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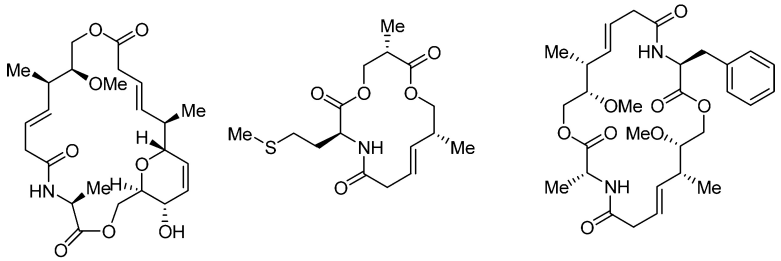

21-member macrocycle
2 fused rings
7 stereocenters

13-member macrocycle
3 stereocenters

22-member macrocycle
6 stereocenters

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Synthesis of a Library of Complex Macrodiolides Employing Cyclodimerization of Hydroxy Esters

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The synthesis of complex macrodiolides involving microwave-accelerated transesterification of chiral, nonracemic, hydroxy esters is described. Methodology development studies indicate that both microwave power and reaction temperature play an important role in the efficiency of cyclodimerizations. Hydroxy ester monomer pairs were evaluated using an analytical rehearsal leading to the preparation of a 127-member library of highly diverse and stereochemically well-defined macrodiolides. Preliminary assays identified a novel macrodiolide antagonist of the κ opioid receptor.

Introduction

For decades, natural products have served as inspiration for chemists engaged in both methodology development and target-oriented synthesis. Recently, considerable emphasis has been placed on the synthesis of chemical libraries that resemble complex natural products.[1,2] Chemical library synthesis in this manner has employed stereochemical[3] and skeletal[4] diversity, as demonstrated by Schreiber and co-workers utilizing diversity-oriented synthesis (DOS).[5] Macrocyclic frameworks present an ideal environment for DOS and exploration of skeletal and stereochemical diversity.[6] Recent studies have also demonstrated the relationship of stereochemical and skeletal structural elements to biological activity.[7] Such relationships have been described for macrolactones, underscoring the importance of macrocyclic conformation on biological activity.[8]

Macrocyclic dilactones (macrodiolides) are well-represented in nature as both homo- and heterodimers (Figure 1)[9] and offer a wide variety of skeletons, ring sizes, and functional groups. Natural products with macrodiolide frameworks are also known to exhibit a wide range of biological properties including antibiotic, antifungal, and antileukemic activities.[9] Based on examination of such structures (cf. Figure 1, **1**−**6**) we envisioned that dimerization[6b,10] of enantio-enriched hydroxy esters may afford complex macrodiolides which may approach the diversity and complexity of those found in Nature.

Herein, we report the development of tin-catalyzed cyclodimerizations of stereochemically well-defined hydroxy esters to afford complex macrolides. Our approach was initiated by synthesis of homodimers utilizing distannoxane catalysis.[11] Further optimization of the cyclodimerization using microwave irradiation[12,13] with fluorous tin catalysts[14] led to subsequent evaluation of a variety of monomeric hydroxy esters in heterodimerization reactions. Successful reaction partners were then incorporated into the synthesis of a library of complex macrodiolides (Figure 2). The library was submitted for biological evaluation in a κ opioid receptor[15] binding assay, leading to identification of a novel receptor antagonist.

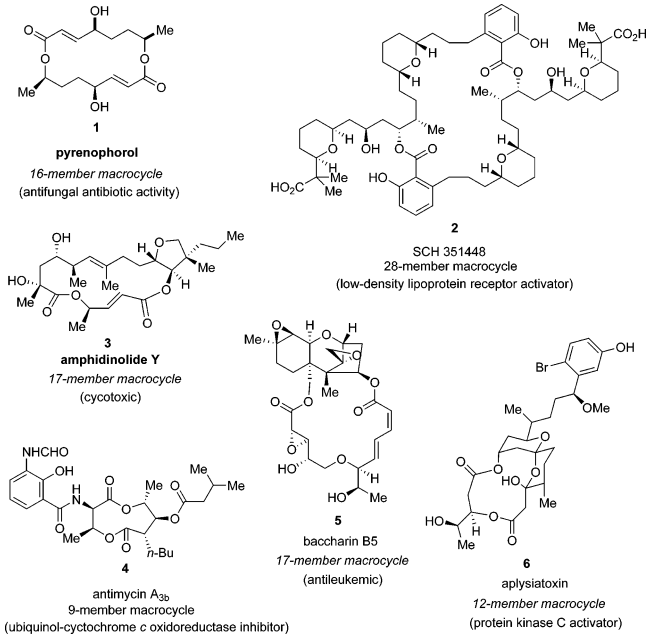

Figure 1. Naturally occurring macrodiolides.

Results and Discussion

Distannoxane-Catalyzed Cyclodimerization. Our interest in C2-symmetric macrocyclic dilactones emerged from the

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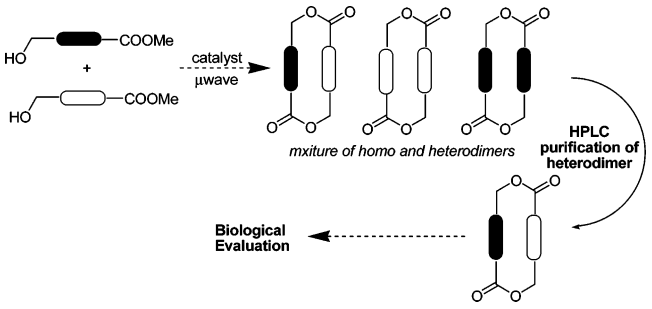


Figure 2. Strategy for the synthesis of heterodimeric macrodilactones.

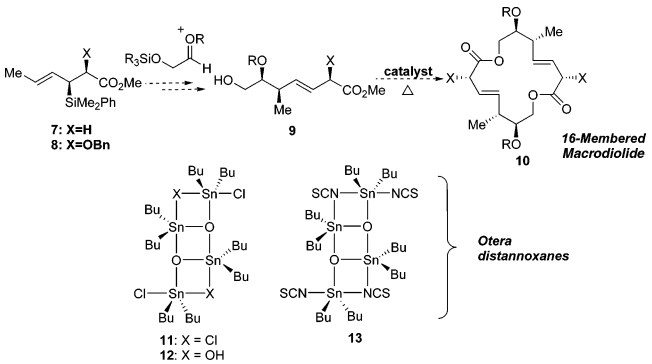


Figure 3. General pathway for distannoxane-catalyzed cyclodimerization.

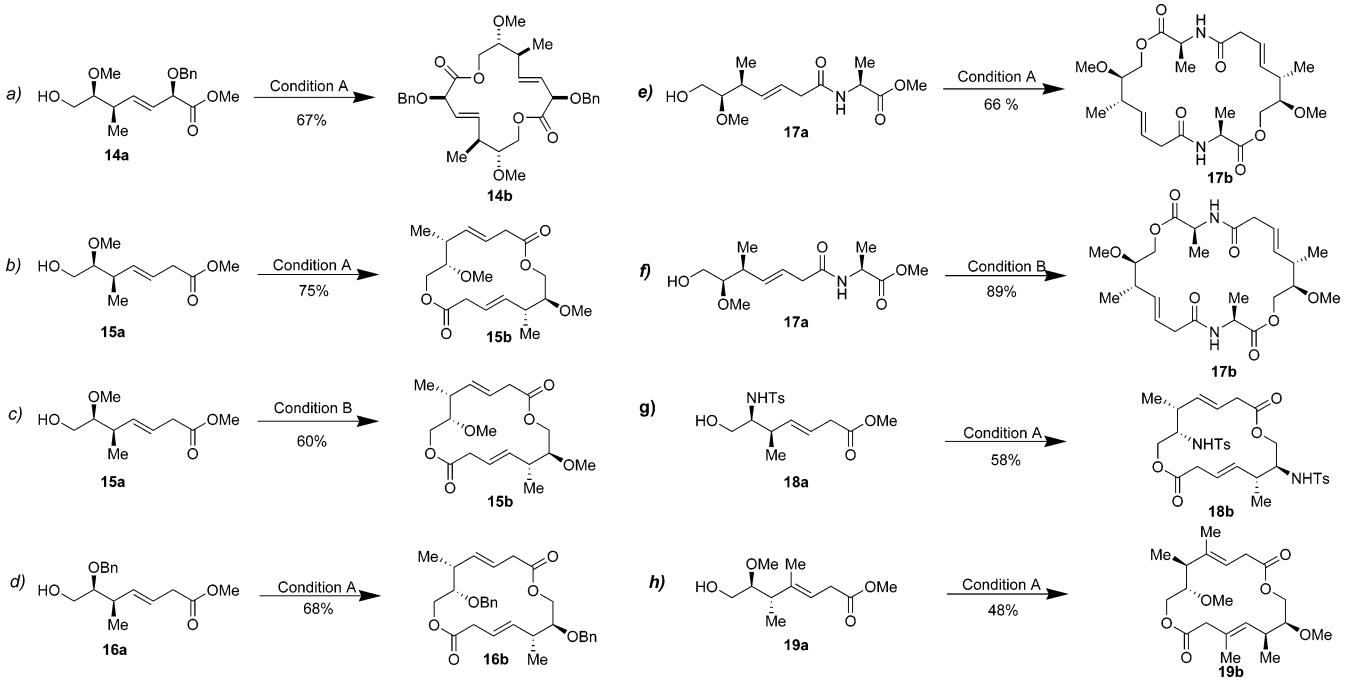
availability of a large number of diverse hydroxy esters obtained through stereoselective addition of crotyl silanes to various electrophiles.[16] Previous studies by Seebach and co-workers demonstrated that attempted dimerization of hydroxy butanoates typically produced mixtures of oligolides.[17] However, we anticipated that, if successful, transesterification of hydroxy esters **9** would lead to initial production of intermediate acyclic dimers, followed by intramolecular transesterification, to afford homodimeric macrodiolides **10** (Figure 3).

Our initial studies[18] demonstrated that cyclodimerization mediated by the Otera distannoxanes[11] (**11**−**13**) provided effective access to homodimers from diverse hydroxy esters. Optimization of temperature, solvent, and concentration led to development of a method for cyclodimerization of a variety of hydroxy esters. Monomeric units containing ethers (**14a**, **15a**, and **16a**), amino acid subunits (**17a**), and sulfonamides (**18a**) afforded moderate to high yields of homodimeric products. In subsequent studies, we demonstrated dramatic acceleration of cyclodimerizations using microwave irradiation (entries c and f, Scheme 1). Initial efforts toward homocyclodimerization thus set the foundation for development of a method to construct diverse heterodimeric macrodiolides.

Optimization of Transesterification Catalyst and Microwave Conditions. Although the Otera distannoxane catalysts worked well in the cyclodimerization process, these catalysts are not effectively removed using parallel purification strategies. Accordingly, we sought alternative catalysts[14] that could be sequestered using streamlined techniques.[19] We thus evaluated the utility of fluorous tin catalysts for cyclodimerization and their subsequent removal using fluorous solid-phase extraction (SPE).[20] Recent reports utilizing fluorous tin reagents in transesterification[14b] and tosylation[14a] prompted us to explore the utility of distannoxane **21** and tin oxide **22**.

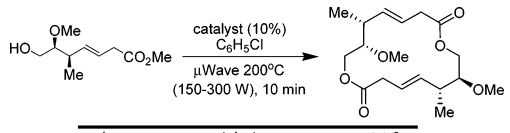
Screening of distannoxanes and tin oxides was therefore initiated to evaluate their catalytic activities for homodimerization of monomer **15a** (Table 1). Fluorous catalyst **21** showed enhanced reactivity (78% yield), as compared to the Otera distannoxane catalysts **11**−**13** (60, 32, and 48% yields, respectively) and tin oxide **20** (27% yield) under microwave

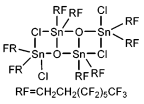
Scheme 1. Representative Examples of Distannoxane-Catalyzed Cyclodimerizations[a,b]



[a] Conditions: (a) 131 °C, C_6H_5Cl, Otera distannoxane **11** (10%), 24 h; (b) C_6H_5Cl, Otera distannoxane **13** (10%), microwave, 200 °C, (150−300 W), 10 min. [b] Isolated yields after column chromatography (SiO_2).

Table 1. Comparison of Tin Catalysts



entry	*catalyst*	*yield*[a]
1	**11**	*60%*
2	**12**	*42%*
3	**13**	*48%*
entry	*catalyst*	*yield*[a]
4	$[[CH_3(CH_2)_3]_2SnO]_n$ **20**	*27%*
5	 **21**	*78%*
6	$[[CF_3(CF_2)_5CH_2CH_2]_2SnO]_n$ **22**	*80%*

[a] Isolated yield after column chromatography (SiO_2).

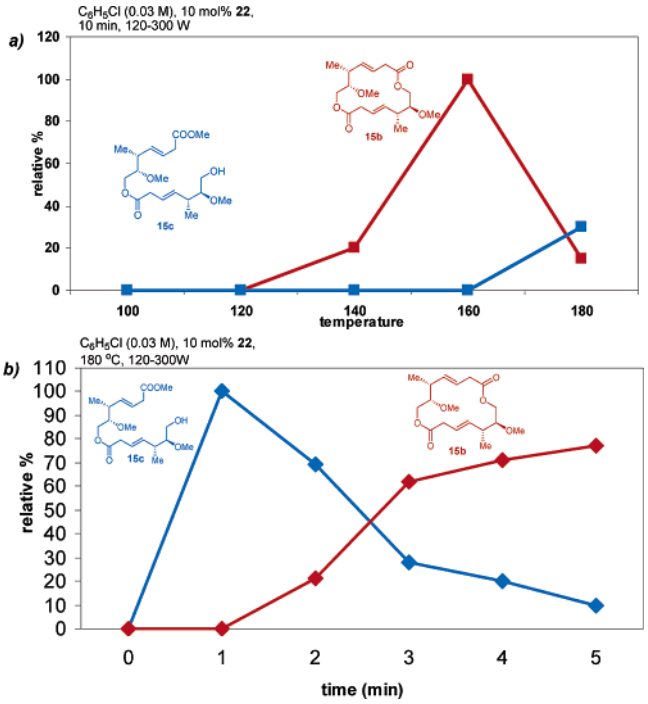
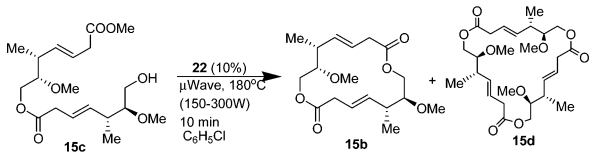


Figure 4. Macrodiolide product distribution as a function of temperature and time. Product distribution determined by HPLC/ELSD area %[22] (5 → 45% CH_3CN (0.01% formic acid)).

irradiation. Furthermore, tin oxide catalyst **22** afforded an optimal yield (80%).

We proceeded to optimize reaction conditions using tin oxide **22** in light of its commercial availability (Fluorous Technologies). To more fully understand the reaction process and optimize microwave conditions, we further examined the effects of both reaction temperature and irradiation time. A temperature screen using substrate **15a** revealed that intermolecular transesterification affording acyclic dimer **15c** began to occur at ~120 °C, and subsequent macrocyclization at ~160 °C (Figure 4). A time analysis (180 °C) indicated that initial intermolecular transesterification to afford **15c** occurs quickly (<1 min), and macrocyclization is the rate-limiting step[21] beginning at ~1 min (Figure 4).[24]

Scheme 2. Equilibration of an Acyclic Dimer[a]



[a] Ratio determined by integration of HPLC/ELSD chromatograms.

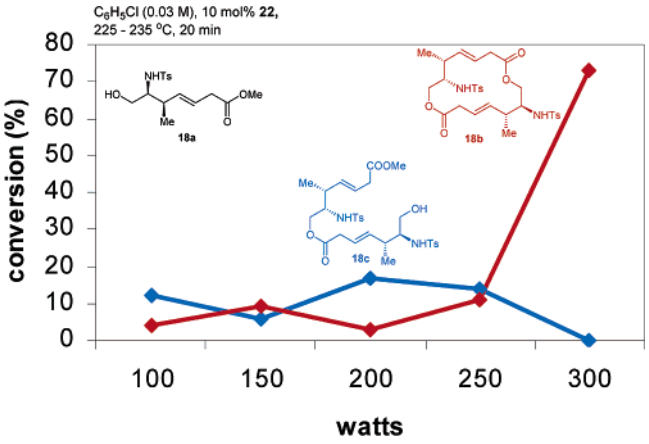


Figure 5. Product distribution related to microwave power. Product distribution determined by HPLC/ELSD area % (5 → 45% CH_3CN (0.01% formic acid)).

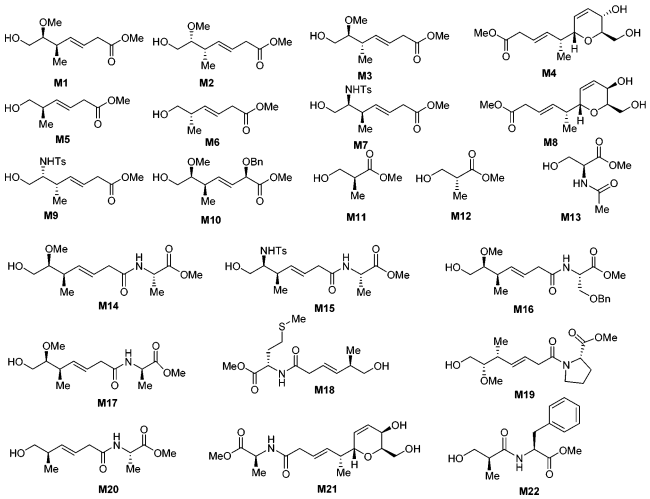


Figure 6. Hydroxyl ester monomers directly accessed using asymmetric crotylations.

Since the cyclodimerization is highly dependent on the intramolecular macrocyclization event, it seemed possible that an equilibrium of linear monomeric, dimeric, and trimeric species[23] may be present. When acyclic dimer **15c** was reacted under standard conditions, we found that both cyclic dimer **15b** and trimer **15d** were present (2.5:1), supporting an equilibrium of acyclic intermediates for this example (Scheme 2). Optimal conditions for cyclodimerization of **15a** entailed microwave irradiation for 5 min at 200 °C (300 W).

A control experiment to directly compare the cyclodimerization using thermal and microwave heating was also performed. Monomer **18a** was heated in a sealed tube using an oil bath at 225 °C (temperature was monitored by an internal fiber-optic probe) in chlorobenzene (0.03 M) and

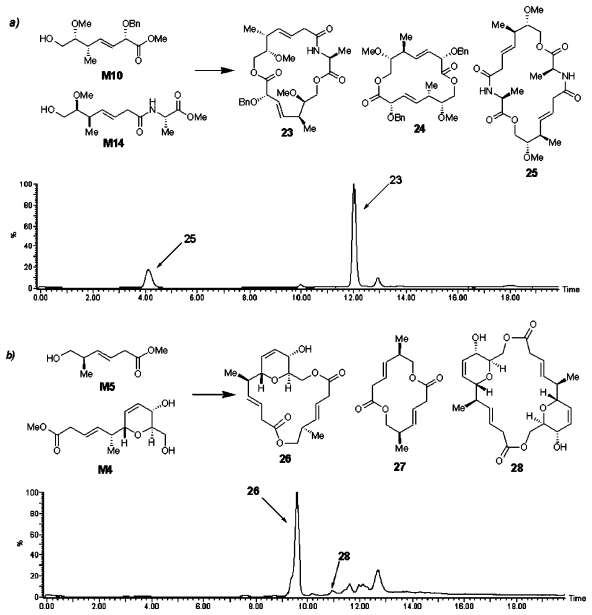


Figure 7. LC/MS/ELSD of "matched" reaction partners. HPLC/ELSD analysis (5 → 45% CH_3CN (0.01% formic acid)).

10 mol % **22**.[24] The reaction proceeded to moderate levels of conversion after 20 min (53%). To further probe the effects of microwave irradiation on this transformation, we investigated homodimerization of **18a** over a range of microwave power (100−300 W) while maintaining the temperature at 225−235 °C for 20 min (Figure 5). Our initial results indicate a likely dependence of macrodiolide formation on microwave power[25] which will be investigated further.

Synthesis of Hydroxy Ester Monomers. We next sought to understand the reactivity scope and limitations for heterocyclodimerization of a diverse set of hydroxy esters. We chose a number of hydroxy esters as reaction partners incorporating stereochemical, functional, and skeletal diversity. The majority of monomers were accessed through Lewis acid-catalyzed crotylation using chiral (*E*)-crotylsilanes (**M1**−**10**, Figure 6).[16] Monomers **M4** and **M8** were obtained by addition of crotylsilanes **7** (Figure 3) to *O*-triacetyl glucal and galactal, respectively (2 mol % $Sc(OTf)_3$, CH_2Cl_2, rt).[26]

Commercially available (*R*) and (*S*)-hydroxyisobutyric acid methyl esters and L-serine methyl ester acetate (**M11**−**13**, Figure 6) were also incorporated into the monomer set. The diversity of the monomer pool was further expanded by synthesis of hybrid monomers containing both polypropionate and amino ester units (**M14**−**22**, Figure 6).[27]

Hybrid monomers were synthesized by saponification of methyl esters followed by HATU-mediated[28] coupling of the corresponding amino acid methyl esters. We selected L- and D-alanine, L-phenylalanine, L-methionine, and L-proline as representative amino acid partners (Figure 6). A total of 22 monomers were subsequently synthesized on an ∼2.5-mmol scale.

Analytical Library Rehearsal. We designed an analytical model library[29] to identify productive monomer pairings and factors influencing the dimerization process. Such an analytical process also allows for conservation of monomers for later use in preparative scale synthesis. The rehearsal involved 1-μmol reactions (1:1 reaction partners) incubated

Table 2. "Matched" and "Mismatched" Reaction Partners[a]

entry	monomer 1	heterodimer	area %[b]
1)	**M22**, **M1**	**29**	35%
2)	**M14**, **M11**	**30**	77%
3)	**M14**, **M6**	**31**	58%
4)	**M18**, **M2**	**32**	45%
5)	**M10**, **M5**	**33**	96%
6)	**M17**, **M3**	**34**	10%

[a] Reactions were incubated for 15 min in the microwave at 225 °C (300 W) in C_6H_5Cl with 10 mol % **22**. [b] Determined by integration of HPLC/ELSD chromatograms.[30]

in C_6H_5Cl (0.03 M) in a microwave synthesizer (CEM Discover/Explorer) for 15 min with 10 mol % **22** at 225 °C (300 W). The 253 ($n \times (n + 1)/2$) reaction mixtures were evaporated, and the crude material was diluted to ∼1.7 mM with CH_3CN. Product distributions were then determined using LC/MS/ELSD[30] analysis.

Under normal circumstances, a heterodimerization process would be expected to produce a 1:2:1 (homodimer/heterodimer/homodimer)[10b,31] mixture based on binomial distribution. However, statistical mixtures were not apparent in most of the reactions carried out in the analytical rehearsal. We found that many reactions produced unknown or nondimeric products. Furthermore, reactions that were successful had a broad range of dimer distributions. Although analysis of the rehearsal data revealed a broad range of reactivity, there were some general trends which emerged. Monomers bearing amino acid units were generally the most successful reaction partners, such as the "matched" reaction of **M10** and **M14** to afford primarily heterodimer **23** (Figure 7a). Reactions

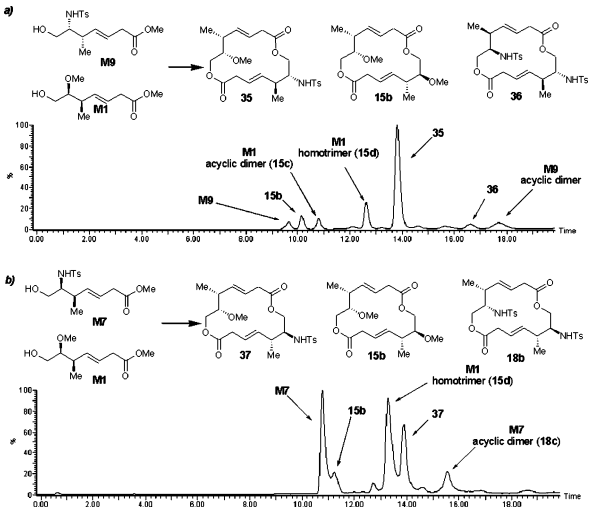


Figure 8. Stereochemical influence on product distribution. HPLC/ELSD analysis (5 → 45% CH_3CN (0.01% formic acid)).

with monomers containing *C*-glycoside units generally proceeded better with the glucal-derived **M4** versus galactal-derived **M8**. Figure 7b illustrates the successful cyclodimerization of **M4** and **M5** to afford **26**. NMR analysis of macrodiolide library members derived from monomers **M4** and **M8** (e.g., Figure 7b) having both primary and secondary alcohols revealed that the diagnostic chemical shift of the methylene adjacent to the primary alcohol was in agreement with acylation of that position.[24]

Table 2 illustrates a number of monomer pairings which afforded a broad range of heterodimeric product levels by HPLC/ELSD analysis.[30] For example, reaction of **M22** and **M1** afforded 35% **29** (HPLC/ELSD area), whereas reaction of **M10** and **M5** afforded nearly exclusively heterodimer **33** (96% HPLC/ELSD area). Product distribution was also influenced by absolute stereochemistry.[3f,4b,32] As shown in Figure 8a, pairing of **M9** and **M1** afforded primarily the desired heterodimer **35**, along with minor side products. In contrast, reaction of the enantiomer **M7** and **M1** afforded low conversion and formation of **15d** as the major product.

Macrodiolide products with large ring sizes (>19), although possible, were found to be disfavored. Reactions involving **M19** and a monomeric series of increasing length illustrate the preference for macrocyclic ring size (Table 3). Reaction of **M19** and **M11** afforded the 15-member macrodiolide **38** as 60% of the product mixture. Products **39** (18-member) and **40** (19-member) were each detected as 65% of their respective reaction mixtures. Macrodiolides **41** (20-member) and **42** (21-member) were clearly less favored as 14 and 28% of their respective product mixtures. Finally, reaction of **M16** and **M19** resulted in no detectable level of the 22-member macrodiolide **43**.

On the basis of evaluation of the first analytical rehearsal data, we formulated criteria for selection of monomer pairs that would produce acceptable yields of heterodimeric products. Analytical scale reactions were considered "successful" if they afforded a LC/ELSD purity of >60 and >25% heterodimeric macrodiolide, respectively. We thought that these criteria would afford an amount of heterodimeric product necessary for purification and subsequent biological analysis. After application of these criteria, 72 of 253 (29%) reactions were deemed suitable for preparative scale library synthesis.

Table 3. Examples of Monomer Pairings to Afford Various Ring Sizes[a]

entry	monomer 1	heterodimer	ring size	area%[b]
1)	M11	38	15	60%
2)	M5	39	18	65%
3)	M2	40	19	65%
4)	M4	41	20	14%
5)	M18	42	21	28%
6)	M16	43	22	0%

[a] **19** + monomer **1** (1:1), 225 °C (300 W), C_6H_5Cl, 10 mol % **22**, 15 m. [b] Determined by integration of HPLC/ELSD chromatograms.[30]

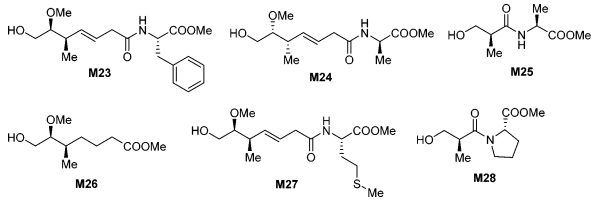


Figure 9. Second generation monomers.

On the basis of the understanding of reactivity gained in the initial studies, a second set of monomers was designed that would have a high likelihood to afford heterodimeric products. Following synthesis of a second set of six monomers (Figure 9), we proceeded with a second analytical rehearsal by pairing second generation (Figure 9) and first generation monomers (Figure 6). We were pleased to find that LC/MS/ELSD analysis of the new analytical set revealed

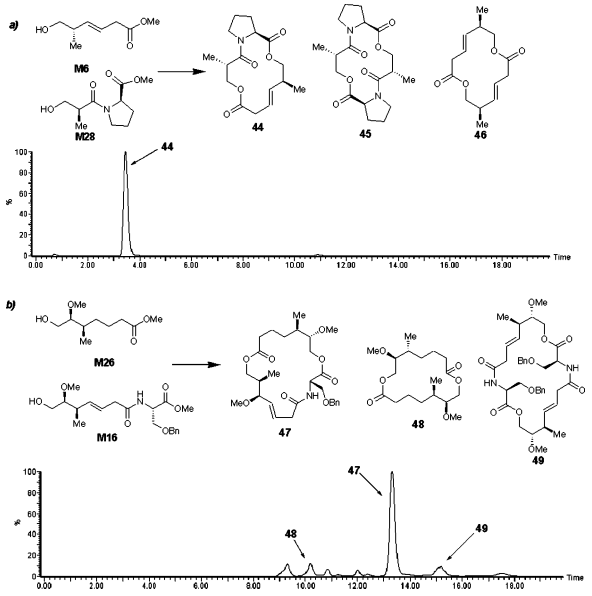
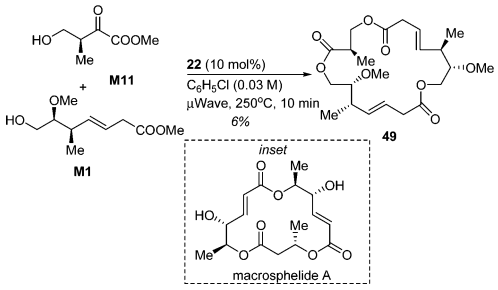


Figure 10. "Matched" reaction partners consisting of second generation monomers. HPLC/ELSD analysis (5 → 45% CH_3CN (0.01% formic acid)).

Scheme 3. Macrotriolide Formation



69 monomer pairs that passed the previously described criteria. This design approach resulted in a 77% increase in success rate. Figure 10 shows select reactions of second generation monomers. The reaction of **M28** with **M5** resulted in clean conversion to heterodimer **44** (Figure 10a). Reaction of **M26** and **M16** afforded primarily the desired heterodimer **47** (Figure 10b).

In addition to heterodimers, there were limited cases in which the major product was an identifiable heterotrimer. For example, reaction of **M1** with **M11** afforded macrotriolide **49** (Scheme 3). Interestingly, heterotrimers were isolated as major products in reactions involving monomers **M1**, **M2**, and **M3** with (*R*)- or (*S*)-isobutyric acid methyl esters (M**11** and M**12**, respectively), an intriguing variation in reactivity of monomer pairs. Naturally occurring macrotriolides, such as the sialyl Lewis × inhibitor macrosphelide A (Scheme 3, inset),[33] suggest future applications of the methodology to prepare complex heteromacrotriolides.

Preparative-Scale Synthesis of a Macrodiolide Library. After completion of the analytical rehearsal, we proceeded to use the successful monomer pairings to synthesize a preparative-scale library. Our strategy was to utilize mass-directed preparative HPLC[34] to obtain pure heterodimeric products from reaction mixtures. Library synthesis was conducted on a 10-μmol scale (1:1 of each reaction partner) in C_6H_5Cl (0.03 M). The reactions were incubated in the CEM Discover/Explorer microwave synthesizer for 15 min

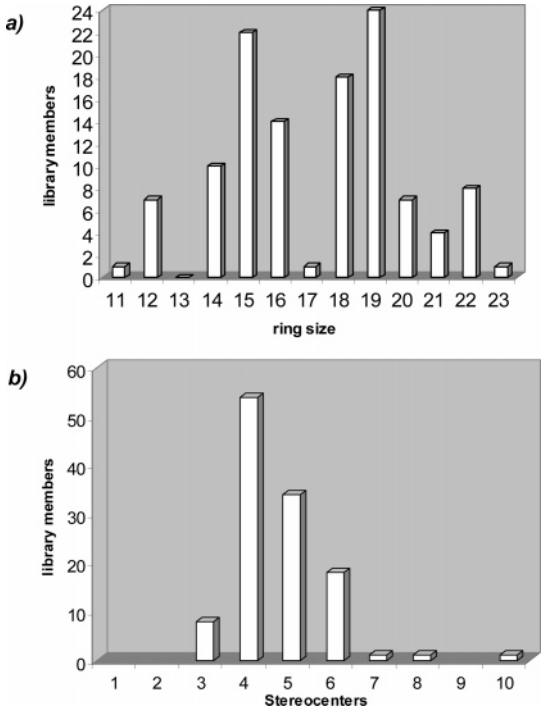


Figure 11. Distribution of ring size and stereocenters.

at 250 °C (300 W). The solvent was removed, and the reaction mixtures were diluted with 250 μL of THF. Reaction solutions were applied to preconditioned (90:10 methanol/water) SPE cartridges containing 500 mg of fluorous silica gel (Fluorous Technologies). The mixtures were further eluted with 5 mL of 90% methanol/water.

Preparative HPLC was conducted on each sample, collecting only the desired heterodimeric product.[35] Acetonitrile/water fractions were finally concentrated and transferred to preweighed Matrix minitubes. Preparative scale reactions resulted in an average of 2.5 mg (9% yield) of heterodimer. Of the 144 monomer pairings that gave acceptable analytical results, 38 reactions did not successfully scale up, despite numerous efforts and reaction optimization. Upon evaluation of the monomers that were unsuccessful, most notable was that the majority contained sulfonamide, sulfide, and benzylic ether functionalities. It is not clear whether the availability of the heteroatoms to competitively chelate the tin catalyst is at fault or if other factors derived from microwave power may be problematic. Although these failed reactions reduced the library size, the overall impact on the breadth of the resulting diversity is low.

Analysis of Library Members. The library was submitted to LC/MS/ELSD analysis for evaluation of final product purities. Of the 127 isolated products, 117 (91%) were found to have a purity (ELSD) >85%, and 106 compounds (83%) had purity (ELSD) >90%. We submitted samples for analysis of trace tin content to verify that the tin catalyst had been effectively removed in the fluorous SPE and preparative HPLC processes. Analysis by ICP-MS revealed that, after fluorous SPE, the tin level was 32 ppm, whereas samples treated by fluorous SPE and preparative HPLC had a tin content of 13 ppm.

To ensure that the tin content was within a suitable range (<10 ppm) for biological assays, we investigated further

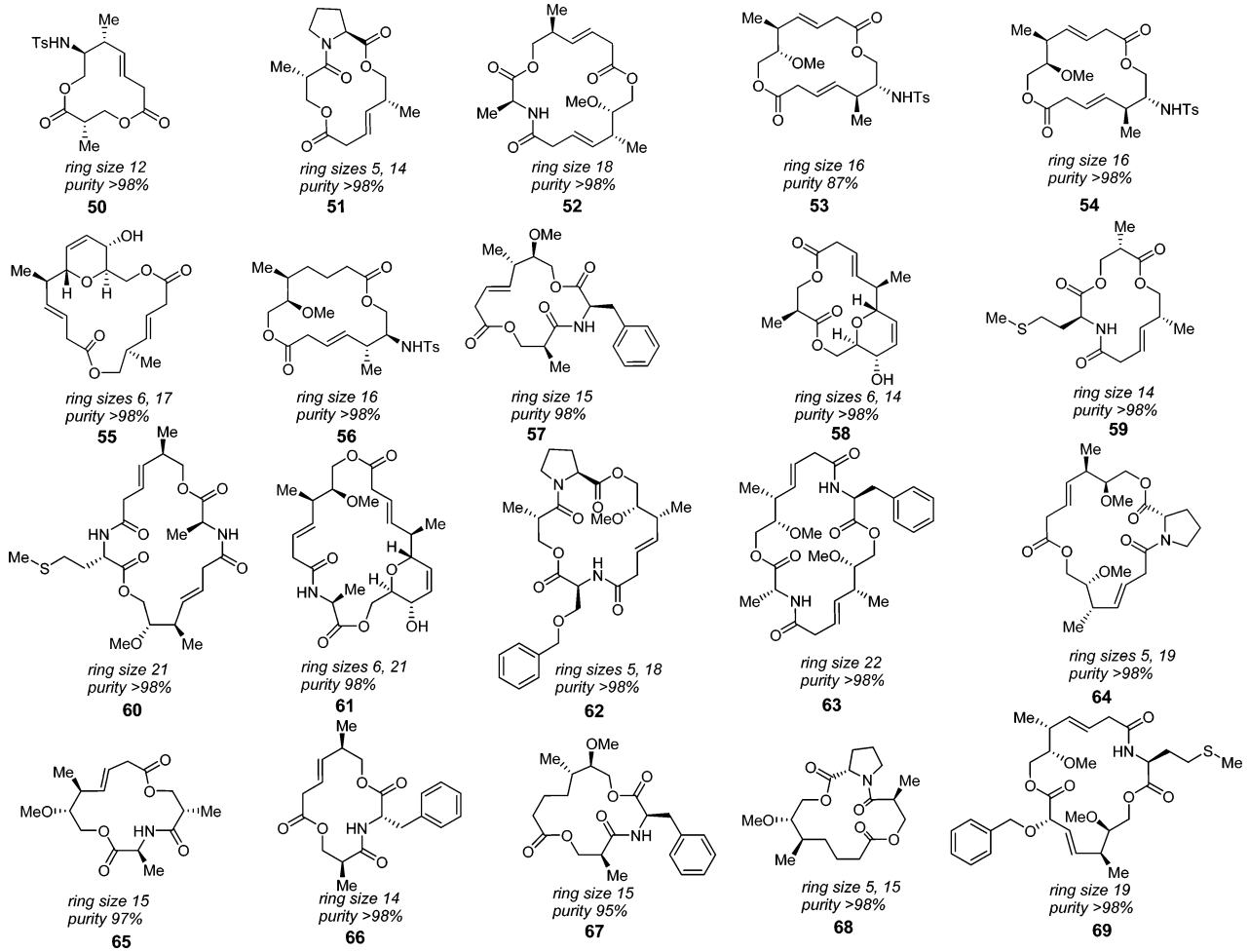


Figure 12. Representative library members. Purities were determined by HPLC/ELSD.

treatment with a triacetic acid (TAA) resin (United Chemical Technologies). We found that after treatment of purified macrodiolide library members with the TAA resin, the tin content was 8 ppm, which was comparable to negative controls.[24] The library members were subsequently dissolved in MeOH and applied to 100 mg of TAA resin and further eluted with 1 mL of MeOH. After solvent removal, samples were aliquoted to daughter plates (0.1 mg) for biological evaluation. Analysis of library members reveals an extraordinary diversity in ring size, stereochemistry, and ring composition. The library members had ring sizes from 11 to 23 (Figure 11a). Examples of 2- and 3-fused-ring systems are represented- and 3−10 stereogenic centers are available (Figure 11b). Figure 12 depicts representative heterodimeric macrodiolide library members, including purity (ELSD) and ring size.

Biological Evaluation of Library Members. In initial studies, the macrodiolide library was assayed for binding to the G protein-coupled κ opioid receptor.[15] Opioid receptor antagonists may have potential utility for the treatment of a variety of neuropsychiatric conditions, including depression (e.g., κ antagonists have antidepressant-like effects of κ in the forced swim test in rats),[36] psychosis, dementia, and HIV infection.[37] Additionally, there is extensive evidence suggesting that κ antagonists may prove useful in the treatment of drug addiction.[38] The binding assay[24] revealed homodimer **70** (Figure 13) as a moderate ligand (K_i = 326 nM). Further

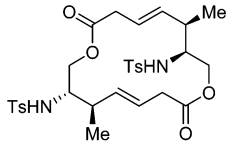


Figure 13. A macrodiolide κ opioid antagonist.

studies revealed that **70** is a κ opioid receptor antagonist. It is noteworthy that the corresponding hydroxy ester monomer (Figure 6, **M7**) was found to be inactive, which implies that the macrocyclic structure is important for binding to the κ opioid receptor. These initial studies should facilitate future design of potent, small molecule κ opioid antagonists. The library of macrodiolides is currently being evaluated in a number of additional biological assays.

Conclusions

We have demonstrated use of a rapid cyclodimerization process to synthesize a library of diverse macrodiolides. A commercially available fluorous tin oxide was found to be very effective under microwave conditions for production of complex macrodiolides and was readily removed using fluorous SPE and metal scavenging. An analytical library rehearsal was performed to select monomer pairings for preparative scale synthesis. The resulting chemical library

of 127 macrodiolides displayed high levels of macrocyclic ring, stereochemical, and functional diversity. Preliminary biological evaluation of the library in κ opioid receptor binding assays led to the identification of a macrodiolide antagonist with moderate affinity for the κ opioid receptor. Further studies on the synthesis and biological evaluation of macrocyclic libraries are currently in progress and will be reported in due course.

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Supporting Information Available. Characterization of library monomers, full details of the analytical and preparative libraries, characterization of select library members, purity data for entire library, and details of biological assays. This material is free of charge via the Internet at http://pubs.acs.org.

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