Little experimental data are available regarding the coordination geometry of Lewis acids to organic carbonyl groups. While the available evidence for coordination with H^+ indicates a geometry corresponding to eq 2 (H-O-C = 115°),[28] calculations indicate that Li^+ prefers a linear geometry (eq 3).[29] We have carried out extensive calculations at the STO-3G and STO-3/21G levels for the interaction of formaldehyde with various first and second row Lewis acids, and the results indicate that a *linear geometry is preferred* when the cation can act as both a σ and π acceptor.[30]

The origin of the nonlinear distortion has not yet been adequately determined. Molecular orbital calculations at the INDO[31,32] level fail to detect any distortion of the "lone-pair" orbitals of **2** and **3**. However, the direction of nonlinear deviation found for a variety of bridged and cyclic ketones in addition to **2** and **3** suggests a steric effect. Although steric repulsion between the shift reagent and substituents on the substrate moiety appears to be unimportant for nitriles,[1,5] the C-O-Eu distance for ketones (ca. 3.7 Å) is shorter than the C-C-N-Eu distance (ca. 5.1 Å) for nitriles by approximately 1.4 Å. In any case, the concept of steric interactions provides a useful device for interpreting and predicting distortions from an otherwise linear arrangement.

Acknowledgment. This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, by grants from the Research Corporation, and by a Fellowship (to D.J.R., 1978-1979) from the Alexander von Humboldt Foundation. Much of the computational work was carried out at the Universität Erlangen-Nürnberg; D.J.R. and N.K.R. express their appreciation to Professor Paul v. R. Schleyer and the Rechenzentrum der Universität Erlangen-Nürnberg for providing working facilities and generous amounts of computing time.

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(32) For example, the orbital coefficients at oxygen of the highest occupied molecular orbital of **2** are -0.002 (2s), 0.580 ($2p_x$), 0.000 ($2p_y$), and 0.000 ($2p_z$) where the C-O bond defines the z axis and the carbon atom of the methyl group lies in the xz plane. Clearly, this "lone-pair" orbital corresponds to an essentially unperturbed p_x orbital, i.e., the orbital shown in eq 3 which is perpendicular to the C-O bond.

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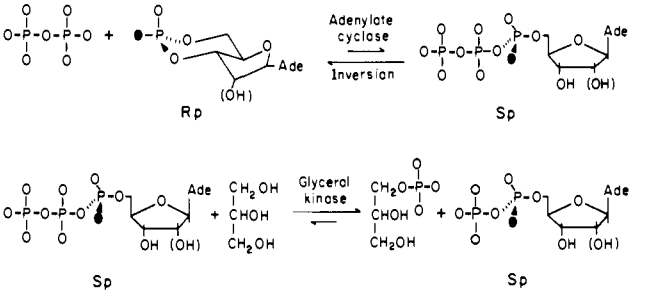
Oxygen Chiral Phosphodiesters. 2. Enzymatic Synthesis and Configurational Analysis of [α-^{18}O]-2′-Deoxyadenosine 5′-Diphosphate

Sir:

The mechanistic investigation of enzymes which catalyze reactions involving nucleoside di- and triphosphates has been facilitated by the use of diastereomeric phosphorothioate analogues in which a nonbridging oxygen atom of a phosphate group is replaced by a sulfur atom.[1,2] For example, the separated diastereomers of ATPαS[3,4] have been used to probe the stereochemical course of a number of adenylyl transfer reactions, thereby providing important information regarding the formation of an adenylated enzyme intermediate during catalysis. The separated diastereomers of ATPβS[3,5-8] have been used to examine the nature of metal ion coordination to the nucleotide, since the stereoselectivity of an enzymatic reaction involving ATPβS often depends on the identity of the divalent metal ion used to promote catalysis. However, mechanistic ambiguity can result, since phosphorothioates are often poor substrates for enzymes. Experiments employing nucleotides which are oxygen chiral at either the α- or β-phosphorus atom would not be subject to this problem. In this communication, we report the syntheses of the first oxygen chiral nucleoside diphosphates, the R_P and S_P diastereomers of [α-^{18}O]-2′-deoxyadenosine 5′-diphosphate ([α-^{18}O]dADP); these materials were prepared from the S_P and R_P diastereomers, respectively, of cyclic [^{18}O]-2′-deoxyadenosine 5′-monophosphate (cyclic [^{18}O]dAMP)[9] by using the adenylate cyclase from *Brevibacterium liquefaciens*[10] as a stereospecific catalyst. We also describe a simple, sensitive, and general method for the determination of the absolute configuration of nucleoside polyphosphates which are oxygen chiral at either the α- or β-phosphorus atom. Our experiments illustrate that the stereochemical course of the reaction catalyzed by the bacterial adenylate cyclase is inversion of configuration whether phosphorothioates[11] or oxygen chiral substrates are used.

Scheme I



[a] Enzymatic synthesis of [α-^{18}O] dADP (or ADP) from cyclic [^{18}O] dAMP (or AMP). The example shown is the preparation of the S_p diastereomer of [α-^{18}O] nucleoside diphosphate from the R_p diastereomer of cyclic [^{18}O] nucleoside monophosphate. ● represents ^{18}O.

The strategy for the stereospecific synthesis of oxygen chiral [α-^{18}O]dADP (or [α-^{18}O]ADP) from oxygen chiral cyclic [^{18}O]dAMP (or cyclic [^{18}O]AMP) is summarized in Scheme I. The adenylate cyclase from *B. liquefaciens* (ATCC 14929) catalyzes the cyclization of ATP (or dATP) to yield cyclic AMP (or cyclic dAMP) and pyrophosphate.[10] At neutral pH, the reaction catalyzed by this enzyme is reversible, with the velocity for the production of ATP from cyclic AMP and pyrophosphate being maximal at pH 7.3. At this pH and in the presence of 5 mM $MgSO_4$, the equilibrium constant for the reaction written in the direction of ATP synthesis is 8 M^{-1}.[12] At millimolar concentrations of reactants and products, the reaction favors the synthesis of cyclic AMP. To favor production of chiral acyclic nucleotide, we have chosen to couple nucleoside triphosphate production to the glycerol kinase reaction.[13]

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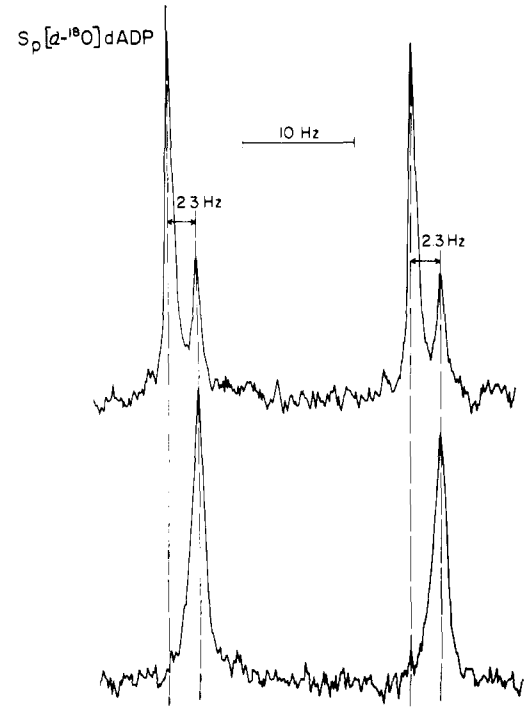


Figure 1. The α-phosphorus region of the 81.0-MHz ^{31}P NMR spectra of [α-^{18}O]dADP predicted to have the S_P configuration at the α-phosphorus. The bottom spectrum is that of the isolated enzymatic product, and the top spectrum is that of the enzymatic product diluted threefold with unlabeled dADP. No ^{18}O perturbation is observed on the resonance for the β-phosphorus atom. The samples were prepared by percolation through 3-mL columns of Chelex-100, lyophilization, and dissolution in 0.10 M EDTA, pH 9.0, containing 20% D_2O. The spectra were obtained with a 500-Hz sweep width and 8 K data points (0.12 Hz/real data point). The approximate chemical shift of the α-phosphorus atom is −10.1 ppm (upfield shift relative to an external capillary containing 85% H_3PO_4).

Experiments recently reported by this laboratory have demonstrated that the reaction catalyzed by the bacterial adenylate cyclase is accompanied by inversion of configuration when ATPαS is used as substrate.[11] The S_P diastereomer of ATPαS is converted to the R_P diastereomer of cyclic AMPS at about one-tenth the rate that ATP is converted to cyclic AMP; this similarity in reaction rates suggests that the same mechanism and stereochemistry should apply to the reaction involving oxygen chiral substrate. Thus, the recent chemical syntheses of oxygen chiral samples of cyclic [^{18}O]dAMP[9] and cyclic [^{18}O]AMP[14] permit the stereospecific enzymatic syntheses of oxygen chiral samples of [α-^{18}O]dADP and [α-^{18}O]ADP. These oxygen chiral nucleoside diphosphates can, of course, be enzymatically converted to oxygen chiral samples of [α-^{18}O]dATP and [α-^{18}O]ATP.

Incubation of either the R_P or the S_P diastereomer of cyclic [^{18}O]dAMP, pyrophosphate, and glycerol in the presence of adenylate cyclase and yeast glycerol kinase[15] resulted in the production of about 50% glycerol phosphate[16] (based on limiting

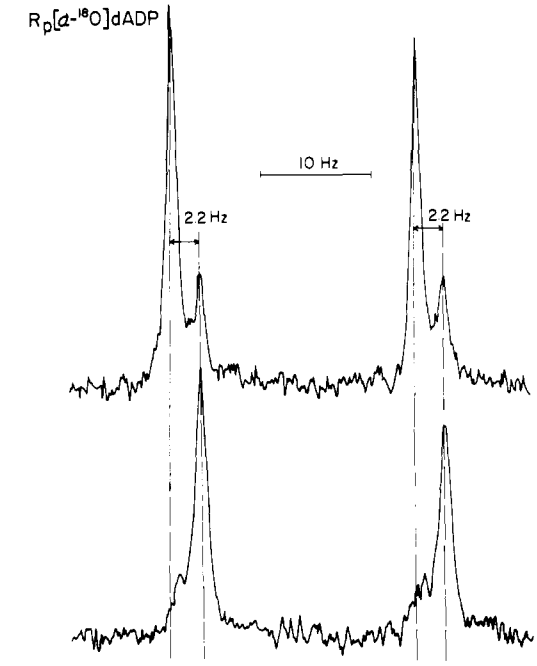
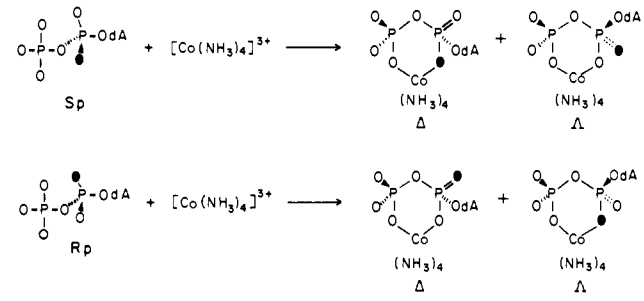


Figure 2. The α-phosphorus region of the 81.0-MHz ^{31}P NMR spectra of [α-^{18}O]dADP predicted to have the R_P configuration at the α-phosphorus. The bottom spectrum is that of the isolated enzymatic product, and the top spectrum is that of the enzymatic product diluted threefold with unlabeled dADP. No ^{18}O perturbation is observed on the resonance for the β-phosphorus atom. Sample preparation and spectral details are identical with those described in the legend to Figure 1.

Scheme II



[a] Configurational analysis of the diastereomers of [α-^{18}O]dADP.

pyrophosphate[17]) after 24 h;[18] examination of each reaction mixture by ^{31}P NMR revealed the presence of nucleoside diphosphate. After gel filtration of the reaction mixtures on Sephadex G-25 to recover active adenylate cyclase, the unreacted oxygen chiral cyclic nucleotides and nucleoside diphosphates were isolated by chromatography on DEAE-Sephadex A-25 (HCO_3^-).

(13) The equilibrium concentration of ATP is calculated to be 0.57 mM or a 19% yield based on pyrophosphate, assuming a value of 8 M^{-1} for the equilibrium constant for the adenylate cyclase reaction and initial concentrations of 30 and 3 mM for cyclic AMP and pyrophosphate. If a value of 150 is assumed for the equilibrium constant for the glycerol kinase reaction, the addition of glycerol kinase and 5 mM glycerol to the reaction will produce an equilibrium concentration of 2.88 mM ADP (96% yield based on pyrophosphate) and 0.026 mM ATP (0.9% yield based on pyrophosphate).

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(16) Measured enzymatically in aliquots by measuring the amount of NAD^+ reduced by glycerol phosphate dehydrogenase; the formation of dADP cannot be measured conveniently by using a coupled enzyme assay.

(17) In the presence of Mg^{2+}, pyrophosphate precipitates as the bismagnesium complex; this requires that the concentrations of both Mg^{2+} and pyrophosphate be kept low. Also, we have found that the formation of ATP from cyclic AMP and pyrophosphate is *inhibited* by increasing concentrations of uncomplexed Mg^{2+}; at 1 mM uncomplexed Mg^{2+}, the K_m for cyclic AMP is about 15 mM and that for pyrophosphate is about 2 mM: Wolin, M. S.; Gerlt, J. A., unpublished observations. The concentration of cyclic dAMP was chosen to be as high as possible to minimize competitive inhibition by dADP.[18]

(18) The yield of glycerol phosphate (and dADP) could not be increased[13] by addition of more adenylate cyclase or glycerol kinase to the reaction mixture. When the production of glycerol phosphate stopped, the adenylate cyclase in the reaction mixture was about 50% as active as when the reaction was initiated. When an analogous reaction was performed on (unlabeled) cyclic AMP, we observed essentially quantitative conversion of the pyrophosphate to glycerol phosphate and ADP, as judged by enzymatic assay for glycerol phosphate and a ^{31}P NMR spectrum of the reaction mixture. Since it is unlikely that the free energy of hydrolysis of cyclic dAMP is significantly different than that of cyclic AMP,[19] we attribute the less than quantitative conversion of pyrophosphate to products due to inhibition of either adenylate cyclase or glycerol kinase by dADP.

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A ^{31}P NMR spectrum of each sample of ^{18}O-labeled dADP was obtained at 81.0 MHz, and the α-phosphorus regions of these spectra are shown in Figures 1 and 2; also shown in the figures are the same regions of spectra obtained under identical conditions of the enzymatic products diluted threefold with unlabeled dADP. The ^{18}O perturbations[20,21] observed in the diluted samples demonstrate that the enzymatic products are highly enriched with ^{18}O; a high degree of enrichment is expected since the starting samples of cyclic [^{18}O]dAMP were enriched to the extent of at least 95%.[9] The ^{18}O perturbations of the α-phosphorus resonances are about 2.2 Hz.

On the basis of our previous stereochemical study of this enzyme, we would predict that the conversion of cyclic [^{18}O]dAMP to [α-^{18}O]dADP would occur with inversion of configuration at the chiral phosphorus atom. However, only one enzyme catalyzing a phosphoryl transfer reaction has been examined stereochemically with both phosphorothioate and oxygen chiral substrates; Knowles' group has determined that the reaction catalyzed by glycerol kinase is accompanied by an inversion of configuration whether a chiral sample of [γ-^{16}O,^{18}O]ATPγS[22] or [γ-^{16}O,^{17}O,^{18}O]ATP[23] is used as the thiophosphoryl group donor. Since we did not feel that this single example is sufficient precedent for the confident assignment of the configurations of our samples of [α-^{18}O]dADP, we independently determined the configurations of our chiral materials.

Configurational assignment at the α-phosphorus atom in oxygen chiral nucleoside diphosphates (or at the β-phosphorus atom in oxygen chiral nucleoside triphosphates) requires isotopic identification of the diastereotopic oxygen atoms.[24] We have found that measurement of the ^{18}O perturbations of the ^{31}P NMR chemical shifts of the α-phosphorus atoms in the diastereomeric pair of α,β-bidentate complexes of [α-^{18}O]dADP with Co(III) is a simple and sensitive method for performing the required configurational analysis; the rationale for this method is summarized in Scheme II.

When dADP is reacted with $[Co(NH_3)_4]^{3+}$ according to the protocol described by Cleland for formation of the α,β-bidentate complexes of ADP with Co(III),[28] a diastereomeric mixture of α,β-bidentate $Co(NH_3)_4$dADP complexes is formed as evidenced by examination of the ^{31}P NMR spectrum of the reaction mixture. After separating the diastereomeric complexes of $Co(NH_3)_4$dADP on a column of cross-linked cycloheptaamylose,[29] we have found that the dADP complexes have spectroscopic properties similar to those reported for the ADP complexes. In particular, the first complex to elute from the cycloheptaamylose column has a negative CD band at 540 nm and is the one whose α-phosphorus resonance is more downfield in the ^{31}P NMR spectrum of the mixture. Cleland has assigned the ADP complex which elutes first from the column to have the Δ screw sense and the second to have the Λ screw sense;[30,31] this assignment should be applicable to the dADP complexes. Thus, this information allows physical distinction of the diastereotopic oxygen atoms in an uncomplexed nucleoside diphosphate.

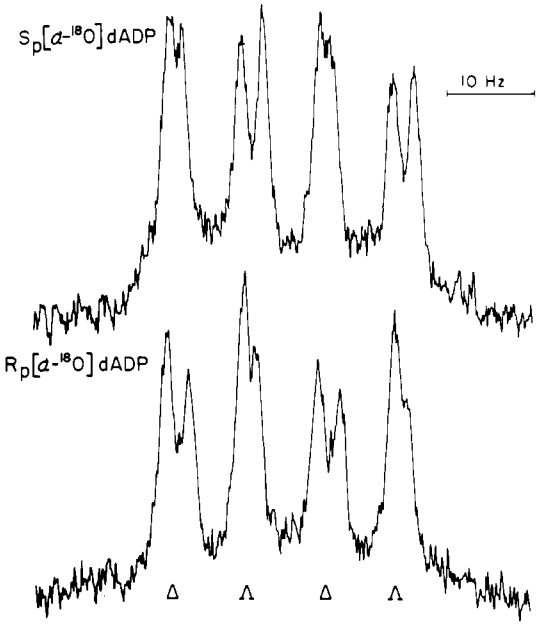

Figure 3. The α-phosphorus region of the 81.0-MHz ^{31}P NMR spectra of $Co(NH_3)_4$dADP prepared from the enzymatic products which had been isotopically diluted with an equal amount of unlabeled dADP. The top spectrum is that of the sample prepared from the [α-^{18}O]dADP predicted to have the S_P configuration, and the bottom spectrum is that of the sample prepared from the [α-^{18}O]dADP predicted to have the R_P configuration. Prior to obtaining the spectra, the mixtures of $Co(NH_3)_4$dADP diastereomers were passed through 3-mL columns of Chelex-100, lyophilized, and dissolved in 0.075 M EDTA, pH 5.5, containing 25% D_2O. The spectra were obtained with a 500-Hz sweep width and 8 K data points. The approximate chemical shift of the center of the multiplets is +0.80 ppm. The first and third sets of resonances are associated with the Δ screw sense diastereomer, and the second and fourth are associated with the Λ screw sense diastereomer (two sets of resonances are present for each diastereomer because of spin–spin coupled to the β-phosphorus atoms).

The required isotopic identification of the diastereotopic oxygen atoms in uncomplexed [α-^{18}O]dADP can be accomplished by a comparison of the ^{18}O perturbations of the α-phosphorus resonances of the $Co(NH_3)_4$dADP diastereomers. The nonbridging P–O bonds at the α-phosphorus atom should have different bond orders as a result of complexation with the cobalt ion, with the P–O bond whose oxygen is coordinated to the cobalt having the smaller bond order.[32] This difference in bond order will cause the ^{18}O perturbations in the $Co(NH_3)_4$dADP diastereomers to be different, with the complex in which ^{18}O is complexed with the Co(III) having the smaller perturbation.[9,33,34]

In Figure 3, we present the α-phosphorus regions of the 81.0-MHz ^{31}P NMR spectra of the $Co(NH_3)_4$dADP complexes obtained from enzymatically produced samples of [^{18}O]dADP which had been isotopically diluted with an equal amount of unlabeled dADP. Examination of the spectrum for the sample synthesized from the R_P diastereomer of cyclic [^{18}O]dAMP reveals that the ^{18}O perturbation in the Δ screw sense complex is about 1.3 Hz and that in the Λ screw sense complex is about 2.4 Hz; these relative values[35] demonstrate that the absolute configuration of this sample of uncomplexed [α-^{18}O]dADP is S_P. In the spectrum for the sample synthesized from the S_P diastereomer of cyclic

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(24) An alternate method of analysis would be to perform a hydrolysis reaction in $H_2{}^{17}O$ with snake venom phosphodiesterase as catalyst and then analyze the chirality of the 5′-dAMP with Knowles' procedure[25] (the snake venom phosphodiesterase is known to catalyze the hydrolysis of the R_P diastereomers of nucleoside phosphorothioates with retention of configuration[26,27]). We did not have sufficient material for this type of analysis due to the apparent inhibition of the reaction by dADP[18] and the amount of adenylate cyclase which can be conveniently prepared.
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(30) Dunaway-Mariano, D.; Cleland, W. W. *Biochemistry* **1980**, *19*, 1496.
(31) The Δ screw sense isomer has the *S* configuration at the α-phosphorus atom, and the Λ screw sense isomer has the *R* configuration at the α-phosphorus; these configurations are independent of the presence of ^{18}O.
(32) The best crystallographic evidence for this statement is provided by the analysis of phosphatobis(ethylenediamine)cobalt(III): Anderson, B.; Milburn, R. M.; Harrowfield, J. MacB.; Robertson, G. B.; Sargeson, A. M. *J. Am. Chem. Soc.* **1977**, *99*, 2652.
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(35) These values differ from those that would be expected if the order of the P–O bond complexed to Co(III) were 1 and that of the uncomplexed bond were 2;[9,33] i.e., these bonds do not appear to be formal single and double bonds.

[^{18}O]dAMP, the ^{18}O perturbation in the Δ complex is 2.5 Hz and that in the Λ complex is 1.3 Hz; these relative values demonstrate that the absolute configuration of this sample of uncomplexed [α-^{18}O]dADP is R_P. These assignments are in agreement with those predicted on the basis of the configurations of the precursor cyclic [^{18}O]dAMP samples and the stereochemical course of the adenylate cyclase reaction determined by using ATPαS as substrate. Thus, the stereochemical course of the reaction catalyzed by this enzyme is inversion of configuration by using either oxygen chiral or phosphorothioate substrates.

These results illustrate the considerable utility of substitution-inert Co(III) complexes in determining the configuration at the α-phosphorus atom of oxygen chiral [α-^{18}O]nucleoside diphosphates. Since substitution-inert β,γ-bidentate complexes of nucleoside triphosphates can be prepared[29] and their screw senses have been assigned,[36] examination of the ^{18}O perturbations of the β-phosphorus atoms in complexes prepared from oxygen chiral [β-^{18}O] nucleoside triphosphates should be the most convenient method for determining their configurations.

The enzymatic syntheses of the diastereomers of [α-^{18}O]ADP are currently in progress.

Acknowledgment. We are grateful to Professor W. W. Cleland for helpful discussions and to Peter Demou, Michael Fuson, and Professor Ian M. Armitage for their assistance in obtaining the high-field ^{31}P NMR spectra. This research was supported by a grant (GM-22350) from the National Institutes of Health. The high-field NMR spectrometer used in this research (Bruker CXP-200) is supported by a grant from the National Science Foundation (CHE-7916120).

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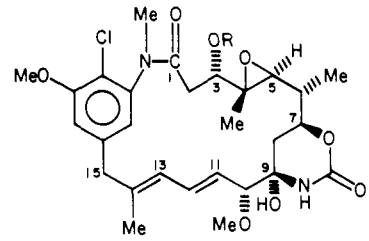
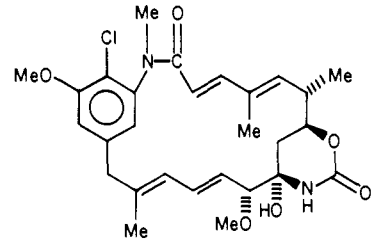
Total Synthesis of (±)-Maytansinol. The Common Precursor to the Maytansinoids

Sir:

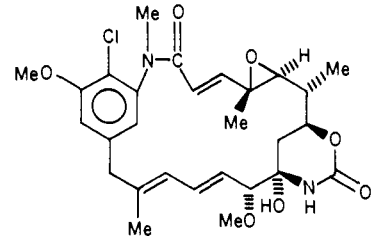
The ansa macrocyclic antitumor substances, maytansinoids, originally isolated and characterized by Kupchan,[1] have been the focus of many pharmacological[2] and synthetic efforts.[3] These highly potent materials are currently undergoing clinical trials under the auspices of the National Cancer Institute. In the last 2 years, there have been successful routes reported for (±)-*N*-methylmaysenine (**2**) in racemic[4] and optically active[5] forms and (±)-maysine **3**,[6] the first naturally occurring maytansinoid. We report herein the total synthesis of (±)-maytansinol **1a** which



1a, R = H
1b, R = $COCH(CH_3)N(CH_3)COCH_3$
1c, R = $COCH_3$



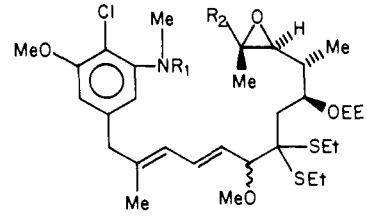
N-methylmaysenine (**2**)



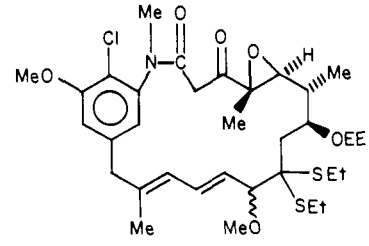
maysine (**3**)

contains all the requisite functionality and stereochemical properties of the antitumor agents maytansine (**1b**), maytanacine (**1c**), and other simple acylated derivatives.[7] Since natural (−)-**1a** has been transformed via routine acylation to (−)-**1b**, (−)-**1c**, and other esters at C-3, this also constitutes the formal total synthesis, in racemic form, for these highly active tumor inhibitors and establishes **1a** as the pivotal precursor to all these interesting substances.

The synthetic scheme leading to (±)-**1a** follows from the key intermediate **4a**[8] which served as the precursor to (±)-maysine.[6]



4a, R_1 = H, R_2 = CHO
4b, R_1 = $COCH_3$, R_2 = CHO
4c, R_1 = $COCH_3$, R_2 = CO_2Me



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