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TOTAL SYNTHESIS OF THE IONOPHORE ANTIBIOTIC X-206. STUDIES RELEVANT TO THE STEREOSELECTIVE SYNTHESIS OF THE C(17)-C(26) SYNTHON.

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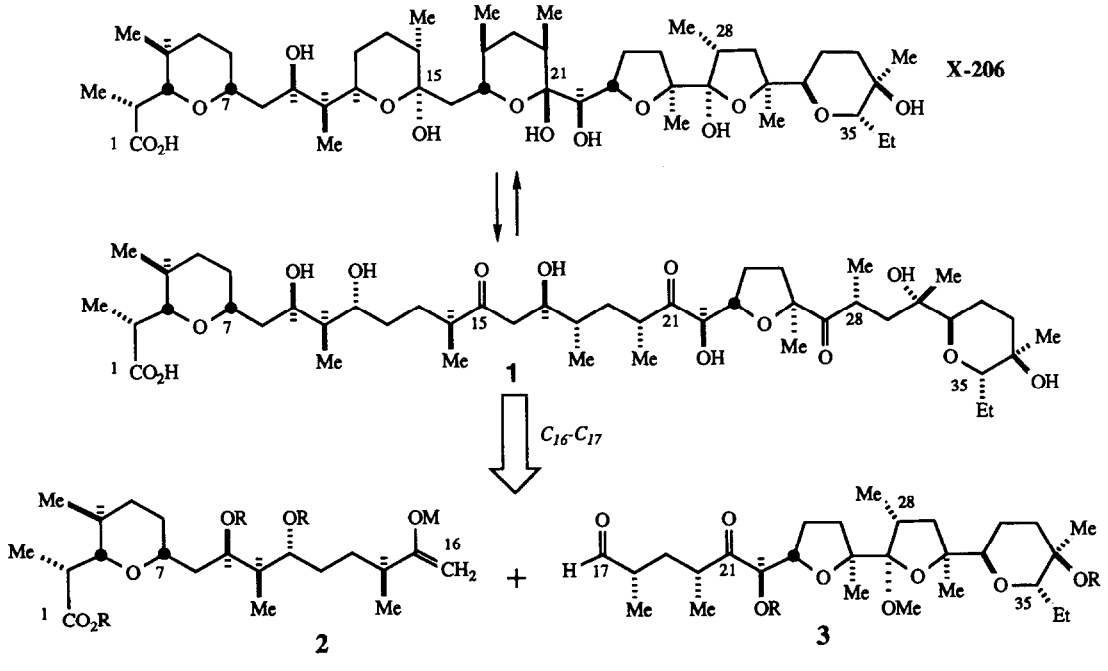
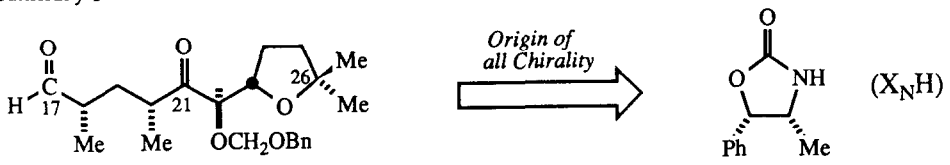
Abstract: A stereoselective synthesis of the keto-aldehyde **4**, which embodies the structural features of the C(17)-C(26) section of the polyether X-206, is described.

Despite recent advances in asymmetric synthesis, the stereochemically complex polyether antibiotics remain as challenging targets for total synthesis.[1] Among the diverse members of this class of substances, X-206[2] merits special attention as a consequence of its general level of architectural complexity. As part of our program aimed at the discovery and application of new methods in acyclic stereocontrol, we have developed a highly convergent approach to the synthesis of X-206 that relies exclusively on asymmetric synthesis to resolve all absolute stereochemical issues. Examination of the hydroxy-ketone tautomer **1** of X-206 reveals that an aldol disconnection of the C_{16}-C_{17} bond divides the molecule into two roughly equal subunits **2** and **3** (Scheme I).

Scheme I



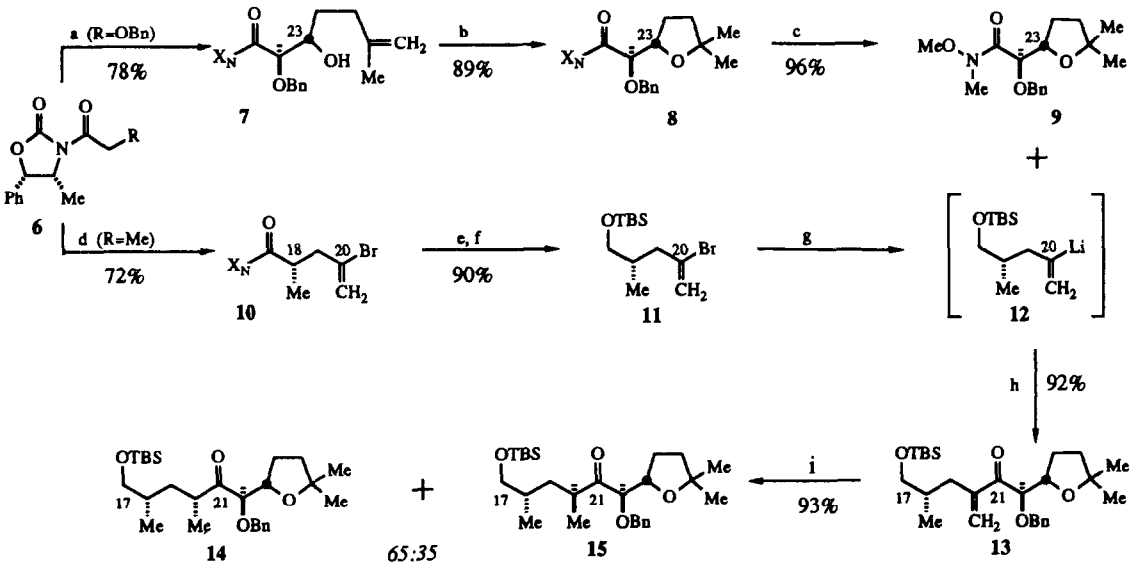
On this basis, the model keto-aldehyde **4** was selected as an initial target in order to investigate possible approaches to the synthesis of the problematic C_{17}-C_{26} section of **3**. In this Letter, we describe the studies leading to an efficient synthesis of **4** in which all chirality originates from the norephedrine-derived auxiliary **5**.



4 **5**

Condensation of the dibutylboron enolate of the imide **6** (R=OBn) with 4-methyl-4-pentenal cleanly established the C_{22} and C_{23} stereocenters (X-206 numbering), giving the aldol adduct **7** with >98% diastereomeric purity (Scheme II).[3] Acid-catalyzed cyclization of **7** produced the crystalline tetrahydrofuran **8** (mp 114-115°C). Since it has been our experience that ketones are not directly accessible from the chiral N-acyl oxazolidones, **8** was converted to the amide **9** with the aluminum amide reagent derived from MeONHMe·HCl and Me_3Al.[4] This reaction has been found to be generally useful in conjunction with these chiral auxiliaries,[5] and the resultant N-methoxy-N-methyl amides are excellent precursors to aldehydes as well as ketones (vide infra).[6] The C_{18} stereocenter was secured by alkylation of the lithium enolate of the imide **6** (R=Me) with 2,3-dibromopropene (THF, -40°C, 9h diastereoselection, 98:2).[7] The product imide **10** (mp 59-60°C) was reduced to the alcohol and then protected as its t-butyldimethylsilyl (TBS) ether **11**. The crucial C_{20} -C_{21} bond construction was achieved in 92% yield by reaction of the amide **9** with the vinyllithium reagent **12**.

Scheme II

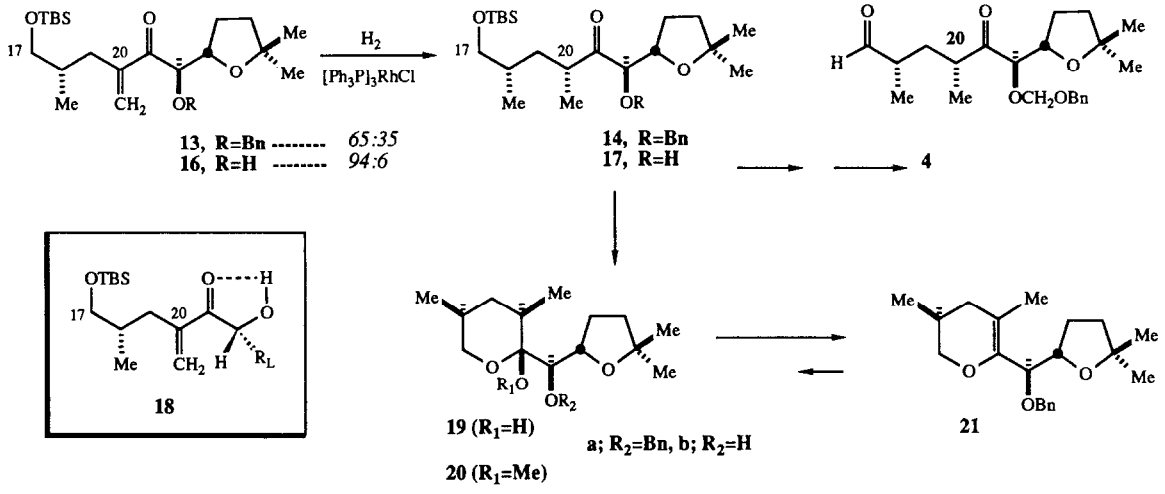


(a) Bu_2BOTf, Et_3N, CH_2Cl_2, -78°C; RCHO, -78°C; (b) CSA, $ClCH_2CH_2Cl$, 80°C; (c) MeONHMe-HCl, Me_3Al, CH_2Cl_2, -15 to 0°C (d) LDA, THf, -78°C; 2,3-dibromopropene, -40°C, 9 h; (e) $LiAlH_4$, -78 to 0°C; (f) TBSCl, Et_3N, cat. DMAP, CH_2Cl_2 (g) 2.0 equiv tert-BuLi, THF, -78°C; (h) THF, -78 to -10°C, 30 min; (i) 15 psi H_2, $(Ph_3P)_3RhCl$, benzene.

Parenthetically, the Weinreb ketone synthesis,[6] which was applied to the construction of **13**, has a number of important attributes. In particular, the stability of the tetrahedral intermediate derived from the N-methoxy-N-methyl amides is exceptional. More complex applications of this reaction will be reported shortly.

During the planning stages of this project it was not readily apparent how one might effectively control the reduction of unsaturated ketone **13** to provide the requisite C_{20} diastereomer **14**. Not suprisingly, hydrogenation of the enone **13** under a variety of conditions proceeded with low levels of asymmetric induction. The best results were obtained with Wilkinson's catalyst, which gave a 65:35 mixture of the diastereomers **14** and **15**. The major hydrogenation product was identified as the desired 20R isomer **14** by conversion to the lactol methyl ether **20a** and subsequent high field NMR analysis.[8]

Scheme III



Recent studies from this laboratory on hydroxyl-directed hydrogenations prompted us to examine the reduction of the related hydroxy ketone **16**.[9] Hydrogenation of this substrate with Wilkinson's catalyst (15 psi H_2, C_6H_6, 25°C) afforded the desired reduction product **17** with considerably improved diastereoselectivity (20R:20S=94:6). There appears to be several possible explanations for the role that the hydroxyl moiety might play in improving hydrogenation selectivity of **13**. The supposition that this ligand is actively involved in catalyst coordination, as has been documented with cationic rhodium catalysts,[9] is not supported by precedent.[10] An alternative explanation for the observed reaction diastereoselection follows from an NMR study of the hydrogenation substrate **16**. Inspection of the coupling constants and benzene-induced solvent shifts in the ^1H NMR spectrum of **16** suggests that this substrate exists largely in the hydrogen-bonded, S-trans conformer **18**.[11] This conformation provides a sterically accessible re-face for catalyst coordination and subsequent reduction to predominate product diastereomer **17**.

In conjunction with our efforts to design a successful approach to the synthesis of X-206, we have utilized **17** to model the C_{17}-C_{26} X-206 synthon and to deduce what refunctionalization reactions might be realistically employed in the actual synthesis plan. For example, in the projected synthesis of keto aldehyde **3** (Scheme I), a series of reactions analogous to the conversion of hydroxy ketone **17** to keto

aldehyde **4** must be feasible. After having surveyed a number of potential protecting groups, we have found that the hydroxyl function in **17** could be protected as its derived benzyloxymethyl ether (1.5 equiv $BrCH_2OBn$, proton sponge, MeCN, 25°C) in high yield. The keto aldehyde **4** was then prepared by successive removal of the silyl protecting group (1.0 N HCl, H_2O-THF, 25°C), and the resultant lactol **19** (R_2=-CH_2OBn) was oxidized (CrO_3·2pyr) in 66% overall yield.[12]

Model experiments directed toward successful manipulation of the lactol functionality at C_{15}, C_{21}, and C_{27} in X-206 and related subunits have also been addressed. We have found that lactol **19a** may be successfully transformed into the anomeric methyl ether **20a** only under carefully defined conditions (cat. $ClCH_2CO_2H$, MeOH, $(MeO)_3CH$, 25°C, 16h). In a complementary experiment, conditions were established for the hydrolysis of **20a** to **19a** (1.0 N HCl-H_2O, 0.1M in THF, 0°C, 16h). In both of these transformations, the dihydropyran **21** is not an intermediate. Much to our surprise, once **21** is formed, the acid catalyzed reconstitution of either **19a** or **20a** has proven to be impossible. Presumably, the delicate balance of steric effects is being expressed in the destabilization of the tetrahydropyrans **19** and **20** relative to the dehydration product **21**.

In conclusion, the model studies outlined in the Letter have played an important role in the development of a successful asymmetric synthesis of antibiotic X-206. The results of these studies will be reported shortly.

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5. The aluminum amide reaction generally succeeds with β-hydroxy imides (i.e. aldol adducts) and with α-heteroatom substituted imides, but ordinarily with α-alkyl imides (i.e. alkylated imides such as **10**) attack at the oxazolidinone carbonyl prevails.
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11. The observed values (in ppm) of $\delta(C_6D_6)$-$\delta(CDCl_3)$ for relevant protons were as follows: vinyl protons, -.58 and -.42; C(22) proton, -.24; hydroxyl proton, +.37. These shifts are consistent with the proposed conformation according to the "carbonyl plane rule": Ronayne, J.; Williams, D.H. In "Annual Review of NMR Spectroscopy"; Mooney, E.F., Ed.; Academic Press: New York, 1969; Vol. 2, pp 83-124.
12. According ^1H NMR analysis ($CDCl_3$), the lactol exists in equilibrium with ca. 10% of the open-chain hydroxyl-ketone tautomer, through which the oxidation is presumed to proceed.

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