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Resolution, Specific Rotation and Absolute Configuration of 2,6,6-Trimethylbicyclo[3.2.0]heptan-*endo*-2-ol and of 2,5-Dimethylbicyclo[3.2.0]heptan-*endo*-2-ol, Key Intermediate in the Synthesis of Grandisol.

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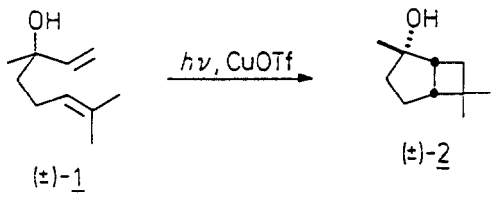
Abstract. Esterification of the title compounds with (1S)-(-)-camphanic acid chloride gave a mixture of diastereoisomeric esters that have been separated by crystallization-column chromatography and converted into enantiomerically pure compounds by reductive cleavage. The purification of diastereoisomers has been performed taking advantage of the different IR (KBr) absorptions of carbonyl groups of each diastereoisomer. The absolute configurations have been assigned to **2** and **4** using an enantiomerically pure sample of (3R)-(-)-linalool that furnished enantiomerically pure (1S,2R,5S)-(+)-**2** by CuOTf-catalyzed photobicyclization.

In 1979 Salomon et al.[1,2] reported an efficient new method for the preparation of bicyclo[3.2.0]heptan-2-ols involving copper(I) trifluoromethanesulfonate (CuOTf) catalyzed $2\pi+2\pi$ photobicyclization of 3-hydroxy-1,6-heptadienes. *endo*-2-Hydroxy epimers of bicyclo[3.2.0]heptan-2-ols were generated stereoselectively in high yields (78-95%) and the preference for stereoselective generation of the less thermodynamically stable epimer was observed to be enhanced (20:1) in the case of 3-hydroxy-3-methyl-1,6-heptadiene derivatives.

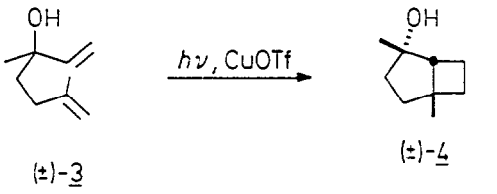
The high stereoselectivity and efficiency of this CuOTf-catalyzed intramolecular photobicyclization has been used to prepare racemic 2,5-dimethylbicyclo[3.2.0]heptan-*endo*-2-ol (**4**), a key intermediate in a successful stereoselective total synthesis of racemic cis-2-isopropenyl-1-methylcyclobutaneethanol (grandisol).[3-6]

As part of a project oriented to devise an easy access to both pure enantiomers of grandisol, we report here the resolution of enantiomers of 2,6,6-trimethylbicyclo[3.2.0]heptan-*endo*-2-ol (**2**), and of 2,5-dimethylbicyclo[3.2.0]heptan-*endo*-2-ol (**4**) via diastereoisomeric ester formation. Our efforts have been focused on the determination of the specific rotation as well as on the assignment of the absolute configuration of compounds **2** and **4**. Actually, we believe that our results could be considered also as unambiguous proof to support the complete stereochemical control of the CuOTf-catalyzed photobicy-

lization of 3-hydroxy-3-methyl-1,6-heptadienes **1** and **3** by which two additional asymmetrical cent re created.



(±)-1 (±)-2 (1)



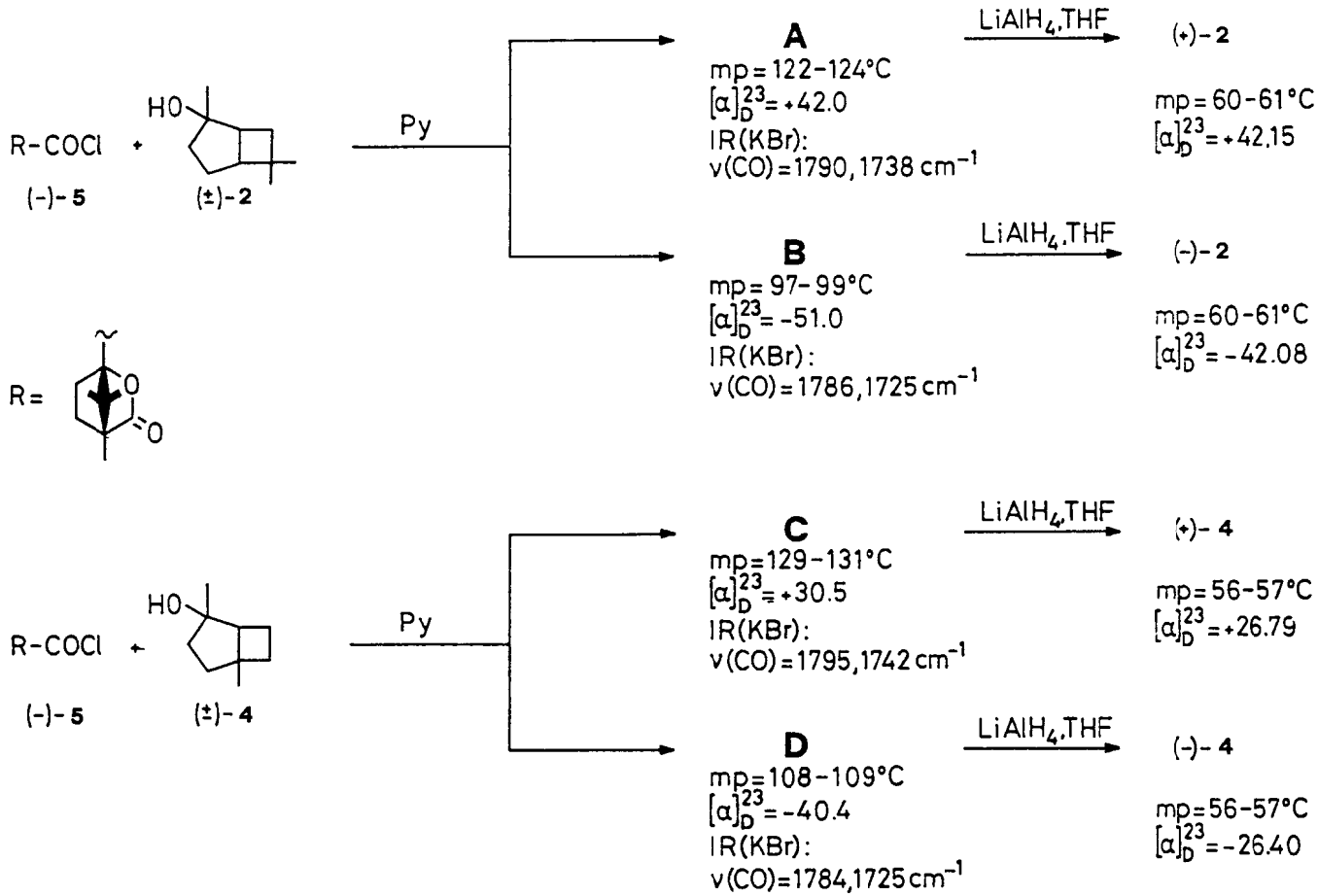
(±)-3 (±)-4 (2)

Pure racemic compounds **2** and **4** were prepared in 95% yield according to the above repor ·ocedures starting from, respectively, racemic **1**[2d] (eq. 1) and **3**[3] (eq.2). From the variety of meth(;ed for resolution of racemic alcohols we chose the separation by fractional crystallization of dias ·oisomeric esters of **2** and **4** with (1S)-(-)-camphanic acid chloride (**5**) introduced by Gerlach[7] 'ficient resolving agent and now commercially available. Compound (-)-**5** reacted with (±)-**2** in ' ·esence of pyridine at 0°C to give a diastereoisomeric mixture of **A** and **B** in almost quantitat eld. Similarly, a diastereoisomeric mixture of **C** and **D** has been obtained starting from racemic he absence of relevant differences in the ^{1}H and ^{13}C NMR spectra of diastereoisomeric couples and **C**, **D** was observed in several different solvents. However, we found that the Gerlach's meth 'fered an important advance never observed previously: in the IR spectra (KBr disk) of the mixt **A** and **B** as well as of the mixture **C** and **D**, multiple carbonyl absorptions were present a; ·mbination of two sharp and strong signals for each of diastereoisomers.

Therefore, we were able to trace the progress of the separation by following the changing abs ion intensities and to determine the ratios of diastereoisomers at any stage of purification using t ethod as easy to apply as is to record an IR spectrum in KBr pellet.

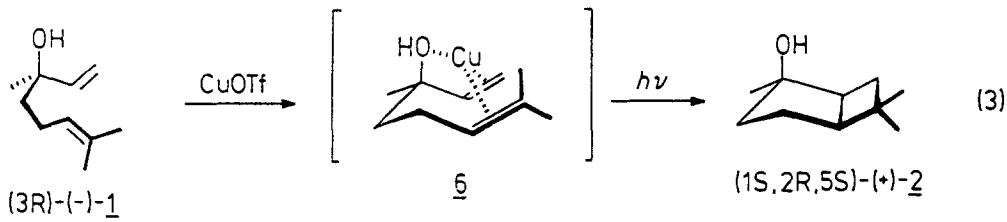
Diastereoisomeric esters obtained from (±)–**2** and (±)–**4** were separated, respectively, into comp ·nts **A** and **B** and into compounds **C** and **D** in several consecutive crystallizations with n-hexane a ccessive column chromatography of the mother liquors. (See experimental part.) Specific rotatio d melting points of pure diastereoisomers **A-D** are reported in Scheme 1 together with the IR (KI ·sorptions, typical of each compound, used as indicators that the separation was complete.

Scheme 1. Resolution of 2-Methylbicyclo[3.2.0]heptan-endo-2-ols 2 and 4



Reductive cleavage of pure diastereoisomers **A-D** with $LiAlH_4$ in tetrahydrofuran gave optically pure enantiomers of **2** and **4** (Scheme 1) in near quantitative yields. It should be noted that both the dextro rotating enantiomers **2** and **4** are derived from the diastereoisomers **A** and **C** respectively, having higher melting points, lower solubility, positive sign of optical rotation and IR (KBr) absorptions (C=O) at higher frequencies with respect to those of the corresponding diastereoisomers **B** and **C** which gave levo rotating enantiomers **2** and **4**.

The absolute configuration assignment for **2**, and accordingly for **4**, was made by using an enantiomerically pure sample of (3R)-(-)-linalool,[8] (-)-**1**. The photobicyclization of this according to the procedure of Salomon gave (+)-**2** (eq. 3) having the same specific optical rotation sign and value observed for the product obtained by reduction of the diastereoisomer **A**. Since the stereospecificity



(3)

of the cuprous triflate catalyzed photobicyclization leading to the formation of 2-methylbicyclo-[3.2.0]heptan-*endo*-2-ols **2** and **4** has been ascribed to the formation of a tridentate ligand as **6**, the absolute configuration of the enantiomer (+)-**2** must be assumed to be (1S,2R,5S). Accordingly the levo rotating alcohol (-)-**2** has the (1R,2S,5R) configuration. Based on the spectroscopical and physico-chemical analogies existing between **A** and **C** as well as between **B** and **D**, summarized in Scheme 1, the (1S,2R,5S)- and the (1R,2S,5R)- configuration have to be assigned to, respectively, (+)-**4** and (-)-**4**.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were recorded as KBr disks. ^{1}H NMR spectra were recorded on a spectrometer operating at 200 MHz. ^{13}C NMR were recorded at 50.3 MHz with a spectrometer by the FT technique. Irradiations were conducted under dry nitrogen in cylindrical Pyrex vessel with a quartz water-cooled double-walled immersion well. Reaction mixtures were stirred magnetically and irradiated internally with a Hanovia medium pressure 450-W mercury vapor lamp. Specific optical rotations were obtained in the solvents specified. Ether and tetrahydrofuran (THF) were distilled prior to use from benzophenone ketyl. (1S)-(-)-Camphanic acid chloride and copper (I) trifluoromethanesulfonate-benzene complex were obtained from Fluka Chemie AG, Buchs (Switzerland). (3R)-(-)-Linalool (95% chemically pure) was obtained from K&K Laboratories, Cleveland, Ohio. It was further purified by spinning band distillation. The distilled material was found to be 99% chemically pure with 98% enantiomeric excess.[8]

Optical Resolution of 2,6,6-Trimethylbicyclo[3.2.0]heptan-*endo*-2-ol (2) via Camphanates A and B. A solution of (±)–alcohol **2** (3.54 g, 23 mmol) in dry pyridine (70ml) was added to an ice-cold, stirred solution of (-)-camphanic acid chloride (4.98 g, 23 mmol) in dry pyridine (20 ml). The mixture was allowed to stand overnight at room temperature poured onto water (100 ml) and extracted with dichloromethane (3x100 ml). The organic layer was washed with 2N hydrochloric acid until acidic pH and then with 5% aqueous sodium bicarbonate (3x20 ml). Evaporation of solvent gave a colorless solid (7.30 g, 91.6% yield). Recrystallization from n-hexane (six times) gave 1.25 g of pure A. Crystals from the mother liquors of the first two crystallizations were collected and purified by column chromatography (silica gel) eluting with n-hexane-diethyl ether 9:1. The first fractions were evaporated and gave 560 mg of pure **B**.

Compound **A**: mp 122-124°C; $[\alpha]_D^{26}$ +42.0 (c 2.00 CHCl3); IR (KBr disk) 1790, 1738 cm^{-1}; ^{1}H NMR δ 0.89, 0.96, 1.04, 1.10, 1.16, 1.42 (3H each, s each, methyls), 1.42-2.45 (11 H, m), 3.03 ppm (1H, m); ^{13}C NMR δ 9.60, 16.65, 16.84, 23.05, 23.29, 23.53, 28.88, 30.68, 31.69, 32.03, 33.97; 37.47, 40.29, 45.23, 53.63, 54.68, 90.01, 91.12, 166.23, 178.26 ppm.

Anal Calcd for $C_{20}H_{42}O_4$: C, 69.31; H, 12.22. Found: C, 69.18; H, 12.15.

Compound **B**: mp 97-99°C; $[\alpha]_D^{26}$ -51.0 (c 2.00 $CHCl_3$); IR (KBr disk) 1786, 1738 cm^{-1}; ^{1}H NMR δ 0.89, 0.96, 1.04, 1.10, 1.16, 1.42 (3H each, s each, methyls), 1.42-2.45 (11 H, m), 3.03 ppm (1 H, m); ^{13}C NMR δ 9.65, 16.69, 16.78, 23.19, 23.39, 23.57, 28.96, 30.62, 31.74, 32.11, 33.95, 37.49, 40.46, 45.21, 53.80, 54.77, 90.10, 91.18, 166.27, 178.30 ppm.

Anal. Calcd for $C_{20}H_{42}O_4$: C, 69.31; H, 12.22. Found: C, 69.18; H, 12.15.

Optical Resolution of 2,5-Dimethylbicyclo[3.2.0]heptan-*endo*-2-ol (4) via Camphana

D. 2,5-Dimethylbicyclo[3.2.0]heptan-*endo*-2-ol (3.85 g, 25 mmol) was treated with (-)-camp chloride (5.41 g, 25 mmol) in pyridine in the same conditions described for compound **1**. Th of the reaction mixture gave a colorless solid (7.36 g, 92%). Recrystallization with n-hexa times) gave 1.300 g, of pure **C**. Crystals obtained from the mother liquors of the two fir lizations were collected and purified by column chromatography (silica gel) eluting with n-h thyl ether 9:1. The first frac tions were evaporated and gave 430 mg of pure **D**.

Compound **C**: mp 129-131°C; $[\alpha]_D^{23}$ +30.5 (c 2.039, $CHCl_3$); IR (KBr disk) 1795, 1742 NMR δ 0.95, 1.04, 1.08, 1.17, 1.40 (3H each, s each, methyls), 1.40-2.01 (10 H, m), 2.32 2.56 ppm (1H, m). ^{13}C NMR δ 9.79, 15.25, 61.88, 17.07, 24.43, 27.94, 27.95, 29.19, 30. 36.93, 37.93, 42.92, 51.66, 53.95, 55.04, 90.67, 91.56, 166.81, 178.91 ppm.

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.18; H, 8.94.

Compound **D**: mp 108-109°C; $[\alpha]_D^{23}$ -40.4 (c 2.050, $CHCl_3$); IR (KBr disk) 1784, 1725 NMR δ 0.97, 1.06, 1.12, 1.19, 1.42 (3H each, s each, methyls), 1.40-2.01 (10 H, m), 2.32 2.56 ppm (1 H, m); ^{13}C NMR δ 9.63, 14.93, 16.72, 16.94, 24.22, 27.69, 28.94, 30.40, 30. 37.55, 42.53, 51.36, 53.80, 54.76, 90.24, 91.16, 166.22, 178.30 ppm.

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.65; H, 8.75.

Reductive cleavage with $LiAlH_4$ - General Procedure

A solution of camphanate **A-D** (10 mmol) in tetrahydrofuran (20 ml) was slowly a suspension of $LiAlH_4$ (0.380 g, 10 mmol) in THF (30 ml) and left under stirring at room te for 12 h. Upon completion of the reaction (TLC control), the mixture was cooled down at saturated aqueous solution of NH_4Cl was added to destroy the hydride in excess. The orga was separated, diethyl ether was added (200 ml) and washed 3 times with water (20 ml), sodium sulfate and evaporated to dryness under reduced pressure:

(1S,2R,5S)-(+)-2,6,6-Trimethylbicyclo[3.2.0]heptan-*endo*-2-ol, (+)-**2**, was obtained in from compound **A**: mp 60-61°C from EtOH/water; $[\alpha]_D^{23}$ +42.15 (c 1.595, CH_3OH).

Anal Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.78; H, 11.83.

(1R,2S,5R)-(-)-2,6,6-Trimethylbicyclo[3.2.0]heptan-*endo*-2-ol, (-)-**2**, was obtained in from compound **B**: mp 60-61°C from EtOH/water; $[\alpha]_D^{26}$ -42.08 (c 1.600, CH3OH).

Anal.Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.73; H, 11.81.

Physico-chemical and spectroscopic data of (+)-**2** and (-)-**2** were in agreement with th racemic compound previously reported.[2d]

(1S,2R,5S)-(+)-2,5-Dimethylbicyclo[3.2.0]heptan-*endo*-2-ol, (+)-**4**, was obtained in 94% yield from compound **C**: mp 56-57°C from EtOH: water and successive sublimation at 65°C/15 mmHg; $[\alpha]_D^{26}$ +26.79 (c 1.628, CH_3OH).

Anal. Calcd for $C_9H_{16}O$: C, 74,94; H, 12.58. Found: C, 74.87; H, 12.62.

(1R,2S,5R)-(-)-2,5-Dimethylbicyclo[3.2.0]heptan-*endo*-2-ol, (-)-**4**, was obtained in 91% yield from compound **D**: mp 56-57°C from EtOH/water and successive sublimation at 65°C/15 mmHg; $[\alpha]_D^{26}$ -26.40 (c 1.622, CH_3OH).

Anal.Calcd for $C_9H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.89; H, 12.65.

The spectroscopic data of (+)-**4** and (-)-**4** were identical with those of the racemic compound previously reported.[3]

Photobicyclization of (3R)-(-)Linalool. The reaction was performed according to the previously reported procedure of Avasthi and Salomon.[2d] A solution of (3R)-(-)-linalool[8] (8.23 g, 53 mmol) and copper(I) trifluoromethanesulfonate-benzene complex (0.5 g) in anhydrous ether (600 ml) was irradiated 15 h with a 450-W Hanovia lamp in a quartz immersion well. After completion of the irradiation, the reaction mixture was quenched with a mixture of crushed ice (100 g) and 30% NH_4OH (10 ml). The deep blue aqueous phase was separated and extracted with ether (2x50 ml). The combined organic extracts were washed with brine and dried over $MgSO_4$. Removal of the solvents by rotary evaporation gave (+) **2** (7.74 g, 94%): mp 60-62°C; $[\alpha]_D^{23}$ +41.48 (c 2.548, CH_3OH). The spectroscopic data of compound (+)-**2** were identical with those of the racemic **2** previously reported.[2d]

Anal.Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.75; H, 11.81.

Acknowledgements.

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