

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/6389751>

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

ARTICLE *in* ORGANIC LETTERS · JUNE 2007

Impact Factor: 6.36 · DOI: 10.1021/ol070405p · Source: PubMed

---

CITATIONS

30

---

READS

18

5 AUTHORS, INCLUDING:



**Shiyang Shang**

University of Colorado Boulder

12 PUBLICATIONS 389 CITATIONS

SEE PROFILE

Published in final edited form as:

Org Lett. 2007 May 10; 9(10): 1895–1898. doi:10.1021/ol070405p.

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

Shiying Shang<sup>†</sup>, Hayato Iwadare<sup>‡</sup>, Daniel E. Macks<sup>‡</sup>, Lisa M. Ambrosini<sup>‡</sup>, and Derek S. Tan<sup>†,‡,§</sup>

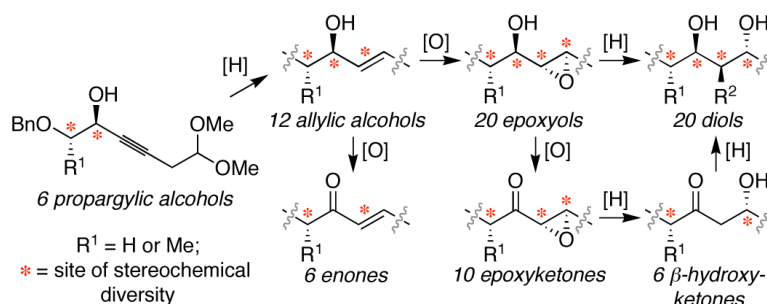
Pharmacology Program, Weill Graduate School of Medical Sciences of Cornell University, Molecular Pharmacology & Chemistry Program, and Tri-Institutional Research Program, Memorial Sloan—Kettering Cancer Center, 1275 York Avenue, Box 422, New York, New York 10021

<sup>†</sup>Weill Graduate School of Medical Sciences

<sup>‡</sup>Molecular Pharmacology & Chemistry Program

<sup>§</sup>Tri-Institutional Research Program.

### 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.<sup>1</sup> Biologically, polyketides are known to bind to a wide range of targets and, thus, can be considered an empirically 'privileged' family of structures.<sup>2</sup> 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.<sup>3</sup> While efforts to date have focused primarily on accessing the polypropionate 1,3-diol motif,<sup>4</sup> an ideal diversity-

tand@mskcc.org.

**Supporting Information Available:** Detailed experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

oriented synthesis would provide access to a wider range of skeletal motifs found in polyketide natural products. Indeed, generating libraries with *both* skeletal<sup>5</sup> and stereochemical diversity<sup>6</sup> is a key current challenge in diversity-oriented synthesis.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup> 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<sup>10</sup> that could be transformed to a variety of polyketide structures. These key intermediates could be generated from  $\alpha$ -alkoxycarbonyl compounds **1** and alkynes **2**, potentially bearing R<sup>1</sup> and R<sup>3</sup> substituents. Terminal benzyl ether and dimethyl acetal groups were selected as functionalities that are directly compatible with biological assays,<sup>11</sup> 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  $\beta$ -hydroxyketones (**9**). R<sup>2</sup> 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  $\beta$ -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<sup>3</sup> = H) by coupling of Weinreb amides **1** (R<sup>1</sup> = H or Me, X = N[Me]OMe) and 3-butylnal dimethyl acetal (**2**, R<sup>3</sup> = H), followed by stereoselective alkynone reduction.<sup>12,13</sup> 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.<sup>14</sup> Alkyne reduction with Red-Al also provided the complementary *E*-allylic alcohols **11**.<sup>15</sup>

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**.<sup>16</sup> Conversely, *anti* epoxidation of *E*-allylic alcohols **11a** and *anti-11b* under matched Sharpless conditions<sup>17</sup> 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 C2 epimeric epoxyols directly (not shown).<sup>13,16</sup> Alcohol inversions using Mitsunobu or oxidation/re-reduction protocols then afforded the remaining epoxyol C2 epimers (not shown).<sup>13</sup> In total, this approach provided serviceable access to all eight epoxyol diastereomers for R<sup>1</sup> = H and 12 out of the 16 possible diastereomers for R<sup>1</sup> = Me.

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<sup>18</sup> and have also been developed by others.<sup>19</sup> We recognized that regioselectivity represented a key concern in these transformations.<sup>20</sup> 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<sub>3</sub>Al combination<sup>21</sup> proved quite effective for these substrates, provided that at least 5 equiv of Me<sub>3</sub>Al 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<sub>3</sub>Al 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<sub>4</sub> cleavage.<sup>22</sup> NMR analyses of 1,3-diol acetonide derivatives using Rychnovsky's <sup>13</sup>C-NMR method<sup>23</sup> and NOESY experiments were then used to confirm relative stereochemical assignments for both the epoxyol precursors and 2-methyl-1,3-diol products.<sup>13</sup> Importantly, this approach provided comprehensive access to all eight 2-methyl-1,3-diol diastereomers in the R<sup>1</sup> = H series (**14a,15a**).

Analogous efforts at nucleophilic opening of the more hindered epoxyols in the R<sup>1</sup> = 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<sub>2</sub> to provide β-hydroxyketones **21**.<sup>24</sup> 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<sup>1</sup> = Me series.<sup>13</sup> 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<sup>2</sup> = H.<sup>13,25, 26</sup>

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 challenges 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

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.

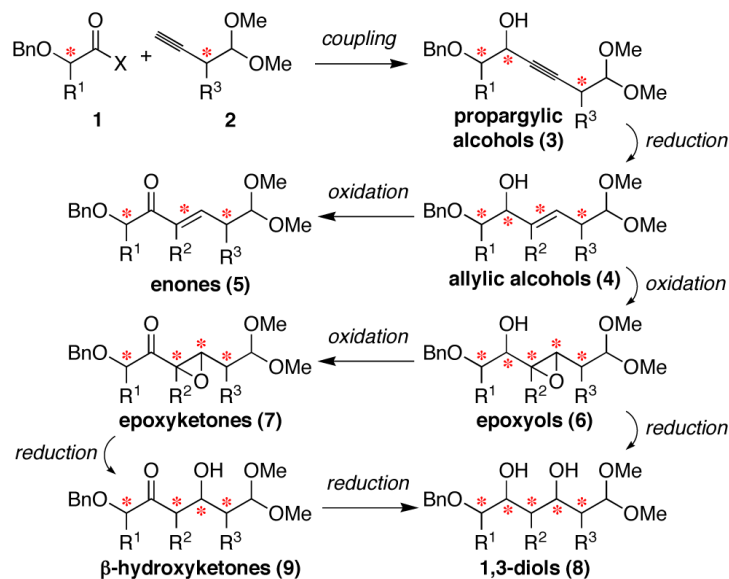
## Acknowledgment

We thank Prof. Jae-Sang Ryu (Ewha University) for helpful discussions and Dr. George Sukenick, Hui Fang, Hui Liu, Sylvi Rusli, and Anna Dudkina for expert mass spectral analyses. D.S.T. is a NYSTAR Watson Investigator, H.I. is a Visiting Scientist from Daiichi Sankyo, L.M.A. was a Summer Undergraduate Research Program student. We gratefully acknowledge financial support from the NIH (P41 GM076267), DOD (CM030085), William Randolph Hearst Fund in Experimental Therapeutics, William H. Goodwin and Alice Goodwin and the Commonwealth Foundation for Cancer Research, and MSKCC Experimental Therapeutics Center.

## References

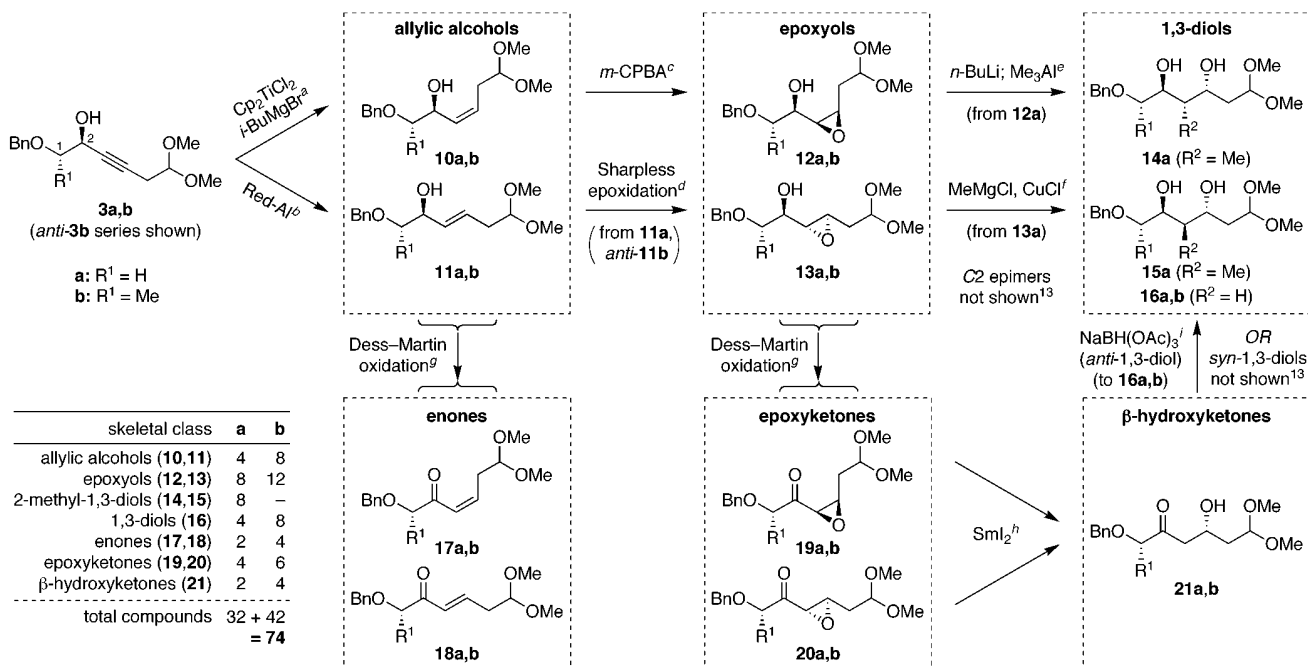
- (1). Shang S, Tan DS. *Curr. Opin. Chem. Biol* 2005;9:248–258. [PubMed: 15939326]
- (2). Evans BE, Rittle KE, Bock MG, DiPardo RM, Freidinger RM, Whitter WL, Lundell GF, Veber DF, Anderson PS, Chang RSL, Lotti VJ, Cerino DJ, Chen TB, Kling PJ, Kunkel KA, Springer JP, Hirshfield J. *J. Med. Chem* 1988;31:2235–2246. [PubMed: 2848124]
- (3)(a). Paterson I, Donghi M, Gerlach K. *Angew. Chem., Int. Ed* 2000;39:3315–3319. (b) Bode JW, Fraefel N, Muri D, Carreira EM. *Angew. Chem., Int. Ed* 2001;40:2082–2085. (c) Smith AB III, Walsh SP, Frohn M, Duffey MO. *Org. Lett* 2005;7:139–142. [PubMed: 15624997] (d) Misske AM, Hoffmann HMR. *Chem. Eur. J* 2000;6:3313–3320. (e) Arjona O, Menchaca R, Plumet J. *J. Org. Chem* 2001;66:2400–2413. [PubMed: 11281781] (f) Reggelin M, Brenig V. *Tetrahedron Lett* 1996;37:6851–6852.
- (4). Bode SE, Wolberg M, Mueller M. *Synthesis* 2006:557–588.
- (5)(a). Lee D, Sello JK, Schreiber SL. *J. Am. Chem. Soc* 1999;121:10648–10649. (b) Lee D, Sello JK, Schreiber SL. *Org. Lett* 2000;2:709–712. [PubMed: 10814416] (c) Kwon O, Park SB, Schreiber SL. *J. Am. Chem. Soc* 2002;124:13402–13404. [PubMed: 12418890] (d) Ding S, Gray NS, Wu X, Ding Q, Schultz PG. *J. Am. Chem. Soc* 2002;124:1594–1596. [PubMed: 11853431] (e) Couladouros EA, Strongilos AT. *Angew. Chem., Int. Ed* 2002;41:3677–3680. (f) Burke MD, Berger EM, Schreiber SL. *Science* 2003;302:613–618. [PubMed: 14576427] (g) Burke MD, Berger EM, Schreiber SL. *J. Am. Chem. Soc* 2004;126:14095–14104. [PubMed: 15506774] (h) Taylor SJ, Taylor AM, Schreiber SL. *Angew. Chem., Int. Ed* 2004;43:1681–1685. (i) Oguri H, Schreiber SL. *Org. Lett* 2005;7:47–50. [PubMed: 15624974] (j) Kumagai N, Muncipinto G, Schreiber SL. *Angew. Chem., Int. Ed* 2006;45:3635–3638. (k) Yeager AR, Min GK, Porco JA Jr. *Schaus SE. Org. Lett* 2006;8:5065–5068. [PubMed: 17048844]
- (6)(a). Sutherlin DP, Armstrong RW. *J. Am. Chem. Soc* 1996;118:9802–9803. (b) Annis DA, Helluin O, Jacobsen EN. *Angew. Chem., Int. Ed* 1998;37:1907–1909. (c) Harrison BA, Gierasch TM, Neilan C, Pasternak GW, Verdine GL. *J. Am. Chem. Soc* 2002;124:13352–13353. [PubMed: 12418865] (d) Kim, Y.-k.; Arai, MA.; Arai, T.; Lamenzo, JO.; Dean, EF., III; Patterson, N.; Clemons, PA.; Schreiber, SL. *J. Am. Chem. Soc* 2004;126:14740–14745. [PubMed: 15535697] (e) Potuzak JS, Moilanen SB, Tan DS. *J. Am. Chem. Soc* 2005;127:13796–13797. [PubMed:

- 16201793] (f) Moilanen SB, Potuzak JS, Tan DS. J. Am. Chem. Soc 2006;128:1792–1793. [PubMed: 16464069]
- (7)(a). Tan DS. Nat. Chem. Biol 2005;1:74–84. [PubMed: 16408003] (b) Burke M,D, Schreiber S,L. Angew. Chem., Int. Ed 2004;43:46–58. (c) Schreiber SL. Science 2000;287:1964–1969. [PubMed: 10720315]
- (8). Fischbach MA, Walsh CT. Chem. Rev 2006;106:3468–3496. [PubMed: 16895337]
- (9). Breslow R. Chem. Soc. Rev 1972;1:553–580.
- (10). The potential utility of propargylic alcohols in diversity-oriented synthesis has been noted previously: Weber L. Curr. Opin. Chem. Biol 2000;4:295–302. [PubMed: 10826979]
- (11)(a). For examples of stable, biologically active dimethyl acetals, see: Cho W-J, Kim E-K, Park IY, Jeong EY, Kim TS, Le TN, Kim D-D, Lee E-S. Bioorg. Med. Chem 2002;10:2953–2961. [PubMed: 12110317] (b) Springer RH, Scholten MB, O'Brien DE, Novinson T, Miller JP, Robins RK. J. Med. Chem 1982;25:235–242. [PubMed: 6279841] (c) Kim CD, Kim HH, Kim YK, Kwak YK, Kim S-O, Yoo S-E, Hong KW. J. Pharmacol. Exp. Ther 2001;296:1085–1090. [PubMed: 11181944]
- (12). Initial attempts to access **3a** directly by various asymmetric alkyne additions to the corresponding aldehydes (reviewed in: Pu L. Tetrahedron 2003;59:9873–9886.) suffered from poor enantioselectivity.
- (13). See Supporting Information for full details.
- (14). Sato F, Ishikawa H, Watanabe H, Miyake T, Sato M. J. Chem. Soc., Chem. Commun 1981:718–720.
- (15). Chan K-K, Cohen N, De Noble JP, Specian AC Jr. Saucy G. J. Org. Chem 1976;41:3497–3505. [PubMed: 978300]
- (16). Adam W, Wirth T. Acc. Chem. Res 1999;32:703–710.
- (17). Katsuki T, Martin VS. Org. React 1996;48:1–299.
- (18)(a). Johnson MR, Nakata T, Kishi Y. Tetrahedron Lett 1979:4343–4346. (b) Finan JM, Kishi Y. Tetrahedron Lett 1982;23:2719–2722.
- (19)(a). Murphy PJ, Procter G. Tetrahedron Lett 1990;31:1059–1062. (b) Miyashita M, Hoshino M, Yoshikoshi A. J. Org. Chem 1991;56:6483–6485. (c) Miyashita M, Yoshihara K, Kawamine K, Hoshino M, Irie H. Tetrahedron Lett 1993;34:6285–6288. (d) Esumi T, Fukuyama H, Oribe R, Kawazoe K, Iwabuchi Y, Irie H, Hatakeyama S. Tetrahedron Lett 1997;38:4823–4826.
- (20). Tius MA, Fauq AH. J. Org. Chem 1983;48:4131–4132.
- (21). Sasaki M, Tanino K, Miyashita M. Org. Lett 2001;3:1765–1767. [PubMed: 11405706]
- (22). Chakraborty TK, Joshi SP. Tetrahedron Lett 1990;31:2043–2046.
- (23)(a). Rychnovsky SD, Skalitzky DJ. Tetrahedron Lett 1990;31:945–948. (b) Rychnovsky SD, Rogers BN, Richardson TI. Acc. Chem. Res 1998;31:9–17.
- (24). Molander GA, Hahn G. J. Org. Chem 1986;51:2596–2599.
- (25). Evans DA, Clark JS, Metternich R, Novack VJ, Sheppard GS. J. Am. Chem. Soc 1990;112:866–868.
- (26). 1,3-Diol **16a** and its C2 epimer could also be accessed directly by reductive epoxide opening of **13a** and its C2 epimer with Red-Al.<sup>13,18b</sup>

**Scheme 1.**

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



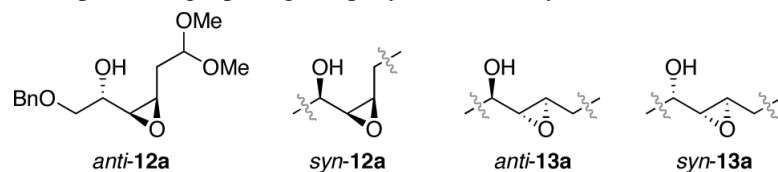
**Scheme 2.**

Synthesis of Six Different Classes of Polyketide Skeletal Motifs with Stereochemical Diversification.<sup>13</sup> <sup>a</sup>  $\text{Cp}_2\text{TiCl}_2$ ,  $i\text{-BuMgBr}$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C} \rightarrow \text{rt}$ , 8–48 h, 81–86%,  $\geq 88:12$  *Z/E*. <sup>b</sup> Red-Al,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C} \rightarrow \text{rt}$ , 3–8 h, 99%,  $\geq 98:2$  *E/Z*. <sup>c</sup>  $m\text{-CPBA}$ ,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C} \rightarrow \text{rt}$  ( $\text{R}^1 = \text{H}$ ) or  $-4^\circ\text{C}$  ( $\text{R}^1 = \text{Me}$ ), 8–24 h, 85–93%,  $\geq 90:10$  dr. <sup>d</sup> D- or L-diethyl tartrate (matched),  $\text{Ti}(\text{O}i\text{-Pr})_4$ ,  $t\text{-BuOOH}$ , 4 Å MS,  $\text{CH}_2\text{Cl}_2$ ,  $-20^\circ\text{C}$  ( $\text{R}^1 = \text{H}$ ) or  $-4^\circ\text{C}$  ( $\text{R}^1 = \text{Me}$ ), 2–3 d, 91–99%, 94:6 dr. <sup>e</sup>  $n\text{-BuLi}$ ,  $\text{Me}_3\text{Al}$ , 1,2-dichloroethane,  $0^\circ\text{C} \rightarrow \text{rt}$ , 2.5 h; then  $\text{NaIO}_4$ ,  $\text{MeCN}/\text{H}_2\text{O}$ ,  $0^\circ\text{C} \rightarrow \text{rt}$ , 2.5 h, 68–73% (two steps),  $\geq 98:2$  dr. <sup>f</sup>  $\text{MeMgCl}$ ,  $\text{CuCl}$ ,  $\text{THF}/\text{Et}_2\text{O}$ ,  $-40^\circ\text{C} \rightarrow \text{rt}$ , 4.5 h; then  $\text{NaIO}_4$ ,  $\text{MeCN}/\text{H}_2\text{O}$ ,  $0^\circ\text{C} \rightarrow \text{rt}$ , 1 h, 68–69% (two steps),  $\geq 91:9$  dr. <sup>g</sup> Dess–Martin periodinane,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C} \rightarrow \text{rt}$ , 1.5–8 h, 85–100%. <sup>h</sup>  $\text{SmI}_2$ ,  $\text{THF}$ ,  $-90 \rightarrow -78^\circ\text{C}$ , 1.5 h, 65–93%. <sup>i</sup>  $\text{NaBH}(\text{OAc})_3$ ,  $\text{AcOH}$ ,  $\text{CH}_3\text{CN}$ ,  $-20^\circ\text{C}$ , 1 h, 87–95%,  $\geq 93:7$  dr.



**Table 1**

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



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

<sup>a</sup> Determined by <sup>1</sup>H-NMR.<sup>b</sup> 5 equiv *n*-BuLi, 8 equiv Me<sub>3</sub>Al, 1,2-dichloroethane, 0 °C → rt, 2.5 h; or 12 equiv Me[M], 6 equiv CuX, 1:1 THF/Et<sub>2</sub>O, −40 °C → rt, 4.5 h.<sup>c</sup> Remainder 5-desmethoxy-2,5-dimethyl-1,3-diol.<sup>13</sup><sup>d</sup> Debenzylated **13a** (94%) and starting material (6%) recovered.<sup>e</sup> Remainder starting material.<sup>f</sup> Remainder 2-chloro-1,3-diol side product.<sup>g</sup> Remainder 2-bromo-1,3-diol side product and starting material.<sup>h</sup> Remainder unidentified decomposition products.