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THE DIOXANONE-TO-DIHYDROPYRAN CLAISEN REARRANGEMENT. SYNTHESIS OF C(7)-C(13) FRAGMENTS OF ERYTHRONOLIDES A AND B

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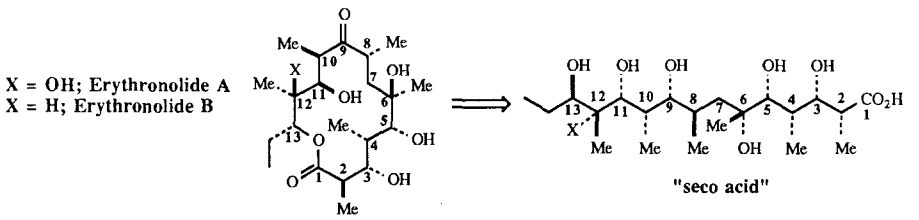
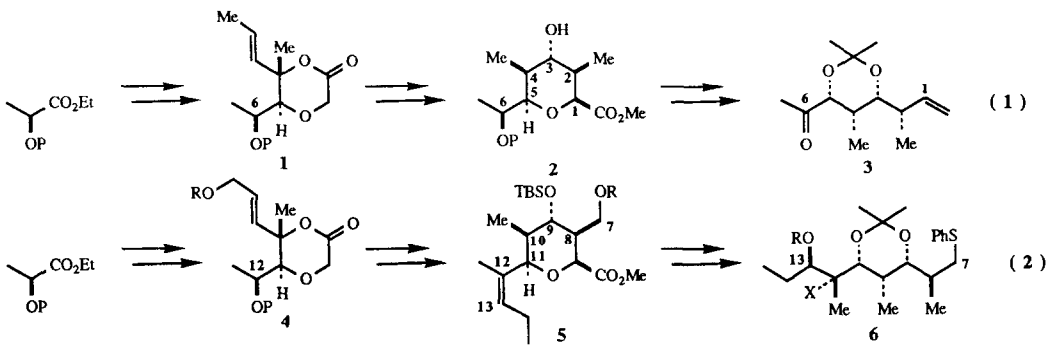
Abstract: Iterative applications of the dioxanone-to-dihydropyran Claisen rearrangement have resulted in the efficient conversion of (*S*)-(-)-ethyl lactate to the erythronolide A and B C(7)-C(13) subunits **19**, **23**, and **27** via the common synthetic intermediates **13** and **22**.

We have developed a variation of the Ireland-Claisen rearrangement[2] in which easily constructed dioxanones are converted to polysubstituted dihydropyrans.[3] Applications of this method to the enantioselective synthesis of ionophore antibiotic hydropyran subunits[4] and polypropionate-derived acyclic arrays[5] of the macrolide antibiotics have been demonstrated and are continuing. In this and the succeeding paper we report extensions of the method which further illustrate its versatility by the enantioselective production of C(7)-C(13) fragments of erythronolides A and B.[6]

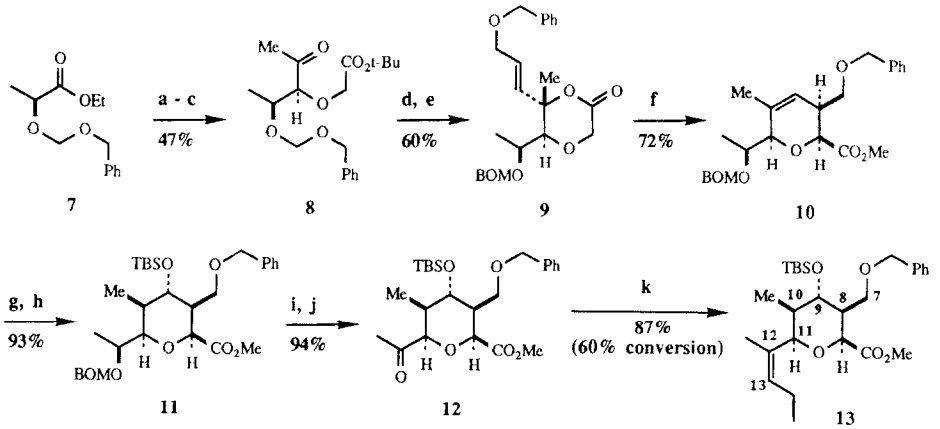


With the indicated seco acid derivatives as targets, a convergent approach has been pursued in which the C(1)-C(6) subunit **3** (eq 1), common to both the erythronolide A and B aglycones, and the two respective C(7)-C(13) subunits, generalized as **6** (eq 2), are to be prepared and coupled. A thirteen step sequence proceeding in 12% overall yield to give the C(1)-C(6) fragment **3** has been completed[5] and is outlined in eq 1. Iterative applications of closely-related chemistry for the production of the C(7)-C(13) fragments are summarized in eq 2 and detailed below. Comparison of the sequences in eqs 1 and 2 reveals the common lactate-derived starting materials and the structurally analogous intermediates (**1** and **4**, **2** and **5**) in the C(1)-C(6) and C(7)-C(13) syntheses.



Elaboration of the benzyloxymethyl-protected (*S*)-(-)-ethyl lactate derivative **7**[7] into a richly functionalized tetrahydropyran **13**, a common intermediate in all of the subsequent chemistry, is detailed in Scheme I. Combining the observations of Comins[8] and Still[9] allowed effective 1,2-chirality transfer by sequential C-C and C-H bond formations at the carbonyl site in **7**, the latter with α-chelation control.[10] The resulting allylic alcohol (anti/syn = 30) was *O*-alkylated under phase-transfer conditions[11] with *t*-butyl bromoacetate and ozonolyzed to give the α-alkoxyketone **8**. Another α-chelation controlled carbonyl addition proceeded in >80:1 diastereoselectivity to give, after lactonization, the dioxanone **9** as the Claisen rearrangement substrate. Conversion to the silyl ketene acetal and thermolysis as previously described[3] transformed the dioxanone **9** into the dihydropyran **10**, mp 85-86°C, wherein there is a steric bias favoring olefin addition from the α-face. Thus the fully functionalized heterocycle **11** was the sole product obtained in 93% yield after hydroboration/oxidation and protection of the resulting secondary alcohol as the *t*-butyldimethylsilyl (TBS) ether.[12] The original *L*-lactate stereocenter was then obliterated by conversion to the ketone **12**. Wittig homologation proceeded in high yield (but modest conversion due to proton transfer) to give the *Z* C(12)-C(13) linkage[13] for elaboration into the erythronolide A- and B C(7)-C(13) subunits. The stereofunctional requirements for the former would be satisfied by *si* face osmylation of the C(12)-C(13) olefin, and those of the latter by *si* face hydroboration.

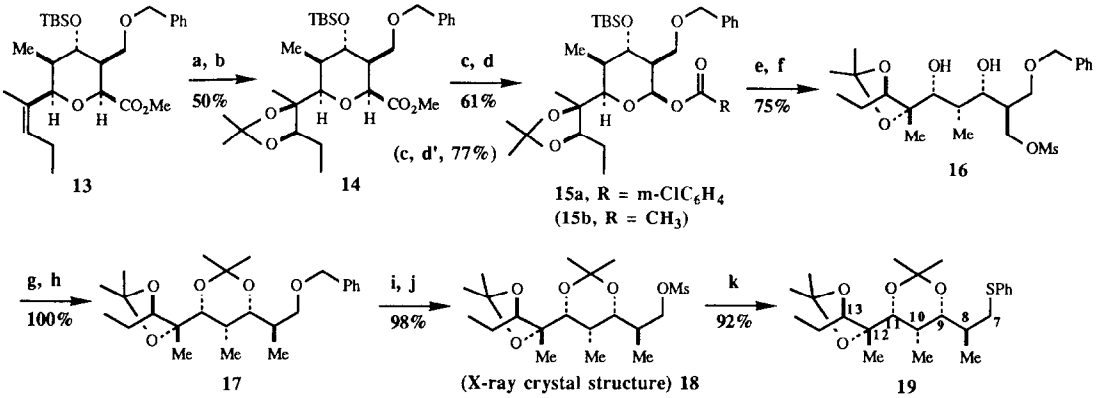
SCHEME I [21]



(a) $LiBH_4$, $H_2C=C(Me)MgBr$, THF, 0°C. (b) $BrCH_2CO_2t$-Bu, PhH, 50% aq NaOH, Bu_4NHSO_4, +10°C. (c) O_3, CH_2Cl_2, -78°C; Me_2S, -78 → 25°C. (d) (*E*)-$BrMgCH=CHCH_2OCH_2Ph$,[22] Et_2O, -78°C. (e) CF_3CO_2H, PhH, reflux. (f) LDA, THF, -78°C, Me_3SiCl, Et_3N; -THF, +$PhCH_3$, 110°C; 5% aq HCl, CH_2Cl_2; CH_2N_2, Et_2O, MeOH, -5°C. (g) BH_3•THF, THF, -78 → 0°C; H_2O_2, aq $OH^{\ominus}$, 0 → 25°C. (h) *t*-$BuMe_2SiOTf$, *i*-Pr_2NEt, CH_2Cl_2, 0°C. (i) BF_3•Et_2O, EtSH, CH_2Cl_2, 0°C. (j) PCC, 3Å molecular sieves, CH_2Cl_2.[23] (k) $Ph_3P=CHCH_2CH_3$, THF, -78 → 25°C.

The conversion of **13** to the C(7)-C(13) erythronolide A fragment **19** proceeded in >20% overall yield by each of the two closely related sequences detailed in Scheme II. Contrary to the Kishi model,[14] the olefin **13** showed a modest preference for *si* face osmylation, leading after protection to the acetonide **14**.[15] This fully elaborated hydropyran was set up for ring cleavage by two methods; carboxy inversion[16] to the *m*-chlorobenzoyl glycoside **15a** and, parenthetically, $Pb(OAc)_4$-induced oxidative decarboxylation[17] in THF/HOAc to give the corresponding acetyl glycoside **15b**. In each case, exhaustive reduction with $LiAlH_4$ accomplished ring scission and desilylation to afford the expected triol. Selective mesylation of the primary hydroxyl therein gave **16** in good overall yield. The straightforward conversion to the erythronolide A C(7)-C(13) fragment **19** proceeded as shown in the Scheme in very high yield, with the stereochemical confirmation secured by x-ray crystallographic analysis of mesylate **18** (mp 112-113°C).[18]

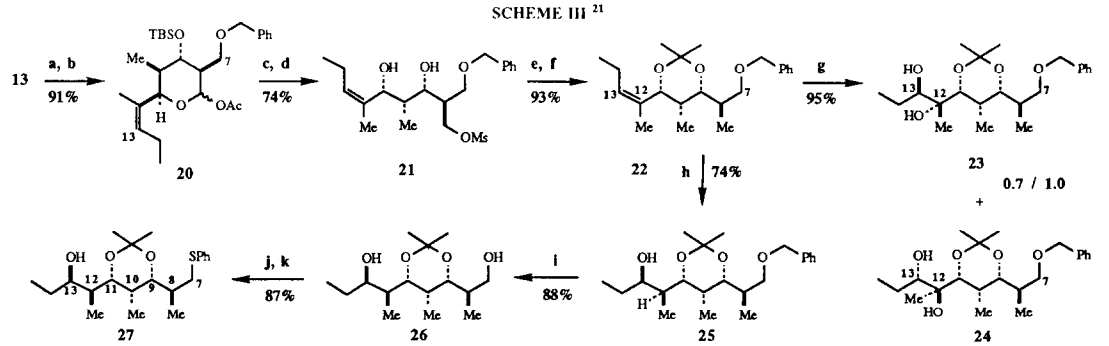
SCHEME II [21]



(a) OsO_4 (cat.), NMMO, aq. THF, 25°C, 24 h.[24] (b) $CH_3C(OMe)_2CH_3$, PPTS,[25] CH_2Cl_2, 25°C, 4.5 h. (c) LiOH, aq. THF, 25°C, 12 h. (d) DCC, *m*-CPBA, CH_2Cl_2, -23 → 0°C. (d') 3.5 equiv $Pb(OAc)_4$, THF-HOAc (10:1), 25°C, 1.5 h. (e) $LiAlH_4$, Et_2O, 0 → 25°C, 20 h. (f) MsCl, *i*-Pr_2NEt, CH_2Cl_2, -24°C. (g) $CH_3C(OMe)_2CH_3$, PPTS, CH_2Cl_2, 25°C, 16 h. (h) $LiEt_3BH$, THF, 60°C, 30 min. (i) Na°, NH_3, Et_2O, 3 min; NH_4Cl. (j) MsCl, *i*-Pr_2NEt, CH_2Cl_2, 0°C. (k) 5.0 equiv PhSNa, EtOH, 0 → 25°C, 5 h.

An alternative and operationally superior elaboration of the common intermediate **13** into C(7)-C(13) fragments for both the "A" and "B" series (**23** and **27**, respectively) is described in Scheme III. Oxidative decarboxylation of the acid derived from **13** afforded the acyl glycoside **20**. In this series, fragmentation of the pyran preceeded C(12)-C(13) functionalization. The common precursor **22** was elaborated to **23** and **25** by osmylation and hydroboration, respectively. Olefin **22** showed a modest preference for *re* face

SCHEME III [21]



(a) LiOH (3 eq), aq. THF. (b) $Pb(OAc)_4$ (3.5 eq), AcOH, THF (1:10), 25°C, 1 h. (c) $LiAlH_4$, Et_2O, 25°C, 16 h. (d) MsCl, *i*-Pr_2NEt, CH_2Cl_2, -78°C, 2 h. (e) $CH_3C(OMe)_2CH_3$, PPTS, CH_2Cl_2, 25°C, 0.5 h. (f) $LiEt_3BH$, THF, reflux, 30 min. (g) OsO_4, pyridine, THF, 4°C, 48 h. (h) 5 equiv BH_3 • THF, THF, -78 → 0°C, 20 h; H_2O quench, 0 → 20°C; 1 equiv H_2O_2, 0.4 equiv $OH^{\ominus}$, 0 → 25°C, 24 h. (i) Na°, NH_3, Et_2O, -33°C, 2 min; NH_4Cl. (j) 1.1 equiv MsCl, 1.3 equiv *i*-Pr_2NEt, CH_2Cl_2, -23°C, 1 h. (k) 6.0 equiv PhSNa, EtOH, 0 → 25°C.

osmylation, as predicted by the Kishi model.[14] In contrast, the desired *si* face hydroboration of **22** is predicted by the Still model,[19] and experiment agreed. The desired product **25** was formed in 74% yield (diastereoselectivity ~10:1) upon hydroboration of **22** with BH_3 • THF, -78 → 0°C. Straightforward conversion to the sulfide **27**, suitable for coupling to the C(1)-C(6) fragment **3**, completed these studies.[20] The efficiency of these sequences is noteworthy, in that the conversions **13** → **23** and **13** → **27** proceeded in 26% and 36% overall yields, respectively.

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20. The identity of several derivatives in this series with those derived from an independent synthetic route (see following paper in this issue) confirms the stereochemical assignments. Specifically, the "C(13)" benzyloxymethyl ether derived from **25**, the diol **26**, the primary mesylate derived therefrom, and the sulfide **27** were identical with the corresponding substances from the alternative route. The usefulness of the C(7) sulfide as a precursor to a nucleophilic coupling partner has been recently demonstrated by Stork.[6e,j]
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