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IONOPHORE SYNTHESIS. AN ENANTIOSELECTIVE ROUTE TO THE LEFT-WING OF INDANOMYCIN (X-14547A).

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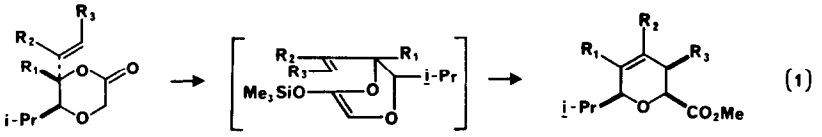
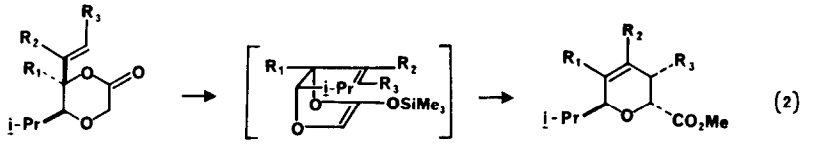
Abstract: An enantioselective synthesis of the tetrahydropyran "left-wing" of the ionophore X-14547A is described, wherein stereoselective 1,2-carbonyl additions and an oxapyranone-to-dihydropyran enolate Claisen rearrangement are key stereocontrol elements.

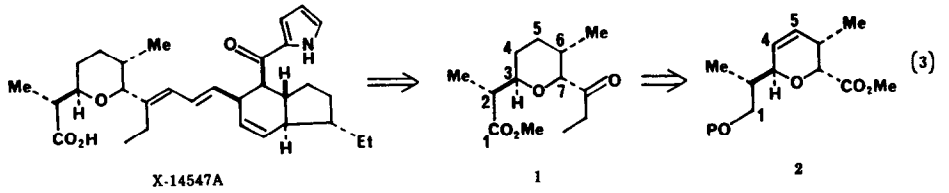
We recently reported[1] a stereoselective synthesis of polysubstituted dihydropyrans from 6-alkenyl-4-oxapyran-2-ones via the Claisen rearrangement[2] variants generalized in eqs 1 and 2. The potential of this method for the synthesis of hydropyran subunits of natural products is apparent upon comparison of the "left-wing" of the ionophore antibiotic X-14547A[3] (recently christened indanomycin)[3m] with the product in eq 2.



(1)



(2)



(3)

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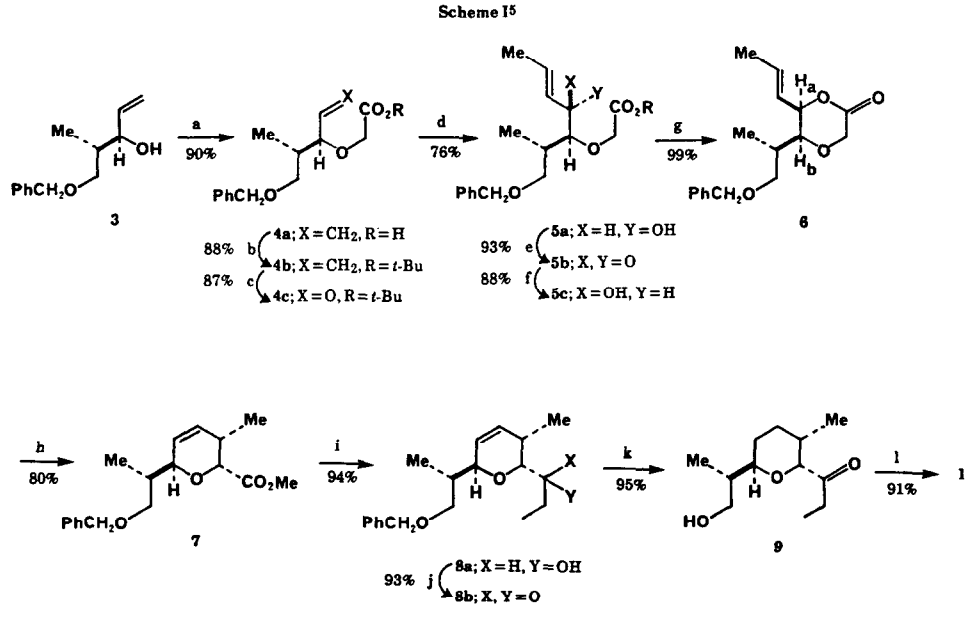
The keto ester **1** (eq 3) is a degradation product[3e] of the antibiotic and has served as an intermediate in the laboratory synthesis of X-14547A.[3h,m,n] Our strategy for the synthesis of **1** was to (a) use the C2 sidechain stereocenter to control the C3, C6 and C7 stereocenters on the heterocycle and (b) form the C6-C7 bond in the key step of the sequence, yielding the γ,δ-unsaturated ester **2** (eq 3). Note that the lack of substitution at the C4 and C5 sites in **1** renders harmless the C4-C5 unsaturation in **2**, the removal of which could be (and was) concurrent with the cleavage of the C1 hydroxyl protecting group. We describe herein a sequence based upon these considerations by which the optically pure left-wing synthon **1** was produced from the allylic alcohol **3** [4] in greater than 25% overall yield.

O-Alkylation of **3** (Scheme I)[5] with bromoacetic acid [NaH (3 eq), $BrCH_2CO_2H$, THF, Δ] proceeded in 90% yield to give the acid **4a**, which was converted to its *t*-butyl ester **4b** (*t*-BuOH, DCC, dimethylaminopyridine, 25°C, 88%).[6] Ozonolytic olefin cleavage unmasked the aldehyde **4c** in 87% yield. Treatment of **4c** with the cuprate derived from *trans*-propenyllithium[7] and CuI·PBu_3 (Et_2O, -78°C) gave in 76% yield a 24:1 mixture[8] of **5a** and its C4 epimer.

Comparison of the predominant diastereomer **5a** with the needed oxapyranone stereochemistry (*cf.* eq 2 and structure **1**) shows that the C4 center must be inverted. This was accomplished by an efficient and highly stereoselective oxidation (PDC, DMF, 0°C, 12 h, 93%)[9] – reduction [$Zn(BH_4)_2$, Et_2O, 0°C, 1.5 h, 88%][10] sequence which converted **5a** via the enone **5b** into the epimer **5c** (**5c**:**5a** > 100:1).[8]

Scheme I[5]



(a) 3 equiv NaH, 1.1 equiv $BrCH_2CO_2H$, THF, reflux. (b) *t*-BuOH, DMAP (0.1 equiv), DCC, 25°C. (c) O_3, CH_2Cl_2, -78°C; Me_2S, -78 → 25°C. (d) *trans* $(MeCH{=}CH)_2CuLi$, Et_2O, -78°C. (e) PDC, DMF, 0°C, 12 h. (f) $Zn(BH_4)_2$, Et_2O, 0°C, 1.5 h. (g) CF_3CO_2H (30 mol %), PhH, reflux, 3 h. (h) LDA, THF, -78°C; Me_3SiCl, Et_3N, -78 → 25°C; remove THF *in vacuo*, add $PhCH_3$, 110°C, 4 h. (i) *i*-Bu_2AlH (1.2 equiv), Et_2O, -78°C; EtMgBr (3 equiv), -78 → 25°C. (j) $H_2Cr_2O_7$, aq acetone, 25°C, 15 min. (k) H_2, 5% Pd/C, EtOH, 25°C, 3.5 h. (l) $H_2Cr_2O_7$, aq acetone, 25°C, 20 min; CH_2N_2, Et_2O, 0°C.

Lactonization with 30 mol % CF_3CO_2H in refluxing benzene proceeded in near quantitative yield to provide the oxapyranone **6** ($J_{a,b} = 2.4$ Hz). Conversion of **6** to the corresponding trimethylsilyl ketene acetal and thermolysis as previously described[1,2d] gave, after hydrolysis and esterification, the dihydropyran **7** (80%) along with 9% recovery of **6**.

With the four sp^3 stereocenters thus established in their correct relative and absolute configurations, it remained to: (1) convert the C7 carbomethoxy residue to an ethyl ketone; (2) reduce the C4-C5 olefin; (3) raise the oxidation state at C1. The first of these requirements was met by treating the ester **7** with 1.2 eq of $(i\text{-Bu})_2AlH$ at -78°C in Et_2O, followed by the addition of 3 eq of EtMgBr (-78 → 25°C). This one-pot operation gave a single diastereomer **8a** (configuration unknown) in 94% yield.[11] Jones oxidation (25°, 15 min, 93%) gave the ethyl ketone **8b**, which was reduced (H_2, 5% Pd/C, EtOH, 25°C) to give the saturated alcohol **9** in 95% yield. Jones oxidation and esterification (CH_2N_2, Et_2O) provided the targeted synthon **1** (91%), $[\alpha]_D^{26} = -23.18°$ (*c* 0.91, $CHCl_3$) [lit.[3e,h] $[\alpha]_D^{25} = -21.96°$ (*c* 0.85, $CHCl_3$)], which was identical by high-field ^1H NMR, IR, and ^{13}C NMR to an authentic sample.[12]

In summary, a highly efficient and enantioselective route to the ionophore synthon **1** has been developed. Application of these findings to the total synthesis of indanomycin (X-14547A) and related ionophorous natural products is in progress and will be reported in due course.

Acknowledgement. We gratefully acknowledge the National Institutes of Health, the National Science Foundation, the Alfred P. Sloan Foundation, and Stuart Pharmaceuticals for generous financial support. High-field NMR spectra were obtained through the NSF Regional NMR Center at the University of South Carolina (CHE 82-07445). We thank Professor K. C. Nicolaou (University of Pennsylvania) for providing spectral data for compound **1**.

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11. Proceeding in two stages, reduction followed by Grignard addition, was precluded by the lability of the corresponding aldehyde. We are currently investigating the scope and stereochemical implications of this one-pot procedure.

12. We thank Professor K. C. Nicolaou (University of Pennsylvania) for comparison data.

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