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Stereocontrolled Approach to 1,4-Disubstituted 1,3-Dienes

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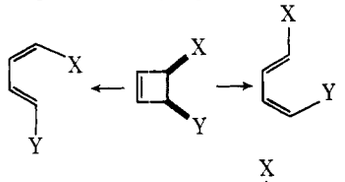
4-Hydroxytricyclo[4.2.1.0^{2,5}]non-7-en-3-one serves as a basic building block for a protected cyclobutene. The rigid tricyclic framework allows stereocontrolled introduction of substituents at the 3,4 positions. Flash vacuum pyrolysis generates cyclopentadiene and a 3,4-disubstituted cyclobutene, which suffers conrotatory opening in situ to give 1,4-disubstituted 1,3-butadienes. The ability to control the stereochemistry of substituent introduction translates into an ability to control diene stereochemistry. Substituents include oxygen, sulfur, and alkyl groups. The synthesis of a diene with a chiral directing substituent is reported.

A resurgence of interest in the applicability of the Diels–Alder reaction in the total synthesis of complex natural products led to an interest in the synthesis of novel dienes as partners.[1-3] Obtention of 1,4-disubstituted dienes is complicated not only by the nature of the substituents but also by the stereochemistry. The utility of 3,4-disubstituted cyclobutenes as represented by eq 1 and 2 is recognized as a most



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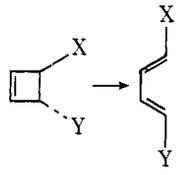
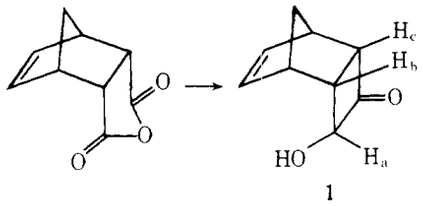


(2)

satisfactory solution[4] with the major problem residing in the synthesis of the requisite cyclobutene.

The Diels–Alder adducts of cyclooctatetraene represent one source of cyclobutenes by cycloreversion which has served as a convenient route to (*E,E*)-1,4-diacetoxy-1,3-butadiene.[5] The



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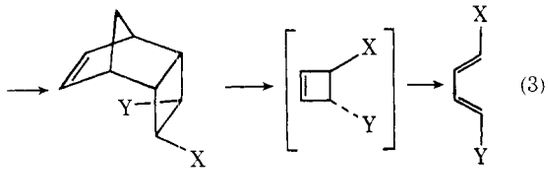
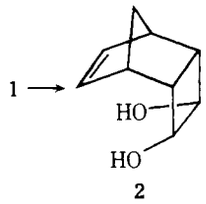


(3)

decreased availability of the key building block detracts from the usefulness of this approach. Jung recognized the potential of the acyloin product of the Diels–Alder adduct of cyclopentadiene and maleic anhydrides to serve this role although his original application proved to be in error in terms of stereochemistry.[6,7] We wish to report the general utility of the route outlined in eq 3 to (*E,E*)-1,3-disubstituted butadienes.

Results

At the outset we needed to establish the stereochemistry of **1**[8] unambiguously since it appears it is this assignment that misled Jung in the stereochemical assignments of his products. The 270-MHz proton NMR spectrum shows H_a as a dd (J = 9.0, 3.8 Hz at δ 4.46), H_b as a ddd (J = 9.0, 7.5, 4.5 Hz at δ 3.25), and H_c as a ddd (J = 7.5, 5.5, 3.8 Hz at δ 3.48). Irradiation at δ 4.46 collapses the signal at δ 3.48 to a dd (J = 7.5, 5.5 Hz) and the resonance at δ 3.25 to a dd (J = 7.5, 4.5 Hz). Irradiation at δ 3.48 collapses the resonance at δ 4.46 to a d (J = 9.0 Hz) and the signal at δ 3.25 to a dd (J = 9.0, 4.5 Hz). Thus, J_{BC} = 7.5 Hz and J_{AB} = 9.0 Hz, implying that all protons bear a cis re-



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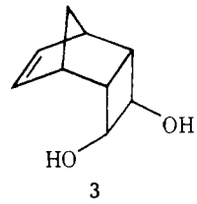

3

lationship in a nearly planar cyclobutanone ring.[9] The endo nature of the hydroxyl group is further confirmed by the reduction to the cis diol **2** since the hydride attack should occur from the exo fact of the molecule. The plane of symmetry as shown by the NMR spectrum precludes the possibility of the alternative *E* product **3**.

The utility of **1** as a substrate to introduce functionality was first explored in conjunction with our interest in the ability of sulfur to serve as a regiochemical control element.[1] The tosylate **4**, readily available by standard methods and being

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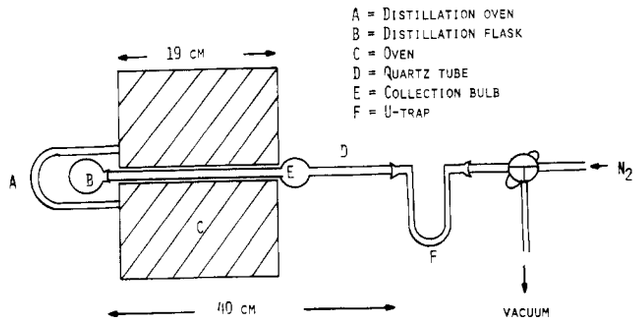
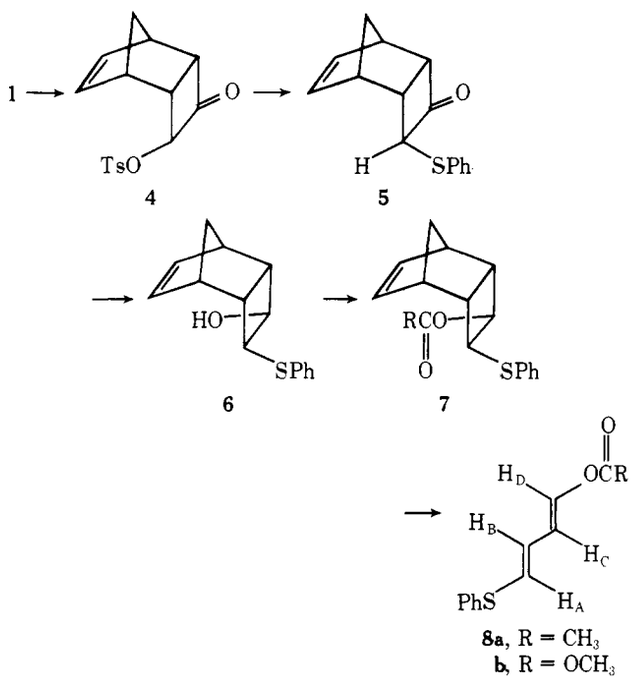


Figure 1. Thermolysis apparatus.

highly crystalline, serves as a convenient storage point. Displacement with sodium thiophenolate in DMF benefits by the addition of a few mole percent tetrahexylammonium bromide



to give **5** quantitatively. Reduction proceeds from the exo fact to give the alcohol **6** which may be readily acylated to **7.** The stereochemistry is clearly discerned by the observed methine proton adjacent to the acyloxy group (R = CH_3, δ 4.71, dd, J = 8.6 and 5.6 Hz) which shows a cis and a trans coupling.

Thermolysis of **7** to the dienes is best performed utilizing an apparatus diagrammed in Figure 1 in which **7** is slowly distilled (temperature of bulb raised from 25 to 240 °C) into an empty glass tube in vacuo at approximately 460 °C. The diene usually collects as a crystalline solid in the cold zone immediately at the exit of the hot zone. Thus, the desired diene emerges quite pure and in virtually quantitative yield. Normally, a small amount of a stabilizer such as a hydroquinone or BHT[10] was added. Obviously, the tosylate can be displaced by other nucleophiles and the oxygen derivatized with other acylating agents. For example, **6** was acylated with both acetic anhydride and methyl chlorocarbonate to give after themolysis **8a** and **8b,** respectively. The efficiency of the method is highlighted by the fact that crystalline diene **8a** is routinely available in 29–33% overall yield from the initial Diels–Alder adduct of cyclopentadiene and maleic anhydride. The sharp melting points and clean spectral properties (see Table I) indicate the homogeneity of the dienes and their *E,E* configuration.

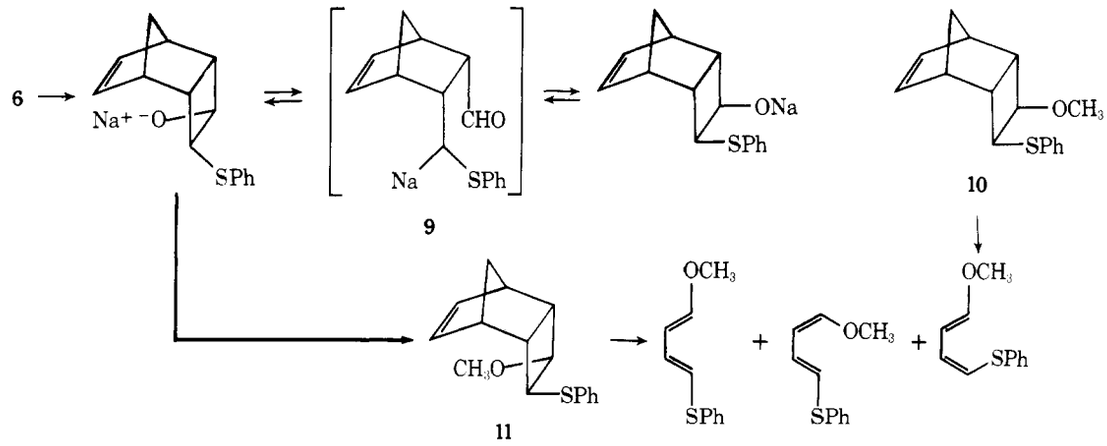
Table I. NMR Properties of Dienes

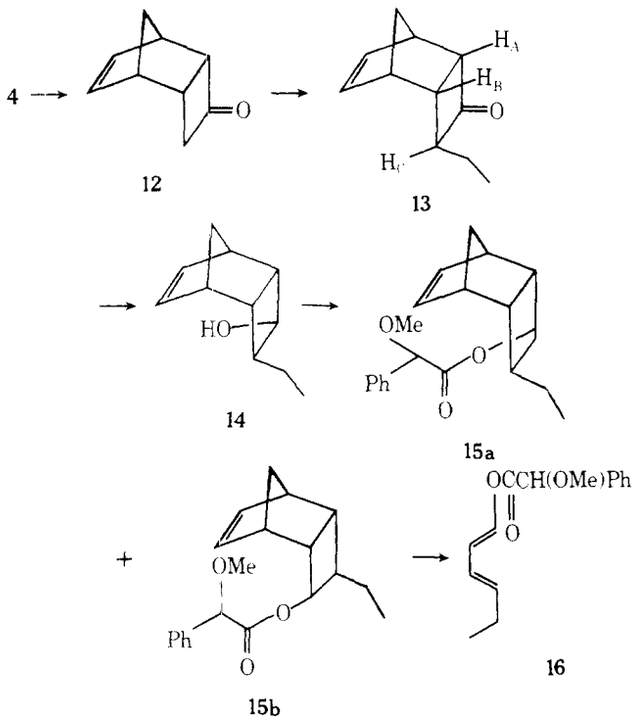
diene		A	B	C	D	J_{AB}, Hz	J_{BC}, Hz	J_{CD}, Hz
8a	^1H	6.31	6.23	6.06	7.32	14.7	10.3	12.1
	^{13}C[a]	129.8[b]	129.7[b]	114.8	135.8			
8b	^1H	6.36	6.24	6.10	7.15	14.7	10.7	11.5

[a] (*E,E*)-1,4-Diacetoxy-1,3-butadiene shows C(1) and C(4) at δ 138.8 and C(2) and C(3) at δ 110.9. [b] These assignments may be reversed.

O-Alkylation of **6** led to the remarkable discovery that isomerization of the cyclobutane accompanied the alkylation. While the mechanism of this isomerization is unclear it could involve C–C cleavage as suggested by structure **9.** The major product **11** (53%) arises by alkylation without this isomerization. Pyrolysis of **10** or **11** led to a mixture of three dienes representing the various geometric isomers. Thus, the very sensitive enol ethers were not available in a geometrically pure state via this method.

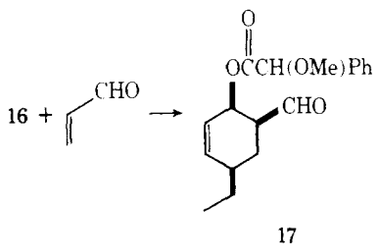
Alkyl-substituted dienes represent easy targets via this method. In conjunction with a synthesis of ibogamine,[11] we required various 1-acyloxy-(*E,E*)-1,3-hexadienes which were readily available from cyclobutanone **12,**[8] the latter derived by chromous chloride[12] reduction of tosylate **4.** Alkylation of the enolate of **12** with ethyl iodide gave the exo ethylated cyclobutanone **13** as indicated by the coupling constants (J_{AB} = 8.8 Hz, J_{BC} = 4.5 Hz). Reduction with sodium borohydride delivers hydride from the exo face to give **14** which can be converted to various oxygen derivatives. The chiral diene **16** becomes available by acylating **14** with (*S*)-*O*-methylmandelyl chloride by the procedure of Dale and Mosher.[13] Since all intermediates are racemic up to this point, a diastereomeric mixture, **15a** and **15b,** is obtained. Pyrolysis proceeded quantitatively as before to give **16** in 97% optically pure form. While the stereochemistry of this diene was difficult to as-





12 13 14 15a 15b 16

certain directly, its Diels–Alder adduct with acrolein led cleanly in 93% yield to an adduct of the all *Z* configuration, i.e., **17**.[11] Thus, the diene must be at least 93% pure *E,E*. Further support for the stereohomogeneity arises from the



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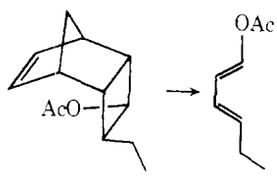
acetate corresponding to **15**, i.e., **18**, which also pyrolyzed to a single diene **19**. Since an authentic sample of **19** as well as its geometric isomer was available, the stereohomogeneity of the method was established.

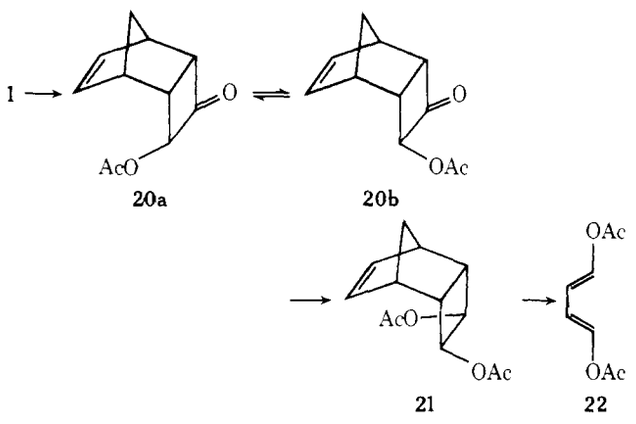


18 19

The synthesis of (*E,E*)-1,4-diacetoxy-1,3-butadiene (**22**) by this route is also quite feasible. Epimerization of the acetate of **1** (i.e., **20**) with DBU reaches a 65:35 ratio which appears to be the equilibrium value. Separation of the isomers, **20a** and **20b**, was readily achieved by medium pressure liquid chromatography. Reduction of **20b** and acetylation produces the expected (*E*)-diacetate **21** which, upon pyrolysis, gives **22**, identical with an authentic sample. Alternatively the mixture of **20a** and **20b** could be carried through to a mixture of **22** and its *E,Z* isomer from which the former could be separated by fractional crystallization.

Conclusions

The rigid framework present in tricyclo[4.2.1.$0^{2,5}$]nonane provides a ready substrate for stereochemically defined introduction of various heteroatom and carbon substituents at the 3,4 positions. Thus, stereochemically defined 1,4-disubstituted 1,3-dienes with a great flexibility for varying the nature of the 1,4 substituents are readily accessible by this route. Special emphasis is placed upon the pyrolysis technique employed since more traditional pyrolysis apparatus clearly lead to inferior results. Thus, a vertically mounted, glass helix packed column at 410 °C led to 20–30% of diene **8a** with varying amounts of starting material and/or decomposition products; whereas, the approach herein led to crystalline diene in virtually quantitative yield. This thermolysis method is the mildest that we have encountered—especially when dealing with highly sensitive materials. The mildness, in part, derives from the minimum amount of contact with glass surfaces. The ease of workup further commends the method.



20a 20b 21 22

Experimental Section

General. Reactions and atmospheric pressure distillations were all performed under a positive pressure of dry nitrogen. Ether and THF were distilled from sodium benzophenone ketyl. Me_2SO, DMF, and HMPA were distilled from calcium hydride. Column chromatography utilized quartz columns packed with W. R. Grace silica gel, grade 62, 60–200 mesh, containing 1.5% phosphor (du Pont 609 Phorphor) which enabled the bands to be visualized. Preparative thick-layer plates utilized Merck silica gel PF-254 or Macherey Nagel MN Kieselgel P/UV 254. The plates were prepared by spreading an aqueous slurry of the silica gel on glass plates, air drying overnight, activating at 120 °C for 2 h, and storing in a closed box. Melting points were determined in open capillaries using a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Proton NMR spectra were recorded on Jeolco MH-100 or Brucker WH-270 spectrometers and carbon NMR spectra on a Jeolco FX-60 spectrometer. NMR chemical shifts are given in parts per million downfield from internal Me_4Si. Coupling constants are stated in hertz with splitting patterns designated s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, and p = pseudo. Mass spectra were recorded on a AEI-MS 902 high-resolution spectrometer at an ionizing current of 100 mA and ionizing voltage of 70 eV. Infrared spectra were obtained on Perkin-Elmer 267 spectrophotometers.

Starting Materials. The dimethyl ester (bp 107–8 °C at 1.2 torr; lit.[14] bp 136–7 °C at 12.5 torr) from the Diels–Alder adduct of maleic anhydride and cyclopentadiene was obtained in 96% yield by dissolving the anhydride in a hot solution of sodium methoxide in methanol, cooling, adding dimethyl sulfate, and then refluxing. The disilyl ether of the ene diol (bp 100–2 °C at 0.9 torr) was obtained in 79% yield by literature methods[8] and its hydrolysis product **1** (mp 135–140 °C) by stirring 150 g (0.509 mol) of silyl ether in 460 mL of water, 460 mL of THF, and 86.6 mL of 36% aqueous hydrochloric acid at reflux for 1.5 h to give 59.8 g (78%) of crystalline product. The previous report[8] did not indicate the melting point of this compound.

(2*S,4*R**,5*R**)-4-(*p*-Toluenesulfonyloxy)tricyclo[4.2.1.$0^{2,5}$]-non-7-en-3-one (4).** To 30 g (0.2 mol) of acyloin **1** dissolved in 300 mL of anhydrous pyridine were added 45.8 g (0.24 mol) of *p*-toluenesulfonyl chloride. The solution was stirred for 22 h at room temperature but became brown within 15 min. The solution was poured into 1200 mL of 3 N aqueous hydrochloric acid and was extracted with dichloromethane (6 × 150 mL). The combined organic layers were washed with 300 mL of 3 N aqueous hydrochloric acid, 300 mL of saturated sodium bicarbonate solution, and 300 mL of saturated sodium chloride solution. After drying (magnesium sulfate), the solvent

was removed in vacuo to leave 61.24 g of light brown crystals. The crude product was filtered through silica gel (length 40 cm, diameter 3 cm, dichloromethane) to give 51 g (84%) of light pink crystals. Further purification was achieved by dissolving the product in refluxing acetone, filtering, and crystallizing first at room temperature and then at −22 °C to give **4**: mp 136–137 °C; IR (CCl_4) 1790, 1378, 1193, 1182 cm^{-1}; NMR ($CDCl_3$) δ 7.82, 7.36 (AB quartet, 2 H, J_{AB} = 8.25 Hz), 6.05 (bs, 2 H), 2.96 (dd, 1 H, J = 8.8, 3.4 Hz), 3.70–2.92 (m, 4 H), 2.46 (s, 3 H), 1.70, 1.42 (AB quartet, 2 H, J_{AB} = 8.3 Hz); MS, *m/e* (rel %) 18 (17), 55 (15), 77 (15), 79 (25), 83 (100), 91 (61), 92 (12), 93 (23), 103 (14), 104 (12), 105 (37), 121 (32), 122 (10), 149 (96), 155 (48). Anal. ($C_{16}H_{16}O_4S$): C,H,S.

(2*S,4*S**,5*R**)-4-(Phenylthio)tricyclo[4.2.1.0^{2,5}]non-7-en-3-one (5).** To 1.08 g (45 mmol) of sodium hydride that had been washed free of mineral oil was added 575 mg (1.323 mmol, 3 mol %) of tetrahexylammonium bromide and 40 mL of deoxygenated, anhydrous DMF. The mixture was cooled to 0 °C and 6.13 g (56 mmol) of thiophenol were added dropwise. The cooling bath was removed and the mixture stirred for 30 min at room temperature. Then 9.26 g (30.44 mmol) of pure tosylate (**4**) was added and the reaction mixture stirred for 3 h at room temperature. The TLC (silica gel, dichloromethane) showed no starting material. The reaction mixture was poured into 200 mL of ether and 400 mL of water, the organic phase separated, and the aqueous layer extracted with ether (3 × 80 mL). The combined etheral layers were washed with 200 mL of 1 N aqueous potassium hydroxide and water (2 × 100 mL), dried (magnesium sulfate), and evaporated in vacuo to leave a light yellow oil that was dried on an oil pump to remove some DMF. Then it was filtered through a silica gel column (length 30 cm, diameter 2 cm, dichloromethane) to give 7.37 g (100%) of colorless oil: IR (CCl_4) 1777, 1582, 1576 cm^{-1}; NMR (CCl_4) δ 7.56–6.96 (m, 5 H), 6.36–6.10 (m, 2 H), 3.86–3.62 (m, 1 H), 3.52–3.38 (m, 1 H), 3.32–3.02 (m, 2 H), 2.78–2.54 (m, 1 H), 1.76, 1.41 (AB quartet, 2 H, J_{AB} = 8.3 Hz); MS, *m/e* (rel %) 32 (42), 38 (11), 39 (99), 40 (16), 45 (26), 50 (18), 51 (48), 55 (18), 63 (16), 65 (60), 66 (48), 69 (22), 77 (59), 78 (25), 79 (24), 91 (28), 103 (16), 104 (16), 105 (100), 106 (11), 109 (58), 110 (39), 115 (12), 119 (11), 123 (13), 133 (21), 147 (27), 163 (21), 176 (73), 218 (40), 242 (6, M^+). Calcd. for $C_{15}H_{14}OS$: 242.0765. Found: 242.0778.

(2*S,3*S**,4*S**,5*R**)-3-Hydroxy-4-(phenylthio)tricyclo-[4.2.1.0^{2,5}]non-7-ene (6).** To a solution of 22.11 g (91.36 mmol) of keto sulfide (**5**) in 150 mL of ethanol at −25 °C was added 7.09 g (183 mmol) of sodium tetrahydridoborate and the reaction mixture was stirred 45 min during which time it was allowed to come to 0 °C. It was poured into a mixture of 300 mL of saturated ammonium chloride solution and 300 mL of ether (very, very carefully; gas evolution!!). The organic phase was separated and the aqueous phase extracted with ether (4 × 100 mL). The combined etheral layers were washed with 200 mL of water and 200 mL of saturated sodium chloride solution and then dried over magnesium sulfate. After removing the solvent, 22.3 g of a colorless oil that crystallized during drying on the oil pump was obtained that recrystallized from 650 mL of hot hexane (cooling in stages to room temperature, −5 °C, and then to −22 °C) to give 15.18 g (68%): mp 74–6 °C; IR (CCl_4) 3620, 3595, 1580 cm^{-1}; NMR ($CDCl_3$) δ 7.4–7.0 (m, 5 H), 6.60–6.25 (m, 2 H), 4.30–3.96 (m, 1 H), 3.32–2.92 (m, 4 H), 2.64–2.34 (m, 1 H), 1.89 (d, 1 H, J = 9.0 Hz), 1.59, 1.14 (AB quartet, 2 H, J_{AB} = 8.3 Hz); MS, *m/e* (rel %) 18 (20), 39 (23), 41 (18), 45 (11), 51 (13), 55 (14), 57 (17), 65 (18), 66 (16), 67 (21), 68 (13), 69 (13), 77 (19), 79 (29), 91 (31), 105 (25), 107 (11), 109 (11), 110 (33), 117 (21), 121 (10), 134 (13), 135 (100), 136 (14), 178 (12), 244 (14, M^+). Calcd for $C_{15}H_{16}OS$: 244.0922. Found: 244.0920.

(2*S,3*S**,4*S**,5*R**)-3-Acetoxy-4-(phenylthio)tricyclo-[4.2.1.0^{2,5}]non-7-ene (7a).** To a solution of 8.5 g (34.83 mmol) of the alcohol (**6**) in 50 mL of pyridine were added 32.46 g (318 mmol) of acetic anhydride. The reaction mixture was stirred at room temperature for 5 h and poured into a mixture of 150 mL of ether and 300 mL of ice cold 3 N aqueous hydrochloric acid; the layers were separated and the aqueous one was extracted with ether (3 × 80 mL). The combined etheral layers were washed with 100 mL of saturated sodium bicarbonate solution (in a beaker) and with 100 mL of saturated sodium chloride solution, dried (magnesium sulfate), and evaporated in vacuo. The residual yellow oil was filtered through a silica gel column (length 30 cm, diameter 2 cm, dichloromethane) to yield 9.6 g (97%): IR (CCl_4) 1745, 1585 cm^{-1}; NMR (CCl_4) δ 7.30–6.94 (m, 5 H), 6.32–6.10 (m, 2 H), 4.71 (dd, 1 H, J = 8.6, 5.6 Hz), 3.40–2.80 (m, 4 H), 2.60–2.36 (m, 1 H), 1.91 (s, 3 H), 1.51, 1.07 (AB quartet, 2 H, J_{AB} = 7.9 Hz); MS, *m/e* (rel %) 18 (15), 39 (9), 43 (100), 66 (9), 77 (11), 79 (12), 91 (19), 105 (12), 109 (9), 110 (9), 117 (42), 135 (36), 286 (10, M^+). Calcd for $C_{17}H_{18}O_2S$: 286.1028. Found: 286.1017.

(*E*,*E*)-1-Acetoxy-4-phenylthiobuta-1,3-diene (8a). The tricyclic acetate **7a** (1.3 g, 4.54 mmol) was distilled into a hot (460 °C) quartz tube (see Figure 1) under a pressure of ca. 1 torr by raising the temperature of the distillation oven from 25 to 240 °C. At the exit from the hot zone, the product crystallized. After all strating material had distilled, the tube was allowed to cool, it was rinsed with ether, and the product was collected in a flask that contained 10 mg of 2,6-di-*tert*-butyl-4-methylphenol. After removing the solvent nearly colorless crystals remained, yielding 995 mg (100%). The NMR spectrum of the product showed no impurities. For additional purification the diene **8a** was recrystallized from 10% ether/90% hexane or hexane at −22 °C to give colorless crystals: mp 65–66 °C; IR (CCl_4) 1771, 1646, 1571 cm^{-1}; NMR, see Table I; MS, *m/e* (rel %) 39 (37), 43 (100), 45 (17), 51 (24), 65 (17), 68 (47), 69 (18), 77 (17), 109 (29), 110 (92), 115 (24), 116 (17), 117 (10), 134 (11), 147 (15), 178 (83), 179 (14), 220 (22, M^+). Calcd for $C_{12}H_{12}O_2S$: 220.0560. Found: 220.0558.

(2*S,3*S**,4*S**,5*R**)-3-(Methoxycarboxy)-4-(phenylthio)tricyclo[4.2.1.0^{2,5}]non-7-ene (7b).** To 300 mg (1.227 mmol) of the alcohol (**6**) in 4 mL of anhydrous pyridine at −40 °C was added dropwise 454 mg (4.8 mmol) of methyl chloroformate. After addition the mixture was allowed to come to room temperature within 1.5 h, stirred at room temperature for 1 h, and then poured into a mixture of 100 mL of ice cold 3 N aqueous hydrochloric acid and 70 mL of ether. The etheral layer was separated and the aqueous phase extracted with 50 mL of ether. The combined organic layers were washed with 100 mL of saturated aqueous sodium chloride solution, dried (magnesium sulfate), and evaporated in vacuo to give a light yellow oil that was filtered through silica gel (length 30 cm, diameter 1 cm, dichloromethane) to yield 326 mg (88%) of a colorless oil: IR (CCl_4) 1747 cm^{-1}; NMR (CCl_4) δ 7.30–6.96 (m, 5 H), 6.36–6.14 (m, 2 H), 4.67 (dd, 1 H, J = 5.6, 8.2 Hz), 3.70 (s, 3 H), 3.46–2.92 (m, 4 H), 2.62–2.36 (m, 1 H), 1.56, 1.12 (AB quartet, 2 H, J_{AB} = 8.2 Hz); MS, *m/e* (rel %) 45 (10), 59 (16), 65 (8), 66 (6), 71 (5), 77 (9), 79 (5), 91 (15), 105 (6), 109 (7), 115 (10), 116 (8), 117 (100), 118 (13), 157 (11), 193 (9), 236 (5), 302 (16, M^+). Calcd for $C_{17}H_{18}O_3S$: 302.0977. Found: 302.0981.

(*E*,*E*)-1-Methoxycarboxy-4-phenylthiobuta-1,3-diene (8b). As for **8a**, 74 mg (0.245 mmol) of carbonate **7b** was pyrolyzed to give 55 mg (97%) of pure diene, mp 85–6 °C, after recrystallization from ether at −22 °C: IR (CCl_4) 1775 cm^{-1}; NMR, see Table I; MS, *m/e* (rel %) 43 (18), 44 (22), 45 (29), 51 (28), 55 (19), 59 (54), 67 (27), 68 (13), 69 (14), 71 (21), 75 (10), 77 (22), 91 (16), 99 (12), 109 (80), 110 (33), 115 (44), 116 (41), 117 (13), 119 (11), 121 (11), 134 (17), 135 (17), 147 (34), 149 (23), 157 (19), 160 (10), 161 (16), 164 (11), 177 (30), 218 (14), 236 (100, M^+), 237 (14). Calcd for $C_{12}H_{12}O_3S$: 236.0507. Found: 236.0505.

(2*S,3*S**,4*S**,5*R**)-3-Methoxy-4-(phenylthio)tricyclo-[4.2.1.0^{2,5}]non-7-ene (11) and (2*S**,5*R**)-3-Methoxy-4-(phenylthio)tricyclo[4.2.1.0^{2,5}]non-7-ene (10).** To 33 mg (1.375 mmol) of sodium hydride that had been washed free of mineral oil in 5 mL of anhydrous DMF at 0 °C was added 278 mg (1.14 mmol) of the alcohol **6**. The mixture was held at 0 °C and stirred until cessation of hydrogen evolution (45 min). The color of the solution was red-brown. Then 284 mg (2 mmol) of methyl iodide was added and the mixture stirred at 0 °C for 30 min during which time the color changed to light yellow. The excess methyl iodide was removed in vacuo and the reaction quenched by pouring it into 100 mL of water and 80 mL of ether. The etheral phase was separated and the aqueous layer was extracted with 80 mL of ether. The combined etheral layers were washed with 80 mL of saturated sodium chloride solution, dried (magnesium sulfate), and evaporated in vacuo to leave a light yellow oil that was chromatographed on a 20 × 40 cm TLC plate (10% ether/90% hexane, 3 × developed) to give two bands: 48 mg (16%) of compound **10** and 156 mg (53%) of compounds **11**.

Methoxy derivative 10: IR (CCl_4) 2825, 1580, 1480 cm^{-1}; NMR (CCl_4) δ 7.34–6.98 (m, 5 H), 6.33 (dd, 1 H, J = 5.3, 1.9 Hz), 6.16 (dd, 1 H, J = 5.3, 3 H), 3.84–3.50 (m, 1 H), 3.34–2.90 (m, 4 H), 3.10 (s, 3 H), 2.60–2.36 (m, 1 H), 1.55, 1.10 (AB quartet, 1 H, J_{AB} = 7.9 Hz); MS, *m/e* (rel %) 44.5 (100), 50 (14), 54 (36), 55 (12), 56 (35), 59 (20), 64 (18), 65 (10), 68 (45), 70 (34), 72 (16), 76 (18), 78 (11), 80 (11), 82 (12), 90 (28), 108 (12), 114 (16), 116 (34), 148 (45), 191 (13), 258 (0.3, M^+). Calcd for $C_{16}H_{18}OS$: 258.1078. Found: 258.1079.

Methoxy derivative 11: IR (CCl_4) 1580, 1480 cm^{-1}; NMR (CCl_4) δ 7.33–6.93 (m, 5 H), 6.59–6.13 (m, 2 H), 3.4–2.6 (m, 6 H), 3.23 (s, 3 H), 1.61, 1.19 (AB quartet, 2 H, J_{AB} = 7.9 Hz); MS, *m/e* (rel %) 41 (31), 45 (50), 51 (18), 53 (10), 55 (13), 65 (22), 66 (10), 69 (22), 71 (31), 77 (23), 79 (14), 91 (42), 105 (12), 109 (14), 115 (25), 116 (12), 117 (70), 121 (13), 122 (11), 135 (19), 149 (100), 150 (11), 192 (47), 258 (12, M^+). Found: 258.1080.

1-Methoxy-4-(phenylthio)-1,3-butadiene. As for **8**, 155 mg (0.6 mmol) of ether **11** was pyrolyzed to give 98 mg (85%) of the diene as an oil that appeared as one spot on TLC (20% ether:80% hexane) but showed the presence of isomers by NMR: IR (CCl_4) 2830, 1632, 1575, 1480 cm^{-1}; NMR (CCl_4) δ 7.4–6.92 (m, 5 H), 6.74–5.36 (m, 4 H), 3.59, 3,56, 3.52 (each a methoxy singlet for a total of 3 H); MS, *m/e* (rel %)

41 (50), 45 (16), 50 (11), 51 (26), 55 (16), 57 (12), 65 (39), 66 (22), 69 (28), 71 (58), 77 (21), 84 (15), 91 (12), 99 (100), 100 (11), 109 (65), 110 (66), 149 (10), 163 (10), 164 (11), 179 (20), 192 (3, M^+). Calcd for $C_{11}H_{12}OS$: 192.0609. Found: 192.0608. The same mixture is obtained by pyrolysis of ether **10**.

Tricyclo[4.2.1.0^{2,5}]non-7-en-3-one (12). To zinc amalgam [from 40 g (0.61 mol) of zinc dust, 3.2 g (0.012 mol) of mercuric chloride, and 2 mL of concentrated aqueous hydrochloric acid] suspended in 80 mL of water containing 8 mL of concentrated aqueous hydrochloric acid was added 20.0 g (0.075 mol) of chromic chloride hexahydrate under an atmosphere of carbon dioxide.[12] After 0.5 h, the initial green solution turned deep blue. The resulting aqueous chromous chloride solution was syringed into a solution of 0.8 g (2.6 mmol) of tosylate **4** in 25 mL of acetone under a nitrogen atmosphere. The resulting mixture was warmed to 60 °C for 0.5 h, allowed to cool to ambient temperature, and then fractionated between ether and saturated brine. The organic layer was washed successively with aqueous potassium carbonate and saturated aqueous sodium chloride to give after drying and concentration 0.35 g (100%) of **12** as an oily white solid: IR (CCl_4) 1774 cm^{-1}; NMR ($CDCl_3$) δ 6.16 (m, 2 H), 3.70 (m, 1 H), 3.08 (m, 2 H), 2.88–2.56 (m, 2 H), 2.25–2.20 (m, 1 H), 1.6 (AB, J = 7.5 Hz, 2 H); MS, *m/e* (rel %) 51 (20), 65 (26), 66 (83), 68 (61), 78 (40), 79 (30), 91 (100), 92 (39), 105 (22), 106 (32), 134 (19, M^+). Calcd for $C_9H_{10}O$: 134.0731. Found: 134.0732.

(2*S,4*S**,5*S**)-4-Ethyltricyclo[4.2.1.0^{2,5}]non-7-en-3-one (13).** A solution of 3.3 g (24.6 mmol) of ketone **12** in 5 mL of dry THF was added to a solution of 24.6 mmol of lithium diisopropylamide in 15 mL of dry THF at −78 °C and the resulting enolate quenched by adding it to 19.2 g of ethyl iodide held at −30 °C. The mixture was allowed to come to room temperature, then fractionated between hexane and aqueous sodium bicarbonate. After standard workup, the mixture was purified by medium-pressure liquid chromatography (Woelm silica gel, 0.032–0.063 mm mesh, 2.5 × 100 cm column) eluting with 6:1 hexane–ether to give 2.1 g (52%) of **13** in fractions 20–30 (collecting 10-mL fractions): IR (CCl_4) 1772, 1455 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 6.11 (m, 2 H), 3.63 (ddd, J = 8.8, 6.0, 3.75 Hz, 1 H), 3.11 (m, 1 H), 3.04 (m, 1 H), 2.50 (dtd, 8.8, 4.5), 2.17 (t, d, d, J = 7.0, 4.5, 3.75 Hz), 1.72 and 1.42 (AB, J = 9 Hz, 2 H), 1.59 (m, 2 H), 0.94 (t, J = 8 Hz, 3 H); MS, *m/e* (rel %) 43 (100), 53 (40), 55 (44), 61 (29), 63 (17), 65 (66), 66 (88), 67 (31), 68 (37), 77 (44), 78 (33), 79 (67), 81 (72), 91 (24), 92 (85), 96 (45), 105 (76), 106 (51), 107 (23), 119 (24), 133 (25), 134 (39), 162 (39, M^+). Calcd for $C_{11}H_{14}O$: 162.1043. Found: 162.1045.

(2*S,3*R**,4*S**,5*S**)-4-Ethyl-3-hydroxytricyclo[4.2.1.0^{2,5}]non-7-ene (14).** Sodium borohydride (0.98 g, 26 mmol) was added in portions to a 0 °C solution of 2.1 g (13 mmol) of ketone **13** dissolved in 10 mL of ethanol. Upon completion of the addition, the mixture was stirred 2 h at ambient temperature and then was fractionated between ether and brine. After the usual workup, 2.05 g (98%) of alcohol **14** was obtained and the material utilized directly in the next step without further purification: IR (CCl_4) 3590, 3280–3500 cm^{-1}; NMR ($CDCl_3$) δ 6.30 (m, 2 H), 3.72 (m, 1 H), 2.96 (m, 3 H), 2.08 (m, 1 H), 1.8–0.9 (m, 6 H), 0.88 (t, J = 7 Hz, 3 H); MS, *m/e* (rel %) 65 (29), 66 (100), 79 (34), 91 (44), 135 (21), 164 (6, M^+). Calcd for $C_{11}H_{16}O$: 164.1197. Found: 164.1201.

(2*S,3*R**,4*S**,5*S**)-3-[(S)-(2′-Methoxy-2′-phenylacetoxy)]-4-ethyltricyclo[4.2.1.0^{2,5}]non-7-ene (15a,b).** To (*S*)-2-phenyl-2-methoxyacetic acid (*o*-methylmandelic acid, 0.11 g, 0.6 mmol) [mp 62–4 °C, $[\alpha]^{25}_D$ 141° (*c* 0.89, C_2H_5OH), 97.4% optically pure[15]] in 12.5 mL of dry benzene was added thionyl chloride (freshly distilled from triphenyl phosphite, 2.0 g, 16.8 mmol). After refluxing for 1 h, the solution was concentrated in vacuo. Benzene (5 mL) and 0.394 g (2.4 mmol) of alcohol **14** dissolved in 0.75 mL of pyridine and 2.5 mL of benzene was added and the resultant mixture stirred 4 h at room temperature. The reaction mixture was poured into equal volumes of benzene and water and the organic layer washed with aqueous potassium carbonate, saturated aqueous sodium chloride, 3 N aqueous hydrochloric acid, and saturated aqueous sodium chloride. After drying ($MgSO_4$) and concentration, the resulting oil was charged onto a medium-pressure liquid chromatography column (15 × 250 mm, Woelm silica gel, 0.032–0.063 mm mesh) and eluted with 10:1 hexane–ether to give 0.11 g (55%) of the esters **15a** and **15b:** $[\alpha]^{25}_D$ 27° (*c* 0.31, $CHCl_3$); IR (CCl_4) 1750, 1458 cm^{-1}; NMR ($CDCl_4$) δ 7.32 (m, 5 H), 5.88 (m, 1.5 H), 5.24 (m, 0.5 H), 4.68 (s, 0.5 H), 4.61 (s, 0.5 H), 4.48 (m, 1 H), 3.40 (s, 1.5 H), 3.36 (s, 1.5 H), 3.16–2.48 (m, 3 H), 2.04 (m, 1 H), 1.88–0.56 (m, 8 H); MS, *m/e* (rel %) (at 20 eV) 66 (12), 121 (100), 312 (0.02, $M^{+\cdot}$). Calcd for $C_{20}H_{29}O_3$: 312.1730. Found: 312.1725. Anal. for ($C_{20}H_{24}O_3$): C,H.

(*E,E*)-1-[(*S*)-2′-Methoxy-2′-phenylacetoxy]-1,3-hexadiene (16). As for the other diene 100 mg (0.32 mmol) of the esters **15a** and **15b** was pyrolyzed to give 79 mg (100%) of the desired diene **16:** $[\alpha]^{25}_D$ 13° (*c* 2.04, $CHCl_3$); IR (CCl_4) 1778 cm^{-1}; NMR ($CDCl_3$) 7.36 (m, 6 H), 6.40–5.44 (m, 3 H), 4.80 (s, 1 H), 3.40 (s, 3 H), 2.04 (m, 2 H), 0.96 (t, J = 7 Hz, 3 H); MS, *m/e* (rel %) 77 (37), 91 (21), 105 (23), 110 (20), 121 (91), 122 (100), 218 (15), 246 (7, $M^{+\cdot}$). Calcd for $C_{15}H_{18}O_3$: 246.1246. Found: 246.1256.

(2*S,4*R**,5*R**)-4-Acetoxytricyclo[4.2.1.0^{2,5}]non-7-en-3-one (20a).** In normal fashion, 15.0 g (0.10 mol) of acyloin **1** was acetylated with 12.0 g (0.11 mol) of acetic anhydride in 25 mL of pyridine to give 16.2 g (84%) of acetate **20a,** bp 90–2 °C (0.1 torr), which crystallized upon standing in the refrigerator, mp 47–49 °C (hexane–ether 6:1): IR (CCl_4) 1790, 1745 cm^{-1}; NMR ($CDCl_3$) δ 6.1 (dd, J = 6, 3 Hz, 1 H), 5.94 (dd, J = 6, 3 Hz, 1 H), 5.26 (dd, J = 8, 3.5 Hz, 1 H), 3.56 (m, 1 H), 3.36 (m, 1 H), 3.14 (m, 2 H), 2.04 (s, 3 H), 1.76 and 1.54 (AB, J = 8 Hz, 2 H); MS, *m/e* (rel %) 51 (21), 55 (31), 65 (46), 66 (54), 71 (21), 77 (35), 78 (40), 79 (42), 80 (31), 83 (29), 84 (77), 91 (44), 93 (23), 104 (27), 105 (22), 121 (28), 122 (27), 150 (34), 192 (0.2, $M^{+\cdot}$). Calcd for $C_{11}H_{12}O_3$: 192.0792. Found: 192.0786.

(2*S,4*S**,5*R**)-4-Acetoxytricyclo[4.2.1.0^{2,5}]non-7-en-3-one (20b).** To a solution of 7.5 g (0.039 mol) of ketoacetate **20a** in 20 mL of THF was added 1.19 g (7.8 mmol) of DBU and the mixture heated at 50 °C for 24 h. It was poured into a mixture of 50 mL of ethyl acetate and 50 mL of aqueous sodium bisulfate. The resulting organic layer was worked up in normal fashion to give a crude oil which was a 65:35 ratio of **20b** and **20a** as determined by the intensity of the signals at δ 4.58 (for **20b**) vs. δ 5.26 (for **20a**). Separation of the isomers was achieved using the medium pressure liquid chromatography column previously described and eluting with 7:1 hexane–ether to give 2.1 g of recovered **20a** and 4.1 g of **20b** as a colorless oil: IR (CCl_4) 1790, 1755 cm^{-1}; NMR ($CDCl_3$) δ 6.28 (m, 2 H), 4.58 (dd, J = 3, 2.5 Hz, 1 H), 3.98 (m, 1 H), 3.24 (m, 2 H), 2.96 (m, 1 H), 2.10 (s, 3 H), 1.80 and 1.48 (AB, J = 8 Hz, 2 H); MS, *m/e* (rel %) 65 (24), 66 (62), 78 (22), 84 (36), 91 (21), 150 (33), 192 (0.11). Calcd for $C_{11}H_{12}O_3$: 192.0784. Found: 192.0786.

(2*S,3*S**,4*S**,5*R**)-4-Acetoxy-3-hydroxytricyclo[4.2.1.0^{2,5}]-non-7-ene.** In the normal fashion, 2.6 g (13 mmol) of ketoacetate **20b** was reduced with 0.51 g (13 mmol) of sodium borohydride in 10 mL of absolute ethanol (2 h at 0 °C) to give 2.5 g (95%) of the alcohol: IR (CCl_4) 3590, 3460, 1720 cm^{-1}; NMR ($CDCl_3$) δ 6.44 (dd, J = 6, 3 Hz, 1 H), 6.24 (dd, J = 6, 3 Hz, 1 H), 4.32 (dd, J = 4, 3.5 Hz, 1 H), 4.12 (m, 1 H), 3.04 (m, 3 H), 2.55 (m, 1 H), 2.4 (m, 1 H), 2.06 (s, 3 H), 1.56 and 1.24 (AB, J = 8 Hz, 2 H); MS, *m/e* (rel %) 66 (90), 67 (24), 77 (26), 79 (44), 86 (44), 91 (45), 92 (20), 105 (47), 108 (28), 134 (32), 151 (22), 194 (0.01, $M^{+\cdot}$). Calcd for $C_{11}H_{14}O_3$: 194.0945. Found: 194.0943.

(2*S,3*S**,4*S**,5*R**)-3,4-Diacetoxytricyclo[4.2.1.0^{2,5}]non-7-ene (21).** In normal fashion 2.5 g (13 mmol) of the above alcohol was acetylated with 1.45 g (14 mmol) of acetic anhydride in 20 mL of pyridine (24 h at rt) to give 2.78 g (90%) of **21:** IR (CCl_4) 1735 cm^{-1}; NMR ($CDCl_3$) δ 6.28 (m, 2 H), 4.86 (dd, J = 9, 4.5 Hz, 1 H), 4.56 (dd, J = 4.5, 4.0 Hz, 1 H), 3.18 (m, 1 H), 2.98 (m, 2 H), 2.54 (m, 1 H), 2.0 (s, 6 H), 1.54 and 1.16 (AB, J = 8.5 Hz, 2 H).

(*E,E*)-1,4-Diacetoxy-1,3-butadiene (22). The diester **21** (0.81 g, 3.6 mmol) was pyrolyzed in the normal fashion to give 0.52 g (89%) of diene **22,** mp 101–103 °C (lit.[5] mp 102–4 °C). Spectral data agreed with those of an authentic sample.

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Registry No.—**1,** 52748-15-9; **4,** 67737-75-1; **5,** 67700-02-1; **6,** 67700-03-2; **7a,** 67737-76-2; **7b,** 67700-04-3; **8a,** 67700-05-4; **8b,** 67700-06-5; **10,** 67700-07-6; **11,** 67737-77-3; **12,** 35150-63-1; **13,** 67700-08-7; **14,** 67700-09-8; **15a,** 67700-10-1; **15b,** 67772-74-1; **16,** 67177-15-5; **20a,** 67737-78-4; **20b,** 67737-79-5; **21,** 67700-11-2; **22,** 15910-11-9; 2(*S**),3(*S**),4(*S**),5(*R**)-4-acetoxy-3-hydroxytricyclo[4.2.1.0^{2,5}]non-7-ene, 67700-12-3; (*E,E*)-1-methoxy-4-phenylthio-1,3-butadiene, 67700-13-4; (*E,Z*)-1-methoxy-4-phenylthio-1,3-butadiene, 67700-14-5; (*Z,E*)-1-methoxy-4-phenylthio-1,3-butadiene, 67700-15-6; *p*-toluenesufonyl chloride, 98-59-9; thiophenol, 108-98-5; methyl chloroformate, 79-22-1; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; *O*-methylmandelic acid, 26164-26-1; (*S*)-*O*-methylmandelyl chloride, 55137-68-3.

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Preparation of Rearranged Allylic Isocyanates from the Reaction of Allylic Alkoxides with Cyanogen Chloride

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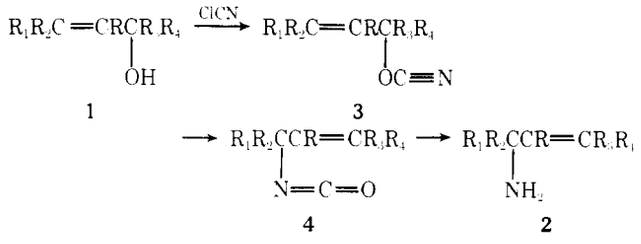
As a potential room temperature method for allylically transposing hydroxyl and amino functions, the reaction of cyanogen chloride with the lithium salt of four representative allylic alcohols was examined. Such treatment results in the formation, in good yield, of a mixture of the allylically rearranged isocyanate and a dimeric carbamate. The allylic isocyanate **4** results from rapid [3,3] sigmatropic rearrangement of the initially formed allylic cyanate **3**, and the dimeric carbamate results from the addition of the starting alkoxide to **4**. Similar treatment of the propargylic alcohol, 2-octyn-1-ol, did not result in the formation of the allenyl isocyanate **19**, but afforded 1-chloro-2-octyne in 70% yield.

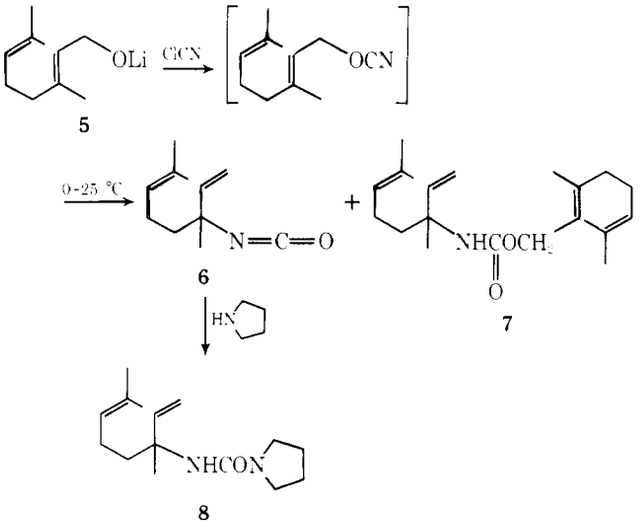
Previous reports from our laboratory have demonstrated that the [3,3] sigmatropic rearrangement of allylic trichloroacetimidates[2,3] is a superior method for the 1,3 transposition[4] of alcohol and amine functions (**1** → **2**). With a goal of developing similar methodology in which the thermal rearrangement[5] could be accomplished at or below room temperature, we were attracted to the procedure of Scheme I. Attempts[6] to prepare allylic cyanic esters[7] have invariably led to the formation of allylic isocyanates, and such results have been interpreted to mean that the allyl cyanate to allyl isocyanate rearrangement (**3** → **4**)[8] occurs rapidly at room temperature. The direct synthesis of alkyl cyanates from the reaction of alkoxides and cyanogen halides has been reported.[7,10] However, good yields have been obtained by this procedure with bridgehead[10a] and acidic alcohols[10b,c] only. Typically encountered[11] problems are further transformations of the initially formed alkyl cyanates,[11] leading to the formation of iminocarbonates,[12] isocyanates,[10a,13] cyanate or isocyanate trimers, and alkenes. We anticipated that many of these problems would be avoided in the reaction of an allylic alkoxide with a cyanogen halide if the initially formed allylic cyanate **3** underwent rapid rearrangement to isocyanate **4**. In this paper we report what to our knowledge is the first study of the reaction of allylic and propargylic alcohols with cyanogen chloride. As detailed below, the methodology of Scheme I was found to be synthetically useful for the introduction of nitrogen at highly hindered positions.

Scheme I



Results and Discussion

Sequential treatment of a tetrahydrofuran (THF) solution of geraniol at 0 °C with *n*-butyllithium (1 equiv) and cyanogen chloride (1 equiv) and subsequent reaction for 3 h at room temperature afforded a mixture of linalyl isocyanate **6** and the dimeric carbamate **7**. Isocyanate **6** was isolated in 40% yield by direct distillation of the crude reaction mixture at reduced pressure, and it was characterized by reaction with pyrrolidine to afford the known[3] urea **8**. Carbamate **7** was isolated in 50%



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