SYNTHESIS OF POTENTIAL PRECURSORS OF CORYMBOLONE AND CORYMBOLOL

Antonio J. C. de Souza, Helena M. C. Ferraz
Instituto de Química - USP - C. P. 20.780 - S. Paulo - SP
Beatriz S. M. Tenius
Instituto de Química - UFRGS - Porto Alegre - RS

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Using the Wieland-Miescher ketone as starting material, the functionalized A-ring of the title compounds was synthesized.

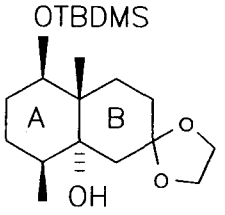
Keywords: sesquiterpenes; synthesis; corymbolone; corymbolol.

INTRODUCTION

Corymbolone (**1**) is a sesquiterpene keto-alcohol first isolated in 1985 from *Cyperus corymbosus Rottboll*[1]. More recently, Corymbolone was also isolated from *C. articulatus* along with another eudesmane sesquiterpene, the diol α-Corymbolol (**2a**)[2]. A crude drug prepared from the rhizomes of these species is used in indigenous medicine as a contraceptive[1].

Our continuous interest in the synthesis of sesquiterpenoid natural products, as well as the absence of any previous synthesis of Corymbolone (**1**) or α-Corymbolol (**2**) in literature, led us to formulate a retrosynthetic approach to these compounds, starting from the known Wieland-Miescher ketone (**3**)[3] as illustrated in Scheme I.

In this paper we wish to report our results[4] concerning the preparation of intermediates with suitably functionalized A-ring (namely, the derivatives **4** and **5**) for the synthesis of **1**, **2a** and **2b**. This later is an epimer of the natural α-Corymbolol, and has already been obtained by reduction of Corymbolone[2].



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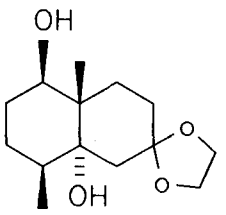

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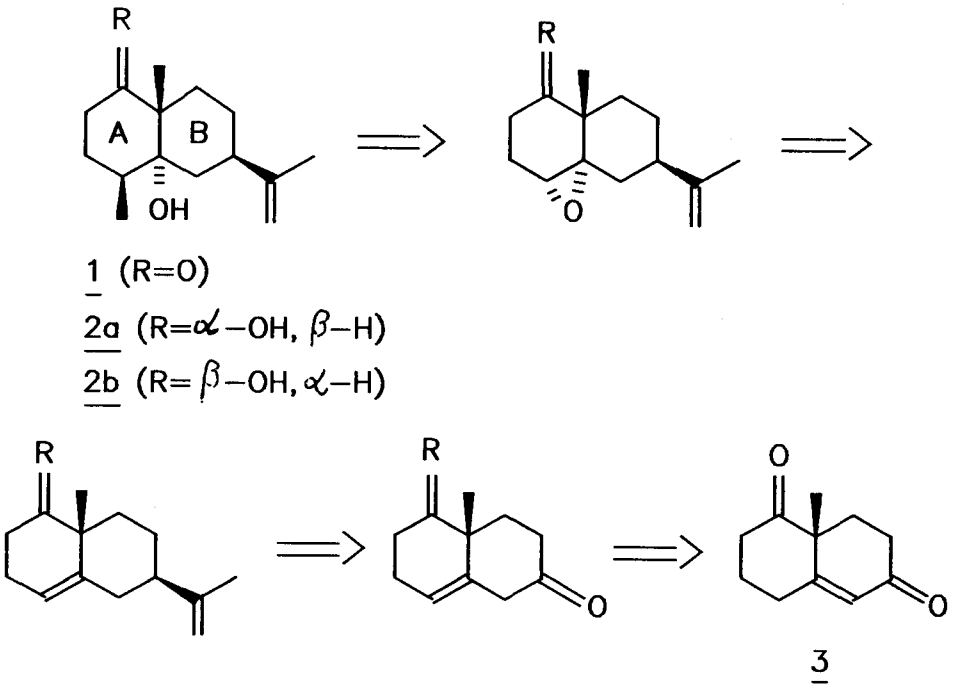
The functionality present at the B-ring - an equatorial isopropenyl group at C_7 - could be introduced, for example, by homologation of the carbonyl to an acetyl group, followed by olefination.

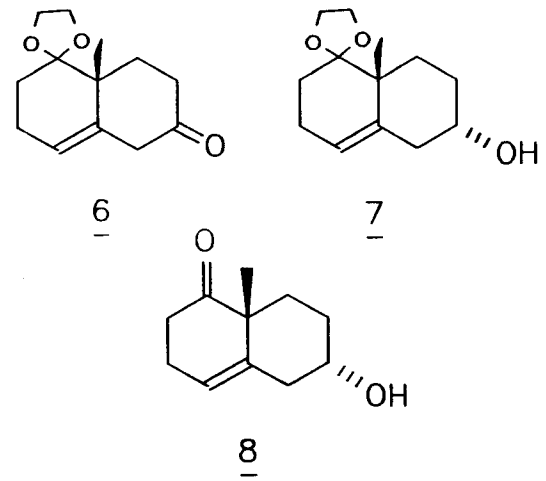


Scheme I

RESULTS AND DISCUSSION

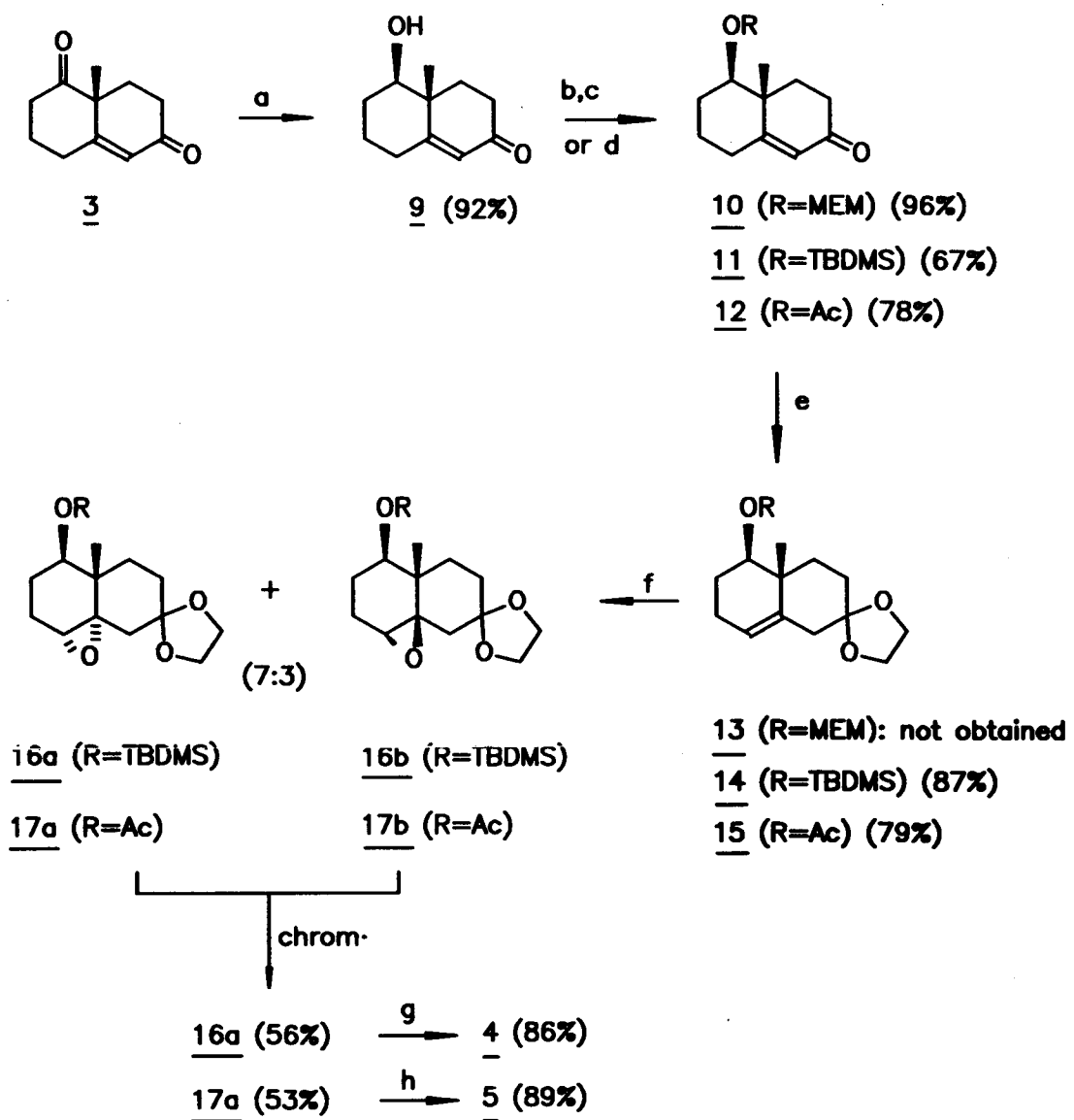
The general strategy for the construction of the ring A of the title compounds consisted of: a) reduction of the carbonyl group at C_1 of the ketone **3**, followed by an adequate protection of the resulting alcohol; b) migration of the double bond from the C_5-C_6 to the C_4-C_5 position; c) stereoselective α-epoxidation of the C_4-C_5 double bond; d) trans-diaxial opening of the α-epoxide with introduction of an axial methyl group at C_4.

In a previous paper[5] we presented the results of our attempts to promote the stereoselective α-epoxidation of the C_4-C_5 double bond on model compounds **6**, **7** and **8**, all prepared from the same ketone **3**. Of the three compounds, only **8** gave satisfactory results (93% yield of the desired α-epoxide). Probably the ketal group at C_1 is responsible for the lack of stereoselectivity in the epoxidation of **6** and **7**.



6 **7**

8



3 **9** (92%)

10 (R=MEM) (96%)
11 (R=TBDMS) (67%)
12 (R=Ac) (78%)

13 (R=MEM): not obtained
14 (R=TBDMS) (87%)
15 (R=Ac) (79%)

16a (R=TBDMS) **16b** (R=TBDMS)

17a (R=Ac) **17b** (R=Ac)

16a (56%) → **4** (86%)

17a (53%) → **5** (89%)

Reagents and conditions:
a) $NaBH_4$/ EtOH/ 0°, 15 min; b) MEMCl/ i-Pr_2EtN/ CH_2Cl_2/ r.t., 12h; c) TBDMSCl/ imidazole/ DMF/ r.t., 9h; d) Ac_2O/ py/ DMAP/ r.t., 5h; e) $HOCH_2CH_2OH$/ pTSA/ PhH/ reflux, 12h; f) MCPBA/ CH_2Cl_2/ r.t., 3h; g) Me_2CuLi/ Et_2O/ r.t., 72h; h) MeMgI/ CuI/ Et_2O/ r.t., 8h.

Scheme II

Based on this observation, we decided to start the synthesis with the known equatorial alcohol **9**, thus avoiding the presence of an axial substituent at C_1. This alcohol is easily obtained from ketone **3**, by treatment with sodium borohydride[6].

The correct stereochemistry at C_1 in the target molecule **2a**, could be achieved through known methodologies of inversion of configuration[7]. The other desired product (**1**) could be obtained by a simple oxidation of the hydroxyl group at C_1.

The proposed synthetic route, as well as the obtained results, are summarized in Scheme II.

The protection of the hydroxyl group at **9** was effected with three different reagents, namely methoxyethoxymethyl chloride (MEM Cl)[8], tert-butyldimethylsilyl chloride (TBDMS Cl)[9], and acetic anhydride, affording the corresponding protected alcohols **10**, **11**, **12**, in 96%, 67% and 78% yields, respectively. The goal was to verify which protecting group worked best in later steps of the synthesis.

Of the protecting groups tried, only the MEM group (compound **10**) did not lead to good results in the deconjugative ketalization step, furnishing a complex mixture of products, among which the expected ketal **13** was not observed (by ^{1}H-NMR analysis).

The next step consisted in the epoxidation of **14** and **15**, using m-chloroperbenzoic acid (MCPBA). The corresponding α-epoxides **16a** and **17a** were obtained as the main products, together with a small amount of the β-epoxides **16b** and **17b**, respectively (ca. 7:3 by ^{1}H-NMR analysis, in both cases). The isomeric mixtures were then separated by column chromatography, giving pure epoxides **16a** and **17a** in 56% and 53% yields, respectively.

The opening of the epoxide **16a** was tried with a number of organometallic reagents, and under different reaction conditions. The best result was obtained through treatment of **16a** with lithium dimethylcuprate, (with an excess of 10 equivalents[10]) which afforded the alcohol **4** in 86% yield. Efforts to promote this opening with methyl lithium and methyl magnesium iodide/cuprous iodide were unsuccessful.

In contrast, the Grignard reagent, in the presence of cuprous iodide, proved to be efficient for opening the epoxide **17a**, although with the expected lost of the acetoxy group at C_1. Thus, the diol **5** was obtained in 89% yield.

At this point, the synthetic problems concerning the construction of the A-ring are solved, since both intermediates **4** and **5** have the properly functions of the title compounds.

Studies directed towards the transformation of **4** and **5** into the synthetic product β-Corymbolol (**2b**), as well as into the natural compounds α-Corymbolol (**2a**) and Corymbolone (**1**) are in progress in our laboratory.

EXPERIMENTAL

Melting points (Kofler hot stage) are uncorrected. NMR spectra were obtained on a Bruker AC-200 spectrometer, in $CDCl_3$, using TMS as internal standard.

1β-Hydroxy-10-methyl-Δ^5-octal-7-one (9)[6]:

Obtained in 92% yield from Wieland-Miescher ketone (**3**), following the described procedure[6].

1β-t-Butyldimethylsilyloxy-10-methyl-Δ^5-octal-7-one (11)[9]:

Obtained in 67% yield from alcohol **9**, following the described procedure[9].

1β-t-Butyldimethylsilyloxy-7,7-ethylenodioxy-10-methyl-Δ^4-octalin (14):

A solution of **11** (5.2 g, 17.7 mmol), ethyleneglycol (4.38 g) and p-toluenosulfonic acid (0.05 g) in anhydrous benzene (46 ml) was refluxed for 20h in a Dean-Stark apparatus. After extraction with chloroform (3 x 30 ml), the organic layer was washed with H_2O and with saturated NaCl solution, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica-gel (hexane: ethyl acetate (9:1) as eluent), giving an unstable amorphous solid which was used in next step without further purification.

Yield: 5.2 g (87%)

^{1}H-NMR: δ= 5.20 (bs, 1H); 3.91 (m, 4H); 3.46 (dd, J=4.6 and 11.0 Hz, 1H); 2.5-1.1 (m, 10H); 1.02 (s, 3H); 0.79 (s, 9H); 0.10 (s, 6H) ppm.

^{13}C-NMR: δ= -4.2, -3.1, 17.0, 18.1, 24.7, 25.0, 27.6, 30.9, 35.7, 39.6, 41.3, 63.9, 64.2, 78.0, 109.4, 121.3, 139.4 ppm.

1 β-t-butyldimethylsilyloxy-4α-epoxy-7,7-ethylenodioxy-10-methyl decalin (16a)

To a solution of **14** (5.0g, 14.8 mmol) in dichloromethane (28 ml) was added dropwise, at O^{0}C, a solution of MCPBA (3.2g, 18.6 mmol) in dichloromethane (100 ml). The mixture was stirred for 3h at room temperature and then poured into a 10% solution of sodium bisulfite (30 ml). The organic layer was separated and washed with 5% solution of $NaHCO_3$ and with saturated NaCl solution, dried with $MgSO_4$ and concentrated. The crude product (7:3 mixture of **16a** and **16b** by NMR) was chromatographed on silica gel (hexane: ethyl acetate (8:2) as eluent) to give pure α-epoxide **16a**; m.p. 61-63^{0}C.

Yield: 2.9 g (56%)

^{1}H-NMR: δ=3.92 (m, 4H), 3.73 (m, 1H), 2.75 (m, 1H), 2.30 (d, J=14 Hz, 1H), 2.0-1.1 (m, 9H), 1.01 (s, 3H), 0.83 (s, 9H), 0.1 (s, 6H) ppm.

^{13}C-NMR: δ= -4.1, -3.0, 13.8, 18.1, 21.7, 25.0, 25.1, 30.8, 37.3, 38.8, 57.0, 64.1, 64.3, 66.0, 72.4, 109.9 ppm.

Calculated for $C_{19}H_{34}O_4Si$: C=64.40%; H=9.60%;
Found: C=64.64%; H=9.66%.

1β-t-Butyldimethylsilyloxy-4β,10β-dimethyl-5α-hydroxy-7,7-ethylenodioxy decalin (4):

To a suspension of cuprous iodide (3.8g, 20 mmol), in anhydrous ethyl ether (50 ml), at O^{0}C, under N_2 atmosphere, was added a 1M solution of methyllithium in ether (42 ml, 42 mmol). To the resulting solution was added dropwise a solution of the epoxide **16a** (0.71g, 2.0 mmol) in anhydrous ethyl ether (2 ml) and stirring was continued for 72 h at room temperature. The mixture was cooled and poured into a saturated solution of NH_4Cl(80 ml). The formed precipitate was filtered-off through Celite and the organic layer was washed with saturated NaCl solution, dried over $MgSO_4$ and the solvent was evaporated. The residue was chromatographed on silica-gel (hexane: ethyl acetate (9:1) as eluent), giving an oil (0.64 g, 86%), which was not purified further.

^{1}H-NMR: δ=4.3 (bs, 1H); 3.94 (m, 4H), 3.86 (m, 1H), 2.14 (d, J=14Hz, 1H), 2.11 (m, 1H), 1.7-1.2 (m, 10H), 0.97 (s, 3H), 0.95 (d, J=7.4Hz, 3H), 0.86 (s, 9H), 0.0 (s, 6H) ppm.

^{13}C-NMR: δ= -4.2, -3.1, 15.3, 16.8, 18.2, 25.1, 26.1, 26.8, 29.8, 31.1, 39.6, 42.6, 64.2, 64.8, 74.2, 77.8, 110.3 ppm.

Obs.: The microanalysis was performed after hydrolysis of the ketal-group of **4**, which gave the corresponding ketone (m.p. 161-163°C) in 96% yield.

Calculated for $C_{18}H_{34}O_3Si$: C=66.25%; H=10.42%;
Found: C=66.02%; H=10.29%.

1β-Acetoxy-10-methyl-Δ⁵-octal-7-one (12):

A mixture of the alcohol **9** (2.05g, 11.3 mmol), pyridine (10 ml), acetic anhydride (7 ml) and dimethylaminopyridine (a few crystals) was stirred for 5h at room temperature. The pyridine was removed by distillation, the residue was dissolved in $CHCl_3$ and washed with 10% HCl solution, water and saturated NaCl solution. The organic layer was dried with $MgSO_4$ and the solvent was evaporated. The residue was distilled (b.p. 110-120°/ 0.3 mm Hg) giving an oil which was not further purified.

Yield: 1.97g (78%).

^{1}H-NMR (CCl_4), 60MHz: δ=5.8 (m, 1H), 4.7 (m, 1H), 2.0 (s, 3H), 2.9-1.3 (m, 10H), 1.1 (s, 3H) ppm.

1β-Acetoxy-7,7-ethylenodioxy-10-methyl-Δ⁴-octalin (15):

Following the same procedure described for **14**, the compound **15** was obtained as a white solid (m.p. 92-94°C), after recrystallization from petroleum ether (yield: 79%).

^{1}H-NMR: δ= 5.33 (d, J=2.4Hz, 1H); 4.81 (dd, J=5.3 and 10.1 Hz, 1H); 3.93 (m, 4H); 2.06 (s, 3H); 2.57-1.28 (m, 10H); 1.15 (s, 3H) ppm.

^{13}C-NMR: δ= 17.6, 21.2, 23.6, 24.3, 30,8, 34.6, 38.1, 41.0, 64,2, 64.4, 79.4, 121.7, 133.2, 138.4, 170.6 ppm.

1β-Acetoxy-4α-epoxy-7,7-ethylenodioxy-10-methyl decalin (17a)

Following the same procedure described for **16a** an epimeric mixture (7:3) of **17a** and **17b** was obtained. The crude product was chromatographed on silica gel (hexane: ethyl acetate (7:3) as eluent) to give pure α-epoxide **17a**; m.p. 136 - 138°C (yield: 53%).

^{1}H-NMR: δ= 4.99 (dd, J=5.2 and 11.6Hz, 1H); 3,95 (m, 4H); 2.83 (d, J=2.9 Hz, 1H); 2.36 (d, J=14.1 Hz, 1H); 2.00 (s, 3H); 2.18-1.18 (m, 9H); 1.14 (s, 3H) ppm.

^{13}C-NMR: δ= 14.6, 21.0, 21.1, 21.3, 30.1, 30.5, 36.3, 38.5, 56.7, 64.1, 64.6, 65.6, 75.0, 108.5, 170.3 ppm.

Calculated for $C_{15}H_{22}O_5$: C=63.81%; H=7.85%;
Found: C=63.35%; H=7.67%.

1β,5α-dihydroxy-4β,10β-dimethyl-7,7-ethylenodioxy decalin (5):

To a suspension of magnesium (42 mg, 1.8 mmol) in anhydrous ether (10 ml), with a few crystals of iodine, under N_2 atmosphere, was added dropwise a solution of methyl iodide (250 mg, 1.8 mmol) in anhydrous ether (10 ml). The mixture was refluxed for 15 minutes, cooled to room temperature, and cuprous iodide (33 mg, 0.2 mmol) was added. To the resulting solution was added dropwise a solution of the epoxide **17a** (100mg, 0.4 mmol) in anhydrous ether (1 ml) and stirring was continued for 1 h at room temperature. The mixture was poured into a saturated solution of NH_4Cl (15 ml), and the organic layer was washed with saturated NaCl solution, dried over $MgSO_4$ and the solvent was evaporated. The residue was chromatographed on silica gel (chloroform: ethyl acetate (7:3) as eluent), giving a solid which was recrystalized from hexane: ethyl acetate (9:1); m.p. 96-98°C.

Yield: 80 mg (89%)

^{1}H-NMR: δ=4.34 (sl, 1H); 3.94 (m, 5H); 2.17 (d, J=14.3 Hz, 1H); 1.97-1.22 (m, 12 H); 0.97 (d, J=8.6 Hz, 3H); 1.02 (s, 3H).

^{13}C-NMR: δ=15.2, 16.4, 26.0, 26.3, 30.8, 31.2, 39.2, 39.5, 42.1, 63.8, 64.2, 73.8, 77.4, 110.1 ppm.

Calculated for $C_{14}H_{24}O_4$: C=65.6%, H=9.3%;
Found: C=65.1%; H=9.3%.

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