[^{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.

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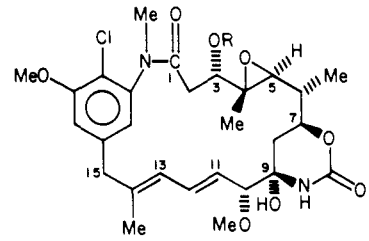
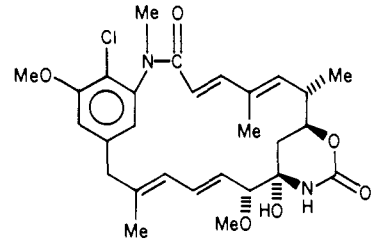
Total Synthesis of (±)-Maytansinol. The Common Precursor to the Maytansinoids

Sir:

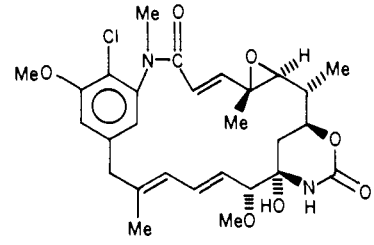
The ansa macrocyclic antitumor substances, maytansinoids, originally isolated and characterized by Kupchan,[1] have been the focus of many pharmacological[2] and synthetic efforts.[3] These highly potent materials are currently undergoing clinical trials under the auspices of the National Cancer Institute. 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 = $COCH_3$



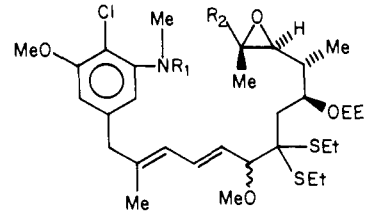
N-methylmaysenine (2)



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

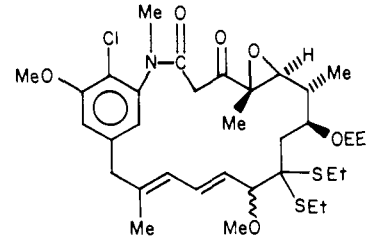


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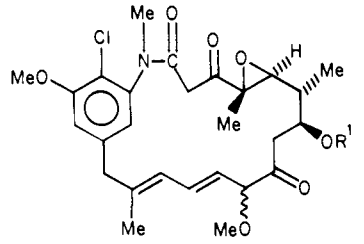
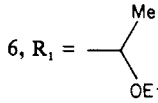
Table I. ^{1}H NMR Data for Synthetic and Natural Maytansinol

proton(s)	synthetic (±)-1a	authentic (-)-1a	authentic (from ref 1 (-)-1a at 100 MHz)
C-4 Me (s)	0.82	0.82	0.84
C-6 Me (d)	1.30 (J = 6.5 Hz)	1.32 (J = 6.5 Hz)	1.32 (J = 6 Hz)
C-14 Me (s)	1.70	1.70	1.68
C-2 H (a portion, AB q)	2.54 (J = 9.7 Hz)	2.54 (J = 9.7 Hz)	
N-Me (s)	3.20	3.20	3.20
C-10 OMe (s)	3.35	3.35	3.36
C-9 OH (br s)	3.60	3.60	3.64
Ar-OMe (s)	3.98	3.98	3.98
C-7 H (m)	4.28–4.35	4.29–4.35	4.36
C-11 H (d of d)	5.50 (J = 9, 15 Hz)	5.50 (J = 9, 15 Hz)	5.53 (J = 9, 15 Hz)
C-13 H (m)	6.13, 6.16	6.13, 6.16	6.19–6.39
C-13 H (m)	6.22, 6.40, 6.43, 6.44	6.22, 6.40, 6.43, 6.44	
NH (m)	6.47	6.47	
ArH	6.81, 6.91	6.81, 6.91	6.81, 7.05
unassigned m	3.10–3.49, 2.11–2.29	3.10–3.49, 2.10–2.29	

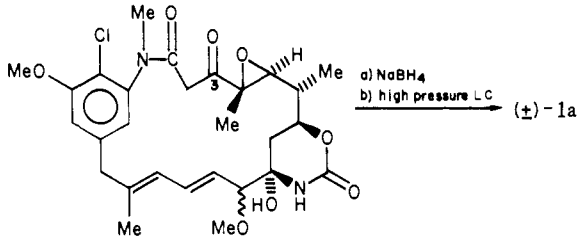
Acetylation (CH_3COCl, pyridine, 0 °C, 3 h) of the secondary amine gave the N-acetyl compound **4b**[9] in 97% yield, and the aldehyde was oxidized (10 equiv of $AgNO_3$, 20 equiv of NaOH, THF–H_2O, 25 °C, 2 h) to the acid and immediately treated with diazomethane–ether at 0 °C to give the methyl ester **4c** in 65% yield.[10] The cyclization to **5** was accomplished in 58% yield by using 4 equiv of lithium (hexamethylsilyl)amide (−78 °C, THF, 5×10^{-3} M, 4 h) and once again showed that anionic ring closures in large rings were indeed a feasible process.[6,11] The next event to be accomplished was the proper removal of the protecting groups at C-7 and C-9. It was necessary to first remove the ethyl thioketal to **6**[12] [2.2 equiv of $HgCl_2$, 2.6 equiv of $CaCO_3$, CH_3CN–H_2O (4:1), 25 °C, 1.5 h] which proceeded in 98% yield, followed by hydrolytic removal of the ethoxyethyl group (1.0 N HCl, THF, 0 °C, 2 h) to **7**.[13] If the ethoxyethyl group was removed prior to the thioketal, extensive decomposition of the molecule resulted, presumably due to the acidic lability of the allylic methyl ether at C-10. Introduction of the cyclic carbinolamide was performed by treating the β-hydroxy ketone **7** with 8.0 equiv of phenyl chloroformate and 8.0 equiv of pyridine in ether–THF (1:1) at 0 °C for 1 h. This gave **8**[14] which was immediately added to excess



6, R_1 =



7, R_1 = H
8, R_1 = CO_2Ph



9

ammonia dissolved in THF at −78 °C and allowed to stir overnight, furnishing **9**[15] in ~50–55% yield.

The remaining step to be carried out required reduction of the C-3 carbonyl in **9**, and this was performed by using sodium borohydride [THF–MeOH (1:1), −40 °C, 30 min] and gave, in 94% yield, an epimeric mixture of four compounds, the major product (~45%) being isolated with the aid of high-pressure liquid chromatography (high-pressure LC). Comparison of this product with authentic natural (−)-maytansinol[16] was rather gratifying, indicating total identity with high-pressure LC (μ-porasil, 30 cm, 5% MeOH–$CHCl_3$, 4.5 min), PTLC (silica gel, 7% MeOH–$CHCl_3$, R_f 0.15), mass spectroscopy, UV, and ^{1}H NMR spectra (Table I).[17]

The completion of this synthetic goal leading to (±)-maytansinol now allows us to pursue the asymmetric synthesis[18] of natural and unnatural derivatives as well as suitable analogues for biological assay. This work is currently in progress.

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(8) Compound **4a** was formed in the previous study[6] as a 1:1 mixture of epimers at C-10 and an undetermined epimeric mixture of ethoxy ethyl ethers at C-7. The latter was removed at a later stage, whereas the C-10 epimers were ultimately separated in the final isolation of **1a**.

(9) High-pressure LC analysis (Waters 244; μ-porasil, 30 cm) in 20% THF–hexane at a flow rate of 3 mL/min gave two peaks, 4.8 and 5.2 min (1:1), shown to be epimers at C-10. The epimeric centers at C-7 were shown in an independent experiment not to interfere with the analysis at C-10. Physical data for **4b**: IR (film) 2710, 1725, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50, 1.52 (3, 2 s, C-4 Me due to epimers at C-10), 1.74 (3, s, C-14 Me), 1.81 (3, s, N-Ac), 3.20 (3, s, N-Me), 3.26 (3, s, C-10 OMe), 3.38 (2, br s, C-15 H), 3.95 (3, s, Ar-OMe), 6.77 (2, br s, ArH), 8.84, 8.87 (1, s, CHO due to epimers at C-10).

(10) **4c**: IR (film) 1737, 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.58, 1.60 (3, s, C-4 Me, as a 1:1 mixture of epimers at C-10), 3.71 (3, s, CO_2Me). High-pressure LC analysis (μ-porasil, 30% THF–hexane, 2 mL/min) showed 4.4 and 4.7 min for epimers at C-10. Purification by PTLC (20% acetone–hexane) gave purified material as a 1:1 mixture of C-10 epimers, R_f 0.2.

(11) **5**: IR ($CHCl_3$) 1718, 1655 cm^{-1}; UV (MeOH) λ_{max} 344, 328, 289, 280, 255, 235 nm; ^{1}H NMR ($CDCl_3$) δ 3.20 (3, s, N–Me), 3.22 (3, s, C-10 OMe), 3.90 and 3.92 ($ArOCH_3$ as a 1:1 epimeric mixture due to C-10); ^{13}C NMR ($CDCl_3$) 203.4, 203.6 (C-3 carbonyl). High-pressure LC (μ-porasil, 30% THF–hexane, 2 mL/min) gave a peak at 2.8 min; purification by PTLC, same solvent, gave R_f 0.28.

(12) **6**: IR (CH_2Cl_2) 1710, 1648 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.21 (3, s, N–Me), 3.40 (3, s, C-10 OMe), 3.94 (3, s, ArOMe), 4.53–4.92 [m, –C*H*-(Et)(OEt)]. Purification by PTLC (30% acetone–hexane) gave R_f 0.11.

(13) **7**: IR (film) 3415, 1716, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.15, 3.18 (3, s, N–Me as a 1:1 mixture of epimers from C-10), 3.38 (3, s, C-10 OMe), 3.94 (3, s, ArOMe).

(14) **8** was not isolated except for a sample to assess the extent of the carbonate formation: IR (CH_2Cl_2) 1755 (carbonate), 1713, 1650 cm^{-1}.

(15) **9**: IR (CH_2Cl_2) 3100–3500 (NH, OH), 1710, 1651, 1635 (carbinolamide) cm^{-1}. High-pressure LC analysis (μ-porasil, 30 cm; 5% MeOH–$CHCl_3$, 2 mL/min) gave a peak at 2.3 min.

(16) We are grateful to Dr. T. Kishi of the Takeda Company, Osaka, for providing us with authentic (−)-maytansinol for comparison.

(17) Physical data comparison of synthetic and natural maytansinol. (a) Ultraviolet spectrum (MeOH, nm): natural (−)-**1a** 232, 244, 252, 281, 288 (cf. ref 1); synthetic (±)-**1a** 233, 243, 252, 281, 288. (b) Mass spectrum (70 eV): natural (−)-**1a** 503 (26), 485 (32), 468 (29), 453 (19), 450 (22), 374 (15), 294 (43), 236 (100), 224 (62); synthetic (±)-**1a** 503 (31), 485 (100), 468 (63), 453 (44), 450 (22), 374 (42), 294 (25), 236 (77), 224 (48). (c) Proton magnetic resonance spectrum (360 MHz, $CDCl_3$, δ): see Table I.

(18) The C-3 to C-7 fragment of the molecule has been prepared via asymmetric synthesis to enantiomerically pure material. This work will be reported in due course.

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