Scheme 3-18

The influence of the acidity of the proton in the *C*-α position to the carbonyl functional group, has been investigated, by reacting, under the ring closing conditions, the sulfonamides **12a,b** and **13a,b** deriving from glycine and phenylalanine methyl esters **14a, 15a** and *tert*-butyl esters **14b**, **15b.**

The *N*-sulfonylation of these esters, especially in the case of methyl glycinate, gave modest yields (Table 3-13, entry 3) of the sulfonamides **12,13**. The condensation process was investigated by varying the base and the reaction conditions, and we found that the best result was obtained by reacting the free amino ester with an equimolar amount of sulfonyl chloride and pyridine, as the activating agent, in DCM solution and in the presence of TEA as a base (Table 3-14, entries 3,4).

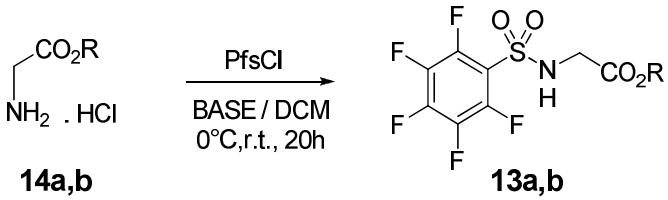


15a,b/14a **12a,b/13a**

Scheme 3-19

	R	R′	Sulfonamide (%)
1	CH_2Ph	Me	**12a** 70
2	CH_2Ph	*t*-Bu	**12b** 62
3	H	Me	**13a** 45

Table 3-13



14a,b **13a,b**

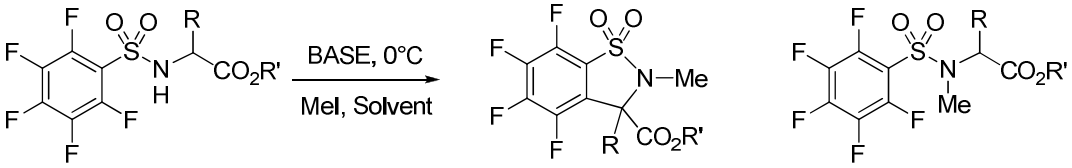
Scheme 3-20

	R	Base	Sulfonamide (%)
1	Me	TEA	**13a** 38
2	Me	N-Me Morpholine	**13a** 45
3	Me	Pyridine-TEA	**13a** 94
4	*t*-Bu	Pyridine-TEA	**13b** 75

Table 3-14

Sulfonamides **12a,b** and **13a,b** were reacted both under PTC conditions (Table 3-15, entry 1) and under many other anhydrous basic conditions (entries 2-9,11), varying the nature of the solvent and the base. Results indicate, for the phenylalanine derivative, a good reactivity for the *N*-alkylation (entries 1,8), but a very scarce reactivity toward the ring closure, and the desired compound **16** was isolated only as a side product (entries 2,5).

The results are even worst with the methyl sulfonamidoglycinate **13a,b**. In fact, no trace of the expected 3-carboxy mono-substituted benzosultam were detected, but the 3-methyl-3-carboxy derivative **20** was isolated as the sole cyclized product (Scheme 3-22).



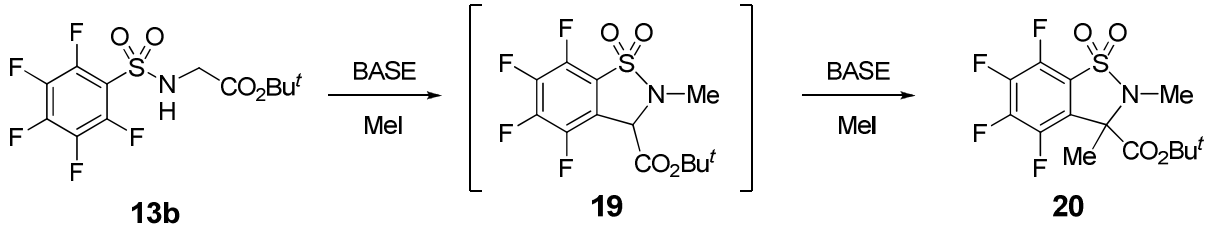
Scheme 3-21

	Substrate	R	R′	Solvent	Base	t [h]	Sultam	Sulfonamide
1	**12a**	CH_2Ph	Me	MeCN	K_2CO_3, $TEBA_{cat}$	20	---	**17a** 80
2	**12a**	CH_2Ph	Me	MeCN	NaH	16	**16a** 12	**17a** 44
3	**12a**	CH_2Ph	Me	DMSO	NaH	18	---	**17a** 35
4	**12a**	CH_2Ph	Me	DMA	NaHMDS	2	---	---
5	**12b**	CH_2Ph	*t*-Bu	THF-DMF	NaH	16	**16b** 15	**17b** 34
6	**13a**	H	Me	DMA	NaH	20	---	**18a** 35
7	**13a**	H	Me	DMA	NaH	1,5	---	**18a** 37
8	**13a**	H	Me	DMA	NaH	20	---	---
9	**13b**	H	*t*-Bu	DMA	NaH	2	---	**18b** 72
10	**13b**	H	*t*-Bu	MeCN	K_2CO_3, $TEBA_{cat}$	40	---	**18b** 60
11	**13b**	H	*t*-Bu	THF-DMF	NaH	22	**20** 12	**18b** 18

Table 3-15

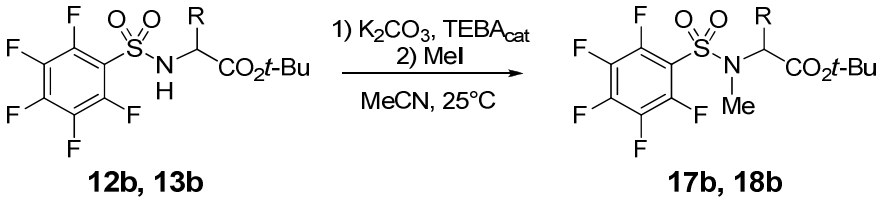
The presence of **20**, arising from *C*-methylation of the mono-*N*-methylated sultam **19**, proves that **19** under strong basic conditions is rapidly deprotonated and then methylated: this

behavior is probably due to the increased acidity of the *C*-α proton that, after the cyclization, is adjacent to the electron withdrawing aromatic fluorinated moiety.



Scheme 3-22

Some additional tests were performed on the *N*-methyl sulfonamides **17b** and **18b**, obtained under SL-PTC conditions, in acetonitrile (Scheme 3-23, Table 3-16).

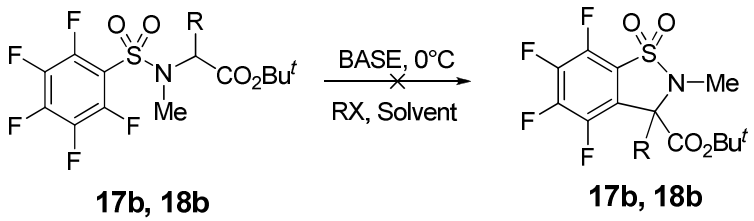


Scheme 3-23

	R	Sulfonamide (%)
1	CH_2Ph	**17b** 80
2	H	**18b** 65

Table 3-16

The cyclization of these compounds (Scheme 3-24, Table 3-17) furnished large amounts of 21 (Figure 3-1) and unidentified by-products (entries 1-4), proving that this reaction is not applicable to derivatives of amino acids different from phenylglycine and indicating the probable fundamental role of the aromatic ring for the success of the cyclization.



Scheme 3-24

	R	Solvent	Base	T [°C]	t [h]	Sultam (%)
1	CH_2Ph	DMA	NaH	0-r.t.	20	---
2	CH_2Ph	MeCN	DBU	r.t.	16	---
3	H	THF	LDA	-78-0	10	---
4	H	DMA	NaH	0-r.t.	20	**21** 18*

Table 3-17

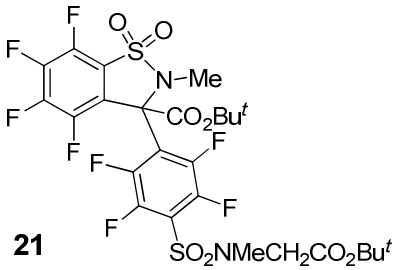
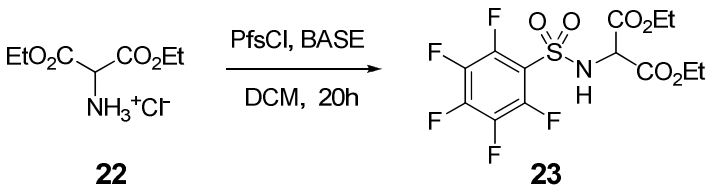


Figure 3-1

Intra-intermolecular aromatic disubstitution product

The high acidity of the *C-α* proton seems one of the determining features for the ring-closure of sulfonamides to benzosultams and to verify this postulate, we decided to synthesize another sulfonamide containing a strongly acid proton. Our choice fell on the sulfonamide **23** derived from the commercially available diethylaminomalonate **22** that was sulfonylated in 50% non-optimized yield (Scheme 3-25, Table 3-18) In the sulfonamide **23**, two electron-withdrawing ester groups activate the C-*α* proton, i.e., with respect to the arylglycinate derivatives, one ester group substitutes the aromatic ring in determining the acidity of the C_α-proton, which can be removed by the mild bases used until now.

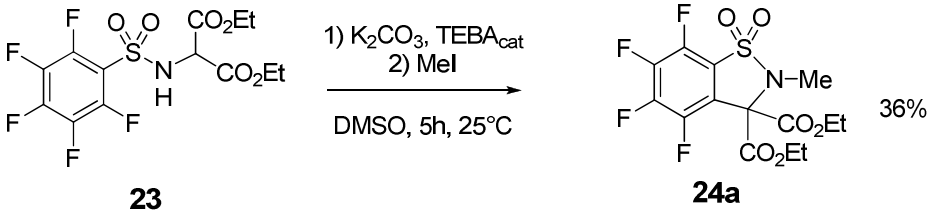


Scheme 3-25

	Base	T[°C]	23 (%)
1	K_2CO_3	25	7
2	DIEA	0	---
3	Pyridine-TEA	0	35
4	Pyridine-TEA	0-25	50

Table 3-18

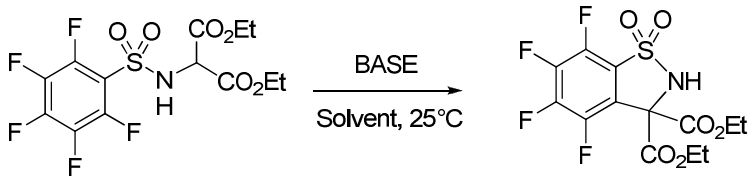
Cyclization of this sulfonamide gave the 3,3-dicarboxy-*N*-methylsultam **24a** in low, but significative yield (36%), confirming that the acidity of the proton effectively influences the formation of the sultam (Scheme 3-26);



23 **24a**

Scheme 3-26

Higher yields were reached by cyclization of the diethylaminomalonate derivative **23** under the optimized homogeneous conditions with DBU (Scheme 3-27, Table 3-19).



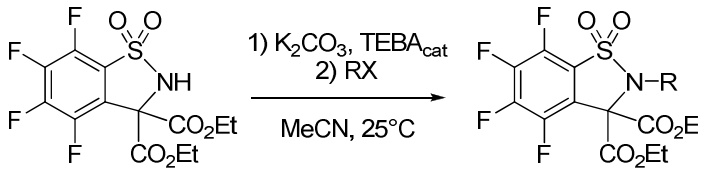
23 **25**

Scheme 3-27

	Solvent	Base	T[°C]	t [h]	25 (%)
1	DMF	K_2CO_3, $TEBA_{cat}$	0	48	48
2	DMA	NaH	0-25	16	61
3	MeCN	DBU	25	4	66

Table 3-19

Even sultam **25**, as done for the phenylglycine derived benzosultam, was *N*-alkylated under SL-PTC conditions, obtaining the correspondent *N*-alkyl sultams in good yields (Scheme 3-28, Table 3-20).



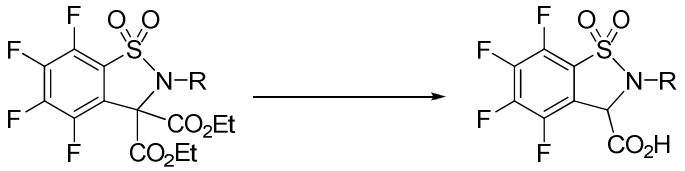
25 **24a-c**

Scheme 3-28

	RX	t [h]	Sultam (%)
1	MeI	5	**24a** 88
2	AllBr	12	**24b** 95
3	BnBr	18	**24c** 70

Table 3-20

With the sultams **25** and **24a-c** in our hand, we investigated the decarboxylative conditions, to obtain the mono-3-carboxy-benzosultams. Despite that many authors describe the use of strong nucleophile under heating for the decarboxylation of malonate derivatives[92], we found that our substrate under these conditions gave by-products through replacement of the aromatic fluorine atoms (Table 3-21, entries 1-2).



Scheme 3-29

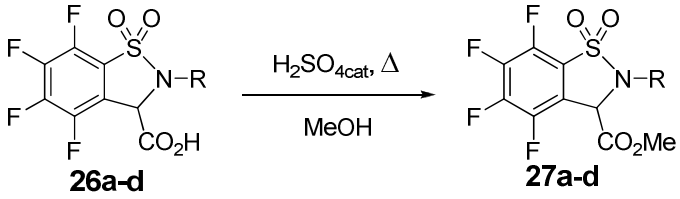
	R	Sulfonamide	Reagents	Solvent	T[°C]	t [h]	Sultam
1	H	**25**	NaCl, H_2O	DMSO	180	0,2	---
2	H	**25**	NaF, TBAF	THF	80	2	---
3	H	**24a**	H_2O, H_2SO_{4cat}	AcOH	100	3	**26a** 95
4	Me	**24b**	H_2O, H_2SO_{4cat}	AcOH	100	18	**26b** 79
5	All	**24c**	H_2O, H_2SO_{4cat}	AcOH	100	50	**26c** 85
6	Bn	**24d**	H_2O, H_2SO_{4cat}	AcOH	100	100	---
7	Bn	**24d**	H_2O, H_2SO_{4cat}	$CH_3CH_3CO_2H$	120	72	**26d** 83

Table 3-21

On the other hand, treatment of the (tetrafluorobenzo)sultams **24,25** with strong acids under heating gave quite complete conversion into the desired carboxylic acid, that can be isolated without any purification. While *N*-methyl **24b** and *N*-allyl **24c** derivatives showed the same behavior under these decarboxylative conditions (entries 4-5), giving the corresponding acids in good yields, even if in longer reaction times, the *N*-benzyl derivative **24d** is not reactive (entry

6), probably due to its low solubility in AcOH. This problem was easily solved by hydrolyzing benzosultam **24c** using propionic acid instead of acetic acid (entry 7).

Finally, the carboxylic acids **26** have been converted into the corresponding methyl esters **27** by Fisher esterification with methanol and sulfuric acid as catalyst (Scheme 3-30, Table 3-22).



Scheme 3-30

	R	Sultam (%)
1	H	**27a** 90
2	Me	**27b** 93
3	Bn	**27c** 75

Table 3-22

These (tetrafluorobenzo)sultams present a high degree of chemical diversity. Actually, they can be functionalized both on the fluorinated moiety, on the nitrogen atom, on the carboxylic functional group and, eventually, on the aromatic ring present in the 3-position. However, in order to synthesize new and more versatile compounds and to go deeper inside into the reaction mechanism, we decided to investigate the role of the fluorine substituents by preparing and reacting differently halogenated sulfonamides. The commercially available (polyfluorobenzo)sulfonyl chlorides **5b-e** (Figure 3-2), even if show a large variety of substitution, do not allow a complete screening, thus we prepared a series of sulfonyl chlorides bearing different substituents on the aromatic fluorinated moiety.

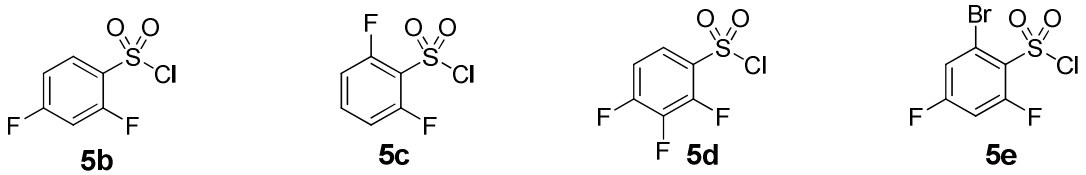
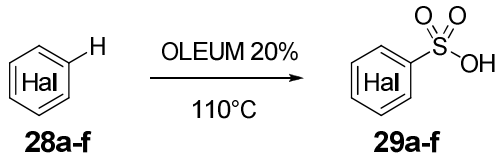


Figure 3-2

We choose, as starting compounds, the commercially available (polyfluoro)halobenzenes **vv** that were sulfonated with 20% oleum, following a literature procedure applied on several chlorinated analogues.[93] Good yields were obtained for all the sulfonic acids (Scheme 3-31, Table 3-23), but *o*-bromo substituted ones **28a,e**, due to the bulky *ortho* substituent that partially inhibits the aromatic electrophilic attack (entries 1,5).



28a-f **29a-f**

Scheme 3-31

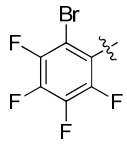
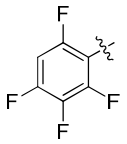
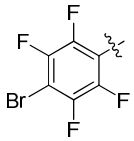
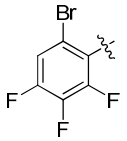
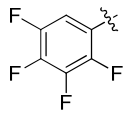
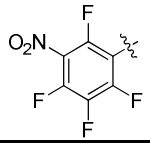
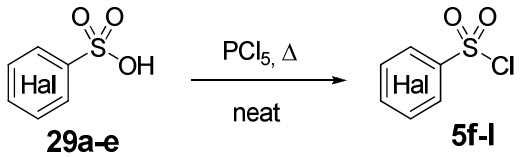
	Hal	t [h]	Sulfonic acid (%)		Hal	t [h]	Sulfonic acid (%)
1		7	**29a** 77	4		4,5	**29d** 90
2		6	**29b** 90	5		7	**29e** 60
3			**29c** 82	6		20	---

Table 3-23

In the case of deactivated 3-nitro derivative **28f**, no reaction was observed (entry 6), even in longer reaction times. The sulfonic acids were subsequently chlorinated (Scheme 3-32, Table 3-24) by reaction at 110-120 °C for 15 minutes with neat phosphorus pentachloride, followed by a rapid quench in ice and extraction. With this protocol, we do not observe any substitution at the aromatic ring by the chloride anion.



29a-e **5f-l**

Scheme 3-32

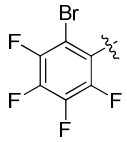
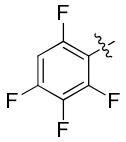
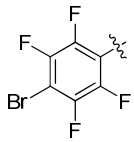
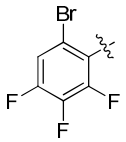
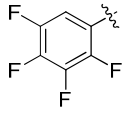
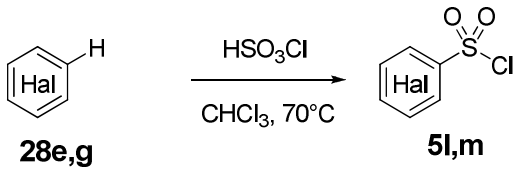
	Hal	Sulfonyl chloride (%)		Hal	Sulfonyl chloride (%)
1		**5f** 80	4		**5i** 78
2		**5g** 89	5		**5l** 78
3		**5h** 73			

Table 3-24

For the more activated 1-bromo-3,4,5-trifluorobenzene (**28e**) and 1,3,5-trifluorobenzene (**28g**) we performed also a direct chlorosulfonation (Scheme 3-33, Table 3-25).



28e,g **5l,m**

Scheme 3-33

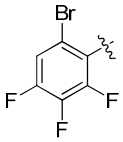
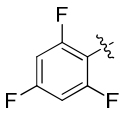
	Hal	t [h]	Sulfonyl chloride (%)
1		7	**5l** 60
2		5	**5m** 62

Table 3-25

The sulfonyl chlorides **5** were condensed with phenylglycine methyl ester to give the corresponding pure sulfonamides **30a-l** in good yield, after crystallization or chromatographic purification (Scheme 3-34, Table 3-26).

5b-m **6a** **30a-l**

Scheme 3-34

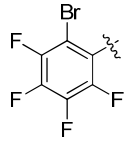
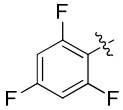
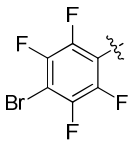
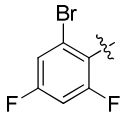
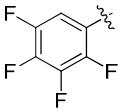
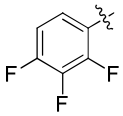
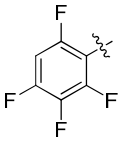
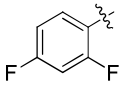
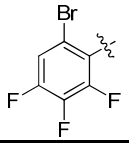
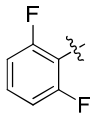
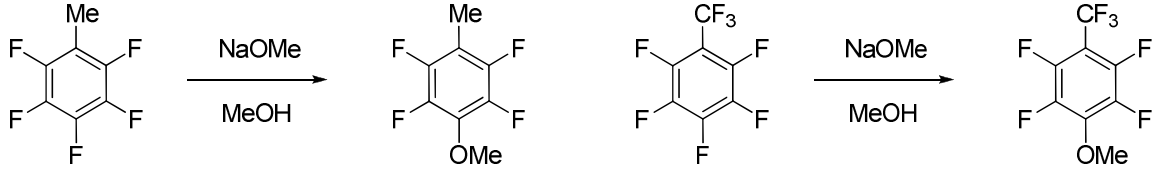
	Hal	Sulfonamide (%)		Hal	Sulfonamide (%)
1		**30a** 82	6		**30f** 70
2		**30b** 86	7		**30g** 89
3		**30c** 61	8		**30h** 93
4		**30d** 67	9		**30i** 88
5		**30e** 60	10		**30l** 81

Table 3-26

From the literature is known that, in the nucleophilic aromatic substitution, the attack of the nucleophile on fluorinated substrates is governed by fluorine atom positions, rather than by the activating affects of other functional groups eventually present in the aromatic ring (Scheme 3-35);



Scheme 3-35

Moreover, considering the basis of the orientating preferences of fluorine atoms, it has been determined that (from the analysis of the relative rate constants, Figure 3-3), for an aromatic fluorine leaving group, the fluorine in *meta*-position is powerfully activating, while the *ortho*-fluorine is less activating, and the *para*-fluorine has an effect similar to a hydrogen substituent.

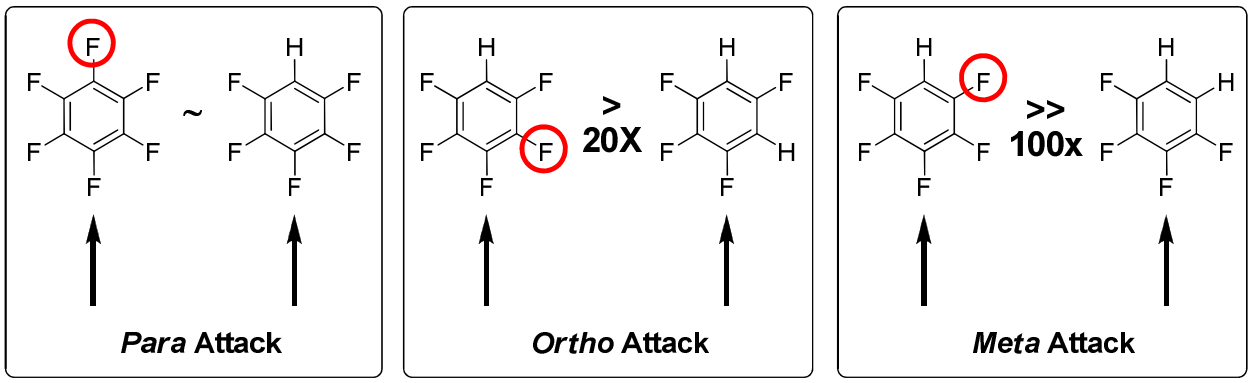
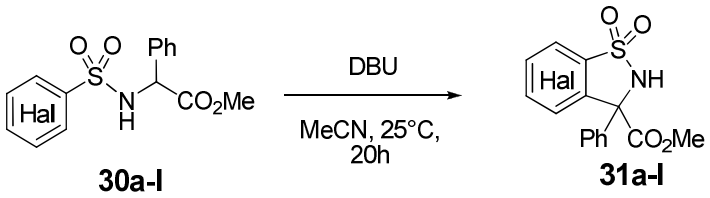


Figure 3-3

Cyclization of the differently halogenated sulfonamides, in effect, gave a decreasing yield with the decrease of the activation of the *ortho*-fluorine atom toward the SNAr (Scheme 3-36, Table 3-27).

In particular, sulfonamides which lack of a fluorine substituent in *meta* to the leaving group, do not give the corresponding sultam (entries 3, 8-9). On the contrary, 2,4,6 trihalosulfonamides gave the desired compounds in good yields, and particularly good in the case of the 5-bromosubstituted benzosultam, obtained in a 64% overall yield from the starting halobenzene.

Another interesting feature is the reaction of sulfonamide **30d** which would lead to two different regioisomers, but we isolated only the regioisomer derived from the major activation of the fluorine in *ortho*-position to the leaving group, proving that the fluorine in 2-position is much more activated in a SNAr reaction.



Scheme 3-36

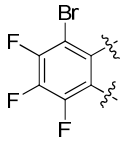
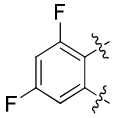
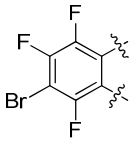
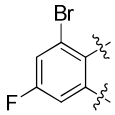
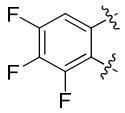
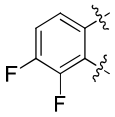
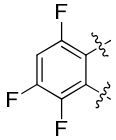
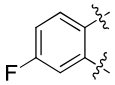
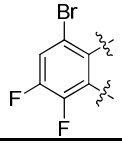
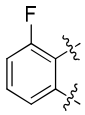
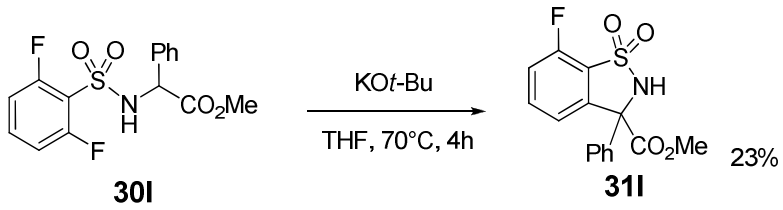
	Hal	t [h]	Sultam (%)		Hal	t [h]	Sultam (%)
1		24	**31a** 78	6		30	**31f** 72
2		24	**31b** 92	7		24	**31g** 64
3		160	**31c** 30	8		30	---
4		20	**31d** 92	9		30	---
5		24	**31e** 92	10		30	---

Table 3-27

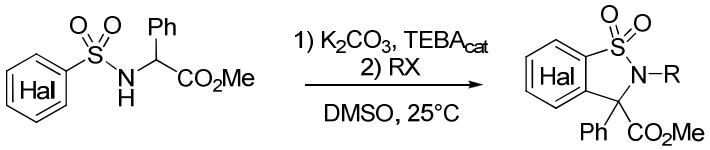
For the less activated sulfonamides **30h-l**, i.e. containing less fluorine atoms, neither stronger bases, nor harsher conditions gave acceptable results and, e.g., only 23% yield of 7-fluoro benzosultam **31l** was obtained (Scheme 3-37):



Scheme 3-37

Regarding the SL-PTC "one-pot" cyclization of these less fluorinated sulfonamides, results confirmed the superiority of homogeneous conditions. In fact, the expected sultams are isolated

in poor yields, especially in the case of the less activated (5,7-difluorobenzo)sultam **33** and (5-fluoro-7-bromobenzo)sultam **34** (Scheme 3-38, Table 3-28).



Scheme 3-38

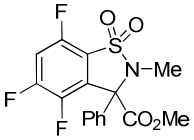
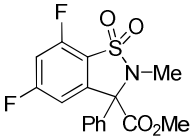
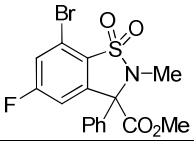
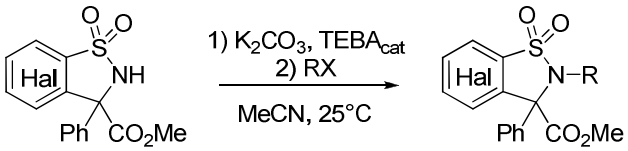
	RX	t	Sultam	(%)
1	MeI	18		**32** 89
2	MeI	45		**33** 51
3	MeI	26		**34** 68

Table 3-28

Sultams **31a,d,f** were SL-PTC *N*-alkylated in good yields, as usual. The results, on the whole,



Scheme 3-39

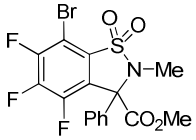
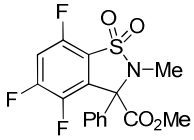
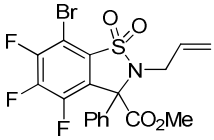
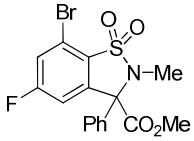
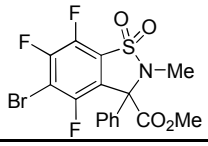
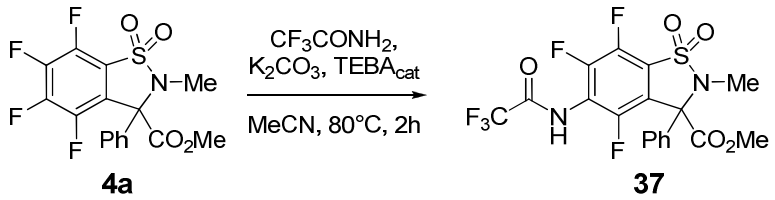
	RX	t [h]	sultam	(%)		RX	t [h]	Sultam	(%)
1	MeI	20		**35a** 94	4	MeI	16		**32** 92
2	AllBr	16		**35b** 77	5	MeI	40		**34** 82
3	MeI	20		**36** 90					

Table 3-29

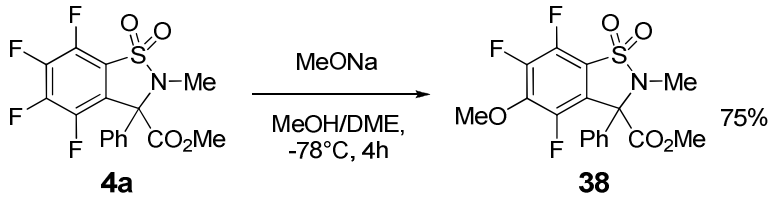
confirmed that the combination between homogeneous cyclization and consecutive SL-PTC *N*-alkylation is much more interesting for the preparation of *N*-alkyl benzosultams (Scheme 3-39, Table 3-29).

N-Methyl (tetrafluorobenzo)sultam **4a** has been employed in the study of aromatic nucleophilic substitution of fluorine atoms. Regarding the mono-substitution, we obtained good results in the introduction of a nitrogen atom by treatment of **4a** with trifluoroacetamide, under SL-PTC conditions. The most labile position is the fluorine in 5-position, probably due the activation both by fluorine in 7-position and by the sulfonyl group in 1-position, and the 5-trifluoroacetamido derivative **37** was isolated as sole product in good yield (Scheme 3-40).



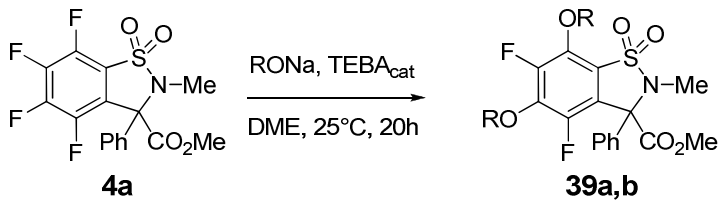
Scheme 3-40

In a similar way, treatment of **4a** with sodium metoxyde at -78°C in THF gave the analogous oxygenated substitution product **38** (Scheme 3-41).



Scheme 3-41

When an excess of the alcolate is used and harsher conditions are employied, the only observed product were the 5,7 disubstituted compounds **39** (Scheme 3-42, Table 3-30) proving that, for the previously seen reasons, even the fluorine atom in 7-position is enough activated as leaving group. As a conclusion, in the mono-substitution the preference for the 5-position is probably due to the steric hindrance given by the sulfonyl functional group.

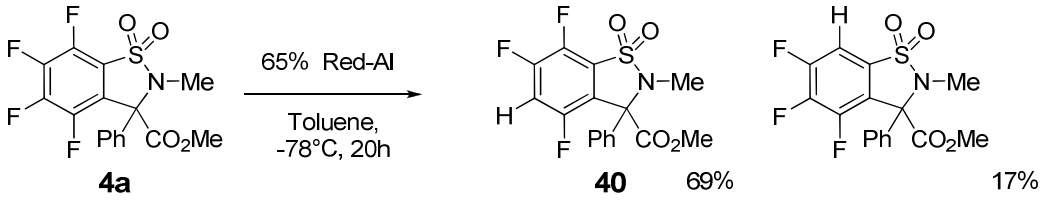


Scheme 3-42

	R	Sultam (%)
1	Me	**39a** 82
2	Ph	**39b** 92

Table 3-30

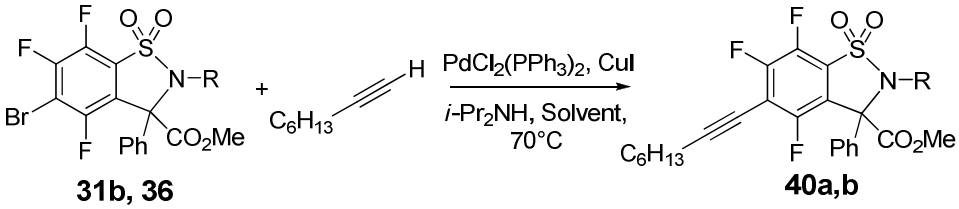
While the reaction of benzosultam **4a** with reducing agents, such as sodium naphtalenide and Red-Al® at room temperature, gave only decomposition products, quite interesting are the results obtained with Red-Al® at -78°C. Under these conditions, in fact, we obtained selective removal of the fluorine in 5-position, along with a minor amount of the sultam in which fluorine in 7-position was removed (Scheme 3-43).



Scheme 3-43

For the brominated sultams **31b** and **36**, we tested the reactivity of the bromine-carbon bond, despite few coupling reactions on fluorinated aromatic rings are reported in literature.[94]

The first reaction analyzed was the Sonogashira coupling with 1-octine (Scheme 3-44, Table 3-31) but the scarce results prompt us to take as standard an easier reaction and our attention fell on the Suzuki coupling with phenylboronic acid.

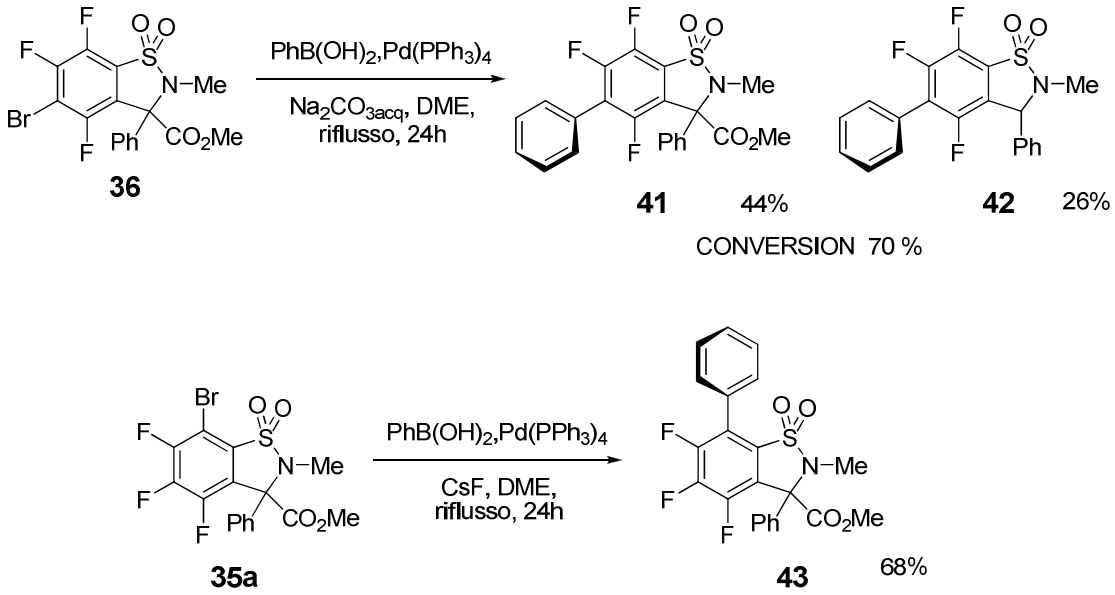


Scheme 3-44

	Solvent	t [h]	R	Sultam (%)
1	DMF	8	Me	**40b** 12
2	THF	9	H	**40a** 31
3	THF	7	Me	**40b** 39

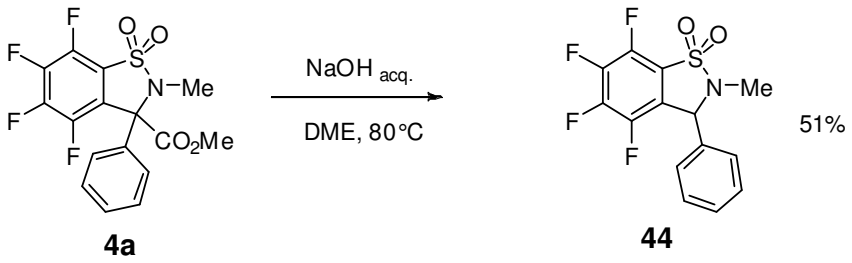
Table 3-31

Preliminary results gave a good conversion of the substrate but a low selectivity and, together with the coupling product **41**, one third of the products is the decarboxylated sultam **42** (Scheme 3-45). After a brief screening for anhydrous Suzuki coupling conditions, we found that cesium fluoride is the base of choice and the biaryl derivative **43** has been obtained in 68% yield.



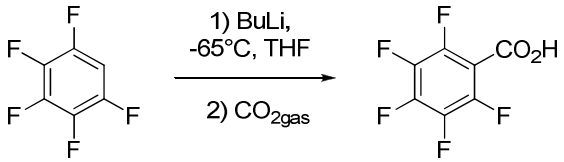
Scheme 3-45

The presence of the decarboxylative product **42** prompted us to investigate the behavior of **4a** under aqueous basic conditions: preliminary results gave a 51% yield of **44** opening the way to the obtainment of 3-aryl monosubstituted benzosultams.



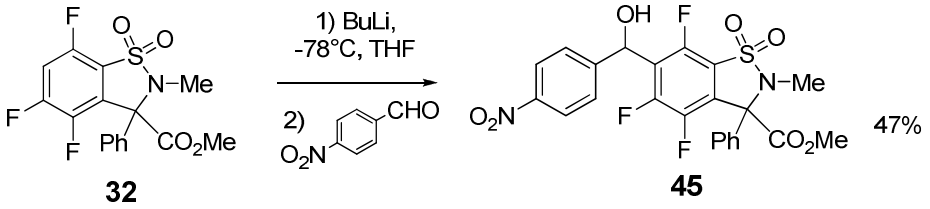
Scheme 3-46

Finally, the aromatic proton in the fluorinated moiety of sultam **32** is acid enough to be lithiated. Actually, few examples are reported in literature for the lithiation of simple aromatic polyfluoro compounds like pentafluorobenzene (Scheme 3-47) or 1,3-difluorobenzene, and reaction with a series of electrophilic reagents (metallic and metalloidal halides, ethyl formate, *N*-methylformanilide, benzaldehyde, halogens, sulfur, water, and carbon dioxide).[95]



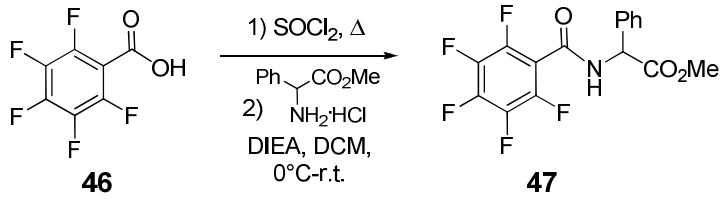
Scheme 3-47

As a consequence, treatment of **32** with buthyl lithum at -78°C followed by the addition of the reactive *p*-nitro benzaldehyde, gave an interesting yield of the secondary alcohol (Scheme 3-48): this preliminary result open the way to further functionalizations of the less fluorinated sultams, not only as electrophiles but also as nucleophiles.



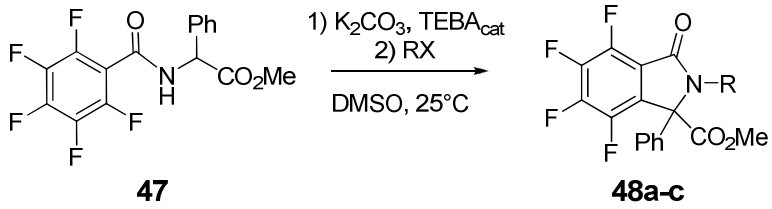
Scheme 3-48

As an extension of our work, we decided to apply the whole methodology to the synthesis of the lactamic analogues: in a preliminary investigation, commercially available pentafluoro benzoic acid **46** has been converted into the corresponding sulfonyl chloride then condensed with phenylglicine methyl ester (Scheme 3-49).



Scheme 3-49

The desired amide **47**, obtained in 47% overall yield, has been cyclized under the homogeneous conditions and gave interesting yields of the tetrafluoro isoindolones **48a-c**.



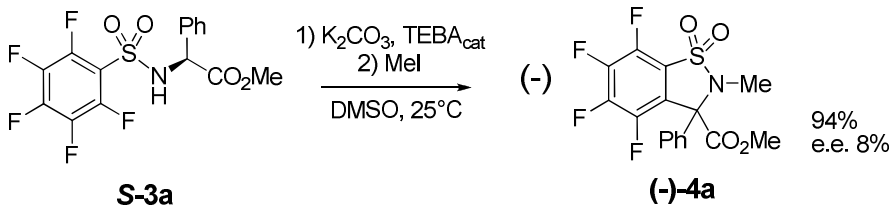
Scheme 3-50

	RX	t [h]	Lactam (%)
1	MeI	26	**48a** 86
2	AllBr	20	**48b** 56
3	BnBr	20	**48c** 40

Table 3-32

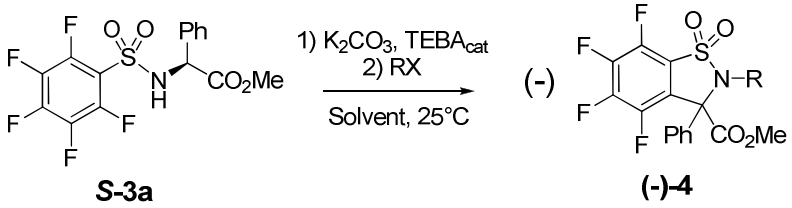
3.2 Stereochemistry of Benzosultams

After having defined the optimal conditions to reach the highest yields for the cyclization step, we turned our attention to the stereoselective synthesis of our sultams: in fact, as we have seen in the previous chapter, the synthesis of optically pure benzo[*d*]sultams is a subject of great interest, even in the light of the very small number of synthetic methods available in literature.
When we performed the SL-PTC "one pot" reaction on the optically pure sulfonamide ***S*-3a**, we found small but encouraging enantiomeric excess (e.e.) of benzosultams (Scheme 3-51) with the prevalence of the (-) isomer.



Scheme 3-51

Moreover, the variation of the alkylating agent led to a continuous, even if low, increase of e.e.'s with the increasing dimension of the alkylic residue, along with decreasing yields (Scheme 3-52, Table 3-33).



Scheme 3-52

	Solvent	RX	t[h]	y	e.e.
1	DMSO	EtI	20	83	16
2	DMSO	*n*-PrI	24	50	25
3	DMF	MeI	48	47	13

Table 3-33

The complete absence of an external source of stereochemical information, suggested to investigate the nature and the determinant parameters of the auto-induced stereoselectivity in the cyclization process.

Firstly, the phase transfer agent was changed, but it did not lead to any substantial modification in the e.e. values and, on the contrary, lower yields were found in the case of more lipophilic onium salts (Table 3-34) probably due to their scarce solubility in DMSO. Even the use of chiral PT agent, such as *N*-methyl-*N*-dodecylephedrinium bromide (MDE-Br^-) or the cinchonidine derived "Corey's catalyst", failed and we obtained the corresponding sultam in low yields and e.e.'s (entries 5-6).

	PT catalyst	t[h]	y	e.e.
1	$Et_3BnN^+Cl^-$	20	94	8
2	$Me_4N^+OH^- 5H_2O$	40	62	0
3	$Me_3BnN^+F^-$ H_2O	40	73	<5
4	$C_{12}Me_{25}N$ $Me_3^+Cl^-$ H_2O	40	73	15
5	MDE-Br^-	40	65	10
6	Corey's Catalyst	30	72	<5

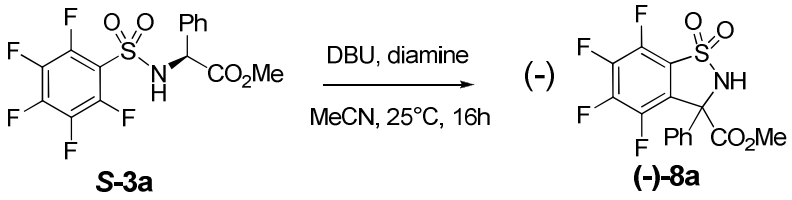
Table 3-34

In the light of the very scarce results obtained under heterogeneous conditions, we turned our attention to the cyclization under homogeneous conditions.

Since the ring-closing of sulfonamide ***S*-3a** with DBU as a base, as described here before, leads to the racemic benzosultam, we decided to evaluate the use of an additive in the system sulfonamide-DBU, looking for possible interactions additive-base-substrate capable to induce the formation of a chiral adduct, which can evolve enantioselectively toward the desired benzosultam.

Preliminary positive results have been obtained by reacting ***S*-3a** with DBU, in acetonitrile at 25 °C in the presence of 0.2 molar equivalents of a diamine (Scheme 3-53): the choice fell both on simple diamines (*Table* 3-35, entries 1-4) and on more complex chiral diamines (entries 5-8). All these reactions gave an almost quantitative yield of **8a** and the e.e. ranging from 19 to 23%. Results show that the bases induces a general effect, maybe due to a modulation of the DBU basicity, rather than to the chiral complex formation; this can be deduced from the reaction of the achiral bases (entries 1-4) and from the use of both the enantiomers of 1,2-diaminocyclohexane (entries 6-7), and of their racemic mixture (entry 8).

All these reactions, in fact, lead to nearly identical e.e. values, with prevalence of the same enatiomer **(-)-8a**.



Scheme 3-53

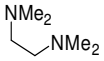
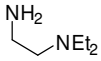
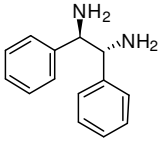
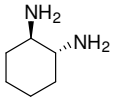
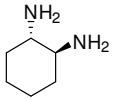
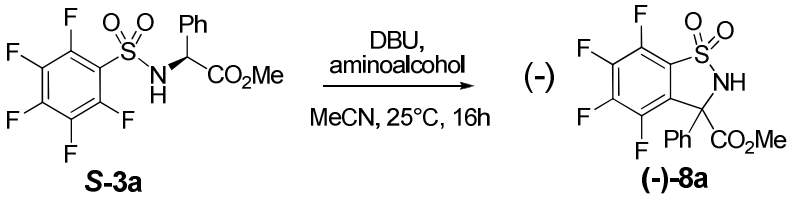
	Diamine	y	e.e.
1		98	21
2		98	20
3		98	19
4		98	23
5		98	21
6		97	23
7		98	22
8	*rac*-diamino cyclohexane	98	22

Table 3-35

Similar results were obtained by addition, as an additive, both of a chiral amino alcohol (Scheme 3-54, Table 3-36) and of cinchona alkaloid derivatives (entries 4-6), compounds that are often used in asymmetric synthesis. The use of α-amino acids (entries 7-8) gave the desired sultam **8a** with unchanged e.e. values, even if in longer reaction times (respectively 80 and 120 h).



Scheme 3-54

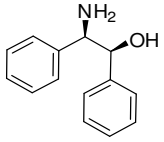
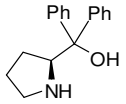
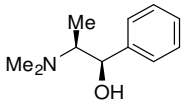
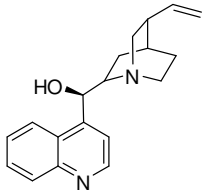
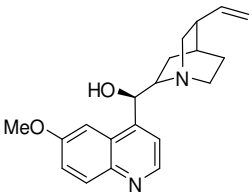
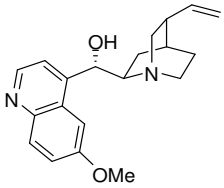
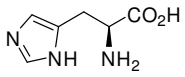
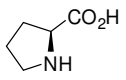
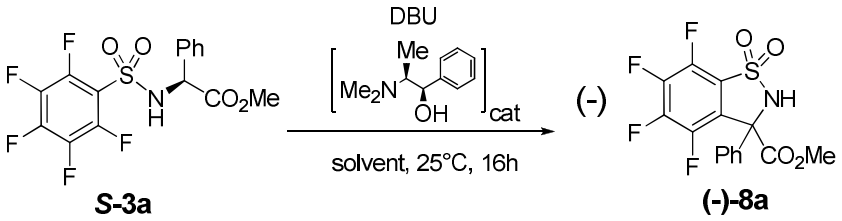
	Amino alcohol	y	e.e.
1		95	23
2		95	16
3		98	22
4		98	22
5		95	19
6		95	23
7		90	20
8		96	23

Table 3-36

Taking the (1*R*,2*S*)-*N*-methylephedrine (NME) as the standard additive, we conducted several experiments varying the solvent (Table 3-37): the best e.e.'s were obtained in ethereal solvents like THF (entry 2) and DME (entry 3). In DCM (entry 4) we found both e.e.'s and yields very

low, while in the aromatic solvents chlorobenzene and toluene quantitative yields and, conversely, poor e.e. values were obtained (entries 5-6).

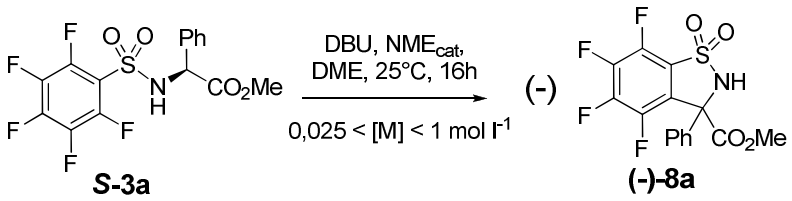


Scheme 3-55

	Solvent	y	e.e.
1	MeCN	98	22
2	THF	98	24
3	DME	98	33
4	DCM	85	14
5	4-Cl-Ph	98	18
6	Toluene	95	18

Table 3-37

Experiments carried out with DBU and NME at different concentrations of the starting sulfonamide ***S*-3a** (Table 3-38) , confirmed that the previously used molarity (0.25 mol l^{-1}) is the best one, even if the values do not change significantly in the range between 0.25—1.0 mol l^{-1}; in very diluted solution (0.025 mol l^{-1}, entry 5) we obtained much lower values of e.e. for **8a**.



Scheme 3-56

	M [mol l^{-1}]	y	e.e.
1	1	98	28
2	0.5	96	29
3	0.25	98	33
4	0.05	98	24
5	0.025	90	17

Table 3-38

In Table 3-39 are summarized the results reached with different amines (entries 1-3), diamines (entry 4), guanidines (entry 5) and amidines (entry 6): these compounds, used with the system ***S*-3a**–DBU in DME at 25°C, gave the same yields of benzosultam **8a** with the same e.e.

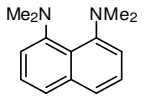
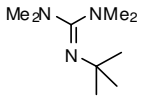
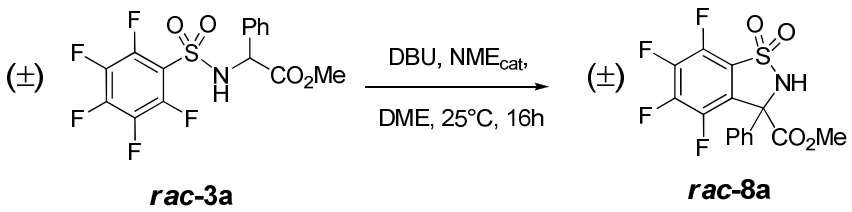
	Diamine	**y**	**e.e.**
1	TEA	97	36
2	DIA	97	35
3	Pyridine	97	36
4		97	34
5		97	35

Table 3-39

This behavior, rather than to the formation of complexes, is therein ascribable to the overall effect of the added second base on the system and to the formation of adducts [enolate]-[basic system]-[starting sulfanamide], in which the optically pure starting material ***S*-3a** acts as a chiral auxiliary.

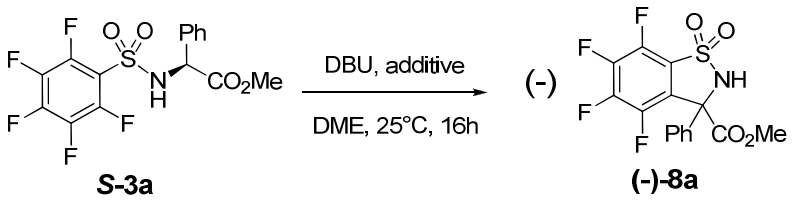
Moreover, the reaction of the racemic sulfonamide ***rac*-3a** under the enantioselective conditions, confirmed our hypothesis, giving quantitative yield of the racemic compound ***rac*-8a** (Scheme 3-57).



***rac*-3a** ***rac*-8a**

Scheme 3-57

Other chiral additives have been employed (Scheme 3-58), but we found similar stereochemical efficiency: the best effects were reached always with diamines (Table 3-40, entries 1-3) while the bis(phenol) (entry 4) completely stopped the reaction and the bis(phosphine) (entry 5) gave analogue results to that obtained with (triphenyl)phosphine (entry 6).



Scheme 3-58

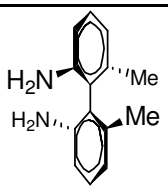
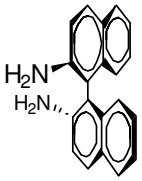
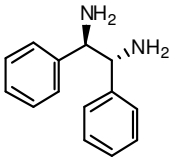
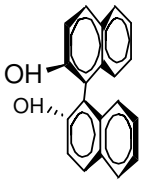
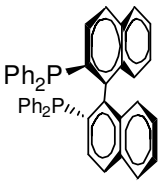
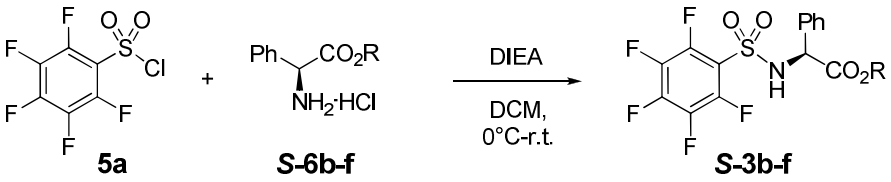
		Additive	y	e.e.
1	(R)		97	36
2	(R)		96	34
3	(R,R)		98	33
4	(R)		---	---
5	(R)		98	28
6		PPh_3	90	27

Table 3-40

In order to analyze the influence of the steric hindrance of the ester, sulfonamides bearing different ester groups have been synthesized. The condensation of ethyl, propyl, butyl, benzyl, and metoxyethyl phenylglycinates with (pentafluorobenzene)sulfonyl chloride, under the previously optimized conditions, gave the desired sulfonamides **3b-f** in good yields (Scheme 3-59, Table 3-41).

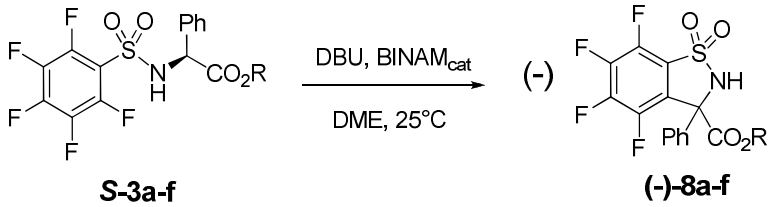


Scheme 3-59

	R	sulfonamide (%)
1	Et	***S*-3b** 74
2	*i*-Pr	***S*-3c** 75
3	*t*-Bu	***S*-3d** 89
4	Bn	***S*-3e** 52
5	CH_2CH_2OMe	***S*-3f** 77

Table 3-41

These sulfonamides ***S*-3b-f** have been cyclized with DBU/BINAM in DME (Scheme 3-60, Table 3-42);

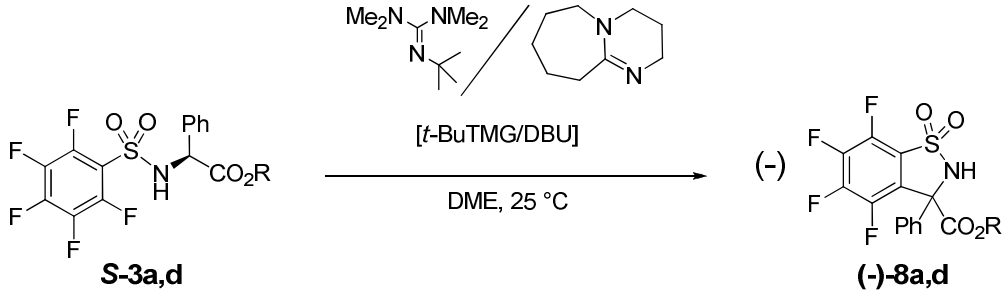


Scheme 3-60

	R	T [°C]	t [h]	Sultam (%)	e.e.
1	Me	25	16	**(-)-8a** 96	34
2	Et	25	16	**(-)-8b** 94	43
3	*i*-Pr	25	20	**(-)-8c** 97	47
4	*t*-Bu	25	20	**(-)-8d** 91	51
5	Bn	25	16	**(-)-8e** 91	18
6	$MeOCH_2CH_2$	25	18	**(-)-8f** 97	17
7	Me	0	40	**(-)-8a** 80 (83)	49
8	Et	0	70	**(-)-8b** 91	53
9	*t*-Bu	0	160	**(-)-8d** 66 (73)	64
10	Me	-20	160	---	---

Table 3-42

A significant increase of sultam **(-)-8a** e.e. was reached - from the 34% to the 51% - passing from methyl to *t*-butyl sulfonamido ester (entries 1-4). Quite unexpected have been the low e.e.'s obtained with benzyl (entry 5) and methoxyethyl (entry 6) esters. In the case of the benzylic ester **S-3e**, this behavior is probably due to a unfavourable π-interactions between the aromatic rings present in the molecule. An analogous interaction of the electrons of the non-bonding orbital in the methoxyethyl ester **S-3f** can be responsible for the low e.e. Lowering the reaction temperature to 0 °C (entries 7-9) drastically decreased the reaction rate, while at -20 °C (entry 10) the ring-closing process was completely stopped. Finally, the analysis of sulfonamide **(-)-8a** and **(-)-8d** cyclizations at non-complete conversion times (entries 7, 9) detected higher e.e.'s (e.e. ≥ 10). In the light of the possibility to choose between chiral and achiral base/additive, we focused our attention on the good results obtained with *t*-BuTMG (Table 3-39, entry 5). Interesting results were achived using the system *t*-BuTMG/DBU in variable molar ratios (Scheme 3-61, Table 3-43): a large molar amount of *t*-BuTMG (entries 1–3) with decreasing quantity of DBU led to a prolongation of the reaction time, but gave good e.e.'s. The best e.e. for the methyl ester **(-)-8a** was obtained using equimolar amount of the two bases (entry 5) and, similarly, the *t*-butyl ester ***S*-3d** gave the desired sultam **(-)-8d** in a similar e.e. in longer times (entry 6), proving one more time the dependence of the reaction rate on the steric hindrance.

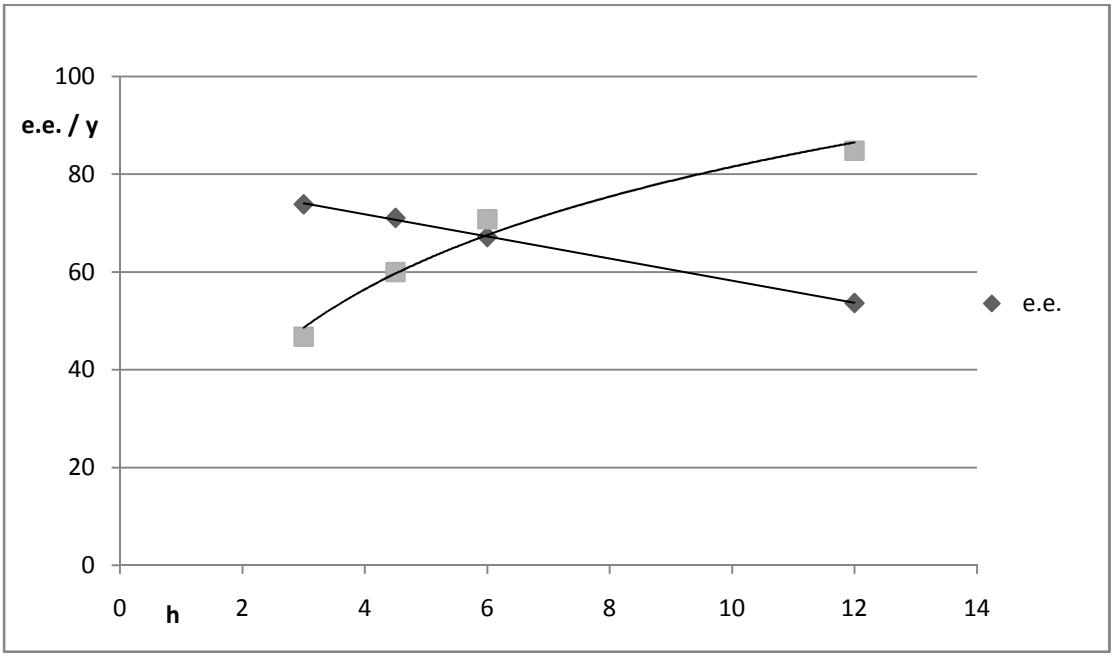


Scheme 3-61

	R	*t*-BuTMG (mol)	DBU (mol)	t [h]	Sultam (%)	e.e.
1	Me	4	2	20	**(-)-8a** 96	50
2	Me	4	0,5	20	**(-)-8a** 96	48
3	Me	4	0,25	30	**(-)-8a** 93	47
4	Me	2	1	20	**(-)-8a** 95	48
5	Me	1	1	20	**(-)-8a** 91	53
6	*t*-Bu	1	1	144	**(-)-8d** 90	54

Table 3-43

The mechanism of the cyclization of sulfonamides to sultams, that envisages the corresponding achiral enol species as an intermediate and the long reaction times (Table 3-42, entries 5-7 or *Table* 3-43, entry 6) suggested us to monitor the product's e.e. variation along the reaction time. The HPLC monitoring of sulfonamide ***S*-3d** cyclization with DBU and BINAM (0,2 eq.) (Graphic 3-4) indicated effectively a decrease in the (-)**-8d** e.e., probably due to a partial racemization of the starting sulfonamide ***S*-3d**.



Graphic 3-4

To study the influence of the base nature on the sultam stereoselective formation, ***S*-3a** was cyclized in the presence of a series of organic soluble bases, having comparable pK_b, and catalytic amounts of BINAM or DMAP (Table 3-44). Results were not encouraging and all the desired sultams were obtained with lower e.e.'s (entries 2-7) or, in some cases, as racemic compounds. Moreover, very poor yields were obtained with *N*-methyl-triazabycyclodecene (entry 2). On the contrary (entry 7), very interesting results were reached with *t*-butyltetramethylguanidine (*t*-BuTMG) that, in the presence of a catalytic amount of DMAP, gave in a longer reaction time the sultam **8a** in higher e.e. and, as the most surprising and interesting feature, in the opposite configuration **(+)** to that obtained with the other bases.

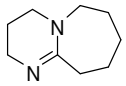
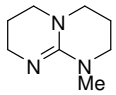
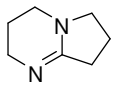
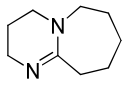
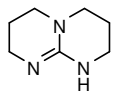
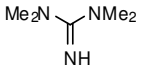
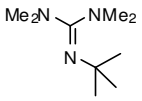
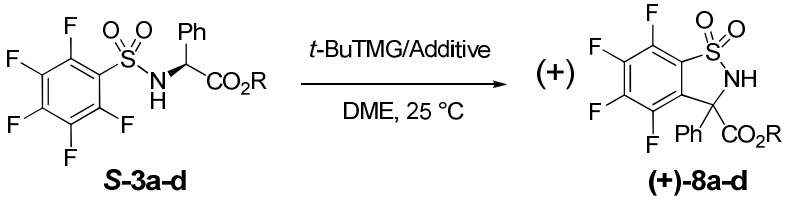
	Diamine	Additive	t [h]	Sultam (%)	e.e.
1		(R)-BINAM	18	**(-)-8a** 97	36
2		(R)-BINAM	20	**(-)-8a** 56	38
3		(R)-BINAM	16	**(-)-8a** 94	14
4		DMAP	16	**(-)-8a** 97	36
5		DMAP	16	**(-)-8a** 95	< 5
6		DMAP	16	**(-)-8a** 90	< 5
7		DMAP	16	**(+)-8a** 25	55

Table 3-44

Our attention was then focused on the cyclization with *t*-BuTMG by varying temperature, steric hindrance of the ester, and additive (Scheme 3-62, Table 3-45). Results indicated that, under all the conditions used, the cyclization is very slow. This can be effectively a problem given that the longer the reaction time, the higher the probability that the starting sulfonamide racemizes. The final and astounding result we found was that no additive is required when *t*-BuTMG is used as a base! Under these conditions, **(+)-3d** in 90% yield and 80% e.e - the higher e.e. for this process attained until now – was isolated. Unfortunately, *t*-butyl ester ***S*-3d**, that is expected to give higer e.e., cyclized very slowly giving after 1 week 37% of the desired product **(+)-8d** having 87% e.e.



Scheme 3-62

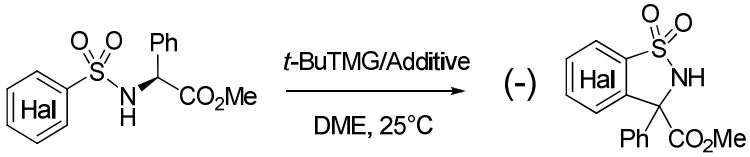
	R	T [°C]	t [h]	Additive	Sultam (%)	e.e.(%)
1	Me	25	20	DMAP	**(+)-8a** 25	**55**
2	Me	25	20	BINAM	**(+)-8a** 67	**77**
3	*t*-Bu	25	20	BINAM	**(+)-8d** < 10	**84**
4	Me	0	168	BINAM	---	**---**
5	*t*-Bu	25	144	---	**(+)-8d** 37	**87**
6	Me	25	90	---	**(+)-8a** 95	**80**

Table 3-45

We can concude that this reaction, passing through an achiral intermediate and cyclizing with achiral bases and/or additives, is a clear example of self-induction of chirality. What makes this reaction much particular is the possibility to obtain both the enantiomers of the desired sultam from a unique enantiomer of the sulfonamide, simply by changing the achiral base.

The real problem is that the complete understanding of all the factors that influence the stereochemistry of this cyclization seems very difficult, consequently we are far from a proposal of the transition state.

The best base/additive conditions, i.e. the DBU/*t*-BuTMG basic system, were applied to the cyclization of the differently halogenated sulfonamides ***S*-30a-e** (Scheme 3-63, Table 3-46), reaching good yields and modest e.e.'s of the resulting benzosultams.



***S*-30a,b,e** **(-)-31a-e**

Scheme 3-63

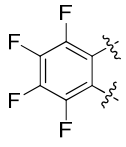
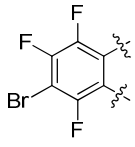
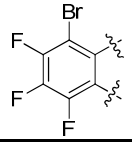
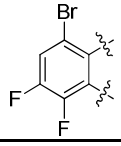
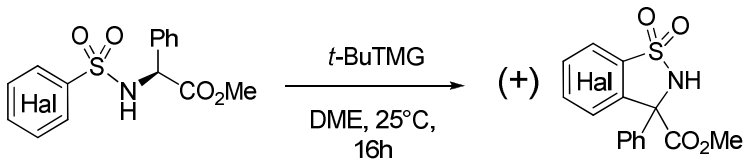
	Hal	sultam (%)	e.e.(%)		Hal	sultam (%)	e.e.(%)
1		**(-)-8a** 95	**53**	3		**(-)-30b** 98	**38**
2		**(-)-30a** 87	**38**	4		**(-)-30e** 93	**38**

Table 3-46

As found in the case of the (pentafluorobenzene)sulfonamide ***S*-3a**, the **c**yclization of (polyhalobenzene)sulfonamides ***S*-30a,b,d,e** using *t*-BuTMG alone, gave **(+)-31a,b,d,e** in very good yield and e.e., that decreases with the decrease of the activation toward the aromatic nucleophilic substitution. Furthermore, analogously to that found for **(+)-8a**, the (polyhalobenzo)sultams **(+)-31a,b,d,e** presented an inversion of configuration, respect to that observed with other bases (Scheme 3-64, Table *3-47*).



***S*-30a,b,d,e** **(+)-31a,b,d,e**

Scheme 3-64

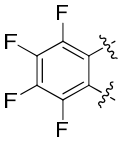
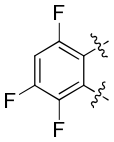
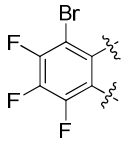
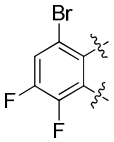
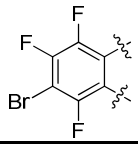
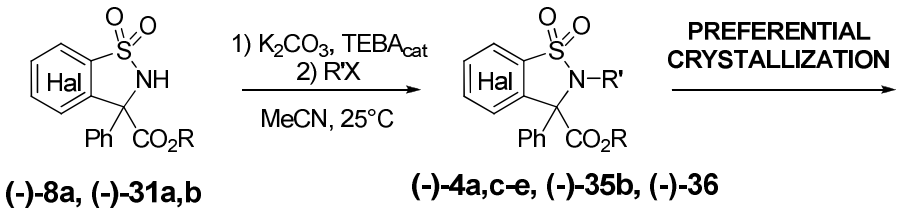
	Hal	sultam (%)	e.e.(%)		Hal	sultam (%)	e.e.(%)
1		**(+)-8a** 95	80	4		**(+)-31d** 94	79
2		**(+)-31a** 92	82	5		**(+)-31e** 89	50
3		**(+)-31b** 93	76				

Table 3-47

Finally an important step forward in the obtainment of enantiopure benzosultams, was the *N*-alkylation of our heterocycles. The non-racemic sultams were reacted with different alkyl halides, under SL-PTC conditions, and the *N*-alkyl derivatives **4a,c-e** were recrystallized: all these benzosultams crystallized preferentially and were isolated in pratically enantiopure form (Scheme 3-65, Table 3-48).



Scheme 3-65

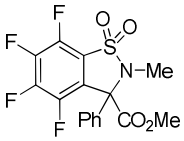
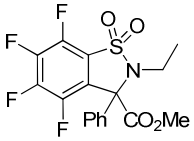
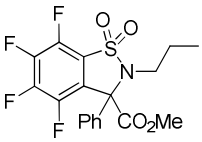
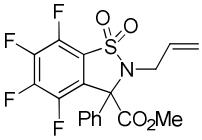
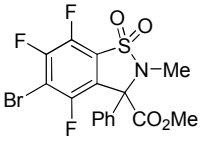
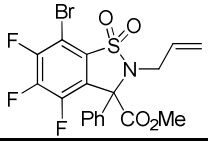
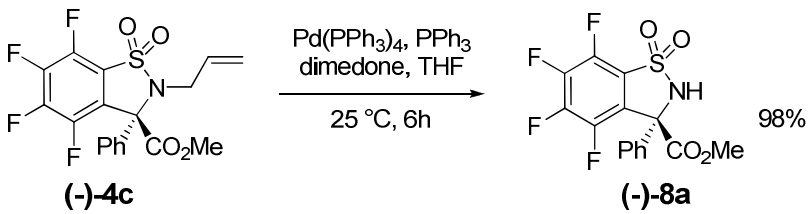
	R	R′X	num	sultam	starting e.e.	final e.e.	Solvent
1	Me	Me	**(-)-4a**		34	95	***i*PA**
2	Me	Et	**(-)-4d**		22	99	***i*PA**
3	Me	*n*-Pr	**(-)-4e**		44	99	***i*PA**
4	Me	All	**(-)-4c**		38	99	***i*-Pr$_2$O-ETP**
5	Me	Me	**(-)-36**		33	95	***i*PA**
6	Me	All	**(-)-35b**		35	81	***i*-Pr$_2$O-ETP**

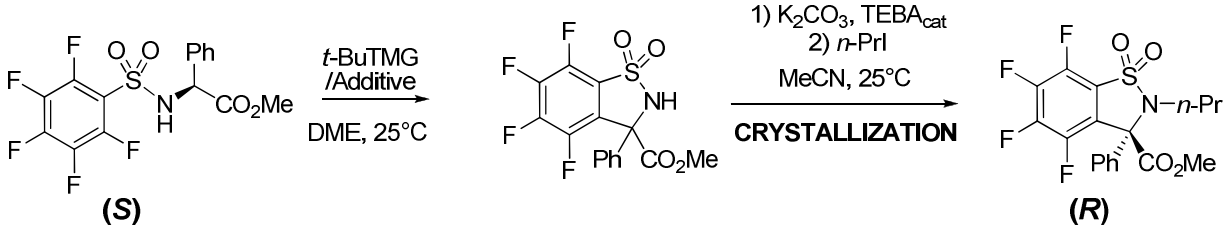
Table 3-48

The non-alkylated sultam **(-)-8a** was the unique compound that did not crystallize with this technique, but was obtained through deprotection of the *N*-allyl derivative **(-)-4c** (Scheme 3-66).



Scheme 3-66

The single crystal X-ray analysis allowed us to assign the right configuration: so, for the cyclization with DBU and *t*-BuTMG we observed (Figure 3-4) the retention product ***R*-4e** starting from ***S*-3a** (Scheme 3-67); the descriptor change occurs only for a change in priority and the reaction, even if occurring with retention, formally goes through inversion of configuration.



Scheme 3-67

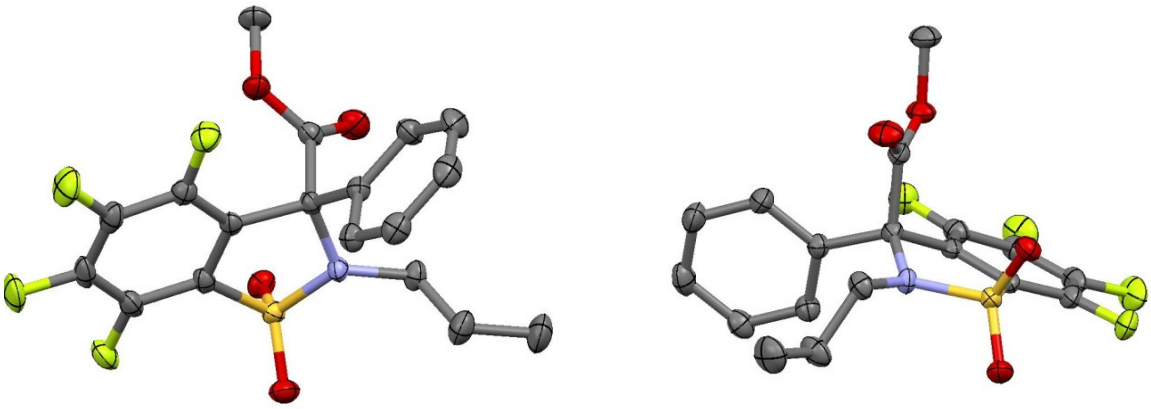
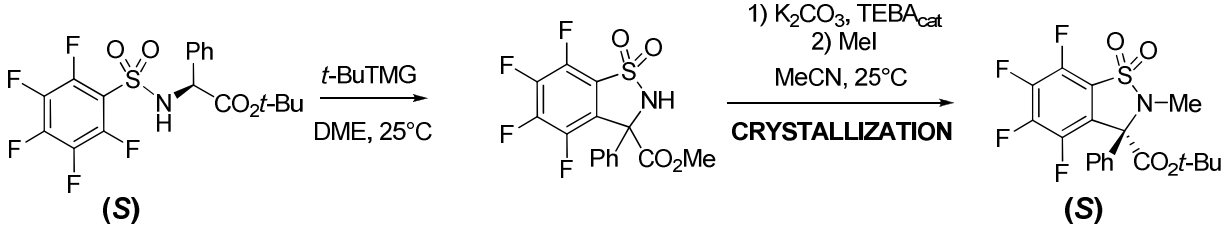


Figure 3-4

On the other hand, cyclization with *t*-BuTMG as the unique base, led to the inversion product ***S*-** (Figure 3-5).



Scheme 3-68

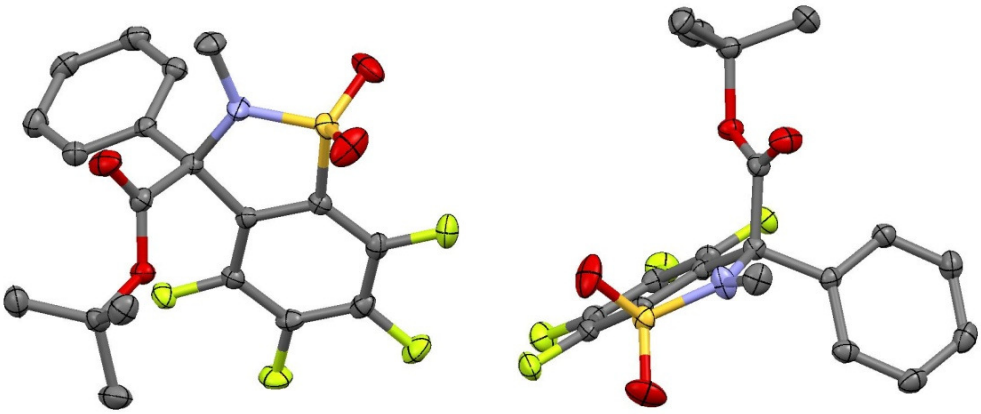


Figure 3-5

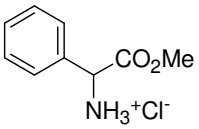
4 EXPERIMENTAL PART

Materials and Methods.

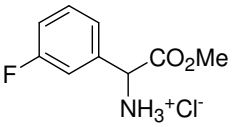
All reactions were carried out in flame-dried glassware with magnetic stirring. Isolated yields refer to homogeneous materials (TLC, HPLC, NMR). Reagent-grade commercially available reagents and solvents were used; anhydrous solvents (DMSO, MeCN, DME, NMP, and DMPU) were used as purchased. TLC was performed using 0.25 mm silica-gel pre-coated plates and visualized by UV-254 light and CAM staining. Silica-gel (particle size 0.040–0.063 mm) was used for flash column chromatography (FCC) and medium pressure liquid chromatographic (MPLC). Melting points are corrected. HPLC analyses were performed using an EC 250/4.6 NUCLEOSIL 100-5 column and, for chiral HPLC analyses, a 250/4.6 Chiracel OD column. IR spectra are reported in frequency of absorption (cm^{-1}). $[\alpha]_D$'s were measured at 589 nm, using a 10 cm x 5 ml cell and *c* is in g/100 ml. NMR spectra were recorded at: 500.13, 300.13 and MHz for ^{1}H; 125.77, 75.00 MHz for ^{13}C; 282.407 MHz for ^{19}F. TMS was used as external reference; δ are in ppm and *J* are in Hz.

Amino-arylacetic Acids and Methyl Amino-arylacetate Hydrochlorides

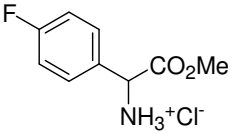
Starting amino-phenyl-,[96] amino-(3-fluoro-phenyl)-,[97] amino-(4-fluoro-phenyl)-,[1,2] amino-(4-chlorophenyl)-,[1,2] amino-(4-bromo-phenyl)-,[1] amino-*p*-tolyl-,[2] amino-(3-methoxy-phenyl)-,[1] amino-(4-methoxy-phenyl)-,[2] and amino-(4-benzyloxy-phenyl)-acetic acids[98] were synthesised following literature methods, amino-(thiophen-3-yl)-acetic acid was purchased from Sigma. The α-amino acids were then converted into the corresponding methyl ester hydrochlorides by reaction with $SOCl_2$ and dry MeOH,[99] whereas L-phenylglycine methyl ester hydrochloride was purchased from Aldrich. To compare with literature products, several free esters were obtained by neutralization of the corresponding hydrochlorides with cold, saturated $NaHCO_3$ solution and Et_2O extraction. The physical and/or spectroscopic characteristics of the isolated products are as follows.



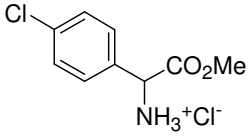
Methyl amino-phenylacetate hydrochloride (6a). Mp 220-223 °C (dec.) (lit.[100] mp 223-224 °C).



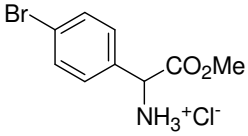
Methyl amino-(3-fluorophenyl)-acetate hydrochloride (9a). Free amino ester, oil (lit.[101] 21 °C).



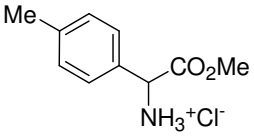
Methyl amino-(4-fluorophenyl)-acetate hydrochloride (9b). Free amino ester, mp 37-38 °C (lit.[6] mp 39 °C).



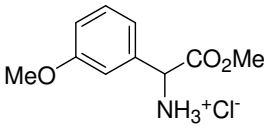
Methyl amino-(4-chlorophenyl)-acetate hydrochloride (9c). Mp 193-196 °C (dec.) (lit.[102] 194-197 °C).



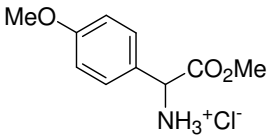
Methyl amino-(4-bromophenyl)-acetate hydrochloride (9d). Free amino ester, mp 54 °C (lit.[6] 54 °C).



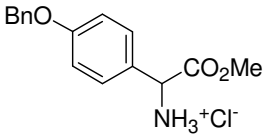
Methyl amino-*p*-tolyl-acetate hydrochloride (9e). Mp 192-193 °C (dec.). ^{1}H NMR (300 MHz, D_2O) δ 7.37 (s, 4H), 5.26 (s, 1H), 3.83 (s, 3H), 2.87 (s, 3H). [103] Anal. Calcd. for $C_{10}H_{14}ClNO_2$: C, 55.69; H, 6.54; N, 6.49. Found C, 55.72; H, 6.56; N, 6.44.



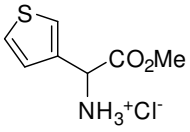
Methyl amino-(3-methoxyphenyl)-acetate hydrochloride (9f). Mp 182-183 °C (dec.). ^{1}H NMR (300 MHz, D_2O) δ 7.50 (t, 1H, *J* = 8.0 Hz), 7.17-7.09 (m, 3H), 5.29 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H). Anal. Calcd. for $C_{10}H_{14}ClNO_3$: C, 51.84; H, 6.09; N, 6.05. Found: C, 51.80; H, 6.13; N, 6,09.



Methyl amino-(4-methoxyphenyl)-acetate hydrochloride (9g). Mp 185-187 °C (dec.) (lit.[104] 187-189 °C).



Methyl amino-(4-benzyloxyphenyl)-acetate hydrochloride (9h). Mp 210-212 °C (dec.) (lit.[105] 212-213 °C).

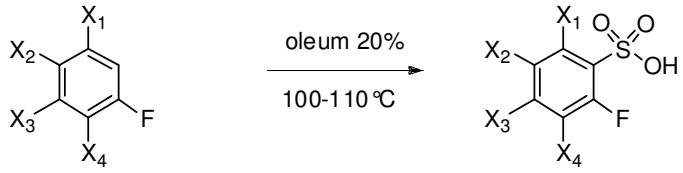


Methyl amino-(thiophen-3-yl)-acetate hydrochloride (9i). Mp 230-232 °C (dec.). ^{1}H NMR (300 MHz, CD_3OD) δ 7.63 (d, 1H, *J* = 3.0 Hz), 7.30 (dd, 1H, *J* = 5.1, 3.0), 7.12 (d, 1H, *J* = 5.1 Hz), 5.50 (s, 1H), 3.85 (s 3H).[106] Anal. Calcd. for $C_7H_{10}ClNO_2S$: C, 40.48; H, 4.85; N, 6.74. Found C, 40.52; H, 4.88; N, 6.69.

Amino-phenylacetate Hydrochlorides

Starting (*R*) Ethyl 2-amino-phenylacetate **(6b)**,[107] (*R*) *i*-Propyl 2-amino-phenylacetate **(6c)**,[108] (*R*) *t*-Butyl 2-amino-phenylacetate **(6d)**,[109] (*R*) Benzyl 2-amino-phenylacetate **(6e)**,[110] (*R*) (2-methoxy)ethyl 2-amino-phenylacetate **(6f)**,[111] were synthesised following literature methods,

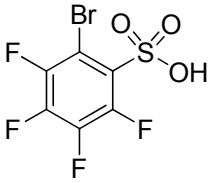
Synthesis of Sulfonic Acids 29a-e: General Procedure.



To the halobenzene is added fuming sulfuric acid (20% SO_3) and the resulting solution is heated at 110 °C until no starting material was not detectable by TLC; the solution is then carefully poured into ice and extracted with Et_2O. After drying over $MgSO_4$ and evaporation of the solvent under vacuum (RV), the sulfonic acid **29a-e** is obtained and used without any further purification in the next step. Starting materials, product, yield, physical and analytical data are as follows.

2-Bromo-3,4,5,6-tetrafluorobenzenesulfonic acid (29a).

Compound	PM	mmol	g	mL
1-Bromo-2,3,4,5-tetrafluoro benzene **(28a)**	228,98	10	2,28	
20 % oleum				10



29a, $C_6HBrF_4O_3S$
MW 309,03

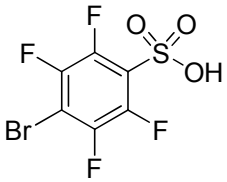
7h, 2,4 g, 77%;

brown solid, mp 79-82°C,

- ^{19}F NMR (282 MHz, $CDCl_3$) δ -125.6 (m, 1F), -134.6 (m, 1F), -149.8 (m, 1F), 153.9 (m, 1F).
- Anal. Calcd. for $C_6HBrF_4O_3S$: C, 23.32; H, 0.33. Found: C, 23.34; H, 0.31.

4-Bromo-2,3,5,6-tetrafluorobenzenesulfonic acid (29b).

Compound	PM	mmol	g	mL
3-Bromo-1,2,4,5-tetrafluoro benzene **(28b)**	228,98	10	2,28	
20 % oleum				10



29b, $C_6HBrF_4O_3S$
MW 309,03

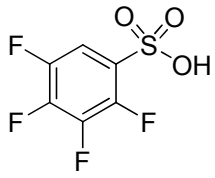
6h, 3,16 g, 90%;

white solid, mp 79,5-80,5°C,

- ^{19}F NMR (282 MHz, $CDCl_3$) δ -133.1 (m, 2F), -137.6 (m, 2F).
- Anal. Calcd. for $C_6HBrF_4O_3S$: C, 23.32; H, 0.33. Found: C, 43.37; H, 0.36.

2,3,4,5-Tetrafluorobenzenesulfonic acid (29c).

Compound	PM	mmol	g	mL
1,2,3,4-Tetrafluoro benzene **(28c)**	150,08	13	1,95	
20 % oleum				12



29c, $C_6H_2F_4O_3S$
MW 230,14

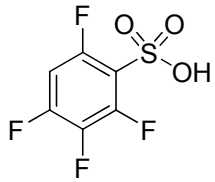
4 h, 2,45 g, 82%;

white solid, mp 63-64°C,

- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (m, 1H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.1 (m, 1F), -126.7 (m, 1F), -132.0 (m, 1F), -164.2 (m, 1F).

2,3,4,6-Tetrafluorobenzenesulfonic acid (29d).

Compound	PM	mmol	g	mL
1,2,3,5-Tetrafluoro benzene **(28d)**	150,08	13	1,95	
20 % oleum				12



29d, $C_6H_2F_4O_3S$
MW 230,14

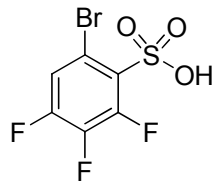
4.5 h, 2,68 g, 90%;

white solid, mp 63-64°C,

- ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (m, 1H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.1 (m, 1F), -126.7 (m, 1F), -132.0 (m, 1F), -164.2 (m, 1F).
- Anal. Calcd. for $C_6H_2F_4O_3S$: C, 31.31; H, 0.88. Found: C, 31.34; H, 0.91.

2-Bromo-4,5,6-trifluorobenzenesulfonic acid (29e).

Compound	PM	mmol	mg	mL
5-Bromo-1,2,3-trifluoro benzene **(28e)**	210,98	3,79	800	
20 % oleum				10



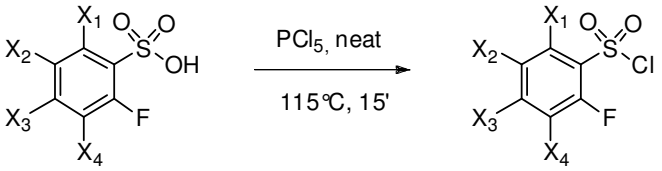
29e, $C_6H_2BrF_3O_3S$
MW 289,89

7h, 655 mg, 60%;

brown solid, mp 86-88°C,

- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (ddd, *J* = 9.1, 6.5, 2.5 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -124.2 (m, 1F), -126.9 (m, 1F), -156.9 (m, 1F).
- Anal. Calcd. for $C_6H_2BrF_3O_3S$: C, 24.76; H, 0.69. Found: C, 24.75; H, 0.72.

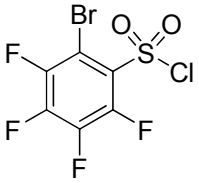
Synthesis of Sulfonyl Chlorides 5f-l: General Procedure.



To the sulfonic acid and phosphorus pentachloride are put together in a round bottom flask and heated until complete fusion of the two compounds; the mixture is heated for further 15 min than rapidly cooled and carefully poured into ice and extracted with Et_2O. After drying over $MgSO_4$ and evaporation of the solvent under vacuum (RV), the sulfonyl chloride **5f-l** is obtained and used without any further purification in the next step. Starting materials, product, yield, physical and analytical data are as follows.

2-Bromo-3,4,5,6-tetrafluorobenzene sulfonyl chloride (5f).

Compound	PM	mmol	g	mL
2-Bromo-3,4,5,6-tetrafluorobenzenesulfonic acid **(29a)**	309,03	7,76	2,4	
Phosphorus pentachloride	208,24	32,2	6,7	



5f, $C_6BrClF_4O_2S$
MW 327,48

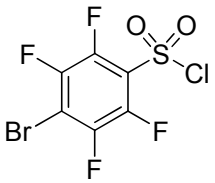
2,4 g, 80%;

brown solid, mp 62,5-63,5°C,

- ^{19}F NMR (282 MHz, $CDCl_3$) δ -121.4 (m, 1F), -127.9 (m, 1F), -140.5 (m, 1F), 150.3 (m, 1F).

4-Bromo-2,3,5,6-tetrafluorobenzene sulfonyl chloride (5g).

Compound	PM	mmol	g	mL
4-Bromo-2,3,5,6-tetrafluorobenzenesulfonic acid **(29b)**	309,03	3,88	1,2	
Phosphorus pentachloride	208,24	16	3,35	



5g, $C_6BrClF_4O_2S$
MW 327,84

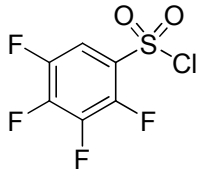
1,13g, 89%;

white solid, mp 48-49°C,

- ^{19}F NMR (282 MHz, $CDCl_3$) δ -127.9 (m, 2F), -134.2 (m, 2F).

2,3,4,6-Tetrafluorobenzene sulfonyl chloride (5h).

Compound	PM	mmol	g	mL
2,3,4,5-Tetrafluorobenzenesulfonic acid **(29c)**	230,14	11,2	2,59	
Phosphorus pentachloride	208,24	45	9,38	



5h, $C_6HClF_4O_2S$
MW 248,58

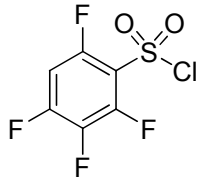
2,03 g, 73%;

brown wax,

- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 1H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -130.8 (m, 1F), -133.5 (m, 1F), -143,4 (m, 1F), -148.9 (m, 1F).

2,3,4,6-Tetrafluorobenzene sulfonyl chloride (5i).

Compound	PM	mmol	g	mL
2,3,4,6-Tetrafluorobenzenesulfonic acid **(29d)**	230,14	11,2	2,59	
Phosphorus pentachloride	208,24	45	9,38	



5i, $C_6HClF_4O_2S$
MW 248,58

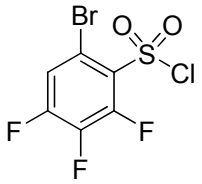
2,16 g, 78%;

brown wax,

- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (ddt, J = 9.6, 5.7, 2.4 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -107.8 (m, 1F), -116.9 (m, 1F), -125,9 (m, 1F), -159.6 (m, 1F).

2-Bromo-4,5,6-trifluorobenzene sulfonyl chloride (5l).

Compound	PM	mmol	mg	mL
6-Bromo-2,3,4-trifluorobenzenesulfonic acid **(29e)**	289,89	2,07	0,600	
Phosphorus pentachloride	208,24	10,5	2,16	



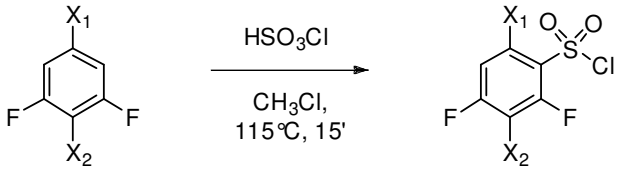
5l, $C_6HBrClF_3O_2S$
MW 309,49

502 mg, 78%;

brown wax,

- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (ddd, *J* = 8.9, 6.7, 2.4 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -120.0 (m, 1F), 121.1 (m, 1F), -154.0 (m, 1F).

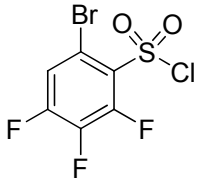
Synthesis of Sulfonyl Chlorides 5l,m: General Procedure.



To a solution of the halobenzene in chloroform at 0°C, is carefully added the chlorosulfonic acid under magnetic stirring; once the addition is complete, the resulting solution is heated until completion (TLC analysis). The mixture is then warmed and carefully poured into ice then extracted with chloroform. The organic phase is dryed over $MgSO_4$ and after evaporation of the solvent under vacuum (RV), the sulfonyl chloride **5l,m** is obtained and used without any further purification. Starting materials, product, yield, physical and analytical data are as follows.

6-Bromo-2,3,4-trifluorobenzene sulfonyl chloride (5l).

Compound	PM	mmol	mg	mL
5-Bromo-1,2,3-trifluorobenzene **(28e)**	210,98	2	422	
Chlorosulfonic acid	116,52	10	1,16g	
Chloroform				10



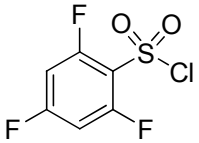
5l, $C_6HBrClF_3O_2S$
MW 309,49

371,4 mg, 60%;

Analytical data identical to that of page 12

2,4,6-trifluorobenzene sulfonyl chloride (5m).

Compound	PM	mmol	mg	mL
1,3,5-trifluorobenzene **(28g)**	132,08	2	264,2	
Chlorosulfonic acid	116,52	5	1,16g	
Chloroform				10



5m, $C_6H_2F_3O_2S$
MW 230,59

285,9 mg, 62%;

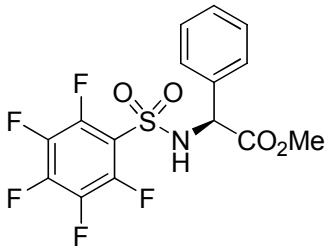
- brown oil,
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (t, 2H, *J* = 8.1 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -92.5 (m, 1F), -100.7 (m, 2F).

Synthesis of Sulfonamides 3a-e, 10a-i, 30a-l, 12a,b: General Procedure

To a suspension of alkyl 2-arylaminoacetate hydrochloride (10 mmol) in dry dichloromethane (40 mL), DIEA (21 mmol) was added at 25 °C in 10 min. The reaction mixture was stirred for furhter 10 min, then cooled to 0°C and sulfonyl chloride (10 mmol) was added dropwise. The resulting solution was allowed to reach 25 °C and stirred until no starting material was not detectable by TLC, then was diluted with dichloromethane (20 mL), washed with 3% HCl (3×15 mL), saturated $NaHCO_3$ solution (2×15 mL) and brine (20 mL), dried over $MgSO_4$, filtered. After evaporation of the solvent under vacuum (RV), the crude recrystallized from ethanol/water (1 : 9), or purified by FCC or MPLC, gave the desired sulfonamides. Starting materials, product, yield, chromatographic eluant, physical and analytical data are as follows.

(*S*)-Methyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-3a).

Compound	PM	mmol	g	mL
S-Methyl 2-amino-2-phenylacetate hydrochloride **(*S*-6a)**	201,65	10	2,02	
Pentafluorobenzene sulfonyl chloride **(5a)**	266,57	10	2,67	
DIEA (ρ = 0,755 g/mL)	129,24	21		3,59
DCM				40



***S*-3a**, $C_{15}H_{10}F_5NO_4S$
MW 395,30

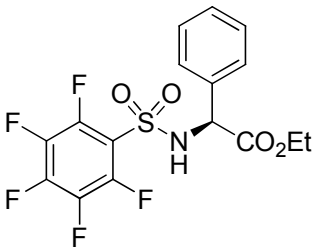
20h, 3.56 g, 90%;

Ethanol-water (9 : 1), white solid, mp 120-121°C,

- $[\alpha]_D^{20}$ +79.8 (*c* 1, $CHCl_3$), (EtOH/water – 9 : 1).
- ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.19 (m, 5H), 6.42 (d, 1H, *J* = 7.5 Hz), 5.28 (d, 1H, *J* = 7.5 Hz), 3.72 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -146.9 (m, 1F), -159.8 (m, 2F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 143.9 (dm, *J* = 258.6 Hz), 143.6 (dm, *J* = 261.6 Hz), 137.4 (dm, *J* = 258.4 Hz), 133.8, 129.2, 128.9, 127.3, 116.7, 59.9, 53.4.
- IR (nujol) 3331, 1741, 1644, 1522, 1300, 1214, 1101, 985, 885 cm^{-1}
- Anal. Calcd. for $C_{15}H_{10}F_5NO_4S$: C, 45.58; H, 2.55; N, 3.54. Found: C, 45.52; H, 2.58; N, 3.59.

(*S*)-Ethyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-3b).

Compound	PM	mmol	mg	mL
S-Ethyl 2-amino-2-phenylacetate hydrochloride **(*S*-6b)**	215,68	1	215,7	
Pentafluorobenzene sulfonyl chloride **(5a)**	266,57	1	266,6	
DIEA (ϱ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



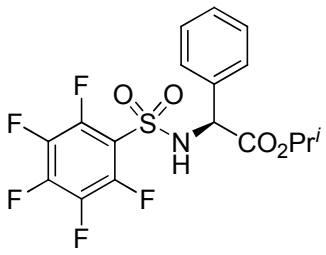
***S*-3b**, $C_{16}H_{12}F_5NO_4S$
MW: 409,33

20h, 302,9 mg, 74%;

- FCC - AcOEt/hexane (1 : 6), white solid, mp 100-102°C
- $[\alpha]_D^{20}$ +71.5 (*c* 1, $CHCl_3$).
- ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.20 (m, 5H), 6.25 (d, 1H, *J* = 7.5 Hz,), 5.24 (d, 1H, *J* = 7.8 Hz), 4.27-4.06 (m, 2H), 1.73 (t, 3H, *J* = 7.2 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -146.9 (m, 1F), -159.8 (m, 2F).
- IR (nujol) 3342, 1746, 1642, 1522, 1301, 1216, 1110, 973 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{12}F_5NO_4S$: C, 43.11; H, 2.94; N, 3.14. Found: C, 43.08; H, 2.92; N, 3.12.

(*S*)-Isopropyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-3c).

Compound	PM	mmol	mg	mL
S-isopropyl 2-amino-2-phenylacetate hydrochloride **(*S*-6c)**	229,70	1	229,7	
Pentafluorobenzene sulfonyl chloride **(5a)**	266,57	1	266,6	
DIEA (ϱ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



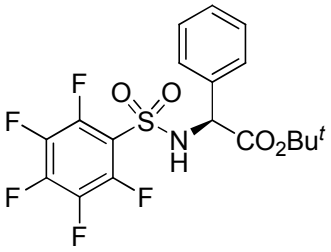
***S*-3c,** $C_{17}H_{14}F_5NO_4S$
MW: 423,35

20h, 317,5 mg, 75%;

- FCC - AcOEt/hexane (1 : 8), white solid, mp 91-92°C
- $[\alpha]_D^{20}$ +54.9 (*c* 1, $CHCl_3$).
- ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.17 (m, 5H), 6.27 (d, 1H, *J* = 7.6 Hz), 5.21 (d, 1H, *J* = 7.6 Hz), 5.05-4.97 (m, 1H), 1.22 (d, 3H, *J* = 6.3 Hz), 1.04 (d, 3H, *J* = 6.3 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.6 (m, 2F), -147.0 (m, 1F), -159.9 (m, 2F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 144.1 (dm, *J* = 261.7 Hz), 143.6 (dm, *J* = 259.5 Hz), 137.4 (dm, *J* = 257.3 Hz), 134.1, 129.0, 128.8, 127.2, 119.0, 70.9, 60.1, 21.5, 21.1.
- Anal. Calcd. for $C_{17}H_{14}F_5NO_4S$: C, 48.23; H, 3.33; N, 3.31. Found: C, 45.24; H, 2.34; N, 3.33.

(*R*)-*tert*-butyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-3d).

Compound	PM	mmol	mg	mL
R-*tert*-butyl 2-amino-2-phenylacetate hydrochloride **(*S*-6d)**	243,73	1	243,7	
Pentafluorobenzene sulfonyl chloride **(5a)**	266,57	1	266,6	
DIEA (ρ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



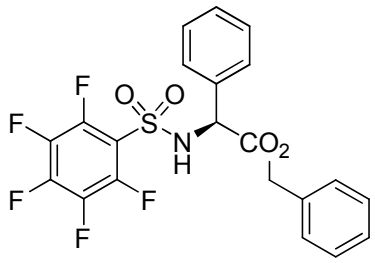
***S*-3d,** $C_{18}H_{16}F_5NO_4S$
MW: 437,38

24h, 389,3 mg, 89%;

- FCC - AcOEt/hexane (1 : 12), white solid, mp 91-92°C
- $[\alpha]_D^{20}$ +82.4 (*c* 1, $CHCl_3$).
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.17 (m, 5H), 6.23 (d, 1H, *J* = 7.6 Hz), 5.14 (d, 1H, *J* = 7.7 Hz), 1.34 (s, 9H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -147.3 (m, 1F), -160.1 (m, 2F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 144.4 (dm, *J* = 266.0 Hz), 144.0 (dm, *J* = 258.4 Hz), 138.0 (dm, *J* = 265.9 Hz),134.8, 129.3, 129.2, 127.6, 119.3, 84.4, 60.8, 28.0.
- IR (nujol) 3333, 1739, 1645, 1526, 1298, 1218, 1106, 981, 888 cm^{-1}.
- Anal. Calcd. for $C_{18}H_{16}F_5NO_4S$: C, 49.43; H, 3.69; N, 3.20. Found: C, 49.40; H, 3.70; N, 3.21.

(*R*)-Benzyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-3e).

Compound	PM	mmol	mg	mL
(R)-Benzyl 2-amino-2-phenylacetate hydrochloride **(*S*-6e)**	277,75	1	277,8	
Pentafluorobenzene sulfonyl chloride **(5a)**	266,57	1	266,6	
DIEA (ρ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



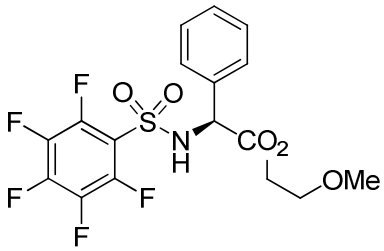
***S*-3e,** $C_{21}H_{14}F_5NO_4S$
MW: 471,40

20h, 245,1 mg, 52%;

- FCC - AcOEt/hexane (1 : 8), white solid, mp 125-127°C, $[\alpha]_D^{20}$ +51.1 (*c* 0.4, $CHCl_3$).
- ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.20 (m, 8H), 7.15-7.12 (m, 2H), 6.42 (d, 1H, *J* = 7.8 Hz), 5.32 (d, 1H, *J* = 7.8 Hz), 5.18 (d, 1H, *J* = 12.2 Hz), 5.07 (dt, 1H, *J* = 12.2 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -146.6 (m, 1F), -159.8 (m, 2F).
- Anal. Calcd. for $C_{21}H_{14}F_5NO_4S$: C, 53.51; H, 2.99; N, 2.97. Found: C, 53.52; H, 3.02; N, 2.99.

(*R*)-2-Metoxyethyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-3f).

Compound	PM	mmol	mg	mL
(R)-2-Metoxyethyl 2-amino-2-phenylacetate hydrochloride **(*S*-6f)**	245,70	1	245,7	
Pentafluorobenzene sulfonyl chloride **(5a)**	266,57	1	266,6	
DIEA (ϱ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



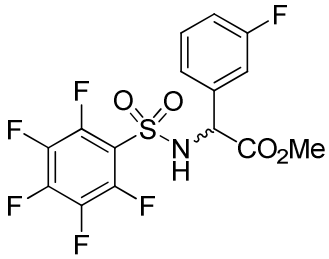
S-3f, $C_{17}H_{14}F_5NO_5S$
MW: 439,35

24h, 338,3 mg, 77%;

- FCC - AcOEt/hexane (1 : 4), white solid, mp 94.5-95.5°C, $[\alpha]_D^{20}$ +29.7 (*c* 1, $CHCl_3$).
- ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.23 (m, 5H), 6.26 (d, 1H, *J* = 7.7 Hz), 5.31 (d, 1H, *J* = 7.7 Hz), 4.32 (dt, 1H, *J* = 12.0, 4.7 Hz), 4.19 (dt, 1H, *J* = 12.0, 4.5 Hz), 3.47 (t, 1H, *J* = 4.6 Hz), 3.23 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -146.8 (m, 1F), -159.8 (m, 2F).
- Anal. Calcd. for $C_{17}H_{14}F_5NO_5S$: C, 46.47; H, 3.21; N, 3.19. Found: C, 43.45; H, 3.22; N, 3.19.

***rac*- Methyl 2-(3-fluorophenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido) acetate (10a).**

Compound	PM	mmol	g	mL
rac- Methyl 2-amino-2-(3-fluorophenyl) acetate hydrochloride **(9a)**	219,64	10	2,20	
pentafluorobenzene sulfonyl chloride **(5a)**	266,57	10	2,67	
DIEA (ϱ = 0,755 g/mL)	129,24	21		3,59
DCM				40



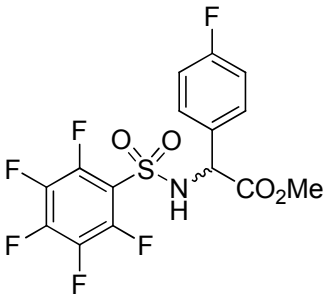
10a, $C_{15}H_9F_6NO_4S$
MW: 413,29

20h, 3.35 g, 81%;

- white solid, mp 108.5-109.5°C (EtOH/water – 9 : 1).
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.22 (m, 1 H), 7.05-6.92 (m, 3 H), 6.34 (d, 1H, *J* = 7.4 Hz), 5.27 (d, 1H, *J* = 7.4 Hz), 3.73 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.3 (s, 1F), -136.5 (m, 2F), -146.1 (m, 1F), -159.3 (m, 2F).
- IR (nujol) 3238, 1747, 1643, 1519, 1329, 1201, 1101, 991, 897 cm^{-1}.
- Anal. Calcd. for $C_{15}H_9F_6NO_4S$: C, 43.59; H, 2.19; F, 27.58; N, 3.39. Found: C, 43.63; H, 2.15; N, 3.41.

***rac*- Methyl 2-(4-fluorophenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido) acetate (10b).**

Compound	PM	mmol	g	mL
rac- Methyl 2-amino-2-(4-fluorophenyl) acetate hydrochloride **(9b)**	219,64	10	2,20	
pentafluorobenzene sulfonyl chloride **(5a)**	266,57	10	2,67	
DIEA (ϱ = 0,755 g/mL)	129,24	21		3,59
DCM				40



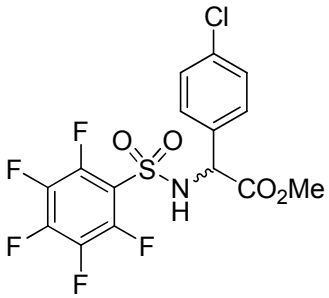
10b, $C_{15}H_9F_6NO_4S$
MW: 413,29

20h, 3.30 g, 80%;

- white solid, mp 125-126 °C (EtOH/water – 9 : 1).
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.20 (m, 2H), 6.99-6.93 (m, 2H), 6.30 (d, 1H, *J* = 7.2 Hz), 5.27 (d, 1H, *J* = 7.2 Hz), 3.71 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.6 (s, 1F), -136.5 (m, 2F), -146.1 (m, 1F), -159.4 (m, 2F).
- IR (nujol) 3274, 1746, 1649, 1520, 1305, 1171, 1107, 991, 892 cm^{-1}.
- Anal. Calcd. for $C_{15}H_9F_6NO_4S$: C, 43.59; H, 2.19; F, 27.58; N, 3.39. Found: C, 43.65; H, 2.21; N, 3.37.

***rac*- Methyl 2-(4-chlorophenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido) acetate (10c).**

Compound	PM	mmol	g	mL
rac- Methyl 2-amino-2-(4-chlorophenyl) acetate hydrochloride **(9c)**	236,10	10	2,36	
pentafluorobenzene sulfonyl chloride **(5a)**	266,57	10	2,67	
DIEA (ϱ = 0,755 g/mL)	129,24	21		3,59
DCM				40



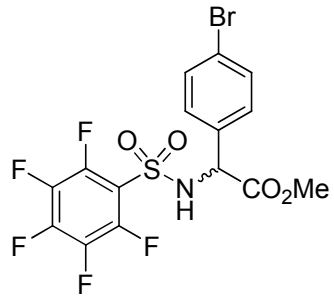
10c, $C_{15}H_9ClF_5NO_4S$
MW: 429,75

20h, 3.35 g, 78%;

- FCC - AcOEt/hexane (1 : 9), pasty wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.23 (m, 2H), 7.19-7.16 (m, 2H), 6.23 (d, 1H, *J* = 7.2 Hz), 5.25 (d, 1H, *J* = 7.2 Hz), 3.72 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -146.0 (m, 1F), -159.2 (m, 2F).
- IR (nujol) 3268, 1738, 1634, 1509, 1294, 1160, 1100, 990 cm^{-1}.
- Anal. Calcd. for $C_{15}H_9ClF_5NO_4S$: C, 41.92; H, 2.11; N, 3.26. Found: C, 42.00; H, 2.08; N, 3.21.

***rac*- Methyl 2-(4-bromophenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido) acetate (10d).**

Compound	PM	mmol	g	mL
rac- Methyl 2-amino-2-(4-bromophenyl) acetate hydrochloride **(9d)**	280,55	10	2,81	
pentafluorobenzene sulfonyl chloride **(5a)**	266,57	10	2,67	
DIEA (ϱ = 0,755 g/mL)	129,24	21		3,59
DCM				40



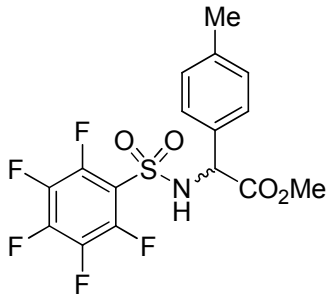
10d, $C_{15}H_9BrF_5NO_4S$
MW: 474,20

20h, 3.89 g, 82%;

- FCC - AcOEt/hexane (1 : 9), white solid, mp 110-111°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.38 (m, 2H), 7.13-7.10 (m, 2H), 6.33 (d, 1H, *J* = 7.3 Hz), 5.24 (d, 1H, *J* = 7.3 Hz), 3.72 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -146.0 (m, 1F), -159.2 (m, 2F).
- IR (nujol) 3271, 1748, 1522, 1363, 1286, 1253, 1180, 1110, 989, 617 cm $^{-1}$.
- Anal. Calcd. for $C_{15}H_9BrF_5NO_4S$: C, 37.99; H, 1.91; N, 2.95. Found: C, 38.03; H, 1.94; N, 2.95.

***rac*- Methyl 2-(4tolyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido) acetate (10e).**

Compound	PM	mmol	g	mL
rac- Methyl 2-amino-2-(4-tolyl) acetate hydrochloride **(9e)**	215,68	10	2,16	
pentafluorobenzene sulfonyl chloride **(5a)**	266,57	10	2,67	
DIEA (ϱ = 0,755 g/mL)	129,24	21		3,59
DCM				40



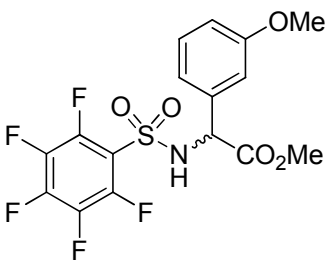
10e, $C_{16}H_{12}F_5NO_4S$
MW: 409,33

20h, 3.68 g, 90%;

- FCC - AcOEt/hexane (1 : 9), white solid, mp 115,5-116,5 °C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10-7.07 (m, 2H), 7.03-7.01 (m, 2H), 6.40 (d, 1H, *J* = 7.2 Hz), 5.24 (d, 1H, *J* = 7.2 Hz), 3.71 (s, 3H), 2.26 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.4 (m, 2F), -147.7 (m, 1F), -160.2 (m, 2F).
- ^{13}C NMR (75 MHZ, $CDCl_3$) δ 169.8, 144.1 (dm, *J* = 255.5 Hz), 143.8 (dm, *J* = 255.6 Hz), 139.4, 137.3 (dm, *J* = 265.4 Hz), 130.7, 129.4, 127.3, 116.9, 59.7, 53.3, 20.8.
- IR (nujol) 3251, 1744, 1643, 1519, 1298, 1210, 1176, 1099, 992, 897 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{12}F_5NO_4S$: C, 46.95; H, 2.95; N, 3.42. Found: C, 46.99; H, 3.00; N, 3.38.

***rac*- Methyl 2-(3-methoxyphenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido) acetate (10f).**

Compound	PM	mmol	g	mL
rac- Methyl 2-amino-2-(3-methoxy phenyl) acetate hydrochloride **(9f)**	231,68	10	2,32	
pentafluorobenzene sulfonyl chloride **(5a)**	266,57	10	2,67	
DIEA (ϱ = 0,755 g/mL)	129,24	21		3,59
DCM				40



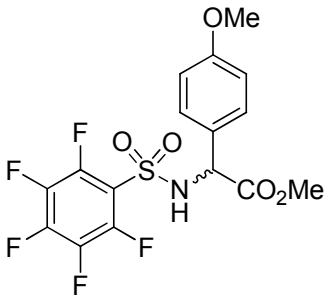
10f, $C_{16}H_{12}F_5NO_5S$
MW: 425,33

20h, 3.61 g, 85%;

- FCC - AcOEt/hexane (1 : 9), white solid, mp 88-89 °C.
- ^{1}H NMR (300 MHZ, $CDCl_3$) δ 7.16-7.11 (m, 1H), 6.79-6.70 (m, 3H), 6.56 (d, 1H, *J* = 7.7 Hz), 5.23 (d, 1H, *J* = 7.7 Hz), 3.72 (s, 3H), 3.71 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -147.2 (m, 1F), -160.2 (m, 2F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 159.9, 143.9 (dm, *J* = 256.5 Hz), 143.5 (dm, *J* = 259.5 Hz), 137.4 (dm, *J* = 251.2 Hz), 135.1, 130.1, 119.5, 116.9 (t, *J* = 12.0 Hz), 114.4, 112.8, 59.9, 55.1, 53.3.
- IR (nujol) 3295, 3244, 1740, 1729, 1644, 1520, 1311, 1179, 1101, 995, 891 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{12}F_5NO_5S$: C, 45.18; H, 2.84; N, 3.29. Found: C, 45.23; H, 2.87; N, 3.25.

***rac*- Methyl 2-(4-methoxyphenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido) acetate (10g).**

Compound	PM	mmol	g	mL
rac- Methyl 2-amino-2-(4-methoxy phenyl) acetate hydrochloride **(9g)**	231,68	10	2,32	
pentafluorobenzene sulfonyl chloride **(5a)**	266,57	10	2,67	
DIEA (ϱ = 0,755 g/mL)	129,24	21		3,59
DCM				40



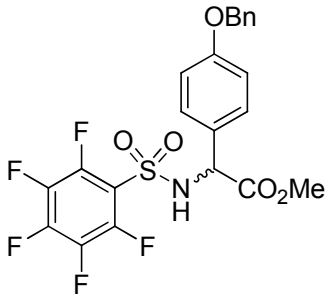
10g, $C_{16}H_{12}F_5NO_5S$
MW: 425,33

20h, 3.40 g, 80%;

- FCC - AcOEt/hexane (1 : 9), white solid, mp 115-116 °C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.10 (m, 2H), 6.74-6.71 (m, 2H), 6.27 (d, 1H, *J* = 7.5 Hz), 5.22 (d, 1H, *J* = 7.5 Hz), 3.74 (s, 3H), 3.71 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -147.2 (m, 1F), -160.0 (m, 2F).
- IR (nujol) 3263, 1748, 1610, 1518, 1303, 1174, 1091, 990 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{12}F_5NO_5S$: C, 45.18; H, 2.84; N, 3.29. Found: C, 45.21; H, 2.89; N, 3.31.

***rac*- Methyl 2-(4-(benzyloxy)phenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido) acetate (10h).**

Compound	PM	mmol	g	mL
rac- Methyl 2-amino-2-(4-(benzyloxy) phenyl)acetate hydrochloride **(9h)**	307,77	10	3,08	
pentafluorobenzene sulfonyl chloride **(5a)**	266,57	10	2,67	
DIEA (ϱ = 0,755 g/mL)	129,24	21		3,59
DCM				40



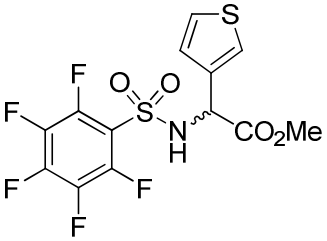
10h, $C_{22}H_{16}F_5NO_5S$
MW: 501,42

24h, 4.16 g, 83%;

- FCC - AcOEt/hexane (1 : 12), white solid, mp 103,5-104,5 °C.
- ^{1}H NMR (300MHz, $CDCl_3$) δ 7.40-7.33 (m, 5H), 7.13-7.10 (m, 2H), 6.83-6.79 (m, 2H), 6.20 (d, 1H, *J* = 7.1 Hz), 5.22 (d, 1H, *J* = 7.1 Hz), 4.97 (s, 2H), 3.71 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -147.0 (m, 1F), -159.8 (m, 2F).
- IR (nujol) 3275, 1741, 1627, 1518, 1310, 1176, 1100, 996, 884 cm^{-1}.
- Anal. Calcd. for $C_{22}H_{16}F_5NO_5S$: C, 52.70; H, 3.22; N, 2.79. Found: C, 52.74; H, 3.19; N, 2.83.

***rac*- Methyl 2-(thiophen-3-yl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido) 3-phenylpropanoate (10i).**

Compound	PM	mmol	mg	mL
rac- Methyl 2-amino-2-(thiophen-3-yl)acetate hydrochloride **(9i)**	207,68	1	208	
pentafluorobenzene sulfonyl chloride **(5a)**	266,57	1	267	
DIEA (ϱ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



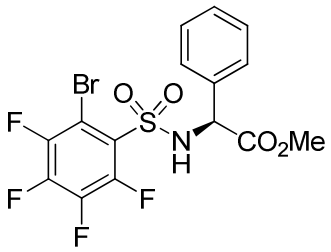
10i, $C_{13}H_8F_5NO_4S_2$
MW: 401,33

20h, 301 mg, 75%;

- FCC - AcOEt/hexane (1 : 9), white solid, mp 150-151 °C.
- ^{1}H NMR (300MHz, $CDCl_3$) δ 7.26 (d, 1H, *J* = 3.0 Hz), 7.20 (dd, 1H, *J* = 5.0, 3.0 Hz), 6.89 (dd, 1H, *J* = 5.0, 0.9 Hz), 6.17 (d, 1H, *J* = 7.8 Hz), 5.41 (d, 1H, *J* = 7.8 Hz), 3.74 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.6 (m, 2F), -146.5 (m, 1F), -159.5 (m, 2F).
- IR (nujol) 3288, 1729, 1615, 1530, 1340, 1165, 982, 895 cm^{-1}.
- Anal. Calcd. for $C_{13}H_8F_5NO_4S_2$: C, 38.91; H, 2.01; N, 3.49. Found: C, 38.96; H, 2.07; N, 3.44.

(*S*)-Methyl 2-(2-Bromo-3,4,5,6-tetrafluorophenylsulfonamido)-2-phenylacetate (30a).

Compound	PM	mmol	mg	mL
S-Methyl 2-amino-2-phenylacetate hydrochloride **(6a)**	201,65	1	201,6	
2-bromo-3,4,5,6-tetrafluorobenzene sulfonyl chloride **(5f)**	327,48	1	327,5	
DIEA (ϱ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



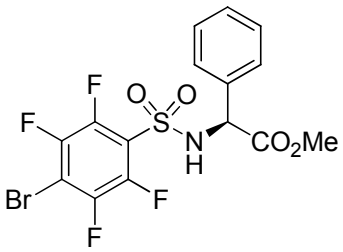
30a, $C_{15}H_{10}BrF_4NO_4S$
MW: 456,21

30h, 374,1 mg, 82%;

- FCC - AcOEt/hexane (1 : 9), white solid, mp 74-76°C
- $[\alpha]_D^{20}$ +68.1 (*c* 1, $CHCl_3$).
- ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.17 (m, 5H), 6.49 (d, 1H, *J* = 7.1 Hz,), 5.24 (d, 1H, *J* = 7.3 Hz), 3.72 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -124.3 (m, 1F), -130.1 (m, 1F), -146.9 (m, 1F), -152.9 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 148.5-138.5 (m, 4 C-F Ar), 134.1, 129.5, 129.1, 127.8, 126.7, 105.5 (d, *J* = 17.1 Hz), 60.5, 53.8.
- Anal. Calcd. for $C_{15}H_{10}BrF_4NO_4S$: C, 39.49; H, 2.21; N, 3.07. Found: C, 39.47; H, 2.19; N, 3.08.

(*S*)-Methyl 2-(4-Bromo-2,3,5,6-tetrafluorophenylsulfonamido)-2-phenylacetate (30b).

Compound	PM	mmol	mg	mL
S-Methyl 2-amino-2-phenylacetate hydrochloride **(6a)**	201,65	1	201,6	
4-bromo-2,3,5,6-tetrafluorobenzene sulfonyl chloride **(5g)**	327,48	1	327,5	
DIEA (ϱ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



30b, $C_{15}H_{10}BrF_4NO_4S$
MW: 456,21

24h, 392,3 mg, 86%;

• FCC - AcOEt/hexane (1 : 9), white solid, mp 107-108°C, $[\alpha]_D^{20}$ +51.3 (*c* 1, $CHCl_3$).

• ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.19 (m, 5H), 6.21 (d, 1H, *J* = 5.7 Hz), 5.27 (d, 1H, *J* = 5.3 Hz), 3.72 (s, 3H).

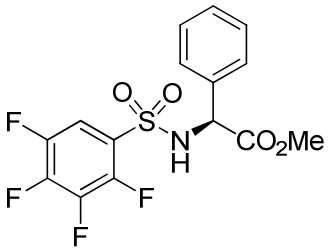
• ^{19}F NMR (282 MHz, $CDCl_3$) δ -130.9 (m, 2F), -136.2 (m, 2F).

• ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 145.3 (dd, *J* = 256.1, 15.2 Hz), 143.7 (dd, *J* = 257.7, 16.5 Hz), 134.3, 129.5, 129.3, 126.7, 120.7, 105.5 (t, *J* = 22.1 Hz), 60.4, 53.8.

• Anal. Calcd. for $C_{15}H_{10}BrF_4NO_4S$: C, 39.49; H, 2.21; N, 3.07. Found: C, 39.51; H, 2.24; N, 3.09.

(*S*)-Methyl 2-(2,3,4,5-tetrafluorophenylsulfonamido)-2-phenylacetate (30c).

Compound	PM	mmol	mg	mL
S-Methyl 2-amino-2-phenylacetate hydrochloride **(6a)**	201,65	1	201,6	
2,3,4,5-tetrafluorobenzene sulfonyl chloride **(5h)**	248,58	1	248,6	
DIEA (ϱ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



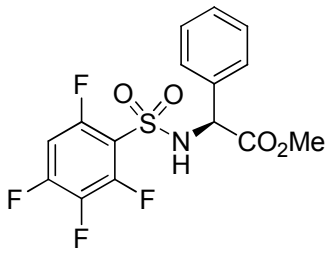
30c, $C_{15}H_{11}F_4NO_4S$
MW: 377,31

24h, 230,2 mg, 61%;

- FCC - AcOEt/hexane (1 : 9), white wax,
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H), 7.03-6.94 (m, 1H), 6.32 (d, 1H, *J* = 7.6 Hz,), 5.24 (d, 1H, *J* = 7.6 Hz), 3.73 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -134.6 (m, 1F), -136.4 (m, 1F), -146.8 (m, 1F), -151.6 (m, 1F).
- Anal. Calcd. for $C_{15}H_{11}F_4NO_4S$: C, 47.75; H, 2.94; N, 3.71. Found: C, 47.79; H, 2.95; N, 3.74.

(*S*)-Methyl 2-(2,3,4,6-tetrafluorophenylsulfonamido)-2-phenylacetate (30d).

Compound	PM	mmol	mg	mL
S-Methyl 2-amino-2-phenylacetate hydrochloride **(6a)**	201,65	1	201,6	
2,3,4,6-tetrafluorobenzene sulfonyl chloride **(5i)**	248,58	1	248,6	
DIEA (ϱ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



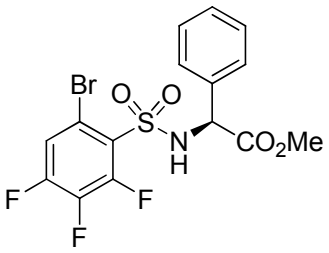
30d, $C_{15}H_{11}F_4NO_4S$
MW: 377,31

20h, 252,8 mg, 67%;

- FCC - AcOEt/hexane (1 : 9), white solid, mp 61-62°C,
- $[\alpha]_D^{20}$ +83.1 (*c* 1, $CHCl_3$).
- ^1H NMR (300 MHz, $CDCl_3$) δ 7.23-7.18 (m, 5H), 6.73-6.63 (m, 1H), 6.23 (d, 1H, *J* = 7.6 Hz,), 5.26 (d, 1H, *J* = 7.7 Hz), 3.70 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.6 (m, 1F), -124.1 (m, 1F), -128.3 (m, 1F), -162.4 (m, 1F).
- Anal. Calcd. for $C_{15}H_{11}F_4NO_4S$: C, 47.75; H, 2.94; N, 3.71. Found: C, 47.73; H, 2.91; N, 3.72.

(*S*)-Methyl 2-(6-Bromo-2,3,4-trifluorophenylsulfonamido)-2-phenylacetate (30e).

Compound	PM	mmol	mg	mL
S-Methyl 2-amino-2-phenylacetate hydrochloride **(6a)**	201,65	1,6	325	
6-Bromo-2,3,4-trifluorobenzene sulfonyl chloride **(5l)**	309,49	1,6	500	
DIEA (ϱ = 0,755 g/mL)	129,24	3,36		0,445
DCM				7



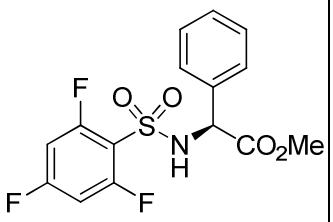
30e, $C_{15}H_{11}BrF_3NO_4S$
MW: 438,22

24h, 424 mg, 60%;

- FCC - AcOEt/hexane (1 : 9), white wax,
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.16 (m, 6H), 6.61 (d, 1H, *J* = 7.6 Hz,), 5.22 (d, 1H, *J* = 7.6 Hz), 3.66 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -123.3 (m, 1F), -126.6 (m, 1F), -157.0 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 151.6 (dm, *J* = 262.9 Hz), 150.1 (dm, *J* = 256.1 Hz), 150.1 (dt, *J* = 255.4, 16.1 Hz), 133.7, 128.9, 128.6, 127.2, 118.7 (d, *J* = 20.0 Hz), 115.0, 59.9, 53.1.
- Anal. Calcd. for $C_{15}H_{11}BrF_3NO_4S$: C, 44.11; H, 2.53; N, 3.20. Found: C, 44.12; H, 2.51; N, 3.22.

(*S*)-Methyl 2-(2,4,6-trifluorophenylsulfonamido)-2-phenylacetate (30f).

Compound	PM	mmol	mg	mL
S-Methyl 2-amino-2-phenylacetate hydrochloride **(6a)**	201,65	1	201,6	
2,4,6-trifluorobenzene sulfonyl chloride **(5m)**	230,59	1	230,6	
DIEA (ϱ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



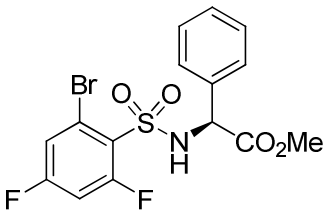
30f, $C_{15}H_{12}F_3NO_4S$
MW: 359,32

24h, 251,5 mg, 70%;

- white solid, mp 119-121°C, (EtOH)
- $[\alpha]_D^{20}$ -99.2 (*c* 1, $CHCl_3$), (EtOH).
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.17 (m, 5H), 7.13 (dt, 2H, *J* = 7.9, 2.2 Hz), 6.10 (d, 1H, *J* = 7.8 Hz,), 5.25 (d, 1H, *J* = 7.8 Hz), 3.68 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -99.6 (m, 1F), -103.6 (m, 2F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 165.3 (dt, *J* = 255.7, 15.5 Hz), 160.5 (ddd, *J* = 257.8, 15.1, 6.6 Hz), 134.8, 129.3, 129.2, 127.6, 116.0, 102.0 (t, *J* = 28.1 Hz), 60.2, 53.6.
- Anal. Calcd. for $C_{15}H_{12}F_3NO_4S$: C, 50.14; H, 3.37; N, 3.90. Found: C, 50.13; H, 3.38; N, 3.92.

(*S*)-Methyl 2-(2-Bromo-4,6-difluorophenylsulfonamido)-2-phenylacetate (30g).

Compound	PM	mmol	mg	mL
S-Methyl 2-amino-2-phenylacetate hydrochloride **(6a)**	201,65	1	201,6	
2-Bromo-4,6-difluorobenzene sulfonyl chloride **(5e)**	291,50	1	291,5	
DIEA (ϱ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



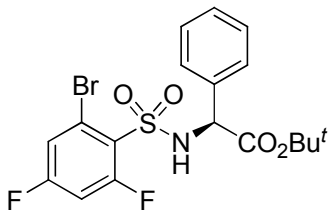
30g, $C_{15}H_{12}BrF_2NO_4S$
MW: 420,23

24h, 374 mg, 89%;

- FCC - AcOEt/hexane (1 : 5), pale brown solid, mp 71.5-72.5°C
- $[\alpha]_D^{20}$ +91.5 (*c* 1, $CHCl_3$).
- ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.17 (m, 5H), 7.13 (dt, 1H, *J* = 7.8, 2.2 Hz), 6.67 (ddd, 1H, *J* = 10.6, 8.3, 2.5 Hz), 6.38 (d, 1H, *J* = 7.7 Hz,), 5.22 (d, 1H, *J* = 7.7 Hz), 3.67 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -98.2 (m, 1F), -102.7 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 164.3 (dd, *J* = 208.4, 14.0 Hz), 164.3 (dd, *J* = 211.4, 14.2 Hz), 134.5, 129.3, 129.2, 127.6, 123.3 (d, *J* = 11.9 Hz), 119.3 (d, *J* = 22.9 Hz), 105.5 (t, *J* = 26.6 Hz), 60.3, 53.7.
- Anal. Calcd. for $C_{15}H_{12}BrF_2NO_4S$: C, 42.87; H, 2.88; N, 3.33. Found: C, 42.85; H, 2.89; N, 3.29.

(*R*)-*tert*-butyl 2-(2-Bromo-4,6-difluorophenylsulfonamido)-2-phenylacetate (50).

Compound	PM	mmol	mg	mL
R-tert-butyl 2-amino-2-phenylacetate hydrochloride (***S*-6d)**	243,73	1	243,7	
2-Bromo-4,6-difluorobenzene sulfonyl chloride **5e**	291,50	1	291,5	
DIEA (ρ = 0,755 g/mL)	129,24	2,1		0,359
DCM				4



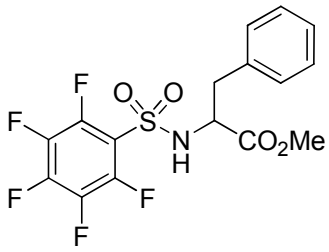
50, $C_{18}H_{18}BrF_2NO_4S$
MW: 462,31

30h, 379,1 mg, 82%;

- FCC - AcOEt/hexane (1 : 10),wax
- $[\alpha]_D^{20}$ +43.2 (*c* 0.2, $CHCl_3$).
- ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.17 (m, 5H), 7.13 (dt, 1H, *J* = 7.9, 2.2 Hz), 6.67 (ddd, 1H, *J* = 10.7, 8.2, 2.6 Hz), 6.33 (d, 1H, *J* = 7.8 Hz,), 5.09 (d, 1H, *J* = 7.9 Hz), 1.31 (s, 9H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -98.1 (m, 1F), -103.0 (m, 1F).
- Anal. Calcd. for $C_{18}H_{18}BrF_2NO_4S$: C, 46.76; H, 3.03; N, 3.33. Found: C, 46.77; H, 3.06; N, 3.32.

Synthesis of Methyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido) 3-phenylpropanoate (12a).

Compound	PM	mmol	mg	mL
Phenylalanine methyl ester hydrochloride **(13a)**	225,64	1	225,6	
pentafluorobenzene sulfonyl chloride (**5a)**	266,57	1	267	
DIEA (ϱ = 0,755 g/mL)		1,05		
DCM				6



12a, $C_{16}H_{12}F_5NO_4S$
MW: 409,33

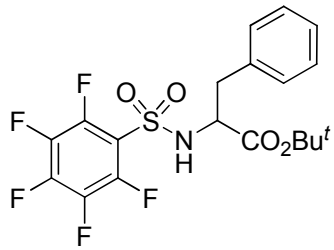
1,5 h, 286,5 mg, 70%;

Ethanol-water (1 : 1), white solid, mp 130-131 °C.

- ^{1}H NMR (300MHz, $CDCl_3$) δ 7.22-7.19 (m, 3H), 7.11-7.07 (m, 2H), 5.60 (d, 1H, *J* = 9.2 Hz), 4.54-4.47 (m, 1H), 3.73 (s, 3H), 3.19 (dd, 1H, *J* = 13.9, 4.8 Hz), 2.97 (dd, 1H, *J* = 13.9, 8.1 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -146.8 (m, 1F), -159.5 (m, 2F).
- IR (nujol) 3225, 1722, 160', 1501, 1342, 1171, 1110, 1096, 998 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{12}F_5NO_4S$: C, 46.95; H, 2.95; N, 3.42. Found: C, 46.96; H, 2.98; N, 3.44.

Synthesis of *tert*-Butyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-3-phenyl propanoate (12b).

Compound	PM	mmol	mg	mL
Phenylalanine *tert*-butyl ester hydrochloride **13b**	257,76	1	211,6	
pentafluorobenzene sulfonyl chloride (**5a)**	266,57	1	267	
DIEA (ϱ = 0,755 g/mL)		1,05		
DCM				6

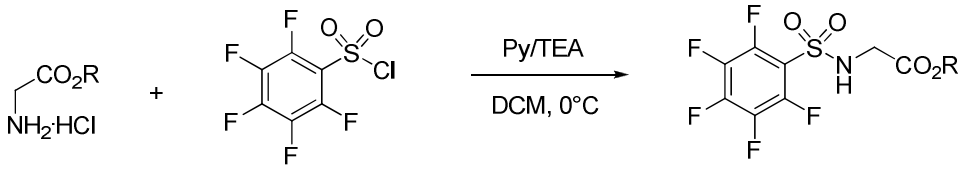


12b, $C_{19}H_{18}F_5NO_4S$
MW: 451,09

18 h, 279,7 mg, 62%;

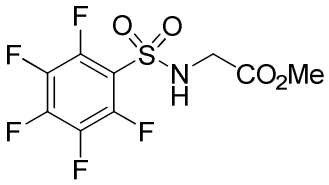
- FCC - AcOEt/hexane (1 : 10), white solid, mp 103.5-104.5°C.
- ^{1}H NMR (300MHz, $CDCl_3$) δ 7.27-7.11 (m, 5H), 5.75 (d, 1H, *J* = 6.5 Hz), 4.45-4.33 (m, 1H), 3.13 (dd, 1H, *J* = 13.9, 5.5 Hz), 2.96 (dd, 1H, *J* = 13.9, 7.6 Hz), 1.38 (s, 9H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.4 (m, 2F), -147.1 (m, 1F), -159.6 (m, 2F).
- IR (nujol) 3218, 1726, 1602, 1498, 1348, 1177, 1116, 1097, 990 cm^{-1}.
- Anal. Calcd. for $C_{19}H_{18}F_5NO_4S$: C, 50.55; H, 4.02; N, 3.10. Found: C, 50.57; H, 4.03; N, 3.12.

Synthesis of Alkyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido) acetate (14a,b): General Procedure.



To a suspension of glycine ester hydrochloride **15a,b** (1 mmol) in dry DCM (4 mL) cooled at 0°C, triethylamine (1,1 mmol) was added dropwise; the mixture was stirred for 15' then a solution of pentafluorobenzene sulfonyl chloride (1 mmol) and pyridine (1 mmol) in DCM (1 mL) was added slowly and the resulting yellow mixture was stirred at 0°C. The reaction was monitored until completion (TLC control) and the solution was then diluted with DCM (10 mL) and washed with aqueous 3% hydrochloric acid (1×5 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated under reduced pressure (RV), and purified by FCC. Yield, chromatographic eluant, physical and analytical data are as follows.

Synthesis of Methyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido) acetate (14a).



14a, $C_9H_6F_5NO_4S$
MW: 319,29

1 h, 399,1 mg, 94%;

• FCC - AcOEt/hexane (1 : 7), white solid, mp 93-94 °C.

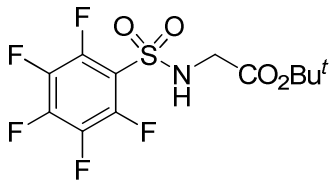
• ^{1}H NMR (300MHz, $CDCl_3$) δ 5.58 (t, 1H, *J* = 5.5 Hz), 4.06 (d, 2H, *J* = 5.5 Hz), 3.72 (s, 3H).

• ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.9 (m, 2F), -146.0 (m, 1F), -158.9 (m, 2F).

• IR (nujol) 3252, 1737, 1644, 1521, 1376, 1169, 1131, 1102, 997, 862 cm^{-1}.

• Anal. Calcd. for $C_9H_6F_5NO_4S$: C, 33.86; H, 1.89; N, 4.39. Found: C, 33.88; H, 1.92; N, 4.40.

Synthesis of *tert*-Butyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido) acetate (14b).



14b, $C_{12}H_{12}F_5NO_4S$
MW: 361,28

24 h, 271 mg, 75%;

• FCC - AcOEt/hexane (1 : 16), white solid, mp 104.5-105.5 °C.

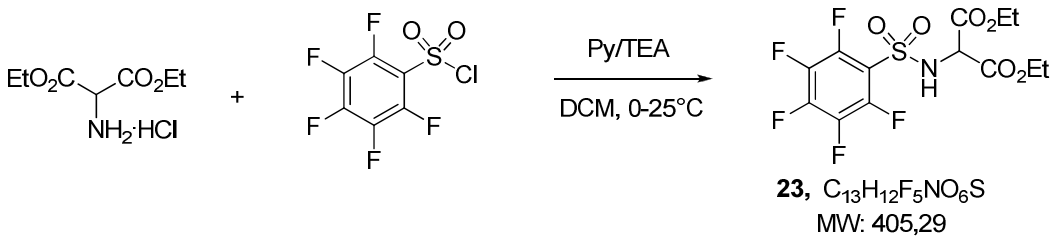
• ^{1}H NMR (300MHz, $CDCl_3$) δ 5.52 (t, 1H, *J* = 5.6 Hz), 3.92 (d, 2H, *J* = 5.6 Hz), 1.40 (s, 9H).

• ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.6 (m, 2F), -146.5 (m, 1F), -159.4 (m, 2F).

• IR (nujol) 3309, 1740, 1644, 1521, 1377, 1180, 1158, 1105, 992, 885 cm^{-1}.

• Anal. Calcd. for $C_{12}H_{12}F_5NO_4S$: C, 39.89; H, 3.35; N, 3.88. Found: C, 39.91; H, 3.36; N, 3.90.

Synthesis of Diethyl 2-(pentafluorophenylsulfonamido) malonate (23).



23, $C_{13}H_{12}F_5NO_6S$
MW: 405,29

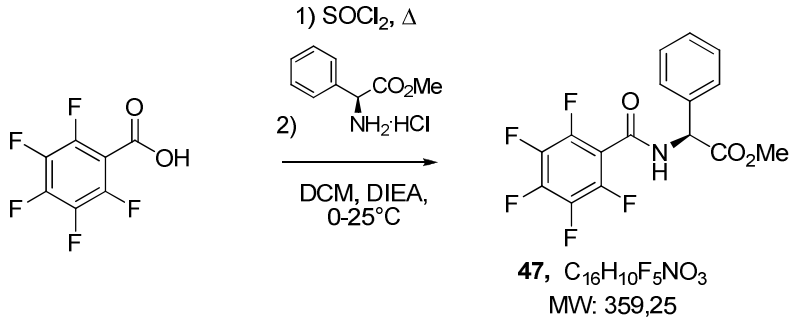
Compound	PM	mmol	mg	mL
Diethylamino malonate hydrochloride **(22)**	211,64	1	211,6	
pentafluorobenzene sulfonyl chloride **(5a)**	266,57	1	267	
TEA (ϱ = 0,725 g/mL)		1,05		
Pyridine		1,05		
DCM				6

To a suspension of diethylamino malonate hydrochloride **22** in dry DCM cooled at 0°C, triethylamine was added dropwise; the mixture was stirred for 15' then a solution of pentafluorobenzene sulfonyl chloride and pyridine in DCM was added slowly and the resulting yellow mixture was allowed to warm to room temperature. The reaction was monitored until completion (16 h, TLC control) and the solution was then diluted with DCM (10 mL) and washed with aqueous 3% hydrochloric acid (1×5 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated under reduced pressure (RV), and purified by FCC (AcOet/Hexane 1 : 9) giving the sulfonamide **23** as a white solid.

20h, 202,7 mg, 50%;

- FCC - AcOEt/hexane (1 : 9), white wax.
- ^{1}H NMR (200MHz, $CDCl_3$) δ 6.37 (d, 1H, *J* = 8.6 Hz), 4.95 (d, 1H, *J* = 6.8 Hz), 5.41 (q, 4H, *J* = 7.1 Hz), 3.74 (t, 6H, *J* = 7.1 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.6 (m, 2F), -146.0 (m, 1F), -159.3 (m, 2F).
- Anal. Calcd. for $C_{13}H_{12}F_5NO_6S$: C, 38.52; H, 2.98; N, 3.46. Found: C, 38.52; H, 3.01; N, 3.47.

Synthesis of (*S*)-Methyl 2-(perfluorobenzamido)-2-phenylacetate (47).



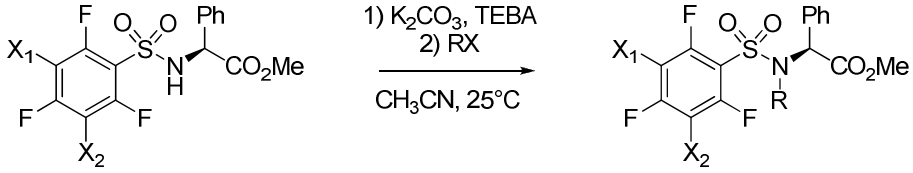
47, $C_{16}H_{10}F_5NO_3$
MW: 359,25

Compound	PM	mmol	g	mL
pentafluorobenzoic acid **(46)**	212,06	10	2,12	
$SOCl_2$ (ϱ = 1,638 g/mL)				3
(*S*)- Methyl 2-amino-2-phenylacetate hydrochloride **(6a)**	207,68	10	2,08	
DIEA (ϱ = 0,755 g/mL)	129,24	22	2,84	
DCM				30

The pentafluorobenzoic acid is dissolved in $SOCl_2$ and the resulting mixture was heated under magnetic stirring for 20h; then the solution is cooled, the excess of $SOCl_2$ removed by RV evaporation and the residue dissolved in DMC (10 mL). This solution is dropped into a solution of the phenylglycine, DIEA in DCM (20 mL) cooled at 0°C and the reaction was monitored until completion (16 h, TLC control AcOEt : hexane – 1 : 3). The mixture was then diluted with DCM (30 mL) and washed with aqueous 3% hydrochloric acid (2×15 mL), saturated $NaHCO_3$ solution (2×15 mL) and brine (20 mL), dried over $MgSO_4$, filtered. After evaporation of the solvent under vacuum (RV), the crude purified by FCC or MPLC, gave sulfonamide **47** as a white solid.

- 24h, 1,62 g, 47%;
- white solid, mp 137,5-138,5 °C.
- $[\alpha]_D^{20}$ +92.9 (*c* 1, $CHCl_3$).
- ^1H NMR (300MHz, $CDCl_3$) δ 7.71 (d, 1H, *J* = 7.2 Hz), 7.32-7.30 (m, 5H), 5.63 (d, 1H, *J* = 7.2 Hz), 3.68 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -140.9 (m, 2F), -151.5 (m, 1F), -161.1 (m, 2F).
- IR (nujol) 3303, 1731, 1660, 1556, 1520, 1495, 1359, 1330, 1312, 1274, 1224, 1186, 1095, 1070, 994, 789, 727, 695 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{10}F_5NO_3$: C, 53.49; H, 2.81; N, 3.90. Found: C, 53.51; H, 2.81; N, 3.92.

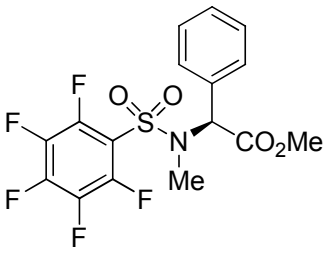
SL-PTC *N*-Alkylation of Sulfonamides 3a, 12b, 13b: General Procedure.



To a solution of sulfonamide (1 mmol) and TEBA (23 mg, 0.1 mmol) in dry MeCN (2 mL) at 25 °C, anhydrous K_2CO_3 (276 mg, 2 mmol) was added. This suspension was stirred for 10 min, then a solution of the alkylating agent (1.5 mmol) in MeCN (1 mL) was added under vigorous stirring, and the reaction was monitored by TLC (AcOEt : hexane – 1 : 9) until completion. The mixture was then diluted with AcOEt (5 mL), washed with brine (2 × 2 mL), dried over $MgSO_4$ and filtered. The solvent was removed under vacuum, the crude was purified by FCC – AcOEt/hexane (1 : 15); alkylating agent, product, yield, chromatographic eluant, physical and analytical data are as follows.

(*S*)-Methyl 2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)-2-phenylacetate (*S*-7a)

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-2-phenylacetate **(*S*-3a).**	395,30	1	395	
Potassium carbonate	138,21	2	276	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
Methyl Iodide	141,94	1,5	213	
Acetonitrile				3



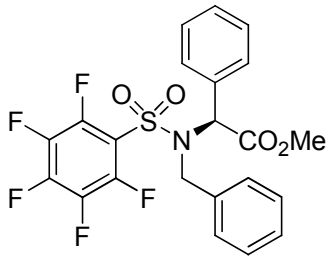
S-7a, $C_{16}H_{12}F_5NO_4S$
MW: 409,04

24 h, 368 mg, 90%;

- white solid, mp 67-69 °C (EtOH/water – 9 : 1).
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.23 (m, 5H), 6.04 (s, 1H), 3.72 (s, 3H), 2.84 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.3 (m, 2F), -146.4 (m, 1F), -159.7 (m, 2F).
- IR (nujol) 1744, 1644, 1541, 1296, 1271, 1222, 1173, 1098, 1025, 699, 678 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{12}F_5NO_4S$: C, 46.95; H, 2.95; N, 3.42. Found: C, 47.02; H, 3.00; N, 3.37.

(*S*)-Methyl 2-(*N*-benzyl-2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-7b)

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-2-phenylacetate **(*S*-3a).**	395,30	1	395	
Potassium carbonate	138,21	2	276	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
Benzyl Bromide	141,94	1,1	188	
Acetonitrile				3



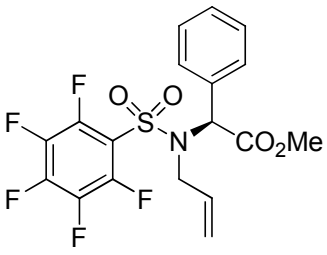
S-7b, $C_{22}H_{16}F_5NO_4S$
MW: 485,42

20 h, 427 mg, 88%;

- FCC - AcOEt/hexane (1 : 12), white solid, mp 106-108 °C
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H), 7.05-6.95 (m, 5H), 6.17 (s, 1H), 4.80 (d, 1H, *J* = 15.4 Hz), 4.25 (d, 1H, *J* = 15.4 Hz), 3.79 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.3 (m, 2F), -147.0 (m, 1F), -160.2 (m, 2F).
- IR (nujol), 1744, 1530, 1351, 1292, 1240, 1106, 669 cm^{-1}.
- Anal. Calcd. for $C_{22}H_{16}F_5NO_4S$: C, 54.43; H, 3.32; N, 2.89. Found: C, 54.48; H, 3.35; N, 2.92.

(*S*)-Methyl 2-(*N*-allyl-2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-7c)

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-2-phenylacetate **(*S*-3a).**	395,30	0,6	237,2	
Potassium carbonate	138,21	1,2	166,2	
Triethylbenzyl ammonium chloride	227,81	0,1	10	
Allyl Bromide	120,98	0,9	98	
Acetonitrile				2,5



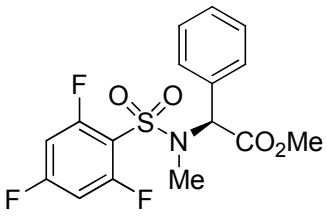
S-7c, $C_{18}H_{14}F_5NO_4S$
MW: 435,37

40 h, 122 mg, 48%;

- FCC - AcOEt/hexane (1 : 12), white wax
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.35 (m, 3H), 7.28-7.26 (m, 2H), 6.06 (s, 1H), 5.42-5.28 (m, 1H), 4.82 (d, 1H, *J* = 17.0 Hz), 4.77 (d, 1H, *J* = 9.9 Hz), 3.98 (dd, 1H, *J* = 16.4, 4.7 Hz), 3.82 (dd, 1H, *J* = 16.4, 6.9 Hz), 3.74 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.0 (m, 2F), -146.4 (m, 1F), -159.6 (m, 2F).
- Anal. Calcd. for $C_{18}H_{14}F_5NO_4S$: C, 49.66; H, 3.24; N, 3.22. Found: C, 49.63; H, 3.24; N, 3.20.

(*S*)-Methyl 2-(2,4,6-trifluoro-N-methylphenylsulfonamido)-2-phenylacetate (51)

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,4,6-trifluorophenyl sulfonamido)-2-phenylacetate **(30f).**	359,34	1,8	395	
Potassium carbonate	138,21	3,5	276	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
Methyl Iodide	141,94	2,6	369,4	
Acetonitrile				3



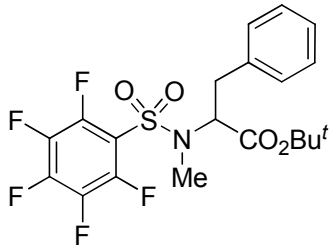
51, $C_{16}H_{14}F_3NO_4S$
MW: 373,35

28 h, 409 mg, 61%;

- FCC - AcOEt/hexane (1 : 5), white solid, mp 89.5-90.5°C
- ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.38-7.34 (m, 3H), 7.26-7.23 (m, 2H), 6.78 (t, 2H, *J* = 8.7), 6.00 (s, 1H), 3.68 (s, 3H), 2.83 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -99.3 (m, 1F), -102.0 (m, 2F).
- ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 164.8 (dt, *J* = 256.6, 16.1 Hz), 160.6 (ddd, *J* = 258.2, 15.5, 6.5 Hz), 133.1, 128.8, 128.7, 128.6, 101.8 (t, *J* = 18.8 Hz), 62.8, 52.1, 30.5.
- IR (nujol) 1748, 1647, 1538, 1301, 1270, 1225, 1173, 1099, 1027, 698, 685 cm^{-1}.

***tert*-Butyl 2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)-3-phenylpropionate (17b)**

Compound	PM	mmol	mg	mL
tert-Butyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-3-phenylpropionate **(12b).**	451,09	1	451,1	
Potassium carbonate	138,21	2	276	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
Methyl Iodide	141,94	1,5	213	
Acetonitrile				3



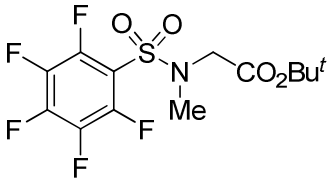
17b, $C_{20}H_{20}F_5NO_4S$
MW: 465,43

24 h, 372,3 mg, 80%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.16 (m, 5H), 4.86 (dd, 1H, *J* = 10.4, 5.3 Hz), 3.30 (dd, 1H, *J* = 14.5, 5.4 Hz), 3.05 (s, 3H), 2.91 (dd, 1H, *J* = 14.5, 10.5 Hz), 1.41 (s, 9H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -134.9 (m, 2F), -147.5 (m, 1F), -159.9 (m, 2F).
- IR (nujol) 1738, 1641, 1541, 1299, 1273, 1221, 1176, 1110, 1024, 699, 675 cm^{-1}.
- Anal. Calcd. for $C_{20}H_{20}F_5NO_4S$: C, 51.61; H, 4.33; N, 3.01. Found: C, 51.63; H, 4.36; N, 3.02.

***tert*-Butyl 2-(2,3,4,5,6-pentafluoro-N-methylphenylsulfonamido)-acetate (18b)**

Compound	PM	mmol	mg	mL
tert-Butyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-acetate **(13b).**	361,28	1	361,3	
Potassium carbonate	138,21	2	276	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
Methyl Iodide	141,94	1,5	213	
Acetonitrile				3

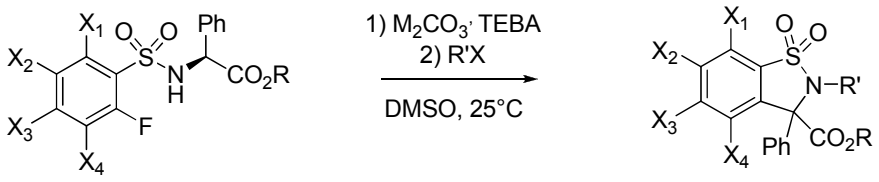


18b, $C_{13}H_{14}F_5NO_4S$
MW: 375,31

20 h, 243,9 mg, 65%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (s, 2H), 3.07 (s, 3H), 1.40 (s, 9H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.3 (m, 2F), -147.0 (m, 1F), -160.0 (m, 2F).
- IR (nujol) 1742, 1641, 1541, 1298, 1269, 1219, 1175, 1095, 1024, 695, 677 cm^{-1}.
- Anal. Calcd. for $C_{13}H_{14}F_5NO_4S$: C, 41.60; H, 3.76; N, 3.73. Found: C, 41.62; H, 3.77; N, 3.71.

SL-PTC 'One-Pot' Synthesis of *N*-Alkyl-benzo[*d*]sultams 7a-f: General Procedure.

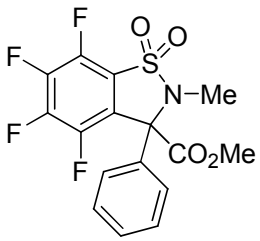


To a solution of sulfonamide and TEBA in dry solvent at 25 °C, anhydrous alkaline metal carbonate was added. The resulting heterogeneous mixture was stirred for 10 min, then the alkylating agent RX was added and the reaction was monitored by TLC (AcOEt : hexane – 1 : 6) until completion. The mixture was diluted with water and extracted with DCM and concentrated; the residue was diluted with AcOEt (10 mL) and washed with brine (5×10 mL), dried over $MgSO_4$ and filtered. After evaporation of the solvent (RV), the crude was purified by MPLC.

Starting alkylating agent (RX), dry solvent, anhydrous base, reaction time, product, yield, physical and analytical data are as follows.

Methyl 4,5,6,7-tetrafluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4a).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido)-2-phenylacetate **(3a).**	395,30	1	395	
Cesium carbonate	325,82	2	652	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
Methyl Iodide	141,94	1,5	213	
DMSO				5



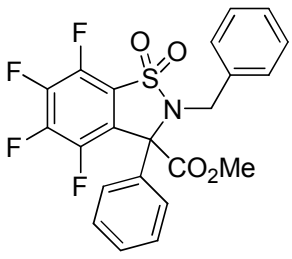
4a, $C_{16}H_{11}F_4NO_4S$
MW: 389,32

1.5h, 366 mg, 94%;

- white solid, mp 166°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.40 (m, 3H), 7.26-7.23 (m, 2H), 3.91 (s, 3H), 2.84 (s, 3H).
- ^{19}F NMR (282, MHz, $CDCl_3$) δ -135 (m, 1F), -140.3 (m, 1F), -145.3 (m, 1F), -149 (m, 1F).
- ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 144.3 (dt, *J* = 261.6, 13.8 Hz), 143.4 (ddd, *J* = 261.6, 12.6, 3.8 Hz), 141.5 (dt, *J* = 261.6, 13.8 Hz), 141.0 (dd, *J* = 262.8, 13.8 Hz), 132.7, 129.9, 129.2, 127.4, 122.3 (dd, *J* = 13.4, 3.5 Hz), 118.2 (dd, *J* = 17.5, 3.1 Hz), 71.8, 53.8, 25.4.
- IR (nujol) 1748, 1638, 1516, 1495, 1296, 1256, 1230, 1170, 1077, 977, 916, 880, 693, 629, 614 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{11}F_4NO_4S$: C, 49.36; H, 2.85; N, 3.60. Found: C, 49.31; H, 2.81; N, 3.64.
- HRMS (ESI positive) Calcd. for $C_{16}H_{11}F_4NNaO_4S$ $[M+Na]^+$: 412.02371. Found: 412.02401.

Methyl 4,5,6,7-tetrafluoro-2-benzyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4b).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido)-2-phenylacetate **(3a).**	395,30	1	395	
Sodium carbonate	105,99	4	424	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
Benzyl Bromide	171,03	1,5	257	
DMSO				5



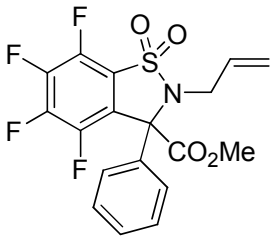
4b, $C_{22}H_{15}F_4NO_4S$
MW: 465,42

20 h, 149 mg, 32%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.31 (m, 5H), 7.25-7.20 (m, 5H), 4.70 (d, 1H, *J* = 16.1 Hz), 4.35 (d, 1H, *J* = 16.1 Hz), 3.60 (s, 3H).
- ^{19}F NMR (282 MHZ, $CDCl_3$): δ -135.2 (m, 1F), -140.1 (m, 1F), -144.9 (m, 1F), -148.9 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 144.4 (dt, *J* = 262.2, 15.2 Hz), 143.1 (dd, *J* = 259.9, 12.2 Hz), 141.5 (dm, *J* = 262.3 Hz), 141.2 (dm, *J* = 259.8 Hz), 135.2, 133.1, 129.7, 129.0, 128.2, 128.0, 127.8, 127.6, 122.3 (d, *J* = 13.9 Hz), 118.1 (d, *J* = 15.2 Hz), 72.5, 53.5, 45.3.
- IR (nujol) 1747, 1642, 1512, 1504, 1330, 1254, 1174, 1076, 996, 980, 914, 881, 829, 698, 607 cm^{-1}.
- Anal. Calcd. for $C_{22}H_{15}F_4NO_4S$: C, 56.77; H, 3.25; N, 3.01. Found: C, 56.81; H, 3.20; N, 3.06.

Methyl 4,5,6,7-tetrafluoro-2-allyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4c).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido)-2-phenylacetate **(3a).**	395,30	1	395	
Sodium carbonate	105,99	4	424	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
Allyl Bromide	120,98	1,5	182	
MeCN				5



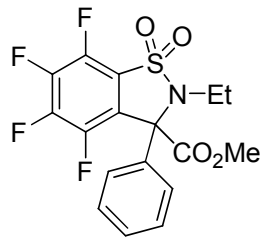
4c, $C_{18}H_{13}F_4NO_4S$
MW: 415,36

24 h, 191 mg, 46%;

- white solid; mp 111-112°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.38 (m, 3H), 7.31-7.27 (m, 2H), 5.88-5.75 (m, 1H), 5.20-5.08 (m, 2H), 4.03-3.78 (m, 2H), 3.89 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.2 (m, 1F), -140.5 (m, 1F), -145.2 (m, 1F), -149.1 (m, 1F).
- IR (nujol) 1748, 1643, 1516, 1498, 1302, 1262, 1230, 1171, 1077, 977, 916, 880, 691 cm^{-1}.
- Anal. Calcd. for $C_{18}H_{13}F_4NO_4S$: C, 52.05; H, 3.15; N, 3.37. Found: C, 52.00; H, 3.19; N, 3.34.

Methyl 4,5,6,7-tetrafluoro-2-ethyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4d).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido)-2-phenylacetate **(3a).**	395,30	1	395	
Potassium carbonate	138,21	2	276	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
Ethyl Iodide	155,97	1,5	234	
DMSO				5



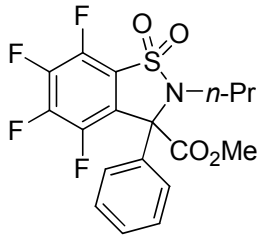
4d, $C_{17}H_{13}F_4NO_4S$
MW: 403,35

20 h, 334 mg, 83%;

- white solid, mp 109.5-110.5°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.38 (m, 3H), 7.30-7.26 (m, 2H), 3.91 (s, 3H), 3.47-3.27 (m, 2H), 1.21 (t, 3H, *J* = 7 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.3 (m, 1F), -140.5 (m, 1F), -145.3 (m, 1F), -149 (m, 1F).
- IR (nujol) 1749, 1642, 1511, 1495, 1298, 1268, 1182, 1161, 1079, 942, 727, 699, 636, 603 cm^{-1}.
- Anal. Calcd. for $C_{17}H_{13}F_4NO_4S$: C, 50.62; H, 3.25; N, 3.47. Found: C, 50.59; H, 3.29; N, 3.43.

Methyl 4,5,6,7-tetrafluoro-2-propyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4e).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido)-2-phenylacetate **(3a).**	395,30	1	395	
Cesium carbonate	325,82	4	1300	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
n-Propyl Iodide	170,01	1,5	255	
DMSO				5



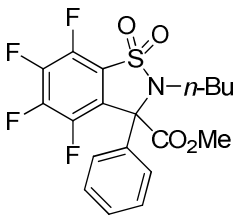
4e, $C_{18}H_{15}F_4NO_4S$
MW: 417,37

16 h, 209 mg, 50%;

- white solid, mp 56-57°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.25 (m, 5H), 3.90 (s, 3H), 3.34-3.10 (m, 2H), 1.71-1.56 (m, 2H), 0.79 (t, 3H, *J* = 7.5 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.4 (m, 1F), -140.5 (m, 1F), -145.3 (m, 1F), -149.1 (m, 1F).
- IR (nujol) 1748, 1639, 1510, 1497, 1300, 1232, 1209, 1167, 1078, 993, 876, 699 cm^{-1}.
- Anal. Calcd. for $C_{18}H_{15}F_4NO_4S$: C, 51.80; H, 3.62; N, 3.36. Found: C, 51.75; H, 3.60; N, 3.41.

Methyl 4,5,6,7-tetrafluoro-2-butyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4f).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido)-2-phenylacetate **(3a).**	395,30	1	395	
Potassium carbonate	138,21	2	276	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
n-Butyl Iodide	184,04	1,5	276	
NMP				5



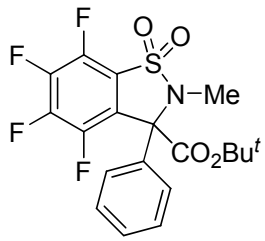
4f, $C_{19}H_{17}F_4NO_4S$
MW: 431,40

20 h, 267 mg, 62%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.36 (m, 3H), 7.29-7.27 (m, 2H), 3.89 (s, 3H), 3.89-3.14 (m, 2H), 1.63-1.55 (m, 2H), 1.27-1.15 (m, 2H), 0.80 (t, 3H, *J* = 7.35 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.4 (m, 1F), -140.6 (m, 1F), -145.4 (m, 1F), -149.2 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 144.3 (dt, *J* = 262.3, 14.8 Hz), 143.5 (dd, *J* = 260.5, 11.5 Hz), 141.5 (dt, *J* = 261.7, 14.1 Hz), 141.1 (dd, *J* = 261.7, 12.5 Hz), 134.1, 130.1, 129.5, 128.0, 122.7 (d, *J* = 13.3 Hz), 118.9 (d, *J* = 18 Hz), 72.8, 54.2, 43.3, 31.5, 20.4, 13.8.
- IR (nujol) 1744, 1633, 1510, 1488, 1290, 1248, 1239, 1170, 1077, 977, 910, 880, 693 cm^{-1}.
- Anal. Calcd. for $C_{19}H_{17}F_4NO_4S$: C, 52.90; H, 3.97; N, 3.25. Found: C, 52.96; H, 4.00; N, 3.20.

***Tert*-butyl 4,5,6,7-tetrafluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (49).**

Compound	PM	mmol	mg	mL
(R)-*tert*-butyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido)-2-phenylacetate **(3d).**	437,38	0,5	219	
Potassium carbonate	138,21	1	138	
Triethylbenzyl ammonium chloride	227,81	0,05	11	
Methyl Iodide	141,94	0,75	106	
DMSO				1,25



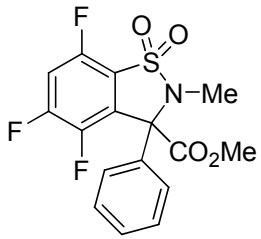
49, $C_{19}H_{17}F_4NO_4S$
MW: 431,40

20 h, 86 mg, 40%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.27 (m, 5H), 2.84 (s, 3H), 1.53 (s, 9H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.2 (m, 1F), -140.6 (m, 1F), -146.0 (m, 1F), -149.6 (m, 1F).
- IR (nujol) 1747, 1628, 1511, 1488, 1295, 1245, 1242, 1173, 1075, 976, 915, 883 cm^{-1}.
- Anal. Calcd. for $C_{19}H_{17}F_4NO_4S$: C, 52.90; H, 3.97; N, 3.25. Found: C, 52.88; H, 3.96; N, 3.22.

Methyl 4,5,7-trifluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (32).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,3,4,6-tetrafluoro phenylsulfonamido)-2-phenylacetate **(30d).**	377,31	0,35	138,7	
Potassium carbonate	138,21	1	138	
Triethylbenzyl ammonium chloride	227,81	0,075	17	
Methyl Iodide	141,94	0,75	106,5	
DMSO				2



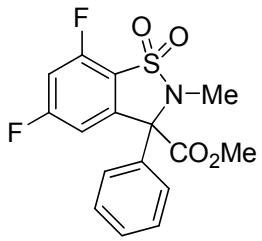
32, $C_{16}H_{12}F_3NO_4S$
MW: 371,33

18 h, 121 mg, 89%;

- FCC - AcOEt/hexane (1 : 5), white solid; mp 137.5-138.5°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.38 (m, 3H), 7.29-7.25 (m, 2H), 7.14 (ddd, 1H, *J* = 9.6, 7.5, 5.2 Hz), 3.90 (s, 3H), 2.82 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.6 (m, 1F), -123.8 (m, 1F), -139.9 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 155.8 (dt, *J* = 259.1, 12.6 Hz), 151.4 (dd, *J* = 256.9, 11.2 Hz), 143.4 (dd, *J* = 256.7, 13.9 Hz), 133.4, 130.1, 129.6, 127.9, 126.3, 118.7 (d, *J* = 20.2 Hz), 108.7 (t, *J* = 23.4 Hz), 72.5, 54.1, 25.7.
- Anal. Calcd. for $C_{16}H_{12}F_3NO_4S$: C, 51.75; H, 3.26; N, 3.77. Found: C, 51.77; H, 3.29; N, 3.78.

Methyl 5,7-difluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (33).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,4,6-trifluorophenyl sulfonamido)-2-phenylacetate **(30f).**	359,32	1	359,3	
Potassium carbonate	138,21	2	275	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
Methyl Iodide	141,94	1,5	213	
DMSO				4



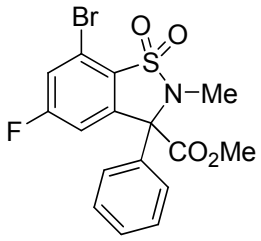
33, $C_{16}H_{13}F_2NO_4S$
MW: 353,34

45 h, 180 mg, 51%;

- FCC - AcOEt/hexane (1 : 3), white solid; mp 170-171°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.38 (m, 3H), 7.18-7.15 (m, 2H), 7.02-6.92 (m, 2H), 3.89 (s, 3H), 2.80 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -99.5 (m, 1F), -111.1 (m, 1F).
- IR (nujol) 1742, 1639, 1521, 1495, 1301, 1262, 1235, 1173, 1071, 979, 915, 889, 692 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{13}F_2NO_4S$: C, 54.39; H, 3.71; N, 3.96. Found: C, 54.42; H, 3.72; N, 3.98.

Methyl 5-fluoro-7-bromo-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (34).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2-bromo-4,6-difluorophenyl sulfonamido)-2-phenylacetate **(30g).**	420,23	0,5	210	
Potassium carbonate	138,21	1	138	
Triethylbenzyl ammonium chloride	227,81	0,05	11	
Methyl Iodide	141,94	1,75	245	
DMSO				4

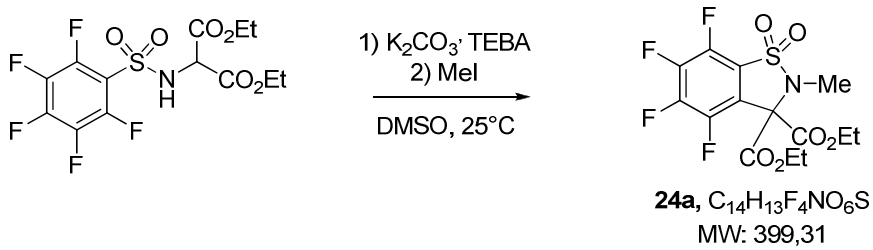


34, $C_{16}H_{13}BrFNO_4S$
MW: 414,25

26 h, 140,8 mg, 68%;

- FCC - AcOEt/hexane (1 : 12), white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.39 (m, 5H), 7.19-7.12 (m, 2H), 3.89 (s, 3H), 2.84 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -102.8 (m, 1F).
- Anal. Calcd. for $C_{16}H_{13}BrFNO_4S$: C, 46.39; H, 3.16; N, 3.38. Found: C, 46.37; H, 3.17; N, 3.36.

Diethyl 4,5,6,7-tetrafluoro-2-methyl-2,3-dihydrobenzo[*d*]isothiazole-3,3-dicarboxylate 1,1-dioxide (24a).



24a, $C_{14}H_{13}F_4NO_6S$
MW: 399,31

Compound	PM	mmol	mg	mL
Diethyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido) malonate **(23).**	405,29	1	405,3	
Potassium carbonate	138,21	2	275	
Triethylbenzyl ammonium chloride	227,81	0,1	23	
Methyl Iodide	141,94	1,5	213	
DMSO				4

5 h, 143,7 mg, 36%;

• FCC - AcOEt/hexane (1 : 9), white wax.

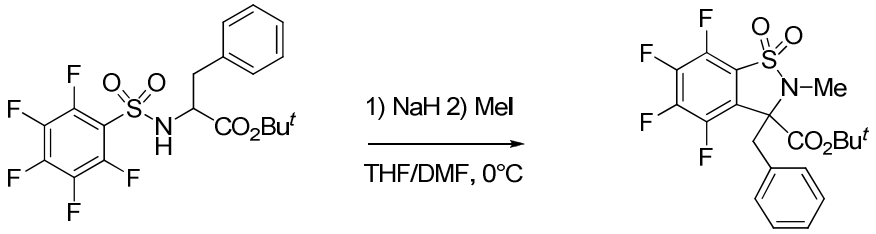
• ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38-4.28 (m, 4H), 3.12 (s, 3H), 2.95 (t, 6H, *J* = 7.1 Hz).

• ^{19}F NMR (282 MHz, $CDCl_3$) δ -133.0 (m, 1F), -139.7 (m, 1F), - 144.9 (m, 1F), -147.4 (m, 1F).

• IR (nujol) 1742, 1646, 1501, 1371, 1313, 1242, 1169, 1035, 915, 843 cm^{-1}.

• Anal. Calcd. for $C_{14}H_{13}F_4NO_6S$: C, 42.11; H, 3.28; N, 3.51. Found: C, 42.13; H, 3.29; N, 3.53.

Synthesis of *tert*-Butyl 4,5,6,7-tetrafluoro-2-methyl-3-benzyl-2,3-dihydro benzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (16b).



16b, $C_{20}H_{19}F_4NO_4S$
MW: 445,43

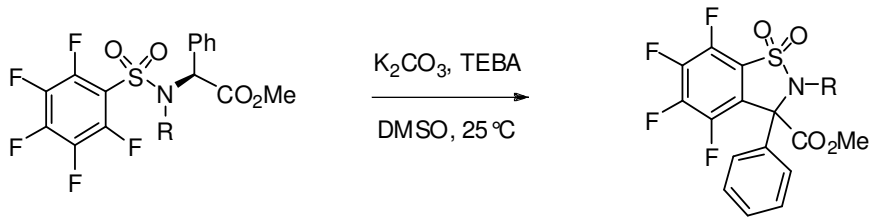
Compound	PM	mmol	mg	mL
Diethyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido) malonate **(23).**	451,41	0,3	135,4	
Sodium Hydride 60%	24	1,2	48	
Methyl Iodide	141,94	0,9	127,7	
THF - DMF				2 + 0,1

In a flame-dried round bottomed flask, 60% sodium hydride was rinsed with anhydrous *n*-pentane and, after cooling at 0°C, a solution of the sulfonylamido ester in anhydrous THF was added. The reaction mixture was stirred until hydrogen evolution ended (ca. 30 min.) then a solution of methyl iodide in anhydrous THF was added. The reaction mixture was stirred at 0°C until the reaction was judged complete by TLC analysis then was quenched with saturated NH_4Cl solution. After extraction with AcOEt and evaporation under reduced pressure, the crude was purified by flash column chromatography on silica gel. Yield, reaction time, chromatographic eluant, physical spectroscopic and analytical data are as follows

4 h, 19,5 mg, 15%;

- FCC - AcOEt/hexane (1 : 10), white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.14 (m, 3H), 7.01-6.98 (m, 2H), 3.54 (dd, 1H, *J* = 15.1, 2.2 Hz), 3.47 (d, 1H, *J* = 15.1 Hz), 3.01 (s, 3H), 1.44 (s, 9H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -137.9 (m, 1F), -139.4 (m, 1F), - 146.5 (m, 1F), -148.9 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 143.7 (dt, *J* = 260.3, 14.0 Hz), 142.3 (dd, *J* = 255.5, 11.7 Hz), 141.2 (dd, *J* = 259.6, 12.5 Hz), 140.9 (dt, *J* = 260.0, 13.7 Hz), 132.9, 129.5, 128.5, 127.8, 119.6, 118.4, 85.1, 71.0, 36.3, 27.7, 24.7.
- Anal. Calcd. for $C_{20}H_{19}F_4NO_4S$: C, 53.93; H, 4.30; N, 3.14. Found: C, 53.91; H, 4.31; N, 3.13.
- MS (ESI positive) Calcd. for $C_{20}H_{19}F_4NNaO_4S$ $[M+Na]^+$: 468.1. Found: 468.2.
- Anal. Calcd. for $C_{14}H_{13}F_4NO_6S$: C, 42.11; H, 3.28; N, 3.51. Found: C, 42.12; H, 3.30; N, 3.50.

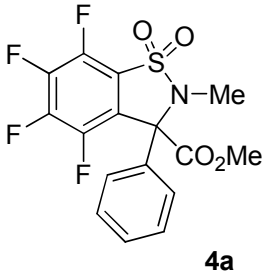
SL-PTC Ring Closing Reactions of *N*-Alkylsulfonamides 7a-c and 51.



number **number**

To a solution of *N*-alkyl-sulfonamide (0.2 mmol) and TEBA (5 mg, 0.02 mmol) in dry DMSO (1 mL) at 25 °C, anhydrous Cs_2CO_3 (130 mg, 0.4 mmol) was added. This suspension was vigorously stirred for 15 min, monitoring by TLC (AcOEt : hexane – 1 : 9), then diluted with water (2 mL), extracted with DCM (3×10 mL). The solvent was removed under vacuum (RV). The residue was diluted with AcOEt (10 mL), washed with brine (5×2mL), dried over Mg_2SO_4 filtered and, after evaporation of the solvent (RV), purified by MPLC (AcOEt : hexane – 1 : 12) to give the desired N-alkyl benzosultam. Starting sulfonamides, product, yield and chromatographic eluants are as follows.

Methyl 4,5,6,7-tetrafluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide 4a.



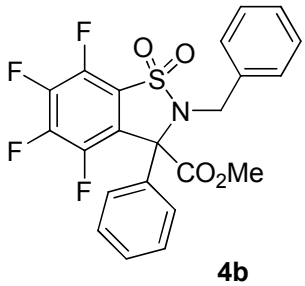
4a

Starting sulfonamide **7a**, 82 mg,

sultam **4a**, 142 mg, 91%,

MPLC (AcOEt : hexane – 1 : 12)

Methyl 4,5,6,7-tetrafluoro-2-benzyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4b).



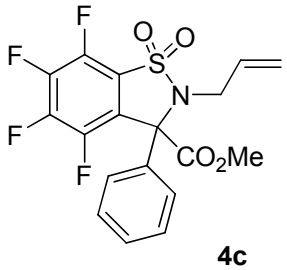
4b

Starting sulfonamide **7b**, 97 mg,

sultam **4b**, 42 mg, 45%,

MPLC (AcOEt : esano – 1 : 12

Methyl 4,5,6,7-tetrafluoro-2-allyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4c).



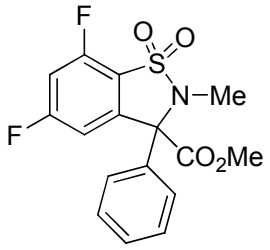
4c

Starting sulfonamide **7c**, 97 mg,

sultam **4c**, 55,6 mg, 61%,

MPLC (AcOEt : esano – 1 : 9

Methyl 4,6-difluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide 33.



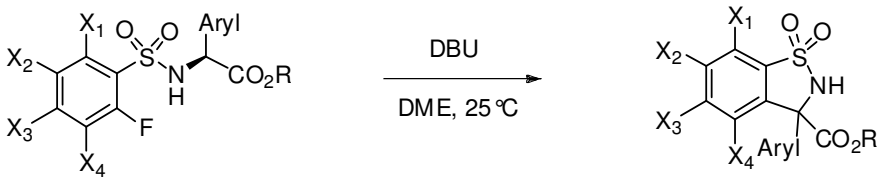
33

Starting sulfonamide **51**, 75 mg,

sultam, 43 mg, 61%,

MPLC (AcOEt : hexane – 1 : 12)

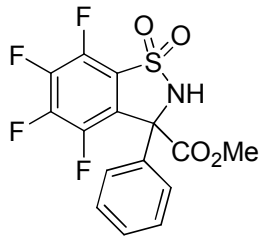
Synthesis of Benzo[*d*]sultams 8a-d, 11a-i, 31a-l: General Procedure.



To a solution of sulfonamide (1 mmol) in dry DME (4 mL), DBU (4 mmol) in DME (1mL) was added and the mixture was stirred at 25 °C until completion (TLC control). The solution was then diluted with AcOEt (10 mL), washed with aqueous 5% citric acid (3×10 mL), saturated $NaHCO_3$ solution (2×10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure (RV), giving the sultams, in some case without any further purification. Starting sulfonamides, reaction time, product, yield, physical and analytical data are as follows.

Methyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (8a).

Compound	PM	mmol	g	mL
(S)-Methyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido)-2-phenylacetate **(*S*-3a).**	395,30	10	3,95	
DBU (ρ = 1,018 g/mL)	152,24	40	6,09	
DME				50



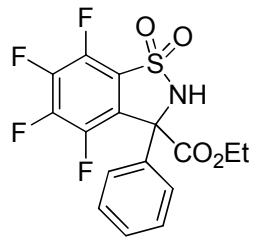
8a, $C_{15}H_9F_4NO_4S$
MW: 375,29

4 h, 3.60 g, 96%;

- white solid; mp 98-99°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.34 (m, 5H), 6.38 (s, 1H), 3.93 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.5 (m, 1F), -140.1 (m, 1F), -144 (m, 1F), -147.9 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 144.6 (dt, *J* = 262.2, 14.3 Hz), 143.6 (ddd, *J* = 261.8, 12.4, 3.3 Hz), 141.6 (dt, *J* = 262.1, 14.2 Hz), 140.9 (dd, *J* = 261.6, 12.5 Hz), 135.4, 129.6, 129.0, 126.2, 121.8 (d, *J* = 14.3 Hz), 119.6 (d, *J* = 17.8 Hz), 69.9, 54.3.
- IR (nujol) 3280, 1748, 1637, 1512, 1376, 1319, 1257, 1173, 1035, 914 cm^{-1}.
- Anal. Calcd. for $C_{15}H_9F_4NO_4S$: C, 48.01; H, 2.42; N, 3.73. Found: C, 47.96; H, 2.44; N, 3.73.

Ethyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (8b).

Compound	PM	mmol	mg	mL
(R)-Ethyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido)-2-phenylacetate **(*S*-3b).**	409,33	1	409,3	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



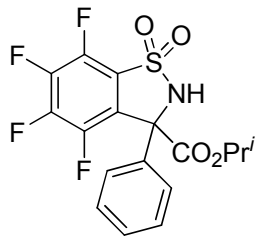
8b, $C_{16}H_{11}F_4NO_4S$
MW: 389,32

16 h, 366 mg, 94%;

- white solid; mp 83.5-84.5°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.37 (m, 5H), 5.98 (s, 1H), 4.50-4.08 (m, 2H), 3.93 (t, 3H, *J* = 6.3 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.1 (m, 1F), -139.6 (m, 1F), -143.8 (m, 1F), -147.5 (m, 1F).
- IR (nujol) 3245, 1742, 1643, 1518, 1369, 1314, 1252, 1173, 1033, 909 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{11}F_4NO_4S$: C, 49.36; H, 2.85; N, 3.60. Found: C, 49.34; H, 2.82; N, 3.59.

Isopropyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (8c).

Compound	PM	mmol	mg	mL
(R)-Isopropyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido)-2-phenylacetate **(*S*-3c).**	423,36	1	423,4	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



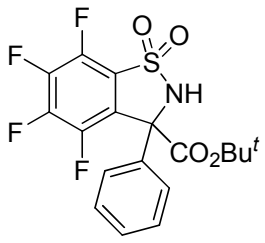
8c, $C_{17}H_{13}F_4NO_4S$
MW: 403,35

20 h, 379,1 mg, 94%;

- white solid; mp 95.5-96.5°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.36 (m, 5H), 6.09 (s, 1H), 5.27-5.18 (m, 1H), 1.34 (d, 3H, *J* = 6.3 Hz), 1.29 (d, 3H, *J* = 6.3 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -131.9 (m, 1F), -139.8 (m, 1F), -144.0 (m, 1F), -147.7 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 145.2 (dt, *J* = 261.1, 14.4 Hz), 144.2 (dd, *J* = 257.6, 11.6 Hz), 142.1 (dt, *J* = 260.7, 14.4 Hz), 141.4 (dd, *J* = 260.6, 11.7 Hz), 136.2, 129.9, 129.5, 126.8, 122.5 (d, *J* = 15.2 Hz), 120.4 (d, *J* = 17.6 Hz), 73.5, 70.5, 21.8.
- IR (nujol) 3229, 1746, 1644, 1523, 1362, 1315, 1256, 1171, 1033, 920 cm^{-1}.
- Anal. Calcd. for $C_{17}H_{13}F_4NO_4S$: C, 50.62; H, 3.25; N, 3.47. Found: C, 50.60; H, 3.26; N, 3.45.

***tert*-Butyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (8d).**

Compound	PM	mmol	mg	mL
(R)-*tert*-Butyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido)-2-phenylacetate **(*S*-3d).**	437,38	1	437,4	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



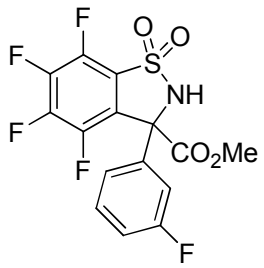
8d, $C_{18}H_{15}F_4NO_4S$
MW: 417,37

16 h, 379,8 mg, 91%;

- white solid; mp 108-109°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.39 (m, 5H), 6.16 (s, 1H), 1.52 (s, 9H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.0 (m, 1F), -140.1 (m, 1F), -144.4 (m, 1F), -148.1 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 146.5-139.1 (4 C-F Ar), 136.1, 129.5, 129.1, 125.9, 120.5, 119.5, 86.6, 70.5, 27.9.
- IR (nujol) 3233, 1745, 1641, 1523, 1363, 1315, 1257, 1171, 1040, 903 cm^{-1}.
- Anal. Calcd. for $C_{18}H_{15}F_4NO_4S$: C, 51.80; H, 3.62; N, 3.36. Found: C, 51.81; H, 3.63; N, 3.39.

Methyl 4,5,6,7-tetrafluoro-3-(3-fluorophenyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (11a).

Compound	PM	mmol	mg	mL
rac-Methyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-2-(3-fluorophenyl)acetate **(10a).**	413,29	1	413,3	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



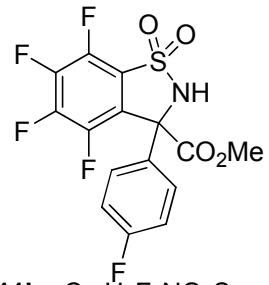
11a, $C_{15}H_8F_5NO_4S$
MW: 393,29

5 h, 373 mg, 95%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.33 (m, 1H), 7.19-7.06 (m, 3H), 6.4 (br, 1H), 3.94 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.9 (s, 1F), -132.5 (m, 1F), -139.7 (m, 1F), -143.5 (m, 1F), -147.3 (m, 1F).
- ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 162.8 (d, *J* = 247.7 Hz), 144.9 (dt, *J* = 262.8, 13.8 Hz), 143.7 (ddd, *J* = 260.4, 11.3, 2.5 Hz), 141.9 (dt, *J* = 262.8, 13.8 Hz), 141.1 (dd, *J* = 260.3, 11.3 Hz), 137.8, 130.9 (d, *J* = 7.5 Hz), 122.2, 121.3 (dd, *J* = 14.3, 3.1 Hz), 119.7 (dd, *J* = 18, 2.5 Hz), 116.9 (d, *J* = 20.1 Hz), 114.0 (d, *J* = 23.9 Hz), 69.4, 54.8.
- IR (nujol) 3275, 1752, 1631, 1508, 1376, 1324, 1263, 1175, 1031, 840 cm^{-1}.
- Anal. Calcd. for $C_{15}H_8F_5NO_4S$: C, 45.81; H, 2.05; N, 3.56. Found: C, 45.84; H, 2.09; N, 3.52.

Methyl 4,5,6,7-tetrafluoro-3-(4-fluorophenyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (11b).

Compound	PM	mmol	mg	mL
rac-Methyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-2-(4-fluorophenyl)acetate **(10b).**	413,29	1	413,3	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



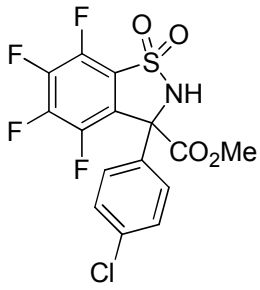
11b, $C_{15}H_8F_5NO_4S$
MW: 393,29

5 h, 385 mg, 98%;

- white solid; mp 83.5-84.5°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.33 (m, 2H), 7.10-7.04 (m, 2H), 6.32 (s, 1H), 3.93 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.2 (s, 1F), -132.8 (m, 1F), -139.6 (m, 1F), -143.5 (m, 1F), -147.3 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 163.7 (d, *J* = 249.3Hz), 145.2 (dt, *J* = 261.1, 14.8 Hz), 144.0 (ddd, *J* = 258.3, 12.9, 2.9 Hz), 142.3 (dt, *J* = 261.1, 14.1 Hz), 141.6 (dd, *J* = 258.3, 12.4 Hz), 131.8, 129.0, 122.1 (d, *J* = 14.3 Hz), 120.1 (d, *J* = 17.2 Hz), 116.6 (d, *J* = 22.3 Hz), 69.8, 55.1.
- IR (nujol) 3272, 1750, 1635, 1508, 1376, 1321, 1261, 1175, 1038, 914, 843 cm^{-1}.
- Anal. Calcd. for $C_{15}H_8F_5NO_4S$: C, 45.81; H, 2.05; N, 3.56. Found: C, 45.82; H, 2.09; N, 3.60.

Methyl 4,5,6,7-tetrafluoro-3-(4-chlorophenyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (11c).

Compound	PM	mmol	mg	mL
rac-Methyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-2-(4-chlorophenyl)acetate **(10c).**	429,75	1	429,8	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



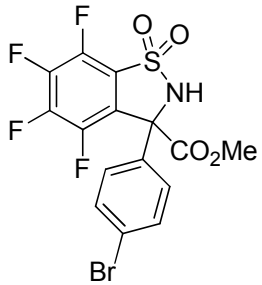
11c, $C_{15}H_8ClF_4NO_4S$
MW: 409,74

5 h, 365 mg, 91%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.30 (m, 4H), 6.26 (s, 1H), 3.94 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.7 (m, 1F), -139.5 (m, 1F), -143.4 (m, 1F), -147.1 (m, 1F).
- ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 144.9 (dt, *J* = 264.1, 15.1 Hz), 143.7 (ddd, *J* = 261.6, 12.6, 5.0 Hz), 141.9 (dt, *J* = 264.1, 15.1 Hz), 141.2 (dd, *J* = 261.6, 12.6 Hz), 136.1, 134.0, 129.4, 127.9, 121.4 (dd, *J* = 15.1, 3.8 Hz), 119.7 (dd, *J* = 17.6, 3.8 Hz), 69.4, 54.8.
- IR (nujol) 3284, 1739, 1648, 1507, 1379, 1325, 1270, 1185, 1028, 911 cm^{-1}.
- Anal. Calcd. for $C_{15}H_8ClF_4NO_4S$: C, 43.97; H, 1.97; N, 3.42. Found: C, 44.03; H, 2.00; N, 3.45.

Methyl 4,5,6,7-tetrafluoro-3-(4-bromophenyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (11d).

Compound	PM	mmol	mg	mL
rac-Methyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-2-(4-bromophenyl)acetate **(10d).**	474,20	1	474,2	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



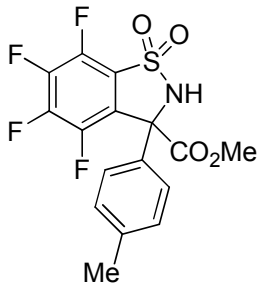
11d, $C_{15}H_8BrF_4NO_4S$
MW: 454,19

5 h, 422 mg, 93%;

- white solid; mp 49-49.5 °C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2H), 7.27-7.24 (m, 2H), 5.93 (s, 1H), 3.93 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.7 (m, 1F), -139.6 (m, 1F), -143.5 (m, 1F), -147.2 (m, 1F).
- ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 144.9 (dt, *J* = 262.8, 15.1 Hz), 143.7 (ddd, *J* = 261.6, 12.6, 3.8 Hz), 141.9 (dt, *J* = 262.8, 14.8 Hz), 141.1 (dd, *J* = 261.6, 12.6 Hz), 134.6, 132.3, 128.1, 124.1, 121.4 (dd, *J* = 14.6, 3.3 Hz), 119.7 (dd, *J* = 18.2, 2.9 Hz), 69.5, 54.8.
- IR (nujol) 3276, 1738, 1630, 1518, 1361, 1302, 1257, 1174, 1044, 906 cm^{-1}.
- Anal. Calcd. for $C_{15}H_8BrF_4NO_4S$: C, 39.67; H, 1.78; N, 3.08. Found: C, 39.61; H, 1.72; N, 3.13.

Methyl 4,5,6,7-tetrafluoro-3-(4-tolyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (11e).

Compound	PM	mmol	mg	mL
rac-Methyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-2-(4-tolyl)acetate **(10e).**	409,33	1	409,3	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



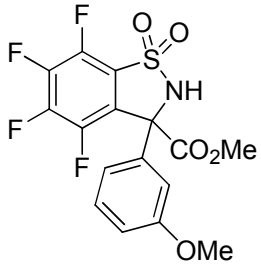
11e, $C_{16}H_{11}F_4NO_4S$
MW: 389,32

6 h, 385 mg, 99%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.17 (m, 4H), 6.32 (s, 1H), 3.93 (s, 3H), 2.34 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.4 (m, 1F), -140.1 (m, 1F), -144.0 (m, 1F), -147.9 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 144.6 (dt, *J* = 276.7, 15.8 Hz), 143.7 (dd, *J* = 261.9, 12.1 Hz), 141.6 (dm, *J* = 276.5 Hz), 141.1 (dd, *J* = 261.9, 12.8 Hz), 140.0, 132.5, 129.8, 126.2, 122.1 (d, *J* = 11.2 Hz), 119.8 (d, *J* = 15.4 Hz), 69.8, 54.4, 21.0.
- IR (nujol) 3238, 1720, 1509, 1391, 1355, 1324, 1294, 1189, 1169, 1061, 1039, 911 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{11}F_4NO_4S$: C, 49.36; H, 2.85; N, 3.60. Found: C, 49.32; H, 2.88; N, 3.62.

Methyl 4,5,6,7-tetrafluoro-3-(3-metoxyphenyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (11f).

Compound	PM	mmol	mg	mL
rac-Methyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-2-(3-metoxyphenyl)acetate **(10f).**	425,33	1	425,3	
DBU (ρ = 1,018 g/mL)	152,24	4	609	
DME				5



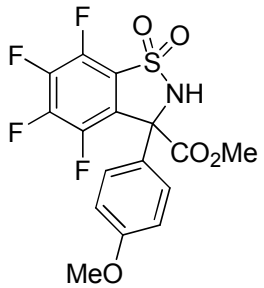
11f, $C_{16}H_{11}F_4NO_5S$
MW: 405,32

6 h, 397 mg, 98%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.27 (m, 1H), 6.93-6.90 (m, 3H), 6.32 (s, 1H), 3.93 (s, 3H), 3.76 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.0 (m, 1F), -140.1 (m, 1F), -143.9 (m, 1F), -147.8 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 160.0, 144.7 (dt, *J* = 261.7, 14.3 Hz), 143.8 (dd, *J* = 262.5, 12.1 Hz), 141.7 (dt, *J* = 261.6, 14.3 Hz), 141.1 (dd, *J* = 262.5, 12.0 Hz), 136.9, 130.2, 121.7 (d, *J* = 11.3 Hz), 119.7 (d, *J* = 14.2 Hz), 118.4, 114.7, 112.7, 69.8, 55.3, 54.5.
- IR (nujol) 3261, 1748, 1603, 1455, 1436, 1358, 1326, 1261, 1177, 1047, 909 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{11}F_4NO_5S$: C, 47.41; H, 2.74; N, 3.46. Found: C, 47.44; H, 2.77; N, 3.42.

Methyl 4,5,6,7-tetrafluoro-3-(4-metoxyphenyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (11g).

Compound	PM	mmol	mg	mL
rac-Methyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-2-(4-metoxyphenyl)acetate **(10g).**	425,33	1	425,3	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



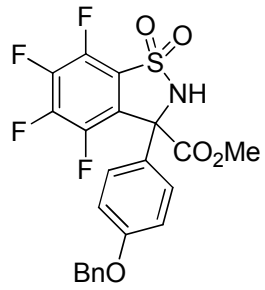
11g, $C_{16}H_{11}F_4NO_5S$
MW: 405,32

8 h, 385 mg, 95%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.23 (m, 2H), 6.88-6.85 (m, 2H), 5.9 (s, 1H), 3.91 (s, 3H), 3.78 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.7 (m, 1F), -140.2 (m, 1F), -144.1 (m, 1F), -148.1 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 160.5, 144.7 (dt, *J* = 264.2, 14.3 Hz), 143.7 (dd, *J* = 261.9, 12.1 Hz), 141.6 (dt, *J* = 264.2, 14.4 Hz), 140.9 (dd, *J* = 261.9, 12.1 Hz), 127.7, 127.2, 122.2 (*J* = 13.6 Hz), 119.8 (d, *J* = 17.4 Hz), 114.1, 69.7, 55.3, 54.4.
- IR (nujol) 3270, 1750, 1600, 1458, 1436, 1352, 1326, 1258, 1170, 1050, 912 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{11}F_4NO_5S$: C, 47.41; H, 2.74; N, 3.46. Found: C, 47.44; H, 2.77; N, 3.42.

Methyl 4,5,6,7-tetrafluoro-3-(4-benzyloxyphenyl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (11h).

Compound	PM	mmol	mg	mL
rac-Methyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-2-(4-benzyloxyphenyl) acetate **(10h).**	501,42	1	501,4	
DBU (ρ = 1,018 g/mL)	152,24	4	609	
DME				5



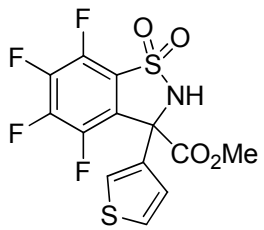
11h, $C_{22}H_{15}F_4NO_5S$
MW: 481,42

12 h, 390 mg, 81%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.33 (m, 5H), 7.31-7.25 (m, 2H), 7.00-6.96 (m, 2H), 6.13 (s, 1H), 5.06 (s, 1H), 3.93 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.5 (m, 1F), -140.0 (m, 1F), -143.9 (m, 1F), -147.9 (m, 1F).
- IR (nujol) 3284, 1739, 1645, 1508, 1371, 1304, 1255, 1170, 1022, 906 cm^{-1}.
- Anal. Calcd. for $C_{22}H_{15}F_4NO_5S$: C, 54.89; H, 3.14; N, 2.91. Found: C, 54.92; H, 3.06; N, 2.88.

Methyl 4,5,6,7-tetrafluoro-3-(thiophen-3-yl)-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (11i).

Compound	PM	mmol	mg	mL
rac-Methyl 2-(2,3,4,5,6-pentafluorophenyl sulfonamido)-2-(thiophen-3-yl)acetate **(10i).**	401,33	0,4	160	
DBU (ϱ = 1,018 g/mL)	152,24	1,6	243,6	
DME				2



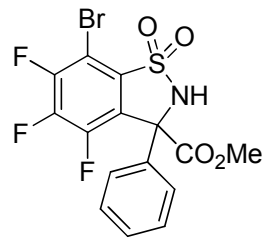
11i, $C_{13}H_7F_4NO_4S_2$
MW: 381,32

8 h, 134 mg, 88%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, 1H, *J* = 3.5 Hz), 7.34 (dd, 1H, *J* = 5.2, 3.5 Hz), 7.12 (d, 1H, *J* = 5.2 Hz), 5.3 (s, 1H), 3.92 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -133.2 (m, 1F), -139.7 (m, 1F), -143.8 (m, 1F), -147.8 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 146. (dt, *J* = 264.8, 13.9 Hz), 143.6 (dd, *J* = 261.5, 11.5 Hz), 141.7 (dt, *J* = 264.7, 13.9 Hz), 141.0 (dd, *J* = 261.4, 11.6 Hz), 135.8, 127.5, 125.8, 124.9, 122.1, 119.3, 66.9, 54.7.
- IR (nujol) 3280, 1753, 1639, 1499, 1378, 1318, 1248, 1172, 1032, 912, 840 cm^{-1}.
- Anal. Calcd. for $C_{13}H_7F_4NO_4S_2$: C, 40.95; H, 1.85; N, 3.67. Found: C, 40.99; H, 1.88; N, 3.70.

Methyl 7-bromo-4,5,6-trifluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (31a).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2-Bromo-3,4,5,6-tetrafluoro phenylsulfonamido)-2-phenylacetate **(30a).**	456,94	1	456,9	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



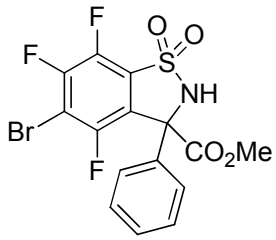
31a, $C_{15}H_9BrF_3NO_4S$
MW: 436,20

24 h, 383,9 mg, 88%;

- pale yellow solid; mp 62.5-63.5°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.34 (m, 5H), 6.24 (s, 1H), 3.93 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -120.2 (m, 1F), -128.3 (m, 1F), -146.2 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 151.0 (dt, *J* = 256.6, 13.1 Hz), 147.4 (dm, *J* = 262.0 Hz), 144.1 (dt, *J* = 262.2, 16.3 Hz), 136.1, 131.1, 130.2, 129.6, 126.8, 124.5 (d, *J* = 14.4 Hz), 99.9 (d, *J* = 19.3 Hz), 69.0, 55.0.
- IR (nujol) 3237, 1743, 1644, 1522, 1367, 1310, 1251, 1170, 1037, 925 cm^{-1}.
- Anal. Calcd. for $C_{15}H_9BrF_3NO_4S$: C, 41.30; H, 2.08; N, 3.21. Found: C, 41.32; H, 2.08; N, 3.22.

Methyl 5-bromo-4,6,7-trifluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (31b).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(4-Bromo-2,3,5,6-tetrafluoro phenylsulfonamido)-2-phenylacetate **(30b).**	456,94	1	456,9	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



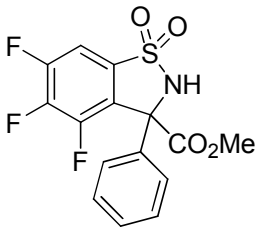
31b, $C_{15}H_9BrF_3NO_4S$
MW: 436,20

24 h, 401,3 mg, 92%;

- pale yellow solid; mp 116-118°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.36 (m, 5H), 6.55 (br, 1H), 3.91 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -103.8 (m, 1F), -119.6 (m, 1F), -141.5 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 151.2 (d, *J* = 258.2 Hz), 149.3 (dd, *J* = 256.9, 13.5 Hz), 140.4 (dd, *J* = 256.5, 12.5 Hz), 135.4, 129.6, 129.0, 126.3, 124.4, 121.3 (d, *J* = 19.2 Hz), 107.0 (t, *J* = 23.9 Hz), 69.8, 54.3.
- IR (nujol) 3232, 1744, 1643, 1529, 1365, 1312, 1251, 1175, 1033, 926 cm^{-1}.
- Anal. Calcd. for $C_{15}H_9BrF_3NO_4S$: C, 41.30; H, 2.08; N, 3.21. Found: C, 41.32; H, 2.09; N, 3.22.

Methyl 4,5,7-trifluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (31c).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,3,4,6-tetrafluoro phenylsulfonamido)-2-phenylacetate **(30c).**	377,31	1	377,3	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



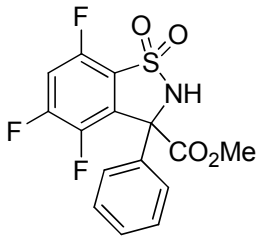
31c, $C_{15}H_{10}F_3NO_4S$
MW: 357,30

160 h, 107,2 mg, 30%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dt, *J* = 6.4, 1.9 Hz), 7.41-7.34 (m, 5H), 5.94 (s, 1H), 3.95 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -125.1 (m, 1F), -127.2 (m, 1F), -149.3 (m, 1F).
- IR (nujol) 3245, 1741, 1634, 1523, 1377, 1321, 1256, 1168, 1043, 911 cm^{-1}..
- Anal. Calcd. for $C_{15}H_{10}F_3NO_4S$: C, 50.42; H, 2.82; N, 3.92. Found: C, 50.44; H, 2.86; N, 3.94.

Methyl 4,5,7-trifluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (31d).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,3,4,6-tetrafluoro phenylsulfonamido)-2-phenylacetate **(30d).**	377,31	1	377,3	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



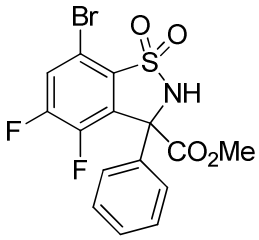
31d, $C_{15}H_{10}F_3NO_4S$
MW: 357,30

20 h, 328,7 mg, 92%;

- white solid; mp 207.5-209.5°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.39 (m, 5H), 7.21-7.14 (m, 1H), 5.95 (s, 1H), 3.95 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.8 (m, 1F), -122.6 (m, 1F), -137.6 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 154.6 (dm, *J* = 247.5 Hz), 151.3 (dm, *J* = 247.5 Hz), 142.1 (dd, *J* = 262.5, 15.0 Hz), 135.8, 129.7, 129.2, 127.2, 126.4, 119,5, 108.9 (t, *J* = 30.0 Hz), 70.2, 54.5.
- IR (nujol) 3241, 1746, 1631, 1521, 1380, 1318, 1254, 1171, 1038, 909 cm^{-1}..
- Anal. Calcd. for $C_{15}H_{10}F_3NO_4S$: C, 50.42; H, 2.82; N, 3.92. Found: C, 50.39; H, 2.82; N, 3.93.

Methyl 7-Bromo-4,5-difluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (31e).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2-Bromo-4,5,6-trifluoro phenylsulfonamido)-2-phenylacetate **(30e).**	438,21	1	438,2	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



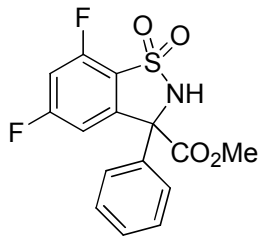
31e, $C_{15}H_{10}BrF_2NO_4S$
MW: 418,21

24 h, 384,7 mg, 92%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.7, 2.9 Hz), 7.38-7.35 (m, 5H), 6.16 (s, 1H), 3.93 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -126.4 (m, 1F), -133.9 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 153.5 (dd, *J* = 259.4, 12.7 Hz), 146.2 (dd, *J* = 261.4, 14.2 Hz), 135.8, 132.0, 129.2, 129.0, 126.4, 125.8, 124.6 (d, *J* = 21.9 Hz), 110.1 (t, *J* = 4.1 Hz), 68.5, 54.4.
- Anal. Calcd. for $C_{15}H_{10}BrF_2NO_4S$: C, 43.08; H, 2.41; N, 3.35. Found: C, 43.09; H, 2.38; N, 3.36.

Methyl 5,7-difluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (31f).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2,4,6-trifluoro phenylsulfonamido)-2-phenylacetate **(30f).**	359,32	1	359,3	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



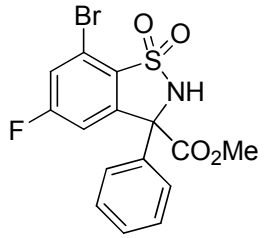
31f, $C_{15}H_{11}F_2NO_4S$
MW: 339,31

30 h, 244,4 mg, 72%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.37 (m, 5H), 7.24 (dd, 1H, *J* = 8.3, 1.9 Hz), 7.00 (dt, 1H, *J* = 8.3, 2.0 Hz), 6.18 (s, 1H), 3.93 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -98.6 (m, 1F), -110.1 (m, 1F).
- IR (nujol) 3246, 1741, 1639, 1518, 1380, 1315, 1261, 1169, 1034, 905 cm^{-1}.
- Anal. Calcd. for $C_{15}H_{11}F_2NO_4S$: C, 53.10; H, 3.27; N, 4.13. Found: C, 53.08; H, 3.25; N, 4.13.

Methyl 7-bromo-5-fluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (31g).

Compound	PM	mmol	mg	mL
(S)-Methyl 2-(2-Bromo-4,6-difluorophenyl sulfonamido)-2-phenylacetate **(30g).**	420,23	1	420,2	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5



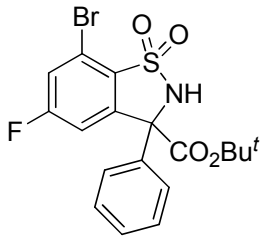
31g, $C_{15}H_{11}BrFNO_4S$
MW: 400,22

24 h, 256,1 mg, 64%;

- white solid; mp 119-120°C.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, 1H, *J* = 7.9, 2.1 Hz), 7.38-7.36 (m, 6H), 6.14 (s, 1H), 3.93 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -102.2 (m, 1F).
- Anal. Calcd. for $C_{15}H_{11}BrFNO_4S$: C, 45.02; H, 2.77; N, 3.50. Found: C, 45.03; H, 2.80; N, 3.52.

***tert*-Butyl 7-bromo-5-trifluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (52).**

Compound	PM	mmol	mg	mL
(R)-*tert*-butyl 2-(2-Bromo-4,6-difluorophenyl phenylsulfonamido)-2-phenylacetate **(50).**	462,31	1	462,3	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5

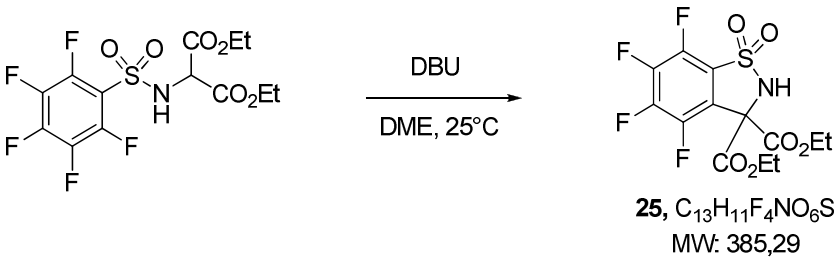


Number, $C_{18}H_{17}BrFNO_4S$
MW: 442,30

24 h, 265,4 mg, 60%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, 1H, *J* = 7.8, 2.2Hz), 7.40-7.34 (m, 6H), 6.25 (s, 1H), 1.50 (s, 9H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -102.6 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 165.0 (d, *J* = 257.3 Hz), 143.5 (d, *J* = 9.5 Hz), 138.7, 132.3, 129.6, 129.5, 126.6, 122.8 (d, *J* = 26.0 Hz), 117.3 (d, *J* = 10.3 Hz), 114.0 (d, *J* = 25.1 Hz), 86.9, 69.9, 28.4.
- Anal. Calcd. for $C_{18}H_{17}BrFNO_4S$: C, 48.88; H, 3.87; N, 3.17. Found: C, 48.85; H, 3.85; N, 3.16.

Diethyl 4,5,6,7-tetrafluoro-2,3-dihydrobenzo[*d*]isothiazole-3,3-dicarboxylate 1,1-dioxide (25).

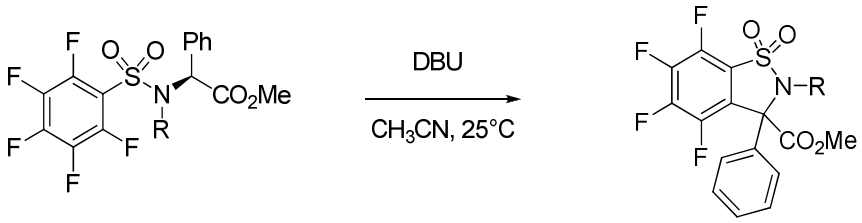


Compound	PM	mmol	mg	mL
Diethyl 2-(2,3,4,5,6-pentafluoro phenylsulfonamido) malonate **(23).**	405,29	1	405,3	
DBU (ϱ = 1,018 g/mL)	152,24	4	609	
DME				5

20 h, 258,1 mg, 67%;

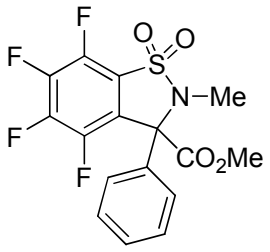
- white solid; mp 87-89°C.
- ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.23 (s, 1H), 4.38 (dq, 4H, *J* = 7.2, 1.9 Hz), 1.33 (t, 6H, *J* = 7.1 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -131.6 (m, 1F), -139.4 (m, 1F), -143.5 (m, 1F), -146.2 (m, 1F).
- ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.2, 144.9 (dt, *J* = 260.7, 14.7 Hz), 144.0 (dd, *J* = 264.2, 9.6 Hz), 142.2 (dt, *J* = 261.5, 14.1 Hz), 141.1 (dd, *J* = 258.6, 12.3 Hz), 120.0 (d, *J* = 17.9 Hz), 117.3 (d, *J* = 14.3 Hz), 67.8, 64.7, 15.0.
- IR (nujol) 3255, 1751, 1635, 1493, 1375, 1323, 1251, 1176, 1036, 918, 838 cm^{-1}.
- Anal. Calcd. for $C_{13}H_{11}F_4NO_6S_2$: C, 40.53; H, 2.88; N, 3.64. Found: C, 40.54; H, 2.87; N, 3.65.

Ring Closing Reactions of *N*-Alkylsulfonamides 7a,b under Homogeneous Conditions: General Procedure.



To a solution of *N*-alkyl-sulfonamide (0.2 mmol) in dry Acetonitrile (0,8 mL) at 25 °C, DBU (1 mmol) in Acetonitrile (0,2 mL) was added and the mixture was stirred at 25 °C until completion (TLC control). The solution was then diluted with AcOEt (10 mL), washed with aqueous 5% citric acid (3×10 mL), saturated $NaHCO_3$ solution (2×10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure (RV) Starting sulfonamides, reaction time, product, yield are as follows.

Methyl 4,5,6,7-tetrafluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4a).



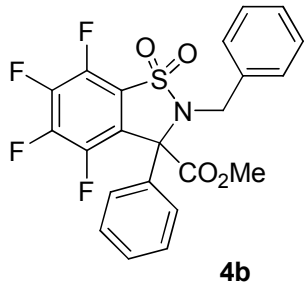
4a

Starting sulfonamide **7a**, 82 mg;

sultam **4a,** 47,4 mg, 61%,

MPLC (AcOEt : hexane – 1 : 12).

Methyl 4,5,6,7-tetrafluoro-2-benzyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4b).



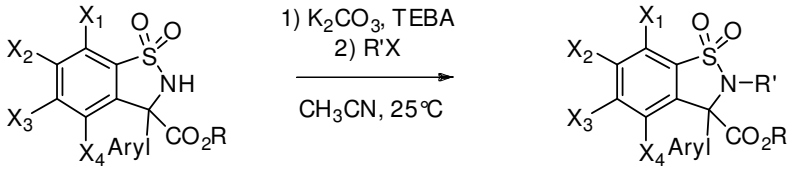
4b

Starting sulfonamide **7b**, 97 mg;

sultam **4b**, 42 mg, 45%,

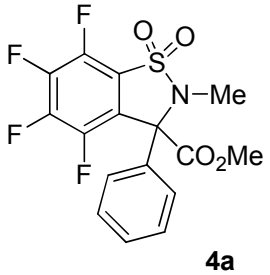
MPLC (AcOEt : esano – 1 : 12).

N-Alkylation of Benzo[*d*]sultams 8a; 31a,b,d-g and 25: General Procedure.



To a solution of sultam (0,25 mmol) and TEBA (5,7 mg, 0,025 mmol) in dry acetonitrile (1 mL) at 25 °C, anhydrous potassium carbonate (51,8 mg, 0,375 mmol) was added. The resulting heterogeneous mixture was stirred for 10 min, then the alkylating agent R'X (0,375 mmol) was added and the reaction was monitored by TLC until completion. The mixture was filtered through a celite pad and, after evaporation of the solvent (RV), the crude was purified by FCC. Starting sulfonamide and alkylating agent (RX), reaction time, product, yield and eluant are as follows.

Methyl 4,5,6,7-tetrafluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carbossilate 1,1-dioxide (4a).



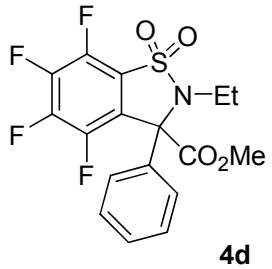
4a

Starting sultam **8a**, 93,8 mg; MeI, 53,2 mg;

sultam **4a**, 142 mg, 91%,

MPLC (AcOEt : hexane – 1 : 12).

Methyl 4,5,6,7-tetrafluoro-2-ethyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4d).



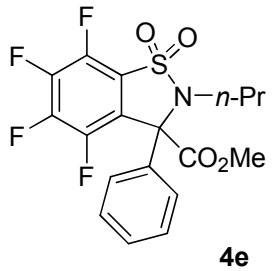
4d

Starting sultam **8a**, 93,8 mg; EtI, 58,5 mg;

sultam **4d**, 87,2 mg, 95%,

MPLC (AcOEt : esano – 1 : 12).

Methyl 4,5,6,7-tetrafluoro-2-*n*-propyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4e).



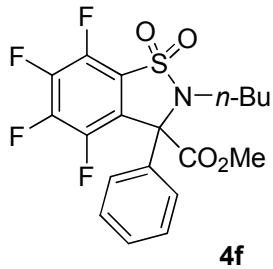
4e

Starting sultam **8a**, 93,8 mg; *n*-PrI, 63,7 mg;

sultam **4e**, 83,9 mg, 88%,

MPLC (AcOEt : esano – 1 : 12).

Methyl 4,5,6,7-tetrafluoro-2-*n*-butyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4f).



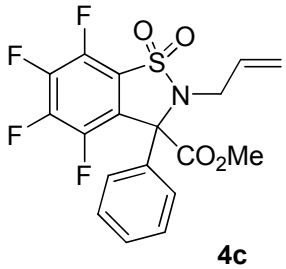
4f

Starting sultam **8a**, 93,8 mg; n-BuI, 69,2 mg;

sultam **4f**, 88,4 mg, 82%,

MPLC (AcOEt : esano – 1 : 12).

Methyl 4,5,6,7-tetrafluoro-2-allyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4c).



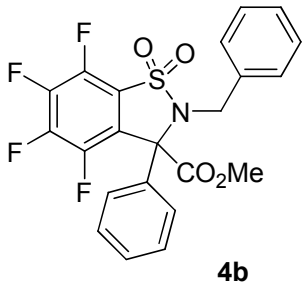
4c

Starting sultam **8a**, 93,8 mg,; AllBr, 45,4 mg;

sultam **4c**, 85,1 mg, 82%,

MPLC (AcOEt : esano – 1 : 9).

Methyl 4,5,6,7-tetrafluoro-2-benzyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4b).



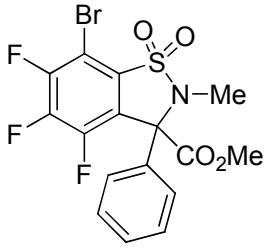
4b

Starting sultam **8a**, 93,8 mg; BnBr, 64,1 mg;

sultam **4b**, 116,3 mg, 80%,

MPLC (AcOEt : esano – 1 : 9).

Methyl 7-bromo-4,5,6-trifluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carbossilate 1,1-dioxide (35a).



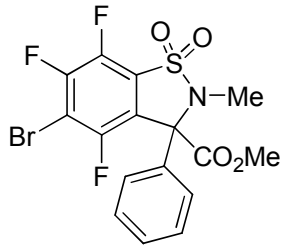
35a

Starting sultam **31a**, 109 mg; MeI, 53,2 mg;

sultam **35a**, 106,2 mg, 94%,

MPLC (AcOEt : hexane – 1 : 9).

Methyl 5-bromo-4,6,7-trifluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carbossilate 1,1-dioxide (36).



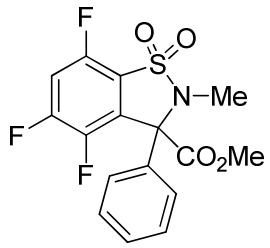
36

Starting sultam **31b**, 109 mg; MeI, 53,2 mg;

sultam 3**6**, 101,3 mg, 90%,

MPLC (AcOEt : hexane – 1 : 9).

Methyl 4,5,7-trifluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carbossilate 1,1-dioxide (32).



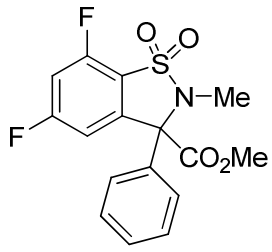
32

Starting sultam **31d**, 89,3 mg; MeI, 53,2 mg;

sultam **32**, 85,4 mg, 92%,

MPLC (AcOEt : hexane – 1 : 9).

Methyl 5,7-difluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carbossilate 1,1-dioxide (33).



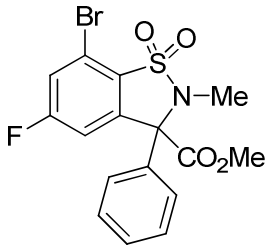
33

Starting sultam **31f**, 93,3 mg; MeI, 53,2 mg;

sultam **33**, 65,4 mg, 74%,

MPLC (AcOEt : hexane – 1 : 12).

Methyl 7-bromo-5-fluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carbossilate 1,1-dioxide (34).



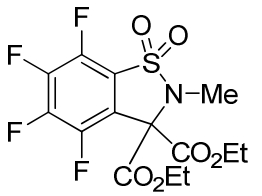
34

Starting sultam **31g**, 84,8 mg; MeI, 53,2 mg;

sultam **34**, 72,4 mg, 82%,

MPLC (AcOEt : hexane – 1 : 12).

Diethyl 4,5,6,7-tetrafluoro-2-methyl-2,3-dihydrobenzo[*d*]isothiazole-3,3-dicarboxylate 1,1-dioxide (24a).



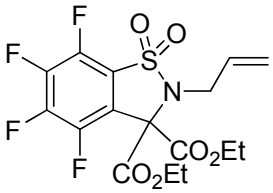
24a, $C_{14}H_{13}F_4NO_6S$
MW: 399,31

Starting sultam **25**, 96,3 mg; MeI, 53,2 mg;

sultam **24a**, 82,8 mg, 86%,

- FCC - AcOEt/hexane (1 : 9).

Diethyl 4,5,6,7-tetrafluoro-2-allyl-2,3-dihydrobenzo[*d*]isothiazole-3,3-dicarboxylate 1,1-dioxide (24b).

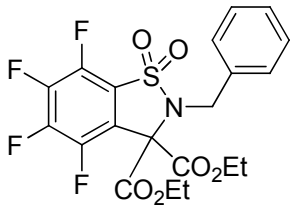


24b, $C_{16}H_{15}F_4NO_6S$
MW: 425,35

Starting sultam **25**, 96,3 mg

- 24 h, 101 mg, 95%;
- FCC - AcOEt/hexane (1 : 9), white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92-5.81 (m, 1H), 5.32 (dd,1H, *J* = 16.9, 1.1 Hz), 5.21 (dd,1H, *J* = 10.3, 1.1 Hz), 4.31-4.23 (m, 6H), 1.29 (t, 6H, *J* = 7.1).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -133.1 (m, 1F), -139.8 (m, 1F), - 144.8 (m, 1F), -147.4 (m, 1F).
- Anal. Calcd. for $C_{16}H_{15}F_4NO_6S$: C, 45.18; H, 3.55; N, 3.29. Found: C, 45.19; H, 3.55; N, 3.27.

Diethyl 4,5,6,7-tetrafluoro-2-benzyl-2,3-dihydrobenzo[*d*]isothiazole-3,3-dicarboxylate 1,1-dioxide (24c).

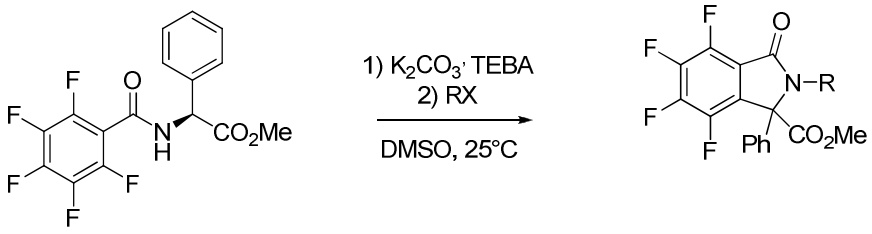


24c, $C_{20}H_{17}F_4NO_6S$
MW: 475,41

Starting sultam **25**, 96,3 mg

- 20 h, 83,2 mg, 70%;
- FCC - AcOEt/hexane (1 : 9), white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.38 (m, 2H), 7.36-7.27 (m, 3H), 4.87 (s, 2H), 4.04-3.91 (m, 4H), 1.45 (t, 6H, *J* = 7.1).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -133.0 (m, 1F), -139.9 (m, 1F), - 144.9 (m, 1F), -147.6 (m, 1F).
- Anal. Calcd. for $C_{16}H_{13}BrFNO_4S$: C, 50.53; H, 3.60; N, 2.95. Found: C, 50.51; H, 3.59; N, 2.94.

SL-PTC 'One-Pot' Synthesis of *N*-Alkyl-benzo[*d*]sultams 48a-c: General Procedure.

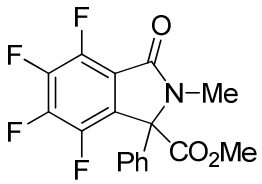


To a solution of sulfonamide and TEBA in dry DMSO at 25 °C, anhydrous potassium carbonate was added. The resulting heterogeneous mixture was stirred for 10 min, then the alkylating agent RX was added and the reaction was monitored by TLC (AcOEt : hexane – 1 : 6) until completion. The mixture was diluted with water and extracted with DCM and concentrated; the residue was diluted with AcOEt (10 mL) and washed with brine (5×10 mL), dried over $MgSO_4$ and filtered. After evaporation of the solvent (RV), the crude was purified by FCC.

Starting alkylating agent (RX), reaction time, product, yield, eluant, physical and analytical data are as follows.

Methyl 4,5,6,7-tetrafluoro-2-methyl-3-oxo-1-phenylisoindoline-1-carboxylate (48a).

Compound	PM	mmol	mg	mL
(*S*)-methyl 2-(perfluorobenzamido)-2-phenylacetate **(47).**	359,27	1	359,3	
Potassium carbonate	138,21	2,5	345,8	
Triethylbenzyl ammonium chloride	227,81	0,2	45,6	
Methyl Iodide	141,94	1,5	291,6	
DMSO				4

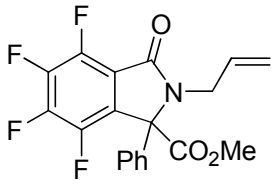


48a, $C_{17}H_{11}F_4NO_3$
MW: 353,27

- 26 h, 279 mg, 79%;
- FCC - AcOEt/hexane (1 : 12), white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.37 (m, 3H), 7.12-7.09 (m, 2H), 3.87 (s, 3H), 2.95 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -138.6 (m, 1F), -143.3 (m, 1F), - 147.9 (m, 1F), -152.1 (m, 1F).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 162.5, 143.4 (dt, *J* = 257.6, 14.6 Hz), 143.1 (dd, *J* = 262.4, 13.1 Hz), 142.5 (dd, *J* = 256.4, 9.1 Hz), 141.4 (dt, *J* = 255.2, 13.9 Hz), 132.7, 129.3, 129.1, 128.9, 127.3 (d, *J* = 12.2 Hz), 126.5, 114.2 (t, *J* = 11.2 Hz), 73.3, 53.3, 26.7.
- IR (nujol) 1742, 1703, 1514, 1429, 1400, 1252, 1094, 1026, 5 746, 693 cm^{-1}.
- Anal. Calcd. for $C_{16}H_{13}BrFNO_4S$: C, 46.39; H, 3.16; N, 3.38. Found: C, 46.38; H, 3.17; N, 3.37.

Methyl 4,5,6,7-tetrafluoro-2-allyl-3-oxo-1-phenylisoindoline-1-carboxylate (48b).

Compound	PM	mmol	mg	mL
(*S*)-methyl 2-(perfluorobenzamido)-2-phenylacetate **(47).**	420,23	0,25	89,8	
Potassium carbonate	138,21	0,5	76,2	
Triethylbenzyl ammonium chloride	227,81	0,05	11,4	
Allyl Bromide	104,03	0,375	40	
DMSO				1

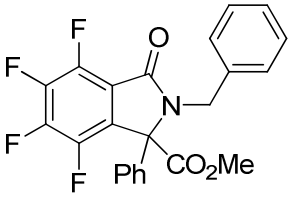


48b, $C_{19}H_{13}F_4NO_3$
MW: 379,31

- 20 h, 53 mg, 56%;
- FCC - AcOEt/hexane (1 : 8), white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.42 (m, 3H), 7.24-7.21 (m, 2H), 5.75-5.65 (m, 1H), 5.08 (s, 1H), 5.03 (d, *J* = 7.5 Hz), 4.28 (dd, *J* = 15.3, 4.5 Hz), 3.92 (dd, *J* = 15.8, 6.3 Hz), 3.86 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -138.4 (m, 1F), -142.9 (m, 1F), - 147.7 (m, 1F), -152.0 (m, 1F).
- IR (nujol) 1747, 1718, 1500, 1435, 1392, 1249, 1095, 1024, 993, 746, 698 cm^{-1}.

Methyl 4,5,6,7-tetrafluoro-2-allyl-3-oxo-1-phenylisoindoline-1-carboxylate (48c).

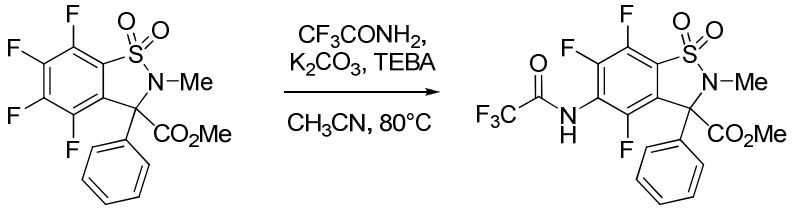
Compound	PM	mmol	mg	mL
(*S*)-methyl 2-(perfluorobenzamido)-2-phenylacetate **(47).**	420,23	0,25	89,8	
Potassium carbonate	138,21	0,5	76,2	
Triethylbenzyl ammonium chloride	227,81	0,05	11,4	
Benyl Bromide		0,375	64,2	
DMSO				



47, $C_{23}H_{15}F_4NO_3$
MW: 429,36

- 20 h, 43,3 mg, 40%;
- FCC - AcOEt/hexane (1 : 9), white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.42 (m, 3H), 7.25-7.22 (m, 5H), 7.15-7.12 (m, 2H), 5.12 (d, *J* = 15.6 Hz), 4.40 (d, *J* = 15.6 Hz), 3.40 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -138.4 (m, 1F), -143.1 (m, 1F), - 147.6 (m, 1F), -151.9 (m, 1F).
- IR (nujol) 1753, 1724, 1513, 1429, 1247, 1022, 993, 727, 697 cm^{-1}.

Methyl 5-(2,2,2-trifluoroacetamido)-4,6,7-trifluoro-2-methyl-3-phenyl-2,3-dihydrobenzo [*d*] isothiazole-3-carboxylate 1,1-dioxide (37).



37, $C_{18}H_{12}F_6N_2O_5S$
MW: 482,35

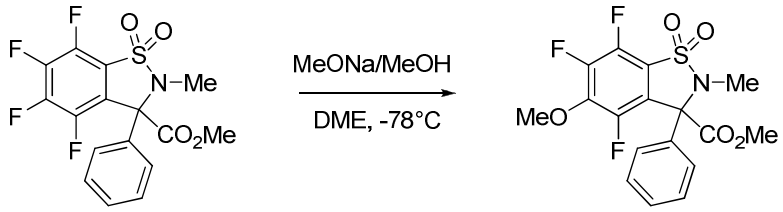
Compound	PM	mmol	mg	mL
Methyl 4,5,6,7-tetrafluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide **(4a).**	389,33	0,3	117	
CF_3CONH_2	113,04	0,3	34	
K_2CO_3	138,21	0,6	83	
Triethyl benzylammonium chloride	227,81	0,03	7	
Acetonitrile				0,3

To a solution of *N*-methyl-sultam in dry acetonitrile the base, TEBA and the trifluoro acetamide were added and the resulting suspension was heated under magnetical stirring monitoring by TLC (AcOEt : hexane – 1 : 5) until completion, then quenched with few drop of a saturate NH_4Cl solution. The solvent was removed under vacuum (RV) and the crude was purified by flash column chromatography.

43 h, 130 mg, 90%;

- FCC - AcOEt/hexane (1 : 7), white solid, mp 191-193 °C
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.37 (m, 3H), 7.34-7.24 (m, 2H), 3.90 (s, 3H), 2.82 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.5 (s, 3F), -117.4 (m, 1F), -131.3 (m, 1F), -141.9 (m, 1F).
- ^{13}C NMR (75 MHz, CDCl3) δ 167.3, 155.7 (t, *J* = 38.6 Hz), 149.3 (d, *J* = 260.0 Hz), 147.2 (dd, *J* = 260.3, 13.1 Hz), 140.9 (dd, *J* = 256.4, 14.1 Hz), 133.3, 130.1, 129.5, 127.9, 122.4 (d, *J* = 17.3 Hz), 121.7 (d, *J* = 11.7 Hz), 119.8 (t, *J* = 16.7 Hz), 115.9 (q, *J* = 285.4 Hz), 72.2, 54.1, 25.7.

Methyl 5-metoxy-4,6,7-trifluoro-2-methyl-3-phenyl-2,3-dihydrobenzo [*d*]isothiazole-3-carboxylate 1,1-dioxide (38).



38, $C_{17}H_{14}F_3NO_5S$
MW: 401,36

Compound	PM	mmol	mg	mL
Methyl 4,5,6,7-tetrafluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide **(4a).**	389,33	0,2	77,8	
MeONa	54,03	0,2	11,1	
DME				0,3
MeOH				0,5

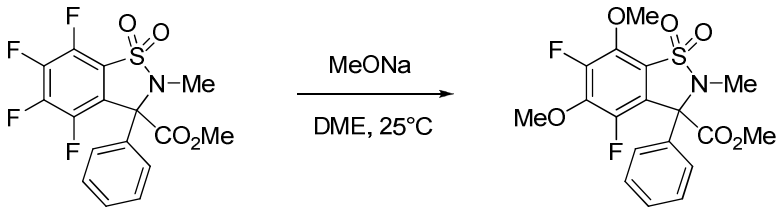
To a solution of *N*-methyl-sultam in dry DME at -78 °C, a solution of MeONa in MeOH was added under magnetical stirring. This mixture was monitored by TLC (AcOEt : hexane – 1 : 7) until completion, then warmed to room temperature and quenched with few drop of a saturate NH_4Cl solution. The solvent was removed under vacuum (RV) to give the crude product without any further purification.

4 h, 60 mg, 75%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 4.04 (t, 3H, *J* = 17.5 Hz), 3.89 (s, 3H), 2.81 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -131.1 (m, 1F), -142.4 (m, 1F), -146.2 (m, 1F).

Methyl 5,7-dialkoxy-4,6-difluoro-2-methyl-3-phenyl-2,3-dihydrobenzo [*d*]isothiazole-3-carboxylate 1,1-dioxide (39a,b).

Methyl 5,7-dimetoxy-4,6-difluoro-2-methyl-3-phenyl-2,3-dihydrobenzo [*d*]isothiazole-3-carboxylate 1,1-dioxide (39a).



39a, $C_{18}H_{17}F_2NO_6S$
MW: 413,39

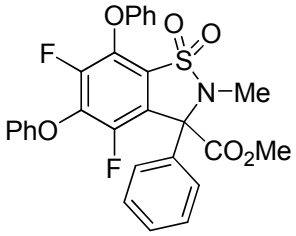
Compound	PM	mmol	mg	mL
Methyl 4,5,6,7-tetrafluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide **(4a).**	389,33	0,2	77,8	
MeONa	54,03	0,4	22,2	
DME				0,5

To a solution of *N*-methyl-sultam in dry DME MeONa was added and the resulting mixture was stirred monitoring by TLC (AcOEt : hexane – 1 : 5) until completion, then quenched with few drop of a saturate NH_4Cl solution. The solvent was removed under vacuum (RV) to give the crude product without any further purification.

20 h, 67,8 mg, 82%;

- white wax.
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 4.16 (s, 3H), 3.98 (s, 3H), 3.87 (s, 3H), 2.80 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -139.0 (m, 1F), -147.5 (m, 1F).

Methyl 5,7-phenoxy-4,6-difluoro-2-methyl-3-phenyl-2,3-dihydrobenzo [*d*]isothiazole-3-carboxylate 1,1-dioxide (39b)

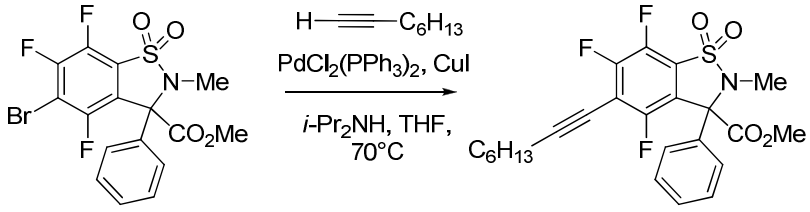


39b, $C_{28}H_{21}F_2NO_6S$
MW: 537,53

24 h, 98,9 mg, 92%;

- white wax
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-6.83 (m, 15H), 3.92 (s, 3H), 2.86 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.2 (m, 1F), -117.1 (m, 1F).

Methyl 5-(oct-1-inyl)-4,6,7-trifluoro-2-methyl-3-phenyl-2,3-dihydrobenzo [*d*]isothiazole-3-carboxylate 1,1-dioxide (40b).



40b, $C_{24}H_{24}F_3NO_4S$
MW: 479,51

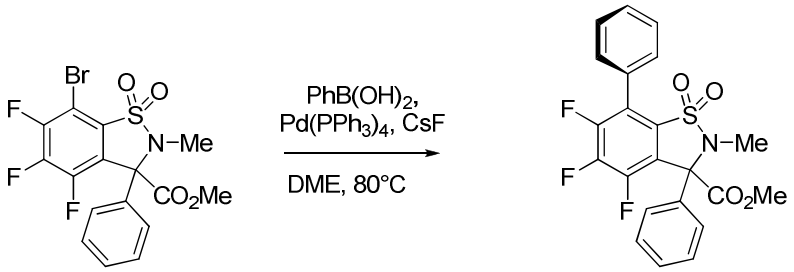
Compound	PM	mmol	mg	mL
Methyl 5-Bromo-4,6,7-trifluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide **(36).**	450,23	0,2	90,1	
1-Octine	110,20	0,3	33,1	
$PdCl_2(PPh_4)_2$	701,90	0,01	7	
CuI	190,45	0,01	2	
Diisopropyl amine				1
THF				1

To a degased solution of the sultam and the amine in dry THF was added the alkyne and the catalyst, was heated under magnetical stirring monitoring by TLC (AcOEt : hexane – 1 : 4) until completion. The mixture is then cooled and filtered through a celite pad then, anidrifyed over $MgSO_4$ and the solvent was removed under vacuum (RV); the crude was purified by flash column chromatography to give the desired compound.

7 h, 39,3 mg, 41%;

- FCC - AcOEt/hexane (1 : 8), yellow wax
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.38 (m, 3H), 7.28-7.25 (m, 2H), 3.89 (s, 3H), 2.82 (s, 3H), 2.44 (t, 2H, *J* = 7.1 Hz), 1.62-1.53 (m, 2H), 1.45-1.41 (m, 2H), 1.39-1.24 (m, 4H), 0.88-0.84 (m, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.4 (m, 1F), -126.5 (m, 1F), -144.5 (m, 1F).

Methyl 7-Phenyl-4,5,6-trifluoro-2-methyl-3-phenyl-2,3-dihydrobenzo [*d*]isothiazole-3-carboxylate 1,1-dioxide (43).



43, $C_{24}H_{17}F_5N_2O_5S$
MW: 540,46

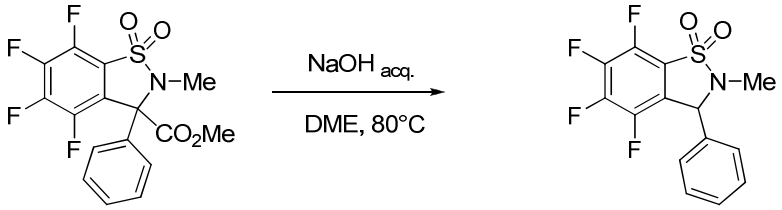
Compound	PM	mmol	mg	mL
Methyl 7-Bromo-4,5,6-trifluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide **(35a).**	436,13	0,2	87,3	
Phenylboronic acid	121,03	0,325	39,3	
$Pd(PPh_3)_4$	1155	0,033	37,5	
CsF	151,9	0,433	65,8	
DME				1,2

A solution of the sultam, the boronic acid and cesium fluoride in dry DME, was degased with Argon and, after adding the catalyst, was heated under magnetical stirring monitoring by TLC (AcOEt : hexane – 1 : 9) until completion. The mixture is then cooled and filtered through a celite pad then, anidrifyed over $MgSO_4$ and the solvent was removed under vacuum (RV); the crude was purified by flash column chromatography to give the desired compound.

6,5 h, 58,8 mg, 68%;

- FCC - AcOEt/hexane (1 : 9), pale yellow wax
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-7.61 (m, 2H), 7.54-7.51 (m, 3H),7.43-7.40 (m, 3H), 7.32-7.29 (m, 2H), 3.93 (s, 3H), 2.80 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -130.9 (m, 1F), -131.7 (m, 1F), -150.3 (m, 1F).
- ^{13}C NMR (75 MHz, CDCl3) δ 167.5, 149.7 (dd, *J* = 254.5, 10.8 Hz), 146.1 (dd, *J* = 260.6, 12.2 Hz), 143.1 (dt, *J* = 258.3, 16.1 Hz), 133.5, 130.1, 129.9, 129.5, 129.0, 128.6, 127.5, 127.1, 123.2 (t, *J* = 16.1 Hz), 70.8, 53.6, 25.4.

4,5,6,7-Tetrafluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (44).



44, $C_{14}H_9F_4NO_2S$
MW: 331,29

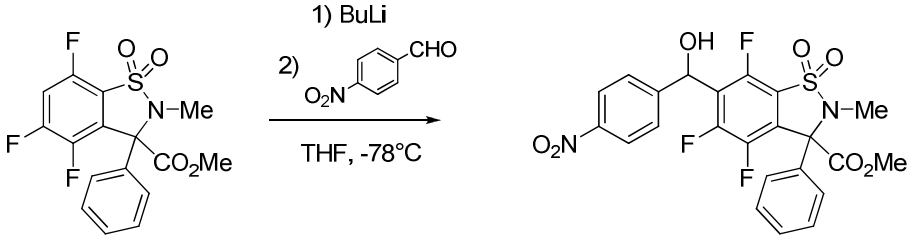
Compound	PM	mmol	mg	mL
Methyl 4,5,6,7-tetrafluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide **(4a).**	389,32	0,3	116,8	
NaOH	40	0,6	24	
H_2O				0,5
DMF				4

A solution of the sultam in aqueous sodium hydroxide-DMF was heated under magnetical stirring monitoring by TLC (AcOEt : hexane – 1 : 9) until completion. The mixture is then cooled and the solvent was removed under vacuum (RV); the crude was purified by flash column chromatography to give the desired compound.

48 h, 50,6 mg, 51%;

- FCC - AcOEt/hexane (1 : 9), white wax
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.39 (m, 3H), 7.37-7.33 (m, 2H), 5.36 (s, 1H), 2.84 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -139.9 (m, 2F), -145.7 (m, 1F), -150.0 (m, 1F).
- IR (nujol) 1635, 1492, 1293, 1249, 1228, 1173, 1076, 977, 914, 881, 690, 630 cm^{-1}.

Methyl 6-(hydroxy(4-nitrophenyl)methyl)-4,5,7-trifluoro-2-methyl-3-phenyl -2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (45).



45, $C_{23}H_{17}F_3N_2O_7S$
MW: 522,45

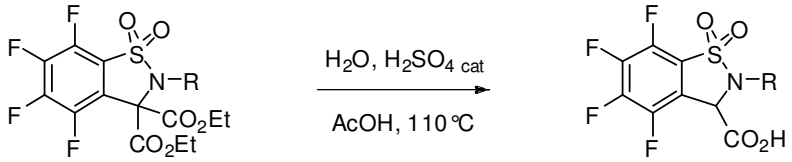
Compound	PM	mmol	mg	mL
Methyl 4,5,7-trifluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide **(32).**	371,34	0,3	112	
Buthyllitium 1M		0,31		0,31
p-nitro benzaldehyde	151,15	0,36	54,7	
THF				3,5

To a solution of the sultam in dry THF, a solution of Buthyllitium in THF was added dropwise under Argon atmosphere at -78°C; the solution, which turns deeply red in color, is stirred for 30' than quenched with the aldheide and let react monitoring the reaction by TLC (AcOEt : hexane – 1 : 3) until completion, than interrupted with NH_4Cl_{acq} and warmed to room temperature; Extraction with Ethyl acetate, anidrification over $MgSO_4$ and remotion of the solvent under vacuum (RV) furnishes the crude, which was purified by flash column chromatography to give the desired compound.

4 h, 72,9 mg, 47%;

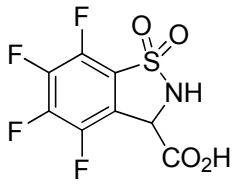
- FCC - AcOEt/hexane (1 : 3), white wax
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22-8.18 (m, 2H), 7.64-7.61 (m, 2H), 7.41-7.38 (m, 3H), 7.25-7.21 (m, 2H), 6.38 (s 1H), 3.89 (s, 3H), 3.64 (br 1H), 2.81 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -121.4 (m, 1F), -126.3 (m, 1F), -137.7 (m, 1F).

Decarboxylation of 4,5,6,7-Tetrafluoro-2-alkyl-2,3-dihydrobenzo[*d*]iso thiazole-3,3-dicarboxylate 1,1-dioxide (25 and 24a-c): General Procedure.



The sultam (0,2 mmol) si dissolved in a mixture of AcOH-H_2O (0,9 mL, 2 : 1) then H_2SO_4 was added and the solution was heated until completion, monitoring the reaction by TLC (AcOEt : hexane – 1 : 3), The mixture is then cooled, to pH4 by addition of solid $NaHCO_3$ then extracted with ethyl acetate; anidrification over $MgSO_4$ and remotion of the solvent under vacuum (RV) furnishes the pure product, without any further purification. Starting sulfonamide, reaction time, product and yield are as follows.

4,5,6,7-tetrafluoro-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (26a)

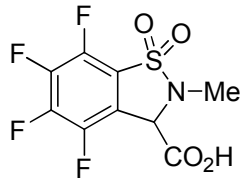


26a, $C_8H_3F_4NO_4S$
MW: 285,17

3 h, 54,2 mg, 95%;

- white wax
- ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 7.25 (br, 2H), 5.61 (s, 1H).
- ^{19}F NMR (282 MHz, $(CD_3)_2CO$) δ -137.6 (m, 1F), -143.3 (m, 1F), -147.8 (m, 1F), -151.3 (m, 1F).
- IR (nujol) 3206, 1739, 1617, 1511, 1457, 1292, 1243, 1177, 1125, 1066, 1037, 911, 841 cm^{-1}.

4,5,6,7-tetrafluoro-2-methyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (26b)

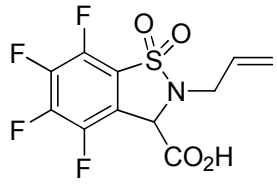


26b, $C_9H_5F_4NO_4S$
MW: 299,20

18 h, 47,3 mg, 79%;

- white wax
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (br, 1H), 5.03 (s, 1H), 3.05 (s, 3H).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -138.1 (m, 1F), -139.0 (m, 1F), -144.7 (m, 1F), -147.8 (m, 1F).
- IR (nujol) 3151, 1741, 1615, 1514, 1456, 1295, 1244, 1176, 1129, 1059, 1028, 911, 844 cm^{-1}.

4,5,6,7-tetrafluoro-2-allyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (26c)

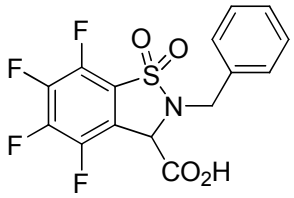


26c, $C_{11}H_7F_4NO_4S$
MW: 325,24

50 h, 55,3 mg, 85%;

- white wax
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (br, 1H), 5.90-5.77 (m, 1H), 5.42 (d, 1H, *J* = 11.7 Hz), 5.38 (d, 1H, *J* = 4.7 Hz), 5.16 (s, 1H), 4.20.(dd, 1H, *J* = 15.1, 5.1 Hz), 3.91.(dd, 1H, *J* = 15.1, 8.3 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -137.7 (m, 1F), -138.9 (m, 1F), -144.7 (m, 1F), -147.8 (m, 1F).
- IR (nujol) 3148, 1744, 1613, 1514, 1457, 1291, 1246, 1174, 1126, 1061, 1032, 914, 846 cm^{-1}.

4,5,6,7-tetrafluoro-2-benzyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (26d)

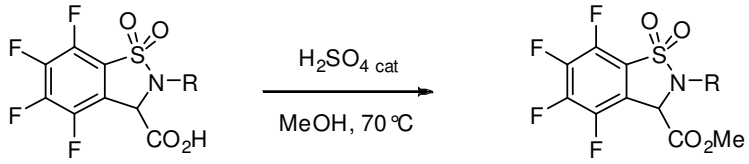


26d, $C_{15}H_9F_4NO_4S$
MW: 375,29

72 h, Propionic acid used instead of acetic acid 62,3 mg, 83%;

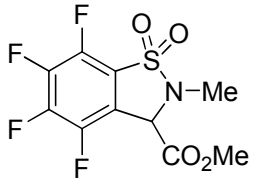
- white wax
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (br, 1H), 5.90-5.77 (m, 1H), 5.42 (d, 1H, *J* = 11.7 Hz), 5.38 (d, 1H, *J* = 4.7 Hz), 5.16 (s, 1H), 4.20.(dd, 1H, *J* = 15.1, 5.1 Hz), 3.91.(dd, 1H, *J* = 15.1, 8.3 Hz).
- ^{19}F NMR (282 MHz, $CDCl_3$) δ -137.7 (m, 1F), -138.9 (m, 1F), -144.7 (m, 1F), -147.8 (m, 1F).

Esterification of 4,5,6,7-Tetrafluoro-2-alkyl-2,3-dihydrobenzo [*d*]isothiazole-3-carboxylate 1,1-dioxide (26a-d): General Procedure.



The sultam (0,2 mmol) si dissolved in a mixture of AcOH-H_2O (0,9 mL, 2 : 1) then H_2SO_4 was added and the solution was heated until completion, monitoring the reaction by TLC (AcOEt : hexane – 1 : 3), The mixture is then cooled, to pH4 by addition of solid $NaHCO_3$ then extracted with ethyl acetate; anidrification over $MgSO_4$ and remotion of the solvent under vacuum (RV) furnishes the pure product, without any further purification. Starting sulfonamide, reaction time, product and yield are as follows.

Methyl 4,5,6,7-tetrafluoro-2-methyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (27b).

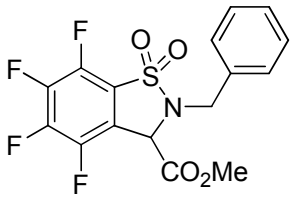


27b, $C_{10}H_7F_4NO_4S$
MW: 313,23

20 h, 58,3 mg, 93%;

- FCC - AcOEt/hexane (1 : 7), white wax
- ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 5.03 (s, 1H), 3.85 (s, 3H), 3.02 (s, 3H).
- ^{19}F NMR (282 MHz, $(CD_3)_2CO$) δ -138.9 (m, 1F), -139.5 (m, 1F), -145.3 (m, 1F), -148.4 (m, 1F).
- ^{13}C NMR (75 MHz, CDCl3) δ 166.0, 144.6 (dt, *J* = 261.3, 14.4 Hz), 143.3 (dd, *J* = 258.2, 11.9 Hz), 142.3 (dm, *J* = 261.2 Hz), 142.0 (dd, *J* = 260.1, 12.8 Hz), 119.7 (d, *J* = 19.3 Hz), 116.4 (d, *J* = 17.0 Hz), 61.2, 54.3, 30.0.
- Anal. Calcd. for $C_{10}H_7F_4NO_4S$: C, 38.35; H, 2.25; N, 4.47. Found: C, 38.37; H, 2.28; N, 4.48.

Methyl 4,5,6,7-tetrafluoro-2-benzyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (27c).

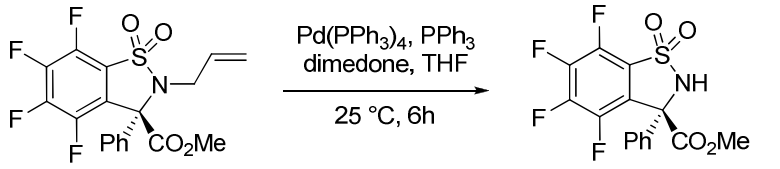


27c, $C_{16}H_{11}F_4NO_4S$
MW: 389,32

44 h, 58,4 mg, 75%;

- FCC - AcOEt/hexane (1 : 4), white wax
- ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.33 (m, 5H), 4.91 (s, 1H), 4.74 (d, *J* = 14.8 Hz), 4.42 (d, *J* = 14.8 Hz), 3.70 (s, 3H).
- ^{19}F NMR (282 MHz, $(CD_3)_2CO$) δ -138.7 (m, 1F), -139.0 (m, 1F), -145.2 (m, 1F), -148.3 (m, 1F).
- ^{13}C NMR (50 MHz, CDCl3) δ 165.8, 144.1 (dt, *J* = 262.2, 16.1 Hz), 142.9 (dd, *J* = 258.6, 13.9 Hz), 142.0 (dm, *J* = 261.0 Hz), 141.6 (dm, *J* = 259.9 Hz), 133.1, 119.4, 116.2, 57.4, 53.6, 46.6.
- Anal. Calcd. for $C_{16}H_{11}F_4NO_4S$: C, 49.36; H, 2.85; N, 3.60. Found: C, 49.32; H, 2.83; N, 3.57.

Deprotection of 4,5,6,7-Tetrafluoro-2-allyl-3-phenyl-2,3-dihydrobenzo [*d*]isothiazole 1,1-dioxide ((-)-4c).



(-)-4c **(-)-8a,** $C_{15}H_9F_4NO_4S$ MW: 375,29

Compound	PM	mmol	mg	mL
Methyl 4,5,6,7-tetrafluoro-2-allyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide **((-)-4a).**	415,36	0,2	83,1	
$Pd(PPh_3)_4$	1155	0,01	11,6	
Dimedone	140,18	0,24	33,6	
THF				1

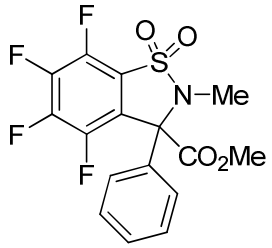
A solution of the sultam, triphenylphosphine and dimedone in dry THF, was degased with Argon and, after adding the catalyst, was magnetical stirred monitoring by TLC (AcOEt : hexane – 1 : 4) until completion. The mixture is then cooled and the solvent was removed under vacuum (RV); the crude was purified by flash column chromatography to give the desired compound.

5 h, 73,6 mg, 98%;

- FCC - AcOEt/hexane (1 : 5)

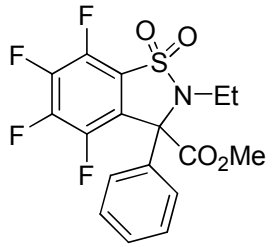
Enantiomeric excess HPLC determination: Analytical Methods.

Methyl 4,5,6,7-tetrafluoro-2-methyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carbossilate 1,1-dioxide (4a).



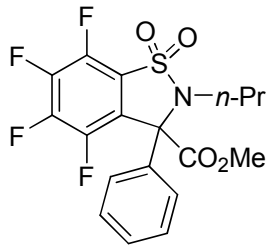
4a, CHIRALCEL OD ®, Hexane – Isopropanol 8 : 2,
Flow rate 1 mL/min, P= 15 bar, t_1 = 5.4 min, t_2 = 6.7 min.

Methyl 4,5,6,7-tetrafluoro-2-ethyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4d).



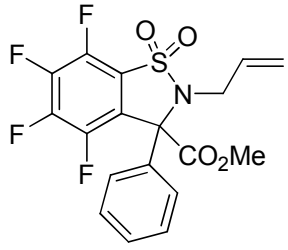
4d, CHIRALCEL OD ®, Hexane – Isopropanol 8 : 2,
Flow rate 1 mL/min, P= 15 bar, t_1 = 4.9 min, t_2 = 6.3 min.

Methyl 4,5,6,7-tetrafluoro-2-*n*-propyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4e).



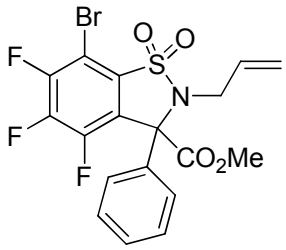
4e, CHIRALCEL OD ®, Hexane – Isopropanol 9 : 1,
Flow rate 0.6 mL/min, P= 7 bar, t_1 = 8.7 min, t_2 = 10.6 min.

Methyl 4,5,6,7-tetrafluoro-2-allyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4c).



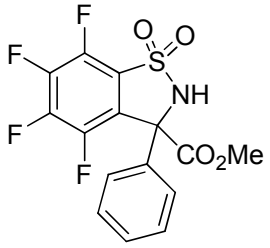
4e, CHIRALCEL OD ®, Hexane – Isopropanol 9 : 1,
Flow rate 0.7 mL/min, P= 8 bar, t_1 = 8.3 min, t_2 = 9.5 min.

Methyl 7-bromo-4,5,6-trifluoro-2-allyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (4c).



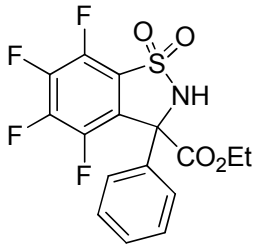
4e, CHIRALCEL OD ®, Hexane – Isopropanol 9 : 1, Flow rate 0.7 mL/min, P= 8 bar, t_1 = 10.2 min, t_2 = 13.2 min.

Methyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (8a).



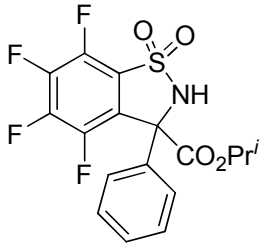
8a, CHIRALCEL OD ®, Hexane – Isopropanol 8 : 2 + 0,2% TFA, Flow rate 0.7 mL/min, P= 10 bar, t_1 = 9.9 min, t_2 = 10.7 min.

Ethyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (8b).



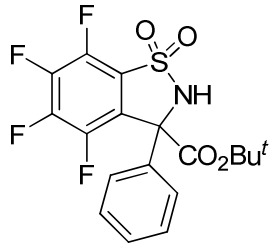
8b, CHIRALCEL OD ®, Hexane – Isopropanol 9 : 1 + 0,2% TFA, Flow rate 1 mL/min, P= 13 bar, t_1 = 8.9 min, t_2 = 10.0 min.

***iso*-Propyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (8c).**



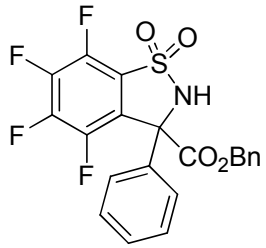
8c, CHIRALCEL OD ®, Hexane – Isopropanol 9 : 1 + 0,2% TFA, Flow rate 1 mL/min, P= 13 bar, t_1 = 7.1 min, t_2 = 9.5 min.

***tert*-Butyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (8d).**



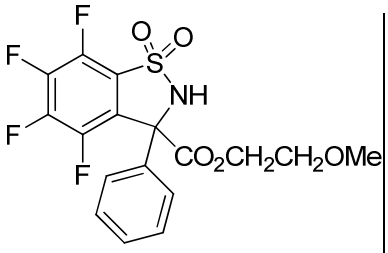
8d, CHIRALCEL OD ®, Hexane – Isopropanol 9 : 1
+ 0,2% TFA,
Flow rate 1 mL/min, P= 13 bar, t_1 = 6.2 min, t_2 = 7.0 min.

Benzyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (8e).



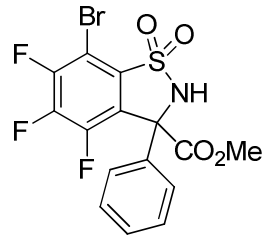
8e, CHIRALCEL OD ®, Hexane – Isopropanol 8 : 2
+ 0,2% TFA,
Flow rate 0.6 mL/min, P= 8 bar, t_1 = 14.5 min, t_2 = 15.4 min.

Methoxyethyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (8f).



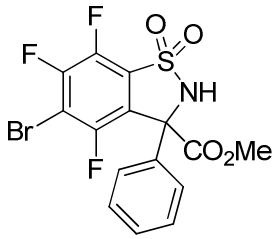
8f, CHIRALCEL OD ®, Hexane – Isopropanol 8 : 2
+ 0,2% TFA,
Flow rate 0.8 mL/min, P= 11 bar, t_1 = 9.4 min, t_2 = 10.9 min.

Methyl 7-Bromo-4,5,6-trifluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (31a).



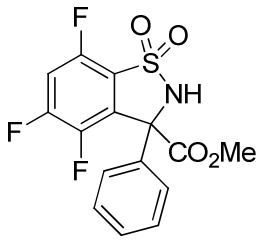
31a, CHIRALCEL OD ®, Hexane – Isopropanol 8 : 2
+ 0,2% TFA,
Flow rate 1 mL/min, P= 14 bar, t_1 = 8.2 min, t_2 = .10.6 min

Methyl 5-bromo-4, 6,7-trifluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (31b).



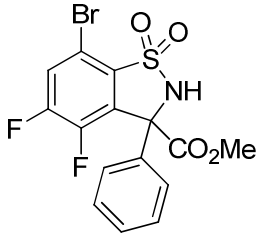
31b, CHIRALCEL OD ®, Hexane – Isopropanol 12 : 1 + 0,2% TFA,
Flow rate 1 mL/min, P= 12 bar, t_1 = 13.0 min, t_2 = 14.0 min.

Methyl 5,4,7-trifluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (31d).



31d, CHIRALCEL OD ®, Hexane – Isopropanol 9 : 1 + 0,2% TFA,
Flow rate 1 mL/min, P= 8 bar, t_1 = 14.0 min, t_2 = 15.5 min.

Methyl 7-bromo-4,5-difluoro-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-3-carboxylate 1,1-dioxide (31e).



31e, CHIRALCEL OD ®, Hexane – Isopropanol 8 : 2 + 0,2% TFA,
Flow rate 1 mL/min, P= 13 bar, t_1 = 10.0 min, t_2 = 11.8 min.

5 BIBLIOGRAPHY

[1]See for example http://nobelprize.org/nobel_prizes/medicine/laureates/1939/press.html

[2] Dogmagk, G.; Einbeitrag zur chemotherapie der bakterielle infectionen. *Dtsch Med Wchschr,* **1935**; *61*; 250.

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