STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF CALCIMYCIN (A-23187)

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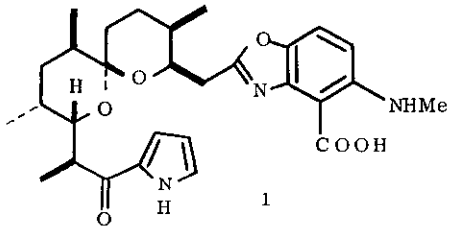
The polyether antibiotics continue to receive considerable attention because of their role in transporting ions across cell membranes.[1] Our synthetic efforts in this area have been focussed on calcimycin (A-23187), a divalent cation ionophore isolated from cultures of Streptomyces chartreusensis.[2] Examination of the structure of calcimycin (1) reveals the presence of a novel 1,7-dioxaspiro[5.5]undecane skeleton which, in principle, can be readily constructed from an appropriately functionalized acyclic substrate (cf. 2). With this strategy in mind, we devised synthetic routes to the C(1) to C(11) acyclic fragment 3 and the benzoxazole unit 4.



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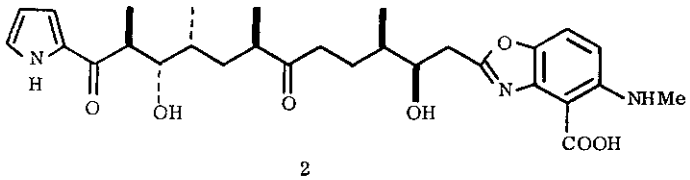

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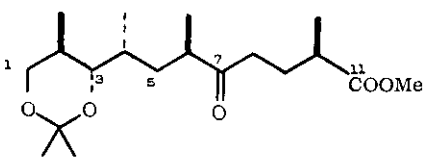

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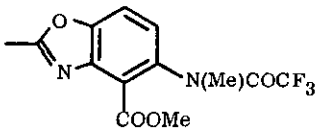

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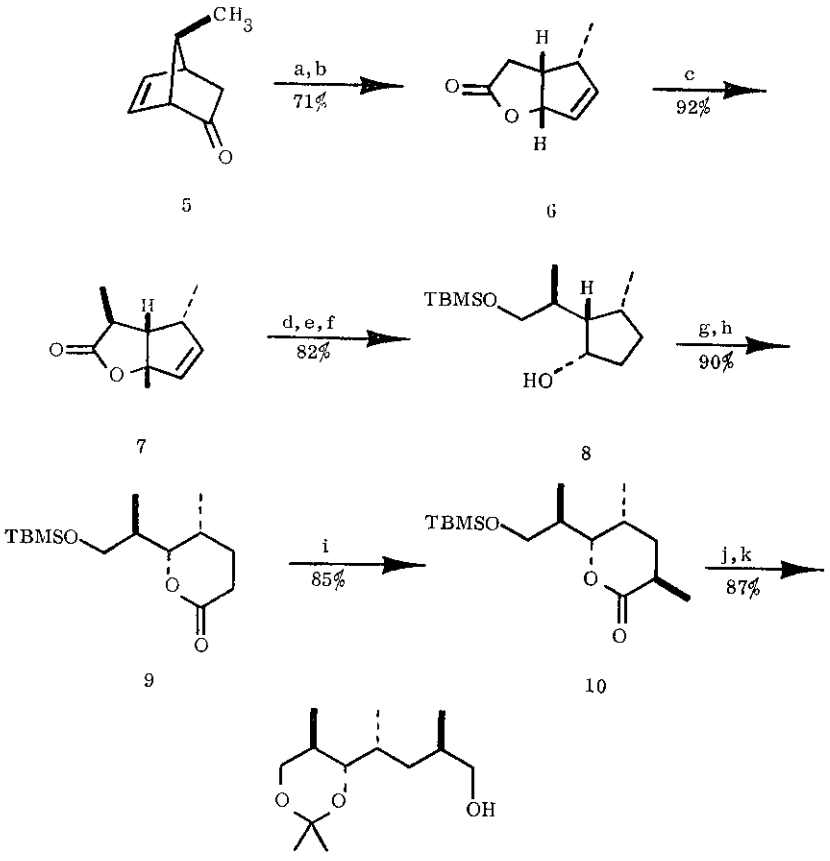
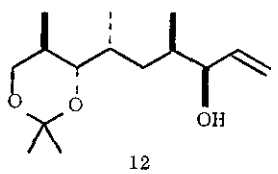
SCHEME I



a, H_2O_2, OH^-; b, $BF_3 \cdot Et_2O$; c, LDA, THF, MeI; d, $LiAlH_4$; e, H_2, PtO_2, EtOAc; f, t-Bu(Me)$_2$SiCl, DMAP, Et_3N; g, $CrO_3 \cdot 2Py$; h, MCPBA; i, LDA, THF, MeI; j, $LiAlH_4$; k, acetone, $CuSO_4$, TsOH.

The fully elaborated C(1) to C(7) segment 11 of intermediate 3 was constructed in a stereospecific fashion from the bicyclo[2.2.1]heptenone 5 employing the methodology in Scheme I. With the configuration at C(2), C(3), C(4), and C(6) established we turned our attention to elaboration of the remaining chiral center at C(10). Oxidation of 11 with Collins reagent followed by addition of vinylmagnesium bromide to the resulting aldehyde gave rise (60 %) to allylic alcohol 12 as the major product in accordance with Cram's rule.

Conversion of 12 into its corresponding propanoate derivative followed by application of the Ireland modification of the Claisen rearrangement[3] utilizing the E-O-silylketene acetal gave after treatment with flouride ion and diazomethane the trans olefinic ester 13 in ca. 80 % overall yield as the sole product. Hydroxylation (OsO_4) of the C(7), C(8) double bond afforded a mixture of hydroxy γ-lactones which upon oxidation with pyridinium chlorochromate[4] gave keto lactone 14 in 87 % yield. Reductive cleavage ($Ca/NH_3/-60^oC$) of the C(8), oxygen bond and subsequent esterification (CH_2N_2) of the resultant keto acid produced key intermediate 3 in 85 % overall yield.



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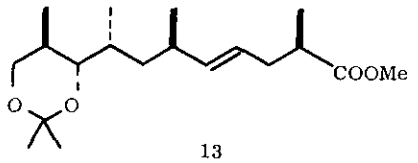

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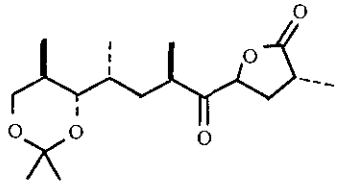

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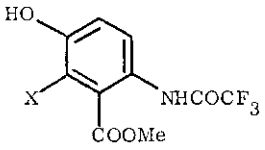
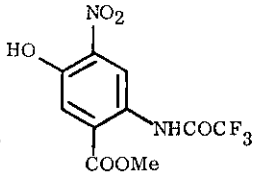
The synthesis of benzoxazole 4 was achieved in a straightforward manner. Trifluoroacetylation (TFAA, CH_2Cl_2, Py) of methyl 5-hydroxyanthranilate[5] afforded 15a, mp 140-141°C, in 95 % yield. Much to our surprise, mono-nitration (HNO_3, CH_3NO_2) of 15a generated (94 %) a 2:1 mixture of the desired nitrophenyl 15b and the corresponding 4-nitro derivative 16 which could be easily separated chromatographically. Reduction (H_2, 10 % Pd-C, EtOAc) of 15b provided an 88 % yield of 15c, mp 170-171°C, which upon treatment with acetyl chloride in refluxing xylene gave in 91 % yield benzoxazole 17, mp 156-157°C. Methylation (MeI, K_2CO_3, acetone) of 17 generated

in near quantitative yield the required, fully protected benzoxazole 4, mp 99.5-100.0°C.



15a, X = H
15b, X = NO_2
15c, X = NH_2



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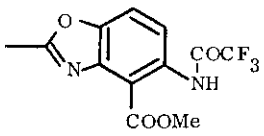

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With benzoxazole 4 and the C(1) to C(11) structural fragment 3 available, efforts are underway to combine these two building blocks in hopes of being able to realize the total synthesis of calcimycin.

ACKNOWLEDGEMENTS

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