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AN ENANTIOSPECIFIC SYNTHESIS OF THE SPIROKETAL PORTION OF AVERMECTIN B_{1a}

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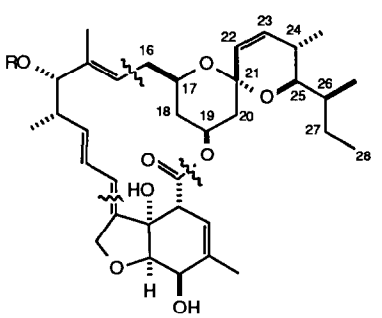
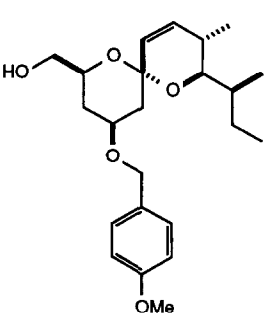
SUMMARY: The acetonide of (3S,5S)-5,6-dihydroxy-3-p-methoxybenzyloxyhexanal, prepared from laevoglucosan, reacted with the cerium derivative of (3S,4R,5S)-3,5-dimethyl-4-t-butyldimethyl silyloxy-1-heptyne, prepared from (2S)-2-methylbutanol, to give a carbinol that was converted in four steps to the spiroketal segment of avermectin B_{1a}.

The potent anthelmintic and antiparasitic activity associated with the avermectins[1] has elicited numerous and exceptionally diverse contributions from synthesis.[2] The endeavors directed toward de novo synthesis of these Streptomyces metabolites and the companion milbemycins has resulted in some noteworthy achievements, including a recent total synthesis of avermectin A_{1a}.[3] Our plan for the synthesis of avermectin B_{1a} envisions construction and convergence of the three subunits identified in its trisected formula (1). A route to the hexahydrobenzofuran moiety of 1 was reported in a recent Letter[4] and we now describe an enantiospecific synthesis of 2, representing the spiroketal component (C-16 to C-28) of avermectin B_{1a}.[5]

A structural element common to certain avermectins that distinguishes them from milbemycins is a sec-butyl substituent at C-25. In consequence, a stereogenic carbon is present at C-26. This feature, together with the additional five stereogenic centers of the spiroketal of 1, suggested an approach in which alkylation of (2S)-2-methylbutanal (3) would be effected with a crotyl anion species to give an alkyne incorporating C-22 to C-28. This could then be coupled to a glucose-derived aldehyde (C-16 to C-21) and the resulting carbinol transformed to 2.[6]

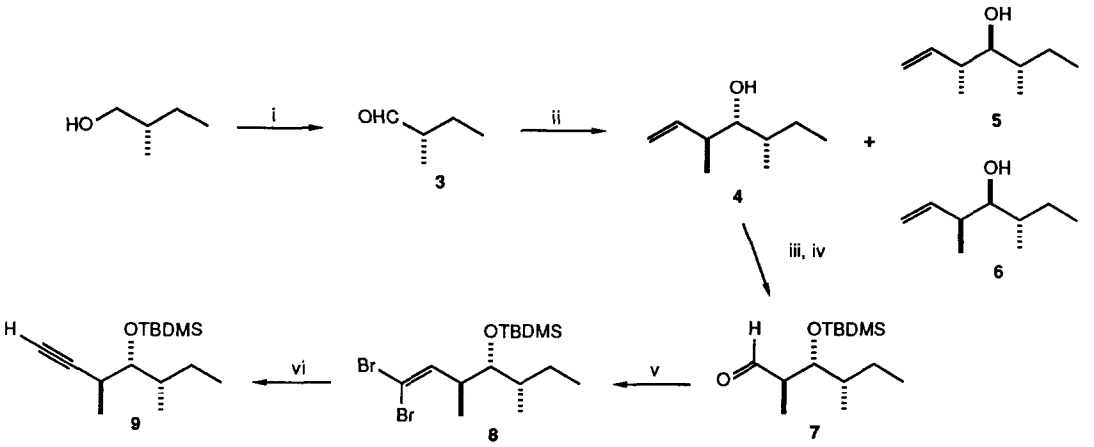


1 (R = L-oleandrosyl-L-oleandrosyl)



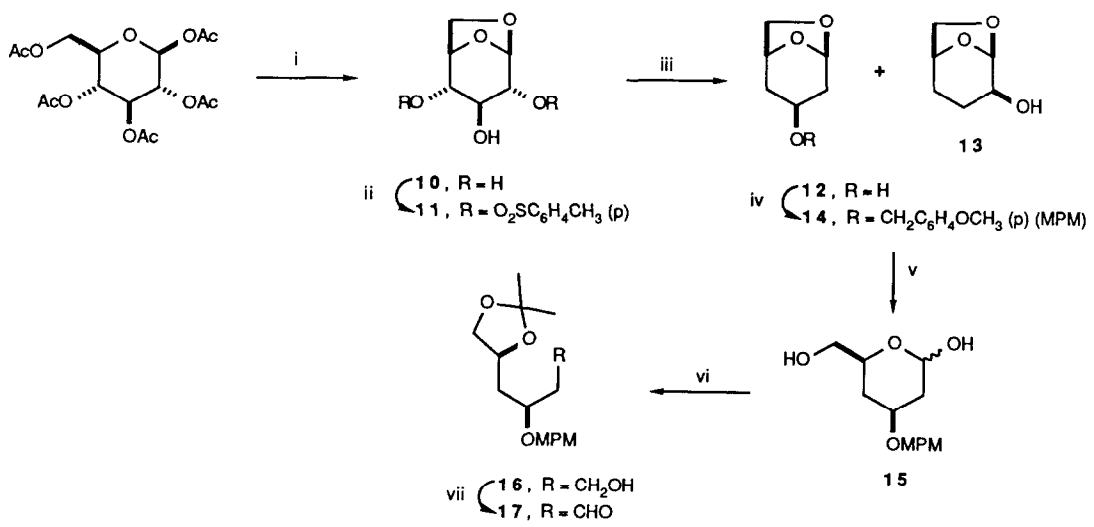
2

The aldehyde **3** was obtained with no loss of optical purity[7] by Swern oxidation[8] of (2S)-2-methyl-1-butanol and was reacted with crotyl bromide in the presence of a chromium(II) reagent prepared in situ from chromium(III) chloride and lithium aluminum hydride.[9]



Scheme 1. Reagents and conditions: i, $(COCl)_2$, DMSO, Et_3N, -60°C (82%); ii, $CrCl_3$, $LiAlH_4$, then $CH_3CH{=}CHCH_2Br$, THF, 25°C; iii, t-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, 0°C (86%); iv, O_3, CH_2Cl_2-MeOH, then Me_2S, -78°C (92%); v, CBr_4, PPh_3, Zn dust, CH_2Cl_2, 25°C (83%); vi, n-BuLi (2 equiv), THF, -78°C to 25°C, 2 h (86%).

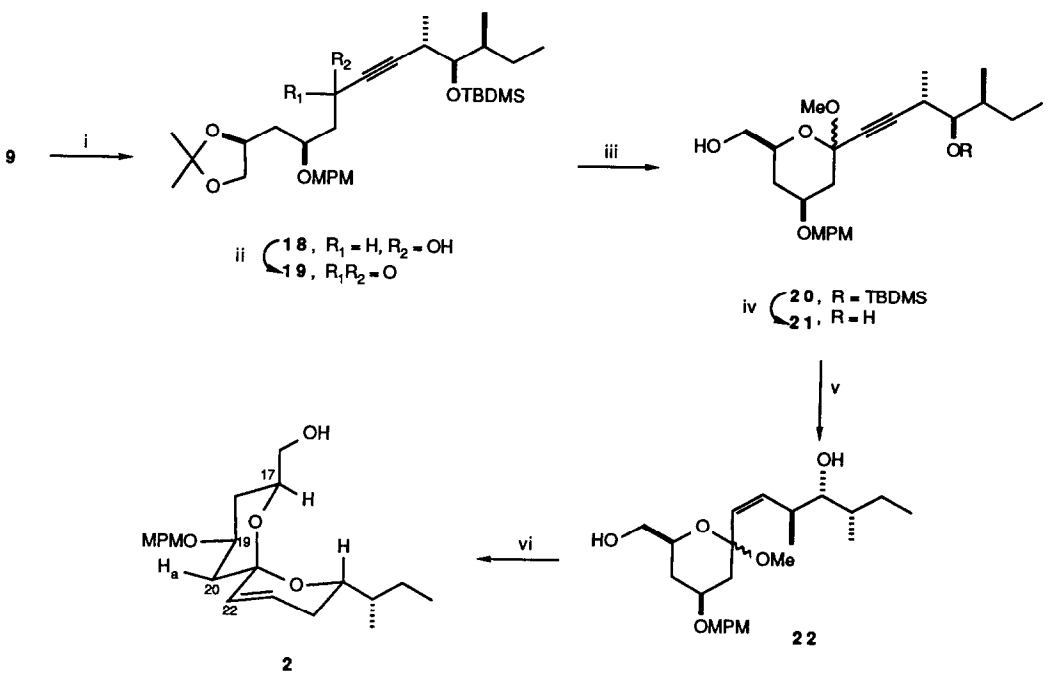
Diastereomeric alcohols **4**, **5**, and **6** were produced in the ratio 61:30:9 respectively, from which the desired alcohol **4** was separated chromatographically in 53% yield. This substance, after protection as its t-butyldimethylsilyl (TBDMS) ether, was ozonized to aldehyde **7**. The latter was converted to the substituted heptyne **9** via dibromo olefin **8** (Scheme 1).[10]



Scheme 2. Reagents and conditions: i, ref 9; ii, p-TsCl, pyridine-$CHCl_3$, 25°C, 50 h (90%); iii, $LiBHEt_3$ (6 equiv), THF, 25°C, 48 h (55%); iv, KH, p-$MeOC_6H_4CH_2Cl$, THF, 0°C, (80%); v, H_2O-THF (1:1), p-TsOH (cat), reflux, 5 h (78%); vi, $LiAlH_4$, THF, 25°C, 3 h, then $Me_2C(OMe)_2$, camphorsulfonic acid (cat), CH_2Cl_2, 1 h (56%); vii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 -60°C (82%).

The second component required for **2** was prepared from laevoglucosan (**10**), itself acquired by a known route from glucose pentaacetate.[11] The superfluous oxygen substituents at C-2 and C-4 were excised by reduction of ditosylate **11**[12] with lithium triethylborohydride, a process that led through intervening epoxides to **12** accompanied by **13** (~5:1) respectively.[13] Protection of **12** as its p-methoxybenzyl (MPM) ether **14**, followed by acidic hydrolysis of the anhydro bridge, yielded lactol **15**. The triol obtained upon reduction of **15** was selectively protected as its acetonide **16** and the resulting heptanol derivative was subjected to Swern oxidation to give aldehyde **17** (Scheme 2).[14]

Alkylation of **17** with the lithium acetylide derived from **9** gave a poor yield of **18** together with much recovered alkyne. However, the less basic alkynylcerium[15] reagent from **9** was more satisfactory and afforded a 67% yield of the desired alkynyl carbinol **18**. This alcohol was readily oxidized to ketone **19**. Elaboration of **19** was carried out in a straightforward sequence that entailed (i) acidic methanolysis, which removed the acetonide and led to methoxy acetal **20**, (ii) deprotection of the silyl ether to give diol **21**, and (iii) partial hydrogenation of the alkyne to cis olefin **22**, followed by a final acid-catalyzed cyclization to yield **2** (Scheme 3).[6] The spiroketal **2**, $[\alpha]_D$ + 100.6°, was obtained as a single stereoisomer, the structure of which was established by a detailed ^1H NMR study.[16] In particular, a n.O.e. experiment in which H-22 (δ 5.56) was irradiated resulted in a 5.5% enhancement of H-20a (δ 1.43) but no enhancement of either H-17 or H-19. This result defines the configuration of the spiro carbon unambiguously.



Scheme 3. Reagents and conditions: i, n-BuLi, THF, -78°C, then $CeCl_3$, 0.5 h, then **17** (67%); ii, MnO_2, CH_2Cl_2, 2 h (75%); iii, MeOH, camphorsulphonic acid (cat), 1 h (84%); iv, n-$Bu_4N^+F^-$, THF, 50°C, 1 h (85%); v, H_2, Pd/$BaSO_4$, quinoline, MeOH, 0.5 h; vi, Et_2O, camphorsulphonic acid, 10 min (83% from **21**).

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7. The optical purity of **3** can be assayed by reaction with (2R,3R)-butan-1,2-diol and examination of the resulting acetal by ^{13}C NMR spectroscopy.
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16. ^1H NMR data for **2** (400 MHz, $CDCl_3$): δ 0.88 (3H, d, 7.0, C-26 Me), 0.92 (3H, d, 7.0, C-24 Me), 0.93 (3H, t, 7.0, C-27 Me), 1.33 (1H, ddd, 12.0, 11.0, 11.0, H-18a), 1.36 (1H, m, H-27), 1.39 (1H, m, H-27), 1.43 (1H, dd, 12.0, 11.0, H-20a), 1.57 (1H, m, H-26), 1.93 (1H, dddd, 12.0, 4.5, 4.5, 2.5, H-18e), 2.12 (1H, ddd, 12.0, 4.5, 2.0, H-20e), 2.26 (1H, dqdd, 10.0, 7.5, 3.0, 2.0, H-24), 3.39 (1H, dd, 10.0, 2.0, H-25), 3.59 (1H, dd, 15.0, 9.0, H-16), 3.63 (1H, brd, 15.0, H-16), 3.80 (3H, s, OMe), 3.89 (1H, dddd, 10.0, 7.0, 4.0, 2.5, H-17), 3.94 (1H, dddd, 11.0, 11.0, 4.0, 4.0, H-19), 4.48 (2H, s, OCH_2Ar), 5.56 (1H, dd, 10.0, 3.0, H-22), 5.74 (1H, dd, 10.0, 2.0, H-23), 6.87 (2H, d, 9.0), and 7.25 (2H, d, 9.0).

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