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Stereoselective Synthesis of a Family of Alternating Polyols from Six-Carbon Epoxyalkynol Modules

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Polyacetate structures of 1, 3, 5, ... alternating polyol chains are found in a variety of natural products, such as polyene macrolides roxaticin,[1] mycoticin,[2] nystatin,[3] RK-397,[4] and other compounds with a variety of biological activities and therapeutic utility. Several other synthetic routes to alternating polyols[5] have been applied to the stereoselective preparation of polyketide natural products.[6] However, these strategies either use relatively small synthons, requiring a large number of carbon−carbon bond-forming steps, or have stereochemical limitations. Herein we report a new synthetic strategy for assembling polyacetate substructures, which is based on cross-couplings of six-carbon modules.

Our approach involves preparation of the protected six-carbon epoxyalkynol **4** by enzyme-catalyzed resolution[7] of **1**,[8] followed by a sequence of virtually nonstereoselective epoxidation and hydrolytic kinetic resolution[9] (Scheme 1). Each of the four stereoisomers of epoxide **4** and diol **5** is produced from either enantiomer of **1** with very high diastereoselectivity.[10,11] The alkynyldiol **5** is converted into a six-carbon nucleophilic module **7** (4 stereoisomers possible) for coupling[12] with the epoxide six-carbon electrophilic module **4** (4 stereoisomers possible), affording diyne **8** bearing 12 carbons and four chiral oxygen substituents (16 stereoisomers possible, Scheme 2). Our efficient preparation and coupling of these modules permits maximum stereochemical diversity in product structures, which is a particularly timely concern with potential applications to combinatorial and parallel synthesis.

The internal alkyne in compound **8** can be differentiated by directed reactions from the hydroxyl group at C-8 arising from epoxide opening. The hydration transformation from **8** was selectively achieved through iodocyclization[13] of the *tert*-butyl carbonate derivative of alkynyl alcohol **8**, followed by radical deiodination (Scheme 3). The β-hydroxyketone **10** was revealed upon basic hydrolysis of cyclic carbonate **9**.[14] β-Hydroxyketone **10** can be reduced with either 1,3-*anti*-[15] or *syn*-stereoinduction[16] from the C-8 hydroxyl group, demonstrating the potential of our strategy for stereoselective preparation of all 32 stereoisomers of polyol **11**.[11]

This strategy was tested in a stereoselective synthesis of the alternating polyol with stereochemistry corresponding to the C11−C28 substructure of the polyene macrolide natural product RK-397. Boron-chelated reduction[16] of the (2*R*,4*S*,8*S*,10*S*)-isomer of **10** afforded *syn*-diol **11** and the less polar cyclic boronate ester **12** (Scheme 4), which were both converted into terminal alkyne−acetonide **13**. Coupling of the 12-carbon nucleophilic module **13** with electrophilic epoxide (2*S*,4*R*)-**4** gave the 18-carbon chain product **14**, which was converted as before into the fully protected 18-carbon alternating polyol chain **15**, which possesses stereochemistry corresponding to the C11−C28 fragment of the natural product RK-397 (**16**).

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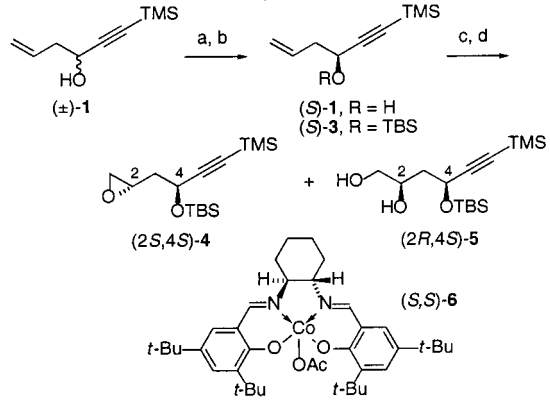
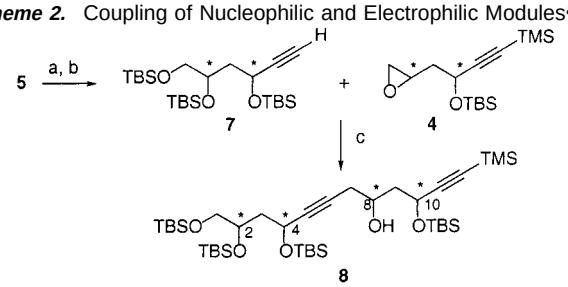
Scheme 1. Stereoselective Preparation of Six-Carbon Modules[a]



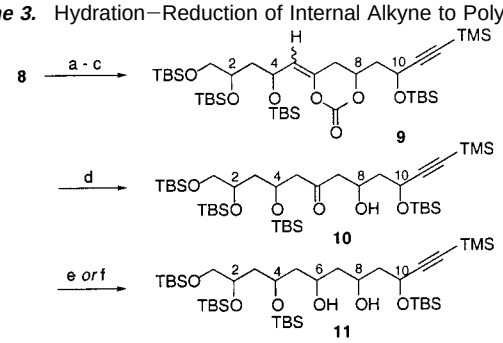
[a] Conditions: (a) *Pseudomonas* (AK), vinyl acetate, 4 Å MS, hexanes; (*S*)-**1**, R = H (48% yield, 98% ee) + (*R*)-**2**, R = Ac (48% yield, >99% ee). (b) TBSCl, imidazole, DMF (96% yield). (c) *m*-CPBA, CH_2Cl_2 (83% yield, 1.1:1 dr). (d) (*S*,*S*)-**6** (5 mol %), THF/H_2O; (2*S*,4*S*)-**4** (54% yield) + (2*R*,4*S*)-**5** (40% yield).

Scheme 2. Coupling of Nucleophilic and Electrophilic Modules[a]



[a] Conditions: (a) K_2CO_3, MeOH. (b) TBSCl, imidazole, DMF. (c) **7**, *n*-BuLi, hexane, THF, −78 to 0 °C; then BF_3−OEt_2, −78 °C; then **4**, −78 °C to room temperature.

Scheme 3. Hydration−Reduction of Internal Alkyne to Polyol **11**[a]



[a] Conditions: (a) $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2. (b) IBr, CH_2Cl_2−toluene, 0 °C. (c) Bu_3SnH, Et_3B, hexane, 0−20 °C. (d) H_2O_2, LiOH, THF−H_2O. (e) Et_2BOMe, $NaBH_4$, THF−MeOH, −78 °C. (f) $Me_4NBH(OAc)_3$, HOAc−MeCN, −40 to −20 °C.

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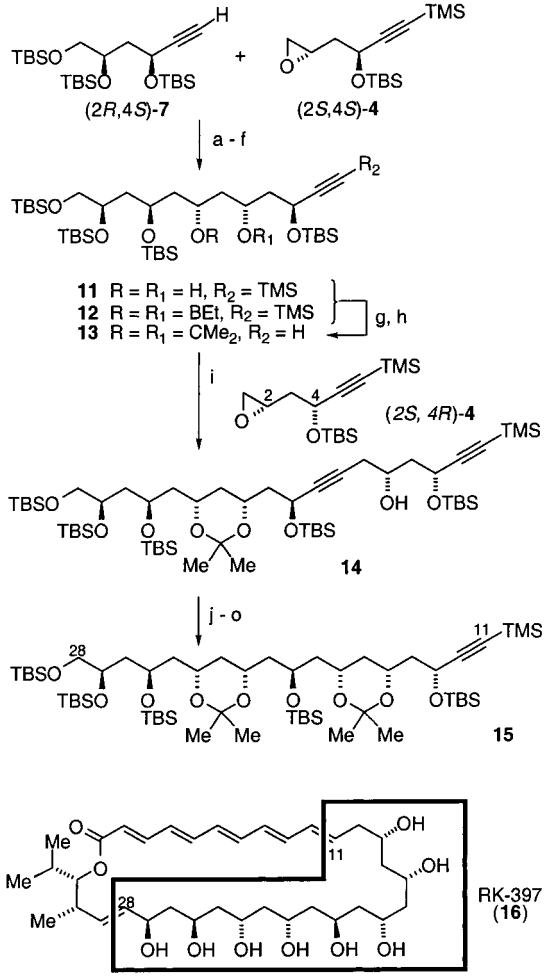
Scheme 4. Synthesis of the C11−C28 Substructure of RK-397[a]



[a] Conditions: (a) *n*-BuLi, hexane, THF, −78 to 0 °C; then $BF_3{-}OEt_2$, −78 °C; then **4**, −78 °C to room temperature (83%). (b) $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2 (97%). (c) IBr, CH_2Cl_2−toluene, 0 °C. (d) Bu_3SnH, Et_3B, hexane, 0−20 °C (64%, 2 steps). (e) H_2O_2, LiOH, THF−H_2O (78%). (f) Et_2BOMe, $NaBH_4$, THF−MeOH, −78 °C. (g) K_2CO_3, MeOH. (h) $Me_2C(OMe)_2$, cat. TsOH (71%, 3 steps). (i) *n*-BuLi, THF, −78 °C; then $BF_3{-}OEt_2$, −78 °C; then **4**, −78 °C to room temperature (54%). (j) $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2 (93%). (k) IBr, CH_2Cl_2−toluene, 0 °C. (l) Bu_3SnH, BEt_3, hexane, 0 °C to room temperature (62%, 2 steps). (m) H_2O_2, LiOH, THF−H_2O (58%). (n) Et_2BOMe, $NaBH_4$, THF−MeOH, −78 °C. (o) $Me_2C(OMe)_2$, cat. TsOH (72%, 2 steps).

In conclusion, a new strategy for construction of alternating polyols has been developed based on coupling of six-carbon epoxyalkynol modules. Preparation of the 18-carbon structure of protected polyol **15** requires only two carbon−carbon bond-forming steps from modules **4** and **7**. Our demonstrated preparations of all isomers of these modules **4** and **7** and the use of *syn*- or *anti*-reductions of β-hydroxyketones **10** suggest that there are no limitations on the stereoisomeric alternating polyols that can be generated.

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Supporting Information Available: Experimental details, spectroscopic and analytical data for compounds **1**−**5** and **7**−**15**, including a complete table of all stereoisomeric products **4** and **5** obtained by hydrolytic kinetic resolution, and ^1H and ^{13}C NMR spectra of **15** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The relative and absolute configuration was confirmed by X-ray crystallographic analysis of the bis-*p*-bromobenzoate ester of (2*S*,4*S*)-**5**. Stereochemistry of the remaining isomers of diols **5** and epoxides **4** was assigned by analogy with the literature and comparison with (2*S*,4*S*)-**5**.
(11) See the Supporting Information for details on preparation of all stereoisomers of **4**, **5**, and **7**, as well as representative stereoisomers of **8**, **10**, and *syn*- and *anti*-diols **11**.
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