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Brown Allylation: Application to the Synthesis of Natural Products

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Dedicated to Professor Franco Cozzi on the occasion of his 70th birthday.

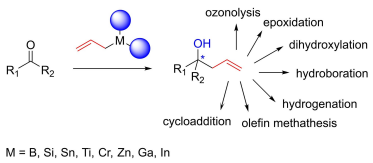
Asymmetric allylation represents an important reaction applied in the natural product synthesis. The stereoselective introduction of an allyl group allows to obtain versatile chiral building blocks, which may further undergo various transformations due to the presence of the carbon–carbon double bond. In this review, we address the Brown allylation, which involves the conversion of aldehydes into homoallylic alcohols using B-allyldiisopinocampheylborane as a chiral reagent. We provide a comprehensive overview of the reaction and highlight its application in the synthesis of natural products, while assessing its performance in comparison to other approaches. The total of 17 syntheses have been described, including the synthesis of biologically active macrolides disciformycin B, biselyngbyolide B, peloruside A, and gliomasolide A, bis-piperidine alkaloid (−)-anaferine and dysoxylactam A.

Introduction

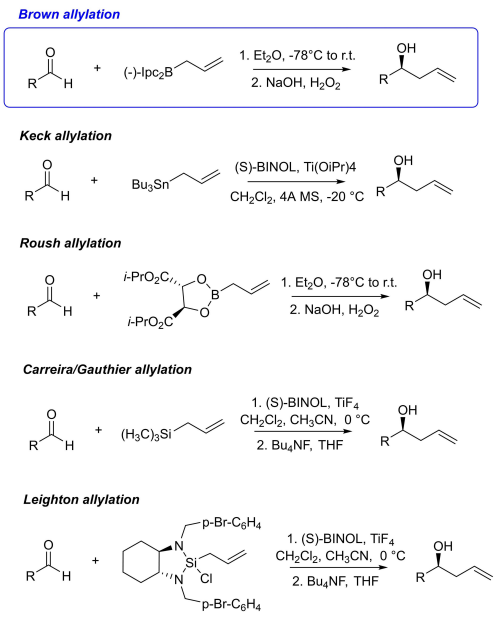
Natural products are known for their structural complexity and abundant stereochemistry, which is often crucial for their biological activity.[1,2] This makes stereoselective synthetic methods, such as asymmetric allylation, of great interest to natural product synthesis.[3] The asymmetric allylation is of prime importance due to a number of reasons. First, introduction of the allylic moiety to carbonyl compounds or imines leads not only to the formation of a new functionality (respectively hydroxyl or amino group), but also adds a carbon–carbon double bond. The latter can then undergo various transformations, such as cycloaddition, olefin metathesis, ozonolysis, dihydroxylation, epoxidation, hydroboration, hydrogenation, hydroformylation, hydration, etc., producing versatile synthetic intermediates. Particularly valuable building blocks can be obtained if the allylation is performed in a stereoselective fashion[4] (Scheme 1).

As a result, many researchers aimed to optimize the reaction throughout the years, particularly in terms of stereocontrol. While several stoichiometric and catalytic approaches have been developed, the use of chiral organometallic reagents in stoichiometric amounts is one of the most exploited in the synthesis of natural products and other complex organic molecules. The reaction succeeds with a wide variety of metals (B, Si, Sn, Ti, Cr, Zn, Ga, In), therefore many different allyl metal reagents are available for carrying out diastereo- and enantioselective allylations.[5,6]

Some of the most notable are the ones of Brown, Keck, Carreira/Gauthier, Roush, and Leighton (Scheme 2).[7–11] The substrates utilized in the asymmetric allylations may be



Scheme 1. Asymmetric allylation using chiral organometallic reagents.



Scheme 2. Common asymmetric allylations.

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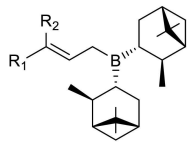
aldehydes, ketones or imines, with aldehydes certainly being the most commonly described.[4,12–18]

As Brown allylation is one of the most applied procedures and has been also the one utilized by our research group, it has served as an inspiration for this review.[19,20] Here, we provide the comprehensive overview of the reaction conditions and mechanism and emphasize the application of Brown allylation in natural product chemistry. Moreover, the relevant data regarding Brown crotylation have been included. The application examples gathered here cover the most pertinent contributions of the 2004–2020 period.

Brown allylation and crotylation

Starting from 1960s, the reaction of 'allyl' boranes with carbonyl compounds has been extensively studied over the years.[21,22] One of the important breakthroughs was the development of pinane-derived borane reagent by Herbert C. Brown, which provided a highly efficient way to perform allylboration (Figure 1). Brown's reagent, the chiral B-allyldiisopinocampheylborane, $(Ipc)_2$B-allyl, was reported to react with various aldehydes to furnish the corresponding homoallylic alcohol in good yields and high enantiomeric excess.[23,24] It is worth noting that Herbert C. Brown received the Nobel Prize in Chemistry for his work with organoboranes in 1979.

According to Denmark classification of allylations, based on their stereochemical outcome, Brown allylation belongs to type I, where the metal activates the carbonyl of the aldehyde to form a closed six-membered chair-like transition state (Zimmerman-Traxler, Scheme 4). Due to the rigid six-membered transition state observed with boron, steric interactions between the axial Ipc ligands and the allyl group are minimized, leading to an excellent stereocontrol, superior to many other 'allyl' metalations. On the contrary, in type II allylation, the allylmetal derivative reacts with the aldehyde through an open transition state (e.g. Keck allylation).[5]



Brown's reagent

Figure 1. Brown's reagent, (−)-Ipc2BX.

For what concerns the reaction conditions, the standard allylation procedure comprises a slow addition of $(Ipc)_2$B-allyl to the aldehyde of interest, commonly solubilized in Et_2O or THF, at −78 °C. Reaction temperature has a crucial effect on the enantioselectivity. It was observed that the latter increases along with temperature reduction from 0 °C to −78 °C, however cooling from −78 °C to −100 °C did not produce any further improvements. As a result, −78 °C is considered the usual temperature of work.[25] In practice, lower temperatures are also applied quite frequently, as demonstrated by some examples further. Colder temperature may be particularly helpful in larger scale reactions, ensuring that the internal temperature is as cold as possible. Although solvents do not affect the reaction significantly, Et_2O and THF have shown to be the optimal ones in terms of reactivity, as well as enantioselectivity. While the preparation of the Brown reagent from α-pinene or borane-methyl sulfide (BMS) can be considered experimentally simple, due to its sensitivity it is generally more convenient to prepare $(Ipc)_2$B-allyl *in situ* without prior isolation.[7,26] $(Ipc)_2$B-allyl can be prepared from chlorodiisopinocampheylborane, $(Ipc)_2$B–Cl, or diisopinocampheyl(methoxy)borane, $(Ipc)_2$B-OMe, and allylmagnesium bromide. Mg^{2+} salts formed during this reaction constitute another important factor. It is postulated that MgBr(OMe) creates a complex with the boron atom, inhibiting the rate of the reaction.[24] Therefore, a better reaction rate can be achieved in the absence of Mg^{2+}, which must be removed by filtration prior to the addition of Brown's reagent to the

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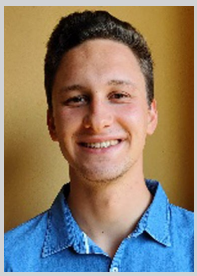
Zlata Boiarska obtained her MSc in Pharmacy from the Jagiellonian University, Poland. Currently she is pursuing a PhD in Chemistry at the University of Milan, Italy, within the European Joint Doctorate "TubInTrain". Her work is focused on the organic synthesis of biologically active small molecules and molecular probes.



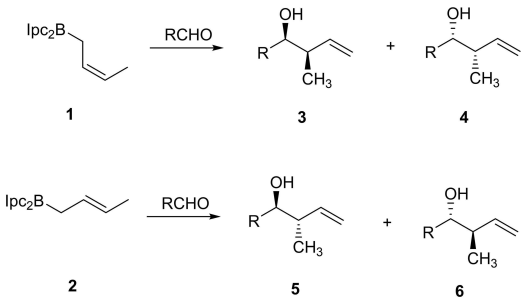
Tommaso Braga, born in 1998, obtained his Bachelor degree in Chemistry at the University of Milan in 2020. In his Bachelor thesis he focused on the Brown and Keck asymmetric allylation reactions. He is currently pursuing his Master in Chemistry at the same University.

electrophile. After the reaction is complete, an alkaline oxidative work-up is needed to finally obtain the desired alcohol.

Apart from the allylation, Brown's reagent can be also used to perform crotylations.[27] $(Ipc)_2B$-(*Z*)-crotyl (**1**) or $(Ipc)_2B$-(*E*)-crotyl (**2**) is made, allowing to obtain β-methylhomoallyl alcohol. As a result, both diastereoselectivity (**3** + **4** vs **5** + **6**) and absolute stereochemical control for a given enantioselectivity (**3** vs **4** or **5** vs **6**) have to be considered (Scheme 3).

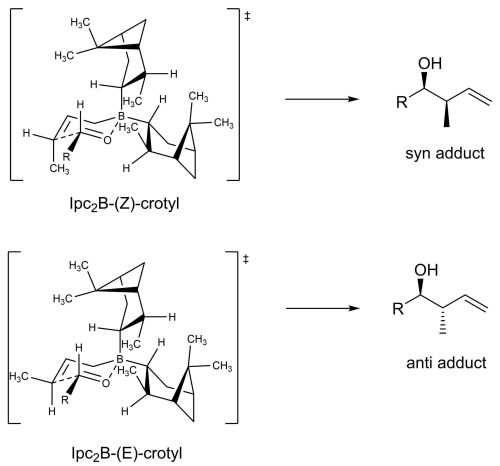
The configuration of the product depends on (*Z*)- or (*E*)-configuration of the crotyl group, which may preferentially furnish *syn* or *anti* adduct, respectively (Scheme 4).[20]

The conditions of the Brown crotylation are similar to those of the allylation. However, in case of crotylation, it is even more important to prepare the $(Ipc)_2B$-crotyl reagents *in situ*, as they



pinene	R	3:4	e.e.	5:6	e.e.
+	CH_3	95:5	90	95:5	90
-	CH_3	4:96	92	4:96	92
+	Ph	94:6	88	94:6	88
+	CH_2=CH	95:5	90	95:5	90

Scheme 3. Brown's crotylation.



Scheme 4. Brown's crotylation transition states.

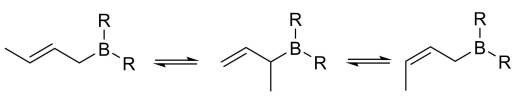


Figure 2. Borotropic rearrangement.

can easily isomerize during storage via borotropic rearrangement (Figure 2). It interferes with the double bond geometry of the reagent, dealing with E/Z stereoisomerism, and consequently leads to the formation of mixtures of products. The rate of isomerization depends greatly on the nature of the other groups on the boron: allyldialkylborane > allylalkylborinate > allylboronate.[29,30]

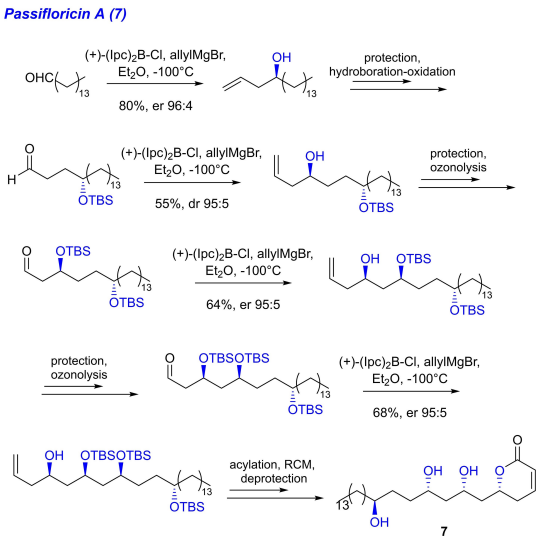
Applications in natural product synthesis

Both Brown's asymmetric allylation and crotylation have been widely applied in the synthesis of natural products, furnishing secondary alcohols as key intermediates in generally good yields and high enantiomeric excess.

In this minireview we have gathered the most prominent examples of Brown's reaction in natural product synthesis, covering the 2004–2020 period. Natural products have been classified by their origin and described in chronological order of publication.

Plant natural products

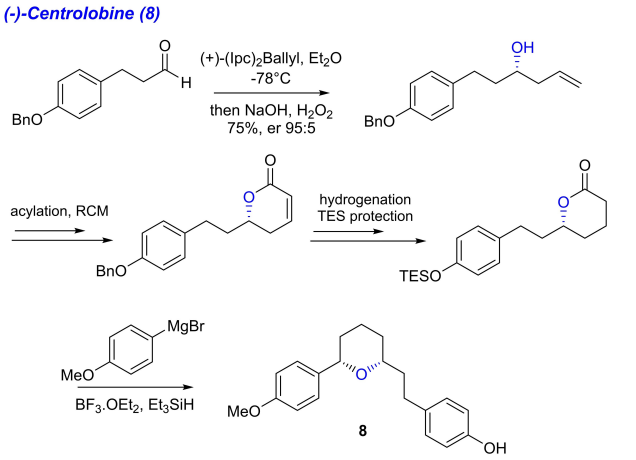
Passifloricin A (7) is a polyketide-type α-pyrone, isolated by Echeverri *et al.* from the resin of *Passiflora foetida* var. *hispida*, a species from the *Passifloraceae* family that grows in tropical zones of America.[31] The compound was found to exert antiprotozoal and antifungal properties.[32] Later, Murga *et al.*, aimed to establish the absolute configuration of the natural product, synthesized several isomers of the compound. Importantly, the synthetic concept relied on Brown's asymmetric allylations as the method to create the 1,3-polyol system with its four stereocenters of each isomer, whereas the lactone moiety was made by means of ring-closing metathesis, (Scheme 5).



Scheme 5. Brown's allylation in the synthesis of passifloricin A.

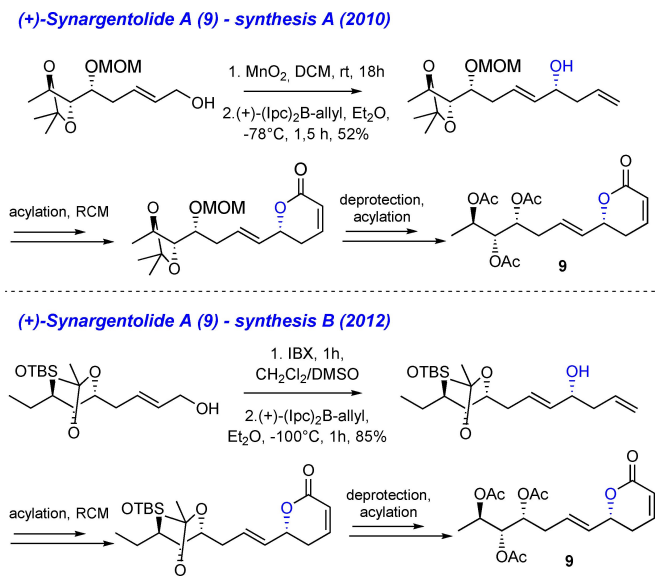
Brown allylations were performed sequentially in the same way: the aldehyde reacted with $(Ipc)_2$B-allyl prepared *in situ* from (+)-$(Ipc)_2$B-Cl and allylmagnesium bromide, after which the the product underwent hydroxyl group protection, hydroboration and Swern oxidation, to be once again subjected to the same allylation conditions, followed by two sequences of silylation and ozonolysis-allylation. All allylations were performed at −100 °C, using Et_2O as a solvent and gave the desired products in high diastereomeric ratio (96:4 for the first one 95:3 for the following 3 reactions) To furnish the other isomers, same conditions using (−)-$(Ipc)_2$B-Cl were applied. The correct structure of passifloricin A was confirmed by NMR.[33]

(−)-Centrolobine (8) is a naturally occurring β-C-glycoside with anti-Leishmanial activity, isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinum potabile* found in Amazon forests. Its structure contains two stereogenic centers, the asymmetric attainment of which included Brown allylation and stereoselective Et_3SiH reduction in the first and in the last step, respectively. By means of Brown allylation, the chiral benzyl protected homoallylic alcohol, obtained from the aldehyde precursor, was achieved in 75% yield with an e.e. of 94%. Similarly to passifloricin A synthetic strategy, it was followed by acylation with acryloyl chloride and subsequent RCM, furnishing a lactone moiety. An interesting nucleophilic addition/reduction sequence was applied after to obtain (−)-Centrolobine (Scheme 6).[34]



Scheme 6. Brown's allylation in the synthesis of (−)-centrolobine.

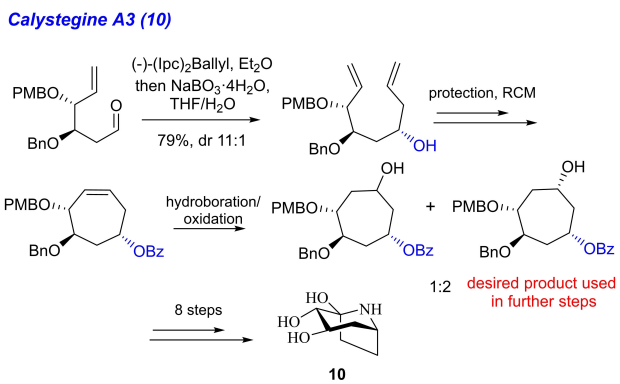
(+)-Synargentolide A (9) is a polyhydroxylated δ-lactone isolated from *Syncolostemon argenteus* extract, found in the South African midlands.[35] This natural product exhibits antitumor, antifungal and antimicrobial activity.[36] Two independent asymmetric syntheses have reported the use of Brown allylation to furnish the configuration of lactone carbon stereocenter (Scheme 7, synthesis A and B respectively). The Brown allylation-RCM sequence has been used in the final steps of both synthetic strategies.[37,38]



Scheme 7. Brown's allylation in the synthesis of (+)-synargentolide A.

Calystegine A3 (10) is a polyhydroxylated nortropane first isolated from *Calystegia sepium* in 1988.[39] It shows significant inhibition of glycoside hydrolases, in particular β-glucosidase and both α- and β-galactosidases. From the chemical point, the common feature of *Calystegine* family is the great number of hydroxyl groups present on the bicyclic ring system.[40] Calystegine A3 has been successfully synthesised in 17 steps from 2-deoxy-D-glucose, using Brown allylation to obtain the desired alcohol intermediate. The reaction proceeded with good diastereocontrol (11:1) in 79% yield (Scheme 8). It is also worth noting that Brown allylation in this case was superior to diastereoselective addition of allyltin reagents and Keck allylation, which were attempted previously in the synthesis, but didn't lead to the desired product.[41]

(+)-Broussonetine H (11) belongs to the family of polyhydroxy alkaloids, isolated from the mulberry tree *Broussonetia kazinoki*. It is a potent and selective inhibitor of β-glycosidases.[42] Broussonetines commonly feature a polyhydroxylated pyrrolidine adjoined to a 13-carbon side chain. In the case of (+)-broussonetine H, 1'-hydroxyl group of pyrrolidine was made in a stereodivergent fashion via Brown allylation (Scheme 9). Different reaction conditions were investigated in order to optimize yields and stereochemical control, reaching



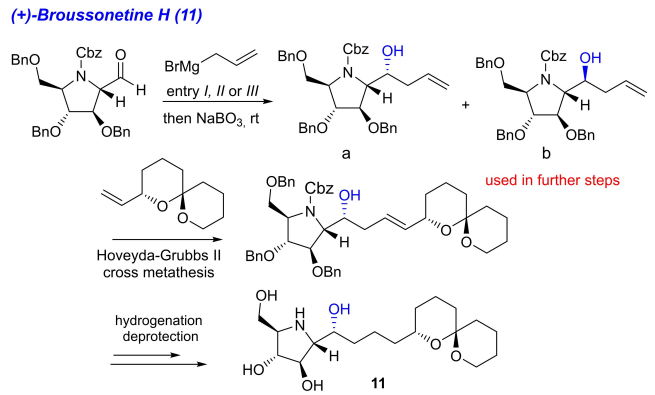
Scheme 8. Brown's allylation in the synthesis of calystegine A3.

15:1 ratio and 83% yield when applying (+)-$(Ipc)_2$B-Cl at −100 °C in Et_2O as the solvent (Table 1). Interestingly, the pyrrolidine fragment obtained within Brown allylation was then subjected to cross metathesis with enantiomeric spiroketal to obtain the intriguing structure of (+)-Broussonetine H.[43]

Paecilomycin C (12) is a β-resorcylic acid lactone, isolated recently from the solid mycelial culture of *Paecilomyces sp.*.[44] This macrolide has a broad spectrum of biological activities including antifungal, antimalarial, antitumor, antibacterial. One of the stereogenic centres of paecilomycin C was installed using a Brown allylation in 72% yield (d.r. = 9:1) (Scheme 10). After the protection of hydroxyl group, the allylation product underwent cross metathesis reaction and followed by 10 more steps, including substrate directed epoxidation and Julia–Kocienski olefination, the synthesis of the natural product was successfully concluded.[45]

(−)-Anaferine (13) is a bis-piperidine alkaloid isolated for the first time in 1962 from the root extract of *Withania somnifera*, a plant widely exploited in the Ayurvedic medicine. It presents anti-inflammatory, anti-stress, immunomodulatory, adaptogenic, anticancer and neuroprotective activities.[46] Architecturally, it is composed by two rings, connected through their C-2 atoms by a 2-propanone bridge. The work on the synthesis of this compound has been done in our group. Total synthesis of (−)-anaferine in 9% overall yield included 13 steps, the third of which was a Brown allylation that allowed to obtain the desired stereoisomer with a d.r. of 85:15 (Scheme 11).[19] It is worth noting that a key homoallylic alcohol, which served as a starting in this total synthesis, has been prepared from 2-piperidine ethanol via Brown allylation as the crucial step once again (e.e. = 84%).[20]

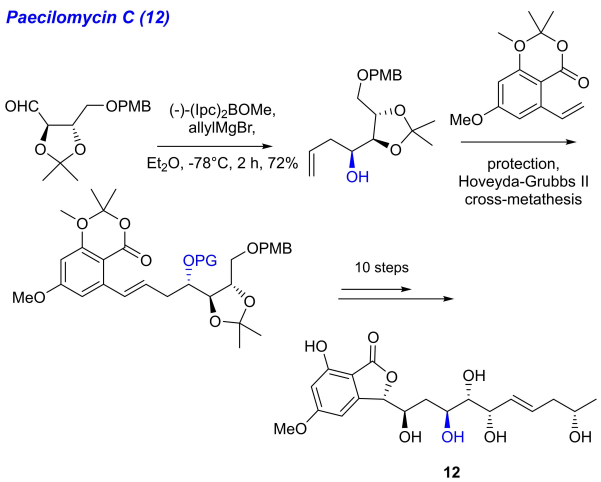
Dysoxylactam A (14) is a novel macrocyclolipopeptide, isolated from the bark of a Chinese plant named *Dysoxylum hongkongense*. This natural product acts as a potent multi-drug resistance reverser, able to significantly inhibit P-gp in cancer cells.[47] Structurally, it consists of a stereochemically rich macrocycle possessing a dense combination of unusual structural features, including a L-valine and a highly functionalized polyketide fragment with an amide linkage between the carboxyl group of the polyketide moiety and the amino group of the L-valine residue. In the synthesis of dysoxylactam A, Brown crotylation was used to forge C-13 and C-14 stereogenic centers. The aldehyde precursor reacted with Brown's $(Ipc)_2$B-(Z)-crotyl (1), prepared from (+)-$(Ipc)_2$B-OMe, and yielded the syn homoallylic alcohol in 87% yield (Scheme 12).[48]



Scheme 9. Brown's allylation in the synthesis of (+)-broussonetine H.

Table 1. Optimization of Brown allylation for (+)-broussonetine synthesis. d.r., diastereomeric ratio.

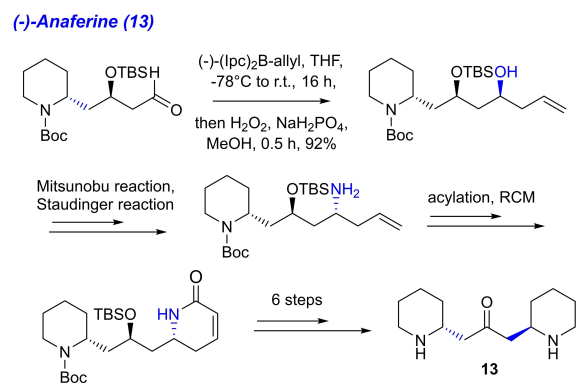
Entry	Conditions	Yield [%]	a: b d.r. (Scheme 9)
a	(+)-$(Ipc)_2$B-Cl, THF, −78 °C	68	6:1
b	(+)-(Ipc)2B-Cl, Et_2O, −100 °C	83	15:1
c	(−)-(Ipc)2B-Cl, Et_2O, −100 °C	71	1:11



Scheme 10. Brown crotylation in the synthesis of paecilomycin C.

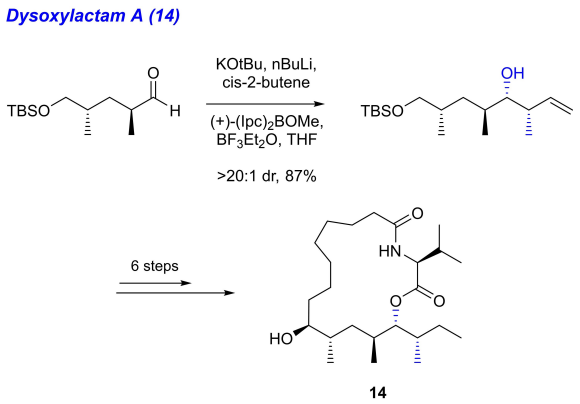
Fungal natural products

Penicillinolide A (15) ia a bioactive metabolite of the marine fungus *Penicillium sp.* SF-5292 with anti-inflammatory activity, isolated in 2013.[49] Its structure consists of 10-membered ring containing a lactone (decanolide) embedded with three stereogenic centers. In the first stereoselective total synthesis of penicillinolide A, Brown's asymmetric allylation using (−)-

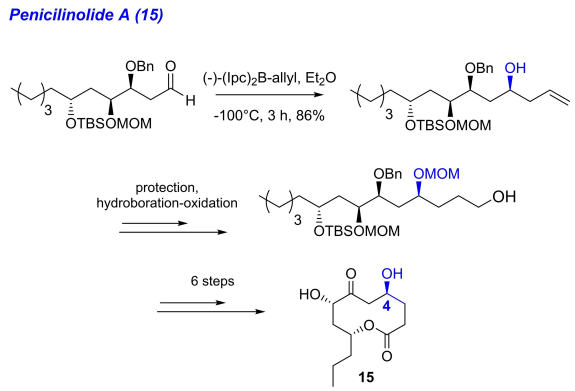


Scheme 11. Brown's allylation in the synthesis of (−)-anaferine.

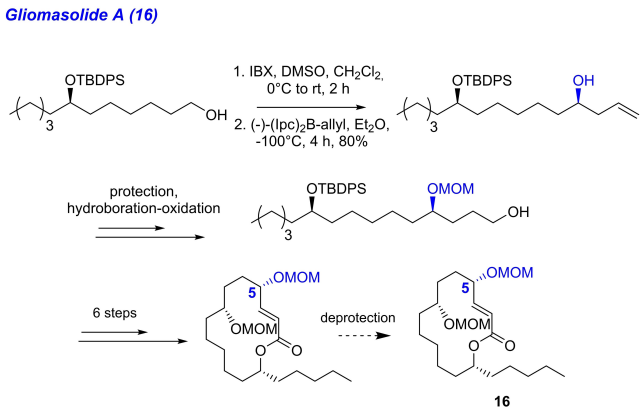
$(Ipc)_2$B-allyl in diethyl ether at −100 °C was used to obtain C-4 (Scheme 13). The authors stated that the NMR spectra showed the only desired diastereoisomer. Such obtained product then underwent protection and hydroboration-oxidation sequence, after which 6 more steps (including oxidation of the intermediate alcohol and Yamaguchi reaction to furnish decanolide core) afforded penicilinolide A.[50]



Scheme 12. Brown crotylation in the synthesis of dysoxylactam A.



Scheme 13. Brown allylation in the synthesis of penicilinolide A.



Scheme 14. Brown allylation in the synthesis of gliomasolide A.

Gliomasolide A (16) is a 14-membered macrolide, isolated by Xu and co-workers from a sponge-derived fungus *Gliomastix sp.* ZSDS1-F7-2. Gliomasolides A–E displayed anticancer activity against HeLa (human epithelial carcinoma cell line) cells, exhibiting moderate inhibitory effect with an IC50 value of 10.1 mM.[51] Gliomasolide A displays three stereogenic centers (5*S*, 8*R*, 14*R*), a n-pentane chain attached at C-14 position and a (*E*)-α,β-unsaturated acid functional group that is locked as a 14-membered macrolactone with the C-14 hydroxyl group. The configuration of C-5 was obtained by a Brown allylation: the primary alcohol was oxidized with 2-iodoxybenzoic acid (IBX) and it was immediately subjected to Brown's asymmetric allylation to give homoallylic alcohol in 80% yield over 2 steps (Scheme 14). Same as in penicilinolide synthesis, the product of Brown allylation was subjected to protection and hydroboration-oxidation sequence. Followed by 6 more steps, the di-MOM protected gliomasolide A was successfully synthesized, the efficient deprotection hasn't been reported. Interestingly, Keck allylation has also been used in this synthesis to obtain the desired configuration of another carbon stereocenter, C-14.[52]

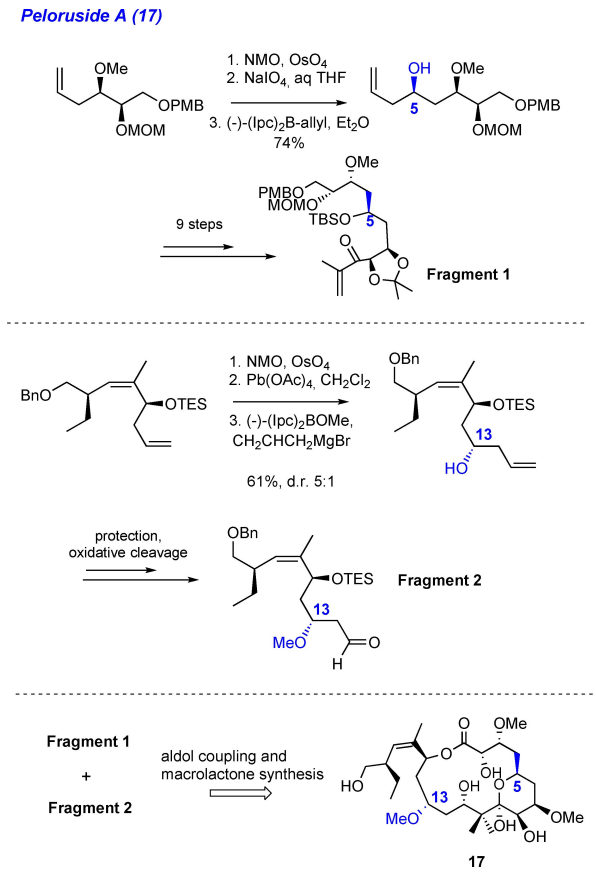
Marine natural products

Peloruside A (17) is a 16-membered macrolide, originally isolated in 1999 from the New Zealand marine sponge *Mycale hentscheli* by Northcote and West.[53] It is a microtubule-stabilizing agent with potent antimitotic activity.[54] Peloruside A contains 10 stereogenic centers, a 6-membered pyranose ring, a gem-dimethyl moiety, and a side-chain with *Z*-configured trisubstituted olefin. In one of its asymmetric total synthesis, C-5 and C-13 stereocenters were introduced by a Brown's allylation (Scheme 15). Importantly, it was used to obtain both main fragments, which then were joined in stereoselective aldol reaction, followed by Yamaguchi macrolactonization to furnish peloruside A.[55]

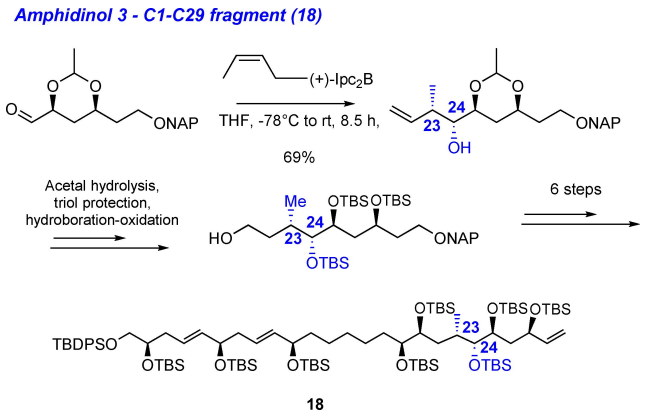
Amphidinol 3 (18) is a marine natural product produced by the dinoflagellate *Amphidinium klebsii*.[56] It shows antifungal and hemolytic activity.[57] This natural product is composed by a long acyclic carbon chain with a high density of stereogenic centers. Two of them, namely at C-23 and C-24, were introduced by Brown asymmetric crotylation (Scheme 16).[58]

Bacterial natural products

Biselyngbyaside (19) is a macrolactone that was isolated from a marine Cyanobacterium *Lyngbya sp.*, collected in the Okinawa prefecture. It showed antitumoral effects against HeLa S3 cells, acting as a cell proliferation inhibitor.[59] From a structural point of view, the macrolactone has six double bonds and three allylic hydroxyls (at C-3, C-7, and C-17) with a specified configuration. Synthesis of the C1–C13 fragment of biselyngbyaside has been published, in which the stereocenter at C-7 was introduced by Brown allylation of the aldehyde precursor. The allyl alcohol was obtained in 66% yield as a mixture of diastereoisomers in a



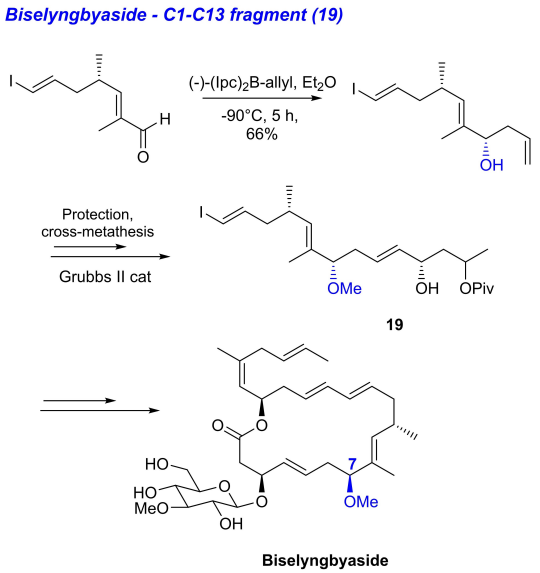
Scheme 15. Brown allylation in the synthesis of peloruside A.



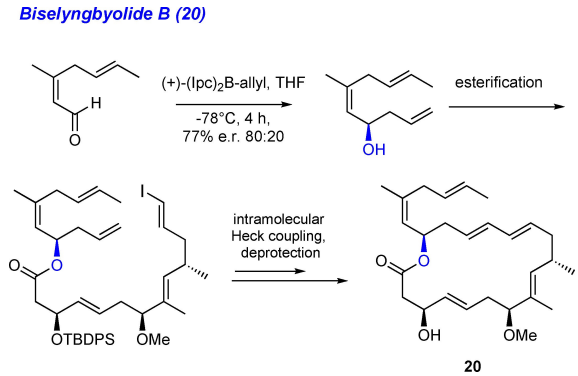
Scheme 16. Brown crotylation in the synthesis of amphidinol 3 C1–C29.

ratio of approximately 18:1 (Scheme 14). Upon protection the allylation product was subjected to cross metathesis reaction, furnishing the desired C1-C13 fragment of biselyngbyaside. 18:1 (Scheme 17).[60]

Biselyngbyolide B (20) is another active macrolide extracted from a marine Cyanobacterium *Lyngbya sp.* It showed inhibitory activity against the growth of human cervical cancer (HeLa) and leukemia (HL60) cells.[61] Structurally it is an 18-membered macrolide embedded with four stereogenic centers. The total



Scheme 17. Brown allylation in the synthesis of biselyngbyaside.



Scheme 18. Brown allylation in the synthesis of biselyngbyolide B.

synthesis of biselyngbyolide B passes through the intermediate alcohol, obtained by a Brown allylation with 80% enantiomeric excess and 77% yield. The allylation was followed by esterification and intramolecular Heck coupling, yielding biselyngbyolide B (Scheme 18).[61]

Solomonamide B (21) is one of the solomonamide macrocycles, known due to their high anti-inflammatory activity. Solomonamide B, together with solomonamide A, were isolated from the marine sponge *Theonella swinhoei*.[62] Eight possible stereoisomers of solomonamide macrocycles were prepared by changing the stereochemical pattern of its non-peptide fragment AHMOA. Brown crotylation was used as a key reaction in this synthesis, allowing to obtain the isomer with 2R, 3S, 4R configuration. Starting with d-methionine, treatment with $(Ipc)_2$B-(E)-crotyl (2) afforded the desired crotylated compound with planned stereochemistry in good yield as a single isomer (Scheme 19). It then underwent acetonide protection, reductive ozonolysis and pyrolytic syn-elimination to give the important

intermediate, later used for ligand-free intramolecular Heck reaction.[63]

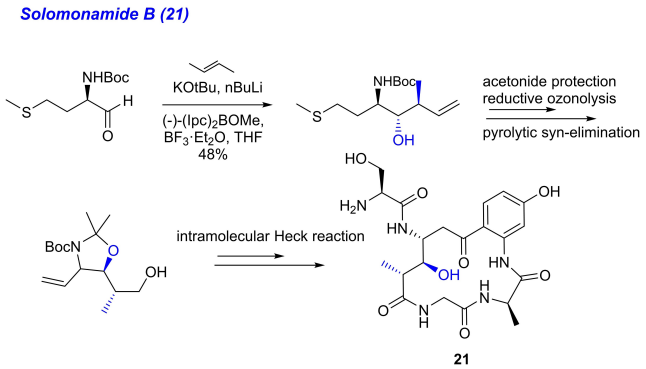
Disciformycin B (22) is a polyketide-derived macrolide, isolated in 2014 by Müller and co-workers from the myxobacterium *Pyxidicoccus fallax* strain AndGT8.[64] The biological assessment of this compound revealed significant antibacterial activity against Gram-positive bacteria, including methicillin- and vancomycin-resistant *Staphylococcus aureus* (MRSA/VRSA) strains. The stereoselective Brown allylation of isomerization-prone angelic aldehyde is a key step in the recently published synthesis of this compound. After the esterification the installed allyl group was subjected to RCM (Scheme 20).[65]

Building blocks for natural products

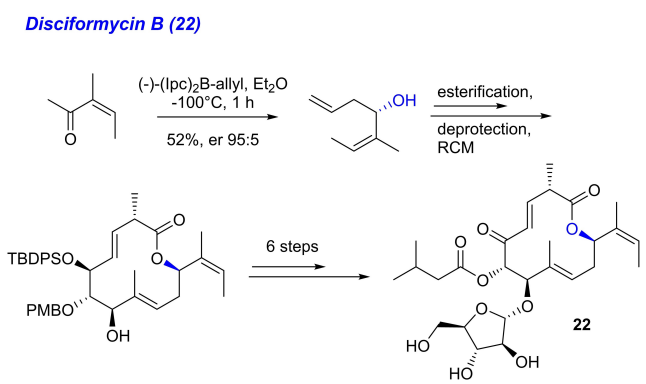
Asymmetric synthesis of new polycyclic nitrogen containing compounds serving as valuable building blocks for a series of natural products has been accomplished in our group. In particular, the synthesized molecules present the isomeric scaffold of some alkaloids. A sequence of seven reactions including Brown allylation has been used to efficiently convert the economic starting 2-piperidine ethanol into a small library of enantiomerically pure, nitrogen containing compounds (23, 24, 25). Racemic aldehyde, obtained from 2-piperifine ethanol, underwent Brown allylation accessing all the four stereoisomers of the homoallylic alcohol (Scheme 21). It was treated with both (+)- and (−)-(Ipc)$_2$B-allyl, obtained *in situ* from respective (Ipc)$_2$B-Cl and allylmagnesium bromide, followed by the chromatographic separation of diastereomers. Each of the diastereomers then underwent Mitsunobu reaction, acylation and RCM, after which either intramolecular aza-Michael addition was applied to obtain compound 23 or Eschweiler-Clarke conditions to produce 24 or 25.[20]

Conclusions

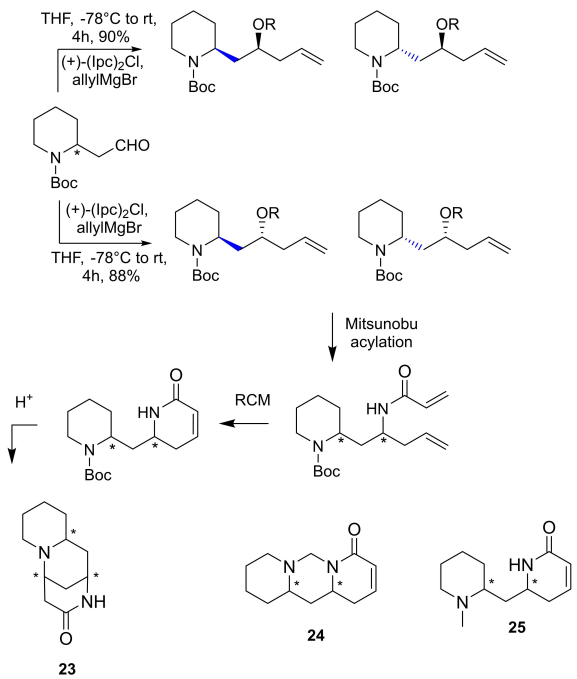
This minireview highlights the value of Brown asymmetric allylation in the synthesis of important intermediates and building blocks for various natural products. As shown, enantioenriched homoallylic alcohols constitute key fragments of diverse complex natural products, which synthesis often presents a challenging task. Brown allylation and crotylation reactions described allowed the synthesis of desired products in high yields and enantioselectivity, speaking in favour of this reaction. The possible drawbacks include the use of stoichiometric quantities of chiral reagent and therefore stoichiometric byproduct formation, as well as the effort needed to prepare the desired chiral allymetal reagent. While a lot of work has been done to address these issues and to develop efficient catalytic asymmetric allylations as an alternative, traditional Brown allylation often remains efficient, simpler, and less costly solution, prompting research to still use it in modern synthesis, as demonstrated by some examples shown in this review. Importantly, it allows to obtain both enantiomeric forms with the same efficiency and can be applied even to structurally



Scheme 19. Brown crotylation in the synthesis of solomonamide B



Scheme 20. Brown crotylation in the synthesis of disciformycin B.



Scheme 21. Brown allylation to obtain the described polyheterocyclic scaffold.

complex structures. 16 natural products reported proved not only the extensive application of Brown allylation and/or crotylation from the point of chemical diversity, but also the medicinal significance, since the majority of the compounds showed potent biological activity. Apart from total synthesis chemistry, our work on new polyheterocyclic scaffolds has also been mentioned, demonstrating that Brown allylation can be applied to a natural product-inspired, diversity-oriented synthesis.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Brown asymmetric allylation · Crotylation · Natural products

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