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Stereochemical Diversity through Cyclodimerization: Synthesis of Polyketide-like Macrodiolides

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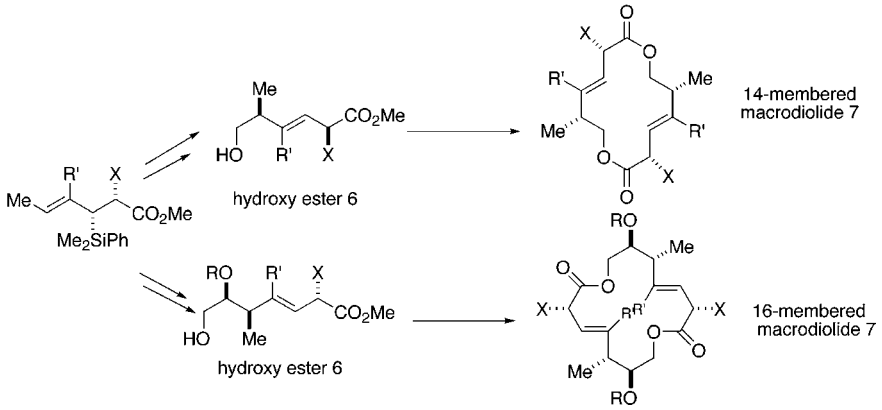
ABSTRACT



An expeditious procedure for the direct formation of stereochemically well-defined macrodiolides is described. Cyclodimerizations of enantioenriched C7 and C8 hydroxy esters 6 in the presence of catalytic amounts of distannoxane transesterification catalysts afford 14- to 22-membered macrodiolides 7–9 bearing up to six stereocenters. Additional structural diversity is introduced by further stereoselective reactions on selected macrodiolides 7a, 7g, 10a, and 11.

For decades natural products have served as inspiration for chemists engaged in target-oriented synthesis and methodology development. An emerging area involves diversity-oriented synthesis[1] of libraries that resemble natural products.[2,3] An underdeveloped strategy in library synthesis is one involving stereochemistry as a diversity element. This approach has been used to prepare cyclic RGD peptides,[4] β-turn peptidomimetics,[5] C-trisaccharides,[6] and other natural-product-like compounds[7] but infrequently in the context of polypropionate-containing molecules.[8] We have been engaged in the development of allylic silanes bearing C-

[†] Cornell University.

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(2) Recent reviews: (a) Wessjohann, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 303. (b) Hall, D. G.; Manku, S.; Wang, F. *J. Comb. Chem.* **2001**, *3*, 125. (c) Ganesan, A. *Pure Appl. Chem.* **2001**, *73*, 1033. (d) Breinbauer, R.; Vetter, I. R.; Waldmann, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2878.

(3) For selected examples, see: (a) Lee, D.; Sello, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10648. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G. Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939. (c) Pelish, H.; Westwood, N.; Feng, Y.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 6740. (d) Brohm, D.; Phillippe, N.; Mertzger, S.; Bhargava, A.; Muelle, O.; Lieb, F.; Waldmann, H. *J. Am. Chem. Soc.* **2002**, *124*, 13171.

(4) Annis, D. A.; Helluin, O.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1998**, *37*, 190.

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centered chirality. These reagents have been successfully employed in Lewis acid promoted crotylations, producing highly diastereo- and enantio-enriched polypropionate-like hydroxy esters.[9] We reasoned that these intermediates could be employed in a transesterification sequence to rapidly assemble stereochemically diverse macrodiolides reminiscent of polyketide-derived natural products (Figure 1).[10]

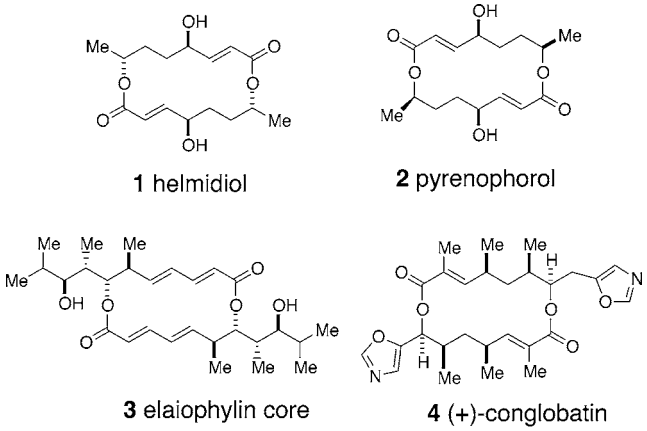

Figure 1. Structures of representative macrodiolide natural products.

Figure 2 summarizes the synthesis of stereochemically well-defined 14- and 16-membered macrodiolides resembling known polyketide-derived natural products. Our approach to these *C*2-symmetric macrocycles emerged from studies on the cyclooligomerization of hydroxybutanoates documented by Seebach.[11] However, these substrates typically produce mixtures of oligolides and may be limited in library synthesis. We anticipated that transesterification of hydroxy esters **6** would lead to initial production of an intermediate acyclic dimer, followed by intramolecular transesterification, to afford a macrodiolide product. This outcome was based on the assumption that cyclization of an initially formed dimer would be more favorable than oligomerization. In this Letter, we report that enantioenriched hydroxy esters (**6a**−**i**) are useful substrates for macrodiolide formation using distannoxane transesterification catalysts,[12] producing stereochemically diverse homo- and heterodimers (**7**, **8**, and **9**) in an efficient complexity-generation step.

(7) (a) Koide, K.; Finkelstein, J. M.; Ball, Z.; Verdine, G. L. *J. Am. Chem. Soc.* **2001**, *123*, 398. (b) Stavenger, R. A.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3417. (c) Harrison, B. A.; Gierasch, T.; Neilan, C.; Pasternak, G. W.; Verdine, G. L. *J. Am. Chem. Soc.* **2002**, *124*. 13352.

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(9) Panek, J. S.; Yang, M.; Muler, I. *J. Org. Chem.* **1992**, *57*, 4063.

(10) (a) Helmidiol: Ruediger, K.; Zeek, A.; Grabley, S.; Thiericke, R.; Zerlin, M. *J. Nat. Prod.* **1996**, *59*, 539. (b) Pyrenophorol: Kis, Z.; Furger, P.; Sigg, H. *Experientia* **1969**, *25*, 123. (c) Elaiophylin: Fiedler H P.; Worner W.; Zahner H.; Kaiser H P.; Keller-Schierlein W.; Muller A. *J. Antibiot.* **1981**, *34*, 1107. (d) Conglobatin: Westley, J. W.; Liu, C.; Evans, R. H.; Blount, J. F. *J. Antibiot.* **1979**, *32*, 874.

(11) Plattner, D. A.; Brunner, A.; Dobler, M.; Muller; H.; Petter, W.; Zbinden, P.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 2004.

(12) Otera, J. *Chem. Rev.* **1993**, *93*, 1449. (b) Shimizu, I.; Nakagawa, H. *Tetrahedron Lett.* **1992**, *33*, 4957.

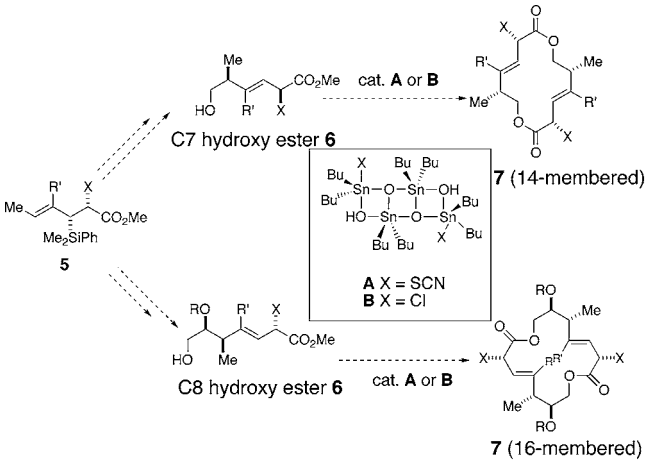
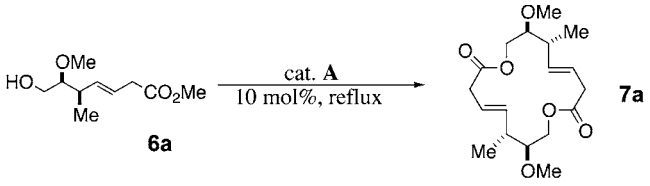


Figure 2. Cyclodimerization of nonracemic chiral hydroxy esters.

The feasibility of cyclodimerizations was studied using solvents and concentrations known to be effective in distannoxane-promoted transesterifications (Table 1). Consistent

Table 1. Effect of Solvent and Concentration on Cyclodimerization



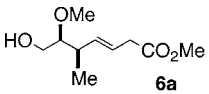
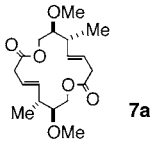
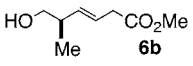
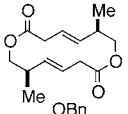
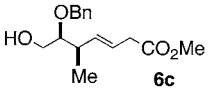
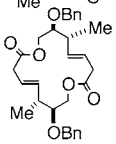
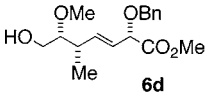
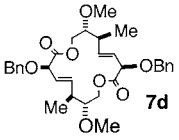
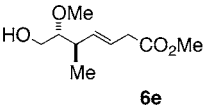
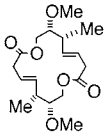
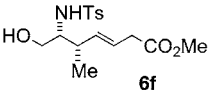
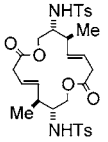
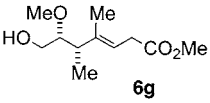
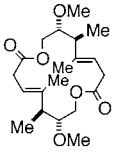
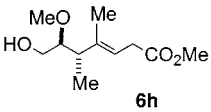
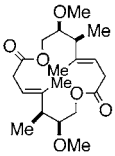
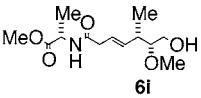
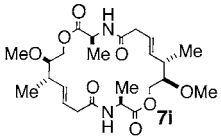
entry	solvent[a]	yield (%)[b]	entry	concn in C_6H_5Cl (M)	yield (%)[b]
1	toluene (0.02 M)	30	5	0.01	75
2	heptane (0.02 M)	20	6	0.05	50
3	benzene (0.025 M)	58	7	0.02	30
4	chlorobenzene (0.01 M)	75	8	0.5	10

[a] All reactions were run at reflux under a N_2 atmosphere (36−48 h). [b] Isolated yield of **7a** after silica chromatography.

with literature precedent, reactions were found to be sensitive to solvent choice; heptane afforded mainly products from oligomerization and use of toluene afforded the benzyl ester of the hydroxy-ester substrate with trace amounts of homodimer. Best results were obtained using chlorobenzene at reflux with monomer **6a**[9,13]to afford 16-membered macrodiolide **7a** in high yield (entries 4 and 5). Not unexpectedly, reactions performed at higher dilution resulted in efficient conversion to **7a** with reduced amounts of oligomers (entries 5 and 6).

After establishing reproducible reaction conditions, we examined a series of stereochemically complementary monomers to generate structurally diverse macrodiolides. As shown in Table 2, cyclodimerization of hydroxy esters **6a**−**i** using catalyst **A** (10 mol %) proceeded to afford homodimers **7a**−**i** in moderate to high yield, together with varying

Table 2. Homodimers Produced by Cyclodimerization

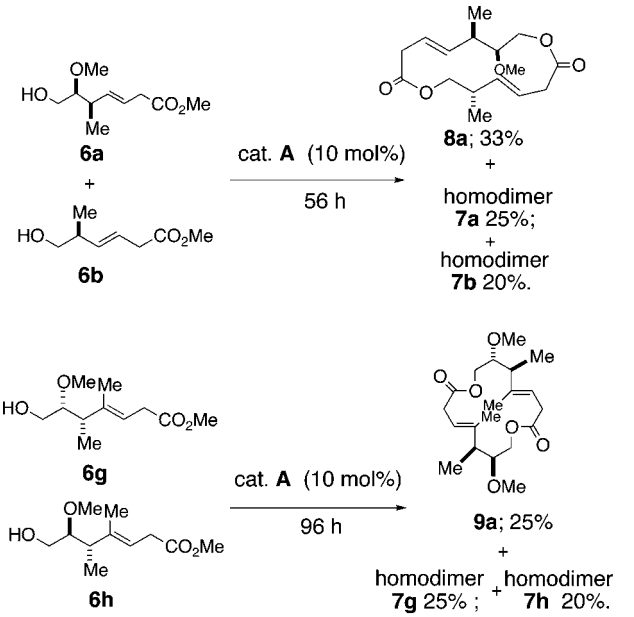
entry	substrate	macrodiolide	yield (%)[a], time, (dimer : trimer)[b]
1	 **6a**	 **7a**	75, 48 h (10:1)
2	 **6b**	 **7b**	80, 48 h (>10:1)[d]
3	 **6c**	 **7c**	68, 72 h (11.8:1)
4	 **6d**	 **7d**	84, 48 h c
5	 **6e**	 **7e**	45, 48 h (3.7:1)
6	 **6f**	 **7f**	58, 96 h (4.7:1)
7	 **6g**	 **7g**	65, 48 h (14:1)
8	 **6h**	 **7h**	48, 72 h c
9	 **6i**	 **7i**	66, 24 h c

[a] All reactions were conducted in C_6H_5Cl (0.01 M) with 10 mol % catalyst **A** at reflux. [b] Ratios were determined by HPLC/MS using ELS detection. [c] Trimer not detected. [d] Ratio was determined by ^1H NMR (400 MHz, $CDCl_3$).

amounts of macrotriolides. The methodology is suitable for preparation of 14- (entry 2), 16- (entries 1 and 3−8), and 22-membered (entry 9) macrodiolides, the latter incorporating both peptide and polyketide features.[14] In preliminary studies, we have found that the cyclodimerization may be accelerated using microwave irradiation.[15] Treatment of monomer **6a** with 10 mol % distannoxane catalyst **B** (0.02 M, C_6H_5Cl) at 200 °C (300 W) in a Discovery-Explorer microwave system for 7 min led to production of macrodiolide **7a** (60%).[16]

Cyclodimerization products may be further diversified through the transesterification of two different monomers to produce heterodimers. This reaction sequence produces a separable mixture of macrodiolides (two homodimers and a heterodimer). Scheme 1 summarizes preliminary experiments

Scheme 1. Heterodimeric Macrodiolides Produced by Cyclodimerization



concerning the generation of heterodimeric macrolides **8** and **9** through cyclodimerization of hydroxy esters **6a** and **6b** and **6g** and **6h** (a 1:1 mixture of *syn*/*anti* diastereomers).

Further functionalization of macrodiolides was investigated in an effort to create additional structural diversity (Scheme 2).[3a] Stereoselective epoxidations of olefins in medium ring and macrocyclic molecules are well-documented and may afford high levels of stereocontrol.[17] Electrophilic epoxidation of macrodiolide **7a** (disubstituted olefin) afforded bisepoxides **10a** and **10b** (dr = 2.5:1). In contrast, epoxidation of macrodiolide **7g** containing a trisubstituted olefin led to bisepoxide **11** as a single diastereomer.

Single X-ray crystal structure analyses of **7a** and **7g** (Scheme 2) show that, in the solid state, both molecules adopt a conformation that minimizes $A^{1,3}$-strain.[18] Peripheral epoxidation[17] leads to major bis-epoxides **10a** and **11**, which both adopt conformations similar to those of their olefin

(13) Craig, E. M.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293.

(14) For the biosynthesis of hybrid peptide-polyketide natural products, see: Du, L.; Shen, B. *Curr. Opin. Drug Discovery Dev.* **2001**, *4*, 215.

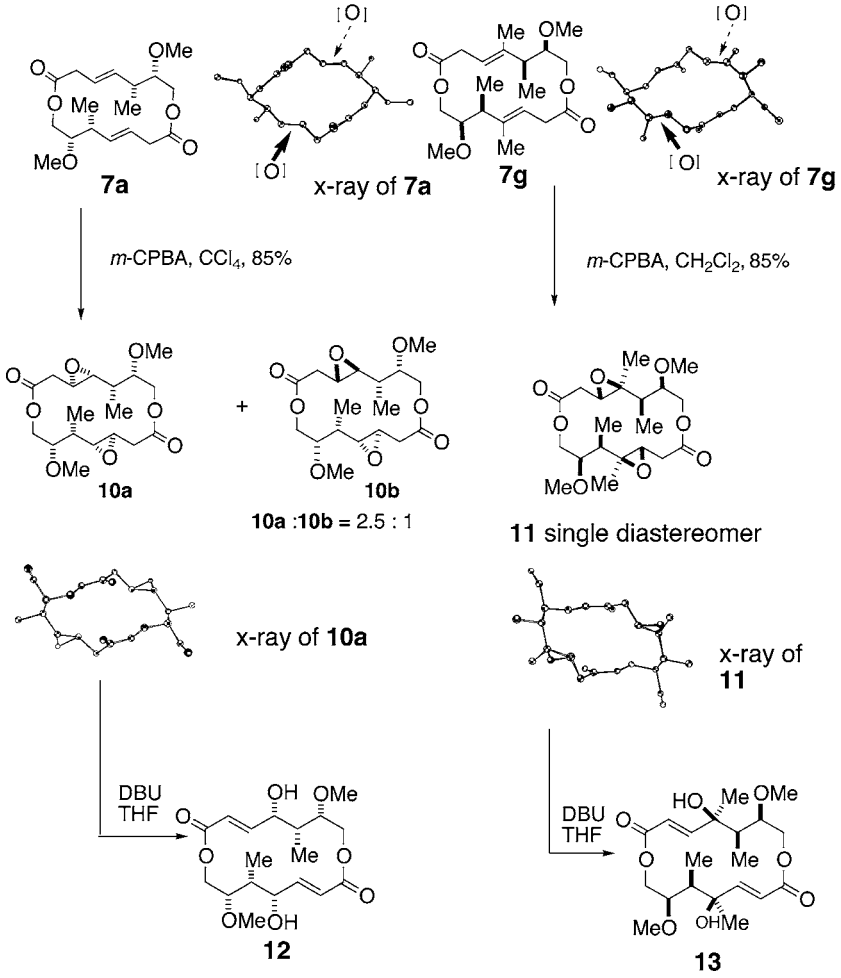
(15) Recent review: Wilson, N. S.; Roth G. P. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 620.

(16) Use of distannoxane catalyst **A** for this transformation (ca. 0.015 M) led to a 25−37% isolated yield of **7a** in a short reaction time of 10 min.

(17) For seminal papers on macrocyclic stereocontrol, see: (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (b) Local conformer effects in macrocycles: Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5059. (c) Vedejs, E.; Dent, W. H.; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 5437.

(18) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

Scheme 2. Postfunctionalization through Bis-epoxidation



precursors in the solid state. In this case, substitution of the double bond dramatically increases the diastereoselectivity of the epoxidation, likely as a result of increased conformational rigidity of **7g**.[17b] Further diversification was achieved by treatment of the macrodiolide bis-epoxides with DBU, which promoted epoxide ring opening to afford α,β-unsaturated macrolides **12** and **13**. For the initial cases examined, excellent yields (>90%) for the ring-opening reactions were obtained, producing structures bearing close analogies to known macrodiolide natural products (cf. Figure 1).

In summary, we have developed a short reaction pathway for the rapid synthesis of stereochemically well defined 14- to 22-membered macrodiolides. Cyclodimerization of two identical hydroxy esters using distannoxane catalysis affords highly functionalized homodimers. The corresponding heterodimers were obtained by combining two different monomeric hydroxyesters. Additional structural diversity is introduced by further stereoselective post-functionalization of macrodiolides (epoxidation followed by base-catalyzed ring opening). Parallel synthesis of complex macrodiolide and related compounds is currently under investigation and will be reported soon.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds and X-ray crystallographic files (in CIF format) for compounds **7a**, **7g**, **10a** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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