Synthesis of the Diastereomeric Mixture (2*RS*)-2-[(1*R*)-3-Cyclohexenyl]propanal

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Bulgarian rose oil contains among other components Δ^1-*p*-menthen-9-al, which is isolated as a partially epimerized diastereomeric mixture of the 4-methyl derivatives of *5a* and *5b* (Chart 1).[1] These compounds are important constituents in perfumes and to obtain them from natural sources is expensive.* Ohloff *et al.*[1] have reported the synthesis of these aldehydes with an optical purity of *ca.* 60 % from (+)-limonene.

3-Cyclohexene-1-carboxylic acid which has been resolved and configurationally assigned [2-4] has been demonstrated to be a useful chiral starting material for the synthesis of optically active substituted fatty alcohols [6] and dicarboxylic acids.[7] The present communication reports the synthesis of (2*RS*)-2-[(1*R*)-3-cyclohexenyl]-propanal, *7a*+*7b*, from (*R*)-3-cyclohexene-1-carboxylic acid, *1*, by the sequence outlined in Chart 1. These aldehydes are lower homologues of Δ^1-*p*-menthen-9-al.

(*R*)-3-Cyclohexene-1-carboxylic acid, *1*, was converted with methyllithium to the methyl ketone, *2*, which with methylenetriphenylphosphorane [8] gave (*R*)-4-isopropenylcyclohexene, *3*. Hydroboration of *3* with 9-borabicyclo[3.3.1]nonane (9-BBN) yielded an optically active diastereomeric mixture of (2*R*)-2-[(1*R*)-3-cyclohexenyl]-1-propanol and (2*S*)-2-[1*R*)-3-cyclohexenyl]-1-propanol, *4a* and *4b*, respectively. Finally, oxidation of this mixture with silver carbonate on Celite,[10,11] gave the diastereomeric mixture of (2*R*)-2-[(1*R*)-3-cyclohexenyl]-propanal, *5a*, and (2*S*)-2-[(1*R*)-3-cyclohexenyl]-propanal, *5b*.

The NMR spectrum of the mixture revealed that the two diastereomers were present in unequal amounts. The chemical shifts of the aldehyde doublets and also of other sets of signals were too close (even at 270 MHz) to allow an accurate estimation of the relative amounts of *5a* and *5b*.

The asymmetric induction apparently occurs in the hydroboration step and to determine the degree of stereoselectivity, we performed the following sequence of reactions. The dextrorotatory diastereomeric mixture *5a*−*5b* was catalytically hydrogenated to the enantiomeric pair *6a*−*6b* (Chart 1). The hydrogenated mixture was optically active which confirmed that asymmetric induction had taken place in the hydroboration step. The aldehyde mixture was then allowed to autoxidize to the enantiomeric acids *7a*−*7b* whose optical properties and absolute configurations have been determined.[12,13] From these values (*cf.* Experimental), assuming that no epimerization or racemization occurs in the oxidation steps, a stereoselectivity of 20 % in the hydroboration step is calculated.

The hydroboration reaction has been demonstrated to proceed *via* a *cis* four-center addition process.[14] Also, considerable asymmetric induction has been found to occur with chiral hydroborating agents [15] and when achiral hydroboranes react with chiral olefins.[16] Our findings are in agreement with these observations.

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. Preparative LC separations were performed at atmospheric pressure on Merck Kiselgel 60, particle diameter 0.063−0.200 mm. The eluents were con-

* Often structural alterations in olfactory constituents lead to interesting changes in their odours. The *5a*−*5b* mixture has a sweet hyacinth-like odour.

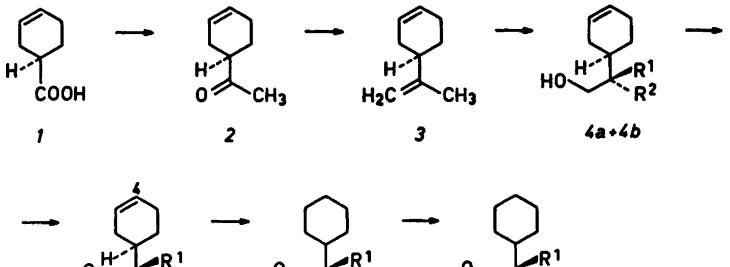

Chart 1. Series *a*: $R^1 = CH_3$, $R^2 = H$; Series *b*: $R^1 = H$, $R^2 = CH_3$.

tinuously analysed with a Pye Unicam LCM2 detector. High pressure LC was performed with a Waters Model 6000 solvent delivery system and R401 RI detector fitted to a 9 mm × 30 cm stainless steel column packed with Porasil. 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-Cyclohexenyl methyl ketone, 2. (*R*)-3-Cyclohexene-1-carboxylic acid, *1*, (2.8 g, 22 mmol), $[\alpha]_D$ +90° (MeOH, $c=5$), which corresponds to 95 % optical purity,[2-4] was dissolved in 60 ml of anhydrous ethyl ether. The solution was kept under dry nitrogen at 0 °C while a 2 M etheral solution of methyllithium (44 mmol) was added dropwise for 30 min. After 1.5 h at room temperature the white suspension was poured into a mixture of ice and 50 ml of 1 M hydrochloric acid. The layers were separated and the water phase was extracted with 4 × 25 ml of ethyl ether. The combined ether extracts were washed once with a saturated solution of sodium carbonate, twice with water, and then dried with anhydrous calcium sulfate. Evaporation of the ethyl ether gave 1.9 g (71 %) of crude product, which was further purified by distillation in a micro distillation apparatus, giving 1.02 g of pure (GC) *2*, b.p. 34 °C/1 Torr (litt.[5] b.p. 78–80 °C/17 Torr), $[\alpha]_D$ +100.2° ($CDCl_3$, $c=4$).

^{1}H NMR (60 MHz): δ 1.2–2.9 (7 H, m), 2.12 (3 H, s) and 5.57 (2 H, s). MS [*m/e* (% rel. int.)]: 125 (5), 124 (47), 109 (13), 95 (6), 91 (8), 83 (5), 82 (6), 81 (81), 80 (28), 79 (51), 78 (8), 77(17), 67 (5), 66 (10), 65 (8), 55 (8), 53 (27), 52 (8), 51 (15), 50 (8), 43 (100), 42 (7), 41 (21), 39 (34), 27 (29), 15 (18). Mol. wt., obs. 124.086 (3), calc. for $C_8H_{12}O$ 124.089.

IR (film): 1710 cm^{-1} (>C=O). UV [abs. ethanol (ε)]: 275 (17) nm.

(R)-4-Isopropenylcyclohexene, 3. Freshly distilled *2* (1.02 g, 8.2 mmol) was added to a solution of methylenetriphenylphosphorane [8] (13.7 mmol) in 20 ml of dimethyl sulfoxide. The solution was stirred for 30 min in a dry nitrogen atmosphere and then distilled giving 607 mg (61 %) of *3* containing traces of dimethyl sulfoxide, $[\alpha]_D$ +67.7° ($CHCl_3$, $c=4$), b.p. *ca.* 50 °C/2 Torr (litt.[17] b.p. 157 °C). The yield of *3* was increased to 70 % when a dry ice trap was used during the distillation and the traces of dimethyl sulfoxide in the distillate were eliminated by chromatography over silica gel (pentane eluent).

^{1}H NMR (60 MHz): δ 1.1–2.5 (7 H, m), 1.70 (3 H, m), 4.62 (2 H, s), 5.58 (2 H, s).

(2RS)-2-[(1R)-3-Cyclohexenyl]-1-propanol, 4a + 4b. 9-BBN (1.02 g, 8 mmol) was dissolved in 12.5 ml of dry tetrahydrofuran. (*R*)-4-Isopropenylcyclohexene (412 mg, 3.4 mmol) in 3 ml of tetrahydrofuran was added to the 9-BBN solution in a dry nitrogen atmosphere.[9] The solution was stirred for 30 min, 5 M sodium hydroxide solution (2.5 ml) was added, followed by 30 % hydrogen peroxide (2 ml). The temperature was kept at 60 °C and the stirring was continued for 1 h. The water phase was saturated with potassium carbonate, separated from the organic phase, and extracted twice with tetrahydrofuran. The combined tetrahydrofuran extracts were dried with potassium carbonate over night. Evaporation and distillation gave 412 mg of product, b.p. *ca.* 70 °C/1 Torr. Liquid chromatography on 40 g silica gel with gradient elution (benzene–ethyl acetate) gave 294 mg (62 % yield) of *4a + 4b*, $[\alpha]_D$ +59.7° ($CDCl_3$, $c=8$). GLC showed the product to have more than 99 % purity.

^{1}H NMR (60 MHz): δ 0.91 (3 H, d), 1.1–2.3 (8 H, m), 2.62 (1 H, s), 3.2–3.9 (2 H, m), 6.70 (2 H, s).

MS [*m/e* (% rel. int.)]: 140 (1.4), 122 (26), 107 (30), 93 (26), 81 (42), 80 (70), 79 (43), 78 (23), 77 (19), 67 (32), 55 (21), 54 (16), 53 (12), 41 (23), 39 (16). Mol. wt., obs. 140.118 (3), calc. for $C_9H_{16}O$ 140.120.

(2RS)-2-[(1R)-3-Cyclohexenyl]propanal, 5a + 5b. Silver carbonate on Celite [10,11] (10 g, 17.5 mmol) was added to a solution of *4a + 4b* (224 mg, 1.6 mmol) in 90 ml of benzene. Benzene-water (5 ml) was azeotropically distilled off and the reaction mixture was refluxed for 12 h. The progress of the oxidation was followed by GLC. The reaction suspension was filtered and the benzene solution was evaporated under reduced pressure giving 172 mg (78 % yield) of *5a + 5b*, $[\alpha]_D$ +62.6° ($CDCl_3$, $c=7$).

^{1}H NMR (60 MHz): δ 1.07 (3 H, d), 1.1–2.6 (8 H, m), 5.52 (2 H, s), 9.55 (1 H, pair of d).

MS [*m/e* (% rel. int.)]: 138 (5), 124 (14), 107 (16), 93 (16), 91 (22), 85 (17), 83 (22), 81 (98), 80 (100), 79 (98), 78 (31), 77 (33), 67 (59), 55 (48), 54 (43), 53 (31), 51 (14), 43 (34), 41 (60), 39 (45). Mol. wt., obs. 138.103 (3), calc. for $C_9H_{14}O$ 138.104.

(RS)-2-Cyclohexylpropanal, 6a + 6b. A solution of *5a + 5b* (63 mg, 0.5 mmol) in 3 ml of ethyl acetate was catalytically hydrogenated at atmospheric pressure with 5 mg of 10 % Pd/C as catalyst. The suspension was filtered and evaporated to give 29 mg of *6a + 6b*, $[\alpha]_D$ −9.5° ($CHCl_3$, $c=4$).* The product was used in the next step without further purification.

(RS)-2-Cyclohexylpropanoic acid, 7a + 7b. Crude *6a + 6b* (29 mg, 0.22 mmol) was allowed to autoxidize for 4 weeks at room temperature to the corresponding acids. The product was purified by high pressure LC (10 % ethyl acetate in hexane) to give *7a + 7b*, $[\alpha]_{578}^{25}$ −3.7° ($CHCl_3$, $c=0.2$), m.p. 53–55 °C.[12,13] GLC showed the product to be more than 98 % pure. ^{1}H NMR (270 MHz): δ 0.93–1.38

* Calculated value from an experiment starting with 27 % optically pure (*S*)-3-cyclohexene-1-carboxylic acid.

(5 H, m), 1.13 (3 H, d), 1.51–1.82 (6 H, m), 2.23–2.34 (1 H, q) and 10.11 (1 H, very broad s).

The sequence of experiments described was also performed with the *S* form of *1* of 27 % optical purity as starting material. The results were in each aspect in agreement with those presented above.

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