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A Practical Synthesis of the Milbemycin SB-201561

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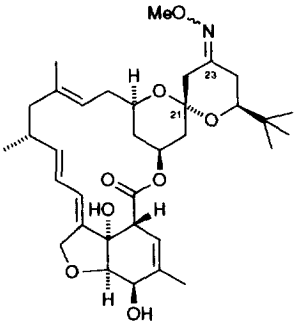
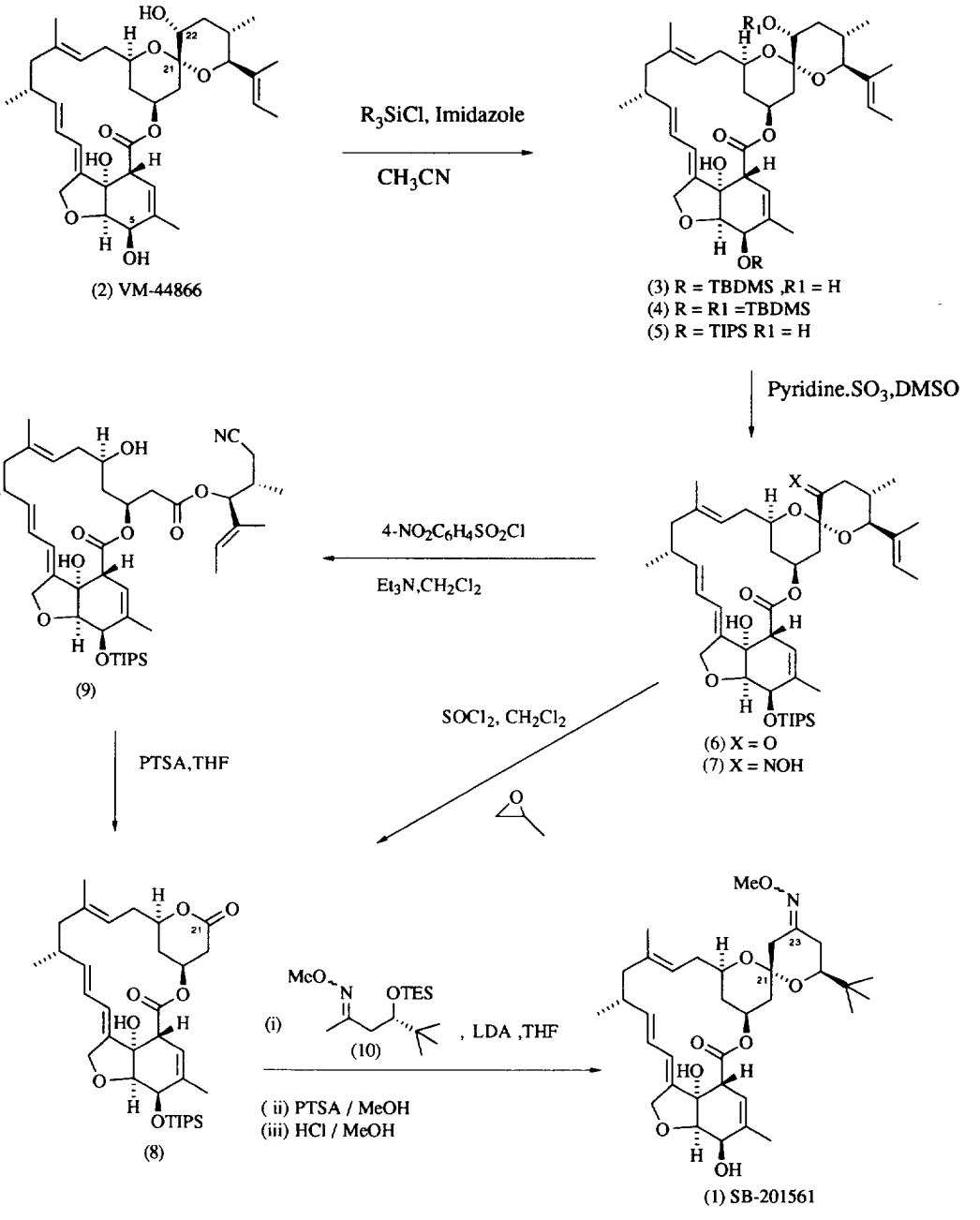
Abstract: *A 6-step synthesis of the potent anthelmintic SB-201561 is described. The key stage of the synthesis is a novel Beckmann type oxime fragmentation to give a lactone, followed by a 2-step reassembly of the spiroketal moiety.* Copyright © 1996 Elsevier Science Ltd



(1) SB-201561 (E/Z 1:1)

Milbemycins form a group of potent anthelmintic agents, and as such continue to attract much interest amongst the synthetic chemistry community.[1] SB-201561 (1), which exists as a 1:1 mixture of E- and Z-isomers, was identified as an active member of this class,[2] and as part of a programme aimed at developing this compound we required a synthesis of (1) which could be used to prepare 100 g amounts in the laboratory and could ultimately form the basis of a full scale manufacturing route operable on a multi-kilogram scale.

The starting point for our endeavours was the metabolite VM-44866 (2).[3] Our basic strategy was to try and degrade the top spiroketal portion to a suitable intermediate that would then permit us to reassemble the spiroketal with the required functionality. Initially the 5-hydroxyl position was protected as its TBDMS ether (3) (Scheme 1), however the reaction selectivity was poor, with up to 25% of the 5,22-bis-silylated compound (4) being produced. A further drawback was the fact that (3) was not crystalline. After screening a range of alternative protecting groups it was found that changing the protective group to TIPS gave much better


R3SiCl, Imidazole
CH3CN
(2) VM-44866
(3) R = TBDMS ,R1 = H
(4) R = R1 =TBDMS
(5) R = TIPS R1 = H
Pyridine.SO3,DMSO
4-NO2C6H4SO2Cl
Et3N,CH2Cl2
(6) X = O
(7) X = NOH
(9)
SOCl2, CH2Cl2
PTSA,THF
(8)
(i)
(10)
, LDA ,THF
(ii) PTSA / MeOH
(iii) HCl / MeOH
(1) SB-201561

Scheme 1

selectivity (>10:1), and the resulting ether (5) was crystalline. It was also found that if the silylation was carried out in acetonitrile the product crystallised directly from the reaction, greatly simplifying isolation. Oxidation of the C-22 hydroxyl function of (5) was best accomplished by means of a Swern procedure, using DMSO / pyridine sulphur trioxide complex.[4] The resulting rather unstable ketone (6) was oximated *in situ* to give oxime (7) in excellent overall yield. It was found initially that (7) could be converted to lactone (8) in two steps by means of a Beckmann fragmentation,[5] using 4-nitrobenzenesulfonyl chloride / Et_3N to give the ester (9), which was lactonised to (8) by treatment with PTSA in THF. This procedure was found to be unreliable on scale-up and was superseded by a one-step conversion in which (7) was simply treated with thionyl chloride in dichloromethane containing propylene oxide to give (8) directly in good yield.[6]

Having cleaved the top spiroketal portion of (2) we now faced the task of reassembling this portion of the molecule with the functionality required for (1). This was ultimately realised in very direct fashion: reaction of the lactone (8) with the anion derived from oxime ether (10),[7] followed by acid catalysed deprotection/spiroketalisation, produced the target (1) in good yield.

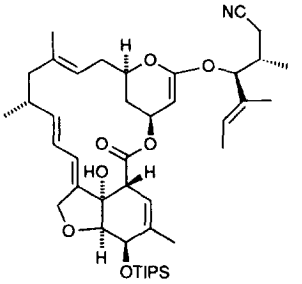
The overall sequence (2) → (1) was carried out on a 0.5 kg scale in 30% overall yield, and fulfilled our objective of forming the basis of a full scale manufacturing route to (1).

Acknowledgements

We thank Analytical Sciences at Great Burgh and Tonbridge for spectral data and HPLC analysis.

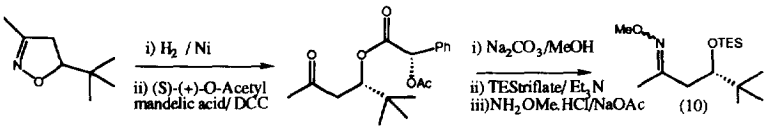
References and Notes

1. Davies H. G., Green R. H., *Chem. Soc. Rev.*, 1991, **20**, 211-269 and 271-339
2. Baker G. H., Blanchflower S. E., Dorgan R. J. J., Morgan D. O., Shelly D. R, Eur. Pat. App., EP 421,568, 10/5/91
3. Hood J. D., Banks R. M., Brewer M. D., Fish J. P., Manger B. R., Poulton M. E., *J. Antibiotics*, 1989, **42**, 1593-98
4. Tidwell T. T., *Org. React.*, 1990, **39**, 297-572
5. Baker G. H., Dorgan R. J. J., Hussain N., Macaulay G. S., Morgan D. O., *Tetrahedron Letters*, 1994, **35**, 2381-84
6. The exact mechanism of this remarkable transformation is not totally clear, however, if the reaction is carried out in the presence of triethylamine a rather unstable product is isolated which was tentatively assigned as (11).

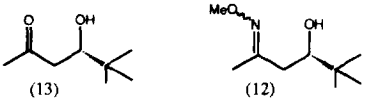


(11)

7. (10) was prepared from the corresponding Aldol product, using the following sequence:



It was later found that use of the dianion derived from (12) gave comparable yields to those obtained using (10). Initial attempts at using the corresponding ketone enolate derived from (13) gave poorer yields owing to competitive lactone deprotonation.



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