

Improved Chemistry of *myo*-Inositol: A New Synthetic Strategy to Protected 1-Keto- and 1,2-Keto-Inososes

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A refresh and improvement of the well-known *myo*-inositol chemistry is reported here, setting up a new synthetic protocol to obtain orthogonally protected compounds, with a special focus on the preparation of 2-O-alkylated compounds. A gram scale synthesis of the 2-allyl compound was performed and optimized in terms of yield. This intermediate is the precursor of *chiro*-1-inosose, for which synthetic procedures are lacking. Taking advantage of the easily handled allyl group, we were

able to transform this keto compound into both the 1,2-diketone and 3-deoxy-1,2-diketone, intermediates of biological transformations used in several patented applications. Finally, to access *poly*-hydroxylated-(aminomethyl)cyclohexane compounds, the reaction of the keto compound with cyanide was optimized, affording cyanohydrins obtained as single stereoisomer, the precursor of the above compound.

Introduction

Inositols are a class of *pseudo*-sugars, characterized by a polyhydroxylated cyclohexane ring, which differ in the relative configuration of the stereocenters. Among them, *myo*-inositol (Scheme 1) is the most common, traditionally obtained by acid hydrolysis of inositol hexakisphosphate (phytate), extracted from corn and rice. It can also be obtained by fermentation of glucose or glycerol by *Escherichia coli*.^[1] Its chemistry, along with that of its derivatives, mostly phosphates, has been extensively explored due to their involvement in several biological pathways. For example, it is an important growth-promoting factor of mammalian cells, regulates the ion channel permeability, phosphate levels, and metabolic flux.^[2,3] Its emerging role in the treatment of various diseases – such as various types of cancer, polycystic ovary syndrome (PCOS), Alzheimer's disease, affective disorder, mild cognitive disorder, bipolar disorder, depression, suicidal tendency, Down's syndrome, left ventricular stiffness, fatty liver disease, and lipodystrophy – was recently reviewed^[4] and reported in several papers.^[5–8] Additionally, *myo*-inositol has been used for the

preparation of natural compounds^[9] as well as resins^[10] and polymers.^[11,12]

Due to its availability in large amounts at low cost and the specific relative configuration of its stereocenters (*cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol), *myo*-inositol is a useful starting material for the preparation of various compounds. For this reason, a plethora of orthogonally substituted compounds have been prepared, including ethers, acetals, carbonates/thiocarbonates, sulfonates, and acylated compounds, just to name a few.^[9,13–17]

Inososes are important compounds involved in the biological synthesis of *myo*-inositol^[18] and can be obtained through various selective enzymatic or microbial oxidations of inositols.^[18–21]

Several inosose stereoisomers are known, some of which have been tested as *in vitro* inhibitors of A β aggregation.^[4] A review of the literature reveals that their synthesis is lacking, particularly starting from *myo*-inositol. Among them, *scyllo*-inosose,^[22–25] *epi*-inosose,^[25–27] and *myo*-inosose-5^[28] can be obtained through enzymatic transformation or chemical oxidation (Scheme 1). Focusing on *chiro*-1-inosose (1; Scheme 1), only two synthetic procedures have been reported: an enzymatic protocol from *myo*-inositol^[29] and a chemical oxidative process from 1 L-*chiro*-inositol,^[8] a very expensive reagent.

Moving to the 1,2-diketo-compound 2 and monodeoxy-diketone 3 (Scheme 1), it has been reported that they are intermediates in the biological transformation of *myo*-inositol^[20,21,30] and, in the case of compound 3, also of *sylo*-inosose.^[18] Alternatively, they can be obtained through oxidative processes from inositols by using metals.^[31,32] Compound 3 is particularly valuable for the synthesis of quercitol derivatives, which are used for the preparation of potential pharmaceutical derivatives.^[18] The use of these scaffolds is also mentioned in several patents as intermediates for various applications, such as the preparation of OLEDs,^[33] polycarbonate resins^[34] and materials for energy storage devices.^[35]

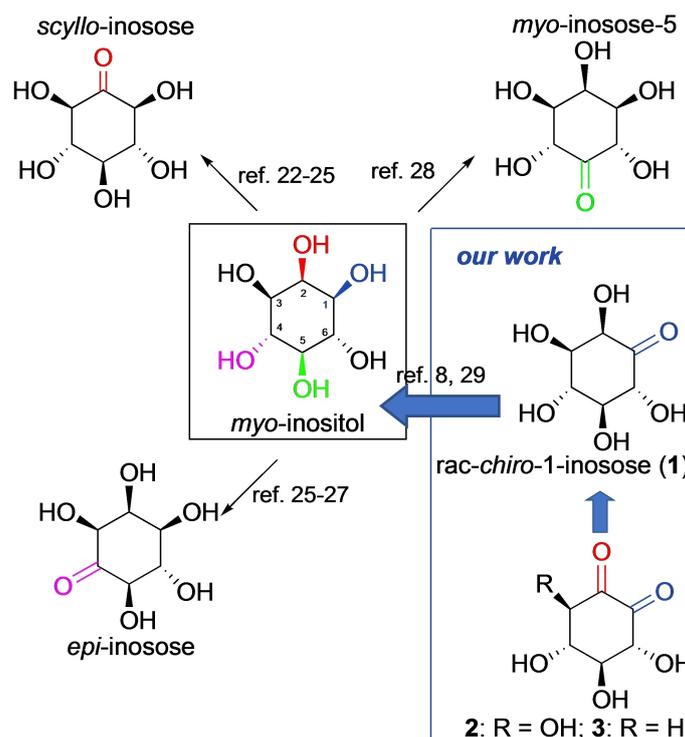
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Scheme 1. Inososes from *myo*-inositol.

The lack of procedures for obtaining *chiro*-1-inosose **1**, its orthogonally protected compounds, as well as diketones **2** and **3** starting from **1**, prompted us to investigate their synthesis. It should be pointed out that the synthesis of the precursors of the key ketone **1** was optimized and scaled-up to 10 g. Additionally, since *myo*-inositol is the only achiral starting material used, all synthesized compound, when chiral, were obtained in racemic form.

We also focused on the reactivity of a *chiro*-1-inosose derivative with cyanide, yielding cyanohydrins, which are good precursors for the synthesis of *polyhydroxylated*-(aminomethyl)cyclohexane compounds. To the best of our knowledge, no examples of the reactivity of inososes with cyanide have been reported in the literature. Only a few examples of inositol-like carbonitriles have been found,^[36,37] which are deoxygenated at the 1,2-carbons, as well as amino-methyl derivatives^[38,39] obtained from other synthetic strategies.

All newly synthesized compounds were fully characterized by NMR, allowing the configuration of the new stereocenters to be determined. Moreover, since a clear spectroscopic characterization of ketones **1–3** has not been reported in the literature, significant effort was made, primarily to identify the main isomers of diketone derivatives present in solution.

Finally, the regioselective ring opening of the orthoformate derivative of inositol by a Grignard reagent (Bodroux-Chichibabin reaction) was investigated through computational studies.

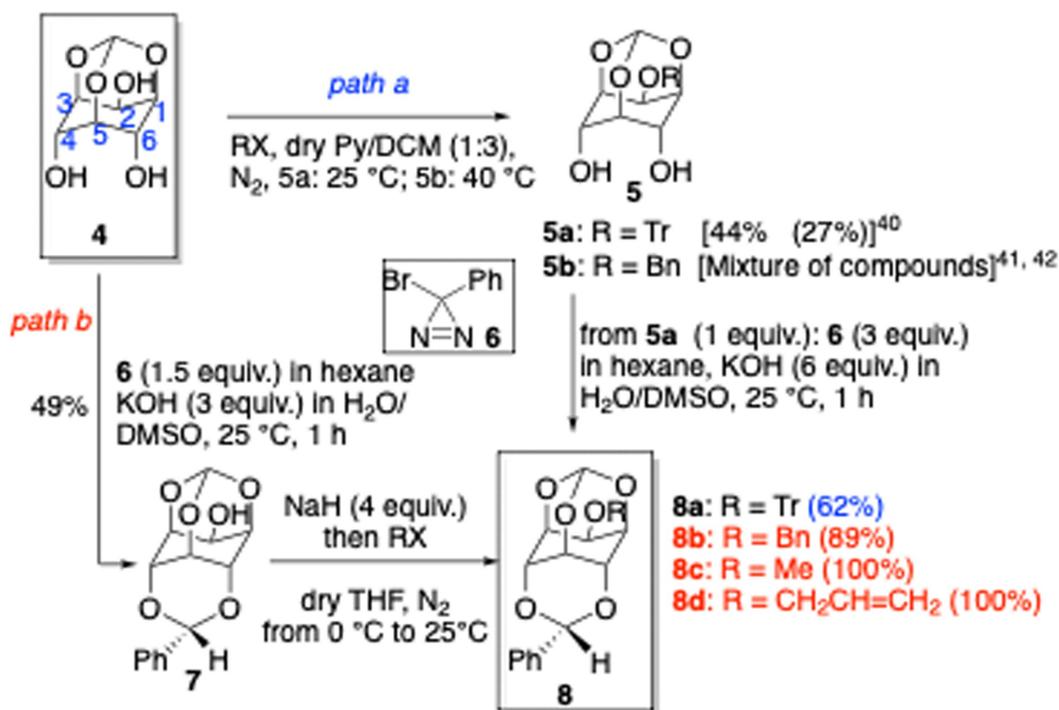
Results

Optimization of the Protecting Groups

In order to obtain protected intermediates from which the hydroxy group at C-1 can be selectively oxidized to a keto-group, two different strategies were considered and reported in Scheme 2. *Myo*-Inositol orthoformate **4**, prepared according to a known procedure from *myo*-inositol,^[24] is the key reagent for obtaining either the partially protected compounds **5** or the fully protected derivatives **8 a–d** (*paths A* and *B* in Scheme 2).

To obtain compounds **5**, we focused on trityl (Tr) and benzyl (Bn) derivatives. The synthesis of the trityl derivative **5 a** (27 %) has already been reported in the literature.^[40] Nevertheless, we succeeded in increasing the yields (44%) by optimizing the protocol: TrCl was used in a larger amount (2.7 equiv.) in pyridine/CH₂Cl₂ (3:1), at reflux for a longer time (42 h). According to the literature,^[41,42] we failed to obtain derivative **5 b** (BnBr, pyridine/DCM, 25 °C) because of the formation of a mixture of different benzylated regioisomers.

Starting from **5 a**, the hydroxy groups at C-6 and C-4 were protected as a benzyl acetal. 3-Bromo-3-phenyl-3*H*-diazirine (**6**)^[43] was used as the key reagent, whose synthesis was optimized, increasing the yields from 37% to 52%. The fully protected known compound **8 a** (62%), obtained as a single diastereoisomer, was prepared by using **6** (3 equiv.) in hexane in the presence of KOH (6 equiv.) operating in H₂O/DMSO (25 °C). Higher yields are reported for the synthesis of **8 a** from **5** and **6**,^[40] but we failed to achieve this goal even though several reaction conditions were tested. To obtain the acetonide, we



Scheme 2. Synthesis of orthogonally protected derivatives of *myo*-inositol 5, 7 and 8.

also attempted another protocol: **5a** was treated with dry acetone in the presence of tetrabutylammonium tribromide as a catalyst (pH=4–5).^[44] Nonetheless, we observed the deprotection of the OTr group, affording orthoformate **4**.

To improve the yields of the fully protected compounds **8**, with the possibility of manipulating orthogonal deprotection, a different strategy was used (*path b*). Orthoformate **4** was first transformed into benzylidene acetal **7** (49%) by optimizing the previously reported conditions (**6**: 1.5 equiv.; KOH: 3 equiv.). Compound **7** is a new, favourable intermediate for obtaining alkylated compound at OH-2. By using different alkyl halides and operating in the presence of NaH in dry THF (from 0 to 25 °C), the new benzyl (**8b**, 89%), methyl (**8c**: quantitative yields), and allyl (**8d**, quantitative yields) derivatives were isolated in excellent yields. It should be pointed out that the use of **8c** is reported,^[45] but, to the best of our knowledge, neither its synthesis nor its characterization was found in the literature. On the other hand, we failed to obtain the trityl compound **8a** starting from **7**. In summary, the proposed methodology (*path b*) represents a new, efficient protocol to selectively obtain 2-alkoxy derivatives **8**, containing a small/medium-sized alkyl group, in two steps from the single intermediate **4**, in overall yields ranging from 45 to 50%. On the other hand, the use of the known *path a* from **4** yielded worse results in terms of selectivity of alkylation, but it proves efficient when using the large trityl group.^[41,42]

In a second step, we focused on the orthoformate ring opening to obtain OH-1 deprotected acetals **9** (Table 1 and Table TS1 for a complete set of experiments). Several procedures are reported in the literature for orthoformate ring

opening of *myo*-inositol derivatives, using either reducing agents or organometallic compounds.^[46] The use of the Bodroux-Chichibabin reaction involving Grignard reagents is the most effective method to control the desired regioselectivity. Specifically, this reaction is known starting from the methoxy derivative **8c**, affording **9c**.^[45] No by-products were reported for this reaction. To verify the effect of the substituents on this reaction and aiming to characterize possible by-products, the reaction was thoroughly investigated starting from compounds **8a–d** and MeMgI (4 equiv.). The trityl compound **8a** is unreactive at 25 °C in toluene and gave a complex mixture at different temperatures (from 40 to 60 °C; entry 1). Similar behaviour was observed using benzene. In this case, a significant amount of the deprotected compound **7** was isolated, probably formed during the work-up (entry 2).

All the condition tested starting from the benzyl compound **8b** failed, even using different solvents (entry 3), with complete recovery of the starting material.

Starting from **8c**, operating as reported in the literature,^[45] we succeeded in the formation of the known alcohol **9c** in benzene, but in very low yield (34%) compared to the reported one (47%). In our case, the isopropyl by-product **10c** (21%, entry 4) was also isolated, derived from the reaction of a second methyl carbanion with the ethylidene acetal **9c** (see computational studies for the mechanism). We attempted to optimize this reaction by decreasing the amount of MeMgI (2 equiv., entry 6 in TS1) but a more complex crude product was obtained with a lower yield of **9c** (10%). After optimizing the reaction on the allyl compound **8d** (see below), we were able to obtain

Table 1. Orthoesters **8** ring opening by Bodroux-Chichibabin reaction: synthesis of compounds **9 c, d**.

Entry	Reagents ^[a]	Solvent	T (°C)	Time (h)	Products
1	8 a	Toluene	0→ ^[b]	^[b]	starting material or complex mixture
2	8 a	Benzene	0→65	18	complex mixture/7 (47%) ^[c]
3	8 b	^[d]	0→55	18	starting material
4	8 c	Benzene	0→55	18	9 c (34%)/ 10 c (21%) ^[e]
5	8 c	Toluene	0→40	24	9 c (50%)/ 10 c (17%) ^[f]
6	8 d	Benzene	0→55	18	9 d (17%)/ 10 d (52%) ^[e]
7	8 d	Toluene	0→40	42	9 d (47%)/ 10 d (7%) ^[e]
8	8 d	Toluene	0→40	24	9 d (58%)/ 10 d (10%) ^[f]

[a] **8** (1 equiv.)/MeMgI (3 M in Et₂O, 4 equiv.) in a dry solvent from 0 °C to the temperature and for the time indicated in the Table. [b] Reaction performed at different temperatures: 25 (5 h), 40 (18 h), 55 (18 h), 60 (18 h) °C. [c] Compound **7** probably formed from **8 a** during the work-up. [d] Reaction performed in different solvents: benzene, THF and toluene. [e] Quenching with a saturated solution of NH₄Cl under stirring (6.7 mL NH₄Cl for 1 mL MeMgI; 0 °C; 5 min.) [f] After quenching with a saturated solution of NH₄Cl (36 mL for 1 mL MeMgI; pH = 7; 0 °C), the stirring was continued for 30 min. at 25 °C, then the reaction mixture was worked-up.

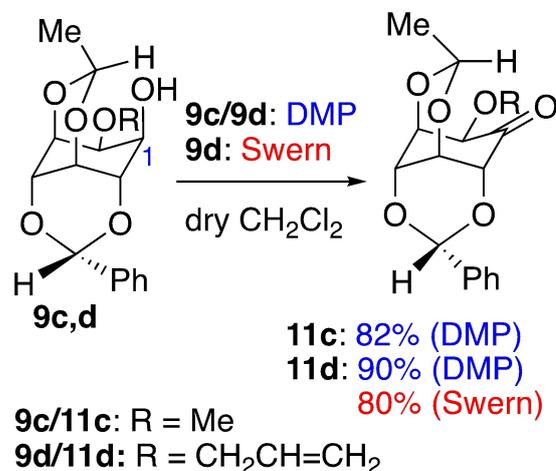
compound **9 c** in 50% yield together with the by-product **10 c** (17%; entry 5).

Finally, we focused on the allyl-compound **8 d**. By changing the solvent, temperature, reaction time and the work-up, we optimized the reaction yields. As with **8 c**, alcohol **9 d** (17%) and a large amount of isopropyl ether **10 d** (52%) were obtained in benzene at 55 °C (entry 6). The use of a coordinating solvent, such as THF or 1,2-dimethoxyethane (entry 9 in TS1), failed and the starting material was recovered. Toluene was found to be the best solvent, increasing the yield of **9 d** (37%) compared to **10 d** (30%) (entry 10 in TS1). Decreasing the temperature to 40 °C required more time (42 h; entry 7), but gave increased yields (**9 d**: 47%; **10 d**: 7%).

Due to Mg coordination to oxygen, quenching the reaction and the consequent work-up proved to be very important (Table TS1, entries 11–12, notes *h, i*). In summary, the best results were achieved operating with 4 equiv. of MeMgI in toluene at 40 °C for 24 h. After quenching the reaction with a saturated solution of NH₄Cl to pH=7 at 0 °C (5 min.), the mixture was further stirred at 25 °C for 30 min, affording **9 d** (58%) and **10 d** (10%) (entry 8).

Synthesis of 1-Keto and 1,2-Diketo-Compounds and Reactivity

The oxidation of the hydroxy group in compounds **9 c, d** was then performed (Scheme 3). Starting from **9 d**, both Dess-Martin periodinane [DMP (1.2 equiv.) in dry CH₂Cl₂, from 0 to 25 °C, 3 h] and Swern conditions [COCl₂ (1.5 equiv.), dry DMSO (1.7 equiv.), dry TEA (4 equiv.) in dry CH₂Cl₂, -78 °C (1 h) then 25 °C (2 h)] were tested. Ketone **11 d** was isolated in 90 and 80% yields,



Scheme 3. Synthesis of ketones **11 c, d**.

respectively. Considering the higher yields, DMP was used for the oxidation of **9c** affording **11c** in 82% yields.

Allyl-compound **11d**, possessing an easily manipulated protecting group compared to the methyl group, was chosen for further studies and prepared on a multi-gram scale, along with its precursors. Starting from **4** (23 g), allyl compound **8d** was prepared (two steps, 19 g), then transformed into ketone **11d** (two steps, 10 gr). Compound **11d** was obtained with an overall yield of 27% (4 steps) from **4**. Ketone **11d** is a valuable intermediate for obtaining both ketone **1** and 1,2-diketones **2** and **3**, as well as their protected derivatives.

The allyl group of **11d** was first removed [tetrakis(triphenylphosphine)palladium (0.05 equiv.)/ dimesone (2 equiv.), THF, 25 °C, 18 h] affording **1a** (70%). The ketal protecting groups were then removed [TFA/H₂O (9:1), 25 °C, 1.30 h], giving the unprotected ketone **1** in 95% yield (Scheme 4).

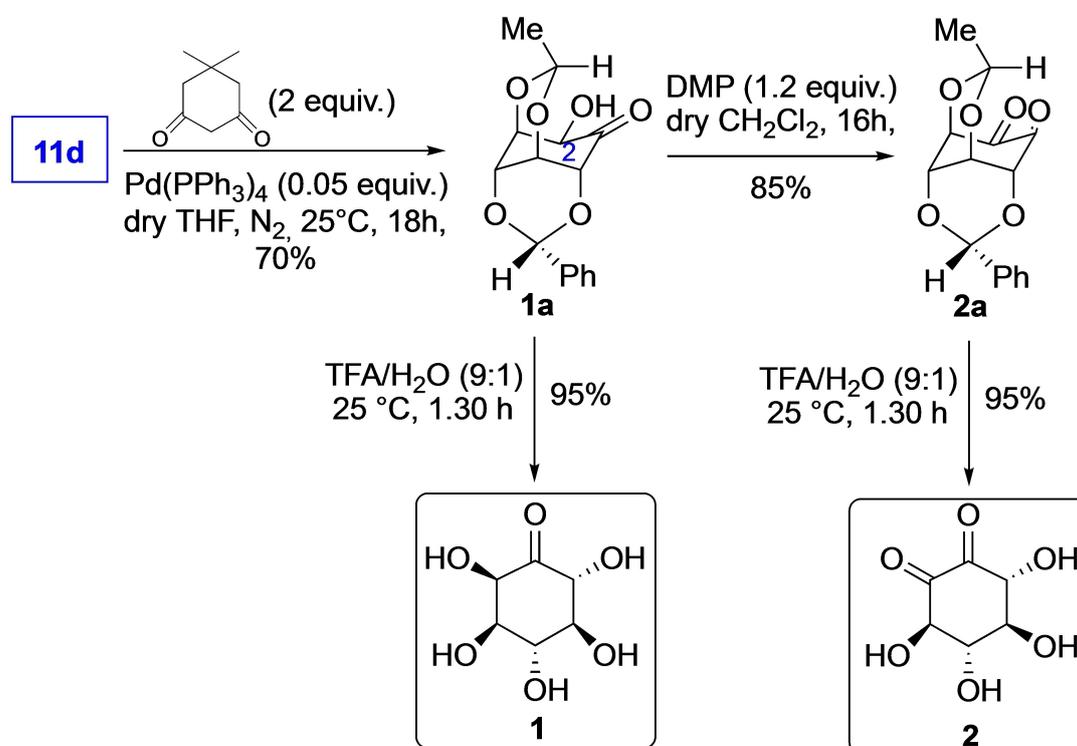
Compound **1a** is also the precursor of ketone **2** (Scheme 4). The OH-2 oxidation was performed with DMP (1.2 equiv. in dry CH₂Cl₂, from 0 to 25 °C, 16 h), giving **2a** in 85% yields. The deprotection of the acetal functions was performed as reported for **1a**, giving **2** in 95% yields.

The transformation of **11d** into ketones **3** (Scheme 5) was achieved by first performing an elimination reaction, giving compound **12**. The elimination reaction of inosose derivatives affording an analogue of **12** has been reported in literature, emphasizing the importance of base selection: while triethylamine (TEA) allows obtaining an unsaturated ketone, the use of a stronger base affords aromatic compounds.^[47] To optimize the reaction conditions, different bases and temperature were

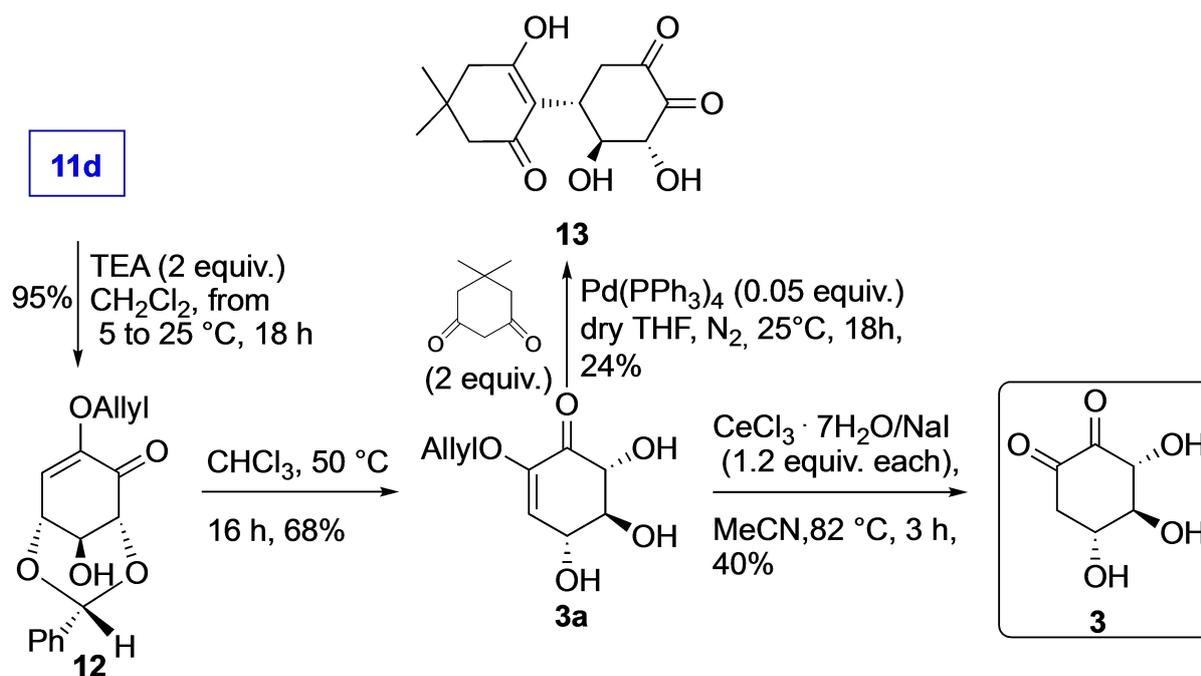
tested. TEA (2 equiv., 0.1 M in CH₂Cl₂ from 5 to 25 °C) worked very well, affording the expected unsaturated compound **12** in 95% yield. The use of stronger bases such as lithium diisopropylamide [LDA, (1.5 equiv, 1.8 M in THF/eptane/ethylbenzene) in CH₂Cl₂ from -78 to 25 °C, 18 h] and lithium bis(trimethylsilyl)amide [LHMDS (2.5 equiv., 1 M in THF) in THF from -78 to 25 °C, 2 h], gave **12** in 58% and 70% yields, respectively. No traces of aromatic compounds were detected, underlining the importance of the selected allyl protecting group, essential for maintaining the cyclohexanone system.

The acetal function of compound **12** was deprotected in CHCl₃ at 40 °C (16 h), taking advantage of the intrinsic acidity of this solvent, affording **3a** (68%). It should be underlined that we did not observe this behaviour in CHCl₃ for ketones **11c, d**. Accordingly, the deprotection of **12** using these mild conditions must be ascribed to the strong constrained cyclohexane ring in which three sp² carbons are present, in addition to the acetal function.

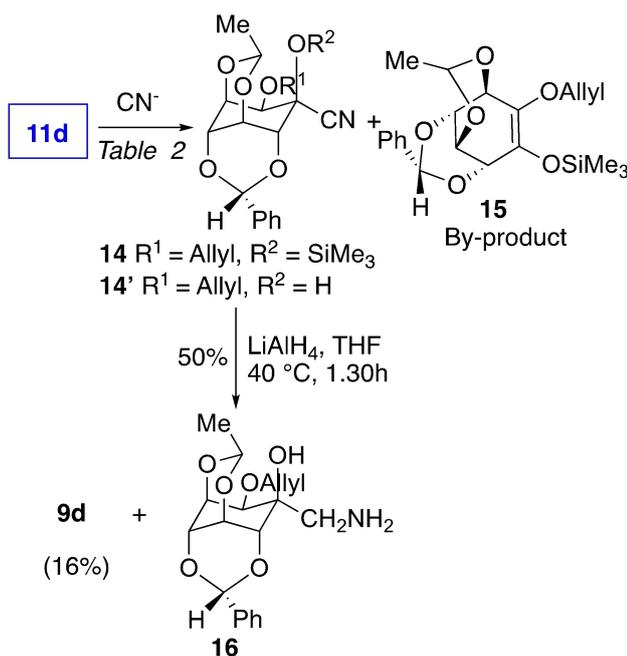
The deprotection of OH-2 of **3a** was performed according to the above-reported deallylation protocol, but only the unexpected compound **13** (24%; Scheme 5) was isolated, derived from the condensation of scaffold **3a** with dimesone, according to a mechanism of transition metal-catalyzed allylic alkylation [see Supporting information for a possible mechanism (Scheme S1) and NMR characterization].^[48] We succeeded in obtaining **3** using CeCl₃·7H₂O and NaI in MeCN (80 °C, 3 h). Its purification was not easy due to its solubility in H₂O and the presence of inorganic salts. After purification of the crude product on ion-exchange resins, compound **3** was isolated in 40% yields.



Scheme 4. Synthesis of ketone **1** and 1,2-diketone **2**.



Scheme 5. Synthesis of 1,2-diketones 3 and 13.



Scheme 6. Synthesis of cyanohydrins 14/14' and amino compound 16.

Synthesis of Cyanohydrin and Aminomethyl-Cyclohexane Derivatives

Finally, we focused on the synthesis of cyanohydrins 14, the precursors of amino compound 16 (Scheme 6). The reactivity of ketone 11d was tested using different cyanide reagents and reaction conditions to obtain both OH-protected 14 or unprotected 14' compounds (Table 2 and Table TS2 in SI for the complete list of experiments). The reaction of 11d with TMSCN in MeCN in the presence of CsF (entry 1, Table 2) gave the protected compound 14 in 89% yield. As by-product, the silyl enol ether 15 was isolated in 4% yield. The use of LiF instead of CsF gave 15 (10%) together with the unreacted starting material (entry 2, Table 2). 11d did not react with NaCN/TMSCl (entry 3, Table TS2) or KCN/NaHSO₃ (entry 4, Table TS2) mixtures. Only the elimination product 12 was found using NH₄Cl/KCN/TBACl (pH 5; entry 5 Table TS2). Unprotected cyanohydrin 14' was isolated in 85% yield by treatment with Et₂AlCN in toluene (entry 3, Table 2). As demonstrated by NMR analyses (see Supporting Information and Figure S1), a single diastereoisomer was obtained in which the nucleophilic attack occurs on the face containing the benzylidene acetal group. In this

Entry	Reagents (equiv.) ^[a]	Solvent	Time (h)	Product/s
1	TMSCN (1.3), CsF (0.1)	dry MeCN	4	14 (89%) + 15 (4%)
2	TMSCN (1.3), LiF (1.1)	dry MeCN	18	15 (10%) ^[b]
3	Et ₂ AlCN (2.2 eq)	dry Toluene	^[c]	14' (85%)

[a] The reaction was performed at 25 °C. [b] Recovered starting material 11d. and change. [c] The reaction was cooled at 0 °C for 2 h, then heated at 25 °C for 3 h.

way, the stereochemistry of hydroxy groups of *myo*-inositol is maintained.

The Strecker reaction was also tested (Table TS2, entries 7–9), but we failed due to the basic conditions: only the elimination product **12** was isolated.

The reduction of the nitrile **14** was performed using LiAlH₄ (4 equiv.) in THF (Scheme 6): **14** is stable at 25 °C but gives the desired amine **16** in low yields (26%) with a mixture of by-products when the reaction was run at reflux. The reaction was successful at 40 °C (1.30 h): amine **16** was isolated in 50% yield. Unexpectedly, alcohol **9d** (16%) was also obtained, probably formed by deprotection of OH-1 in **14**, giving **14'**, followed by cyanide loss, giving ketone **11d**, which was then reduced to alcohol **9d**.

Spectroscopic Characterization

All synthesized compounds were characterized by analytical (MS) and spectroscopic experiments (¹H, ¹³C, COSY, NOESY, HSQC experiments), and the data are summarized in Figure S1 (Supporting Information). Special attention was paid to the stereochemistry of the benzylidene and ethylidene stereocenters: in all compounds, the phenyl group is located below the cyclohexane ring due to the boat conformation of the acetal ring (see also computational studies below), confirming literature data.^[40] As for the ethylidene acetal, the proton is oriented toward the substituted C-1 carbon.

The spectroscopic characterization of ketones 1–3 was not trivial due to the formation of both the hydrate form of ketone(s) and the enols, coexisting in equilibrium and affording complex mixtures, as also underlined in the literature.^[49]

The exact mass of ketone **1** (HRMS, C₆H₁₀O₆ + Na⁺: 201.0374) confirms its complete deprotection. The enzymatic synthesis of **1**, directly from *myo*-inositol, has been reported, but limited NMR information was provided to attest the correct stereochemistry.^[21,32,49] The ¹³C NMR spectrum recorded in D₂O (125.8 MHz) showed the absence of the keto function but the presence of the typical signal of its hydrate form at δ 94.5, confirming the reported data.^[49] All chemical shifts were assigned according to *J* values and NOE experiments (Figures 1A and S2 in SI), proving the structure assigned in the literature.

The exact mass of diketone **2** agrees with the complete deprotection of **2a** (HRMS, C₆H₈O₆ + Na⁺: 201.0374). A very complex ¹H NMR spectrum was obtained, showing the presence of several species (Figure S3, B). As reported, diketone **2** is present in solution in equilibrium with its enol forms and can also give aromatic compounds.^[32]

A detailed NMR analysis, not reported in literature, was performed to identify some isomers (Figures 1B and S3 in SI). The ¹³C NMR spectrum shows the presence of both the keto function(s) (δ 204.5 main peak, 204.7) and the corresponding hydrate forms (δ 94.9 main peak, 94.8, 94.4 and 94.1). The main isomer is represented by the fully hydrated form I: a symmetric system is detected at δ 3.51 (dd) and δ 3.34 (dd), characterized by the same *J* values (*J*_{1,2} = 6.9, *J*_{1,4} = 2.7 Hz), suggesting the presence of equatorial protons. The high-field resonances of these protons are consistent with the hydrate form. Signals at lower field (δ > 4) are also present, consistent with the presence of H_α to a keto group. The signal at δ 4.60 (d, *J* 9.5 Hz) correlates with two species (COSY/TOCSY experiments; Figures S74, S75). For the first isomer (four signals correlate in the above experiments), the structure of monohydrate ketone **II** was

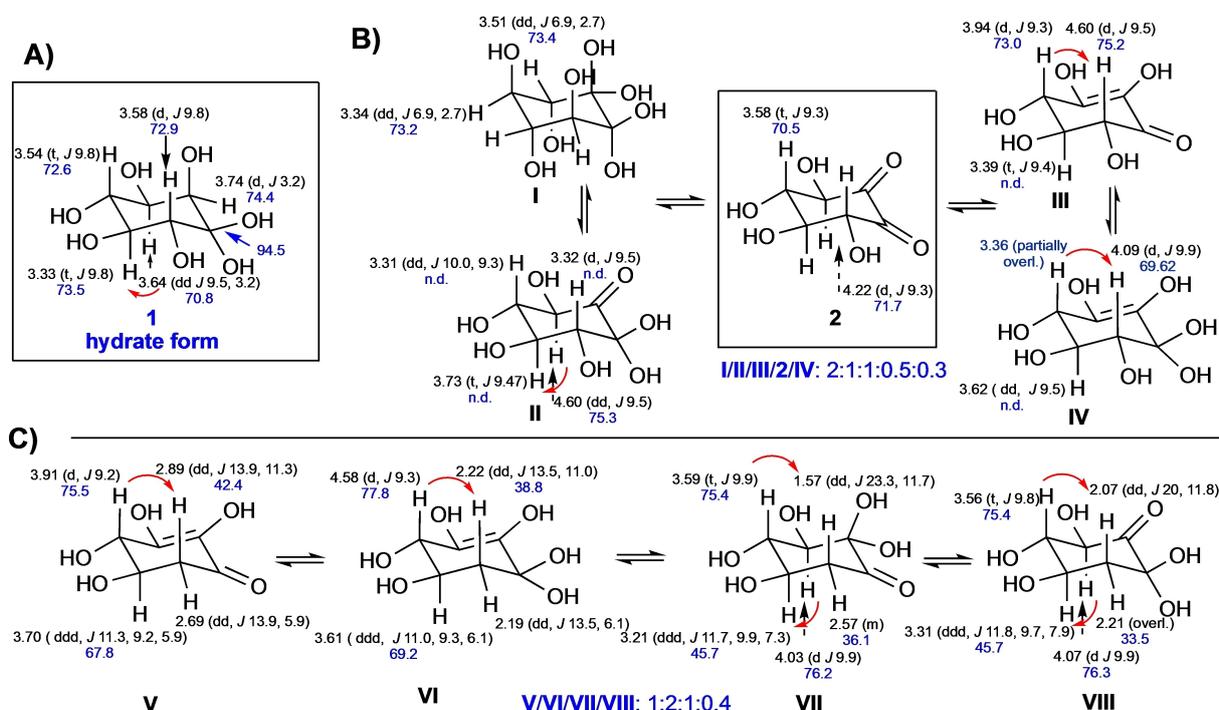


Figure 1. ¹H/¹³C NMR chemical shifts and NOEs (red) for A) ketone **1**, B) diketone **2**, C) diketone **3** and isomeric ratio

proposed due to the high-field resonance of H-3. All the OH groups are in the equatorial position ($J_{1,2}=10-9.3$ Hz), and spatial proximity between H-4 and H-6 was detected (Figure S3C). The main second isomer corresponds to the mono-enol form III (three signals correlate in the above experiment) in which only axial protons are present ($J_{1,2}=9.5-9.3$ Hz), also confirmed by the NOESY experiment (NOE between H-4/H-6; Figure S3C). Unfortunately, we were unable to detect the quaternary carbons in the ^{13}C NMR spectrum. The structure of the hydrate form of enol III was assigned to isomer IV, characterized by similar $J_{1,2}$ and NOE, but chemical shifts at higher field for H4/H6 (Figure S3C). The distribution of these isomers is reported in Figure 1, as well as the chemical shifts and NOEs.

The formation of ketone 3 is confirmed by MS spectroscopy: the molecular peak was found in both ESI-MS (ESI-, $\text{C}_6\text{H}_7\text{O}_5$; 159.36) and in HRMS (HRMS/cESI-, $\text{C}_6\text{H}_7\text{O}_5$; 158.9340). While the literature claims that the ^1H NMR spectrum of 3 is too complex to identify the different compounds, and only the corresponding dihydrazone was characterized,^[21] we were able to identify four main isomers (Figure 1C). Besides some signals in the aromatic region, COSY/TOCSY and NOESY experiments confirmed the assigned structures (Figures S4B-C, S92, S93), with isomers V and VI being the enol forms of ketone 3, the second one as a hydrate compound, and VII and VIII corresponding to the hydrate form of one of the two keto functions.

Computational Studies for Bodroux-Chichibabin Reaction

To understand the mechanism, regioselectivity and stereoselectivity of this reaction, DFT calculations were done at the $\omega\text{B97X-D/Def2TZVP/CPCM}(\text{Et}_2\text{O})//\omega\text{B97XD/6-31+G(d,p)}$ level, a

method previously shown to be effective in similar studies,^[50,51] as detailed in the Computational Methods section of the Supplementary Information (SI). To simplify calculations, we used a model system in which the benzylidene acetal was replaced with a formyl acetal bearing the 2-OMe substituent (s8c). Its reaction with MgMe_2 yields intermediate s9c and product s10c (see Scheme S2 in the Supporting Information). The geometries of reactants, intermediates, and products were optimized, and their energies were evaluated as described in the Computational Studies (Methods section, see SI). Initial models of s8c were based on both chair and boat conformations for the 1,3-dioxane ring containing acetal oxygens O4 and O6. The boat conformation was favored by 4.2 kcal/mol over the chair, likely due to reduced steric hindrance. Indeed, a longer distance was measured between the methylene hydrogens and H6 or H2 in the boat and chair conformation (2.23 and 1.82 Å, respectively). Accordingly, all other derivatives were modelled in boat conformation.

In addition, as Mg complexes can adopt various coordination states – tetrahedral, trigonal bipyramidal, and square bipyramidal^[52-54] – the geometries of $\text{MgMe}_2 \cdot \text{Et}_2\text{O}_n$ ($n=2, 3$ and 4) were optimized and compared in terms of overall stability. The hexacoordinated configuration was the most stable, with ΔH values of 8.0 and 9.6 kcal/mol lower than the tetra- and pentacoordinated complexes, respectively; therefore, hexacoordination was assumed for further analysis (see SI for additional details). We then evaluated the chelation of MgMe_2 reagent to orthoester oxygens (O1, O3, O5) and acetal oxygens (O4, O6) in s8c (Figure 2). We found that coordination at orthoester O5 was slightly favored, being 1.0 and 1.2 kcal/mol more stable than O1 and O3 chelation, respectively. Coordination at O4 and O6 was significantly less favorable, with ΔH values 3.7 and 3.1 kcal/mol higher than O5 chelation, respectively.

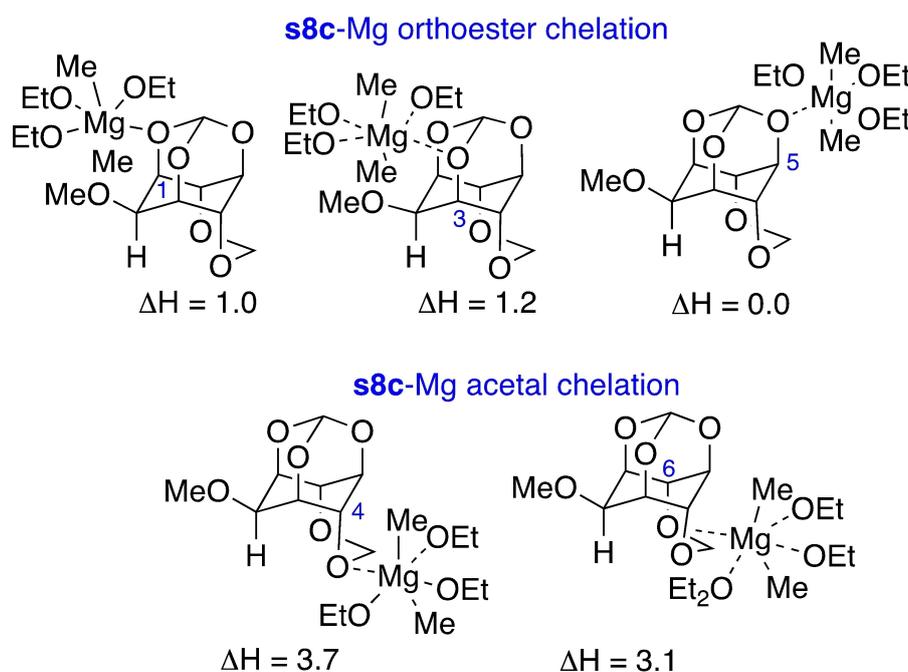


Figure 2. A) s8c-Mg chelation at orthoester function; B) s8c-Mg chelation at acetal function; in both cases, ΔH values are reported in kcal/mol.

Starting from the reactants $\text{MgMe}_2(\text{Et}_2\text{O})_4$ and **s8c**, set at $\Delta H=0$, chelation of **s8c** at O5 proceeds exothermally ($\Delta H = -2.3$ kcal/mol) with the release of one Et_2O molecule (Figure 3). In the resulting complex **s8c**· $\text{MgMe}_2(\text{Et}_2\text{O})_3$, the ideal orientation of the Me group favors nucleophilic attack at the orthoester carbon, with O1 acting as the leaving group and forming **s9c**· $\text{MgMe}(\text{Et}_2\text{O})_3$, with $\delta\Delta H$ of -38.7 kcal/mol. This intermediate exhibits dual Mg coordination by anionic O1 and the OMe group at C2, with Mg–O1 and Mg–O2 distances of 1.96 and 2.25 Å, respectively. An alternative regioisomer, where O3 serves as the leaving group, yielding Mg coordination by O3 and O2 (see Figure S11, SI), is 4.7 kcal/mol less stable, consistent with the scheme in Figure 3. Again, the proper orientation of the Me group in **s9c**· $\text{MgMe}(\text{Et}_2\text{O})_3$ facilitates a second Me transfer, with O5 as the leaving group, producing **s10c**· $\text{Mg}(\text{Et}_2\text{O})_3$ at a $\delta\Delta H$ of -32.2 kcal/mol. Another potential regioisomer, with the *i*Pr group at C5 and formed when O3 acts as the leaving group (Figure S13, SI), was 1.6 kcal/mol less stable, in line with the observed experimental regiochemistry.

Conclusions

An alternative and new straightforward protocol to obtain orthogonally protected *myo*-inositols **8** in excellent yields and characterized by different substituents at OH-2 was developed, starting from the common intermediate **7**. These compounds are precursors for obtaining ketones **11** via intermediates **9**. It must be underlined that the choice of the OH-2 protecting group is crucial for achieving good yields in the preparation of compounds **9**. Sterically hindered substituents, such as trityl or benzyl groups, probably prevent coordination of the Grignard reagent to O-2, as claimed by some authors,^[45] thus preventing orthoformate ring opening. On the other hand, the methyl and allyl compounds work well, affording **9c, d**, which are then oxidized to **11c, d**.

Considering the ease of handling the allyl group, we developed a protocol to obtain keto compound **11d** on a gram scale by optimizing the reaction conditions. Ketone **11d** is very sensitive to basic conditions, affording the elimination product **12**. Compounds **11d** and **12** are key intermediates for accessing

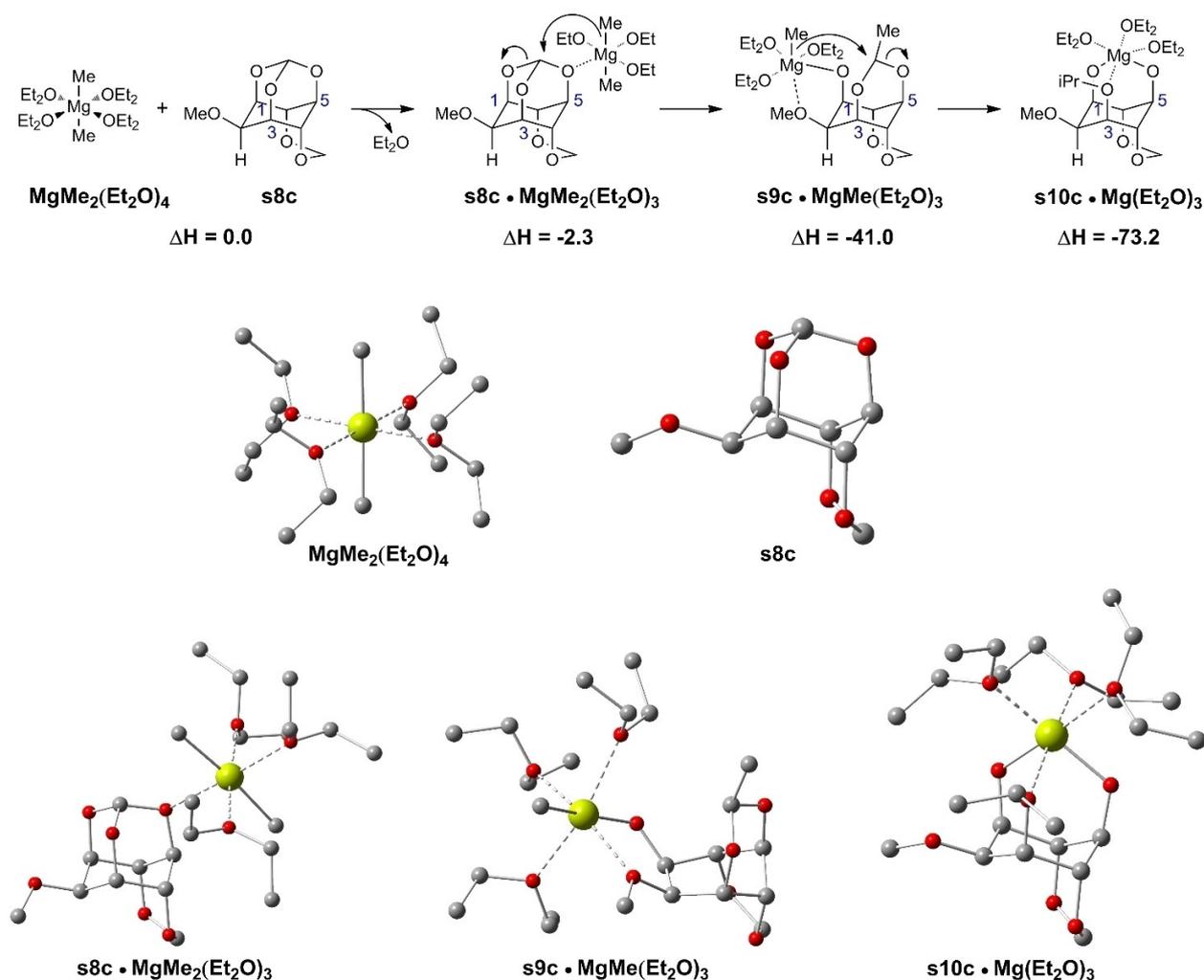


Figure 3. Bodroux-Chichibabin reaction from compounds **s8c** affording **s10c**: proposed mechanism and optimized geometries; ΔH values, referred to the total enthalpy computed for isolated reactants, are reported in kcal/mol.

both keto compound **1** and diketo-derivatives **2** and **3**, for which few synthetic procedures have been reported.

Finally, to access to polyhydroxylated aminomethylcyclohexane compound **16**, the reaction of ketone **11d** with cyanide was optimized, affording cyanohydrins **14**, which were then reduced to amino compound **16**. It must be underlined that these compounds have never been reported in the literature and that the cyanide reaction is highly diastereoselective, forming a single stereoisomer. Because alcohol **9d** was also obtained as a by-product during nitrile reduction, we can assume that the nucleophilic attack at the ketone function in both cases occurs on the face containing the benzylidene acetal group, thus maintaining the orientation of OH-groups as in the starting *myo*-inositol.

Supporting Information Summary

The supporting Information contains Tables TS1 and TS2 with a complete set of the experiments performed, NMR studies for the synthesized compounds, the mechanism for the formation of compound **13** and NMR discussion, the synthesis of compounds **1–16** and NMR spectra, the computational studies on Grignard reaction from orthoformate **s8c** and references.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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