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A Unified Synthetic Approach to Polyketides Having Both Skeletal and Stereochemical Diversity

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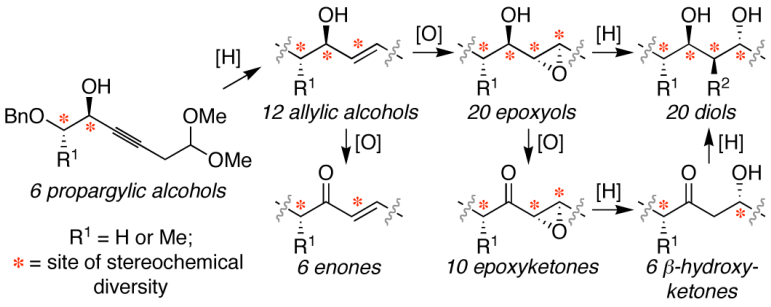
Abstract



An efficient systematic approach to the diversity-oriented synthesis of polyketides has been developed to provide both skeletal and stereochemical diversity. Each synthetic intermediate is also a desired polyketide fragment and no protecting group manipulations are required. A first-generation synthesis provides a 74-membered polyketide library comprising six different skeletal classes, each in one to five steps from propargylic alcohol precursors. A study of epoxyol opening reactions revealed unusual reactivity trends based on epoxide configuration.

Polyketide natural products exhibit a tremendous variety of biological activities and chemical structures, making them attractive starting points for the synthesis of natural product-based libraries.[1] Biologically, polyketides are known to bind to a wide range of targets and, thus, can be considered an empirically 'privileged' family of structures.[2] Chemically, polyketides present significant challenges in diversity-oriented synthesis, in that flexible, highly efficient synthetic approaches are required to allow systematic modification of biologically active compounds identified from the resulting libraries. To access this biological and chemical diversity, several approaches to polyketide libraries have been advanced.[3] While efforts to date have focused primarily on accessing the polypropionate 1,3-diol motif,[4] an ideal diversity-

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oriented synthesis would provide access to a wider range of skeletal motifs found in polyketide natural products. Indeed, generating libraries with *both* skeletal[5] and stereochemical diversity[6] is a key current challenge in diversity-oriented synthesis.[7] Toward these ends, we report herein a unified approach to the diversity-oriented synthesis of polyketides and a first implementation that provides 74 stereochemically diverse polyketides falling into six different structural classes.

At the outset of our efforts, we noted that the polyketide skeleton arises biosynthetically from reiterative couplings of simple malonate building blocks, with tailoring reactions generating most of the structural diversity, primarily through variations in oxidation state and stereochemical configuration.[8] We envisioned a conceptually related synthetic approach in which simple precursors are transformed stereoselectively to a variety of polyketide structures through formal alterations in oxidation state, with each synthetic intermediate also representing a desired polyketide fragment. Such an approach can be considered 'biomimetic' under Breslow's original broad definition.[9] Importantly, in contrast to polyketide total synthesis, in which a variety of synthetic approaches can be interchanged as necessary, diversity-oriented synthesis requires that these various polyketide motifs be accessed in a unified, systematic fashion.

Thus, we formulated the general synthetic strategy outlined in Scheme 1, using propargylic alcohols **3** as versatile synthetic precursors[10] that could be transformed to a variety of polyketide structures. These key intermediates could be generated from α-alkoxycarbonyl compounds **1**and alkynes **2**, potentially bearing R^1 and R^3 substituents. Terminal benzyl ether and dimethyl acetal groups were selected as functionalities that are directly compatible with biological assays,[11] and are also potential handles for further functionalization. Subsequent reductive and oxidative transformations would then provide six different polyketide skeletal motifs: allylic alcohols (**4**), enones (**5**), epoxyols (**6**), epoxyketones (**7**), 1,3-diols (**8**), and β-hydroxyketones (**9**).R^2 substituents could potentially be installed in conjunction with any of the formal reduction steps and the 1,3-diols **8** could be accessed from either epoxyols **6** or β-hydroxyketones**9**. Alcohol deoxygenation reactions can also be anticipated to provide corresponding deoxypolyketide fragments (not shown).

To begin exploring this concept, we synthesized propargylic alcohols **3** (R^3 = H) by coupling of Weinreb amides **1** (R^1 = H or Me, X = N[Me]OMe) and 3-butynal dimethyl acetal (**2**, R^3 = H), followed by stereoselective alkynone reduction.[12,13] We then investigated transformation of the key intermediates **3** to various polyketide motifs (Scheme 2). With a view toward future solid phase implementations, we sought homogeneous reaction conditions for stereospecific alkyne reduction to *Z*-allylic alcohols **10**. Gratifyingly, Sato's titanocene-catalyzed hydromagnesiation reaction provided an effective solution.[14] Alkyne reduction with Red-Al also provided the complementary *E*-allylic alcohols **11**.[15]

We next sought to oxidize allylic alcohols **10** and **11** to epoxyols **12** and **13**, respectively, using stereoselective epoxidation reactions. As hoped, *syn* epoxidation of *Z*-allylic alcohols **10** using *m*-CPBA provided the *cis*,*syn*-epoxyols **12**.[16] Conversely, *anti* epoxidation of *E*-allylic alcohols **11a** and *anti*-**11b** under matched Sharpless conditions[17] provided the *trans*,*anti*-epoxyols **13**, although *syn*-**11b** proved unreactive in this case. Interestingly, however, *syn*-**11b** was amenable to *syn* epoxidation with *m*-CPBA in unusually high stereo-selectivity, providing one of the desired *C*2 epimeric epoxyols directly (not shown).[13,16] Alcohol inversions using Mitsunobu or oxidation/re-reduction protocols then afforded the remaining epoxyol *C*2 epimers (not shown).[13] In total, this approach provided serviceable access to all eight epoxyol diastereomers for R^1 = H and 12 out of the 16 possible diastereomers for R^1=Me.

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We then explored nucleophilic epoxide-opening reactions to provide canonical polypropionate 2-methyl-1,3-diols **14a** and **15a**. Related epoxide-based approaches were pioneered by Kishi[18] and have also been developed by others.[19] We recognized that regioselectivity represented a key concern in these transformations.[20] To address this issue, we evaluated a wide range of reaction conditions with both*cis*- and *trans*-epoxyol substrates (Table 1). Notably, we discovered that epoxide configuration had a pronounced effect upon reaction outcome.

For *cis*-epoxyols *anti*-**12a** and *syn*-**12a**, epoxide opening with methyl cuprate nucleophiles generally favored formation of the undesired 1,2-diols and/or halogenated side products. However, Miyashita's *n*-BuLi/Me_3Al combination[21] proved quite effective for these substrates, provided that at least 5 equiv of Me_3Al were used to accommodate the five Lewis basic sites in the substrates. Interestingly, we discovered that the reaction required the use of chlorinated solvents, with 1,2-dichloroethane providing higher yields than methylene chloride. Further studies of the mechanistic implications of this intriguing finding are ongoing.

In contrast, for *trans*-epoxyols *anti*-**13a** and *syn*-**13a**, the *n*-BuLi/Me_3Al combination was ineffective, leading only to debenzylation of the starting material in the case of *anti*-**13a** and to undesirable regioselectivity in the case of *syn*-**13a**. However, examination of a variety of methyl cuprates revealed that MeMgCl/CuCl provided effective access to the desired 1,3-diol products for these substrates. Interestingly, the choice of cuprate counterion had a significant effect upon regioselectivity, with chloride providing enhanced selectivity for 1,3-diol formation compared to bromides, iodides, and cyanides.

In both the *cis*- and *trans*-epoxyol series, residual undesired 1,2-diols were then conveniently separated after $NaIO_4$ cleavage.[22] NMR analyses of 1,3-diol acetonide derivatives using Rychnovsky's ^{13}C-NMR method[23] and NOESY experiments were then used to confirm relative stereochemical assignments for both the epoxyol precursors and 2-methyl-1,3-diol products.[13] Importantly, this approach provided comprehensive access to all eight 2-methyl-1,3-diol diastereomers in the R^1 = H series (**14a**,**15a**).

Analogous efforts at nucleophilic opening of the more hindered epoxyols in the R^1 = Me series (**12b**, **13b**) were thwarted by complete regioselectivity for 1,2-diol formation under all conditions tested. However, expansion of the synthetic route to include additional desired polyketide motifs provided a useful alternative solution. Dess—Martin oxidation of allylic alcohols **10** and **11**provided enones **17** and **18**, respectively, while oxidation of epoxyols **12** and **13** provided epoxyketones **19** and **20**, respectively. The epoxyketones could then undergo reductive epoxide opening with SmI_2 to provide β-hydroxyketones **21**.[24] All three of these structural classes represent desired polyketide motifs. NOESY analysis of 1,2-diol cyclic carbonates derived from β-hydroxyketones **21b** provided direct confirmation of relative stereochemical assignments for the epoxyol precursors in the R^1 = Me series.[13] At this point, directed reductions of β-hydroxyketones **21** provided *anti*-1,3-diols **16** and their *syn*-1,3-diol congeners (not shown), representing all 12 possible 1,3-diol diastereomers for R^2 = H.[13,25,26]

In conclusion, we have developed an efficient, unified diversity-oriented synthesis of polyketides that provides both skeletal and stereochemical diversity. Our first-generation synthesis has provided a 74-membered polyketide library comprising six different skeletal classes. Overall, this work addresses three important current challeges in the field of diversity-oriented synthesis. First, our synthesis provides substantial skeletal diversity, and in an unusual context involving acyclic molecules. Second, our route provides a unified approach to these various polyketide motifs. Third, the synthetic route is highly efficient, providing each polyketide motif in only one to five steps from propargylic alcohols **3**, with each synthetic

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intermediate also representing a desired polyketide motif and with no protecting group manipulations required. While this has been accomplished by strategic application of established chemistry, the extensive synthetic investigations undertaken to achieve these high yields and stereoselectivities required in diversity-oriented synthesis have revealed interesting new avenues for further chemical investigations. Further expansion of this synthetic approach to provide more comprehensive access to these and other polyketide motifs and screening of the resulting polyketide libraries against a variety of targets is ongoing. The availability of this unified synthetic approach will allow systematic evaluation of skeletal and stereochemical modifications to biologically active compounds identified therein. Moreover, the results of these screens will provide important insights into the effectiveness of natural product-based libraries at addressing diverse biological targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(26). 1,3-Diol **16a** and its *C*2 epimer could also be accessed directly by reductive epoxide opening of **13a** and its *C*2 epimer with Red-Al.[13,18b]

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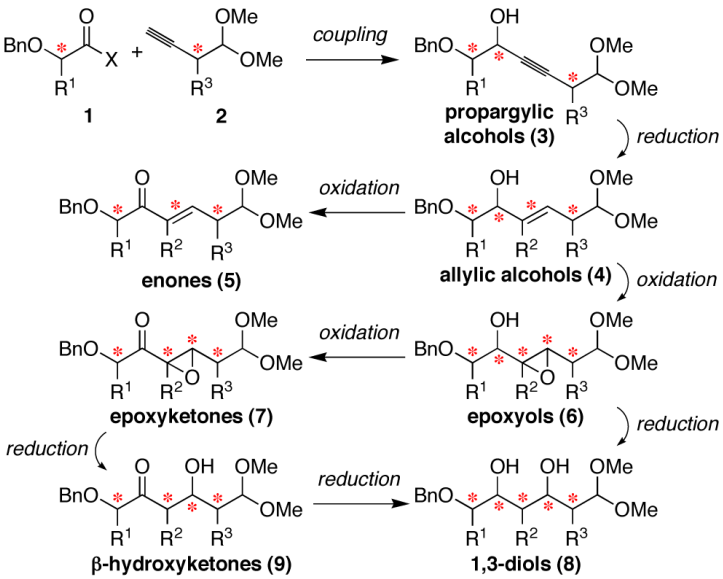
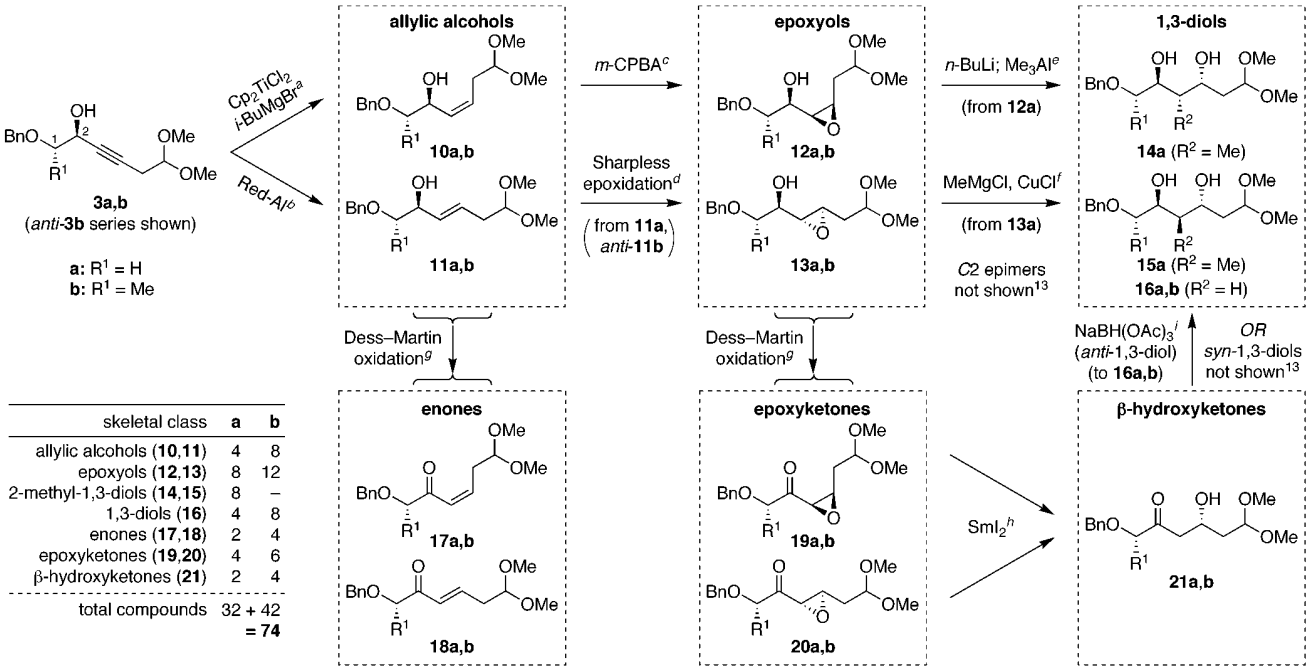


Scheme 1.

Unified Strategy for Synthesis of 6-Carbon Polyketide Fragments Having Skeletal and Stereochemical Diversity (**4**–**9**).[a] a R^1, R^2, R^3 = H or Me; (*) = site of stereochemical diversity.



skeletal class	a	b
allylic alcohols (**10**,**11**)	4	8
epoxyols (**12**,**13**)	8	12
2-methyl-1,3-diols (**14**,**15**)	8	–
1,3-diols (**16**)	4	8
enones (**17**,**18**)	2	4
epoxyketones (**19**,**20**)	4	6
β-hydroxyketones (**21**)	2	4
total compounds	32 + 42 = 74	

Scheme 2.

Synthesis of Six Different Classes of Polyketide Skeletal Motifs with Stereochemical Diversification.[13] [a] Cp2TiCl2, *i*-BuMgBr, Et_2O, 0 °C → rt, 8–48 h, 81–86%, ≥88:12 *Z*/*E*. [b] Red-Al, Et_2O, 0 °C → rt, 3–8 h, 99%, ≥98:2 *E*/*Z*. [c] *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C → rt (R^1 = H) or –4 °C (R^1 = Me), 8–24 h, 85–93%, ≥90:10 dr. [d] D-or L-diethyl tartrate (matched), $Ti(Oi\text{-}Pr)_4$, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −20 °C (R^1 = H) or −4 °C (R^1 = Me), 2–3 d, 91–99%, 94:6 dr. [e] *n*-BuLi, Me_3Al, 1,2-dichloroethane, 0 °C → rt, 2.5 h; then $NaIO_4$, MeCN/H_2O, 0 °C → rt, 2.5 h, 68– 73% (two steps), ≥98:2 dr. [f] MeMgCl, CuCl, THF/Et_2O, −40 °C → rt, 4.5 h; then $NaIO_4$, MeCN/H_2O, 0 °C → rt, 1 h, 68–69% (two steps), ≥91:9 dr. [g] Dess— Martin periodinane, CH_2Cl_2, 0 °C → rt, 1.5–8 h, 85–100%. [h] SmI_2, THF, −90 → −78 °C, 1.5 h, 65–93%. [i] $NaBH(OAc)_3$, AcOH, CH_3CN, −20 °C, 1 h, 87–95%, ≥93:7 dr.

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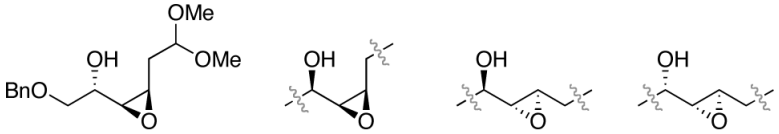
Table 1

Nucleophilic Ring Opening of Epoxyols to 2-Methyl-1,3-diols.



anti-**12a** *syn*-**12a** *anti*-**13a** *syn*-**13a**

conditions[b]	product ratio (1,3-diol:1,2-diol)[a]			
	***anti*-12a**	***syn*-12a**	***anti*-13a**	***syn*-13a**
n-BuLi/Me_3Al	**79:9**[c]	88:12	0:0[d]	4:20[e]
MeMgCl/CuCl	32:9[f]	33:60[f]	77:23	78:22
MeMgBr/CuBr	26:7[g]	33:62[g]	68:32	
MeMgBr/CuI	12:19[g]	28:51[g]	48:26[g]	
MeMgBr/CuCN	17:3[g]	21:58[g]	50:22[g]	
MeLi/CuI	24:15[h]	4:96	48:52	
MeLi/CuCN	17:12[h]	2:6[e]	58:42	

[a] Determined by ^{1}H-NMR.

[b] 5 equiv *n*-BuLi, 8 equiv Me_3Al, 1,2-dichloroethane,0 °C → rt, 2.5 h; or 12 equiv Me[M], 6 equiv CuX,1:1 THF/Et_2O, –40 °C → rt, 4.5 h.

[c] Remainder 5-desmethoxy-2,5-dimethyl-1,3-diol.[13]

[d] Debenzylated **13a** (94%) and starting material (6%)recovered.

[e] Remainder starting material.

[f] Remainder 2-chloro-1,3-diol side product.

[g] Remainder 2-bromo-1,3-diol side product and starting material.

[h] Remainder unidentified decomposition products.