Reaction of 18 under alkoxycarbonylation conditions[9,26] involved a mixture of $PdCl_2(CH_3CN)_2$ (0.1 mol equiv) and $CuCl_2$ (3.0 mol equiv) in methyl alcohol under a positive pressure of CO (1.1 atm). After 3.3 h at 25 °C, the crude product was obtained and chromatographed to provide a mixture of **21a** and **21b** (70% yield). Analytical HPLC indicated a ratio of **21a/21b** = 3:1. The major component (**21a**, trans) was obtained by crystallization as orange needles, mp 134–136 °C. The minor product (**21b**, cis) was also obtained by crystallization from the mother liquor, mp 144–148.5 °C and the isomers were identified by NMR spectral analysis.[27] Treatment of the phenol ethers with BBr_3 causes demethylation to the phenol for both **21a** and **21b** and complete isomerization of the cis arrangement in **21b** into the natural trans series, **22** (84% yield of **22**). The ester **22** has been converted to (±)-deoxyfrenolicin (**1c**) and correlated with a sample of (+)-frenolicin derived from nature.[9a]

Reaction of **20** under the same alkoxycarbonylation conditions (25 °C/6 h) produced pyrano ester isomers **23a** and **23b** in 89% yield and a ratio of trans/cis = 3:2. The major isomer (**23a**) was isolated by crystallization from hexane–ethyl acetate, mp 132.5–135 °C. The minor isomer (**23b**) was crystallized from the mother liquor, mp 144.5–145 °C; it can be equilibrated with **23a** in sulfuric acid.[4] The phenol methyl ether is cleaved with $AlCl_3$ and the methyl ester is hydrolyzed with dilute aqueous base to give nanaomycin A (**1a**).[4a,b] A formal synthesis of **1a** is completed.

Acknowledgment. We acknowledge support for this work from the National Institutes of Health, through Research Grant AI-15916 and a postdoctoral fellowship to E. Spiess.

(25) Characterization data for **19**: mp 126–127 °C; ^1H NMR ($CDCl_3$) δ 7.65 (d, 1 H, J = 9.0 Hz), 7.38 (t, 1 H, J = 9.0 Hz), 7.08 (d, 1 H, J = 9.0 Hz), 6.0–5.4 (m, 1 H), 5.0–4.85 (m, 2 H), 4.4–4.0 (m, 4 H), 3.88 (s, 3 H), 3.55 (d, J = 9.0 Hz), overlapping with 3.4–2.25 (m, 4.3 H together), 2.25 (s, 3 H); IR ($CHCl_3$) 3080 (w), 3000 (m), 2900 (m), 2840 (w), 1710 (s), 1690 (s), 1640 (w), 1585 (s), 1470 (s), 1440 (m), 1290 (s) cm^{-1}. Anal. C, H. Characterization of **20**: mp 76–78 °C; ^1H NMR ($CDCl_3$) δ 7.63–7.4 (m, 2 H), 7.13 (dd, 1 H, J = 8.5, 2.5 Hz), 6.0–5.58 (m, 1 H), 5.2–4.65 (m, 3 H), including apparent dq at δ 4.78 (1 H, J = 11, 7 Hz). Irradiation at δ 1.50 gives δ 4.8 (d, 1 H, J = 1 Hz), 3.92 (s, 3 H), 3.63 (d, 1 H, J = 11 Hz; collapses to s with irradiation at δ 4.7), 3.36 (dt, 2 H, J = 6, 1.5 Hz), 1.51 (d, 3 H, J = 7.0 Hz); IR ($CHCl_3$) 3500 (br), 3080 (w), 3000 (m), 2930 (s),2840 (w), 1650 (s), 1630 (s), 1570 (s) cm^{-1}. Anal. C, H.

(26) For discussion of this general reaction, see: (a) Stille, J. K.; Hines, L. F.; Fries, R. W.; Wong, P. K.; James, D. E.; Lau, K. *Adv. Chem. Ser.* **1974**, *No. 132*, 90. (b) Collman, J. P.; Hegedus, L. S. "Principles and Applications of Organotransition Metal Chemistry"; University Science Books: Mill Valley, CA, 1980, pp 585, 604. (c) James, D. E.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810. The problems assocatied with Pd-promoted addition of nucleophiles to alkenes followed by carbonylation have been discussed recently; the same paper described examples of intramolecular addition of amine nucleophiles with CO trapping which are efficient in a limited number of examples: Hegedus, L. S.; Allen, G.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583.

(27) The stereochemistry of each isomer (**21a, 21b**) was determined by analogy with the eleutherin–isoleutherin system: Cameron, D. W.; Kingston, D. G. I.; Sheppard, N.; Lord Todd *J. Chem. Soc.* **1964**, 98. The pseudochair arrangement with the C-11 alkyl group equatorial is preferred. In the ^1H NMR spectra, the homoallylic (homobenzylic) coupling between H at C-12 and H at C-9 is greater when the C-9 H is pseudo-axial (eleutherin, C-9 shows J = 3.5 and 2.9 Hz for coupling to the $H_{a'}$ and $H_{e'}$ at C-12). The CH_2 unit at C-12 in **21b** gave rise to two ddd patterns at δ 2.84 (pseudoequatorial H with J = 18, 2.6, 2.6 Hz) and δ 2.21 (pseudo-axial H with J = 18, 10.4, and 3.9 Hs). The homoallylic coupling constants are therefore 3.9 Hz (C-9 axial/C-12 axial) and 2.6 Hz (C-9 ax/C-12 eq), consistent with a cis-pyran configuration.

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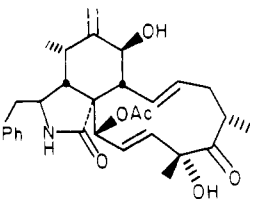
Model Study for Synthesis of the Cytochalasin D Cycloundecanone Ring System

Summary: Thiocarbonyl Diels–Alder additions are used to assemble **6** and **12**, precursors of sulfur-bridged cycloundecenones **3a,b**, via ylide rearrangement. Either **6** or **12** is converted into allylic iodides upon reaction with Me_3SiI, and internal S-alkylation followed by a 2,3-shift gives the desired **3**. A novel method for α-sulfur bond cleavage in ketone **3b** or **3i** with $PhMe_2SiLi$ described. Complete desulfurization of **3** with Raney Ni affords 5-acetoxycycloundecanone (**17**).

Sir: Cytochalasin D is an important tool for probing aspects of cell membrane function.[1] The molecule contains an 11-membered carbocycle in addition to an isoindolone unit, derivatives of which we have recently synthesized.[2] Cycloundecanes are found in other natural products, but the cytochalasin carbocycle is unique in its complexity and poses a major challenge.[3] Our plans for cycloundecanone construction include ring expansion methods, one of which is described here.

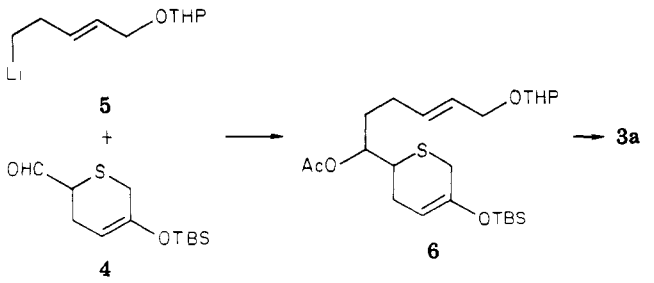


cytochalasin D

Earlier work in our laboratory has shown that sulfur-bridged lactones of 10 or 11 members can be made via the [2,3] sigmatropic rearrangement of bicyclic sulfonium ylides.[4] Application of this concept to carbocycle synthesis requires the preparation of a functionalized thian-3-one such as **1**. Ring expansion via internal S-alkylation and ylide generation would be expected to form the sulfur-bridged cycloundecanone **3**.

Two different routes to the desired ylide precursor **1** have been developed, both of which rely upon thiocarbonyl Diels–Alder additions. In the shorter route (a series, Scheme I) the adduct of the transient thioaldehyde NCCSH[5] with 2-(*tert*-butyldimethylsiloxy)-1,3-butadiene is converted into **4** by DIBAL reduction (84%). Condensation of **4** with the organolithium reagent **5** followed by

Scheme I. Route a



(1) Tanenbaum, S. W., Ed. "Frontiers of Biology"; North-Holland Publishing Co.: New York, 1980; Vol. 46.

(2) Vedejs, E.; Campbell, J. B., Jr.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534.

(3) For a previous study directed at the cyochalasin cycloundecane ring by a fragmentation approach, see: Clark, D. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1979**, *101*, 3567.

(4) Vedejs, E.; Gapinski, D. M.; Hagen, J. P. *J. Org. Chem.* **1981**, *46*, 5451.

(5) Vedejs, E.; Eberlein, T. H.; Varie, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1445.

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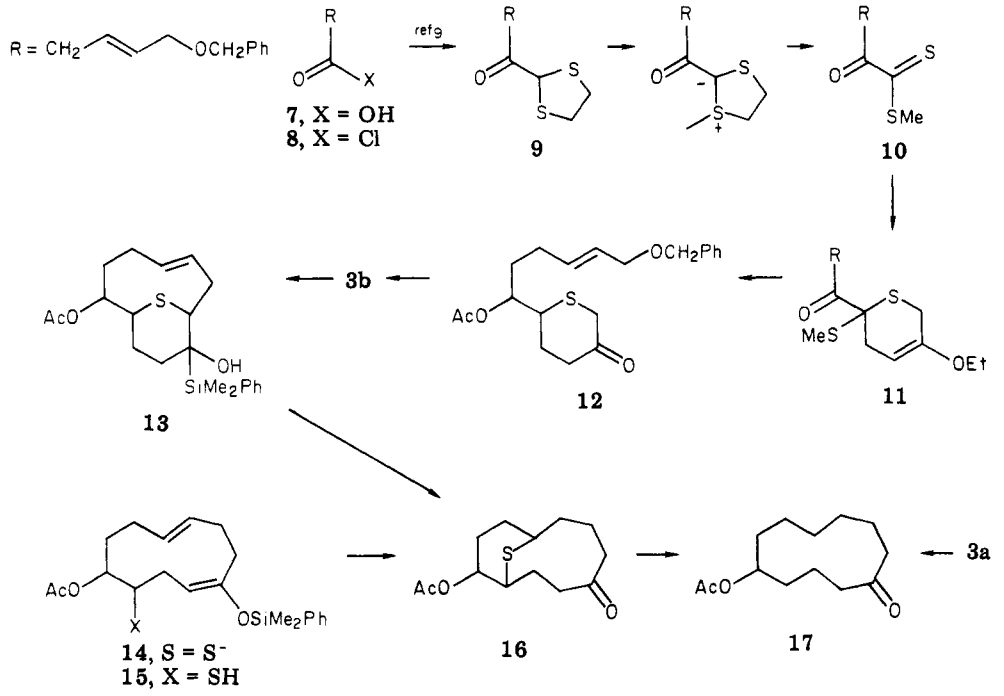
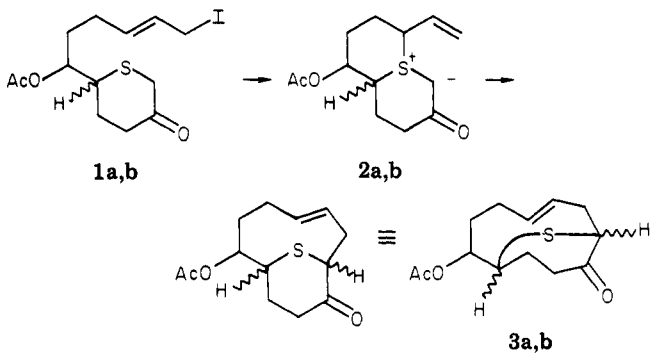
Scheme II. Route b





Steglich acylation[6] affords **6** (40%, 9:1 diastereomer mixture) together with 20% of recovered aldehyde **4**. Generation of **5** is difficult at best, and useful results have only been achieved by reaction of *tert*-butyllithium with the precursor bromide at −78 °C.

Stepwise conversion of **6** (major diastereomer) into **1a** is possible by enol ether hydrolysis and treatment with $(CH_3)_3SiCl/NaI$.[7] However, the same net result can be achieved simply by reacting **6** with 3 equiv of $(CH_3)_3SiCl/NaI$ in acetonitrile. Heating the allylic iodide from this reaction with K_2CO_3 in acetonitrile affords **3a** as a mixture of separable diastereomers (60–70%, 4:1 ratio).[8] Both products have characteristic NMR signals for a *trans*-thiacyclonon-4-ene and must differ in bridgehead stereochemistry.

Attempts to perform the capricious addition of organolithium reagent **5** to **4** on larger than a 1.0-mmol scale have been unsatisfactory. We therefore examined an alternative route to **1** which has some advantages on scaleup (the b series, Scheme II). Conversion of acid chloride **8** into 2-acyl-1,3-dithiolane (**9**) followed by ylide generation and cycloreversion affords the α-oxo dithioester **10** as a transient species.[9] In the presence of 2-ethoxybutadiene, a Diels–Alder adduct, **11**, is obtained in 64% yield. After dethiomethylation ($CH_3C_6H_4S^-Na^+$/DMF), stereospecific reduction with $LiBH(sec\text{-}Bu)_3$, Steglich acylation, and enol ether hydrolysis (HCl–THF–H_2O), the thian-3-one **12** is obtained as a single diastereomer. Conversion to **1b** is possible with $(CH_3)_3SiI$ (50% isolated after chromatography),[10] and treatment with K_2CO_3 in CH_3CN affords **3b** (45%). Once again, two separable trans olefin products are formed in a 4:1 ratio,[11] but neither **3b** diastereomer is identical with the sulfur-bridge cycloundecenones from the "a" route. Intermediates and final products in the two series must therefore differ in relative stereochemistry between the adjacent acetate and sulfur-bearing carbons.

Initial attempts to convert the two sets of diastereomeric products **3a** and **3b** into a single common derivative for structure verification focused on a novel method for reductive elimination of sulfur α to carbonyl. Treatment of the major **3b** diastereomer with $LiSi(CH_3)_2C_6H_5$[12] at −78 °C followed by careful neutralization affords a silyl carbinol, **13** (88%). We hoped that base-initiated C to O silyl migration with concomitant expulsion of mercaptide anion[13] would afford **14** and after neutralization the mercaptan **15**. Desulfurization of **15** by using tri-*n*-butyltin hydride or other methods might then afford 8-acetoxycycloundec-4-en-1-one, an ideal structure for comparing the **3a** and **3b** series of ring-expansion products.

In fact, treatment of **13** with KH followed by silyl ether hydrolysis does give a product of α-sulfur bond cleavage.

(6) Höfle, G.; Vorbrüggen, H.; Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.

(7) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

(8) Characterization of **3a** (major diastereomer): mp 101–104 °C; IR 1730, 1705 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 5.89 (1 H, ddd, J = 15.7, 11.5, 5.0 Hz), 4.93 (1 H, dd, J = 11.5, 6.5 Hz), 3.70 (1 H, d, J = 6.3 Hz), 2.80 (3 H, m), 2.6–2.1 (6 H, m), 2.04 (3 H, s), 1.92 (1 H, ddd, J = 12.5, 12.5, 6.3 Hz), 1.65 (1 H, ddd, J = 13.9, 4.0, 3.8 Hz); mass spectrum, m/e 254.0976 (calcd for $C_{13}H_{18}O_3S$ 254.0978).

(9) Vedejs, E.; Arnost, M. J.; Dolphin, J. M.; Eustache, J. *J. Org. Chem.* **1980**, *45*, 2601.

(10) This reaction has proved more difficult than conversion of the allylic tetrahydropyranyl ether into an allylic iodide used in the "a" series. Freshly distilled $(CH_3)_3SiI$ at 0 °C in CH_2Cl_2 gives the best results.

(11) Characterization of **3b** (major diastereomer): mp, 92–93 °C; IR 1735, 1705 cm^{-1}; 270-MHz NMR ($CDCl_3$) δ 5.81 (1 H, ddd, J = 16.1, 10.7, 2.9), 5.04 (2 H, m), 3.61 (1 H, dd, J = 5.5, 1.8 Hz), 3.28 (1 H, dd, J = 12.1, 4.0 Hz), 3.13 (1 H, ddd, J = 18.0, 12.5, 7.3 Hz), 2.65 (1 H, br d, J = 14 Hz), 2.49 (1 H, m), 2.3–1.6 (7 H, m), 2.05 (3 H, s); mass spectrum, m/e 254.0974 (calcd for $C_{13}C_{18}O_3S$ 254.0978).

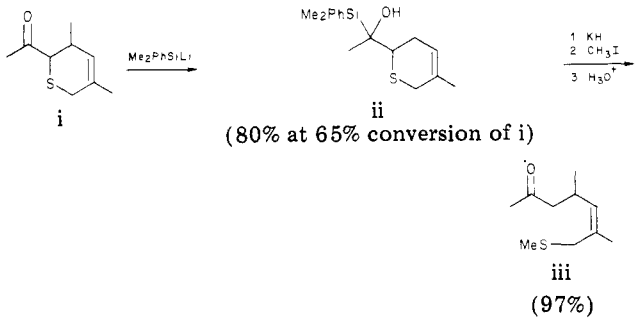
(12) George, M. V.; Peterson, D. J.; Gilman, H. *J. Am. Chem. Soc.* **1960**, *82*, 403.

However, the free mercaptan is unstable and cylizes spontaneously to form a sulfide lacking vinyl protons in the NMR spectrum, tentatively identified as **16**. The same overall result is achieved more efficiently by reaction of **13** with CsF/DME (89% yield of **16** after chromatography). In view of the instability of mercaptan **15**, correlation of the a and b series was performed by using Raney nickel desulfurization. Thus, treatment of either **3a** or of **16** with W-2 Raney nickel affords 5-acetoxycycloundecanone **17**[14] as the sole product. This experiment confirms the formation of a carbocyclic periphery in both a and b series ring expansions.

Work is continuing to evaluate this route to cycloundecenones in cytochalasin synthesis.

Registry No. 3a, 83076-86-2; **4**, 83076-81-7; (*E*)-**5**, 83076-82-8; **6** (isomer 1), 83076-83-9; **6** (isomer 2), 83148-35-0; **6** iodide (isomer 1), 83076-84-0; **6** iodide (isomer 2), 83076-85-1; (*E*)-**8**, 83095-35-6; (*E*)-**9**, 83076-87-3; (*E*)-**10**, 83076-88-4; (*E*)-**11**, 83076-89-5; **12**, 83076-90-8; **13**, 83076-91-9; **16**, 83076-92-0; **17**, 83076-93-1; i, 83076-94-2; ii, 83076-95-3; (*Z*)-iii, 83076-96-4; cytochalasin D, 22144-77-0; 2-ethoxybutadiene, 4747-05-1; $Me_2PhSiLi$, 3839-31-4.

(13) (a) Analogous expulsion of an α leaving group initiated by C to O silyl migration: Corey, E. J.; Tius, M. A.; Jagabandhu, D. *J. Am. Chem. Soc.* **1980**, *102* 1742. Reich, H. J.; Kelly, M. J. *Ibid.* **1982**, *104*, 1119. (b) The analogous C–S cleavage of i[9] can be performed by using $Me_2PhSiLi$. In this case, treatment of silylcarbinol ii with KH followed by methyl iodide results in clean conversion to the acyclic sulfide iii. Use of Me_3SiLi in place of $Me_2PhSiLi$ is not satisfactory due to increased enolization.



i ii (80% at 65% conversion of i) iii (97%)

(14) Characterization of **17**: IR 1720, 1705 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 4.88 (1 H, m), 2.8–2.5 (2 H, m), 2.4–2.2 (2 H, m), 2.05 (3 H, s), 1.9–1.3 (14 H, m); mass spectrum, *m/e* 226.1566 (calcd for $C_{13}H_{22}O_3$ 226.1569).

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Chiral Leaving Groups in Nucleophilic Displacement Reactions. Solvolysis of 2-Octyl Camphor-10-sulfonate (Casylate) Stereoisomers

Summary: Small kinetic differences between the diastereomeric pairs in aqueous ethanolysis of the four stereoisomeric 2-octyl casylates are consistent with a crowded S_N2 transition state.

Sir: Wilson and Cram recently showed[1] that in aromatic nucleophilic substitution a chiral leaving group may provide the driving force for asymmetric synthesis. Since the steric demands should vary with the displacement mechanism, we have studied solvolytic reactivity of some model aliphatic systems undergoing k_s, k_Δ, and k_c reactions.[2] In each case, we used the readily available (+)- or (−)-camphor-10-sulfonate ester,[3] which we call casylates, as the chiral leaving group. A second chiral component (solvent or substrate) was used to provide diastereomeric transition states for comparison. Our preliminary results show reactivity differences with diastereomers of each substrate type and interesting differences among the mechanistic classes. The reactivity of the four 2-octyl casylate stereoisomers is treated in this communication.

2-Octyl substrates have long been known to follow a S_N2-like mechanism (k_s substrate)[4] in solvents of moderate nucleophilicity.[5] Multiple conductimetric rate measurements[6] of solvolytic reactions of the D- and L-2-octyl D-

Table I. Solvolysis Rates of 2-Octyl Casylates

isomer	% EtOH (v/v)	T, °C	10^4k, s^{-1}	$\Delta H^\ddagger$, kcal/mol	$\Delta S^\ddagger$, eu
D,D	80E	25.0	6.48[a]	18.7[b]	−19.8[b]
		49.4	0.673 ± 0.025		
		56.1	1.42 ± 0.04		
		64.2	2.80 ± 0.07		
		68.8	4.20 ± 0.10		
		75.0	6.59 ± 0.22		
		85.0	12.5 ± 0.91		
L,D	80E	25.0	4.76[a]	19.7[b]	−17.0[b]
		49.4	0.619 ± 0.006		
		56.1	1.21 ± 0.01		
		56.8	1.27 ± 0.06		
		70.1	4.84 ± 0.04		
		75.0	6.65 ± 0.28		
		85.0	13.3 ± 0.22		
L,L	60E	55.0	2.66[a]	20.9	−11.4
		51.0	1.80 ± 0.01		
		64.6	6.92 ± 0.05		
	80E	56.1	1.44 ± 0.03		
	90E	55.0	0.841[a]	16.2	−28.2
		54.9	0.838 ± 0.003		
		79.2	4.95 ± 0.04		
	95E	55.0	0.726 ± 0.035		
	100E	55.0	0.491 ± 0.008		
D,L	60E	55.0	2.70[a]	20.9	−11.5
		51.0	1.80 ± 0.03		
		64.6	6.91 ± 0.03		
	80E	56.1	1.14 ± 0.01		
	90E	55.0	0.553[a]	19.4	−19.0
		54.9	0.550 ± 0.002		
		79.2	4.60 ± 0.04		
	95E	55.0	0.438 ± 0.002		
	100E	55.0	0.347 ± 0.004		

[a] Extrapolated from rates at other temperatures. [b] From 22 separate kinetic runs at the six temperatures shown, r = 0.998.

(1) Wilson, J. M.; Cram. D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881–884.

(2) Harris, J. M. *Prog. Phys. Org. Chem.* **1974**, *11*, 89–173.

(3) D-(+)-Casyl chloride, mp, 66–67 °C, was prepared by the procedure of P. D. Bartlett and L. H. Knox ("Organic Syntheses"; Wiley: New York, 1973; Collect Vol. V, pp 196–198) from the optically pure acid monohydrate (Eastman or Aldrich) or was purchased from Tridom (Fluka). L-Casyl chloride, mp 66–67 °C, was prepared from the 95% optically pure ammonium salt of the L-acid (Aldrich), using the Bartlett–Knox procedure. Esters were prepared by the tosylate procedure of Schleyer (Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 1180).

(4) A variety of 2-octyl substrates have been shown to give complete inversion in a variety of solvents including ethanol and water; cf. Sukenik, C. N.; Bergman, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 6613–6623; Weiner H.; Sneen, R. A. *Ibid.* **1965**, *87*, 288–291 and references therein; also see Filippo, J. S., Jr.; Silberman, J. *Ibid.* **1981**, *103*, 5588–5590.

(5) Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1–67.

0022-3263/82/1947-4386$01.25/0