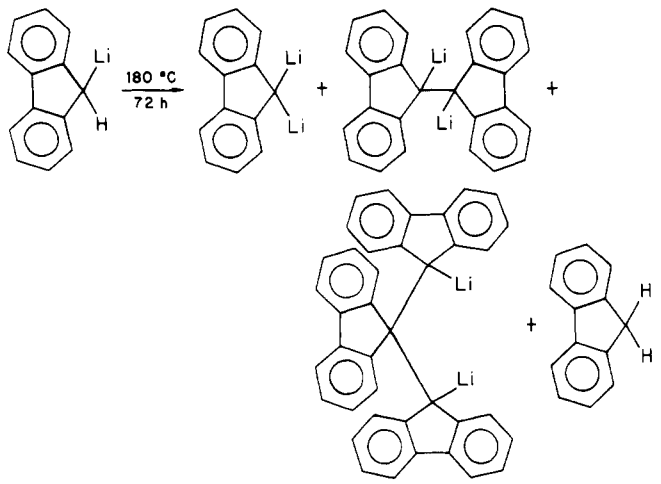

fluorene (15%), 9,9′-bifluorenyl (70%), and 9,9′:9,9″-terfluorenyl (15%) which were separated by thermal-gradient sublimation and identified by mass spectra. Hydrolysis with EtOD gave the same mixture but each compound was found to contain two deuteriums by mass spectral analysis:[6] 9,9-dideuteriofluorene [parent peak and base peak at *m/e* 168]; 9,9′-dideuterio-9,9′-bifluorenyl [parent peak at *m/e* 332 (12%), base peak at *m/e* 166]; 9,9″-dideuterio-9,9′:9,9″-terfluorenyl [parent peak at *m/e* 496 (27%), base peak at *m/e* 330]. Only signals due to phenyl protons appeared in their ^{1}H NMR spectra indicating that 9, 9′, and 9″ positions were all occupied by deuterium atoms.

The reaction of the dark brown powder with chlorotrimethylsilane in diethyl ether gave 9-(trimethylsilyl)-fluorene, 9,9′-bis(trimethylsilyl)-9,9′-bifluorenyl, and 9,9″-bis(trimethylsilyl)-9,9′:9′,9″-terfluorenyl which were identified by mass and ^{1}H NMR spectral analyses: 9-(trimethylsilyl)fluorene [mass spectrum, parent peak at *m/e* 238 (90%), base peak at *m/e* 165; ^{1}H NMR δ −0.26 (9 H), 3.68 (1 H), 7.03–7.77 (8 H)]; 9,9′-bis(trimethylsilyl)-9,9′-bifluorenyl [mass spectrum, parent peak at *m/e* 474 (7%), base peak at *m/e* 193; ^{1}H NMR δ–0.18 (18 H), 6.668–7.90 (16 H)]; 9,9″-bis(trimethylsilyl)-9,9″-terfluorenyl [mass spectrum, parent peak at *m/e* 638 (3%), base peak at *m/e* 165; ^{1}H NMR δ 0.07 (18 H), 6.90–7.90 (24 H)]. Like other *gem*-dilithium compounds,[7] 9,9-dilithiofluorene did not give 9,9-bis(trimethylsilyl)fluorene but a hydrogen is abstracted (probably from the solvent) and monotrimethylsilylation to produce 9-(trimethylsilyl)fluorene was observed.

Presently very little is known about the mechanism of the Kawa–Lagow-modified Ziegler thermal rearrangement. An unpublished study on ^{13}C-labeled methyllithium pyrolysis has indicated only that the rearrangement is intermolecular or possibly a combination of intramolecular and intermolecular with respect to methyllithium tetramers. The range of reaction products in the present study are very interesting in this regard and a labeling study which is underway may shed more light on the mechanism of this reaction.

A feature of the Schleyer–Pople[8] proposal for planar carbon is stabilization by two lithium atoms via π acceptor and α donor character. For example, in the planar cis form of dilithiomethane, the two π-electrons are delocated in a cylic arrangement, isoconjugate with the cyclopropenium ion. Currently, we are attempting to add an additional conjugated system such as phenyl or vinyl groups into *gem*-dilithium compounds so that the "homoaromatic" π system in the planar form should be more stable.

Acknowledgment. We are grateful to the National Science Foundation (CHE-8210708) for support of this work.

Registry No. Fluorene, 86-73-7; *n*-butyllithium, 109-72-8; 9-lithiofluorene, 881-04-9; 9,9-dilithiofluorene, 101248-45-7; 9,9′-dilithio-9,9′-bifluorenyl, 56833-94-4; 9,9″-dilithio-9,9′:9′,9″-terfluorenyl, 101315-86-0; 9,9′-bifluorenyl, 1530-12-7; 9,9′:9,9″-terfluorenyl, 1064-37-5; 9-(trimethylsilyl)fluorene, 7385-10-6; 9,9′-bis(trimethylsilyl)-9,9′-bifluorenyl, 76241-26-4; 9,9″-bis(trimethylsilyl)-9,9′:9′,9″-terfluorenyl, 101315-87-1.

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(6) The mass spectra of all three dideuterio compounds were identical with the reported spectra.[9]
(7) Kawa, H.; Manley, B. C.; Lagow, R. J. *J. Am. Chem. Soc.* 1985, in press.
(8) Collins, J. B.; Dill, J. D.; Jemmis, E. D.; Apeloig, Y.; Schleyer, P. v. R.; Seeger, R.; Pople, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 5419.
(9) Minabe, M.; Suzuki, K. *J. Org. Chem.* **1975**, *40*, 1298.

A Stereoselective Synthesis of the Hydronaphthalene Substructure of Kijanolide

Summary: The synthesis of a hydronaphthalene substructure of the antitumor antibiotic kijanimicin is described in which four of the seven chiral centers are introduced via a diastereoselective intramolecular Diels–Alder cyclization of an *all*-(*E*)-2,8,10,12-tetradecatetraenal.

Sir: We recently found that enals display exceptional dienophilic reactivity in Lewis acid-promoted intramolecular Diels–Alder cyclizations leading to hydronaphthalenes.[1] Such cyclizations proceed at −78 to −20 °C in a few hours with high endo selectivity. The remarkable rate enhancement and high stereoselectivity engendered by the aldehyde–Lewis acid combination suggest possible applications to the hydronaphthalene substructure of kijanolide and tetronolide, aglycones of the antitumor antibiotics kijanimicin[2a] and tetrocarin A.[2b] Accordingly, disconnection of C-2/C-3 and C-16/C-17 or C-18/C-19 of, e.g. kijanolide leads to a hydronaphthalene such as A whose assemblage could be formulated via cyclization of enal B (Figure 1).

While our preliminary work along these lines with simple 2,8,10-undecatrienals showed great promise,[1] we were concerned that the additional substituents on a more complex system such as B would raise the Diels–Alder activation energy to a point where the Lewis acid catalyst would cause decomposition of the sensitive trienyl ether moiety.[3] We were also uncertain as to the effect of the

(1) (a) Marshall, J. A.; Audia, J. E.; Grote, J. *J. Org. Chem.* **1984**, *49*, 5277. (b) Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron*, in press. (c) Marshall, J. A.; Audia, J. E.; Grote, J. *J. Org. Chem.*, in press.
(2) (a) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; McFarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1497. Mallams, A. K.; Puar, M. S.; Rossman, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3938. (b) Hirayama, N.; Kasai, M.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Tetrahedron Lett.* **1980**, *21*, 2559.

0022-3263/86/1951-1633$01.50/0

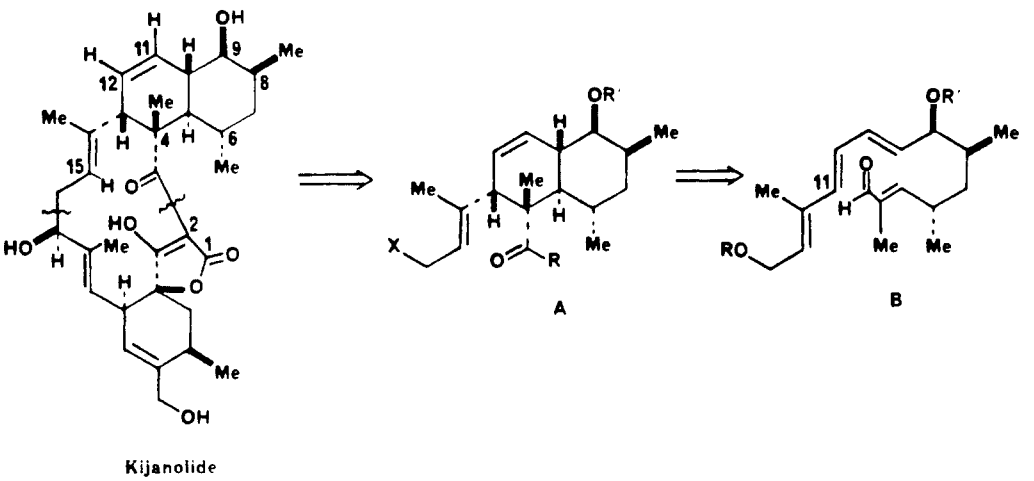


Figure 1. Proposed route to kijanolide via hydronaphthalene A.

Table I. ^{1}H NMR Comparison of Kijanolide with Bicyclic Aldehydes A16 and A17

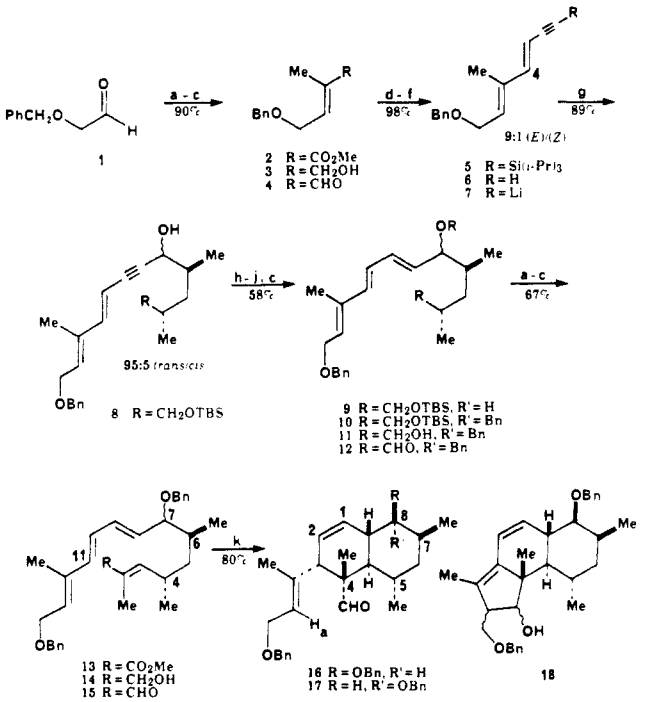
kijanolide[a]			A16 and A17				
				A16		A17	
signal[b]	δ	pattern	signal[c]	δ	pattern	δ	pattern
H-15	5.18	ddd; 9.1, 2.0, 1.0	H-a	5.52	ddd; 6.2, 1.1, 1.1	5.65	m
H-12	5.39	ddd; 10.4, 5.0, 2.5	H-2	5.42	ddd; 10.2, 4.6, 2.7	5.44	ddd; 10.0, 4.6, 2.7
H-11	6.02	ddd; 10.4, 2.0, 2.0	H-1	6.15	ddd; 10.2, 1.8, 1.8	5.52	bd, 10.0
H-9	3.11	dd; 10.5, 4.9	H-8	3.30	dd; 11.0, 5.1	3.43	br s
Me-4	1.62	s	Me-4	1.59	s	1.59	s
Me-6	0.68	d, 6.6	Me-5	0.68	d, 6.0	0.67	d, 6.6
Me-8	0.97	d, 7.0	Me-7	1.01	d, 7.1	1.00	d, 7.3

[a] Methyl ether at C-9, see ref 2a. [b] Kijanolide numbering, see Figure 1. [c] Hydronaphthalene numbering, see Chart I.

added C-11 vinyl substituent on the diastereoselectivity of the cyclization; hydronaphthalene A possesses three potentially axial substituents.

The synthesis of tetraenal B (**A15**) is detailed in Chart I. Aldehyde **A4**, prepared from α-(benzyloxy)acetaldehyde (**A1**)[4] by the sequence shown, afforded a 90:10 mixture of (*E*)- and (*Z*)-dienynes **A5** upon condensation with the TIPS-protected[5] propargylic Wittig reagent (step d).[6] The lithio derivative **A7** of the deprotected acetylene **A6** readily added to the aldehyde (step g) prepared from mono TBS-protected *trans*-2,4-dimethyl-1,5-pentanediol[7] to give a mixture of propargylic carbinol epimers **A8**. In addition to the 10% impurity derived from (4*Z*)-**A5**, alcohol **A8** contained 5% of material with syn dimethyl substituents, a consequence of an impurity in the starting 2,4-dimethylglutaric acid.[8]

Chart I. Series A Compounds[a,b]



[a] Bn = CH_2Ph, TBS = *t*-BuSiMe$_2$. [b] (a) $Ph_3P{=}C(Me)CO_2Me$, CH_2Cl_2; (b) DIBAH, Et_2O, −78 °C; (c) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2; (d) $Ph_3P{=}CHC{\equiv}CSi(i\text{-}Pr)_3$, −78 °C; (e) Bu_4NF, THF, 0–23 °C; (f) *n*-BuLi, THF, −78 °C; (g) *rel*-(2*R*,4*R*)-TBSOCH$_2$CH(Me)CH$_2$CH(Me)CHO (0.7X), THF, −40 °C; (h) Red-Al, Et_2O, 0–23 °C; (i) *n*-BuLi, HMPA, $PhCH_2Br$, THF; (j) Bu_4NF, THF, 23 °C; (k) Me_2AlCl, CH_2Cl_2, −78 to −25 °C, 4.5 h.

Reduction of propargylic alcohol **A8** with Red-Al yielded the (*E*,*E*,*E*)-trienol **A9**. Benzylation followed by desilylation and oxidation gave the aldehyde **A12** which was homologated via Horner–Emmons condensation, DIBAH

(3) Attempted Lewis acid cyclizations of 2,8,10-undecatrienoic esters possessing allylic ether substituents fail owing to extensive decomposition of the starting materials. (a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200. (b) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611. (c) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825. (d) Takeda, K.; Shingagawa, M.; Koizuma, T.; Yoshii, E. *Chem. Pharm. Bull.* **1982**, *30*, 4000. (e) Snider, B. B.; Burbaum, B. W. *J. Org. Chem.* **1983**, *48*, 4370. (f) For a recent review, see: Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. An ether substituent at C-4 appears to accelerate the cyclization. Funk, R. L; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180.

(4) Prepared via Swern oxidation[9] of β-(benzyloxy)ethanol using a nonaqueous workup to avoid hydration of the aldehyde.

(5) Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1982**, *23*, 719.

(6) Prepared from the corresponding bromide. Marshall, J. A.; Peterson, J. C.; Lebioda, L. *J. Am. Chem. Soc.* **1984**, *106*, 6006.

(7) Allinger, N. L. *J. Am. Chem. Soc.* **1959**, *81*, 232. The oxidation was effected by the method of Swern.[9]

(8) *trans*-2,4-Dimethylglutaric acid is separated from minor amounts of the cis isomer by fractional crystallization. Material of greater than 95% purity can thus be obtained. Reduction of the dimethyl ester with lithium aluminum hydride affords the diol.[7]

reduction, and Swern oxidation[9] to give the *all-(E)*-tetraenal **A15**. Our initial cyclization of this sensitive intermediate with Me_2AlCl in CH_2Cl_2 at ca.–10 to –15 °C for 28 h gave rise to a complex mixture containing two major products, dienal **A17** and the tricyclic alcohol **A18**.[10] Cyclization at –78 to –30 °C for 4.5 h, on the other hand, afforded a 1:1 mixture of the expected carbinyl epimers **A16** and **A17** in nearly 80% yield.[11,12] Pure samples could be obtained via chromatography on silica gel. Detailed ^1H NMR analysis and comparison with the spectrum of a kijanolide derivative (Table I) supports the structure assignments.[2a] The epimeric hydronaphthalenes **A16** and **A17** showed little contamination by other diastereoisomers as judged by the high-field ^1H NMR spectra. When allowances are made for impurities in enal **A15** (C-4 epimer and 10-*Z* isomer), the yield of cyclic products **A16** and **A17** approaches 90%.

Conceivably the unwanted 8α epimer **A17** could be inverted via deprotection, oxidation and reduction to the desired 8β epimer **A16**.[13] However, a more satisfactory solution would entail synthesis of an acyclic precursor (**A15**) with the correct absolute configuration at C-4, C-6, and C-7 for direct cyclization to optically active **A16**.[15] The efficient transformation of the epimers **A15** to a 1:1 mixture of **A16** and **A17** demonstrates the feasibility of this approach. Work along these lines is currently in progress.

Acknowledgment. Support for this work was provided by a research grant from the National Cancer Institute of the NIH (CA 34243). We thank the South Carolina NSF Regional NMR Center for cooperation in obtaining high-field spectra.

(9) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(10) The structure assignment is based upon high-field ^1H NMR analysis. Although the product is an apparent mixture of epimeric centers in the five-membered ring, the benzyloxy carbinyl proton is clearly axial. Thus only the equatorial benzyloxy epimer **A16** undergoes this ene-type cyclization.

(11) Typically a 0.1 M solution of enal was cooled to –78 °C, and an equimolar quantity of 1 M Me_2AlCl in hexanes was added dropwise. Our previous experience suggests that the *Z* isomer contaminant of **A15** will not cyclize under these conditions. The minor contaminants present in **A16** and **A17** are therefore most likely related to the ca. 5% cis-dimethyl isomer of **A15**.

(12) The C-11 unsubstituted analogue of **A15** was found to cyclize under comparable conditions to a 1:1 epimeric mixture analogous to **A16** and **A17**. The stereochemistry of these cyclizations is consistent with a product-like transition state with the tether ring in a chair and the Diels–Alder ring in a boat conformation. Diastereoselectivity stems from the preferred equatorial orientation of the C-5-methyl grouping in this boat-chair conformation. Relative energies of the diastereomeric boat-chair conformers, calculated via Still's Model program,[14] can be used to predict the major cyclization product.[1c,13] For recent ab initio calculations in support of such a picture, see: Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1984**, *25*, 4609.

(13) Audia, J. E. Ph.D. Thesis, University of South Carolina, **1985**, pp 59–62, 75–87.

(14) Cf.: Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

(15) *trans*-2,4-Dimethylglutaric acid has been resolved and both enantiomers are known. Möeller, E. *Lunds Univ. Arsskr. Avd. 2* **1919**, *15*, 56; *Chem. Abstr.* **1920**, *14*, 942. Grunfeld, N.; Stanton, J. L.; Yuan, A. M.; Ebetino, F. H.; Browne, L. J.; Gude, C.; Huebner, C. F. *J. Med. Chem.* **1983**, *26*, 1277. For a review on asymmetric reductions of acyclic ketones leading to chiral alcohols of predictable configuration, see: Midland, M. M.; Grandbois, E. R.; Howard, S. I.; Morrison, J. D. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 2, Chapters 2 and 3, pp 45–89.

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Received December 3, 1985

A Direct, Regio- and Stereoselective 1α-Hydroxylation of (5*E*)-Calciferol Derivatives

Summary: Selenium-IV reagents, particularly buffered selenious acid, afford a regio- and stereoselective 1α-hydroxylation of the trialkylsilyl ethers of (5*E*)-calciferols leading to a convenient synthesis of 1α-hydroxycholecalciferol, 1α-hydroxycalciferol, and 1α,25-dihydroxycholecalciferol.

Sir: While the high potency and striking effects of 1α-hydroxylated vitamin D derivatives on calcium metabolism have stimulated many efforts to prepare such compounds, even the best syntheses are relatively inefficient and/or indirect.[1] Simple allylic hydroxylation of a triene such as **1** or its isomer **5** (Chart I) has been an obvious and beguiling possibility, but to quote from a pertinent paper,[2] "Direct allylic oxidation of Vitamin D is feasible but, because of difficulty in controlling the site, extent and stereochemistry of hydroxylation it is not (at least as yet) an efficient process." We now report an efficient process for the regio- and stereoselective 1α-hydroxylation of (5*E*,7*E*)-trienes such as **5**–**8**. This procedure permits a simple, rather direct synthesis of 1α-hydroxylated vitamin D derivatives.

We noted that while either cholecalciferol (**1**) or its 5*E* isomer (**5**) [available in high yield from the former through electrocyclic addition of SO_2 ($SO_2/C_6H_6/H_2O$) followed by stereospecific thermal elimination of SO_2 (EtOH, $NaHCO_3$) from adducts[3] **9a** and **9b**] gave unpromising mixtures of products upon reaction with SeO_2 in most solvents, a cleaner reaction took place in methanol or solvent mixtures containing methanol and afforded variable amounts of four isomeric 1-hydroxylated products (**10**, **11**, **12**, and **13**), together with a rich mixture of byproducts, several of which contained selenium. While addition of standard reoxidants, e.g., H_2O_2 or $(CH_3)_3CO_2H$,[4] did not improve the reaction, addition of periodate salts [$NaIO_4$, $(C_4H_9)_4NIO_4$] (4 equiv) suppressed formation of selenium-bearing byproducts and increased the yield of **10**, **11**, **12**, and **13** (30% combined). Use of bulky ester blocking groups at 3 (for instance **6**), by suppressing the fortuitous equilibration about the 5,6 bond which accompanied the hydroxylation of **1** or **5**, revealed that while the 5*E* isomer **6** was quickly hydroxylated to afford only 5*E* products (**14** and **15**), the 5*Z* isomer **2** reacted sluggishly to afford both 5*E* and 5*Z* products in poor yield. Throughout this communication

(1) (a) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Rizzardo, E. *J. Am. Chem. Soc.* **1973**, *95*, 2748; *J. Chem. Soc., Chem. Commun.* **1974**, 203. (b) Furst, A.; Labler, L.; Meiner, W.; Pfoertner, K. H. *Helv. Chim. Acta* **1973**, *56*, 1708 and references there cited. (c) Kaneko, C. I.; Yamada, S.; Sugimoto, A.; Eguchi, Y.; Ishikawa, M.; Suda, T.; Suzuki, M.; Kakuta, S.; Sasaki, S. *Steroids* **1974**, *23*, 75. (d) Kaneko, C. I.; Sugimoto, A.; Eguchi, Y.; Yamada, s.; Ishikawa, M.; Sasaki, S.; Suda, T. *Tetrahedron* **1974**, *30*, 2701. (e) Emke, A.; Hands, D.; Midgley, J. M.; Whalley, W. B.; Ahmad, R. *J. Chem. Soc., Perkin A. Trans 1* **1977**, 820. (f) Guest, D. W.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1695. (g) Mihailovic, M. L. J.; Lorenc, L. J.; Pavlovic, V. *Tetrahedron Lett.* **1977**, 441. (h) Pelc, B. *Steroids* **1977**, *30*, 193. (i) Paaren, H. E.; DeLuca, H. F.; Schnoes, H. K. *J. Org. Chem.* **1980**, *45*, 3253. (j) Mourino, A. *Synth. Commun.* **1978**, *8*, 127. (k) Kocienski, P. J.; Lythgoe, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1400. (l) Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans 1* **1980**, 1405. (m) Lythogoe, B. *Chem. Soc. Rev.* **1980**, *9*, 449. (n) Georghiou, P. E. *Ibid.* **1977**, *6*, 83. (o) Freeman, D.; Archer, A.; Mazur, Y. *Tetrahedron Lett.* **1975**, 261. (p) Cohen, Z.; Keinan, E.; Mazur, Y.; Ulman, A. *J. Org. Chem.* **1976**, *41*, 2651.

(2) Paaren, H. E.; Hammer, D. E.; Schnoes, H. K.; DeLuca, H. F. *Proc. Natl. Acad. Sci.* **1978**, *75*, 2080.

(3) (a) Yamada, S.; Takayama, H. *Chem. Lett.* **1979**, 583. (b) Reischl, W.; Zbiral, E. *Helv. Chim. Acta* **1979**, *62*, 1763. Reischl, W.; Zbiral, E. *Monatsh. Chem.* **1979**, *110*, 1463. (c) Yamada, S.; Suzuki, T.; Takayama, H.; Miyamoto, K.; Matsunaga, I.; Nawata, Y. *J. Org. Chem.*, **1983**, *48*, 3483.

(4) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

0022-3263/86/1951-1635$01.50/0