Synthesis of an Optically Active α-Methylene Lactone Starting from Isosaccharinic Acid

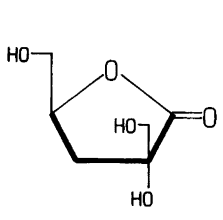
Klaus Bock,* Ines Maya Castilla, Inge Lundt and Christian Pedersen

Department of Organic Chemistry, The Technical University of Denmark, Building 201, DK-2800 Lyngby, Denmark

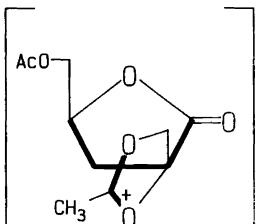
Bock, K., Castilla, I. M., Lundt, I. and Pedersen, C., 1987. Synthesis of an Optically Active α-Methylene Lactone Starting from Isosaccharinic Acid. – Acta Chem. Scand. B 41: 13–17.

Treatment of isosaccharinic acid, *1*, with hydrogen bromide in acetic acid led to a mixture of bromolactones, *3* and *4*, which was converted to (*S*)-4-acetoxymethyl-α-methylene-γ-butyrolactone, *7*, in high yield. Saturation of the double bound gave optically pure (2*S*, 4*S*)-4-acetoxymethyl-2-methyl-γ-butyrolactone, *6*, which was further converted to (*S*)-methylsuccinic acid, *10*, and (*S*)-α-methyl-γ-butyrolactone, *8*, in good yields. Treatment of the bromolactones *3* and *4* with strong base followed by esterification and acetylation gave methyl-4-*O*-acetyl-2-acetoxymethyl-2,5-anhydro-3-deoxy-D-*threo*-pentanoate, *11*, and the corresponding 1,4-lactone *12* in good yield.

The synthesis of α-methylene-γ-lactones has drawn considerable attention during the last decade due to the interesting biological activity of this type of compound, as discussed in recent reviews.[1,2] Numerous synthetic methods for the preparation of α-methylene-γ-lactones both from achiral[1-6] and from chiral[1,2,7-10] precursors have been published. In this publication, we present a simple preparation of optically pure (*S*)-4-acetoxymethyl-α-methylene-γ-butyrolactone, *7*, starting from the easily available isosaccharinic acid, *1*, and demonstrate that simple optically active compounds can be prepared in high yield from *7*.

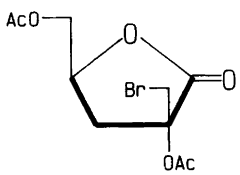


1

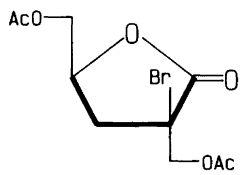


2

*To whom correspondence should be addressed.



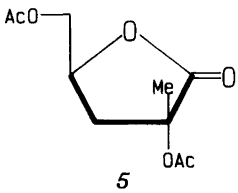
3



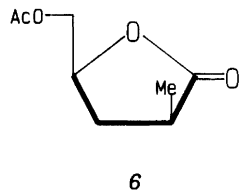
4

Results and discussion

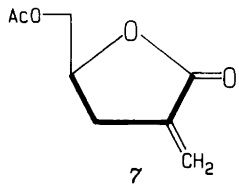
Treatment of isosaccharinic acid, *1*,[11] with hydrogen bromide in acetic acid (HBA) gave, presumably via the acetoxonium ion intermediate[12] *2*, a mixture of the acetoxybromo lactones *3* and *4* in a ratio of 9:2. The structures of *3* and *4* were determined primarily from their ^1H and ^{13}C NMR spectral data (see Experimental). Hydrogenolysis of the reaction mixture (H_2, Pd/C 5 %) in EtOAc with Et_3N as the acid acceptor yielded predominantly (40 % yield) the α-methyl lactone *5* which showed a singlet in the ^{13}C and ^1H NMR spectra at 24.8 ppm and δ 1.63, respectively. Furthermore, small amounts of (2*S*,4*S*)-4-acetoxymethyl-2-methyl-γ-butyrolactone, *6*, were isolated. This last product was presumably formed via the α-methylene lactone *7*. The stereoche-



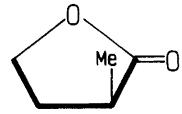
5



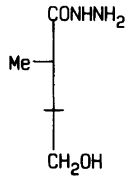
6



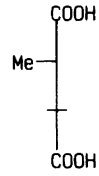
7



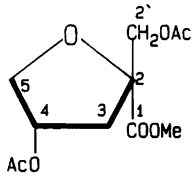
8



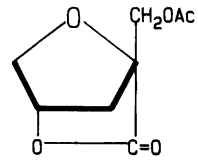
9



10



11



12

mistries of compounds *3* and *4* are proposed on the basis of reaction of the acetoxonium ion intermediate *2* with bromide ions.

The α-methylene lactone *7* could, however, be prepared in almost quantitative yield when the mixture of the bromides *3* and *4* was treated with Zn dust in $EtOH/H_2O$ containing a small amount of HCl. Since *7* is rather unstable, it was characterized only through its NMR parameters (^1H and ^{13}C) and optical rotation. Attempts to purify the compound by distillation or chromatography led in most cases to polymerised material. Hydrogenation of the double bond with hydrogen over palladium on carbon gave a high yield (92%) of the (2*S*, 4*S*)-4-acetoxymethyl-2-methyl-γ-butyrolactone *6* which could be characterized by all its physical parameters.

The optical purity of compounds *6* and *7* was proved by transformation of *6* to the known (*S*)-methylsuccinic acid, *10*, and to (*S*)-α-methyl-γ-butyrolactone, *8*. The α-methyl lactone *6* was hydrolysed with base, and after neutralization the free acid was oxidized with periodate to the aldehyde. The latter was immediately oxidized with permanganate to (*S*)-methylsuccinic acid, *10*, or reduced with sodium borohydride to (*S*)-α-methyl-γ-butyrolactone, *8*. The acid *10* had m.p. 108–112 °C and $[\alpha]_D^{20}$ −17.2°. The reported[13] values for (*R*)-methylsuccinic acid are m.p. 112 °C and $[\alpha]_D$ +16.88°, suggesting that the α-methylene lactone *7* and the α-methyl lactone *6* were optically pure. The (*S*)-α-methyl-γ-butyrolactone *8* was converted into its hydrazide *9* which had m.p. 115–117 °C and $[\alpha]_D$ +39.4° in $CHCl_3$ (*c* 0.125) and +42° in water. The reported values[14] for the enantiomeric compound are m.p. 116–117 °C and $[\alpha]_D$ −48.9° in chloroform (*c* 1.43). It was not possible to dissolve the compound in chloroform at the concentration given in Ref. 14. The highest concentration we could obtain was *c* = 0.125.

Treatment of the mixture of bromolactones *3* and *4* with excess base followed by esterification and acetylation gave the tetrahydrofuran derivative *11* in 30% yield, together with the corresponding lactone *12* in 18% yield. Isolation of the crystalline lactone *12* proved that the stereochemistry at C-2 and C-4 in *11* and *12* is as shown. This was also demonstrated by a ^1H NMR nuclear Overhauser enhancement (NOE) experiment on compound *11*, since irradiation of H-4 gave NOE on the two H-2′ protons and vice versa.

Experimental

Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 241 polarimeter. NMR spectra were obtained on Bruker WH-90 and AM-500 NMR instruments. The spectra of protected compounds were measured in $CDCl_3$. Unprotected compounds were measured in D_2O relative to the internal reference: acetone (δ 2.22) for ^1H NMR spectra and dioxane (67.4 ppm) for ^{13}C NMR spectra. Microanalyses were performed by Novo Microanalytical Laboratory, Copenhagen, Denmark. TLC was performed on silica gel-coated plates (Merck

F-254), the compounds being visualised by charring with sulfuric acid.

2,5-Di-O-acetyl-2-bromo-2-deoxy-α-D-isosaccharino-1,4-lactone (3). Hydrogen bromide in acetic acid (33 %, 75 ml) was added to calcium α-D-isosaccharinate, *1*,[11] (10 g) and the mixture stirred for 3 h at room temp. The mixture was then diluted with $CHCl_3$, washed with water, dried ($MgSO_4$) and evaporated to give 11.7 g (78 %) of a syrup which consisted of the bromolactone *3* and its isomer *4* in a 9:2 ratio as determined from a ^{13}C NMR spectrum. Purification by preparative TLC using EtOAc/pentane (1:2) as the eluant gave *3* as a syrup: $[\alpha]_D^{20}$ +86.1° (*c* 1, $CHCl_3$). ^1H NMR data for *3* (500 MHz, $CDCl_3$): δ 5.03 (1H, H-4), 4.36 (1H, H-5; J_{54} 2.5 Hz, $J_{55'}$ 12.5 Hz), 4.23 (1H, H-5′; $J_{5'4}$ 5.0 Hz), 3.73 (1H, H-2′; $J_{2'2''}$ 10.0 Hz), 3.62 (1H, H-2″), 2.57 (1H, H-3; J_{34} 8.7 Hz, $J_{33'}$ 15.0 Hz), 2.52 (1H, H-3′; $J_{3'4}$ 6.2 Hz), 2.18 (3H, OAc) and 2.10 ppm (3H, OAc). ^{13}C NMR data for *3* ($CDCl_3$): 170.4 (C-1), 79.1 (C-2), 74.8 (C-4), 64.5 (C-5), 35.0, 33.5 (C-2′, C-3) and 20.5 ppm (OAc). The next fraction gave *4* also as a syrup with the following ^1H NMR parameters ($CDCl_3$): 4.84 (1H, H-4), 4.52 (1H, H-2′; $J_{22'}$ 10.0 Hz), 4.48 (1H, H-2″), 4.41 (1H, H-5; J_{54} 6.2 Hz, $J_{55'}$ 12.5 Hz), 4.23 (1H, H-5′), 3.06 (1H, H-3; J_{34} 8.7 Hz, $J_{33'}$ 15.0 Hz), 2.66 (1H, H-3′; $J_{3'4}$ 6.2 Hz), 2.14 (3H, OAc) and 2.08 (3H, OAc). ^{13}C NMR data for *4*: 171.3 (C-1), 75.3 (C-4), 66.9 (C-2′), 64.2 (C-5), 37.0 (C-3), 36.6 (C-2) and 20.7 ppm (OAc).

(2R, 4S)-2-O-Acetyl-4-acetoxymethyl-2-methyl-γ-butyrolactone (5). A solution of the bromolactones *3* and *4* (1 g) in EtOAc (20 ml) containing Et_3N (2 ml) was hydrogenated overnight with palladium on charcoal (0.3 g) at room temp. The mixture was filtered and concentrated, dissolved in CH_2Cl_2, washed with 1M HCl and water, dried ($MgSO_4$) and concentrated. The syrupy residue (0.5 g) was a mixture of *5* and *6* in a 1:0.7 ratio as seen from the ^1H NMR spectrum. Preparative TLC (1:2 EtOAc/hexane, 3 elutions) gave pure *5* (0.130 g, 40 %): $[\alpha]_D^{20}$ +64.2° (*c* 1.4, $CHCl_3$). Anal. $C_{10}H_{14}O_6$: C, H. ^1H NMR (500 MHz, $CDCl_3$): δ 4.95 (1H, H-4), 4.33 (1H, H-5; J_{54} 3.0 Hz, $J_{55'}$ 12.4 Hz), 4.13 (1H, H-5′; $J_{5'4}$ 4.9 Hz), 2.64 (1H, H-3; J_{34} 9.2 Hz, $J_{33'}$ 14.2 Hz), 2.14 (1H, H-3′; $J_{3'4}$ 6.1 Hz), 2.10 (6H, OAc) and 1.63 (3H, CH_3). ^{13}C NMR ($CDCl_3$): 170.4 (C-1), 77.1 (C-2), 74.1 (C-4), 64.7 (C-5), 35.8 (C-3), 24.8 (Me) and 20.6 ppm (OAc).

Characterization of *6* was carried out as described below.

(S)-4-Acetoxymethyl-2-C-methylene-γ-butyrolactone (7). To a solution of the bromodeoxylactones *3* and *4* (1 g) in EtOH (22 ml) was added zinc dust (8 g) and the mixture was stirred for 30 min at room temp. 4M HCl (1.2 ml) was then added and the stirring continued for 30 min. The Zn dust was filtered off and the filtrate concentrated to dryness. The residue was dissolved in CH_2Cl_2 and washed with 4M HCl and water. The extract was dried ($MgSO_4$) and concentrated to give a syrup (0.54 g, 80 %): $[\alpha]_D^{20}$ +56.3° (*c* 0.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 6.26 (1H, H-2′; J_{gem} 0 Hz), 5.69 (1H, H-2″), 4.77 (1H, H-4), 4.29 (1H, H-5; J_{54} 3.5 Hz, $J_{55'}$ 12.2 Hz), 4.19 (1H, H-5′; $J_{5'4}$ 5.4 Hz), 3.08 (1H, H-3; $J_{32'} = J_{32''}$ 3.0 Hz, J_{34} 8.4 Hz, $J_{33'}$ 17.2 Hz), 2.76 (1H, H-3′; $J_{3'2'} = J_{3'2''}$ 2.9 Hz, $J_{3'4}$ 5.4 Hz) and 2.08 (3H, OAc). ^{13}C NMR ($CDCl_3$): 170.6 (C-1), 133.5 (C-2), 122.6 (C-2′), 74.1 (C-4), 65.2 (C-5), 29.6 (C-3) and 20.6 ppm (OAc).

This compound was not sufficiently stable to obtain an elementary analysis.

(2S,4S)-4-Acetoxymethyl-2-methyl-γ-butyrolactone (6). A solution of *7* (0.64 g) in EtOAc (20 ml) was hydrogenated overnight with palladium on carbon. The mixture was filtered and the filtrate concentrated to give pure *6* as a liquid residue. Yield 0.60 g (92 % calculated from *5*, 74 % calculated from 1.4 g of *1*): $[\alpha]_D^{20}$ +43.6° (*c* 1.1, $CHCl_3$). Purification by preparative TLC (EtOAc/hexane, 1:2) gave an analytical sample with $[\alpha]_D^{20}$ +45.1° (*c* 0.7, $CHCl_3$). Anal. $C_8H_{12}O_4$: C, H. ^1H NMR (500 MHz, $CDCl_3$): δ 4.59 (1H, H-4), 4.33 (1H, H-5; J_{54} 3.0 Hz, $J_{55'}$ 12.6 Hz), 4.12 (1H, H-5′; $J_{5'4}$ 6.0 Hz), 2.72 (1H, H-2; $J_{2,Me}$ 7.2 Hz), 2.49 (1H, H-3; J_{32} 9.0 Hz, J_{34} 6.0 Hz, $J_{33'}$ 12.3 Hz), 1.81 (1H, H-3′; $J_{3'2}$ 12.3 Hz, $J_{3'3}$ 9.8 Hz), 2.11 (3H, OAc) and 1.33 (3H, CH_3). ^{13}C NMR ($CDCl_3$): 178.6 (C-1), 75.3 (C-4), 65.0 (C-5), 35.2, 32.7 (C-2, C-3), 20.7 (OAc) and 12.2 ppm (Me).

Hydrazide of (S)-*4-hydroxy-2-methylbutyric acid* (9). Compound *6* (0.77 g) was dissolved in water containing KOH (0.67 g) and the solution kept at room temperature for 24 h. The reaction mixture

was neutralized with 4M HCl and $NaIO_4$ (0.95 g) added in the dark. After 5 h, water was removed, ethanol added and inorganic salts filtered off. The filtrate was concentrated and the residue dissolved in water (8 ml) and EtOH (5 ml), cooled in ice and stirred with Amberlite IR-120 (H^+) resin. Sodium borohydride (170 mg, 1 mol. equiv.) was added in portions at such a rate that the pH did not rise above 5. After the addition was complete (~15 min), stirring was continued for an additional 30 min. The resin was collected and washed with MeOH, and the combined filtrates and washings were concentrated. MeOH was distilled twice from the residue to remove boric acid. The residue was dissolved in water, 4M HCl added (pH 2) and the solution kept overnight at room temp. It was then extracted with CH_2Cl_2 (3×20 ml) and the extract concentrated to give *8* as a liquid residue (0.42 g, 95%). ^1H NMR (90 MHz, $CDCl_3$): δ 4.50–4.00 (2H, H-4, H-4′), 2.90–1.60 (3H, H-3, H-3′, H-2), 1.30 (3H, CH_3).

Crude *8* (0.42 g) was dissolved in MeOH (2.5 ml), hydrazine hydrate (0.5 ml) in water (0.12 ml) was added and the solution was kept at 5 °C overnight. Concentration to a small volume gave the hydrazide *9* as a crystalline material (0.25 g, 50%); m.p. 105–107 °C. Recrystallization from EtOAc gave *9*, with m.p. 116–117 °C; $[\alpha]_D^{20}$ +39.4° (*c* 0.125, $CHCl_3$) [Lit.[14] m.p. 116–117 °C, $[\alpha]_D^{20}$ −48.9° (*c* 1.43, $CHCl_3$)], $[\alpha]_D^{20}$ +42° (*c* 0.7, water). ^1H NMR (500 MHz, D_2O): δ 3.94 (1H, H-4; $J_{43} = J_{43'}$ 7.0 Hz), 3.87 (1H, H-4′; $J_{4'3} = J_{4'3'}$ 6.5 Hz, $J_{4'4}$ 11.0 Hz), 2.79 (1H, H-2; $J_{2,Me}$ 7.0 Hz), 2.13 (1H, H-3; J_{32} 8.5 Hz, $J_{33'}$ 12.5 Hz), 1.97 (1H, H-3′; $J_{3'2}$ 7.0 Hz) and 1.45 (3H, CH_3). ^{13}C NMR (D_2O): 174 (C-1), 60.2 (C-4), 36.3 (C-2, C-3) and 17.6 ppm (Me).

(S)-*Methylsuccinic acid* (10). Compound *6* (0.66 g) was treated with KOH and $NaIO_4$ as mentioned above. The residue obtained was oxidized with a solution of $KMnO_4$ (0.81 g) in water (3 ml). After removing the MnO_2 by filtration, Amberlite IR-120 (H^+) resin was added (6 ml). The resin was filtered off and the water evaporated to give a solid residue (0.47 g, 88%); m.p. 102 °C. Recrystallization from water gave *10*, with m.p. 108–112 °C, $[\alpha]_D^{20}$ −17.2° (*c* 0.9, EtOH) [Lit.[13] m.p. 112 °C, $[\alpha]_D^{20}$ +16.88° (*c* 2.16, EtOH) for (*R*)-methylsuccinic acid]. ^1H NMR (500 MHz, D_2O): δ 2.89 (1H, H-2; $J_{2,Me}$ 7.2 Hz), 2.70 (1H, H-3; J_{32} 8.9 Hz, $J_{33'}$ 17.0 Hz), 2.58 (1H, H-3′; $J_{3'2}$ 5.3 Hz) and 1.22 ppm (3H, Me).

*Methyl 4-O-acetyl-2-acetoxymethyl-2,5-anhydro-3-deoxy-D-*threo*-pentanoate* (11) *and 2-acetoxymethyl-2,5-anhydro-3-deoxy-D-*threo*-pentono-1,4-lactone* (12). The mixture of bromodeoxylactones *3* and *4* (0.9 g) was dissolved in a solution of KOH (0.85 g) in water (15 ml) and boiled for 1 h. After neutralisation with pyridine and evaporation to dryness, the residue was acetylated with pyridine/acetic anhydride for 2 h. Working up as usual gave a syrupy residue (0.5 g, 63%) which was crystallized from EtOH to give crystalline *12* (60 mg, 11%); m.p. 101–103, $[\alpha]_D^{20}$ +139.6° (*c* 1.3, $CHCl_3$). Anal. $C_8H_{10}O_5$: C, H. ^1H NMR (500 MHz, $CDCl_3$): δ 5.16 (1H, H-4; $J_{45} = J_{45'}$ 0 Hz), 4.58 (1H, H-2′), 4.55 (1H, H-2″; $J_{2'2''}$ 12.6 Hz), 4.11 (1H, H-5), 3.91 (1H, H-5′; $J_{55'}$ 8.4 Hz), 2.22 (1H, H-3; J_{34} 2.4 Hz, $J_{35'}$ 1.2 Hz), 2.11 (3H, OAc) and 2.07 (1H, H-3′; $J_{3'3}$ 10.8 Hz, $J_{3'4}$ 0 Hz). ^{13}C NMR ($CDCl_3$): 170 (C-1), 82.3 (C-2), 78.9 (C-4), 70.9 (C-2′), 59.3 (C-5), 41.1 (C-3) and 20.7 ppm (Me).

The syrupy compound *11* was obtained pure from the mother liquor by preparative TLC (EtOAc/hexane, 1:2, 3 elutions). Yield 0.2 g (30%), $[\alpha]_D^{20}$ −4.9° (*c* 0.86, $CHCl_3$). Anal. $C_{11}H_{16}O_7$: C, H. ^1H NMR (500 MHz, $CDCl_3$): δ 5.30 (1H, H-4), 4.40 (1H, H-2′), 4.24 (1H, H-2″; $J_{2'2''}$ 11.5 Hz), 4.23 (1H, H-5; J_{54} 1.0 Hz) 4.10 (1H, H-5′; $J_{5'5}$ 10 Hz, $J_{5'4}$ 5.5 Hz), 3.80 (3H, Me), 2.51 (1H, H-3; J_{34} 0 Hz), 2.25 (1H, H-3′; $J_{3'3}$ 9.0 Hz, $J_{3'4}$ 6 Hz) and 2.08, 2.03 (OAc). ^{13}C NMR ($CDCl_3$): 172.2 (C-1), 84.7 (C-2), 74.2, 73.7 (C-2′, C-4), 66.8 (C-5), 52.7 (O–Me), 39.0 (C-3) and 20.9, 20.7 ppm (OAc).

The preparative TLC furthermore yielded 28 mg of compound *12*, bringing the total yield of *12* to 98 mg (18%).

Acknowledgements. The Fourier transform NMR spectrometers were provided by the Danish Natural Science Research Council and the Carlsberg Foundation. One of us (I.M.C.) wishes to thank the Danish Ministry of Foreign Exchange for a grant to work in Denmark.

References

1. Hoffmann, H. M. R. and Rabe, J. *Angew. Chem. 97* (1985) 96.
2. Petragnani, N., Ferraz, H. M. C. and Silva, G. V. J. *Synthesis* (1986) 157.
3. Okuda, Y., Nakatsukasa, S., Oshima, K. and Nozaki, H. *Chem. Lett.* (1985) 481.
4. Haider, A. *Synthesis* (1985) 271.
5. Murray, A. W. and Reid, R. G. *J. Chem. Soc., Chem. Commun.* (1984) 132.
6. Saimoto, H., Nishio, K., Yamamoto, H., Shinoda, M., Hiyama, T. and Nozaki, H. *Bull. Chem. Soc. Jpn. 56* (1983) 3093.
7. Bravo, P., Resnati, G. and Viani, F. *Tetrahedron Lett. 26* (1985) 2913.
8. Papageorgiou, C. and Benezra, C. *J. Org. Chem. 50* (1985) 157.
9. Martin, L. D. and Stille, J. K. *J. Org. Chem. 47* (1982) 3630.
10. Nair, V. and Sinhababu, A. K. *J. Org. Chem. 45* (1980) 1893.
11. Whistler, R. L. and BeMiller, J. N. *Methods Carbohydr. Chem. 2* (1963) 477.
12. Bock, K., Lundt, I. and Pedersen, C. *Carbohydr. Res. 104* (1982) 79.
13. Berner, E. and Leonardsen, R. *Justus Liebigs Ann. Chem. 538* (1939) 1.
14. Seidel, C. F. and Stoll, M. *Helv. Chim. Acta 42* (1959) 1830.

Received June 25, 1986.