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ANSA MACROLIDE SYNTHESIS

PREPARATION OF THE AROMATIC PORTION OF MAYTANSINE

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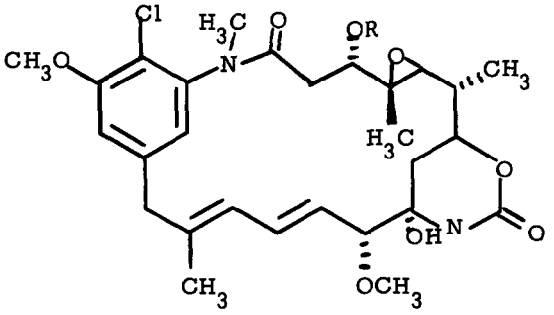
Progress towards the stereospecific synthesis of clinically interesting maytansinoids 1[1] requires an efficient route to the tetrasubstituted aromatic ("western") fragment commonly found in these ansa macrolides.[2] An unusual assemblage of three different vicinal heteroatoms, the selection of an appropriate nitrogen protecting group, and the need for a preparatively practical route are three features which considerably complicate this objective. In this letter we disclose the development of a six-step route to 2-chloro-3-methoxy-5-bromomethyl-N-methylacetanilide 8, a versatile intermediate which satisfies our present prerequisites for maytansine total synthesis.



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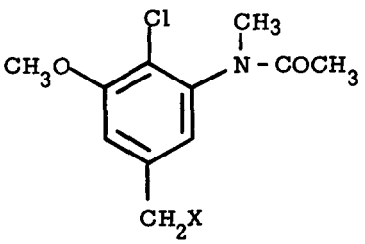
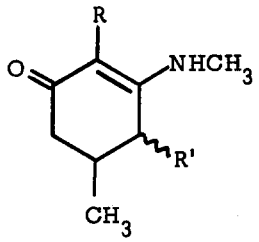


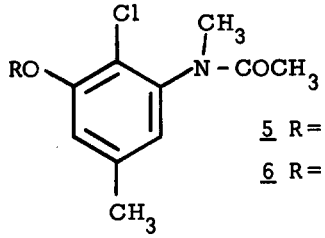
7 X=H
8 X=Br

Condensation of 5-methylcyclohexane-1,3-dione[3] with 40% aqueous methylamine furnishes 2 (mp 118-119°) in 70% yield after crystallization.[4] Chlorination of 2 is best accomplished with N-chlorosuccinimide (1 equiv) in CH_2Cl_2 at rt, and the resulting chloroenaminoketone 3 [72%, mp 188-89°; NMR δ (DMSO-d_6) 7.00 (broad s, 1H, NH), 2.89 (d, 3H, J=5), 1.08

(d, 3H, J=6); mass spectrum (EI) M^+ 173, 175, ratio 3:1] oxidized further by the addition of Br_2 in CCl_4 (1 equiv) at 0°.



2 R, R' = H
3 R = Cl, R' = H
4 R = Cl, R' = Br



5 R = $COCH_3$
6 R = H

A mixture of monochlorobromides 4 is formed in this reaction from which one isomer crystallizes [64%, mp 123-124°; NMR ($CDCl_3$) 5.7 (broad s, 1H, NH), 4.81 (d, 1H, J=3, CH-Br), 3.15 (d, 3H, J=5, N-CH_3), 1.18 (d, 3H, J=6); IR ($CHCl_3$) 6.1, 6.3μ; mass spectrum (EI) m/e 251 (M+):253:255 ratio 1:1.06:0.31]. However 4 is usually not purified, rather the mixture is treated directly with acetic anhydride/TsOH at 110° for 90 min to effect dehydrobromination. Thus the overall yield of 5[4] from 3 is 85-90% [mp 88°; NMR ($CDCl_3$) 7.00 (s, 2H), 3.18 (s, 3H, N-CH_3), 2.33 (broad s, 6H, O-$COCH_3$ and Ar-CH_3), 1.80 (s, 3H, N-$COCH_3$); IR (mull) 5.62, 6.00μ; mass spectrum (EI) M+ 255, 257 ratio 3:1]. Saponification of 5 (K_2CO_3, CH_3OH) affords the corresponding phenol 6 which may be isolated[4] (mp 199-200°) or preferably methylated *in situ* (CH_3I, K_2CO_3, CH_3OH, 6 hr reflux) to give methoxyacetanilide 7 [91%; NMR ($CDCl_3$) 6.87, 6.78 (2 singlets, each 1H, Ar-H), 3.92 (s, 3H, OCH_3), 3.18 (s, 3H, N-CH_3), 2.38 (s, 3H, Ar-CH_3), 1.81 (s, 3H, N-$COCH_3$)].[4] Finally oxidation of 7 at the aromatic methyl group may be effected selectively in 76-80% yield by reaction with NBS (1.1 equiv) in CCl_4 (reflux, 4-5 hr, sunlamp irradiation) [NMR ($CDCl_3$) 7.05 (2 overlapping s, 2H), 4.44 (s, 2H, CH_2Br), 3.95 (s, 3H), 3.18 (s, 3H), 1.82 (s, 3H)].

Conversion of 8, now available in good overall yield (33%), into maytansine is currently under investigation.[5]

REFERENCES (1) S.M. Kupchan, A.R. Branfman, A.T. Sneden, A.K. Varma, R.G. Dailey Jr., Y. Komoda, Y. Nagao, J. Amer. Chem. Soc., 97, 5294 (1975).
(2) For other progress reports on maytansine see (a) A.I. Meyers et al., Tetrahedron Lett., 717 (1974), 1745 (1975), 1749 (1975); (b) E.J. Corey, M.G. Bock, ibid., 2643 (1975)
(3) A.W. Crossley, N. Renouf, J. Chem. Soc 602 (1915)
(4) Satisfactory elemental analysis has been obtained for this compound.
(5) The authors acknowledge generous financial support from the National Institutes of Health (Grant # CA 19686) and the Eli Lilly Company.