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STEREOCHEMICAL CONTROL IN THE SYNTHESIS OF THE CYCLOHEXYL PORTION OF THE MILBEMYCIN SKELETON

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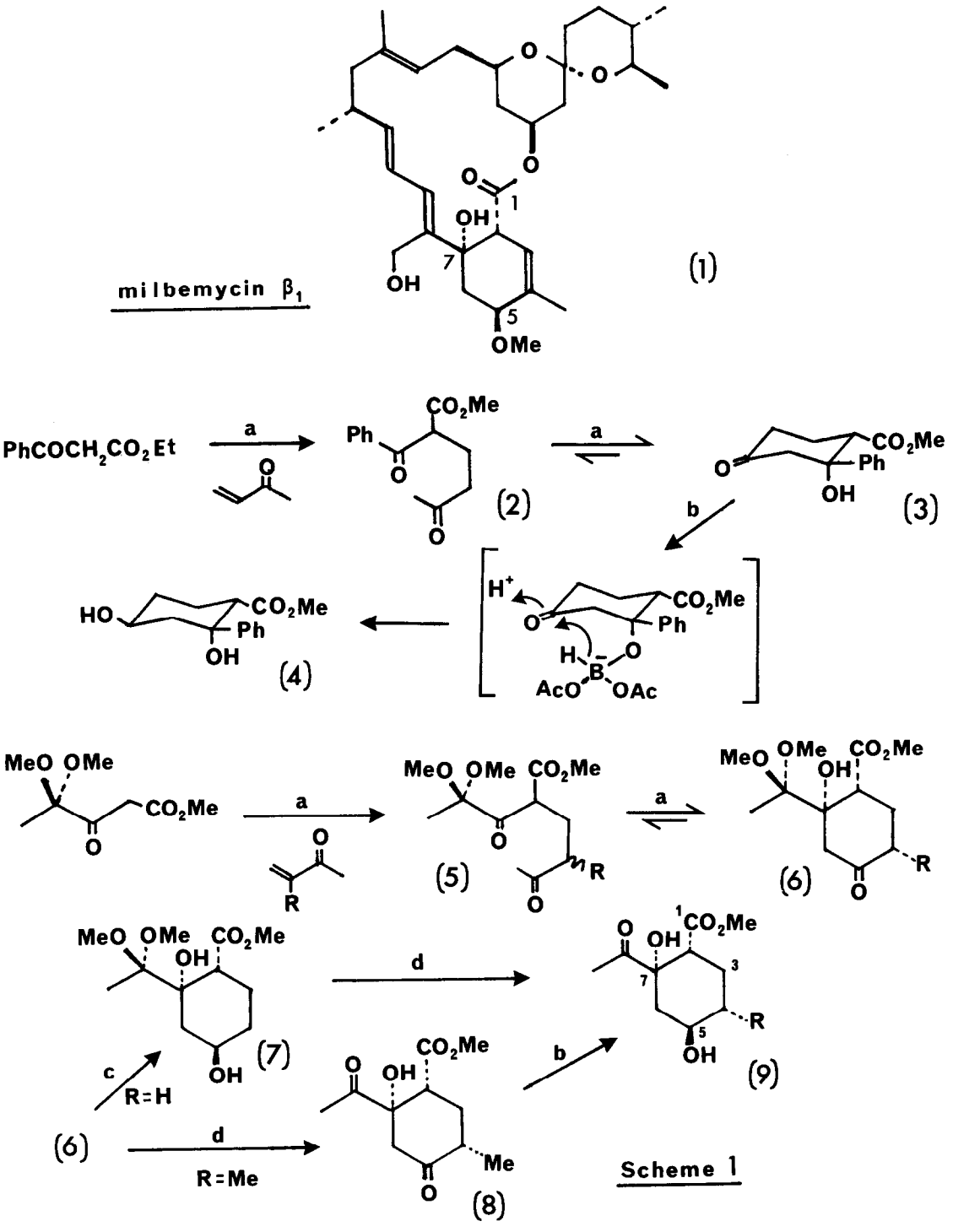
Abstract: Robinson annulation of β-keto esters and stereospecific reduction of the resulting ketols with sodium triacetoxyborohydride gives dihydroxy cyclohexane carboxylates with the carbon and oxygen framework of part of the milbemycins.

As part of an investigation into the total synthesis of the insecticidal milbemycins[1] (e.g. milbemycin β_1 (1)[2]) and their analogues, we were attracted by the simplicity of an approach to the cyclohexyl ring using the method of Robinson annulation[3]. Although more often applied to decalin systems, it also allows access to cyclohexanes with appropriate oxygen functionality for elaboration, if the sequence is stopped at the stage of a cyclic ketol. In many applications of the Robinson procedure, the ketol is dehydrated to an enone, but this usually requires a separate acid-catalysed step[4].

In monocyclic cases, previous authors have not commented on the stereochemical outcome[5], but we find that the reaction is stereoselective in giving a cis disposition of carbonyl and (axial) hydroxyl in all cases we have examined[6]. Thus, under the conditions of DeBoer[5a], ethyl benzoylacetate (0.5 M) and methyl vinyl ketone (0.5 M) in methanolic sodium hydroxide at 20°C gave (3) in 74% yield. The hydrogen-bonded hydroxyl proton gives a characteristic signal at 4.2 δ in the proton nmr in $CDCl_3$, revealing the axial geometry of the substituent. This is the outcome that would be expected on thermodynamic grounds given the equilibrating conditions of formation of the ring from (2) and the bulky nature of methoxycarbonyl and phenyl groups.

In certain cases displacement of the equilibrium from (2) to (3) proved difficult. Uncyclised material was the sole product of carrying out the Michael addition in dry ether in the presence of a catalytic quantity of sodium hydride. In contrast, alcoholic solvents and sodium hydroxide as base were found to promote the desired cyclisation: even when the product did not crystallise from the reaction mixture, driving the reaction to completion, (as with (3)), the ratio of open and cyclised forms could in general be influenced by variation of temperature. Dehydration to enone was not observed under these mildly basic conditions.



Reagents: a) NaOH, MeOH b) $NaBH(OAc)_3$, HOAc c) $NaBH(OAc)_3$, EtOAc d) H^+, Acetone

Two closely related sequences which are typical of those examined and of more relevance to milbemycin studies are shown in Scheme 1. When R=H, an isolated yield of (6) of 85% was obtained from a reaction run at 0°C: at work-up, thin layer chromatography showed no remaining uncyclised (5)[5b], which however was shown to predominate if the reaction was run at 20°C or above, leading to poor isolated yields of (6) in that case. In contrast, when R=CH_3 and the temperature was kept below 20°C, the first Michael addition was barely perceptible by tlc and heating was required to move away from starting materials[7]. Equilibration in boiling methanol gave the desired ketol as the major component of the product mixture and it was obtained in 50% yield after isolation by flash chromatography on silica gel. The additional methyl group was determined by nmr to be stereospecifically equatorial, again as expected under the equilibrating conditions[8].

Milbemycins have equatorial hydroxy or methoxy substituents at C-5[1]. Sodium borohydride reduction of (3) in isopropanol or tetrahydrofuran as solvent gave a mixture of diols isomeric at C-5 (milbemycin numbering). These were readily separated by chromatography and the C-5 axial diol found to predominate. A much more selective reagent is sodium triacetoxy borohydride[9], following the work of Saksena[10]. This uses the axial hydroxy on C-7 to direct hydride attack stereospecifically. Thus, addition of the hydroxy ketone (3) in acetic acid or tetrahydrofuran to a two-fold molar excess of the reagent solution gave the desired 5-equatorial, 7-axial diol (4) in 80% yield after crystallisation. The undesired isomer available from the non-selective reduction was not detectable by tlc in the reaction mixture.

In the case of the more acid-sensitive substrate ((6),R=H) the reduction was carried out in dry ethyl acetate using crude sodium triacetoxyborohydride precipitated as a moisture-sensitive white powder by addition of dry ether to a reaction between sodium borohydride and glacial acetic acid. With (8), the reaction was both regio- and stereo- specific and gave ((9),R=CH_3) in 57% yield.

In conclusion, the reaction between suitable β-keto esters and α-β unsaturated ketones, followed by cyclisation to ketol and stereospecific reduction with sodium triacetoxy borohydride provides in two simple steps a versatile route to the carbon skeleton of the cyclohexyl ring of milbemycins bearing the correct hydroxylation pattern. This methodology has already been used to produce simplified milbemycin analogues[11]. It is now being adapted to a total synthesis of the full milbemycin skeleton[12].

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6. All the reactions reported in this paper were done on racemic material: it would be expected that the basic conditions would racemise any Michael adduct like (2), which had been produced stereochemically pure by other means, leading to racemic (3).
7. Methyl 4,4-Dimethoxy-3-oxopentanoate was prepared in tetrahydrofuran by the method of S Danishefsky, R Zamboni, M Kahn, and S J Etheredge, J. Amer. Chem. Soc., 103, 3460 (1981). All other starting materials are commercially available or were prepared by standard methods.
8. The stereochemical outcome was most readily established on the diol products where the C-4 methyl is no longer subject to base-catalysed epimerisation and the coupling to axial hydrogens on C-3 and C-5 can readily be seen in the proton nmr.
   Data for (9), R=CH_3: M.p. 83-84°C (Ether/Petroleum ether). ^{1}H-nmr (400 MHz), ($CDCl_3$):1.10,3H,d,J=8Hz;1.40,1H_{6a},dt,J=13Hz,0.5Hz;1.50,1H_{4a},m;1.65,1H_{3a},q,J= 13Hz; 1.70,1H_{OH},s;1.97,2$H_{3e,6e}$,m;2.32,3H_9,s;3.02,1H_{2a},dd,J=13Hz,5Hz;3.62,1H_{5a},m; 3.65,3H_{OMe},s;4.30,1H_{OH},d,J=0.5Hz.
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