Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 1293–1299

TETRAHEDRON

Asymmetric synthesis of (+)-1-deoxynojirimycin and (+)-castanospermine

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Received 27 September 2002; revised 27 November 2002; accepted 19 December 2002

Abstract—Asymmetric total syntheses of (+)-1-deoxynojirimycin (**1**) and (+)-castanospermine (**2**) are described. Starting from diene **3**, the required absolute stereochemistry is introduced by an asymmetric hydroxylation followed by epoxidation. An intramolecular cyclization of amine **17** gives access to the corresponding tetrasubstituted piperidine **18**, which is a precursor to compounds **1** and **2**. (+)-Deoxynojirimicyn (**1**) was obtained in 36% yield over 11 steps from diene **3**, while (+)-castanospermine (**2**) was achieved in 13% after 19 steps from the same starting material.

1. Introduction

(+)-Deoxynojirimycin (**1**) and (+)-castanospermine (**2**) are naturally occurring polyhydroxylated alkaloids known as aza-sugars. Several structurally related congeners are known, of which some are shown in Figure 1. (+)-Castanospermine (**2**) was first isolated as the major alkaloid component from the seeds of *Castanospermum australe*,[1] and later of the dried pod of *Alexa leiopetala*,[2] and was found to be a powerful inhibitor of α- and β-glucosidases,[3–6] while (+)-1-deoxynojirimycin (**1**) was extracted from the roots of mulberry trees[7] and also inhibits α-glucosidases I and II.[8] In addition, compounds **1** and **2** also show promising anitiviral[9] and anticancer properties.[9,10] It has also been found that derivatives of **1** and **2** exhibit interesting biological properties.[8,11] Due to the interesting biological activities of compounds **1** and **2**, as well as derivatives thereof, there is a current interest in developing stereocontrolled syntheses of these alkaloids.

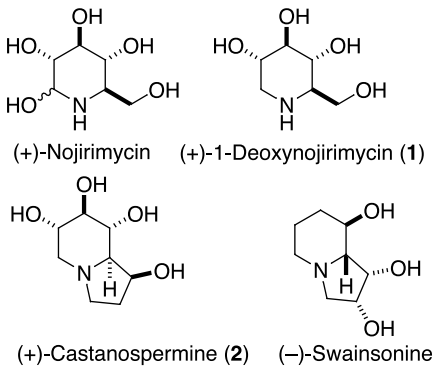

Figure 1. Examples of naturally occurring polyhydroxylated alkaloids.

To date several syntheses of compounds **1**[8] and **2**[11] have been described. Due to their highly oxygenated architecture and structural relationship with natural sugars, a number of the developed routes have made clever use of the intrinsic chirality of various carbohydrate precursors, mainly glucose and sorbose. As a result, however, these routes are limited by their lack of stereochemical flexibility. So far only few methods have been developed that allow for control of the absolute and relative stereochemistry of the contiguous stereocenters required for alkaloids **1** and **2**. To date, one of the more flexible and efficient entries to various polyhydroxylated indolizidine alkaloids is based on the use of tandem [4+2]/[3+2] cycloaddition of nitroalkenes, developed by Denmark and co-workers.[12] This strategy has been used for the preparation of several hydroxylated indolizidine and pyrrolizidine alkaloids.

We previously reported an enatioselective synthesis of **1** (14 steps, 20% overall yield) in which a regio- and stereoselective opening of vinylepoxide **4**, itself prepared from **3**, was used to secure piperidine **5** (Scheme 1).[13] Conversion of **5** into aldehyde **6**, which was then reduced and deprotected to give (+)-1-deoxynojirimycine (**1**), was uneventful. At the outset, it was also planned to use derivative **5** or **6** as intermediate for the preparation of (+)-castanospermine (**2**). All attempts, however, to realize this goal proved unsuccessful. Protection of the hydroxyl moiety in **6** to give **8** failed, most likely due to a facile retro aldol reaction. To circumvent this, **5** was converted into **7**, but then oxidation of **7** into **8** proved to be unacceptably slow and low yielding. The problems with this approach resided in the

Keywords: amino alcohols; asymmetric synthesis; alkaloids.

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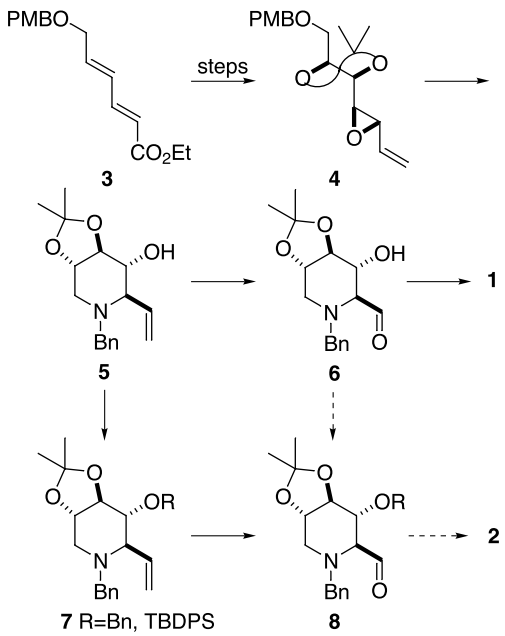


Scheme 1.

difficulties encountered in preparing aldehyde **8** and it was decided to develop an alternative approach from diene **3** towards alkaloids **1** and **2**. Herein are detailed the results from this effort.

2. Results and discussion

2.1. Synthesis of (+)-1-deoxynojirimycin (1)

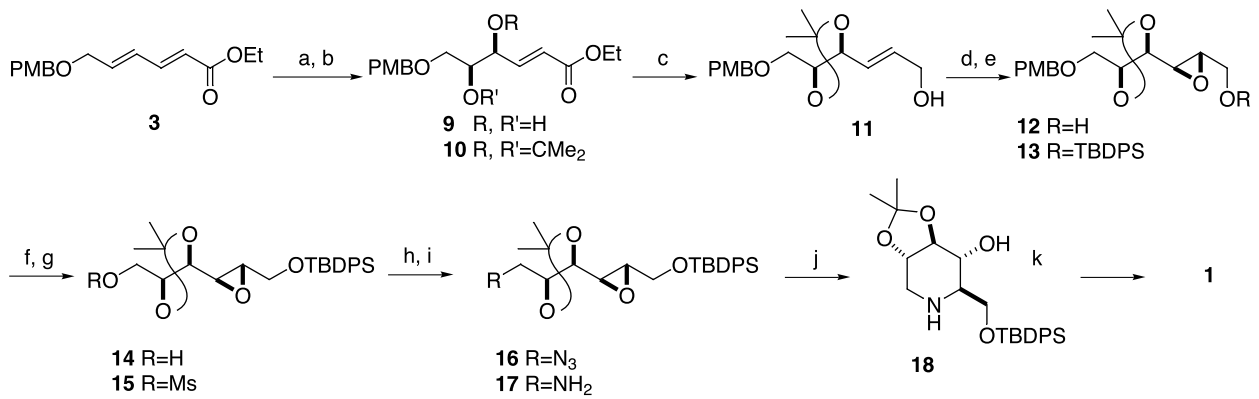
Formation of the four contiguous stereocenters required for **1** can be achieved by asymmetric dihydroxylation of diene **3** followed by epoxidation (Scheme 2). It has previously been shown that the enantioselectivity obtained in asymmetric dihydroxylation of 6-hydroxyhexa-2,4-dienoic acid derivatives is sensitive to the nature of the hydroxyl protecting group.[13–15] For reasons of orthogonality with other projected protecting groups, the *p*-methoxybenzyl ether **3** was selected as a suitable starting material.[16] Dihydroxylation of this material using AD-mix-α led to the expected diol **9** in 80% yield and 97% ee,[17] which was easily improved to 99.5% ee by a single recrystallization.[18] The diol moiety in **9** was protected as an acetonide to give **10**[19] (97%) and subsequent DIBAL reduction of the ester functionality yielded allylic alcohol **11** (93%). Epoxidation of **11** using the catalytic Sharpless epoxidation resulted in poor yield of **12**,[20] but could be realized by utilizing the stoichiometric protocol to afford **12** in 80% yield and high diastereoselectivity (de>95%). As noted previously, epoxidation of substrates similar to **11** using (+)-tartrate esters constitutes a mis-matched combination and, indeed, subjecting **11** to *m*-CPBA gave **12** and its diastereomer in 50% de favoring the unwanted diastereomer.[21] Protection of the hydroxyl group in **12** as a TBDPS ether then gave **13** (97%).

Removal of the PMB group yielded **14** (92%), the primary hydroxyl group of which was activated towards nucleophilic attack by conversion into mesylate **15** (100%). Somewhat surprisingly, **15** proved to be inert when subjected to benzylamine and the starting material was recovered. Instead, mesylate **15** could be converted into azide **16** (91%) without opening of the epoxide, and then reduced to amine **17** using Staudinger conditions (83%). Subjecting **17** to refluxing EtOH resulted in a smooth and quantitative cyclization into piperidine derivative **18**. As expected, only the product derived from a 6-*endo-tet* cyclization was detected; the corresponding *5-exo-tet* process being disfavored since it would produce a *trans*-fused bicyclo[3.3.0]-nonane type of system.[22]

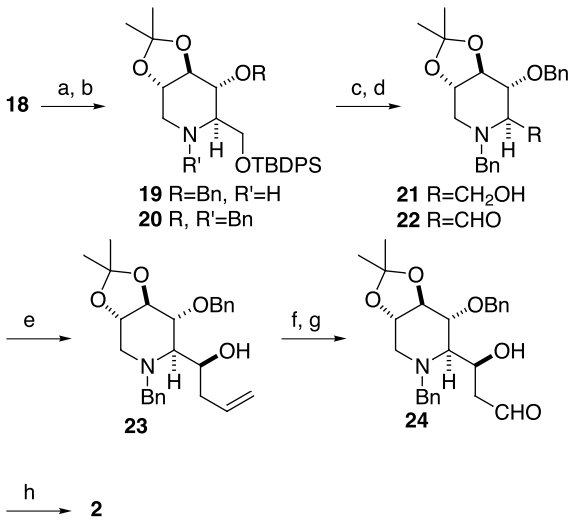
Concomitant removal of both the silyl and acetonide protecting groups in key intermediate **18** by aq. HCl in refluxing EtOH then gave (+)-1-deoxynojirimycin (**1**) in quantitative yield, its physical data being in accordance with literature values.[23] By this reaction sequence **1** was obtained in 11 steps and 36% overall yield from diene **3**.

2.2. Synthesis of (+)-castanospermine (2)

In order to proceed with the synthesis of (+)-castanospermine (**2**) and avoid the problems encountered in our earlier route it was necessary to protect both the secondary hydroxyl and amine functionalities in **18**. Initial attempts to benzylate the hydroxyl group in **18** using standard basic conditions resulted in partial migration of the silyl group,[24]



Scheme 2. (a) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, 80%l; (b) 2-methoxypropene, *p*-TsOH (cat.), DMF, 97%; (c) DIBAL, −78°C, CH_2Cl_2, 93%; (d) (+)-DIPT, Ti(O*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, −20°C, 80%; (e) *t*-BuPh$_2$SiCl, Et_3N, DMAP, CH_2Cl_2, 97%; (f) DDQ, CH_2Cl_2, H_2O, 92%; (g) MsCl, *i*-Pr$_2$EtN, CH_2Cl_2, 100%; (h) NaN_3, DMF, 70°C, 91%; (i) Ph_3P, THF, H_2O, 83%; (j) EtOH, △, 100%; (k) HCl (37%), MeOH, 100%.



Scheme 3. (a) KHMDS (2.2 equiv.), BnBr (3 equiv.), THF, −78°C, 82%; (b) BnBr (1.3 equiv.), K_2CO_3 (2.6 equiv.), CH_3CN, △, 97%; (c) *n*-Bu_4NF, THF, rt, 100%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 93%; (e) $CH_2CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2, −65 to −60°C, 71%; (f) OsO_4, NMO, *t*-BuOH–THF–H_2O (10:3:1); (g) $NaIO_4$, $NaHCO_3$, THF–H_2O (1:1), 84% (2 steps); (h) H_2, Pd/C, then TFA, 81%.

while acid catalyzed methods only gave degradation of the starting material (Scheme 3). This was eventually resolved by using KHMDS and BnBr in THF at −78°C, which yielded compound **19** (82%). Protection of the amine moiety gave **20** (97%) and removal of the silyl group afforded primary alcohol **21** (100%), which was converted to aldehyde **22** (93%) by a Swern oxidation. Introduction of the final stereocenter required for **2** by a Sakurai reaction on aldehyde **22** proved more problematic than anticipated.[25] Subjecting **22** to $TiCl_4$ and allyltrimethylsilane at −78°C gave no reaction, while higher temperatures resulted in what appeared to be concomitant addition to the carbonyl group and removal of the acetonide. Other Lewis acids examined did not promote the addition while the use of allylmagnesium chloride gave **23** in 1:1 diastereoselectivity. After careful optimization **23** could be obtained in reasonable yield and excellent diastereoselectivity by addition of $TiCl_4$ to a mixture of **22** and allyltrimethylsilane at −65°C and stirring the resultant mixture at this temperature 15 h (71%, >95% de). Completion of the synthesis was then straightforward. Dihydroxylation of **23** gave the corresponding triol as a mixture of diastereomers that upon treatment with $NaIO_4$ resulted in the somewhat labile aldehyde **24** (84%, 2 steps). Finally, reductive amination of this material followed by acidic workup gave (+)-castanospermine (**2**) in 81% yield.[26]

3. Conclusion

In conclusion, we have developed a route to (+)-1-deoxynojirimycin (**1**) that also allows for the preparation of (+)-castanospermine (**2**). The required stereochemistry was introduced by a sequential use of the Sharpless asymmetric dihydroxylation and epoxidation reactions, while the remaining stereocenter in **2** was created by a highly selective Sakurai reaction. Starting from diene **3**, (+)-1-deoxynojirimycin (**1**) was prepared in 36% yield over 11 steps and (+)-castanospermine (**2**) was obtained in 19 steps and 13% overall yield starting from the same diene.

4. Experimental[27]

4.1. Data for compounds

4.1.1. (*E*)-Ethyl (4*S*,5*S*)-4,5-dihydroxy-6-(4-methoxybenzyloxy)-hex-2-enoate (9). To a stirred solution of AD-mix-α (5.0 g), $K_2OsO_4{\cdot}2H_2O$ (0.011 g, 0.03 mmol), and methanesulfonamide (0.344 g, 3.62 mmol) in *t*-BuOH–H_2O (36 mL, 1:1), was added **3** (1.0 g, 3.62 mmol) at 0°C. After stirring at 0°C for 46 h, Na_2SO_3 (5.7 g) was added. The mixture was stirred for an additional l2 h at rt and then diluted with EtOAc (40 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2×20 mL). The combined organic phases were washed with 2 M KOH. Drying ($MgSO_4$), filtration and concentration, followed by flash chromatography (pentane–EtOAc 2:1) of the residue afforded diol **9** (0.90 g, 80%) as white crystals in 97% ee. One recrystallization (*i*-PrOH–hexane) afforded >99.5% ee. Mp 65–66°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J=8.8 Hz, 2H), 6.90 (m, 3H), 6.14 (dd, J=15.7, 1.8 Hz, 1H), 4.49 (m 2H), 4.38 (dt, 1H, J=4.5, 1.8 Hz, 1H), 4.20 (q, J=7.2 Hz, 2H), 3.82 (s, 3H), 3.76 (m, 1H), 3.61 (m, 2H), 1.29 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 159.4, 145.8, 129.4 (2C), 129.2 (2C), 122.4, 113.9, 73.4, 72.1, 71.9, 71.2, 60.5, 55.3, 14.3; IR (film) 3428, 2933, 2871, 2360, 1716, 1513, 1249 cm^{-1}; $[\alpha]_D$=−24.2 (*c* 1.08, $CHCl_3$); HRMS (CI) calcd for $C_{16}H_{22}O_6$ (M): 310.1416, found: 310.1422.

4.1.2. (*E*)-Ethyl 3-[(4*S*,5*S*)-5-(4-methoxybenzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enoate (10). To a solution of **9** (0.100 g, 0.32 mmol) in DMF (8 mL) was added 2-methoxypropene (0.121 mL, 1.29 mmol) and a few crystals of *p*-TsOH. The mixture was stirred over night after which it was poured into Et_2O (20 mL) and washed with water and then brine. Drying ($MgSO_4$), filtration and concentration, followed by flash chromatography (heptane–EtOAc 8:1) of the residue afforded acetonide **10** (0.108 mg, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2H), 6.89 (m, 3H), 6.09 (dd, J=15.7, 1.4 Hz, 1H), 4.54 (s, 2H), 4.41 (m, 1H), 4.21 (q, J=7.1 Hz, 2H), 3.95 (dt, J=8.4, 4.7 Hz, 1H), 3.82 (s, 3H), 3.66 (d, J=4.7 Hz, 2H), 1.46 (s, 3H), 1.44 (s, 3H), 1.30 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 159.7, 144.5, 130.2, 129.8, 123.0, 114.3, 110.6, 80.0, 77.9, 73.7, 69.4, 61.0, 55.7, 27.4, 27.1, 14.7; IR (film) 2987, 2935, 2360, 1720, 1513, 1249 cm^{-1}; $[\alpha]_D$=−22.8 (*c* 1, $CHCl_3$); HRMS (CI+) calcd for $C_{19}H_{26}O_6$ (M): 350.1729, found: 350.1734.

4.1.3. (*E*)-3-[(4*S*,5*S*)-5-(4-Methoxybenzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-ol (11). To a solution of **10** (4.30 g, 12.3 mmol) in CH_2Cl_2 (40 mL) at −78°C was added DIBAL (4.8 mL, 27.0 mmol). After 0.5 h at −78°C the reaction was carefully quenched by dropwise addition of MeOH before the cooling bath was removed. The reaction mixture was then poured into aq. Rochelle salt. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. Drying ($MgSO_4$), filtration,

concentration and flash chromatography (heptane–EtOAc 1:1) afforded **11** (3.70 g, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (br d, J=8.7 Hz, 2H), 6.88 (br d, J=8.7 Hz, 2H), 5.92 (ddt, J=15.5, 5.0, 0.6 Hz, 1H), 5.71 (ddt, J=15.5, 7.4, 1.6 Hz, 1H), 4.52 (s, 2H), 4.24 (t, J=7.9 Hz, 1H), 4.13 (br s, 2H), 3.90 (m, 1H), 3.80 (s, 3H), 3.56 (m, 2H), 1.83 (br s, 1H), 1.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 134.6, 130.4, 129.8, 128.1, 114.2, 109.8, 80.5, 79.0, 73.6, 69.5, 63.0, 55.7, 27.4; IR (film) 3423, 2987, 2869, 2360, 1513, 1247 cm^{-1}; $[\alpha]_D$=−7.3 (*c* 0.66, $CHCl_3$); HRMS (CI+) calcd for $C_{17}H_{23}O_5$ (M−H): 307.1546, found: 307.1564.

4.1.4. (2*R*,3*R*)-3-[(4*S*,5*R*)-5-(4-Methoxybenzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]oxiranylmethanol (12). To a solution of Ti(O*i*-Pr)$_4$ (0.034 mL, 0.116 mmol) in CH_2Cl_2 (1.0 mL) at −20°C was added (+)-diisopropyl tartrate (0.031 mL, 0.145 mmol). After stirring for 10 min, **11** (0.030 g, 0.097 mmol, in 1 mL CH_2Cl_2) was added. After stirring for 20 min at −20°C *t*-BuOOH (5.2 M in toluene; 0.037 mL, 0.194 mmol) was added and the resultant mixture was stored in a freezer at −20°C over night. The reaction was quenched by addition of sat. aq. Na_2SO_4 (0.5 mL) and Et_2O (1 mL). The resultant mixture was stirred for 1 h at rt after which it was filtered through a pad of Celite®. The filtrate was diluted with Et_2O (5 mL) and stirred for 20 min with 1 M NaOH (2 mL). The phases were separated and the aqueous phase was extracted twice with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography (heptane–EtOAc 1:1) of the residue afforded **12** (0.025 g, 80%) as a colorless oil in >95% de. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J=8.6 Hz, 2H), 6.88 (dd, J=8.7 Hz, 2H), 4.50 (s, 2H), 4.13 (m, 1H), 3.85 (d, J=2.1 Hz, 1H), 3.81 (s, 3H), 3.76 (dd, J=8.0, 4.7 Hz, 1H), 3.66 (dd, J=10.0, 4.8 Hz, 1H), 3.54 (dd, J=9.9, 5.6 Hz, 2H), 3.08 (m, 2H), 1.92 (br s, 1H), 1.41 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 129.6, 129.4, 113.7, 109.9, 78.7, 76.5, 73.3, 69.7, 60.6, 55.7, 55.3, 54.6, 27.0, 26.6; IR (film) 3448, 1513, 1249, 1087 cm^{-1}; $[\alpha]_D$=−11.4 (*c* 0.51, $CHCl_3$); HRMS (CI+) calcd for $C_{17}H_{23}O_6$ (M−H): 323.1495, found: 323.1499.

4.1.5. *t*-Butyl-[3-(2*R*,3*R*)-((4*S*,5*R*)-5-(4-methoxybenzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)oxiranylmethoxy]diphenylsilane (13). To a solution of Et_3N (1.8 equiv., 2.01 mL, 14.46 mmol) in CH_2Cl_2 (50 mL) was added DMAP (5 mol%,48 mg) and TBDPSCl (3.134 mL, 12.05 mmol). After 5 min **12** (2.595 g, 8.03 mmol) in CH_2Cl_2 (10 mL) was added. The resultant mixture was stirred at rt for 16 h, then poured into sat. $NaHCO_3$ and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Flash chromatography (heptane–EtOAc 6:1) of the residue gave **13** (4.402 g, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.43 (m, 6H), 7.22 (d, J=8.6 Hz, 2H), 6.87 (d, J=8.3 Hz, 2H), 4.51 (m, 2H), 4.12 (dt, J=8.0, 5.0 Hz, 1H), 3.81 (m, 1H), 3.80 (s, 3H), 3.77 (dd, J=8.0, 5.3 Hz, 1H), 3.72 (m, 1H), 3.60 (dd, J=15.4, 5.0 Hz, 2H), 3.09 (m, 1H), 3.00 (dd, J=5.3, 2.3 Hz, 1H), 1.5 (s, 6H), 1.1 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 136.0, 135.9, 133.6, 133.5, 130.2, 129.9, 128.2, 114.2, 110.4, 78.9, 73.7, 70.1, 63.4, 56.1, 55.7, 55.3, 27.4, 27.2, 27.0, 19.6; IR (film) 2923, 2861, 1624, 1527, 1263, 1111 cm^{-1}; $[\alpha]_D$=−15 (*c* 0.7, $CHCl_3$); HRMS (CI-CH_4) calcd for $C_{33}H_{41}O_6Si$ (M−H): 561.2672, found: 561.2666.

4.1.6. (4*S*,5*R*)-5-[(2*R*,3*R*)-3-(*t*-Butyldiphenylsilanyloxymethyl)-oxiranyl]-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (14). To a solution of **13** (1.08 g, 1.921 mmol) in CH_2Cl_2 (30 mL) and H_2O (1.2 mL) at 0°C was added DDQ (480 mg, 2.114 mmol) in portions. The resultant mixture was stirred at rt for 3 h and then sat. $NaHCO_3$ (10 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residual oil was purified by flash chromatography (pentane–EtOAC 3:1) to give **14** (780 mg, 92%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.45 (m, 6H), 4.05 (dt, J=8.7, 3.5 Hz, 1H), 3.85 (m, 4H), 3.62 (m, 1H), 3.13 (dt, J=3.5, 2.3 Hz, 1H), 3.01 (dd, J=4.8, 2.3 Hz, 1H), 1.85 (dd, J=8.3, 4.8 Hz, 1H), 1.50 (s, 6H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 134.3. 132.2, 132.1, 128.9, 126.9, 126.9, 109.0, 77.2, 75.5, 62.2, 60.6, 54.4, 53.8, 26.1, 25.8, 25.5, 18.3; IR (film) 3402, 2930, 2875, 1652, 1256, 1124 cm^{-1}; $[\alpha]_D$=−13.2 (*c* 0.22, $CHCl_3$); HRMS (FAB+) calcd for $C_{25}H_{34}O_5SiNa$ (M+Na): 465.2073, found: 465.2075.

4.1.7. (4*S*,5*R*)-5-[(2*R*,3*R*)-3-(-*t*-Butyldiphenylsilanyloxymethyl)-oxiranyl]-2,2-dimethyl-1,3-dioxolan-4-yl)methanesulfonate (15). To a solution of **14** (720 mg, 1.63 mmol) in CH_2Cl_2 (35 mL) at 0°C was added *i*-Pr_2EtN (994 μL, 5.705 mmol) and CH_3SO_2Cl (315 μL, 4.075 mmol). The resultant mixture was stirred over night at rt and then poured into aq. $NaHCO_3$. The phases were separated and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Remaining by-products were removed under vacuum (oil pump, 60°C) to give **15** (859 mg, 100%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 6H), 7.40 (m, 4H), 4.39 (dd, J=11.3, 4.5 Hz, 1H), 4.35 (dd, J=11.3, 3.9 Hz, 1H), 4.16 (dt, J=8.1, 3.2 Hz, 1H), 3.89 (dd, J=8.3, 4.8 Hz, 1H), 3.85 (t, J=4.0 Hz, 2H), 3.20 (dt, J=3.52, 2.3 Hz, 1H), 3.08 (s, 3H), 3.01 (dd, J=4.6, 2.3 Hz, 1H), 1.30 (s, 6H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.5, 132.1, 132.1, 128.9, 126.9, 109.8, 74.4, 67.0, 61.5, 54.6, 53.1, 36.8, 26.05, 25.8, 25.7, 18.3; IR (film) 2932, 2858, 1472, 1360, 1259, 1177, 1112 cm^{-1}; $[\alpha]_D$=−13.2 (*c* 1, $CHCl_3$); HRMS (FAB+) calcd for $C_{26}H_{36}O_7SSiNa$ (M+Na): 543.1849, found: 543.1852.

4.1.8. (4*S*,5*R*)-5-((2*R*,3*R*)-3-(*t*-Butyldiphenylsilanyloxymethyl)-oxiranyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methylazide (16). Compound **15** (1.02 g, 1.96 mmol) was dissolved in DMF (30 mL) and NaN_3 (156.6 mg, 2.255 mmol) was added. The flask was then sealed and warmed to 80°C over night. The solution was then cooled to rt and the DMF was removed under reduced pressure. The residue was taken up in Et_2O–H_2O (50 mL, 1:1), the phases were separated and the aqueous phase extracted with Et_2O (3×50 mL). The combined organic layers were washed with H_2O, dried ($MgSO_4$) and concentrated. The residual oil was

purified by flash chromatography (pentane–EtOAc 35:10) to give **16** (802 mg, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 4H), 7.34 (m, 6H), 3.98 (dt, J=8.1, 4.3 Hz, 1H), 3.74 (m, 3H), 3.48 (dd, J=13.1, 4.3 Hz, 1H), 3.23 (dd, J=13.1, 4.5 Hz, 1H), 3.05 (dt, J=3.8, 2.0 Hz, 1H), 2.86 (dd, J=4.8, 2.3 Hz, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.9, 133.4, 133.5, 130.3, 128.2, 110.9, 77.9, 76.9, 63.4, 55.8, 54.8, 51.8, 27.3, 27.1, 27.0, 19.6; IR (film) 2930, 2861, 2097, 1444, 1375, 1250, 1118 cm^{-1}; $[\alpha]_D$=−28.9 (c 0.95, $CHCl_3$); HRMS (FAB+) calcd for $C_{25}H_{33}N_3O_4SiNa$ (M+Na): 490.2138, found: 490.2134.

4.1.9. (4*S*,5*R*)-5-((2*R*,3*R*)-3-(*t*-Butyldiphenylsilanyloxymethyl)-oxiranyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methylamine (17). To a solution of **16** (800 mg, 1.713 mmol) in THF–H_2O (25 mL, 10:1) was added Ph_3P (516 mg, 1.97 mmol) and the resultant mixture was stirred at rt over night. The solvents were then removed and the residue was purified by flash chromatography (EtOAc→EtOAc–MeOH–NH_4OH 9:1:0.1) to give **17** (632 mg, 83%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 4H), 7.44 (m, 6H), 3.87 (ddd, J=9.7, 6.3, 3.8 Hz, 1H), 3.75 (d, J=4.0 Hz, 2H), 3.61 (dd, J=8.0, 4.8 Hz, 1H), 3.05 (dt, J=3.8, 2.3 Hz, 1H), 2.89 (dd, J=4.8, 2.3 Hz, 1H), 2.87 (dd, J=13.6, 3.8 Hz, 1H), 2.75 (dd, J=13.6, 6.3 Hz, 1H), 2.40 (bs, 2H), 1.34 (s, 3H), 1.33 (s, 3H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.9, 133.4, 133.5, 130.3, 128.2, 110.9, 77.9, 76.9, 63.4, 55.8, 54.8, 51.8, 27.3, 27.1, 27.0, 19.6; IR (film) 2962, 1471, 1429, 1114, 1105, 1100 cm^{-1}; $[\alpha]_D$=−23 (c 0.2, $CHCl_3$); HRMS (EI+) calcd for $C_{25}H_{35}NO_4Si$ (M): 441.2335, found: 441.2346.

4.1.10. (3a*S*,6*R*,7a*S*,7*R*)-6-(*t*-Butyldiphenylsilanyloxymethyl)-2,2-dimethyl-hexahydro-1,3-dioxolo[4,5-*c*]pyridin-7-ol (18). A solution of **17** (630 mg, 1.428 mmol) in EtOH (50 mL) was heated to reflux for 65 h. The solvents were then removed and the residue was dissolved in Et_2O. The organic phase was washed with aq. Na_2CO_3, dried (Na_2SO_4) and the solvents were removed. Flash chromatography of the residue (pentane–EtOAc 1:1→EtOAc) gave **18** (567 mg, 90%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 4H), 7.35 (m, 6H), 3.83 (dd, J=10.1, 4.0 Hz, 1H), 3.79 (dd, J=10.1, 4.0 Hz, 1H), 3.70 (t, J=8.9 Hz, 1H), 3.33 (t, J=8.9 Hz, 1H), 3.27 (m, 2H), 2.67 (dd, J=12.6, 11.3 Hz, 1H), 2.47 (dt, J=8.6, 4.0 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 133.2, 130.4, 128.3, 110.9, 84.4, 76.6, 72.2, 64.0, 61.4, 47.1, 27.3, 27.1, 19.6; IR (film) 2888, 2858, 1428, 1228, 1114, 1080, 1027 cm^{-1}; $[\alpha]_D$=+9 (c 0.8, $CHCl_3$); HRMS (CI+) calcd for $C_{25}H_{35}NO_4Si$ (M): 441.2335, found: 441.2331.

4.1.11. (+)-1-Deoxynojirimycin (1). To **18** (47 mg, 0.106 mmol) in MeOH (1 mL) was added HCl (37%, 1 mL) and the resultant mixture was stirred at 70°C for 4 h. After cooling to rt, the mixture was diluted with EtOH (1 mL) and 10 mL of CH_3CN (10 mL) followed by removal of the solvents. The residual oil was purified by flash chromatography ($CHCl_3$–MeOH 1:1) to give the known **1**·HCl salt (17 mg, 100%) as white crystals. Mp 201–202°C (lit.[23] 202–204°C); ^{1}H NMR (500 MHz, D_2O) δ 3.95 (dd, J=11.7, 3.1 Hz, 1H), 3.88 (dd, J=11.7, 5.1 Hz, 1H), 3.78 (ddd, J=12.2, 9.5, 5.1 Hz, 1H), 3.59 (t, J=9.5 Hz, 1H), 3.52 (t, J=9.5 Hz, 1H), 3.48 (dd, J=12.2, 5.1 Hz, 1H), 317 (ddd, J=3.1, 5.2, 9.5 Hz, 1H) 2.95 (t, J=12.2 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 79.1, 70.9, 70.1, 62.9, 60.9, 49.0; $[\alpha]_D$=+46.9 (c 0.11, H_2O) [lit.[23] $[\alpha]_D$=+47.1 (c 0.17, H_2O)].

4.1.12. (3a*S*,6*R*,7a*S*,7*R*)-5-Benzyl-6-(*t*-butyldiphenylsilanyloxymethyl)-2,2-dimethyl-hexahydro-1,3-dioxolo[4,5-*c*]pyridin-7-ol (19). To a stirred solution of **18** (18.2 mg, 0.041 mmol) and benzyl bromide (14.7 μL, 0.124 mmol) in THF (1 mL) at −78°C was added KHMDS (70.5 μL, 1.23 M in THF). The reaction mixture was stirred at −78°C for 2 h and then allowed to slowly warm to rt over night. The reaction was quenched by addition of aq. Na_2CO_3 (2 mL) and the resultant mixture was extracted twice with Et_2O. The combined organic phases were dried ($MgSO_4$), concentrated and flash chromatographed (Et_2O–pentane 3:7) to give **19** (18 mg, 82%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.40–7.15 (m, 11H), 4.87 (d, J=11.4 Hz, 1H), 4.47 (d, J=11.4 Hz, 1H), 3.98 (dd, J=9.95, 3.9 Hz, 1H), 3.91 (dd, J=9.95, 2.6 Hz, 1H), 3.62 (t, J=9.1 Hz, 1H), 3.51 (t, J=8.9 Hz, 1H), 3.35 (m, 2H), 2.72 (dt, J=11.5, 2.04 Hz, 1H), 2.47 (dt, J=11.5, 2.63 Hz, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 136.0, 133.6, 130.2, 128.6, 128.2, 128.0, 127.8, 110.5, 85.2, 78.0, 76.9, 72.3, 63.4, 60.87, 47.2, 27.4, 27.3, 27.3, 19.8; IR (film) 2956, 2931, 1429, 1380, 1232, 1112, 1083 cm^{-1}; $[\alpha]_D$=+25.4 (c 1.01, $CHCl_3$); HRMS (EI+) calcd for $C_{32}H_{41}NO_4Si$ (M): 531.2805, found: 531.2816.

4.1.13. (3a*S*,6*R*,7a*S*,7*R*)-5-Benzyl-7-benzyloxy-6-(*t*-butyldiphenylsilanyloxymethyl)-2,2-dimethyl-hexahydro-1,3-dioxolo[4,5-*c*]pyridine (20). To a solution of **19** (140 mg, 0.253 mmol) in CH_3CN (3 mL) was added benzyl bromide (40.6 μL, 0.343 mmol) and K_2CO_3 (94.8 mg, 0.685 mmol, dried and powdered). The resultant heterogeneous solution was heated at reflux for 5 h. After cooling to rt the solids were filtered off and the solvents removed. Flash chromatography (pentane–Et_2O 9:1) of the residue gave **20** (153 mg, 97%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 6H), 7.52 (m, 2H), 7.40–7.10 (m, 12H), 4.85 (d, J=11.4 Hz, 1H), 4.45 (d, J=11.4 Hz, 1H), 4.34 (d, J=13.8 Hz, 1H), 4.12 (dd, J=10.1, 1.0 Hz, 1H), 4.01 (dd, J=10.1, 3.8 Hz, 1H), 3.65 (t, J=8.6 Hz, 1H), 3.47 (m, 2H), 3.39 (d, J=13.8 Hz, 1H), 3.12 (dd, J=10.5, 3.1 Hz, 1H), 2.50 (dd, J=7.3, 2.2 Hz, 1H), 2.18 (dt, J=9.8, 4.8 Hz, 1H), 1.41 (s, 3H), 1.43 (s, 3H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.3, 135.7, 135.6, 133.3, 133.2, 129.5, 128.7, 128.1, 128.1, 127.8, 127.6, 127.6, 127.5, 127.3, 126.8, 110.5, 84.9, 75.8, 73.7, 72.2, 66.7, 62.24, 57.07, 52.5, 26.94, 26.9, 26.8, 19.2; IR (film) 3068, 2931, 2858, 1454, 1380, 1232, 1110 cm^{-1}; $[\alpha]_D$=+5.7 (c 1.99, $CHCl_3$); HRMS (EI+) calcd for $C_{39}H_{47}NO_4Si$ (M): 621.3274, found: 621.3278.

4.1.14. (3a*S*,6*R*,7a*S*,7*R*)-(5-Benzyl-7-benzyloxy-2,2-dimethyl-hexahydro-[1,3]dioxolo[4,5-*c*]pyridin-6-yl)methanol (21). To a solution of **20** (150 mg, 0.241 mmol) in THF (6 mL) was added n-Bu_4NF·$2H_2O$ (133 mg, 0.411 mmol) in one portion. The reaction mixture was then stirred at rt for 14 h followed by removal of the

solvents. Flash chromatography (pentane–Et_2O 3:2) of the residue gave **21** (92 mg, 100%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.22 (m, 10H), 4.94 (d, J=11.3 Hz, 1H), 4.64 (d, J=11.3 Hz, 1H), 4.08 (d, J=9.1 Hz, 1H), 3.98 (t, J=11.9 Hz, 1H), 3.92 (t, J=11.3 Hz, 1H), 3.8 (t, J=8.8 Hz, 1H), 3.4 (m, 3H), 3.22 (dd, J=10.0, 3.6 Hz, 1H), 2.48 (d, J=9.1 Hz, 1H), 2.41 (d, J=6.8 Hz, 1H), 2.32 (t, J=9.9 Hz, 1H), 1.43 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 137.1, 129.1, 128.5, 128.4, 127.8, 127.5, 111.1, 84.2, 75.8, 73.7, 72.9, 64.8, 64.7, 58.0, 57.1, 52.7, 27.0, 26.8; IR (film) 3440, 1641, 1454, 1382, 1230, 1153, 1074 cm^{-1}; $[\alpha]_D$=+21.0 (c 0.4, $CHCl_3$); HRMS (CI+) calcd for $C_{23}H_{30}NO_4$ (M+H): 384.2175, found: 384.2171.

4.1.15. (3a*S*,6*S*,7a*S*,7*R*)-5-Benzyl-7-benzyloxy-2,2-dimethyl-hexahydro-1,3-dioxolo[4,5-*c*]pyridine-6-carbaldehyde (22). To a solution of DMSO (59 μL, 0.783 mmol) in CH_2Cl_2 (4 mL) at −78°C was added $(COCl)_2$ (28 μL, 0.392 mmol). After stirring for 15 min at −78°C 15 min **21** (100 mg, 0.261 mmol) in CH_2Cl_2 (1 mL) was added. The resultant solution was then stirred −78°C→−40°C for 4 h. and then recooled to −78°C before addition of Et_3N (145.3 μL, 1.044 mmol). The resultant pale yellow solution was warmed to rt and stirred for 1 h before it was quenched by addition of sat. $NaCO_3$ (5 mL). The phases were separated, the aqueous phase extracted with Et_2O (2×15 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residual oil was dissolved in Et_2O, the organic phase was washed with H_2O, then triturated with pentane (25% V/V) and finally washed with H_2O (10 mL). This process was repeated thrice and then the organic phase was dried ($MgSO_4$) and concentrated to give crude **22** (92 mg, 93%) as a colorless oil. Compound **22** can be stored at −20°C for a short period of time but was normally taken on directly to the subsequent step. ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, J=4.5 Hz, 1H), 7.38–7.19 (m, 10H), 4.84 (d, J=11.8 Hz, 1H), 4.61 (d, J=11.8 Hz, 1H), 3.82 (t, J=8.8 Hz, 1H), 3.78 (d, J=13.7 Hz, 1H), 3.55 (dt, J=9.1, 3.9 Hz, 1H), 3.45 (d, J=6.6 Hz, 1H), 3.42 (d, J=13.7 Hz, 1H), 3.19 (dd, J=9.9, 3.8 Hz, 1H), 2.97 (dd, J=8.7, 4.5 Hz, 1H), 2.23 (t, J=9.8 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 137.5, 136.0, 129.0, 128.3, 128.2, 128.0, 127.7, 127.5, 111.4, 83.5, 74.1, 72.9, 72.2, 59.3, 52.0, 31.0, 27.0, 26.9.

4.1.16. (1*S*)-1-((3a*S*,6*S*,7a*S*,7*R*)-5-Benzyl-7-benzyloxy-2,2-dimethylhexahydro-1,3-dioxolo[4,5-*c*]pyridin-6-yl)-but-3-en-1-ol (23). To a solution of aldehyde **22** (73 mg, 0.19 mmol) and allyltrimethylsilane (0.120 mL, 0.95 mmol) in CH_2Cl_2 (4 mL) was added $TiCl_4$ (1 M in CH_2Cl_2; 0.20 mL, 0.20 mmol) at −65°C. After 15 h at −78°C, a saturated solution of NH_3 in EtOH (0.2 mL) was added and the reaction mixture allowed to attain rt. The mixture was poured into Et_2O (5 mL) and H_2O (5 mL). The organic phase was washed with brine and then dried (Na_2SO_4). Flash chromatography (pentane–EtOAc 20:1→15:1) gave **23** (57 mg, 71%) as an oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.20 (m, 10H), 5.81 (m, 1H), 5.04 (m, 1H), 4.99 (m, 1H), 4.91 (d, J=11.5 Hz, 1H), 4.69 (d, J=11.5 Hz, 1H), 4.08 (br d, J=8.4 Hz, 1H), 4.01 (d, J=13.9 Hz, 1H), 3.84 (dd, J=8.3, 0.8 Hz, 1H), 3.73 (br s, 1H), 3.58 (d, J=13.9 Hz, 1H), 3.53 (t, J=9.0 Hz, 1H), 3.46 (m, 1H), 3.19 (dd, J=10.5, 4.2 Hz, 1H), 2.69 (dd, J=8.2, 3.3 Hz, 1H), 2.40 (m, 1H), 2.34 (t, J=10.4 Hz, 1H), 2.05 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 137.9, 136.3, 129.2, 129.0, 128.9, 128.8, 128.5, 127.6, 117.1, 111.5, 84.6, 77.9, 74.0, 72.8, 71.4, 67.4, 58.7, 53.6, 38.8, 27.4, 27.3; IR (film) 3450, 2985, 1640 cm^{-1}; $[\alpha]_D$=+37.5 (c 2.50, $CHCl_3$); HRMS (FAB+) calcd for $C_{26}H_{34}NO_4$ (M+H): 424.2488, found: 424.2484.

4.1.17. (3*S*)-3-((3a*S*,6*R*,7a*S*,7*R*)-5-Benzyl-7-benzyloxy-2,2-dimethylhexahydro-1,3-dioxolo[4,5-*c*]pyridin-6-yl)-3-hydroxypropionaldehyde (24). To a solution of **23** (54 mg, 0.127 mmol) in *t*-BuOH–THF–H_2O (2 mL, 10:3:1) was added NMO (29 mg, 0.254 mmol) and OsO_4 (cat.). After stirring at rt for 3 h sat. Na_2SO_3 (1 mL) was added and the resultant mixture was stirred for 1 h. The mixture was extracted with Et_2O (3×5 mL) and the combined organic phases were dried ($MgSO_4$). Removal of the solvents gave a residue that was filtered through a plug of silica to give the corresponding diol (48 mg) as a 1:1 mixture of diastereomers (^1H NMR). This mixture was not further purified but taken on to the next step.

To the diol from above (53 mg) in THF–H_2O (1 mL, 1:1) was added $NaHCO_3$ (44 mg, 0.525 mmol) and $NaIO_4$ (45 mg, 0.210 mmol). After stirring at rt for 3 h the mixture was poured into Et_2O–H_2O, the phases were separated and the aqueous phase extracted with Et_2O (2×5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (pentane–EtOAc 4:1) of the residue gave **24** (45 mg, 84% from **24**) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (br s, 1H), 7.40–7.19 (m, 10H), 4.93 (d, J=11.4 Hz, 1H), 4.71 (m, 1H), 4.69 (d, J=11.4 Hz, 1H), 3.95 (m, 1H), 3.94 (d, J=14.4 Hz, 1H), 3.81 (br t, J=8.7 Hz, 1H), 3.69 (d, J=14.4 Hz, 1H), 3.52 (br t, J=8.7 Hz, 1H), 3.47 (m, 1H), 3.20 (dd, J=10.5, 4.0 Hz, 1H), 2.72 (dd, J=8.7, 3.4 Hz, 1H), 2.56 (br d, J=16.3 Hz, 1H), 2.41 (t, J=10.5 Hz, 1H), 2.36 (ddd, J=16.3, 9.8, 2.5 Hz, 1H), 1.47 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 138.4, 137.5, 129.1, 129.0, 128.9, 128.7, 128.7, 127.8, 111.6, 84.4, 73.8, 72.8, 67.0, 66.9, 58.3, 53.8, 48.0, 27.3, 27.2; IR (film): 3459, 2985, 1725 cm^{-1}; $[\alpha]_D$=+44.5 (c 2.50, $CHCl_3$).

4.1.18. (+)-Castanospermine (2). A mixture of **24** (37 mg 0.087 mmol) and 10% Pd/C (5 mg) in EtOAc (3 mL) was stirred at rt under H_2 for 24 h. The mixture was then filtered through Celite® and the solvents were evaporated. The residue was taken up in TFA–H_2O (2 mL, 8:1) and stirred rt for 10 h. Removal of the solvents gave a white solid that was recrystallized from CH_2Cl_2–MeOH (3:1) to give the **2**·TFA salt (23 mg, 89%) as white crystals. Mp 174–176°C; ^1H NMR (500 MHz, D_2O) δ 4.65 (m, 1H), 3.83, (m, 2H), 3.74 (m, 1H), 3.67 (m, 1H), 3.55 (br t, J=9.2 Hz, 1H), 3.15 (m, 2H), 2.95 (br t, J=11.5 Hz, 1H), 2.52 (m, 1H), 2.05 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 79.7, 74.1, 70.6, 70.4, 69.2, 55.5, 54.6, 34.4; $[\alpha]_D$=+54.7 (c 0.25, H_2O); IR (KBr) 3368, 2841, 1673 cm^{-1}; HRMS (FAB+) calcd for $C_8H_{16}NO_4$ (**2**+H): 190.1079, found:190.1082.

The **2**·TFA salt (23 mg, 0.076 mmol) from above was subjected ion-exchange chromatography (Dowex 1-X, OH^-

form, 100–200 mesh, H_2O). Removal of the solvents followed by lyophilization gave **2** (13 mg, 81% from **24**) as white crystals. Mp 209–211°C dec (lit.[28] mp 212–215°C); ^{1}H NMR (500 MHz, D_2O) δ 4.41 (dd, J=7.2, 4.4, 1.7 Hz, 1H), 3.61 (ddd, J=10.4, 9.3, 5.1 Hz, 1H), 3.60 (br t, J=9.6 Hz, 1H), 3.33 (t, J=9.1 Hz, 1H), 3.18 (dd, J=5.1 Hz, 1H), 3.09 (td, J=9.1, 2.2 Hz, 1H), 2.34 (dddd, J=14.2, 9.4, 7.3, 2.4 Hz, 1H), 2.22 (q, J=9.1 Hz, 1H), 2.06 (t, J=10.7 Hz, 1H), 2.02 (dd, J=9.8, 4.4 Hz, 1H), 1.71 (dtd, J=14.2, 8.8, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 81.8, 74.2, 72.9, 72.4, 71.8, 58.2, 54.4, 35.5; $[\alpha]_D$=+82.4 (c 0.35, H_2O) [lit.[28] $[\alpha]_D$=+76.8 (c 0.1, H_2O)].

Acknowledgements

This work was supported financially by the Swedish Research Council. We are grateful to Mr Jan Blid for assistance with NMR measurements.

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