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A Total Synthesis of (±)-Eremophilenolide

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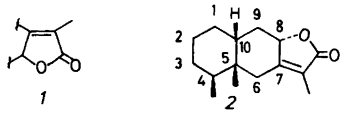
(±)-Eremophilenolide was synthesized in 18 % overall yield from cyclohexanone. The A/B-ring system was prepared *via* butenylcyclohexenol-annulation and the 2-furanone unit *via* α-epoxy-ketone-ynamine reaction.

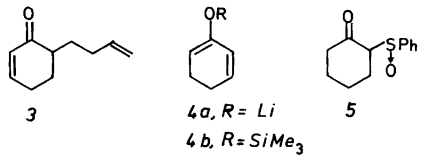
Recently a new, two-step synthesis of the 3-methyl-2(5*H*)-furanoid structural unit (*1*) from α-epoxy-ketones and 1-diethylaminopropyne was reported from this laboratory.[1] The recent results[2] in organoselenium chemistry to convert ketones to α-epoxyketones in two steps encouraged me to apply the above method for the total syntheses of some representative sesquiterpenes. (±)-Eremophilenolide (*2*) was selected for a target molecule and this report details the subsequent chemical transformations leading to *2*.



Scheme 1.

Two total syntheses of *2* have been published,[3,4] but both of these approaches lead to mixtures of *cis-trans*-isomers in the A/B ring system of *2* at some stage of the synthetic scheme. Therefore it was thought that some improvements in the synthesis of *2* could be achieved using the new method to prepare the furanone unit *1*.

One attractive possibility to prepare *cis*-decalin is based on the observation of Johnson and Harding[5] that 6-(3-butenyl)-2-cyclohexenol gives the appropriate ring structure upon treatment with formic acid. This method was later modified by Cohen[6] culminating in the total synthesis of racemic fukinone. However, one of the main problems in their synthetic scheme was the preparation of the key intermediate, the enone *3*. Starting from anisaldehyde, the required *3* was obtained in six steps in poor overall yield.



Scheme 2.

After ring closure of methylated *3* both rings of the product *8* (Scheme 4) contain functional groups. This opens possibilities for many kinds of ring transformations and for syntheses of other compounds having the *cis*-decalin ring system. Thus some new alkylation procedures to prepare the key intermediate *3* were examined.

RESULTS

The most direct method to prepare *3* would be the alkylation (with 4-iodo-1-butene) of the kinetic enolate (*4a* or *4b*) of 2-cyclohexenone generated with lithium di-isopropylamide (LDA).[7,8] This method, however, failed giving in every experiment only yellow polymeric material. A second approach was the alkylation of the dianion of the sulfoxide *5* prepared with LDA.[9] According to precedent, only monoalkylation should take place at C-6. The controlling sulfoxide group should then be removed upon pyrolysis to give a ring double bond. Treatment of the dianion of *5* with 4-iodo-1-butene gave the desired monoalkylated product which was pyrolyzed in refluxing carbon tetrachloride. After preparative TLC, an analytically pure sample of *3*

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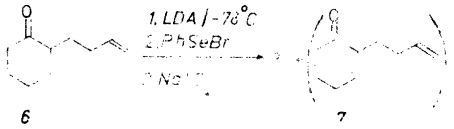
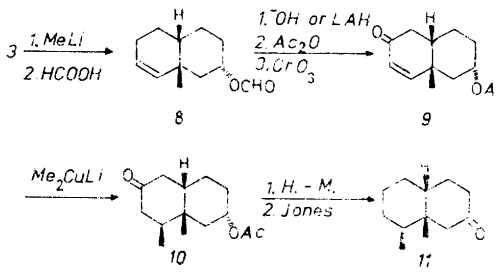
(by NMR) was obtained. However, overall yield based on 5 was only 33 %.

An alternative strategy consists of the introduction into the α-butenylcyclohexanone kinetic enolate of 6 a suitable leaving group, to furnish the α,β-enone system. Thus, cyclohexanone enolate reacted with 4-iodo-1-butene in the presence of triethylboron,[10,11] an efficient additive to minimize polyalkylation, giving in every reaction performed typically over 85 % yield of 2-butenylated cyclohexanone 6. Treatment of 6 with LDA at −78 °C gave the kinetic enolate which was allowed to react with phenylselenyl bromide, followed by oxidation with sodium periodate to furnish the enone 3 in 65 % overall yield based on cyclohexanone (Scheme 3).[12] According to NMR assignments compound 3 contained less than 5 % the undesired isomer 7.



Scheme 3.

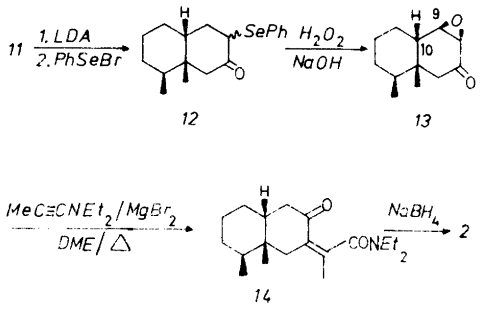
For the cyclization and oxidation of 3 the procedure of Marshall and Cohen[9] was followed, giving 9 in 72 % overall yield (Scheme 4). The



Scheme 4.

remaining methyl group was introduced *via* 1,4-addition of lithium dimethylcopper. Better yields (up to 94 %) than reported[9] were obtained when the reactions were carried out at −20 °C.

The Huang-Minion reduction of 10 followed by the Jones oxidation[9] gave in 76 % overall yield decalone 11 possessing the correct A,B-ring system of (±)-eremophilenolide. The tosylhydrazone–sodium borohydride or catecholborane reduction methods did not improve the yield of 11.



Scheme 5.

Finally the 3-methyl-2(5*H*)-furanoid unit was constructed using a selenium intermediate and 1-diethylaminopropyne (Scheme 5). The decalone 11 was treated with LDA–PhSeBr as described by Reich *et al.*,[12] giving in 87 % yield the 8-phenylselenenylated product 12. To transform the selenide 12 directly to an α-epoxydecalone *via* selenoxide fragmentation and double bond oxidation, a modification of the method by Sharpless *et al.*[13] was employed. Oxidation of 12 with excess of hydrogen peroxide in alkaline medium furnished the α-epoxydecalone 13 in 76 % yield. The epoxide ring was assigned the β-stereochemistry based on the small coupling constant between the protons at C-9 and C-10 ($J = 2$ Hz) and because the oxidant can approach the molecule more easily from the β-face than from the hindered α-face.

The reaction of 13 with 1-diethylaminopropyne *via* oxetene rearrangement took place smoothly at room temperature in dimethoxyethane (DME) and in the presence of magnesium bromide.[4] The reaction mixture was refluxed after the reaction to achieve *in situ* rearrangement of the epoxide ring into ketone in the presence of $MgBr_2$, a mild Lewis-acid. After purification, the amide decalone 14 was isolated in 83 % yield. The stereochemistry at the double bond was exclusively (*Z*) based on NMR assignments and reported results.[4] Ring closure to the furanone system was effected with sodium borohydride reduction of the ketocarbonyl, which was followed by spontaneous cyclization and expulsion of diethylamine. (±)-Eremophilenolide was isolated in 91 % yield (18 % from cyclohexanone).

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 700 spectro-

photometer. The NMR spectra were determined with Jeol FX 60 spectrometer in chloroform-*d*. Preparative TLC was performed with Silica Gel $60_{253+366}$ ethyl acetate – chloroform (1:9) as eluent. In column chromatography, the method of Still *et al.*,[14] "flash chromatography", was used. Solvents were dried by standard methods.

4-Iodo-1-butene. Di-iodobutane (64 ml) was heated in a vacuum distillation apparatus equipped with a magnetic stirrer in an oil bath (bath temperature 110 °C) under vacuum at 70–80 mmHg while triphenyl phosphate (135 ml) was added dropwise. Crude 4-iodo-4-butene distilled slowly from the reaction mixture. Redistillation at 84–88 °C/120 mmHg gave 28 g (32 %) of pure 4-iodo-1-butene.

6-(3-butenyl)-2-cyclohexenone (3). Method A (analytically pure sample was prepared this way): The procedure of Griego and Pogonowsky[10] was employed. Thus, 3.00 g of 5 gave after alkylation and pyrolysis 660 mg (33 %) of *3* as a colourless oil. B.p. 88–90 °C/2.0 mmHg (lit.[6] 87–89 °C/1.7 mmHg) IR (film): 1680, 1645 cm^{-1}. NMR: δ 1.10–2.80 (9H, m), 5.01 (1H, m), 4.76 (1H, m), 5.40–5.90 (1H, m), 5.80 (1H, dt, *J* 10.0 and 1.5 Hz), 6.78 (1H, dt, *J* 10.0 and 4.0 Hz).

Method B. 2-(3-Butenyl)-cyclohexanone (6). Cyclohexanone was alkylated with 4-iodo-1-butene and sodium hydride (or potassium hydride) in the presence of triethylboron.[10,11] In several batches in 5 g scale the yields of *6* were typically over 90 % after column chromatography ($CHCl_3$ as eluent).

Employing the method of Reich *et al.*[12] the alkylated ketone *6* was phenylselenenylated with PhSeBr under kinetically controlled conditions at −78 °C. After flash chromatography the selenide was oxidized with $NaIO_4$ in wet methanol[12] to give *3* after spontaneous fragmentation. Overall yield from cyclohexanone 82 %. According to NMR studies the product *3* contained less than 5 % undesired 2-(3-butenyl)-2-cyclohexenone.

cis-5β-Methyl-7α-acetoxy-3-octal-2-one (9). The compound *9* was prepared as described[9] in 72 % yield.

cis-4β,5β-Dimethyl-7α-acetoxy-2-decalone (10). A solution of lithium dimethylcopper(I) was prepared from 1.48 g (1.2 equiv.) of copper(I) iodide in 40 ml of dry ether to which 9.1 ml of 1.7 M methyllithium was added at −20 °C under Ar. To this solution 1.00 g of ketoacetate *9* in 20 ml of dry ether was added with stirring. After 2 h, during which time the mixture warmed up to room temperature, NH_4Cl solution was added. The organic layer was separated, dried with Na_2SO_4 and the solvent was evaporated. Preparative TLC afforded 1.00 g (94 %) of *10*, a viscous oil with spectral data like reported.[6] In several runs performed the yields were over 85 % (55 % reported[6]).

cis-4β,5β-Dimethyl-7-decalone (11). The Huang-Minlon reduction of 600 mg of *10* gave 413 mg (82 %) of 7-decalol[6] which was oxidized to the 7-decalone *11* by the Jones procedure.[6] Yield 380 mg (93 %); viscous oil. IR (film): 1710, 1310 cm^{-1}. NMR: δ 0.85 (3H, d, *J* 7 Hz), 1.00 (3H, s), 1.50–2.60 (14H, m). The reduction of tosylhydrazone of *10* with $NaBH_4$[16] or catecholborane[17] did not improve the overall yield of *11*.

cis-4β,5β-Dimethyl-8ξ-phenylseleno-7-decalone (12). The 7-decalone *11* (500 mg) was phenylselenenylated with LDA/PhSeBr[12] giving after preparative TLC 810 mg (87 %) of *12*; m.p. 56–57 °C (hexane/$CHCl_3$). NMR: δ 0.90 (3H, d, *J* 7 Hz), 1.03 (3H, s), 1.50–2.50 (12H, m), 3.92 (1H, broad t), 7.32 (3H, broad s), 7.46 (2H, broad s). Found: C 64.38; H 7.15. Calc. for $C_{18}H_{24}OSe$: C 64.47; H 7.21.

cis-4β,5β-Dimethyl-8,9β-epoxy-7-decalone (13). The oxidation method by Sharpless *et al.*[13] was modified to achieve both selenoxide fragmentation and oxidation of the enone formed in one reaction step. To a mixture of the selenide *12* (300 mg) and 0.5 ml aqueous NaOH (2 M) in 5 ml of methanol 0.8 ml of 30 % H_2O_2 (8 equiv.) was added at 0 °C. The mixture was stirred for 5 h and allowed to reach room temperature. Water was added and the product was extracted with ether. The organic mixture was washed with water, dried with Na_2SO_4 and solvent was evaporated. After preparative TLC, a viscous oil (solidified slowly) was obtained. Yield 132 mg (76 %); m.p. 34–36 °C (hexane). IR (tablet): 1715, 820 cm^{-1}. NMR: δ 0.95 (3H, d, *J* 7 Hz), 1.02 (3H, s), 1.55–2.50 (10H, m), 3.24 (1H, d, *J* 4.5 Hz), 3.62 (1H, dd, *J* 4.5 and 2.0 Hz). MS: *m/e* 194 (M^+). Found: C 73.98; H 9.17. Calc. for $C_{12}H_{18}O_2$: C 74.20; H 9.33.

(Z)-cis-4β,5β-Dimethyl-8-decalone-7-ylidene-N,N-diethylmethacrylcarboxamide (14). To a mixture of 100 mg of *13* and 8.6 μl (1.2 equiv.) of 1-diethylaminopropyne in 5 ml of dry DME 120 mg (1.2 equiv.) of dry $MgBr_2$ (prepared from 1,2-dibromoethane and magnesium) was added at room temperature under Ar. Stirring was continued for 1.5 h during which time a brown sirup developed on the wall of the reaction falsk. The mixture was refluxed stirring vigorously for 1.5 hr to ensure the rearrangement of the epoxide ring. After cooling, 20 ml of aqueous NH_4Cl solution was added and organic compounds were taken in ether. After work-up and preparative TLC, a very viscous oil was obtained. Yield 130 mg (83 %). IR (film): 1680 (unsaturated ketone), 1630 (amide) cm^{-1}. NMR: δ 0.84 (H, d *J* 7 Hz), 1.02 (3H, s), 1.10 (6H, t, *J* 7 Hz), 1.87 (3H, s), 1.52–2.50 (12H, m), 3.44 (4H, broad q, *J* 7 Hz). Found: C 74.58; H 10.08; N 4.50. Calc for $C_{19}H_{31}NO_2$: C 74.72; H 10.22; N 4.59.

(±)-Eremophilenolide (3). Reduction of 65 mg

of *14* in 5 ml of abs. ethanol at room temperature with 200 mg (excess) of $NaBH_4$ for 3 h gave after preparative TLC 45 mg (91 %) of *3*; m.p. 111–112 °C (hexane/$CHCl_3$; lit.[4] 111.0–111.5 °C). The IR and NMR spectra were identical with those of the natural compound. ^{13}C NMR ($CDCl_3$, TMS): δ C_{12} 174.92 (s), C_7 161.03 (s), C_{11} 146.35 (s), C_8 80.38 (d), C_4 40.26 (d), C_5 36.49 (s), C_{10} 35.06 (d), C_{14} 21.69 (q), C_{13} 16.10 (q), C_{15} 8.31 (q), C_1, C_2, C_3, C_6 and C_9 20.65 (t), 26.75 (t), 30.00 (t), 30.65 (t) and 31.95 (t).

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