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A STEREOSELECTIVE SYNTHESIS OF A FUNCTIONALIZED TRICYCLO$[6.3.1.0^{3,8}]$-DODEC-4-ENE BY AN INTRAMOLECULAR DIELS-ALDER REACTION1)

Kozo SHISHIDO, Kou HIROYA, Yutaka UENO, Keiichiro FUKUMOTO,*
Tetsuji KAMETANI,† and Toshio HONDA†
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980
†Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41,
Shinagawa-ku, Tokyo 142

An intramolecular Diels-Alder reaction of the cyclohexatrienone derivatives gives the title compounds, which have a useful structural feature for constructing basic carbon frameworks of some kinds of natural products, in a stereoselective manner.

In connection with our current studies directed towards total synthesis of natural products using an intramolecular Diels-Alder reaction,2) we planned to get a useful and common synthon for constructing basic carbon frameworks of various kinds of natural products by the cycloaddition. For this purpose, we chose 7-substituted (3α)-12-oxotricyclo$[6.3.1.0^{3,8}]$-dodec-4-ene (1) as a synthetic target because of the suitably positioned functionalities in 1 for assembling e.g., the left half part of the aconitine type alkaloid cardiopetaline3) (2), the basic skeleton of sesquiterpenoid α-cedrene4) (3), and of diterpenoid stemodin5) (4) as shown in Fig. 1. Here we describe a

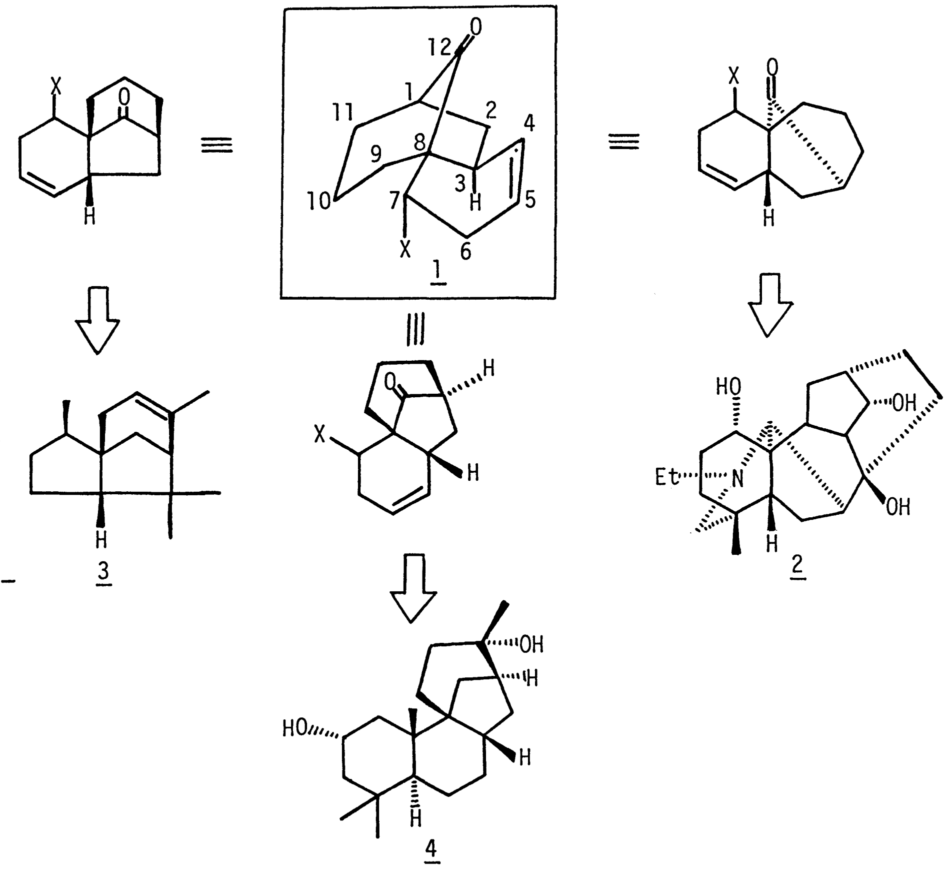
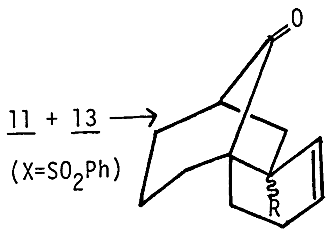


Fig 1.



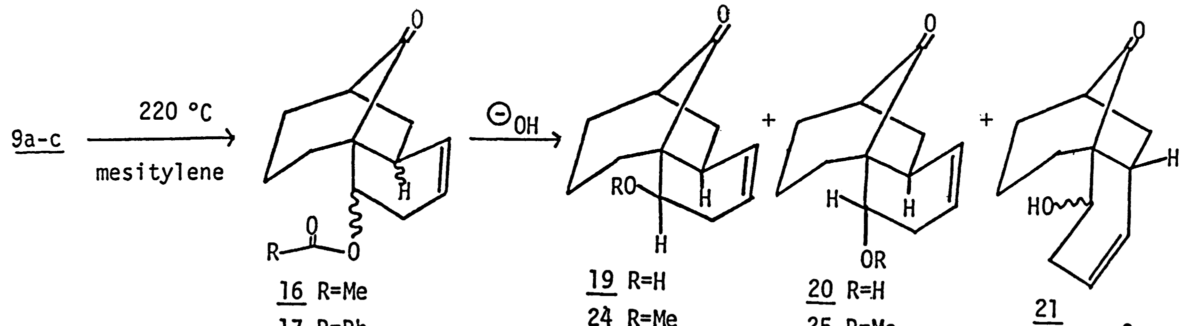
14 R=α-H
15 R=β-H

Scheme 2.

the preference of the exo-conformer (10) in the transition state during the thermolysis (Scheme 1). The confirmation of the structure was made by X-ray crystallographic analysis[13)] of 11 (X=SO$_2$Ph).

On the other hand, the results of the cycloadditions of the acyloxy series (9a-c) are summarized in Scheme 3.

The thermolysis of this series resulted in four products which were the diastereomers about two chiral centers, at C-3 and C-7. Despite of the homogeneity[10)] of the starting trienones (9a-c), the occurrence of an epimerization at C-7 might be explainable by equilibration via retro Diels-Alder reaction and re-addition under such considerable harsher thermal conditions (at 220 °C for 38 - 60 h). The stereochemistry at C-3 in the major isomers was correlated with that of 14 by treating a mixture of 19 and 20,[14)] obtained by the basic hydrolysis of 16, 17, and 18, with a condition of deoxygenation[15)] [i) SO$_2$Cl$_2$, pyridine then Me$_2$NH ii) Na, liq. NH$_3$, MeOH, THF iii) PCC] (Scheme 4).



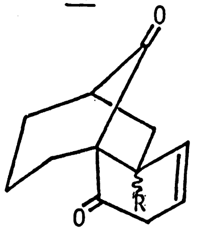
16 R=Me
17 R=Ph
18 R=^{i}Pr

19 R=H
24 R=Me

20 R=H
25 R=Me

21

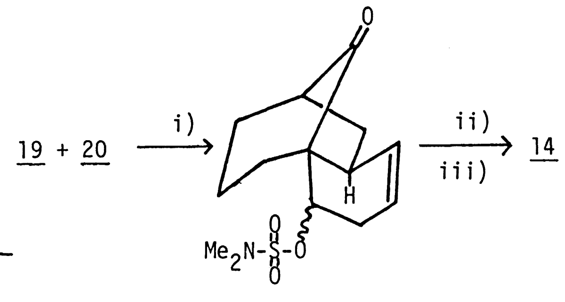
Compound	Time/h	Product	Yield/%	Ratio 19 : 20 : 21
9a	50	16	46.6	12.0 : 2.6 : 1
9b	38	17	40.0	2.7 : 2.1 : 1
9c	60	18	50.0	12.4 : 7.7 : 1



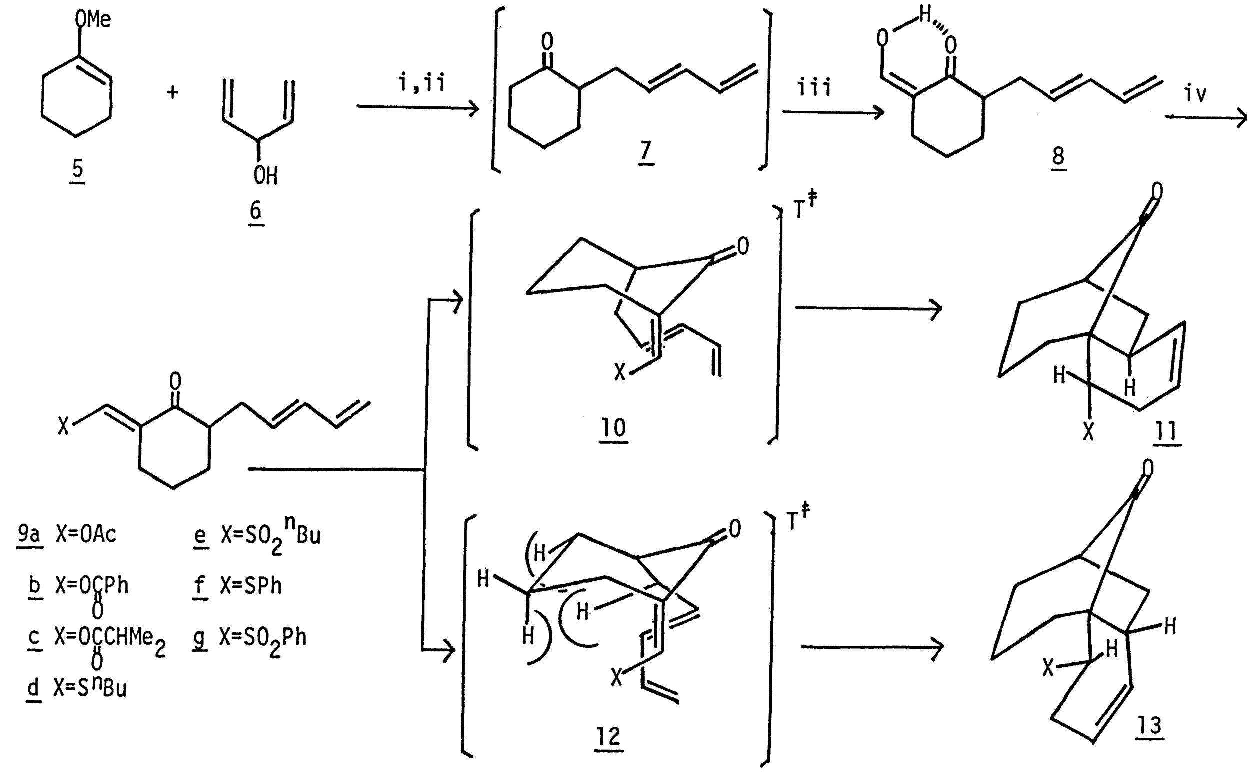
22 R=α-H
23 R=β-H

Scheme 3.

About both structures[16)] of 19 and 20, it was confirmed by an independent PCC oxidation of both compounds affording the same diketone (22).[17)] Whereas the another cycloadduct (21), an unseparable mixture of two diastereomers, was oxidized with PCC to give a single diketone (23) indicating that 21 should be the isomeric at C-7. In conclusion, higher stereoselectivities (14.6 : 1 for 9a and 20.1 : 1 for 9c) about the configuration of C-3 was achieved in the thermolysis of 9a and 9c and it was found that the presence of the sp^3 carbon adjacent to the carbonyl group on the dienophile part would be necessary for the increased stereoselectivity of the cycloaddition.



Scheme 4.



i) Hg(OAc)$_2$, NaOAc ii) CSA iii) NaH, HCO$_2$Et, benzene iv) a: Ac$_2$O, pyridine, DMAP (cat.), CH$_2$Cl$_2$ b: (PhCO)$_2$O, pyridine, DMAP (cat.), CH$_2$Cl$_2$ c: (Me$_2$CHCO)$_2$O, pyridine, DMAP (cat.), CH$_2$Cl$_2$ d: ^{n}BuSH, p-TsOH (cat.), benzene e: 9d, 2 equiv. MCPBA, CH$_2$Cl$_2$ f: MsCl, pyridine DMAP (cat.) then PhSH g: 9f, 2 equiv. MCPBA, CH$_2$Cl$_2$

Scheme 1.

simple and stereoselective route to the tricyclic ketone (1) by an intramolecular Diels-Alder reaction.[6)]

Reaction of divinylcarbinol[7)] (6) with an excess 1-methoxycyclohexene (5) in the presence of a catalytic amount of mercuric acetate at 112 °C followed by further heating with a catalytic amount of d-10-camphorsulfonic acid at the same temperature gave 2-(2,4-pentadienyl)cyclohexanone (7) via Claisen rearrangement.[8)] The crude 7 was then converted to the hydroxymethylene ketone[9)] (8) in 80.0% overall yield from 6. An introduction of the substituents on the dienophile part could be achieved by standard procedures as shown in Scheme 1 affording the trienones[10)] (9a-g).

Table 1.

Compound	X	Yield/%	Products	Ratio
9e	SO$_2$^{n}Bu	74.5	11 + 13	5.6 : 1$^{a)}$
9g	SO$_2$Ph	72.0	11 + 13	3.4 : 1

a) A ratio of products determined by LC.

An intramolecular Diels-Alder reaction was conducted as an about 50 mmol solution in toluene using a sealed tube at 180 °C[11)] for 20 h. The results of the cycloadditions are summarized in Table 1.

Two products (11 and 13) thus obtained were the diastereomers at C-3, which could be supported by the fact that the mixture of the cycloadducts, 11 and 13 (X=SO$_2$Ph), was treated with lithium in liq. ammonia in the presence of ethanol followed by PCC oxidation to give two ketones,[12)] 14 and 15 (Scheme 2).

The stereochemistry of the major cycloadduct (11) was deduced from because of

Thus, we could develop an efficient and highly stereoselective route for constructing the functionalized tricyclo[6.3.1.$0^{3,8}$]dodec-4-ene system, which should be the potential synthon for assembling basic carbon frameworks of some kinds of natural products, by using an intramolecular Diels-Alder reaction as a key step.

Further experiments aimed at constructing the carbon frameworks of natural products shown in Fig. 1. are in progress.

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6) During the course of this work, the same type of the intramolecular Diels-Alder reaction for total synthesis of quadrone was reported by Schlessinger and Vandewalle, independently. R. H. Schlessinger, J. L. Wood, A. P. Poss, R. A. Nugent, and W. H. Parsons, J. Org. Chem., 48, 1146 (1983); J. M. Dewanckele, F. Zutterman, and M. Vandewalle, Tetrahedron, 39, 3235 (1983).
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9) Ir (neat), 1630 cm^{-1}; NMR (CCl_4), δ 14.50 (1H, br.s), 8.50 (1H, m), 6.56 - 4.56 (5H, m).
10) The configuration of the dienophile enone in 9a-g was homogeneous from ^1H NMR and ^{13}C NMR spectra and was assigned as "E" from the chemical shift of the β-proton of the enone. cf.) S. Danishefsky, J. Morris, G. Mullen, and R. Gammill, J. Am. Chem. Soc., 104, 7591 (1982). For 9a: IR ($CHCl_3$), 1770, 1690, 1620 cm^{-1}; NMR ($CDCl_3$), δ 7.98 (1H, t, J = 2 Hz), 2.20 (3H, s). For 9f: IR (neat), 1687 cm^{-1}; NMR ($CDCl_3$), δ 6.68 (1H, m).
11) Although the Lewis acid [Et_2AlCl, $AlCl_3$, or $B(OMe)_3$] catalyzed cyclization was also examined under various conditions, no cycloadducts were obtained.
12) For 14: IR ($CHCl_3$), 1735 cm^{-1}; NMR ($CDCl_3$), δ 5.48 (2H, br.s). For 15: IR ($CHCl_3$), 1735 cm^{-1}; NMR ($CDCl_3$), δ 5.92 - 5.44 (2H, m). The ketone 14 is completely different from 15 on TLC using three different kinds of solvents.
13) Detailed analytical data will be shown later in the full paper.
14) IR ($CHCl_3$), 3530, 1720 cm^{-1}; NMR ($CDCl_3$), δ 5.52 (2H, m).
15) T. Tsuchiya, I. Watanabe, M. Yoshida, F. Nakamura, T. Usui, M. Kitamura, and S. Umezawa, Tetrahedron Lett., 1978, 3365.
16) For the methyl ether (24): NMR ($CDCl_3$) δ 3.40 (1H, t, J = 2 Hz, C-7H). For 25: NMR ($CDCl_3$), δ 3.08 (1H, dd, J = 10 and 6 Hz, C-7H).
17) IR ($CHCl_3$), 1740, 1710 cm^{-1}; NMR ($CDCl_3$), δ 5.72 (2H, br.s).

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