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Note

Total synthesis and identification of two diastereoisomers of 1-methyl-2-[*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl]ethyl β-L-fucopyranoside

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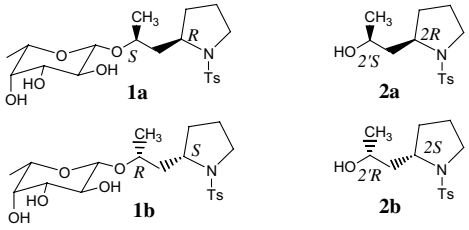
Abstract—The reaction of a racemic mixture of (2*R*,2′*S*)- and (2*S*,2′*R*)-*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl-2-propanol, prepared from (*S*)-proline, with 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl trichloroacetimidate led to both diastereoisomers of the title compound after *O*-deacetylation.

Keywords: L-Proline; β-Aminoalcohols; β-L-Fucopyranosides

Pyrrolidine alkaloids,[1–3] such as hygroline and pseudohygroline, [(2*S*,2′*S*)- and (2*S*,2′*R*)-*N*-methyl-2-(2′-hydroxypropyl)pyrrolidines, respectively] possess interesting biological activities.[4,5] These compounds have been isolated from plants.[1,6–9] All four stereoisomers have previously been synthesized.[3] One of them has been found as an aglycone in 1-methyl-2-(1-methyl-2-pyrrolidinyl)ethyl 6-deoxy-3-*O*-[(*Z*)-2-methyl-2-buten-oyl)-α-galactopyranoside isolated from *Schizanthus integrifolius* Phil. (Solanaceae), the absolute configuration of fucose and hygroline moieties has not yet been determined.[10] In our ongoing research work on the synthesis of glycoheterocyclic compounds, we were interested in the preparation of diastereomerically pure β-L-fucopyranosides **1a** and **1b**, having only a fucosyl and a pyrrolidinyl moiety, for biological activity tests, the starting alcohols being a racemic mixture of (2*R*,2′*S*)- and (2*S*,2′*R*)-*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl-2-propanol **2a** and **2b.**



We have first synthesized a mixture of all four stereoisomers **2a**–**d** in seven steps starting from (*S*)-proline **3** (Scheme 1). Compounds **4**–**7** were prepared as described in the literature.[11,12] Treatment of **7** with $(COCl)_2$, followed by reaction with the sodium salt of diethyl malonate afforded diester **8** in 78% yield. Decarboxylation of **8** under acidic conditions at 100 °C gave ketone **9** in 79% yield, unfortunately as a racemic mixture. Reduction of **9a**,**b** gave alcohols **2a**–**d**.

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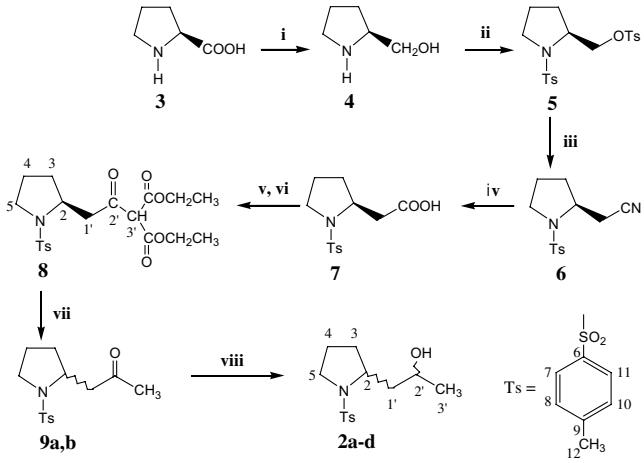


Scheme 1. Reagents and conditions: (i) $Zn(BH_4)_2$, THF, Δ, 10 h, 61%; (ii) TsCl, Py, rt, 12 h, 89%; (iii) NaCN, Me_2SO, rt, 72 h, 90%; (iv) AcOH, 37% HCl, 100 °C, 4 h, 66%; (v) $(COCl)_2$, DMF, CH_2Cl_2, rt, 4 h; (vi) NaH, $CH_2(CO_2CH_2CH_3)_2$, THF, Δ, 3 h, 78%; (vii) 4 M H_2SO_4, 100 °C, 12 h, 79%; (viii) (1) 2 equiv $NaBH_4$, MeOH, 0 °C, 1 h; (2) 2 M HCl, 0 °C, 96% (**2a**,**b**:**2c**,**d**—2.1:1).

TLC [1.5:1.0 petroleum ether–EtOAc] of the mixture **2a**,**d** showed two spots of R_f values 0.4 and 0.5 under ultraviolet light. Each spot constituted racemic mixtures of 2*R*,2′*S*–2*S*,2′*R* and 2*S*,2′*S*–2*R*,2′*R*. Each enantiomeric pair was separated by liquid chromatography over silica gel in the ratio of 2:1 (**2a**,**b**:**2c**,**d**). The one having R_f value of 0.4 (**2a**,**b**) produced crystals from which a suitable crystal was picked up and subjected to X-ray analysis (Fig. 1, Table 1). It showed the relative configuration at positions 2 and 2′, which could either be 2*R*,2′*S* or 2*S*,2′*R*. Compound **2b** was synthesized enantiomerically pure starting from compound **6** as shown in Scheme 2 and gave similar ^1H NMR spectra as the racemic mixture (**2a**,**b**).

These *N*-tosyl alcohols **2a**,**b** and **2c**,**d** have not been reported in the literature and the ^1H NMR spectra of **2a**–**d** are consistent with the proposed structures. Compounds **2b** and **9a** were found to be enantiomerically pure by ^1H NMR spectroscopy as verified by the chiral shift reagent europium tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorate.

The next step was the glycosidation process, which was performed using the trichloroacetimidate method.[13] Acetylation of L-fucose followed by hydrolysis gave the known 2,3,4-tri-*O*-acetyl-α/β-L-fucopyranose.[14,15] This compound was treated with trichloroacetonitrile in dichloromethane with DBU as the catalyst to give 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl trichloroacetimidate **11**.[16] Reaction of optically pure **2b** with **11** in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 gave a single compound **12b** in 78% yield, having the configuration 2″*S*,2′*R*, R_f value of 0.45 on TLC in 1.5:1.0 petroleum ether–EtOAc. On the other hand, the reaction of the racemic mixture **2a**,**b** with **11** in the presence of TMSOTf in CH_2Cl_2 gave a mixture of diastereoisomers showing two spots on the TLC plate: one with R_f value of 0.45 corresponding to **12b**, the other one with R_f value of 0.52 and so corresponding to **12a**. With careful

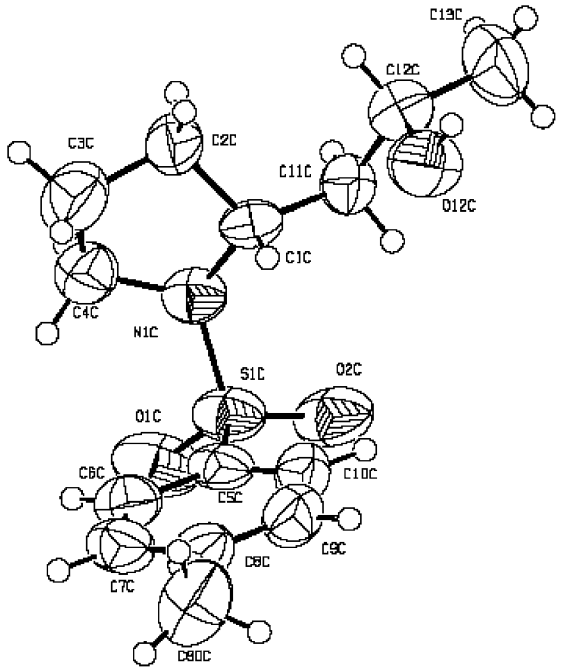
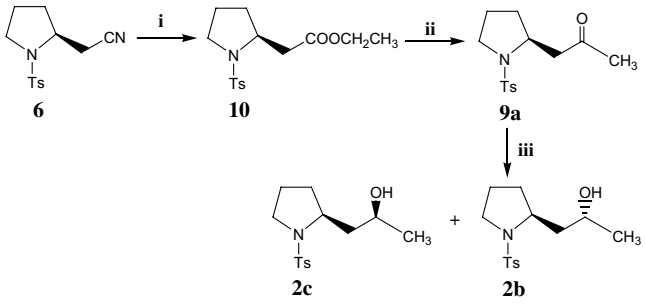


Figure 1. Structure of compound **2a**,**b**.

Table 1. Crystal data and structure refinement of **2a**,**b**

Empirical formula	$C_{14}H_{21}NO_3S$
Formula weight	283.38
Temperature (K)	293 (2)
Radiation wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
a (Å)	13.188(3), $\alpha = 90°$
b (Å)	7.7314(15), $\beta = 100.85(3)°$
c (Å)	14.682(3), $\gamma = 90°$
Volume (Å^3)	1470.2(5)
Z	1
Calculated density (Mg m^{-3})	1.280
Absorption coefficient (mm^{-1})	0.224
F(000)	608
Crystal size (mm)	$1.0 \times 0.2 \times 0.2$
Θ Range for data collection (°)	1.91–27.53
Limiting indices	$-17 \leqslant h \leqslant 16$, $0 \leqslant k \leqslant 10$, $0 \leqslant l \leqslant 19$
Reflections collected/unique	3339/3339 [$R_{int} = 0.0000$]
Completeness to θ (%)	98.9
Absorption correction	None
Max and min transmission	0.9566 and 0.8071
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3339/0/193
Goodness-of-fit on F^2	1.449
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0782$, $wR_2 = 0.1799$
R indices (all data)	$R_1 = 0.1649$, $wR_2 = 0.2500$
Largest diff. peak and hole (e A^{-3})	1.048 and −0.959



Scheme 2. Reagents and conditions: (i) EtOH, HCl(gas), rt, 24 h, 60%; (ii) (1) 1 equiv Tebbe's reagent 0.5 M in toluene, THF, 0 °C, 30 min; (2) Et_2O, 0.1 M NaOH; (3) 1 M HCl, $CHCl_3$, rt, 1.5 h, 79% from **10**; (iii) (1) 2 equiv $NaBH_4$, MeOH, 0 °C, 1 h; (2) 2 M HCl, 0 °C, 96% (**2b**:**2c**—2.1:1).

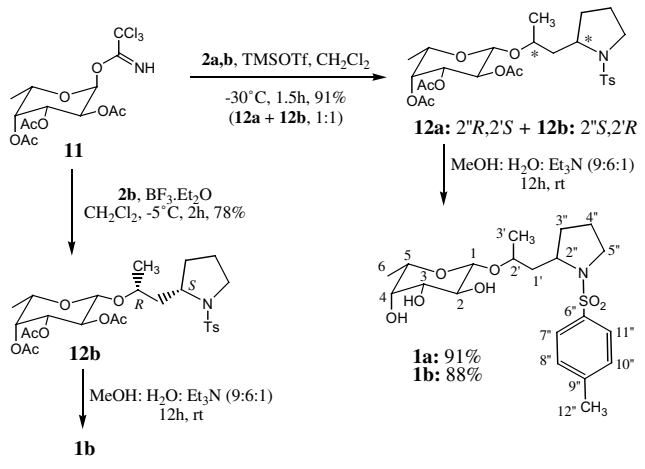
handling, these two compounds were separated and their specific rotations and spectroscopic data obtained (Scheme 3).

Deacetylation of **12a** and **12b** was performed individually using 9:6:1 methanol–water–triethylamine,[17] which gave **1a** and **1b** in excellent yields (Scheme 3).

Compounds **1a** and **1b** were evaluated for their cytotoxic activity with tumor cells HEp2 (larynx carcinoma) and NCI-H_{292} (lung carcinoma). The methodology used for this test was in accordance with the protocol for Screening Chemical Agents and Natural Products.[18] Unfortunately the results of the cytotoxic evaluation in vitro showed that compounds **1a** and **1b** were inactive up to a concentration of 10 μg/mL.

1. Experimental

Melting points were determined on a Electrothermal digital melting point apparatus (model IA9100) and are uncorrected. Specific rotations were measured with a Perkin–Elmer polarimeter model 241. ^1H and ^{13}C NMR spectra were recorded on a Brüker AM 300 spectrophotometer using TMS as internal standard. Silica gel 60 (230–400 mesh) has been employed for liquid chromatography. Petroleum ether used in the experiments had a boiling range of 40–65 °C.



Scheme 3.

1.1. Diethyl (−)-(*S*)-{[*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl]acetyl}malonate (8)

To (−)-(*S*)-[*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl]acetic acid **7** (1.0 g, 3.53 mmol) in CH_2Cl_2 (10.0 mL) was added two drops of DMF and oxalyl chloride (0.5 mL, ~1.5 equiv) at 0 °C. The mixture was stirred for 4 h at room temperature and concentrated to dryness. Diethyl malonate (2.7 mL, 17.66 mmol) and 60% NaH (0.70 g, 17.66 mmol) in dry THF (10.0 mL) were stirred for 30 min at room temperature. Addition of the generated acid chloride in dry THF (15.0 mL) to this malonate suspension followed by stirring for 4 h at 70 °C completed the reaction. Addition of water, extraction with CH_2Cl_2, drying the soln over Na_2SO_4 and solvent removal provided the crude product. Purification by column chromatography over silica gel using 4:1 petroleum ether–EtOAc gave 1.17 g (78%) of an oil characterized as a 1:1 keto-enolic mixture of **8**: TLC (4:1 petroleum ether–EtOAc): R_f 0.54; $[\alpha]_D^{25}$ −101.8 (*c* 1.05, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ 13.25 (s, 0.5H, OH), 7.76 (d, 2H, *J* 8.2 Hz, H-7, H-11), 7.33 (d, 2H, *J* 7.9 Hz, H-8, H-10), 4.50 (s, 0.5H, H-3′), 4.29 (q, 4H, *J* 7.1 Hz, –OCH_2–), 4.01–3.94 (m, 1H, H-2), 3.49–3.41 (m, 1H, H-5), 3.39 (dd, 0.5H, *J* 3.1 Hz, *J* 18.2 Hz, H-1′), 3.18 (dd, 0.5H, *J* 4.5 Hz, *J* 13.7 Hz, H-1′), 3.10–3.03 (m, 1H, H-5), 3.01 (dd, 0.5H, *J* 9.8 Hz, *J* 18.2 Hz, H-1′), 2.66 (dd, 0.5H, *J* 10.0 Hz, *J* 13.7 Hz, H-1′), 2.44 (s, 1.5H, H-12), 2.43 (s, 1.5H, H-12), 1.83–1.45 (m, 4H, H-3, H-4), 1.34–1.28 (4t overlapping, 6H, *J* 6.9 Hz, aliph.–CH_3). Anal. Calcd for $C_{20}H_{27}NO_5S\cdot 1/4H_2O$: C, 55.86; H, 6.44. Found: C, 55.91; H, 6.41.

1.2. *N*-(*p*-Tolylsulfonyl)-2-pyrrolidinylacetone (9a,b)

Diethyl (−)-(*S*){[*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl]acetyl}malonate **8** (1.10 g, 2.59 mmol) in 4 M H_2SO_4 (55.0 mL) was stirred for 12 h at 100 °C. The mixture was neutralized with satd aq $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with water (3 × 100 mL), dried (Na_2SO_4) and concentrated to yield the crude product. Purification by column chromatography over silica gel using 7:3 petroleum ether–EtOAc gave **9a**,**b**, which after crystallization from petroleum ether–CH_2Cl_2 yielded colourless crystals (575 mg, 79%): mp 101–102 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 2H, *J* 8.2 Hz, H-7, H-11), 7.33 (d, 2H, *J* 7.9 Hz, H-8, H-10), 3.94–3.89 (m, 1H, H-2), 3.47–3.40 (m, 1H, H-5), 3.25 (dd, 1H, *J* 3.2 Hz, *J* 17.8 Hz, H-1′), 3.12–3.04 (m, 1H, H-5), 2.65 (dd, 1H, *J* 9.7 Hz, *J* 17.8 Hz, H-1′), 2.43 (s, 3H, H-12), 2.17 (s, 3H, H-3′), 1.82–1.72 (m, 2H, H-3), 1.61–1.43 (m, 2H, H-4); ^{13}C

NMR (75.5 MHz, $CDCl_3$): δ 207.57 (C-2′), 143.94 (C-6), 134.03 (C-9), 130.15 (C-7, C-11), 128.00 (C-8, C-10), 56.26 (C-2), 51.04 (C-1′), 49.55 (C-5), 32.47 (C-3), 30.94 (C-3′), 24.18 (C-4), 21.91 (C-12). The NMR spectra agreed with the literature data.[19]

1.3. Ethyl (−)-(*S*)-[*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl]acetate (10)

(−)-(*S*)-[*N*-(*p*-Tolylsulfonyl)-2-pyrrolidinyl]acetonitrile **6** (1.0 g, 3.79 mmol) in absolute EtOH (40.0 mL) saturated with HCl gas was stirred for 24 h at room temperature. Solvent removal under diminished pressure, dissolution of the residue in ice-cold water followed by treatment with $NaHCO_3$ furnished an alkaline soln with a pH value of ~9.0. Extraction with CH_2Cl_2, drying (Na_2SO_4), filtration and solvent removal left an oil. Liquid chromatography of the above material over silica gel using a mixture of 1:1 petroleum ether–diethyl ether gave 0.71 g (60%) of chromatographically pure product having the R_f value of 0.5 (1:1 petroleum ether–diethyl ether): $[\alpha]_D^{25}$ −103.2 (*c* 1.04, CH_2Cl_2); IR (cm^{-1}): 1735 (*v* C=O), 1250 and 1050 (*v* C–O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 2H, *J* 8.2 Hz, H-7, H-11), 7.32 (d, 2H, *J* 8.2 Hz, H-8, H-10), 4.14 (2q overlapping, 2H, *J* 7.1 Hz, –OCH_2–), 3.99–3.93 (m, 1H, H-2), 3.48–3.41 (m, 1H, H-5), 3.17–3.11 (m, 1H, H-5), 3.10 (dd, 1H, *J* 3.9 Hz, *J* 16.0 Hz, H-1′), 2.53 (dd, 1H, *J* 10.1 Hz, *J* 16.0 Hz, H-1′), 2.44 (s, 3H, H-12), 1.90–1.51 (m, 4H, H-3, H-4), 1,27 (t, 3H, *J* 7.1 Hz, aliph. –CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.62 (CO), 143.92 (C-6), 134.48 (C-9), 130.10 (C-7, C-11), 127.94 (C-8, C-10), 60.83 (–OCH_2–), 56.95 (C-2), 49.56 (C-1′), 41.77 (C-5), 32.00 (C-3), 24.12 (C-4), 21.88 (C-12), 14.57 (aliph.–CH_3). The IR and NMR spectra agreed with the literature data.[19]

1.4. (−)-(*S*)-[*N*-(*p*-Tolylsulfonyl)-2-pyrrolidinyl]acetone (9a)

Tebbe's reagent (2.0 mL, 0.5 M in toluene) was added to ester **10** (0.31 g, 1.0 mmol) dissolved in THF (3.0 mL) at 0 °C, and the mixture was stirred for 30 min at room temperature. Soon after, ether (15.0 mL) and seven drops of 0.1 M NaOH were added, and the soln was stirred for an additional 30 min. Drying (Na_2SO_4), filtration over celite and solvent removal left the crude product. This was then dissolved in $CHCl_3$ (15.0 mL) and six drops of 2.0 M HCl were added to it followed by stirring for 1.5 h at room temperature. Water (30.0 mL) was added to the soln followed by neutralization with $NaHCO_3$. Extraction with CH_2Cl_2 (3 × 30 mL), drying (Na_2SO_4), filtration and solvent removal provided the crude product (0.28 g). Column chromatography over silica gel using 1.5:1.0 petroleum ether–EtOAc gave pure **9a**, which after crystallization from petroleum ether–CH_2Cl_2 yielded colourless crystals (0.22 g, 79%): mp 94–96 °C; $[\alpha]_D^{25}$ −116.9 (*c* 1, CH_2Cl_2). The NMR spectra agreed with those of compounds **9a**,**b** given above.

1.5. *N*-(*p*-Tolylsulfonyl)-2-pyrrolidinyl-2-propanol (2a,b and 2c,d)

Sodium borohydride (148 mg, 3.91 mmol) was added at 0 °C to racemic **9a**,**b** (550 mg, 1.96 mmol) dissolved in MeOH (40.0 mL), and the reaction mixture was stirred for 1 h at this temperature. To the soln, 2.0 M HCl was added followed by stirring for an additional 10 min. Neutralization of this soln with aq $NaHCO_3$, extraction with CH_2Cl_2 and work-up yielded two diastereoisomers, which were separated by column chromatography over silica gel using 1.5:1.0 petroleum ether–EtOAc of **2a**,**b** (359 mg) and **2c**,**d** (171 mg) (2.1:1). The combined yield was 96%. These compounds were recrystallized in 5:1 hexane–EtOAc.

Compound **2a**,**b**: TLC (1.5:1 petroleum ether–EtOAc): R_f 0.4; mp 76–78 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, 2H, *J* 8.2 Hz, H-7, H-11), 7.33 (d, 2H, *J* 8.1 Hz, H-8, H-10), 3.93–3.85 (m, 2H, H-2, H-2′), 3.45–3.37 (m, 1H, H-5), 3.22–3.14 (m, 1H, H-5), 2.42 (s, 3H, H-12), 2.03–1.44 (m, 6H, H-1′, H-3, H-4), 1.26 (d, 3H, *J* 6.2 Hz, H-12); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 143.84 (C-6), 134.80 (C-9), 130.09 (C-7, C-11), 128.04 (C-8, C-10), 66.64 (C-2′), 58.59 (C-2), 49.24 (C-5), 46.43 (C-1′), 31.67 (C-3), 24.79 (C-3′), 24.38 (C-4), 21.91 (C-12).

Compound **2c**,**d**: TLC (1.5:1 petroleum ether–EtOAc): R_f 0.5; mp 87–89 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, 2H, *J* 8.2 Hz, H-7, H-11), 7.33 (d, 2H, *J* 8.1 Hz, H-8, H-10), 4.20–4.16 (m, 1H, H-2′), 4.10–4.02 (m, 1H, H-2), 3.46 (br s, 1H, OH), 3.42–3.34 (m, 1H, H-5), 3.22–3.13 (m, 1H, H-5), 2.43 (s, 3H, H-12), 1.88–1.31 (m, 6H, H-1′, H-3, H-4), 1.23 (d, 3H, *J* 6.4 Hz, H-12); ^{13}C NMR (75.5 MHz, $CDCl_3$): 144.12 (C-6), 134.70 (C-9), 130.19 (C-7, C-11), 127.98 (C-8, C-10), 64.10 (C-2′), 58.10 (C-2), 48.80 (C-5), 45.84 (C-1′), 31.70 (C-3), 24.46 (C-4), 23.26 (C-3′), 21.93 (C-12).

1.6. (−)-(2*S*,2′*R*)- and (−)-(2*S*,2′*S*)-*N*-(*p*-Tolylsulfonyl)-2-pyrrolidinyl]-2-propanol (2b and 2c)

Starting from enantiomerically pure ketone **9a** and following the procedure described above, **2b** and **2c** were obtained in a (2.1:1) ratio and separated on column chromatography. Yield 96%.

Compound **2b**: R_f 0.4; mp 84–85 °C; $[\alpha]_D^{25}$ −98.0 (*c* 1.04, CH_2Cl_2). Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.33; H, 7.47. Found: C, 59.26; H, 7.31.

Compound **2c**: R_f 0.5; mp 92.5–94 °C; $[\alpha]_D^{25}$ −20.5 (*c* 0.83, CH_2Cl_2). Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.33;

H, 7.47. Found: C, 59.69; H, 7.72. The NMR spectra for **2b** and **2c** agreed with those of compounds **2a**,**b** and **2c**,**d** above.

1.7. 1-Methyl-2-[*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl]ethyl 2,3,4-tri-*O*-acetyl-β-L-fucopyranoside (12a and 12b)

To a cold (−30 °C) suspension of **2a**,**b** (150 mg, 0.53 mmol) and trichloroacetimidate **11** (345 mg, 0.79 mmol) in dry CH_2Cl_2 (5.0 mL) containing a small amount of 4 Å molecular sieves under argon atmosphere was added TMSOTf (20 μL). After stirring for 1.5 h, the reaction mixture was treated with 1.5 g of $NaHCO_3$ and filtered. Water was then added and the mixture was extracted with CH_2Cl_2 (3 × 20.0 mL). Drying (Na_2SO_4) and solvent removal provided crude diastereoisomers **12a** and **12b**, which were separated by column chromatography over silica gel using 1.5:1 petroleum ether–EtOAc. The ratio of **12a** (126.8 mg) and **12b** (139 mg) was ~1:1. The combined yield was 91%.

Compound **12a**: TLC (1.5:1.0 petroleum ether–EtOAc): R_f 0.52; $[\alpha]_D^{25}$ +64.7 (*c* 1, CH_2Cl_2); mp 146–147 °C (petroleum ether–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 2H, *J* 8.2 Hz, H-7″, H-11″), 7.34 (d, 2H, *J* 7.9 Hz, H-8″, H-10″), 5.22 (d, 1H, $J_{4,3}$ 3.4 Hz, H-4), 5.15 (dd, 1H, $J_{2,1}$ 7.7 Hz, $J_{2,3}$ 10.5 Hz, H-2), 5.04 (dd, 1H, $J_{3,2}$ 10.5 Hz, $J_{3,4}$ 3.4 Hz, H-3), 4.50 (d, 1H, $J_{1,2}$ 7.7 Hz, H-1), 4.02–3.91 (m, 1H, H-2′), 3.80–3.71 (m, 2H, H-2″, H-5), 3.44–3.36 (m, 1H, H-5″), 3.23–3.15 (m, 1H, H-5″), 2.43 (s, 3H, H-12″), 2.18 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 1.99 (s, 3H, $COCH_3$), 1.84–1.37 (m, 6H, H-3″, H-4″, H-1′), 1.21 (d, 3H, *J* 6.0 Hz, H-3′), 1.17 (d, 3H, $J_{6,5}$ 6.4 Hz, H-6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.31 (CO), 169.87 (CO), 169.19 (CO), 142.78 (C-6″), 134.20 (C-9″), 129.21 (C-7″, C-11″), 127.37 (C-8″, C-10″), 98.60 (C-1), 72.13 (C-2′), 71.06 (C-3), 70.05 (C-4), 68.71 (C-2), 68.60 (C-5), 56.94 (C-2″), 48.66 (C-5″), 42.76 (C-1′), 30.72 (C-3″), 23.50 (C-4″), 21.16 (C-12″), 20.46 ($COCH_3$), 20.39 ($COCH_3$), 20.29 ($COCH_3$), 19.23 (C-3′), 15.17 (C-6); HRFABMS $[M+H]^+$ calcd for $C_{26}H_{38}NO_{10}S$: 556.2217. Found = 556.2222.

Compound **12b**: TLC (1.5:1 petroleum ether–EtOAc): R_f 0.44; $[\alpha]_D^{25}$ −50 (*c* 1, CH_2Cl_2); mp 181–182 °C (petroleum ether–EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 2H, *J* 8.2 Hz, H-7″, H-11″), 7.36 (d, 2H, *J* 8.1 Hz, H-8″, H-10″), 5.22 (d, 1H, $J_{4,3}$ 3.5 Hz, H-4), 5.18 (dd, 1H, $J_{2,1}$ 7.9, $J_{2,3}$ 10.3 Hz, H-2), 5.02 (dd, 1H, $J_{3,2}$ 10.3, $J_{3,4}$ 3.5 Hz, H-3), 4.50 (d, 1H, $J_{1,2}$ 7.9 Hz, H-1), 3.89 (m, 1H, H-2′), 3.80 (m, 1H, H-5), 3.69 (m, 1H, H-2″), 3.41–3.33 (m, 1H, H-5″), 3.26–3.18 (m, 1H, H-5″), 2.43 (s, 3H, H-12″), 2.17 (s, 3H, $COCH_3$), 1.98 (s, 3H, $COCH_3$), 1.91 (s, 3H, $COCH_3$), 1.79–1.39 (m, 6H, H-3″, H-4″, H-1′), 1.36 (d, 3H, *J* 6.2 Hz, H-3′), 1.23 (d, 3H, $J_{6,5}$ 6.2 Hz, H-6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.20 (CO), 170.65 (CO), 169.65 (CO), 143.71 (C-6″), 135.02 (C-9″), 130.15 (C-7″, C-11″), 127.95 (C-8″, C-10″), 101.71 (C-1), 76.51 (C-2′), 71.98 (C-3), 70.72 (C-4), 69.73 (C-2), 69.45 (C-5), 57.65 (C-2″), 49.15 (C-5″), 43.84 (C-1′), 31.71 (C-3″), 24.45 (C-4″), 22.06 (C-3′), 21.91(C-12″), 21.16 ($COCH_3$), 21.07 ($COCH_3$), 21.05 ($COCH_3$), 16.59 (C-6). Anal. Calcd for $C_{26}H_{37}NO_{10}S$: C, 56.20; H, 6.71; N, 2.52; S, 5.77. Found: C, 56.20; H, 7.01; N, 2.78; S, 5.85.

1.8. 1-Methyl-2-[*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl]ethyl 2,3,4-tri-*O*-acetyl-β-L-fucopyranoside (12b)

To a cold (−5 °C) suspension of **2b** (20 mg, 0.07 mmol), trichloroacetimidate **11** (61 mg, 0.14 mmol) and 4 Å molecular sieves in dry CH_2Cl_2 (2.0 mL) under argon, was added $BF_3{\cdot}Et_2O$ (20 μL). After stirring for 2 h, the reaction mixture was treated with a satd aq $NaHCO_3$ (4 mL) and filtered. Extraction of the mixture with CH_2Cl_2 (3 × 20 mL), drying (Na_2SO_4) and solvent removal provided the crude product of **12b**, which was purified by preparative TLC over silica gel using 9.7:0.3 toluene–MeOH to yield 30 mg (78%) of pure **12b**. The NMR spectra agreed with those of compound **12b** above.

1.9. 1-Methyl-2-[*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl]ethyl β-L-fucopyranoside (1)

A 1% soln of **12** in 9:6:1 MeOH–water–triethylamine was stirred overnight at room temperature. Water was added and extraction with CH_2Cl_2 (3 × 20 mL), drying (Na_2SO_4), filtration and solvent removal provided the crude product **1**. Column chromatography over silica gel using 9.5:0.5 CH_2Cl_2–MeOH as eluent, gave pure **1**, which after crystallization from 9:1 cyclohexane–CH_2Cl_2, yielded colourless crystals.

Compound **1a**: Starting from **12a**, 91%; $[\alpha]_D^{25}$ +87.3 (*c* 0.48, MeOH); mp 196–198 °C (C_6H_{12}–CH_2Cl_2); ^{1}H NMR (300 MHz, CD_3OD): δ 7.76 (d, 2H, *J* 8.1 Hz, H-7″, H-11″), 7.46 (d, 2H, *J* 7.8 Hz, H-8″, H-10″), 4.22 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1), 4.02–3.93 (m, 1H, H-2′), 3.84–3.73 (m, 1H, H-2″), 3.61–3.48 (m, 4H, H-2, H-3, H-4, H-5), 3.38–3.07 (m, 2H, H-5″), 2.43 (s, 3H, H-12″), 2.21–2.12 (m, 1H, H-1′), 1.78–1.32 (m, 5H, H-3″, H-4″, H-1′), 1.22 (d, 3H, *J* 6.0 Hz, H-3′), 1.18 (d, 3H, $J_{6,5}$ 6.6 Hz, H-6); ^{13}C NMR (75.5 MHz, CD_3OD): δ 144.92 (C-6″), 135.45 (C-9″), 130.90 (C-7″, C-11″), 128.94 (C-8″, C-10″), 102.63 (C-1), 75.12 (C-2′), 73.05 (C-3, C-4), 72.28 (C-2), 71.65 (C-5), 58.87 (C-2″), 50.36 (C-5″), 45.24 (C-1′), 31.83 (C-3″), 24.83 (C-4″), 21.46 (C-12″), 20.79 (C-3′), 16.85 (C-6). Anal. Calcd for $C_{20}H_{31}NO_7S$: C, 55.92; H, 7.27; N, 3.26; S, 7.46. Found: C, 55.99; H, 7.30; N, 3.29; S, 7.43.

Compound **1b**: Starting from **12b**, 88%; $[\alpha]_D^{25}$ −68.3 (*c* 0.36, MeOH); mp 171–172 °C (C_6H_{12}–CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, 2H, *J* 8.4 Hz,

H-7″, H-11″), 7.31 (d, 2H, *J* 8.4 Hz, H-8″, H-10″), 4.26 (d, 1H, $J_{1,2}$ 7.2 Hz, H-1), 3.97–3.91 (m, 1H, H-2′), 3.80–3.61 (m, 5H, H-2, H-3, H-4, H-5, H-2″), 3.39–3.32 (m, 1H, H-5″), 3.15–3.07 (m, 1H, H-5″), 2.41 (s, 3H, H-12″), 2.16–2.07 (m, 1H, H-1′), 1.82–1.77 (m, 1H, H-1′), 1.58–1.44 (m, 4H, H-3″, H-4″), 1.36 (d, 3H, *J* 6.6 Hz, H-3′), 1.33 (d, 3H, $J_{6,5}$ 6.3 Hz, H-6); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 143.33 (C-6″), 134.56 (C-9″), 129.69 (C-7″, C-11″), 127.53 (C-8″, C-10″), 103.85 (C-1), 75.36 (C-2′), 73.89 (C-3), 71.48 (C-4), 70.40 (C-2), 66.08 (C-5), 58.12 (C-2″), 48.77 (C-5″), 45.85 (C-1′), 31.11 (C-3″), 24.28 (C-4″), 22.53 (C-12″), 21.45(C-3′), 16.39 (C-6). Anal. Calcd for $C_{20}H_{31}NO_7S$: C, 55.92; H, 7.27; N, 3.26; S, 7.46. Found: C, 56.26; H, 7.05; N, 2.77; S, 7.99.

Supplementary materials

The crystallographic data were deposited at Cambridge structural database (accession number CCDC 252734). These data can be obtained free of charge from the director, CCDC, 12 Union road, Cambridge CB21EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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