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A short and efficient synthesis of (+)-calystegine B_2

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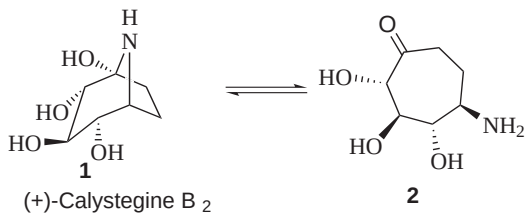
Abstract—A short synthesis of (+)-calystegine B_2 from (D)-glucose has been achieved, which involves as the key step a triple domino zinc-mediated reductive ring-opening, imine formation and allylation reaction of 6-iodoglucopyranose.

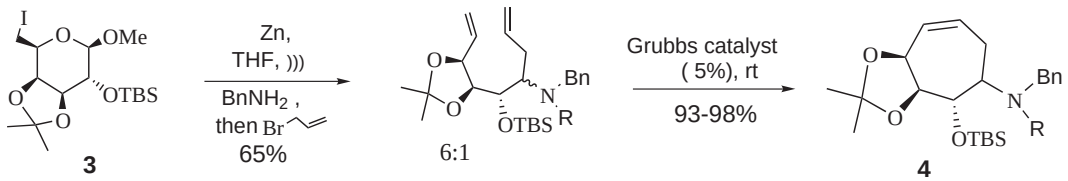
Calystegines[1] are polyhydroxylated nortropane alkaloids, first isolated from the roots of *Calystegia sepium* as plant metabolic mediators in the rhizosphere. Recently, they have been found in tuber tissues and in other plant organs of a large variety of potatoes (*Solanum tuberosum*…). This group of alkaloids is of interest in that most of its members are potent inhibitors of glycosidase enzymes.[2] Among them (+)-calystegine B_2 **1** selectively inhibits the rat liver β-glucosidase activity and the human lysosomal α-galactosidase A (a-Gal A) with an IC_{50} value of 30 μM. Several enantioselective and racemic syntheses of calystegines have been reported.[3–5] All of these proceeded via an appropriately substituted 5-amino-cycloheptanone intermediate (e.g. **2**), which is allowed to ring-close in the last stage of the synthesis into the bicyclic aminoketal structure, e.g. calystegine B_2 **1** (Scheme 1).



Scheme 1.

Previous reports from our laboratory described the synthesis of both (+) and (−)-calystegines B_2 through ring enlargement of the protected pseudosymmetric polyhydroxycyclohexanone derived from D-glucose.[4a,b] An alternative route to the aminocycloheptanone intermediate was also investigated via a Diels–Alder reaction between chiral acylnitroso derivatives and a protected polyhydroxycycloheptadiene.[4c] In yet another approach, both enantiomers of calystegine B_2 were synthesized by Depezay et al. using the intramolecular cycloaddition of an olefinic oxime derived from D-glucose.[5] Despite their success, these syntheses suffer from certain drawbacks, in particular their length since more than ten steps are required to reach the amino cycloheptane system.

In a recent report, we described the facile preparation of highly functionalized cycloheptenes from galactose derivatives. In particular, 6-iodogalactopyranose **3** underwent a zinc-mediated triple domino reaction fol-



Scheme 2.

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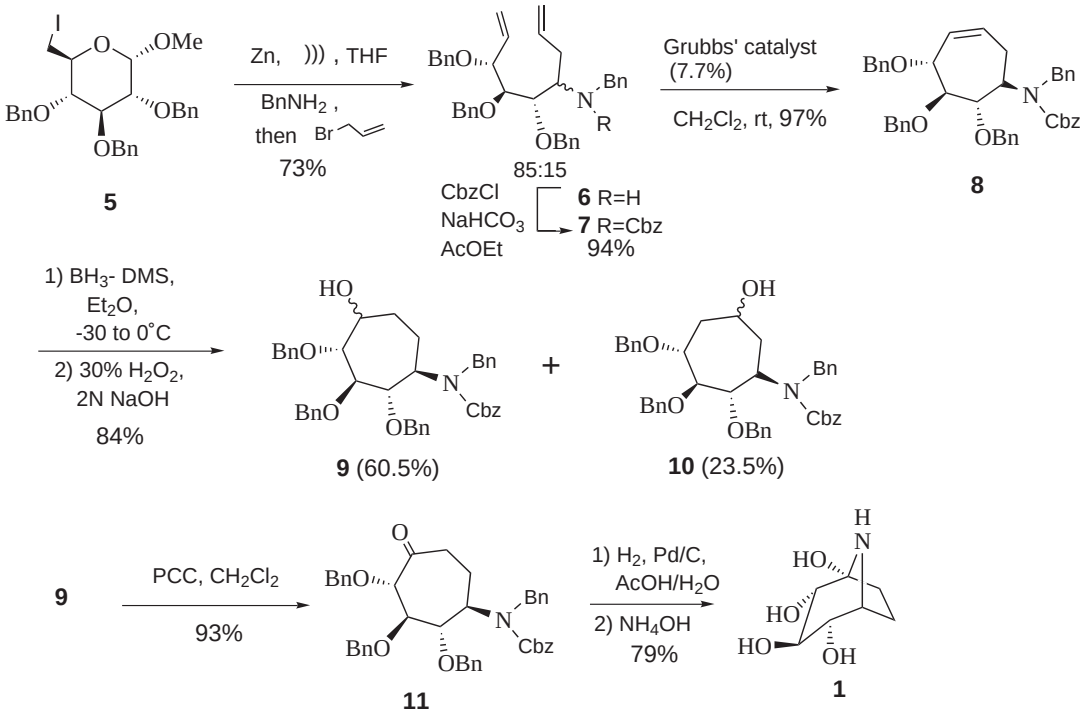

Scheme 3.

lowed by ring-closing olefin metathesis (RCM) to furnish the aminocycloheptene **4** in good yield (Scheme 2).[6] Herein we use this method[7] as the key-step in a concise synthesis of (+)-calystegine B_2.

The synthesis started from 6-iodoglucopyranose **5**,[8] readily prepared from the cheap and commercially available methyl-α-D-glucopyranoside. As for **3**, when **5** was subjected to zinc dust in the presence of benzylamine followed by the addition of allyl bromide in anhydrous THF under sonication, amino diene **6**[9] was obtained as an 85:15 mixture of diastereomers separated by flash column chromatography in 73% combined yield. (Scheme 3).

The *anti* configuration of the new asymmetric center in the major isomer was assigned later on the basis of the RCM reaction product, and confirmed in the final stage of the synthesis. The amino group was then protected as the benzyl carbamate **7**, and the major isomer was submitted to the ring-closing metathesis reaction[10] using Grubbs catalyst (0.077 equiv.) in CH_2Cl_2 at room temperature for 4.5 h to afford **8** as a mixture of atropoisomers in 97% yield. Hydroboration of olefin **8** with borane–methyl sulfide complex (BH_3–DMS) in diethyl ether at 0°C for 18 h followed by oxidative treatment (30% H_2O_2 and 2N NaOH for 3 h) gave a mixture of regioisomeric alcohols **9** and **10** (2.6:1) which were separated by flash chromatography in 84% combined yield. Oxidation of the major regioisomer **9** with pyridinium chlorochromate (PCC) in dichloromethane provided the desired ketone **11** in 93% yield. Finally, full deprotection of the triol and the amine functionality was accomplished by hydrogenolysis with 10% Pd/C in aqueous acetic acid for four days. Purification of the crude product using Dowex® 50W-X8 ion-exchange resin column (0.01 M HCl then 0.5% NH_4OH and 1% NH_4OH), followed by silica gel flash column chromatography (MeOH–H_2O 95:5) afforded **1** in 79% yield. The ^1H, ^{13}C NMR spectra and specific rotations ($[\alpha]_D = +24$ (*c* 1.14, H_2O) obtained from the aqueous solution of **1** are similar to those reported for (+)-calystegine B_2.[4b]

In conclusion, we have described a rapid (six steps from **5**, 25% yield overall) and efficient route to (+)-calystegine B_2, involving as the key-step a triple domino reaction: zinc-mediated reductive ring-opening, imine formation followed by allylation of 6-iodoglucopyranose derivative. This approach could be used for the synthesis of other calystegines.

References

1. For an excellent review on calystegines see: Molyneux, R. J.; Nash, R. J.; Asano, N. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W.; Ed; Elsevier Science: Oxford, 1996; Vol. 11, pp. 303–343.
2. For a recent review on sugar-mimic glycosidase inhibitors including calystegines see: Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680.
3. For racemic and enantioselective syntheses of calystegine A_3 see: (a) Boyer, F.-D.; Ducrot, P.-H.; Henryon, V.; Soulié, J.; Lallemand, J.-Y. *Synlett* **1992**, 357–359. (b) Johnson, C. R.; Bis, S. J. *J. Org. Chem.* **1995**, *60*, 615–623.
4. (a) Boyer, F.-D.; Lallemand, J.-Y. *Synlett* **1992**, 969–971; (b) Boyer, F.-D.; Lallemand, J.-Y. *Tetrahedron* **1994**, *50*,

10443–10458; (c) Faitg, T.; Soulié, J.; Lallemand, J.-Y.; Ricard, L. *Tetrahedron: Asymmetry* **1999**, *10*, 2165–2174.
5. (a) Duclos, O.; Duréault, A.; Depezay, J.-C. *Tetrahedron Lett*. **1992**, *33*, 1059–1062; (b) Duclos, O.; Mondange, M.; Duréault, A.; Depezay, J.-C. *Tetrahedron Lett*. **1992**, *33*, 8061–8064.
6. Hanna, I.; Ricard, L. *Org. Lett*. **2000**, *2*, 2651–2654.
7. For the use of this method for the synthesis of aminocyclohexene see: Hyldtof, L.; Poulsen, C. S.; Madsen, R. *Chem. Commun*. **1999**, 2101–2102. Hyldtof, L.; Madsen, R. *J. Am. Chem. Soc*. **2000**, *122*, 8444–8452.
8. Garegg, P. J.; Johansson, R.; Ortega, C.; Samuelsson, B. *J. Chem. Soc., Perkin Trans 1* **1982**, 681–683.
9. All new compounds were full characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, mass spectrometry and optical rotation. Data for **6** (major isomer)**:** $[\alpha]_D = -19.5$ (*c* 2.84, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.35–7.30 (m, 20 H), 6.00 (ddd, $J = 18$ Hz, $J = 10.5$ Hz, $J = 9$ Hz, 1 H), 5.66 (m, 1 H), 5.34–4.56 (m, 9 H), 4.14 (d, $J = 12$ Hz, 1 H), 4.02 (dd, $J = 7.5$ Hz, $J = 3$ Hz, 1 H), 3.90 (d, $J = 13$ Hz, 1 H), 3.86 (dd, $J = 7.5$ Hz, $J = 2$ Hz, 1 H), 3.76 (dd, $J = 7.5$ Hz, $J = 3$ Hz, 1 H), 3.50 (d, $J = 13$ Hz, 1 H), 2.50 (m, 2 H), 2.29 (m, 1 H), 1.55 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 141.1 (C), 139.4 (C), 138.9 (C), 138.2 (C), 136.4 (CH), 136.3 (CH), 136.4 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 126.9 (CH), 118.4 (CH_2), 116.9 (CH_2), 83.5 (CH), 80.8 (CH), 79.7 (CH), 75.4 (CH_2), 74.8 (CH_2), 70.2 (CH_2), 56.5 (CH), 50.9 (CH_2), 35.2 (CH_2). MS (CI) m/z (%) 548.8 ($[MH]^+$, 100), 506 (10), 160 (30). IR (neat, cm^{-1}): 3063, 3028, 2917, 2850, 1638, 1495, 1453, 1064, 730, 695.
10. For recent reviews concerning ring-closure metathesis reactions, see: (a) Fürstener, A. *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 3012–3043. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.