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DEVELOPMENT OF A SYNTHETIC ROUTE TOWARDS MILBEMYCIN β_1: PREPARATION OF AN ADVANCED MODEL SYSTEM.

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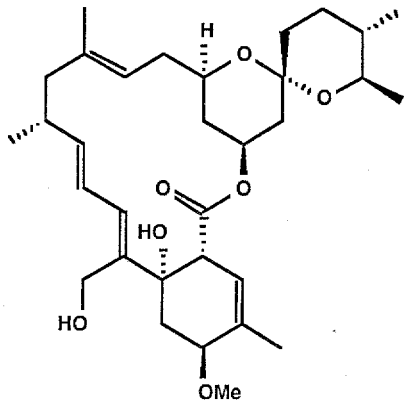
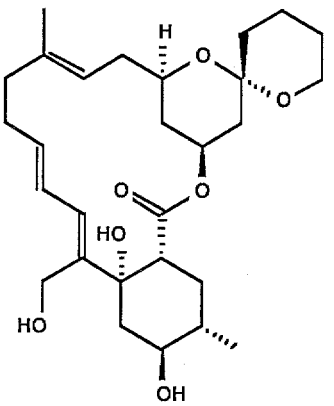
Summary: An advanced model compound for milbemycin β_1 synthesis has been prepared by a new coupling strategy employing alkylative rearrangement of a conformationally biased vinyl sulphone.

The growing importance of milbemycins[1] and the subsequent need to develop syntheses of novel unnatural compounds prompts us to report our approach towards milbemycin β_1 (**1**) illustrated by the preparation of an advanced model compound (**2**).



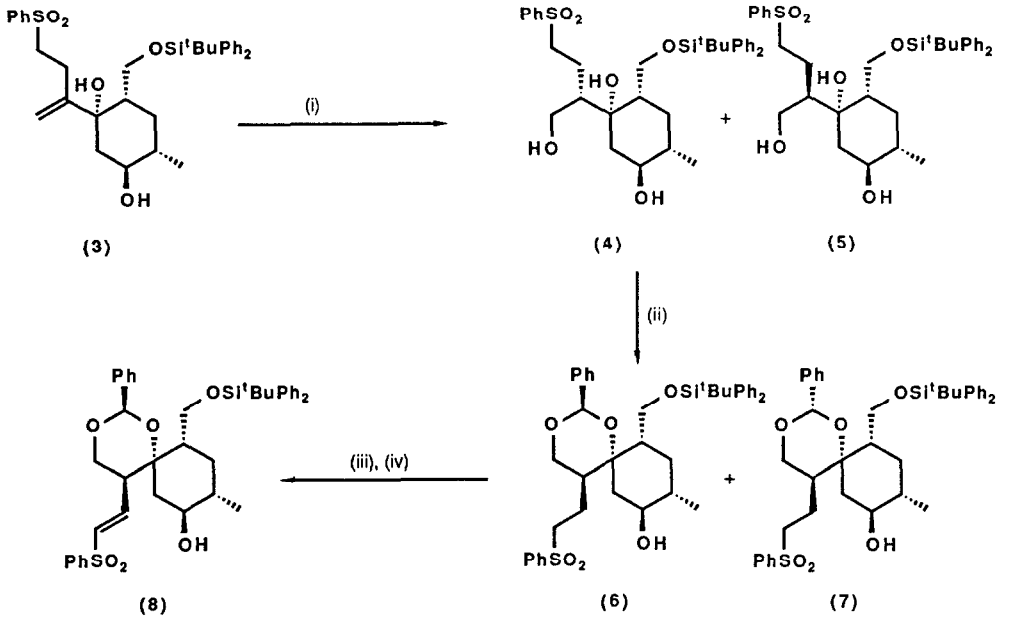
(**1**)



(**2**)

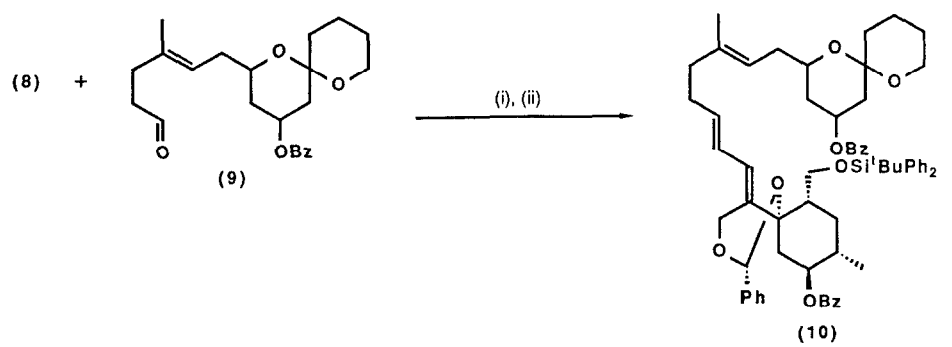
In a preceding letter[2] we have described an efficient preparation of the sulphone (**3**) as a pivotal fragment for milbemycin synthesis. Here we show how this unit may be further converted to a vinyl sulphone, which after anionic coupling[3] and macrolactonisation, affords the skeleton of milbemycin β_1.

Hydroboration of (3) gave a readily separable mixture of diastereoisomeric diols[†] (4) and (5)[Δ,‡] in a 9:2 ratio in 85% yield. Treatment of the major isomer (4) with benzaldehyde and pyridinium tosylate (PPTS) gave a separable 1:1 mixture of the benzylidine acetals (6) and (7) in 97% yield. The acetal (7) was recycled *via* equilibration in the presence of benzaldehyde and PPTS. The sulphone (6) was dehydrogenated to afford exclusively the E-vinylsulphone (8) (69%) by treatment with n-butyllithium and phenylselenenyl chloride followed by *syn*-elimination of the corresponding selenoxides.[§]

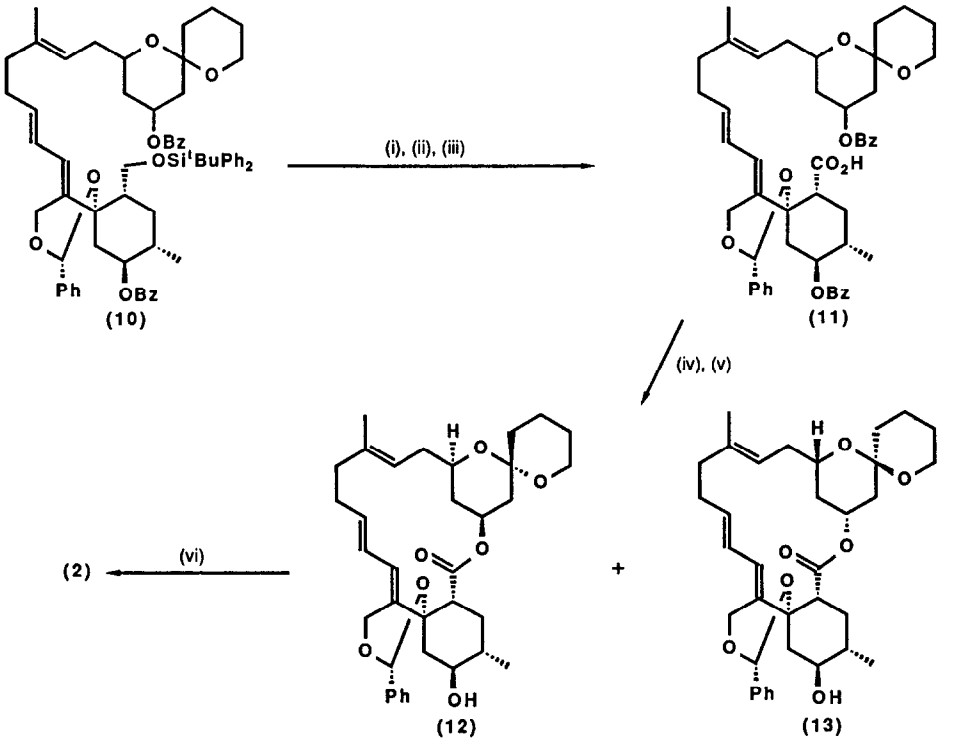


i). $BH_3.Me_2S$, THF, -20°C, 16h then NaOH, H_2O_2, RT, 30min. ii). PhCHO, pyridinium tosylate (1eq.), C_6H_6, 80°C, 2h. iii). ^nBuLi, THF, -78°C, 30min then PhSeCl, -78°C, 15min. iv). m-CPBA/satd. $NaHCO_3$, 10°C, 20min.

The conformation[#] of (8) is such that it may be deprotonated (with 2 equiv. ^tBuLi) to give an anion stable at -78°C, which underwent coupling at the α–carbon atom with the aldehyde (9). This racemic spiroacetal aldehyde was readily available from penta-1,4-diene in six steps by modification of our previously reported route to such units.[4]



i). ^tBuLi, THF, -78°C, 20min then (9) then PhCOCl, -78°C to RT, 3h. ii). 6%Na/Hg, MeOH/THF, Na_2HPO_4 buffer. -30°C, 30min.



i). TBAF, THF, 65°C, 2h. ii). $(COCl)_2$, DMSO, -60°C, 20min then Et_3N, -60°C to RT, 1h. iii). NaO_2Cl, $^tBuOH/H_2O$, KH_2PO_4, $(CH_3)_2C{:}CHCH_3$, RT, 30min. iv). NaOMe, MeOH, RT, 4h. v). 2-Chloro-N-methyl-pyridinium iodide, Et_3N, CH_3CN, 80°C, 12h. vi). CF_3COOH, CH_2Cl_2, 30min.

Benzoylation of the coupled products and treatment of the resulting benzoyloxyphenyl sulphones with sodium amalgam gave the diastereoisomeric E,E-dienes¥ (**10**) in 25% overall yield from (**8**). None of the other possible dienes were isolated in significant quantity, suggesting that steric effects may be operating in the initial coupling to favour the formation of the desired C-8,C-9 double bond geometry. Following methods established in the preceding letter, the silyl ethers (**10**) were deprotected with $^nBu_4NF$ in boiling THF, oxidised under Swern[5] conditions to the corresponding aldehydes and immediately further oxidised to the acids (**11**) with buffered sodium chlorite[6] in an overall 62% yield. The benzoyl groups were removed with sodium methoxide in methanol and the crude products subjected to macrolactonisation[7] with 2-chloro-N-methyl-pyridinium iodide to afford the 16 membered ring lactones (**12**) and (**13**). These were formed in a 1:1 ratio in 36% yield from (**11**). The macrolide (**12**) was quantitatively deprotected to give the milbemycin model derivative (**2**).¶

We believe that the methodology presented above is applicable to the total synthesis of the natural product milbemycin β_1. The results of this study will be reported at a later date.

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Footnotes

† All compounds reported in this paper are racemic.

Δ All new compounds had satisfactory spectral, microanalytical and/or accurate mass data.

‡ Proof of structure of these diols and later compounds relied upon X-ray crystallographic methods; we thank Dr. D.J. Williams, Imperial College, for these results.

§ Dehydrogenation of simple sulphones using the selenation / *syn*-elimination technique has not been reported previously. Other examples of this efficient process to the E-vinylsulphones will be reported separately.

¥ Proof of structure followed from extensive high field n.O.e. experiments.

A full discussion of the possible stereoelectronic effects and their use in the design of this synthesis will be reported later. See also H.D.Banks, *J. Org. Chem.*, **46**, 1743 (1981) and references therein.

¶ Compound (2) δ (500 MHz) 6.28-6.21 (2H, m, 9-H and 10-H), 5.61 (1H, m, 11-H) 5.17 (1H, tt, J 11.6 and 4.7 Hz, 19-H), 5.04 (1H, br t, J 6.6 Hz and 15-H), 4.26 (2H, m, 8'-H_2), 3.74 (1H, m, 17-H), 3.66 (1H, m, 24-H), 3.57 (1H, dt, J 2.5 and 11.3 Hz, 5-H), 3.52 (1H, m, 24-H), 3.28 (1H, d, J 2.7 Hz), 2.87 (1H, dd, J 3.6 and 12.8 Hz, 2-H), 2.40-2.30 (2H, m, 16-H_2), 2.06 (1H, dd, J 4.6 and 13.2 Hz, 13-H), 1.93 (1H, ddd, J 1.9, 4.8 and 12.1 Hz, 20-H), 1.90-1.80 (2H, m, 13-H and 22-H), 1.77 (1H, m, 18-H), 1.72-1.24 (15H, m), 1.51 (3H, s, 14-CH_3), 1.07 (3H, d, J 6.4 Hz, 4-CH_3), 0.88 (1H, q, J 11.8 Hz, 18-H).

References

1. H.G.Davies and R.H.Green, *Nat. Prod. Rep.*, 87 (1986).
2. See preceding communication.
3. M.Julia and J.-M.Paris, *Tetrahedron Lett.*, **14**, 4833 (1973); P.Kocienski, *Phosphorous Sulphur*, **24**, 97 (1985).
4. C.Greck, P.Grice, S.V.Ley and A.Wonnacott, *Tetrahedron Lett.*, **27**, 5277 (1986).
5. A.J.Mancuso and D.Swern, *Synthesis*, 165 (1981).
6. G.A.Kraus and M.J.Taschner, *J. Org. Chem.*, **45**, 1175 (1980); B.S.Bal, W.E.Childers and H.W.Pinnick, *Tetrahedron.*, **37**, 2091 (1981).
7. T. Mukaiyama, M. Usui and K. Saigo, *Chem. Lett.*, 49 (1976).

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