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Synthesis and Characterization of both Enantiomers of *trans*-1,2-Di-(2-hydroxy-2-propyl)-cyclobutane

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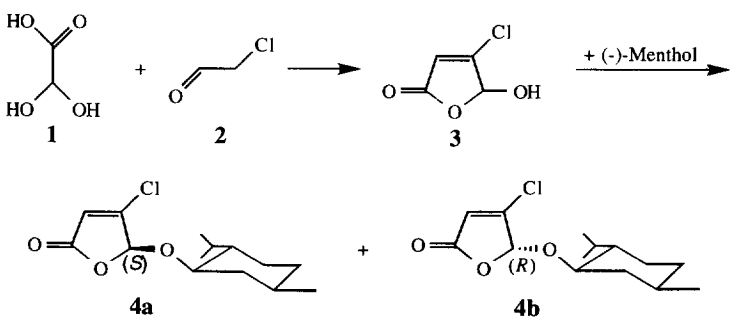
Abstract: Both enantiomers of the title compound are synthesized for the first time in four steps including a [2+2]-photocycloaddition to build up the cyclobutane backbone and a cerium supported reductive permethylation. During the cerium supported process a complete and selective change in the configuration of the cyclobutane ring takes place. The substituents are transformed from the *cis*- to the *trans*-geometry. Copyright © 1996 Published by Elsevier Science Ltd

Rac-trans-1,2-Di-(2-hydroxy-2-propyl)-cyclobutane ***rac*-6** was synthesized for the first time in 1951[1]. The racemate was obtained by subsequent Grignard addition of *rac-trans*-1,2-cyclobutanedicarboxylic acid ester[2]. The latter was the result of a multistep synthesis. To produce enantiomerically pure **6** in this way it is necessary to start with the enantiomers of *trans*-1,2-cyclobutanedicarboxylic acid. In 1924 a resolution and characterisation of these enantiomers[3] by means of quinine was reported without giving any detailed informations of the amounts of isolated products. Later on this method was reproduced[4], but the (-)-acid was described with different physical properties than before, and the (+)-acid could not be isolated in pure form. Recently[5] a resolution of *trans*-1,2-cyclobutanedicarboxylic acid was reported by fractional crystallisation with quinine and chinchonidine.In the present paper we describe a stereoselective new approach to both enantiomers **6** and ***ent*-6** without the need for resolution.

As starting material we used glyoxylic acid monohydrate **1** (an aqueous solution is also suitable), chloroacetic aldehyde **2** and morpholinium chloride in a Mannich-type condensation reaction[6] to give 4-chloro-5-hydroxy-[5H]-furan-2-one **3**[7] in a 60% yield. Acetalization[8] of **3** with (-)-menthol in the presence of catalytic amounts of *p*-toluenesulfonic acid formed both diastereomers of 4-chloro-5-(-)-menthyloxy-[5H]-furan-2-one **4a,b** in yields up to 95% (scheme 1). Repeated crystallization of **4a,b** from *n*-hexane gave the pure (5*S*)-configured diastereomer **4a** (10%).



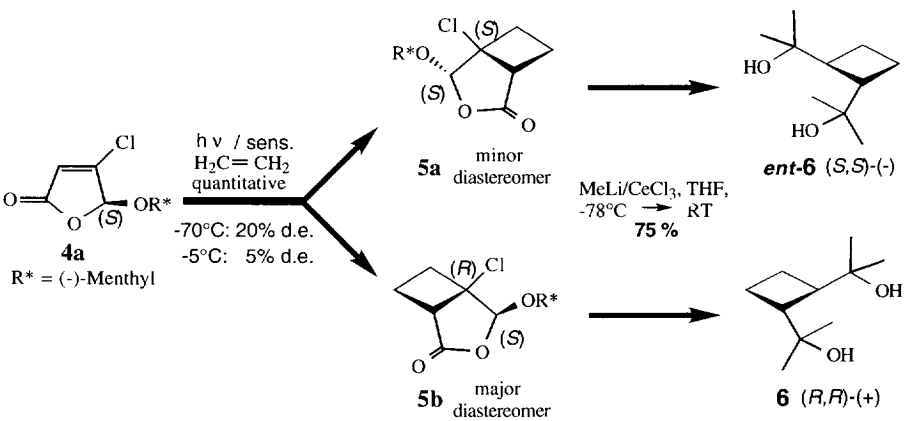
Scheme 1.

According to scheme 2 compound **4a** was irradiated in the presence of ethene. Triplett sensitized [2+2]-photocycloaddition reactions of enones with olefins are well known[9]. In our case acetone was the solvent and was also used as a triplett sensitizer. This photocycloaddition reaction proceeds in excellent yields and is very fast because the halide accelerates the intersystem crossing[10]. We obtained two diastereomeric forms of (4*S*)-5-chloro-4-(-)-menthyloxy-3-oxabicyclo[3.2.0]heptan-2-one **5a,b** which could be separated easily by column chromatography. The first eluated diastereomer **5a** has the (1*R*, 4*S*, 5*S*)-configuration, the second one **5b** the (1*S*, 4*S*, 5*R*)-configuration. Both diastereomers were obtained as syrups. One sample of **5b** however crystallized after a long period stored in the refrigerator to a solid having a m. p. of 54 °C. No side products were observed in this reaction.

In photo cycloaddition reactions of chiral enones and olefins the diastereomeric excess most depends on the temperature[11]. In our case we found that **5b** was always the major diastereomer in the investigated temperature interval. The diastereomeric excess decreased from 20% (-70 °C) to 5% (-5 °C).

Compound **6** was synthezised by treatment of **5** with the organocerium compound "H_3CCeCl_2", which was generated according to the literature[12]. Although the exact reaction mechanism (scheme 3) is not known our results clearly indicate, that the reaction proceeds through the formation of lactol **7**[14]. We were able to show that the product selectivity depended on the reaction temperature. Quenching the reaction mixture after stirring for two hours at -78 °C with saturated aqueous $NaHCO_3$ gave lactol **7**, isolated as a single product in 75% yield. Allowing the mixture to warm up to room temperature very slowly before quenching the reaction resulted in exclusive formation of compound **6** (75% yield).

Using the pure compound **5a** in this reaction gave one of the enantiomers of **6** with an e.e. higher than 98%. **5b** formed the other enantiomer with the same e.e. value. This was demonstrated by chiral gas chromatography. Using **5b** this reaction leads selective to **6**. Using **5a** it leads to ***ent*-6** as shown in scheme 2.

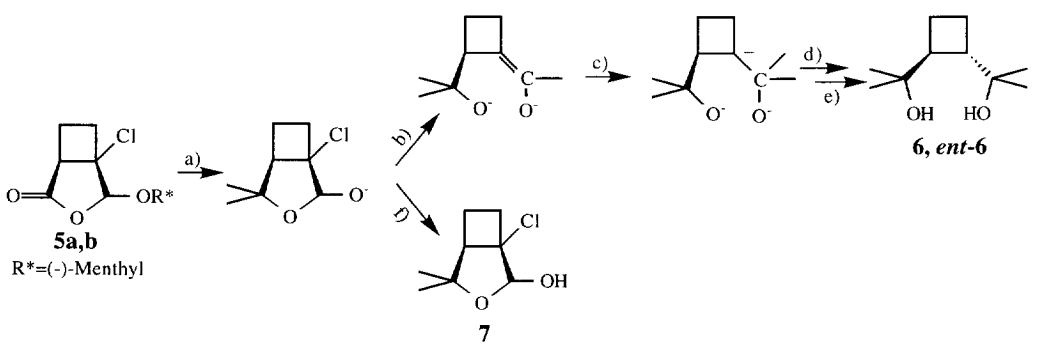


Scheme 2.

Structural determination.

First we determined the configuration of compound **4a** to be (5*S*) by comparative NMR-spectroscopy. As references we used configurationally well known analogues[8; 13]. Based on this assumption it was possible to define **5b** to be the (1*S*, 4*S*, 5*R*)-configurated diastereomer and **5a** to be the (1*R*, 4*S*, 5*S*)-configurated one by NOE-measurements. An X-ray-structure of compound **5b** showed the absolute (1*S*, 4*S*, 5*R*)-configuration and confirmed structural determination by NMR-spectroscopy.

To establish the stucture of **6** and ***ent*-6** we first synthesized the racemic monoacetate. NOE-measurements of this compound indicated the *trans*-structure. The X-ray-analysis of **6** showed the *trans*-structure clearly but unfortunately it could not prove the absolute configuration. Nevertheless **6** posessess the (*R*, *R*)-(+)-*trans*-structure and ***ent*-6** the (S, S)-(-)-*trans*-structure according to their educt structures **5b** (1*S*, 4*S*, 5*R*) and **5a** (1*R*, 4*S*, 5*S*). In conclusion we substantiate this findings by the following. The configuration of the educts **5a,b** and the *trans*-stucture of **6** and ***ent*-6** were established by X-ray-analysis. The enantiomeric purity of **6** and ***ent*-6** was determined by chiral capillary GC. Even while the mechanism leading from **5b** to **6** and from **5a** to **ent-6** is not exactly clear, it is certain that the carbonyl function is first methylated twice. Any assumed mechanism from **5b** to ***ent*-6** and from **5a** to **6** would involve complete inversion of the (1)-position, which is a saturated carbon atom, and also a halogen abstraction followed by a hydrogen saturation with a complete retention in the (5)-position of the educts which is very unlikely. Consequently our proposed mechanism (scheme 3) is plausible.



Scheme 3: Proposed mechanism for the generation of **6** and ***ent*-6.** a) $+2LiCH_3$, $-RO^{*-}$; b) $-HCl,+LiCH_3$; c) $+LiCH_3$; d) $+H^+$; e) $+2H^+$; f) $+H^+$

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Experimental Section

4-Chloro-5-hydroxy-[5H]-furan-2-one 3. Morpholinium chloride (136 g, 1,1 moles) and glyoxylic acid monohydrate **1** (92 g, 1 mol) were stirred in dioxane (300 ml) for one hour. After addition of chloroacetic aldehyde **2** (1 mole, 150 g of a 50% solution in water) the mixture was stirred for additional 30 minutes and

refluxed for 72 hours. To remove dioxane the solution was concentrated under reduced pressure, and the residue was perforated with ether for 6 days. Afterwards the ether layer was dried over $MgSO_4$ and concentrated. The residue was distilled in vacuo to yield 80.6 g (60%) of compound **3**. b.p. 104 °C / 0.01 torr. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 6.25 (OH), 6.24 (d, J = 1Hz, 1H), 6.08 (d, J = 1Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 169.66, 158.38, 119.37, 98.34 ppm.

4-Chloro-5-(-)-menthyloxy-[5H]-furan-2-one 4a,b. Equimolar quantities of 4-chloro-5-hydroxy-[5H]-furan-2-one **3** and (-)-menthol were dissolved in toluene. After addition of a catalytic amount of *p*-toluene sulphonic acid the mixture was heated on a water trap until water separation was finished. After cooling the mixture was washed with aqueous saturated $NaHCO_3$-solution and with water, dried over $MgSO_4$ and concentrated under reduced pressure. The combined yield **4a,b** is 80 to 95%, the **4a / 4b** ratio is 55 / 45.

(5*S*)-4-Chloro-5-(-)-menthyloxy-[5H]-furan-2-one 4a[15]**.** The pure (5*S*)-configured diastereomer **4a** can be isolated by repeated crystallisation of the crude product from *n*-hexane in amounts of 10%. m.p. 118 °C. $[\alpha]_D^{20}$ = +25.26 (c = 1.16, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 6.19 (d, J = 1Hz, 1H), 5.76 (d, J = 1Hz, 1H), 3.55 (d / t, 4.5 / 10.5Hz, 1H), 2.29 (m, 2H), 1.67 (m, 2H), 1.43 (m, 1H), 1.37 (m, 1H),1.11 (m, 1H), 1.01-0.87 (c.a., 2H), 0.94 (d, J = 6.5Hz, 3H), 0.95 (d, J = 7Hz, 3H), 0.82 (d, J = 7Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 125 MHz): δ = 167.74, 156.16, 119.67, 103.65, 84.17, 48.09, 42.16, 34.06, 31.62, 25.29, 23.02, 22.11, 20.85, 15.9 ppm. Anal. Calcd for $C_{14}H_{21}ClO_3$: C, 61.63; H, 7.77; found: C, 61.59; H, 7.72.

(1*R*, 4*S*, 5*S*)-and (1*S*, 4*S*, 5*R*)-5-Chloro-4-(-)-menthyloxy-3-oxabicyclo [3.2.0] heptan-2-one 5a,b. The following describes a typical run. In a standard photoreactor with gas-inlet (sintered glassplug) and a quartz immersion well 1.5 g of (5*S*)-4-chloro-5-(-)-menthyloxy-[5H]-furan-2-one **4a** dissolved in 200 ml of acetone were placed. After the solution was cooled down to -70 °C and saturated with ethene it was irradiated for two hours. As light source a Phillips HPK-125W lamp was used. During the irradiation a slow stream of ethene was bubbled through the reaction mixture. After irradiation the acetone was removed in vacuo. Separation by column chromatography [ethylacetate / *n*-hexane (1:4)] afforded in order of increasing polarity the minor diastereomer **5a** and the major diastereomer **5b** as diastereomerically pure compounds. The total yield of cyclobutanes **5a** and **5b** is quantitative. **5a**: $[\alpha]_D^{20}$ = +60.1 (c = 0.91, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 5.66 (s, 1H), 3.53 (d / t, J = 6.5 / 10.5 Hz, 1H), 3.26 (m, 1H), 3.07 (m, 1H), 2.63 (m, 1H), 2.39 (m, 1H), 2.22 (m, 1H), 2.12 (m, 1H), 2.02 (m, 1H), 1.66 (m, 2H), 1.42 (m, 1H), 1.36 (m, 1H), 1.1 (m, 1H) 1.0 (m, 1H), 0.93 (m, 6H), 0.85 (m, 1H), 0.8 (d, J = 7Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 125 MHz): δ = 174.95, 110.76, 83.65, 65, 48.27, 47.38, 42.29, 34.14, 31.6, 29.75, 25.73, 23.24, 22.12, 20.88, 19.34, 16.15 ppm. Anal. Calcd for $C_{16}H_{25}ClO_3$: C, 63.87; H, 8.39; found: C, 64.29; H, 8.46. **5b**: m.p. 54 °C. $[\alpha]_D^{20}$ = +9.6 (c = 0.99, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 5.37 (s, 1H), 3.49 (d / T, 6.5 / 11Hz, 1H), 3.17 (m, 1H), 2.87 (m, 1H), 2.7 (m, 1H), 2.51 (m, 1H), 2.32 (m, 1H), 2.2 (m, 1H), 2.07 (m, 1H), 1.65 (m, 2H), 1.4 (m, 1H), 1,37 (m, 1H), 1.1 (m, 1H), 0.98 (m, 1H), 0.93 (d, J = 7Hz, 3H), 0.9 (d, J = 7Hz, 3H), 0.84 (m, 1H), 0.77 (d, J = 7Hz, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 125 MHz): δ = 175.95, 106.99, 83, 65.55, 48.22, 45.61, 42.37, 34.27, 34.09, 31.66, 24.96, 22.76, 22.15, 21.01, 20.85, 15.73 ppm. Anal. Calcd for $C_{16}H_{25}ClO_3$: C, 63.87; H, 8.39; found: C, 64.13; H, 8.47.

(*R*, *R*)-(+)-*trans*-1,2-Di-(2-hydroxy-2-propyl)-cyclobutane 6. 37.25 g of cerium chloride ($CeCl_3$*7 H_2O, 100mmol) were dried to constant weight under vacuum (140 °C, 0.1 mm Hg). The resulting powder was cooled under vacuum, and then the flask was flushed with nitrogen. At that time freshly absoluted

tetrahydrofuran (300 ml) was added, and the resulting suspension was stirred overnight. The mixture was cooled to -78 °C, whereupon methyllithium (100 mmol; 62.5 ml of a 1.6 M ether solution) was added dropwise. The yellow suspension was stirred for an additional hour at -78 °C, and a solution of (1*R*, 4*S*, 5*R*)-5-chloro-4-(-)-menthyloxy-3-oxabicyclo [3.2.0] heptan-2-on **5b** (3 g, 10 mmol) in 50 ml of absolute tetrahydrofuran was added dropwise. Afterwards the reaction mixture was allowed to warm up to room temperature very slowly overnight. The resulting brown reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$. The liquid layer was decanted, and the slimy residue was stirred with ether and decanted forming a solid during this procedure. The combined organic phases were concentrated under reduced pressure at 30 °C almost to dryness. The residue was taken up with ether, dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography [ethylacetate / *n*-hexane (1:1)] gave 1.29 g (75%) of **6**. $[\alpha]_D^{20}$ = +10.91 (c = 1.12, $CHCl_3$), m.p = 104 °C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.3 (m, 1H), 1.7 (m, 1H), 1.4 (m, 1H), 1.19 (s, 3H), 1.11 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 70.76, 47.93, 27.95, 24.27, 20.15 ppm. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.7; H, 11,72; found: C, 69.4 ; H, 11.85

(*S*, *S*)-(-)-*trans*-1,2-Di-(2-hydroxy-2-propyl)-cyclobutane *ent*-6.This compound was synthesized in line with **6.** (1*S*, 4*S*, 5*S*)-5-chloro-4-(-)-menthyloxy-3-oxabicyclo [3.2.0] heptan-2-one **5a** was used as educt material instead of **5b**. The yield was 1.24 g (72%). $[\alpha]_D^{20}$ = -11 (c = 0.93, $CHCl_3$). The other physical data and properties are equivalent to those of compound **6**. Chiral gas chromatography: Lipodex-E, 25 m., 130 °C isotherm.

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14. Lactol **7** occurs in the *syn*- and the *anti*-form (ratio *syn* / *anti* = 23.5 / 76.5). Spectral data of the major diastereomer: H-NMR ($CDCl_3$, 500 MHz): δ = 5.57 (s, 1H), 2.78 (m, 1H), 2.69 (m, 1H), 2.22 (m, 1 H), 2.06 (m, 1H), 1.84 (m, 1 H), 1.31 (s, 3H),1.22 (s, 3H).ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 103.66, 81.32, 70.91, 56.42, 27.3, 26.62, 23.12, 16.56 ppm. The hydroxyd-proton appears in the region of 5 ppm. Spectral data of the minor diastereomer: ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 5.4 (s, 1H), 2.89 (m, 1H), 2.49 (m, 1H), 2.38 (m, 1H), 2.14 (m, 1H), 1.87 (m, 1H), 1.41 (s, 3H),1.23 (s, 3H).ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 102.17, 83.64, 73.39, 57.63, 33.26, 29.14, 23.45, 16.53 ppm.The hydroxyd-proton appears in the region of 4 ppm.
15. NMR-data of **4b** were obtained from the mixture of diastereomers. ^{13}C-NMR ($CDCl_3$, 125 MHz): δ = 167.97, 156.33, 119.78, 100.45, 80.59, 47.57, 40.37, 34.13, 31.5, 25.24, 23.08, 22.2, 20.84, 15.7 ppm. In the ^{1}H-NMR-spectrum only the acetalic proton [5.86 (d, J = 1Hz, 1H) ppm] and the C-1-proton of the cyclohexan ring [3.65 (d / t, 4.5 / 10.5Hz, 1H) ppm] were clearly different to those of **4a**.

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