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TOTAL SYNTHESIS OF dl-ELEMOL

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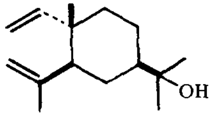
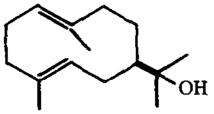
Elemol is a crystalline sesquiterpenic alcohol of structure I (1, 2). The only recorded synthesis of this substance is an indirect preparation from (-)α-santonin which has recently been described (3). This note outlines a direct synthesis of dl-I (4) which involves a novel method for the construction of the characteristic 1,2-divinylcyclohexane unit.

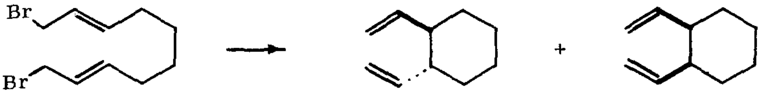


I

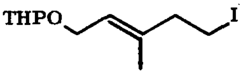


II

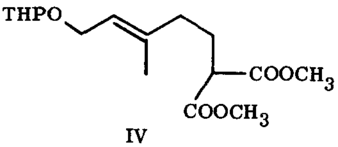
The reaction of acyclic allylic dibromides with nickel carbonyl has previously been used to effect ring closure to form 6-, 8-, and 11- to 18-membered carbocyclic rings (5-7). Of special relevance to the application of this reaction to the synthesis of elemol was the finding that 1,10-dibromo-2,8-decadiene was transformed into a mixture of trans- and cis-1,2-divinylcyclohexanes (ratio 2 : 1) by reaction with nickel carbonyl (7). Although it was shown in the case of the cis product that cis,trans-1,5-cyclodecadiene was not an intermediate, a distinction could not be made between the formation of trans-1,2-divinylcyclohexane by a direct process and formation via trans,trans-1,5-cyclodecadiene. This fact together with previous observations regarding the effect of structure on the course of the nickel carbonyl cyclization, including the application to humulene synthesis (11-membered ring formation) (6), made it seem possible that this approach could lead to a synthesis of the trans,trans-cyclodecadiene II, a probable precursor of elemol (8), as well as elemol (I), and this provided additional incentive for this study.



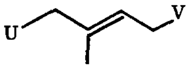
The intermediate required for the cyclization reaction, the dibromide VIId, was synthesized as



III



IV

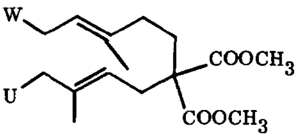


Va, U = Cl, V = CH_3CO_2

Vb, U = $\underline{o}$-TolCO$_2$, V = CH_3CO_2

Vc, U = $\underline{o}$-TolCO$_2$, V = OH

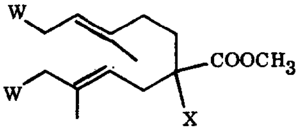
Vd, U = $\underline{o}$-TolCO$_2$, V = Br



VIa, U = $\underline{o}$-TolCO$_2$, W = OTHP

VIb, U = OH, W = OTHP

VIc, U = W = OTHP

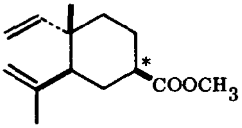


VIIa, W = OTHP, X = CHO

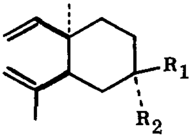
VIIb, W = OTHP, X = H

VIIc, W = OH, X = H

VIId, W = Br, X = H

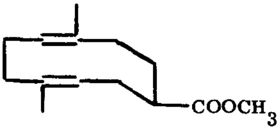


VIII



IXa, R_1 = $COOCH_3$, R_2 = H

IXb, R_1 = H, R_2 = $COOCH_3$



X

follows. The trans iodide III, prepared from the corresponding bromide (6) by treatment with sodium iodide in acetone, was allowed to react with sodio dimethyl malonate in tetrahydrofuran--dimethylformamide (ca. 20 : 1) for 48 hr. at 40° (after an initial period of 1 hr. at 25°) to give IV (9, 10) in 85% yield. Alkylation of the sodio derivative of IV by a similar procedure using the bromide Vd afforded (85% yield) the α-disubstituted malonic ester VIa (9, 10). The bromide Vd (9) was prepared from 1-chloro-2-methyl-4-acetoxy-2-butene (Va) (11) by the sequence: conversion to Vb using benzyltrimethylammonium o-toluate (2 equiv.) in ethanol at 80° for 15 hr., selective acetyl cleavage using 1 equiv. of aqueous ethanolic sodium hydroxide at 25° to form Vc, and reaction with 0.5 molar equiv. of phosphorus tribromide in ether at 0°. Treatment of the α-disubstituted malonic ester VIa with 1.3 equiv. of potassium hydroxide in methanol at 25° for 10 hr. afforded the hydroxy malonic ester VIb (9) which was transformed into the bis-tetrahydropyranyl ether VIc (9) using 1.5 equiv. of dihydropyran in dioxane at 25° with a small amount of p-toluenesulfonic acid catalyst.

Treatment of VIc with 2 equiv. of diisobutylaluminum hydride in pentane--toluene (1 : 3) at -70° for 8 hr. produced the aldehyde VIIa which was deformylated without purification to produce VIIb (79% from VIc) (9) by heating with 0.2 equiv. of sodium methoxide in methanol--toluene at 100° under nitrogen for 0.5 hr. The mono ester VIIb was subjected to acid hydrolysis to form the corresponding dihydroxy ester VIIc (9), and this was converted to dibromo ester VIId (9) (90% from VIIb) by reaction with phosphorus tribromide in ether at -5°.

Slow addition (over 14 hr.) of the dibromo ester VIId in N-methylpyrrolidone to 7 equiv. of nickel carbonyl in N-methylpyrrolidone at 47-50° under an atmosphere of carbon monoxide led to a mixture of isomeric cyclization products (total yield 83%) which was resolved into three components, R_f 0.45, 0.23, 0.08, by tlc analysis using 20% silver nitrate on silica gel with petroleum ether--ether (3 : 1) as eluant. These three materials were separated preparatively by column chromatography of the mixture using the same adsorbent. The products of R_f 0.45, 0.23, and 0.08 were eluted respectively by 1 : 1 petroleum ether--ether, 1 : 3 petroleum ether--ether, and 3 : 5 : 1 petroleum ether--ether--benzene. The most polar fraction (R_f 0.08, 32% yield) consisted of the ester VIII contaminated by ca. 10% of the diastereomer differing in orientation of carboxyl at C*. Reaction of the pure ester VIII (9, 12), obtained by preparative gc, with excess methylmagnesium bromide afforded, after the usual isolation, 85% yield of dl-elemol (I) (13) as needles, m.p. 37-38°. The infrared, n.m.r., and mass spectra of the synthetic product were identical with those of an authentic sample (14) of natural elemol.

The cyclization product from VIId of R_f 0.23 (27% yield) was identified as an 8 : 1 mixture of isomers IXa and IXb (differing in orientation of carboxyl). Both isomers were obtained pure by preparative gc (15).

The product from VIId of R_f 0.45 (11% yield) was identified as the cis, cis or cis, trans isomer of X by analytical and spectroscopic measurements (9, 16) and the finding that thermolysis at 285° (minimum temp.) in the vapor phase yielded mainly IXa and IXb. The trans, trans formulation for X can be ruled out since this structure should afford VIII upon thermolysis (8). In addition, the thermal stability of X at 100° for long periods of time and also the n.m.r. spectrum (8) argue against the trans, trans geometry.

In summary, the reaction of the dibromide VIId with nickel carbonyl has afforded a synthetic route to dl-elemol (I), but not to the isomeric trans,trans-cyclodecadiene II (17).

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2. For absolute configuration see (a) T. G. Halsall, D. W. Theobald, and K. B. Walshaw, J. Chem. Soc. 1029 (1964) and (b) A. D. Wagh, S. K. Paknikar, and S. C. Bhattacharyya, Tetrahedron 20, 2647 (1964).
3. L. J. Patil and A. S. Rao, Tetrahedron Letters 2273 (1967).
4. All synthetic substances reported herein which contain asymmetric centers were obtained as racemates.
5. (a) E. J. Corey and E. Hamanaka, J. Am. Chem. Soc. 86, 1641 (1964); (b) E. J. Corey and M. F. Semmelhack, Tetrahedron Letters 6237 (1966).
6. E. J. Corey and E. Hamanaka, J. Am. Chem. Soc. 89, 2758 (1967).
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8. Since completion of the present study the isolation of a new sesquiterpene, "hedycaryol," possessing structure II has been reported by R. V. H. Jones and M. D. Sutherland, Chem. Commun. 1229 (1968).
9. Infrared and n.m.r. spectra were in excellent agreement with the assigned structure.
10. This intermediate was purified by preparative layer chromatography using silica gel. Since distillation in vacuo was accompanied by considerable decomposition for this substance and also most of the products V-VII, elemental analyses were not obtained for these liquids.
11. W. Oroshnik and R. Mallory, J. Am. Chem. Soc. 72, 4608 (1950).
12. The following data were obtained for VIII. Found: C, 75.45; H, 9.91; molecular ion at m/e 222.1620 (calcd., 222.1620) (AEI-MS-9 double focusing instrument). The infrared spectrum of VIII (CCl_4) exhibited absorption at 5.75 (C=O), 6.08 (C=C), 9.95 and 11.0 $({}^{H}\!\!>\!C{=}CH_2)$, and 11.21 μ $(>\!C{=}CH_2)$. The n.m.r. spectrum of VIII showed sharp methyl singlets at 3.62 and 1.01 ppm (3 H each), olefinic methylene protons (4 H, multiplet) at 4.50-5.02 ppm, and an olefinic methine proton (1 H, ABX quartet) at 5.50-6.03 ppm.
13. Found for dl-I: C, 81.33; H, 11.95; molecular ion at m/e 222.
14. The sample was kindly provided by Prof. O. Jeger, Zurich.
15. The following data were obtained for IXa. Found: C, 75.61; H, 9.97; molecular ion at m/e 222.1620 (calcd., 222.1620); infrared absorption (CCl_4) at 5.75 (C=O), 6.08 (C=C), 9.95, 10.92, and 11.22 μ ($CH{=}CH_2$, $C{=}CH_2$); n.m.r. absorption (CCl_4) (in ppm) at 1.03 (s, 3 H, CH_3), 3.63 (s, 3 H, CH_3), 4.57-5.17 (m, 4 H, 2 $C{=}CH_2$), 6.07-6.60 (q, 1 H, $C\underline{H}{=}CH_2$). Satisfactory analytical and spectroscopic data were also obtained for the diastereomer of IXb.
16. Found for X: C, 75.99; H, 10.30; molecular ion at m/e 222.1260 (calcd., 222.1260).
17. This work was generously supported by the Hoffmann-La Roche Co.