

TOTAL SYNTHESIS OF dl-CHAMAECYNONE,
A TERMITICIDAL NORSESEQUITERPENE

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Chamaecynone (1), originally isolated from *Chamaecyparis formosensis* Matsum., Cupressaceae¹⁾, has become of interest because of its termiticidal activity.²⁾ Although a formal synthesis of chamaecynone from α -santonin has been reported,³⁾ total synthesis of this unusual norsesquiterpene has not been accomplished.

In previous papers⁴⁾, we reported that addition of butadiene to the dienophiles such as 2,5-dialkylcyclohex-2-en-1-ones in the Diels-Alder reaction took place stereoselectively from the opposite side to the C₅-alkyl substituent in the dienophile and that this type of the Diels-Alder reaction would be effectively employed for the synthesis of some eudesmane type sesquiterpenes and some alkaloids.⁴⁾ Consequently, our strategy for the chamaecynone synthesis was based on the assumption that all chiral centers in the molecule would be constructed in a single step by taking advantage of the Diels-Alder reaction of the dienophile (2) with an appropriately substituted diene (6).

The dienophile, 5-ethynyl-2-methylcyclohex-2-en-1-one (2)^{*1} was synthesized as follows. The 1,4-addition of vinylmagnesium bromide-CuI in THF at -40° to 6-methylcyclohex-2-en-1-one gave a stereoisomeric mixture of 2-methyl-5-vinylcyclohexan-1-one (3) (cis/trans=1) in 80% yield. Reduction of 3 with NaBH₄, followed by acetylation, yielded quantitatively a stereoisomeric mixture of the acetates (4), bp 121-122°/32 mmHg. Successive treatments of 4 with bromine, NaNH₂-liq. NH₃, 10% KOH in MeOH and Jones' reagent provided 5-ethynyl-2-methylcyclohexan-1-one (5), bp 87-90°/12 mmHg, in 79% overall yield. Bromination of 5, followed by dehydrobromination with LiBr-Li₂CO₃ gave the desired dienophile (2), colorless plates, mp 46°, in 70% yield.

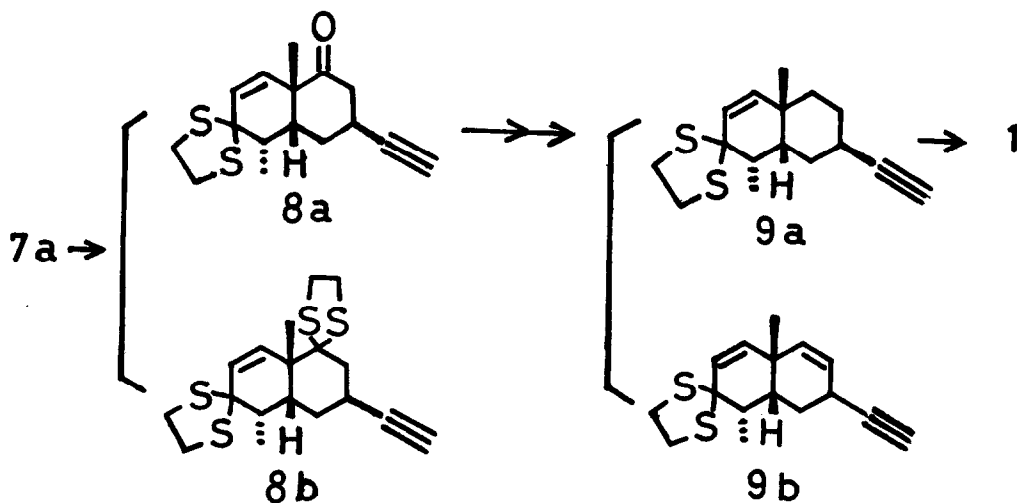
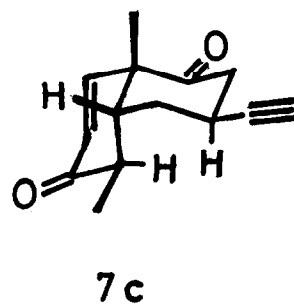
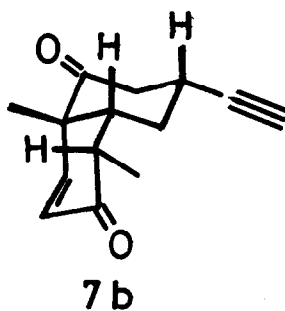
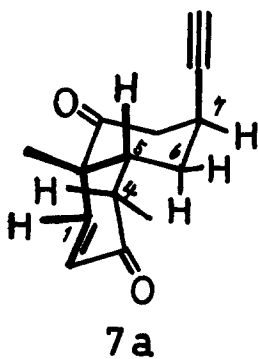
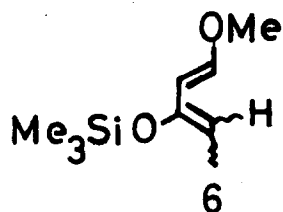
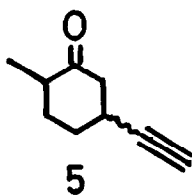
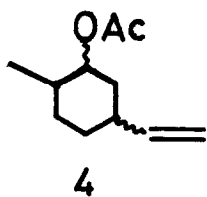
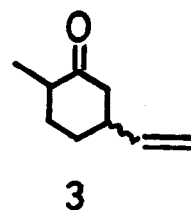
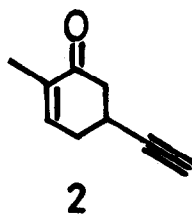
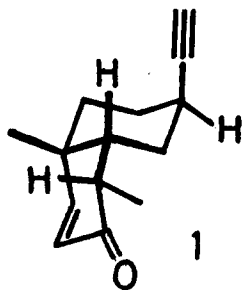
On the other hand, trimethylsilylation of 1-methoxypent-1-en-3-one⁵⁾ with Me₃SiCl-ZnCl₂-Et₃N gave the new diene (6), bp 72-76°/9 mmHg, in 70% yield.

The Diels-Alder reaction of the dienophile (2) with the diene (6) was carried out at 190-210° for 3 days under argon atmosphere and the adducts, without separation, were hydrolyzed with 2N-HCl in THF and chromatographed on

silica gel to give the adducts, (7a), (7b), and (7c) in 16%, 6%, and 4% yields, respectively.

The NMR spectrum of 7a revealed a signal due to C_1 -H at δ 6.32 (1H, d.d., $J=10$, 2 Hz) and a signal assignable to C_5 -H at δ 2.73 (1H, m.).^{*2} The W letter long-range coupling (2 Hz) between C_1 -H and C_5 -H (see formula 7a) suggests the nonsteroidal conformation of the compound (7a). A similar long-range coupling was also observed in the spectrum of 7b (C_1 -H, δ 6.33, d.d., $J=10$, 2 Hz) suggesting the nonsteroidal conformation of 7b. In the NMR spectra of 7a and 7b, irradiation of the signal due to C_{10} -CH₃ group (7a: δ 1.46, 3H, s. and 7b: δ 1.43, 3H, s.) led to 10% and 15% enhancements of the integrated intensity of the C_4 -H signal (7a: δ 2.99, 1H, double q., $J=7$, 4.5 Hz and 7b: δ 2.96, 1H, double q., $J=7$, 3.5 Hz), respectively. These observations suggest the same α configuration of C_4 -CH₃ group in both 7a and 7b. Consequently, the compound (7a) and (7b) are stereoisomeric with respect to the configuration of the ethynyl group. The configuration of the ethynyl group of 7a was deduced from the homonuclear INDOR experiments.^{*3} Thus, the signal due to C_6 -H_{ax.} appeared at δ 1.63 (1H, oct., $J=14$, 13 and 4 Hz). Since the geminal coupling (C_6 -H_{ax.}- C_6 -H_{eq.}) and the diaxial coupling (C_5 -H_{ax.}- C_6 -H_{ax.}) have the values of 13 Hz and 14 Hz or vice versa, the coupling constant value ($J=4$ Hz) is allotted to the coupling between C_6 -H_{ax.} and C_7 -H_{eq.} (δ 3.22, 1H, m.) geminal to the ethynyl group. This suggests the axial conformation of the ethynyl group in 7a. Consequently, the stereostructures of the major product and the minor product are shown by the formulas, (7a) and (7b), respectively. On the other hand, no W letter long-range coupling on the signal due to C_1 -H (δ 6.77, 1H, d., $J=10$ Hz) was observed in the NMR spectrum of 7c, suggesting its steroidal conformation. The equilibrium experiment of 7c with ^tBuOK-^tBuOH at room temperature for 2 hr causes epimerization at the C_4 position to afford a mixture of 7a and 7c in a 2:1 ratio. From these observations, the stereostructure of 7c is presumed to be shown by the formula (7c). Consequently, the major product (7a) serves for the chamaecynone synthesis.}}}}}}

The next step of synthesis is selective reduction of the C_9 carbonyl function of 7a to the methylene group. Since the C_9 carbonyl group is highly hindered by the angular methyl and the axial ethynyl group and the ethynyl group is susceptible to reduction, most of the usual procedures being available for reduction of the carbonyl group were unsuccessful. Then, selective thioketalization of 7a with 4.9 mol of ethanedithiol and 2.9 mol of BF_3 -Et₂O gave the monothioketal (8a) and the dithioketal (8b) in 57% and 13% yields, respectively. Treatment of 8a with p-TsNHNH₂-MeOH-CHCl₃ provided quantitatively the tosylhydrazone which was reduced with NaBH₃CN-anhydrous p-TsOH-sulfolane-DMF to give the thioketal derivative (9a) of dl-chamaecynone and the olefinic compound (9b) resulted from elimination of the tosylhydrazino group, in 10% and 7% yields, respectively. Finally, treatment of the compound (9a) with Tl(NO₃)₃ provided



dl-chamaecynone, mp 77-80° (from n-pentane), in 73% yield. A sample of synthetic dl-chamaecynone was identified with an authentic sample of natural chamaecynone by comparison of their IR (in CCl₄) and NMR spectra.

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Footnotes and References

- *1 All new compounds gave satisfactory analytical and spectroscopic data.
- *2 Measurements of NMR spectra were made for CDCl₃ solutions.
- *3 Details of the results obtained by the homonuclear INDOR experiments will be stated elsewhere.
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