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Carbohydrate Research 340 (2005) 2457–2468
Carbohydrate RESEARCH

Efficient and stereodivergent synthesis of deoxyimino sugars

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Received 6 May 2005; accepted 25 August 2005
Available online 5 October 2005

Abstract—Both *cis*- and *trans*-2-substituted-1,2,3,6-tetrahydro-pyridin-3-ols have been prepared via an aldol condensation–ring-closing metathesis sequence. A stereodivergent synthesis of optionally functionalized deoxyimino sugars was achieved via asymmetric dihydroxylation or epoxidation/nucleophilic substitution of these tetrahydropyridines.

Keywords: Imino sugar; Metathesis; Asymmetric dihydroxylation; Stereodivergent

1. Introduction

Deoxyimino sugars[†] are common structural subunits of a wide variety of naturally occurring alkaloids including the piperidine alkaloids.[1] It has been demonstrated that polyhydroxylated piperidine alkaloids can mimic enzymatic substrates,[2] and can act as transition-state analogs for various enzymes that bind and process glycoproteins.[3] These compounds are known to possess a broad range of pharmacological properties,[4] and as such, synthetic and medicinal chemists have often incorporated these structural motifs into the design of novel biologically active compounds. It is therefore desirable to devise stereodivergent and expedient synthetic strategies that provide access to novel derivatives of these deoxyimino sugars.[5] This manuscript describes the extension of our previously reported aldol condensation–ring-closing metathesis sequence[6] to the synthesis of deoxyimino sugars.

2. Results and discussion

cis- and *trans*-2-Substituted-1,2,3,6-tetrahydro-pyridin-3-ols were prepared via an aldol condensation–ring-closing metathesis (RCM) sequence (Scheme 1). In our hands, acetonides **7** and **8** were ideal intermediates that could be rapidly functionalized to various deoxyimino sugars. These compounds were prepared in ca. 45% overall yield (1:1 ratio) from ester **1**[7] (aldol condensation with acrolein, LAH reduction, acetonide formation, and RCM, Scheme 1). The structure of **7** was assigned unambiguously by its single-crystal X-ray analysis (Fig. 1). In addition, reaction of ester **3** with Grubbs' catalyst afforded the diastereomeric tetrahydropyridines **9** and **10** in 84% yield. The tosyl group of **7** was removed by Red-Al [sodium bis(2-methoxyethoxy)aluminum hydride] to give amine **11** in 84% yield.

Dihydroxylation of *trans*-acetonide **7** (OsO_4, NMO) afforded diols **12** and **13** in 77% and 12% yield, respectively. Dihydroxylation of *cis*-acetonide **8** gave exclusively diol **14** in 83% yield (Scheme 2). Asymmetric

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† Imino sugars are sometimes referred to as 'azasugars', a term that does not conform to IUPAC rules of nomenclature. See www.chem.qmw.ac.uk/iupac/2carb/, Rule 2-Carb-34.1.

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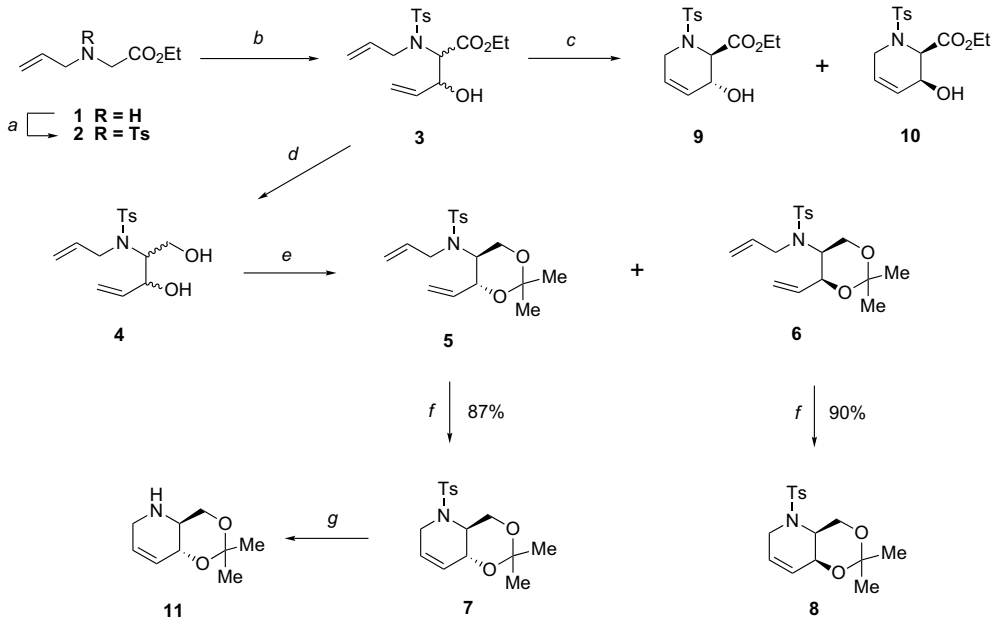
doi:10.1016/j.carres.2005.08.014



Scheme 1. Preparation of acetonides **7** and **8**. Reagents and conditions: (a) TsCl, Et_3N, DMAP, CH_2CI_2; 89%. (b) (1) LDA, THF; (2) Acrolein, THF; 87%. (c) Ru(IV), CH_2Cl_2; 84%. (d) $LiAlH_4$, THF, 87%. (e) $(CH_3)_2C(OMe)_2$, *p*-TsOH, C_6H_6; 55% (for **5**), 36% (for **6**). (f) Ru(IV), CH_2Cl_2. (g) Red-AI, THF; 84%.

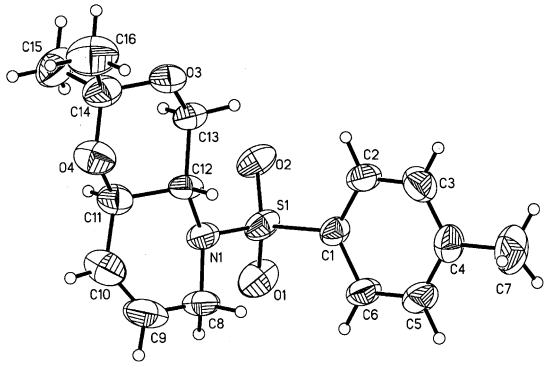


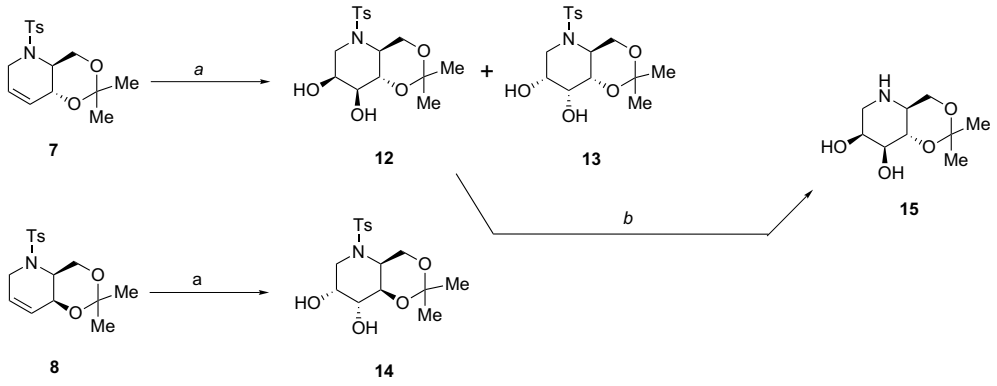
Figure 1. ORTEP view of the single-crystal X-ray diffraction structure of *trans*-2,2-dimethyl-5-(toluene-4-sulfonyl)-4a,5,6,8a-tetrahydro-4*H*-[1,3]dioxino[5,4-*b*]pyridine (**7**) with atomic numbering. Thermal ellipsoids are drawn at the 30% probability level.

dihydroxylation of *trans*-acetonide **7** with the Hsung–Vedejs AD-mix β[8] gave (+)-**13** and (−)-**12** in 42% and 35% yield (Scheme 3). The tosyl groups and acetonides were subsequently removed by Red-Al and HCl–MeOH to give 1,5-dideoxy-1,5-imino-D-allitol (+)-**17**[9] and 1,5-dideoxy-1,5-imino-D-mannitol (+)-**18**.[10]

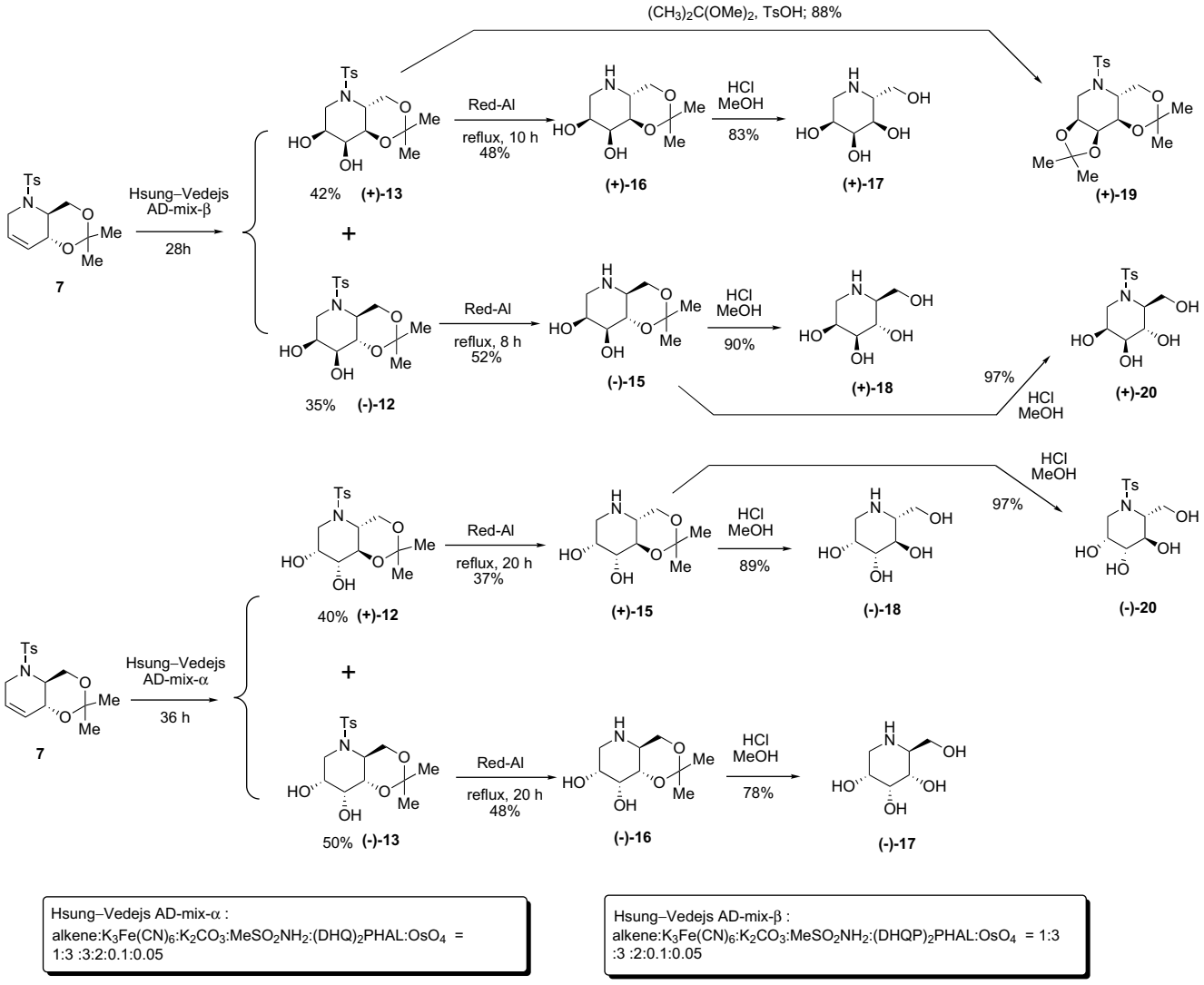
Similarly, reaction of *trans*-acetonide **7** with the Hsung–Vedejs AD-mix α afforded acetonides (−)-**13** and (+)-**12** (50% and 40% yield, respectively). The tosyl groups and acetonide groups were subsequently removed with Red-Al and HCl–MeOH to give (−)-**18**[11] and (−)-**17**.[12] The structure of diol (+)-**13** was unambiguously assigned by the single-crystal X-ray analysis of its diacetonide derivative (+)-**19**, prepared from (+)-**13** with $(CH_3)_2C(OMe)_2$ and *p*-TsOH; 88% yield (Fig. 2).

Isofagomine and siastatin B are potent and structurally complex inhibitors of the liver glycogen phosphorylase (GP)[13] and β-glucuronidase[14] enzymes, which are two important biological targets for the treatment of type-2 diabetes. Surprisingly, very little is known of the structure–activity relationships of these inhibitors.[15] One of the goals of this project was to devise an efficient synthesis of the epoxides of **7**, which could then serve as key intermediates in the preparation of novel analogs of isofagomine and siastatin B. After much experimentation, we found that the reaction of **7** with either dioxirane or MCPBA would lead to the two isomeric epoxides **21** and **22**. Nucleophilic ring opening of the epoxides **21** and **22**, with KCN, Bu_4NI, and Ti(O-*i*-Pr)$_4$ in DMSO, gave **23** and **28**, respectively. Reduction of nitrile **23** with various reducing agents (e.g., $LiAlH_4$, DIBAL-H, $NaBH_4$, etc.) afforded complex mixtures. The use of $BH_3{\cdot}Me_2S$ in THF at reflux afforded the primary amine and concomitantly reduced the acetonide to isopropyl ethers **24** and **25**, which were deprotected with BBr_3 in CH_2Cl_2 at 0 °C to afford aminotriol **26**. Subsequent Birch reduction of the tosyl protecting group of **26** afforded 5-aminomethyl-2-hydroxymethylpiperidine-3,4-diol (**27**). Compound **32** was prepared in a similar way from nitrile **28** (Scheme 4).

In summary, an efficient and stereodivergent synthesis of deoxyimino sugars has been achieved via an aldol–



Scheme 2. Dihydroxylation of acetonides **7** and **8**. Reagents and conditions: (a) OsO_4, NMO/THF–*t*-BuOH–H_2O = 1:3:0.5; 77% (for **12**), 12% (for **13**); 83% (for **14**). (b) Red-Al, THF, reflux; 83%.



Scheme 3. Asymmetric dihydroxylation of acetonide **7**.

RCM sequence. This protocol provides a rapid approach to polyfunctionalized imino sugars. Further synthetic applications of this methodology are under active investigation in our laboratories.

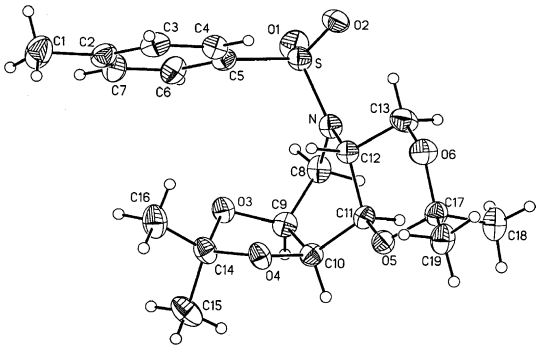
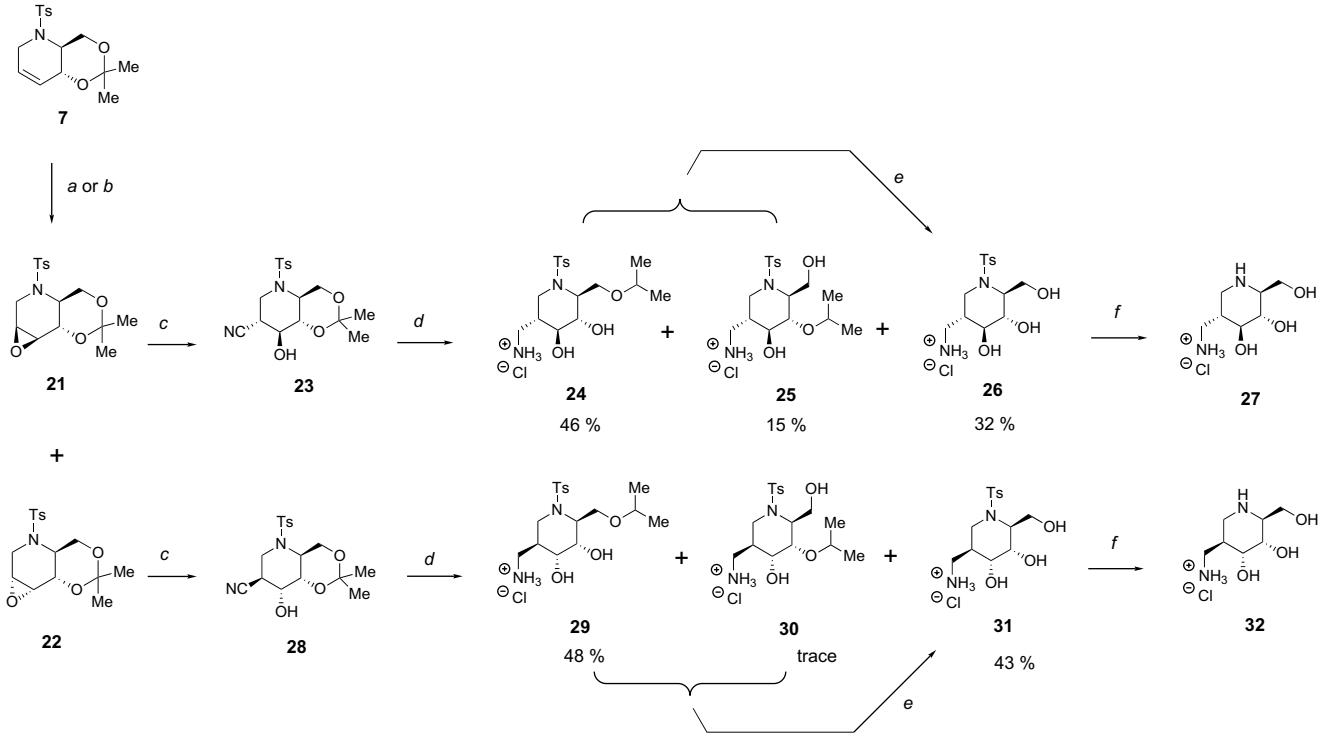


Figure 2. ORTEP view of the single-crystal X-ray diffraction structure of 1,5-deoxy-1,5-imino-2,3:4,6-di-*O*-isopropylidene-D-allitol [(+)-**19**] with atomic numbering. Thermal ellipsoids are drawing on the 30% probability level.

3. Experimental

3.1. General

All solvents were of reagent grade. All chemicals were purchased from Aldrich Chemical Co. Reactions were normally carried out under argon atmosphere in flame-dried glassware. E. Merck Silica Gel 60 (particle size 0.04–0.063 mm) was employed for flash chromatography. The HPLC instrument was equipped with ultraviolet and refractive index detectors. The sample was analyzed and/or separated on a Spherisorb-Si column (25 cm × 10 mm, particle size 8 μm, pore size 60 Å) or a μ-Porasil column (25 cm × 1.0 cm) using a flow rate of 5 mL/min and ultraviolet and refractive index detectors (EtOAc and hexane eluants). The flow rate of the indicated elution solvent was maintained at 5 or 1 mL/min, and the retention time of a compound is recorded accordingly. Melting points are uncorrected. Most compounds were characterized by full spectroscopic (^{1}H, ^{13}C, DEPT, HMQC, COSY, NOESY, LRMS, and HRMS) data. ^{1}H NMR, COSY, and NOESY spectra were obtained in $CDCl_3$ unless otherwise noted at 400 MHz (Bruker DPX-400) or 500 MHz (Varian Unity INOVA-500). ^{13}C NMR spectra, HMBC, HMQC, and DEPT experiments were obtained at 100 or 125 MHz. Mass spectra were recorded on a Finnigan/Thermo Quest MAT 95XL, or on a VG 70-250S GC–MS or Micromass TRIO-2000 GC–MS spectrometer in the electron impact mode. X-ray crystallographic analyses were performed on a Bruker AXS SMART APEX CCD X-ray diffractometer with graphite-monochromated Mo Kα radiation. Alpha values were recorded on a JASCO DIP-1000 digital polarimeter with a Na–Hg lamp and a Na 589-nm filter.



Scheme 4. Epoxidation and nucleophilic reactions of **7**. Reagents and conditions: (a) (1) 1.4×10^4 M Na_2EDTA (aq), CF_3COCH_3, CH_3CN, 0 °C; (2) $NaHCO_3$, Oxone, 0 °C; 45% (for **21**), 37% (for **22**). (b) MCPBA, CH_2Cl_2; 43% (for **21**), 36% (for **22**). (c) KCN, Bu_4NI, Ti(O-*i*-Pr)$_4$, DMSO, rt; 86% (for **23**), 82% (for **28**). (d) (1) $BH_3{\cdot}SMe_2$, THF, reflux, 2 h; (2) 6 M HCl in MeOH. (e) (1) BBr_3, CH_2Cl_2, 0 °C, 1.5 h; (2) H_2O; 80% (for **26**), 78% (for **31**). (f) Na/NH_3, THF, −78 °C; 83% (for **27**), 87% (for **32**).

3.2. Single-crystal X-ray structural analyses

The crystal data and a summary of experimental details for **7** and **19** are given in Table 1. Data collections were performed on a Bruker AXS SMART APEX CCD X-ray diffractometer, with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) in the ϕ–ω scan mode. The structures were solved by a direct method (SHELXL-97), and were refined with full-matrix least-squares on F^2. All the non-hydrogen atoms were refined with anisotropic thermal parameters. All the hydrogen atoms, calculated at idealized positions, were included in structure factor calculations but were not refined. The Flack parameter of **19** was in accordance with the expected absolute structure.

3.3. Ethyl allylaminoacetate (1)

Under an atmosphere of argon, allylamine (15.2 g, 0.27 mmol) was placed in a flask containing Et_2O (20 mL), and the resulting solution was cooled to 0 °C. Ethyl bromoacetate (23.4 g, 0.14 mmol) was added over 30 min. The solution was allowed to warm to 25 °C and was stirred at that temperature for 22 h. The mixture was filtered, and the supernatant was concentrated in vacuo. The residue was distilled under reduced pressure to give **1** as a colorless liquid (40–42 °C, 2 mmHg, 14.4 g, 73%). Lit. 88–89 °C, 30 mmHg,[16] 90 °C, 25 mmHg,[17] 67 °C, 20 mmHg, 75–78 °C,[18] 15 mmHg,[19] 77–80 °C, 15 mmHg,[20] 47 °C, 3 mmHg.[21] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.85–5.75 (m, 1H), 5.16–5.03 (m, 2H), 4.12 (q, J 7.2 Hz, 2H), 3.33 (s, 2H), 3.21–3.19 (m, 2H), 1.77 (br s, 1H), 1.21 (t, J 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.02 (C), 136.68 (CH), 117.15 (CH_2), 61.31 (CH_2), 52.41 (CH_2), 50.57 (CH_2), 14.81 (CH_3). HREIMS: Calcd for $C_7H_{13}NO_2$ (M^+): m/z 143.0946. Found: m/z 143.0946.

3.4. Ethyl allyl(toluene-4-sulfonyl)aminoacetate (2)

To a solution of **1** (140 mg, 1.0 mmol) and DMAP (61 mg, 0.5 mmol) in 9:1 CH_2Cl_2–Et_3N (10 mL) was added 4-toluenesulfonyl chloride (228 mg, 1.2 mmol). The resulting solution was stirred at ambient temperature for 3 h. The solution was diluted with CH_2Cl_2 (40 mL), washed with H_2O (20 mL × 2), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography with 4:1 EtOAc–hexane (R_f 0.45 in 4:1 EtOAc–hexane) to give **2** as a colorless liquid (264 mg, 89% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, J 8.0 Hz, 2H), 7.23 (d, J 8.0 Hz, 2H), 5.58–5.64 (m, 1H), 5.13 (s, 1H), 5.10 (d, J 7.5 Hz, 1H), 4.01 (q, J 7.5 Hz, 2H), 3.94 (s, 2H), 3.83 (d, J 6.5 Hz, 2H), 2.35 (s, 3H), 1.13 (t, J 7.5 Hz, 3H);

Table 1. Crystal data and structure refinement for **7** and **19**

	7	**19**
Molecular formula	$C_{16}H_{21}NO_4S$	$C_{19}H_{27}NO_6S$
Molecular weight (g mol^{-1})	323.4	397.48
Temperature (K)	298	298
Crystal system	Orthorhombic	Monoclinic
Space group	*Pbca*	*Cc*
a (Å)	20.924(2)	15.742(3)
b (Å)	7.9873(10)	10.8070(19)
c (Å)	23.365(3)	11.583(2)
β (°)	90.0	97.583(3)
V (Å^3)	3904.9(8)	1953.2(6)
Z (molecules per cell)	8	4
D_{calcd} (g cm^{-3})	1.100	1.352
Absorption coefficient (mm^{-1})	0.180	0.201
$F(000)$	1376	848
Crystal size (mm)	0.23 × 0.16 × 0.12	0.53 × 0.42 × 0.35
θ Range for data collection (°)	1.74–28.29	2.29–23.32
Index ranges	$-27 \leqslant h \leqslant 25$	$-17 \leqslant h \leqslant 15$
	$-10 \leqslant k \leqslant 9$	$-11 \leqslant k \leqslant 12$
	$-31 \leqslant l \leqslant 25$	$-12 \leqslant l \leqslant 12$
Reflections collected	22,970	4083
Independent reflections	4759	2340
Reflections with [$I \geqslant 2\sigma(I)$]	3106	2277
Function minimized[a]	0.1321, 0.0000	0.0532, 0.1807
Data/restraints/parameters	4759/0/202	2340/2/250
Goodness-of-fit on F^2	1.070	1.046
Final R/wR indices [$I \geqslant 2\sigma(I)$]	0.0658/0.1982	0.0308/0.0773
R/wR Indices (all data)	0.0936/0.2154	0.0317/0.0780
Largest difference peak and hole (e Å^{-3})	0.488/−0.189	0.158/−0.221

[a] $\sum_w (F_0^2 - F_c^2)^2$, $w = 1/[\sigma^2(F_0^2) + x^2 + yP]$, where $P = (F_0^2 + 2F_c^2)/3$.

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.73 (C), 143.35 (C), 136.73 (C), 132.15 (CH), 129.44 (two CH), 127.24 (two CH), 119.69 (CH_2), 61.08 (CH_2), 50.60 (CH_2), 46.85 (CH_2), 21.40 (CH_3), 13.90 (CH_3); HREIMS: Calcd for $C_{14}H_{19}NO_4S$ (M^+): m/z 297.1035. Found: m/z 297.1034.

3.5. Ethyl 2-[Allyl(toluene-4-sulfonyl)amino]-3-hydroxy-pent-4-enoate (3)

Under an atmosphere of argon, lithium diisopropylamide (2.0 M solution in THF–*n*-heptane, 0.22 mL, 0.44 mmol) was added to dry THF (20 mL) at −78 °C. After stirring for 5 min, a solution of **2** (100 mg, 0.34 mmol) in THF (4 mL) was added, and the solution was stirred at −78 °C for 10 min. Acrolein (0.03 mL, 0.36 mmol) was added into the reaction mixture. The reaction was completed in ~15 min and was quenched with EtOH (2 mL) and allowed to warm to room temperature. The solution was diluted with EtOAc (30 mL), washed with H_2O (20 mL × 2), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography with 4:1 EtOAc–hexane (R_f 0.32 in 3:7 EtOAc–hexane) to give **3** as a colorless liquid (105 mg, 87% as two isomers in a 4:3 ratio). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69–7.64 (m, 2H), 7.24–7.18 (m, 2H), 5.95–5.72 (m, 2H), 5.35–5.02 (m, 4H), 4.57–4.35 (m, 2H), 4.07–3.76 (m, 4H), 2.35 (s, 3H), 1.03 (t, J 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, for the major isomer): δ 170.17 (C), 143.51 (C), 137.13 (C), 136.25 (CH), 134.30 (CH), 129.38 (two CH), 129.36 (two CH), 118.52 (CH_2), 117.99 (CH_2), 71.83 (CH), 63.26 (CH), 61.50 (CH_2), 49.81 (CH_2), 21.47 (CH_3), 13.74 (CH_3); HREIMS: Calcd for $C_{17}H_{23}NO_5S$ (M^+): m/z 353.1297. Found: m/z 353.1297.

3.6. *N*-Allyl-*N*-(2-hydroxy-1-hydroxymethyl-but-3-enyl)-4-methylbenzenesulfonamide (4)

To a solution of **3** (200 mg, 0.56 mmol) in THF (15 mL) was added $LiAlH_4$ (64 mg, 1.68 mmol). The resulting mixture was stirred at ambient temperature for 15 min and then quenched with H_2O (10 mL). The solution was diluted with EtOAc (50 mL × 2), washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography with 7:3 EtOAc–hexane (R_f 0.28 in 1:1 EtOAc–hexane) to give **4** as a colorless liquid (152 mg, 87% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69–7.75 (m, 2H), 7.26–7.31 (m, 2H), 5.72–5.86 (m, 2H), 5.05–5.30 (m, 5H), 4.24–4.32 (m, 1H), 3.92–3.98 (m, 2H), 3.71–3.83 (m, 3H), 3.08 (br s, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 2:1 isomeric forms, * denotes minor isomer): δ 143.47* (C), 143.44 (C), 137.98 (CH), 137.55* (CH), 137.38 (C), 137.36* (C), 135.43 (CH), 135.39* (CH), 129.56 (two CH), 129.48* (two CH), 127.44 (two CH), 127.26* (two CH), 117.96* (CH_2), 117.84 (CH_2), 117.42* (CH_2), 116.73 (CH_2), 73.71 (CH), 71.43* (CH), 64.10* (CH), 63.10 (CH), 61.32 (CH_2), 60.72* (CH_2), 48.60 (CH_2), 48.33* (CH_2), 21.38 (CH_3 and $^*CH_3$); HREIMS: Calcd for $C_{15}H_{21}NO_4S$ (M^+): m/z 311.1191. Found: m/z 311.1193.

3.7. *trans*- and *cis*-*N*-Allyl-*N*-(2,2-dimethyl-4-vinyl-[1,3]dioxan-5-yl)-4-methylbenzenesulfonamide (5) and (6)

To a solution of **4** (310 mg, 1.00 mmol) in dry benzene (20 mL) was added 2,2-dimethoxypropane (0.37 mL, 3.00 mmol). The resulting solution was stirred for 5 min at ambient temperature, *p*-TsOH (38 mg, 0.20 mmol) was added, and stirring was maintained at ambient temperature and for ~1.5 h. The reaction was quenched with aq $NaHCO_3$ (15 mL), diluted with EtOAc (50 mL), washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography with 5:95 EtOAc–hexane (**5**: R_f 0.56 in 1:4 EtOAc–hexane; **6**: R_f 0.54 in 1:4 EtOAc–hexane) to give **5** (193 mg, 55% yield) as a colorless oil and **6** (126 mg, 36% yield) as a colorless oil. For **5**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62–7.75 (m, 2H), 7.21–7.27 (m, 2H), 5.70–5.82 (m, 1H), 5.59–5.68 (m, 1H), 5.10–5.32 (m, 4H), 4.40–4.50 (m, 1H), 3.75–3.86 (m, 3H), 3.56–3.68 (m, 2H), 2.39 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.52 (C), 137.61 (C), 135.39 (CH), 135.07 (CH), 129.68 (CH), 129.43 (CH), 127.34 (CH), 127.23 (CH), 118.53 (CH_2), 118.01 (CH_2), 99.18 (C), 70.63 (CH), 61.38 (CH_2), 57.66 (CH), 49.02 (CH_2), 27.42 (CH_3), 21.46 (CH_3), 20.66 (CH_3); HREIMS: Calcd for $C_{18}H_{26}NO_4S$ (M^++1): m/z 352.1583. Found: m/z 352.1586.

For **6**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66–7.68 (m, 2H), 7.24–7.30 (m, 2H), 5.94–6.03 (m, 1H), 5.62–5.71 (m, 1H), 5.20–5.31 (m, 2H), 5.06–5.12 (m, 2H), 4.56–4.59 (m, 1H), 4.29–4.31 (m, 2H), 4.08 (dd, J 12.8, 4.2 Hz, 1H), 3.79–3.82 (m, 1H), 3.66 (dd, J 12.8, 2.1 Hz, 1H), 2.41 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.56 (C), 138.62 (C), 136.39 (CH), 134.77 (CH), 129.87 (two CH), 127.75 (two CH), 117.13 (CH_2), 117.04 (CH_2), 99.60 (C), 72.28 (CH), 63.72 (CH_2), 52.87 (CH), 49.77 (CH_2), 29.13 (CH_3), 21.86 (CH_3), 19.44 (CH_3); HREIMS: Calcd for $C_{18}H_{26}NO_4S$ (M^++1): m/z 352.1583. Found: m/z 352.1581.

3.8. *trans*-2,2-Dimethyl-5-(toluene-4-sulfonyl)-4a,5,6,8a-tetrahydro-4*H*-[1,3]dioxino[5,4-*b*]pyridine (7)

To a solution of **5** (90 mg, 0.26 mmol) in CH_2Cl_2 (10 mL) was added bis(tricyclohexylphosphine)benzylidine ruthenium(IV) chloride (Grubb's catalyst) (10 mg, 0.01 mmol), and the resulting mixture was stirred at ambient temperature for 24 h. The solution was concen-

trated in vacuo, and the crude residue was purified by flash column chromatography with 1:1 EtOAc–hexane (R_f 0.40 in 15:85 EtOAc–hexane) to give the product as a white solid (73 mg, 87% yield); mp 68–70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62–7.66 (m, 2H), 7.30–7.32 (m, 2H), 5.59–5.68 (m, 2H), 4.31–4.38 (m, 3H), 4.11–4.17 (m, 1H), 3.42–3.48 (m, 1H), 2.65–2.69 (m, 1H), 2.41 (s, 3H), 1.47 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.98 (C), 134.65 (C), 129.94 (two CH), 127.67 (CH), 127.43 (two CH), 123.79 (CH), 98.95 (C), 68.69 (CH), 63.19 (CH_2), 55.78 (CH), 48.00 (CH_2), 29.27 (CH_3), 21.49 (CH_3), 18.81 (CH_3); HREIMS: Calcd for $C_{16}H_{21}NO_4S$ (M^+): m/z 323.1191. Found: m/z 323.1191.

3.9. *cis*-2,2-Dimethyl-5-(toluene-4-sulfonyl)-4a,5,6,8a-tetrahydro-4*H*-[1,3]dioxino[5,4-*b*]pyridine (8)

Prepared from **6** according to procedure 3.8. Colorless oil: 90% yield, R_f 0.38 in 15:85 EtOAc–hexane. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70–7.73 (m, 2H), 7.28–7.31 (m, 2H), 5.85–5.89 (m, 1H), 5.73–5.77 (m, 1H), 4.26–4.36 (m, 2H), 4.03–4.09 (m, 1H), 3.85 (t, J 10.2 Hz, 1H), 3.55–3.68 (m, 2H), 2.42 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.71 (C), 136.91 (C), 129.86 (two CH), 127.65 (CH), 126.93 (two CH), 123.01 (CH), 98.40 (C), 65.77 (CH), 57.27 (CH_2), 46.73 (CH), 40.80 (CH_2), 29.63 (CH_3), 23.55 (CH_3), 21.45 (CH_3); HREIMS: Calcd for $C_{16}H_{21}NO_4S$ (M^+): m/z 323.1191. Found: m/z 323.1191.

3.10. Ethyl *trans*- and *cis*-3-hydroxy-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine-2-carboxylate (9) and (10)

To a solution of **3** (90 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) was added bis(tricyclohexylphosphine)benzylidine ruthenium(IV) chloride (Grubb's catalyst) (10 mg, 0.01 mmol), and the resulting mixture was stirred at ambient temperature for 24 h. The solution was concentrated in vacuo, and the crude residue was purified by flash column chromatography with 1:1 EtOAc–hexane (R_f 0.49 in 1:1 EtOAc–hexane) to give the product as a colorless liquid (68 mg, 84% yield as two isomers in a 2:1 ratio). The diastereomers were separated by HPLC. For **9**: R_t (1:4 EtOAc–hexane) 13.4 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65–7.70 (m, 2H), 7.23–7.25 (m, 2H), 5.81–5.91 (m, 2H), 4.82 (d, J 2.0 Hz, 1H), 4.46–4.47 (m, 1H), 4.03–4.08 (m, 1H), 3.90–3.98 (m, 1H), 3.78–3.86 (m, 2H), 2.52 (br s, 1H), 2.35 (s, 3H), 1.02 (t, J 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.08 (C), 143.49 (C), 135.73 (C), 129.36 (two CH), 127.70 (CH), 127.33 (two CH), 124.51 (CH), 64.47 (CH), 61.20 (CH_2), 60.67 (CH), 42.31 (CH_2), 21.35 (CH_3), 13.68 (CH_3); HREIMS: Calcd for $C_{15}H_{19}NO_5S$ (M^+): m/z 325.0984. Found: m/z 325.0961.

For **10**: R_t (1:4 EtOAc–hexane) 11.5 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63–7.70 (m, 2H), 7.23–7.28 (m, 2H), 5.73–5.76 (m, 1H), 5.61–5.66 (m, 1H), 4.92 (d, J 6.1 Hz, 1H), 4.44–4.46 (m, 1H), 3.92–4.04 (m, 2H), 3.80–3.88 (m, 1H), 3.60–3.66 (m, 1H), 2.39 (s, 3H), 1.00 (t, J 7.1 Hz, 3H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.04 (C), 143.65 (C), 136.05 (C), 129.61 (CH), 129.54 (two CH), 127.23 (two CH), 123.28 (CH), 66.27 (CH), 61.51 (CH_2), 55.96 (CH), 42.33 (CH_2), 21.44 (CH_3), 13.71 (CH_3); HREIMS: Calcd for $C_{15}H_{19}NO_5S$ (M^+): m/z 325.0984. Found: m/z 325.0959.

3.11. 2,2-Dimethyl-4a,5,6,8a-tetrahydro-4*H*-[1,3]dioxino[5,4-*b*]pyridine (11)

To a solution of **7** (100 mg, 0.31 mmol) in THF (5 mL) was added Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride, 70% in toluene, 1.1 mL, 3.72 mmol). The resulting solution was heated at reflux for 8 h. The reaction was cooled to 0 °C and quenched by slow addition of 15% NaOH (5 mL), diluted with EtOAc (50 mL × 2), washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography with pure 99:1 EtOAc–Et_3N (R_f 0.15 in EtOAc) to give **11** as a colorless liquid (44 mg, 84%). ^{1}H NMR (acetone-d_6, 400 MHz): δ 5.80–5.58 (m, 2H), 4.18–4.10 (m, 1H), 3.71–3.78 (m, 1H), 3.65 (dd, J 10.8, 13.5 Hz, 1H), 3.45–3.32 (m, 1H), 3.30–3.18 (m, 1H), 2.75–2.47 (m, 2H), 1.47 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz): δ 129.04 (CH), 128.57 (CH), 99.60 (C), 70.41 (CH), 64.84 (CH_2), 55.33 (CH), 46.06 (CH_2), 29.98 (CH_3), 19.45 (CH_3); HREIMS: Calcd for $C_9H_{15}NO_2$ (M^+): m/z 169.1103. Found: m/z 169.1107.

3.12. 2,2-Dimethyl-5-(toluene-4-sulfonyl)-hexahydro-[1,3]dioxino[5,4-*b*]pyridine-7,8-diol (12) and (13)

To a solution of **7** (40 mg, 0.12 mmol) in THF–*t*-BuOH–H_2O (1:3:0.5 mL) was added *N*-methylmorpholine *N*-oxide (NMO, 17 mg, 0.14 mmol), and the solution was stirred for 5 min at ambient temperature. OsO_4 (0.1 mL, 2.5 wt % in *t*-BuOH) was added, and stirring was maintained at ambient temperature for ca. 18 h. The reaction was quenched by the addition of sodium-hydrosulfite (0.2 g), Florisil (2.0 g), and H_2O (5 mL). The mixture was stirred for 30 min, washed with acetone (100 mL), filtered through filter paper, and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography with 4:1 EtOAc–hexane (**12**: R_f 0.21; **13**: R_f 0.30 in 4:1 EtOAc–*n*-hexane) to give **12** (33 mg; 77% yield) as a white solid and **13** (5 mg; 12% yield) as a white solid. For **12**: mp 198–200 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, J

8.2 Hz, 2H), 7.32 (d, *J* 8.1 Hz, 2H), 4.29 (dd, *J* 12.0, 4.8 Hz, 1H), 4.21 (dd, *J* 10.3, 1.5 Hz, 1H), 4.15–3.95 (m, 3H), 3.39 (dd, *J* 9.3, 3.2 Hz, 1H), 2.82 (br s, 3H), 2.56 (d, *J* 12.5 Hz, 1H), 2.40 (s, 3H), 1.46 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.17 (C), 133.80 (C), 130.04 (two of CH), 127.41 (two of CH), 99.18 (C), 72.28 (CH), 71.32 (CH), 66.50 (CH), 62.36 (CH_2), 56.03 (CH), 52.39 (CH_2), 29.15 (CH_3), 21.49 (CH_3), 18.95 (CH_3); MS (*m*/*z*, relative intensity): 357 (M^+, 5), 342 (11), 300 (5), 285 (10), 269 (58), 226 (82), 225 (59), 197 (28), 155 (59), 154 (68), 91 (100); HREIMS: Calcd for $C_{16}H_{23}NO_6S$ (M^+): *m*/*z* 357.1246. Found: *m*/*z* 357.1226.

For **13**: mp 171–173 °C; ^{1}H NMR (1:1 $CDCl_3$–CD_3OD, 500 MHz): δ 7.61 (d, *J* 8.5 Hz, 2H), 7.37 (d, *J* 8.0 Hz, 2H), 4.32 (dd, *J* 4.5, 12.5 Hz, 1H), 4.14 (t, *J* 11.0 Hz, 1H), 3.88 (s, 1H), 3.79–3.77 (m, 1H), 2.76–2.74 (m, 3H), 2.63 (dd, *J* 11.0, 10.5 Hz, 1H), 2.43 (s, 3H), 1.86 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (1:1 $CDCl_3$–CD_3OD, 125 MHz): δ 143.63 (C), 132.36 (C), 129.49 (two CH), 126.81 (two CH), 98.20 (C), 71.61 (CH), 68.37 (CH), 66.04 (CH), 62.36 (CH_2), 79.71 (CH), 47.94 (CH_2), 29.00 (CH_3), 28.02 (CH_3), 17.92 (CH_3); HREIMS: Calcd for $C_{16}H_{23}NO_6S$ (M^+): *m*/*z* 357.1246. Found: *m*/*z* 357.1252.

3.13. 2,2-Dimethyl-5-(toluene-4-sulfonyl)-hexahydro-[1,3]dioxino[5,4-*b*]pyridine-7,8-diol [(+)-13] and [(−)-12]

To a solution of **7** (70 mg, 0.22 mmol) in H_2O–*t*-BuOH (1:1.8 mL) was added potassium ferricyanide (217 mg, 0.66 mmol), potassium carbonate (91 mg, 0.66 mmol), methanesulfonamide (42 mg, 0.44 mmol), and hydroquinidine 1,4-phthalazinediyl diether (15 mg, 0.02 mmol). The solution was stirred for 10 min at 0 °C, OsO_4 (20 μL, 2.5 wt % in *t*-BuOH) was added, and stirring was maintained for 1 h. The solution was slowly warmed to ambient temperature and stirred for an additional 28 h. Sodium sulfite (100 mg) was added, the reaction was stirred for 30 min, and then extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography with EtOAc [(+)-**13**: R_f 0.79; (−)-**12**: R_f 0.52 in EtOAc] to give 33 mg of (+)-**13** (42% yield) as a white solid, and 27 mg of (−)-**12** (35% yield) as a white solid. For (+)-**13**: $[\alpha]_D^{25}$ +32.6 (*c* 0.47, EtOAc); For (−)-**12**: $[\alpha]_D^{25}$ −20.6 (*c* 0.52, EtOAc).

3.14. 2,2-Dimethyl-5-(toluene-4-sulfonyl)-hexahydro-[1,3]dioxino[5,4-*b*]pyridine-7,8-diol [(−)-13] and [(+)-12]

To a solution of **7** (70 mg, 0.22 mmol) in H_2O–*t*-BuOH (1:1, 8 mL) was added potassium ferricyanide (217 mg, 0.66 mmol), potassium carbonate (91 mg, 0.66 mmol), methanesulfonamide (42 mg, 0.44 mmol), and hydroquinone 1,4-phthalazinediyl diether (15 mg, 0.02 mmol). The solution was stirred for 10 min at 0 °C, OsO_4 (20 L, 2.5 wt % in *t*-BuOH) was added, and stirring was maintained for 1 h. The solution was slowly warmed to ambient temperature, and stirring was maintained for 36 h. Sodium sulfite (100 mg) was added, the mixture was stirred for 30 min and then extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography with EtOAc [for (−)-**13**: R_f 0.87. For (+)-**12**: R_f 0.70 in EtOAc] to give 30 mg of (+)-**12** (40% yield) as a white solid and 38 mg of (−)-**13** (50% yield) as a white solid. For (−)-**13**: $[\alpha]_D^{25}$ −33.3 (*c* 0.53, EtOAc); For (+)-**12**: $[\alpha]_D^{25}$ +21.2 (*c* 0.53, EtOAc).

3.15. 2,2-Dimethyl-5-(toluene-4-sulfonyl)-hexahydro-[1,3]dioxino[5,4-*b*]pyridine-7,8-diol (14)

Prepared from **8** according to procedure 3.12. Colorless oil: 83% yield, R_f 0.40 in 8:2 EtOAc–*n*-hexane. ^{1}H NMR (C_6D_6, 400 MHz): δ 7.80 (d, *J* 8.2 Hz, 2H), 6.92 (d, *J* 8.2 Hz, 2H), 4.36 (dd, *J* 12.8, 4.3 Hz, 1H), 4.18 (dd, *J* 4.3, 4.3 Hz, 1H), 4.12–4.08 (m, 1H), 4.03 (d, *J* 4.2, 1H), 3.73–3.90 (m, 3H), 3.65–3.55 (m, 1H), 3.47 (dd, *J* 12.7, 6.4 Hz, 1H), 2.54 (br s, 1H), 1.97 (s, 3H), 1.33 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (C_6D_6, 100 MHz): δ 143.38 (C), 136.81 (C), 129.77 (two CH), 127.92 (two CH), 99.32 (C), 70.18 (CH), 68.68 (CH), 66.19 (CH), 61.71 (CH_2), 49.67 (CH), 46.77 (CH_2), 27.78 (CH_3), 21.51 (CH_3), 21.19 (CH_3); HREIMS: Calcd for $C_{16}H_{23}NO_6S$ (M^+): *m*/*z* 357.1246. Found: *m*/*z* 357.1221.

3.16. 1,5-Dideoxy-1,5-imino-4,6-*O*-isopropylidenemannitol (15)

To a solution of **12** (30 mg, 0.09 mmol) in THF (5 mL) was added Red-Al (sodium bis-(2-methoxyethoxy)aluminum hydride, 70% in toluene, 0.7 mL, 2.61 mmol). The resulting mixture was heated to reflux for 8 h. The reaction mixture was cooled to 0 °C and quenched by slow addition of 15% NaOH (5 mL), diluted with EtOAc (50 mL × 2), washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash column chromatography with 3:7 MeOH–CH_2Cl_2 (1% Et_3N) [R_f 0.13 in 3:7 MeOH–CH_2Cl_2 (1% Et_3N)] to give **15** as a colorless oil (15 mg, 83% yield). ^{1}H NMR (CD_3OD, 500 MHz): δ 4.06 (d, *J* 13.5 Hz, 1H), 3.87–3.90 (m, 1H), 3.76 (dd, *J* 10.0, 5.5 Hz, 2H), 3.56–3.63 (m, 1H), 3.49 (dd, *J* 5.0, 4.5 Hz, 1H), 3.25–3.27 (m, 1H), 3.18–3.21 (m, 1H), 2.91 (d, *J* 10.5 Hz, 1H), 0.89 (s, 6H); ^{13}C NMR (CD_3OD, 125 MHz): δ 100.90 (C), 73.36 (CH), 70.61 (CH), 63.16 (CH_2), 55.74 (CH), 53.61 (CH), 51.06 (CH_2), 29.71 (CH_3), 19.48 (CH_3); HREIMS: Calcd for $C_9H_{17}NO_4$ (M^+): *m*/*z* 203.1158. Found: *m*/*z* 203.1165.

3.17. 1,5-Dideoxy-1,5-imino-4,6-*O*-isopropylidene-L-mannitol [(−)-15]

Prepared from (−)-**12** according to procedure 3.16. Colorless oil: 52% yield, R_f 0.46 in 2:3 MeOH–CH_2Cl_2; $[\alpha]_D^{30}$ −11.5 (*c* 0.14, MeOH).

3.18. 1,5-Dideoxy-1,5-imino-4,6-*O*-isopropylidene-D-mannitol [(+)-15]

Prepared from (+)-**12** according to procedure 3.16. Colorless oil: 37% yield, R_f 0.44 in 2:3 MeOH–CH_2Cl_2; $[\alpha]_D^{28}$ +10.1 (*c* 0.08, MeOH).

3.19. 1,5-Dideoxy-1,5-imino-4,6-*O*-isopropylidene-L-allitol [(−)-16]

Prepared from (−)-**13** according to procedure 3.16. Colorless oil: 48% yield, R_f 0.44 in 2:3 MeOH–CH_2Cl_2; $[\alpha]_D^{30}$ −12.5 (*c* 0.15, MeOH).

3.20. 1,5-Dideoxy-1,5-imino-4,6-*O*-isopropylidene-D-allitol [(+)-16]

Prepared from (+)-**13** according to procedure 3.16. Colorless oil: 48% yield, R_f 0.44 in 2:3 MeOH–CH_2Cl_2; $[\alpha]_D^{31}$ +13.2 (*c* 0.11, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): δ 3.89–3.99 (m, 1H), 3.72–3.82 (m, 2H), 3.40–3.50 (m, 2H), 2.95–3.10 (m, 1H), 2.80–2.90 (m, 1H), 2.45–2.60 (m, 1H), 1.51 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (CD_3OD, 125 MHz): δ 100.33 (C), 74.01 (CH), 70.85 (CH), 69.71 (CH_2), 63.81 (CH), 48.73 (CH), 46.64 (CH_2), 29.51 (CH_3), 19.44 (CH_3); HREIMS: Calcd for $C_9H_{17}NO_4$ (M^+): *m*/*z* 203.1158. Found: *m*/*z* 203.1162.

3.21. 1,5-Dideoxy-1,5-imino-D-allitol [(+)-17]

To a solution of (+)-**16** (10.8 mg, 0.05 mmol) in MeOH (10 mL) was added a solution of methanolic HCl (1 mL, prepared from 0.5 mL concd HCl in 30 mL of MeOH). The resulting mixture was stirred for 6 h at ambient temperature and concentrated in vacuo to give (+)-**17** (8.8 mg; 83% yield); mp 149–150 °C; $[\alpha]_D^{25}$ +30.5 (*c* 0.15, H_2O). ^{1}H NMR (CD_3OD, 500 MHz): δ 4.04 (br s, 2H), 3.80–3.92 (m, 3H), 3.68 (dd, *J* 10.5, 2.0 Hz, 1H), 3.30 (dd, *J* 3.0, 1.5 Hz, 1H), 3.21–3.28 (m, 1H), 3.02–3.10 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz): δ 71.82 (CH), 67.24 (CH), 66.41 (CH), 59.06 (CH_2), 56.60 (CH), 43.38 (CH_2); HREIMS: Calcd for $C_6H_{13}NO_4$ (M^+): *m*/*z* 163.0845. Found: *m*/*z* 163.0814.

3.22. 1,5-Dideoxy-1,5-imino-L-allitol [(−)-17]

Prepared from (−)-**16** according to procedure 3.21. Yield (78%); $[\alpha]_D^{27}$ −31.6 (*c* 0.10, H_2O).

3.23. 1,5-Dideoxy-1,5-imino-L-mannitol [(+)-18]

Prepared from (−)-**15** according to procedure 3.21. White solid: 90% yield; mp 183–184 (dec), lit. 184–186 (dec); $[\alpha]_D^{21}$ +27.3 (*c* 0.15, H_2O); ^{1}H NMR (D_2O, 500 MHz): δ 4.13 (d, *J* 1.0 Hz, 1H), 3.87 (dd, *J* 12.5, 3.0 Hz, 1H), 3.80–3.62 (m, 2H), 3.57 (dd, *J* 9.5, 3.0 Hz, 1H), 3.35–3.26 (m, 3H), 3.18–3.10 (m 1H); ^{13}C NMR (D_2O, 125 MHz): δ 75.16 (CH), 68.62 (CH), 68.46 (CH), 63.10 (CH), 60.85 (CH_2), 50.26 (CH_2); MS (*m*/*z*, relative intensity): 163 (M^+, 28), 132 (50), 105 (82), 87 (100); HREIMS: $C_6H_{13}NO_4$ (M^+): *m*/*z* 163.0845. Found: *m*/*z* 163.0814.

3.24. 1,5-Dideoxy-1,5-imino-D-mannitol [(−)-18]

Prepared from (+)-**15** according to procedure 3.21. Yield (89%); $[\alpha]_D^{21}$ −28.0 (*c* 0.13, H_2O).

3.25. 1,5-Deoxy-2,3:4,6-di-*O*-isopropylidene-1,5-sulfonamino-D-allitol [(+)-19]

Prepared from (+)-**13** according to procedure 3.7. White solid: 88% yield; R_f 0.28 in 1:4 EtOAc–hexane; mp 162–163 °C; $[\alpha]_D^{23.3}$ 27.7 (*c* 0.6, EtOAc); ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.70 (d, *J* 8.2 Hz, 2H), 7.39 (d, *J* 8.1 Hz, 2H), 4.42–4.33 (m, 2H), 4.28 (dd, *J* 8.3, 2.6 Hz, 1H), 4.16 (dd, *J* 10.3, 2.7 Hz, 1H), 3.96 (dd, *J* 15.5, 2.3 Hz, 1H), 3.81 (dd, *J* 11.2, 10.7 Hz, 1H), 3.49 (dd, *J* 15.6, 1.8 Hz, 1H), 3.42–3.32 (m, 1H), 2.41 (s, 3H), 1.48 (s, 3H), 1.30 (s, 3H), 1.16 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz): δ 144.08 (C), 138.18 (C), 130.23 (two CH), 128.68 (two CH), 109.16 (C), 99.51 (C), 73.63 (CH), 71.75 (CH), 69.57 (CH), 64.72 (CH_2), 47.24 (CH), 44.61 (CH_2), 29.34 (CH_3), 25.27 (CH_3), 23.59 (CH_3), 21.31 (CH_3), 19.13 (CH_3); HREIMS: Calcd for $C_{19}H_{27}NO_6S$ (M^+): *m*/*z* 397.1559. Found: *m*/*z* 397.1565.

3.26. 2-Hydroxymethyl-1-(toluene-4-sulfonyl)piperidine-3,4,5- triol [(+)-20]

Prepared from (−)-**15** according to procedure 3.21. Yield (97%); $[\alpha]_D^{23}$ +22.4 (*c* 0.25, H_2O).

3.27. 2-Hydroxymethyl-1-(toluene-4-sulfonyl)piperidine-3,4,5- triol [(−)-20]

Prepared from (+)-**15** according to procedure 3.21. Yield (97%). $[\alpha]_D^{23}$ −20.4 (*c* 0.30, H_2O); ^{1}H NMR (D_2O, 500 MHz): δ 7.66 (d, *J* 8.0 Hz, 2H), 7.27 (d, *J* 8.0 Hz, 2H), 3.94–3.88 (m, 1H), 3.84–3.81 (m, 1H), 3.80–3.74 (m, 1H), 3.70–3.68 (m, 1H), 3.60–3.50 (m, 2H), 3.45–3.35 (m, 1H), 3.11–3.03 (m, 1H), 2.27 (s, 3H); ^{13}C NMR (D_2O, 125 MHz): δ 145.02 (C), 136.02 (C), 129.87 (two CH), 127.33 (two CH), 69.51 (CH),

69.01 (CH), 63.29 (CH), 60.69 (CH), 58.86 (CH_2), 40.39 (CH_2), 20.78 (CH_3); HREIMS: Calcd for $C_{13}H_{19}NO_6S$ (M^+): m/z 317.0933. Found: m/z 317.0936.

3.28. 6,6-Dimethyl-3-(toluene-4-sulfonyl)hexahydro-1,5,7-trioxa-3-aza-cyclopropa[*a*]naphthalene (22) and (21)

To a solution of **7** (144 mg, 0.45 mmol) in CH_3CN (15 mL) was successively added aqueous Na_2EDTA (4×10^{-4} M, 13 mL) and CF_3COCH_3 (1 mL) at 0 °C. A mixture of $NaHCO_3$ (0.40 g, 4.8 mmol) and Oxone (2.0 g) was added to the reaction mixture over 1 h at 0 °C, and the whole mixture was stirred at the same temperature for 30 min. H_2O (15 mL) was added to the reaction mixture, and the solution was extracted with CH_2Cl_2 (40 mL × 2). The extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography with 1:3 EtOAc–hexane (for **21**: R_f 0.64 in 1:1 EtOAc–hexane. For **22**: R_f 0.58 in 1:1 EtOAc–hexane) to give **21** (45.5 mg; 45% yield) and **22** (37.3 mg; 37% yield). For **21**: ^{1}H NMR (C_6D_6, 500 MHz): δ 7.61 (d, J 8.0 Hz, 2H), 6.73 (d, J 8.0 Hz, 2H), 4.37 (d, J 7.0 Hz, 2H), 4.14 (d, J 15.0 Hz, 1H), 3.78 (d, J 10.0 Hz, 1H), 2.91 (d, J 3.5 Hz, 1H), 2.56 (d, J 14.5 Hz, 1H), 2.50–2.41 (m, 1H), 2.39 (br s, 1H), 1.87 (s, 3H), 1.37 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz): δ 143.13 (C), 137.93 (C), 129.66 (two CH), 127.91 (two CH), 99.70 (C), 67.53 (CH), 63.08 (CH_2), 55.54 (CH), 54.29 (CH), 49.38 (CH), 47.60 (CH_2), 29.36 (CH_3), 21.06 (CH_3), 18.55 (CH_3); HREIMS: Calcd for $C_{16}H_{22}NO_5S$ (M^++1): m/z 340.1219. Found: m/z 340.1219.

For **22**: ^{1}H NMR (C_6D_6, 500 MHz): δ 7.51 (d, J 8.5 Hz, 2H), 6.67 (d, J 8.5 Hz, 2H), 4.50–4.57 (m, 1H), 4.44 (dd, J 11.0, 11.5 Hz, 1H), 3.89 (d, J 9.5 Hz, 1H), 3.66 (dd, J 4.0, 14.5 Hz, 1H), 3.02–3.10 (m, 1H), 3.02 (d, 14.5 Hz, 1H), 2.83 (d, J 4.5 Hz, 1H), 2.58 (dd, J 4.0, 4.0 Hz, 1H), 1.85 (s, 3H), 1.41 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (C_6D_6, 125 MHz): δ 143.38 (C), 135.00 (C), 129.88 (two CH), 127.56 (two CH), 99.24 (C), 70.99 (CH), 63.01 (CH_2), 52.03 (CH), 51.19 (CH), 50.21 (CH), 46.18 (CH_2), 29.35 (CH_3), 21.07 (CH_3), 18.73 (CH_3); HREIMS: Calcd for $C_{16}H_{22}NO_5S$ (M^++H): m/z 340.1219. Found: m/z 340.1221.

3.29. 8-Hydroxy-2,2-dimethyl-5-(toluene-4-sulfonyl)hexahydro[1,3]dioxino-[5,4-*b*]pyridine-7-carbonitrile (28) and (23)

To a stirred solution of **21** (24 mg, 0.07 mmol) in dry DMSO (2 mL) was added KCN (44 mg, 0.64 mmol), followed by Bu_4NI (116 mg, 0.32 mmol). After 5 min, titanium tetraisopropoxide (0.12 mL, 0.38 mmol) was slowly injected, and the resulting mixture was stirred at room temperate for 84 h. The solution was diluted with EtOAc (30 mL × 2), washed with water and brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography with 1:1 EtOAc–hexane (R_f 0.35 in 1:1 EtOAc–hexane) to give **23** (22 mg; 86% yield). The same procedure was applied on **22** (24 mg, 0.07 mmol) to give **28** (R_f 0.30 in 1:1 EtOAc–hexane; 21 mg, 82% yield). For **23**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61 (d, J 8.5 Hz, 2H), 7.36 (d, J 8.5 Hz, 2H), 4.22–4.36 (m, 4H), 4.02 (dd, J 13.0, 1.0 Hz, 1H), 3.18 (s, 1H), 2.95 (d, J 13.0 Hz, 1H), 2.70–2.80 (m, 1H), 2.44 (s, 3H), 1.51 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.87 (C), 133.19 (C), 130.40 (two CH), 127.21 (two CH), 116.45 (C), 99.53 (C), 66.30 (CH), 65.58 (CH), 62.08 (CH_2), 55.36 (CH), 51.47 (CH_2), 38.29 (CH), 28.86 (CH_3), 21.57 (CH_3), 18.89 (CH_3); HREIMS: Calcd for $C_{17}H_{23}N_2O_5S$ (M^++1): m/z 367.1328. Found: m/z 367.1325.

For **28**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63 (d, J 8.0 Hz, 2H), 7.34 (d, J 8.0 Hz, 2H), 4.34 (dd, J 12.5, 4.5 Hz, 1H), 4.22 (t, J 11.0 Hz, 1H), 4.09 (dd, J 9.5, 3.0 Hz, 1H), 4.05–4.06 (m, 1H), 3.98 (dd, J 12.5, 2.5 Hz, 1H), 3.07 (t, J 2.5 Hz, 1H), 3.03 (dd, J 12.0, 3.0 Hz, 1H), 2.86 (td, J 10.0, 4.5 Hz, 1H), 2.43 (s, 3H), 1.51 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.50 (C), 133.91 (C), 130.21 (two CH), 127.41 (two CH), 117.34 (C), 99.56 (C), 70.82 (CH), 65.91 (CH), 62.36 (CH_2), 51.93 (CH), 44.70 (CH_2), 32.07 (CH), 29.00 (CH_3), 21.57 (CH_3), 19.20 (CH_3); HREIMS: Calcd for $C_{17}H_{22}N_2O_5S$ (M^+): m/z 366.1249. Found: m/z 366.1249.

3.30. 4,5-Dihydroxy-6-isopropoxymethyl-1-(toluene-4-sulfonyl)-piperidin-3-ylmethylammonium chloride (24), 4-hydroxy-6-hydroxymethyl-5-isopropoxy-1-(toluene-4-sulfonyl)-piperidin-3-ylmethylammonium chloride (25), and 5-aminomethyl-2-hydroxymethyl-1-(toluene-4-sulfonyl)-piperidine-3,4-diol (26)

To a stirred solution of **23** (20 mg, 0.05 mmol) in dry THF (10 mL) was added $BH_3{\cdot}SMe_2$ (10 drops) at 0 °C. The reaction mixture was heated to reflux for 2 h, cooled to ambient temperature and treated with a 6 M solution of HCl in MeOH for 18 h. The solvent was removed in vacuo, and the crude residue was purified by flash chromatography with 1:4 MeOH–CH_2Cl_2 (1% NH_4OH) to 100% MeOH (1% NH_4OH) to give the products. For **24**: Colorless solid: yield, 10.3 mg, 46%; R_f 0.24 in 1:4 MeOH–CH_2Cl_2 (1% NH_4OH); mp 161–163 °C; ^{1}H NMR (CD_3OD, 500 MHz): δ 7.79 (d, J 8.0 Hz, 2H), 7.35 (d, J 8.0 Hz, 2H), 4.12 (t, J 6.0 Hz, 1H), 4.06 (s, 1H), 3.69–3.75 (m, 2H), 3.46–3.57 (m, 3H), 3.09–3.20 (m, 2H), 2.88 (dd, J 12.5, 10.5 Hz, 1H), 2.41 (s, 3H), 1.93–1.97 (m, 1H), 1.09 (d, J 2.0 Hz, 3H), 1.08 (d, J 2.0 Hz, 3H); ^{13}C NMR (CD_3OD, 125 MHz): δ 144.79 (C), 139.46 (C), 130.60 (two CH), 128.56 (two CH),

73.49 (CH), 69.25 (CH), 67.22 (CH_2), 66.28 (CH), 60.62 (CH), 48.49 (CH_2), 42.55 (CH_2), 42.09 (CH), 22.32 (CH_3), 22.27 (CH_3), 21.45 (CH_3); HREIMS: Calcd for $C_{17}H_{29}N_2O_5S$ (M^+−HCl+1): *m*/*z* 373.1792. Found: *m*/*z* 373.1797.

For **25**: Colorless liquid: yield 3.3 mg, 15%; R_f 0.14 in 1:4 MeOH–CH_2Cl_2 (1% NH_4OH); ^1H NMR (CD_3OD, 500 MHz): δ 7.80 (d, *J* 8.0 Hz, 2H), 7.35 (d, *J* 8.0 Hz, 2H), 4.12 (t, *J* 6.0 Hz, 1H), 4.05 (s, 1H), 3.65–3.73 (m, 2H), 3.44–3.55 (m, 3H), 2.94–3.06 (m, 2H), 2.82 (t, *J* 11.0 Hz, 1H), 2.41 (s, 3H), 1.71–1.75 (m, 1H), 1.09 (d, *J* 1.5 Hz, 3H), 1.08 (d, *J* 1.5 Hz, 3H); ^{13}C NMR (CD_3OD, 125 MHz): δ 144.73 (C), 139.53 (C), 130.56 (two CH), 128.59 (two CH), 73.43 (CH), 69.13 (CH), 66.94 (CH_2), 66.09 (CH), 60.72 (CH), 48.49 (CH_2), 44.07 (CH), 42.45 (CH_2), 22.30 (CH_3), 22.23 (CH_3), 21.43 (CH_3); HREIMS: Calcd for $C_{17}H_{29}N_2O_5S$ (M^+−HCl+1): *m*/*z* 373.1792. Found: *m*/*z* 373.1801.

For **26**: Colorless liquid: yield 6.4 mg, 32%; R_f 0.14 in MeOH (1% NH_4OH); ^1H NMR (CD_3OD, 500 MHz): δ 7.79 (d, *J* 8.5 Hz, 2H), 7.34 (d, *J* 7.5 Hz, 2H), 4.13 (s, 1H), 4.07 (t, *J* 6.5 Hz, 1H), 3.63–3.73 (m, 3H), 3.54–3.57 (m, 1H), 3.09–3.19 (m, 2H), 2.82 (t, *J* 13.0 Hz, 1H), 2.41 (s, 3H), 1.93–2.02 (m, 1H); ^{13}C NMR (CD_3OD, 125 MHz): δ 144.7 (C), 139.5 (C), 130.6 (two CH), 128.6 (two CH), 67.9 (CH), 66.2 (CH), 62.3 (CH), 60.4 (CH_2), 48.1 (CH_2), 42.2 (CH_2), 41.9 (CH), 21.4 (CH_3); HREIMS: Calcd for $C_{14}H_{23}N_2O_5S$ (M^+−HCl+1): *m*/*z* 331.1322. Found: *m*/*z* 331.1326.

3.31. 4,5-Dihydroxy-6-isopropoxymethyl-1-(toluene-4-sulfonyl)piperidin-3-ylmethylammonium chloride (29), and 5-aminomethyl-2-hydroxymethyl-1-(toluene-4-sulfonyl)piperidine-3,4-diol (31)

Prepared from **28** according to procedure 3.30. For **29**: Colorless solid: yield 10.7 mg, 48%; R_f 0.29 in 1:4 MeOH–CH_2Cl_2 (1% NH_4OH); mp 162–164 °C; ^1H NMR (CD_3OD, 500 MHz): δ 7.82 (d, *J* 8.0 Hz, 2H), 7.35 (d, *J* 8.5 Hz, 2H), 4.25 (br s, 1H), 3.93 (s, 1H), 3.81 (dd, *J* 11.0, 3.0 Hz, 1H), 3.74 (dd, *J* 13.0, 5.0 Hz, 1H), 3.53–3.56 (m, 1H), 3.46–3.48 (m, 1H), 3.04 (dd, *J* 13.0, 8.0 Hz, 1H), 2.94 (t, *J* 13.0 Hz, 1H), 2.83 (dd, *J* 13.0, 5.0 Hz, 1H), 2.41 (s, 3H), 2.07–2.18 (m, 1H), 1.07 (d, *J* 6.0 Hz, 3H), 1.05 (d, *J* 6.5 Hz, 3H); ^{13}C NMR (CD_3OD, 125 MHz): δ 144.73 (C), 139.51 (C), 130.62 (two CH), 128.57 (two CH), 73.43 (CH), 72.33 (CH), 69.82 (CH), 67.78 (CH_2), 60.89 (CH), 44.77 (CH_2), 42.18 (CH_2), 35.47 (CH), 22.28 (CH_3), 22.25 (CH_3), 21.44 (CH_3); HREIMS: Calcd for $C_{17}H_{29}N_2O_5S$ (M^+−HCl+1): *m*/*z* 373.1792. Found: *m*/*z* 373.1801.

For **31**: Colorless solid: yield 8.6 mg, 43%; R_f 0.17 in MeOH (1% NH_4OH); mp 158–160 °C; ^1H NMR (CD_3OD, 500 MHz): δ 7.83 (d, *J* 6.0 Hz, 2H), 7.33 (d, *J* 7.5 Hz, 2H), 4.19–4.21 (m, 1H), 3.95 (t, *J* 2.5 Hz, 1H), 3.55–3.71 (m, 4H), 2.76–2.83 (m, 2H), 2.53 (q, *J* 6.5 Hz, 1H), 2.40 (s, 3H), 1.79–1.83 (m, 1H); ^{13}C NMR (CD_3OD, 125 MHz): δ 144.52 (C), 139.56 (C), 130.47 (two CH), 128.70 (two CH), 71.54 (CH), 68.95 (CH), 62.74 (CH), 60.87 (CH_2), 44.79 (CH_2), 43.09 (CH_2), 38.67 (CH), 21.45 (CH_3); HREIMS: Calcd for $C_{14}H_{23}N_2O_5S$ (M^+−HCl+1): *m*/*z* 331.1322. Found: *m*/*z* 331.1328.

3.32. 5-Aminomethyl-2-hydroxymethylpiperidine-3,4-diol (27)

Small pieces of sodium metal were added to a solution of **26** (37.6 mg, 0.10 mmol) in liquid ammonia (20 mL) at −78 °C, until a blue color persisted for 5 min. The solution was then warmed to ambient temperature, and the ammonia was allowed to evaporate. The crude residue was purified by flash chromatography with 3:7 NH_4OH–MeOH. (R_f 0.31 in 3:7 NH_4OH–MeOH) to give **27** as a colorless liquid (18.1 mg; 83% yield). ^1H NMR (D_2O, 500 MHz): δ 3.98 (t, *J* 4.0 Hz, 1H), 3.84 (td, *J* 7.5, 4.0 Hz, 1H), 3.60–3.63 (m, 2H), 3.14 (dd, *J* 13.0, 6.0 Hz, 1H), 3.04 (dd, *J* 13.0, 6.0 Hz, 1H), 2.88–2.91 (m, 1H), 2.83 (dd, *J* 13.5, 3.5 Hz, 1H), 2.63 (dd, *J* 13.5, 7.5 Hz, 1H), 1.98–2.03 (m, 1H); ^{13}C NMR (D_2O, 125 MHz): δ 66.16 (CH), 65.98 (CH), 58.92 (CH_2), 57.95 (CH), 44.88 (CH_2), 41.24 (CH), 39.16 (CH_2); HREIMS: Calcd for $C_7H_{16}N_2O_3$·HCl (M^+·HCl): *m*/*z* 176.1161. Found: *m*/*z* 176.1159.

3.33. 5-Aminomethyl-2-hydroxymethylpiperidine-3,4-diol (32)

Prepared from **31** according to procedure 3.32. Colorless oil: 87% yield; R_f 0.32 in 3:7 NH_4OH–MeOH. ^1H NMR (D_2O, 500 MHz): δ 3.72 (dd, *J* 7.0, 3.0 Hz, 1H), 3.56–3.61 (m, 3H), 2.97–3.01 (m, 2H), 2.86–2.91 (m, 2H), 2.57 (dd, *J* 13.5, 7.5 Hz, 1H), 2.03–2.10 (m, 1H); ^{13}C NMR (D_2O, 125 MHz): δ 69.57 (CH), 66.96 (CH), 59.44 (CH_2), 58.14 (CH), 40.65 (CH_2), 40.05 (CH_2), 37.20 (CH); HREIMS: Calcd for $C_7H_{16}N_2O_3$·HCl (M^+−HCl): *m*/*z* 176.1161. Found: *m*/*z* 176.1163.

Acknowledgments

Financial support from Auspex Pharmaceutical Inc. for this work is gratefully acknowledged.

Supplementary data

Crystal information files (CIF) have been deposited with the Cambridge Crystallographic Data Centre. These data may be obtained, on request, from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Tel.: +44-1223-336408; fax: +44-1223-336033; e-mail:

deposit@ccdc.cam.ac.uk) on quoting CCDC-280748 for *trans*-2,2-dimethyl-5-(toluene-4-sulfonyl)-4a,5,6,8a-tetrahydro-4*H*-[1,3]dioxino[5,4-*b*]pyridine (**7**) and CCDC-280749 for 1,5-deoxy-2,3:4,6-di-*O*-isopropylidene-1,5-sulfonamino-D-allitol (**19**). Spectra of all compounds have been compiled (total 261 pages) can be found in the online version at doi:10.1016/j.carres.2005.08.014.

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