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Synthesis of Optically Active Alcohols from 3-Cyclohexene-1-carboxylic Acid

OLOF CEDER and HANS G. NILSSON

Department of Organic Chemistry, University of Göteborg and Chalmers University of Technology, Fack, S-402 20 Göteborg, Sweden

(*S*)-2-Propyl-1-dodecanol has been prepared from (*R*)-3-cyclohexene-1-carboxylic acid by use of the Kolbe electrolytic synthesis and the Wittig reaction. After changes of the number of carbon atoms in the reagents, the same route also allows the preparation of (*R*)-2-propyl-1-dodecanol from (*R*)-3-cyclohexene-1-carboxylic acid. The CD spectra of (*S*)-3-carboxyethyl-γ-butyrolactone, (*R*)-3-carboxyethyl-γ-butyrolactone methyl ester, and (*S*)-3-propyl-γ-butyrolactone are reported.

3-Cyclohexene-1-carboxylic acid, *1*, which is commercially available, has been resolved and the configurations of the enantiomers have been determined.[1–3] This acid is an attractive starting material for a variety of compounds [4,5] and in the present communication we describe the synthesis of optically active branched alcohols from *1*.

Reduction of (*R*)-3-cyclohexene-1-carboxylic acid, *1*, to the alcohol *2* with lithium aluminum hydride proceeded without racemization [2] (Chart 1). Ozonization of *2* followed by oxidative work-up gave the γ-lactone acid *3*.[2] Its structure follows from mass and NMR spectra of the methyl ester and the ring size from a carbonyl absorption at 1778 cm^{-1} in the infrared spectrum. This lactone acid, which contains a free carboxyl function and masked carboxyl and hydroxyl functions, is the key compound in the synthetic sequence, which can be elaborated in several directions. Kolbe electrolysis with a salt of a monocarboxylic acid or with the salt of a half-ester of a dicarboxylic acid converts *3* into a lactone containing an alkyl or an esterified carboxyalkyl side chain. The lactone ring can then be opened and the carboxyl and hydroxyl functions can be modified separately. It should also be observed that both enantiomers of the desired product can be obtained from one enantiomer of *3* by varying the reagents.

We have examplified the described approach with the synthesis of the two forms of 2-propyl-1-dodecanol, *7a* and *7b*. One enantiomer was prepared from *3* in the following way. Kolbe electrolysis of *3* in the presence of sodium acetate replaced the carboxyl group by a methyl group. 3-Propyl-γ-butyrolactone, *4a*, was formed in good yield and dimeric products were easily eliminated by distillation. The lactone was then converted into the hemiacetal

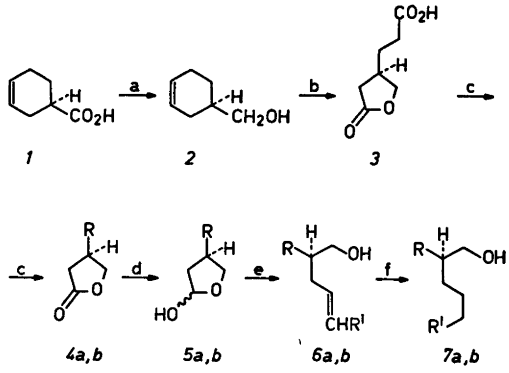

Chart 1. Scheme for the synthesis of optically active 2-alkylated alcohols: a. $LiAlH_4$, b. O_3 − 30 % H_2O_2 + HCOOH, c. Kolbe electrolysis, CH_3COONa or $C_8H_{17}COONa$, d. $[(CH_3)_2CHCH_2]_2AlH$, e. $C_6H_{16}=P(C_6H_5)_3$ or $CH_2=P(C_6H_5)_3$, f. H_2 + Pd/C.

5a by reduction with diisobutylaluminum hydride and the hemiacetal was allowed to react with the Wittig reagent octylidenetriphenylphosphorane.[6] Finally, the olefinic alcohol *6a* was catalytically reduced to the desired saturated alcohol *7a*, which was dextrorotatory.

The other enantiomer was obtained using the same type of reactions. Kolbe electrolysis of *3* in the presence of sodium nonanoate gave the 3-decyl-γ-butyrolactone, *4b*, which was reduced with diisobutylaluminum hydride to the hemiacetal *5b*. With methylenetriphenylphosphorane this compound yielded the unsaturated alcohol *6b*, which finally was reduced to the levorotatory enantiomer of 2-propyl-1-dodecanol, *7b*. The main problem we have encountered in the preparations described is the separation of desired and dimeric products formed in the Kolbe electrolysis.

Intermediates *3* and *4* (Chart 1) are chiral 3-substituted γ-lactones whose chiroptical properties have attracted considerable interest for some time.[7–11] We have therefore recorded the CD spectra for *3*, its methyl ester, and *4a* (*cf.* Exp.). Compounds (*S*)-*3* and (*S*)-*4a* give rise to CD curves displaying positive Cotton effects, while the (*R*)-*3* methyl ester gives a negative one for the n-π^* transition [12] at 218 nm. If we suppose that the preferred conformations of the γ-lactones have the 3-substituents in pseudoequatorial positions, as indicated in Fig. 1, our results are in agreement with the rule proposed by Legrand and Bucourt [9] and the findings by Beecham.[10]

In conclusion, we want to point out that, by variation of the reagents, the types of optically active compounds shown in Fig. 2 can be prepared from 3-cyclohexene-1-carboxylic acid.

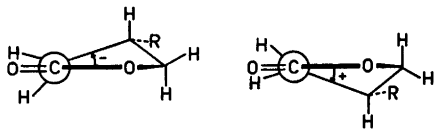

Fig. 1. Preferred conformations of 3-substituted γ-butyrolactones showing the sign of the dihedral angle $O-C(=O)-C_3-C_3$.

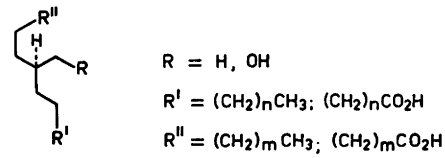

Fig. 2. Optically active compounds from 3-cyclohexene-1-carboxylic acid.

EXPERIMENTAL

General methods. GLC analyses were carried out on a Perkin-Elmer 900 instrument fitted with flame ionization detectors and 3 mm × 180 cm stainless steel columns packed with 3 % SE-30 on Gas Chrom Q. Column chromatographic separations were performed on Merck Kiselgel 60, particle diameter 0.063 – 0.200 mm. The eluents were continuously analysed with a Pye Unicam LCM2 detector. The CD spectra were determined with a Cary 60 instrument. The IR spectra were recorded on a Beckman IR 9 spectrophotometer. MS were determined on an AEI 902 mass spectrometer or on an LKB 9000 mass spectrometer connected to a gas chromatograph. The 270 MHz NMR spectra were determined in $CDCl_3$ with a Bruker WH270 instrument.

(R)-*3-Propyl-γ-butyrolactone*, 4a. (*R*)-3-Carboxyethyl-γ-butyrolactone, *3*, (0.5 g, 3.2 mmol) of 97 % optical purity [2] and acetic acid (3.6 g, 60 mmol) were separately dissolved in 5 and 10 ml of anhydrous methanol, respectively. The solutions were neutralized by dropwise addition of 1 M sodium methoxide solution. The combined methanolic solutions were electrolysed in a Kolbe electrolysis apparatus with mercury cathode and rotating platinum anode.[13] The initial current was 4 A and after 2 h it had decreased to 0.4 A. The reaction mixture was evaporated under reduced pressure, 5 ml of water was added, and the resulting mixture was extracted with 4 × 10 ml of ethyl ether. The combined organic solutions were washed twice with a saturated solution of sodium bicarbonate, twice with water, dried over anhydrous magnesium sulfate, and evaporated giving 500 mg of crude *4a*, $[\alpha]_D + 3.2°$ ($CHCl_3$, *c* 26). IR: 1778 cm^{-1} (lactone carbonyl). ^1H NMR (270 MHz): δ 0.94 (3 H, t), 1.20 – 1.55 (2 H, m), 1.37 (1 H, t), 1.45 (1 H, t), 2.09 – 2.28 (1 H, m), 2.44 – 2.71 (2 H, m), 3.92 (1 H, t), and 4.42 (1 H, t). MS: mol. wt. obs. 128.082 ± 0.003, calc. for $C_7H_{12}O_2$ 128.084.

(R)-*3-Decyl-γ-butyrolactone*, 4b. (*R*)-3-Carboxyethyl-γ-butyrolactone, *3*, (1.0 g, 6.3 mmol) of 97 % optical purity and nonanoic acid (4.0 g, 25.2 mmol) were reacted as described for the preparation of *4a*. The product (2.04 g) was purified by LC on silica gel (gradient elution with benzene – ethyl acetate) giving 300 mg of *4b*, $[\alpha]_D + 5.1°$ ($CHCl_3$, *c* 5), of 95 %

purity (GC). IR: 1778 cm^{-1} (lactone carbonyl). ^1H NMR (270 MHz): δ 0.88 (3 H, t), 1.19–1.39 (16 H, m), 1.39–1.55 (2 H, m), 2.09–2.28 (1 H, m), 2.44–2.71 (2 H, m), 3.92 (1 H, t), and 4.42 (1 H, t). MS: mol. wt. obs. 226.194 ± 0.003, calc. for $C_{14}H_{26}O_2$ 226.193.

(2RS,4R)-2-Hydroxy-4-propyltetrahydrofuran, 5a. In a dry nitrogen atmosphere *4a* (244 mg, 1.9 mmol) was dissolved in 10 ml of anhydrous toluene. A solution of diisobutylaluminium hydride [6,14] (8 mmol) in 10 ml of anhydrous toluene was added dropwise to the cooled, −70 °C, lactone solution over a period of 10 min. The solution was stirred at −70 °C and after 45 min, 10 ml of 4 M 2-propanol in toluene was added dropwise, followed by 2 ml of water. The reaction mixture was allowed to assume room temperature and was filtered. Toluene, as well as 2-propanol and water, was removed by evaporation under reduced pressure giving 100 mg of crude *5a*, $[\alpha]_D + 21°$ ($CHCl_3$, *c* 3). The IR spectrum showed no lactone carbonyl absorption. ^1H NMR (60 MHz): δ 0.92 (3 H, t), 1.1–2.6 (7 H, m), 3.2–4.4 (2 H, m), 4.6 (1 H, broad s), and 5.5 (1 H, broad d).

(2RS,4R)-2-Hydroxy-4-decyltetrahydrofuran, 5b. The lactone *4b* (240 mg, 1.33 mmol) was dissolved in 10 ml of anhydrous toluene and was reacted with diisobutylaluminium hydride (16 mmol) in 10 ml of anhydrous toluene as described above for the preparation of *5a* giving 240 mg of *5b*, $[\alpha]_D + 20°$ ($CHCl_3$, *c* 7). The IR spectrum showed no lactone carbonyl absorption. ^1H NMR (60 MHz): δ 0.7–2.5 (24 H), 3.2–3.7 (2 H, m), 3.7–4.4 (1 H, m), and 5.5 (1 H, broad d).

(R)-2-Propyl-4-dodecen-1-ol, 6a. A solution of octylidentriphenylphosphorane, from octyltriphenylphosphonium bromide [15,16] (2.73 g, 6.0 mmol) in 16 ml of dimethyl sulfoxide, was added dropwise to a solution of the lactol *5a* * (700 mg, 5.4 mmol) dissolved in 4 ml of dimethyl sulfoxide under dry nitrogen atmosphere.[14] The reaction mixture was stirred at 70 °C. After 24 h, 30 ml of water was added. The aqueous phase was extracted with 5 × 15 ml of pentane. The combined organic phases were washed three times with water, dried over anhydrous magnesium sulfate, and evaporated. The crude product was purified by LC on silica gel (benzene) giving 150 mg of *6a*, $[\alpha]_{546} - 2.0°$ (MeOH, *c* 6). ^1H NMR (60 MHz): δ 0.88 (3 H, t), 0.90 (3 H,t), 1.1–1.6 (15 H), 1.80 (1 H, s), 1.9–2.3 (4 H, m), 3.55 (2 H, d), and 5.3–5.6 (2 H, m). MS: mol. wt. obs. 226.226 ± 0.003, calc. for $C_{15}H_{30}O$ 226.230.

(R)-2-Decyl-4-penten-1-ol, 6b. Methylenetriphenylphosphorane [15] (20 mmol) dissolved in 20 ml of dimethyl sulfoxide was added dropwise to a solution of *5b* (180 mg, 0.79 mmol) dissolved in 2 ml of dimethyl sulfoxide [14] under dry nitrogen atmosphere. The reaction mixture was treated as described for the preparation of *6a*. The crude product was purified by preparative TLC on silica gel (benzene) giving 25 mg of *6b*, $[\alpha]_D + 8°$ ($CHCl_3$, *c* 2). MS: $M^+ = 226$. ^1H NMR (60 MHz): δ 0.88 (3 H, t), 1.1–2.3 (22 H), 3.55 (2 H, d), and 4.7–5.3 (3 H, m).

(R)-2-Propyl-1-dodecanol, 7a. Compound *6a* * (140 mg, 0.44 mmol) was dissolved in 15 ml of ethanol and hydrogenated at atmospheric pressure with 8 mg of 10 % Pd/C as catalyst. The suspension was filtered and the filtrate was evaporated giving 110 mg of a product, which was further purified by preparative TLC on silica gel with benzene as eluent. Yield: 53 mg of *7a*,* $[\alpha]_D - 0.7°$ (MeOH, *c* 1). ^1H NMR (270 MHz): δ 0.88 (3 H, t), 0.91 (3 H, t), 1.0–1.6 (24 H), and 3.5–3.6 (2 H, broad d). MS: mol. wt. obs. 210.233 ± 0.003, calc. for $C_{15}H_{30}$ ($M^+ - H_2O$) 210.235.

(S)-2-Propyl-1-dodecanol, 7b. Compound *6b*, (20 mg, 0.08 mmol) was dissolved in 10 ml of methanol and catalytically hydrogenated at 2.7 atm with 6 mg of 10 % Pd/C for 1 h in a Parr hydrogenation apparatus. The suspension was filtered and the filtrate was evaporated. The product was further purified by TLC giving 13 mg of *7b*, $[\alpha]_D + 7°$ ($CHCl_3$, *c* 1.5). ^1H NMR (270 MHz): δ 0.86 (3 H, t), 0.89 (3 H, t), 1.0–1.6 (24 H), and 3.5–3.6 (2 H, broad d). MS: mol. wt. obs. 210.240 ± 0.004, calc. for $C_{15}H_{30}$ ($M^+ - H_2O$) 210.235.

(S)-3-Carboxyethyl-γ-butyrolactone, 3. Crude *(S)-3*, $[\alpha]_D + 0.16°$ (MeOH, *c* 6), was prepared from *(S)-1* of 53 % optical purity as described in Ref. 2. CD: $[\theta]_{218} + 420$ (EtOH).

(R)-3-Carboxyethyl-γ-butyrolactone methyl ester. *(R)-3* methyl ester, $[\alpha]_D - 2.4°$ (ethyl ether, *c* 4), was prepared from optically pure *(R)*-3, esterified with CH_2N_2, and purified by chromatography over silica gel (ethyl ether) twice. CD: $[\theta]_{218} - 790$ (EtOH).

(S)-3-Propyl-γ-butyrolactone, 4a. *(S)-4a*, $[\alpha]_D - 5.3°$ (EtOH, *c* 0.6), was prepared from *(S)*−1 of 53 % optical purity as described for *(R)*−*4a* and was purified by distillation and by chromatography over silica gel (CH_2Cl_2–MeOH, 10:1). CD: $[\theta]_{218} + 540$ (EtOH).

* Prepared in an experimental series starting with *(R)*-3-cyclohexene-1-carboxylic acid of 52 % optical purity. Compound *7a* has, compared to *7b*, a specific rotation which is too low. We can offer no adequate explanation for this finding.

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