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Efficient route to optically pure polyfunctionalized cyclooctanes

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Abstract—A short and efficient synthesis of enantiopure highly functionalized eight-membered carbocyclic rings is described from 1,2:5,6-bis-epoxides issued from D-mannitol. The key cyclization step involves the metathesis of 1,9-diene using Grubbs' catalyst or the pinacolic coupling of 1,8-dialdehyde resulting from the oxidative cleavage of the previous diene. In the specific case of ring-closing metathesis cyclization, the influence of a conformationally restricted diene compared to that of a flexible one has been evaluated.

The conversion of carbohydrate derivatives into carbasugars, sugars for which the endocyclic oxygen atom has been replaced by a methylene group, is well documented for the C5 and C6 series[1] and this has given rise to interesting biologically active compounds such as trehazolamines, conduritols or inositols. However, only a few approaches have been dedicated to analogous routes in the C7[2] and C8[3] series. In the latter case, the unfavorable thermodynamic factors are claimed to limit the access to C8 cyclitols.[4]

As part of our ongoing research on the synthesis of new glycosidases inhibitors and especially on the synthesis of new potential drugs to treat non-insulino-dependant (NID) diabetes, we considered the structure of either voglibose itself or valienamine as an essential core unit of acarbose (Fig. 1).

Both voglibose[5] and acarbose[6] display powerful α-D-glucosidase inhibition and have already found therapeutic application in NID diabetes. In this context, our goal was to develop a straightforward and efficient route to cyclooctanic carbasugar analogs in order to study the effect of an increase in the flexibility of the resulting targets on the expected enhanced adaptability of cyclooctanic structure within the active site of the enzyme. Furthermore, the availability of various configurations of the carbasugar should enable us to examine the consequence of different distributions of the hydroxyl groups on the activity.

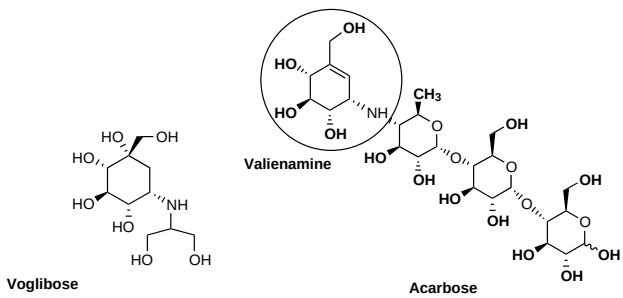

Figure 1. Examples of non-insulino-dependant diabetes therapeutic agents.

Our retrosynthetic analysis (Scheme 1) involves two different pathways, namely the carbocyclization of enantiomerically pure 1,9-diene and the carbocyclization of 1,8-dialdehyde which results from oxidative cleavage of the previous diene. The key step requires either an intramolecular cycloaddition by ring-closing metathesis (RCM) or a pinacolic coupling (PC). The synthetic route begins with C2-symmetrical bis-epoxides easily available from D-mannitol.

Although ring-closing metathesis has been largely used in the synthesis of heterocyclic compounds[7] and in that of C5 to C7 cyclitols,[1a,1c,1e,2a,2b] only a few examples deal with the obtention of C8 cyclitols[3a,3b] and the recent work published in this field[3b,3d] has prompted us to submit our results.[8] First, the regiospecific opening of C2 symmetrical L-*ido* bis-epoxide **2**, readily available from D-mannitol,[9] by an excess of lithium divinyl

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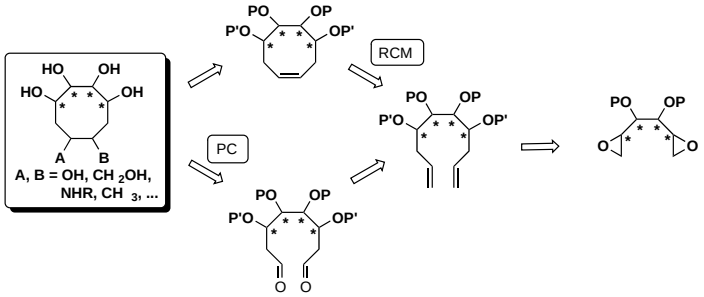
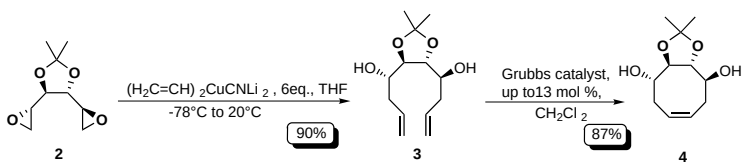


Scheme 1. Retrosynthetic analysis.

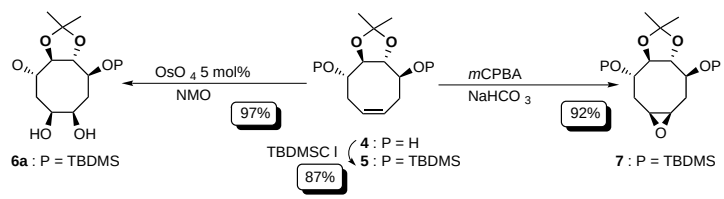
cyanocuprate[10] was carried out at −78°C to cleanly afford the diene **3** in 90% yield[11] (Scheme 2). The carbocyclization involving Grubbs' commercially available ruthenium catalyst [$(PCy_3)_2Cl_2Ru{=}CHPh$, up to 13 mol%], 0.005 M in CH_2Cl_2 at 20°C for 96 h, efficiently gave the expected cyclooctene **4** in 87% yield. The simplicity of both the ^1H and ^{13}C NMR spectra of **4**[12] revealed the retention of the C2-axis of symmetry and showed the formation of the thermodynamically more stable *cis*-cyclooctene. It is worthy of note that, in our case, RCM led to the cyclized product at 20°C without requiring the protection of the two hydroxyl groups of the diol **3**.[13]

Both hydroxyl groups were then protected as their *tert*-butyldimethylsilyl ethers **5** (TBDMSCl, imidazole, DMF) prior to exploring the synthetic potentialities at the newly created double bond of this enantiomerically pure polyhydroxycyclooctenic structure (Scheme 3). *syn*-Dihydroxylation[14] by a 5 mol% aqueous solution of osmium tetroxide, in dichloromethane, in the presence of *N*-methylmorpholine oxide and *tert*-butanol afforded the enantiopure polyhydroxylated cyclooctane derivative **6a** in 97% yield. Alternatively, the epoxidation of the double bond[15] in the presence of *meta*-chloroperbenzoic acid and sodium hydrogenocarbonate cleanly gave the enantiopure epoxide **7** in 92% yield.

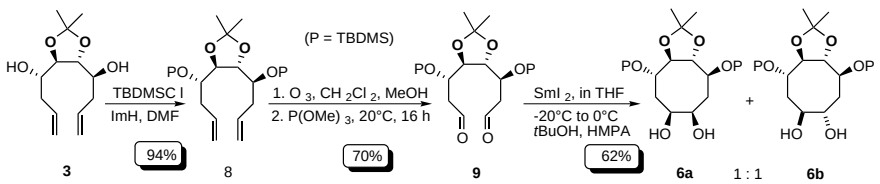
We next turned to the second proposed pathway involving the pinacolic coupling of 1,8-dialdehyde. For that purpose (Scheme 4), the secondary alcohol functions of the diol **3** were protected as their *tert*-butyldimethylsilyl ethers (TBDMSCl, imidazole, DMF) to give the entirely protected compound **8**. Ozonolysis of both double bonds of **8** in dichloromethane and methanol followed by the decomposition of the resulting ozonide by trimethylphosphite, furnished the expected dialdehyde **9** in 70% yield. Reductive coupling was then carried out by samarium diiodide (0.1 M in THF) in the presence of *tert*-butanol and HMPA[16] to promote the cyclization. In these conditions, efficient cyclization occurred affording the cyclooctanediol skeleton in 62% yield as a 1:1 diastereomeric mixture of *cis* and *trans* cycloadducts **6a** and **6b**.[17] The *cis* relation



Scheme 2.



Scheme 3.



Scheme 4.

ship in **6a** has been shown by comparison with the same compound previously obtained by *syn*-dihydroxylation of the cyclooctene **5** resulting from RCM.

Due to the poor observed diastereoselectivity of pinacolic coupling cyclization, it is obvious that RCM followed by *syn*-dihydroxylation or *syn*-epoxidation was a better method to reach the targeted compounds. So, we proceeded to the generalization of the RCM to other substrates displaying different configuration and/or higher flexibility of the backbone in order to test the presumed entropic assistance to the cyclization process of the acetonide moiety in the conformationally restricted diene **3** (Scheme 5). To this end, both D-*manno*-1,9-dienes **12** and **13** were prepared from the corresponding D-*manno*-bis-epoxides[9,18] according to the same conditions as the diene **3**. As for the L-*ido*-acetonide diene **3**, the D-*manno*-acetonide diene **12** was isolated in good yield (80%). However, our previous work[19] has shown that bis-opening of flexible di-*O*-benzyl-bis-epoxide by a nucleophile is competitive with *O*-cyclization involving the alcoholate resulting from the nucleophilic opening of a single epoxide moiety. Nevertheless, the low temperature of the reaction (−78°C) allowed us to minimize the *O*-cyclization and the expected diene **13** was isolated in 30% yield. To our great satisfaction, RCM of both dienes **12** and **13**, in the same conditions as above, efficiently afforded the corresponding cycloadducts **14**[12] and **15**[12] in 65 and 50% non-optimized isolated yield.

In summary, RCM was a powerful method to reach polyhydroxycyclooctene structures displaying diverse configurations and allowing various, either rigid or flexible, protective groups for the central diol. In this study, protection of hydroxyl groups at homoallylic positions proved to be unnecessary since the RCM occurred in good to excellent yield. Furthermore, *syn*-diol or *syn*-epoxide resulting from dihydroxylation or epoxidation of cyclooctenic structure may be considered as key intermediates in the obtention of the targeted C8-amino cyclitols. Work on the synthesis of voglibose mimics is now in progress and will be reported in due course.

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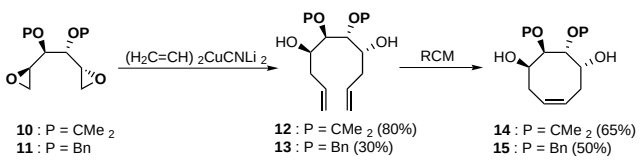

Scheme 5.

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11. All new compounds were characterized by analytical and spectroscopic data. Yields are given for isolated, chromatographically purified products.
12. Selected physical data for **4**, **14** and **15**:**4**: ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 5.78–5.73 (m, 2H, $H_{1,8}$), 3.83–3.74 (m, 2H, $H_{3,6}$), 3.70–3.58 (m, 2H, $H_{4,5}$), 2.46–2.24 (m, 4H, $H_{2,2',7,7'}$), 1.35 (s, 6H, Me), the following coupling constants can be found by proton selective irradiations $J_{2,2'} \approx$ 13.9 Hz, $J_{1,2}=3.5$ Hz, $J_{1,2'}=6.8$ Hz. ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 127.7 ($C_{1,8}$), 108.9 (CMe_2), 82.2, 72.5 ($C_{3,4,5,6}$), 30.3 ($C_{2,7}$), 26.8 (CMe_2). **14**: ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm) 5.81–5.67 (m, 2H, $H_{1,8}$), 4.23 (s, 2H, $H_{4,5}$), 4.19–4.11 (m, 2H, $H_{3,6}$), 2.50–2.31 (m, 4H, $H_{2,2',7,7'}$), 1.42 (s, 6H, Me). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 128.0 ($C_{1,8}$), 108.2 (CMe_2), 77.0, 67.5 ($C_{3,4,5,6}$), 29.0 ($C_{2,7}$), 27.2 (CMe_2). **15**: ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm) 7.36–7.26 (m, 10H, Ph), 5.70–5.60 (m, 2H, $H_{1,8}$), 4.85 (AB, 2H, $J_{A,B}=11.4$ Hz, CH_2Bn), 4.53 (A′B′, 2H,

$J_{A',B'}$ = 11.4 Hz, CH_2Bn), 4.21–4.13 (m, 2H, $H_{4,5}$), 3.91 (m, 2H, $H_{3,6}$), 2.38–2.30 (m, 4H, $H_{2,2',7,7'}$). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 128.5, 128.3, 127.9 (C_{Ar}), 127.6, ($C_{1,8}$), 74.2 ($PhCH_2$), 78.3, 71.0 ($C_{3,4,5,6}$), 29.7 ($C_{2,7}$).

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