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PROGRESS TOWARD THE TOTAL SYNTHESIS OF MAYTANSINOIDS. AN EFFICIENT ROUTE TO TWO MAJOR PRECURSORS (WESTERN-SOUTHERN ZONE)

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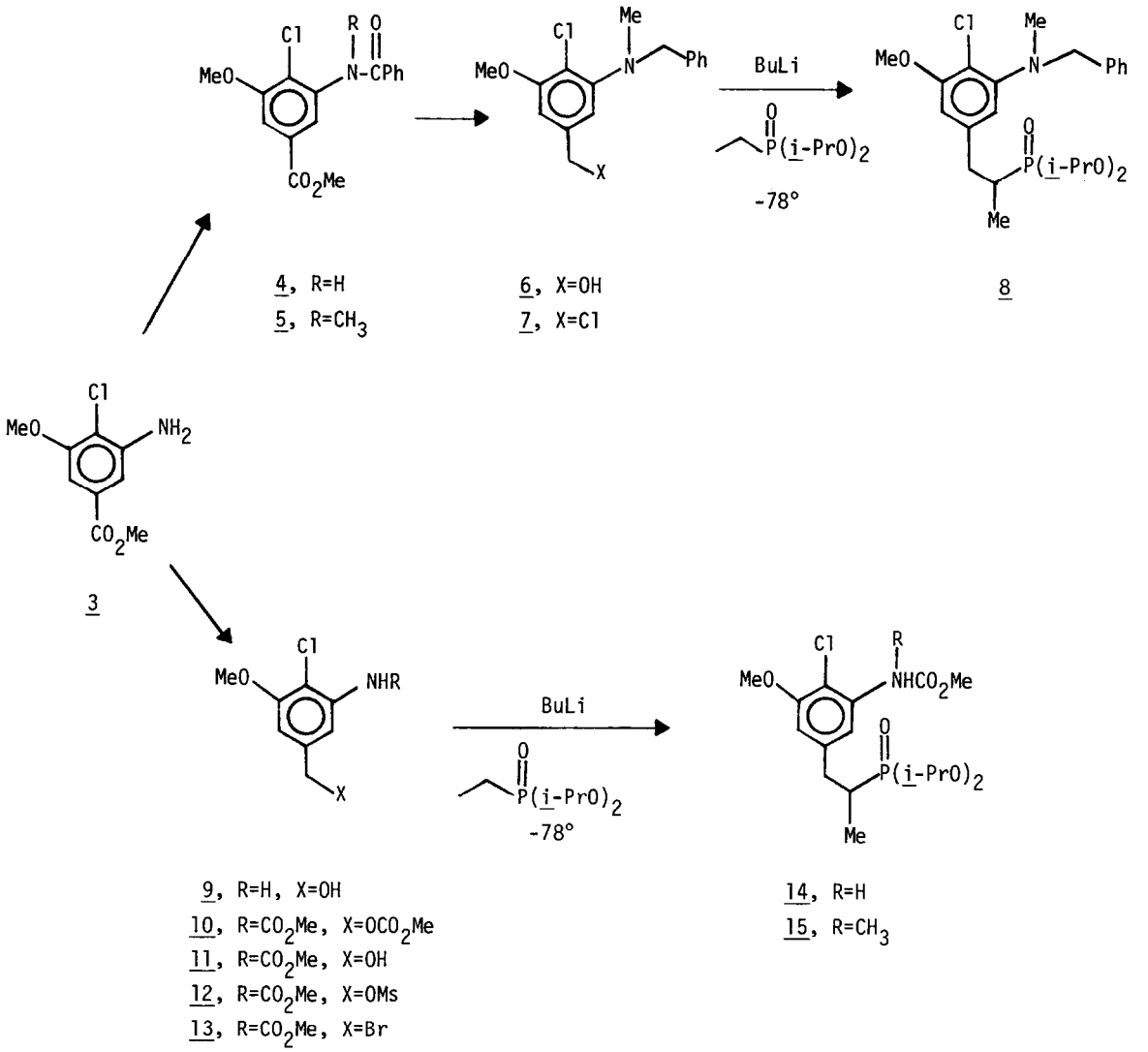
The effort to reach the anti-tumor macrocycle, maytansine,[1] has been rather extensive and reports by various groups in recent years[2] have demonstrated the extreme complexity of the problem. We wish to describe our recent studies which have provided good access to a significant portion of the target molecule in the form of the functionalized intermediates 1 and 2.

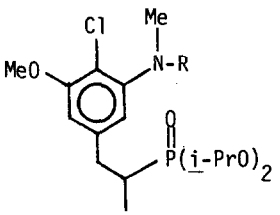
The previously described[1d] aromatic compound 3 served as a common precursor to 1 and 2 by the routes outlined below. Amino ester 3 was transformed into the N-benzoyl derivative 4 (m.p. 148-150°) using benzoyl chloride-triethylamine Methylation to 5 (m.p. 128°) was accomplished with t-BuOH-MeI-DMF and reduction with $LiAlH_4$ (THF, 66°) gave the N-benzyl benzyl alcohol 6 (99%, oil). Without purification, 6 was converted to the chloride 7 (87%) using mesyl chloride, lithium chloride, DMF.[3] A solution of lithiated ethyldiisopropyl phosphonate (THF, -78°) was treated with 7 to afford the phosphonate 8 (65%) as an oil (purified by PLC). The overall yield of 8 from amino ester 3 was 56%. Addition of n-BuLi (-78°, THF) to 8 gave the lithiated phosphonate which was treated, after 22 min, with E-γ,γ-dimethoxycrotonaldehyde (-78°, 40 min), followed by addition of DMF and heating of the mixture (13 h, 100°). This gave the diene 16, which was immediately hydrolyzed (10% HCl-THF, 1.5 h) to the dieneal 1 (50% from 8); ir 2725, 1685, 1635 cm^{-1}; nmr ($CDCl_3$), δ 9.67 (d, J=7 Hz). Multiple elutions on tlc showed only a single spot.[4] The high degree of stereoselectivity in the phosphonate coupling reaction (to 1) is due primarily to the diisopropyl groups on the phosphonate.[5]

The sequence leading to 2 also originates with the amino ester 3. Reduction ($LiAlH_4$, THF) gave 9 (99%, m.p. 100-101°) which was converted to the carbamate-carbonate 10 (89%) with excess methyl chloroformate (CH_2Cl_2, 0°, 30 min). Selective removal of the carbonate (1% K_2CO_3-MeOH, 25°, 15 h), gave the alcohol 11 (88%) which was transformed (1.4 eq MesCl, 1.5 eq Et_3N, CH_2Cl_2, -20°), into the mesylate 12 (100%, m.p. 111-113°). Addition of LiBr in DMF to 12 (25°, 15 h)



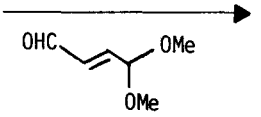
gave the benzyl bromide 13 (96%, m.p. 133-135°) which was alkylated with lithio ethyldiisopropyl phosphonate (1.2 eq LDA, -78°, THF) to furnish 14 (99%). Methylation of the latter (t-BuOK, MeI, THF, 66°) gave the phosphonate 15 (96%). The overall yield of 15 from 3 was 71%. Addition of n-BuLi (THF, -78°) to 15, followed by introduction of E-γ,γ-dimethoxycrotonaldehyde gave 17 as an oil which was directly hydrolyzed [1 N HCl, THF (1:5) 25°, 1.5 h] to give 2 [50% from 15, ir (film) 1679, 1713, 2725; nmr ($CDCl_3$) δ 9.8 (d, J=7 Hz)].[4,6]

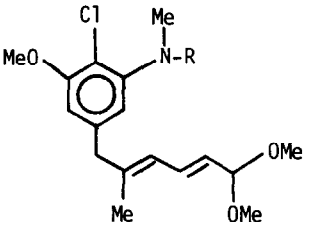
With the precursors 1 and 2 in hand, further studies linking the "northern and eastern zones"[2a,b] should provide the target molecule, maytansine.



8, R=$PhCH_2$

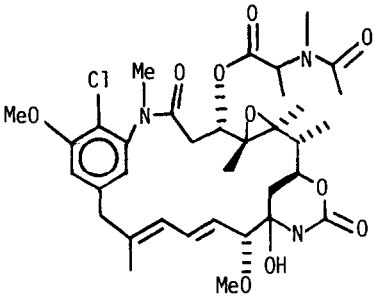
15, R=CO_2Me



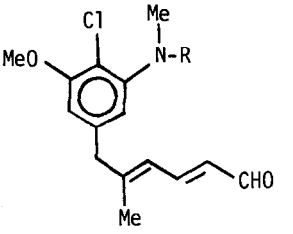


16, R=$PhCH_2$

17, R=CO_2Me



Maytansine



1, R=$PhCH_2$

2, R=CO_2Me

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REFERENCES AND FOOTNOTES

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2. a) A. I. Meyers, C. C. Shaw, D. A. Horne, L. M. Trefonas and R. J. Majeste, Tetrahedron Letters, 1745 (1975); b) A. I. Meyers and R. S. Brinkmeyer, ibid., 1749 (1975); c) A. I. Meyers and C. C. Shaw, ibid., 717 (1974); d) A. I. Meyers and J. M. Kane, ibid., 771 (1977); e) E. J. Corey and M. G. Bock, ibid., 2643 (1975); f) E. J. Corey, et al., ibid., 777 (1977); g) J. E. Foy and B. Ganum, ibid., 775 (1977); h) M. Vandewalle, et al., ibid., 3195 (1977); i) O. E. Edwards and P. T. Ho, Can. J. Chem., 55, 371 (1977); j) W. J. Elliot and J. Fried, J. Org. Chem., 41, 2469 (1976).

3. A. I. Meyers and E. W. Collington, J. Org. Chem., 36, 3044 (1971).

4. Although the product appears to be pure E,E-isomer, the presence of a small amount of the E,Z-isomer cannot be precluded at this time.

5. In collatoral studies, the use of diisopropylphosphonates in Horner-Emmons-Wadsworth couplings with a variety of carbonyl compounds has resulted in very high stereoselectivity (>97%); R. K. Smith, research in progress.

6. Both 1 and 2, as well as all other intermediates, gave satisfactory analytical data.