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Short Synthetic Route to the Enantiomerically Pure (*R*)-(+)-γ-Decalactone

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Abstract: An efficient procedure for the preparation of homochiral (*R*)-(+)-γ-decalactone **4** based on castor oil ozonolysis is described. The key intermediate, (*R*)-(-)-1,3-nonandiol **1**, was transformed into monotosylate **2** and then reacted with sodium cyanide to give (*R*)-(-)-4-hydroxydecanitrile **3**. Treatment of the latter with a dilute hydrochloric acid provided the enantiomerically pure lactone **4**.

Lactones are very common flavour compounds used in the perfume and food industry, and they are useful intermediates in the synthesis of natural products. Among the flavour-active lactones, γ-decalactone is used in fruit and dairy flavours.[1]

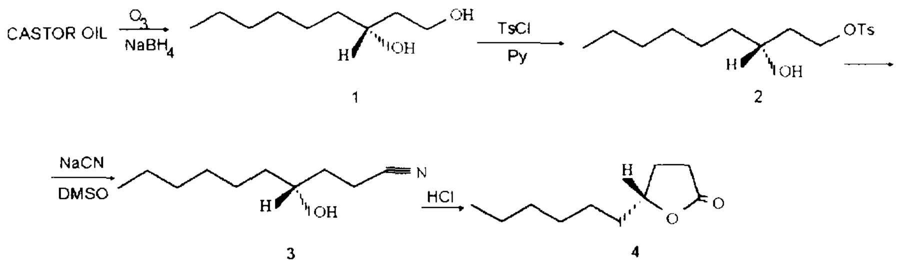
A recent study revealed that dextrorotatory γ-decalactone is the major lactone of ripe fruits both of peaches[2] and nectarines.[3] It is also an important contributor to the apricot[4] and mango[5] aroma.

Sensory characteristics and specific optical rotations of both enantiomers have been described and it is known that the (*R*)-enantiomer is more attractive than its (*S*)-antipode as far as the flavour is concerned.[6]

Generally, commercial synthetic γ-decalactone is the racemate form, but the (+)-γ-decalactone has also been available. It is produced by a microbial process from ricinoleic acid[7] which is a very costly procedure. Therefore, the search for new, efficient routes to this nature-identical microcomponent is justified. and the purpose of this paper is to show a simple and cost-effective synthetic route to the enantiomerically pure (+)-γ-decalactone.

RESULTS AND DISCUSSION

Castor oil contains, up to 90% of the mixed acids, a unique hydroxy acid, (*R*,*Z*)-(+)-12-hydroxy-9-octadecenoic acid or ricinoleic acid.[8] Ozonolysis of the acid provides (*R*)-(-)-1,3-nonandiol **1**.[9] The same outcome could be observed when a commercial castor oil was subjected to ozonolysis.[10] On the basis of the suitable absolute configuration of diol **1** and its availability, the compound was a promising starting material for the preparation of (*R*)-γ-decalactone **4** (Scheme)



Ozonolysis of castor oil in methanol followed by reduction of the resulting intermediate ozonides afforded a product composed of diol **1** and methyl 9-hydroxynonanoate (≅ 1:1, GC). The latter was formed as a result of a spontaneous transesterification of the triglyceride and was difficult to separate from diol **1** by distillation. However, alkaline hydrolysis of the ester allowed isolation of (-)-1,3-nonandiol **1** in 73% yield (based on 85% castor oil).

In light of the literature report,[11] it was tempting to try to transform diol **1** into (*R*)-4-hydroxydecanitrile **3** by a one-pot procedure (*via bis*-trifluoroacetate of the diol), but it did not work well under our conditions and gave a poor result. A much better procedure appeared, which involved a selective tosylation of diol **1** with tosyl chloride providing tosylate **2** in 97% yield. The purity and the structure of the intermediate **2** was confirmed by TLC and IR, and without further purification, the compound was reacted with sodium cyanide in DMSO to give crude 4-hydroxydecanitrile **3**. The product contained 89% of compound **3** and 6% of γ-decalactone **4** the retention time of which was very close to nitrile **3**. Apparently, in the course of the work-up, a partial hydrolysis of the hydroxynitrile and lactonization took place. Fortunately, compound **3** became solid when refrigerated and could be easily purified by a three-fold crystallisation from n-hexane to deliver a chemically pure 4-hydroxydecanitrile **3** (>99%, GC) with an optical rotation $[\alpha]_D^{20}$-20.1° (c=1, MeOH). Its structure was confirmed by spectral analysis (^{13}C- ^{1}H-NMR, IR and MS) and by its acidic hydrolysis to (+)-γ-decalactone **4**. The hydrolysis of nitrile **3** in the presence of a dilute HCl was practically quantitative and the product showed one peak (GC). Spectral examination of the compound proved its identity by comparison with the authentic sample of *gamma*-n-decalactone. This means that an acidic treatment of hydroxynitrile **3** involves both the hydrolysis and lactonization reaction. The measurement of the specific optical rotation of the lactone **4**, $[\alpha]_D^{20}$ +48.5° (c=1.1, MeOH), demonstrated its homochirality.[6] Additionally, this was supported by chiral GC analysis (column Lipodex®B, comparison with the racemic γ-decalactone).

As for the absolute configuration of (-)-4-hydroxydecanitrile **3**, it can be deduced that the compound possesses the original configuration of the substrate diol **1**, and its optical rotation, -20° (in methanol), is specific for the enantiomerically pure (*R*)-configurated enantiomer.

Our approach with (*R*)-(-)-1,3-nonandiol **1** as the starting material, has significant advantages and provides a useful alternative for the preparation of (+)-γ-decalactone by microbial and multi-step chemical methods.[12,13]

EXPERIMENTAL PROCEDURES

General. Commercial-grade castor oil, $[\alpha]_D^{20}$+5.6° (neat), n_D^{20} 1.4778 from *Ricinus communis* was used. All solvents (methanol, pyridine, DMSO, CH_2Cl_2, diethyl ether, n-hexane and ethyl acetate) were freshly distilled prior to their use. NaCN was powdered and previously dried at 120 °C/0.2 mm Hg for 3 h. Crude tosylate **2** was, before the reaction, dried over P_2O_5 for 25 h.
Gas Chromatography (GC). - A Carlo Erba Vega 6000 gas chromatograph with FID, equipped with a column Rtx-1 (30 m), 0.25 mm i.d. was used. Conditions: temperature program 60 - 250 °C (4°/min.), nitrogen as carrier gas (0.8 mL/min.). Chiral GC analysis was performed using capillary column Lipodex®B, 25 m fused silica, column temp. 150 °C, injection temp. 190 °C, He as carrier gas. *Gas Chromatography - Mass Spectrometry (GC-MS).* - A Carlo Erba GC 8000 coupled to MD 800 Fisons Instruments were used. The apparatus was equipped with the same column as for GC analysis. Helium was used as carrier gas; electron ionization, 70 eV. *Thin - Layer Chromatography (TLC).* - Analytical TLC was performed on procoated plates (2.5 x 7.5 cm, silica gel 60 F_{254},0.25 mm, Merck). The chromatograms were developed with hexane:ethyl acetate 60:40 (v/v) for compound **2** and 50:50 (v/v) for hydroxynitrile **3**. *IR spectroscopy.* - The IR spectra were measured as a smear on sodium chloride plates with a Specord 71 spectrophotometer. *NMR Spectroscopy.* - All NMR spectra were recorded on a Bruker AC (200 MHz) spectrometer in $CDCl_3$ solutions. TMS as internal standard and chemical ships in δ (ppm): s - singlet, d - doublet, t - triplet, q - quartiplet and m - multiplet. Resonance multiplicities for carbon-13 were obtained by DEPT technique. *Optical Rotation.* - The optical rotations were measured on Perkin Elmer 241 MC instrument, ±0.01 accuracy.

(R)-(-)-1,3-Nonandiol 1. Castor oil (50 g in 200 mL methanol) was ozonized under the conditions described elsewhere.[10] and the ozonide products were reduced with $NaBH_4$ (7 g, 1.3 equiv) by a portionwise addition of the reducing agent at 0 - 5 °C for 5 h during an intensive stirring. The mixture was stirred at 20 °C for another 2 h and then 200 mL of water was added. A part of methanol and water was distilled in vacuo and the product was extracted with diethyl ether (4 x 200 mL). The combined extracts were washed with water and dried with Na_2SO_4 and the solvent removed. The residue (52 g) was refluxed with 1.2 equiv of NaOH (4% in methanol) for 2 h (to hydrolyze the accompanied methyl 9-hydroxynananoate). After solvent evaporation, diethyl ether (300 mL) was added and the solution was made neutral by several washings with brine. The etheral solution was dried with Na_2SO_4 and the solvent evaporated. The crude product was fractionally distilled to give 16 g (ca. 73% yield) of 1,3-nonandiol **1**; b.p. 110 - 113 °C/0.4 mm Hg. $[\alpha\ ]_D^{20}$-6° (c=1, EtOH) {lit.[9] $[\alpha]_D^{22}$ -5.5° (c=5.8, ethanol)}, IR: 3360, 1130, 1090, 1060, 1010 cm^{-1}. Its MS spectrum coincided with that given earlier.[9]

(R)-(-)-Hydroxydecanitrile 3. To a solution of diol **1** (5 g, 0.031 mol) and dry pyridine (4.8 g, 0.06 mol) in dry CH_2Cl_2 (25 mL) was added tosyl chloride (8g, 0.036 mol) with ice-cooling and the mixture was stirred overnight at 4 °C. The reaction mixture was diluted with diethyl ether (150 mL), washed with water, ice-10% HCl (2 x 30 mL), brine, dried over Na_2SO_4 and concentrated to give 9.6 g of crude tosylate **2**; IR: 3420, 1600, 1365, 1190, 1175, 1100, 960, 910, 820 cm^{-1}. A mixture of the tosylate (9.5 g, 0.03 mol) and NaCN (1.7 g, 0.035 mol) in dry DMSO (30 mL) was stirred for 3 days at room temperature. The reaction mixture was poured into ice-water and extracted with diethyl ether (5 x 80 mL). The combined extracts were washed with water and brine, dried with Na_2SO_4 and concentrated to provide a crude product (4.9 g) of 89% chemical purity (GC) which contained ca. 6% of γ-decalactone (by GC). The crude product while stored overnight in a refrigerator (-15 °C) became solid. The solid (2 g) was three-fold crystallized from hexane to deliver 1.5 g of chemically pure (GC) 4-hydroxydecanitrile **3** in the form of white, minute crystals tending to be liquid (m.p. <15 °C); $[\alpha\ ]_D^{20}$-20.1° (c=1, MeOH). IR: 3430, 2950, 2870, 2250, 1470, 1425, 1080, 1055 cm^{-1}, ^{1}H-NMR: 3.70 (m, 1H), 2.49 (dt, J=7 and 1.1 Hz, 2H), 0.88 (t, J=6.7 Hz, 3H), ^{13}C-NMR: 119.9 (s), 69.5 (d), 37.1 (t), 32.3 (t), 31.5 (t), 30.0 (t), 25.3 (t), 22.3 (t), 13.8 (q), 13.4 (t), MS (*m/z*): 169 (M, 0%), 136 (4), 115 (40), 97 (72), 84 (57), 69 (19), 57 (20), 56 (37), 55 (100), 43 (44), 41 (81).

(R)-(+)-γ-Decalactone 4. A mixture of hydroxynitrile **3** (1.03 g) and 14% HCl (20 mL) was stirred at 100 °C for 5 h. The product was extracted with diethyl ether (3 x 50 mL), washed with the saturate $NaHCO_3$ solution and with water, dried (Na_2SO_4) and the solvent thoroughly evaporated in vacuum to provide 1.2 g of chemically pure (GC, TLC) γ-decalactone **4** (as a colorless liquid); $[\alpha]_D^{20}+48.5°$ (c=1.1, MeOH) {for optically pure[6]: $[\alpha]_D^{20}+48.5°$ (in MeOH)}. Its GC, IR and MS data were identical with those of authentic sample.

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