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AN ALTERNATE ROUTE TO THE C(7)-C(13) SUBUNIT OF ERYTHRONOLIDE B VIA A HYDROPYRAN TEMPLATE

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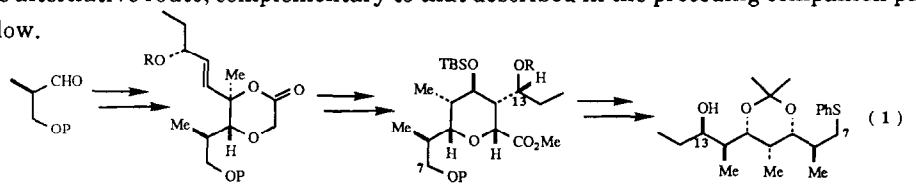
Abstract: Conversion of (*R*)-3-benzyloxy-2-methylpropionaldehyde (4) to the erythronolide B C(7)-C(13) subunit **13** in 15% overall yield is described. Chelation-controlled carbonyl additions and a dioxanone-to-dihydropyran Claisen rearrangement are key steps.

While developing the dioxanone-to-dihydropyran enolate Claisen[2] route from (*S*)-(-)-ethyl lactate to the C(1)-C(6)[3] and C(7)-C(13)[4] polypropionate-derived subunits of the erythronolides B and A,[5] we also pursued the elaboration of (*R*)-3-benzyloxy-2-methylpropionaldehyde as outlined in eq. 1. Specifically, the dioxanone **1** was to be established and converted to the fully functionalized hydropyran template **2**, leading, after heterocycle cleavage, to the homochiral[6] C(7)-C(13) erythronolide B fragment **3**. The details of this alternative route, complementary to that described in the preceding companion paper, are described below.

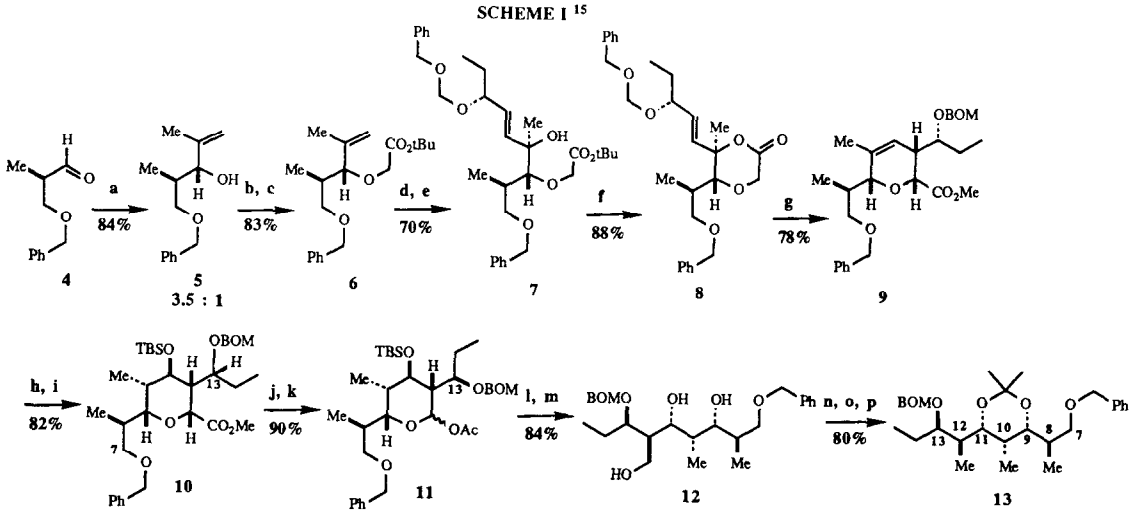


(1)

1 **2** **3**

Addition of the cuprate derived from isopropenyllithium to (*R*)-3-benzyloxy-2-methylpropionaldehyde (4)[7] proceeded to give predominately the allylic alcohol **5**, reflecting β-chelation-controlled

SCHEME I [15]



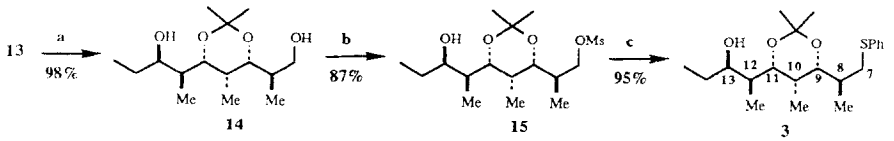
4 **5** (3.5 : 1) **6** **7** **8** **9** **10** **11** **12** **13**

(a) $[H_2C=C(Me)]_2CuLi$, Et_2O, -30°C. (b) NaH, THF, reflux; $BrCH_2CO_2H$. (c) *t*-BuOH, DMAP, DCC. (d) O_3, MeOH, CH_2Cl_2, -78°C; Me_2S. (e) (*E*)-3-(*R*)-$BrMgCH=CHCH(OCH_2OCH_2Ph)CH_2CH_3$, Et_2O, -78°C. (f) CF_3CO_2H, PhH, reflux. (g) LDA, Me_3SiCl, Et_3N, THF, -100 → 25°C; remove THF *in vacuo*, add $PhCH_3$; 110°C, 5 h; H_3O^+; CH_2N_2, Et_2O. (h) BH_3 • THF, -78 → 0°C; H_2O_2, aq. NaOH. (i) *t*-$BuMe_2SiOTf$, *i*-Pr_2NEt, CH_2Cl_2. (j) *n*-PrSLi, HMPA, 25°C.[16] (k) $Pb(OAc)_4$, THF-HOAc (10:1), 25°C. (l) $LiBH_4$, THF, 25°C. (m) *n*-Bu_4NF, THF, (n) MsCl, *i*-Pr_2NEt, CH_2Cl_2, -23°C, 35 min. (o) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, 25°C. (p) $LiEt_3BH$, THF, reflux, 30 min.

addition.[8] *O*-Alkylation and esterification[9] gave **6** which, upon ozonolysis and α-chelation-controlled addition[10] of (*E*)-3-(*R*)-BrMgCH=CHCH(OCH$_2$OCH$_2$Ph)CH$_2$CH$_3$[11] gave in >20:1 diastereomeric excess the tertiary allylic alcohol **7**. Lactonization and enolate Claisen reorganization as previously described[2] transformed **7** via **8** into the dihydropyran **9**, wherein the α-face of the olefin is sterically blocked. Hydroboration/oxidation[12] and protection of the resulting secondary alcohol as the *t*-butyldimethylsilyl (TBS) ether gave the fully elaborated tetrahydropyran **10**. Cleavage of the heterocyclic template was effected by Pb(OAc)$_4$-induced oxidative decarboxylation[13] of the derived acid, followed by exhaustive reduction of the acyl glycoside **11** and desilylation to give the triol **12**. Selective mesylation of the primary hydroxyl therein, followed by acetonide formation and reduction with LiBEt$_3$H gave the erythronolide B C(7)-C(13) subunit **13**, with its six contiguous asymmetric centers in the desired absolute configurations.

As mentioned in the preceding communication, the C(7)-C(13) subunits derived from (*S*)-(-)-ethyl lactate and from **4** were structurally correlated via several common derivatives. For example, **13** was converted to **3** as shown in Scheme II. This served to confirm the identity of the products derived from the two optically active starting materials and provided in **3** a C(7) anion precursor[14] for coupling with an electrophilic C(1)-C(6) subunit.[3]

SCHEME II [15]



(a) Na°, NH_3, Et_2O, -33°C, 2 min; NH_4Cl. (b) MsCl, *i*-Pr_2NEt, CH_2Cl_2, -23°C, 1 h. (c) 6 equiv PhSNa, EtOH, 0 → 25°C, 5 h.

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References and Notes

1. Research Fellow of the Alfred P. Sloan Foundation, 1984-88, recipient of a National Science Foundation Presidential Young Investigator Award, 1984-89.
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5. For a bibliography of synthetic efforts in this area, see ref. 6 in the preceding paper in this issue.
6. The term "homochiral" is used here in the sense employed by Masamune[6a] and Sharpless[6b] as a synonym for optically pure. (a) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67.
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14. The usefulness of the C(7) sulfide as a precursor to a nucleophilic coupling partner has been demonstrated recently by Stork (refs. 6e, j in preceding paper).
15. Yields cited in the Schemes are for chromatographically and spectroscopically homogeneous substances. All structural assignments are supported by IR, high-field ^{1}H NMR (300 or 400 MHz), ^{13}C NMR, and mass spectrometric and combustion analyses.
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