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Studies Related to Maytansinoids

By DEREK H. R. BARTON,* STEPHEN D. GÉRO, and CHRISTOPHER D. MAYCOCK (Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France)

MAYTANSINE (1)¹ is a naturally occurring ansa macrolide of considerable clinical interest as an anticancer agent.² A number of research groups have made notable efforts towards its partial and total synthesis.³

Summary A rapid and high yielding route to optically active β -carbamoyloxy ketones of use in the synthesis of maytansinoids has been devised, starting from quinic acid.



As part of a project aimed, ultimately, at the convergent synthesis of a modified maytansinoid and its congeners, in an enantiomerically pure form, we have prepared the epoxide (2), which is to become the C-6—C-11 portion of the macrocycle. We report also the preparation of the carbamate (3) which may retain some of the biological properties of maytansine. These, and other potentially usefully functionalised molecules, have been elaborated from D-(-)-quinic acid (4),⁴ a relatively easily obtainable pseudo-carbo-hydrate.



Treatment of the β -hydroxyketone (5)⁴ with benzoyl chloride in pyridine afforded the monobenzoate (6) (90%), m.p. 120-121 °C, $[\alpha]_{\rm D} + 68^{\circ}$ (c, 1.45 in CHCl₃). Reaction of (6) with ethanedithiol and zinc iodide resulted in the diol

† Details of this will be published elsewhere.

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(7) (80%), m.p. 115—116 °C, $[\alpha]_{\rm D} \pm 0^{\circ}$ (c, 1.47 in CHCl₃); c.d. (EtOH) $\lambda_{\rm max}$ 223 nm ($\Delta \epsilon$ +1.75), by a simultaneous acetalisation of the carbonyl function and liberation of the *cis*-diol system. The diol (7) was then oxidised, using triphenylbismuth carbonate,⁵ to the dialdehyde (8) which could not be isolated. It was, therefore, immediately reduced with sodium borohydride to give the expected product (10) (25%), $[\alpha]_{\rm D}$ +23.2° (c, 15.6 in CHCl₃), along with (9) (50%), a liquid, $[\alpha]_{\rm D}$ +3.7° (c, 0.96 in CHCl₃), the latter being the product resulting from benzoyl group migration. The secondary ester (10) could be converted into (9) (85%) using NNN'N'-tetramethylguanidine. The ester (9) was characterised as its bis-*p*-nitrobenzoate, m.p. 64— 65 °C, $[\alpha]_{\rm D}$ +9.5° (c, 1.48 in CHCl₃).



Selective protection of the free primary alcohol function of (9) was achieved using chloromethyl methyl ether to give the oily methoxymethyl ether (12) (55%), $[\alpha]_{\rm D} - 1 \cdot 1^{\circ} (c, 18\cdot3 \text{ in CHCl}_3)$, which was converted into its mesylate (13) (90%), $[\alpha]_{\rm D} - 19\cdot9^{\circ} (c, 5\cdot5 \text{ in CHCl}_3)$. Methanolysis of (13) (sodium methoxide in methanol) afforded the epoxide (2) (80%), $[\alpha]_{\rm D} - 1\cdot6^{\circ} (c, 0.76 \text{ in CHCl}_3)$, as an oil.

Acylation of the secondary alcohol function of (12) with p-nitrophenyl chloroformate in pyridine, followed by ammonolysis (ammonia in Bu^tOH) furnished the carbamate (14) (80%). Regeneration of the ketone from the dithioacetal (14) with phenylseleninic anhydride⁶ and propylene oxide gave (3), m.p. 71-72 °C. Surprisingly, (3) did not spontaneously cyclise as has been observed for model compounds of a similar type.⁷ The acyclic structure of (3) was indicated by the resonance frequencies for the protons adjacent to the carbonyl group,⁸ and by the occurrence of a signal at δ 204·7 p.p.m. in its ¹³C n.m.r. spectrum. As a consequence, the model compounds (15) and (16) have been prepared in racemic form and also appear not to be cyclic.[†]

The absolute configuration at the asymmetric carbon atom in (9) is epimeric to that found at C-7 in the naturally occurring maytansinoids, hence a route to its enantiomer (11) was also developed from (5).



The latter was treated as before with ethanedithiol and zinc iodide giving the triol (17) (80%), m.p. 127–128 °C, $[\alpha]_{\rm D}$ -35° (c, 1.25 in EtOH), which was reprotected as its

cyclohexylidene derivative (18) (85%), m.p. 143-144 °C, $[\alpha]_{\rm p}$ – 45° (c, 1.76 in CHCl₃), by reaction with 1,1-dimethoxycyclohexane and sulphuric acid in dimethylformamide.



Oxidation of the remaining hydroxy-group was effected (90%) with oxalyl chloride and dimethyl sulphoxide⁹ and the product (19), m.p. 184–186 °C, $[\alpha]_D$ +15° (c, 1.03 in CHCl₃), reduced with lithium tri-t-butoxyaluminium hydride. The required alcohol (20), m.p. 121-122 °C, $[\alpha]_{\rm p}$ +16° (c, 3.65 in CHCl₃), was obtained in 70% yield, whereas the alcohol (18) was only recovered in 6% yield. Acid-catalysed alcoholysis of the benzoate (21), m.p. 84-86 °C, $[\alpha]_D - 24^\circ$ (c, 1.33 in CHCl₃), rapidly produced the diol (22) (90%), m.p. 178–179 °C, $[\alpha]_{\rm D}$ –27° (c, 1.7 in EtOH).

Triphenylbismuth carbonate oxidation followed by reduction, as before, furnished the diol (11) (50%) as an oil, $[\alpha]_{\rm p} - 3.9^{\circ}$ (c, 1.1 in CHCl₃). This compound exhibited n.m.r. and i.r. spectra identical to those obtained for enantiomer (9).

We have demonstrated here the feasibility of preparing chiral compounds useful for the synthesis of simplified maytansinoids.

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