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# Short syntheses of enantiopure calystegine $B_2$, $B_3$, and $B_4$

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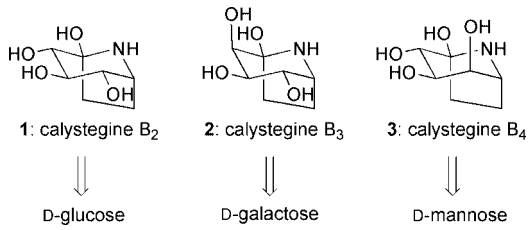
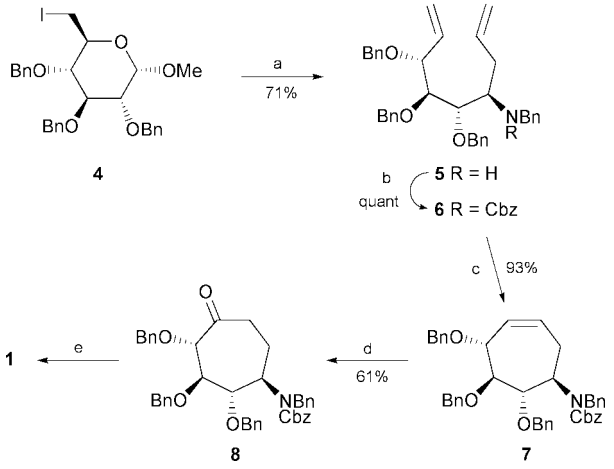
**Calystegine $B_2$, $B_3$, and $B_4$ have been prepared in 5 steps from the benzyl protected methyl 6-iodoglycopyranosides of glucose, galactose and mannose, respectively, by using a zinc-mediated domino reaction followed by ring-closing olefin metathesis as the key steps.**

Many polyhydroxylated alkaloids are important glycosidase inhibitors due to their structural resemblance to sugars.[1] A special class of these alkaloids is the calystegines which consist of a polyhydroxy-nortropane ring system.[2] Up to date, 14 different calystegines have been isolated from various plant species. Their structures have been elucidated mainly by NMR spectroscopy and they have been divided into four different classes: A, B, C and N. The absolute configuration, however, is known only for calystegine $B_2$ (**1**) and the configuration of all the remaining calystegines is presumed to be analogous to that of **1** based on biosynthetic considerations.[2] So far, only calystegine $A_3$ and $B_2$ have been prepared by chemical synthesis.[3]

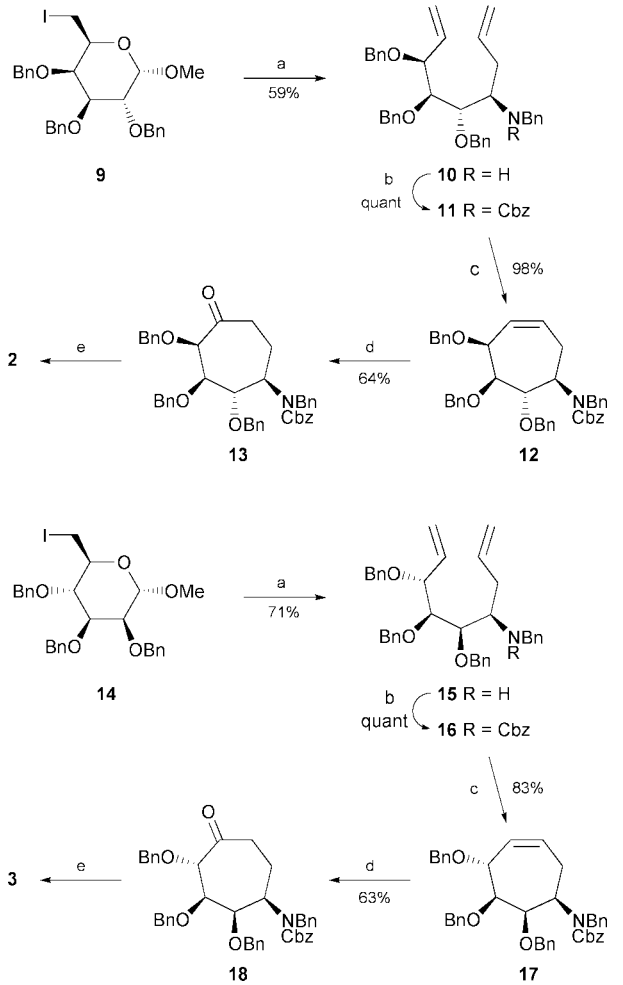



We have recently introduced a zinc-mediated domino reaction followed by ring-closing olefin metathesis for synthesis of polyhydroxylated carbocycles from sugars.[4,5] The domino reaction allows for the stereocontrolled introduction of an amino group and is then well suited for preparing the seven-membered carbocycle in the calystegines. Herein, we exploit these reactions for short syntheses of calystegine $B_2$, $B_3$ (**2**) and $B_4$ (**3**) starting from glucose, galactose and mannose, respectively.[6] Calystegine $B_2$ and $B_4$ are potent inhibitors of β-glucosidase and trehalase.[7]

The starting material for all three syntheses is the corresponding benzyl protected methyl 6-deoxy-6-iodo-α-D-glycopyranoside (Scheme 1). Sonicating a mixture of glucopyranoside **4** and excess zinc dust in dry THF caused a reductive fragmentation to generate the 5,6-unsaturated aldehyde[8] which was trapped *in situ* as the corresponding benzyl imine. Slow addition of allyl bromide to the mixture led to allylation of the imine to give a 5:1 mixture of amino dienes. The major diastereomer **5**[3a] was isolated in 71% yield and the stereochemistry verified after completing the synthesis of **1**. Cbz-protection of the amino group gave **6**† which was metathesised into cycloheptene **7** with the saturated *N*-heterocyclic carbene catalyst $(PCy_3)(C_3H_4N_2mes_2)Cl_2Ru{=}CHPh$.[4,9,10] The double bond in **7** is slightly polarized and can be hydroborated[11] followed by oxidation[12] in




**Scheme 1** *Reagents and conditions*: (a) Zn, $BnNH_2$, $CH_2{=}CHCH_2Br$, THF, sonication, 40 °C; (b) CbzCl, $KHCO_3$, EtOAc, $H_2O$; (c) 2% $(PCy_3)(C_3H_4N_2mes_2)Cl_2Ru{=}CHPh$, $CH_2Cl_2$, rt; (d) $BH_3$·THF, THF, −50 → 0 °C, then NaOH, $H_2O_2$, 0 °C, then Dess-Martin periodinane, $CH_2Cl_2$, rt; (e) $H_2$, Pd/C.




**Scheme 2** *Reagents and conditions*: (a) Zn, $BnNH_2$, $CH_2{=}CHCH_2Br$, THF, sonication, 40 °C; (b) CbzCl, $KHCO_3$, EtOAc, $H_2O$; (c) 2% $(PCy_3)(C_3H_4N_2mes_2)Cl_2Ru{=}CHPh$, $CH_2Cl_2$, rt; (d) $BH_3$·THF, THF, −50→ 0 °C, then NaOH, $H_2O_2$, 0 °C, then Dess-Martin periodinane, $CH_2Cl_2$, rt; (e) $H_2$, Pd/C.

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a one pot procedure to give a 3:1 mixture of ketones. Major ketone isomer **8** was isolated in 61% yield and hydrogenated to give calystegine $B_2$ ($[\alpha]_D^{20}$ +23.8 (*c* 0.31, $H_2O$)). NMR data and optical rotation were in accordance with those reported for the natural product.[13]

The same sequence was then applied to the synthesis of calystegine $B_3$ and $B_4$ (Scheme 2). Subjecting galactose-derived iodoglycoside **9** to the domino reaction gave a 2:1 mixture of amino dienes. Major diastereomer **10**‡ was isolated in 59% yield and then converted into cycloheptene **12**. Hydroboration and oxidation gave a 3:1 mixture of ketones and the major isomer **13** was isolated in 64% yield. Hydrogenation then furnished calystegine $B_3$ ($[\alpha]_D^{20}$ +75.6 (*c* 0.55, $H_2O$)) with NMR data and optical rotation in accordance with the data for the natural compound.[13] Subjecting mannose-derived iodoglycoside **14** to the domino reaction gave a 8:1 mixture of amino dienes and the major diastereomer **15**§ was isolated in 71% yield. The stereochemical outcome in these allylations is noteworthy. In all three cases the major product is the (*R*)-benzylamine which is the correct stereochemistry for the calystegines. The major product **15** from mannose is consistent with predictions from the Felkin-Anh model while the major isomers from glucose and galactose are not. This, however, does correspond with our previous experience on zinc-mediated alkylations of glucose and mannose substrates.[4a] Finally, amine **15** was converted into cycloheptene **17** which was hydroborated and oxidised to give a 3:1 ratio of ketones. The major isomer **18** was isolated in 63% yield and deprotected to give calystegine $B_4$ ($[\alpha]_D^{20}$ −46.4 (*c* 0.18, $H_2O$)). NMR data and optical rotation were similar to those reported for the natural product.[7]

In conclusion, a general strategy for preparation of the calystegines has been devised. Calystegine $B_3$ and $B_4$ have been prepared for the first time and their absolute configuration confirmed. These syntheses should hold great promise for making the calystegines and their analogues more readily available for biological investigations.

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## Notes and references

† All Cbz-protected compounds showed mixtures of rotamers by NMR.

‡ Spectral data for **10**: $\delta_H$ ($CDCl_3$) 7.35–7.22 (m, 20H), 5.98 (ddd, 1H, *J* 17.9, 10.0, 8.5), 5.65 (m, 1H), 5.31 (bd, 1H, *J* 10.0), 5.15 (bd, 1H, *J* 17.5), 5.00 (m, 2H), 4.92 (d, 1H, *J* 11.1), 4.84 (d, 1H, *J* 11.1), 4.72 (d, 1H, *J* 11.1), 4.56 (d, 1H, *J* 12.8), 4.53 (d, 1H, *J* 12.4), 4.29 (d, 1H, *J* 11.9), 4.18 (bs, 1H), 3.90 (d, 1H, *J* 13.2), 3.83 (dd, 1H, *J* 7.8, 3.2), 3.67 (d, 1H, *J* 13.2), 3.56 (bs, 1H), 2.66 (bs, 1H), 2.45 (m, 1H), 2.29 (m, 1H); $\delta_C$ ($CDCl_3$) 140.5, 139.1, 139.0, 138.7, 135.8, 135.1, 128.2–126.6 (20C), 118.9, 116.7, 82.6, 81.5, 80.1, 74.7, 74.5, 69.7, 56.7, 50.7, 34.5.

§ Spectral data for **15**: $\delta_H$ ($CDCl_3$) 7.43–7.25 (m, 20H), 6.00 (ddd, 1H, *J* 17.7, 10.4, 8.1), 5.79 (m, 1H), 5.39 (bd, 1H, *J* 17.5), 5.34 (bd, 1H, *J* 10.4), 5.10 (bd, 1H, *J* 17.9), 5.09 (bd, 1H, *J* 9.8), 4.83 (d, 1H, *J* 11.5), 4.75 (d, 2H, *J* 11.5), 4.71 (d, 1H, *J* 11.9), 4.58 (d, 1H, *J* 11.1), 4.44 (d, 1H, *J* 11.9), 4.29 (m, 1H), 3.89 (m, 1H), 3.83 (d, 1H, *J* 12.8), 3.82 (m, 1H), 3.77 (d, 1H, *J* 12.8), 3.08 (dt, 1H, *J* 8.0, 3.9), 2.51 (m, 1H), 2.36 (m, 1H); $\delta_C$ ($CDCl_3$) 140.6, 138.8, 138.6, 138.5, 136.4, 136.2, 128.8–125.9 (20C), 118.1, 117.0, 82.3, 81.1, 79.4, 74.4, 73.1, 70.4, 57.1, 51.7, 34.6.

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