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PROGRESS TOWARD THE TOTAL SYNTHESIS OF MAYTANSINOIDS. A FACILE ROUTE TO THE AROMATIC MOIETY (WESTERN ZONE)

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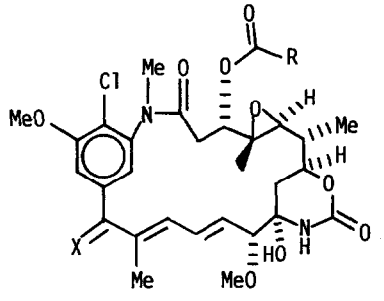
The potent anti-leukemic maytansinoids 1 (a-c)[1] have been the synthetic goal of several groups. Approaches to the "northern", "southern", and "eastern" regions of these complex substances were recently reported.[2,3] The so-called "western" zone of 1 contains an unusual aromatic substitution array which at first glance does not appear to present a formidable synthetic challenge. However, the introduction of three contiguous hetero substituents (MeO, Cl, NH_2), in addition to a suitable functional group for linkage to the "southern" zone, is not readily obvious from traditional methodology.[4] We



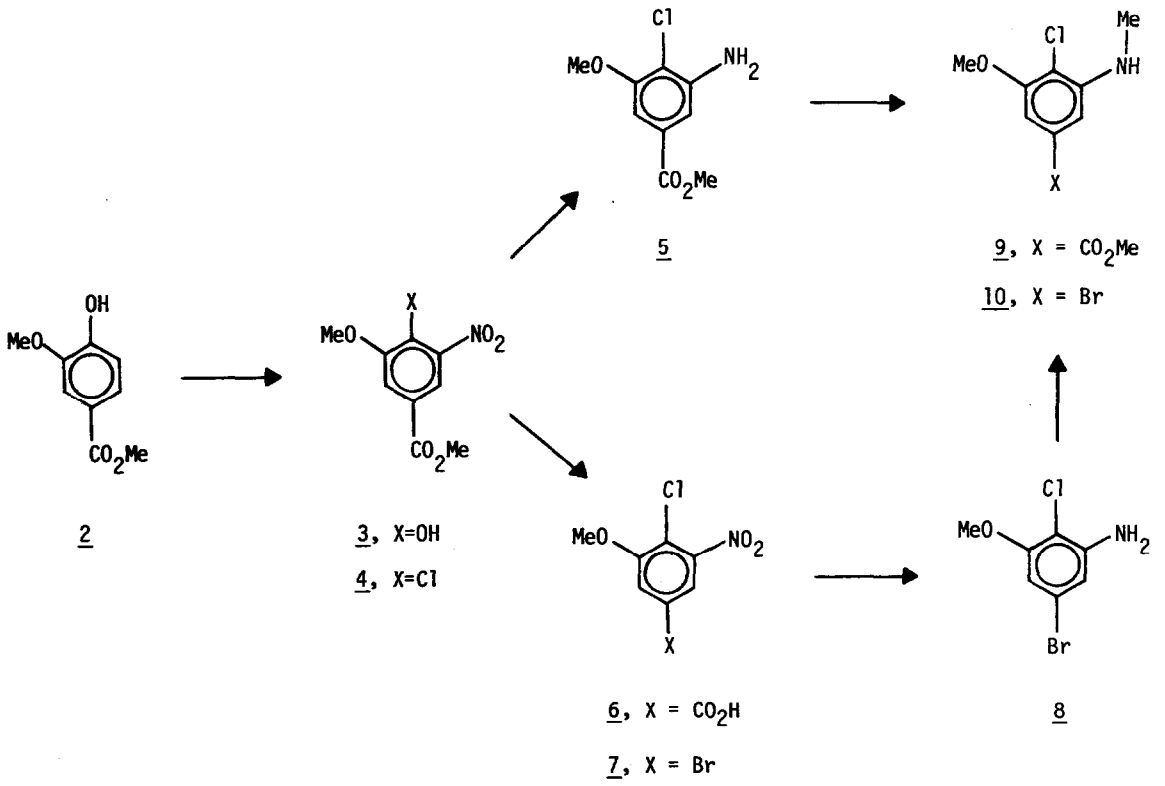
1a, X=H_2, R=N-acetylglycine

1b, X=H, OH

1c, X=O

wish to describe a rather simple solution to this problem which leads to the appropriately substituted aromatic ring (9 and 10), containing substituents for further elaboration to the target macrocycle.

Commercially available methyl vanillate (Aldrich) 2 was nitrated ($HOAc-HNO_3$, 0°) to give the nitro derivative 3 [86%; mp 154-155°; nmr ($CDCl_3$) δ 8.45 (d, J=2, 1H), 7.80 (d, J=2, 1H), 4.04 (s, 3H), 3.98 (s, 3H)].[5] Treatment of 3 with thionyl chloride-DMF, under reflux, furnished the chloro-derivative 4 in 61% yield [mp 103-104°, nmr ($CDCl_3$) δ 8.04 (d, J=2, 1H), 7.78 (d, J=2, 1H), 4.07 (s, 3H), 4.00 (s, 3H); ir (KBr) 1735, 1720, 1540, 1360 cm^{-1}; m/e 245 ($M^{+\cdot}$), 247 (1:0.3)]. The ready formation of 4 provides a key aromatic intermediate possessing the requisite substitution mentioned above. Reduction ($SnCl_2$-HOAc) of 4 gave the aniline 5 in 75% yield [low melting solid; nmr



($CDCl_3$) δ 7.18 (d, J=2, 1H), 7.05 (d, J=2, 1H), 4.3 (br.s, exchanges with D_2O, 2H), 3.97 (s, 3H), 3.94 (s, 3H)]. Monomethylation of 5 using the method of Kadin[6] or methylation of the trifuloroacetyl derivative (MeI, NaH) produced the N-methyl derivative 9 in 50-80% yields [mp 84-86°; nmr ($CDCl_3$) δ 7.03 (s, 2H), 4.54 (br.s, exchangeable with D_2O, 1H), 3.93 (s, 6H), 2.98 (d, J=5, 3H, collapses to singlet on D_2O addition); m/e 229 ($M^{+\cdot}$), 231 (1:0.3)]. This sequence leading to 9 allows complete versatility in attaching the "southern" zone via nucleophilic (organometallic) reagents while amide coupling is possible with the "northern" zone. On the other hand, 4 may be elaborated further by hydrolysis (10% aq. KOH) to 6 [93%; mp 217-218°; ir (KBr) 3600-2400, 1700, 1545, 1370 cm^{-1}] and treatment with HgO-Br_2 (CCl_4, reflux)[7] to give the bromide 7 [55%; mp 110-112°; nmr ($CDCl_3$) δ 7.58 (d, J=2, 1H), 7.28 (d, J=2, 1H), 4.02 (s, 3H); m/e 265 ($M^{+\cdot}$), 267, 269 (1:1.2:0.25)]. Reduction ($SnCl_2$-HOAc) gave the aniline 8 [75%; nmr ($CDCl_3$) δ 6.60 (d, J=2 1H), 6.48 (d, J=2, 1H), 4.20 (br.s, exchanges with D_2O, 2H), 3.88 (s, 3H)] which was monomethylated, as above, to 10 [75%; low melting solid; nmr ($CDCl_3$) δ 6.48 (s, 2H), 4.50 (br.s, exchanges with D_2O, 1H), 3.89 (s, 3H), 2.92 (d, J=5, 3H, collapses to singlet with D_2O)]. The acquisition of 10 furnishes an aromatic precursor which can be utilized in coupling to the "southern" zone via its organolithium or Grignard derivative.[2] Thus, the routes outlined above provide correctly substituted aromatic precursors for incorporation into the macrocycle and future developments will dictate which aromatic (9 or 10) will be most suitable for this task.

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