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Asymmetrized tris(hydroxymethyl)methane as precursor of iminosugars: application to the synthesis of isofagomine

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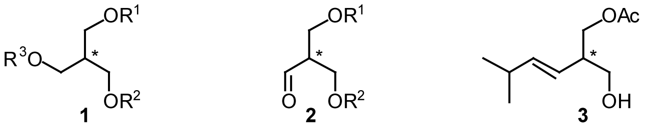
Abstract—A new synthetic application of asymmetrized tris(hydroxymethyl)methane (THYM*), readily obtained in both enantiomeric forms through a chemoenzymatic procedure, is reported. In this case THYM* precursor **3** was elaborated by ring closing metathesis into some enantiopure branched tetrahydropyridines, that have been used as precursors of the potent glycosidase inhibitor *isofagomine* **28**. © 2002 Elsevier Science Ltd. All rights reserved.

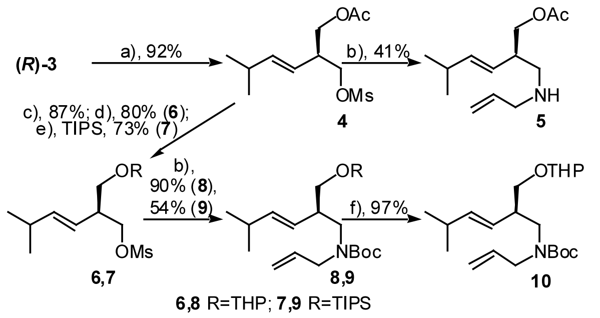
Asymmetrized tris(hydroxymethyl)methane **1** (THYM*) (Scheme 1) and its synthetic equivalent bis(hydroxymethyl) acetaldehyde **2** (BHYMA*) constitute a family of readily accessible chiral building blocks, that have found many synthetic applications in our group.[1] One of the most useful precursors of **1** or **2** is represented by monoacetate **3**, whose synthesis in both enantiomeric forms by asymmetrization of prochiral precursors catalyzed by lipase from porcine pancreas (PPL)[2] was already described by us.[3]

Actually, derivative **3** contains a masked aldehydic functionality, that can be introduced by the oxidative cleavage of the double bond without racemization and can be successively reduced to the corresponding alcohol. THYM* and BHYMA* have been submitted to several transformations involving: (a) the substitution of one oxygenated moiety with a suitable nucleophile without the formation of new stereocentres;[1] (b) the stereoselective functionalization of one or two branches with the creation of new stereogenic centres;[1] (c) the stereoselective elaboration, which has been performed also intramolecularly,[4] of suitable alkenes obtained after olefination of BHYMA*.[1] Now we report a new application of THYM*, starting directly from **3**. The double bond was not oxidatively cleaved at an early stage; on the contrary, it was used as functional group for a cyclization reaction, performed through a ring closing metathesis (RCM), after the substitution of one hydroxy group of **3** with a *N*-Boc protected allylamine moiety.[5] This transformation was realized following two similar routes, differing by the order of introduction of the Boc protecting group and the terminal olefin unit.

In the first route (Scheme 2) the *N*-Boc protected amines to be used as substrates in RCM reaction,[6] were prepared by nucleophilic substitution with allylamine of a *O*-activated (as mesylate) derivative of **3**,[7] followed by protection of N as Boc. This substitution was per-



Scheme 1.



Scheme 2. *Reagents and conditions*: (a) MsCl, Et_3N, CH_2Cl_2, −30°C; (b) allylamine, 80°C; (c) KOH, MeOH, 0°C; (d) DHP, *p*-TSA, CH_2Cl_2, 0°C; (e) TIPS-Cl, imidazole, DMF, rt; (f) Boc_2O, 1,2-dichloroethane, reflux.

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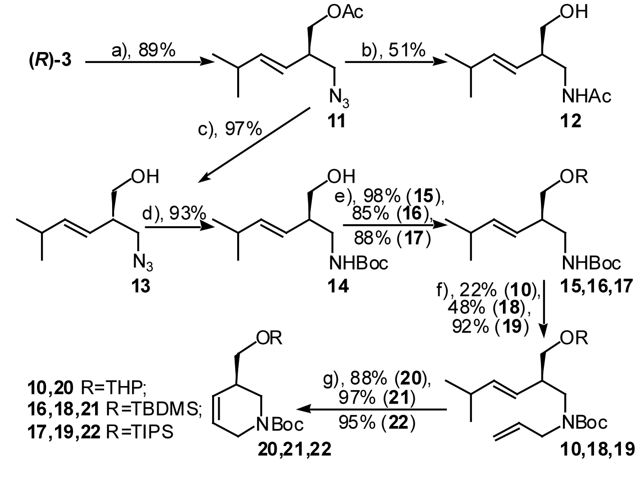
formed on three different *O*-protected mesylates with satisfactory results only for the *O*-THP derivative **8** (90% yield). Since we were interested in defining an efficient protocol for the preparation of different *O*-protected analogous of **10** to be submitted to RCM reaction, we decided to follow another route (Scheme 3), involving the transformation of **3** into the corresponding carbamate, followed by the allylation of its anion. For this purpose, **3** was transformed (via mesylate) into the corresponding azide **11**, which was reduced with Staudinger method.[8] However, while starting from **11** we were able to isolate only amide **12**, deriving most likely from an intramolecular acyl transfer during hydrolysis of the intermediate iminophosphorane,[9] the reduction of azido alcohol **13**, obtained by *Pseudomonas cepacia* (PCL) catalyzed hydrolysis of **11**, furnished the expected amine which was transformed in situ into *N*-Boc derivative **14**, according to a modified literature procedure.[10] The free alcoholic function of this intermediate was then protected in three different ways (THP, TBDMS, TIPS)[11] and the corresponding carbamates were allylated under classical basic conditions to give the required *O*-protected allyl derivatives with an overall yield varying from 22% (**10**) to 92% (**19**).[12]

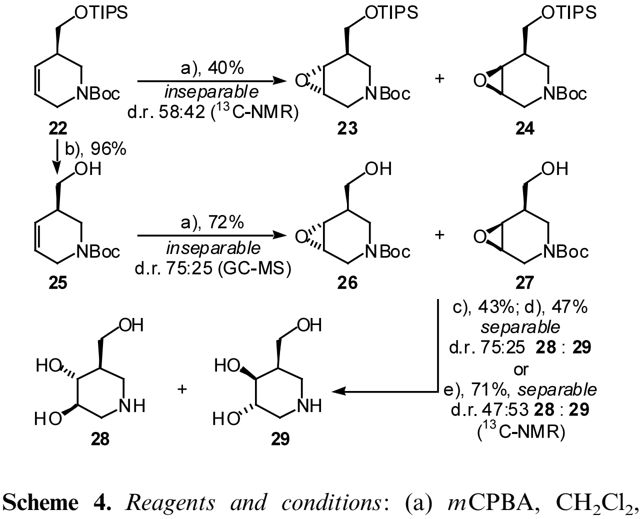
With three different *O*-protected allyl carbamates in hand, we started to study the RCM reaction. We examined different reaction conditions and, at the end, the best results were obtained using the protocol described in Scheme 3. The excellent yields of the obtained tetrahydropyridines (**20**–**22**) suggest that the steric hindrance of the branched substrates used as precursors and the formation of a substituted olefin (isopropylethylene) as by-product instead of classical ethylene, do not influence negatively the course of this reaction, which occurred smoothly whatever the protection of the hydroxy group. No acyclic derivatives, arising from intermolecular metathesis, could be detected, thus allowing us to work also in solutions more concentrated than usual.



Scheme 3. *Reagents and conditions*: (a) 1. MsCl, Et_3N, CH_2Cl_2, −30°C; 2. NaN_3, DMF, 50°C; (b) PPh_3, THF/H_2O, 55°C; (c) PCL, THF/H_2O 1:3, pH 7, rt; (d) 1. PPh_3, THF/H_2O, rt; 2. Boc-ON, Et_3N, rt; (e) DHP, *p*-TSA, CH_2Cl_2, 0°C (**15**) or $R^1{}_2R^2SiCl$, imidazole, rt [R^1=Me, R^2=*t*Bu (**16**), R^1=R^2=*i*Pr (**17**)]; (f) allyl bromide, NaH, DMF, rt; (g) Grubb's catalyst, 0.028 M (**20**), 0.014 M (**21**) or 0.036 M (**22**) in CH_2Cl_2, reflux.

It is noteworthy that, although different unsaturated six-membered nitrogen heterocycles, have been synthesized in the last few years using a RCM for the cyclization step,[13] the synthesis of these new chiral building blocks, obtained through an 8-step sequence in 62% overall yield from (*R*)-**3** (compound **22**), represents, to best of our knowledge, the only example in which the acyclic precursor has been prepared through a chemoenzymatic procedure, involving an asymmetrization and not a kinetic resolution[14] Moreover, with our methodology, both configuration at the stereogenic centre are in principle available.[2]

These tetrahydropyridines can be seen as useful intermediates for the synthesis of iminosugars, a class of sugar shaped compounds that have found a growing interest in the last years for their properties as glycosidase and glycosyltransferase inhibitors.[15] Compounds **20**–**22** constitute actually a series of useful intermediates for the synthesis of *isofagomine* **28**, a mimic of glucose,[16,17] and of its 'gulo' stereoisomer **29**,[18] since very similar racemic derivatives[19,20] have been transformed into the final products, by epoxidation of the double bond, followed by hydrolysis of the oxirane ring and protecting groups removal (Scheme 4). To demonstrate the possibility to use THYM* as precursor of these compounds, we converted **22**, the intermediate easier to be prepared in a multigram scale, into **28** and **29**, following the literature procedure. We were surprised by the scarce reactivity of the double bond with respect to the epoxidation, which required unusual harsh conditions in order to go to completion with an appreciable rate. Compounds **23** and **24** were obtained only in moderate yield and with modest diastereomeric ratio. The best results, either in terms of rate, yield and d.r. were obtained on the unprotected alcohol **25**, thus suggesting that the stereoselectivity can not be attributed mostly to sterical reasons.



Scheme 4. *Reagents and conditions*: (a) *m*CPBA, CH_2Cl_2, reflux; (b) Bu_4NF, THF, rt; (c) 3% $HClO_4$ in Me_2CO, rt; (d) AcOEt/3 M HCl 2:1, rt; (e) 1% aq KOH, reflux.

Other methods, tested in order to improve most of all the stereoselectivity, like for example Jacobsen catalyst in the presence of *m*CPBA or NaClO,[21] or *t*-BuOOH in the presence of VO(acac)$_2$[22] were absolutely unsatisfactory: with the first conditions only traces of the desired epoxides were obtained starting from **22**, while, with the second reagent, an extensive decomposition of the starting compound **25** was observed. The mixture of the diastereomeric epoxides could not be separated[23] and was converted as such, by acidic or basic hydrolysis, into the final products, that were quite easily separated by chromatography. Under acidic conditions, compounds **28** and **29** were obtained in moderate overall yield but with complete retention of the d.r. of the starting epoxides. On the other hand, the basic hydrolysis of **26** and **27**, furnished **28** and **29** with and a remarkable changement of the d.r., with stereoisomer **29** prevailing in this case. These data suggest that, only under acidic conditions, the epoxide opening is regioselective. Finally, the spectroscopic data of both triols agree with those reported in literature[17,19] and, in particular, the optically rotatory value of **28** fits well with the reported one,[24] thus demonstrating that the whole sequence proceeded without racemization. We are now trying to investigate more in detail the mechanistically aspects of the last reactions, that have never been pointed out in similar projects. Furthermore, we are also studying other stereoselective additions to the double bond of **22** and **25** in order to synthesize new highly functionalized piperidine derivatives of great interest for their potential biological activity. Our data will be reported in due course.

Acknowledgements

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