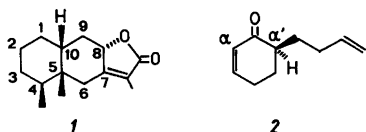# The Total Synthesis of (+)-Eremophilenolide

S. I. PENNANEN

Department of Chemistry, University of Kuopio, P.O.B. 138, SF-70101 Kuopio 10, Finland

Naturally occurring (+)-eremophilenolide was synthesized in 7 % overall yield from cyclohexenone (with an optical yield of 89 %). The key step in the synthetic scheme was the enantioselective alkylation of cyclohexenone followed by the construction of the cis A/B-ring system via butenylcyclohexenol annulation and of the 2-furanone unit via the α-epoxyketone − ynamine reaction.

More than 70 different eremophilane-type naturally occurring sesquiterpenes have been isolated and subjected to structural elucidation. Some of these have been totally synthesized. Normally eremophilaneterpenes have several asymmetric centres and total syntheses have involved optically inactive (±)-mixtures with only few exceptions.

Scheme 1.

Recently a total synthesis of the racemic (±)-eremophilenolide (1) was published by this author.[1] The reaction scheme used, except the beginning, is stereocontrolled and makes it possible to plan the total synthesis of the natural (+)-eremophilenolide (1). The absolute configuration of 1 has been established by Novotný et. al.[2] as in 1 (Scheme 1).
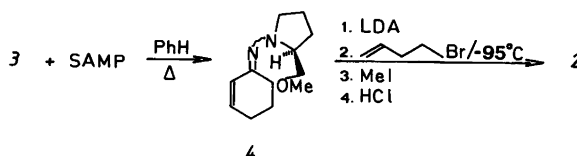
From the synthetic point of view the earlier the correct chirality of the molecule can be introduced the better. Looking at the synthetic scheme of (±)-1[1] it can be reasoned that the key chiral center is at C-10 which is the α' carbon of the starting enone 2 (Scheme 1). After that the appropriate ring system, the cis-vicinal methyl groups and 2-(5H)-furanoid moiety could be constructed.[1] The stereochemistry of 2 at the α' carbon must be (S) as shown.

During the last few years several papers dealing with enantioselective alkylation of ketones have been published. The excellent procedure by Enders and Eichenauer[3] was expected to give ready access to (S)-2. These authors have alkylated various types of ring ketones using the reagent (S)-1-amino-2-(methoxymethyl)pyrrolidene (SAMP).
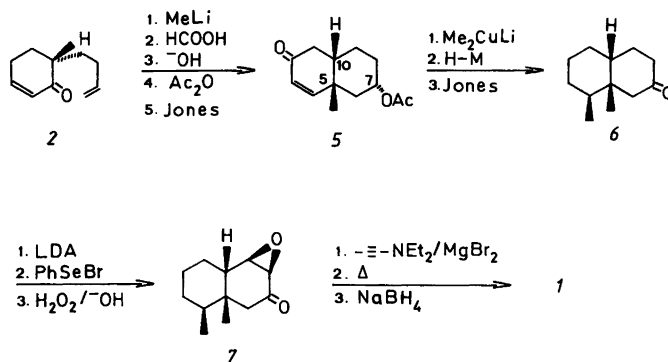
RESULTS

SAMP gave readily, with cyclohexenone (3), the hydrazone (4) (94 %) which was subjected to litiation with litium di(isopropyl)amide (LDA) followed by a treatment with 4-bromo-1-butene at −95 °C. The regeneration of the keto group was performed with methyl iodide/HCl giving the enone 2 in 26 % overall yield from 3 (Scheme 2).

Chiral α-ketones are sensitive towards racemization not only in alkaline medium, but under acidic

Scheme 2.

Scheme 3.

Reagents (Scheme 3):

Compound **2** →
1. MeLi
2. HCOOH
3. ⁻OH
4. Ac₂O
5. Jones
→ Compound **5** →
1. Me₂CuLi
2. H–M
3. Jones
→ Compound **6** →
1. LDA
2. PhSeBr
3. H₂O₂/⁻OH
→ Compound **7** →
1. –≡–NEt₂/MgBr₂
2. Δ
3. NaBH₄
→ **1**

conditions as well. To minimize racemization, the hydrazone was rapidly hydrolyzed (*ca.* 10 min), and the crude *2* purified by preparative TLC (silica gel/chloroform), with the next step performed (treatment with MeLi) as soon as possible to secure the chirality.

The details of the following reactions from *2* to *1* are as described previously[1] (Scheme 3).

All the intermediates starting from *2* were solids compared to the very viscous syrups of the racemic mixture, thus facilitating the purification. (+)-Eremophilenolide (*1*) was isolated in 27 % yield starting from the chiral enone *2* and only in 7 % yield from 2-cyclohexenone.

ENANTIOMERIC PURITY OF THE INTERMEDIATE 6

Recently some good methods for studying the enantiomeric purity of optically active compounds have been published.[4,5] The idea is to introduce another known chiral centre (normally an amino acid or its derivative) in the compound to be studied. The mixture of diastereomers formed is then monitored by using high-pressure liquid chromatography (HPLC; diastereomers[4] have normally a separation factor α of 1.2−1.4). For the preparation of a mixture of diastereomers, the ketone *6* was refluxed with SAMP in toluene to give the adduct *8* (Scheme 4) as the expected *E/Z*-mixture[3] (about 1:1). These isomers had $\Delta R_f \approx 0.8$ on a TLC-plate (silica gel, 0.25 mm, ether).

When the isomer mixture *8* (purified by preparative TLC) was analyzed by HPLC (details in the experimental), two strong peaks (ratio about 1:1)

6 + SAMP $\xrightarrow[\Delta]{\text{Toluene}}$ **8**
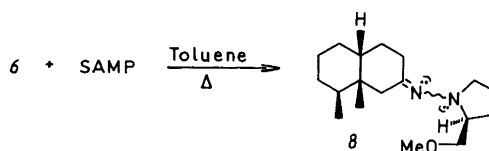
Scheme 4.

with retention times 4.3 and 4.9 min were observed. Both of these peaks had small satellite peaks with retention times 4.0 and 4.6 min. The small peaks (about 7 % of the peak area of the large ones) were supposed to be diastereomers arising from the undesired enantiomer of *6*. The intermediate *6* had to be used in the further synthetic steps in spite of the small amounts of enantiomeric impurities.

EXPERIMENTAL

For general remarks, see the preceding paper.[1] The $[\alpha]_D$ values were measured on a Perkin-Elmer 141 polarometer. The purity of the adduct of SAMP with 6 was determined on a Waters HPLC-M 6000 A instrument, monitored at 254 nm with a Waters M 440 detector (2.1 × 250 mm column packed with Merck Lichrosorb Si 60; solvent 10 % methylene chloride/hexane; flow rate 2.1 ml/min). The hydrazone *4* was prepared from cyclohexenone and SAMP in benzene with azeotropic distilation.[3] The adduct *4* was purified (in about 5 g scale) by "flash column chromatography"[6] (ether as eluent) giving the *E*- and *Z*-isomers of the hydrazone *4* which were combined for further reactions. For the physical and spectral properties of most intermediates, see Ref. 1.

(S)-6-(3-Butenyl)-2-cyclohexenone (2). The prepared enone *2* (highly viscous oil) gave $[\alpha]_D^{20} = +39.7°$ ($c=1.0$, C_6H_6). The $[\alpha]_D$-value of *2* is not available in literature. However, it seems reasonable when compared to $[\alpha]_D^{20} = +43.4°$ and $[\alpha]_D^{20} = +29.4°$ of 6-methyl and 6-ethyl-2-cyclohexenone, respectively, having the same chirality at α' carbon as *2*.[3]

(5S,7S,10S)-5-Methyl-7-acetoxy-3-octal-2-one (5). M.p. 74−75 °C (reported[7] for the racemic mixture m.p. 63.5−65.5 °C) $[\alpha]_D^{20} = +19.8°$ ($c=2.0$, $CHCl_3$).

(4S,5S,7S,8R,9R)-4,5-Dimethyl-8,9-epoxy-7-decalone (7). M.p. 62−63 °C; $[\alpha]_D^{20} = -47.6°$ ($c=2.0$, $CHCl_3$).

(+)-Eremophilenolide (1). The uncorrected melting point of 124−125 °C (undepressed on admixture with an authentic sample) was determined (reported m.p. 125 °C[2]; the m.p. of the racemic mixture 111.0−111.5 °C[1]). The measured $[\alpha]_D^{20}$ was +14.7° ($c=3.67$, $CHCl_3$) compared to the reported[2] one $[\alpha]_D^{20} = +16.6°$, thus giving the optical yield of 89 %.

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