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Double Dioxanone-to-Dihydropyran Reorganization. Construction of a C(1)-C(13) Erythronolide Template.

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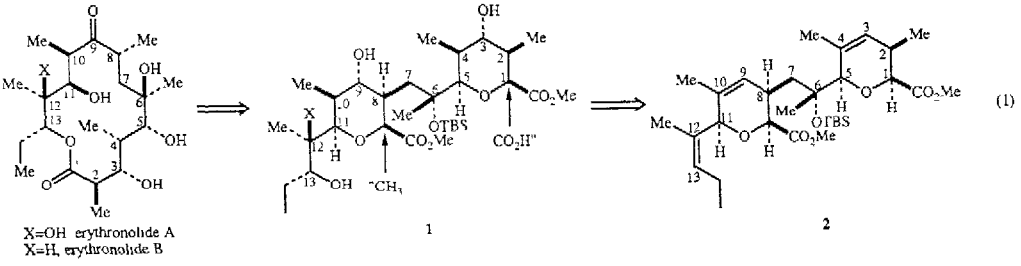
Abstract. Convergent, stereoselective construction of the lactate-derived bis(dioxananone) 16 and two concurrent [3,3] sigmatropic transformations thereof result in the trienic bis(dihydropyran) 2, a potential precursor of the intact C(1)-C(13) erythronolide array

Synthetic efforts directed at macrolide and polyether antibiotics have resulted in numerous methods for duplicating the stereochemical details present on carbon chains of polyketide origin.[2] General strategies featuring acyclic stereocontrol, carbohydrate modification, cyclic template elaboration and cleavage, and stereoselective macrocycle transformations have been developed.[2b-e] The recurring stereotriads[2a] bearing alternating methyl and hydroxyl groups (as in erythronolides A and B) have stimulated the use of reiterative procedures such as aldol couplings,[3] cyclocondensations,[4] and lactone adornment.[5]

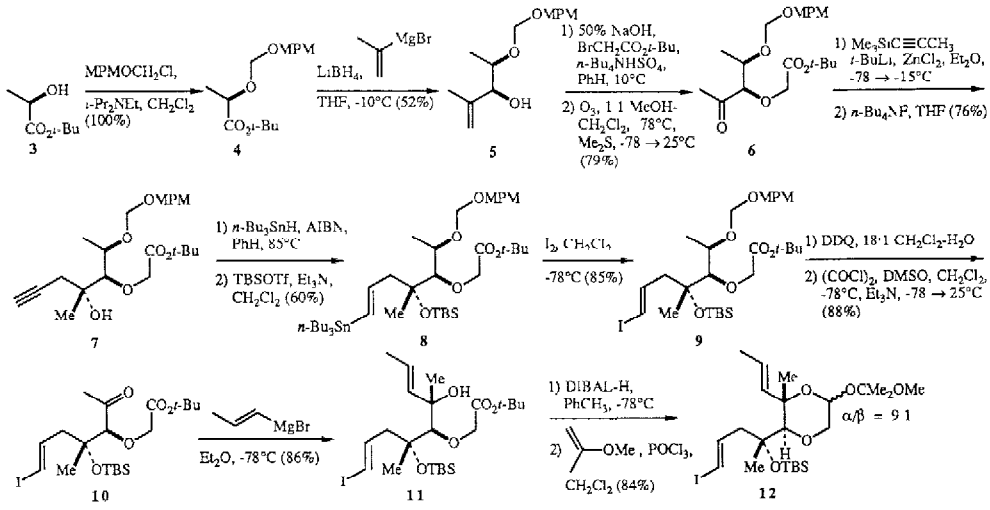
We have reported sequences affording C(1)-C(6) and C(7)-C(13) subunits of erythronolides A and B with control of relative and absolute stereochemistry.[6] However, inefficient coupling of these subunits[7] has led us to investigate an alternative construction of the intact C(1)-C(13) arrays. The prior work involved iterative application of the dioxanone-to-dihydropyran Ireland-Claisen rearrangement.[8] Described herein is the first example of a "double" dioxanone-to-dihydropyran reorganization involving two [3,3] sigmatropic rearrangements occurring together in the same molecule.



(1)

The basis for this approach is illustrated in eq. 1. Reorientation of the C(1)-C(13) seco acid chain of the erythronolides leads to the bis(tetrahydropyran) **1**, equivalent in stereochemistry and functionality, save for the indicated C(1) carboxyl group and C(8) methyl substituent, and the oxidation level at C(9). The two tetrahydropyrans in **1** are nearly identical in substituent type and stereochemistry, and it is projected that hydroboration of the three olefin moieties in bis(dihydropyran) **2** will establish the six asymmetric centers at C(3), C(4), C(9), C(10), C(12) and C(13) for erythronolide B.[9] Production of **2** by the title reaction is described herein.

SCHEME I



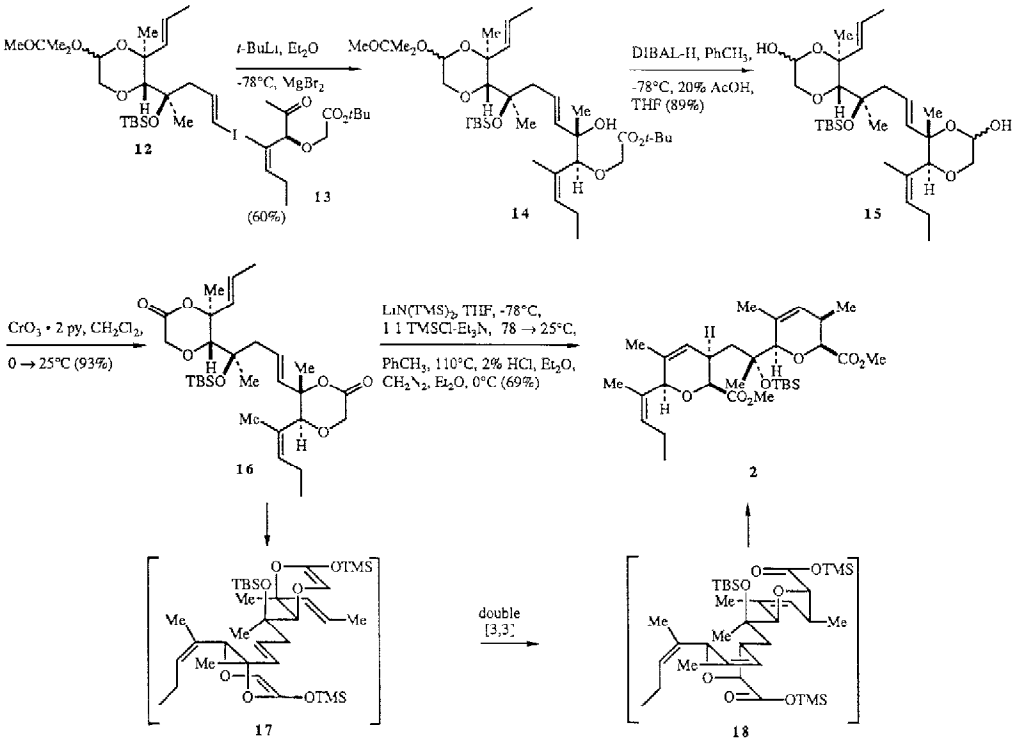
Quantitative protection of (*R*)-*i*-butyl lactate (**3**) as the (*p*-methoxyphenyl)methoxylmethyl ether **4** (Scheme I)[10] was followed by the *in situ* sequential addition of carbon and hydride nucleophiles to the ester carbonyl,[11] the latter occurring with chelation-control to afford alcohol **5**. *O*-Alkylation under phase transfer conditions[12] followed by ozonolytic cleavage provided ketone **6**, which underwent chelation-controlled addition[13] of the propargylic zincate derived from 1-(trimethylsilyl)propyne.[14] Silyl cleavage afforded the homopropargylic alcohol **7**, from which the *trans*-vinyl iodide **10** was prepared by standard methods.[15] A third chelation-controlled α-alkoxy ketone nucleophilic addition[13] established in 86% yield the tertiary allylic carbinol center in **11**, which was converted to the mixed acetal **12** by ester reduction with diisobutyl aluminum hydride and protection of the resultant lactol.[16]

Lithium-halogen exchange[17] and transmetallation[18] of **12** (Scheme II) provided a vinyl Grignard species that was coupled with the α-alkoxy ketone **13** (prepared in three steps from ketone **6**).[19] Again, chelation-control[13] resulted in clean production of the tertiary allylic carbinol stereochemistry depicted in **14**. Lactol closure as before and mild acid hydrolysis gave the bis(hemiacetal) **15**, which underwent Collins oxidation[20] to the bis(dioxanone) **16**[21a] in high yield.

Deprotonation of **16** with excess lithium hexamethyldisilazide, addition of chlorotrimethylsilane, and thermolysis of the unisolated bis(silylketene acetal) **17** gave, after standard work-up[8] the bis(dihydropyran) **2**[21b] in 69% yield. Inspection of the bracketed structures **17** and **18** clarifies the stereogenicity transfers that occur during the two [3,3] sigmatropic shifts.

In summary, the optically pure trienic bis(dihydropyran) **2**, possessing seven asymmetric (thirteen stereogenic) centers, is available in 18 linear steps from (*R*)-lactate **3**. High stereoselectivity in all carbon-carbon bond formations arose from the special attributes of α-alkoxy ketones[13,19] or pericyclic transition state constraints, by which trigonal carbon geometries gave rise to tetrahedral carbon stereochemistries. The demonstrated feasibility of the double dioxanone-to-dihydropyran rearrangements makes available extended arrays rich in stereochemical and functional detail. Elaboration of **2** and related templates is currently under investigation.

SCHEME II



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21. (a) ^1H NMR data for bis(dioxanone) **16**: (200 MHz, $CDCl_3$) δ 5.87 (dq, *J* = 15 6, 6.5 Hz, 1H), 5.80 (ddd, *J* = 15.1, 9.4, 5.4 Hz, 1 H), 5.53 (dq, *J* = 15 6, 1 6 Hz, 1H), 5.43 (br t, *J* = 7.6 Hz, 1 H), 5.42 (br d, *J* = 15.1 Hz, 1 H), 4.42 (ABq, J_{AB} = 17.9 Hz, $\Delta\nu_{AB}$ = 43.8 Hz, 2 H), 4.31 (s, 1 H), 4.28 (ABq, J_{AB} =17.5 Hz, $\Delta\nu_{AB}$ = 73 9 Hz, 2 H), 3.22 (s, 1 H), 2.68 (dd, *J* = 13 1, 9.4 Hz, 1 H), 2.14 (ddd, *J* = 13 1, 5.4, 1 6 Hz, 1 H), 2.14-1.82 (m, 2 H), 1.78-1.74 (m, 6 H), 1.64 (s, 3 H), 1.50 (s, 3 H), 1.27 (s, 3 H), 0.96 (t, *J* = 7.4 Hz, 3 H), 0.87 (s, 9 H), 0.11 (s, 3 H), 0.08 (s, 3 H).
(b) ^1H NMR data for bis(dihydropyran) **2**: (200 MHz, $CDCl_3$) δ 6.08 (br d, *J* = 6.5 Hz, 1 H), 5.57 (br d, *J* = 6.1 Hz, 1 H), 5.40 (br t, *J* = 7.5 Hz, 1 H), 4.95 (br s, 1 H), 4.25 (d, *J* = 2.9 Hz, 1 H), 4 16 (d, *J* = 3.5 Hz, 1 H), 3.91 (br s, 1 H), 3.73 (s, 6 H), 2.72-2.62 (m, 1 H), 2.48-2.30 (m, 1 H), 2.21-2 03 (m, 2 H), 1.78 (br s, 3 H), 1.76 (dd, *J* = 13.4, 10.7 Hz, 1 H), 1.62 (br s, 3 H), 1.59 (dd, *J* = 13.4, 2.8 Hz, 1 H), 1.48 (s, 6 H), 0 96 (t, *J* = 7.5 Hz, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.87 (s, 9 H), 0.15 (s, 3 H), 0.14 (s, 3 H)

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