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PROGRESS TOWARD THE TOTAL SYNTHESIS OF MAYTANSINE. A MODEL SYSTEM CONTAINING THE C-7 TO C-16 MOIETY (SOUTHERN AND EASTERN ZONE)

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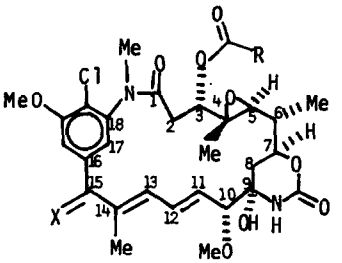
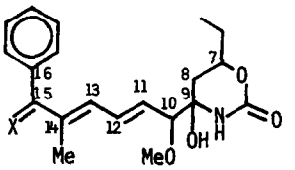
In the previous communication[1] we have described a stereoselective approach to the northern zone of the maytansinoids 1 (a-c).[2] This report deals with the synthesis of an advanced model 2 (a,b) possessing the appropriately functionalized carbon chain from C-7 to C-16 including the fused cyclic carbamate which we have termed the "southern and eastern" zones of the macrolide.





1a, X=H_2, R = N-acetyl glycine

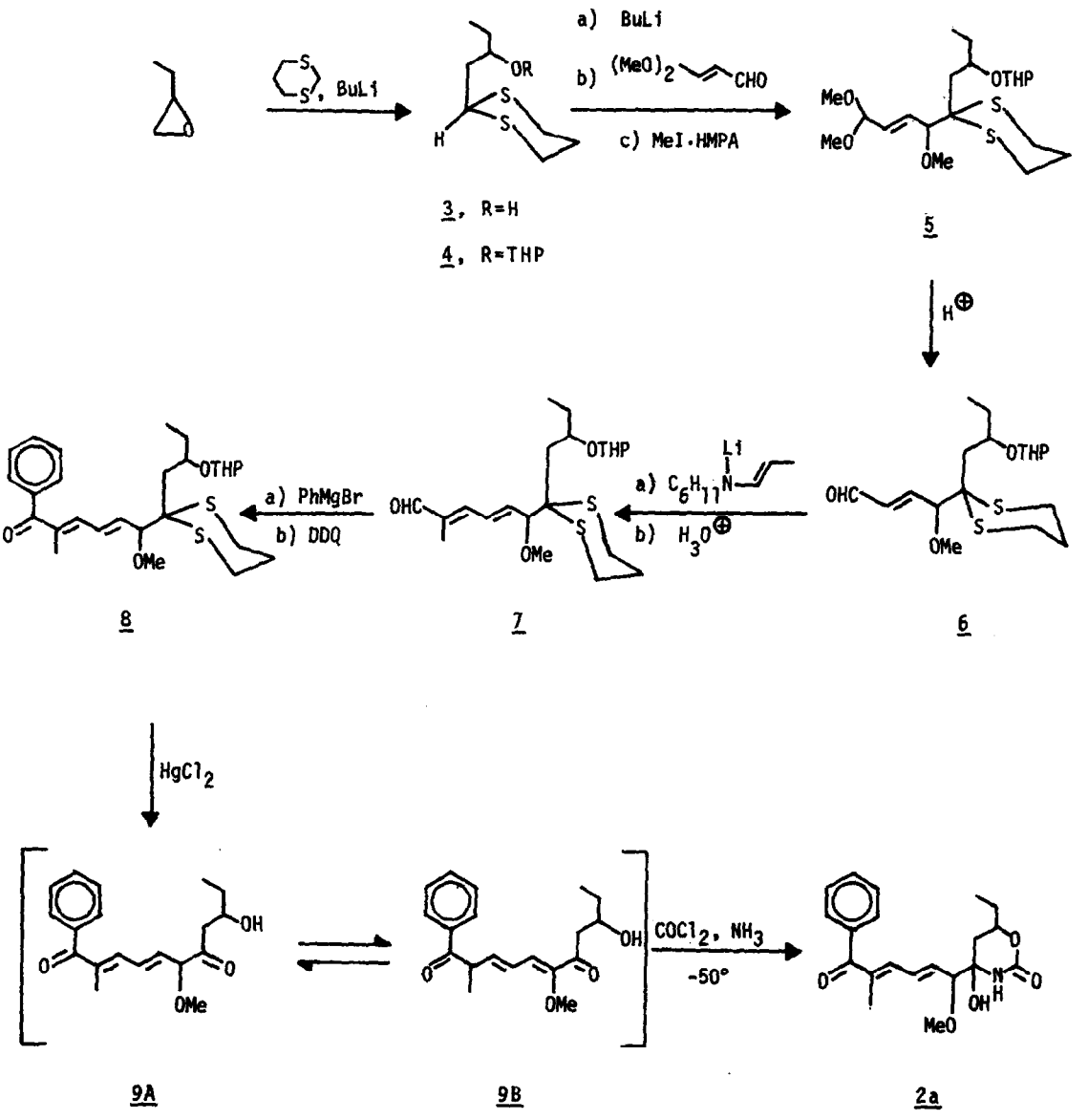
1b, X=H, OH

1c, X=O

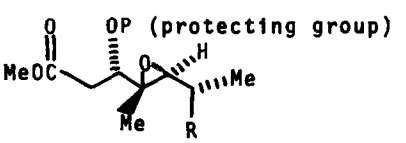
2a, X=O

2b, X=H, OH

The synthetic approach to 2 was initiated by alkylation of 2-lithio-1,3-dithiane[3] with 1,2-epoxybutane (-25°, 48 h) producing the dithiane alcohol 3 (98%, oil) which was transformed into its tetrahydropyranyl ether 4 (94%) by addition of dihydropyran (ether, 20°, TsOH). Reforming the lithio salt (BuLi, -30°) of 4 followed by addition (-78°) of the monoacetal of fumaraldehyde[4] produced the expected adduct which was converted *in situ* (MeI-HMPA, 1:1) to the methyl ether 5 (80%, R_f 0.60, 4:1 hexane-acetone). Although diastereomers are possible, only a single homogeneous spot was observed on tlc. Selective cleavage of the acetal (oxalic acid, 5°, THF-H_2O, 5:1,


BuLi
a) BuLi
b) (MeO)2 CHO
c) MeI·HMPA
3, R=H
4, R=THP
5
H⊕
6
a) C6H11N Li
b) H3O⊕
7
a) PhMgBr
b) DDQ
8
HgCl2
9A
9B
COCl2, NH3
-50°
2a

6 h) furnished the aldehyde 6 [96%; R_f 0.46, 4:1 hexane-acetone; ir 1695 cm^{-1}, nmr ($CDCl_3$) δ 9.7 (d, 8 Hz, 1), 6.3 (d of d, J=8, 16 Hz, 1), 7.05 (d of d, J=6, 15 Hz, 1), 3.4 (s, 3)]. A three carbon homologation of 6 was accomplished using Wittig's aldol method[5] (N-cyclohexylpropyl imine, lithium diisopropylamide, -78°, 6 h) and directly dehydrating the hydroxy intermediate (aq. oxalic acid, 0°) to afford the E,E-dienal 7 purified by preparative tlc [80%; ir 1690, 1635, 1605 cm^{-1}; nmr ($CDCl_3$) δ 9.7 (s, 1), 6.75 (m, 3), 1.9 (s, 3), 3.4 (s, 3); R_f 0.45 (hexane-acetone, 4:10]. Treatment of 7 with phenylmagnesium bromide (ether, 5°) gave the intermediate allylic alcohol (λ_{max}^{EtOH} 246 nm) as a mixture of diastereomers and this was oxidized[6] (DDQ, THF, 25°) without further purification to the ketone 8 [85% from 7, λ_{max}^{EtOH} 287 nm; ir 1650, 1635, 1605, 1580 cm^{-1}; nmr ($CDCl_3$) δ 2.13 (s, 3), 3.40 (s, 3), 6.8 (m, 3), R_f 0.26]. Removal of the dithiane and tetrahydropyranyl protecting groups in 8 was accomplished in a single step using mercuric chloride (CH_3CN-H_2O, 4:1, 25°, 5 h)[7] producing 9 (70%) as an equilibrium mixture of 9A and 9B containing 80% of the latter.[8] The mixture was treated successively[9] with phosgene (1.0 equiv collidine, ether-benzene, 25°) and then with methanolic ammonia (-50°) furnishing the cyclic carbamate 2a; (mp 56°; 50%, λ_{max}^{EtOH} 287 nm; ir 3560, 3430, 1720, 1650, 1635, 1605, 1585; nmr ($CDCl_3$) δ 1.0 (t, 3), 1.7 (m, 5), 2.15 (s, 3), 3.40 (s, 3), 3.72 (m, 1), 4.5 (m, 2), 5.9 (m, 1), 6.8 (m, 2), 7.6 (m, 5); m/e 341 (M^+-18) 0.3%, 298 [M^+-(H_2O + HNCO) 1.1%]. It is noteworthy that the mass fragmentation of 2a exhibits the same behavior as that of the maytansines in that the molecular ion is virtually absent and only the M^+-18 and M^+-61 (H_2O + HNCO) are visible.[2] Reduction with sodium borohydride converted 2a to 2b[10] which corresponds to the exact southern portion of colubrinol,[2] an ansa macrolide differing from the maytansines only at C-15, yet also possessing comparable anti-tumor activity. It should now be feasible to repeat this sequence using the appropriately substituted northern zone[1] 10, after conversion of the formyl group to the epoxy derivative 11. Furthermore, the Grignard reagent of the appropriately substituted aromatic portion is required in the transformation of 7 to 8. Work is continuing toward these goals.[11]



10 R=CHO

11 R= -HC—CH_2 (epoxide)

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3. For a review of dithiane chemistry, c.f. D. Seebach, Synthesis, 1, 17 (1969).

4. This aldehyde was formed in two steps from furan. First, reaction of furan with bromide in methanol gave 1,1,4,4-tetramethoxy-2-butene [S. M. Makin and N. I. Telegrina, J. Gen. Chem., USSR, 32, 1032 (1962)]. Hydrolysis to the aldehyde was performed (80-85%) using 25% perchloric acid (1.0 equiv of water) at 0° in THF solution, bp 55° (2.5 mm), G. A. Kogan, et. al., Bull. Acad. Sci. USSR, Div. Chem. Sei., 2093 (1962) report 78° (11 mm).

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8. Under certain conditions, we could isolate 9a in pure form. An equilibration study (via nmr) indicated that the equilibrium 9A-9B is established very quickly (~15 min) if a trace of s-collidine is added. Although $K_{eq}^{\sim}=4$ for 9A ⇌ 9B, the formation of 2a was ~50% indicating that the unfavorable equilibrium was not detrimental to the cyclic carbamate formation.

9. A. I. Meyers and C. C. Shaw, Tetrahedron Letters, 717 (1974).

10. Physical data for 2b, λ_{max}^{EtOH} 244 nm; ir 3550, 3440, 1720 cm^{-1}; nmr ($CDCl_3$) δ 0.9 (t, 3), 1.70 (br.s, 3), 1.7 (m, 6), 3.4 (s, 3), 3.6 (m, 2), 4.8 (m, 3), 5.2 (s, 1), 6.4 (m, 1), 7.4 (s, 5).

11. It has readily been observed that the t-Boc derivative of m-bromo-(N-methyl) aniline, when converted to its Grignard reagent, added smoothly to aldehydes similar to 7. (Dr. D. A. Horne, research in progress.) No effort was expended in separating stereoisomers in 2a since this model could not be used in further synthetic steps.