temperature and Freon solvent are apparently also important factors in the selectivity. The facility of the reactions is enhanced by the fact that the color of the diazo compound is dissipated during fluorination, and the color change serves as an internal visual indicator for the reaction endpoint.

The selectivity and safety of fluorination with dilute elemental fluorine in Freon solution at low temperature have inspired increased research into this simple fluorination procedure.[13,14] Although Freon is nonpolar and relatively inert, its role in enhancing fluorination selectivity in unclear. Further studies on the synthetic and mechanistic aspects of the fluorination of diazo compounds are in progress in our laboratory.

Experimental Section

General Procedures. Temperature readings are uncorrected. ^{19}F NMR spectra were recorded in $CDCl_3$ solution with internal $CFCl_3$ (ϕ 0.0) on a JEOL FX-90Q spectrometer at 84.6 MHz. Fluorine gas (10%) diluted with nitrogen was purchased from Matheson Gas Company. *Although dilute fluorine gas is much safer than the concentrated gas, the gas cylinder was stored behind a blockade, and all reactions were performed behind a shield in a well-ventilated hood.*

Diazo Compounds. Diphenyldiazomethane,[15] 9-diazofluorene,[15] 9-diazoanthrone,[16] diethyl diazomalonate,[19] diazodeoxybenzoin,[18] diazocyclohexanone,[19] and 2-diazodimedone[15] were prepared by known literature procedures.

Fluorination Procedure. The reaction between diphenyldiazomethane and dilute fluorine exemplifies all of the reactions and is described here as a general procedure. Diphenyldiazomethane (2.0 g, 0.01 mol) in 75 mL of $CFCl_3$ contained in a 100-mL round-bottomed flask cooled to −70 °C in dry ice–acetone was treated with dilute fluorine (10%) delivered from the tank through $^1/_8$ in. copper tubing. The rapidly stirred solution was treated with dilute fluorine at a rate of about six bubbles per second. The mixture became colorless after about 15 min. Pure nitrogen was used to purge the residual fluorine, and the Freon was removed on a rotary evaporator to yield a light yellow oil. Column chromatography on a 20-cm pressurized silica gel column (Silica Gel 60 TLC) with 9:1 hexane–chloroform eluant gave 1.45 g (71%) of pure difluorodiphenylmethane as a colorless liquid: ^1H NMR ($CDCl_3$) δ 7.2 m, aromatic), 7.5 (m, aromatic). Anal. Calcd for $C_{13}H_{10}F_2$: C, 76.47; H, 4.90; F, 18.63. Found: C, 76.60; H, 5.2; F, 18.41.

9,9-Difluorofluorene: mp 37–43 °C; ^1H NMR δ 7.4 (m, aromatic). Anal. Calcd for $C_{13}H_8F_2$: C, 77.23; H, 3.96; F, 18.81. Found: C, 77.02; H, 4.11; F, 19.60.

Diethyl difluoromalonate: colorless liquid; ^1H NMR δ 1.3 (t, CH_3), 4.4 (q, CH_2). Anal. Calcd for $C_7H_{10}O_4F_2$: C, 42.86; H, 5.10; F, 19.39. Found: C, 42.89, H, 5.31; F, 19.60.

Difluorodeoxybenzoin: mp 40–42 °C; ^1H NMR δ 7.2 (m, aromatic). Anal. Calcd for $C_{14}H_{10}OF_2$: C, 72.41; H, 4.31; F, 16.38. Found: C, 72.10; H, 4.53; F, 16.68.

10,10-Difluoroanthrone: mp 140–141 °C (lit.[20] mp 141–142 °C); ^1H NMR δ 7.4 (aromatic); IR 1660 cm^{-1} (C=O).

2,2-Difluorodimedone: mp 104–106 °C; ^1H NMR δ 1.2 (s, CH_3), 2.4 (s, CH_2). Anal. Calcd for $C_8H_{10}O_2F_2$: C, 54.55; H, 5.68; F, 21.59. Found: C, 54.78; H, 5.73; F, 21.91.

2,2-Difluorocyclohexanone: colorless liquid; ^1H NMR δ 2.0, 2.5 (cyclohexane), 3.5 (m, CH_2 next to CF_2); ^{19}F NMR ϕ 111 (t, CF_2); difficult to purify and heat sensitive. Anal. Calcd for $C_6H_8OF_2$: C, 53.37; H, 5.97. Found: C, 53.90; H, 5.79.

Acknowledgment. This research was supported by the Office of Research, SIUE. We thank Mr. Phil James for performing several fluorination experiments.

Registry No. 1,1′-(Diazomethylene)bisbenzene, 883-40-9; 9-diazo-9*H*-fluorene, 832-80-4; 2-diazo-5,5-dimethyl-1,3-cyclohexanedione, 1807-68-7; 10-diazo-9(10*H*)-anthracenone, 1705-82-4; diazodiphenylethanone, 3469-17-8; diethyl diazopropanedioate, 5256-74-6; 2-diazocyclohexanone, 3242-56-6; 1,1′-(difluoromethylene)bisbenzene, 360-11-2; 9,9-difluoro-9*H*-fluorene, 342-58-5; 2,2-difluoro-5,5-dimethyl-1,3-cyclohexanedione, 76185-12-1; 10,10-difluoro-9(10*H*)-anthracenone, 1735-34-8; 2,2-difluoro-1,2-diphenylethanone, 365-01-5; diethyl difluoropropanedioate, 680-65-9; 2,2-difluorocyclohexanone, 29548-93-4.

(12) C. R. Patrick ("Advances in Fluorine Chemistry", M. Stacy, J. Tatlow, A. Sharpe, Eds., Vol. 2, Butterworths, London, 1961, p 1) gives $\Delta H_f(CH_2F_2)$ as −106 kcal/mol; R. Shaw, ref 7d, Chapter 4, gives ΔH_f (CH_2N_2) as +46 kcal/mol.

(13) Reviewed by R. J. Lagow and J. L. Margrave, *Prog. Inorg. Chem.*, **26**, 161 (1979).

(14) Several recent examples include: S. Rozen and M. Brand, *J. Org. Chem.*, **46**, 733 (1981); S. Rozen and C. Gal, *J. Fluorine Chem.*, **16**, 557 (1980); S. Rozen, *Tetrahedron Lett.*, 5067 (1980); I. Ruppert, *Tetrahedron Lett.*, 4893 (1980); S. Rozen and M. Brand, *Tetrahedron Lett.*, 4543 (1980); S. Rozen, C. Gal, and Y. Faust, *J. Am. Chem. Soc.*, **102**, 6860 (1980); S. Rozen, *J. Fluorine Chem.*, **16**, 19 (1980).

(15) J. B. Miller, *J. Org. Chem.*, **24**, 560 (1959).

(16) M. Regitz, *Annalen*, **676**, 101 (1964).

(17) M. Regitz and A. Liedhegener, *Chem. Ber.*, **99**, 3128 (1966).

(18) J. B. Hendrickson and A. Wolf, *J. Org. Chem.*, **33**, 3610 (1968).

(19) M. Rosenberger, P. Yates, J. Hendrickson, and P. Wolf, *Tetrahedron Lett.*, 2285 (1964).

(20) D. Applequist and R. Searle, *J. Org. Chem.*, **29**, 987 (1964).

1-Bromobenzocyclobutene: A Convenient Entry into the Benzocyclobutene Ring System[1]

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The thermally induced benzocyclobutene–*o*-quinodimethane interconversion has been exploited recently for the construction of complex polycyclic compounds.[2] The synthetic design involves interception of a nascent *o*-quinodimethane by a remote multiple bond in an intramolecular Diels–Alder reaction. The requisite starting material for such a process is a benzocyclobutene appropriately elaborated at the 1-position. Conventional approaches to the benzocyclobutene ring system center around cyclization of exotically substituted acyclic precursors or cycloaddition of benzyne to an olefinic moiety.[3] We describe here a novel, direct route to 1-bromobenzocyclobutene[4] (**1**), a material which may be converted in good yield to 1-substituted benzocyclobutenes of varied functionality.

1-Bromobenzocyclobutene is formed in isolated yields of 18–45% when cycloheptatriene (3 equiv) is allowed to react with bromoform, potassium carbonate, and 18-crown-6 at 140 °C—conditions favoring the formation of dibromocarbene[5] (eq 1). In accord with the literature, starting material is recovered unchanged at lower reaction temperatures or in the absence of the crown ether. Compound **1** is accompanied in the crude reaction mixture by dibromide **2**, several minor unidentified components, and substantial quantities of intractable material. Three additional side products were detected by GC analysis when the higher boiling bromoform was used as the reaction medium (vide infra).

(1) Presented in part at the 12th Central Regional Meeting of the American Chemical Society, Pittsburgh, PA, Nov 12–14, 1980.

(2) For a timely review, see Oppolzer, W. *Synthesis* **1978**, 793.

(3) Synthetic entries to the benzocyclobutene ring system have been reviewed: Thummel, R. P. *Acc. Chem. Res.* **1980**, *13*, 70. Klundt, I. L. *Chem. Rev.* **1970**, *70*, 471.

(4) (a) Cava, M. P.; Napier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2255. (b) Horner, L.; Kirmse, W.; Muth, K. *Chem. Ber.* **1958**, *91*, 430.

(5) Fedorynski, M.; Wojciechowski, K.; Matacz, M.; Makosza, M. *J. Org. Chem.* **1978**, *43*, 4682.

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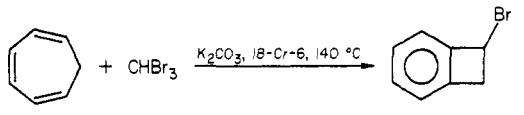
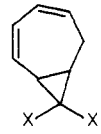


1

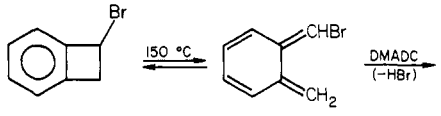
$PhCH_2CHBr_2$ (1)

2



3a, X = Br
b, X = Cl

Efforts to bolster the yield of 1 have been frustrated by the intrinsic inefficiency of dibromocarbene addition to cycloheptatriene and by the evanescence of 1 under the reaction conditions. Although a significant amount of bromoform remains unreacted,[6] maximum yields of 1 were realized within 9–10 h, whereupon its concentration began to diminish steadily. Ironically, the high temperature which is required to effect the initial dibromocyclopropanation serves simultaneously to destroy the product; a control experiment indicated that 1 was completely consumed after 20 h in boiling bromoform. The volatile products of this decomposition, as yet uncharacterized, appear to be identical, by VPC analysis, with the byproducts of the synthesis of 1. When the thermolysis was carried out in the presence of dimethyl acetylenedicarboxylate, the formation of these decomposition products was dramatically inhibited. Formed in their place was diester 4, suggesting that the destruction of 1 occurs, at least in part, by way of *o*-quinodimethane 5 (eq 2).



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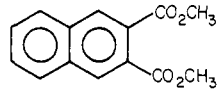
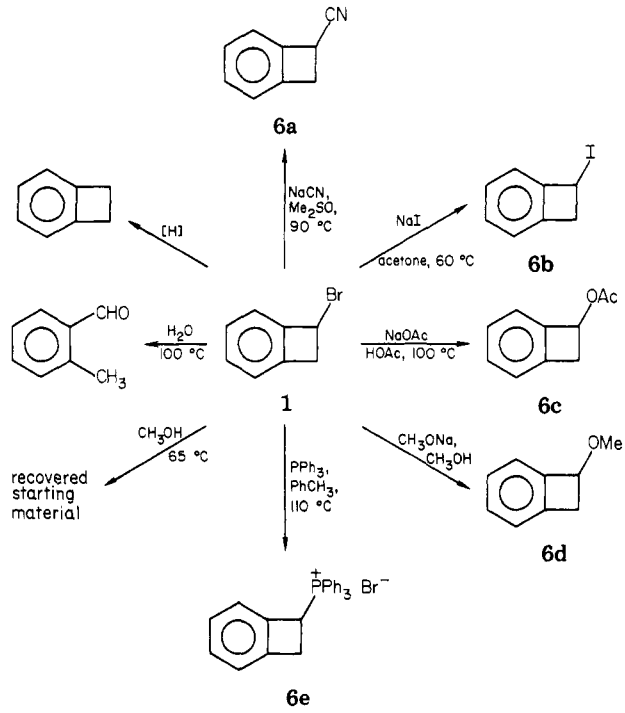


(2)

4

Formation of 1 directly from cycloheptatriene warrants further comment. The likely intermediate in this process is the dibromocyclopropane **3a**.[7] Indeed, **3a**, prepared independently by the standard procedure, afforded 1 and 2 in the ratio of 3:1, essentially the same proportions as above, upon rearrangement in refluxing toluene. Experimental difficulties in obtaining pure **3a** rendered the two-step approach vastly inferior to the one-pot method. Precedent for the structural reorganization of **3a** is found in the thermal behavior of **3b**. ter-Borg and Bickel[8] reported that rearrangement of **3b** in ethylbenzene produced the chloro analogues of 1 and 2, although in this case the benzocyclobutene was the minor product. The pathway proposed by these authors for the formation of 1-chlorobenzocyclobutene, namely, solvolytic opening of the halocyclopropane ring, electrocyclic ring closure, and aromatization with loss of hydrogen halide, adequately accounts for the formation of 1 in the current example.

Scheme I



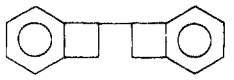
The ease of preparation of 1 prompted a brief investigation of its utility as an electrophile in the benzocyclobutene series. Previous reports of the chemistry of 1 are fragmentary at best.[4,9] We report here that 1 serves as a convenient precursor to substituted benzocyclobutenes of diverse functionality. The results are summarized in Scheme I.

Although 1 is a secondary benzylic halide, we suspected that its reactivity might be diminished as a consequence of the strained four-membered ring. We were pleased to discover that prototype S_N2 reactions of 1 proceeded smoothly and efficiently. For example, the synthetically useful nitrile **6a** was prepared by displacement with cyanide ion by the published procedure.[9a] Treatment of 1 with iodide in refluxing acetone afforded the previously unreported iodide **6b**. The known acetate **6c**[10] and methyl ether **6d**[11] were prepared by standard methods. There was no evidence of benzocyclobutadiene formation in the latter reaction, although *t*-BuOK is known to effect dehydrohalogenation of 1.[4a] Further transformations of **6a** and **6c** have been described elsewhere.[3]

In contrast, 1 reacts slowly with triphenylphosphine, even at 110 °C, to yield phosphonium salt **6e**, and fails to react under solvolytic conditions (anhydrous methanol, 65 °C). Care must be taken to exclude moisture from these reactions because at elevated temperatures 1 was found to undergo hydrolysis, with skeletal reorganization, to *o*-tolualdehyde. Presumably the initial hydrolysis product is benzocyclobutenol, which is known to rearrange to tolualdehyde under mild conditions,[12] but the possibility of ring opening and hydrolysis of vinyl bromide 5 has not been explicitly excluded.

(6) Ca. 70–80% of the bromoform has been consumed when the reaction is terminated.
(7) Van Vuuren, P. J.; Fletterick, R. J.; Meinwald, J.; Hughes, R. E. *J. Am. Chem. Soc.* **1971**, *93*, 4394.
(8) ter-Borg, A. P.; Bickel, A. F. *Recl. Trav. Chim. Pays-Bas* **1961** *80*, 1217.
(9) (a) Cava, M. P.; Little, R. L.; Napier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2257. (b) Horner, L.; Subramaniam, P. V. *Tetrahedron Lett.* **1965**, 101. (c) Skorcz, J. A.; Kaminski, F. E. *J. Med. Chem.* **1965**, *8*, 732. (d) Sanders, A.; Bauch, T.; Magatti, C. V.; Lorenc, C.; Giering, W. P. *J. Organomet. Chem.* **1976**, *107*, 359 (e) Bubb, W. A.; Sternhell, S. *Aust. J. Chem.* **1976**, *29*, 1685.
(10) Wasserman, H. H.; Solodar, J. *J. Am. Chem. Soc.* **1965**, *87*, 4002.
(11) DeCamp, M. R. Ph.D. Thesis, Princeton University, 1972.
(12) (a) Cava, M. P.; Muth, K. *J. Am. Chem. Soc.* **1960**, *82*, 652. (b) Arnold, B. J.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1972**, 30.

Reduction of 1 to the parent hydrocarbon could be effected by either Bu_3SnH or Bu_3SnCl–$LiAlH_4$.[13] This constitutes an efficient two-step synthesis of benzocyclobutene which compares favorably with other published methods.[14] Other transformations of 1 were less productive. NaN_3 (ethanol, 80 °C) converted 1 to a complex mixture of benzocyclobutenes which included the azide; the presence of the azide in the crude reaction mixture was confirmed by reduction to 1-aminobenzocyclobutene[9e] with $LiAlH_4$. Carbonation of the Grignard reagent derived from 1 afforded benzocyclobutenecarboxylic acid in low yield.[15] The principal neutral product, isolated as a pair of diastereomers, was tentatively identified as dimer 7. The



7

coupling reaction is not uncharacteristic of benzylic halides. Substance 7 was also obtained as the only detectable hydrocarbon product upon attempted alkylation of 1 with either CH_3MgBr or $(CH_3)_2CuLi$. Thus, although its reactivity is reduced somewhat relative to unstrained benzylic bromides, we expect 1 to enjoy renewed synthetic popularity, especially as it is now readily available via a one-pot reaction.

Experimental Section[16]

1-Bromobenzocyclobutene (1). A 250-mL flask, equipped with condenser, drying tower, and efficient magnetic stirrer, was charged with cycloheptatriene (freshly distilled, 27.6 g, 300 mmol), bromoform (freshly distilled, 25.3 g, 100 mmol), anhydrous K_2CO_3 (15.0 g, 109 mmol), and 18-crown-6 (0.75 g). The reaction vessel was immersed in an oil bath preheated to 145 °C. Progress of the reaction was monitored by regular VPC analysis. After ca. 10 h the reaction mixture was cooled, diluted with an equal volume of acetone, and treated with 10 g of silica gel. The insoluble solid residue was separated by suction filtration and the filter cake was washed with acetone until the washings were colorless. The liquid phases were combined and concentrated (rotary evaporator), and the residual cycloheptatriene was recovered by distillation at reduced pressure. The viscous, dark brown residue was added dropwise with stirring to 150 mL of hot petroleum ether (30–60). After filtration to remove precipitated solids, the solution was concentrated (rotary evaporator) and distilled in vacuo through a 15-cm Vigreaux column to afford 1 of >90% purity, contaminated only by 2. Pure 1 (4.78 g, 26%; 33% based on recovered bromoform) was obtained as a faintly yellow liquid by redistillation, bp 48–51 °C (0.75 mm) [lit.[4b] 55–59 °C (1 mm)]. It was stored at −15 °C until use.

1-Iodobenzocyclobutene (6b). A solution of 1 (1.83 g, 10.0 mmol) and NaI (4.5 g, 3 equiv) in 20 mL of acetone was heated at reflux for 12 h. The crude reaction mixture was concentrated and partitioned between water and ether. The organic layer was separated, washed with water and brine, and dried ($MgSO_4$). Solvent removal afforded the crude iodide as a nondistillable red liquid (2.05 g, 89% yield) free of NMR detectable impurities. The analytical sample was obtained by preparative TLC (hexane, R_f 0.45–0.65): ^1H NMR ($CDCl_3$) δ 3.6 (dd, J = 15 Hz, J' = 2 Hz, 1.0 H), 4.1 (dd, J = 15 Hz, J' = 4 Hz, 1.0 H), 5.7 (q, J = 4 Hz, J' = 2 Hz, 1.0 H), 7.1–7.6 (m, 4.0 H); mass spectrum, m/e (relative intensity) 230 (M^+, 2), 188 (3), 127 (4), 103 (M − I, 100), 91 (5), 63 (4), 51 (10).

Phosphonium Salt (6e). A mixture of 1 (1.83 g, 10.0 mmol) and triphenylphosphine (5.4 g, 2 equiv) was maintained at 110 °C in 10 mL of toluene for 48 h. The finely divided white solid which precipitated was collected and dried in vacuo (2.06 g, 46% yield), mp 218–222 °C dec, unchanged by recrystallization: ^1H NMR ($CDCl_3$) δ 3.0–3.6 (m, 2 H), 4.4–5.0 (m, 1 H), 7.0–8.5 (aromatics, 19 H). Anal. Calcd for $C_{26}H_{22}BrP$: C, 70.12; H, 4.98. Found: C, 70.16; H, 5.18.

Acknowledgment. Partial support of this work by the Horace H. Rackham School of Graduate Studies of the University of Michigan is gratefully acknowledged. We thank Mr. Vittorio J. Bruni for the preparation of **3a**.

Registry No. 1, 21120-91-2; **6b**, 78329-06-3; **6c**, 78329-07-4; 7 (isomer 1), 78329-08-5; 7 (isomer 2), 78329-09-6; cycloheptatriene, 544-25-2; bromoform, 75-25-2; benzocyclobutene, 694-87-1.

(13) Sanders, A.; Giering, W. P. *J. Org. Chem.* **1973**, *38*, 3005.
(14) Brewer, P. D.; Tagat J.; Hergrueter, C. A.; Helquist, P. *Tetrahedron Lett.* **1977**, 4573 and references therein.
(15) Horner et al.[3b] report isolation of the acid in 53% yield.
(16) Melting points are uncorrected. Routine NMR spectra were recorded on a Varian T-60 spectrometer in $CDCl_3$ solution with Me_4Si as an internal standard. Mass spectra were obtained with a Finnegan 4023 GC–MS instrument. Gas chromatography was performed on a Varian Aerograph 1720-5 gas chromatograph employing a 6 ft × $^1/_4$ in. 5% SF-96 column at 175 °C with He as the carrier gas.

Synthesis of *trans*-2,5-Dimethylpyrrolidine by Intramolecular Amidomercuration

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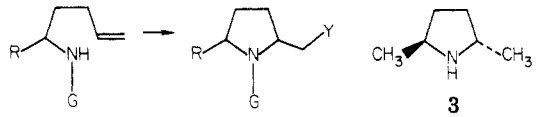
As part of another synthetic project, we became interested in the stereoselectivity of the electrophile-initiated cyclization of δ-alkenyl amine derivatives (1 → 2). In the



1 2 3

course of examining this question, we have developed an efficient, highly stereoselective synthesis of *trans*-2,5-dimethylpyrrolidine (3), a structure which has proven to be of interest as an easily resolved chiral amine containing a C_2 axis of symmetry.[1,3] The procedure described herein should also be applicable to the synthesis of other *trans*-dialkylpyrrolidines.[5,6]

The synthesis of 3 is outlined in Scheme I. The known conversion of the commercially available ketone 4 into oxime 5 proceeds in 88–97% yield.[4] Reduction of the oxime with lithium aluminum hydride and direct acylation of the crude product gave the amide derivatives 6 in 95–99% yields. Treatment with mercuric acetate in tetrahydrofuran followed by reduction with sodium borohydride gave the cyclization product 7 in yields of 90–98%. Careful examination of the product 7a by ^1H and ^{13}C NMR (XL-200) shows only trace signals for the cis isomer.[7]

(1) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1977**, *42*, 1663. Amine 3 was prepared through a procedure developed by P. Dervan[2] utilizing 2,5-hexanediol as starting material.
(2) Dervan, P. B.; Uyehara, T. *J. Am. Chem. Soc.* **1976**, *98*, 2003–2005.
(3) A mixture of *cis*- and *trans*-2,5-dimethylpyrrolidine is commercially available, but this mixture is not easily separated.[4]
(4) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863–869.
(5) For another highly stereoselective approach to *trans*-2,5-dialkylpyrrolidines, see Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193–94.
(6) *trans*-2,5-Dialkylpyrrolidines are characteristic components of the poison gland products of a variety of ant species: Pedder, D. J.; Fales, H. M.; Jaouni, T.; Blum, M; MacConnel, J.; Crew, R. M. *Tetrahedron* **1976**, 2275–2279; Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron Lett.* **1979**, 1031–1034; Jones, T. H.; Frank, J. B.; Blum, M. S.; Fales, H. M. *Tetrahedron Lett.* **1980**, 789–792 and references cited therein.
(7) The proportion of cis isomer is estimated to be approximately 2% by comparison with a sample containing added cis isomer. Authentic 7a was prepared by acetylation of a sample of 3 kindly provided by J. Whitesell.[1] A mixture of 7a and the corresponding cis acetamide was prepared by acetylation of the commercially available mixture of *cis*- and *trans*-2,5-dimethylpyrrolidine.[3]

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