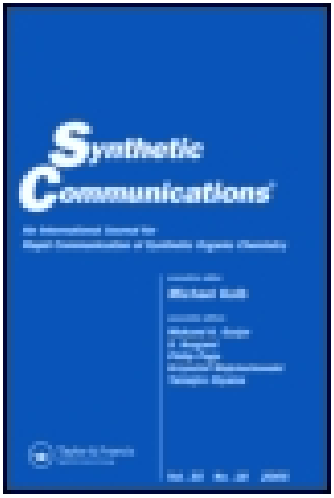

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A Convenient Synthesis of Chiral, Non-Racemic [4aS,8aR]-5,5,8a-Trimethyl Octahydro-2,2-(1,3-Dioxolane)-Naphthalene

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A CONVENIENT SYNTHESIS OF CHIRAL, NON-RACEMIC [*4aS,8aR*]-5,5,8a-TRIMETHYL OCTAHYDRO-2,2-(1,3-DIOXOLANE)-NAPHTHALENE

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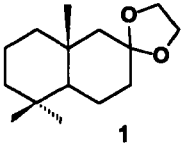
Abstract: *(-)-(4aS,8aR)-5,5-8a-trimethyl-trans-decaline* ***1*** *was prepared in a stereoespecific synthesis of 4 steps and 38% yield. The key-step involves an asymmetric Robinson annulation via Michael addition of chiral imine.*

In connection with our projected synthesis of bicyclic diterpenes of labdane-type, we required a convenient stereoselective preparation of [*4aS,8aR*]-5,5,8a-trimethyloctahydro-2,2-(1,3-dioxolane)-naphthalene (**1**). A large number of naturally occuring 5,5,8a-trimethyl-*trans*-decaline exhibiting diverse biological activities are known[1]. As representative example, Ambrox®[2] constitute a famous target molecule in perfumary. Besides this, compound **1** should be seen as an versatile intermediate in the construction of related diterpenes, due to the possibility of functionalization at the ketone moiety after deprotection. However, a convenient method for the preparation of such intermediate was not avaiable[3].



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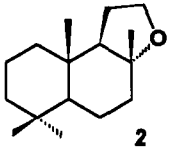

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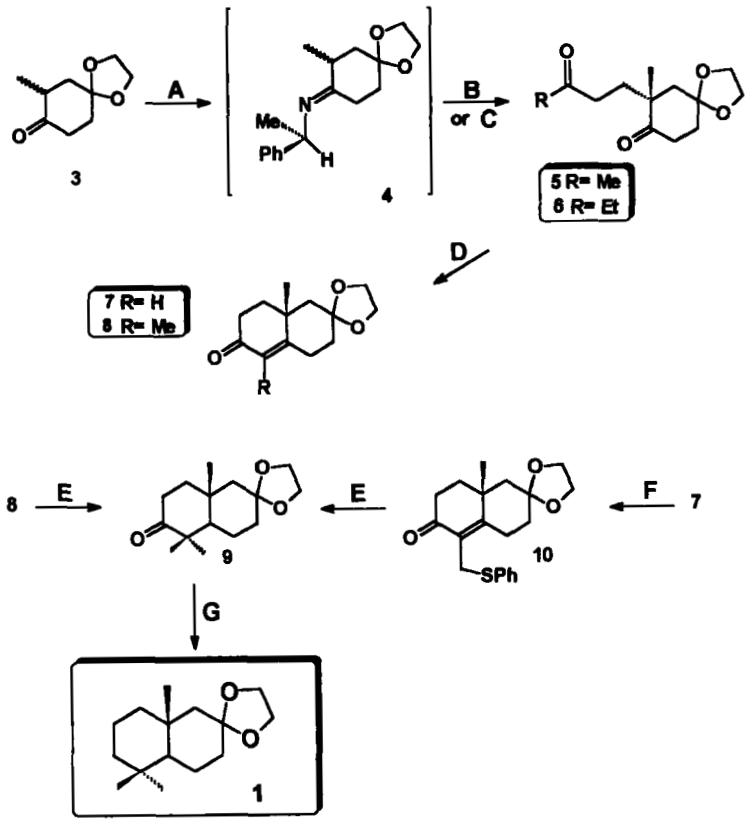
SCHEME 1



A) (R)-(+)-1-phenylethylamine, cat TsOH, benzene, 99%; B) MVK,THF,r.t.,3 days, and then 20% aq. AcOH,73%; C) EVK,THF,r.t.,3 days, and then 20% aq. AcOH, 71%; D) MeONa / MeOH, 5h, 55° C, 87%; E) Li-NH_3, *t*-BuOH, THF, MeI, 88%; F) PhSH, HCHO, Et_3N, EtOH, reflux, 4 days, 87%; G) DEG, KOH, hydrazine, 110°C, 3h, 70%.

We reported here a short synthetic sequence for the preparation of **1** using the "deracemizing alkylation of chiral imines"[4] as the key step to introduce the stereogenic centers. The sequence of reactions used in our approach is outlined in scheme 1.

The starting material, 4,4-ethylenedioxy-2-methyl cyclohexanone (**3**) was prepared by alkylation of available 4,4-ethylenedioxy cyclohexanone.[5] The addition of the chiral imine derivative **4**, prepared from (*R*)-(+)-1-phenylethylamine, to methyl vinyl ketone and ethyl vinyl ketone yielded, after hydrolysis, diketones **5** and **6**, respectively, as the only stereoisomer detected by ^{1}H and ^{13}C NMR. Cyclization of **5** and **6** with sodium methoxide in methanol afforded octalones **7** and **8** in 87% yield. Alkylation of the enolate avaiable *via* lithium-liquid ammonia reduction[6,7] of enone **8** led to decalone **9** in 88% yield. Alternatively, compound **9** could be acessed trough reductive alkylation of enone **10**, prepared by treatment of octalone **7** with aqueous formaldehyde, thiophenol and triethylamine in ethanol, by means of a thioanalogous Mannich reaction, according to the protocol of Kirk and Petrow[8,9]. Finally, Wolff-Kishner reduction[10] of keto group of decalone **9** afforded decaline **1** in 70% yield.

In summary, our four-steps approach to protected decalone **1**, a versatile potential *building block* for the synthesis of labdanes diterpenes, offers excellent yield, high stereoseletivity and convenience.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ solution with a Varian VXR-200 and INOVA-30 instruments. Chemical shifts (δ) are reported in ppm downfield from internal tetramethyl silane. ^{1}H NMR data are reported in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) and number of protons. Infrared spectra were determined with a Mattson Galaxy series FT-3000 spectrophotometer and melting points were determined with digital melting point apparatus Electrothermal iA 9000 series. Silica gel 60 F_{254} plates were used for TLC; 230-400 mesh silica gel were used for chromatography. All chemicals and solvents were of analytical grade and were used without further purification. THF was distilled from sodium/benzophenone under nitrogen immediately before use.The reactions were carried out under argon when necessary. Organic extracts were dried over $MgSO_4$. Gas chromatography analysis were carried out with a Shimadzu GC-174 chromatograph DB-1 column. Specific rotations were mesured at $25^{0}C$ on a Perkin Elmer-Polarimeter 145 at 589 nm (sodium line).

[*1R*]-1-methyl-1(3-butanone)-3-ethylenedioxi-2-oxocyclohexanone (5):

To a solution of 4.5 g (27 mmol) of compound **3** in 16 mL benzene placed in a 50 mL round-bottomed flask equipped with a Dean-Stark apparatus was added 4.1 mL (32 mmol) of (*R*)-(+)-1-phenylethylamine, followed by catalytic amount of p-toluenesulfonic acid. The reaction mixture was refluxed for 5 h, with azeotropic removal of water. After cooling, the reaction mixture was concentrated under reduced pressure and then distilled (10^{-2} mmHg – 152° C) to afford 6.34 g (90%) of **3.** To a solution of **3** in 7.9 mL of THF was added dropwise, methyl vinyl ketone (3.4 mL – 58 mmol), and the reaction mixture was stirred at room temperature, under argon, for 3 days. After that, 10 mL of a solution of 20% aqueous acetic acid was added and the mixture was stirred for 3 h. The solvents were removed under reduced pressure, and 1N HCl (10 mL) was added to the residual oil. The mixture was then extracted with ether and organic phases were treated with brine, dried and concentreted in vacuo to afford 6.24 g of crude material. Flash chromatography on silica gel (hexane: EtOAc, 10:1) gave diketone **5** (4.43 g - 19 mmol – 71%).

5: b.p.= 98-102° C (0.3 mmHg).
IR(film): 2969, 1710, 1456, 1363 cm^{-1}
^1H NMR ($CDCl_3$): δ 4.0 (m, 4H), 2.6 to 1.6 (m,10H), 2.16 (s, 3H), 1.14 (s, 3H).
^{13}C NMR ($CDCl_3$): δ 214.0, 208.2, 107.3, 64.5 and 64.3, 46.9, 45.3, 38.5, 35.7, 34.4, 31.9, 30.0, 21.5.

[*1R*]-1-methyl-1(3-pentanone)-3-ethylenedioxi-2-oxocyclohexanone (6):

This diketone was obtained as described above, as a pale yellow oil in 70% yield.

6: b.p.= 67-69° C (0.2 mmHg)
IR(film): 2969, 1710, 1456, 1363 cm^{-1}
^1H NMR ($CDCl_3$): δ 4.0 (m, 4H), 2.70 to 1,65 (m, 12H), 1.11 (s, 3H), 1.04 (s, 3H).
^{13}C NMR ($CDCl_3$): δ 214.0, 210.8, 107.3, 64.4 and 64.2, 46.9, 45.3, 37.1, 35.9, 35.7, 34.4, 32.0, 23.7, 7.8.

(+)-[*4aR*]-4,4a,5,6,7,8-hexahydro-4a-methyl-6,6'-(1,3-dioxolane)-2(3H)-naphthalenone (7):

1.7 g (7 mmol) of compound **5** was added to a solution of 0.42 g (18 mmol)

of Na in 50 mL methanol under nitrogen. After 5 h at 55° C, the methanol was evaporated under reduced pressure and after ether extraction, the organic layer was treated with water, brine, dried and concentrated in vacuo. 1.35 g (6 mmol; 86% yield) of compound **7** was obtained after flash chromatography (EtOAc:hexane = 1:10).

7: m.p. = 78.9 – 80.2° C (hexane/AcOEt, 95:5)
$[\alpha]_D^{20}$= + 167 (c 2; EtOH)
IR(film): 2933, 2891, 1668, 1619cm^{-1}.
^{1}H NMR ($CDCl_3$): δ 5.76 (s, 1H), 4.0 (m, 4H), 2.72 (m, 1H), 2.50 (m, 3H), 1.8 (m, 6H), 1.36 (s,3H).
^{13}C NMR ($CDCl_3$): δ 199.4, 168.2, 124.5, 108.0, 64.8 and 63.8, 47.9, 38.6, 36.6, 34.9, 33.6, 30.5, 23.4.

(+)-[*4aR*]-4,4a,5,6,7,8-hexahydro-1,4a-dimethyl-6,6'-(1,3-dioxolane)-2(3H)-naphthalenone (8):

This octalone was prepared from diketone **6** following the same procedure as described above, in 86% yield.

8: m.p. = 52.7-53.6° C (hexane/AcOEt, 95:5)(lit[11] 54-54.5° C)
$[\alpha]_D^{20}$= + 135 (c 0,8; CH_2Cl_2)
IR(film): 2931, 2870, 1666, 1613 cm^{-1}.
^{1}H NMR ($CDCl_3$): δ 4.0 (m, 4H), 2.60 (m, 4H),1.79 (s, 3H), 1.61 (d,1H).
^{13}C NMR ($CDCl_3$): δ 198.8, 160.5, 128.6, 107.6, 64.5 and 63.6, 48.3, 37.8, 36.8, 34.4, 33.3, 25.4, 23.5, 10.9.

[*4aR*]-4,4a,5,6,7,8-hexahydro-1-(methylthiophenyl)-4a-methyl-6,6'-(1,3-dioxolane)-2(3H)-naphthalenone (10):

A solution of 1.4 g (6 mmol) of compound **7** with 1.5 equiv. of freshly distilled thiophenol, 1.63 equiv. of 37% aqueous formaldehyde, 1.26 equiv. of triethylamine and 150 mL of ethanol was heated to reflux under nitrogen for 4 days. The solution was cooled and extracted with 5% potassium hydroxide and ether. The organic layer was washed with 5% potassium hydroxide, brine,dried and concentrated in vacuo. 1.7g (5.20 mmol, 87% yield) of compound **10** was obtained after flash chromatography (EtOAc:hexane = 1:40).

10: IR(film): 3055, 2935, 1668, 1088, 737, 702 cm^{-1}.
^1H NMR ($CDCl_3$): δ 7.4 to 7.2 (m, 5H arom.), 3.8 to 4.1 (m, 6H), 2.4 to 2.7 (m, 3H), 1.3 to 1.8 (m, 7H), 1.33 (s, 3H).
^{13}C NMR ($CDCl_3$): δ 196.7, 164.6,136.0, 131.4, 129.3, 129.2, 128.6, 126.7, 107.4, 64.6, 63.7, 48.3, 37.6, 37.3, 34.6, 33.3, 28.8, 26.0, 23.8.

(-)-[*4aR,8aS*]-1,1',8a-trimethylhexahydro-6,6'-(1,3-dioxolane)-2(3H)-naphthalenone (9):

By reductive alkylation of phenylthioenone 10:

A solution of 1.7 g (5.2 mmol) of phenylthioenone **10**, 2 equiv. of anhydrous *tert*-butyl alcohol, and 50 mL of anhydrous THF was added to a stirred solution of 3 equiv. of lithium in 170 mL of anhydrous liquid ammonia over a 20-30 min period. The solution was allowed to stir for another 45 min, whereupon 205 mL of THF was added followed by rapid addition of 15 equiv. of methyl iodide dissolved in 50 mL of THF. The reaction mixture was stirred for 30 min after which the ammonia was allowed to evaporate. The residue was diluted with ether and extracted with water, brine, dried and concentrated in vacuo. 0.95 g (3.8mmol, 74% yield) of compound **9** was obtained after flash chromatography (EtOAc:hexane = 1:40).

By reductive alkylation of octalone 8

To a solution of 1.4 g (5.9 mmol) of compound **8** , 5.9 mmol of anhydrous *tert*-butyl alcohol, 24 mL of anhydrous THF, and 177 mL of anhydrous liquid ammonia under a kindly stream of nitrogen, was added 103 mg (17.6 equiv.) of lithium wire. The blue color persisted for 10 min. To the colorless enolate solution was added 3.7 mL of methyl iodide freshly distiled. After the reaction mixture was stirred for 1 h, the ammonia was evaporated over a 1 h period by using a steam bath. The product was diluted in water and extracted with ether. The etheral solution was washed with brine, dried and concentrated in vacuo. 1.3 g (5.19 mmol; 88% yield) of compound **9** was obtained after flash chromatography (EtOAc:hexane = 1:20).

9: m.p. = 71.8 – 73.5° C
IR(film): 2945, 2877, 1704 cm^{-1}
^1H NMR ($CDCl_3$): δ 4.1 to 3.8 (m, 4H), 2.68 (ddd, J= 16.2 Hz, 12.5 Hz, 6.5 Hz,

1H), 2,36 (ddd J= 16.2 Hz, 6.5 Hz, 3.0 Hz, 1H), 2.0 to 1.0 (m,18H), 1.21 (s, 3H), 1.11 (s, 3H), 1.04 (s, 3H).
^{13}C NMR ($CDCl_3$): δ 108.7, 64.6 and 63.7, 52.7, 50.7, 47.5, 40.1, 35.9, 34.9, 34.4, 26.1, 21.5, 20.9,19.0.

(-)-[*4aR,8aS*]-1,1',8a-trimethyloctahydro-6,6'-(1,3)-naphthalene (1):

A solution of 0.75 g (3 mmol) of ketone **9** in 20 mL of diethylene glycol, 0.5 g of KOH and 1 mL of hydrazine hydrate was heated at 110° C under nitrogen for 3 h. After that the temperature was raised to 220° C for 3 h. The reaction mixture was then cooled, poured into water and extracted with ether. The etheral solution was washed with brine, dried and concentrated in vacuo. 0.50 g (2.1 mmol; 70% yield) of compound **1** was obtained after flash chromatography (EtOAc:hexane = 1:20).

1: $[\alpha]_D^{20}$ = - 64 (c 0.05, CH_2Cl_2)
IR (film): 2925, 1098 cm^{-1}
^1H NMR ($CDCl_3$): δ 4.1 to 3.7 (m, 4H), 2.0 to 0.7 (m, 10 H), 1.03 (s, 3H), 0.88 (s, 3H), 0.81 (s, 3H).
^{13}C NMR ($CDCl_3$): δ 109.3, 64.5 and 63.4, 53.6, 52.2, 42.4, 36.9, 35.3, 33.3, 21.4, 20.2, 19.8.

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