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Fragmentations and Rearrangements of 22-hydroxyl substituted Milbemycins - Synthesis of a key lactone intermediate

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Abstract: Beckmann fragmentation of 22-oximino milbemycins resulted in the cleavage of the C21-C22 bond to produce a key lactone intermediate which can be used to synthesise new spiroacetals. Cleavage of the C21-O25 bond and recyclisation to produce a furyl derivative is also described.

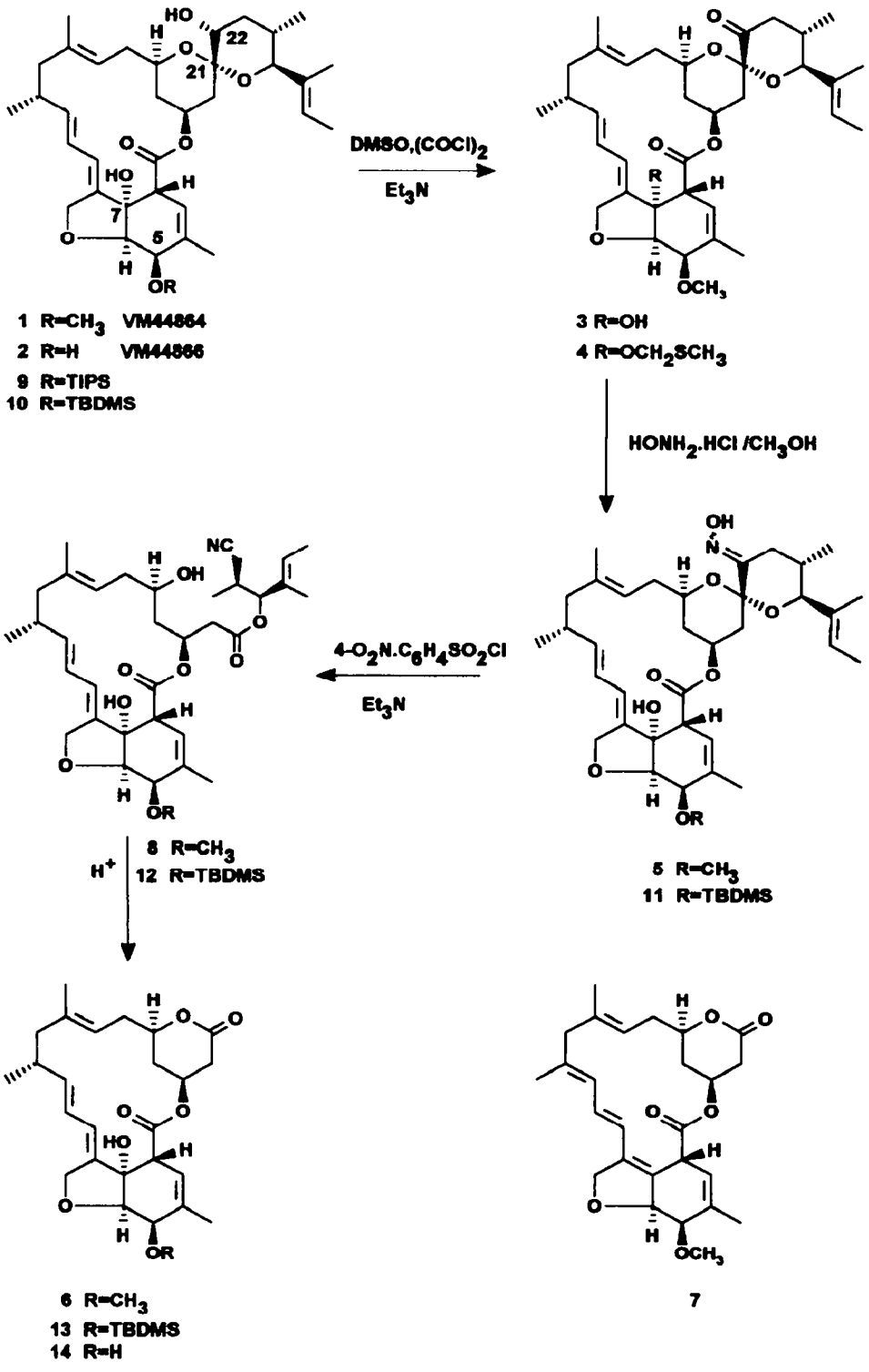
We have previously reported [1,2] the isolation and structure elucidation of a novel series of milbemycin fermentation products. One particularly interesting structural feature of the major members of this group, VM 44864 and VM 44866 (1 and 2 respectively) is the 22-hydroxyl group. We reasoned that as these milbemycins were α -hydroxy acetals it should be possible to cleave the 21-22 carbon-carbon bond and hence generate a lactone intermediate (for example 6) which could be used for further elaboration of new spiroacetals.

The Beckmann fragmentation of the 22-oximino derivative proved to be an efficient procedure for achieving this fragmentation[3].

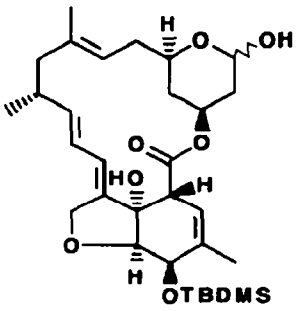
Oxidation of VM 44864 under standard Swern conditions [DMSO, $(COCl)_2$, CH_2Cl_2] gave the 22- ketone (3) in good yield in addition to a small amount of the 7-methylthiomethyl derivative (4). Reaction of ketone (3) with hydroxylamine hydrochloride gave an essentially quantitative yield of the desired oxime (5) which upon treatment with polyphosphoric acid trimethylsilyl ester (PPSE)[4] (i/ PPSE, CH_2Cl_2, 20°, ii/ H_2O) gave the triene (7)[5] as the major product and a small amount of the desired lactone (6).

Encouraged by this result we decided to activate the oxime thereby enabling milder conditions to be used which should prevent triene formation. Sulphonylation of the oxime with p-nitrobenzenesulphonyl chloride in the presence of triethylamine yielded directly the nitrile (8) and this upon treatment with acid gave the desired lactone (6)[6] in good overall yield.

Selective protection of the 5-hydroxyl group over the slightly more hindred 22-hydroxyl group in VM 44866 was achieved by silylation with either TBDMS chloride to give (10), in 73%yield, in addition to the 5,22-diTBDMS derivative (23%) or more efficiently with TIPS chloride to give (9) with less than 10% of the di-TIPS derivative. Oxidation and oximination of (10) gave the oxime (11) as a single isomer of undetermined stereochemistry in an 84% overall yield and this upon reaction with 4-nitrobenzenesulphonyl chloride yielded the ester (12) which was converted directly to the lactone (13), by treatment with 4-toluenesulphonic acid, in a 78% yield from (11). Removal of the TBDMS protecting group under acid conditions gave the 5-hydroxy lactone (14). Reduction of the lactone (13) with DIBAL gave the lactol (15) as an anomeric mixture in 82% yield.


DMSO,(COCl)2
Et3N
HONH2.HCl /CH3OH
4-O2N.C6H4SO2Cl
Et3N
H+
1 R=CH3 VM44864
2 R=H VM44866
9 R=TIPS
10 R=TBDMS
3 R=OH
4 R=OCH2SCH3
5 R=CH3
11 R=TBDMS
8 R=CH3
12 R=TBDMS
6 R=CH3
13 R=TBDMS
14 R=H
7

The presence of the two acetal oxygen atoms ß- to the 22-OH group profoundly affects its reactivity. Thus, the 22-mesylate (16) [(1)/CH_3SO_2Cl/pyridine, 0°C] proved remarkably resistant to displacement by a variety of nucleophiles and even under forcing conditions (e.g.NaN_3/DMF 60°C, 48h) the mesylate group remained intact although migration of the 3,4-double bond occured and (17), the Δ2 isomer of the mesylate, was formed as a mixture of diastereoisomers. In an attempt to facilitate these displacements under milder conditions and thereby avoid the conjugation reaction, the triflate derivative (18) was prepared [1/$(CF_3SO_2)_2O$ / C_5H_5N /-30°C→ 0°C]. The triflate was isolated, though not fully characterised, and treatment with variety of nucleophiles (eg Et_4NOAc) in acetone gave, in moderate yield, after an aqueous workup the rearrangement product (19) of undetermined stereochemistry. A possible mechanism is shown in scheme 1.



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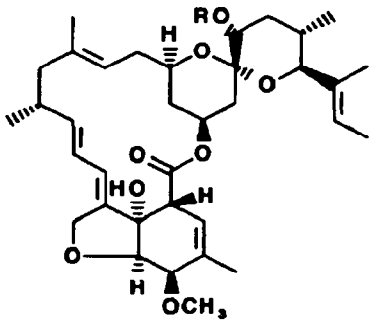
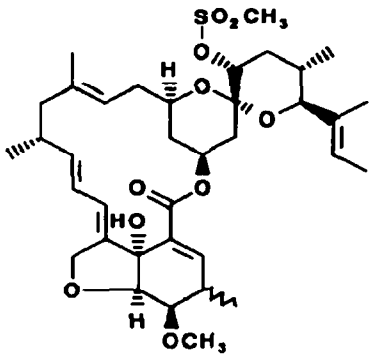


16 R=SO_2CH_3
18 R=SO_2CF_3



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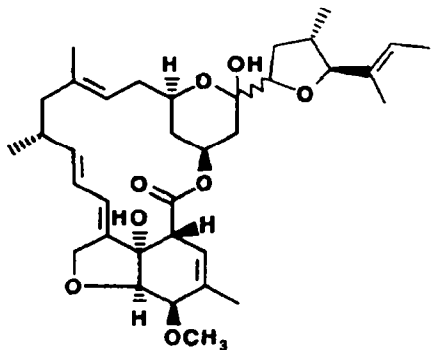

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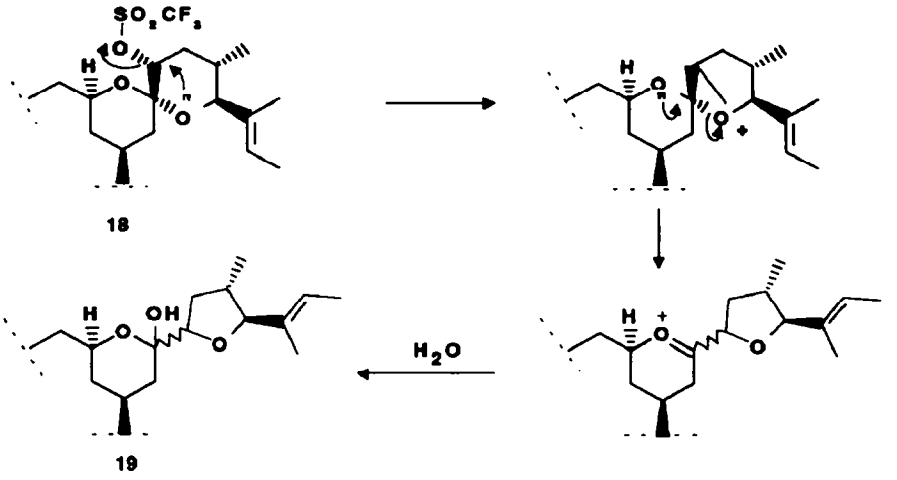

scheme 1

The use of these key intermediates in the synthesis of new spiroacetals will be described in subsequent papers.

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4. Tsuneo Imamoto, Hideki Yokoyama, & Masataka Yokoyama, *Tetrahedron. Lett.* 1981, **22**, 1803-4.
5. ^{13}C (δ $CDCl_3$), 169.9, 169.4, 140.2, 139.8, 137.0, 133.9, 128.3, 125.9, 125.9, 122.4, 120.3, 118.5, 86.5, 78.8, 75.6, 75.1, 66.6, 60.5, 47.5, 42.6, 36.2, 33.0, 32.4, 22.9, 19.2, 17.7,
6. ^{13}C (δ $CDCl_3$), 172.9, 168.4, 142.6, 139.9, 139.1, 136.4, 123.6, 119.5, 118.8, 118.0, 80.6, 77.8, 76.7, 76.6, 68.1, 66.1, 57.8, 48.4, 45.6, 36.8, 35.9, 34.6, 34.1, 22.3, 19.9, 15.7.

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