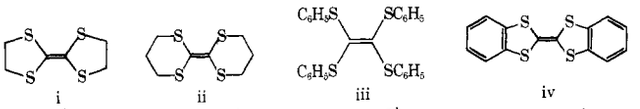
Registry No.—**1**, 177-29-7; **5**, 51795-67-6; **6**, 51795-68-7; **9**, 24719-68-4; **10**, 51795-69-8; **11**, 51795-70-1; mercaptoacetic acid, 68-11-1; ethanedithiol, 540-63-6; 1,3-propanedithiol, 109-80-8.

Supplementary Material Available. Listings of atomic coordinates and thermal parameters for **6** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2374.

References and Notes

(1) R. H. DeWolfe, "Carboxylic Ortho Acid Derivatives," Academic Press, New York, N. Y., 1970, Chapter 6.
(2) H. J. Backer and G. L. Wiggerink, *Recl. Trav. Chem. Pays-Bas*, **60**, 453 (1941).
(3) A. Schöberl and G. Wiehler, *Justus Liebigs Ann. Chem.*, **595**, 101 (1955).
(4) Compound i exhibits uv absorption at 358 mμ (ε 470). Symmetrical tetrathioethylenes exhibit no infrared C=C bands, but we have examined the laser Raman spectra of several and find that these bands appear at exceptionally low frequencies as listed below (recorded with solid samples). We are greatly indebted to Mrs. Fie Chang for recording these data.



i, 1550 cm^{-1}; ii, 1460 cm^{-1}; iii, 1450 cm^{-1}; iv, 1530 cm^{-1}

(5) A. Reissert and A. Moré, *Chem. Ber.*, **39**, 3298 (1906).
(6) D. S. Breslow and H. Skolnik, "Multi-Sulfur and Sulfur and Oxygen Five- and Six-Membered Heterocycles," Interscience, New York, N. Y., 1966, Part One, 323.
(7) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970).
(8) See paragraph at end of paper regarding supplementary material.
(9) Melting points are uncorrected. Nmr spectra were recorded on Varian T-60 and HA-100 instruments and are reported in parts per million from internal tetramethylsilane. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC-110B instruments, respectively. Elemental analyses were conducted under the supervision of Dr. F. Scheidl of our microanalytical laboratory.
(10) D. L. Coffen, J. Q. Chambers, D. R. Williams, P. E. Garrett, and N. D. Canfield, *J. Amer. Chem. Soc.*, **93**, 2258 (1971).

Stereospecific Synthesis of 3,7-Disubstituted Bicyclo[3.3.0]octanes[1]

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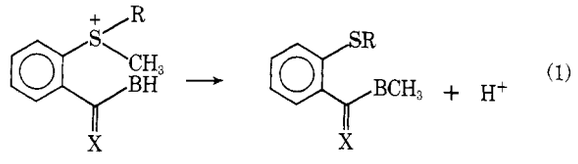
The synthesis of several 3,7-disubstituted bicyclo[3.3.0]octanes has been accomplished by a series of stereospecific reactions, starting with the monoethylene ketal of 3,7-bicyclo[3.3.0]octanedione. The configurations at carbons 3 and 7 were established by the use of pmr spectroscopy.

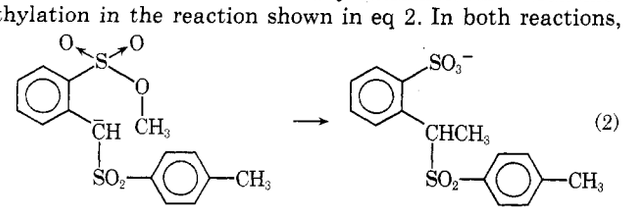
As part of a project aimed at understanding biochemical one-carbon transfer, we have been studying several types of molecules in order to elucidate the stereochemistry and the nature of catalysis involved in nonenzymic transalkylation reactions.[3] Specifically, we are interested in providing a chemical model for enzyme-catalyzed methylations involving *S*-adenosylmethionine (SAM).[4] In a previous paper[5] we noted the stability of **1** under conditions where one might observe intramolecular transmethylations (eq 1). Independently, Eschenmoser and his coworkers[6] were unable to observe any intramolecular transmethylation in the reaction shown in eq 2. In both reactions,



(1)

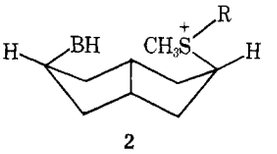
1

a, R = CH_3; X = H_2; BH = NH_2 ⟶ a, R = CH_3; X = H_2; B = NH
b, R = CH_3; X = O; BH = OH ⟶ b, R = CH_3; X = O; B = O
c, R = CN; X = O; BH = OH
d, R = CN; X = O; BH = NH_2 ⟶ c,d, R = CN; X = O; B = O



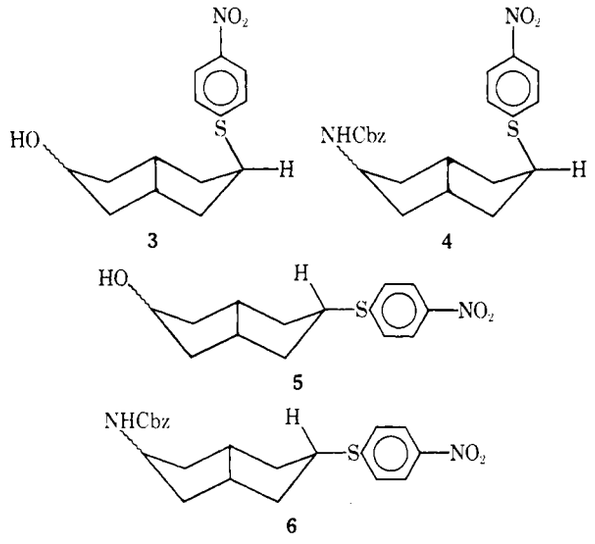
(2)

a six-membered cyclic intermediate can conceivably be formed, but no product resulting from intramolecular nucleophilic attack at the sp^3 carbon was obtained. Failure of these reactions may be ascribed to the inability of the atoms involved to achieve the required linear geometry in the transition state. This is in marked contrast to the numerous intramolecular reactions involving six-membered cyclic intermediates occurring at sp^2 carbons.[7] We have continued to examine models[8] of compounds in which the nucleophile, the leaving group, and the electrophilic center can be aligned in the collinear array required for a nucleophilic displacement. A molecule which can achieve such a conformation is the methylsulfonium salt **2** of a 3,7-disubstituted bicyclo[3.3.0]octane.



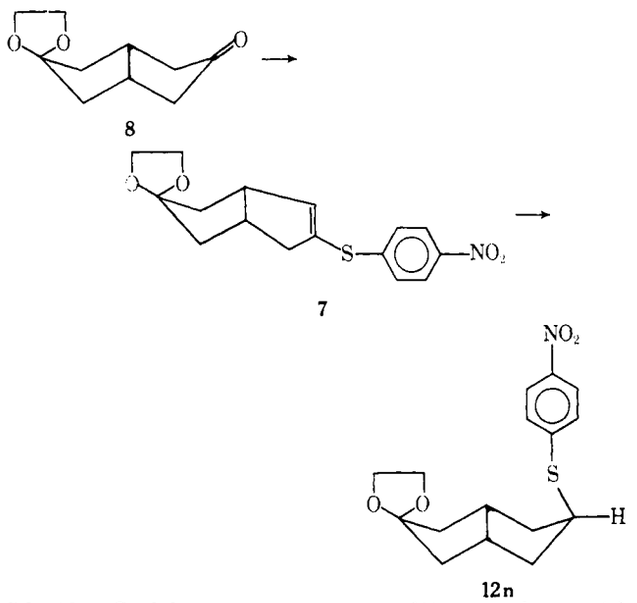
2

Tabushi and his coworkers[9] have shown that 3-substituted bicyclo[3.3.0]octanes prefer a "W" conformation. Models of **2** indicate that the rigid backbone of this bicyclic ring system allows an endo nucleophilic base (BH) at C-7 and the methyl of an endo sulfonium moiety at C-3 to come in close proximity to one another. Only a small deviation from the fully extended "W" conformation brings the nucleophilic and electrophilic centers within bond-making distance for a possible intramolecular transmethylation reaction. The compound in which RS of **2** is homocysteine appears to be a plausible model for enzymic methylations involving SAM. There are very little data on the 3,7-disubstituted bicyclooctanes in the literature.[10a] We have carried out the synthesis of some stereospecifically substituted bicyclooctane derivatives, **3**–**6**, and the results of these efforts are the subject of this paper.



3 4 5 6

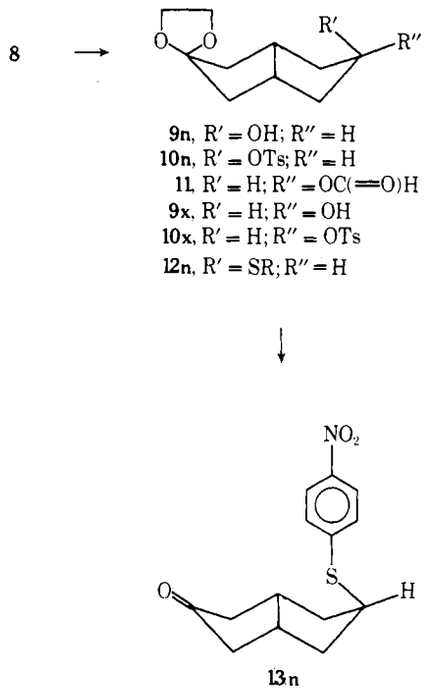
Our initial approach to **3** was to attempt the preparation of vinyl sulfide **7** from the known bicyclo[3.3.0]octane-3,7-dione monoethylene ketal (**8**).[10a] Sulfide **7** could then be stereospecifically reduced to the endo ketal sulfide **12n**. Cyclohexanone was reported[11] to condense with benzenethiol in the presence of *p*-toluenesulfonic acid to give phenyl cyclohexenyl sulfide in one step. Similarly, we were able to convert cyclopentanone to the corresponding *p*-nitrophenyl cyclopentenyl sulfide in good yield. However, the analogous reaction between **8** and benzenethiol gave a complex mixture with none of the desired product.



8 7 12n

We then turned our attention to the reaction sequence in Scheme I. Tabushi and his coworkers[9] reported the reduction of bicyclo[3.3.0]octan-3-one to the corresponding alcohol with a ratio of endo OH:exo OH of 4:1. In our hands, reduction of **8** by $LiAlH_4$ gave exclusively the endo product **9n**, which was readily converted to the tosylate **10n**. However, when treated with sodium acetate, the tosylate of *endo*-bicyclo[3.3.0]octan-3-ol was known to give extensive olefin formation.[12] Recently, Corey[13] and Weinshenker[14] described the use of tetraalkylammonium formates as mild reagents for effecting displacement reactions with only minor olefin formation. When **10n** was mixed with tetra-*n*-butylammonium formate in acetone at ambient temperature the product consisted of a mixture of exo formate **11** and an olefinic material in a ratio of *ca.* 5:1 estimated by nmr. This mixture was solvolyzed to the

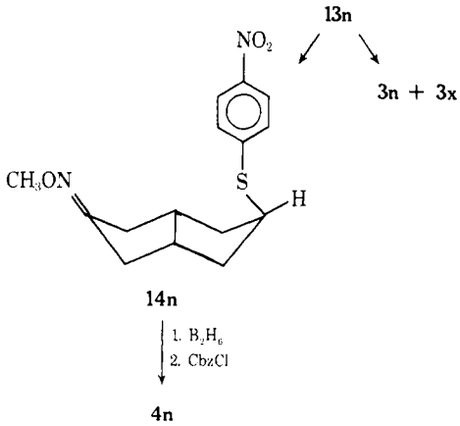
Scheme I



9n, R′ = OH; R″ = H
10n, R′ = OTs; R″ = H
11, R′ = H; R″ = OC(=O)H
9x, R′ = H; R″ = OH
10x, R′ = H; R″ = OTs
12n, R′ = SR; R″ = H

13n

exo alcohol **9x**, which was then tosylated to give **10x**. To convert the exo tosylate **10x** to the endo sulfide **12n** we used the reagent tetra-*n*-butylammonium *p*-nitrobenzenethiolate. Although a recent paper described kinetic studies of displacement reactions with tetraalkylammonium thiophenolates,[15] we are not aware of the use of these reagents for the synthetic preparation of sulfides. Thus, formation of the endo sulfide **12n** was effected in good yield with no presence of isomeric exo sulfide **12x**. The ketal group was removed by acid-catalyzed ketal exchange with acetone. Reduction of the resulting ketone **13n** with $NaBH_4$ gave the desired endo hydroxy compound **3n** together with a small amount of the exo hydroxy isomer **3x** (endo:exo = 7:1). Treatment of **13n** with *O*-methyl oxime hydrochloride produced the oxime **14n** in good yield. Reduction of **14n** by diborane and derivatization of the resulting amine with carbobenzyloxy chloride (CbzCl) gave only the endo *N*-carbobenzyloxyamino sulfide **4n**.



14n 4n

Stereochemistry. Reduction of bicyclo[3.3.0]octan-3-one is known to give the endo alcohol **15n** as the major product, and results from attack of the carbonyl function from the least hindered exo side.[12] Tabushi and his coworkers[9] found that the α protons of the endo alcohol **15n** and its acetate **16n** are more shielded than the α protons of the isomeric exo alcohol **15x** and its acetate **16x**. For nmr

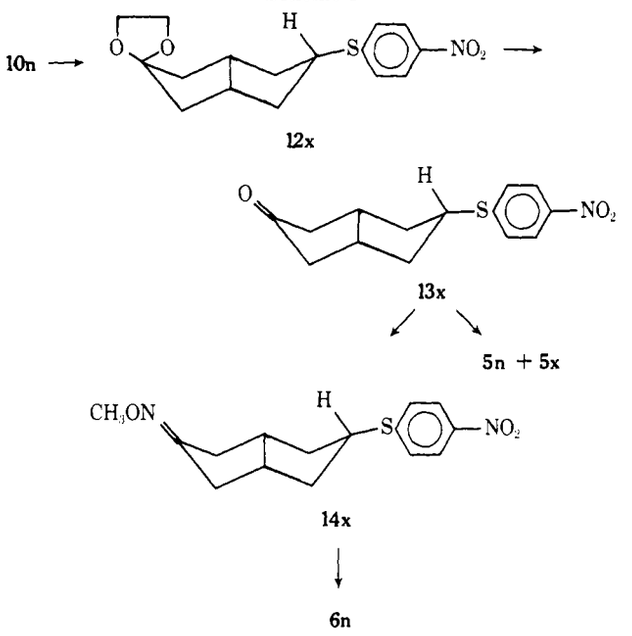
Table I[a]

Compd	H_3	H_7	Compd	H_3	H_7
15n	3.93[b]		**15x**	4.16[b]	
16n	4.92[b]		**16x**	5.18[b]	
9n	4.14		**9x**	4.37	
10n	4.83		**10x**	5.05	
12n	3.65		**12x**	3.96	
13n	3.83		**13x**	3.98	
14n	3.72		**14x**	3.83	
3n	3.57	4.35	**5n**	4.13	4.13
3x	3.58	4.47	**5x**	3.73	4.45

[a] Chemical shifts in δ units. [b] Data from Tabushi, *et al.*[9]

comparison, we prepared the series of exo sulfides **5** and **6**, using analogous reactions as in the endo series (Scheme II). The exo sulfide series also provide access to the corresponding methylsulfonium compounds, in which the nucleophile and methyl group are not correctly aligned for intramolecular methyl transfer. These sulfonium compounds, in contrast to **2**, should not undergo facile transmethylation, and therefore could be used in control experiments to probe the stereochemical requirements of the reaction.

Scheme II

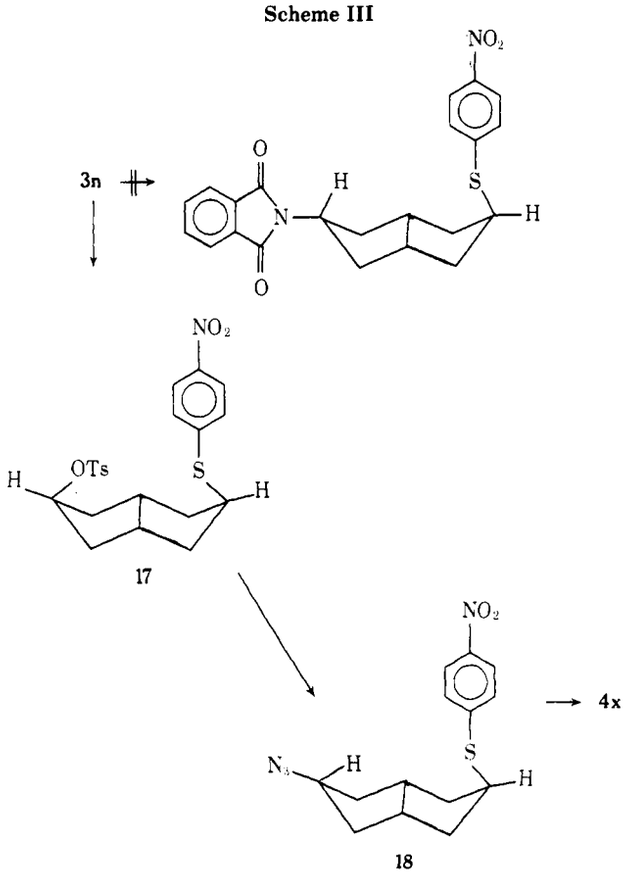


The chemical shifts of the α H's in the endo and exo series along with those obtained by Tabushi are listed in Table I. We observe a similar upfield shift of the α H's in the endo sulfides compared to the exo sulfides. The difference of 0.23 ppm between **15n** and **15x** is identical with the difference between **9n** and **9x**. The position of the H_7 proton of the hydroxy sulfide **3n** at δ 4.35 compared to δ 4.47 of **3x** confirms the endo configuration of the hydroxy moiety of **3n**. Similarly, the upfield shift of the H_7 proton of **5n** relative to that of **5x** indicates the endo geometry of the hydroxy group of **5n**. The chemical shift of the α H's of the sulfides also vary within each series. In particular, a difference of 0.4 ppm is observed between the H_3 protons of **5n** and **5x**. This difference may be an indication of the influence of the endo hydroxy at C-7 of **5n** on the endo proton at C-3. Such an influence demonstrates the close proximity of the two endo groups. This is encouraging in terms of bringing the nucleophile of **2** in close proximity to the sulfonium moiety.

Reduction of ketoxime acetates by diborane is known to occur stereospecifically from the less hindered side.[16] In support of this mode of attack, we obtained exclusively the endo alcohol **9n** when the ketone **8** was treated with diborane. However, since it is critical that the nucleophile at C-7 of **2** be in the endo configuration, we felt it important to establish beyond a doubt the geometry of the C-7 substituent. For this reason, we converted the endo hydroxy sulfide **3n** to the exo *N*-carbobenzyloxyamino sulfide **4x** for direct comparison with its endo isomer **4n**.

Mitsunobu and coworkers[17] reported that an optically active alcohol could be converted to an optically active amine by treatment with diethyl azodicarboxylate, triphenylphosphine, and phthalimide at room temperature. We carried out the analogous reaction with **3n**, but recovered only starting material (Scheme III). Therefore, we prepared the tosylate **17** and converted it to the exo azido sulfide **18**. Reduction of the azide **18** by diborane followed by CbzCl treatment gave the exo *N*-carbobenzyloxyamino sulfide **4x**. The isomers **4n** and **4x** have identical R_f values on tlc and identical elemental composition. Their ir spectra are identical except in the 1000–1300-cm^{-1} region. A broad multiplet at δ 3.3–4.4 is observed in the nmr spectrum of **4n**; this peak is assigned to the protons α to the sulfide and *N*-Cbz-amino groups. In the exo isomer **4x**, the multiplet at δ 4.13 is assigned to the proton α to the *N*-carbobenzyloxyamino group and, analogous to other sulfides, the higher field multiplet at δ 3.43 is attributed to the proton α to the sulfide moiety. Finally, the two isomers differ in melting point by 25°.

Scheme III



Experimental Section[18]

Cyclopentenyl *p*-Nitrophenyl Sulfide. A mixture of cyclopentanone (0.84 g, 10 mmol), 1.55 g (10 mmol) of *p*-nitrobenzenethiol, *ca.* 0.1 g of *p*-toleuenesulfonic acid, and 30 ml of toluene was refluxed for 22 hr with continuous water removal. The solution was then extracted several times with 6 *N* aqueous NaOH and the combined aqueous solution was backwashed with $CHCl_3$. The organic phases were combined and dried. The solvents were removed under vacuum and the residue was distilled. A yellow liquid weighing 1.15 g (52%) was obtained: bp 127° (0.07 mm); ir

1500, 1340 cm^{-1} (NO_2); nmr δ 8.05, 7.3 (4 H, two sets of d, J = 9 Hz, ArH), 6.15 (1 H, m, HC=C), 2.25 (6 H, m, ring protons).

Anal. Calcd for $C_{11}H_{11}NO_2S$: C, 59.69; H, 5.01; N, 6.29. Found: C, 59.83; H, 4.95; N, 6.42.

Bicyclo[3.3.0]octane-3,7-dione Monoethylene Ketal (8). The dione[19] (17.0 g, 0.123 mol) was heated overnight with ethylene glycol (7.61 g, 0.123 mol) and a catalytic amount of *p*-toluenesulfonic acid in 200 ml of benzene while the water formed was continuously removed. The mixture was extracted with aqueous $NaHCO_3$ solution and dried. Benzene was removed and the residue was passed through a silica gel column with ether as the eluent. The first eluate consisted of 6.57 g of the diketal, nmr 3.78 (8 H, s, 2 OCH_2CH_2O), 1.35–2.80 (10 H, m, ring protons). The second eluate was a mixture primarily of the monoketone 8 with a trace of the diketal (8.67 g). A pure sample of 8 gave the following data: ir (neat) 1740 cm^{-1} (C=O); nmr δ 3.77 (4 H, s, OCH_2CH_2O), 1.3–3.0 (10 H, m, ring protons). The third fraction, weighing 2.15 g, was the unreacted dione plus a small trace of monoketone 8. These spectral data are in agreement with those previously obtained.[10b]

3-*endo*-Hydroxybicyclo[3.3.0]octan-7-one Ethylene Ketal (9n). A. By Reduction with $LiAlH_4$. The monoketone (5.15 g) prepared as described above was heated at reflux for 1 hr with 1.07 g of $LiAlH_4$ in 30 ml of ether. Excess $LiAlH_4$ was destroyed by addition of MeOH and H_2O. Insoluble solids were removed by filtration and the aqueous phase was extracted with $CHCl_3$. The organic phases were combined and concentrated. The residue was eluted on a silica gel column with ether. The first eluate contained unreacted diketal (0.76 g) and the second eluate was pure hydroxy ketal **9n** (3.07 g, 69%) obtained as a colorless oil: ir 3360 cm^{-1} (OH); nmr δ 4.14 (1 H, p, J = 6 Hz, HCO), 3.83 (s, 4 H, OCH_2CH_2O), 3.0 (1 H, s, OH), 2.5–1.2 (m, 10 H, ring protons).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.69. Found: C, 64.95; H, 8.77.

B. By Reduction with BH_3. The usual Brown procedure was employed.[20] The crude product from 182 mg of unpurified monoketone 8 weighed 143 mg. Its nmr, tlc, and ir indicated only the presence of the endo hydroxy ketal **9n** and a trace of diketal.

3-*endo*-*p*-Toluenesulfonatobicyclo[3.3.0]octan-7-one Ethylene Ketal (10n). *p*-Toluenesulfonyl chloride (6.1 g, 0.032 mol) was added slowly to a solution of 2.94 g (0.016 mol) of **9n** in 50 ml of dry pyridine with stirring and cooling. After stirring for another hour in the cold, it was left at room temperature overnight. The mixture was then poured into ice water, and the precipitate was collected and redissolved in ether. The ether solution was dried and concentrated, leaving a white solid. This material was recrystallized from ether–petroleum ether mixture, giving two crops of material (3.07 g, 57%): mp 85–86°; ir 1350, 1170 cm^{-1} (SO_2); nmr δ 7.77, 7.32 (4 H, two sets of d, J = 9 Hz, ArH), 4.83 (1 H, p, J = 6.5 Hz, CHOTs), 3.84 (4 H, s, OCH_2CH_2O), 2.8–1.4 (13 H, m, $ArCH_3$ and ring protons).

Anal. Calcd for $C_{17}H_{22}O_5S$: C, 60.34; H, 6.55. Found: C, 60.53; H, 6.53.

3-*exo*-Hydroxybicyclo[3.3.0]octan-7-one Ethylene Ketal (9x). Tetra-*n*-butylammonium formate[21] (62.5 mmol) and 4.2 g (12.5 mmol) of the endo tosylate **10n** were dissolved in 150 ml of dry acetone. The mixture was allowed to stand overnight at room temperature. Acetone was then evaporated and the residue was extracted several times with ether. The ethereal solution was concentrated to a small volume and then passed through a silica gel column using ether as the eluent. Evaporation of ether from the eluate gave 2.18 g of a colorless oil: nmr δ 7.96 [s, OC(=O)H], 5.58 (m, HC=CH), 5.35 (p, J = 3 Hz, CHO), 3.82 (s, OCH_2CH_2O), 3.0–1.2 (m, ring protons). The peak intensity of the formyl proton *vs.* the vinylic protons was 7:3, giving a ratio of 5:1 of the formate **11** to the olefinic by-product.

The formate mixture was stirred for 4.5 hr in a solution of 20 g of anhydrous K_2CO_3 and 250 ml of anhydrous MeOH. The solid was then filtered, and MeOH was removed from the filtrate. The residue was partitioned between ether and water, the ether phase was dried and concentrated, and the oily residue was purified on a silica gel column with ether as the eluent. The eluate consisted of two fractions. The first fraction (0.17 g), with nmr δ 5.6 (2 H, m, HC=CH), 3.83 (4 H, s, OCH_2CH_2O), 3.4–1.2 (m, 9.2 H, ring protons), is in accord with the olefin obtained in the previous step. The second fraction **9x** weighed 1.4 g (61% from the tosylate): ir (neat) 3400 cm^{-1} (OH); nmr δ 4.37 (1, H, p, J = 5 Hz, CHO), 3.83 (4 H, s, OCH_2CH_2O), 3.17 (1 H, s, OH), 3.0–1.3 (10 H, m, ring protons).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.69. Found: C, 64.94; H, 8.88.

3-*exo*-*p*-Toluenesulfonatobicyclo[3.3.0]octan-7-one Ethylene Ketal (10x). The exo alcohol **9x** (1.1 g, 6 mmol) was treated with *p*-toluenesulfonyl chloride (3.44 g, 18 mmol) as before except that the work-up was modified as follows. The reaction mixture was poured into ice–water. The resulting aqueous solution, in which no precipitate appeared, was extracted with $CHCl_3$ and the dried $CHCl_3$ extract was concentrated *in vacuo*. The remaining pyridine was evaporated by a mechanical pump and the final trace was removed by an aqueous cupric chloride wash. The product weighed 1.4 g (69%): mp 55–60° (recrystallized from petroleum ether); ir 3400 cm^{-1} (OH); nmr δ 7.77, 7.32 (4 H, two sets of d, J = 9 Hz, ArH), 5.05 (1 H, p, J = 4 Hz, HCOTs), 3.81 (4 H, s, OCH_2CH_2O), 3.0–1.2 (13 H, m, $ArCH_3$ and ring protons).

Anal. Calcd for $C_{17}H_{22}O_5S$: C, 60.34; H, 6.55. Found: C, 60.23; H, 6.43.

3-*endo*-*p*-Nitrophenylthiobicyclo[3.3.0]octan-7-one Ethylene Ketal (12n). Tetra-*n*-butylammonium *p*-nitrobenzenethiolate was prepared by mixing a solution of 64.87 g (25 mmol) of 10% aqueous tetra-*n*-butylammonium hydroxide in 60 ml of MeOH with a solution of *p*- nitrothiophenol (4.267 g, 27.5 mmol) in 60 ml of MeOH. The mixture was concentrated *in vacuo* and then lyophilized overnight. The excess thiophenol was removed by washing the red crystals with ether several times.

To the red solid was added 1.69 (5 mmol) of the exo tosylate **10x** followed by 250 ml of freshly distilled CH_3CN. The solution was allowed to stand at room temperature for 48 hr. At this time, the solvent was removed and the solid was extracted in a Soxhlet extractor overnight with ether. The ethereal solution was concentrated, leaving a yellow solid (0.81 g). Additional product could be obtained from repeated extractions. A total of three extractions gave 1.66 g of crude **12n**. A small sample was purified by preparative tlc and recrystallized from 95% ethanol: mp 143–145°; ir 1470, 1320 cm^{-1} (NO_2); nmr δ 8.10, 7.34 (4 H, two sets of d, J = 9 Hz, ArH), 3.87 (4 H, s, OCH_2CH_2O), 3.65 (1 H, p, J = 6 Hz, CHSAr), 3.0–1.3 (10 H, m, ring protons).

Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.81; H, 5.95; N, 4.35. Found: C, 59.55; H, 5.92; N, 4.35.

3-*endo*-*p*-Nitrophenylthiobicyclo[3.3.0]octan-7-one (13n). The crude ketal sulfide **12n** (1.61 g, 5 mmol) was refluxed in dry acetone (200 ml) with 30 mg of *p*-toluenesulfonic acid for 4 hr. Acetone was evaporated and the residue was extracted between $CHCl_3$ and saturated $NaHCO_3$. The $CHCl_3$ phase was dried and concentrated, leaving a (yellow solid) residue weighing 1.4 g. A small quantity of pure **13n** was obtained by preparative tlc: mp 95–96°; ir 1730 cm^{-1} (C=O); nmr δ 8.09, 7.33 (4 H, two sets of d, J = 9 Hz, ArH), 3.83 (1 H, p, J = 7 Hz, CHSAr), 3.2–1.2 (m, 10 H, ring protons).

Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.53; H, 5.39; N, 5.24.

Reduction of 3-*endo*-*p*-Nitrophenylthiobicyclo[3.3.0]octan-7-one (13n). The crude keto sulfide **13n** (70 mg, 0.25 mmol) dissolved in 3 ml of dry THF was added to a mixture of $NaBH_4$ (37.8 mg, 1 mmol) in 0.2 ml of MeOH in the cold. Stirring was continued at room temperature for 2 hr. Solvent was then removed, the residue was covered with ether, and excess $NaBH_4$ was destroyed with 1 *N* aqueous HCl. The ether layer was separated, and the aqueous phase was extracted several more times with ether. The combined ether fractions were dried and concentrated. The residue was chromatographed on a preparative tlc plate. The major yellow band followed by a minor yellow band were extruded and washed with $CHCl_3$. Evaporation of the solvent gave 40 mg from the major band and 6 mg from the minor band. The yield from tosylate **10x** to the hydroxy sulfides was 66%. The major product **3n** had the following characteristics: mp 115–117°; ir 3200 cm^{-1} (OH); nmr δ 8.15, 7.36 (4 H, 2 sets of d, J = 9 Hz, ArH), 4.35 (1 H, m, HCO), 3.57 (1 H, m, CHSAr), 2.8–1.0 (11 H, m, ring protons + OH).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.14; N, 5.01. Found: C, 60.07; H, 6.19; N, 4.75.

The minor product **3x** had the following characteristics: mp 132°; ir 3280 cm^{-1} (OH); nmr δ 8.17, 7.36 (4 H, two sets of d, J = 9 Hz, ArH), 4.47 (1 H, p, J = 5 Hz, CHO), 3.58 (1 H, m, HCSAr), 3.0–0.8 (11 H, m, ring protons + OH).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.14; N, 5.01. Found: C, 60.01; H, 6.19; N, 5.02.

3-*endo*-*p*-Nitrophenylthio-7-(*O*-methyl)oximinobicyclo[3.3.0]octane (14n). A mixture of 753 mg (2.7 mmol) of crude

keto sulfide **13n** and 226 mg (2.7 mmol) of *O*-methyl oxime hydrochloride in 15 ml of absolute EtOH and 15 ml of dry pyridine was refluxed overnight. The solvents were evaporated and the residue was extracted between 1 *N* aqueous HCl and ether. The ether wash was dried and concentrated and a residue weighing 575 mg was obtained. Part of the product was purified by preparative tlc, and a pure sample had the following characteristics: mp 78°; ir 1640 cm^{-1} (C=N); nmr δ 8.08, 7.3 (4 H, two sets of d, J = 9 Hz, ArH), 3.8 (3 H, s, OCH_3), 3.72 (1 H, m, CHSAr), 2.5 (8 H, m, ring protons), 1.45 (2 H, m, ring protons).

Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.79; H, 5.92; N, 9.15. Found: C, 58.92; H, 5.92; N, 9.12.

3-*endo*-*p*-Nitrophenylthio-7-*endo*-*N*-carbobenzyloxyaminobicyclo[3.3.0]octane (4n). The crude oximino sulfide **14n** (546.3 mg, 1.8 mmol) dissolved in 18 ml of dry THF was treated with 7.2 ml of a 1 *M* BH_3 in THF solution (7.2 mmol of BH_3) in the cold over N_2. After addition, the solution was refluxed for 2 hr and cooled, and excess BH_3 was destroyed with 2 ml of H_2O followed by 5.4 ml of 5% aqueous HCl solution. The mixture was heated to reflux for another hour, and the THF was removed by evaporation. The yellow residue was extracted with 170 ml of water and ether. The aqueous phase was covered with 130 ml of ether and made basic with 10.8 ml of 5% aqueous NaOH solution, and carbobenzyloxy chloride (7.2 mmol, 1.08 ml) was then added slowly to the mixture. Stirring was continued for 3 hr, and the phases were separated. The aqueous phase was extracted several times with ether, and the ethereal solutions were combined and washed with 1 *N* aqueous HCl solution. Finally, the ether phase was dried and concentrated. The residue was purified by trituration with petroleum ether, recrystallization from ether–petroleum ether mixture, and final purification by preparative tlc. A total of 398 mg of pure **4n** was obtained: mp 91–93°; ir 3400 (NH), 1709 cm^{-1} (C=O); nmr δ 8.09, 7.31 (4 H, two sets of d, J = 9 Hz, ArH), 7.32 (5 H, s, PhH), 5.1 (2 H, s, CH_2Ph), 4.87 (1 H, d, J = 7 Hz, NH), 4.4–3.3 (2 H, br m, HCN, HCSAr), 2.4 (6 H, m, ring protons), 1.47 (4 H, m, ring protons).

Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.05; H, 5.86; N, 6.79. Found: C, 64.33; H, 6.00; N, 6.85.

3-*exo*-*p*-Nitrophenylthiobicyclo[3.3.0]octan-7-one Ethylene Ketal (12x). The same procedure for the preparation of ketal sulfide **12n** was employed. From 676.4 mg (2 mmol) of the tosylate **10n**, 682 mg of crude sulfide **12x** was obtained. A small quantity of **12x** purified by preparative tlc and then recrystallized from 95% ethanol gave the following characteristics: mp 120–122°; ir 1500, 1335 cm^{-1} (NO_2); nmr δ 8.10, 7.33 (4 H, two sets of d, J = 9 Hz, ArH) 3.96 (1 H, m, CHSAr), 3.89 (4 H, s, OCH_2CH_2O), 2.8 (2 H, m, ring protons), 2.3–1.4 (8 H, m, ring protons).

Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.81; H, 5.95; N, 4.35. Found: C, 59.81; H, 5.78; N, 4.29.

3-*exo*-*p*-Nitrophenylthiobicyclo[3.3.0]octan-7-one (13x). The same procedure for the preparation of keto sulfide **13n** was used. The crude ketal sulfide **12x** from above (682 mg) gave 583 mg of crude keto sulfide **13x**. A sample of **13x** was purified by preparative tlc and recrystallization from ethanol and water: mp 98–100°; ir 1730 cm^{-1}; nmr δ 8.11, 7.33 (4 H, two sets of d, J = 9 Hz, ArH), 3.98 (1 H, p, J = 7 Hz, CHSAr), 3.0–1.6 (10 H, m, ring protons).

Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.68; H, 5.42; N, 4.86.

Reduction of Keto Sulfide 13x by $NaBH_4$. The keto sulfide **13x** (70 mg, 0.25 mmol) was reduced as described for the reduction of **13n** to give two products which were separated by preparative tlc. The major, fast-running material **5n** weighed 57 mg: mp 86–88°; ir 3500 cm^{-1} (OH); nmr δ 8.12, 7.35 (4 H, two sets of d, J = 9 Hz, ArH), 4.13 (2 H, two sets of overlapping p, HCO, HCSAr), 3.0–1.0 (11 H, m, ring protons + OH).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.14; N, 5.01. Found: C, 60.26; H, 5.92; N, 4.75.

The slower moving, minor product **5x** weighed 12 mg: mp 83–85°; ir 3200 cm^{-1} (OH); nmr δ 8.1, 7.3 (4 H, two sets of d, J = 9 Hz, ArH), 4.45 (1 H, m, HCO), 3.73 (1 H, p, J = 7 Hz, CHSAr), 2.9 (2 H, m, ring protons), 2.0–1.0 (9 H, m, ring protons + OH).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.14; N, 5.01. Found: C, 60.41; H, 6.37; N, 5.03.

3-*exo*-*p*-Nitrophenylthio-7-(*O*-methyl)oximinobicyclo[3.3.0]octane (14x). The crude keto sulfide **13x** (277 mg, 1.0 mmol) was treated with *O*-methyl oxime hydrochloride (91.9 mg, 1.1 mmol) in 5 ml each of pyridine and absolute ethanol as described for the preparation of **14n**. The product after work-up gave 250 mg of yellow solid. A pure sample was obtained by preparative tlc: mp 71–72°; ir 1640 cm^{-1} (weak C=N); nmr δ 8.09, 7.3 (4 H, two sets of d, J = 9 Hz, ArH), 3.83 (1 H, m, HCSAr), 3.8 (3 H, s, OCH_3), 3.0–1.8 (10 H, m, ring protons).

Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.79; H, 5.92; N, 9.15. Found: C, 59.09; H, 6.15; N, 8.96.

3-*exo*-*p*-Nitrophenylthio-7-*endo*-*N*-carbobenzyloxyaminobicyclo[3.3.0]octane (6n). The reduction of the oximino sulfide **14x** and formation of the carbobenzyloxy derivative of the amino sulfide were carried out in a similar fashion as in the preparation of **4n**. The crude **14x** (190 mg, 0.62 mmol) in 6 ml of THF was reduced with 2.48 ml of a 1 *M* solution of BH_3 in THF, while 37.2 μl (2.48 mmol) of CbzCl was used for derivatizing the amine. The product (147 mg) melted at 67–93°. A sample purified by preparative tlc and recrystallized from a petroleum ether–ether mixture melted at 92–94°: ir 3380 (NH), 1710 cm^{-1} (C=O); nmr δ 8.06, 7.32 (4 H, two sets of d, J = 9 Hz, ArH), 7.3 (5 H, s, PhH), 5.09 (2 H, s, CH_2Ph), 4.93 (1 H, d, J = 6 Hz, NH), 3.8 (2 H, m, HCN, HCSAr), 3.0–0.8 (10 H, m, ring protons).

Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.05; H, 5.86; N, 6.79. Found: C, 64.09; H, 6.08; N, 6.78.

3-*endo*-*p*-Nitrophenylthio-7-*endo*-*p*-toluenesulfonatobicyclo[3.3.0]octane (17). The hydroxy sulfide **3n** (150 mg, 0.536 mmol) was tosylated in the usual manner with 286 mg (1.5 mmol) of tosyl chloride in pyridine. The product consisted of 24 mg of unreacted hydroxy sulfide and 117 mg (60%) of tosylate **17** which was purified by preparative tlc: mp 98–100°; ir 1340, 1175 cm^{-1} (SO_2); nmr δ 8.07 (2 H, d, J = 9 Hz, ArH), 7.77 (2 H, d, J = 9 Hz, Ar'H), 7.3 (4 H, d, J = 9 Hz, ArH, Ar'H), 4.97 (1 H, p, J = 5 Hz, CHOTs), 3.5 (1 H, m, CHSAr), 2.9–1.1 (13 H, m, ring protons, plus s, $ArCH_3$).

Anal. Calcd for $C_{21}H_{23}NO_5S_2$: C, 58.19; H, 5.34; N, 3.23. Found: C, 57.99; H, 5.29; N, 3.29.

3-*endo*-*p*-Nitrophenylthio-7-*exo*-azidobicyclo[3.3.0]octane (18). The tosylate **17** (86.6 mg, 0.2 mmol) in 1 ml of dry HMPT was added to 65 mg (1 mmol) of NaN_3. The solution was stirred at ambient temperature for 2 hr. The entire mixture was chromatographed on a preparative plate, and the major yellow band extruded. The yellow material thus isolated weighed 52 mg (85.5%): mp 51–52°; ir 2100 cm^{-1} (N_3); nmr δ 8.05, 7.28 (4 H, two sets of d, J = 9 Hz, ArH), 4.01 (1 H, p, J = 6 Hz, HCN_3), 3.57 (1 H, septet, J = 5 Hz, HCSAr), 3.0–0.8 (10 H, m, ring protons).

Anal. Calcd for $C_{14}H_{16}N_4O_2S$: C, 55.24; H, 5.30; N, 18.41. Found: C, 55.37; H, 5.50; N, 18.15.

3-*endo*-*p*-Nitrophenylthio-7-*exo*-*N*-carbobenzyloxyaminobicyclo[3.3.0]octane (4x). The azido sulfide **18** (30.4 mg, 0.1 mmol) in 1 ml of THF was mixed with 0.4 ml of a 1 *M* solution of BH_3 in THF (0.4 mmol) in the cold over N_2. The solution was refluxed for 2.5 hr and cooled, and excess BH_3 was destroyed with 1 ml of H_2O followed by 0.4 ml of a 1 *N* aqueous HCl solution. THF was removed *in vacuo*, and the residue was dissolved in *ca.* 20 ml of H_2O, extracted with ether, and filtered. The filtrate was covered with 20 ml of ether and made basic with 0.8 ml of 1 *N* aqueous NaOH solution, and 60 μl (0.4 mmol) of CbzCl was then added. The biphasic mixture was stirred for another 2 hr and the phases were separated. The aqueous phase was extracted several times with ether, and the ethereal solutions were combined, dried, and concentrated. The residue was purified by preparative tlc. The product (25 mg, 61%) had the following properties: mp 116–118°; ir 3400 (NH), 1710 cm^{-1} (C=O); nmr δ 8.10 (2 H, d, J = 9 Hz, ArH), 7.33 (7 H, s overlapping with d, PhH and ArH), 5.1 (2 H, s, $PhCH_2$), 4.8 (d, J = 8 Hz, NH), 4.13 (1 H, m, CHN), 3.43 (1 H, m, CHSAr), 3.0–1.0 (10 H, m, ring protons).

Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.05; H, 5.86; N, 6.79. Found: C, 64.05; H, 6.06; N, 6.95.

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Registry No.—3n, 51716-27-9; **3x,** 51773-30-9; **4n,** 51716-28-0; **4x,** 51773-33-2; **5n,** 51773-34-3; **5x,** 51773-35-4; **6n,** 51773-36-5; **8,** 51716-62-2; 8 dione derivative, 51716-63-3; **9n,** 51716-64-4; **9x,** 51773-37-6; **10n,** 51716-65-5; **10x,** 51773-38-7; **11,** 51716-66-6; **12n,** 51716-67-7; **12x,** 51773-39-8; **13n,** 51716-68-8; **13x,** 51716-69-9; **14n,** 51716-70-2; **14x,** 51716-71-3; **17,** 51716-72-4; **18,** 51716-73-5; cyclopentenyl *p*-nitrophenyl sulfide, 51716-74-6; cyclopentanone, 120-

92-3; *p*-nitrobenzenethiol, 1849-36-1; tetra-*n*-butylammonium formate, 35733-58-5; tetra-*n*-butylammonium *p*-nitrobenzenethiolate, 20627-93-4; *O*-methyl oxime hydrochloride, 4229-44-1; carbobenzyloxy chloride, 501-53-1; *p*-toluenesulfonyl chloride, 98-59-9.

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Stereoselective Synthesis of 3-Exo-Substituted 2-*endo*-Acyl-5-norbornene Derivatives[1]

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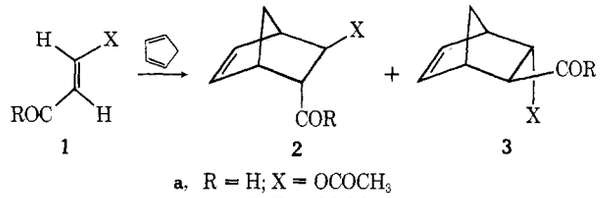
The stereoselective addition of a variety of nucleophiles (ROH, RSH) to several 2-acylnorbornadienes provides an efficient synthesis of the title compounds. The allyl ethers derived from the addition of allyl alcohol are stable to many synthetic transformations and readily liberate the 3-exo alcohol on reductive cleavage.

During the course of model studies for the synthesis of several tetracyclic sesquiterpenes,[2] we required an efficient preparation of various 3-exo-substituted 2-*endo*-acylnorbornenes (*e.g.*, **2**). In particular we had need of a substituent at C-3 which could be readily converted to an hydroxyl group but which would also survive further intended synthetic transformations. To this end we have investigated the reaction of cyclopentadiene with trans-β-substituted α,β-unsaturated carbonyl compounds and the addition of nucleophiles to 2-acylnorbornadienes. We have also determined that allyl ethers are effective as masked alcohols, thus satisfying our final criterion.

The results of the Diels–Alder reaction between trans-β-substituted α,β-unsaturated carbonyl compounds (**1**) and cyclopentadiene are summarized in Table I. As expected for an uncatalyzed reaction, the product with an endo acyl group was always predominant, the isomer ratios ranging from 2.6:1 to 5.6:1.[3-6] Predictably the addition of catalytic amounts of cupric[7] and stannic[8] salts led to significant increases in both the rate and stereoselectivity of the Diels–Alder reaction.[9] The rather low yields (not optimized) are apparently due to extensive polymerization of the diene and resultant difficulties in the isolation procedure. However, the high specificity of the reaction makes the catalyzed procedure preferable when isomerically pure adducts are desired.



1 2 3

a, R = H; X = $OCOCH_3$
b, R = H; X = $OCOC_6H_5$
c, R = CH_3; X = $OCOCH_3$
d, R = i-C_3H_7; X = $OCOCH_3$
e, R = OH; X = Cl
f, R = CH_3; X = OCH_3

Table I
Reaction of Cyclopentadiene with Several Acrylic Dienophiles (1)

Dienophile	Catalyst	Yield, %[a]	[2]:[3][b]
1a[c]		75	2.6:1
1b[c]		50	3:1
1c[d]		58	2.6:1
1d		67	3.5:1
1d	$SnCl_4$[e]	47	>15:1
1e[f]		87	5.6:1
1f		0	
1f	$Cu(BF_4)_2$[g]	11	>15:1
1f	$SnCl_4$	51	15:1

[a] Isolated yields, not optimized. [b] Reference 5. [c] Reference 20. [d] Reference 21. [e] Reference 9. [f] Reference 22. [g] Reference 8.

Although the acyl esters **2a–d** were thus available in quantity, they did not prove to be synthetically useful, since treatment with most basic reagents led to significant decomposition of starting material.[10] A more generally useful procedure was found to be the conjugate addition of nucleophiles to 2-acylnorbornadienes (**5**). For instance,