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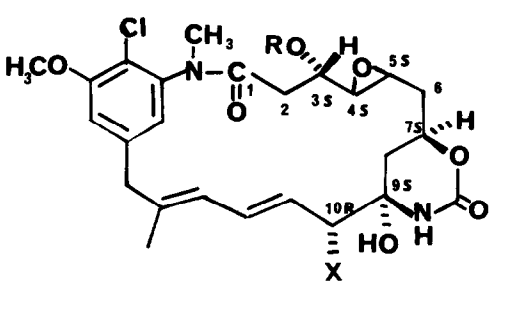
STUDIES RELATED TO THE SYNTHESIS OF MAYTANSINOIDS.

Derek H.R. Barton, Michel Bénéchie, Françoise Khuong-Huu,
Pierre Potier and Victor Reyna-Pinedo

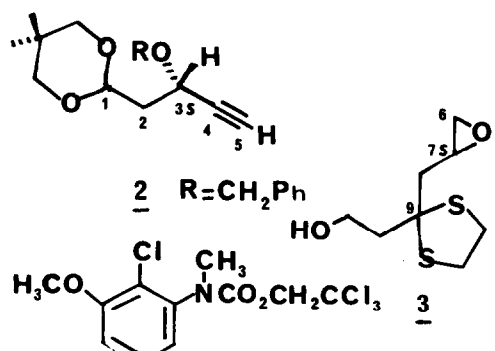
(Institut de Chimie des Substances Naturelles, C.N.R.S,
91190 Gif-sur-Yvette, France)

Abstract - Two approaches to the partial synthesis of C_1-C_5 of a bis-nor maytansinoid 1 have been investigated starting on the one hand with (S)-(−)-malic acid and on the other, with D-(+)-ribonolactone.

Maytansinoids are interesting naturally occurring[1] antitumor agents[2]. Extensive work has already been carried out on the synthesis of maytansine itself[3]. In a projected partial synthesis of the bis-nor-4,6-maytansinoid 1 (R = H, or ester) in the correct absolute configuration, we have investigated two approaches to the acetylenic acetal 2. This acetal bears at C-3 an hydroxyl group in the correct absolute configuration and by coupling with the epoxide 3[4] would lead, after further manipulation, to the C_1-C_{11} moiety of 1. After oxidation of the acetal function of 2 to an acid, the amide linkage could, then, been established with the amine function of 4[5] (R, variable).



1 X = H or OCH_3

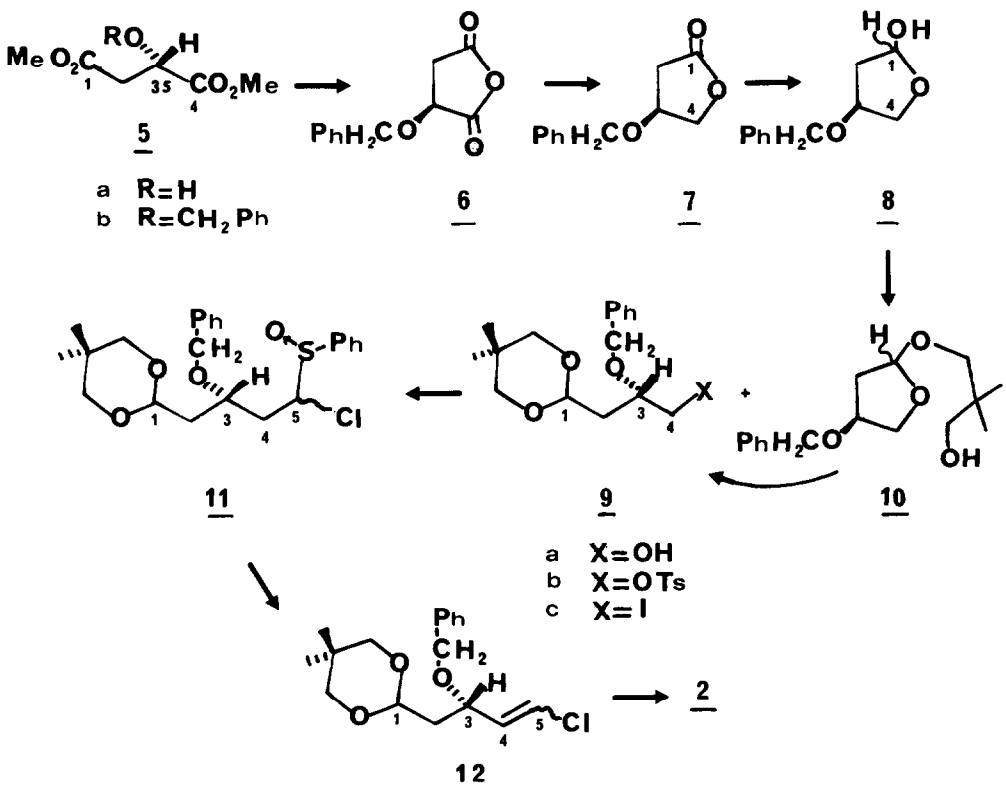


2 R = CH_2Ph

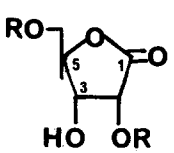
3

4

Two routes to 2 have been investigated. In the first, dimethyl (S)-(-)-malate 5a was converted (benzyl bromide -Ag_2O in ethyl acetate at room temperature) (84%) into its O-benzyl derivative 5b, oil, $[\alpha]_D$ - 63° ($CHCl_3$ c = 1,6). Saponification of the ester functions, followed by treatment with acetyl chloride in reflux, gave the anhydride 6 which was reduced ($NaBH_4$ in THF[6]) to the lactone 7, mp 70-71° (acetone), $[\alpha]_D$-29° ($CHCl_3$ c = 1) (61% yield for the three steps). Diisobutylaluminium hydride reduction[7] of 7 effected at -40° afforded the epimeric lactols 8 (65%). The lactol ring was opened upon acetalisation (2,2-dimethylpropane-1,3-diol, p-toluene sulphonic acid) to give 9a, oil, $[\alpha]_D$-5° ($CHCl_3$ c = 1,6). This reaction gave a mixture of 9a and 10. When the glycoside 10 was treated in acidic conditions, a further amount of 9a was obtained. The yield of 9a was 80% in two operations. Tosylation of 9a led to 9b which was transformed quantitatively (NaI-acetone) into the iodo derivative 9c, mp 29-30°, $[\alpha]_D$-6° ($CHCl_3$ c = 2). Reaction of 9c with the lithium derivative of $ClCH_2SOC_6H_5$[8] afforded the chlorosulfoxide 11 (72%). This gave the vinylchlorides 12 (80%) on heating at 140° in xylene. The mixture of E and Z-vinylchlorides when treated with dimsylsodium gave the desired acetylenic compound 2, oil, $[\alpha]_D$-84° (55%). With n-BuLi as base the yield was 35%. Pure E-vinylchloride, mp 77°(MeOH), $[\alpha]_D$-55°, led to 2 in 60% yield when reacted with n-BuLi.

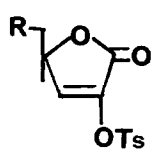


The second route to acetal 2 began with D-(+)- ribonolactone 13a, which on treatment with tosyl chloride in pyridine 1 h at -20° and then 5 h at -10° gave the 2,5-ditosylate 13b (52%), mp 122°, $[\alpha]_D$ + 2° ($CHCl_3$ c = 0,9), $[\alpha]_D$ + 8° (EtOH c = 1, litt. + 9°[9]). The olefinic compounds 14a, 14b and 15 were also isolated. Derivative 13b was transformed quantitatively (LiBr-acetone) to the dibromides 16 which were reduced (NaI, TFA, acetone[10]) to the 5-bromo compound 17a (53%) and the 5-iodo analogue 17b[11] (7%). Compound 17a was converted (benzylbromide, Ag_2O, ethyle acetate) (90%) to its O-benzyl derivative 17c, oil, $[\alpha]_D$ + 17° ($CHCl_3$ c = 4,1), the lactone ring of which was reduced (diisobutylaluminium hydride -75° to -60° in 50 min. then 30 min. at -60°) (68%) to the lactol 18. Upon acetalisation (2,2-dimethylpropane-1,3-diol, p-toluene sulphonic acid), 18 led to a mixture of 19 (29%) and 20a (42%). Acidic treatment of 19 gave a further amount of 20a. The yield of compound 20a was 52% in two operations. Tosylation of 20a afforded 20b (80%) which when treated with sodium isopropylate in refluxing isopropanol gave a poor yield (24%) of the vinyl bromides 21a. The mesylate 20c with KOH in n-propanol at 88° led to the E-vinylbromide 21a (16%), mp 82-84°, $[\alpha]_D$ - 65° ($CHCl_3$ c = 1,4) and the ketone 22 (51%). These results led us to prepare (NaI, acetone, refluxing overnight) (70%) the olefin 21b starting from 20b. Bromation of 21b (pyridinium bromide perbromide, THF, -50°) (59%) and debromation (dimsylsodium) gave the desired compound 2 (40%).



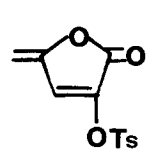
13

a R=H
b R=Ts



14

a R=OH
b R=OTs



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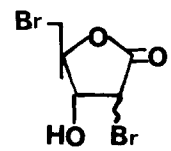

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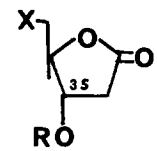
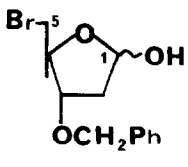


17

a R=H X=Br
b R=H X=I
c R=CH_2Ph X=Br



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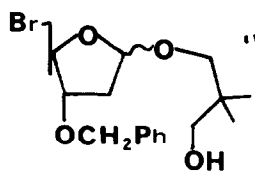

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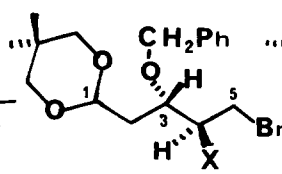
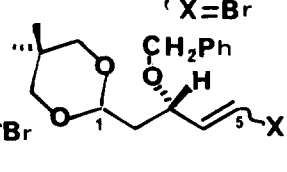


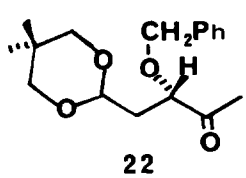


20

a X=OH
b X=OTs
c X=OMs
d X=Br

21

a X=Br
b X=H



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