Stereoselective Total Synthesis of (–)-α-Eudesmol, a P/Q-Type Calcium Channel Blocker

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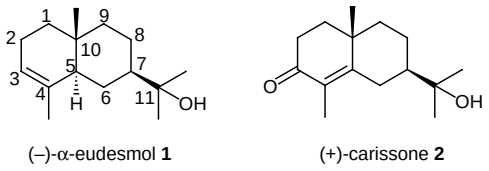
Abstract: Practical and stereoselective total synthesis of (−)-α-eudesmol **1**, a P/Q-type calcium channel blocker, has been achieved with the key step being a cyclopropane ring opening accompanying introduction of a hydroxyl group. (+)-Carissone is used as a key intermediate.

Key words: α-eudesmol, natural products, total synthesis, stereoselective, ring opening

The already-known sesquiterpene, α-eudesmol, has been isolated from many species of the plant kingdom.[1] Recently, in our laboratory, α-eudesmol isolated from *Juniperus virgantea* was found to display a P/Q-type calcium channel inhibitory activity.[2] P/Q-type calcium channels are only present in the central nervous system, especially at the synaptic terminal, and participate in the release of neurotransmitters. [3] As excess release of neurotransmitters causes neuronal degeneration, the P/Q-type calcium channel blocker is considered to be effective for treatment of cerebral apoplexy, Alzheimer's disease and migraine.

Syntheses of α-eudesmol have been achieved by some groups, however, most use semi-synthesis from other natural products[4] and do not allow synthesis of the antipode of α-eudesmol. Also, the total synthesis reported by the Li group consists of many steps.[5]

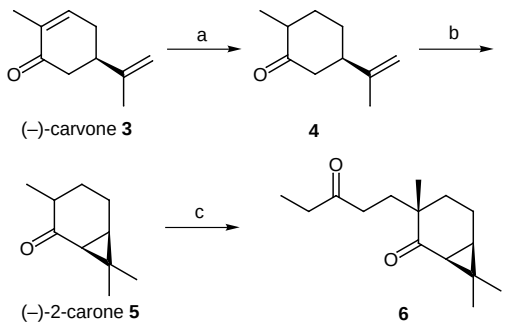
We tried to develop a simpler total synthesis of both enantiomers of α-eudesmol for two purposes. The first was to obtain a supply of α-eudesmol for pharmacological evaluation, as it can not be obtained from *Juniperus virgantea* in large quantities. The second was to determine the biological activity of the antipode of α-eudesmol. We describe herein a practical and stereoselective total synthesis of (–)-α-eudesmol **1** with the key step being cyclopropane ring cleavage accompanying introduction of a hydroxyl group.



(–)-α-eudesmol **1** (+)-carissone **2**

Figure 1

(–)-α-Eudesmol **1** possesses three asymmetric carbons (C-5, C-7 and C-10), a double bond at the C_3–C_4 position and a hydroxyl group at the C-11 position. Our synthetic design employs (+)-carissone **2**[6] as a key intermediate because it has the same stereochemistry at C-7 and C-10 as (–)-α-eudesmol **1** and a hydroxyl group at the C-11 position. (–)-Carvone **3** was chosen as the starting material, because both enatiomers of carvone are readily available commercially.

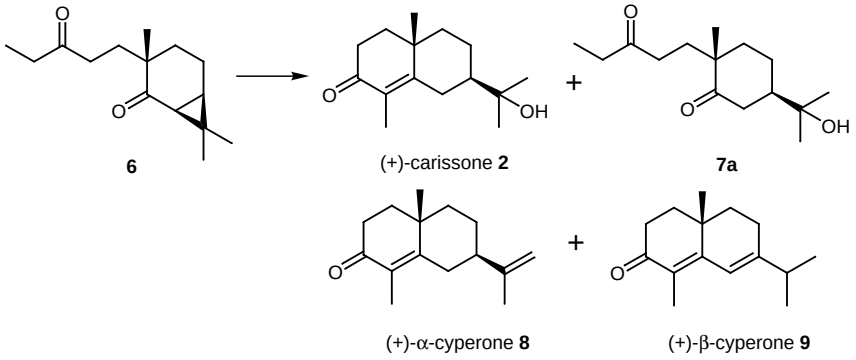


Scheme 1 [a] Li, THF, *t*-BuOH, 85% (Ref 7); [b] HCl (gas), $CHCl_3$ then KOH, MeOH, 82% (Ref 8); [c] EVK, KOH, EtOH, 85% (Ref 9).

First, (–)-carvone **3** was stereoselectively converted into diketone **6** by known methods (Scheme 1).[7–9] Because the Michael reaction of (–)-2-carone **5** with ethyl vinyl ketone (EVK) led stereoselectively to diketone **6** which possessed the desired stereochemistry at the C-10 position,[9] these methods were applied to the synthesis of (+)-carissone **2**, the key intermediate. Robinson annulation of diketone **6** was tried, but, the reaction did not proceed at all, which may suggest that ring strain of the bicyclic structure **6** inhibits the cyclization reaction. Accordingly, cyclopropane ring opening was next investigated.

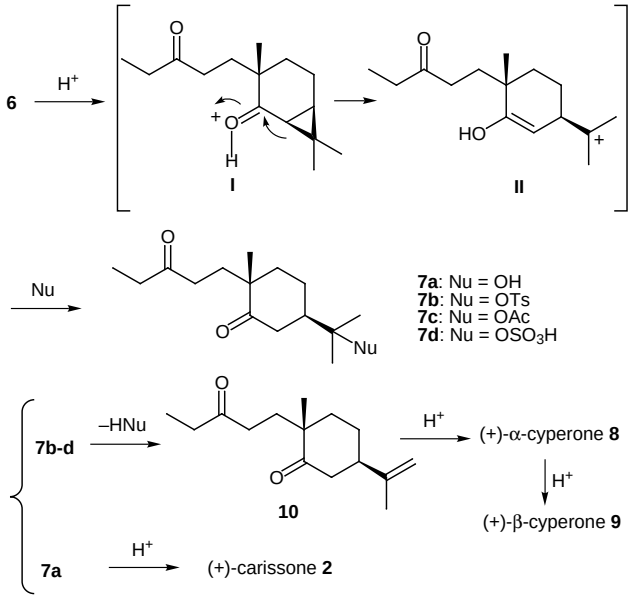
Some synthetic studies related to the ring opening of cyclopropyl ketone have been reported.[10] What was necessary was to develop a method for the cyclopropyl ketone ring opening followed by introduction of a hydroxyl group at the C-11 position. The results of acid-catalyzed cyclopropane ring opening are summarized in the Table. Treatment of diketone **6** with acids such as boron trifluoride diethyl etherate (BF_3•OEt_2), sulfuric acid (H_2SO_4) and acetic acid (AcOH) led to (+)-β-cyperone **9**, an undesired product (entry 1, 2 and 3). However, by using *para*-

Table Cyclopropane ring opening followed by cyclization.



Entry	Conditions	Isolated yields
1	BF_3•OEt_2 (10 eq.), AcOH, r.t., 2 h	**9** (68%)
2	H_2SO_4 (1.0 eq.), AcOH, r.t., 1 h	**9** (70%)
3	H_2SO_4 (1.0 eq.), dioxane, r.t., 2 h	**9** (65%)
4	TsOH•H_2O (1.5 eq.), dioxane, r.t., 24 h	**2** (12%), **8** (33%), **9** (14%)
5	TsOH•H_2O (1.5 eq.), H_2O (200 eq.), dioxane, r.t., 18 h	**7a** (63%)
6	TsOH•H_2O (1.5 eq.), H_2O (200 eq.), dioxane, 60 °C, 15 h	**2** (81%)

toluenesulfonic acid monohydrate (TsOH•H_2O), (+)-carissone **2**, a desired product and (+)-α-cyperone **8**, a dehydrated product of (+)-carissone **2**, were obtained as major products (entry 4). Based on these results, the proposed mechanism of the transformation of cyclopropyl ketone **6** into (+)-β-cyperone **9** and (+)-carissone **2** is presented in Scheme 2. In the presence of H_2SO_4 and/or AcOH and/or TsOH, nucleophilic addition against the C-11 carbocation of ring-opening intermediate **II** leads to compounds **7b-d** (Nu = OSO_3H, OAc, OTs). The elimination reaction of **7b-d** to **10** smoothly proceeds and then the acid-catalyzed cyclization of **10** occurs to afford (+)-α-cyperone **8**. The acid-catalyzed isomerization of (+)-α-cyperone **8** to (+)-β-cyperone **9** has already been reported.[11] The use of TsOH•H_2O as an acid gives **7a** and **7b**, because both TsOH and H_2O act as nucleophiles. Compound **7a** is converted into (+)-carissone **2** without dehydration. Accordingly, in the presence of excess of H_2O, acid-catalyzed ring opening followed by cyclization of **6** was expected to selectively lead to **2**. As expected, in the presence of excess of H_2O (200 equiv.), TsOH-catalyzed ring opening of **6** selectively afforded **7a**, a precursor of **2** (entry 5). Increasing the reaction temperature accelerated cyclization of **7a** to give (+)-carissone **2** in 81% yield (entry 6).[12] This method of introducing a hydroxyl group at the C-11 position enabled practical and stereoselective synthesis of (+)-carissone **2**.

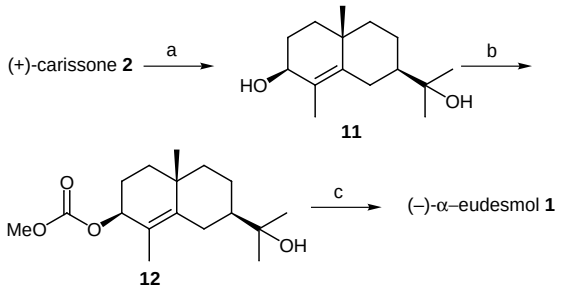


Scheme 2 Proposed mechanism of the transformation of cyclopropyl ketone **6** into (+)-β-cyperone **9** and (+)-carissone **2**.

Finally, conversion of (+)-carissone **2** into (–)-α-eudesmol **1** was investigated.[4a] The crucial generation of *trans* decalin **1** was effected by palladium-catalyzed hydrogenolysis of allylic carbonate **12** (Scheme 3).[13] Reduction

of the carbonyl group of **2** with $NaBH_4$-$CeCl_3$ gave the corresponding 3β-alcohol **11** (92%) as a major product.[14] Compound **11** was regioselectively transformed into allylic carbonate **12**. The palladium-catalyzed regioselective and stereospecific decarboxylation−hydrogenolysis of allylic carbonate **12** afforded (–)-α-eudesmol **1** without hindrance of the reaction by the non-protected hydroxyl group of **12**.[15] Total synthesis of (–)-α-eudesmol **1** has been achieved in seven steps with an overall yield of 42% from (–)-carvone **3**.[16] The antipode **13** of (–)-α-eudesmol **1** was synthesized from (+)-carvone by the above procedures.

The inhibition of calcium influx in rat cerebral synaptosome by the P/Q-type calcium channel blocker α-eudesmol was examined. The activities of both enantiomers of α-eudesmol **1** and **13** were almost same (IC_{50} = 2.6 and 2.0 μM., respectively).[2]



Scheme 3 [a] $NaBH_4$, $CeCl_3$•$7H_2O$, EtOH−H_2O, −40 − 0 °C, 92%; [b] $ClCO_2Me$, pyridine, CH_2Cl_2, 0 °C, >99%; [c] $Pd(OAc)_2$ (0.2 eq.), *n*-Bu_3P (0.2 eq.), HCO_2NH_4 (2.0 eq.), THF, r.t., 2 h, 95%.

In summary, practical and stereoselective total synthesis of (–)-α-eudesmol **1**, a P/Q-type calcium channel blocker, has been achieved with the key step being the cyclopropyl ketone ring opening followed by introduction of a hydroxyl group at the C-11 position This method of introducing a hydroxyl group may be applicable to syntheses of other natural products

Acknowledgement

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(12) Preparation of (+)-carissone **2**: A solution of **6** (411 mg, 1.74 mmol) and *para*-toluenesulfonic acid monohydrate (496 mg, 2.61 mmol) in H_2O (6.3 mL, 350 mmol) and 1,4-dioxane (6.0 mL) was heated for 15 h at 60 °C. After cooling, sodium bicarbonate solution (20 mL) was added and the reaction mixure was extracted with ethyl acetate (2 × 20 mL). The organic phase was washed with brine and dried over Na_2SO_4. Removal of solvent and chromatographic purification (*n*-hexane/ethyl acetate = 3/1) yielded **2** (333 mg, 81%) as a colorless solid; mp 76.0−77.0 °C; $[\alpha]_D^{22}$ = +138.7°+11.0° (*c* 0.163, $CHCl_3$) (lit. (Ref 6c)+136.6° ($CHCl_3$)); IR ν_{max}: 3609, 1654, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (s, 3H), 1.25 (s, 3H), 1.26 (s, 3H), 1.31−1.60 (m, 4H, including OH), 1.66−1.84 (m, 4H), 1.78 (d, 3H, *J* = 1.2 Hz), 1.91 (dt, 1H, *J* = 1.2 and 13.5 Hz), 2.39 (dt, 1H, *J* = 16.5 and 4.2 Hz), 2.52 (ddd, 1H, *J* = 7.5, 12.0 and 17.1 Hz), 2.86 (dt, 1H, *J* = 13.8 and 2.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.8 (q), 22.3 (q), 22.5 (t), 26.6 (q), 27.4 (q), 28.7 (t), 33.7 (t), 35.8 (s), 37.2 (t), 41.8 (t), 49.6 (d), 72.2 (s), 128.7 (s), 162.9 (s), 199.1 (s); FABMS m/e 237 [$(M+H)^+$]; *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.05; H, 10.17.
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(15) To the best of our knowledge, this is the first example of application of an allylic carbonate with a non-protected hydroxyl group, such as **12**, to the palladium-catalyzed hydrogenolysis of an allylic carbonate (or formate).
(16) An analytical sample of (−)-α-eudesmol **1** was recrystallized from *n*-pentane, mp 85.0−86.0 °C; $[\alpha]_D^{24}$ = −8.1°+0.5° (*c* 1.008, $CHCl_3$) (lit. (Ref 4c) −8.0° ($CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (s, 3H), 0.91−1.17 (m, 2H), 1.21 (s, 3H), 1.22 (s, 3H), 1.28−1.66 (m, 7H, including OH), 1.62 (brs, 3H), 1.82−2.20 (m, 4H), 5.32 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.5 (q), 21.2 (q), 22.4 (t), 22.9 (t), 24.3 (t), 26.8 (q), 27.6 (q), 32.2 (s), 37.8 (t), 40.1 (t), 46.6 (d), 50.0 (d), 73.0 (s), 121.0 (d), 135.2 (s); LSIMS m/e 222 [M^+]; *Anal.* Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.86; H, 11.73.

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