Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 4362

www.rsc.org/obc

PAPER

Total synthesis of *ent*-calystegine B4 *via* nitro-Michael/aldol reaction†

Akio Kamimura,*[a] Koichiro Miyazaki,[a] Shuzo Suzuki,[a] Shingo Ishikawa[a] and Hidemitsu Uno[b]

Received 22nd February 2012, Accepted 10th April 2012
DOI: 10.1039/c2ob25386k

Optically active *ent*-calystegine B4 was prepared in 13 steps from commercially available chiral L-dimethyl tartrate. The synthesis was achieved by the Michael addition and the aldol reaction of nitromethane to form cycloheptanone in a stereoselective manner. Reduction of the nitro group in the presence of Boc_2O accomplished an efficient conversion to amino cycloheptanone, which readily afforded the desired *ent*-calystegine B4.

Introduction

Calystegines are a family of polyhydroxylated nortropane alkaloids, which were first isolated in 1988 from Calystegia sepium.[1] So far, more than 10 calystegines have been isolated.[2] The calystegine family can be categorized according to the number of hydroxyl groups present as follows: calystegine A containing three hydroxyl groups, calystegine B containing four hydroxyl groups, and calystegine C containing five hydroxyl groups. Calystegine shows bioactivity similar to castanospermine and swainsonine, which are known to be glycosidase inhibitors.[3] The structure of calystegine contains a bicyclic ring unit that is simultaneously formed by aminocycloheptanone.[4] Thus, the total synthesis of calystegine will be achieved by developing a new method for the construction of the cycloheptane ring. Several synthetic efforts have been reported to date.[5]

Aliphatic nitro compounds are useful synthetic building blocks because activation by the nitro group facilitates the formation of carbon–carbon bonds under mild conditions.[6] The nitroaldol and nitro-Michael reactions are representative methods for this purpose.[7] We are interested in an intramolecular nitroaldol reaction to for medium sized ring structure.[7b,8] If the activation of nitromethane for the carbon–carbon bond formation effectively works twice, it will provide a short-step synthesis of cycloheptanes. In this paper, we report a new method to prepare *ent*-calystegine B4 using nitromethane as the key unit for the formation of the cycloheptane structure.

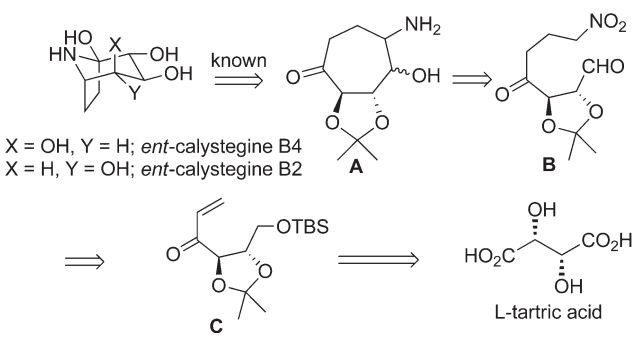
[a]*Department of Applied Molecular Bioscience, Graduate School of Medicine, Yamaguchi University, Ube 755-8611, Japan. E-mail: ak10@yamaguchi-u.ac.jp; Fax: +81 836 85 9231; Tel: +81 836 85 9231*
[b]*Department of Chemistry, Graduate School of Science and Engineering, Ehime University, Matsuyama 790-8577, Japan*

†Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR data for compounds **2**–**4** and **6**–**13** and CIF data and ORTEP charts for **11** and **12**. CCDC 857315 (**11**) and 868308 (**12**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25386k

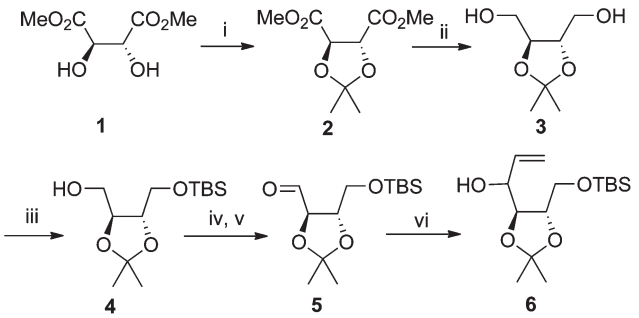
Results and discussion

The outline of our synthesis is depicted in Scheme 1. It is known that the bridged structure will be spontaneously formed when aminocycloheptane **A** is generated. Our aim was to form aminocycloheptanone **A** more efficiently. The nitro group was expected to be a good precursor of the amino unit and a good activating group for the formation of cycloheptanone. Thus, we planned to form the ring from intermediate **C** and nitromethane *via* Michael addition followed by intramolecular aldol reaction of **B**. The formation of calystegine B2 or B4 depends on the stereoselectivity of the nitroaldol reaction; if the OH occupies the pseudo-axial position, calystegine B4 will be prepared, whereas the OH group comes to pseudo-equatorial position, calystegine B2 will be generated. The precursor **C** will be converted from optically active tartaric acid, which is readily available in both enantiomers. In this study, we have started with more readily available L-tartrate, which will afford antipode of naturally occurring calystegine B.

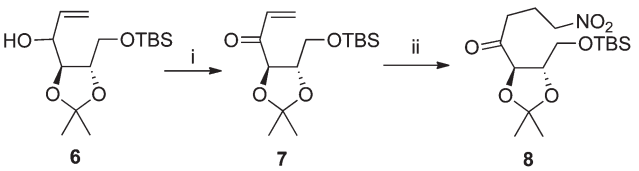
The first stage of the synthesis was the conversion of natural dimethyl L-tartrate **1** to compound **6** (Scheme 2). Treatment of **1** with 2,2-dimethoxypropane gave dimethylacetal **2**, which was reduced by $LiAlH_4$ to afford diol **3** in 75% yield.[9] Monoprotection of **3** was achieved by a reported method using cyclopentyl methyl ether (CPME) and mono-TBS ether **4** was obtained in



Scheme 1 Retrosynthetic analysis for *ent*-calystegine B.



Scheme 2 *Reagents and conditions*; i, $(CH_3)_2C(OMe)_2$, *p*-TsOH, $CHCl_3$, reflux, 5 h, 88%; ii, $LiAlH_4$, THF, reflux, 3 h, 75%; iii, TBSCl, NaH, CPME, 82%; iv, $(COCl)_2$/DMSO/CH_2Cl_2; v, Et_3N; vi, CH_2=CHMgBr/THF, 55% (2 steps).



Scheme 3 *Reagents and conditions*; i, Dess–Martin periodinane/CH_2Cl_2; ii, CH_3NO_2/base/rt, see Table 1.

Table 1 Conjugate addition of nitromethane to **7**

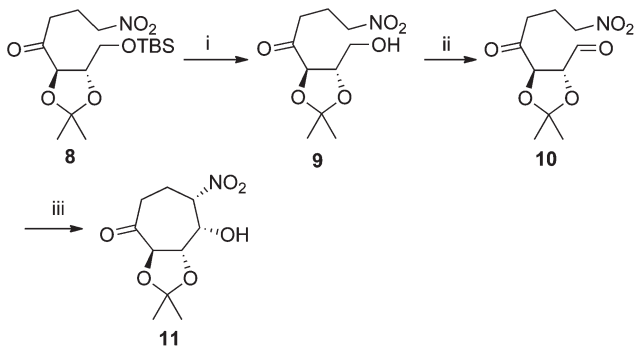
Entry	Base	Solvent	Time (h)	Yield[a] (%)
1	Et_3N	CH_3CN	2	18
2	DBU	DMF	24	35
3	TMG	DMF	36	63

[a] Isolated yield.

82% yield.[10] The Swern oxidation led to quantitative conversion of **4** into aldehyde **5**; however, we proceeded to next step without purification owing to lability of **5**. A vinyl group was introduced by treatment with vinyl magnesium bromide to form allyic alcohol **6**, which was isolated in 55% yield. Compound **6** contained the two diastereomers in about 1 : 1 ratio.

Oxidation of **6** was carried out using Dess–Martin periodinane,[11] forming the corresponding vinyl ketone **7** quantitatively (Scheme 3). This vinyl ketone was very unstable and readily polymerized when concentrated and maintained at room temperature for several hours. Thus, the next stage, the nitro-Michael reaction with nitromethane, was performed without purification of **7**. Exposure of **7** to nitromethane in the presence of catalytic amounts of a base resulted in the formation of **8**. The yield of **8** depended on the reaction conditions. The results are summarized in Table 1.

The reaction catalysed by Et_3N afforded **8** in 18% yield (entry 1). The use of tetramethylguanidine (TMG) and DBU, which are known as effective bases for the nitro-Michael reaction,[6c] improved the yield of **8** to 35% and 63% (entries 2 and 3), respectively, although the reaction time required was more than 24 h. Compound **8** was a stable compound and easily handled in further stages.



Scheme 4 *Reagents and conditions*; i, AcOH–THF–MeOH, 62%; ii, Dess–Martin periodinane/CH_2Cl_2; iii, TMG/DMF/rt, 40% (2 steps).

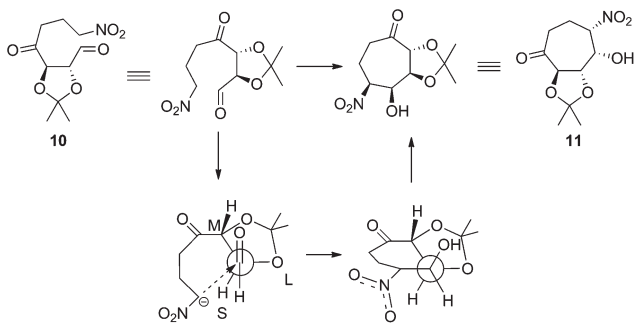
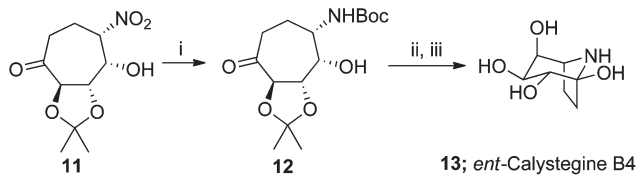


Fig. 1 Plausible origin of the stereoselectivity of the nitroaldol reaction.

We examined several conditions for the removal of the TBS group from **8** and found that the treatment with acetic acid afforded nitroalcohol **9** in 62% yield, although HF-pyridine afforded **9** in 57% yields (Scheme 4). Oxidation of the primary alcohol was achieved by Dess–Martin periodinate oxidation.[11] We performed the subsequent intramolecular nitroaldol reaction without further purification because aldehyde **10** was unstable. The intramolecular nitroaldol reaction proceeded smoothly in the presence of TMG as the catalyst, affording the desired cycloheptane **11** in 40% yield as a single isomer. Stereochemistry determined by X-ray crystallographic analysis showed the configuration unambiguously.[12] This stereoselectivity allowed us to prepare *ent*-calystegine B4.

The reaction appears to favour the Felkin–Anh type nucleophilic attack that affords an *S*-configuration at the C8 hydroxyl position. Subsequent protonation at the C7 nitronate occurred in a thermodynamically controlled manner to afford **9**, because the nitro group occupies the pseudo-equatorial position that avoids steric congestion (Fig. 1).[13,14]

The final stage of our synthesis continued with the reduction of **11** to amino cycloheptane (Scheme 5).[15] Although simple hydrogenation occurred smoothly, it was very difficult to isolate the reduced compounds. This was probably due to the instability of aminoketone that was expected to be generated under the reaction conditions. Thus, we investigated the entrapment of the amino group by conversion to *tert*-butyl carbamate (Boc) amide that prevented the undesirable side reaction by the amino group. Treatment of **11** under hydrogenation conditions in the presence



Scheme 5 *Reagents and conditions*; i, $(Boc)_2O$/Pd-C/H_2/THF/rt, 84%; ii, 12 M HCl/THF; iii, Dowex-SBR/MeOH, 50% (2 steps).

of Boc_2O formed Boc-protected cycloheptanone **12** in 84% yield. The structure of **12** was unambiguously determined by X-ray crystallographic analysis.[16] This was isolated as a single isomer, indicating that no undesirable epimerization occurred. The final stage was global deprotection under acidic conditions. Exposure of **12** to a catalytic amount of conc. HCl readily formed the calystegine B4 HCl salt. The crude salt was isolated by the simple removal of the solvent under reduced pressure. Conversion of the HCl salt to *ent*-calystegine B4 was carried out by treatment with Dowex acidic resin in MeOH. This procedure offered a significant advantage because removal of water, which is a usually troublesome procedure requiring freeze dry apparatus, was not necessary. *ent*-Calystegine B4 **13** was readily isolated by passing a MeOH solution of the crude product through a Dowex short column and then removing MeOH by using a conventional rotary evaporator. ^{13}C NMR data for compound **13** were identical to the data for previously reported calystegine B4.[3d] The observation that H4 signal appeared at 3.74 ppm as triplet (J = 3.1 Hz) also supports the structure. The optical rotation was positive, and our compound was an antipode of the natural product.

Conclusion

In conclusion we have successfully achieved the total synthesis of *ent*-calystegine B4 in 13 steps starting from commercially available L-tartrate. The key reaction was the intramolecular nitroaldol reaction that yielded polyhydroxylated cycloheptanone. The reaction occurred in a stereoselective manner to form nitrocycloheptanone as a single isomer. Conversion of the nitro group to amine was readily achieved under pressurized hydrogenation conditions in the presence of Boc_2O. We believe that the intermediate Boc-amide cycloheptanone would be useful for conversion to other calystegine compounds such as A3. Although we prepared antipodes of naturally occurring calystegine, natural forms would be synthesized if the starting material was D-tartrate. We think this procedure will provide a convenient synthesis of calystegine alkaloids.

Experimental section

General

All ^1H and ^{13}C NMR spectra were recorded on JEOL Delta-500 or Lambda-500 (500 MHz for ^1H and 125 MHz for ^{13}C) spectrometer. High resolution mass spectra (HRMS) were measured at Tokiwa Instrumentation Centre, Yamaguchi University and Integrated Centre for Sciences, Ehime University, Matsuyama, Japan. All reactions in this paper were performed under a nitrogen atmosphere unless otherwise mentioned. Dess–Martin periodinane was prepared by a reported procedure.[11] Other compounds were purchased from Aldrich Co. Ltd. and were used without further purification. Anhydrous THF was purchased from Kanto Kagaku Co. Ltd. CPME was donated from Zeon Co. Ltd.

Preparation of (4*R*,5*R*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (2)

A solution of **1** (114.5 g, 0.643 mol), 2,2-dimethoxypropane (81.471 g, 0.785 mol) and *p*-toluenesulfonic acid hydrate (1.2272 g, 6.45 mmol) in $CHCl_3$ (350 mL) was heated at refluxing temperature for 5 h. The reaction mixture was neutralized by adding K_2CO_3 (1.271 g) and filtered. The filtrate was concentrated *in vacuo* to give compound **2** in 88% yield (118.75 g), which was used for the next step without further purification. Oil; $[\alpha]_D$ −37.46° (c 1.34, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (2H, s), 3.82 (6H, s), 1.49 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 113.8, 52.7, 26.3; IR (neat) ν 2995, 1743, 1207, 1109 cm^{-1}; HRMS (ESI M + Na) m/z 241.0691. Calcd for $C_9H_{14}O_6Na$ 241.0688.

Preparation of ((4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)-dimethanol (3)

A solution of **2** (10.91 g, 50 mmol) in THF (20 mL) was slowly added to a suspension of $LiAlH_4$ (5.6925 g, 150 mmol) in THF (40 mL). The reaction mixture was heated at refluxing temperature for 3 h. After cooling, EtOAc (10 mL) was added slowly, and the resulting mixture was filtered. The filtrated was concentrated *in vacuo* and the residue was purified by flash chromatography (silica gel/hexane–EtOAc) to give compound **3** in 75% yield (6.1295 g). Pale yellow oil; $[\alpha]_D$ +1.86° (c 2.58, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.16–3.93 (2H, m), 3.84–3.79 (2H, m), 3.73–3.67 (2H, m), 2.03–1.98 (2H, m), 1.57 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 109.3, 78.4, 62.2, 26.9; IR (neat) ν 3200–3600, 2987, 1045 cm^{-1}.

Preparation of ((4*S*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (4)

Under a nitrogen atmosphere, a solution of **3** (18.99 g, 50.5 mmol) in CPME (20 mL) was added to a suspension of NaH (2.351 g, 60%, 59.13 mmol) in CPME (180 mL) over 15 min at 0 °C. TBSCl (8.018 g, 53.2 mmol) in CPME (20 mL) was added to the reaction mixture at 0 °C and the resulting solution was stirred at the same temperature for additional 15 min and at room temperature for 3 h. Saturated NH_4Cl aq (30 mL) was added and the organic phase was separated. The aqueous solution was extracted with EtOAc (100 mL × 3). Organic phases were combined, washed with brine (20 mL) and dried over Na_2SO_4. After filtration, the organic solution was concentrated. The residue was purified by flash chromatography (silica gel/hexane–EtOAc 50 : 1, 30 : 1 then 10 : 1) to give **4** in 82% yield (11.399 g). Colorless oil; $[\alpha]_D$ +16.90° (c 1.28, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.06–3.74 (3H, m), 3.76–3.51 (3H, m), 2.79–2.58 (1H, m), 1.37 (3H, s), 1.36 (3H, s), 0.86

(9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 109.1, 80.1, 78.0, 63.7, 62.7, 27.0, 26.9, 25.8, 18.3, −5.5, −5.6; IR (neat) ν 3200–3600, 1371, 1251, 1080 cm^{-1}; HRMS (ESI M + H) m/z 277.1838. Calcd for $C_{13}H_{29}O_4Si$ 277.1835.

Preparation of 1-((4*S*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (6)

DMSO (10.0 mL, 140.8 mmol) was added to a solution of oxalyl chloride (12.5 mL, 145.95 mmol) in CH_2Cl_2 (300 mL) at −78 °C over 20 min. A solution of compound **5** (29.784 g, 107.7 mmol) in CH_2Cl_2 (50 mL) was added to the solution at the same temperature over 30 min. Et_3N (34.0 mL, 243.9 mmol) was added to the reaction mixture over 30 min. The resulting solution was stirred for an additional 30 min at the same temperature and then at room temperature for 4 h. Water (100 mL) was added and the organic phase was separated. The water phase was extracted with CH_2Cl_2 (30 mL × 3). The organic phases were combined and dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. The resulting crude aldehyde **5** (33.842 g) was used to the next step without further purification. Crude aldehyde **5** (33.756 g,) was dissolved in THF (350 mL) and cooled to 0 °C. A THF solution of vinyl magnesium bromide (1.0 M, 140 mL, 140 mmol) was added to the solution over 1 h, and the reaction mixture was stirred at room temperature for 60 h. Saturated NH_4Cl aq (120 mL) was added to the reaction mixture and THF was removed by using a rotary evaporator. The aqueous residue was extracted with EtOAc (50 mL × 3) and the organic phase was dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel/hexane–EtOAc) to give **6** in 55% yield (18.047 g). Isolated as a mixture of the two diastereoisomers. Pale yellow viscous oil; $[\alpha]_D$ +24.2° (c 0.99, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (1H, ddd, J = 16.5, 10.4, 5.7 Hz), 5.41 (1H for major isomer, dt, J = 17.2, 1.6 Hz), 5.39 (1H for minor isomer, dt, J = 17.2, 1.6 Hz), 5.26 (1H, dt, J = 10.6, 1.5 Hz), 4.25–4.18 (1H, m), 4.01–3.94 (1H, m), 3.82 (2H, ddd, J = 17.1, 9.7, 3.7 Hz), 3.74–3.66 (1H, m), 3.12 (1H for major isomer, d, J = 2.2 Hz), 2.68 (1H for minor isomer, d, J = 7.8 Hz), 1.42 (3H for minor isomer, s), 1.41 (3H for major isomer, s), 1.40 (3H for minor isomer, s), 1.39 (3H for major isomer, s), 0.91 (9H for major isomer, s), 0.90 (9H for minor isomer, s), 0.10 (6H for major isomer, s), 0.08 (6H for minor isomer, s); ^{13}C NMR (68 MHz, $CDCl_3$) δ 137.3, 136.6, 116.9, 116.7, 111.7, 109.5, 81.9, 81.6, 78.8, 77.3, 72.8, 71.9, 64.1, 63.8, 27.1, 27.0, 26.9, 26.8, 25.9, 18.4, 18.3, −5.5, −5.6.; IR (neat) ν 3600–3200, 1707, 1371, 1217, 1051 cm^{-1}; HRMS (ESI M + H) m/z 303.1990. Calcd for $C_{15}H_{31}O_4Si$ 303.1992.

Preparation of 1-((4*R*,5*S*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-one (8)

Dess–Martin periodinane (3.1798 g, 7.5 mmol) was added to a solution of **6** (1.5084 g, 5.0 mmol) in CH_2Cl_2 (50 mL) at room temperature and the resulting mixture was stirred for 30 min. The $Na_2S_2O_3$ (12 g) solution in saturated $NaHCO_3$ aq (55 mL) was added to the reaction mixture and the resulting mixture was extracted with ether (3 × 50 mL). The organic phase was washed with $NaHCO_3$ and brine, and then dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel/hexane–EtOAc) to give **7** in 92% yield (1.3782 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (1H, dd, J = 17.5, 10.6 Hz), 6.45 (1H, dd, J = 17.5, 1.7 Hz), 5.83 (1H, dd, J = 10.6, 1.6 Hz), 4.54 (1H, d, J = 7.2 Hz), 4.14 (1H, dt, J = 11.1, 3.9 Hz), 3.87 (1H, dd, J = 11.2, 3.8 Hz), 3.77 (1H, dd, J = 11.2, 3.9 Hz), 1.46 (3H, s), 1.40 (3H, s), 0.90 (9H, s), 0.08 (3H, s), −0.01 (3H, s).

TMG (0.1 g) was added to a solution of **7** (1.3782 g, 4.59 mmol) and CH_3NO_2 (1.58 mL, 22.9 mmol) in DMF (3 mL), and the resulting solution was allowed to stand at room temperature for 14 h. aq. NH_4Cl (10 mL) was added and the mixture was extracted with ether (3 × 50 mL). The organic phase was washed with brine, and then dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel/hexane–EtOAc) to give **8** in 69% yield (1.1409 g). Pale yellow oil; $[\alpha]_D$ +31.83° (c 0.98, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44 (2H, t, J = 6.6 Hz), 4.34 (1H, d, J = 7.6 Hz), 4.02 (1H, dt, J = 7.4, 3.6 Hz), 3.88 (1H, dd, J = 11.3, 3.5 Hz), 3.75 (1H, dd, J = 11.3, 3.8 Hz), 2.90–2.76 (2H, m), 2.32–2.24 (2H, m), 1.44 (3H, s), 1.41 (3H, s), 0.89 (9H, s), 0.07 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.8, 111.0, 81.1, 78.9, 74.5, 62.8, 34.9, 26.8, 26.4, 25.9, 25.6, 20.6, −3.6, −5.5; IR (KBr) ν 2929, 1722, 1554, 1373 cm^{-1}; Anal. Calcd for $C_{16}H_{31}NO_6Si$: C, 53.16; H, 8.64; N, 3.87. Found: C, 53.32; H, 8.71; N, 3.89.

Preparation of 1-((4*R*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-one (9)

A solution of **8** (688.8 mg, 1.907 mmol) in AcOH–THF–H_2O (1.8 mL : 0.6 mL : 0.6 mL) was allowed to stand at 40 °C for 14 h. Saturated $NaHCO_3$ aq (20 mL) was added and THF was removed *in vacuo*. The resulting aqueous mixture was extracted with CH_2Cl_2 (3 × 50 mL) and organic phase was dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel/hexane–EtOAc) to give **9** in 62% yield (292.0 mg). Colorless oil; $[\alpha]_D$ +21.24° (c 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (2H, t, J = 6.6 Hz), 4.30 (1H, d, J = 8.0 Hz), 4.08 (1H, dt, J = 8.0, 3.6 Hz), 3.93 (1H, ddd, J = 12.0, 4.4, 3.4 Hz), 3.74 (1H, ddd, J = 13.4, 8.6, 3.8 Hz), 3.00–2.73 (2H, m), 2.38–2.18 (2H, m), 1.95 (1H, dd, J = 8.6, 4.5 Hz), 1.47 (3H, s), 1.42 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.1, 110.8, 81.0, 78.2, 74.3, 61.9, 34.9, 26.5, 25.9, 20.3; IR (neat) ν 3600–3200, 2924, 1717, 1552, 1373, 1091 cm^{-1}; Anal. Calcd for $C_{10}H_{17}NO_6$: C, 48.48; H, 6.93; N, 5.67. Found: C, 48.30; H, 6.95; N, 5.41.

Preparation of (3a*R*,7*S*,8*S*,8a*S*)-8-hydroxy-2,2-dimethyl-7-nitrotetrahydro-3a*H*-cyclohepta[*d*][1,3]dioxol-4(5*H*)-one (11)

Dess–Marin periodinane (556.8 mg, 1.31 mmol) was added to a solution of **9** (211.6 mg, 0.876 mmol) in CH_2Cl_2 (16 mL) at room temperature and the resulting mixture was stirred for 60 min. The $Na_2S_2O_3$ (2.2 g) solution in saturated $NaHCO_3$ aq (11 mL) was added to the reaction mixture and the resulting mixture was extracted with ether (3 × 50 mL). The organic phase

was washed with $NaHCO_3$ and brine and then dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo* to give crude **10** in 221.5 mg, which was used in the next step without further purification. Crude **10** (221.5 mg) was dissolved in DMF (400 mL) and TMG (1 drop) was added. The reaction mixture was allowed to stand for 48 h. DMF was removed under reduced pressure. The residue was subjected to flash chromatography (silica gel/hexane–EtOAc) to give **11** in 40% yield (86.2 mg). The product was further purified by recrystallization from CH_2Cl_2. White solid; mp 152–153 °C; $[\alpha]_D$ +53.8° (c 1.18, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (1H, d, J = 10.0 Hz), 5.08–5.05 (1H, m), 4.42 (1H, d, J = 11.6 Hz), 3.94 (1H, dd, J = 10.0, 1.8 Hz), 2.84 (1H, ddd, J = 19.5, 5.9, 2.5 Hz), 2.77 (1H, ddd, J = 14.3, 4.3, 2.4 Hz), 2.76–2.72 (1H, m), 2.49–2.45 (1H, m), 2.42 (1H, ddd, J = 16.3, 10.4, 2.7 Hz), 1.56 (3H, s), 1.48 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.4, 111.8, 86.3, 78.1, 68.2, 37.7, 26.7, 26.6, 18.9, 0.1; IR (KBr) ν 3500–3200, 1985, 1722, 1556, 1375, 1165, 1084 cm^{-1}; Anal. Calcd for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.17; N, 5.71. Found: C, 49.01; H, 6.22 N, 5.68.

Preparation of *tert*-butyl ((3*aS*,4*S*,5*S*,8*aR*)-4-hydroxy-2,2-dimethyl-8-oxohexahydro-3*aH*-cyclohepta[*d*][1,3]dioxol-5-yl)carbamate (12)

A mixture of **11** (96.4 mg, 0.39 mmol), Boc_2O (440.8 mg, 2.02 mmol) and 10% Pd/C (98.6 mg) in THF (17 mL) was shaken at room temperature in an autoclave under a hydrogen atmosphere at 5 MPa for 16 h. Pd/C was removed by filtration on Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel/hexane–EtOAc) to give compound **12** in 84% yield (103.7 mg). White solid; mp 186–187 °C; $[\alpha]_D$ −38.8° (c 0.78, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (1H, d, J = 8.7 Hz), 5.06 (1H, d, J = 10.0 Hz), 4.29 (1H, s), 3.90 (1H, dd, J = 10.0, 1.5 Hz), 3.68 (1H, t, J = 10.1 Hz), 2.72 (1H, s), 2.65 (1H, ddd, J = 20.0, 5.9, 2.1 Hz), 2.44 (1H, ddd, J = 19.7, 13.2, 2.5 Hz), 2.25 (1H, dd, J = 25.5, 12.4 Hz), 1.79–1.69 (2H, m), 1.45 (3H, s), 1.43 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.6, 155.1, 110.9, 80.0, 78.4, 77.8, 69.0, 52.6, 38.9, 28.5, 26.9, 26.5, 23.3; IR (KBr) ν 3500–3400, 2980, 1714, 1697, 1494, 1163 cm^{-1}; Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.15; H, 7.93 N, 4.26.

Preparation of (+)-calystegine B4 (13)

HCl aq (12 M, 0.1 mL) was added to a solution of **12** (44.1 mg, 0.14 mmol) in THF (1.5 mL) at room temperature and the reaction mixture was stirred for 4 h. The resulting mixture was concentrated to a solid under reduced pressure. The residue was dissolved in MeOH (3 mL) and passed through a Dowex SBR column. The eluent was concentrated *in vacuo* to give (+)-calystegine B4 in 50% yield (11.6 mg). Colorless oil; $[\alpha]_D$ +81.21° (c 0.39, H_2O) (lit.[3d] −63.0° (c 0.65, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 3.74 (1H, t, J = 3.1 Hz), 3.56 (1H, s), 3.56 (1H, s), 3.36 (1H, dd, J = 7.8, 3.0 Hz), 2.15–2.00 (1H, m), 2.00–1.91 (1H, m), 1.54–1.39 (2H, m); ^{13}C NMR (126 MHz, D_2O) δ 92.4, 79.4, 74.7, 73.6, 59.0, 29.6, 24.9; HRMS (FAB M + H) m/z 176.0926. Calcd for $C_7H_{14}O_4N$ 176.0923.

Acknowledgements

We are grateful for the financial support from Yamaguchi University based on The YU Strategic Program for Fostering Research Activities (2010–2011).

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