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Article

The Enantioselective Synthesis of (*R*)-(+)-6-Isopropenyl-3-Methyl-2-Cycloheptenone

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(*R*)-(+)-6-isopropenil-3-metil-2-cicloeptenona foi sintetizada a partir de (*R*)-(-)-carvona, por redução e formação do éter-enólico-trialquilsilil, ciclopropanação com iodeto de metileno e dietil-zinco, seguida por oxidação de Saegusa com cloreto férrico e finalmente, desidroalogenação com base. O produto final, um quiron para a síntese de produtos naturais sesquiterpênicos do tipo guaiano, foi obtido em cinco etapas com 38% de rendimento global.

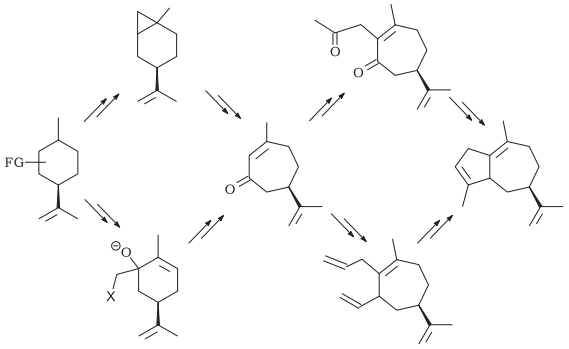
(R)-(+)-6-isopropenyl-3-methyl-2-cycloheptenone is synthesized from (*R*)-(-)-carvone by reduction and trialkylsilyl-enolether formation, cyclopropanation with methylene iodide and diethylzinc, followed by a Saegusa type oxidation with ferric chloride and finally dehydrochlorination with base. The title compound is obtained in five steps and 38% overall yield, being a useful chiron for guaiane sesquiterpene natural products.

Keywords: cycloheptenone, carvone, ring expansion, perhydroazulene, enantioselectivity

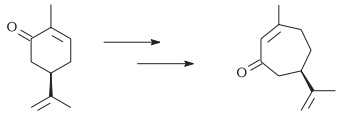
Introduction

The total synthesis of guaiane sesquiterpenes[1] is of current interest due to innumerous examples of these natural products with relevant biological activities, and the challenge of the perhydroazulene carbon skeleton containing two methyl and an isopropyl groups. Our interest in their synthesis has led us to develop methods for the transformation of *para*-menthane monoterpenes into single isomer cycloheptenones,[2-4] and then by pent-annelation[5,6] into the required complete carbon skeleton. Scheme 1 outlines our synthetic strategy which involves two quite different routes for the ring expansion, by cyclopropanation and central sigma bond cleavage[2,3] or nucleophilic addition and rearrangement.[4] The intermediate cycloheptenone can then by pent-annelated by more classical ionic reactions (allylation, Wacker oxidation and intramolecular aldol reaction)[5] or by the ring closing metathesis[6] of a suitable neighboring allyl-vinyl derivative.

Thus far we have developed several distinct methodologies for the ring expansion of different *para*-menthane monoterpenes, and in this paper we would like to describe a new route which transforms readily available (*R*)-(-)-carvone (**1**) into the desired (*R*)-(+)-6-isopropenyl-3-methyl-2-cycloheptenone (**2**) in five steps and 38% overall yield (Scheme 2), with complete regioselectivity and retention of stereochemical integrity.



Scheme 1. FG = functional group(s).



Scheme 2.

Results and Discussion

The enantiodivergent strategy we have developed[3] requires a double bond in the *para*-menthane structure at the C-1 to C-2 centers for the (*R*)-cycloheptenone enantiomer or the C-1 to C-6 centers for the (*S*)-enantiomer (Scheme 3).

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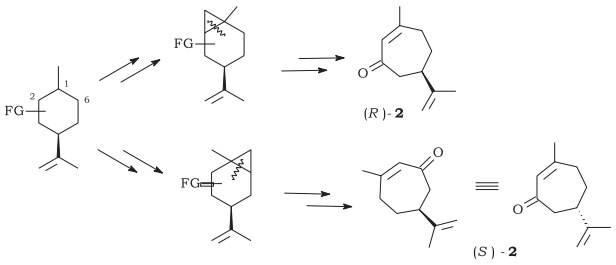
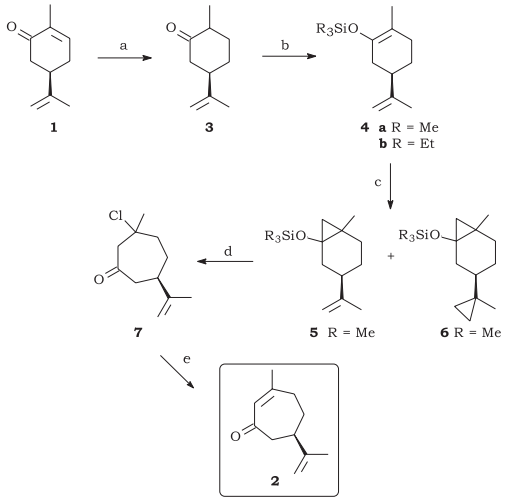


Scheme 3. FG = functional group(s).

Herein we describe an enantio- and regioselective route to the (*R*)-enantiomer of **2** by regioselective formation of the trialkylsilyl-enolether **4** of dihydrocarvone (**3**) followed by chemoselective cyclopropanation and oxidative cleavage of the common sigma bond. Elimination of HCl with base completes the synthesis of **2** (Scheme 4).

A similar strategy was used by Marques *et al.*[7] in the synthesis of the sesquiterpene africanol, for the ring expansion of 2,5,5-trimethyl-cyclohexanone.



Scheme 4. Reagents and conditions: a) Zn^o, KOH, MeOH/H_2O, reflux, 9 hours, 84%; b) R_3SiCl, NaI, Et_3N, CH_3CN, room temp., (R = Me) 1 hour 89%; (R = Et) 4 hours, 73%; c) CH_2I_2 (1 equiv.), Et_2Zn (1mol L^{-1} in hexane), toluene/CH_2Cl_2, 2 hours, room temp., 83%, (95:05 **5**:**6**, R = Me); d) $FeCl_3$, DMF/CH_2Cl_2, 1 hour at 0 °C, 2 hours at room temp., 82%; e) NaOAc, MeOH, reflux, 2 hours, 74%.

The reduction of the conjugated double bond of (*R*)-(-)-carvone (**1**) can be readily effected with zinc dust in alkaline methanol/water as we have developed[3] in our laboratory, as a simple modification of the well known electron transfer methods, thus producing dihydrocarvone (**3**) as an epimeric mixture. The weak base catalyzed enolization leads to the thermodynamically preferred enolate which is captured by both trimethylsilyl chloride and triethylsilyl chloride, leading to enolethers **4a** and **4b** in excellent overall yields from carvone (**1**).[3]

The key step of chemoselective cyclopropanation of **4** to produce the substituted nor-carane **5** was executed by the Furukawa modification[8] of the Simmons-Smith reaction,[9] using methylene iodide in the presence of diethylzinc. This reaction was found to be very capricious with respect to reproducibility and highly influenced by the two reagents. Methylene iodide is not easily purified by standard methods including distillation and chromatography on silica gel without substantial loss of reagent. In the event, we purify methylene iodide by quick treatment with the minimum quantity of silica gel whereupon the reagent becomes colorless for a short time. In a similar fashion, solutions of diethylzinc are of variable reactivity depending upon concentration, solvent and even batch, and diethylzinc is best acquired as a dilute solution (approximately molar) in hexane.

We have found very little difference between the reactivities of the trimethylsilyl ether **4a** or the triethylsilyl ether **4b**, the same being true for their stabilities with respect to the reagents. Thus the cyclopropanation reactions described below were all performed with the more readily available trimethylsilyl ether **4a**.

In the first procedure described in the experimental section, we have utilized the very surprising catalytic effect of a dry oxygen atmosphere[10] on this cyclopropanation reaction. This method gave us the best results of 83% yield of **5** and **6** in a 95 to 5 relation. This reaction was performed in toluene and dichloromethane (1:1) for 2 hours at room temperature with one equivalent of methylene iodide. Gas chromatographic analysis of the diastereomeric mixture of **5** gave a 6% diastereomeric excess of an undetermined isomer, confirming the expected lack of stereoselectivity of the cyclopropanation at the internal double bond.

The standard procedure[8] with maintenance of the dry nitrogen atmosphere and conducted in toluene as solvent, gave variable results of chemoselectivity and isolated crude yields of **5** and **6**, as described in the second procedure. Although higher yields can be obtained with the use of more methylene iodide and diethyl zinc, as expected the chemoselectivity for **5** over **6** decreases substantially. A third method was attempted based on a publication by Charette *et al.*[11] In this method the solvent is dimethoxyethane which is proposed to have a complexing effect on the organo-zinc carbenoid. In the event, and with large excesses of methylene iodide and diethylzinc in dichloromethane for extended reaction times, no reaction was observed and starting material was recovered.

The separation and purification of **5** and **6** is not trivial, and requires careful column chromatography. We obviously investigated many different reaction conditions

to avoid formation of the bis-cyclopropane **6** but with no success, which indicates similar kinetics of the reactions at the two double bonds. Although we had expected much higher reactivity at the trialkylsilyl-enol ether site for electronic arguments, we interpret this as being due to the reactivity of the methylene zinc carbenoid and possible steric effects. However, the cyclopropanation reaction is still highly chemoselective for the desired double bond, but the bis-cyclopropanated product **6** is still present to the extent of 5% in subsequent reactions.

The Saegusa oxidation[12] of mono-cyclopropanated **5** with dry ferric chloride in dimethylformamide led easily to the ring expanded 3-epimeric mixture of the 3-chloro-cycloheptanone **7** in 82% yield. Finally, treatment with sodium acetate in methanol at reflux furnished the conjugated cycloheptenone **2** in 74% yield. Alternatively, we have executed these two reactions without isolation of intermediate **7**, although the yield is comparable, and this procedure is also described in the experimental section.

Gas chromatographic analyses on chiral columns were performed, and demonstrate unequivocally that the cycloheptenone **2** has the same extremely high enantiomeric excess as starting material (*R*)-(-)-carvone (**1**), and therefore maintenance of stereochemical integrity. Determination of the optical activity allowed comparison with samples prepared earlier in our laboratory[3] and also confirm very high enantiomeric excess. The previous samples[3,4] have optical rotations (α_D) of +51.0 (c 1.47, ($CHCl_3$) and +49.0 (c 0.13, $CHCl_3$) respectively, whereas the present work shows optical rotations of +61.3 and +56.0 (c 0.02, $CHCl_3$) in two different procedures. These small differences are certainly due to the presence of trace chemical impurities and not to different enantiomeric excesses.

Conclusions

We have demonstrated the efficient synthesis of the single isomer (*R*)-(+)-cycloheptenone **2** in five steps from (*R*)-(-)-carvone (**1**). With the exception of the cyclopropanation reaction, the other reactions are all easily amenable to execution at the 10 to 20 gram scale, use relatively simple reagents and require very little chromatographic purification. This allows us to prepare large quantities of the desired cycloheptenone **2** in a relatively short time.

Experimental

General

^1H and ^{13}C NMR spectra were obtained on a Bruker DRX-400 spectrometer at 400 and 100 MHz, and on a Bruker ARX-200 spectrometer at 200 and 50 MHz respectively, with $CDCl_3$ as solvent. Chemical shifts are in ppm downfield from a tetramethylsilane internal standard. Infrared spectra were recorded on Bomen Michelson model 102 FTIR or Hartman & Braun MB, and the most intense or representative bands are reported (in cm^{-1}). Mass spectra were determined by APCI with MeOH using a Micromass Quattro LC/MS spectrometer. Melting points were determined on a Micro Química model APF 301 apparatus and are uncorrected. Radial chromatography was performed on a Chromatotron® model 8924 with 2 mm plates of silica gel 60, PF 254 with calcium sulphate, E. Merck 7749. Gas liquid chromatographic analyses were performed on a Shimadzu GC-17A, equipped with a DB-1 capillary column (0.25 mm × 30 m) and using nitrogen as carrier gas. The chiral GC analyses were performed on a heptakis-2,6-dimethyl-3-pentyl-b-cyclodextrin column on a HP Agilent 6890 series gas chromatograph, with nitrogen as carrier gas, at the Chemistry Institute, UNICAMP, in Campinas. The optical rotation measurements were determined on a Perkin-Elmer model 241 polarimeter. The micro-analytical data were obtained on a Fisons EA 1108 CHNS-O Analyser. Reactions with compounds sensitive to air or moisture were performed under a dry nitrogen atmosphere. Solvents and reagents were used directly from the manufacturer, or purified when required by standard procedures. Anhydrous solvents were dried by refluxing over sodium wire in the presence of the benzophenone ketyl as indicator. Methylene iodide was purified by swirling in a conical flask with the minimum quantity of chromatographic quality silica gel, and decantation under nitrogen pressure. Diethylzinc is an approximately 1 molar solution in hexane, obtained from Aldrich, and analyzed previous to use by the usual methodology for butyllithium solutions.

Dihydrocarvone (**3**), the trimethylsilyl-enolether **4a** and the triethylsilyl-enolether **4b** were prepared by our published procedures.[3]

*Cyclopropanation of the trimethylsilyl-enolether **4a** to (3R)-3-isopropenyl-6-methyl-1-trimethylsilyloxy-bicyclo-[4.1.0.]-heptane **5***

Method (i). To a solution of trimethylsilyl-enolether **4a** (1.413 g, 6.29 mmol) in dry toluene and CH_2Cl_2 (1:1; 6.30 mL), under dry nitrogen and at ice bath temperature, was slowly added a solution of Et_2Zn (1.0 mol L^{-1} in hexane, 6.30 mL, 6.30 mmol), and then drop-by-drop CH_2I_2 (0.30 mL, 6.30 mmol). The inert atmosphere and ice bath were

removed and the reaction mixture was stirred under a dry oxygen atmosphere. After 2 h, the mixture was stirred with a saturated solution of NH_4Cl (8 mL) for 10 min. The suspension was filtered through Celite® with a hexane wash, the organic layer was then washed with a solution of NH_4Cl and NH_4OH (95:0.5) and a saturated solution of NH_4Cl, dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated. The crude product (1.494 g) was purified by column chromatography on silica gel, using hexane with 2% of Et_3N as eluent, to afford 1.235 g (83%) of **5** as a yellow oil; $[\alpha]_D^{29}$ +54.0 (c=0.03; $CHCl_3$).

An analytical sample was prepared by further purification by column chromatography on silica gel, using hexane: EtOAc (98:2) with 2% of Et_3N as eluent. IR ν_{max}/ cm^{-1}: 840, 983, 1250,1447,1691,2855, 2925, 3068. ^1H NMR (400MHz, $CDCl_3$) δ: 0.15 (broad s, 9H), 0.39-0.46 (m, 2H), 1.18 (s, 3H), 1.67 (s, 3H), 2.13-2.18 (m, 1H), 4.63-4.65 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.4, 20.7, 20.8, 23.8, 25.7, 28.1, 31.7, 40.9, 42.1, 60.2, 108.5, 149.9. MS (APCI), *m/z* $[M+H]^+$= 239. $[\alpha]_D^{27}$ + 70.5 (c = 0.42; $CHCl_3$). Anal. Calc. for $C_{14}H_{26}SiO$: C, 70.52; H, 10.99: Found: C, 70.33; H, 10.75.

Method (ii). To a solution of trimethylsilyl-enolether **4a** (571 mg, 2.54 mmol) in anhydrous toluene (3.28 mL), under dry nitrogen at aprox. –10 °C, was slowly added a solution of Et_2Zn (1.0 mol L^{-1} in hexane, 4.58 mL, 4.58 mmol), and then drop-by-drop CH_2I_2 (0.28 mL, 3.52 mmol, 1.38 equiv.). The cooling bath was removed after 15 min, and the reaction was followed by gas chromatographic analysis. The reaction mixture was stirred at room temperature for 2.5 h, and then a saturated solution of NH_4Cl (2 mL) was added and allowed to stir for 10 min. The suspension was filtered through Celite® and washed with hexane, the organic layer was then washed with a saturated solution of NH_4Cl, dried over anhydrous Na_2SO_4, filtered, and the solvent evaporated to give the crude product (589 mg). GC analysis indicated the presence of 20% starting material **4a**, and products **5** and **6** in a 4 to 1 proportion, as determined by peak areas.

*(6R)-3-chloro-6-isopropenyl-3-methyl-cycloheptanone (**7**)*

Method (i). To a solution of **5** (589 mg, with traces of **6**) in DMF (2.10 mL) and CH_2Cl_2 (0.10 mL) at O °C, was added dropwise a solution of $FeCl_3$ (1.160 g, 7.14 mmol; purified by refluxing with $SOCl_2$) in DMF (4.60 mL). The reaction mixture was stirred for 1 h, at O °C and another 2 h at room temperature. A solution of HCl (1.0 mol L^{-1}, 10 mL) was then added and the product was extracted with hexane (7 x 10 mL). The organic layer was washed successively with a solution of HCl (1.0 mol L^{-1}, 10 mL), a saturated solution of $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated to give **7** (407 mg, 82%).

Method (ii). To a solution of **5** (1.235 g, with traces of **6**) in THF (0.30 mL) and CH_2Cl_2 (6.35 mL), at O °C and under a nitrogen atmosphere, was added drop-by-drop a suspension of anhydrous $FeCl_3$ (3.30 g, 20.31 mmol) and silica gel (3.30 g) in THF (13.50 mL). After 1 h the cooling bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The nitrogen atmosphere was removed and the reaction mixture was treated directly as described in procedure (*ii*) below.

*(6R)-6-isopropenyl-3-methyl-2-cycloheptenone (**2**)*

Method (i). A solution of **7** (483 mg) in MeOH (30 mL) and a saturated solution of NaOAc (10.0 mL) in MeOH (30 mL) was stirred and the MeOH was evaporated. To the reaction mixture was added MeOH (30 mL), and stirred under reflux for 2 h. The solvent was evaporated and the crude product was purified by column chromatography on silica gel using hexane: EtOAc (9:1) as eluent, to afford **2** in 74% yield as a colorless oil. IR ν_{max}/cm^{-1}: 891, 1442, 1652, 2931, 3072. ^1H NMR (400MHz, $CDCl_3$) δ: 1.73 (broad s, 3H), 1.75-1.83 (m, 1H), 1.91-2.00 (m, 1H), 1.96 (bs, 3H), 2.32-2.38 (m, 1H), 2.49-2.55 (m, 2H), 2.66-2.69 (m, 2H), 4.73 (m, 2H), 5.93 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 27.4, 31.2, 33.7, 40.6, 47.8, 110.0, 129.8, 148.3, 158.5, 202.5. $[\alpha]_D^{29}$ + 61.3 (c = 0.02; $CHCl_3$).

Method (ii). The previously obtained solution of **7** (1.235 g) in MeOH (50 mL) and a saturated solution of NaOAc (20 mL) was stirred and refluxed during 2 h. The product was isolated as described above in procedure (*i*). The crude product was purified by column chromatography on silica gel, using hexane: EtOAc (9:1) as eluent, to afford **2** as a colorless oil in 77% yield. MS (APCI), *m/z* $[M+H]^+$= 165. $[\alpha]_D^{29}$ + 56.0 (c = 0.02; $CHCl_3$).

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