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THE INTRAMOLECULAR NITRILE OXIDE—OLEFIN [3 + 2] CYCLOADDITION ROUTE TO THE MAYTANSINOIDS

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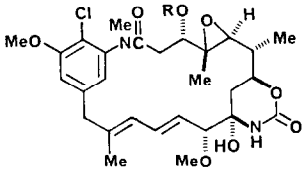
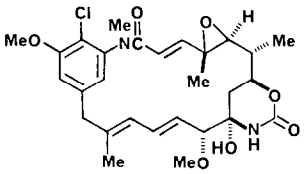
ABSTRACT: The macrocyclization of the olefinic nitrile oxide 24 to the ansa-macrolide skeleton 26, a model for a novel approach to the maytansinoids, is described.

Since Kupchan's[1] report in 1972 of the isolation and structure determination of the ansa-macrolide maytansine (1) and its cogeners (2,3), considerable efforts to synthesize these intriguing substances have been expended. After initial reports indicating excellent progress, three independent syntheses were achieved.[2] As part of our ongoing program utilizing [3 + 2] cycloaddition chemistry for the synthesis of natural products, we wish to report a synthesis of the maytansine skeleton via a novel macrocyclization route that is particularly useful for this class of materials.



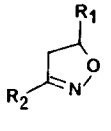
1 MAYTANSINE (R=ACYLAMINO)

2 MAYTANSINOL (R=H)



3 MAYSINE

From the outset we were intrigued with the possibility of closing the 19-membered ring of maytansine with a [3 + 2] cycloaddition reaction.[3] An intramolecular nitrile oxide-olefin cyclization would yield an isoxazoline 4 imbedded in the resulting ring. Thus, it was important to verify that this heterocycle could then be further elaborated into functionality present in the target molecule. The obvious choice is the cyclic hydroxy carbamate system 5 often implicated in the mechanism of action of this antitumor class of compounds.



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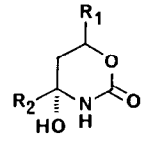

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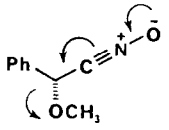

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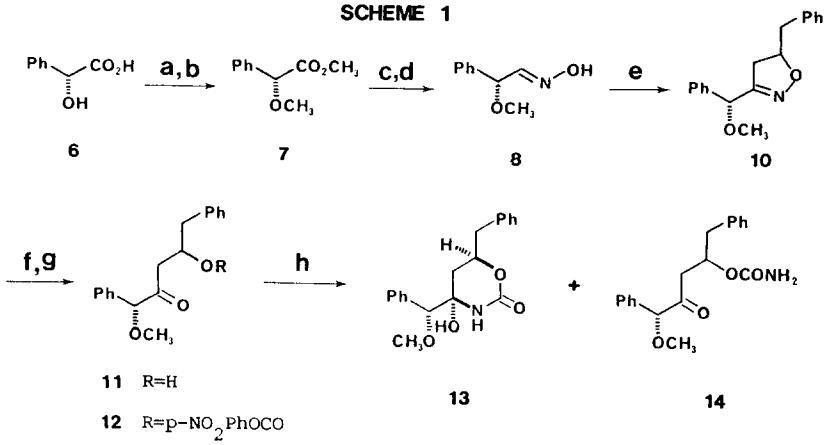
To this end, D-(-)-mandelic acid (6) was converted to methyl mandelate O-methyl ether (7)[4], which possesses the same absolute configuration as C(10) of maytansine (Scheme 1). The phenyl moiety was chosen to represent the diene system attached to C(10) in the 'southern zone' of the target. Conversion of 7 to the optically active oxime 8 was accomplished by DIBAL reduction to the aldehyde and treatment with hydroxylamine. A facile intermolecular nitrile oxide-olefin cycloaddition occurred when 8 was oxidized with Clorox® in a two-phase system[5] in the presence of allyl benzene. This afforded the desired isoxazoline 10, regiospecifically (two diastereomers), in 70% yield. Fortunately, the intermediate nitrile oxide exhibited no tendency to decompose by the elimination mechanism shown in 9. Conversion of 10 to the corresponding cyclic hydroxy carbamate 13, m.p. 128-129°, was achieved by a hydrolytic reduction[6] to the β-hydroxy ketone 11[7] and treatment with p-nitrophenyl chloroformate followed by ammonia. A small amount (15%) of the uncyclized isomer 14 could also be isolated by chromatography. This surprisingly stable molecule, which does not go to 13 under the reaction conditions, could be converted to 13 by either DBU/THF or 1N HCl/CH_3CN. This 'open form' material presumably arises from attack of ammonia at the formate-derived carbonyl of the intermediate 12 leading directly to 14, whereas reaction at the ketone site of 12 to form a hemi-aminal followed by cyclization accounts for the production of 13.

SCHEME 1

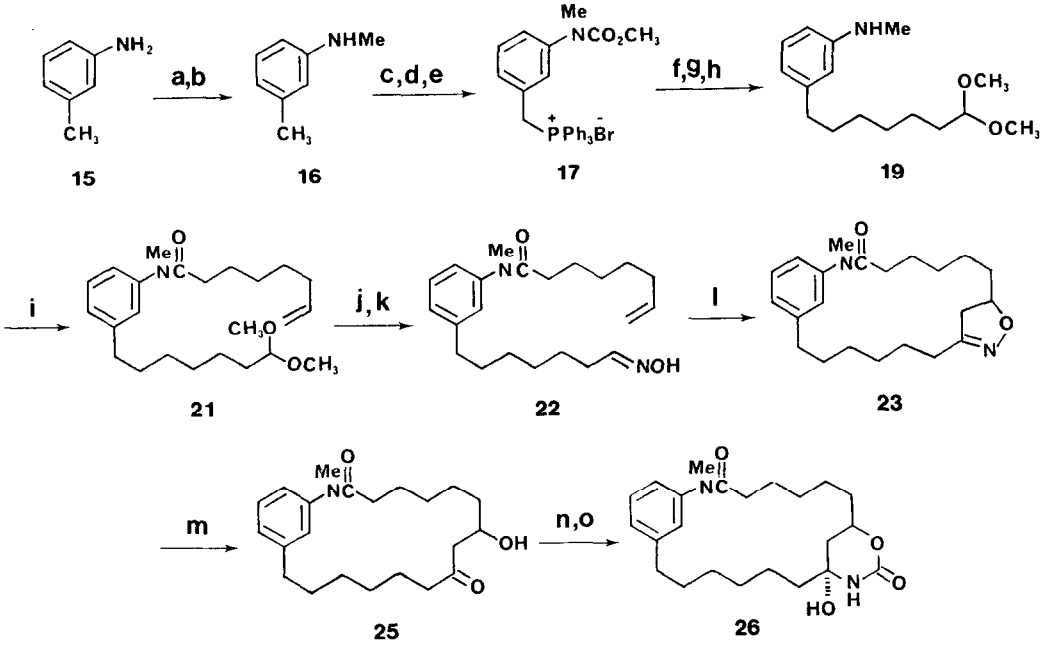


a c-H_2SO_4, CH_3OH/reflux, 2.5 h; b CH_3I, Ag_2O/DMF/RT, 24 h; c DIBAL/CH_2Cl_2/-78°→-30°, 2 h, d NH_2OH/EtOH/RT, 1.5h; e allylbenzene, Clorox®, NEt_3/Ch_2Cl_2/RT, 1 h; f H_2, Raney Ni/CH_3OH-H_2O-HOAc/RT, 16h; G p-nitrophenyl chloroformate, pyridine/CH_2Cl_2/0°, 30 min; h NH_3/CH_3OH-CH_2Cl_2/-78°→-20°, 1 h.

Encouraged by these results, we prepared m-methylaminotoluene (16) from m-toluidene (15) (Scheme 2). After protection of nitrogen as its methyl carbamate, allylic bromination and treatment with triphenylphosphine afforded the desired phosphonium salt 17. Wittig reaction with the acetal aldehyde 18[8], followed by catalytic hydrogenation of the resulting styrene and deprotection yielded the N-methyl aniline derivative 19. Acylation with 7-octenoyl chloride (20) led to amide 21 which was converted to the key intermediate oximino-olefin 22 by standard methods. In spite of some pessimistic projections of the yield in the crucial macrocyclization, an initial yield of 51% of the 19-membered cycloaduct 23[10], m.p. 95-96°, was obtained by phase-transfer oxidation of 22 as in the bimolecular model. An even better synthesis of 23 was achieved when the nitro-olefin 24[11], readily prepared from phosphonium salt 17, was treated with p-chlorophenylisocyanate, affording the desired

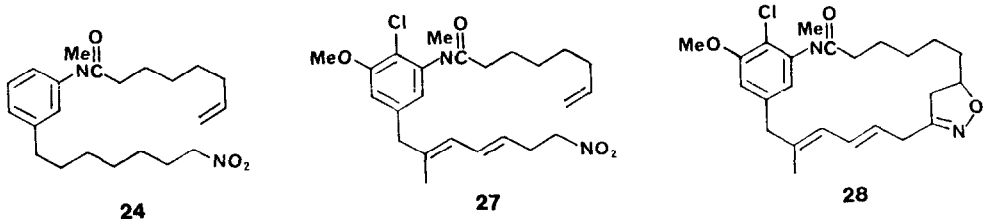
macrocycloadduct 23 in 82% isolated yield! Hydrolytic reduction to the β-hydroxy macrocycle 25, m.p. 109-110°, and conversion to the targeted maytansine analog 26[12], m.p. 119-120°, following the lines of the model study, completed the required transformation. Interestingly, compound 26, a highly simplified version of maytansine, exhibited *in vitro* anti-tumor activity against human colon tumor cells (ID_{50} = 2.12 μg/mL). This is presumably attributed to the presence of the cyclic hydroxy carbamate group in 26, the proposed 'active site' of the maytansinoids.[13]

SCHEME 2



a CH_3CO_2COH/THF/RT, 2 h; b BH_3-Me_2S/THF/reflux, 3 h; c $ClCO_2CH_3$, pyridine/CH_2Cl_2/0°, 1h; d NBS/CCl_4/reflux, 6 h; e Ph_3P/toluene/reflux, 36 h; f ^tBuOK/THF/0°, 30 min, then $OHC(CH_2)_4CH(OCH_3)_2$, 0° → RT, 4 h; g H_2, 10% Pd-C, $NaHCO_3$/MeOH/RT, 5 h; h 12M-KOH/EtOH/reflux, 16 h; i CH_2=$CH(CH_2)_5COCl$ (20), pyridine/CH_2Cl_2/0° → RT, 5 h; j 75% aq HOAc/50°, 1 h; k NH_2OH/EtOH/H_2O/RT, 1 h; l Clorox, n-Bu_4NOH/CH_2Cl_2/72 h; m H_2, Raney-Ni/MeOH-H_2O-HOAc-CH_2Cl_2/RT, 5 h; n p-nitrophenyl chloroformate, pyridine/CH_2Cl_2/0°, 25 min; o NH_3/CH_3OH-CH_2Cl_2/-78° → 0°, 1 h.

One additional model study was required before a final assault on maytansine employing this methodology could be justified. Our concern was directed toward the presence of the diene system in the natural product and its possible complication of the key nitrile oxide-olefin cycloaddition step. Therefore, the highly functionalized nitro-triene 27 was



synthesized[14] and shown to undergo the desired macrocyclization to the isoxazoline 28. This satisfying transformation proceeded in 50% yield (unoptimized) and augurs well for the completion of the total synthesis of maytansine by this route.

In summary, intramolecular nitrile oxide-olefin [3 + 2] cycloaddition chemistry has been shown to be an important reaction for macrocyclization. Its utility for the total synthesis of the maytansinoids and other macrolides is under intense investigation, and these results and others will be reported in due course.

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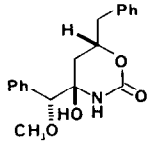
4. McKenzie, A., Wren, H., J. Chem. Soc., 1910, 97, 484.
5. Lee, G.A., Synthesis, 1982, 508.
6. Curran, D.P., J. Am. Chem. Soc., 1982, 104, 4024. Kozikowski, A.P., Adamczyk. M., Tet. Lett., 1982, 23, 3123.
7. The two diastereomers, 12 and its epimer (ratio 57:43) were separated (silica gel 60, EtOAc-Hexane 1:1). The epimer was also converted to the corresponding cyclic hydroxy carbonate 29, m.p. 144-147 (dec).



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8. Schreiber, S.L., Claus, R.E., Reagan, J., Tet. Lett., 1982, 23, 3867.
9. 7-Octenoyl chloride (20) was synthesized from methyl 7-oxo-heptanoate[8] in 3 steps: i. $Ph_3P^+CH_3Br^-$, n-BuLi/THF/0° RT, 3 h; ii. 1N-NaOH/MeOH/RT, 18 h; iii. $SOCl_2$/50°, 3 h.
10. ^1H NMR ($CDCl_3$, 360 MHz) δ 7.31 (1H,t,J=8Hz), 7.12 (1H,d,J=8Hz), 7.00 (1H,d,J=8Hz), 6.99 (1H,s), 4.60 (1H,m), 3.24 (3H,s), 2.84 (1H,dd,J=10Hz,17Hz), 2.63 (2H,m), 2.54 (1H,dd,J=6Hz,17Hz), 2.48 (1H, td, J=5Hz,9Hz), 2.22 (1H,dt,J=5Hz,14Hz), 2.07 (2H,m), 1.65-1.15 (16H).
11. Nitro-olefin 24 was synthesized from the phosphonium salt 17 in 8 steps: i. ^tBuOK/THF/0° 0.5 h, then ω-hydroxyvaleraldehyde O-THP/0°→RT, 4 h; ii. H_2, 10% Pd-C/MeOH/RT, 5 h; iii. 12M-KOH/EtOH/reflux, 16 h; iv. 7-octenoyl chloride (20), pyridine/CH_2Cl_2/0° RT, 5 h; v. Dowex-50X8-400/MeOH/50° , 20 h; vi. CH_3SO_2Cl, NEt_3/CH_2Cl_2/0° , 1 h; vii LiI/DMF/90 3.5 h; viii. $AgNO_2/Et_2O$/0° , 1 day, RT, 12 days.
12. ^1H NMR ($CDCl_3$, 360 MHz) δ 7.33 (1H,t,J=8Hz), 7.15 (1H,d,J=8Hz), 6.99 (2H,m), 5.04 (1H,m), 4.60 (2H,brs), 3.25 (3H,s), 2.65 (4H,m), 2.36 (2H,m), 2.05 (2H, brt,J=7Hz) 1.70-1.15 (16H); mass spectrum m/e 341.2372 (M^+-H_2O-HNCO; calcd for $C_{22}H_{31}NO_2$, 341.2355).
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14. Nitro triene 27 was synthesized from 1-[4-chloro-3-methoxy-5-(methylamino) phenyl]-2-propanone[15] in 11 steps: i. $Ph_3P{=}CHCO_2CH_3$/toluene/reflux, 36 h; ii. DIBAL/CH_2Cl_2/0° , 1.5 h; iii. 7-octenoyl chloride (20), pyridine/CH_2Cl_2/0° 1 h; iv. 1M-NaOH/MeOH/RT, 1 h; v. PBr_3, LiBr, collidine/Et_2O-THF/0° , 25 min; vi. Ph_3P/CH_3CN/RT, 2 h; vii. $LiN(SiMe_3)_2$, 3-hydroxypropanal O-THP ether/THF/ -78°→-20°, 1 h; viii. Dowex-50X8-400/MeOH/RT, 24 h; ix. CH_3SO_2Cl, NEt_3/CH_2Cl_2/0° , 30 min; x. LiI/DMF/80 , 15 h; xi. $NaNO_2$, catechol/DMSO/RT, 16 h.
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