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Synthesis of Adamantane Derivatives. LXVIII.[1] Cycloaddition Reactions of 2-(1-Adamantyl)-1,3-butadiene and -heterodienes

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2-(1-Adamantyl)-1,3-butadiene (**1**) was prepared by *p*-toluenesulfonic acid-catalyzed dehydration of the corresponding allyl alcohol **5**. The Diels–Alder reactions of **1** with a variety of dienophiles proceeded smoothly to give adamantane-substituted six-membered carbo- and heterocycles. Similarly, [4+2]cycloaddition reactions of adamantane-bearing heterodienes afforded some adamantyl-oxazines.

Keywords——adamantylbutadiene; Diels–Alder reaction; heterodiene; heterodienophile; oxazine

Some compounds incorporating an adamantyl group show interesting pharmacological activity (*e.g.*, antivirus activity), and therefore, various adamantane derivatives have been prepared and pharmacologically screened.[2] As a part of our continuing program of research on adamantane derivatives from this viewpoint, we planned the synthesis of adamantane-substituted six-membered rings[3] by means of a straightforward procedure based on [4+2]cycloaddition. For this purpose, a conjugated diene with an adamantyl group at the 2-position is preferred because this minimizes the steric effect of such a bulky substituent.[4] The prototype of this class of compounds is 2-(1-adamantyl)-1,3-butadiene (**1**). However, surprisingly, the diene **1** has not yet been reported. Thus, we started the present work aimed at preparing **1**, and thereafter, its cycloaddition reactions with dienophiles were studied, in addition to those of some adamantane-bearing heterodienes leading to oxazines.

The desired diene **1** was synthesized from 1-adamantanecarboxylic acid (**2**) by the following sequence of reactions; the methyl ketone **3** was prepared from **4** and methylmagnesium iodide in the presence of CuCl according to a recent report by Russian chemists.[5] Addition of vinylmagnesium bromide to **3** afforded the allyl alcohol **5** in a high yield. For the dehydration of **5** several procedures were attempted. Only polymerization was observed when **5** was treated with methanesulfonyl chloride–triethylamine, thionyl chloride–pyridine, or dimethylsulfoxide (DMSO) (150 °C). The acetate **6** was mainly obtained by treatment with acetic anhydride at reflux temperature. Thermolysis of the oxalate **7** at 170 °C under a vacuum[6] afforded the diene **1** in only 35% yield. As a standard acid-catalyzed E_1 reaction, a solution of **5** in benzene in the presence of *p*-toluenesulfonic acid was heated, but concomitant polymerization could not be avoided. Finally, when the solvent was changed to ether under the same conditions, the diene **1** was obtained in 60% yield as a colorless oil. The characteristics of the structure were consistent with the infrared (IR) spectrum [1620 and 1600 cm^{-1}] and the nuclear magnetic resonance (NMR) [$\delta(CCl_4)$ 4.68 and 5.00 (2H, d, J= 1.5 Hz, C_1–H), 4.93, 5.24 and 6.40 (3H, ABX, J=2 and 10 Hz, 2 and 17 Hz, and 10 and 17 Hz, respectively, C_3– and C_4–H)].

With the diene **1** in hand, [4+2]cycloaddition reactions of **1** with a variety of dienophiles were carried out in an appropriate solvent at room or higher temperature under a nitrogen atmosphere. After the reaction (which was monitored by thin layer chromatography (TLC)) was completed, the products were purified by recrystallization or column chromatography.

TABLE I. Cycloaddition Reaction of **1** with Dienophiles

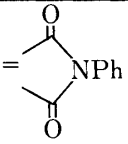
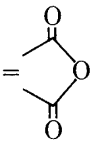
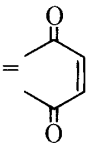
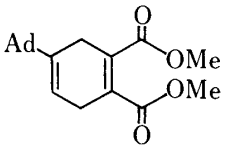
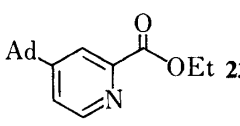
Entry	Dienophile	Reaction conditions and purification[a] 1. solv. 2. temp. 3. time 4. purification	Product	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
1	**8**	B rf 30 min Re (M)	**22a** $R^1, R^2 =$  $R^3 = H$	63	177—180	$C_{24}H_{27}NO_2$	79.74 (79.46	7.53 7.61	3.88 3.88)
2	**9**	H rf 4 h Ch (Si–C)	**22b** $R^1 = R^3 = COOEt$ $R^2 = H$	72	Oil	$C_{22}H_{32}O_4$	77.30 (77.31	8.95 8.94)	
3	**10**	B rf 3.5 h Re (E and T)	**22c** $R^1, R^2 =$  $R^3 = H$	70	148—149	$C_{18}H_{22}O_3$	75.49 (75.46	7.74 7.77)	
4	**11**	B rf 5 h Re (H)	**22d** $R^1, R^2 =$  $R^3 = H$	75	133—136	$C_{20}H_{24}O_2$	81.04 (81.39	8.16 8.39)	
5	**12**	B rf 8 h Re (M)	 **22e**[b]	65	75—76.5	$C_{20}H_{26}O_4$	72.70 (72.72	7.93 7.89)	
6	**13**	B rm 2 h Re (H)	**22f** $R^1 = H, R^2 = CN$ $R^3 = COOMe$	90	88—90	$C_{19}H_{25}NO_2$	76.22 (75.96	8.42 8.29	4.68 5.06)
7	**14**	D[c] −50 °C 2.5 h Re (H)	**22g** $R^1 = H, R^2 = OH$ $R^3 = COMe$	52	67.5—69.5	$C_{18}H_{26}O_2$	78.79 (78.51	9.55 9.65)	
8	**15**	B rm 20 h Ch (Si–C)	**23a** $X = Y = NCOOEt$	87	Oil	$C_{20}H_{30}N_2O_4$	66.27 (66.19	8.34 8.36	7.73 7.79)
9	**16**	C rm 3 d Re (H)	**23b** $X = NPh$ $Y = O$	51	95—98	$C_{20}H_{25}NO$	81.31 (81.29	8.53 8.60	4.74 4.70)
10	**17**	To rf 39 h Ch (Si–B)	**23c**[d] $X = C(COOEt)_2$ $Y = O$	100	Oil	$C_{21}H_{30}O_5$	69.58 (69.54	8.34 8.32)	
11	**18**	B rm 39 h Fi	**23d** $X = S = O$ $Y = NSO_2C_6H_4(4\text{-Me})$	89	120—124	$C_{21}H_{27}NO_3S_2$	62.19 (62.09	6.71 6.69	3.45 3.57)
12	**19**	To[e] 115 °C 25 d Ch (Al–C)	 **23e**[b,d]	42	Oil	$C_{18}H_{23}NO_2$	75.75 (75.59	8.12 8.30	4.91 4.90)

TABLE I. (continued)

Entry	Dienophile	Reaction conditions and purification[a] 1. solv. 2. temp. 3. time 4. purification	Product	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
13	**20**	H rm 15 h Fi	**23f**[d] X=CCl_2 Y=S=O	72	91—96[f]	$C_{15}H_{20}Cl_2OS$	56.43 (56.55	6.31 6.33)	
14	**21**	To rf 2 h Ch (Si-D)	**23g** X=P(=S)C_6H_4(4-OMe) Y=S	85	Oil	$C_{21}H_{27}OPS_2$	64.58 (64.50	6.97 6.91)	

a) 1. Solvent: B, benzene; C, chloroform; D, dichloromethane; E, ether; H, hexane; M, methanol; T, tetrahydrofuran; To, toluene. 2. temp.: rf, reflux; rm, room temperature. 4. purification: Re; recrystallization from the solvent in parentheses; Ch, chromatography on the column with the eluting solvent in parentheses (Si, silica gel; Al, alumina); Fi, filtration of the precipitate.
b) Ad = 1-adamantyl.
c) This reaction was carried out in the presence of 1 eq of $SnCl_4$. The work-up was done as follows; 1) decomposition of the reaction mixture with ice. 2) extraction of the products with CH_2Cl_2. 3) desilylation with 1 N HCl (1 ml)–MeOH (5 ml) at room temperature for 30 min.
d) Only the major regioisomer is given in Table I. The minor isomer was not fully characterized.
e) This reaction was carried out in a sealed glass tube.
f) This melting point was measured for the mixture of regioisomer.

Their structures were deduced by spectral and elemental analyses, while the known reactions of 2-substituted 1,3-butadienes (*e.g.*, isoprene) provided a precedent for the regiochemistry.[7] The results are summarized in Tables I and II.

Among these reactions, the relative diene reactivity of **1** was estimated by hlaf-life measurement by gas chromatography for the reaction with diethyl fumarate (**9**), using myrcene as a reference; it was shown that adamantane-substituted **1** reacted 5 times faster than the less crowded myrcene. This may be explicable in terms of the electron-donating character of an adamantyl group and/or predominance of a cisoid conformation due to its steric bulkiness.

Entries 1—5 show the cycloaddition reactions with symmetrical C=C dienophiles such as *N*-phenylmaleimide (**8**), **9**, maleic anhydride (**10**), *p*-benzoquinone (**11**), and dimethyl acetylenedicarboxylate (**12**). The adducts **22c** and **22d** were further converted to the free diacid **24** by hydrolysis and to the hydroquinone **25** by catalytic isomerization with triethylamine. Although unsymmetrical dienophiles **13** and **14** may afford two regioisomers (*meta* and *para* adducts), only the *para* adduct, formation of which is expected from simple orbital considerations,[4] could be isolated. The synthesis of the α-ketol **22g** is based on the method recently developed by us.[7a] Thus, adamantylcyclohexenes with a hydrophilic group at the *meta* and *para* positions were prepared in fair to good yields.

Adamantane-substituted six-membered heterocycles **23a**—**g** were obtained from the reactions of **1** with heterodienophiles (X=Y; X, Y=C, N, O, S) such as diethyl azodicarboxylate (**15**), nitrosobenzene (**16**), diethyl oxomalonate (**17**), *N*-sulfinyl-*p*-toluenesulfonamide (**18**), ethyl cyanoformate (**19**), dichlorosulfine (**20**),[8] and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (**21**) as shown in entries 8—14. In these cases the regiochemistry is also involved. Except for entries 10, 12 and 13, no appreciable minor regioisomer was isolated. This high selectivity is consistent with the

TABLE II. IR and ^{1}H NMR Spectral Data for Cycloadducts **22** and **23**

Compd.	IR ν_{max} (cm^{-1})[a]	^{1}H NMR (δ)[b]
22a	1700, 1650, 1495	2.2—3.1 (4H, m, CH_2), 3.1—3.3 (2H, m, CH), 5.57 (1H, m, CH=C), 7.1—7.5 (5H, m, Ph)
22b	1730, 1660	1.23 and 1.25 (6H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.2—2.9 (6H, m, ring CH and CH_2), 4.11 (4H, q, J=7 Hz, OCH_2), 5.36 (1H, m, CH=C)
22c	1845, 1770, 1650	2.2—3.0 (4H, m, CH_2), 3.3—3.5 (2H, m, CH), 5.58 (1H, m, CH=C)
22d	1685, 1600	2.1—2.5 (4H, m, CH_2), 3.0—3.3 (2H, m, CH), 5.37 (1H, m, CH=C), 6.65 (2H, s, COCH=C)
22e	1735, 1720, 1680 1650	2.94 (4H, s, CH_2), 3.72 (6H, s, CH_3), 5.41 (1H, m, CH=C)
22f	2230, 1740, 1640	1.9—2.4 and 2.5—2.7 (6H, m, CH_2), 3.83 (3H, s, OCH_3), 5.38 (1H, m, CH=C)
22g	3430, 1700, 1655	1.9—2.8 (6H, m, CH_2), 2.25 (3H, s, $COCH_3$), 3.52 (1H, br s, OH, disappeared with D_2O), 5.37 (1H, m, CH=C)
23a	1710, 1660	1.27 (6H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.15 (4H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 3.4—4.7 (4H, m, ring CH_2), 5.38 (1H, m, CH=C)
23b	1660, 1590, 1490	3.70 (2H, m, NCH_2), 4.47 (2H, m, OCH_2), 5.48 (1H, m, CH=C), 6.7—7.4 (5H, m, Ph)
23c	1745, 1665	1.28 (6H, t, J=7.5 Hz, $OCH_2C\underline{H}_3$), 2.67 (2H, m, C_5–CH_2), 4.26 (4H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 4.41 (2H, m, C_2–CH_2), 5.50 (1H, m, CH=C)[c]
23d	1630, 1590, 1345 1155, 1100	2.43 (3H, s, CH_3), 3.4—5.0 (4H, m, CH_2), 5.62 (1H, m, CH=C), 7.32 and 7.81 (4H, d, J=8.5 Hz, Ph)
23e	1720, 1600	1.45 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.48 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.40 (1H, dd, J=6 and 2.5 Hz, C_5–H), 8.12 (1H, d, J=2.5 Hz, C_3–H), 8.67 (1H, d, J=6 Hz, C_6–H)[d]
23f	1640, 1070	2.8—4.1 (4H, m, CH_2), 5.36 (1H, m, CH=C)[e]
23g	1635, 1590, 1500 1255, 1030	2.8—3.8 (4H, m, CH_2), 3.83 (3H, s, CH_3), 5.92 (1H, m, CH=C), 6.94 (2H, dd, J=9 and 3 Hz, CH=C–OMe), 7.92 (2H, dd, J=14 and 9 Hz, CH=C–P)

a) Measured in KBr disks except for **22b**, **23a** and **23c** (neat) and **23e** and **23g** ($CHCl_3$).
b) Measured in $CDCl_3$ except for **22b**, **22e**, **23a** and **23b** (CCl_4). In all spectra, signals due to adamantane ring protons appeared in the 1.5—2.2 δ region as a multiplet.
c) A signal due to the minor regioisomer appeared at δ 5.30 (m).
d) Signals due to the minor regioisomer appeared at δ 7.75 (dd, J=7.5 and 3 Hz), 8.08 (d, J=7.5 Hz) and 8.80 (d, J=3 Hz).
e) A signal due to the minor regioisomer appeared at δ 5.42 (m),

reported examples.[7] However, in the cycloadduct of **1** with **17**, the *meta* adduct was found to be present (less than 30%) with the *para* adduct depicted in Table I on the basis of proton nuclear magnetic resonance (^{1}H NMR) inspections. The reaction of a diene with **19** was reported a long time ago by Alder,[7e] but no experimental details were given. In our case (**1** and **19**), an extremely prolonged reaction time was required to accomplish the cycloaddition reaction. The products were characterized as 4-(1-adamantyl)picolinic acid ethyl ester (**23e**) and the 5-isomer (less than 15% from the ^{1}H NMR), which were formed by oxidative aromatization of the primary cycloadduct. The structural proofs were based on the comparison of chemical shifts and coupling patterns with those of 4- and 5-alkylpicolinates.[9] Among cycloaddition reactions using **20**, only symmetrical dienes have been employed and reported so far.[7f] In this case (**1** and **20**), a mixture of regioisomers was obtained in a ratio of 3:2. While ^{1}H NMR was not useful to determine the regiochemistry, carbon-13 nuclear magnetic resonance (^{13}C NMR) was suggestive; in addition to signals due to adamantane ring carbons, one pair of signals (major/minor with an average integral ratio of 3:2) appeared at 37.5 (s)/37.2 (s), 48.5 (t)/47.5 (t), 95.4 (s)/94.5 (s), 108.1 (d)/136.8 (s), and 144.3 (s)/115.9 (d)

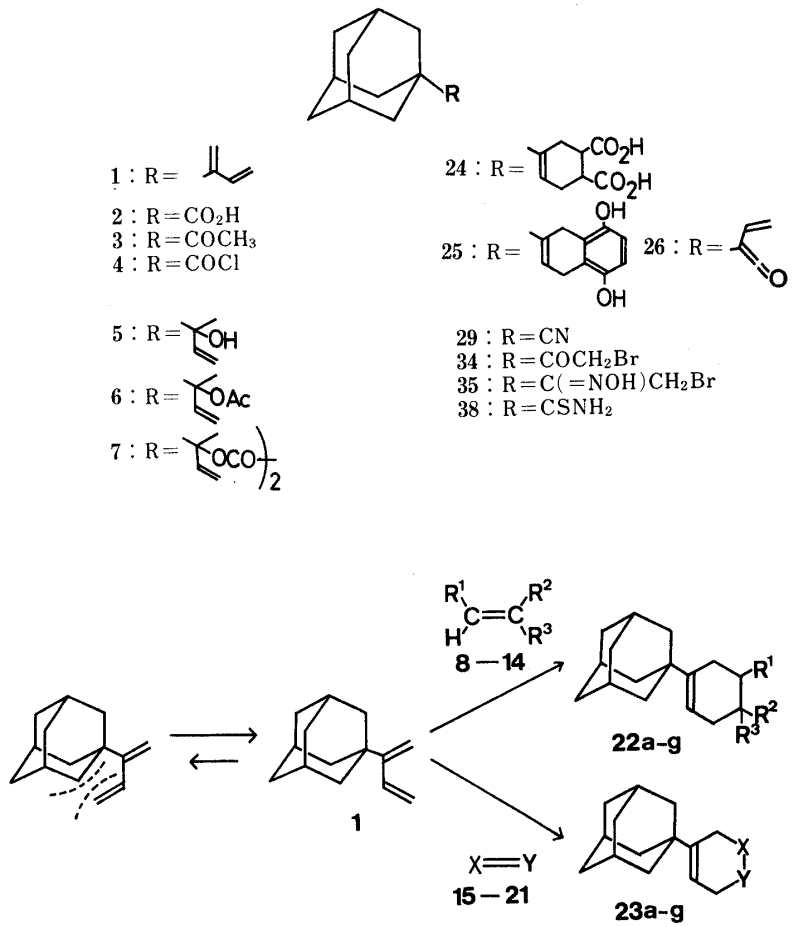


Chart 1

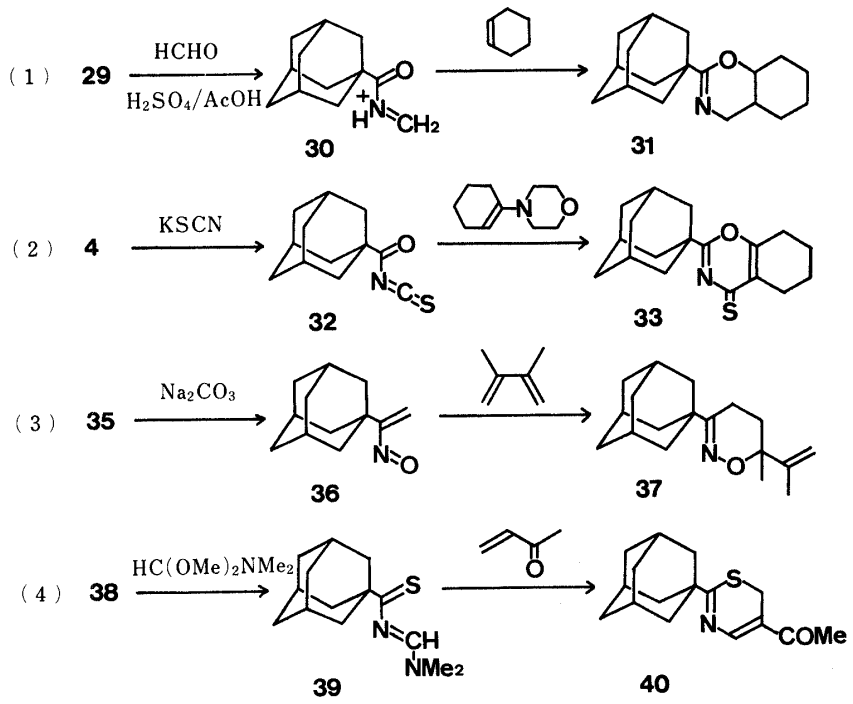


Chart 2

ppm; these can be attributed to C_5-, C_2-, C_6-, C_3- and C_4-carbons of the dihydrothiapyran-1-oxide ring. Less deshielded C_3- and more deshielded C_4-carbon were noted in the major isomer. In view of the greater deshielding effect of $>CCl_2$ than $>S=O$ at the β-position,[10] the major isomer is considered to be that with the adamantyl group at C_4 (*para* adduct, as depicted in Table I).

(1-Adamantyl)vinylketene (**26**) is another type of 4π-component which should be stable in solution.[11] Thus, preparation of **26** or its synthon was attempted. However, we failed in both 1,4-elimination of the corresponding α,β-unsaturated acid chloride and formation of the related α,β-unsaturated silyl ketene acetal.[12]

The use of admantane-substituted heterodienes is an alternative approach to adamantane-heterocycles. In particular, oxazine is interesting because of its potent physiological activity,[13] and it is easily accessible by cycloaddition. Thus we investigated four selected reactions involving heterodienes (Chart 2). (1) Reaction of the *N*-acyliminium salt prepared *in situ* from nitrile and formaldehyde;[14] the 1,3-oxazine **31** was obtained from 1-adamantanecarbonitrile (**29**) and cyclohexene in 33% yield. (2) Reaction of acylisothiocyanate with enamine;[15] 1-adamantanecarbonylisothiocyanate (**32**) [prepared from **4** and KSCN] was treated with 1-morpholino-1-cyclohexene to give the 1,3-oxazine-4-thione **33** in 50% yield. (3) Reaction of nitroso-olefin;[16] the isomeric 1,2-oxazine **37** was obtained by the reaction of the oxime **35** of 1-adamantyl bromomethyl ketone (**34**) with Na_2CO_3 in the presence of 2,3-dimethyl-1,3-butadiene in 59% yield. (4) Reaction of *N*-thioacylformamidine;[17] *N*-(1-adamantanethiocarbonyl)formamidine (**39**) prepared from **38** and dimethylformamide dimethyl acetal was treated with methyl vinyl ketone to give the 1,3-thiazine **40** in 36% yield. All of the above reactions followed the reported mechanism, suggesting that the reactivity of these heterodienes is not altered substantially by the presence of an adamantly substituent.

In this work, adamantane derivatives having a diene-reactive substituent at the bridgehead were found to be useful for the preparation of various adamantane-substituted carbo- and heterocycles by means of [4+2]cycloaddition reactions.

Experimental

IR spectra were determined on a JASCO A-100 spectrophotometer, and data are reported in units of cm^{-1}. All of the crystalline products were scanned in KBr disks except for the oily products (neat). ^1H NMR spectra were determined at 60 MHz in the indicated solvent with a JEOL 60-HL spectrometer, and chemical shifts are reported in δ units downfield from internal tetramethylsilane. In all spectra, signals due to adamantane ring protons were usually recognized in the 1.5—2.2 δ region as a multiplet. ^{13}C NMR spectra were determined on a JEOL JNM-FX60 spectrometer. Spectral patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. Melting points were determined on a Yanaco MP apparatus and are uncorrected. Chromatographic separations were carried out on a silica gel column (Mallinckrodt, 100 mesh) or an alumina column (Woelm N, Akt 1) with the solvent noted.

2-(1-Adamantyl)-1,3-butadiene (1)——First, the acid **2** was converted to the acid chloride **4** with $SOCl_2$,[18] and **4** was reacted with methylmagnesium iodide in ether in the presence of CuCl to give **3**.[5] A solution of **3** (1.78 g, 10 mmol) in THF (10 ml) was added to a solution of vinylmagnesium bromide [prepared from vinyl bromide (6 ml, 20 mmol) and magnesium (0.49 g)] in THF (12 ml) at 0 °C under a nitrogen atmosphere, and the mixture was stirred at room temperature overnight and refluxed for 1 h. Ice was carefully added to this mixture, followed by aq. NH_4Cl, and ether (50 ml) successively. The mixture was shaken, then the organic layer was separated, washed with aq. NaCl, and dried over Na_2SO_4. Evaporation of the solvent gave **5** as a colorless oil (1.95 g, 95%), which had absorptions at 3500, 1640, 1000 and 920 cm^{-1} in the IR spectrum and signals at δ ($CDCl_3$) 1.18 (3H, s, CH_3), 1.35 (1H, s, OH, disappeared with D_2O), 5.08, 5.15 and 6.04 (3H, ABX, $J=2$ and 11 Hz, 2 and 18 Hz, and 11 and 18 Hz, respectively, $CH=CH_2$) in the ^1H NMR spectrum. Without further purification, **5** (1.95 g, 9.5 mmol) was dissolved in ether (40 ml). This solution was refluxed for 4 h in the presence of *p*-toluenesulfonic acid (1.8 g, 9.5 mmol). The reaction mixture was then cooled, neutralized with NaOH, and dried over Na_2SO_4. After evaporation of the solvent, the residual oil was chromatographed on a silica gel column (hexane) to give **1** as a colorless oil (1.05 g, 60%). IR and ^1H-NMR: see text. *Anal.* Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 89.09; H, 10.92. This diene was also obtained by thermolysis of the oxalate **7**; crude **7** [prepared from **5** (0.42 g, 2 mmol) and oxalyl chloride (0.13 g, 1 mmol) by the reported procedure[6]] was

heated in a glass tube oven (Shibata model GTO 250) at 170 °C under a vacuum (3 mmHg). The distilled products were trapped in a bulb cooled with ice and chromatographed as above to give **1** (0.13 g, 35%).

General Procedure for the Cycloaddition Reaction of 1——A solution of **1** (0.19 g, 1 mmol) and a dienophile (1—1.2 mmol) in an appropriate solvent (2 ml) was stirred at room temperature or refluxed if necessary for a specified period under a nitrogen atmosphere. After evaporation of the solvent, the residue was recrystallized or chromatographed using the noted solvent. Otherwise, precipitates were collected by filtration (entries 11 and 13). The products were characterized by spectral and elemental analyses. The reaction conditions, purification method, and physical and analytical data are all summarized in Tables I and II.

Half-life measurement was carried out by following the relative height of a diene peak and the internal standard (biphenyl for **1** and decalin for myrcene) peak on GLC (Varian gas chromatograph, model 1400) at regular intervals. The half-lives were found to be 40 min for **1** and 210 min for myrcene.

Hydrolysis of **22c** was carried out by treating **22c** (0.32 g, 1.1 mmol) with NaOH (0.1 g, 2.5 mmol) in water (2 ml). After acidification, the precipitates collected by filtration were recrystallized from MeOH–H_2O to give **24** (0.28 g, 91%), mp 221—223 °C. IR ν_{max}: 1705. ^{1}H NMR (DMSO-d_6): 2.1—3.1 (6H, m, cyclohexene ring H), 5.31 (1H, m, CH=C), 11.88 (2H, br s, COOH, disappeared with D_2O). *Anal.* Calcd for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 71.05; H, 7.92.

Isomerization of **22d** was carried out by treating **22d** (0.59 g, 2 mmol) with triethylamine (0.28 ml, 2 mmol) in degassed dry benzene (8 ml) at room temperature for 50 min under a nitrogen atmosphere. After acidification with conc. HCl, the precipitates collected by filtration were recrystallized from ether–hexane to give **25** (0.36 g, 60%), mp 231—232 °C. IR ν_{max}: 3320, 1625, 1490. ^{1}H NMR (CD_3COCD_3): 2.93 and 3.28 (4H, br s, C_5– and C_8–H), 5.70 (1H, br s, C_7–H), 6.56 (2H, s, C_2– and C_3–H), 7.48 and 7.53 (2H, s, OH, disappeared with D_2O). *Anal.* Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.07; H, 8.13.

2-(1-Adamantyl)-4*a*,5,6,7,8,8*a*-hexahydro-4*H*-1,3-benzoxazine (31)——A mixture of acetic acid (1 ml), 97% H_2SO_4 (0.2 g, 2 mmol), and 1,3,5-trioxane (60 mg, equivalent to 2 mmol of HCHO) was stirred at room temperature until it became a clear solution. To this solution, **29** (0.32 g, 2 mmol) was added at 50 °C, and stirring was continued for 30 min. The resulting solution was stirred with cyclohexene (0.16 g, 2 mmol) for 3 h at 80 °C. The reaction mixture was poured onto ice containing 20% NaOH (5 ml) and ether (20 ml), and the water layer was washed with ether. The combined ether extracts were washed with water (the temperature should be kept at 0 °C with ice until this work-up) and dried over Na_2SO_4. Evaporation of the solvent left a residue, which was chromatographed on an alumina column (benzene) to give **31** as white crystals (0.18 g, 33%), mp 84—87 °C. IR ν_{max}: 1660. ^{1}H NMR ($CDCl_3$): 1.2—2.2 (9H, m, C_{4a-8}–H), 3.2—3.5 (2H, m, C_4–H), 4.15 (1H, m, C_{8a}–H). *Anal.* Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12. Found: C, 79.04; H, 10.01; N, 5.12.

2-(1-Adamantyl)-5,6,7,8-tetrahydro-1,3-benzoxazine-4-thione (33)——A mixture of **4** (0.4 g, 2 mmol) and KSCN (0.39 g, 4 mmol) in dry benzene (10 ml) was stirred at room temperature for 1 d. After removal of solids by filtration, evaporation of the solvent gave crude **32** as a yellow oil, which has absorptions at 2000 and 1720 cm^{-1} in the IR spectrum. This oil was dissolved in dry $CHCl_3$ (5 ml) and stirred with 1-morpholino-1-cyclohexene (0.17 g, 1 mmol) at room temperature for 1 d. After evaporation of the solvent, the residue was chromatographed on a silica gel column ($CHCl_3$) to give **33** as yellow crystals (0.15 g, 50% based on the enamine), mp 245—247 °C. IR ν_{max}: 1645. ^{1}H NMR ($CDCl_3$): 1.7—2.3 (4H, m, C_6– and C_7–H), 2.3—2.9 (4H, m, C_5– and C_8–H). *Anal.* Calcd for $C_{18}H_{23}NOS$: C, 71.72; H, 7.69; N, 4.65. Found: C, 71.80; H, 7.72; N, 4.64.

3-(1-Adamantyl)-6-methyl-6-(1-methylvinyl)-5,6-dihydro-4*H*-1,2-oxazine (37)——A solution of hydroxylamine sulfate (0.33 g, 2 mmol) in water (0.5 ml) was added to a solution of **34** (0.51 g, 2 mmol) in MeOH (6 ml), and the mixture was stirred at room temperature for 90 min. After evaporation of the solvent, the products were extracted with benzene and the extracts were dried over Na_2SO_4. Evaporation of the solvent left a white solid, which was recrystallized from ether–hexane without warming to give the oxime **35** (0.42 g, 77%), mp 198.5—199.5 °C, which showed absorptions at 3250 and 1640 cm^{-1} in the IR spectrum and signals at δ (DMSO-d_6) 4.60 (2H, s, CH_2Br), 11.26 (1H, br s, OH, disappeared with D_2O) in the ^{1}H NMR spectrum. Anhydrous powdered Na_2CO_3 (0.26 g, 2.4 mmol) was added to a solution of **35** (0.27 g, 1 mmol) and 2,3-dimethyl-1,3-butadiene (0.41 g, 5 mmol) in CH_2Cl_2 (6 ml), and stirring was continued at room temperature for 40 h. The mixture was filtered and the filtrate was evaporated to dryness. The residue was chromatographed on an alumina column ($CHCl_3$) to give **37** (0.16 g, 59%), mp 69.5—71.5 °C. IR ν_{max}: 1645, 1600. ^{1}H NMR ($CDCl_3$): 1.33 (3H, s, C_6–CH_3), 1.77 (3H, br s, C=CCH_3), 1.6—2.2 (4H, m, C_4– and C_5–H), 4.85 and 4.92 (2H, br s, C=CH_2). *Anal.* Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12. Found: C, 79.01; H, 9.82; N, 5.32.

2-(1-Adamantyl)-5-acetyl-6*H*-1,3-thiazine (40)——A mixture of **38** (0.39 g, 2 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (0.27 g, 2.3 mmol) in benzene (1 ml) was stirred at room temperature for 1 d, and then chromatographic separation (silica gel, $CHCl_3$–acetone (95 : 5)) of the resulting yellow solid gave **39** (0.42 g, 84%), which had an absorption at 1620 cm^{-1} in the IR spectrum and signals at δ (CCl_4) 3.12 and 3.22 (6H, s, NCH_3) and 8.26 (1H, s, CH=N) in the ^{1}H NMR spectrum. A solution of **39** (0.25 g, 1 mmol) and methyl vinyl ketone (0.12 g, 1.6 mmol) in benzene (2 ml) was refluxed for 32 h. After evaporation of the solvent, the residue was chromatographed on an alumina column (benzene) to give **40** as yellow crystals (0.1 g, 36%), mp 101—102 °C. IR ν_{max}: 1660, 1600, 1540. ^{1}H

NMR (CCl_4): 2.34 (3H, s, $COCH_3$), 3.45 (2H, s, C_6–H), 7.68 (1H, s, C_4–H). *Anal.* Calcd for $C_{16}H_{21}NOS$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.74; H, 7.68; N, 5.13.

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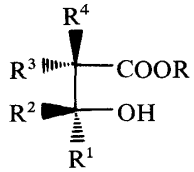

27: R = H *threo* R^1 = 1-adamantyl, R^2, R^3 = H, R^4 = Me
28: R = Me *erythro* R^1 = 1-adamantyl, R^2, R^4 = H, R^3 = Me

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