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TOTAL SYNTHESIS OF (+) - MILBEMYCIN β_1

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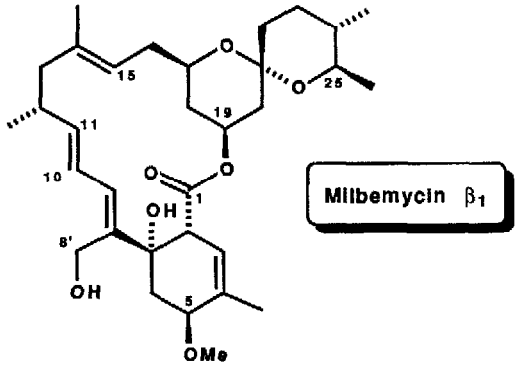
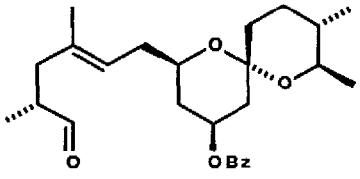
Abstract: *The successful sulphone anion stabilised coupling of a monocyclic C-1 to C-10 unit (3) with the "northern hemisphere" C-11 to C-25 fragment (2) of the milbemycins produces a compound which may be further elaborated in fourteen steps to the macrocyclic natural product (+) - milbemycin β_1 (1).*

The milbemycins and avermectins[1] have attracted considerable chemical and biological interest over the past decade due to their potent antiparasitic and insecticidal properties. Synthesis in the area has been extensive, culminating in several excellent total syntheses of milbemycin β_3,[2] the simplest member of the series, and the elegant construction of the structurally more complex avermectin A1a.[3]

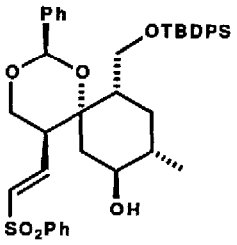


(1)

Our work in this area was initiated by the need to define new methods for the preparation of the inherent spiroacetal unit;[4] we also sought to devise alternative coupling sequences that would be applicable to the whole family of milbemycins and avermectins. Previously we have reported an efficient synthesis of the "northern" C-11 to C-25 fragment (2) common to many milbemycins,[5,6] the preparation of various monocyclic "southern" units such as **3**, and several model studies for coupling and analogue preparation.[6] Here we report the first synthesis of (+) - milbemycin β_1(1),[7] encompassing the methods that we have developed.



(2)



(3)

In an interesting coupling of the optically pure fragments **2** and **3**[6] we found that the sulphone (3) may be reacted with 2 equivalents of t-butyl lithium to afford a dianion which specifically reacts through the C-10 carbon atom to give the hydroxy sulphone products (4) in excellent yield (83%).[8] The conformation of the dianion derived from **3** is restricted such that the possibility of competing β-elimination is prohibited. We were unable to detect any other double bond isomers about the C-9 position during this coupling process. Reductive elimination of **4** using sodium amalgam in methanolic tetrahydrofuran in the presence of Na_2HPO_4 afforded the required E,E-diene (5) which was benzoylated in the usual way to give **6**. Elaboration to the 16-membered macrolide required initial deprotection of the primary t-butyldiphenylsilyl ether using $^nBu_4NF$. Oxidation of the C-1 alcohol was accomplished using a two stage procedure; reaction with tetra-n-propylammonium perruthenate (TPAP)[9] gave the aldehyde, which was then further oxidised to the carboxylic acid (7) using sodium chlorite.[10] After removal of the benzoyl groups with sodium methoxide, the resulting dihydroxy acid (8) was cyclized to the macrolide (9)[11] using the excellent Mukaiyama procedure.[12] Oxidation with TPAP and subsequent removal of the benzylidene acetal with moist trifluoroacetic acid afforded the ketone (10). For the remaining steps of the synthesis we chose to effect the introduction of the important 3,4-double bond by a *syn*-elimination sequence, since other workers have shown that difficulties arise in the related avermectins when unsaturation is present at an early stage in the synthesis, necessitating a less than satisfactory final deconjugation process.[3,13] Reaction of **10** with t-butyldimethylsilyl triflate to simultaneously protect the primary alcohol and form the thermodynamic enol ether was followed by treatment with phenylselenenyl chloride to give the protected ketoselenide (11). Oxidation of **11** to the corresponding selenoxides using the Davis oxaziridine reagent[14] proceeded well, the subsequent elimination affording both the *endo* and *exo* products in a 2:1 ratio. The possibility of aromatisation of the *endo*- enone system made it most convenient to simply work-up the crude mixture with sodium borohydride and cerium (III) chloride[15] to give the alcohols **12**, **13** and **14** in a 1:1:1 ratio, in 81% combined yield. The alcohol (13) could then be recycled to **12** by oxidation (TPAP) and reduction as described above. Methylation of **12** with methyl iodide and silver (I) oxide under ultrasonication, followed by deprotection with HF/pyridine in acetonitrile, gave (+) - milbemycin β_1 (1) in 55% overall yield. The synthetic sample[16] of **1** was identical by ^1H nmr, IR, mass spectral, $[\alpha]_D$ and tlc comparisons (3 solvent systems) to authentic material kindly provided by the Sankyo Company.

We believe that the synthesis described above demonstrates the viability of our approach and coupling strategy for the preparation of this important class of antiparasitic agents.

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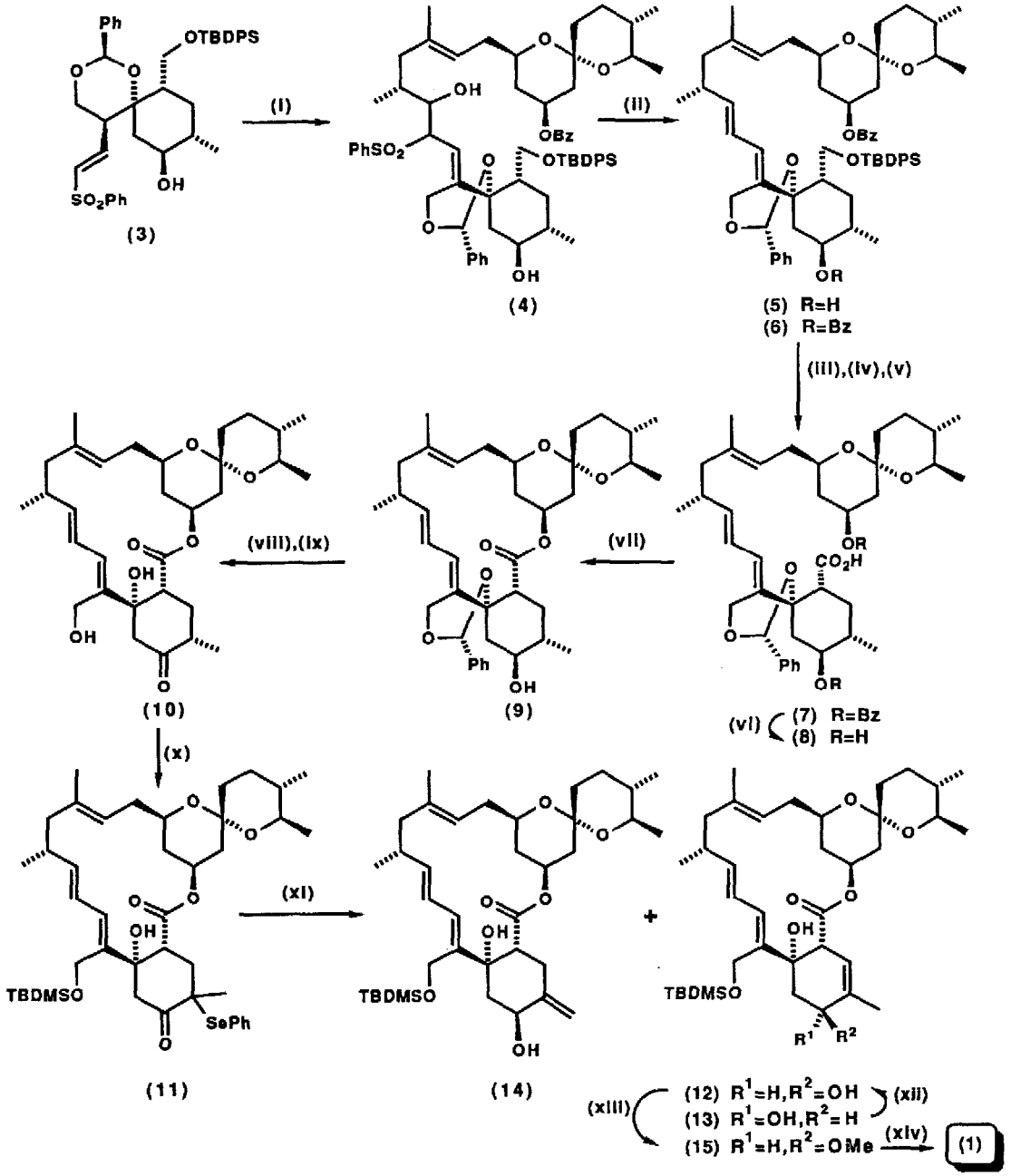

(i) 2.2 eq. t-BuLi, THF, -78°C, then (2), 83%; (ii) 6% Na/Hg, Na_2HPO_4, THF/MeOH, -40°C, then PhCOCl, py, DMAP, 27%; (iii) 2 eq. TBAF, THF, reflux, 91%; (iv) TPAP, NMO, 4Å ground sieves, CH_2Cl_2, 76%; (v) NaO_2Cl, 2-methyl-2-butene, KH_2PO_4, t-BuOH/H_2O; (vi) NaOMe, MeOH; (vii) 2-chloro-1-methyl pyridinium iodide, Et_3N, CH_3CN, reflux, 49% from aldehyde; (viii) TPAP,NMO, 4Å ground sieves, CH_2Cl_2, 83%; (ix) TFA, CH_2Cl_2, 92%; (x) 4 eq. TBDMSOTf, 20 eq. Et_3N, R.T., CH_2Cl_2, then PhSeCl, -78°C, 50%; (xi) 2-Benzenesulphonyl-3-(p-nitrophenyl)oxaziridine, $CDCl_3$, R.T., then $NaBH_4$, $CeCl_3$, MeOH, R.T.; (xii) TPAP, 4Å ground sieves, CH_2Cl_2, then $NaBH_4$, $CeCl_3$, MeOH, R.T.; (xiii) MeI, Ag_2O,))), 73%; (xiv) HF, py, CH_3CN, 75%.

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11. Data for compound (9): $[\alpha]^{20}_D$ = + 3.8° (c = 1.1, $CHCl_3$); δ_H (500MHz, $CDCl_3$) **7.63** (2H, m, Ph), **7.39-7.32** (3H, m, Ph), **6.03** (1H, dd, J 15.2, 10.3 Hz, H-10), **5.97** (1H, s, PhCH), **5.90** (1H, d, J 10.2 Hz, H-9), **5.74** (1H, dd, J 15.3, 5.1 Hz, H-11), **5.46** (1H, tt, J 11.4, 4.6 Hz, H-19), **4.87** (1H, br.d, J 11.2 Hz, H-15), **4.84** (1H, d, J 13.8 Hz, H-8'), **4.54** (1H, d, J 13.8Hz, H-8'), **3.67** (1H, m, H-17), **3.50** (1H, dt, J 11.5, 4.7 Hz, H-5), **3.25** (1H, dq, J 9.8, 6.2 Hz, H-25), **3.04** (1H, dd, J 13.8, 4.2 Hz, H-6_{eq}), **2.90** (1H, dd, J 12.4, 3.6 Hz, H-2), **2.57** (1H, m, H-12), **2.38-2.17** (3H, m), **2.05-1.68** (6H, m) **1.67** (3H, s, Me-14), **1.57-1.12** (6H, m), **1.09-1.05** (6H, m), **1.03** (3H, d, J 6.4 Hz, Me), **1.00-0.84** (3H, m), and **0.82** (3H, d, J 6.6 Hz, Me); m/z (FAB from 3-nitrobenzyl alcohol) 621 (MH^+), 602 (M^+-H_2O), and 515 (MH^+-PhCHO); (Observed MH^+, 621.3791. Calc. for $C_{38}H_{53}O_7$ MH, 621.3791).
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16. Data for compound (1): $[\alpha]^{20}_D$=+129.1° (c = 0.3, $CHCl_3$); δ_H (500MHz, $CDCl_3$) **6.41** (1H, d , J 11.3 Hz, H-9), **6.25** (1H, dd, J 14.7, 11.3 Hz, H-10), **5.45** (1H, dd, J 14.7, 9.8 Hz, H-11), **5.39** (1H, tt, J 11.5, 4.7 Hz, H-19), **5.25** (1H, m, H-3), **4.87** (1H, m, H-15), **4.26** (1H, dd, J 12.1, 6.1 Hz, H-8'), **4.17** (1H, dd, J 12.1, 4.6 Hz, H-8'), **4.04** (1H, br m, H-5), **3.78** (1H, d, J 1.6 Hz, OH-7), **3.55** (1H, m, H-17), **3.48** (1H, m, H-2), **3.36** (3H, s, MeO-5), **3.24** (1H, dq, J 9.7, 6.2 Hz, H-25), **2.47** (1H, m, H-12), **2.27-2.16** (3H, m, H_2-16 and H-13), **1.93-1.75** (5H, m), **1.80** (3H, s, Me-4), **1.64** (1H, m), **1.59** (3H, s, Me-14), **1.56-1.37** (5H, m), **1.25-1.19** (1H, m, H-20), **1.11** (3H, d, J 6.3 Hz, Me-25), **1.03** (3H, d, J 6.3 Hz, Me-12), **0.82** (3H, d, J 6.6 Hz, Me-24), and **0.77** (1H, q, J 11.6 Hz, H-18_{ax}).

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