Pergamon

Tetrahedron Vol. 51, No. 41, pp. 11177-11182, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4020/95 $9.50+0.00

0040-4020(95)00680-X

Synthetic Studies Toward Pseurotin A

Part 4[1]

Stereocontrolled Synthesis of Highly Functionalized C_5-γ-Lactols

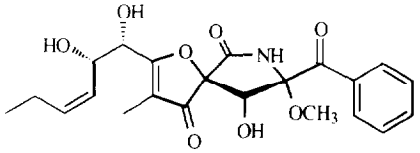
Zhuang Su and Christoph Tamm*

Institut für Organische Chemie der Universität, St. Johanns-Ring 19, 4056 Basel, Switzerland

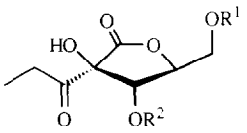
Abstract: Starting with the protected hydroxyaldehyde **5** the two epimeric hydroxy-γ-lactols were synthesized as intermediates for the stereocontrolled synthesis of pseurotin A (**1**). For further differentiation of the various OH groups the carbonated γ-lactol **14** was synthesized as well.

In the preceding communication[1] we have described the synthesis of the γ-lactone **2** which is a key intermediate in our approach to the total synthesis of pseurotin A (**1**), a secondary metabolite of *Pseudorotium ovalis* **Stolk**.

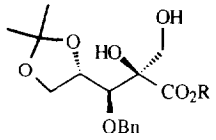
Scheme 1



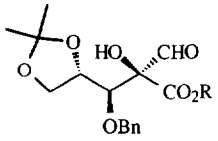
Pseurotin A (**1**)



2



3

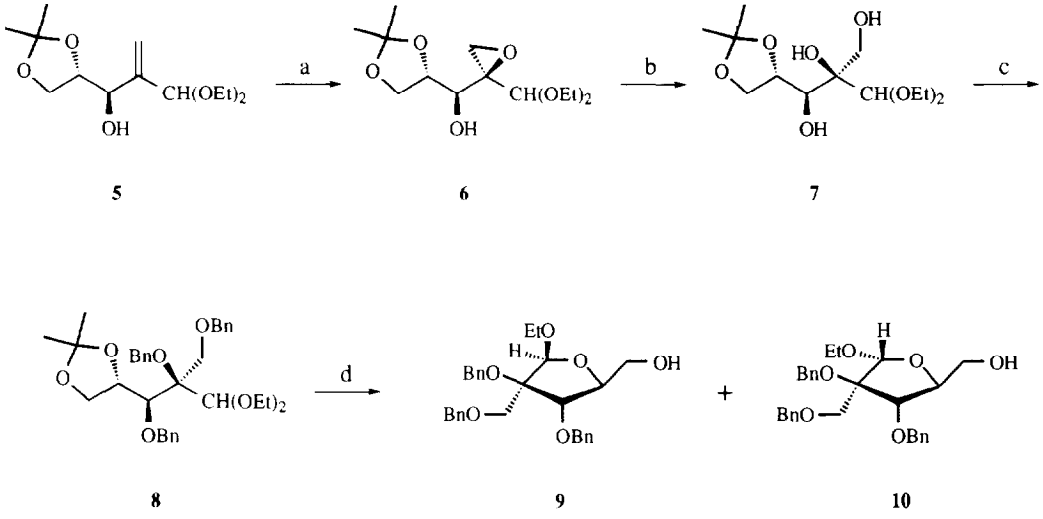


4

In the ten step synthesis one important reaction, the selective oxidation of the α,β-dihydroxy ester **3** to the α-hydroxy-α-formylester **4** which was required for a subsequent chain extension by a *Grignard* reaction, proved to be experimentally critical because of the instability of **4**. In order to overcome this difficulty we have synthesized new C_5-γ-lactols which represent more advanced and suitably functionalized intermediates for the stereocontrolled synthesis of γ-lactone **2**.

Results and Discussion. The protected C_6-hydroxyaldehyde **5**[1] served as starting material. It had been prepared from (S)-glyceraldehyde[2] and diethoxybromopropene[3]. *Sharpless* oxidation[4] of the allylic alcohol **5** using the conditions of *Depezay* and *Merrer*[5] afforded the epoxide **6** (yield 70%) as the only stereoisomer, the second centre of chirality at C(2) being introduced stereospecifically (*Scheme 2*). Cleavage of the epoxide **6** with aqueous NaOH afforded the triol **7**. Subsequent treatment of the latter with more than 3 equiv. benzyl bromide yielded the fully protected compound **8**. After treatment of **8** with HCl the epimeric hydroxy-γ-lactols **9** and **10** were obtained in a ratio of 1:1.

Scheme 2



5 **6** **7**

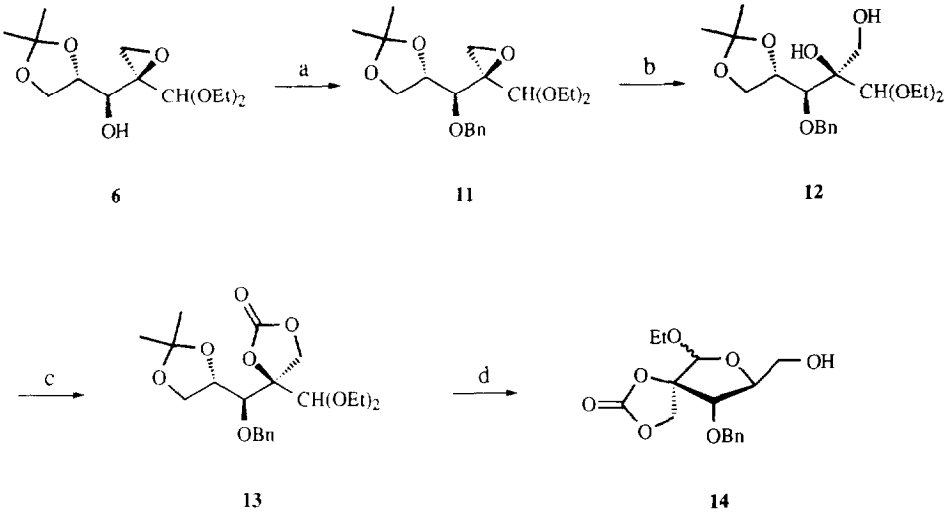
8 **9** **10**

a) $VO(acac)_2$/*t*-BuOOH/C_6H_6 ; b) NaOH/90° ; c) $C_6H_5CH_2Br$/KOH/DMSO ; d) HCl/THF

The ^{1}H-NMR data demonstrated clearly that no δ-lactols had been formed. The substituted γ-lactols **9** and **10** permitted the smooth preparation of the desired highly functionalized γ-lactone **2**. For the further differentiation of the various OH groups the secondary hydroxy group of the epoxide **6** was protected by the benzyl group (*Scheme 3*). The benzyl ether **11** obtained was treated with KOH/DMSO at 100°. Both hydroxy groups of the glycol **12** obtained were protected by treatment with trichloromethylchloroformate in dioxane at 60° using charcoal as catalyst[6]. The final cyclization of the carbonate **13** to the anticipated γ-lactol **14** was achieved in excellent

yield (85%) by treatment with conc. HCl/THF. Thus the problem of the selective protection of the various hydroxyl groups required for the subsequent synthetic work has been solved in a very satisfactory manner. Both compounds, the diol **12** as well as the carbonated γ-lactol **14**, which were synthesized for the first time, are promising building blocks not only for the synthesis of pseurotin A (**1**) but also for other complex natural products.

Scheme 3



a) $C_6H_5CH_2Br$/NaH/DMSO ; b) KOH/DMSO ; c) CCl_3OCOCl/py/dioxane/C ; d) HCl/THF

EXPERIMENTAL PART

General. Moisture-sensitive reactions were carried out in flame-dried glass ware under argon or N_2. Organic extracts were dried (Na_2SO_4) and evaporated below 40°. Analytical samples were dried overnight under reduced pressure or over P_2O_5. TLC: silica gel *60 F254 (Merck)*. Detection with UV light, iodine, 10% H_2SO_4 in MeOH or a $KMnO_4$ solution (2.0 g $KMnO_4$, 4.0 g Na_2CO_3, 100 ml H_2O). Column chromatography (CC): silica gel 60 (0.063-0.200 mm, *Merck* or *Chemische Fabrik Uetikon*). IR: *Perkin-Elmer-781* IR spectrometer. NMR: *Varian Gemini-300* (^1H, 300 MHz; ^{13}C, 75 MHz), *Varian VXR-400* (^1H, 400 MHz; ^{13}C, 101 MHz). Chemical shifts in ppm downfield from internal TMS. MS: *VG-70-250* spectrometer (CI with NH_3).

(1'S,2'S,2R)-2-(Diethoxymethyl)-2-{1'-hydroxy-2',3'-[(1-methylethylidene)dioxy]propyl}oxirane (**6**). To a stirred solution of **5** (99 mg; 0.38 mmol) in anhyd. benzene (5 ml) $VO(acac)_2$ (5 mg) was added at r.t. After carefully adding a solution of tert. butylperoxide in toluene (3M, 0.37 ml) the mixture was stirred overnight under

argon. After diluting with aq. $NaHCO_3$ (20 ml) the reaction mixture was extracted with ether and dried (Na_2SO_4). Removal of the solvent, followed by flash chromatography (silica, petroleum ether/ethyl acetate 84:16) afforded **6** (73 mg; 70%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.15-1.25 (*m*, 6H, $CH(OCH_2CH_3)_2$); 1.33, 1.40 (2*s*, 6H, $C(CH_3)_2$); 2.77 (*d*, 1H, *J* = 2.6, HO-C(1')); 2.87 (*d*, 1H, *J* = 5.0, H^A-C(3)); 2.95 (*d*, 1H, *J* = 5.0, H^B-C(3)); 3.48-3.63 (*m*, 2H, OCH_2CH_3); 3.63-3.82 (*m*, 2H, OCH_2CH_3); 3.90-4.10 (*m*, 4H, H-C(1'), H-C(2'), $H_2C(3')$); 4.54 (*s*, 1H, $CH(OEt)_2$). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 14.9; 25.2; 26.2; 47.0; 59.3; 64.2; 66.4; 69.5; 75.1; 102.9; 109.3. IR (film): υ 3480; 2980; 2930; 2880; 1450; 1380; 1370; 1250; 1210; 1150; 1110; 1060; 850 cm^{-1}. MS (CI): m/z 294 ([M+NH_4]$^+$); 248; 231; 202; 87; 58.

(2R,3S,4S)-2-(Diethoxymethyl)-4,5-[(1-methylethylidene)dioxy]pentane-1,2,3-triol (**7**). A solution of oxirane **6** (0.53 g; 1.92 mmol) in 1M NaOH (10 ml) was stirred for 1.5 h at 90°. After neutralizing, the mixture was extracted with CH_2Cl_2 and the organic extracts were dried (Na_2SO_4). Removal of the solvent, followed by flash chromatography (silica, petroleum ether/ethyl acetate 65:35) gave the desired triol **8** (0.49 g; 85%). IR (film): υ 3450; 2980; 2930; 2890; 1450; 1370; 1250; 1210; 1110; 1070; 920; 800; 740 cm^{-1}.

(2R,3S,4S)-2-(Diethoxymethyl)-4,5-[(1-methylethylidene)dioxy]-1,2,3-tri(benzyloxy)pentane (**8**). A mixture of triol **7** (0.47 g; 1.6 mmol) and KOH (0.28 g; 5 mmol) in anhyd. DMSO (17 ml) was stirred for 1 h. After adding dropwise benzyl bromide (958 mg; 5.6 mmol) the mixture was stirred overnight at r.t. Neutralizing, extraction with ether and drying (Na_2SO_4) gave, after flash chromatography (silica, petroleum ether/ethyl acetate 93:7), pure **8** (632 mg; 70%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.18 (2*t*, 6H, *J* = 7.0, $CH(OCH_2CH_3)_2$); 1.31, 1.41 (2*s*, 6H, $C(CH_3)_2$); 3.43-3.53 (*m*, 2H, OCH_2CH_3); 3.75 (2*q*, 2H, *J* = 9.1, OCH_2CH_3); 3.82 (AB, 1H, J_{AB} = 10.7, H^A-C(1)); 3.92 (*t*, 1H, *J* = 7.5, H^A-C(5)); 3.94 (AB, 1H, J_{AB} = 10.6, H^B-C(1)); 4.11 (*t*, 1H, *J* = 7.3, H^B-C(5)); 4.36 (*d*, 1H, *J* = 1, H-C(3)); 4.50 (*s*, 2H, OCH_2Ph); 4.61 (AB, 1H, J_{AB} = 11.4, OCH^APh); 4.71 (*s*, 1H, $CH(OEt)_2$); 4.77 (AB, 1H, J_{AB} = 11.4, OCH^BPh); 4.82 (AB, 1H, J_{AB} = 11.5, OCH^APh); 4.87 (*dt*, 1H, *J* = 7.0, 1.0, H-C(4)); 5.01 (AB, 1H, J_{AB} = 11.4, OCH^BPh); 7.20-7.40 (*m*, 15H, phenyl). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 15.5 (2); 24.5; 26.4; 64.9; 65.4; 65.7; 66.5; 68.4; 73.5; 75.3; 77.2; 80.7; 82.1; 104.5; 107.0; 126.9; 127.1 (3); 127.2; 127.5 (2); 128.0 (3); 128.1; 128.3; 138.2; 139.4; 139.8. IR (film): υ 3080; 3060; 3020; 2960; 2920; 2860; 1490; 1450; 1370; 1255; 1200; 1150; 1110; 1050; 900; 860; 800; 725; 690 cm^{-1}.

(2S,3R,4S,5S)-3-(Benzyloxymethyl)-3,4-di(benzyloxy)-2-ethoxy-5-hydroxymethyltetrahydrofuran (**9**) and *(2R,3R,4S,5S)-3-(Benzyloxymethyl)-3,4-di(benzyloxy)-2-ethoxy-5-hydroxymethyltetrahydrofuran* (**10**). A mixture of **8** (29 mg; 0.05 mmol) and conc. HCl (2 drops) in THF (2 ml) was stirred at r.t. under argon for 1.5 h. After neutralizing the mixture was extracted with ether, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (silica) to give the two diastereoisomers **9** and **10** (10 mg each; 69%). **9***: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.25 (*t*, 3H, *J* = 7.1, OCH_2CH_3); 2.40 (*dd*, 1H, *J* = 8.0, 4.0, CH_2OH); 3.54-3.64 (*m*, 2H, CH^AOH, OCH^ACH_3); 3.74 (*dd*, 1H, *J* = 3.3, 11.9, CH^BOH); 3.85-3.89 (*m*, 1H, OCH^BCH_3); 3.89 (AB, 1H, J_{AB} = 11.7, C(3)-CH^AOPh); 3.97 (AB, 1H, J_{AB} = 11.1, C(3)-CH^BOPh); 3.98-4.04 (*m*, 1H, H-C(5)); 4.43 (*d*, 1H, *J* = 7.0, H-C(4)); 4.53 (AB, 1H, J_{AB} = 11.7, OCH^APh); 4.56 (*s*, 2H, OCH_2Ph); 4.67 (AB, 1H, J_{AB} = 11.7, OCH^BPh); 4.75 (AB, 1H, J_{AB} = 11.7, OCH^APh); 4.89 (AB, 1H, J_{AB} = 11.7, OCH^BPh); 5.31 (*s*, 1H, H-C(2)); 7.20-7.40 (*m*, 15H, phenyl). ^{13}C-NMR (101 MHz, $CDCl_3$): δ 15.3; 63.3; 64.7; 68.6; 71.1; 73.0; 73.8; 82.1; 82.8; 86.1; 102.2; 126.3; 127.2 (2); 127.6; 127.7; 127.8 (2); 127.9 (2); 128.1; 128.2; 128.3; 128.4; 138.0 (2); 139.5. IR (film): υ 3460; 3080; 3060; 3020; 2970; 2920; 2860; 1480; 1450; 1360; 1310; 1200; 1150; 1100; 1040; 900; 840; 730; 690 cm^{-1}.

10*: ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.22 (*t*, 3H, *J* = 7.1, OCH_2CH_3); 2.05 (*t*, 1H, *J* = 5.7, CH_2OH); 3.42-3.49 (*m*, 1H, CH^AOH); 3.52-3.59 (*m*, 1H, OCH^ACH_3); 3.65-3.72 (*m*, 1H, CH^BOH); 3.75-3.85 (*m*, 1H, OCH^BCH_3); 3.89 (*d*, 1H, *J* = 3.8, H-C(4)); 3.96 (*d*, 2H, *J* = 3.4, OCH_2Ph); 4.20 (*ddd*, 1H, *J* = 3.3, 3.8, 7.1, H-C(5)); 4.53 (*d*, 2H, J = 3.7, OCH_2Ph); 4.57 (AB, 1H, J_{AB} = 12.3, OCH^APh); 4.59 (*d*, 2H, *J* = 2.4, OCH_2Ph); 4.64 (AB, 1H, J_{AB} = 12.3, OCH^BPh); 5.11 (*s*, 1H, H-C(2)); 7.23-7.48 (*m*, 15H, phenyl). IR (film): υ 3460; 3080; 3060; 3020; 2960; 2920; 2860; 1480; 1450; 1360; 1200; 1150; 1100; 1030; 900; 840; 730; 690 cm^{-1}. * may be reversed

(2R,1'S,2'S)-2-(Diethoxymethyl)-2-{1'-benzyloxy-2',3'-[(1-methylethylidene)dioxy]propy}oxirane (**11**). To a solution of **6** (89 mg; 0.32 mmol) in dry DMSO (6 ml) sodium hydride (20 mg; 1.5 eq.) was carefully added under argon. After stirring for 45 min benzyl bromide (82 mg; 0.479 mmol) was added dropwise and the mixture sirred overnight. The solution was poured in ice/water and neutralized, extracted with ether and dried (Na_2SO_4). Removal of the solvent, followed by flash chromatography (silica, petroleum ether/ethyl acetate 90:10) yielded pure **11** (94 mg; 80%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.15-1.25 (2*t*, 6H, 2 OCH_2CH_3); 1.35, 1.41 (2*s*, 6H, $C(CH_3)_2$); 2.82 (*s*, 2H, $H_2C(3)$); 3.45-3.76 (*m*, 4H, 2 OCH_2CH_3); 3.88-4.04 (*m*, 2H, $H_2C(3')$); 4.10 (*d*, 1H, *J* = 4.5, H-C(1')); 4.31 (*ddd*, 1H, *J* = 4.5, 6.7, 11.3, H-C(2')); 4.59 (*s*, 1H, $CH(OEt)_2$); 4.71 (*s*, 2H, OCH_2Ph); 7.25-7.38 (*m*, 5H, phenyl). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 15.3 (2); 25.5; 26.4; 46.0; 59.8; 64.1; 64.4; 65.9; 75.2; 75.9; 76.5; 102.1; 109.2; 128.0; 128.4; 128.7; 138.9. IR (film): υ 3060; 3030; 2980; 2930; 2880; 1450; 1380; 1370; 1250; 1210; 1150; 1110; 1065; 850; 730; 690 cm^{-1}.

(2R,3S,4S)-3-Benzyloxy-2-(diethoxymethyl)-4,5-[(1-methylethylidene)dioxy]pentane-1,2-diol (**12**). Under argon 3M KOH (3 ml) was added to a solution of **11** (75 mg; 0.2 mmol) in DMSO (7 ml) at 100°. After refluxing for 8 h the mixture was cooled to r.t., neutralized and extracted with ether. Drying (Na_2SO_4), concentration *in vacuo* and flash chromatography (silica) of the crude product afforded **12** (59 mg; 75%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.15-1.25 (2*t*, 6H, 2 OCH_2CH_3); 1.38, 1.44 (2*s*, 6H, $C(CH_3)_2$); 2.88 (*m*, 1H, HO-C(1)); 2.91 (*s*, 1H, HO-C(2)); 3.26-3.40 (*m*, 1H, OCH^ACH_3); 3.60-3.86 (*m*, 5H, $H_2C(1)$, OCH^BCH_3, OCH_2CH_3); 4.04 (*d*, 1H, *J* = 2.8, H-C(3)); 4.04-4.14 (*m*, 2H, $H_2C(5)$); 4.47 (*dt*, 1H, *J* = 7.2, 2.8, H-C(4)); 4.63 (AB, 1H, J_{AB} = 11.3, OCH^APh); 4.64 (*s*, 1H, $CH(OEt)_2$); 4.97 (AB, 1H, J_{AB} = 11.3, OCH^BPh); 7.26-7.38 (*m*, 5H, phenyl). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 15.1; 15.3; 24.9; 26.2; 62.9; 65.0; 65.3; 67.5; 75.4; 75.8; 76.5; 78.3; 106.2; 107.9; 127.8; 127.9; 128.5; 138.7. IR (film): υ 3450; 3100; 3070; 3040; 2980; 2940; 2900; 1380; 1370; 1260; 1210; 1110; 1060; 865; 840; 735; 700 cm^{-1}.

(1'S,2'S,3R)-3-{1'-Benzyloxy-2',3'-[(1-methylethylidene)dioxy]propy}-3-(diethoxymethyl) ethylene carbonate (**13**). Pyridine (75 µl) and activated charcoal (50 mg) were added under argon to a solution of **12** (23 mg; 0.06 mmol) in dioxane (3 ml). After stirring for 5 min at r.t. trichloromethyl chloroformate (57 mg; 0.29 mmol) was added. The mixture was heated to 50-60° for 1.5 h, followed by stirring overnight at r.t. After filtration through Celite and silica the solvents were removed and the residue was purified by flash chromatography to give **13** (22 mg; 89%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.21 (2*t*, 6H, 2 OCH_2CH_3); 1.35, 1.43 (2*s*, 6H, $C(CH_3)_2$); 3.34-3.45 (*m*, 1H, OCH^ACH_3); 3.65-3.88 (*m*, 3H, OCH^BCH_3, OCH_2CH_3); 3.93 (*d*, 1H, *J* = 4.4, H-C(1')); 4.06-4.16 (*m*, 2H, $H_2C(3')$); 4.28 (AB, 1H, J_{AB} = 8.5, H^A-C(4)); 4.29-4.36 (*m*, 1H, H-C(2')); 4.58 (AB, 1H, J_{AB} = 8.7, H^B-C(4)); 4.64 (AB, 1H, J_{AB} = 11.0, OCH^APh); 4.78 (s, 1H, $CH(OEt)_2$); 4.84 (AB, 1H, J_{AB} = 11.0, OCH^BPh); 7.30-7.40 (*m*, 5H, phenyl). IR (film): υ 3090; 3060; 3030; 2980; 2920; 1815; 1450; 1380; 1270; 1250; 1210; 1160; 1090; 1070; 850; 765; 735; 695 cm^{-1}.

(5R,6RS,8S,9S)-6-Ethoxy-8-hydroxymethyl-2-oxo-1,3,7-trioxaspiro[4.4]nonane (**14**). A mixture of **13** (10 mg; 0.024 mmol) and conc. HCl (3 drops) in THF (1 ml) was stirred under argon for 2 h. After neutralizing the reaction mixture was extracted with ether. The extracts were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash chromatography. **14** (6.7 mg, 85%) was obtained as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.27 (*t*, 3H, *J* = 7.3, OCH_2CH_3); 2.05 (*t*, 1H, CH_2-O*H*); 3.50-3.55 (*m*, 1H, C*H*-OH); 3.60-3.75 (*m*, 2H, OCH_2CH_3); 3.78-3.88 (*m*, 1H, OCH^ACH_3); 3.88-3.95 (*m*, 1H, H-C(8)); 4.25 (AB, 1H, J_{AB} = 8.8, H^A-C(4)); 4.57 (*d*, 1H, J = 6.6, H-C(9)); 4.62 (AB, 1H, J_{AB} = 11.5, OCH^APh); 4.69 (AB, 1H, J_{AB} = 11.5, OCH^BPh); 4.82 (*s*, 1H, H-C(6)); 4.88 (AB, 1H, J_{AB} = 8.7, H^B-C(4)); 7.30-7.40 (*m*, 5H, phenyl). IR (film): υ 3460; 3090; 3030; 2970; 2930; 1815; 1450; 1380; 1260; 1200; 1160; 1100; 1060; 770; 730; 700 cm^{-1}.

Acknowledgement: Financial support of these investigations by the *Swiss National Science Foundation* is gratefully acknowledged.

REFERENCES

1. Part 3: Su, Z.; Tamm, Ch. *Helv. Chim. Acta* **1995**, 78, *in press.*
2. Hubschwerlen, Ch. *Synthesis* **1986**, 962.
3. Smith III., A. B.; Levenberg, P. A.; Jerris, P. J.; Scarborough, Jr., R. M.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, 103, 1505.
4. Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, 12, 63.
5. Depezay, J. C.; Merrer, Y. L. *Tetrahedron Lett.* **1978**, 2869; *iidem*, *Carbohydr. Res.* **1980**, 83, 273.
6. Katakai, R.; Lizuka, Y. *J. Org. Chem.* **1985**, 50, 715.

(*Received in Germany* 19 *July* 1995; *accepted* 16 *August* 1995)