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Preparation and reactions of 2-allyl-5-deoxymannose derivatives

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Abstract—Reaction of Danishefsky diene with benzyloxyethanal led to a pyrone which was transformed in 4–6 steps to different 5-deoxymannose derivatives, useful intermediates for the synthesis of natural product such as hemibrevetoxin.

1. Introduction

Hemibrevetoxin B is a natural marine product of a family of red tide toxins possessing biological properties including antimicrobial activity and neurotoxicity.[1] This 6,6,7,7-tetracyclic ether contains 10 stereogenic centres. (Fig. 1) More complex structures including the brevetoxins, maitotoxins, ciguatoxins or others have been reported.[2]

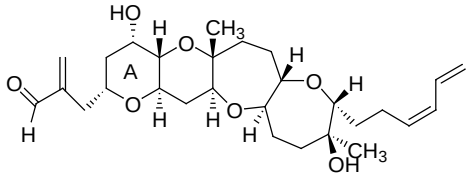
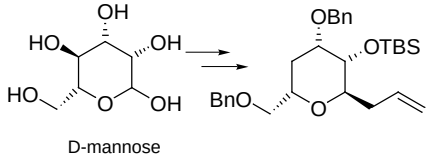


Figure 1.

The total synthesis of hemibrevetoxin B has been accomplished by several groups.[3] Except for the Nakata strategy,[3d] the approaches required the construction of the A-ring first. For example, Nicolaou[3b] reported the preparation of this ring in 12 steps from D-mannose (Scheme 1). Our interest in the synthesis of hemibrevetoxin, by a iterative method,[4] led us to research a shorter preparation of 2-alkyl-5-deoxymannose derivatives.[5]



Scheme 1.

2. Results

2.1. Preparation of racemic 2-α-allyl-6-benzyloxy-5-deoxymannose derivatives

Our approach was based on the work of Danishefsky concerning the hetero Diels–Alder reaction of aldehydes with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene. Following the already described procedure,[6] the racemic enone **1** was prepared and stereoselectively reduced by diisobutylaluminum hydride to the allylic alcohol **2** (Scheme 2). Reaction of this latter compound with *m*-chloroperbenzoic acid in the presence of methanol gave the diol **3a**. Only one diastereoisomer was obtained, the stereochemistry of which was deduced from its ^{1}H NMR spectra. Similarly, the reactions were conducted in the presence of 2-methoxyethanol and benzylalcohol to give, respectively, the diols **3b** and **3c**. In view of the subsequent allylation reaction, different protecting groups for the diols were then examined. Reaction of diols **3a–c** with excess of acetic anhydride led to the diacetates **4a–c**. In acetonitrile, in the presence of a catalytic amount of boron trifluoride diethyl etherate, only the diacetate **4b** led to the desired allylic compounds **5** and **6**, in seven days. The structure of these two diastereoisomers was determined from their ^{1}H NMR spectra, and confirmed in the case of compound **5**, by comparison to the spectra of diol **7** (Scheme 2), formed by cleavage of the two acetate functions, with those reported in the literature.[3b]

To improve the rate of the allylation reaction, we decided next to examine the behaviour of the dibenzyl ethers **8a**,**b**. As expected, these compounds were much more reactive (2 days for compound **8a** and 12 h for compound **8b**) and in both cases the allylic compounds **9**, **10** were obtained in good yields (Scheme 2). The stereochemistry of these two diastereoisomers was deduced from their ^{1}H NMR spectra, 2D NOESY experiment and confirmed in the case of

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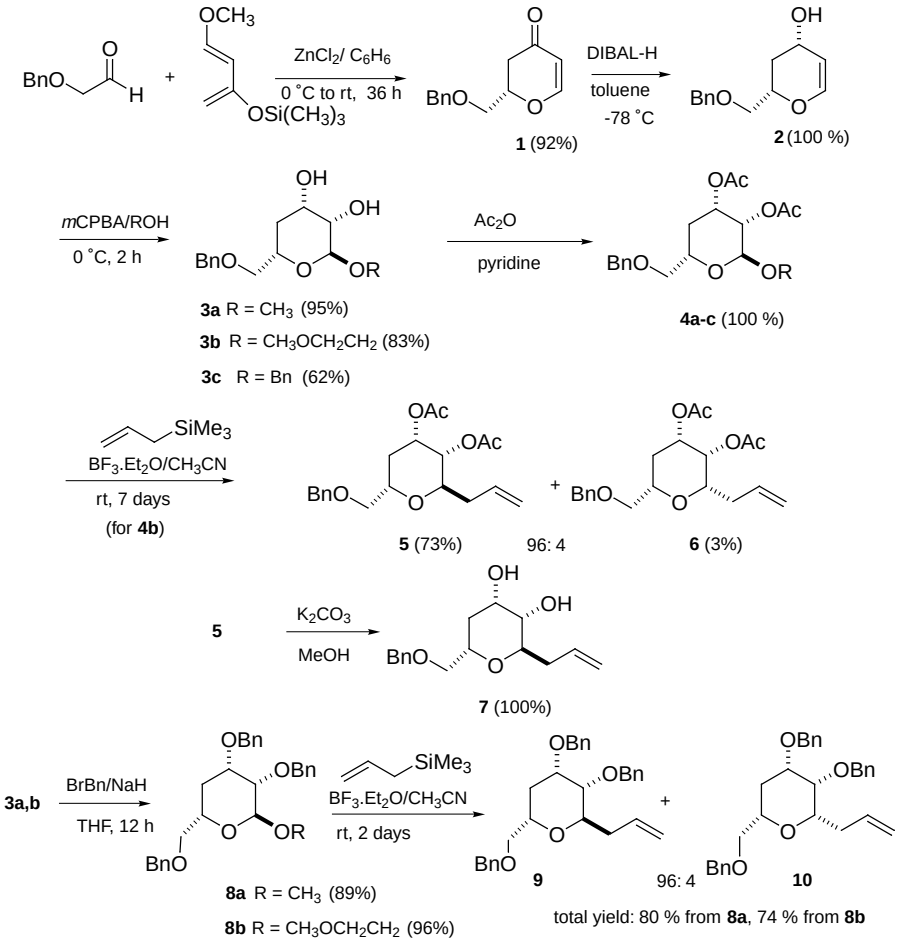
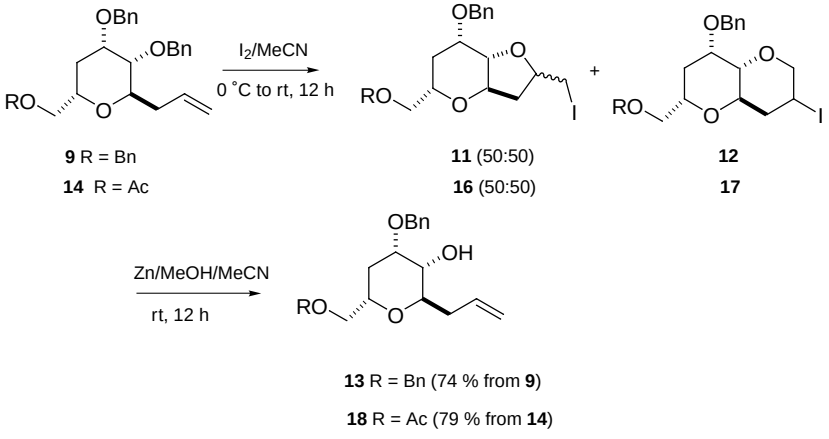


Scheme 2.

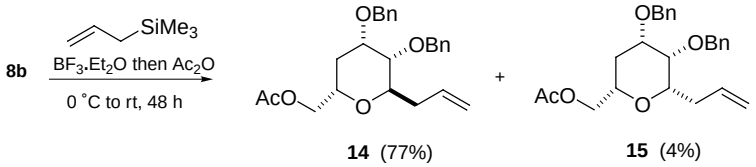
compound **9** by comparison of its NMR spectra with those of the product formed by dibenzylation of the diol **7**.

2.2. Differentiation of the alcohol functions of 2-α-allyl-5-deoxymannose derivatives

In our objective to prepare intermediates which can be useful for the synthesis of hemibrevetoxin, it would be interesting to find procedures to discriminate between the three benzyl ether functions of compound **9**. Differentiation between the two benzyl functions in the 3 and 4 position was easily realised by iodoetherification.[7] In acetonitrile in the presence of iodine compound **9** led to a mixture of the two products **11**, **12** (mixture of two diastereoisomers) which after reaction with zinc in methanol–THF was converted to the 3-hydroxy compound **13** (Scheme 3). This two step selective cleavage of a benzyl ether has precedent in the literature.[8]



Scheme 3.



Scheme 4.

Wong reported that allylation of 6-benzyloxymethyl sugars led in one pot to 6-acetyloxymethyl derivatives if, the reaction was quenched by addition of acetic anhydride.[9] We applied this procedure to the allylation of compound **8b**, and obtained a mixture (95:5) of the two diastereoisomers **14**, **15** (Scheme 4). As in the case of compound **9**, reaction of compound **14** with iodine in acetonitrile led to a mixture of the two iodoethers **16**, **17** which after reaction with zinc led to the monoalcohol **18** (Scheme 3).

Cleavage of the acetate function on the mixture of products **16**, **17** and protection as a *t*-butyldiphenylsilylether led to a mixture of compounds **19**, **20** which by reaction with zinc yielded the alcohol **21** (Scheme 5).

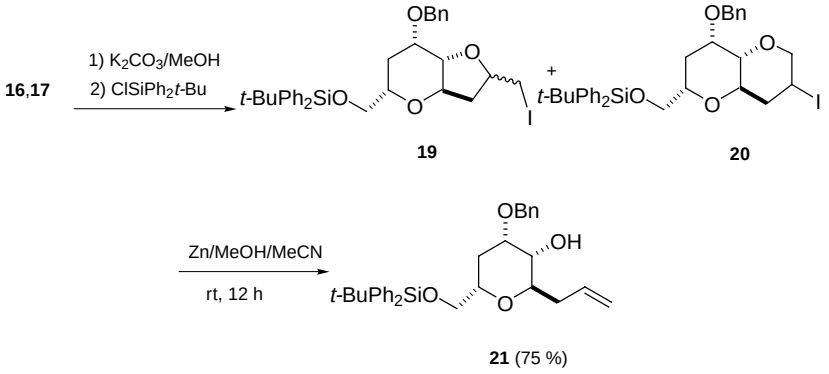
2.3. Preparation of enantiomerically enriched 2-α-allyl-6-benzyloxy-5-deoxymannose derivatives

Numerous methods have been reported for asymmetric hetero-Diels–Alder.[10] We chose the method described by Jacobsen, for the simplicity of the reaction conditions.[11] Reaction of the Danishefsky diene with benzyloxyethanal in the presence of the Jacobsen catalyst[12] led to enone (*S*)-**1** in moderate yield (60%). Its enantiomeric excess (90%) was determined by chiral gas chromatography on 4,4-dimethoxy-2-hydroxymethyltetrahydropyran. This latter was formed by reduction of enone (*S*)-**1** by hydrogen in methanol in the presence of Pd/C. Reduction of the ketone function of enone **1** with DIBAL–H at −78°C led to allylic alcohol (2*S*,4*S*)-**2** ($[\alpha]_D$=+9.1, *c*=1, $CHCl_3$) followed by epoxidation using *m*-chloroperbenzoic acid in the presence of methoxyethanol led in quantitative yield to the enantiomerically enriched diol (2*S*,3*S*,4*S*,6*S*)-**3b** ($[\alpha]_D$=+26.6, *c*=1, $CHCl_3$) (see Scheme 2). Its enantiomeric excess measured by chiral HPLC was found to be 76%. The partial racemisation observed seemed to occur during the enone reduction step. After benzylation, enantiomerically enriched compound (2*S*,3*S*,4*S*,6*S*)-**8b** ($[\alpha]_D$=+17.0, *c*=1, $CHCl_3$) was transformed, as in the racemic series, into the allylic compounds **9**, **10** (96:4) (overall yield: 76%). The major diastereoisomer **9** was treated with iodine in acetonitrile leading to a mixture of compounds **11**, **12** (see Scheme 3) which after reaction with zinc provided the desired enantiomerically enriched monoalcohol (2*R*,3*S*,4*S*,6*S*)-**13** (overall yield: 74%) $[\alpha]_D$=+19.5 (*c*=1, $CHCl_3$).

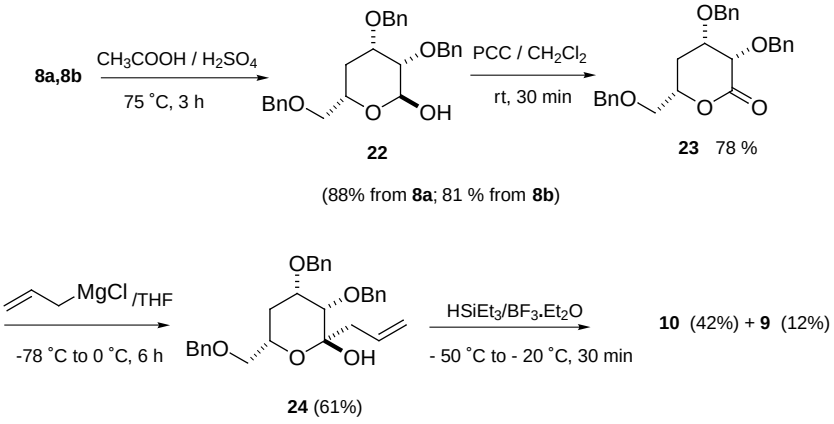
2.4. Preparation of 2-β-allyl-6-benzyloxy-5-deoxymannose derivatives

β-*C*-Glycosidic natural products have been reported,[13] and due to the interesting biological properties of compounds possessing this stereochemistry,[14] it seemed interesting to prepare the still unknown 2-β-allyl-5-deoxymannose derivatives. Numerous methods have been reported to prepare 2-β-*C*-glycosides.[15] We decided to use the method published by Kishi.[16] Reaction (80°C, 36 h) of **8a** or **8b** with a mixture (1:1) of sulphuric acid (1N) and acetic acid led to the hemiacetal **22** (Scheme 6). This compound was oxidised into the unstable lactone **23** by PCC in methylene chloride. Without purification, the addition of allylmagnesium chloride at −40°C to this lactone led to the desired unstable alcohol **24**, whose stereochemistry was deduced from its ^1H, ^{13}C and 2D spectra. Reduction of the alcohol function using a large excess of triethylsilane in methylene chloride in the presence of boron trifluoride led to a 80:20 mixture of the two diastereoisomers **10**, **9**.

In conclusion, in this study we have shown that we were able to prepare different 5-deoxymannose derivatives in racemic and enantiomerically enriched forms. These compounds should be interesting intermediates for the synthesis of products possessing this deoxy sugar.



Scheme 5.



Scheme 6.

3. Experimental

3.1. General

NMR spectra were recorded on 250 and 400 MHz spectrometers. Tetrahydrofuran and ether were distilled under argon from sodium-benzophenone. Dichloromethane was distilled from calcium hydride. Acetonitrile and pentane were distilled from phosphoric anhydride. (+)-Dihydropyrone **1** was prepared as previously reported[6] in 93% yield.

3.1.1. Preparation of (2*S,4*S**)-2-benzyloxymethyl-3,4-dihydro-2*H*-pyran-4-ol 2.** A solution of enone **1** (0.86 g, 3.94 mmol) in toluene (8 mL) was cooled to −78°C. To this was added dropwise a 1 M solution in toluene of diisobutylaluminum hydride (5 mL, 5 mmol). After 15 min, methanol was added (10 mL), followed by a saturated solution of Rochelle salt (15 mL) and the mixture was allowed to warm to rt. The reaction mixture was extracted with ethyl acetate (4×20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (70:30 ether–hexane) afforded 0.87 g (100%) of pyranol **2**.

3.1.2. Preparation of (2*S,3*S**,4*S**,6*S**)-6-benzyloxymethyl-2-methoxy-tetrahydropyran-3,4-diol 3a.** A solution of pyranol **2** (2.0 g, 9.09 mmol) in methanol (60 mL) was stirred for 10 min at 0°C before addition dropwise of a solution of *m*-chloroperbenzoic acid (2.6 g, 9.90 mmol) in methanol. The solution was maintained at 0°C for 2 h before addition of a saturated solution of sodium bicarbonate (30 mL). The mixture was stirred for 12 h at rt. The pH of the solution was found to be between 7 and 8 and was extracted with methylene chloride (2×50 mL). The organic phase was then washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography (2.5:97.5 methanol–ether) afforded 2.31 g of diol **3a** as a white solid. Mp: 80–85°C. ^{1}H NMR (250 MHz, D_2O–$CDCl_3$) δ 1.59 (m, 2H), 3.36 (s, 3H), 3.54 (d, J=4.5 Hz, 2H), 3.70 (dd, J=1.9, 3.3 Hz, 1H), 3.91 (m, 2H), 4.58 (s, 2H), 4.77 (d, J=1.5 Hz, 1H), 7.30 (s, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.4, 54.7, 65.4, 67.1, 68.6, 72.5, 73.3, 101.4, 127.6–128.3 (5C), 137.7. IR (film) 3395, 3020, 1450, 1360, 1020–1100 cm^{-1}. Anal. calcd for $C_{14}H_{20}O_5$: C, 62.18; H, 7.41. Found: C, 62.67; H, 7.51.

3.1.3. Preparation of (2*S,3*S**,4*S**,6*S**)-6-benzyloxymethyl-2-(2-methoxyethoxy)-tetrahydropyran-3,4-diol 3b.** The reaction was conducted as reported for the preparation of compound **3a** using methoxyethanol as alcohol. Oil, 83%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.61–1.69 (m, 2H), 2.25 (bs, 1H), 2.41 (bs, 1H), 3.33 (s, 3H), 3.49–3.58 (m, 5H), 3.37–3.81 (m, 2H), 3.95 (m, 2H), 4.45 (s, 2H), 4.80 (d, J=1.3 Hz, 1H), 7.30 (s, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.4, 58.6, 65.2, 66.1, 67.2, 68.4, 71.2, 72.4, 73.0, 100.3, 127.4–128.1 (5C), 137.7. IR (film) 3400, 3080, 2920, 1490, 1450, 740–695 cm^{-1}. HMRS calcd for $C_{16}H_{24}O_6Na$ (MNa^+): 335.147056. Found: 335.147058. Anal. calcd for $C_{16}H_{24}O_6$: C, 61.03; H, 7.72. Found: C, 61.52; H, 7.74.

3.1.4. Preparation of (2*S,3*S**,4*S**,6*S**)-2-benzyloxy-6-benzyloxymethyltetrahydropyran-3,4-diol 3c.** This compound was prepared using the procedure reported for the diol **3a** using benzyl alcohol. Oil. ^{1}H NMR (250 MHz, D_2O–$CDCl_3$) δ 1.70 (m, 2H), 3.53 (d, J=4.4 Hz, 2H), 3.74 (t, J=2.2 Hz, 1H), 3.97 (m, 2H), 4.49 (d, J=11.8 Hz, 1H), 4.57 (s, 2H), 4.72 (d, J=11.8 Hz, 1H), 4.96 (d, J≤0.5 Hz, 1H), 7.33 (m, 10H).

3.1.5. Preparation of (2*S,3*S**,4*S**,6*S**)-6-benzyloxymethyl-3,4-bisacetyloxy-2-methoxytetrahydropyran 4a.** To diol **3a** (0.3 g, 1.12 mmol) was added acetic anhydride (0.316 mL, 3.36 mmol) and triethylamine (0.622 mL, 4.48 mmol). After one night at rt, the mixture was concentrated under vacuum and the residue was purified by flash chromatography (SiO_2, 35:65 ether–pentane) to give 0.375 g of diacetate **4a** as an oil (95%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.72 (m, 2H), 1.91 (s, 3H), 2.03 (s, 3H), 3.28 (s, 3H), 3.46 (m, 2H), 3.94 (m, 1H), 4.50 (s, 2H), 4.66 (d, J=1.6 Hz, 1H), 5.00 (d, J=3.2 Hz, 1H), 5.60 (ddd, J=11.9, 5.3, 3.2 Hz, 1H), 7.23 (s, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.7, 28.0, 54.7, 66.5, 67.1, 67.6, 72.1, 73.0, 99.0, 127.8–128.1 (5C), 137.9, 169.7, 170.0. MS *m/z*: 352, 320, 292, 277, 149, 133, 121, 92, 91, 75, 43. Anal. calcd for $C_{18}H_{24}O_7$: C, 61.55; H, 6.95. Found: C, 61.35; H, 6.86.

3.1.6. Preparation of (2*S,3*S**,4*S**,6*S**)-6-benzyloxymethyl-3,4-bisacetyloxy-2-(2-methoxyethoxy)-tetrahydropyran 4b.** This compound was obtained using the procedure reported for the diacetate **4a**. Oil, 100%. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.80 (m, 2H), 2.00 (s, 3H), 2.08 (s,

3H), 3.36 (s, 3H), 3.59 (m, 5H), 3.79 (m, 1H), 4.09 (m, 1H), 4.50 (2d, J=12.1 Hz, 2H), 4.88–4.89 (d, J=1.3 Hz, 1H), 5.12 (d, J=2.0 Hz, 1H), 5.29 (ddd, J=3.2, 5.4, 11.6 Hz, 1H), 7.32 (s, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.8, 28.1, 58.8, 66.7, 67.3, 67.8, 71.3, 72.2, 73.2, 98.2, 127.4–128.2 (5C), 138.0, 169.8, 170.0. Anal. calcd for $C_{20}H_{28}O_8$: C, 60.61; H, 7.18. Found: C, 60.59; H, 7.12.

3.2. Allylation of compound 4b

To a solution of diacetate **4b** (0.06 g, 0.15 mmol) in acetonitrile (2 mL) at 0°C was added allyltrimethylsilane (0.25 mL, 0.15 mmol), followed 15 min later by $BF_3{\cdot}Et_2O$ (0.125 mL, 0.1 mmol). The reaction was warmed to rt and stirred for 12 h. Then allyltrimethylsilane (0.25 mL, 0.15 mmol) and $BF_3{\cdot}Et_2O$ (0.125 mL, 0.1 mmol) were added and the reaction was stirred for another 12 h. The reaction mixture was stirred for 7 days more, with sequential addition each 12 h of allyltrimethylsilane and $BF_3{\cdot}Et_2O$. The reaction was quenched with $NaHCO_3$ (sat., 2 mL), extracted with methylene chloride (2×10 mL), washed with brine, dried (Na_2SO_4) and concentrated. Flash chromatography (30:70 ether–pentane) afforded 40 mg (74%) of allyl compounds **5**, **6** (mixture 96:4 of two diastereoisomers in ^{1}H NMR spectra).

3.2.1. (2*R,3*S**,4*S**,6*S**)-2-Allyl-6-benzyloxymethyl-3,4-bisacetyloxytetrahydropyran 5.** (Major diastereoisomer) ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.88 (m, 2H), 2.02 (s, 3H), 2.12 (s, 3H), 2.46 (m, 2H), 3.56 (ddd, J=4.5, 6.0, 10.1 Hz, 2H), 4.00 (m, 2H), 4.58 (s, 2H), 5.16 (m, 4H), 5.79 (m, 1H), 7.33 (s, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 20.9, 21.0, 28.8, 33.8, 66.7, 68.6, 69.0, 72.2, 73.3, 75.0, 117.2, 127.5–128.3 (5C), 133.1, 138.0, 170.0, 170.3. Anal. calcd for $C_{20}H_{26}O_6$: C, 66.26; H, 7.23. Found: C, 65.95; H, 7.33. HMRS calcd for $C_{20}H_{30}O_6N$ (MNH_4^+) 380.20729. Found: 380.20731.

3.2.2. Preparation of (2*R,3*S**,4*S**,6*S**)-2-allyl-6-benzyloxymethyl-tetrahydropyran-3,4-diol 7.** To a solution of diacetate **5** (0.04 g, 0.11 mmol) in methanol (2 mL) was added K_2CO_3 (2 mg). The mixture was stirred for 2 h at rt. The solvent was removed under vacuum and THF (3 mL) was added to the residue. After filtration the solvent was removed under vacuum. The crude allyl diol **7** (33 mg, 100%) could be used without purification. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.75 (m, 1H), 1.98 (dt, J=5.0, 13.8 Hz, 1H), 2.35 (m, 2H), 3.15 (bs, 1H), 3.19 (bs, 1H), 3.41–3.62 (m, 4H), 3.84–3.96 (m, 2H), 4.56 (bs, 2H), 5.05–5.15 (m, 2H), 5.81 (m, 1H), 7.24–7.37 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 32.0, 34.7, 65.6, 68.9, 69.9, 73.2, 73.5, 75.2, 117.2, 127.6–128.4 (5C), 134.2, 137.5. HMRS calcd for $C_{16}H_{22}NaO_4$(MNa^+) 301.14157. Found: 301.14157.

3.2.3. Preparation of (2*S,3*S**,4*S**,6*S**)-3,4-bisbenzyloxy-6-benzyloxymethyl-2-methoxy-tetrahydropyran 8a.** To sodium hydride (2 g, 83.7 mmol) washed twice with pentane under argon, was added, at 0°C THF (50 mL), and dropwise a solution of diol **3a** (2.9 g, 11.9 mmol) in THF (50 mL). Thirty minutes after the end of the addition of the diol, benzyl bromide (4.25 mL, 35.6 mmol) was introduced. After one night at rt, methanol (10 mL) was added at 0°C. After filtration over Celite, the solution was concentrated under vacuum and the residue was purified by flash chromatography (30:70 ether–pentane) to give 3.88 g (98%) of compound **8a**. Oil ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (m, 1H), 1.93 (d, J=12 Hz, 1H), 3.30 (s, 3H), 3.53 (ddd, J=4.4, 6.3, 10.0 Hz, 2H), 3.67 (bs, 1H), 3.81 (dt, J=4.4, 10.6 Hz, 1H), 3.88 (m, 1H), 4.50 (bs, 2H), 4.59 (2d, J=12.0 Hz, 2H), 4.73 (2d, J=12.4 Hz, 2H), 4.77 (s, 1H), 7.33 (m, 15H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 28.7, 54.1, 67.7, 69.6, 71.6, 72.2, 72.8 (2C), 73.5, 99.6, 126.8–127.9 (15C), 138.0 (3C). Anal. calcd for $C_{27}H_{30}O_5$: C, 74.68; H, 7.14. Found: C, 74.62; H, 6.96.

3.2.4. Preparation of (2*S,3*S**,4*S**,6*S**)-3,4-bisbenzyloxy-6-benzyloxymethyl-2-(2-methoxy-ethoxy)-tetrahydropyran 8b.** This compound was obtained using the procedure reported for the dibenzyl ether **8a**. Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (m, 2H), 3.34 (s, 3H), 3.47–3.62 (m, 6H), 3.80 (m, 1H), 3.92 (m, 2H), 4.52 (s, 2H), 4.58 (d, J=12.0 Hz, 2H), 4.75 (2d, J=12.4 Hz, 2H), 4.94 (d, J=1.0 Hz, 1H), 7.32 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.9, 58.7, 66.0, 67.9, 69.9, 71.3, 72.4, 72.7, 72.9, 73.0, 73.7, 98.8, 127.5 (15C), 138.2 (2C). Anal. calcd for $C_{30}H_{36}O_6$: C, 73.15; H, 7.39. Found: C, 73.35; H, 7.37. HMRS calcd for $C_{30}H_{36}O_6Na$ (MNa^+) 515.24095. Found: 515.24095.

3.3. Allylation of compound 8a

To a solution of tribenzyl ether **8a** (0.117 g, 2.37 mmol) in acetonitrile (6 mL) was added allyltrimethylsilane (0.81 mL, 5.11 mmol) at 0°C, followed 15 min later by $BF_3{\cdot}Et_2O$ (0.2 mL, 1.64 mmol). The reaction was warmed to rt and stirred for 12 h. Then allyltrimethylsilane (0.414 mL, 2.61 mmol) and $BF_3{\cdot}Et_2O$ (0.1 mL, 0.83 mmol) were added and the reaction was stirred for another 12 h. The same amounts of silane and $BF_3{\cdot}Et_2O$ were again added and after 12 h the reaction was quenched with $NaHCO_3$ solution (sat., 4 mL), extracted with methylene chloride (2×15 mL), washed with brine, dried (Na_2SO_4) and concentrated. Flash chromatography (20:80 ether–pentane) afforded 0.815 g (80%) of allyl compounds **9**, **10** (mixture 96:4 of the two diastereoisomers from ^{1}H NMR spectra).

3.3.1. (2*R,3*S**,4*S**,6*S**)-2-Allyl-3,4-bisbenzyloxy-6-benzyloxymethyl-tetrahydropyran 9.** (Major diastereoisomer): ^{1}H NMR (250 MHz, $CDCl_3$) 1.78 (dt, J=4.0, 13.0 Hz, 1H), 2.00 (m, 1H), 2.32 (m, 2H), 3.46 (t, J=3.0 Hz, 1H), 3.50 and 3.74 (ddd, J=5.1, 6.7, 10.0 Hz, 2H), 3.78 (m, 1H), 3.90 (m, 1H), 4.08 (m, 1H), 4.43–4.65 (m, 6H), 5.04 (m, 2H), 5.78 (m, 1H), 7.32 (m, 15H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.8, 34.3, 69.3, 69.6, 70.8, 71.3, 71.6, 72.4, 72.7, 74.3, 116.5, 126.1–127.7 (15C), 133.8, 137.8 (3C). Anal. calcd for $C_{30}H_{34}O_4$: C, 78.57; H, 7.47. Found: C, 77.97; H, 7.48.

3.3.2. (2*S,3*S**,4*S**,6*S**)-2-Allyl-3,4-bisbenzyloxy-6-benzyloxymethyl-tetrahydropyran 10.** (Minor diastereoisomer):^{1}H NMR (400 MHz, $CDCl_3$) 1.90 (m, 2H), 2.31 (m, 1H), 2.47 (m, 1H), 3.28 (t, J=7.0 Hz, 1H), 3.47 (dd, J=4.0, 9.2 Hz, 1H), 3.57–3.69 (m, 4H), 4.52–4.68 (m, 6H), 5.02 (m, 2H), 5.66 (m, 1H), 7.26–7.41 (m, 15H). ^{13}C NMR

(50 MHz, $CDCl_3$) δ 29.3, 35.9, 70.0, 72.9, 73.3, 73.4, 74.0, 75.6, 78.5, 79.2, 117.0, 127.1–128.7 (15C), 134.6, 138.2, 138.4, 138.8. HMRS (MNa^+) calcd 481.23547. Found: 481.23547.

3.3.3. Preparation of (2*R,3*S**,4*S**,6*S**)-2-allyl-4-benzyloxy-6-benzyloxymethyl-tetrahydropyran-3-ol 13.** To a solution of tribenzyl ether **9** (0.59 g, 1.29 mmol) in acetonitrile (20 mL) was added at 0°C iodine (0.982 g, 3.86 mmol). After stirring for 14 h in the dark, ether (150 mL) and sodium sulphite (sat. solution, 20 mL) were added. The aqueous phase was extracted with ether (2×100 mL) and the organic phase was washed with brine (sat. solution, 50 mL), dried ($MgSO_4$) and concentrated. The crude residue was dissolved in a 1:1 mixture methanol–THF (10 mL), and zinc powder (0.6 g) was added. After 15 min, five drops of acetic acid were added, and the mixture stirred for 48 h. The mixture was filtered with Celite. The solution was extracted with ether (3×300 mL), and the organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (40:60 pentane–ether) to afford 0.35 g (74%) of alcohol **13** as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.88 (m, 2H), 2.36 (m, 3H), 3.48 (dd, J=5.3, 10.0 Hz, 1H), 3.69 (m, 2H), 3.79 (m, 1H), 3.90 (m, 1H), 3.98 (m, 1H), 4.58 (m, 4H), 5.10 (m, 2H), 5.84 (m, 1H), 7.33 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.2, 34.2, 67.6, 68.7, 69.8, 71.8, 72.9, 74.6, 116.7, 127.2–128.1 (10C), 134.1, 137.5, 137.9. HMRS (MNa^+) calcd 391.18852. Found: 391.18852.

3.3.4. Preparation of (2*R,3*S**,4*S**,6*S**)-2-allyl-6-acetyloxymethyl-3,4-bisbenzyloxytetrahydropyran-3-ol 14.** The reaction was carried out as reported for the allylation of compound **8a**. However, before the quenching of the reaction, acetic anhydride was added (6 mL for 4 mmol of compound **8b**) and the solution was stirred 3 h. Work-up was then carried out as for the allylation of compound **8a**. After flash chromatography (20:80 ether–pentane) a mixture 96:4 of the two diastereoisomers **14**, **15** was obtained (77%). ^{1}H NMR for **14** (250 MHz, $CDCl_3$) δ 1.74 (dt, J=4.0, 13.0 Hz, 1H), 1.95 (m, 1H), 2.08 (s, 3H), 2.29 (t, J=7.0 Hz, 2H), 3.42 (dd, J=2.8, 4.7 Hz, 1H), 3.76–3.95 (m, 2H), 4.06–4.16 (m, 2H), 4.35 (dd, J=8.0, 11.7 Hz, 1H), 4.56 (s, 2H), 4.62 (s, 2H), 5.00 (m, 2H), 5.73 (m, 1H), 7.37 (m, 10H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.8, 29.1, 34.7, 65.7, 68.6, 70.5, 71.3, 71.7, 72.4, 75.1, 117.0, 127.5–128.8 (10C), 134.2, 138.1, 138.2, 170.9. HMRS (MNa^+) calcd 433.19909. Found: 433.19909.

3.3.5. Preparation of (2*R,3*S**,4*S**,6*S**)-2-allyl-4-benzyloxy-6-acetyloxymethyltetrahydropyran-3-ol 18.** The reaction was carried out from compound **14** as reported for the preparation of alcohol **13** (79%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.84 (m, 2H), 2.08 (s, 3H), 2.32 (m, 3H), 3.67 (m, 1H), 3.81 (m, 1H), 3.91 (m, 1H), 4.00 (m, 1H), 4.07 and 4.68 (ddd, J=3.6, 3.8, 11.6 Hz, 2H), 4.54 (d, J=11.6 Hz, 1H), 4.65 (d, J=11.6 Hz, 1H), 5.11 (m, 2H), 5.84 (m, 1H), 7.35 (m, 5H). Anal. calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.55; H, 7.61.

3.3.6. Preparation of (2*R,3*S**,4*S**,6*S**)-2-allyl-4-benzyloxy-6-(*t*-butyldiphenylsilanyloxymethyl)-tetrahydropyran-3-ol 21.** After reaction of acetate **14** (1 g, 2.03 mmol) with iodine (1.48 g, 5.80 mmol) in acetonitrile (30 mL), as reported for the preparation of compound **8a**, the crude mixture of iodo ethers **16**, **17** was diluted with methanol (40 mL) and a catalytic amount of K_2CO_3 (0.05 g) was added. After stirring for one night at rt, the methanol was removed under vacuum and the residue was diluted in THF (30 mL). After filtration over Celite, the solvent was removed under vacuum. The crude mixture of iodo alcohols (100% yield) was diluted in dry THF (30 mL), and imidazole (0.544 g, 8 mmol) and DMAP (40 mg) were added. After 1 h of stirring at rt, the mixture was cooled at 0°C and *t*-butyldiphenylchlorosilane (0.9 mL, 4 mmol) was added. The solution was stirred for 12 h at rt. The solvent was removed, and the residue was purified by flash chromatography (10:90 ether–pentane). Then the mixture of silyliodo ether was treated with zinc as reported for the preparation of alcohol **13**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.88 (m, 2H), 2.32 (m, 2H), 2.38 (m, 1H), 3.82–3.96 (m, 6H), 4.53–4.64 (2d, J=12 Hz, 2H), 5.06 (m, 2H), 5.81 (m, 1H), 7.37 (m, 11H), 7.56 (m, 4H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.2, 26.8 (3C), 28.4, 65.8, 68.2, 70.2, 70.3, 73.4, 74.9, 117.0, 127.6–129.6 (15C), 133.5 (2C), 134.4, 135.6, 137.7. HMRS calcd for $C_{32}H_{40}NaSiO_4$: (MNa^+) 539.25935. Found: 539.25935.

3.3.7. Preparation of (2*S,3*S**,4*S**,6*S**)-3,4-bisbenzyloxy-6-benzyloxymethyltetrahydropyran-2-ol 22.** A solution compound **8a** (0.146 g, 0.32 mmol) in a mixture of acetic acid (30 mL) and sulphuric acid (1 M sol, 0.65 mL) was heated at 75°C for 48 h. The solution was then concentrated under vacuum and the residue was dissolved in methylene chloride (100 mL). The organic phase was washed with sodium bicarbonate (sat. sol., 20 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (30:70 ether–pentane) afforded 0.114 g (81%) of compound **22** as a white solid. Mp 108–110°C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.85 (m, 2H), 2.55 (d, 1H), 3.55 (ddd, J=3.5, 6.0, 10.6 Hz, 2H), 3.72 (bs, 1H), 3.92 (ddd, J=2.9, 4.4, 11.7 Hz, 1H), 4.17 (m, 1H), 4.59 (m, 4H), 4.75 (2d, J=12.5 Hz, 2H), 5.28 (d, J=1.5 Hz, 1H), 7.30 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.7, 67.5, 69.8, 72.3, 72.8, 72.9, 73.2, 93.1, 127.5 (15C), 137.6, 138.0 (3C), 138.2. Anal. calcd for $C_{27}H_{30}O_5$: C, 74.68; H, 7.14. Found: C, 74.62; H, 6.96.

3.3.8. Preparation of (3*S,4*S**,6*S**)-3,4-bisbenzyloxy-6-benzyloxymethyltetrahydropyran-2-one 23.** To a solution of hemiketal **22** (0.15 g, 0.355 mmol) in methylene chloride (12 mL) was added molecular sieve 4 Å in powder (0.4 g). The mixture was stirred for 15 min at rt, then cooled at 0°C, and PCC (0.344 g, 1.6 mmol) was added. After 50 min, the reaction was quenched by addition of a mixture pentane–ether (1:2). After filtration, the filtrate was concentrated under vacuum. The residue was washed with a mixture pentane–ether (1:2) (150 mL). Concentration of the organic phase afforded the unstable lactone **23** as an oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.06 (m, 1H), 2.20 (m, 1H), 3.55 (ddd, J=4.5, 6.0, 10.4 Hz, 2H), 4.13 (m, 2H), 4.40 (m, 1H), 4.60 (m, 4H), 4.81 (d, J=12.3 Hz, 1H), 5.03 (d, J=12.3 Hz, 1H), 7.34 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.9, 71.2, 72.1, 72.2, 73.2, 73.9, 75.9, 128.0 (15C), 137.3 (3C), 169.3. HMRS calcd for $C_{27}H_{28}O_5Na$ (MNa^+) 455.18344. Found: 455.18344.

3.3.9. Preparation of (2*S,3*S**,4*S**,6*S**)-2-allyl-3,4-bis-benzyloxy-6-benzyloxymethyl-tetrahydropyran-2-ol 24.** A solution of lactone **23** (0.16 g, 0.347 mmol) in THF (20 mL) was cooled at −78°C, and a solution (0.5 M in THF) of allylmagnesium chloride (0.345 mL, 0.173 mmol) was added. The mixture was warmed to rt and stirred for 15 h. The mixture was cooled at −78°C and another solution of Grignard reagent was added (0.173 mL, 0.0865 mmol). The mixture was warmed to −20°C then cooled again to −78°C. The same addition protocol was carried out 10 times. The reaction was then quenched at −78°C by addition of ammonium chloride (sat. sol., 5 mL) and warmed to rt. The aqueous phase was extracted with dichloromethane (100 mL). The organic phase was dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (30:70 ether–pentane) to afford the unstable allyl alcohol **24** (61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (m, 2H), 2.19 (dd, J=9.5, 13.7 Hz, 1H), 2.51 (m, 1H), 2.75 (dd, J=5.3, 13.7 Hz, 1H), 3.43–3.68 (ddd, J=4.4, 6.0, 10.0 Hz, 2H), 3.67 (d, J=2 Hz, 1H), 4.05 (m, 2H), 4.51–5.00 (2d+m, J=11.4 Hz, 6H), 5.18 (m, 2H), 5.80 (m, 1H), 7.24–7.36 (m, 15H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 29.0, 43.4, 69.3, 70.6, 73.1, 73.4, 74.5, 75.9, 76.1, 98.5, 120.4, 128.0 (15C), 132.5, 139.0 (3C). HMRS calcd for $C_{30}H_{34}O_5Na$ (MNa^+) 497.23038. Found: 497.23039.

3.3.10. Preparation of (2*S,3*S**,4*S**,6*S**)-2-allyl-3,4-bisbenzyloxy-6-benzyloxymethyl-tetrahydropyran 10.** To a solution of alcohol **24** (0.149 g, 0.134 mmol) in methylene chloride (6 mL) and triethylsilane (4 mL) at −35°C was added slowly $BF_3{\cdot}Et_2O$ (0.125 mL, 1.1 mmol). The solution was stirred for 45 min after the end of the addition and sodium bicarbonate (sat. solution, 2.5 mL) was added dropwise. After warming to rt, the aqueous phase was extracted with methylene chloride (3×20 mL). The organic phases were dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (15:85 ether–pentane) to afford a mixture (80:20) of the two diastereoisomers **10** and **9** (54%).

References

1. Prasad, A. V. K.; Shimizu, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6476–6477.
2. Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1–49 and references cited.
3. (a) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1992**, *114*, 7935–7936. (b) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558–3575. (c) Kadota, I.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6597–6606. (d) Morimoto, M.; Matsukura, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6365–6368. (e) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6200–6209. (f) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380–1386.
4. Simart, F.; Brunel, Y.; Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13557–13566.
5. For a preliminary report of this work see: Saleh, T.; Rousseau, G. *Synlett* **1999**, 617–619.
6. Danishefsky, S.; Kerwin, J. F.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358–360.
7. Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963–3964.
8. (a) Cipolla, L.; Lay, L.; Nicotra, F. *J. Org. Chem.* **1997**, *62*, 6678–6681. (b) Jégou, A.; Pacheco, C.; Veyrières, A. *Tetrahedron* **1998**, *54*, 14779–14790.
9. Hung, S.-C.; Lin, C.-C.; Wong, C.-H. *Tetrahedron Lett.* **1997**, *38*, 5419–5422.
10. (a) Waldmann, H. *Synthesis* **1994**, 535–551. (b) Jorgensen, K. A.; Johannsen, M.; Yao, S. L.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605–613.
11. Schaus, S. E.; Brânalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876–4877.
12. Schaus, S. E.; Brânalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403–405.
13. (a) Zheng, W.; De Mattei, J.-P.; Wu, J.-W.; Duan, J.-W.; Cook, L. H.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946–7968. (b) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C.; Winkler, T. *J. Org. Chem.* **1995**, *60*, 953–959. (c) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6811–6814.
14. (a) Bertozzi, C.; Bednarski, M. *Carbohydr. Res.* **1992**, *223*, 243–253. (b) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752–753. (c) Cipolla, F.; Nicotra, F.; Vismara, E.; Guerrini, M. *Tetrahedron* **1997**, *53*, 6163–6170.
15. (a) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545–8599. (b) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913–9959.
16. Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.