4.78 (1 H, br s, exchangeable), 4.8 (1 H, d, J = 11 Hz), 5.16 (1 H, br s), 5.2 (1 H, d, J = 14 Hz), 7.2 (15 H, m); IR (film) 3400, 3000, 2900, 2840, 1670, 1440, 1360, 1260, 1080, 1030, 810, 740, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 481 (M^+, 0.3), 462 (1.4), 408 (10.2), 407 (10.9), 406 (3.1), 391 (8.7), 390 (30.7), 372 (10.3), 344 (4.4), 298 (9.7), 284 (9.4), 280 (25.2), 278 (3.1), 270 (10.5), 254 (5.8), 250 (4.3), 210 (3.3), 188 (10.6), 181 (10.2), 160 (4.3), 147 (3.2), 135 (3.9), 91 (100); calcd for $C_{32}H_{35}NO_3$ m/e 481.2617, found m/e 481.2592 (5.3 ppm error).

3β-Benzyl-5α,6-dimethyl-8α-(hydroxymethyl)-9β-hydroxy-2,3α,4β,5β,8β,9-hexahydro-1*H*-isoindol-1-one (36). To a solution of 5 mg (0.83 mmol) of lithium metal in 3 mL of ammonia was added a solution of 12 mg (0.03 mmol) of **35** in 1 mL of dry THF. A solution of 100 mg of dibenzyl ether in 2 mL of THF was added to the reaction mixture, followed by water, and the mixture was evaporated. The residue was taken up in ethyl acetate, washed with water, brine, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The crude product was purified by column chromatography, eluting with THF/hexane (1/1) to give 6 mg (80%) of crystalline diol **36**: mp 189–190 °C; ^{1}H NMR (100 MHz) δ 1.38 (3 H, d, J = 7 Hz), 1.8 (3 H, br s), 2.5 (4 H, m), 3.06 (2 H, m), 3.9 (2 H, m), 4.12 (1 H, br s, exchangeable), 4.32 (1 H, br s, exchangeable), 5.12 (1 H, br s), 5.96 (1 H, br s), 7.2 (5 H, m); ^{13}C NMR δ 14.812, 20.090, 33.741, 44.844, 46.179, 55.765, 56.372, 63.228, 81.672, 120.623, 127.054, 128.813, 128.934, 137.428, 141.554, 177.350; IR ($CHCl_3$) 3400, 2920, 2840, 1680, 1485, 1450, 1430, 1370, 1320, 1270, 1100, 1020 cm^{-1}; mass spectrum, m/e (relative intensity) 301 (M^+, 1.6), 300 (0.2), 283 (13.9), 210 (100), 192 (62.5), 182 (26.6), 172 (18), 164 (28.5), 162 (37.2), 120 (20), 119 (69), 95 (57.8), 94 (38.0), 91 (92.8), 83 (24.2), 79 (22.1), 70 (70.0); calcd for $C_{16}H_{23}NO_3$ m/e 301.1678, found m/e 301.1679 (0.4 ppm error).

3β-Benzyl-5α,6-dimethyl-8α-(acetoxymethyl)-9β-hydroxy-2,3α,4β,5β,8β,9-hexahydro-1*H*-isoindol-1-one (37). A mixture of 8 mg (0.026 mmol) of alcohol **36**, 0.5 mL of pyridine, and 0.2 mL of acetic anhydride was stirred at room temperature for 2 h. Pyridine and acetic anhydride were evaporated under vacuum to give 8 mg (89%) of acetate **37** which was used directly in the next step: ^{1}H NMR δ 1.38 (3, H, d, J = 6.5 Hz), 1.9 (3 H, br s), 2.16 (3 H, s), 2.4–3.3 (6 H, m), 3.4 (1 H, br s), 4.36 (1 H, dd, J = 6.5, 11 Hz), 4.68 (1 H, dd, J = 7.6, 11 Hz), 5.42 (1 H, br s), 5.56 (1 H, br s), 7.35 (5 H, m); mass spectrum, m/e (relative intensity) 343 (M^+, 100), 301 (8), 283 (23), 282 (10), 90 (6).

3β-Benzyl-5α,6α-dimethyl-6β,7β-epoxy-8α-(acetoxymethyl)-9β-hydroxy-2,3α,4β,5β,6,7α,8β,9-octahydro-1*H*-isoindol-1-one (41). Method A. To a solution of 8 mg (0.023 mmol) of alkene **37** in 1 mL of methylene chloride was added 6 mg (0.03 mmol) of *m*-chloroperbenzoic acid. The mixture was stirred overnight at room temperature and was filtered. The filtrate was washed with saturated $NaHSO_3$ solution, saturated $NaHCO_3$, water, and brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo gave the β-epoxide **41** containing a trace of the α-epoxide. Epoxide **41** was purified by preparative TLC developed with ethyl acetate/hexane (3/1): ^{1}H NMR δ 1.11 (3 H, d, J = 7 Hz), 1.3 (3 H, s), 2.1 (3 H, s), 2.26 (2 H, m), 2.8 (3 H, m), 3.65 (1 H, m), 4.5 (1 H, dd, J = 8.6, 11.4 Hz), 4.73 (1 H, dd, J = 6.3, 11.4 Hz), 5.65 (1 H, br s), 7.25 (5 H, m).

Method B. A mixture of 0.75 mg (0.002 mmol) of authentic cytochalasin E degradation product **40**,[25] 5 drops of pyridine, and 2 drops of acetic anhydride was stirred for 2 h at room temperature. Pyridine and acetic anhydride were evaporated under vacuum, and the residue was purified by preparative TLC, eluting with ethyl acetate/hexane (3/1) to give acetate **41** identical in NMR and TLC with the synthetically derived material prepared in method A.

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Registry No. 5, 26489-01-0; **6**, 67245-12-9; **7**, 67245-14-1; **8**, 79631-90-6; (*E*)-**9**, 79631-91-7; (*Z*)-**9**, 79631-92-8; **10**, 79631-93-9; **11**, 79631-94-0; **12**, 79631-95-1; **13**, 70849-69-3; **14**, 70849-70-6; **15**, 79703-01-8; **16**, 70849-72-8; **17**, 79631-96-2; **18**, 70849-76-2; **19**, 70849-73-9; **20**, 79631-97-3; **21**, 70849-77-3; **24**, 70849-78-4; **25**, 79631-98-4; **26**, 79631-99-5; **27**, 79632-00-1; **29**, 79632-01-2; **30**, 1631-26-1; **31**, 79632-02-3; **32**, 79632-03-4; **33**, 79632-04-5; **34**, 79632-05-6; **35**, 79632-06-7; **36**, 79632-07-8; **37**, 79632-08-9; **41**, 79632-09-0; *N*-ethylmaleimide, 128-53-0.

Direct and Efficient Synthesis of β-L-Rhamnopyranosides†

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Methyl α-L-rhamnopyranoside (1) was converted in a single-stage procedure to crystalline methyl 4-*O*-benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnopyranoside (**2**). This compound served as a stable derivative from which 4-*O*-benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnopyranosyl bromide (**3**) could be derived in essentially quantitative yield by reaction with dibromomethyl methyl ether. The glycosyl halide **3** was used to prepare three β-L-rhamnopyranosides by reaction with the selectively blocked glycosides methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**4**), methyl 4-*O*-acetyl-2-*O*-benzoyl-α-L-rhamnopyranoside (**5**), and methyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside (**6**). Good to moderate yields of the corresponding β-linked rhamnose disaccharides **7–9** were obtained. The yields and stereospecificity of the glycosylation reaction were highest for the relatively reactive secondary hydroxyl groups HO-4 and HO-3. Reduced stereospecificity and moderate yield of the β anomer were associated with the most unreactive hydroxyl group HO-2.

L-Rhamnose occurs in plant glycosides,[1,2] glycolipids,[3] and immunologically important polysaccharides.[4,5] Several groups including our own have synthesized di-[6-8] and oligosaccharides[9-11] containing two or three α-linked rhamnopyranoside residues as models for immunodeterminants of polysaccharide antigens. It is unusual to find naturally occurring L-rhamnose in other than the α-L-

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pyranosidic linkage, although several reports of β-L-rhamnopyranose residues in polysaccharides have appeared.[4,12,13] The more accessible chemical and physical methods such as optical rotation[12] and even NMR chemical shifts and homonuclear proton coupling constants[5,14,15] may not always provide unambiguous assignment of rhamnopyranose anomeric configuration. One such reassignment of a β- to α-L-rhamnopyranose unit has occurred in the *Salmonella* lipopolysaccharides.[16] It is therefore desirable to develop a reliable method of β-L-rhamnopyranoside synthesis to provide compounds for comparative purposes and to extend the scope of glycoside synthesis for potentially active glycosides.

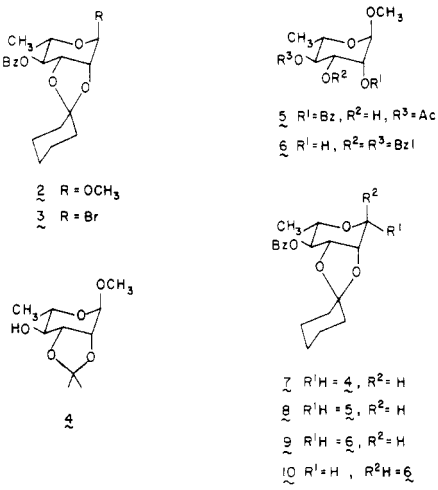
We recently described, in a preliminary report, a new and efficient route to β-L-rhamnopyranosides.[14] Simultaneously independent work was presented describing a different but related approach to this problem.[17] Subsequently, two simple alkyl β-L-rhamnopyranosides have been synthesized via 1-*O*-sulfonate esters.[18]

We now describe in detail the direct and facile synthesis of the rhamnopyranosyl bromide **3**, which is demonstrated to be an effective derivative for synthesis of β-L-rhamnopyranosides, by the preparation of three isomeric 1,2-, 1,3-, and 1,4-linked rhamnose disaccharide glycosides **13**, **12**, and **11**.

Results and Discussion

The synthesis of β-L-rhamnopyranosides is a specific example of a long-standing problem, the efficient and stereospecific synthesis of 1,2-*cis*-hexopyranosides possessing an axial C-2 hydroxyl group, most often the manno configuration. Solutions to this problem generally follow the approach of Gorin and Perlin,[19] who employed a nonparticipating protecting group at 0-2, in this case a 2,3-carbonate.[19] More recently others have used benzyl ethers[20] and methanesulfonate esters[18] for β-mannopyranoside synthesis. However, the most practical and efficient synthesis of β-D-mannopyranosides is the approach developed by Garegg and co-worker.[21] Acetalation of D-mannose yields crystalline 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranose from which the corresponding glycosyl chloride is readily prepared.[22] Disaccharide synthesis with this derivative provides β-D-mannopyranosides with high stereoselectivity except in the case of particularly unreactive aglycons.[21]

Chart I



Methyl α-L-rhamnopyranoside (**1**) was acetalated with 1-ethoxycyclohexene in acetonitrile solution. Without isolation of the crude product, in situ benzoylation of this ketal gave crystalline methyl 4-*O*-benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnopyranoside (**2**) in 72% yield (Chart I). Conversion of the methyl rhamnopyranoside **2** to a glycosyl halide by conventional procedures such as HBr/acetic acid and HBr/dichloromethane or via acetolysis were precluded by the presence of the acid-labile acetal group. Dibromomethyl methyl ether and its chloro analogue have been used to effect such conversions,[23] but this method has not enjoyed widespread use. In our hands we have found both chloro and bromo and analogoues to be particularly effective for mild, one-step conversion of methyl glycosides to glycosyl halides containing both acetal and benzyl ether protecting groups.[24] Thus reaction of **2** with dibromomethyl methyl ether[23] converted this glycoside rapidly and essentially quantitatively into the rhamnopyranosyl bromide **3**. ^{13}C and ^{1}H NMR data require that this product, **3**, obtained by filtration and evaporation of the solvent, be at least 95% pure. Consequently, throughout this work the bromide **3** was used for glycosylation reactions without further processing or purification. The speed and ease with which **3** is prepared from **2** is well suited to the lability of such glycosyl halides, which should be freshly prepared for each glycosylation reaction.

In order to test the efficancy of **3** for stereospecific synthesis of β-L-rhamnopyranosides, we chose selectively blocked derivatives of methyl α-L-rhamnopyranoside. Methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**4**) and methyl 4-*O*-acetyl-2-*O*-benzoyl-α-L-rhamnopyranoside (**5**) provide examples of aglycons of good to moderate reactivity containing protecting groups of different functionality. The third compound, methyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside, has been demonstrated to be relatively unreactive toward glycosyl halides except under the most forcing condtions.[8] Methyl 4-*O*-acetyl-2-*O*-benzoyl-α-L-rhamnopyranoside (**5**) was synthesized by reaction of **1** with trimethyl orthobenzoate, according to the procedure of Garegg and Hultberg.[25] Acetylation and

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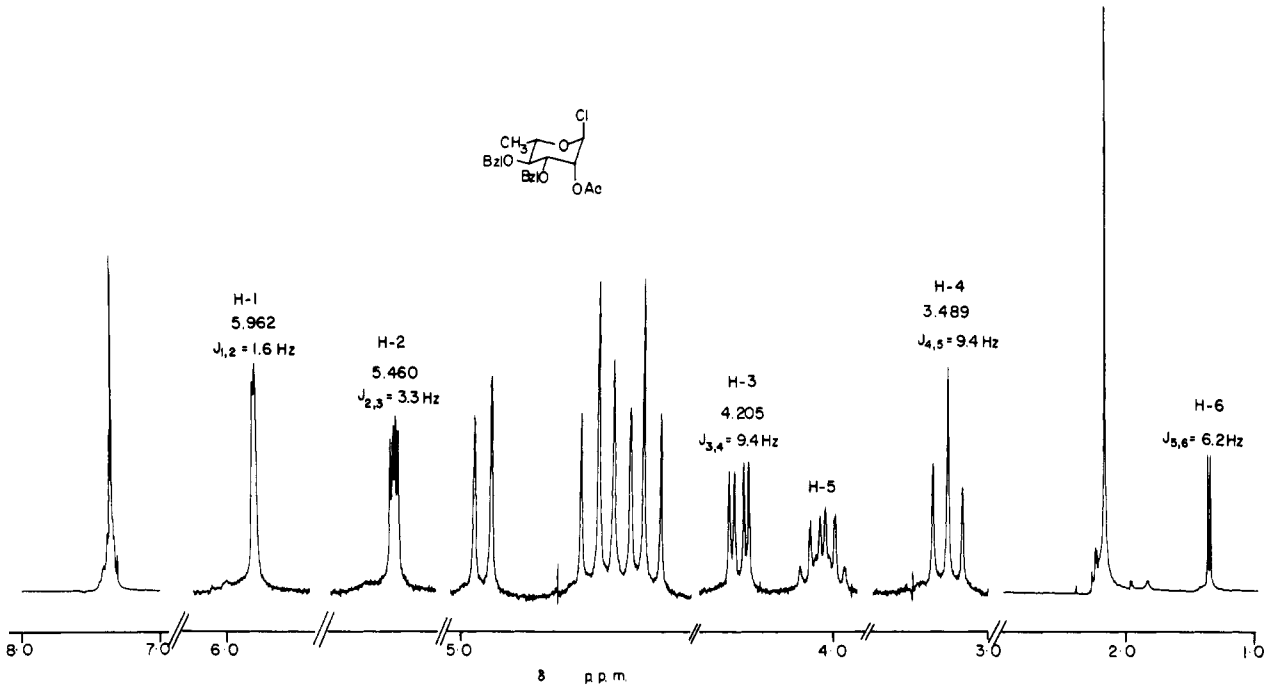

Figure 1. 300-MHz ^1H NMR spectrum of 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl chloride illustrating shifts and ^3J coupling constants which confirm the expected $^1C_4$ chair conformer.

regiospecific ring opening of the 2,3-orthobenzoate gave crystalline **4** in 76% yield. Methyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside may be prepared from 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl chloride in the manner described for the more complex 8-(methoxycarbonyl)octyl α-L-rhamnopyranoside.[10] However, as we have previously shown, trifluoromethanesulfonic acid and *N,N*-tetramethylurea (1:1) in a catalytic amount effect quantitative and regiospecific opening of 1,2-orthoacetates,[26] and this method is that of choice for the preparation of **6**. Thus, 3,4-di-*O*-benzyl-α-L-rhamnopyranose 1,2-orthoacetate in dichloromethane was quantitatively converted to methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranoside which was deacetylated to give **6** in 90% yield.

Although not used in this work, the derivative 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranosyl chloride has been demonstrated to be a very convenient and efficient building unit for oligosaccharide synthesis.[10,11,27] A recent suggestion in the literature[18] that this derivative is impure deserves some comment. We have reinvestigated the ^1H NMR of this compound by recording its 300-MHz spectrum (Figure 1). This shows, as expected on the basis of modern conformational analysis, that the glycosyl chloride exists exclusively in the $^1C_4$ chair conformation and, furthermore, that a single anomer is present. Since we reported a $J_{3,4}$ coupling constant of 9.5 Hz in our initial publication,[27] there is little doubt that this compound exists as a single conformer in solution, the $^1C_4$ (L) chair. The chemical shift of the H-1 proton further indicates the α anomer for this compound. Srivastava and Schuerch suggested that our reported first-order J_{AB} coupling constants of 10.6 and 10.2 Hz indicated the $^4C_1$ chair conformer and also that the reported compound was, in fact, a mixture of α- and β-glycosyl chlorides.[18] The spectrum displayed in Figure 1 establishes on the basis of the ^3J values that the compound is a single isomer and adopts the $^1C_4$ conformation. Furthermore, this observation indicates that first-order J_{AB} coupling constants of methylene protons in the ether linkage to pyranosides may not be used in an empirical manner to deduce the conformation of the pyranose rings to which they are attached.

Glycosylation of the selectively blocked rhamnopyranosides was performed under standard conditions. Freshly prepared rhamnopyranosyl bromide **3** (1.4 molar equiv) was reacted with 1.0 molar equiv of rhamnopyranosides **4–6** in dry dichloromethane by using excess silver carbonate as the promoter, with molecular sieves to remove water. The yields of β-L-rhamnopyranosides ranged from 73% for the 1,4-linked disaccharide **7**, with no detectable α anomer, to 38% for the β-1,2-linked disaccharide **9**, which was accompanied by a 35% yield of α anomer **10**. Removal of blocking groups from the fully protected disaccharides was accomplished in the usual manner. Methyl 4-*O*-(β-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**11**) was obtained by transesterification of **7** and acid hydrolysis of the acetal groups. Methyl 3-*O*-(β-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**12**) was obtained from **8** in similar fashion. Methyl 2-*O*-(β-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**13**) was obtained from **9** by transesterification of the benzoate ester followed by hydrogenolysis in 80% aqueous acetic acid. Removal of benzyl ethers was accompanied by hydrolysis of the acetal function.

From these results the glycosyl bromide **3** is seen to be an effective and stereospecific derivative for β-L-rhamnopyranoside formation, where the aglycons possess good to moderate reactivity. However, in the face of increasingly unreactive aglycons such as methyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside (**6**) and 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside[14] only moderate stereospecificity and yields are observed. This observation is not unexpected in light of similar findings in the synthesis of β-D-mannopyranosides.[21] Despite the loss of stereoselectivity, in limited cases 4-*O*-benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnopyranosyl bromide (**3**) is an effective and accessible derivative for β-L-rhamnopyranoside synthesis. This approach compares favorably with the other approaches to such glycosides.[17–19] The blocking groups employed are readily removed under mild conditions and also permit the use of **3** for sequential chain extension in oligosaccharide

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synthesis at the 0-4 position of β-L-rhamnopyranoside residues.

Experimental Section

General methods used were as described in earlier work from this laboratory.[8] Column chromatography employed a medium-pressure LC system.[28] Routine ^{13}C and ^{1}H were recorded at 20 and 79.9 MHz, respectively. High-resolution spectra were obtained with a Bruker CXP-300 instrument operating at 75 and 300 MHz. Proton chemical shifts are expressed relative to internal tetramethylsilane (Me_4Si) for chloroform-*d* solutions, and in deuterium oxide solution sodium 3-(trimethylsilyl)propionate-2,2,3,3,-d_4 was the internal reference. Carbon-13 shifts are respectively referenced to internal and external Me_4Si for chloroform-*d* and deuterium oxide solutions. Skellysolve B refers to a hexane fraction, supplied by Getty Refining and Marketing Co., which was redistilled prior to use.

Methyl 4-*O*-Benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnopyranoside (2). Methyl α-L-rhamnopyranoside (1;[29,30] 5.3 g, 30 mmol) and *p*-toluenesulfonic acid (100 mg) were dissolved in acetonitrile (50 mL), and 1-ethoxycyclohexane (5.7 g, 45 mmol) in acetonitrile (25 mL) was added dropwise to the stirred solution. After 1 h at room temperature the reaction mixture was evaporated to a syrup, which was taken up in pyridine (40 mL), and a solution of benzoyl chloride (6.3 g, 45 mmol) in pyridine (10 mL) was added dropwise. After a further 1 h at room temperature the reaction mixture was diluted with dichloromethane, washed with ice-cold dilute, aqueous, hydrochloric acid and water, dried over sodium sulfate, and evaporated to a syrup, which crsytallized from Skellysolve B to give 7.8 g (72% yield) of **2**: $[\alpha]_D$ +2.2° (*c* 1.0, $CHCl_3$); mp 95.5–97.0 °C; ^{1}H NMR (chloroform-*d*) δ 8.2–7.2 (m, 5 H, aromatics), 5.18 (dd, 1 H, H-4), 4.96 (s, 1 H, H-1), 3.41 (s, 3 H, OMe), 2.0–1.0 (m, 10 H, cyclohexylidene), 1.22 (d, 3 H, $J_{5,6}$ = 6.3 Hz, H-6); ^{13}C NMR (chloroform-*d*) 98.3 (C-1), 75.7 (C-3), 75.5 (2 C, C-2, C-4), 64.1 (C-5), 55.0 (OMe), 17.2 (C-6). Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.44; H, 7.00.

4-*O*-Benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnopyranosyl Bromide (3). Dibromomethyl methyl ether[31] (0.3 mL) and zinc bromide (~30 mg) were added to a solution of **2** (0.50 g, 1.4 mmol) in chloroform (5 mL).[3] The reaction mixture was stirred at 50 °C for 1 h, filtered through glass wool, evaporated, and dried under vacuum to give 0.55 g (~100%) of **3** as a yellow syrup: $[\alpha]_D$ −72.6° (*c* 1.4, CHC_3). ^{13}C and ^{1}H NMR indicate the syrup to be at least 95% pure, and it was immediately used in the following glycosidation steps: ^{1}H NMR (chloroform-*d*) δ 8.3–7.0 (m, 5 H, aromatics), 6.68 (s, 1 H, H-1), 5.25 (dd, 1 H, H-4), 2.0–1.0 (m, 10 H, cyclohexylidene), 1.26 (d, 3 H, $J_{5,6}$ = 6.2 Hz, H-6), ^{13}C NMR (chloroform-*d*) 86.6 (C-1), 79.4 (C-2), 74.6 (C-3), 74.2 (C-4), 69.8 (C-5), 16.9 (C-6).

Methyl 4-*O*-Acetyl-2-*O*-benzoyl-α-L-rhamnopyranoside (5). A mixture of **1**[29,30] (1.8 g, 10 mmol), trimethyl orthobenzoate (2.3 g, 13 mmol) and *p*-toluenesulfonic acid (50 mg) in acetonitrile (25 mL) was stirred at room temperature. After 1 h pyridine (10 mL) followed by acetic anhydride (5 mL) was added and the reaction left overnight. Evaporation of the solvents gave a syrup that was twice taken up in and evaporated at 50 °C with aqueous acetic acid (80%, 2 × 50 mL). The resulting syrup crystallized from aqueous ethanol to give 2.5 g (76%) of **4**: $[\alpha]_D$ +51.5° (*c* 1.2, $CHCl_3$); mp 132–133 °C; ^{1}H NMR (chloroform-*d*) δ 8.20–7.20 (m, 5 H, aromatics), 5.30 (dd, 1 H, $J_{1,2}$ = 1.6 Hz, $J_{2,3}$ = 3.5 Hz, H-2), 4.99 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 9.8 Hz, H-4), 4.79 (d, 1 H, H-1), 4.12 (dd, 1 H, H-3), 3.39 (s, 3 H, OMe), 2.12 (s, 3 H, OAc), 1.25 (d, 3 H, $J_{5,6}$ = 6.3 Hz, H-6), ^{13}C NMR (chloroform-*d*) 98.4 (c-1), 74.8 (C-2), 73.2 (C-4), 68.5 (C-3), 66.0 (C-5), 55.2 (OMe), 21.0 (OAc), 17.5 (C-6). Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.29; H, 6.22. Found: C, 59.44; H, 6.09.

Methyl 3,4-Di-*O*-benzyl-α-L-rhamnopyranoside (6). A solution of trifluoromethanesulfonic acid (0.1 mL) and tetramethylurea (0.2 mL) in dichloromethane (10 mL) was added to 3,4-di-*O*-benzyl-β-L-rhamnopyranose 1,2-(methyl orthoacetate)[21] (2.2 g, 5.5 mmol) in 20 mL of dichloromethane. After 1 h at room temperature all the starting material had reacted to give methyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rhamnopyranoside. This solution was diluted with dichloromethane (50 mL), extracted with 5% potassium hydrogen carbonate, dried, and concentrated. The resultant syrup (2 g) was dissolved in methanol (25 mL) containing a catalytic amount of sodium methoxide. After 18 h the solution was neutralized with Rexyn 101(H^+) (Fisher) and evaporated. Purification by silica gel chromatography (Skellysolve B–ethyl acetate 2:1) gave 1.6 g (90%) of **6**: $[\alpha]_D$ −50.0° (*c* 1.5, CHC_3) [lit.[6] $[\alpha]_D$ −46.4° (*c* 1.7, $CHCl_3$)].

Methyl 4-*O*-(4-*O*-Benzoyl-2,3-*O*-cyclohexylidene-β-L-rhamnopyranosyl)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (7). A stirred mixture of methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**4**;[30] 0.22 g, 1.0 mmol) and silver carbonate (0.8 g, 2.9 mmol) in dry dichloromethane (10 mL) containing 4-Å molecular sieves was cooled to −40 °C. The bromo sugar **3** (0.55 g, 1.4 mmol) from the above preparation dissolved in dichloromethane (5 mL) was added. The reaction mixture was stirred at −40 °C for a further 2 h, allowed to reach room temperature, stirred overnight, filtered, evaporated, and separated on a silica gel column (Skellysolve B–ethyl acetate, 4:1) to give 0.40 g (73%) of syrupy **7**; $[\alpha]_D$ +19.0° (*c* 2.1, $CHCl_3$); ^{1}H NMR (chloroform-*d*) δ 8.2–7.2 (m, 5 H, aromatic), 3.34 (s, 3 H, OMe), 2.20–1.0 (m, 22 H, cyclohexylidene, isopropylidene, H-6); ^{13}C NMR (chloroform-*d*) 98.9, 98.2 (2 C, C-1′ and C-1), 82.6 (C-4), 54.7 (OMe), 17.9, 17.8 (2 C, C-6′ and C-6).

Methyl 4-*O*-Acetyl-2-*O*-benzoyl-3-*O*-(4-*O*-benzoyl-2,3-*O*-cyclohexylidene-β-L-rhamnopyranosyl)-α-L-rhamnopyranoside (8). Coupling of **5** (0.33 g, 1.0 mmol) and **3** (0.55 g, 1.4 mmol) was carried out as described for the synthesis of **7**. After column chromatography (Skellysolve B–ethyl acetate, 4:1) this gave 0.38 g (58%) of syrupy **8**: $[\alpha]_D$ +44.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR (chloroform-*d*) δ 8.2–7.2 (m, 10 H, aromatics), 3.37 (s, 3 H, OMe), 2.13 (s, 3 H, OAc), 2.20–1.0 (m, 16 H, cyclohexylidene, H-6); ^{13}C NMR (chloroform-*d*) 98.9, 94.6 (2 C, C-1′ and C-1), 55.1 (OMe), 18.5, 17.7 (2 C, C-6′ and C-6).

Methyl 2-*O*-(4-*O*-Benzoyl-2,3-*O*-cyclohexylidene-β-L-rhamnopyranosyl)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (9) and Methyl 2-*O*-(4-*O*-Benzoyl-2,3-*O*-cyclohexylidene-α-L-rhamnopyranosyl)-3,4-di-*O*-benzyl-α-L-rhamnopyranoside (10). Coupling of **6** (0.36 g, 1.0 mmol) and **3** (0.55 g, 1.4 mmol) was carried out as described for the synthesis of **7**. After column chromatography (Skellysolve B–ethyl acetate, 4:1) this gave 0.24 g (35%) of **10**: $[\alpha]_D$ −17.0° (*c* 1.6, $CHCl_3$); ^{1}H NMR (chloroform-*d*) δ 8.2–7.0 (m, 15 H, aromatics), 3.33 (s, 3 H, OMe), 2.0–1.0 (m, 16 H, cyclohexylidene, H-6), ^{13}C NMR (chloroform-*d*) 100.3 (C-1), 99.2 (C′-1), 54.8 (OMe), 18.2 (C-6), 17.2 (C-6′). Also obtained was 0.26 g (38%) of **9**: $[\alpha]_D$ +27.6° (*c* 1.2, $CHCl_3$); ^{1}H NMR (chloroform-*d*) δ 8.2–7.0 (m, 15 H, aromatics), 3.36 (s, 3 H, OMe), 2.2–1.0 (m, 16 H, cyclohexylidene, H-6); ^{13}C NMR (chloroform-*d*) 99.3, 97.8 (2 C, C-1′ and C-1), 54.8 (OMe), 18.3, 18.2 (2 C, C-6′ and C-6).

Methyl 4-*O*-(β-L-Rhamnopyranosyl)-α-L-rhamnopyranoside (11). Compound **7** (0.40 g, 0.7 mmol) was dissolved in methanol (50 mL) containing a catalytic amount of sodium methoxide, and the mixture was left at room temperature for 2 h. The reaction mixture was neutralized with Rexyn 101(H^+) and evaporated to a syrup that was taken up in aqueous trifluoroacetic acid (90%, 10 mL), left at 0 °C for 2 h, evaporated, and coevaporated with ethanol (2 × 25 mL). This gave a syrup that was purified on a silica gel column (ethyl acetate–methanol–water, 7:2:1) to give 0.22 g (93%) of the product **11**: $[\alpha]_D$ −12.1 (*c* 1.2, water) [lit.[7] $[\alpha]_D$ −16.5 (*c* 2.5, water)]; ^{1}H NMR (D_2O, 93 °C) δ 4.71 (d, 2 H, H-1, H′-1), 1.35 (d, 3 H, $J_{5,6}$ = 5.8 Hz, H-6), 1.33 (d, 3 H, $J_{5,6}$ = 5.7 Hz, H′-6); ^{13}C NMR (D_2O) δ 101.8 ($J_{C1,H1}$ = 173.9 Hz, C-1), 101.6 ($J_{C1',H1'}$ = 155.4 Hz, C-1′), 83.7 (C-4), 73.8, 73.4, 73.0 (3 C, C-3′, C-5′, C-4′), 71.7 (C-2), 70.5, 70.3 (2 C, C-2′, C-3), 68.0 (C-5), 56.0 (OMe), 17.8, 17.7 (2 C, C-6′, C-6). Anal. Calcd for $C_{13}H_{24}O_9$: C, 48.14; H, 7.46. Found: C, 47.75; H 7.71.

Methyl 3-*O*-(β-L-Rhamnopyranosyl)-α-L-rhamnopyranoside (12). Compound **8** (0.38 g, 0.6 mmol) was dissolved in methanol (20 mL) containing a catalytic amount of sodium methoxide and left overnight. The reaction was twice taken up

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in and evaporated with aqueous trifluoracetic acid (90%, 2 × 10 mL) followed by coevaporation with water (2 × 10 mL) to give a syrup that was purified on a silica gel column (ethyl acetate–methanol–water 85:10:5) to give 0.19 g (97%) of the product **12**: $[\alpha]_D$ +15.0° (*c* 1.6, water); ^{1}H NMR (D_2O, 80 °C) δ 4.73 (dd, 2 H, H-1 H-1′), 1.33 (d, 6 H, $J_{5,6} \approx J_{5,6}$ = 5.6 Hz, H-6, H-6′); ^{13}C NMR (D_2O) 101.8 ($J_{C1,H1}$ = 170.6 Hz, C-1), 98.4 ($J_{C1',H1'}$ = 159.7 Hz, C-1′), 78.7 (C-3), 73.8, 73.4, 73.1 (3 C, C-3′, C-5′, C-4′), 72.1 (C-4), 71.6 (C-2), 69.3 (C-2′), 68.5 (C-5), 55.9 (OMe), 18.0, 17.9 (2 C, C-6′, C-6). Anal. Calcd for $C_{13}H_{24}O_9$: C, 48.14; H, 7.46. Found: C, 47.98; H, 7.60.

Methyl 2-*O*-(β-L-Rhamnopyranosyl)-α-L-rhamnopyranoside (13). Compound **9** (0.22 g, 0.3 mmol) was dissolved in methanol (25 mL) containing a catalytic amount of sodium methoxide and left at room temperature for 2 h. The reaction mixture was neutralized with Rexyn 101(H^+) and evaporated to a syrup that was taken up in aqueous acetic acid (80%, 25 mL) and hydrogenated at 70 psi of H_2 overnight. The reaction was filtered through Celite 505 (Baker), evaporated, and purified on a silica gel column (ethyl acetate–methanol–water, 7:2:1) to give 85 mg (81%) of **13**: $[\alpha]_D$ +37.4° (*c* 1.4, water); ^{1}H NMR (D_2O, 80 °C) δ 4.78 (d, 1-H, $J_{1,2}$ = 1.7 Hz, H-1′), 4.69 (d, 1 H, $J_{1,2}$ = 0.9 Hz, H-1); ^{13}C NMR (D_2O) 99.7 (2 C, $^1J_{C1,H1}$ = 161.5, $^1J_{C1',H-1'}$ = 170.5 Hz, C-1, C-1′). 78.6 (C-2), 73.7 (2 C, C-3, C-3′), 73.5 (C-5′), 73.1 (C-4′), 72.1 (C-4), 70.8 (C-2′), 69.7 (C-5), 56.0 (OMe), 17.9, 17.7 (2 C, C-6′ and C-6). Anal. Calcd for $C_{13}H_{24}O_9$: C, 48.14; H, 7.46. Found: C, 47.94; H, 7.56.

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20′-Deethylanhydrovinblastine

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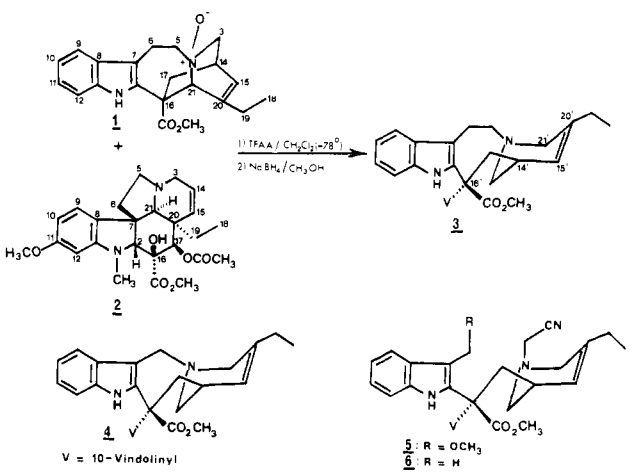
Racemic 20-deethylcatharanthine of synthetic origin has been coupled with vindoline by the fragmentative coupling method via the amine oxide. After reduction in methanol (16′*S*,14′*R*)-20′-deethylanhydrovinblastine is formed, accompanied by two methanol adducts, 15′-methoxy-20′-deethyl-15′,20′-dihydroanhydrovinblastine, which are epimeric at $C_{16'}$ and $C_{14'}$. If this step is performed in tetrahydrofuran, the yield of 20′-deethylanhydrovinblastine is increased and an equal yield of the 16′*R*,14′*S* epimer is obtained.

The discovery in our laboratory of a coupling reaction between catharanthine *N*-oxide (**1**) and vindoline (**2**) induced by a Polonovski fragmentation[1] has resulted in the preparation of anhydrovinblastine (**3**)[2] (Scheme I) and the main antitumor alkaloids extracted from the Madagascan periwinkle *Catharanthus roseus*.[3] In addition, derivatives **4**, **5**, and **6**,[4,5] having a modified skeleton, were synthesized. Some of them have shown interesting antitumor activities against leukemia L1210 and P-388 in mice and are currently under clinical evaluation.

The efficient total synthesis of (±)-20-deethylcatharanthine (**7**) by Sundberg and Bloom[6,7] prompted us to investigate the fragmentation reaction with the corresponding N_b-oxide **8** in the presence of vindoline (**2**). Besides comparing the behavior of (±)-20-deethylcatharanthine N_b-oxide (**8**) and catharanthine N_b-oxide (**1**),

Scheme I



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