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Synthesis of differentially protected cyclopentitol: its application towards the stereoselective synthesis of 5-*epi*-calditol

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Abstract—The synthesis of differentially protected cyclopentitol derivative **5** is described using ring-closing metathesis of a diene derived from D-mannose. Subsequent chemical modifications such as catalytic osmylation and chain extension using glycidyl triflate completed the synthesis of 5-*epi*-calditol.

Cyclopentitols are unique derivatives isolated frequently as subunits of biologically active natural products (Fig. 1). Calditol (**1**) was isolated as a cell wall component of the extreme thermoacidophile *Sulfolobus solfatiricus* (a bacterium present in hot springs and responsible for the production of sulfuric acid from elemental sulfur).[1] Its absolute structure was the subject of speculation for a long time and Sinaÿ and co-workers resolved the issue once and for all by the total synthesis of calditol and its possible isomers.[2] Trehazolin (**2**) and bacterohopanetriol ethers **3** and **4** are some other natural products, which contain cyclopentitol as a subunit.[3,4] Samarium iodide mediated intramolecular pinacol coupling of suitably disposed ketoaldehydes seemed to be a popular strategy in the synthesis **1**–**4**.[2,5] Intrigued by the structural similarity between the cyclopentitol moieties of **1**–**4**, we initiated a programme directed towards the synthesis of these subunits preferably using a common starting point. Herein we report the synthesis of a differentially protected cyclopentitol derivative **5**, its stereo- selective dihydroxylation and conversion of the resulting diol into 5-*epi*-calditol **6**.

The synthesis began with the one carbon Wittig olefination of the known lactol **7** (derived from the crossed aldol reaction between diisopropylidene mannofuranose and formaldehyde in the presence of K_2CO_3 in methanol)[6] using $Ph_3P{=}CH_2$ to procure the olefin **8** in 83%

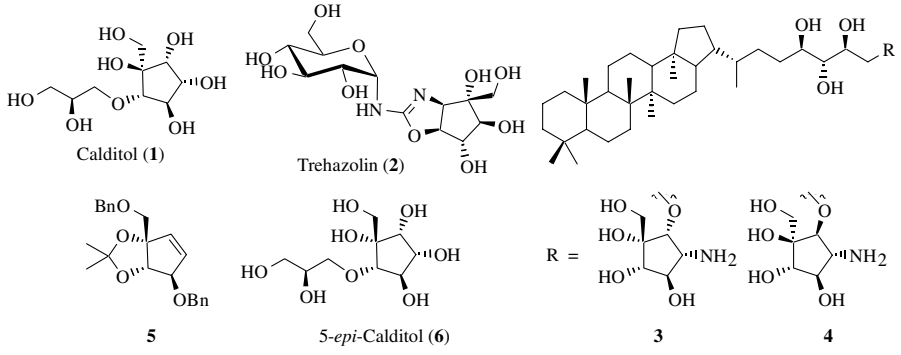

Figure 1.

Keywords: Calditol; Cyclopentitols; Ring closing metathesis; Second generation Grubbs' catalyst; Catalytic osmylation.
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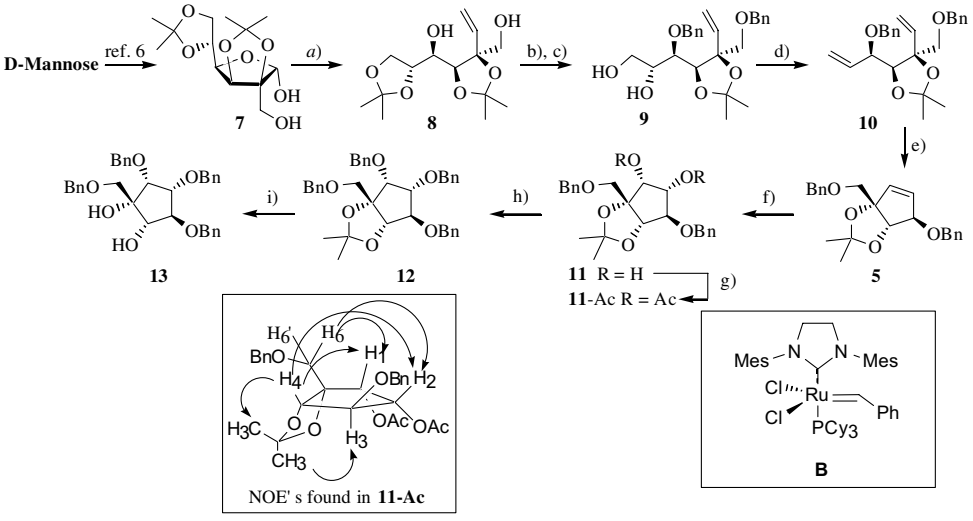
yield. The structure of olefin **8** was confirmed by ^{1}H NMR spectroscopy, in which signals due to the olefinic protons appeared at 5.32 and 5.92 ppm.

Protection of the diol **8** as the corresponding dibenzyl ether using benzyl bromide and NaH in DMF, followed by selective hydrolysis of the 5,6-isopropylidene group using 0.8% H_2SO_4 in methanol, gave the diol **9** in 82% overall yield. The resulting diol **9** was then treated with methanesulfonyl chloride and triethylamine in CH_2Cl_2 to afford the bis-mesylated compound in quantitative yield, which was subjected to elimination (by treating with sodium iodide in refluxing 2-butanone) without any further purification to afford the diene **10** in 70% yield.[7] The structure of diene **5** was confirmed by its ^{1}H NMR spectrum, in which six olefinic proton signals were present between 5.2–5.7 ppm.[8] As expected, our initial efforts to bring about the ring closing metathesis of diene **10** using the first generation Grubbs' catalyst met with failure. Although, Eustache and co-workers reported the successful RCM of a similar diene using Schrock's catalyst,[9] however, because of the superior stability as well as easy availability of the Grubbs' second generation catalyst we intended to use it in the present context. Gratifyingly, the RCM of **10** with second generation Grubbs' catalyst (**B**) was facile and the key cyclopentitol derivative **5** was obtained in 81% yield along with the unreacted **10** (11%).[10] The structure of compound **5** was confirmed by its ^{1}H NMR spectrum, in which only two olefinic proton signals were present at 5.90 (dd, $J = 2.3$, 5.8 Hz) and 6.05 (d, $J = 5.8$ Hz).[11]

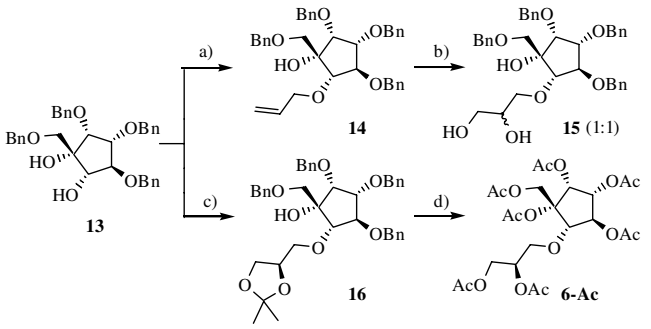
We next focused our attention on the diastereoselectivity of the dihydroxylation of **5**. Eustache and co-workers reported the dihydroxylation of a similar cyclopentitol derivative (albeit protected as its benzyl ethers) with an ≈2:1 diastereomeric ratio, the major being the one in which dihydroxylation occurred from the α-face.[9] The dihydroxylation of **5** was carried out using osmium tetroxide and *N*-methylmorpholine N-oxide in acetone/water solvent system and occurred exclusively from the α-face giving the diol **11**. For characterization, the diol **11** was converted to its diacetate **11-Ac** by treatment with acetic anhydride in pyridine. In the ^{1}H NMR spectrum of **11-Ac**, H(1) and H(2) appeared downfield at 5.21 (d, $J = 5.2$ Hz) and 5.29 (dd, $J = 7.3$, 5.2 Hz) ppm, respectively.[12] The observed NOE's between H(1) and H(6)/H(6′), H(4) and H(1)/H(2) in the NOESY spectrum of **11-Ac** clearly indicated a *syn*-spacial relation between these protons thus confirming its assigned structure (Scheme 1). After confirming the configuration of the resulting diol **11**, we proceeded to accomplish the synthesis of 5-*epi*-calditol. Treatment of the diol **11** with NaH and benzyl bromide in DMF followed by deprotection of the acetonide group with 80% aq acetic acid afforded **13** in 76% yield.

Our intended strategy for the installation of the glycidyl ether unit was the selective allylation of HO-C(4) of **13** and the Sharpless asymmetric dihydroxylation of resulting allyl ether. Selective allylation of **13** was carried out by treatment with 1.2 equiv each of NaH and allyl bromide in THF, the allyl ether **14** was obtained in 76% yield. Attempted asymmetric dihydroxylation of **14** using ADmix-β gave poor diastereoselectivity (inseparable 1:1 epimeric mixture).[13] After being met with discouraging results in the asymmetric dihydroxylation, we next focused our attention on alkylation of the diol **13** directly with the corresponding glycerol derivative (Scheme 2).

After initial investigations with different 2,3-*O*-isopropylidine (*R*)-glyceryl halides as well as with the corresponding 1-*O*-sulfonates, we found that **13** could be selectively alkylated (63% yield) by using 2,3-*O*-isopropylidine-(*R*)-glycerol-1-*O*-triflate and *n*-BuLi in THF. Deprotection of 5-*epi*-calditol **16** followed by peracetylation using acetic anhydride in pyridine and catalytic



Scheme 1. Reagents and conditions: (a) $PPh_3CH_3^+I^-$, $NaNH_2$, THF/EtO_2, 0 °C–rt, 10 h, 83%; (b) NaH, BnBr, DMF, 0 °C–rt, 4 h, 90%; (c) 0.8% w/v H_2SO_4/H_2O, MeOH, rt, 6 h, 91%; (d) MsCl, Et_3N, CH_2Cl_2, rt, 4 h, then NaI, 2-butanone, reflux, 6 h, 70% (overall); (e) **B** (2 mol%), C_6H_6, reflux, 6 h, 81%; (f) OsO_4, NMO, acetone/H_2O, rt, 12 h, 80%; (g) Ac_2O, pyridine, DMAP (cat), rt, 4 h, 89%; (h) NaH, BnBr, DMF, 0 °C–rt, 6 h, 95%; (i) 80% acetic acid/H_2O, 60 °C, 4 h, 80%.



Scheme 2. Reagents and conditions: (a) NaH, allyl bromide, THF, 0 °C–rt, 2 h, 76%; (b) ADmix-β, *t*-BuOH/H_2O, 0 °C, 18 h, 78%; (c) *n*-BuLi, 2,3-*O*-isopropylidene-(*R*)-glycerol-1-*O*-triflate, THF, −78–0 °C, 6 h, 63%; (d) Pd/C, H_2, MeOH/AcOH (1:0.01), 6 h, then Ac_2O, pyridine, DMAP (cat), 12 h, 61% (overall).

dimethylaminopyridine gave the hepta-acetyl-5-*epi*-calditol **6-Ac** in 61% overall yield. The spectral and analytical properties as well as the optical rotation of **6-Ac** are comparable with the reported values.[14]

To conclude, we have provided a simple preparative procedure for the synthesis of differentially protected cyclopentitol **5**, and its application towards the diastereoselective synthesis of 5-*epi*-calditol. Presently, work towards the synthesis of naturally occurring aminocyclopentitol derivatives from **5** using the Overman aza-Claisen rearrangement or epoxidation and subsequent inter/intramolecular opening with amino-nucleophiles is in progress.

Acknowledgements

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8. Spectral data of diene **10**: $[\alpha]_D^{25}$ +30.6 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.49, 1.56 (2s, 6H), 3.44 (d, $J = 10.5$ Hz, 1H), 3.47 (d, $J = 10.5$ Hz, 1H), 3.88 (t, $J = 8.3$ Hz, 1H), 4.38 (d, $J = 8.3$ Hz, 1H), 4.49 (d, $J = 12.4$ Hz, 1H), 4.52 (d, $J = 12.4$ Hz, 1H), 4.62 (d, $J = 12.3$ Hz, 1H), 4.64 (d, $J = 12.3$ Hz, 1H), 5.20 (dd, $J = 1.8$, 10.8 Hz, 1H), 5.27–5.32 (m, 2H), 5.46 (dd, $J = 1.8$, 17.1 Hz, 1H), 5.64 (ddd, $J = 8.3$, 10.8, 17.1 Hz, 1H), 5.77 (dd, $J = 10.8$, 17.1 Hz, 1H), 7.23–7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.5, 27.8, 70.0, 72.9, 73.5, 79.5, 80.3, 84.0, 108.2, 116.4, 120.2, 127.1, 127.5, 128.0, 128.2, 134.0, 136.2, 138.1, 138.5. Anal. Calcd for $C_{25}H_{30}O_4$: C, 76.11, H, 7.66. Found: C, 76.32, H, 7.55.
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11. Spectral data of cyclopentene **5**: $[\alpha]_D^{25}$ −41.7 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.36, 1.42 (2s, 6H), 3.61 (d, $J = 10.3$ Hz, 1H), 3.66 (d, $J = 10.3$ Hz, 1H), 4.42 (br s, 1H), 4.47 (d, $J = 2.3$ Hz, 1H), 4.54 (d, $J = 11.8$ Hz, 1H), 4.62 (s, 2H), 4.68 (d, $J = 12.1$ Hz, 1H), 5.90 (dd, $J = 2.3$, 5.8 Hz, 1H), 6.05 (br d, $J = 5.8$ Hz, 1H), 7.28–7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.7, 28.1, 71.5, 73.5, 84.4, 87.4, 94.7, 112.2, 127.4, 127.5, 128.2, 128.3, 132.0, 137.6, 138.1, 138.2. Anal. Calcd for $C_{23}H_{26}O_4$: C, 75.38, H, 7.15. Found: C, 75.14, H, 7.02.
12. Spectral data of diacetate **11-Ac**: $[\alpha]_D^{25}$: +47.6 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.35–1.47 (2s, 6H), 2.04–2.09 (2s, 6H), 3.60 (d, $J = 10.6$ Hz, 1H), 3.61 (d, $J = 10.6$ Hz, 1H), 4.12 (dd, $J = 2.9$, 7.3 Hz, 1H), 4.45 (d, $J = 2.9$ Hz, 1H), 4.58 (d, $J = 12.1$ Hz, 1H), 4.59 (d, $J = 12.0$ Hz, 1H), 4.63 (d, $J = 12.1$ Hz, 1H), 4.70 (d, $J = 12.0$ Hz, 1H), 5.21 (d, $J = 5.2$ Hz, 1H), 5.29 (dd, $J = 5.2$, 7.3 Hz, 1H), 7.25–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.7, 20.8, 27.1, 27.4, 72.0, 72.9, 73.1, 73.9, 75.6, 85.0, 85.1, 86.6, 114.1, 127.6, 127.7, 127.8, 128.4, 128.5, 137.6, 137.8, 169.3, 169.5. Anal. Calcd for $C_{27}H_{32}O_8$: C, 66.93, H, 6.66. Found: C, 66.56, H, 6.42.
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14. Spectral data of hepta-*O*-acetyl-5-*epi*-calditol (**6-Ac**): $[\alpha]_D^{25}$ +16.2 (*c* 0.6, $CHCl_3$); lit.[2] $[\alpha]_D^{20}$: +17.9 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 2.06–2.12 (7s, 21H), 3.52 (dd, $J = 4.3$, 10.1 Hz, 1H), 3.78 (dd, $J = 0.8$, 2.4 Hz, 1H), 3.88 (dd, $J = 4.8$, 10.1 Hz, 1H), 4.13 (dd, $J = 6.9$, 12.0 Hz, 1H), 4.17 (d, $J = 12.8$ Hz, 1H), 4.29 (dd, $J = 3.9$, 12.0 Hz, 1H), 4.87 (d, $J = 12.8$ Hz, 1H), 5.10–5.18 (m, 1H), 5.20 (t, $J = 5.7$ Hz, 1H), 5.32 (dd, $J = 2.8$, 6.3 Hz, 1H), 5.61 (dd, $J = 0.8$, 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.4, 20.7, 20.8, 20.9, 21.2, 61.9, 62.5, 69.2, 70.1, 71.7, 73.3, 80.5, 82.8, 83.2, 169.4, 169.6, 170.0, 170.1, 170.5. Anal. Calcd for $C_{23}H_{32}O_{15}$: C, 50.36, H, 5.88. Found: C, 50.52, H, 5.72.