# A Short-Step Synthetic Approach to Eudesmane Skeleton. A Synthesis of (±)-β-Eudesmol and Related Eudesmane Sesquiterpenes

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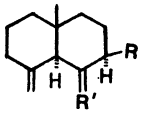
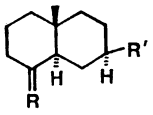
**Synopsis.** The formal total syntheses of (±)-β-eudesmol and its related sesquiterpenes such as cryptomeridiol and neointermediol were accomplished by an efficient method using aldol cyclization as the key step starting from the known 3-vinyl-2-cyclohexen-1-one.

Although several different syntheses of eudesmane sesquiterpenes including (±)-β-eudesmol (**1**), one of the representatives of this class[1-3] have been reported, most of these approaches involved construction of the decalin ring system via the conventional Robinson annelation reaction. In the synthetic trial of **1**, approaches without recourse to this reaction have been reported recently.[4-7]

In connection with our interest in the development of an efficient general method for the synthesis of the eudesmane class of sesquiterpenoids, we have developed a short step approach to construct the eudesmane skeleton. This has enabled us to synthesize formally the well-known β-eudesmol (**1**) as well as cryptomeridiol (**4**)[8] and neointermediol (**5**).[9]





**1** R: -C(OH)($CH_3$)$_2$, R′: =$H_2$

**2** R: -CH($CH_3$)$_2$, R′: 

**3** R: -CH($CH_3$)$_2$, R′: =O

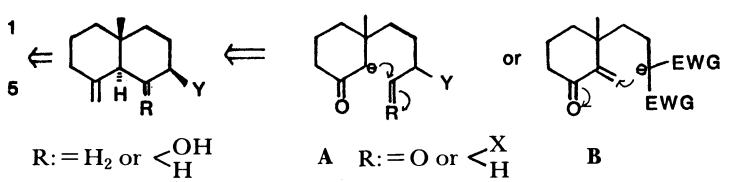
**4** R:  , R′: -C(OH)($CH_3$)$_2$

**5** R:  , R′: -$CH_2$=$CHCH_3$

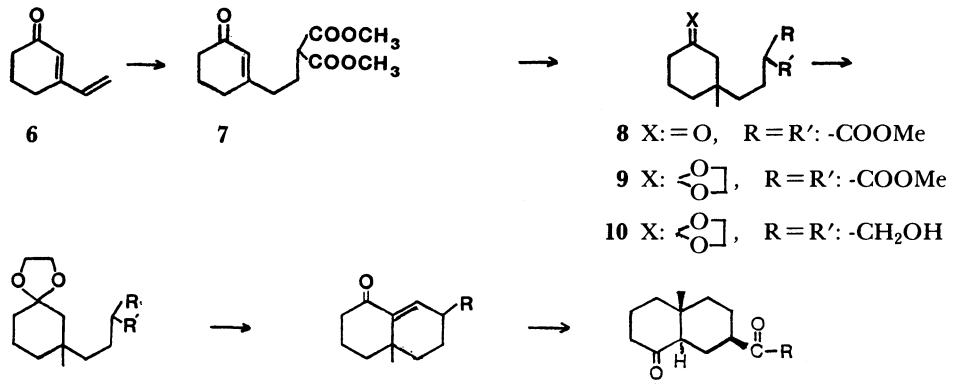
Our synthetic strategy (Scheme 1) is based on the device of synthon like A or B as a common key intermediate and its intramolecular cyclization by aldol condensation (A) or Michael reaction (B) for the general construction of the eudesmane type of sesquiterpenes. These are represented by the above-mentioned β-eudesmol (**1**) and its close relatives, **4**, **5** and selinene[10] and C(6) oxygenated compounds, juneol (**2**)[11] and acolamone (**3**).[12] In this note the study of the synthon A is described.

Treatment of 3-vinyl-2-cyclohexen-1-one (**6**), readily available from 1,3-cyclohexanedione, with dimethyl malonate in methanol (MeOH) in the presence of sodium methoxide ($NaOCH_3$) gave mainly the 1,6-Michael adduct (**7**) (50%) along with a small amount of a dialkylation product. Conjugate addition of lithium dimethylcuprate (I) [$(CH_3)_2CuLi$] in dry ether at 0 °C provided methylated cyclohexanone (**8**) in good yield (88.4%). Acetalization of **8** with ethylene glycol [*p*-toluenesulfonic acid monohydrate (TsOH)/benzene] gave acetal diester (**9**) in almost quantitative yield. This was in turn subjected to reduction with lithium aluminum hydride ($LiAlH_4$) in ether to afford the corresponding dihydroxy acetal (**10**) (78%). Selective benzylation of **10** with benzyl bromide in tetrahydrofuran (THF) in the presence of tetrabutylammonium iodide (*n*-$Bu_4NI$) furnished almost exclusively the desired monobenzyl ether (**11a**) along with the dibenzyl ether (**11b**) [**11a** : **11b**=98 : 2]. Oxidation of **11a** with pyridinium dichromate (PDC) in dichloromethane ($CH_2Cl_2$) at room temperature afforded acetal aldehyde (**12**) in almost quantitative yield.

With the key intermediate **12** in hand, attention was turned to the crucial intramolecular aldol condensation. When **12** was exposed to the action of a 1 M (1 M=1 mol dm$^{-3}$) HCl in THF (1 : 2) at room temperature overnight, the desired α,β-unsaturated ketone **13** was constructed in a single step as a result of the simultaneous aldolization and dehydration (37%) along with the intermediary keto aldehyde (20%), which upon treatment of TsOH in benzene afforded additional **13** (ca. 7.5%). **13**: $C_{19}H_{24}O_2$ (MW 284). MS *m*/*z*: 284 ($M^+$). IR (KBr): 1687, 1620 (enone), 1068 cm$^{-1}$. Catalytic hydrogenation of **13** in the presence of 10% Pd-C in ethanol (EtOH)/ethyl acetate (AcOEt)(1 : 1) at room temperature proceeded smoothly with the concomitant cleavage of the benzyl group to furnish the keto alcohol (**14**)(66%). Oxidation of **14** with PDC in $CH_2Cl_2$ at room temperature followed by immediate treatment of the resulting unstable aldehyde **15** with Jones reagent in acetone afforded the keto carboxylic acid (**16**). This was, in turn, esterified with diazomethane ($CH_2N_2$) in ether to give the corresponding keto carboxylic acid methyl ester (**17**), IR (KBr): 1739, 1715 cm$^{-1}$. The ester




Scheme 1. Retrosynthetic analysis for the eudesmane skeleton.




**11a** R: $-CH_2OH$, R': $-CH_2OCH_2Ph$ **13** R: $-CH_2OPh$ **15** R: -H **17a** R: -OMe (8aαH)
**11b** R=R': $-CH_2OCH_2Ph$ **14** R: $-CH_2OH$ **16** R: -OH **17b** R: -OMe (8aβH)
**12** R: -CHO, R': $-CH_2OCH_2Ph$ ($\Delta^8$-dihydro)

Scheme 2. Synthetic approach to (±)-β-eudesmol and its close relatives.

**17** was found to be a 76 : 24 mixture of two components by the examination of its gas chromatographic data [Rt: 11.3 and 12.2]. On the other hand, $^1H$ NMR showed methyl signals at δ 1.17 and 0.82, methoxyl methyl signals at δ 3.67 and 3.68, and other signals between δ 1.1 and 2.4. The comparison of this data with that of the diastereomers[6] of **17** suggested that **17** was a mixture of **17a** and **17b** in an approximately 3 : 1 ratio. This was determined by evaluating the integration trace of the methyl and methoxyl methyl peaks described above. The ratio was in good agreement with that obtained from the GC-MS data; the presence of the C(2)-epimer of **17b** was easily ruled out since the $^1H$ NMR of **17** exhibited no signals below δ 2.4 .[6]

Since, not only the 4a-methyl-8-oxo-2-decalin carboxylic acid (**16**) and its ester **17a, b** but also the above-mentioned mixture of four diastereomers of **17** have already been converted to β-eudesmol (**1**), which, in turn, has been converted to cryptomeridiol (**4**)[8] and neointermediol (**5**).[9] The synthesis of the former compounds (**16** and/or **17a, b**) constitute a formal total synthesis of (±)-β-eudesmol as well as (±)-**4** and (±)-**5**. Furthermore, since **17a** and **17b** could essentially be convertible to other isomeric eudesmols (α-, γ-eudesmol)[13] and its close relatives such as costal[14] and costic acid etc.,[14] this sequence should provide a general method of constructing the eudesmane sesquiterpenes exemplified by eudesmols.

## Experimental

IR spectra were recorded on a Hitachi EPI-G3 spectrophotometer. Mass spectra were taken on a JEOL JMS-D300 instrument (JMA-2000 data analysis system). $^1H$ NMR spectra were recorded with JMN-GX-400 with TMS as an internal standard. TLC was performed on a Kieselgel 60 $F_{254}$ plate (Merck) using ether-hexane (gradient).

**Preparation of 7:** To a cold (0 °C) stirred solution of $NaOCH_3$ (220 mg) in dry MeOH (15 ml) was added dropwise a solution of dimethyl malonate (2.4 g) in dry MeOH (15 ml) and then a solution of 3-vinyl-2-cyclohexen-1-one (**6**) (1.83 g) in dry MeOH (15 ml). The mixture was stirred at 0 °C for 2 h and then at room temperature overnight. The mixture was quenched with 2 M HCl, evaporated, and extracted with ether. The ether extract was washed with sat. NaCl and dried ($MgSO_4$). Removal of the solvent in vacuo left a crude oil, which was purified by chromatography on silica gel to give **7** as an oil, 1.90 g (ca. 50%), MS *m/z*: 254 ($M^+$). IR (KBr): 1749, 1733, 1644, 1620 $cm^{-1}$. From the polar fraction the dialkylation product, 371 mg (6.6%). MS *m/z*: 376 ($M^+$) ($C_{21}H_{28}O_6$) was obtained.

**Conjugate Addition of $(CH_3)_2CuLi$ to 7 (8):** To a cold (0 °C) stirred suspension of CuI (2.53 g) in dry ether (100 ml) was added dropwise $CH_3Li$ (1.6 M hexane, 16.2 ml) under $N_2$ atmosphere and then **7** (1.5 g) in dry ether (120 ml). The mixture was stirred at 0 °C for 2 h and then at room temperature overnight. The mixture was quenched with sat. $NH_4Cl$, extracted with ether, washed with $H_2O$ and dried over $CaCl_2$. Removal of the solvent at diminished pressure afforded 1.47 g of viscous oil, which was purified by chromatography on silica gel (ether : hexane=4 : 6) to give 1.26 g (88.4%) of an essentially pure oil, **8** (TLC homogeneous; ether : hexane=1 : 1). CI-MS *m/z*: 271 ($M^+$+1) ($C_{14}H_{22}O_5$, MW 270). IR (KBr): 1751, 1733, 1710 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ=0.98 (3H, s), 1.1—2.43 (12H, m), 3.3 (1H, d, 7), 3.75 (6H, s).

**$LiAlH_4$ Reduction of 9:** To a stirred suspension of $LiAlH_4$ (450 mg) in dry ether (80 ml) was added dropwise a solution of **9** (982 mg) in dry ether (60 ml) under ice-cooling. The mixture was refluxed for 2 h. The mixture was quenched carefully with sat. $NH_4Cl$, filtered and the filtered cake thoroughly washed with $CH_2Cl_2$. The filtrate was partitioned between the organic phase and the aqueous phase. The latter phase was extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ was washed with sat. NaCl and dried ($MgSO_4$). Removal of the solvent at reduced pressure left a viscous oil, which was purified by chromatography on silica gel eluting with ether to afford 630 mg (78%) of **10** as an oil. IR (KBr): 3387 (OH) $cm^{-1}$, which was used directly in the next step, and the recovered product, 79 mg (11.8%).

**Preparation of Monobenzyl Ether (11a):** To a stirred solution of **10** (600 mg) in dry THF (28 ml) was added NaH (104 mg) under $N_2$. After adding a catalytic amount of $Bu_4NI$, a solution of benzyl bromide (426 mg) in dry THF (12 ml) was added. The mixture was diluted with ether, washed with 2 M HCl and sat. NaCl and dried over $MgSO_4$. Evaporation of the solvent left a crude oil, which was purified by chromatography on silica gel. 10% ether-hexane fraction furnished 47 mg (4.6%) of dibenzyl ether (**11b**). MS *m/z*: 438 ($M^+$) ($C_{28}H_{38}O_4$, MW 438). IR (KBr): 1092, 1070 (sh), 1048, 944, 734, 697 $cm^{-1}$, and the ether eluant gave 710 mg (87.9%) of monobenzyl ether (**11a**) as an oil. MS *m/z*: 348 ($M^+$) ($C_{21}H_{32}O_4$, MW 348). IR (KBr): 3422, 1092, 1070 (sh), 1048,

944, 734, 697 $cm^{-1}$.

**Cyclization of 11a (13):** To a stirred solution of **11a** (100 mg) in $CH_2Cl_2$ (4 ml) was added PCC (80 mg) and the mixture was stirred at room temperature for 5 h. The reaction mixture was filtered through a pad of silica gel. The filtrate was evaporated to give a viscous oil **12**, IR (KBr): 1727 (-CHO), 1096 $cm^{-1}$, This was dissolved in 2 M HCl : THF (1 : 2) (1 ml) and stirred at room temperature overnight under an argon atmosphere. To the mixture sat. NaCl was added and it was extracted with ether, washed with sat. NaCl and dried ($MgSO_4$). Evaporation of the solvent followed by purification by chromatography on silica gel afforded 20 mg (ca. 30%) of **13** (oil), IR (KBr): 1687, 1620, 1086 $cm^{-1}$, MS *m/z*: 284 ($M^+$) ($C_{19}H_{24}O_2$, MW 284) and the intermediary keto aldehyde, 21 mg (20%), IR (KBr): 1728, 1287, 1129 (sh), 1115, 1068 $cm^{-1}$, which gave the additional enone **13** (5 mg, 7.5%) upon treatment with TsOH in refluxing benzene.

**17a and 17b:** 15 mg of **13** was dissolved in EtOH-AcOEt (1 : 1) (2 ml) and 10%-Pd/C (catalytic) was added. The mixture was stirred at room temperature under $H_2$ atmosphere for 4 days. After filtration of the mixture, the solvent was evaporated and the residue was purified by chromatography on silica gel to give 8 mg (66%) of **14**, which was dissolved in $CH_2Cl_2$ (1.5 ml), and PCC (12 mg) was added. The mixture was stirred for 3 h at room temperature. After filtration, the solvent was evaporated and the residue was purified by chromatography on silica gel to give 6 mg (79.9%) of the corresponding keto aldehyde (**15**). This was immediately dissolved in acetone (1 ml) and several drops of Jones reagent was added. After a few minutes a small amount of isopropyl alcohol was added. Filtration of the mixture followed by evaporation of the solvent left 5 mg (77.0%) of keto carboxylic acid (**16**), IR (KBr): 3500—2400, 1712 $cm^{-1}$. The above acid (**16**)(5 mg) was dissolved in ether (0.5 ml) and excess $CH_2N_2$ in ether was added. Evaporation of the solvent furnished 5 mg (ca. 100%) of the corresponding methyl ester (**17a** and **17b**). IR (KBr): 1739, 1715 $cm^{-1}$. GC-MS (2% OV-1, 200 °C), **17b**; $R_t$ 11.3 min, *m/z*: 224 ($M^+$), 209 ($M^+$−15). **17a**; $R_t$ 12 min, *m/z*: 224 ($M^+$), 209 ($M^+$−15). $C_{13}H_{20}O_3$ (MW 224). $^1H$ NMR (400 MHz) $\delta$=0.82 (s), 3.67 ($OCH_3$) and 1.17 (s), 3.68 ($OCH_3$) [76 : 24]. High-resolution MS: *m/z* 224.1408 for **17a**, 224.1384 for **17b** [Theor. 224.1384 for $C_{13}H_{20}O_3$].

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