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THE ESTER ENOLATE CLAISEN REARRANGEMENT. SYNTHESIS OF A C(1)–C(6) ERYTHRONOLIDE FRAGMENT

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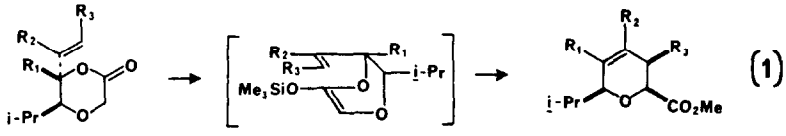
Abstract: An enantioselective route to the C(1)–C(6) erythronolide unit **10** is described, involving the dioxanone-to-dihydropyran enolate Claisen rearrangement (**7** → **8**), regio- and stereoselective hydroboration to give **9a**, and reductive fragmentation of the heterocyclic template (**9c** → **10**).

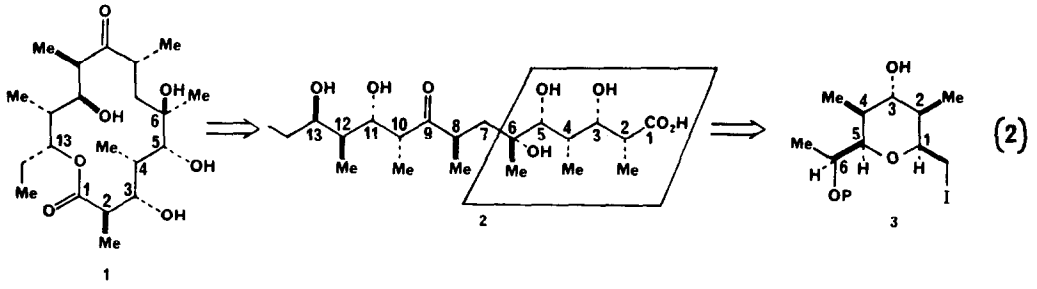
The stereocontrolled synthesis of polysubstituted dihydropyrans via a variant of the enolate Claisen rearrangement has recently been described.[1] This process of dioxanone-to-dihydropyran conversion is generalized in eq. 1 for one stereochemical series. The all-*cis* orientation of the substituents at the three sp^3-carbon stereocenters in the product suggested that stereoselective electrophilic addition to the olefin



(1)

residue could be effected to give a tetrahydropyran with five contiguous asymmetric carbons in the ring. The realization of this, followed by a cleavage of the heterocyclic template, has provided an efficient route to a synthon for the C(1)–C(6) portion of the erythronolide B aglycone (1) as described herein.[2]

The correlation of the macrolide subunit via the seco acid **2** with the appropriate tetrahydropyran system **3** is shown in eq. 2. The heterocycle **3** contains the C(2)–C(5) stereocenters in their correct absolute configurations, a β-halo ether for the reductive fragmentation of the C(1)–O bond, and an



(2)

1 2 3

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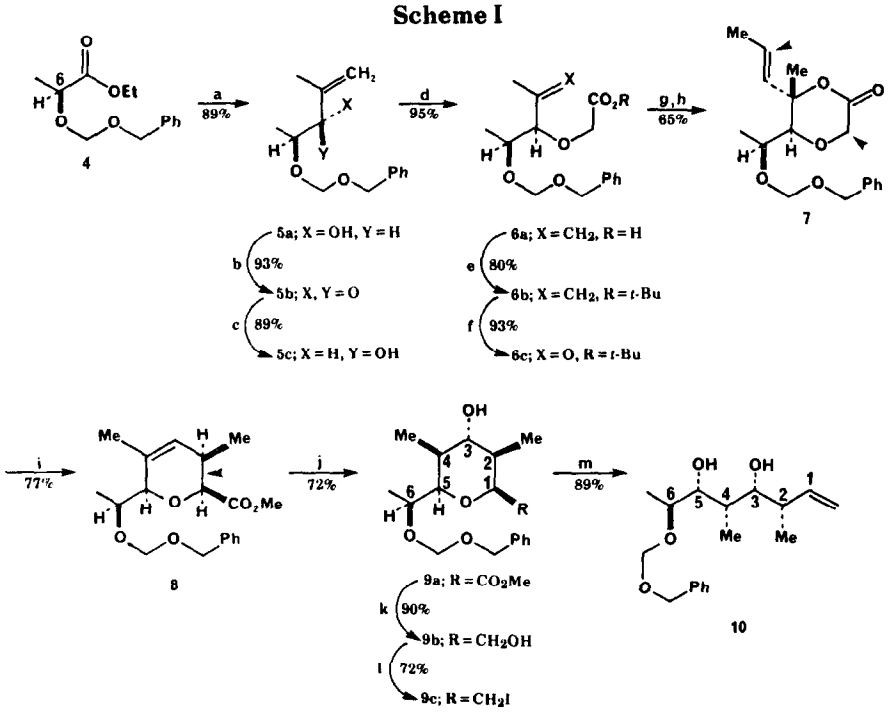
incipient methyl ketone at C(6).[3] This ultimately unnecessary C(6) stereocenter serves to guide the selective introduction of stereochemistry at the C(5) – C(1) sites, as detailed in Scheme I.[4]

The known derivative[5] of ethyl (+)-lactate was subjected to a one-pot reduction/Grignard addition procedure to afford a 4:1 mixture of allylic alcohols **5a** and **5c** in 89% yield. Swern oxidation[6] of this mixture gave the enone **5b** (93%) which was subjected to reduction at -78°C with $Zn(BH_4)_2$ in Et_2O[7] to give **5c** in 89% yield with 20:1 diastereoselectivity.[8] This two step oxidation/"chelation-controlled" reduction thus reversed the configurational outcome of the Dibal/Grignard addition with greatly enhanced selectivity, and dictated the choice of lactate starting material stereochemistry.

The elaboration of **5c** to a dioxanone enolate Claisen substrate mirrored the previously published procedure.[1] O-alkylation with the carboxylate of bromoacetic acid, conversion to the *t*-butyl ester, and ozonolysis gave the methyl ketone **6c** in 71% overall yield. Treatment of **6c** with 2.2 eq of the Grignard reagent derived from *trans*-propenyllithium[9] and anhydrous $MgBr_2$[10] in Et_2O gave, after lactonization with 30 mol % trifluoroacetic acid in refluxing benzene, the dioxanone **7** (mp 55 – 57°C) in 65% overall yield.[11] Thermolysis of the silyl ketene acetal derived from **7** in the manner previously described[1,12]

Scheme I



(a) *i*-Bu_2AlH, Et_2O, -78°C, 1 h; $H_2C=C(CH_3)MgBr$, THF, -78 → 25°C, 3 h. (b) $(COCl)_2$, CH_2Cl_2, DMSO, Et_3N, -60 → 25°C. (c) $Zn(BH_4)_2$, Et_2O, -78°C, 40 min. (d) NaH (3 eq), $BrCH_2CO_2H$, THF, reflux, 15 h. (e) *t*-BuOH, CH_2Cl_2, DMAP, DCC, 0 → 25°C, 2 h. (f) O_3, 1:1 CH_2Cl_2/MeOH, -78°C; Me_2S, -78 → 25°C. (g) *trans*-$CH_3CH=CHMgBr$, Et_2O/PhH, -78°C. (h) 30 mol % CF_3CO_2H, PhH, reflux, 7 h. (i) 2.0 eq LDA, THF, Me_3SiCl/Et_3N, -78°C; $PhCH_3$, 110°C, 4 h; $H_3O^{\oplus}$; CH_2N_2, Et_2O. (j) B_2H_6 • THF (10 eq), THF, -78 → 0°C; aq NaOH, H_2O_2. (k) $LiAlH_4$, Et_2O, -78°C, 30 min. (l) Ph_3P, PhH, pyridine, I_2. (m) Zn dust, DME, reflux, 36 h.

afforded, after hydrolysis and esterification, the dihydropyran **8** in 77% yield. Thus the rearrangement resulted in the coupling of the designated sites in dioxanone **7** to give the C–C bond signified in **8**, with the vicinal stereochemistry shown.

Treatment of the dihydropyran **8** with excess diborane in THF at 0°C gave, after standard oxidative work-up, the hydroboration product **9a** in 72% yield; no other stereo- or regioisomers could be detected. Thus the expected steric protection of the β-face of the trisubstituted olefin in **8** was fully enforced.[13]

Reduction of the methyl ester to the primary alcohol **9b** ($LiAlH_4$, Et_2O, -78°C, 90%) and conversion to the iodide **9c** (Ph_3P, I_2, pyridine, PhH, reflux, 72%)[14] set up the cleavage of the heterocyclic template. This reductive fragmentation was cleanly accomplished with activated zinc dust[15] in refluxing dimethoxyethane to give the erythronolide C(1)–C(6) synthon **10** in 89% yield.[16]

The conversion of the ethyl L-(+)-lactate derivative **4** into the homochiral C(1)–C(6) synthon **10** thus required thirteen steps which proceeded in 11% overall yield. Each of the four new stereocenters was introduced with ≥20:1 diastereoselectivity. Application of this method to the production of C(7)–C(13) synthons for erythronolides A and B is in progress.

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3. This disconnection between C(7) and a C(6) methyl ketone is reminiscent of that employed by Stork in ref. 2e.

4. Yields cited in the Scheme are for chromatographically and spectroscopically homogeneous substances. All structural assignments are supported by IR, 400 MHz ^{1}H NMR, ^{13}C NMR, and mass spectrometric and elemental analyses.

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8. The diastereomer ratio was measured by analytical HPLC and by ^{13}C NMR.

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11. The diastereoselectivity in the addition of the vinyl Grignard reagent to the ketone was ≥20:1 by ^{1}H NMR at 400 MHz. Use of *trans*-propenyllithium gave only a 2:1 diastereoselectivity. For a recent pertinent paper, see: Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 424.

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13. The ^{1}H NMR data listed below for the C(3) acetate from **9a** indicate that the substituents at C(2), C(3), and C(4) are all axially oriented: (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 4.86 (narrow m, 1H), 4.80 (AB q, 2H, J_{AB} = 6.99 Hz, $\Delta\nu_{AB}$ = 44.63 Hz), 4.60 (s, 2H), 4.45 (d, 1H, J = 3.32 Hz), 3.88 (dq, 1H, J = 9.14, 5.94 Hz), 3.75 (s, 3H), 3.55 (dd, 1H, J = 9.14, 2.81 Hz), 2.11-2.08 (m, 2H), 2.09 (s, 3H), 1.36 (d, 3H, J = 5.96 Hz), 1.12 (d, 3H, J = 7.58 Hz), 1.04 (d, 3H, J = 7.56 Hz).

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15. The zinc dust was activated by washing repeatedly with 5% HCl, then water, methanol, and ether in turn, followed by drying under vacuum. See: Tsuda, K.; Ohki, E.; Nozoe, S. *J. Org. Chem.* **1963**, *28*, 783.

16. The ^{1}H NMR data listed below for the acetonide derived from **10** confirm the indicated stereochemistry. For related systems with comparable data, see: Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247. (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 5.61 (m, 1H), 5.10 (dd, 1H, J = 17.1, 0.79 Hz), 5.02 (dd, 1H, J = 10.37, 1.90 Hz), 4.80 (AB q, 2H, J_{AB} = 7.06 Hz, $\Delta\nu_{AB}$ = 49.06 Hz), 4.55 (AB q, 2H, J_{AB} = 11.75 Hz, $\Delta\nu_{AB}$ = 11.65 Hz), 3.74 (dq, 1H, J = 8.85, 5.92 Hz), 3.60 (dd, 1H, J = 8.70, 2.09 Hz), 3.46 (dd, 1H, J = 10.9, 2.03 Hz), 2.35-2.29 (m, 1H), 1.87-1.82 (m, 1H), 1.40 (s, 6H), 1.23 (d, 3H, 5.91 Hz), 1.04 (d, 3H, 6.46 Hz), 0.89 (d, 3H, 6.75 Hz).

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