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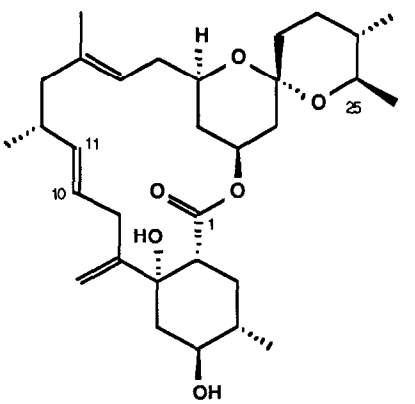
SYNTHESIS OF A NOVEL 3,4-DIHYDROMILBEMYCIN ANALOGUE.

Christine Greck, Peter Grice, A. Brian Jones, and Steven V. Ley*

Department of Chemistry, Imperial College, London, SW7 2AY, U.K.

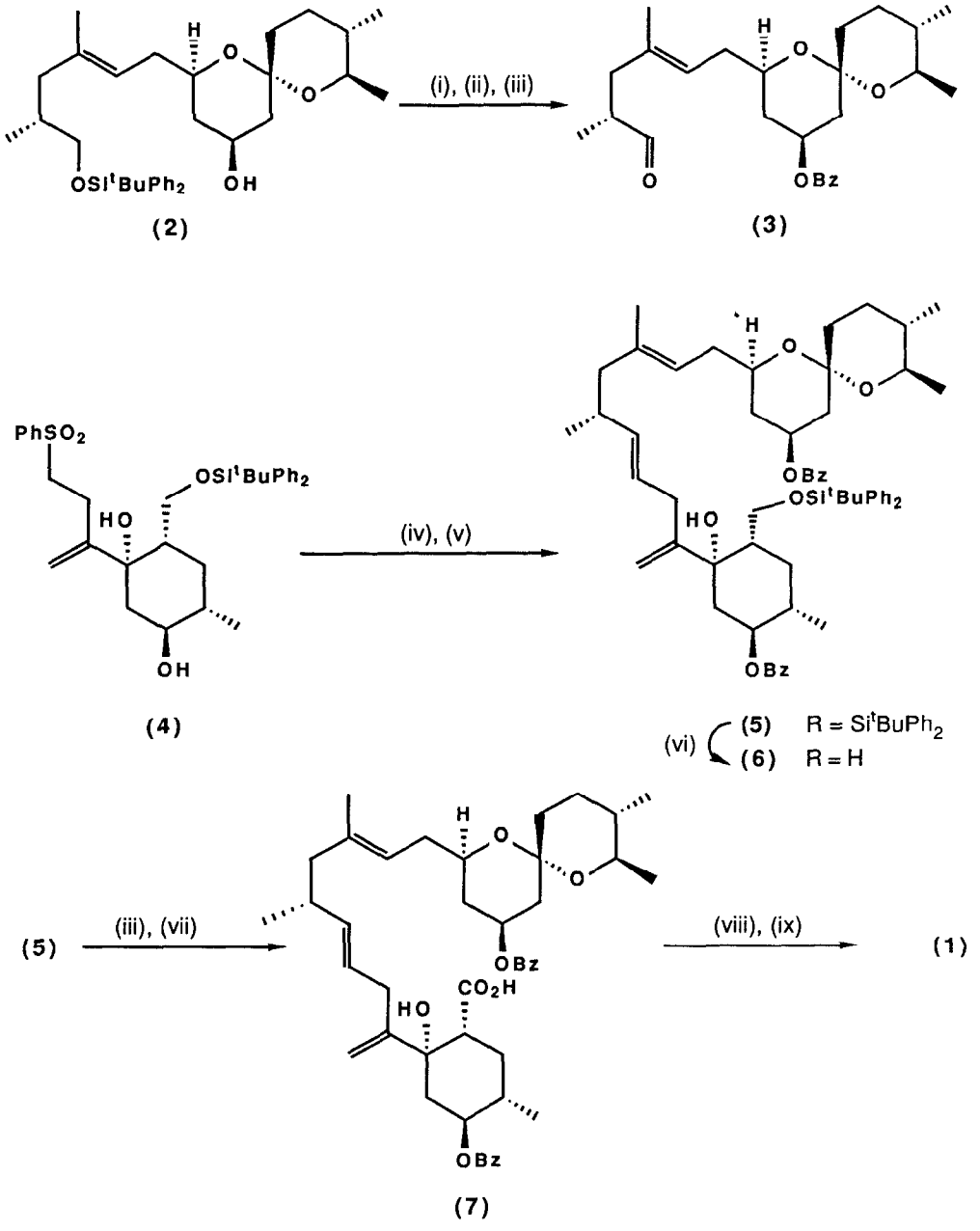
Summary: The synthesis of a 3,4-dihydromilbemycin derivative has been achieved by Julia coupling of the trianion of a C-1 to C-10 'southern' fragment with a C-11 to C-25 'northern' unit.

In view of the interest in milbemycin and avermectin synthesis[1,2] we wish to report the preparation of a 3,4-dihydro milbemycin analogue (**1**). This letter describes the coupling of our previously synthesised northern (C-11 to C-25) unit[3] with a 3,4-dihydromonocyclic southern (C-1 to C-10) fragment[4] and their further elaboration to a 16 membered macrocyclic structure.



(1)

The chiral milbemycin spiroacetal northern fragment (**2**)[3] was converted to the aldehyde (**3**) in 69% overall yield by benzoylation with benzoyl chloride in the presence of DMAP, deprotection with tetra-n-butylammonium fluoride in the normal way, followed by oxidation with a two fold excess of the Swern reagent.[5]



i). PhCOCl, pyridine, DMAP, 16h. ii). TBAF, THF, 4h. iii). $(COCl)_2$, DMSO, -60°C, 20min then Et_3N, -60°C to RT 1h. iv). ^nBuLi, THF, -78°C, 30min then (3) then PhCOCl, -78°C to RT, 2h. v). 6%Na/Hg, MeOH/THF, Na_2HPO_4 buffer, -30°C, 30min. vi). TBAF, THF, RT, 15min. vii). NaO_2Cl, ^{t}BuOH/H_2O, KH_2PO_4, $(CH_3)_2C{:}CHCH_3$, RT, 3h. viii). NaOMe, MeOH, RT, 10h. ix). 2-Chloro-N-methyl-pyridinium iodide, Et_3N, CH_3CN, 80°C, 12h.

The trianion from the chiral sulphone (**4**)[4] (generated in solution by treatment of (**4**) with 3 equiv. ^{n}BuLi in THF at -78°C) was reacted with the aldehyde (**3**) and the adduct quenched with benzoyl chloride. Reductive elimination of the crude benzoyloxyphenyl sulphones with Na/Hg[6] gave the 10-E alkene (**5**) in an unoptimised 30% yield. Deprotection of (**5**) with $^{n}Bu_4NF$ in THF afforded the alcohol (**6**) (87%). Several methods were investigated for the oxidation of this alcohol to the carboxylic acid. By far the most successful procedure involved Swern oxidation to the aldehyde (85%) followed by immediate oxidation with sodium chlorite in the presence of a potassium di-hydrogen phosphate buffer and 2-methylbut-2-ene which delivered (**7**) in essentially quantitative yield. After removal of the benzoyl groups by treatment with sodium methoxide in methanol and recovery through a non-aqueous work-up, the crude triol seco acid was subjected to macrolactonisation using the excellent Mukaiyama procedure.[8] The milbemycin analogue (**1**) was obtained in a satisfying 60% yield for the two steps.

Further chemical elaboration of (**1**) to milbemycin β_1 was not investigated at this stage in favour of an alternative route.[9]

Nonetheless this represents the most advanced totally synthetic intermediate for the preparation of the non-aromatic milbemycins reported to date.

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Footnotes

All new compounds gave satisfactory spectral microanalytical and/or accurate mass measurement data.

Compound (**4**) $[\alpha]_D$ + 9.7° (c = 1.4, $CHCl_3$); δ (250 MHz) 7.95-7.32 (15H, m, Ph), 5.32 (1H, s, 1'$_A$-H), 4.90 (1H, s, 1'$_B$-H), 4.38 (1H, br s,. 1-OH), 3.80 (1H, d, J 11.2 Hz, 1"-H), 3.65 (1H, m 5-H), 3.45 (1H, d, J 11.2 Hz 1"-H), 3.24 (2H, m, 4'-H_2), 2.44 (2H, m, 3'-H_2), 1.94 (1H, dd, J 26.0 and 13.0 Hz, 3-H), 1.81 (1H, dd, J 13.0 and 4.0 Hz, 6-H), 1.62 (2H, m, 6-H and 5-OH), 1.39 (3H, m, 2-H, 3-H and 4-H), 1.10 (3H, d, J 7.5 Hz, 4-Me), and 1.04 (9H, s, ^{t}Bu):

Compound (**1**) $[\alpha]_D$ + 38.9° (c = 0.4, $CHCl_3$); δ (500 MHz), 5.44 (1H, ddd, J 4.2, 9.7 and 14.9 Hz, 10-H), 5.32 (1H, d J 1.1 Hz, 28-H), 5.29 (1H, tt, J 4.8 and 11.5Hz, 19-H), 5.12 (1H, dd, J 9.4 and 15.0 Hz, 11-H), 4.94 (1H, m, 15-H), 4.80 (1H, d, J 1.20 Hz, 28-H), 3.69 (1H, m, 5-H), 3.59 (1H, m, 17-H), 3.25 (1H, m, 25-H), 2.95 (1H, d, J 2.8 Hz, 7-OH), 2.79 (1H, dd, J 3.5 and 12.7 Hz, 2-H), 2.69 (1H, m, 9-H), 2.60 (1H, dd, J 9.6 and 17.5 Hz, 9-H), 2.44 (1H, m, 12-H), 2.20 (3H, m, 13-H and 16-H_2), 1.93-1.63 (5H, m, 3-H, 6-H, 13-H, 18-H and 20-H), 1.60-1.35 (11H, m, 3-H, 4-H, 6-H, 14-Me, 20-H, 22-H_2 and 23-H_2), 1.25 (2H, m, 5-OH and 24-H), 1.11 (3H, d, J 6.3 Hz, 25-Me) 1.08 (3H, d, J 6.4 Hz, 4-Me), 0.99 (3H, d, J 6.7 Hz, 12-Me), 0.82 (3H, d, J 6.6 Hz, 24-Me), and 0.75 (1H, q, J 12.0 Hz, 18-H);

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