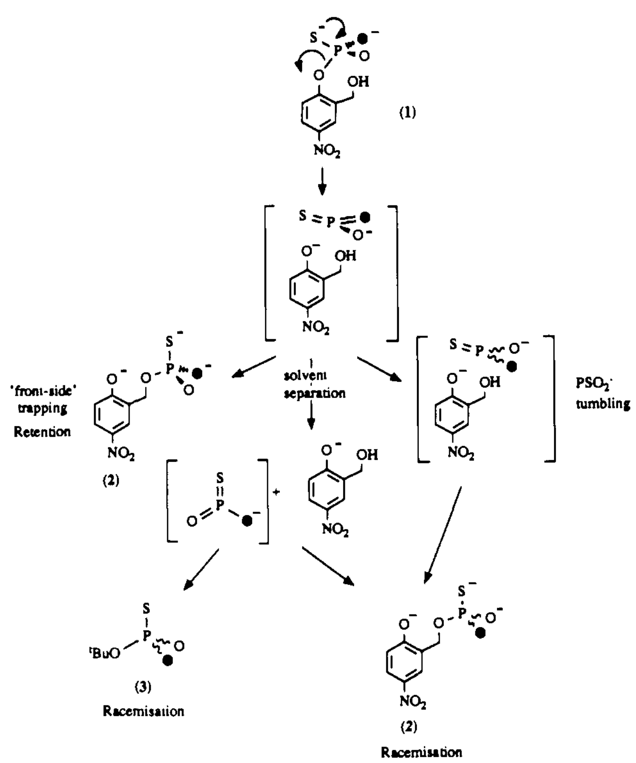
Scheme I



considerably more convenient than that for isotopically chiral phosphate esters.[7] When a concentrated aqueous solution of the dianion of **1** is rapidly diluted into a large volume of *tert*-butyl alcohol, **1** reacts rapidly to give comparable yields of 2-hydroxy-5-nitrobenzyl thiophosphate (**2**) and *tert*-butyl thiophosphate (**3**), with only small amounts of inorganic thiophosphate, Scheme I. The starting material **1** and the two products **2** and **3** were subjected to our published stereochemical analysis.[7] The starting material was shown to be present in ≥90% ee, and the assignment of the R_p configuration follows from the synthesis. As expected, the *tert*-butyl [^{18}O]thiophosphate (**3**) was completely racemic, confirming a fully dissociative mechanism involving a "free" monomeric thiometaphosphate intermediate, in accord with expectations based on our previous studies.[6] Although the product (**2**) of the formally intramolecular thiophosphoryl transfer reaction experienced some racemization (ca. 60%), there was a significant stereospecific pathway. On the basis of the absolute configuration deduced from the stereochemical analysis and confirmed by comparison with independently synthesized material, this pathway proceeds with retention of configuration.

The observed racemization during the formation of **2** could be accounted for in a number of ways, including tumbling of the thiometaphosphate within the dissociation complex or return from a solvent-separated species. However, the pathway proceeding with retention must arise from "front-side" trapping of monomeric thiometaphosphate within the initial dissociation complex. The alternative possibility involving formation and pseudorotation of a pentacovalent intermediate is highly unlikely for two reasons: (i) in base, the first-formed pentacoordinate intermediate would involve placement of an oxyanion (or S$^-$) in the apical position, for which there is no reliable precedence;[8] (ii) increasing amounts of water included in the reaction mixture lead to a decrease in the amounts of the rearranged product (**2**) and an increase in inorganic thiophosphate, presumably because of competition for a common intermediate, namely, caged thiometaphosphate. This is the first demonstration of a dissociative phosphoryl transfer reaction occurring with retention.[9] Interestingly, this study taken with other results demonstrates that a dissociative or preassociative stepwise pathway can occur with *inversion, racemization, or retention*, depending on conditions (solvent, etc.) and the constraints placed on the nucleophile and the reactive intermediate. It also suggests that, if enzymes do accelerate a formally dissociative reaction, there exists the possibility for a front-side nucleophilic displacement on an enzyme-shielded metaphosphate intermediate. This possibility is reminiscent of the difficulties in distinquishing an enzyme-shielded oxycarbonium ion and a genuine glycosyl-enzyme intermediate in glycosyl transferases that proceed with overall retention.[10]

Acknowledgment. This work was supported by the SERC (studentship to R.M.) and is a publication from the Leicester Centre for Molecular Recognition.

Registry No. 1, 136537-94-5; **2**, 136537-95-6; **3**, 136537-96-7.

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[7] Cullis, P. M.; Misra, R.; Wilkins, D. J. *Tetrahedron Lett.* **1987**, *28*, 4211.

[8] If (1) were to undergo an associative reaction the nucleophile and the leaving group would initially have to span apical-equatorial positions with the nucleophile forced to approach from an adjacent position since a six membered ring cannot span the two apical sites (six membered rings may offer some stabilization of the pentacoordinate intermediate but considerably less than a five membered ring). The pentacoordinate intermediate that this would have to involve would therefore place one of the remaining ligands (-O$^-$ or -S$^-$) in the other apical position. The low apicophilicity of such groups would make this a relatively high energy pathway.

[9] A previous chemical 'mutase-like' reaction studied by Knowles and coworkers (Buchwald, S. L.; Pliura, D. H.; Knowles, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 4916) reported the stereochemical course of an intramolecular phosphoryl transfer of monophosphates derived from propane diol under acid conditions to be retention of configuration but this reaction is an associative reaction involving an adjacent attack and pseudorotation of the resulting phosphorane, a reaction type known to proceed with retention.

[10] Sinnott, M. L. in *Enzyme Mechanisms*, eds. Page, M. I.; Williams, A.; Royal Society of Chemistry, **1987**, p. 259.

Isolation and Crystal Structure of a Technetium(V) Nitrido Complex Containing a Coordinated Transient State of *N*-(2-Aminoethyl)carbamic Acid

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We reported recently the synthesis and characterization of the technetium(V) nitrido complexes $[\mathrm{TcN(L^1)_2Cl}]^+$ and $[\mathrm{TcN(L^2)Cl}]^+$ [$\mathrm{L^1 = H_2N(CH_2)}_n\mathrm{NH_2}$, n = 2, 3; $\mathrm{L^2 = H_2N(CH_2)_3NH(CH_2)_2NH(CH_2)_3NH_2}$].[1] In developing this chemistry, we carried out the reaction of the complex $\mathrm{TcNCl_2(PPh_3)_2}$ with diethylenetriamine ($\mathrm{H_2NCH_2CH_2NHCH_2CH_2NH_2}$ = dien), and surprisingly, we isolated the dicationic complex $[\mathrm{TcN(en)_2(L)}]^{2+}$ (**1**) [en = ethylenediamine; L = *N*-(2-aminoethyl)carbamic acid ($\mathrm{HOOCNHCH_2CH_2NH_2}$)]. The X-ray crystal structure of **1** revealed that the coordinated ligand L lies in a peculiar "transient state" originated by an uncommon weakening of a carbon–nitrogen bond. We report here the synthesis of complex **1** and the description of its crystal structure.

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[1] Marchi, A.; Garuti, P.; Duatti, A.; Magon, L.; Rossi, R.; Ferretti, V.; Bertolasi, V. *Inorg. Chem.* **1990**, *29*, 2091–2096.

0002-7863/91/1513-9680$02.50/0 © 1991 American Chemical Society

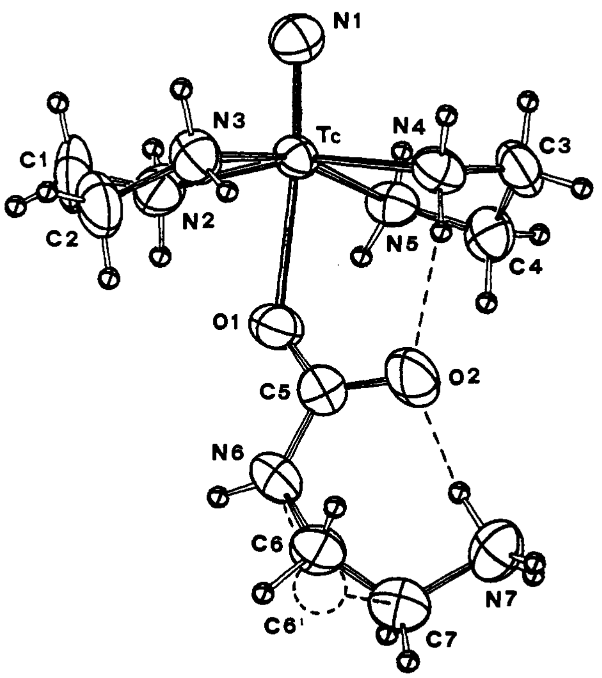

Figure 1. An ORTEP view of the $[TcN_7O_2C_7H_{24}]^{2+}$ cation showing the thermal ellipsoids at 40% probability. The most relevant bond distances are as follow: Tc–N(1) = 1.607 (9), Tc–O(1) = 2.330 (6), C(5)–O(1) = 1.24 (1), C(5)–O(2) = 1.28 (1), C(5)–N(6) = 1.35 (1), N(6)–C(6) = 1.59 (2), N(6)–C(6′) = 1.56 (3), C(6)–C(7) = 1.33 (2), C(6′)–C(7) = 1.41 (4), C(7)–N(7) = 1.46 (1) Å.

The reaction of $TcNCl_2(PPh_3)_2$ with excess dien, in a benzene/ethanol mixture and under aerobic conditions, leads to the formation of the complex $[TcN(en)_2(L)]^{2+}$ (**1**). This product was obtained from the reaction solution by slow precipitation with excess $Na[B(C_6H_5)_4]$ and has been characterized by elemental analysis, IR, ^1H NMR, and mass spectra, and magnetic susceptibility measurements in solution. When the same reaction was carried out under anhydrous and anaerobic conditions, the starting complex $TcNCl_2(PPh_3)_2$ was recovered unaltered. The structure of complex **1** was determined crystallographically (Figure 1).[2] The results show that **1** is a technetium(V) nitrido complex containing two ethylenediamine ligands coordinated in the plane normal to the $[Tc\equiv N]^{2+}$ group, and a unique structural form of *N*-(2-aminoethyl)carbamic acid coordinated in a trans position to the same group through one oxygen atom of the carboxylic group. The resulting coordination around the Tc atom is distorted octahedral, the metal atom being displaced from the least-squares plane defined by the four N atoms of the two en ligands by 0.3268 (5) Å toward the nitrido group. The coordinated *N*-(2-aminoethyl)carbamic acid was found to be in an uncommon "transient state" exhibiting remarkable structural features. The ligand is in a typical zwitterionic form ($^-OOCNHCH_2CH_2NH_3^+$) stabilized by an intramolecular head-to-tail hydrogen bond [N(7)⋯O(2) = 2.61 (1) Å, H(N71)⋯O(2) = 1.64 (12) Å, N(7)–H(N71)⋯O(2) = 149 (8)°], which can be considered very strong on the basis of a statistical analysis carried out on particular classes of compounds, such as amino acids and their derivatives.[3] The additional hydrogen bond between the carboxylic oxygen atom O(2) and the N(4)–H(42) group of one en ligand [N(4)⋯O(2) = 2.82 (1) Å, H(N42)⋯O(2) = 1.99 Å, N(4)–H(N42)⋯O(2) = 145°] may play an important role in further stabilizing the overall structure of the complex. The $C(6)H_2$ group is disorderly and displaced over two positions, which are separated by 1.43 (3) Å, and were refined with occupancies of 0.70 and 0.30. The N(6)–C(6) [1.59 (2) Å] and N(6)–C(6′) [1.56 (4) Å] bond lengths are abnormally long, and this lengthening has to be considered together with the concomitant shortening of the C(6)–C(7) [1.33 (2) Å] and C(6′)–C(7) [1.41 (4) Å] single bond distances. Although these unusual bond lengths always involve carbon atom C(6), which is severely disordered, the extent of their deviations from the corresponding normal bond lengths (C–N, ca. 1.47 Å; C–C, ca. 1.54 Å) cannot be simply ignored. Presumably, the ligand L has been trapped in a partially degraded state inside the crystal structure of the final complex as a consequence of the stabilizing effect of the crystal forces. Indeed, the coordination of L to the substitution-labile site trans to the $Tc\equiv N$ linkage would play a minor role in stabilizing this transient species, and this conclusion is partially supported by the observed instability of **1** in various solvents. The net charge of the complex is 2+, and thus, it constitutes the first example of a dicationic complex containing the $Tc\equiv N$ multiple bond.

While at present the mechanism of formation of complex **1** remains undetermined, some important conclusions can be drawn about the origin of the en and L substituents in **1** on the basis of the following experimental evidence.

1. The starting dien ligand (Fluka) was checked by HPLC and gas chromatography, and we did not detect any traces of ethylenediamine or any other contaminant that might be ascribed to the presence of *N*-(2-aminoethyl)carbamic acid in the analyzed sample. The same results were obtained by analyzing a CH_2Cl_2 solution of dien bubbled with CO_2 for 1 h at room temperature. These findings reasonably eliminate the possibility that ethylenediamine and *N*-(2-aminoethyl)carbamic acid were present as contaminants prior to reaction.

2. The reaction of $TcNCl_2(PPh_3)_2$ with freshly distilled dien, carried out under an inert atmosphere, did not give rise to complex **1**, the starting compound being recovered unaltered from the reaction solution. Instead, the introduction of a stream of CO_2 into the same reaction led readily to the isolation of **1**, suggesting that the presence of CO_2 is essential for obtaining the formation of complex **1**.

3. It has been reported previously that the reaction of $TcNCl_2(PPh_3)_2$ with excess en, under aerobic conditions, gave rise to the complex $[TcN(en)_2Cl]^+$.[1] No evidence of the production of *N*-(2-aminoethyl)carbamic acid in this reaction has been found, a fact which seems to indicate that, in the synthesis of **1**, the ligand L does not originate from the previous formation of en, which successively reacts with CO_2 (either as a free ligand or coordinated to the metal atom) to produce the corresponding carbamic acid.

These observations strongly support the hypothesis that the species en and L are generated as a consequence of the metal-promoted degradation of dien during the reaction with the complex $TcNCl_2(PPh_3)_2$. Such a reaction constitutes the first reported observation of this type of process. However, further studies are required in order to establish the exact role played by each species in the formation of complex **1** and to determine the factors stabilizing the unique structural form of L.

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Registry No. [**1**][BPh_4]$_2$, 137174-99-3; [**1**][PF_6]$_2$, 137175-01-0; dien, 111-40-0; $TcNCL_2(PPh_3)_2$, 77933-40-5; CO_2, 124-38-9.

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[2] Crystal data for $TcN_7O_2C_{55}H_{64}B_2$: monoclinic, *Ia* (alt. *Cc*, No. 9), $a = 22.903$ (6) Å, $b = 9.346$ (3) Å, $c = 25.731$ (5) Å, $\beta = 91.76$ (2)°, $V = 5505$ (2) Å^3, $Z = 4$, $D_{calcd} = 1.17$ g cm^{-3}, $D_{found} = 1.13$ g cm^{-3}, λ(Mo Kα) = 0.71069 Å (graphite monochromator), $\mu = 2.96$ cm^{-1}. An Enraf-Nonius CAD-4 diffractometer was used to collect 6124 independent reflections ($2° \leq \theta \leq 27°$) on a yellow orange crystal. Of these, 3463 were observed [$I \geq 3\sigma(I)$]. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods (SIR88: Burla, M. C.; Camalli, M.; Cascarano, C.; Giacovazzo, C.; Polidori, G.; Spagna, R.; Viterbo, D. *J. Appl. Crystallogr.* **1989**, *22*, 389–396). All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in idealized positions except for H(N71), involved in a strong hydrogen bond, which was refined isotropically. $R = 0.052$, $R_w = 0.064$. All computations were performed using CAD4-SDP (Frenz, B. A., College Station, TX, and Enraf-Nonius, Delft, The Netherlands, 1978) and PARST (Nardelli, M. *Comput. Chem.* **1983**, *7*, 95–100) systems of programs.

[3] Ramakrishnan, C.; Prasad, N. *Int. J. Protein Res.* **1971**, *3*, 209–213. Taylor, R.; Kennard, O.; Versichel, W. *Acta Crystallogr., Sect. B* **1984**, *40*, 280–285. Gorbitz, C. H. *Acta Crystallogr., Sect. B* **1989**, *45*, 390–394.

Supplementary Material Available: Details of the crystal structure determination, tables of positional parameters, calculated positional parameters of hydrogen atoms, general temperature factor expressions, bond distances, and bond angles for $[TcN_7O_2C_7H_{24}][BC_{24}H_{20}]_2$, ORTEP views of the two $[BC_{24}H_{20}]^-$ anions, details of the preparation and characterization of the complex $[TcN(en)_2(L)][B(C_6H_5)_4]_2$, and a general reaction scheme (20 pages); listing of observed and calculated structure factors for $[TcN_7O_2C_7H_{24}][BC_{24}H_{20}]_2$ (18 pages). Ordering information is given on any current masthead page.

Synthetic Studies Directed toward the Eremantholides. 2. A Novel Application of the Ramberg–Bäcklund Rearrangement to a Highly Stereoselective Synthesis of (+)-Eremantholide A

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Received August 12, 1991

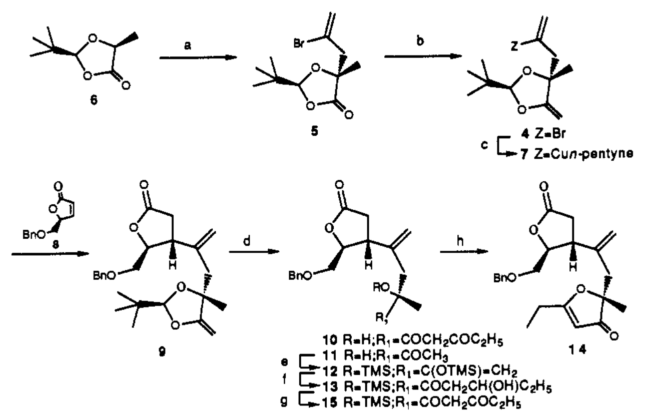
Eremantholide A (**1**) is a member of the furanoheliangolides isolated by LeQuesne and co-workers from *Eremanthus elaeagnus*.[1,2] The structure and relative stereochemistry of **1** were confirmed by X-ray crystallographic analysis of a derivative.[1] The absolute configuration of **1** (as shown) was predicated upon the biogenetic relationship of the furanoheliangolides to the germacranolides, which possess a common absolute configuration at C_7. The structure of **1** is unusual and highly strained since the molecular geometry requires that the endocyclic C_4–C_5 double bond be twisted 88° out of the plane of the 3(2*H*)-furanone ring. Eremantholide A (**1**) is also of interest because it exhibits significant levels of in vitro antitumor activity against a variety of tumor cell lines.[3,4]

The synthesis of other naturally occurring 3(2*H*)-furanones, such as jatrophone, has been reported,[5] and **1** has also been the target of several synthetic efforts, including our own preliminary studies.[6-8] Herein, we report the first stereoselective total synthesis of (+)-eremantholide A (**1**), which also confirms the assignment of its absolute configuration.

Our strategy required an α-hydroxy ketone synthon convertible into the 3(2*H*)-furanone and methodology to effect medium-ring closure and creation of the strained nine-membered-ring olefin.[7] Intact 3(2*H*)-furanone derivatives did not prove suitable; thus cyclic acetal **4** was employed, which was available from (*R*)-(−)-lactic acid via **5** (Scheme I).[9]

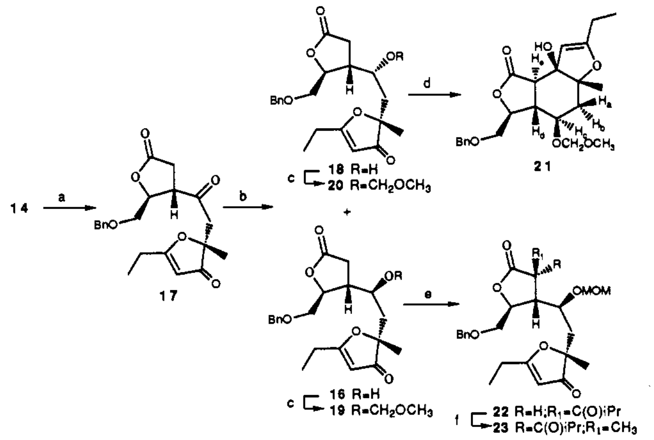
Alkylation of the (2*S*,4*S*)-(+)-lactolide **6**[9] with 2,3-dibromopropene afforded the (2*S*,4*R*)-(+)-lactolide **5** (mp 35–36 °C, >98% de) in 74% yield.[9,10] Lactolide **5** was elaborated to the desired vinyl bromide **4**, in 83% yield, by exposure to Tebbe reagent prepared in situ.[11,12] Bromide **4** was converted to the sensitive mixed cuprate reagent **7** by successive treatment with *t*-BuLi and cuprous *n*-pentyne in the presence of HMPT at −40 °C.[13,14] Addition of the optically pure butenolide **8**[15] then provided lactone (+)-**9** ($[\alpha]^{23}_D$ +5.5° (*c* 2.82, $CHCl_3$)), as a single diastereomer, in 79% yield.

Scheme I[a]



[a] Reagents: (a) LDA (1.2 equiv), THF, −78 °C, 3 h, then $H_2C{=}C(Br)CH_2Br$ (2.5 equiv), dropwise, −78 → −70 °C, 18 h; (b) Cp_2TiCl_2–$Al(CH_3)_3$ (3 equiv), THF–$PhCH_3$, 0 → 25 °C, 4 h then 25 °C, 10 h; (c) *t*-BuLi (2 equiv), Et_2O, −78 °C, ~1.5 h, then added to $Cu{\equiv}nC_3H_7$ (1 equiv), HMPT (1 equiv), Et_2O, −40 °C, 30 min followed by **8** (1 equiv), Et_2O, −40 °C, 2 h, then pH 10 NH_4Cl–NH_4OH, −40 °C → 25 °C, 1 h; (d) aqueous $(CO_2H)_2$ (saturated), HCl (1 drop), THF, 25 °C, 12 h; (e) TMSCl (5 equiv), DBU (5 equiv), CH_2Cl_2, Δ, 12 h; (f) C_2H_5CHO (1.2 equiv), then $BF_3{\cdot}Et_2O$ (1.1 equiv) (dropwise, 5 min), −78 °C, 40 min; (g) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2, 20 °C, 1 h; (h) 5% HCl–THF (1:2, v/v), 25 °C, 8 h.

Scheme II[a]



[a] Reagents: (a) OsO_4 (catalytic), $NaIO_4$ (2.5 equiv), THF–H_2O, 25 °C, 12 h; (b) $NaBH_4$ (1 equiv), CH_3OH, −40 °C, 15 min; (c) $(CH_3O)_2CH_2$ (60 equiv), P_2O_5 (3 equiv), 3-Å molecular sieves, CH_2Cl_2, 25 °C, 40 min; (d) LDA (1 equiv), THF, −78 °C, 2 h; (e) LDA (2.3 equiv), THF, −78 °C, 40 min, then isobutyryl imidazolide (1.1 equiv) in THF (dropwise, 10 min), −78 °C, 1.5 h; (f) NaH (1.3 equiv), DMF, 0 °C, 40 min, then CH_3I (5 equiv), 0 °C, 3.5 h.

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(1) Raffauf, R. F.; Huang, P. C.; Le Quesne, P. W.; Levery, S. B.; Brennan, T. F. *J. Am. Chem. Soc.* **1975**, *97*, 6884.

(2) Le Quesne, P. W.; Levery, S. B.; Menachery, M. D.; Brennan, T. F.; Raffauf, R. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1572.

(3) Geran, R. I.; Greenberg, N. H.; Macdonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep.* **1972**, *3*, 1.

(4) Hladon, B.; Twardowski, T. *Pol. J. Pharmacol. Pharm.* **1979**, *31*, 35.

(5) Smith, A. B., III; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219.

(6) (a) Tam, T. F.; Fraser-Reid, B. *J. Org. Chem.* **1980**, *45*, 1344. (b) McDougal, P. G.; Oh, Y.-I.; VanDerveer, D. *J. Org. Chem.* **1989**, *54*, 91. (c) Smith, A. B., III, and co-workers, unpublished research.

(7) Boeckman, R. K., Jr.; Heckendorn, D. K.; Chinn, R. L. *Tetrahedron Lett.* **1987**, *28*, 3551.

(8) (a) Taken in part from the Ph.D. Dissertations of S. K. Yoon, University of Rochester, Rochester, NY, 1990, and D. K. Heckendorn, University of Rochester, Rochester, NY, 1987. (b) See also: Chinn, R. L. Ph.D. Dissertation, University of Rochester, Rochester, NY, 1987.

(9) Seeback, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313.

(10) All new substances exhibited satisfactory spectroscopic (IR, ^1H, and MS) and HRMS or combustion analytical data.

(11) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

(12) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2386.

(13) For other examples of such a strategy, see: (a) Herrmann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1973**, *95*, 7923. (b) Ziegler, F. E.; Schwartz, J. A. *J. Org. Chem.* **1978**, *43*, 985. (c) Tomioka, K.; Ishiguro, T.; Itaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1313. (d) Hanessian, S.; Murray, P. J. *J. Org. Chem.* **1987**, *52*, 1170.

(14) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

(15) For preparation of the unprotected hydroxymethyl butenolide, see: (a) Vekemans, J. A. J. M.; Franken, G. A. M.; Dapperrens, C. W. M.; Godefroi, E. F.; Chittenden, G. J. F. *J. Org. Chem.* **1988**, *53*, 627. (b) Hafele, B.; Jager, V. *Liebigs Ann. Chem.* **1987**, 85. Benzyl ether **8** was obtained via the procedure of Iversen and Bundle: Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.

0002-7863/91/1513-9682$02.50/0