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Note

Synthesis and unusual glycosidic coupling reaction of substituted 2,7-dioxabicyclo[4.1.0]heptanes: 1,2-anhydro-3,4-di-*O*-benzyl-α-D-fucopyranose

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Most of the D-fucopyranosides occur in cardiac glycosides or in plants as glycosides or oligosaccharide derivatives of steroids. A considerable number of these glycosides, such as strebloside, kamaloside, and the antibiotic chartreusin (a disaccharide of D-fucose and D-digitalose), have been isolated and their structures have been determined [1]. In addition, in some glycoproteins, fucopyranose has been found at the non-reducing end with α-(1 → 2) linkage on Gal, or α-(1 → 3), (1 → 4), or (1 → 6) linkage on GlcNAc [2].

Due to their importance in the synthesis of oligosaccharides and other anomerically-substituted carbohydrate derivatives, 1,2-anhydro sugars have received considerable attention recently because of their excellent reactivity and stereoselectivity [3–11]. We have reported previously on the synthesis and glycosidic coupling reactions of 1,2-anhydro-D, L-rhamno- [12], -D-talo- [13], -D-xylo- [14], -L-arabino- [15], -L-ribo-, -D-lyxo- [16], 6-deoxy-D-gluco- [17], and -D-galacto-pyranose [18] benzyl ethers. Earlier, Schuerch's group described the synthesis of 1,2-anhydro-D-gluco- [19] and -manno-pyranose [20] benzyl ether. We recently reported a method for the preparation of a glycopeptide with 1,2-anhydrosugars as glycosyl donors, affording 1,2-*trans* linked glycosyl serine derivatives in high yields [21]. Here we report the synthesis of 1,2-anhydro-3,4-di-*O*-benzyl-α-D-fucopyranose (**9**) and its coupling reaction with *N*-benzyl-oxycarbonyl-L-serine methyl ester, which gives an unexpected 1,2-*cis* linked fucopyranoside as the sole product in high yield.

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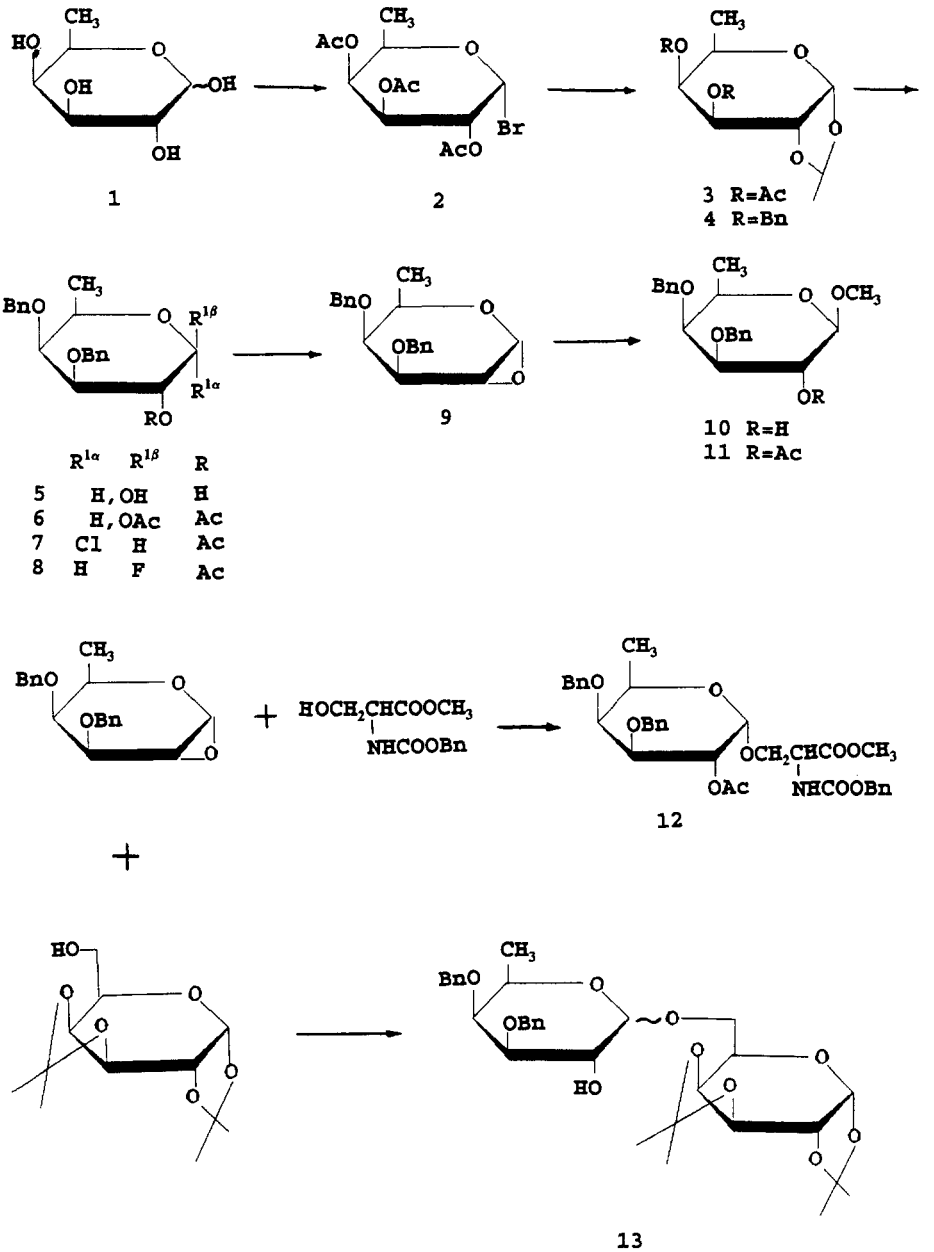
1. Results and discussion

For the synthesis of the 1,2-anhydro sugar **9**, a 1,2-blocked D-fucopyranose was prepared as an intermediate. An initial attempt focused on the synthesis of 3,4-di-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-α-D-fucopyranose. It was found, however, that treatment of the acetobromosugar **2** with methanol and 2,4-lutidine gave a mixture of the *R*- and *S*-isomers of 3,4-di-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-α-D-fucopyranose, together with methyl 2,3,4-tri-*O*-acetyl-β-D-fucopyranoside. The ratio of the methyl glycoside and *ortho* esters was about 1:1, and separation was difficult. To obtain a high yield of a 1,2-protected α-D-fucopyranose, 3,4-di-*O*-acetyl-1,2-*O*-ethylidene-α-D-fucopyranose (**3**) was prepared as a mixture of *R*- and *S*-isomers in a good yield (69%) from **2** according to a reported method [22]. Compound **3** was directly converted to 3,4-di-O-benzyl-1,2-*O*-ethylidene-α-D-fucopyranose (**4**) in a high yield (Scheme 1). Hydrolysis of **4** in 1,4-dioxane with sulfuric acid under reflux gave 3,4-di-*O*-benzyl-D-fucopyranose (**5**). Acetylation of **5** with acetic anhydride-pyridine furnished the 1,2-diacetate (**6**) quantitatively. 2-*O*-Acetyl-3,4-di-*O*-benzyl-α-D-fucopyranosyl chloride (**7**) was obtained in an excellent yield (94%) from compound **6** with hydrogen chloride in diethyl ether. Pure compound **7** was relatively stable at 0°C while crude product **7** was labile even below 0°C. To prepare β-halide suitable for an intramolecular S_N2 reaction from back-side attack, fluorination of **7** with silver fluoride in a mixed solvent of anhydrous acetonitrile and benzene was carried out, and crystalline 2-*O*-acetyl-3,4-di-*O*-benzyl-β-D-fucopyranosyl fluoride (**8**) was obtained as the sole product in high yield. This is different from the fluorination of 2-*O*-acetyl-3,4-di-*O*-benzyl-6-deoxy-α-D-glucopyranosyl chloride [17] and 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-galactopyranose chloride [18] which always give a mixture of α- and β-fluoride under the same conditions. Ring closure of **8** with potassium *tert*-butoxide in tetrahydrofuran for several hours at room temperature was not successful, as the completion of this reaction was slow, and some by-products were formed together with the required 1,2-anhydrosugar. In contrast, ring closure of **8** with potassium *tert*-butoxide in boiling tetrahydrofuran quantitatively afforded syrupy 1,2-anhydro-3,4-di-*O*-benzyl-α-D-fucopyranose (**9**) within 30 min.

Compound **9** was very sensitive to acidic and hydroxylic solvent, and attempts to obtain an accurate elemental analysis of **9** were unsuccessful, but **9** was characterized via ^{1}H NMR spectroscopy with single-frequency decoupling. The ^{1}H NMR spectrum of compound **9** showed an upfield peak for H-2 at 3.14 ppm, which is the salient feature for the 1,2-epoxide ring of carbohydrate compounds [12–18]. Further verification of the structure was performed by alcoholysis of **9** in dry MeOH at room temperature, quantitatively giving methyl 3,4-di-*O*-benzyl-β-D-fucopyranoside (**10**), as expected. Although the physical constants of **10** differ somewhat from the literature values [25], the acetylated derivative **11** gave a similar optical rotation and melting point as reported [25]. The doublet at 4.30 ppm ($^3J_{H1,H2} = 8.0$ Hz) in the ^{1}H NMR spectrum of **11** indicates a β configuration. However, the coupling reaction of **9** with *N*-benzyloxycarbonyl-L-serine methyl ester in the presence of silver triflate (under the conditions designed for the coupling reaction of the 1,2-anhydrogalactopyranose analogue giving 10:1 (β:α) galactopyranosyl serine derivatives [21]) afforded, to our surprise, *O*-(2-*O*-acetyl-3,4-di-*O*-benzyl-α-D-fucopyranosyl)-*N*-benzyloxycarbonyl-L-serine methyl ester

(**12**) in high yield (86%), and no β-linked isomer was detected. The doublet at 5.00 ppm ($^3J_{H1,H2} = 4.0$ Hz) and the doublet of doublets at 5.18 ppm ($^3J_{H1,H2} = 4.0$ Hz; $^3J_{H2,H3} = 10.5$ Hz) are characteristic of H-1 and H-2, respectively, for an α-linked D-fucopyrano-



Scheme 1.

side. To pursue what occurred during the coupling reaction, we tested the reaction of **9** with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose under the same conditions as that used for the preparation of the glycopeptide. We found that again the α-linked disaccharide was the major product (α:β 2:1), although not the sole one as indicated from the ^{1}H NMR spectrum of the product showing a doublet at 5.15 ppm ($^3J_{H1,H2}$ = 3.1 Hz; of the α anomer) and a doublet at 4.42 ppm ($^3J_{H1,H2}$ = 7.8 Hz; H-1 of the β anomer). To determine whether the resulting stereoselectivity was due to silver triflate-assisted isomerization, methyl 3,4-di-*O*-benzyl-β-D-fucopyranoside (**10**) was subjected to the same coupling reaction conditions as used for the preparation of **12**. *No* anomerization of **10** was detected. Based on these results, it seems that the coupling reaction of **9** may proceed via an S_N1 mechanism in which the 1,2-anhydrosugar **9** is converted into a coordinated complex involving the sugar O-5–C-1 delocalized ion and Ag^+ ion of the catalyst. Formation of an α-linkage is apparently favoured from the complex.

2. Experimental

General methods and materials.—A description of general methods and materials was published previously [14].

3,4-Di-O-acetyl-1,2-O-[R,S-ethylidene]-α-D-fucopyranose (**3**).—To a solution of 2,3,4-tri-*O*-acetyl-α-D-fucopyranosyl bromide **2** (2.16 g, 6.14 mmol, prepared by a standard method [23] from **1**) in anhydrous MeCN (20 mL) was added tetrabutylammonium iodide (1.13 g, 3.1 mmol) and $NaBH_4$ (1.16 g, 31 mmol) at 0°C. The mixture was stirred for 24 h at room temperature. TLC (1:1 petroleum ether–EtOAc) indicated that the reaction was complete. Filtration and concentration of the filtrate gave a residue that was diluted with CH_2Cl_2 (50 mL). The solution was washed with water (3 × 30 mL), the organic layer was dried over anhydrous Na_2SO_4 and the dried solution was concentrated to a syrup. Anhydrous EtOAc was added, giving crystalline tetrabutylammonium iodide that could be recovered and reused. Filtration, followed by concentration of the filtrate, gave a residue. Column chromatography (3:1 petroleum ether–EtOAc) of the residue afforded **3** as a mixture of acetal isomers (1.16 g, 69.1%) consisting of *R* and *S* isomers in a ratio of 1:1; $[\alpha]_D$ + 63° (*c* 4.3, $CHCl_3$). The two isomers were separated by analytical LC to give the *R*-isomer as a syrup and the *S*-isomer as crystals; mp 73–74°C; ^{1}H NMR ($CDCl_3$) for the *R*-isomer: δ 5.59 (d, 1 H, $J_{1,2}$ 4.9 Hz, H-1), 5.44 (q, 1 H, *J* 4.9 Hz, C*H*CH_3), 5.21 (dd, 1 H, $J_{3,4}$ 3.4, $J_{4,5}$ 0.7 Hz, H-4), 5.07 (dd, 1 H, $J_{2,3}$ 7.3, $J_{3,4}$ 3.4 Hz, H-3), 4.36–4.25 (m, 1 H, $J_{4,5}$ 0.7, $J_{5,6}$ 6.6 Hz, H-5), 4.05–3.98 (m, 1 H, $J_{1,2}$ 4.9, $J_{2,3}$ 7.3 Hz, H-2), 2.10, 2.06 (2 s, 6 H, CH_3CO), 1.39 (d, 3 H, *J* 4.9 Hz, CH_3CH), 1.21 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6). For the *S* isomer: δ 5.52 (d, 1 H, $J_{1,2}$ 4.9 Hz, H-1), 5.30–5.17 (m, 2 H, $J_{3,4}$ 3.4, $J_{4,5}$ 0.7 Hz, H-4; *J* 4.9 Hz, CH_3C*H*), 4.93 (dd, 1 H, $J_{2,3}$ 7.3, $J_{3,4}$ 3.4 Hz, H-3), 4.36–4.25 (m, 1 H, $J_{4,5}$ 0.7, $J_{5,6}$ 6.6 Hz, H-5), 4.01 (dd, 1 H, $J_{1,2}$ 4.9, $J_{2,3}$ 7.3 Hz, H-2), 2.15, 2.06 (2 s, 6 H, CH_3CO), 1.46 (d, 3 H, *J* 4.9 Hz, CH_3C*H*), 1.21 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6). Anal. Calcd for $C_{12}H_{18}O_7$ (mixture): C, 52.55; H, 6.57. Found: C, 52.16; H, 6.59.

3,4-Di-O-benzyl-1,2-O-[(R, S)-ethylidene]-α-D-fucopyranose (**4**).—To a solution of

compound **3** (1.16 g, 4.23 mmol) in anhydrous toluene (25 mL) was added finely powdered potassium hydroxide (4 g, 71 mmol) under vigorous stirring. The mixture was heated to boiling under reflux, and benzyl chloride (7 g, 35.3 mmol) was added dropwise from the top of the condenser over a 10 min time period. The reaction was refluxed with vigorous stirring for 2 h or more, until TLC (3:1 petroleum ether–EtOAc) indicated that the benzylation was complete. The mixture was subjected to steam distillation to remove the excess benzyl chloride and the by-product dibenzyl ether and then partitioned between CH_2Cl_2 and water. The organic layer was dried and concentrated to a syrup which was purified by chromatography on a column of silica gel with 3:1 petroleum ether–EtOAc as the eluent to give syrupy **4** (1.41 g, 89.8%) as a mixture of *R* and *S* isomers; $[\alpha]_D$ −47° (*c* 2.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) for the *R* isomer: δ 7.50–7.20 (m, 10 H, Ph), 5.60 (d, 1 H, $J_{1,2}$ 4.4 Hz, H-1), 5.34 (q, 1 H, *J* 4.9 Hz, CH_3CH), 4.88, 4.64 (2 d, 2 H, *J* 11.5 Hz, $PhCH_2$), 4.83, 4.64 (2 d, 2 H, *J* 12.3 Hz, $PhCH_2$), 4.42 (dd, 1 H, $J_{1,2}$ 4.4 $J_{2,3}$ 6.8 Hz, H-2), 4.09–3.96 (m, 1 H, $J_{4,5}$ 2.0, $J_{5,6}$ 6.6 Hz, H-5), 3.65–3.50 (m, 2 H,-3, H-4), 1.38 (d, 3 H, *J* 4.9 Hz, CH_3CH), 1.20 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6). For the *S* isomer: δ 7.50–7.22 (m, 10 H, Ph), 5.50 (d, 1 H, $J_{1,2}$ 4.6 Hz, H-1), 5.16 (q, 1 H, *J* 4.9 Hz, CH_3CH), 4.87, 4.64 (2 d, 2 H, *J* 11.8 Hz, $PhCH_2$), 4.82, 4.63 (2 d, 2 H, *J* 12.3 Hz, $PhCH_2$), 4.19 (dd, 1 H, $J_{1,2}$ 4.6, $J_{2,3}$ 6.8 Hz, H-2), 3.98–3.86 (m, 1 H, $J_{4,5}$ 1.8, $J_{5,6}$ 6.6 Hz, H-5), 3.65–3.50 (m, 2 H, H-3, H-4), 1.40 (d, 3 H, *J* 4.9 Hz, $CHCH_3$), 1.22 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.35; H, 7.03. Found: C, 70.85; H, 7.14.

*3,4-Di-*O*-benzyl-α-*D*-fucopyranose* (**5**).—To a solution of **4** (1.1 g, 2.96 mmol) in dioxane (20 mL) was add 1 M sulfuric acid (8 mL), and the mixture was boiled under reflux with stirring for 6 h. TLC (2:1 petroleum ether–EtOAc) indicated that the starting material had disappeared. The mixture was cooled and carefully neutralized with sodium bicarbonate powder, and then evaporated to dryness. The residue was partitioned between water and CH_2Cl_2, and the organic layer was dried (Na_2SO_4), and evaporated to a syrup. Pure **5** (790 mg, 77.5%) was obtained as white crystals after column chromatographic separation of the syrupy mixture with 2:1 petroleum ether–EtOAc as the eluent; m.p. 77–79°C; $[\alpha]_D$ + 82.5° (*c* 1.4, $CHCl_3$); lit. [24] syrup, $[\alpha]_D$ −72° (*c* 1.41, $CHCl_3$ for L enantiomer). Anal. Calcd for $C_{20}H_{24}O_5$; C, 69.75; H, 7.02. Found: C, 69.61; H, 7.12.

*1,2-Di-*O*-acetyl-3,4-di-*O*-benzyl-α-*D*-fucopyranose* (**6**).—Compound **5** (720 mg, 1.94 mmol) was treated with acetic anhydride (1.5 mL) and pyridine (2 mL) according to standard method. A syrupy mixture of compound **6** and its β isomer was obtained in quantitative yield. Upon standing in refrigerator, this syrup yielded white crystalline **6** as the only product; mp 79–81°C; $[\alpha]_D$ −51° (*c* 2.3 $CHCl_3$); ^{1}H NMR ($CDCl_3$) for the α anomer; δ 7.40–7.20 (m, 10 H, Ph), 6.20 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.45 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 10.6 Hz, H-2), 4.90–4.45 (m, 4 H, 2 $PhCH_2$), 4.02 (dq, 1 H, $J_{4,5}$ 1.8, $J_{5,6}$ 6.5 Hz, H-5), 3.82 (dd, 1 H, $J_{2,3}$ 10.6, $J_{3,4}$ 1.8 Hz, H-3), 3.63 (t, 1 H, $J_{3,4} = J_{4,5}$ = 1.8 Hz, H-4), 2.01, 2.06 (2 s, 6 H, 2 CH_3CO), 1.19 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6). Anal. Calcd for $C_2H_{28}O_7$: C, 67.29; H, 6.54. Found: C, 67.11, H, 6.56. ^{1}H NMR ($CDCl_3$) for the β anomer: δ 7.40–7.20 (m, 10 H, Ph), 5.45–5.35 (m, 2 H, H-1, H-2), 4.80–4.50 (m, 4 H, 2 $PhCH_2$), 3.88 (dq, 1 H, $J_{4,5}$ 1.5, $J_{5,6}$ 6.8 Hz, H-5), 3.74–3.69 (m, 1 H, H-4), 3.50 (dd,

1 H, $J_{2,3}$ 10.1, $J_{3,4}$ 1.5 Hz, H-3), 1.95, 2.01 (2 s, 6 H, 2 CH_3CO), 1.15 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6).

2-O-Acetyl-3,4-di-O-benzyl-α-D-fucopyranosyl chloride (**7**).—A solution of compound **6** (450 mg, 1.05 mmol) in dry diethyl ether (8 mL) was saturated with HCl gas under a N_2 atmosphere at 0°C, and the solution was kept at room temperature in a sealed bottle for 2 h. TLC (3:1 petroleum ether–EtOAc) indicated that the reaction was complete. The solution was concentrated to a syrup which was dissolved in CH_2Cl_2 (1 mL), and the solvent evaporated. This procedure was repeated for 6–7 times to remove most of the HCl. The residue was purified on a short silica gel column by flash chromatography with 3:1 petroleum ether–EtOAc as the cluent, giving pure **7** as a syrup (400 mg, 94%); $[\alpha]_D$ +138° (*c* 4.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 10 H, Ph), 6.40 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1), 5.40 (dd, 1 H, $J_{1,2}$ 4.7, $J_{2,3}$ 11.1 Hz, H-2), 5.05–4.60 (m, 4 H, 2 PhCH_2), 4.20 (dq, 1 H, $J_{4,5}$ 1.8, $J_{5,6}$ 7.2 Hz, H-5), 4.05 (dd, 1 H, $J_{2,3}$ 11.1, $J_{3,4}$ 2.0 Hz, H-3), 3.74 (dd, 1 H, $J_{3,4}$ 2.0, $J_{4,5}$ 1.7 Hz, H-4), 2.12 (s, 3 H, CH_3CO), 1.20 (d, 3 H, $J_{5,6}$ 7.2 Hz, H-6). Anal. Calcd for $C_{22}H_{25}ClO_3$: C, 65.27; H, 6.22. Found: C, 65.00; H, 6.58.

2-O-Acetyl-3,4-di-O-benzyl-β-D-fucopyranosyl fluoride (**8**).—To a solution of **7** (100 mg, 0.25 mmol) in 2:5 acetonitrile–benzene (7 mL) was added solid silver fluoride (60 mg, 0.47 mmol). A white precipitate of silver chloride formed immediately. The mixture was stirred vigorously in a dark room for 16 h at room temperature, centrifuged, and the filter cake was washed repeatedly with CH_2Cl_3. The combined washings and supernatant liquor were concentrated to give a syrup. Purification of the syrup by column chromatography (4:1 petroleum ether–EtOAc) yielded **8** as crystals (81 mg, 84.4%); mp 51–52°C; $[\alpha]_D$ +9° (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.39–7.25 (m, 10 H, Ph), 5.48–5.32 (m, 1 H, $J_{1,2}$ 7.0, $J_{2,3}$ 12.0, $J_{2,F}$ 10.2 Hz, H-2), 5.10 (dd, 1 H, $J_{1,F}$ 55, $J_{1,2}$ 7.0 Hz, H-1), 5.00, 4.66 (2 d, 2 H, *J* 11.6 Hz, PhCH_2), 4.72, 4.58 (2 d, 2 H, *J* 12.3 Hz, PhCH_2), 3.70–3.45 (m, 3 H, H-3,4,5), 2.08 (s, 3 H, CH_3CO), 1.30 (d, 3 H, $J_{5,6}$ 5.9 Hz, H-6). Anal. Calcd for $C_{22}H_{25}FO_5$: C, 68.04; H, 6.44. Found: C, 67.85; H, 6.33.

1,2-Anhydro-3,4-di-O-benzyl-α-D-fucopyranose (**9**).—To a stirred and preheated solution of compound **8** (50 mg, 0.13 mmol) in tetrahydrofuran (2 mL) was rapidly added potassium *tert*-butoxide (25 mg, 0.23 mmol) and the mixture was heated in a hot-oil bath to boiling within 1 min. A brown solution formed immediately after addition of the base, and the reaction was continued under reflux for 30 min, at the end of which time TLC (3:1 petroleum ether–EtOAc) indicated that the starting material had disappeared. The mixture was cooled and evaporated to dryness under vacuum. The residue was repeatedly extracted with 3:1 petroleum ether–EtOAc, and the completely colourless extracts were combined and evaporated to dryness. Compound **9** was obtained as a syrup (40 mg, 95.2%); $[\alpha]_D$ −9.2° (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.42–7.20 (m, 10 H, Ph), 5.05 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.95, 4.75 (2 d, 2 H, *J* 10.9 Hz, PhCH_2), 4.83, 4.72 (2 d, 2 H, *J* 12.6 Hz, PhCH_2), 3.76 (d, 1 H, $J_{3,4}$ 2.9, H-4), 3.65 (q, 1 H, $J_{5,6}$ 5.7 Hz, H-5), 3.44 (dd, 1 H, $J_{2,3}$ 2.0, $J_{3,4}$ 2.9 Hz, H-3), 3.14 (dd, 1 H, $J_{1,2}$ 1.5, $J_{2,3}$ 2.0 Hz, H-2), 1.18 (d, 3 H, $J_{5,6}$ 5.7 Hz, H-6).

Methyl 3,4-di-O-benzyl-β-D-fucopyranoside (**10**).—Compound **9** (30 mg, 0.09 mmol) was dissolved in anhydrous MeOH (2 mL) for about 30 min. TLC (2:1 petroleum ether–EtOAc) indicated that the reaction was complete. The solution was concentrated

to afford **10** quantitatively as white crystals; mp 96–98°C; $[\alpha]_D$ −29° (*c* 1.2 $CHCl_3$); lit. [25] mp 109°C; $[\alpha]_D$ −12° (*c* 2.25 $CHCl_3$).

Methyl 2-O-acetyl-3,4-di-O-benzyl-β-D-fucopyranoside (**11**).—Acetylation of compound **10** (20 mg, 0.056 mmol) with pyridine (1.5 mL) and acetic anhydride (0.8 mL) at room temperature for 16 h gave compound **11** in a quantitative yield as white needles; mp 112–113°C; $[\alpha]_D$ −2.9° (*c* 0.6, $CHCl_3$); lit. [25] mp 114°C; $[\alpha]_D$ −3.3° (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 10 H, Ph), 5.15 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.9 Hz, H-2), 4.47, 4.20 (2 d, 2 H, *J* 12.0 Hz, PhCH_2), 4.30 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 4.24, 3.92 (2 d, 2 H, *J* 12.0 Hz, PhCH_2), 3.26 (s, 3 H, OCH_3), 3.53–3.10 (m, 3 H, H-3, 4,5), 1.90 (s, 3 H, CH_3CO), 1.15 (d, 3 H, $J_{5,6}$ 6.0 Hz, H-6).

O-*(2-O-Acetyl-3,4-di-O-benzyl-α-D-fucopyranosyl)*-N-*benzyloxycarbonyl*-L-*serine methyl ester* (**12**).—A mixture of *N*-benzyloxycarbonyl-L-serine methyl ester (76 mg, 0.3 mmol) and powdered 4 Å molecular sieves in dry CH_2Cl_2 (5 mL) was stirred vigorously for 10 min, and compound **9** (80 mg, 0.25 mmol) and AgOTf (70 mg, 0.27 mmol) were then added simultaneously under N_2 protection. The mixture was kept in a dark room with agitation for 1 h at room temperature. Ac_2O (1.0 mL) was added and the mixture was allowed to stand at room temperature overnight. The suspension was filtered to remove solids, and the filtrate was washed with water (3 × 35 mL), dried over Na_2SO_4 then concentrated to a syrup. Purification by analytical LC (2:1 petroleum ether–EtOAc) yielded syrupy **12** (130 mg, 86%); $[\alpha]_D$ +70.3° (*c* 2.0, $CHCl_3$; ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 15 H, Ph), 5.80 (d, 1 H, $J_{NH,CH}$ 8.8 Hz, N-*H*), 5.18 (dd, 1 H, $J_{1,2}$ 4.0, $J_{2,3}$ 10.5 Hz, H-2), 5.13 (s, 2 H, PhCH_2OCO), 5.00 (d, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.94, 4.61 (2 d, 2 H, *J* 11.7 Hz, PhCH_2), 4.68 (s, 2 H, PhCH_2), 4.55–4.40 (m, 1 H, $J_{NH,CH}$ 8.8 Hz, C*H*NH), 4.00 (dd, 1 H, *J* 11.2, *J* 3.1 Hz, one proton of CHCH_2), 3.89–3.76 (m, 3 H, H-3,5, and the other proton of CHCH_2), 3.72 (s, 3 H, OCH_3), 3.64 (d, 1 H, $J_{3,4}$ 1.9 Hz, H-4), 2.0 (s, 3 H, CH_3CO), 1.13 (d, 3 H, $J_{5,6}$ 6.3 Hz, H-6). Anal. Calcd for $C_{34}H_{39}NO_{10}$: C, 65.70; H, 6.28. Found: C, 65.71; H, 6.33.

O-*(2-O-Acetyl-3,4-di-O-benzyl-α,β-D-fucopyranosyl)-(1 → 6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose* (**13**).—To a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (21 mg, 0.08 mmol) in anhydrous CH_2Cl_2 (5 mL) was added 4 Å molecular sieves and AgOTf (14 mg, 0.06 mmol). The mixture was stirred for 10 min at room temperature, and compound **9** (20 mg, 0.06 mmol) was then added under N_2 protection. Work-up of the reaction was the same as described for **12**. Disaccharide **13** (α, β mixture) was obtained as a colourless syrup (19.3 mg, 55%); $[\alpha]_D$ +4.4° (*c* 0.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ7.50–7.30 (m, 10 H, Ph), 5.50 (2 d, 1 H, $J_{1,2}$ 4.8 Hz, H-1), 5.20–5.16 (m, 1 H, H-2′), 5.15 (d, 0.66 H, $J_{1',2'}$ 3.1 Hz, H-1′ of α anomer), 4.96, 4.82 (2 d, 2 H, *J* 10.1 Hz, PhCH_2), 4.66–4.38 (m, 3 H, H-3 of α anomer, *J* 11.4 Hz, PhCH_2, and H-3 of β anomer), 4.42 (d, 0.33 H, $J_{1',2'}$ 7.8 Hz, H-1′ of β anomer), 4.35–4.30 (m, 1 H, H-2), 2.00 (bs, 3 H, CH_3CO), 1.55, 1.46, 1.36, 1.34 (4 s, 12 H, CCH_3), 1.22 (d, 3 × 0.33 H, *J* 6.1 Hz, H-6′ of β anomer), 1.20 (d, 3 × 0.66 H, *J* 6.0 Hz, H-6′ of α anomer).

References

[1] H.M. Flowers, *Adv. Carbohydr. Chem. Biochem.*, 39 (1981) 280–345.
[2] P.J. Garegg and T. Norberg, *Carbohydr. Res.*, 52 (1976) 235–240.

[3] M. Gallant, J.T. Link, and S.J. Danishefsky, *J. Org. Chem.*, 58 (1993) 343–349.
[4] C.H. Marzabadi and C.D. Spilling, *J. Org. Chem.*, 58 (1993) 3761–3766.
[5] K.K.C. Liu and S.J. Danishefsky, *J. Am. Chem. Soc.*, 115 (1993) 4933–4934.
[6] S.J. Danishefsky, K.F. Mcclure, J.T. Randolph, and R.B. Rugger, *Science*, 260 (1993) 1307–1309.
[7] R.G. Dushin and S.J. Danishefsky, *J. Am. Chem. Soc.*, 114 (1992) 3471–3475.
[8] K. Chow and S.J. Danishefsky, *J. Org. Chem.*, 55 (1990) 4211–4214.
[9] R.L. Halcomb and S.J. Danishefsky, *J. Am. Chem. Soc.*, 111 (1989) 6661–6666.
[10] R.R. Schmidt, *Angew Chem., Int. Ed. Engl.*, 25 (1986) 212–235.
[11] A. Delgado and J. Clardy, *J. Org. Chem.*, 58 (1993) 2862–2866.
[12] Q. Chen, F. Kong, and L. Cao, *Carbohydr. Res.*, 240 (1993) 107–117.
[13] J. Liu, F. Kong, and L. Cao, *Carbohydr. Res.*, 240 (1993) 295–300.
[14] G. Yang, F. Kong, and R.R. Fraser, *Carbohydr. Res.*, 258 (1994) 49–58.
[15] G. Yang and F. Kong, *J. Carbohydr. Chem.*, 13 (1994) 909–921.
[16] G. Yang and F. Kong, *Carbohydr. Lett.*, 1 (1994) 137–141.
[17] G. Yang, L. Cao, and F. Kong, *J. Carbohydr. Chem.*, 11 (1992) 379–395.
[18] F. Kong, J. Du, and H. Shang, *Carbohydr. Res.*, 162 (1987) 217–225.
[19] S.J. Sondheimer, H. Yamaguchi, and C. Schuerch, *Carbohydr. Res.*, 74 (1979) 327–332.
[20] H. Yamaguchi and C. Schuerch, *Carbohydr. Res.*, 81 (1980) 192–195.
[21] Y. Du and F. Kong, *J. Carbohydr. Chem.*, 14 (1995) 341–352.
[22] V.I. Betaneli, M.V. Ovchinnikov, L.V. Backinowsky, and N.K. Kochetkov, *Carbohydr. Res.*, 84 (1980) 211–224.
[23] R.L. Whistler and M.L. Wolfrom, *Methods Carbohydr. Chem.*, 2 (1963) 335–336.
[24] M.D. Juszynsky and H.M. Flowers, *Carbohydr. Res.*, 28 (1973) 61–74.
[25] S. Kamiya, S. Esaki, and R. Tanaka, *Agric. Biol. Chem.*, 49 (1985) 55–62.