Preparation of Chiral Lactones from L-Lactic Acid via (*S*)-γ-Methyltetronic Acid

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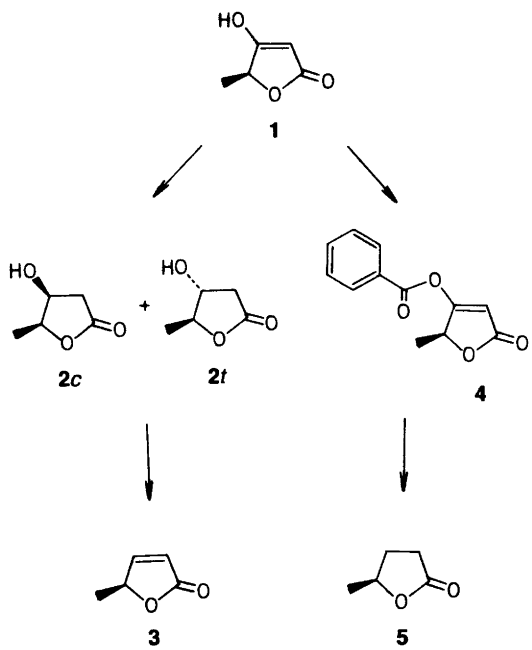
(*S*)-γ-Methyltetronic acid (**1**), prepared in two high-yield steps from ethyl L-lactate, has been reduced to chiral building blocks. Reduction with ammonia–borane gave mainly the *trans* alcohol **2***t*. A new route to butenolide **3** led to a higher optical purity of **3** than was attained by five previous routes. An efficient procedure provided the saturated lactone **5** in two steps from **1**.

Several natural products are derivatives of tetronic acid, i.e. 4-hydroxy-2(5*H*)-furanone, and a variety of techniques for the synthesis of tetronic acids have been developed.[1] However, only a few of these techniques permit the preparation of optically active C–5 (γ-) monosubstituted compounds. We found that lithium bis(trimethylsilyl)amide brings about a facile ring-closure of ethyl 2(*S*)-acetoxypropanoate with little or no racemisation, and crystalline (*S*)-γ-methyltetronic acid (**1**) was thus obtained from ethyl (*S*)-lactate in two steps in an overall yield of about 80 %.[2]

Carbon chain elongation of α-hydroxy acids to tetronic acids, and subsequent reduction producing new asymmetric carbons seem to be a promising synthetic operation. Its usefulness depends upon the availability of suitable reduction methods and we have therefore developed procedures for partial as well as full reduction of **1**. To the best of our knowledge, only two reductions of a tetronic acid are described in the literature.[3,4] Both are catalytic hydrogenations of α,γ-disubstituted tetronic acids which mainly lead to products having all-*cis* configurations. Scheme 1 summarizes the structures of the compounds that we have prepared from **1**.

Excellent yields of mixtures of the hydroxy lactones **2***c* (*cis*) and **2***t* (*trans*) were obtained on reduction of **1** with ammonia–borane or on catalytic hydrogenation over rhodium. ^{13}C NMR analysis or GLC of the acetylated reduction product shows that the former reagent gives **2***c* and **2***t* in a ratio of 25:75 while the latter gives these compounds in a ratio of 85:15. This result is in line with the finding that reduction of ketones with ammonia–borane often gives a high propor-



tion of the thermodynamically most stable product.[5] Six-membered ring analogues of tetronic acids have been found to be reducible with ammonia–borane but not with sodium borohydride or sodium cyanoborohydride,[6] and this probably holds also for tetronic acids. Isomer **2***t* has previously been prepared from ethyl L-lactate in six steps as an intermediate in a synthesis of (+)-blastmycinone.[7] Our route to **2***t* involves only three steps but shows lower stereoselectivity (3:1) and involves an accompanying separation problem (the separation of **2***c* and **2***t* on silica gel was inefficient; other techniques were not tried).

Compound **2***c* has been dehydrated to **3** using methanesulfonyl chloride and triethylamine (94 % yield).[8] Another good method, used for the enantiomer of **2***t*, is benzoylation followed by treatment with ammonia in methanol.[9] We evaluated the classical phosphoryl chloride–pyridine system but obtained a lower yield (68 %). However, our product **3** showed consistently higher optical rotation, $[\alpha]_D + 123°$, than reported for the five previous preparations of **3** or its enantiomer (reported values of $[\alpha]_D$ range from 93.9 to 108°).[8–12] This route to **3** compares favourably with the other routes, also with respect to length and simplicity. Compound **3** and its analogues are useful chiral building blocks which show excellent stereoselectivity on reaction with organocuprates[13] or on epoxidation.[14]

Reduction of **1** to the fully reduced lactone **5** can probably be carried out via **2** and **3**, but a more direct route goes via the enol benzoate **4**. The tetrabutylammonium salt of **1** was easily extracted from water into dichloromethane and then *O*-benzoylated; crystallisation gave a 90 % yield of **4**. Hydrogenation using platinum dioxide afforded **5** in 91 % yield (GLC). This kind of hydrogenolysis, which was first described in 1931 for acyclic enol acetates,[15,16] has not found much use in synthesis. It also works well for an α-methylated six-membered ring analogue.[17] The specific rotation of the product was slightly higher than the highest literature value[18] and the material is therefore assumed to be of high optical purity.

The enantiomers of **3**[9,10] and **5**[19] have previously been prepared from D-ribonolactone. Ethyl L-lactate thus complements D-ribonolactone as an optically pure starting material. In general, it seems to be advantageous to prepare compounds of high optical purity via tetronic acids, which are often crystalline compounds. Crystallisation is a potentially useful technique for increasing the optical purity, and the crystallisation of **1** is probably one reason why **3**, and probably also **5**, could be prepared in superior optical purity.

Experimental

A fused silica capillary column (CP-WAX 52, 25 m) mounted in a Hewlett-Packard 5830 A instrument was used for analytical GLC. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. A JEOL JNM-FX 100 spectrometer was used to record ^1H and ^{13}C NMR spectra. Unless otherwise stated, internal TMS was used as reference for samples in $CDCl_3$. Sodium 2,2-dimethyl-2-silapentane-5-sulfonate was used as reference in DMSO-d_6. IR spectra were recorded on a Perkin-Elmer 257 instrument.

Reduction of **1** *with ammonia–borane.* Ammonia–borane (2.98 g, 96 mmol) was added in portions in the course of ca. 10 min to an ice-cooled solution of **1** (6.84 g, 60 mmol) in methanol (270 ml) and water (30 ml). After stirring for 1 h, at which point the evolution of gas had almost ceased, citric acid (12.6 g) was added in portions over a period of ca. 15 min. The mixture was heated under reflux (18 h), cooled, and the methanol evaporated. Water (40 ml) was added and the reduction products extracted with ethyl acetate (4 × 100 ml). Drying of the combined organic phases (Na_2SO_4), evaporation of the solvent, dissolution in dichloromethane, drying again (Na_2SO_4) and evaporation at ca. 2 kPa (40 °C) left a liquid residue (7.16 g, 103 %) which contained a small amount of solid material. ^{13}C NMR spectroscopy showed a **2***c*:**2***t* ratio of 25:75 (for shifts, see below); purity ca. 95 %.

Reduction of **1** *with* H_2/Rh. A solution of **1** (114 mg, 1 mmol) in ethyl acetate (20 ml) was hydrogenated (5 atm, 22 °C, 60 h) using 5 % Rh/C (40 mg). After filtration the solvent was evaporated. ^{13}C NMR analysis showed a **2***c*:**2***t* ratio of 86:14; purity ca. 95 %.

2*c*. The ^1H NMR spectrum was indistinguishable from that of its enantiomer.[20] The ^{13}C NMR spectrum [(DMSO-d_6): 177.9, 82.4, 69.8, 40.9, 15.4 ppm] agrees well with literature[21] data (solvent not specified).

2*t*. The ^{1}H NMR spectrum ($CDCl_3$) was indistinguishable from that of the enantiomer[9], and its ^{13}C NMR spectrum in DMSO-d_6 was closely similar to that recorded in acetone-d_6.[9] ^{13}C NMR (DMSO-d_6): 177.2, 85.5, 73.1, 38.4, 19.7 ppm.

5(S)-Methyl-2(5H)-furanone (**3**). The crude mixture (4.64 g, 40 mmol) of **2*c*** and **2*t*** obtained in the reduction of **1** with ammonia–borane was dissolved in pyridine (16 ml) and dichloromethane (35 ml). A solution of phosphoryl chloride (9.21 g, 60 mmol) in dichloromethane (15 ml) was added with stirring over a period of 15 min and the mixture was then heated under reflux for 2 h. The major part of the solvent was distilled off through a 20 cm Vigreux column (1 h), diethyl ether (30 ml) was added and then carefully water (30 ml). After separation of the phases, extraction with diethyl ether (5 × 70 ml), and drying (Na_2SO_4) of the combined organic phases, the solvent was distilled off through a 20 cm Vigreux column. Compound **3** was purified on a silica gel column using diethyl ether as eluent and then distilled at 40–41 °C (0.15–0.2 kPa). Yield 2.67 g (68 %); $[\alpha]_D^{20.0}$ + 123° (*c* 1.7, chloroform); five lit. values[8–12] range from 94 to 108°; GLC purity: 97 %. The ^{1}H NMR spectrum was indistinguishable from that published.[9,10] ^{13}C NMR ($CDCl_3$): 172.8, 157.6, 120.6, 79.4 and 18.4 ppm (solvent signal at 77.17 ppm as reference).

Tetrabutylammonium salt of **1**. A mixture of **1** (0.684 g, 6 mmol), dichloromethane (20 ml), tetrabutylammonium hydrogen sulfate (2.237 g, 6.6 mmol) and 1 M aqueous sodium hydroxide (13.2 ml) was shaken and the organic phase separated. After three additional extractions with CH_2Cl_2 and drying of the combined organic phases (Na_2SO_4), the solvent was evaporated and the crude product dried over P_2O_5 (1 h, ca. 0.1 kPa); yield 2.20 g (103 %).

4-Benzoyloxy-5(S)-methyl-2(5H)-furanone (**4**). A mixture of the above tetrabutylammonium salt (6 mmol), dry dichloromethane (20 ml), benzoyl chloride (2.58 g, 18 mmol) and ground, dried potassium carbonate (3.11 g, 18 mmol) was heated under reflux for 2 h. After cooling, filtration and evaporation of the major part of the solvent, diethyl ether (100 ml) was added and the mixture was washed twice with weakly acidic water (pH ca. 4). Replacement of the ether with dichloromethane, drying (Na_2SO_4) and evaporation gave a crude product which was recrystallised by dissolution in the minimum amount of dichloromethane followed by addition of dry diethyl ether. Four crops of **4** gave in all 1.18 g (90 %), m.p. 134–135 °C; $[\alpha]_D^{23}$ –27.4 ° (*c* 1.4, chloroform). IR (KBr): 1762 and 1635 cm^{-1}. ^{1}H NMR ($CDCl_3$): 8.2–7.3 (5 arom. H), 6.28 (d, 1H, J = 1.5 Hz), 5.14 (dq, 1H, J = 1.5 and 6.8 Hz), 1.61 (d, 3H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): 171.7, 171.5, 161.6, 135.0, 130.4, 129.1, 127.3, 100.8, 75.8 and 17.9 ppm.

Dihydro-5(S)-methyl-2(3H)-furanone (**5**). A solution of **4** (109 mg) in dry tetrahydrofuran (4 ml) was hydrogenated using platinum dioxide (15 mg). After 1.5 h the reaction mixture was filtered through a column of basic alumina (0.5 × 6 cm), which also removed the benzoic acid formed. Thorough evaporation of the solvent gave ca. 70 % of **5**. $[\alpha]_D^{21.5}$ –39° (*c* 1.0, CH_2Cl_2); highest lit.[18] value: $[\alpha]_D$ –35.2° (*c* 1.02, CH_2Cl_2). The ^{1}H NMR spectrum ($CDCl_3$, JEOL GSX 270 instrument) was indistinguishable from that of authentic **5** and showed that less than 2 mole % of a benzoyl-containing contaminant was present. The yield determined by GLC using γ-butyrolactone as internal standard was 91 % and the purity 98 %.

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