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STEREOCONTROLLED SYNTHESIS OF SUBSTITUTED 2-ALKOXYTETRAHYDROPYRANS FROM MESO-2,4-DIMETHYLGLUTARIC ANHYDRIDE

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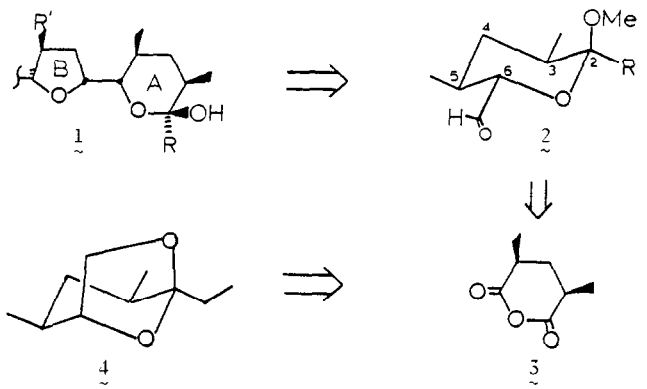
Abstract Methods for efficient synthesis of A-ring fragments present in monensin and several of the nigericin group of ionophores and of α-multistriatin are described

Monensin and members of the nigericin group comprise one of the largest classes of naturally occurring monocarboxylic acid ionophores [2] By virtue of their novel and complex molecular architecture, development of methods for the efficient construction of structural fragments found in these molecules is an area of considerable current interest [3] Part structure 1 illustrates the AB ring system[2] present in several members of the group, including monensin, nigericin, and dianemycin (R=CH_2OH, R'=CH_3), grisorixin and mutalomycin (R=R'=CH_3), and septamycin and antibiotic 6016 (R=CH_3, R'=H) As outlined by the disconnections shown in scheme 1, our approach to the total synthesis of members of this class of ionophores[4] involves

Scheme 1

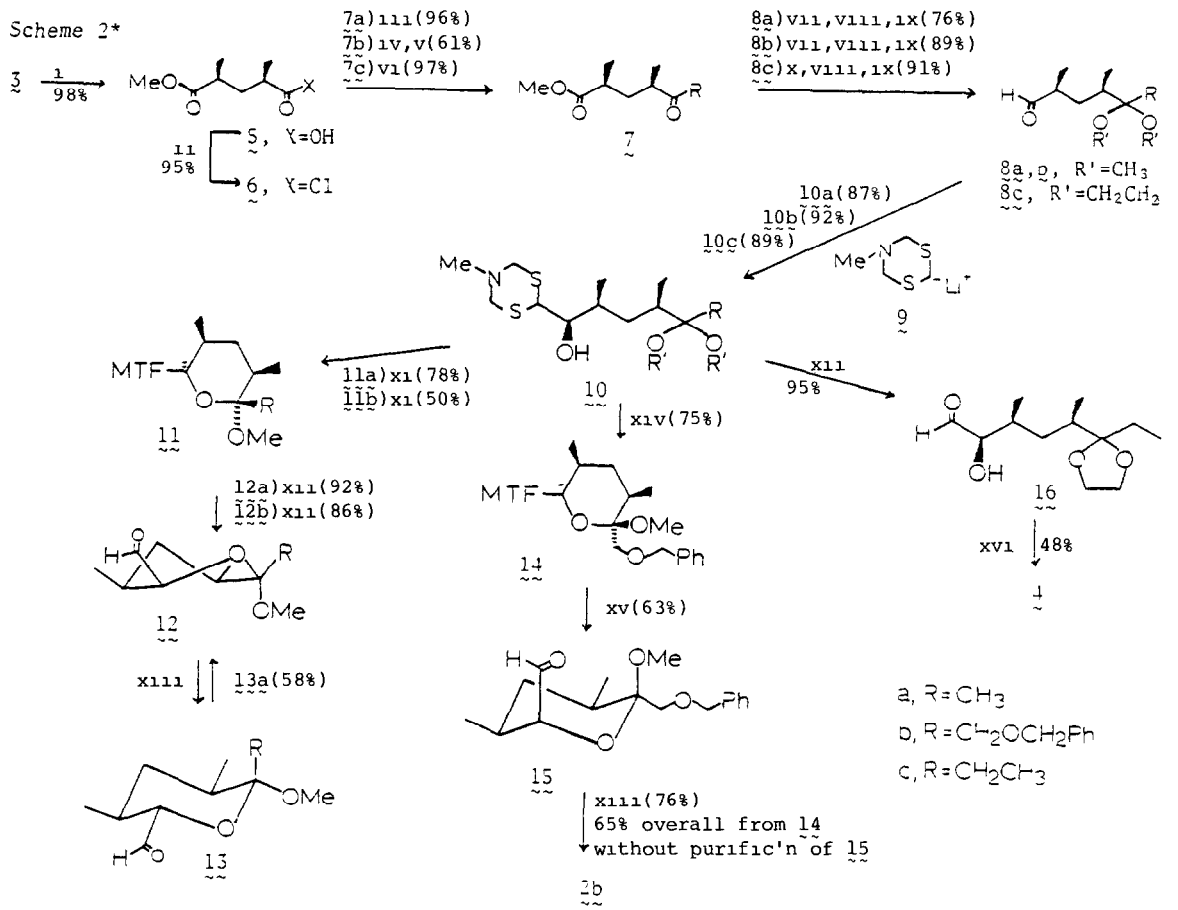


1 2 4 3

use of tetrahydropyran (THP) derivatives of type 2 (R=CH_3 or CH_2OCH_2Ph) as key intermediates containing the elements of the A-ring appropriately functionalized for further manipulation The synthetic plan calls for preparation of THPs of type 2 by sequential addition of two different nucleophiles to the carbonyl groups of the readily available meso-2,4-dimethylglutaric anhydride (3) [5] Stereocontrol at C-6 (numbering as shown for structure 2) would derive from the expected thermodynamic preference for an α-oriented (equatorial) formyl group in 2 We report herein methods for accomplishment of this goal, which also afford a highly efficient preparation of the important pheromone constituent α-multistriatin (4) [6]

The syntheses are shown in scheme 2 [7] Several attempts at direct reaction of various nucleophiles with anhydride 3 failed to provide the desired keto acid The carbonyl groups of 3 were therefore differentiated by the well-known methanolysis reaction[8a] to give half-acid

Scheme 2*



* i) MeOH, reflux, ii) $(COCl)_2$, benzene, iii) Me_2CuLi, iv) CH_2N_2, v) $PhCH_2OH$, BF_4H, vi) CH_3CH_2Cu, vii) $HC(OMe)_3$, MeOH, viii) $LiAlH_4$, ix) CrO_3·2pyr; x) $(HOCH_2)_2$, benzene, TsOH, xi) HPyrOTs, MeOH, xii) HgI_2, HgO, aqu THF; xiii) MeOH, K_2CO_3, reflux, xiv) HPyrOTs, THF, xv) $Hg(CN)_2$, $CaCO_3$, aqu. THF, xvi) $NaCNBH_3$, aqu. THF, pH=2~3

ester 5 followed by conversion to the acid chloride 6. Since initiation of our work, other groups have reported on the utility of half-acid ester 5 for synthesis of natural products, including α-multistriatin[3] and the Prelog-Djerassi lactone.[4] In addition, Sih has recently described a microbiological method for preparation of 5 in >98% enantiomeric purity,[5] further enhancing the attractiveness of this material as a synthetic intermediate.

Initial efforts were directed towards preparation of a septamycin A-ring fragment (R=CH_3 in schemes 1 and 2). Thus, addition of lithium dimethylcuprate to acid chloride 6 to give ketone 7a, followed by protection of the ketone carbonyl as a dimethyl acetal, then transformation of the ester grouping to the aldehyde stage gave 8a in 73% overall yield from 6. The synthesis now requires addition of a formyl anion equivalent which is stable to cyclic ketal forming conditions and may be removed in the presence of a sensitive ketal. Several functional groups routinely utilized as synthons for a formyl group, including a simple vinyl group, nitromethyl, and dithian-1, failed in one or the other of these requirements. The N-methyl-thioformaldine (MTF) grouping of Balanson,[10] however, proved an excellent solution to the

problem Thus, addition of aldehyde 8a to a tetrahydrofuran (THF) solution of lithiothioformaldine (9) at -100°→0°C resulted in formation of adduct 10a in good yield with the expected Cram's rule diastereoselection (>95% of a single diastereomer by ^{13}C NMR analysis) Treatment of hydroxy-ketal 10a with pyridinium tosylate[11] in dry methanol gives the crystaline THP derivative 11a (mp 92-94°C) in 78% isolated yield after flash chromatography The stereochemistry of compound 11a at both C-2 and C-6, and therefore that of 10a at C-6 is unequivocally established by single crystal X-ray analysis [12] THP 11a exists in the crystal in a twist boat conformation in which the α-oriented methoxyl substituent at C-2 enjoys anomeric stabilization

Hydrolysis of the thioacetal function of 11a in the presence of the cyclic ketal is accomplished by allowing 11a to react with mercuric iodide and excess mercuric oxide in aqueous THF affording aldehyde 12a Treatment of this material with potassium carbonate in refluxing methanol for one hour gives a readily separable mixture of epimeric aldehydes 13a and 12a in a 6 1 ratio The desired aldehyde 13a may be obtained in 58% isolated yield by flash chromatography Analysis of the ^1H NMR spectrum of 13a suggests it exists in the indicated chair conformation ($J_{5,6}$ =10Hz) The rather disappointing extent of epimerization is presumably a result of loss of anomeric stabilization in THP 13a While compound 13a is epimeric with septamycin A-ring fragment 2 (R=CH_3) at C-2, 13a represents a useful protected synthon for the septamycin A-ring system since deprotection of the ketal moiety will proceed with epimerization to the thermodynamically preferred β-hydroxyl configuration

Preparation of the desired monensin A-ring fragment 2 (R=CH_2OCH_2Ph) requires addition of a methanol dianion equivalent to acid chloride 6 in place of methyl After several approaches for direct addition of a benzyloxymethyl group failed to provide ketone 7b, the required transformation is accomplished in two steps by diazoketone formation followed by flouroboric acid catalyzed addition of benzyl alcohol Conversion of ketone 7b to hydroxy-ketal 10b proceeds in a straightforward manner, affording 10b in 50% overall yield from acid chloride 6

Treatment of hydroxy-ketal 10b with pyridinium tosylate in methanol gives a single diastereomeric cyclic ketal assigned structure 11b by analogy with the cyclization results obtained with 10a Removal of the MTF grouping and base catalyzed epimerization gives aldehydes 13b and 12b in a 3 1 ratio as judged by ^1H NMR The poor stereoselctivity in the epimerization and great difficulty in separation of these epimeric aldehydes prompted us to search for a more efficient pathway to 2 (R= CH_2OCH_2Ph) Treatment of 10b with pyridinium tosylate in dry THF at reflux for two hours gave the THP derivative 14, epimeric with 11b at C-2, in good yield None of the epimer 11b was detected in the crude reaction mixture, and 11b treated under identical conditions gave an enol ether resulting from elimination of methanol Compound 14, when treated with pyridinium tosylate in methanol gave THP 11b, indicating that 14 is a kinetic product of cyclization in THF, while 11b is thermodynamically favored in methanol

Removal of the MTF grouping of 14 under the same conditions successfully utilized for deprotection of 11 gave a mixture of aldehyde 15 and a bicyclic product resulting from hydrolysis of the methyl ketal However, this deprotection is efficiently accomplished with mercuric cyanide and calcium carbonate in aqueous THF to cleanly afford aldehyde 15 The ^1H NMR spectrum of 15 is best rationalized in terms of the expected chair conformation shown in scheme 2 ($J_{5,6}$ =2Hz) Given the axial orientation of the formyl group of 15, it was anticipated that

epimerization in base would proceed efficiently to the desired α-oriented (equatorial) configuration Indeed, treatment of aldehyde 15 with catalytic potassium carbonate in refluxing methanol gives complete epimerization within the limits of detectability (<2% of 15 at equilibrium) affording the desired monensin A-ring fragment 2 (R=CH_2OCH_2Ph) in 50% overall yield from hydroxy-ketal 10b

The highly stereoselective addition of MTF anion 9 to aldehydes 8a and 8b, coupled with the observed deprotection of hydroxy-ketals 10a and 10b without epimerization suggested an efficient route to α-multistriatin utilizing this approach Thus, ethyl ketone 7c was prepared by treatment of acid chloride 6 with ethyl copper Interestingly, attempted protection of the ketone grouping of 7c as the dimethyl acetal resulted in epimerization of the C-3 methyl However, ethylene ketal formation under standard conditions proceeded smoothly to give aldehyde-ketal 8c after manipulation of the ester function Addition of MTF anion 9 proceeded in a highly stereoselective manner as expected producing hydroxy-ketal 10c, which upon hydrolysis of the thioacetal gave aldehyde 16 in good yield Reduction of the aldehyde functio and concomitant hydrolysis of the ethylene ketal unit then afforded α-multistriatin in seven steps, and 36% overall yield from acid chloride 6

In conclusion, we have developed efficient methods for stereocontrolled synthesis of structural fragments found in several ionophores from readily available materials Also, it may be noted that, to our knowledge, the route provides the most efficient stereocontrolled preparation of α-multistriatin reported to date

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12) Full details of the crystal structure determination of compound 11a will be reported in a full paper describing this work We thank Mr R Curtis Haltiwanger for his invaluable assistance with the X-ray crystallography Questions regarding this aspect of our work should be addressed to him at the University of Colorado

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