ORGANIC LETTERS

2001
Vol. 3, No. 5
731−733

Stereoselective Transformations on D-Glucose-Derived Eight-Membered Ring Carbocycles

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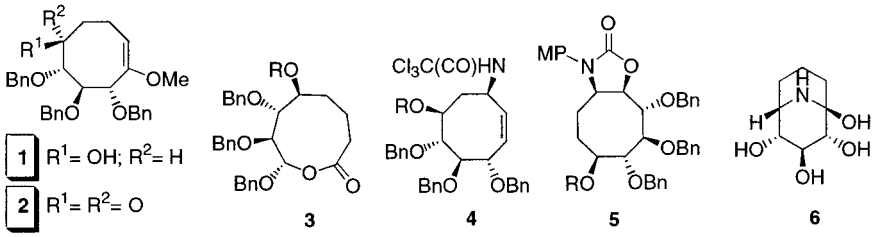
Received December 22, 2000

ABSTRACT



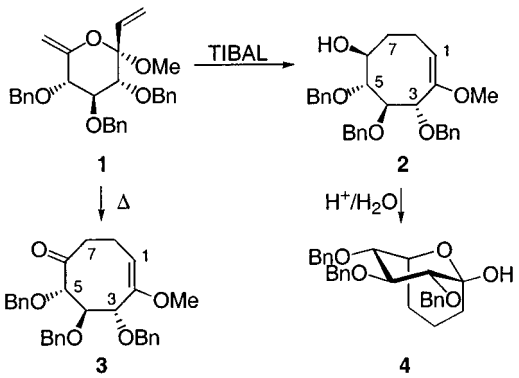
The cyclooctenol derivative 1 can be transformed into the nine-membered ring lactone 3, as well as the amino-containing carbocycles 4 and 5. The corresponding ketone 2 gives access to the conformationally locked azasugar 6.

In a recent paper from our laboratory[1] we revealed inter alia that methyl (4,5,6-tri-*O*-benzyl-1,2,8-trideoxy)-α-D-*xylo*-octa-1,7-dieno-3-ulopyranoside (**1**, see Scheme 1) could be smoothly converted via triisobutylaluminum (TIBAL) mediated Paquette rearrangement,[2,3] or thermally induced [3,3]-sigmatropic Claisen rearrangement, into the respective cyclooctenic compounds **2** and **3**. It was also established that **2** underwent a fast acid-catalyzed ring closure to give the locked L-idose derivative **4**.

We wish to report here several highly stereoselective transformations of the D-glucose-derived eight-membered ring carbocycles **2** and **3**.

To introduce additional functionalities on the cyclic framework of carbocycle **2**, we first explored whether the intrinsically fast acid-catalyzed ring closure (i.e., **2** → **4** in Scheme 1) could be prevented by silylation of the secondary hydroxyl group. Treatment of **2** under standard conditions with *tert*-butyldimethylsilyl chloride and imidazole in DMF

Scheme 1



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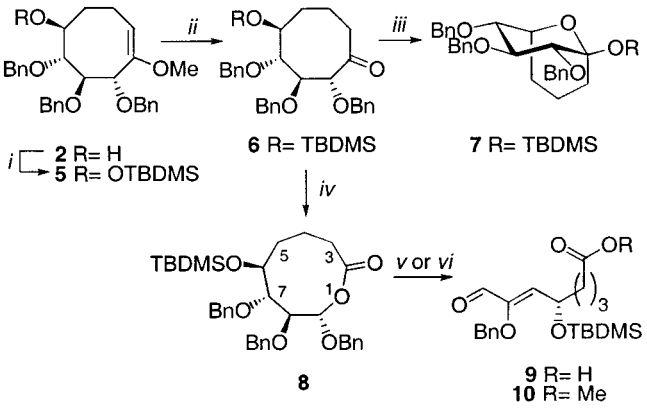
10.1021/ol007047+ CCC: $20.00
Published on Web 02/10/2001

Scheme 2[a]

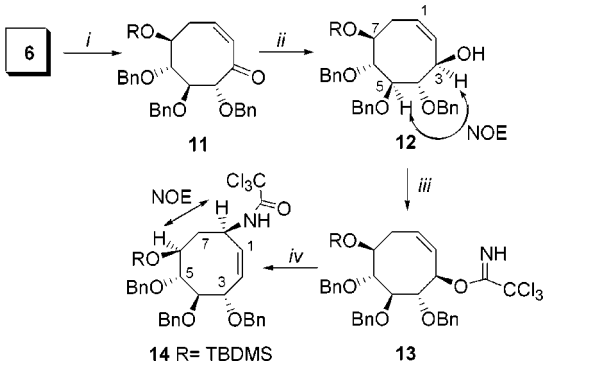


[a] Legend: (*i*) TBSOTf (1.2 equiv), DiPEA (1.2 equiv), CH_2Cl_2, −20 °C, 30 min (95%); (*ii*) *p*-TsOH, aqueous THF, 30 min (93%); (*iii*) *m*-CPBA, CH_2Cl_2, 20 °C, 20 h (95%); (*iv*) *m*-CPBA (4 equiv), $NaHCO_3$ (3 equiv), CH_2Cl_2, 20 °C, 20 h (64%); (*v*) 1 M NaOH, THF, 2 h (84%); (*vi*) NaOMe, MeOH, 2 h (78%).

(see Scheme 2) resulted in the near quantitative isolation of bicyclic compound **4**, instead of the silylated carbocycle **5**. On the other hand, protection of **2** using *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of *N*,*N*-diisopropylethylamine in dichloromethane at −20 °C afforded **5** in an excellent yield. Subjection of **5** to a catalytic amount of acid gave ketone **6** and a small amount of a product with a higher R_f value. At this stage, it was of interest to find out whether **6** would be compatible with a Baeyer−Villiger oxidation under acidic conditions. It turned out that reaction of **6** with *m*-chloroperoxybenzoic acid (*m*-CPBA, 2 equiv) in anhydrous dichloromethane led to the sole formation of the 1-*O*-silyl L-idose derivative **7**, which was in every aspect identical to the minor product observed in the aforementioned acid-catalyzed reaction of **5**. This result indicates that the silyl protecting group in **5** does not inhibit the highly favorable 6-*exo*-*trig* ring-closing reaction under acidic conditions. Fortunately, oxidation of **6** under basic conditions afforded the expected[4] lactone **8**. The regioselectivity of the latter oxidation was corroborated independently by ring opening of **8** with either NaOH or NaOMe to give the respective open-chain derivatives **9** and **10**, the structures of which were fully ascertained by mass spectrometry as well as NMR spectroscopy. The formation of the α,*β*-unsaturated aldehydes **9** and **10** can be readily explained by base-assisted elimination[5] of benzyl alcohol from the initially formed aldehyde.

The ketone function in **6** also offers a suitable handle for the installation of different functionalities on the carbocyclic framework. The latter possibility is demonstrated in the synthesis of the allylic amine derivative **14** (see Scheme 3).

Scheme 3[a]



[a] Legend: (*i*) (a) PhSeCl, EtOAc, 20 °C, 16 h, (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, −78 to −20 °C, 1 h, then DMS, Et_3N, 0 °C, 1 h (52%); (*ii*) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 4 h (56%); (*iii*) CCl_3CN, NaH (60% disp.), CH_2Cl_2, 0 °C, 6 h (57%); (*iv*) K_2CO_3, 1,2-dichlorobenzene, Δ, 2 h (80%).

To this end, **6** was first converted into the α,*β*-unsaturated ketone **11**. Initial attempts to achieve this objective following a standard protocol[6] (i.e., LDA, benzeneselenyl chloride (PhSeCl), then 30% H_2O_2) were unsatisfactory. On the other hand, reaction of **6** with PhSeCl in ethyl acetate,[7] followed by oxidation of the resulting crude selenyl derivative with *m*-CPBA and subsequent elimination,[8] furnished the α,*β*-unsaturated ketone **11** in 52% yield. Luche reduction[9] of **11** with cerium(III) chloride and sodium borohydride in methanol at 0 °C proceeded in a stereoselective fashion to give (3*R*,4*S*,5*R*,6*R*,7*S*)-4,5,6-tri(benzyloxy)-7-*tert*-butyldimethylsilyloxy-3-hydroxycyclooct-1-ene (**12**), as evidenced by NMR spectroscopy. Ensuing Overman rearrangement[10] under the improved conditions of Isobe et al.[11] of the trichloroacetimidate **13**, easily accessible by reaction of **12** with trichloroacetonitrile in the presence of sodium hydride at 0 °C, gave the corresponding (3*S*,4*R*,5*R*,6*S*,8*R*)-3,4,5-tri(benzyloxy)-6-*tert*-butyldimethylsilyloxy-8-trichloroacetamidocyclooct-1-ene (**14**) in 46% yield over two steps. NOESY experiments showed that the stereochemistry of **14** is in full accordance with the proposed structure.

The synthetic usefulness of allylic alcohol **12** was exemplified further by its transformation into the *cis*-oxazolidinone derivative **16** (see Scheme 4) via a two-step sequence recently devised by Nicolaou and co-workers.[12] Accordingly, the requisite urethane function in **15** was obtained by reaction of **12** with *p*-methoxyphenyl isocyanate in the presence of

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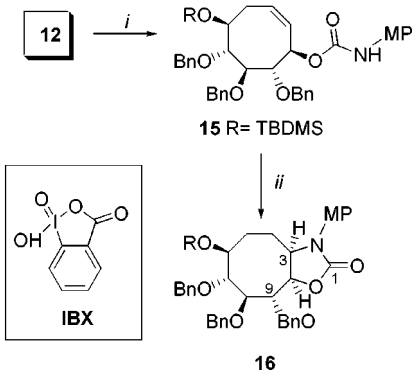
Scheme 4[a]

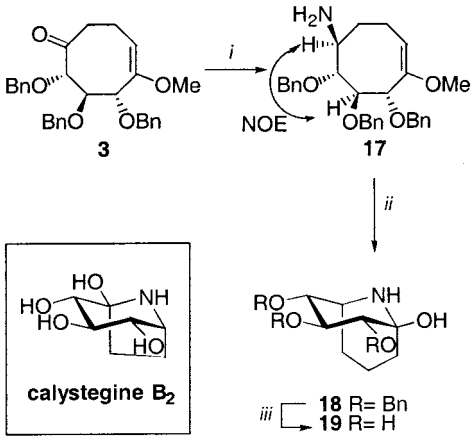


[a] Legend: (*i*) *p*-methoxyphenyl isocyanate (1.1 equiv), NaH (60% disp.), THF, 20 °C, 1.5 h (76%); (*ii*) IBX, THF/DMSO, 90 °C, 16 h (42%).

sodium hydride. Radical-mediated 5-*exo*-*trig* cyclization of **15** under the agency of *o*-iodoxybenzoic acid (IBX)[13] gave oxazolidinone derivative **16**. The presence of the expected *cis*-configuration of H-1 and 2 was inter alia gauged by NMR spectroscopy ($J_{3,10}$ = 6.8 Hz, $J_{9,10}$ = 9.0 Hz).

The acid-catalyzed ring closure of **2** into **4** (Scheme 1) was an incentive to prepare the conformationally restricted azasugar **19** from ketone **3** (see Scheme 5). Subjection of **3** to ammonium formate and reduction of the in situ formed imine with sodium cyanoborohydride in the presence of molecular sieves gave amine **17** with a high degree of diastereoselectivity. The *S*-configuration of the secondary amine function was corroborated by NMR spectroscopy. Treatment of **17** with a catalytic amount of *p*-toluenesulfonic acid for 2 h at ambient temperature furnished the bicyclic compound **18**. ^{1}H NMR spectroscopy clearly indicated that the piperidine ring in **18** adopts a $^4C_1$-conformation, based on the *trans* coupling of H-2, 3, and 4. Hydrogenation of **18** over palladium on activated carbon gave fully deprotected (1*S*,2*R*,3*S*,4*R*,5*S*)-1,2,3,4-tetrahydroxy-9-azabicyclo[3.3.1]-nonane (**19**), which is structurally related to calystegine B_2.[14] The latter naturally occurring compound is an inhibitor in the micromolar range[15] of both β-glucosidase and α-galactosidase.[16] Preliminary experiments showed that azasugar **19** did not exhibit any β-glucosidase or α-galactosidase inhibition.

Scheme 5[a]



[a] Legend: (*i*) $NH_4^+HCO_2^-$, $NaCNBH_3$, 3 Å sieves, MeOH/CH_2Cl_2, 24 h (39%); (*ii*) *p*-TsOH, aqueous THF, 20 °C, 2 h (67%); (*iii*) Pd/C, H_2, EtOH, 48 h (78%).

The results presented in this Letter clearly show that cyclooctenic derivatives **2** and **3** are valuable synthons in the construction of highly functionalized eight-membered ring carbocycles. Although several steps are not fully optimized (i.e., **6** → **11**, **15** → **16**, and **3** → **17**), we are of the opinion that our approach nicely compliments existing methodologies[17] for the synthesis of substituted eight-membered rings. The potential usefulness of structurally related carbocycles, derived from other and orthogonally protected sugars, is currently under investigation and will be presented in due course.

Acknowledgment. The authors thank Fons Lefeber and Cees Erkelens for recording the COSY and NOESY spectra and Hans van den Elst for performing the mass spectrometric analyses.

Supporting Information Available: Experimental procedures and full analytical data for compounds **3**, **10**, **12**, **14**, **16**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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