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Semi-synthetic C23-Substituted Milbemycins via Spiroacetal Cleavage and Resynthesis.

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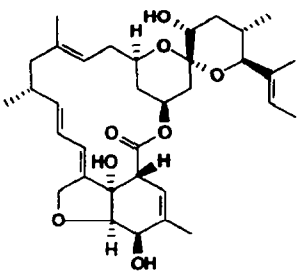
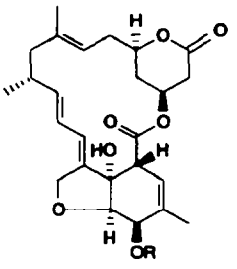
Abstract: The lactone intermediates (2) and (3) are converted by lithium acetylide chemistry followed by mercury catalysed hydration to novel semi-synthetic 23-oxo C24 and C25 substituted milbemycins (7).

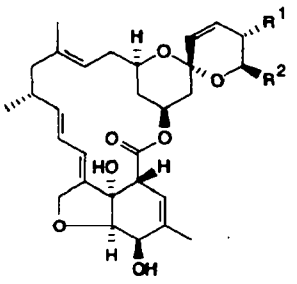
Since the discovery[1] of VM 44866 (1), a milbemycin containing the unusual feature of a hydroxyl group at C22 whilst being unsubstituted at C23, we have been interested in the chemical alteration of its structure in order to modify its biological activity. We had found that the outer spiroacetal ring could be cleaved by a Beckmann fragmentation process giving the lactone (2) or (3).[2] These lactones are key intermediates since it has proved possible to rebuild the outer spiroacetal ring containing novel substituents. We have shown[3] that an efficient way of achieving this is by employing lithium acetylide chemistry leading eventually to semi-synthetic milbemycins of the general type (4) containing a C22-C23 double bond and a variety of substituents at C24 and C25. We now wish to describe an extension to this chemistry leading to novel milbemycins containing functionality at C23, C24 and C25.



(1) VM 44866



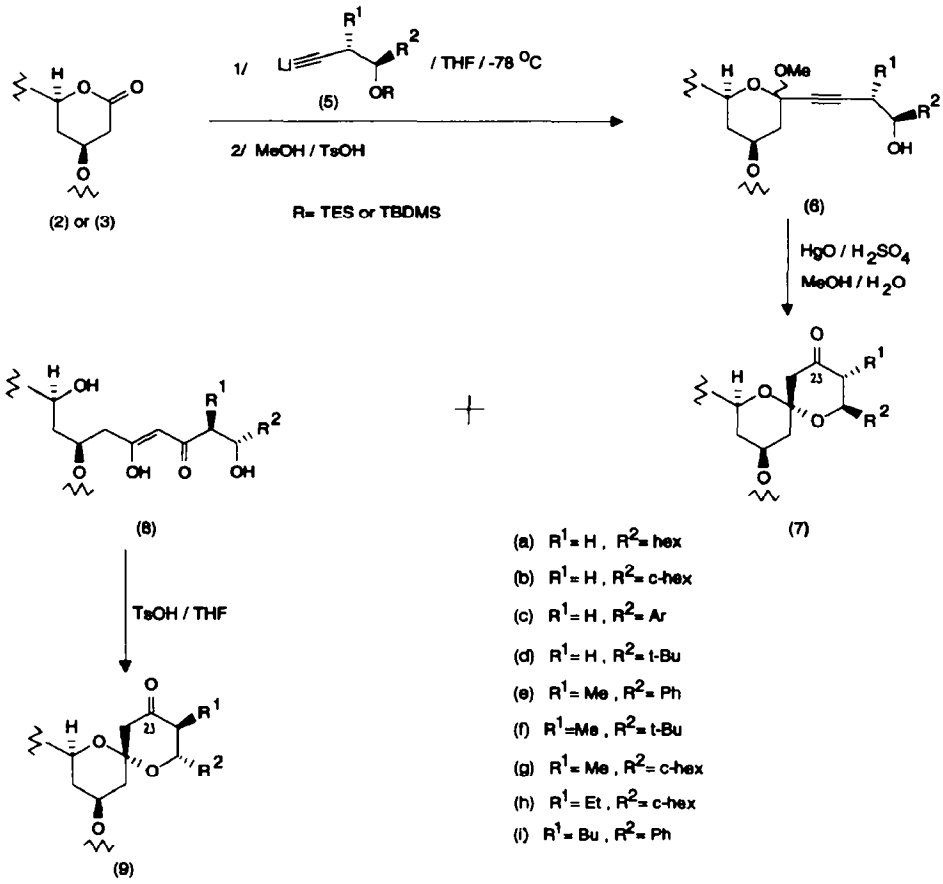
(2) R= TBDMS
(3) R= TIPS



(4)

Addition of the lithium acetylide(5), derived from a (±)-*trans*-substituted homopropargyl alcohol (protected as its TES or TBDMS ether) and butyllithium, to the lactone (2) or (3) followed by acid/methanol treatment gives the methyl acetal (6) as a mixture of diastereoisomers in good yield (50-80%

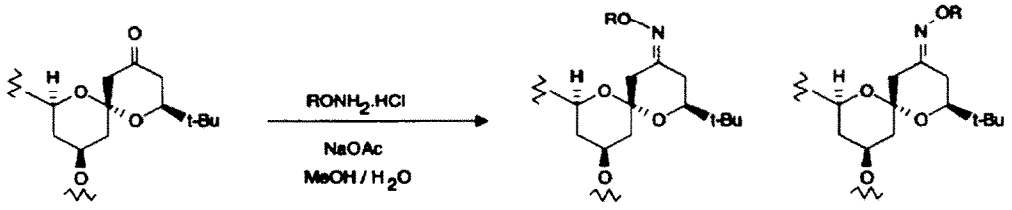
after chromatography). Functionality at C23 is then introduced by hydration of the acetylene with 5 mol% of mercuric oxide in dilute sulfuric acid/methanol at room temperature (Scheme 1). Under these conditions although both diastereoisomers hydrate, the diastereoisomer with 'natural milbemycin' stereochemistry at C25 cyclises significantly faster than the diastereoisomer with 'unnatural milbemycin' stereochemistry at C25, particularly when R^2 is a bulky group. Therefore by careful control of the reaction a mixture of spirocyclic ketone (7) and triol (8) can be obtained which can readily be separated by chromatography. The triol (8) can then be cyclised separately to spiroacetal (9) by prolonged treatment with toluene-4-sulfonic acid in THF.



SCHEME 1

The 23-carbonyl group in structure (7) offers a handle for the introduction of alternative functionality at this position. A series of 23-oximes were prepared. In general when the C24 position was substituted (i.e. $R^1 \neq H$) then a single oxime isomer (E-isomer) was obtained[4] although it was possible to bring about partial isomerisation by prolonged acid treatment. When the C24 position was unsubstituted it was possible to get a mixture of both oxime isomers (Scheme 2).[5] Interestingly as the oxime substituent

gets bulkier the selectivity changes from favouring the Z-isomer to favouring the E-isomer. At present it is not fully understood what factors govern this reversal in selectivity.

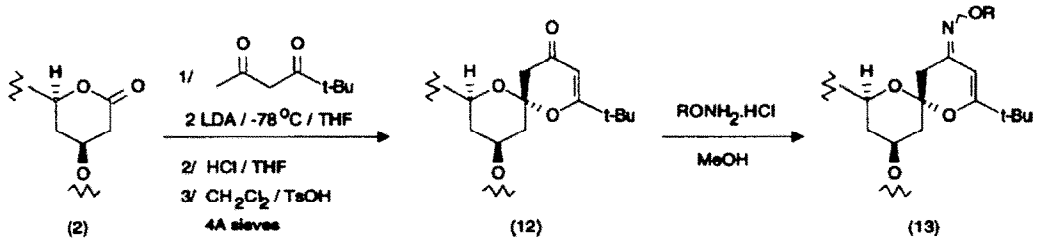


(7d) (10) (11)

R	Z-OXIME	E-OXIME
(a) Me	5	2
(b) 4-NO_2-C_6H_4-CH_2	3	1
(c) Ph_3C	1	2
(d) t-Bu	1	4

SCHEME 2

We were then interested to see what effect introduction of a C24-C25 double bond might have upon the biological activity of these oximes. The required 23-ketone (12) was prepared employing some dianion chemistry similar to that developed by Barrett in his total synthesis of milbemycin β_3.[6] The dianion derived from 5,5-dimethyl-2,4-hexadione[7] and 2 mole equivalents of LDA was reacted with the lactone (2) in THF at -78°C (Scheme 3). Addition was essentially quantitative, however difficulty in bringing about spirocyclisation was encountered. It was first necessary to remove the 5-TBDMS protecting group with dilute hydrochloric acid in THF. Spirocyclisation was finally achieved by treatment with toluene-4-sulfonic acid in dichloromethane in the presence of 4Å molecular sieves in low yield [25% overall yield from (2)]. Oxime formation was then accomplished by reaction with the appropriately substituted hydroxylamine hydrochloride in methanol to give (13). It was necessary to carry-out the oxime formation in the absence of sodium acetate in order to obtain a reasonable rate of reaction and under such conditions a 1:1 mixture of oxime isomers was obtained which could be separated by preparative TLC.



(2) (12) (13)

SCHEME 3

In conclusion we have shown that it is possible to convert the key lactone intermediate (2) or (3) via lithium acetylide chemistry and mercury catalysed hydration to a range of semi-synthetic milbemycins containing novel substituents at C23, 24 and 25. Also using dianion chemistry the lactone (2) has been converted to the 23-oxo-24,25-didehydro milbemycin (12). The biological activity of these compounds will be reported in due course.

ACKNOWLEDGEMENT.

We thank Analytical Services Unit at Great Burgh for all the spectral data.

REFERENCES AND NOTES.

1. a) Hood, J.D.; Banks, R.M.; Brewer, M.D.; Fish, J.P.; Manger, B.R.; Poulton, M.E. *J. Antibiotics*, 1989, **42**, 1593-1598.
   b) Baker, G.H.; Dorgan, R.J.J.; Everett, J.R.; Hood, J.D.; Poulton, M.E. *J. Antibiotics*, 1990, **43**, 1069-1076.
2. Baker, G.H.; Dorgan, R.J.J.; Hussain, N.; Macaulay, G.S.; Morgan, D.O. *First paper in series.*
3. Baker, G.H.; Dorgan, R.J.J.; Hussain, N.; Macaulay, G.S.; Morgan, D.O. *Preceding paper.*
4. One exception was for (7f) when R^1=Me and R^2=t-Bu where a mixture of both possible oxime isomers was obtained.
5. a) All new compounds were characterised by mass-spectroscopy, ^{1}H n.m.r. and ^{13}C n.m.r.
   b) Typical ^{13}C n.m.r. for compound (10a) δ_c (d_6-Acetone) 172.5 (C1), 154.2 (C23), 142.5 (C11), 141.6 (C8), 137.8 (C4 or C14), 137.6 (C4 or C14), 124.9 (C10), 121.8 (C15), 121.0 (C9), 119.2 (C3), 99.4 (C21), 81.6 (C6), 81.3 (C7), 76.7 (C25), 69.2 (C17), 68.7 (C19), 68.5 (C5), 68.3 (C27), 61.2 (NOMe), 49.1 (C13), 46.7 (C2), 41.9 (C20), 36.8 (C18), 36.5 (C12), 36.0 (C22), 35.1 (C16), 34.5 ($\underline{C}Me_3$), 31.3 (C24), 26.1 ($C\underline{Me}_3$), 22.7 (C28), 19.8 (C26) and 15.7 (C29).
   For compound (11a) δ_c (d_6-Acetone) 172.5 (C1), 154.3 (C23), 142.5 (C11), 141.6 (C8), 137.8 (C4 or C14), 137.6 (C4 or C14), 124.8 (C10), 121.8 (C15), 121.0 (C9), 119.2 (C3), 99.8 (C21), 81.6 (C6), 81.3 (C7), 75.4 (C25), 69.3 (C17), 68.6 (C19), 68.5 (C5), 68.3 (C27), 61.3 (NOMe), 49.1 (C13), 46.6 (C2), 41.9 (C20), 41.4 (C22), 36.9 (C18), 36.5 (C12), 35.2 (C16), 34.6 ($\underline{C}Me_3$), 26.1 ($C\underline{Me}_3$), 25.7 (C24), 22.7 (C28), 19.8 (C26) and 15.7 (C29).
6. a) Barrett, A.G.M.; Carr, R.A.E. *J. Org. Chem.*, 1986, **51**, 4840-56.
   b) Attwood, S.V.; Barrett, A.G.M.; Carr, R.A.E.; Richardson, G. *J. Chem. Soc., Chem. Commun.*, 1986, 479-481.
7. 5,5-Dimethyl-2,4-hexadione (b.p. 70-72°C at 24 mmHg) was prepared by the condensation of pinacolone with ethyl acetate employing sodium hydride as base. See Adams, J.T.; Hauser, C.R. *J. Amer. Chem. Soc.*, 1944, **66**, 1220-1222.

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