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Asymmetric Synthesis, Structure, and Reactivity of Unexpectedly Stable Spiroepoxy-β-Lactones Including Facile Conversion to Tetronic Acids: Application to (+)-Maculalactone A

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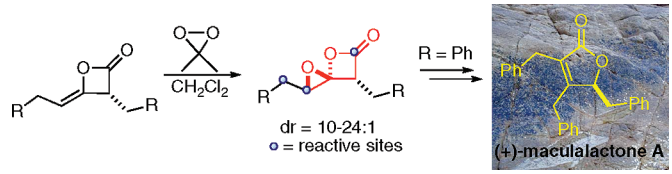
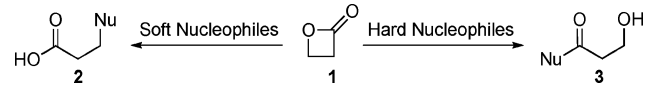


A novel class of small spirocyclic heterocycles, spiroepoxy-β-lactones (1,4-dioxaspiro[2.3]-hexan-5-ones), is described that exhibit a number of interesting reactivity patterns. These spiroheterocycles, including an optically active series, are readily synthesized by epoxidation of ketene dimers (4-alkylidene-2-oxetanones) available from homo- or heteroketene dimerization. An analysis of bond lengths in these systems by X-ray crystallography and comparison to data for known spirocycles and those determined computationally suggest that anomeric effects in these systems may be more pronounced due to their rigidity and may contribute to their surprising stability. The synthetic utility of spiroepoxy-β-lactones was explored, and one facile rearrangement identified under several conditions provides a three-step route from acid chlorides to optically active tetronic acids, ubiquitous heterocycles in bioactive natural products. The addition of various nucleophiles to these spirocycles leads primarily to addition at C5 and C2. The utility of an optically active spiroepoxy-β-lactone was demonstrated in the concise, enantioselective synthesis of the antifouling agent, (+)-maculalactone A, which proceeds in five steps from hydrocinnamoyl chloride by way of a tetronic acid intermediate.

Introduction

Small, strained heterocyclic rings have proven extremely useful in synthetic endeavors and continue to fascinate chemists due to their unusual structure, hybridization, and unique reactivity patterns. Historically, of the small, oxygen-containing heterocyclic rings,[1] epoxides are the most widely used and explored primarily due to their relevance in synthetic endeavors toward polyketide structures; however, recently, oxetanes and β-lactones (2-oxetanones)[2] are being increasingly targeted due to their presence in natural products, their potential as enzyme inhibitors, and their versatility as synthetic intermediates. The inherent strain associated with these heterocycles has led to interesting and sometimes unexpected modes of reactivity. One example is illustrated by the dual reactivity of β-lactones toward nucleophiles (Scheme 1).[3] Nucleophiles can add to either the acyl carbon to give β-hydroxy carbonyl derivatives **3** typically observed with "hard" nucleophiles or the β-carbon to provide β-substituted carboxylic acids **2** with "soft" nucleophiles.[4]

SCHEME 1. Dual Reactivity of β-Lactones



The utility of small, strained heterocyclic rings has also been extended to spiroheterocyclic systems that include oxa- and

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(1) (a) Searles, S., Jr. In *Heterocyclic Compounds with Three- and Four-Membered Rings*; Weissberger, A., Ed; Interscience: New York, 1964; p 983.

(2) (a) Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441. (b) Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403. (c) Wang, Y.; Tennyson, R. L.; Romo, D. *Heterocycles* **2004**, *64*, 605. (d) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545.

(3) For recent examples demonstrating the dual reactivity of β-lactones, see: (a) Lall, M. S.; Ramtohul, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem.* **2002**, *67*, 1536. (b) Yokota, Y.; Cortez, G. S.; Romo, D. *Tetrahedron* **2002**, *58*, 7075. (c) Nelson, S. G.; Spencer, K. L.; Cheung, W. S.; Mamie, S. J. *Tetrahedron* **2002**, *58*, 7081. (d) Nelson, S. G.; Wan, Z.; Stan, M. A. *J. Org. Chem.* **2002**, *67*, 4680. (e) Zhang, W.; Romo, D. *J. Org. Chem.* **2007**, *72*, 8939.

(4) For reviews on hard/soft acid−base theory (HSAB) theory, see: (a) Pearson, R. G. *Coord. Chem. Rev.* **1990**, *100*, 403. (b) Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* **2003**, *103*, 1793.

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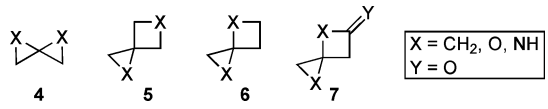
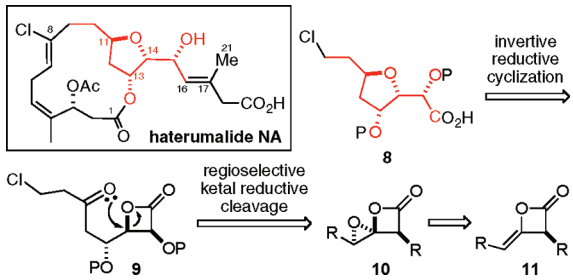


FIGURE 1. Known small, spiroheterocyclic ring systems **4**−**7**.

SCHEME 2. Synthesis of β-Lactone 9 via Reductive Cleavage of Proposed Spiroepoxy-β-Lactone 10 toward Haterumalide Tetrahydrofuran Synthesis

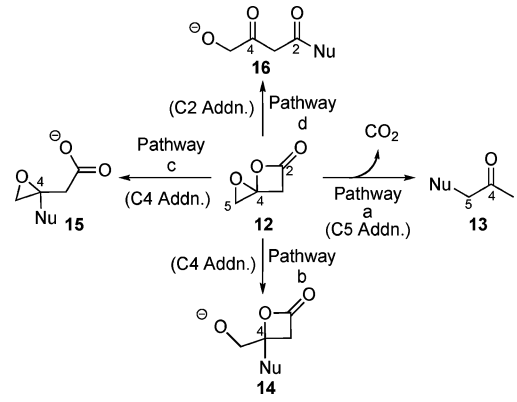


dioxaspiro[2.2]pentanes **4** as well as oxa- and dioxaspiro[2.3]-hexanes **5** and **6** (Figure 1).[5] As part of a total synthesis effort toward the haterumalides,[6] we required access to anti-γ-hydroxy-*cis*-β-lactones such as **9** to be used in a reductive cyclization route[7] to the tetrahydrofuran fragment of this natural product target (Scheme 2). However, existing diastereoselective methods for β-lactone synthesis from chiral α-oxy aldehydes provided only *syn-cis* or *syn-trans* selectivity.[8] This led us to consider the utility of heretofore unknown 1,4-dioxaspiro[2.3]hexan-5-ones (**7**, X = Y = O) that could potentially be accessed by epoxidation of known optically active ketene dimers **11**.[9] A subsequent and likely required in situ regio- and facially selective C−O reductive bond cleavage, due to the expected instability of spiroepoxy-β-lactones **10**, might allow access to the desired *anti-cis*-γ-hydroxy-β-lactone **9**. We previously reported in preliminary form the first synthesis of the dioxaspiro[2.3]hexan-5-one ring system (spiroepoxy-β-lactones) **7**[10] which demonstrated several interesting modes of reactivity. Herein, we provide a full account of our studies of these novel spiroheterocycles, including further details regarding their unique reactivity and a propensity to generate tetronic acids under a number of conditions. In addition, the accessibility of optically active ketene dimers by the method of Calter enabled a concise, five-step, organocatalytic, asymmetric synthesis of (+)-maculalactone proceeding via an optically active tetronic acid derived from a spiroepoxy-β-lactone intermediate.

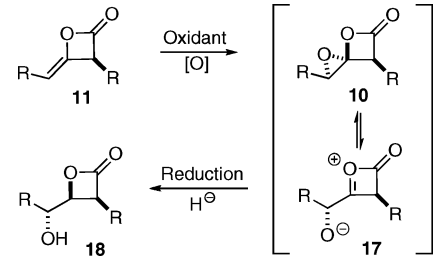
Results and Discussion

The spiroepoxy-β-lactone moiety incorporates three potentially reactive sites into a highly strained ring system by possessing both an epoxide and a β-lactone. Four possible modes of reactivity with nucleophiles can be envisioned upon consideration of the functionalities present in this ring system (Scheme 3). The first mode involves addition of nucleophiles to the distal epoxide C−O bond, pathway a, which would lead to an intermediate γ-substituted β-keto-carboxylate. Subsequent facile decarboxylation would yield an α-substituted ketone **13**. The second mode, pathway b, involves nucleophilic addition to or reduction of an oxocarbenium derived from cleavage of the epoxide ring at the spiroketal center, resulting in a γ-hydroxy-β-lactone **14**, which was the desired reaction manifold toward the requisite β-lactone for a proposed synthesis of the tetrahydrofuran of haterumalide (Scheme 2). Alternatively, a nucleophile could add to an oxocarbenium derived from cleavage of the β-lactone ring at the spirocenter instead of the epoxide (pathway c), which would result in the formation of an epoxy acid **15**. The final possible mode, pathway d, involves nucleophilic addition at the β-lactone carbonyl leading to cleavage of both rings to initially yield a γ-hydroxy-β-ketoacid derivative **16**. The reactivity of these systems has been explored, and the findings to date indicate that pathways a and d predominate; however, some unexpected pathways were also uncovered.

SCHEME 3. Potential Modes of Nucleophilic Addition to Spiroepoxy-β-lactones 12



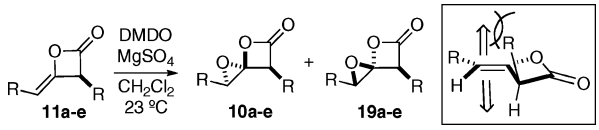
SCHEME 4. Epoxidation of Ketene Homodimers 11 and Possible In Situ Reduction of Derived Oxocarbenium 17



Epoxidation of Homoketene Dimers: Synthesis of Unexpectedly Stable Spiroepoxy-β-lactones. To access the proposed spiroepoxy-β-lactones, we set out to develop appropriate epoxidation conditions for ketene dimers that would leave the β-lactone nucleus intact (Scheme 4). At the outset, the stability of the desired spiroepoxy-β-lactones **10** was unknown and we anticipated that in situ reduction to give β-lactone **18** might be necessary if perhaps oxocarbenium intermediate **17** formed spontaneously. On the basis of ring strain considerations,[11] we expected formation of the β-lactone oxocarbenium **17** rather than the epoxide-containing oxocarbenium derived from ring opening of the β-lactone (pathway c, Scheme 3). This mode of reactivity would enable the desired C−O reductive cleavage to give the desired *anti*-γ-hydroxy-β-lactone **18** if successful.

(5) Duffy, R. J.; Morris, K. A.; Romo, D. *Tetrahedron* **2009**, in press.
(6) (a) Takada, N.; Sato, H.; Suenaga, K.; Arimoto, H.; Yamada, K.; Ueda, K.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 6309. (b) Kigoshi, H.; Hayakawa, I. *Chem. Rec.* **2007**, *7*, 254.
(7) Mitchell, T. A.; Romo, D. *J. Org. Chem.* **2007**, *72*, 9053.
(8) Known, direct methods for β-lactone synthesis from chiral α-oxy aldehydes are either unsuccessful or provide only *syn* selectivity (see ref 2).
(9) (a) Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308. (b) Calter, M. A.; Guo, X.; Liao, W. *Org. Lett.* **2001**, *3*, 1499. (c) Calter, M. A.; Liao, W. *J. Am. Chem. Soc.* **2002**, *124*, 13127. (d) For a review describing use of ketenes in asymmetric synthesis, see ref 2d.
(10) Duffy, R. J.; Morris, K. A.; Romo, D. *J. Am. Chem. Soc.* **2005**, *127*, 16754.
(11) The ring strain of epoxides (25.7 kcal/mol) is greater than that of β-lactones (22.6 kcal/mol).

TABLE 1. Diastereomeric Spiroepoxy-β-lactones 10/19 Obtained via Facially Selective Epoxidation of Ketene Dimers 11[a]



entry	R	compound	dr[b] (**10**:**19**)	% yield[c]
1	*n*-Bu	**10a**	14:1	80
2	$CyCH_2$	**10b**	10:1	76
3	$PhCH_2$	**10c**	24:1	57
4	$TIPSO(CH_2)_4$	**10d**	17:1	40
5	$N_3(CH_2)_4$	**10e**	16:1	61

[a] Epoxidations were performed at ~0.1 M concentration using isolated, purified ketene dimers **11a**−**e**. [b] Ratios determined by analysis of crude reaction mixtures by ^{1}H NMR (500 MHz). [c] Refers to isolated, purified (SiO_2) yields.

Previously, we reported that ketene homodimers **11**, including the optically active series available by the method of Calter,[12] were stable to silica gel chromatography,[9,13] and we employed these methods to access both racemic and optically active ketene dimers utilized in this study. Our initial epoxidation studies involved the use of *m*-CPBA, which gave multiple products even under buffered conditions with added $NaHCO_3$ and pointed to the likely sensitive nature of the targeted spiroepoxy-β-lactones. These results led us to consider a mild, non-nucleophilic, neutral oxidant such as dimethyldioxirane.[14] Exposure of ketene dimer **11** to excess freshly prepared DMDO at low temperatures (−78 °C) gave no reaction. However, exposure of dimer **11** to DMDO at ambient temperature (23 °C) for 5 h led to the production of a single product whose spectral characteristics supported the structure of spiroepoxy-β-lactone **10**. Surprisingly, these novel spirocyclic heterocycles could be isolated and purified by silica gel chromatography under standard conditions. However, the shelf life of these strained intermediates is ~7 days when stored neat at low temperature (i.e., −20 °C). Therefore, it is best to purify and then directly utilize spiroepoxy-β-lactones in subsequent transformations within ~5 days. Storing frozen in benzene can extend the shelf life of the spiroepoxide. The scope of this epoxidation was explored with several other homoketene dimers leading to a number of spiroepoxy-β-lactones **10/19** in moderate to good yields (Table 1). Generally high diastereoselectivities were observed, as expected, due to steric interactions with the α-substituent leading to preferred approach of the oxidant to the opposite face of the alkene (see inset, Table 1). Enrichment of the major diastereomer to >19:1, as determined by ^{1}H NMR (500 MHz), was achieved upon silica gel purification. Phenyl groups, silylethers, and azides with appropriate chain lengths to avoid intramolecular interactions of functional groups and unfavorable inductive effects were tolerated but overall, reductions in yields were observed (Table 1, entries 3−5). Chain lengths <4 carbons led to diminished yields and multiple side products during the epoxidation step and also led to difficulties during ketene dimer substrate synthesis and purification as previously described.[13]

Structural Analysis of a Spiroepoxy-β-lactone by X-ray Analysis: Comparison to Related Small Heterocyclic Rings and Other Spirocyclic Hetero- and Carbocycles. The cyclohexyl-substituted spiroepoxy-β-lactone **10b** could be recrystallized from pentane (slow evaporation at −20 °C) to provide crystals suitable for X-ray analysis (Figure 2). The

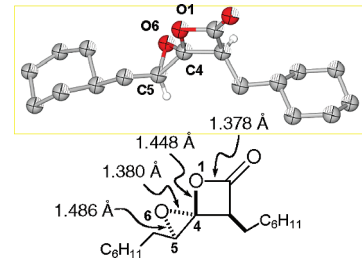


FIGURE 2. X-ray structure (ORTEP) of spiroepoxy-β-lactone **10b** showing selected bond lengths.

derived crystal structure revealed several interesting structural features of these novel spiro systems, and most intriguing was that both the epoxide C4−O6 and the β-lactone C4−O1 bonds were significantly shortened compared to average values for the parent systems (derived from a search of the Cambridge Structural Database) by Δ0.055[15] and Δ0.044 Å, respectively (Table 2).[16] As a direct consequence, the C5−O6 bond is slightly lengthened to 1.486 Å compared to the average bond length of 1.446 Å for β-lactones,[15] while the C4−C5 bond of the epoxide is significantly shortened to 1.380 Å from an average C−C bond length of 1.446 Å for epoxides. Finally, the C4−O1 bond is shortened to 1.448 Å from the more typical 1.492 Å of a β-lactone. These observations can be rationalized based on expected hybridization changes that occur in small rings leading to increased p-orbital character in order to relieve ring strain and result in concomitant increased σ-orbital character in exocyclic bonds leading to shorter bonds. Alternatively, bond shortening could be rationalized by n→σ* overlap of an epoxide (O5) and a β-lactone (O1) lone pair with the σ*-orbitals of the C4−O1 and C4−O6 bond of the epoxide and β-lactone, respectively, indicative of a double anomeric effect. Calculations performed on spiroepoxyoxetanes, spirocyclopropyl oxetanes, and spiroepoxycyclobutanes suggest that, while hybridization effects play a role in bond shortening (Table 2), this is insufficient to explain the degree of bond shortening observed, thus pointing to a greater role of anomeric effects.[17] The observed anomeric effects may be more pronounced in these systems due to the rigidity of the spirocycle and may contribute to the unexpected stability of these systems. The C5−O6 bond of the epoxide is also lengthened, predictive of the greater reactivity of this bond (vide infra).

Reactivity of Spiroepoxy-β-lactones toward Nucleophiles. When spiroepoxy-β-lactone **10b** was exposed to nucleophilic reagents such as tetrabutylammonium chloride (TBACl), the major isolated product was α-chloroketone **20** in low yield (Scheme 5). Similarly, when the same spiro compound was exposed to sodium azide in a THF/H_2O mixture, α-azidoketone **21** was obtained in low yield. Highly polar products and multiple other unidentifiable byproducts, some of which appeared polymeric based on solubility characteristics, accompanied these

(12) Calter, M. A.; Orr, R. K.; Song, W. *Org. Lett.* **2003**, *5*, 4745.

(13) Purohit, V. C.; Richardson, R. D.; Smith, J. W.; Romo, D. *J. Org. Chem.* **2006**, *71*, 4549.

(14) For preparation of DMDO, see: (a) Murray, R. W.; Singh, M. *Organic Syntheses*; Wiley & Sons: New York, 1998; Collect. Vol. IX, p 288. (b) See ref 10 for further details.

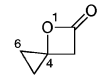
(15) Average O1−C4 bond length for 40 β-lactones found in the Cambridge Structural Database.

(16) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1.

(17) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, 1st ed.; Pergamon Press: New York, 1983.

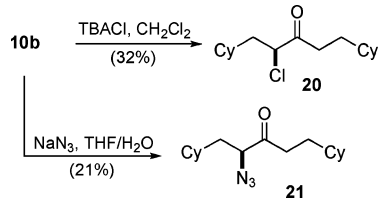
(18) Lotesta, S. D.; Kiren, S.; Sauers, R. R.; Williams, L. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7108.

TABLE 2. Comparison of Calculated[a] and Experimentally Determined C−O Bond Lengths (Å) of β-Lactones, Epoxides, Oxetanes, and Spiro Systems

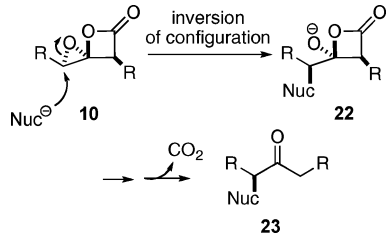
ring system bond[b]								
X1-C4	1.448[c]	1.492[d]	-	1.452[d]	1.393[e]	1.415	1.458	1.531
X1-C2	1.378[c]	1.377	-	1.452[d]	-	-	1.379	-
C4-X6	1.380[c]	-	1.446[d]		1.393[e]	1.399	1.487	1.423
C4-C5	1.437[c]	-	1.466[d]		1.446[e]	1.461	1.487	1.467
C5-X6	1.486[c]	-	-		1.517[e]	1.464	1.527	1.445

[a] All bond lengths were calculated (B3LYP/6-31+G**+zpe) unless noted otherwise. [b] X = O or C. [c] From X-ray structure of spiroepoxy-β-lactone **10b** reported herein. [d] Average X-ray structure derived C−O bond lengths for β-lactones[15] and epoxides.[16] [e] From X-ray structure of spirodiepoxide.[18]

SCHEME 5. Addition of Soft Nucleophiles to Spiroepoxy-β-lactone 10b (pathway a)



SCHEME 6. Proposed Mechanism for Addition of Soft Nucleophiles to Spiroepoxy-β-lactones

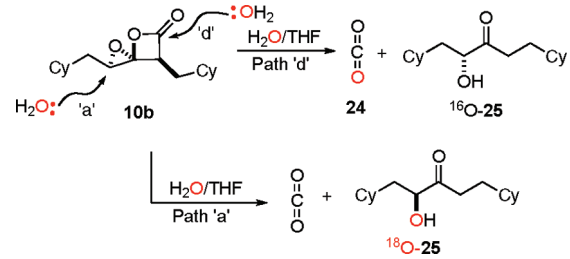


addition products. A plausible mechanism for these nucleophilic additions involves attack with inversion of configuration at the distal epoxide C−O bond to deliver hemiketal **22** which undergoes subsequent decarboxylation providing ketone **20** or **21** (Schemes 5 and 6).

Hydrolysis of Spiroepoxy-β-lactone 10b: Verification of the Site of Attack with $H_2{}^{18}O$. The reaction of spiroepoxy-β-lactone **10b** with water at 23 °C slowly (19 h, pH 6.5) delivered α-hydroxy ketone **25** in 53% yield. There are two plausible mechanisms that would deliver this hydrolysis product, and the operative pathway was distinguished by performing the hydrolysis with isotopically enriched water containing 90% ^{18}O. The two possible mechanisms are (1) water addition at the distal epoxide C−O bond (pathway a) as observed with chloride and azide ions (see Scheme 5), leading to α-hydroxy ketone ^{18}O-**25** incorporating the ^{18}O label, or (2) water addition to the β-lactone carbonyl (pathway d) leading to eventual loss of the ^{18}O label in the form of labeled carbon dioxide **24** via decarboxylation to provide unlabeled α-hydroxy ketone ^{16}O-**25** (Scheme 7).

The outcome of the heavy water hydrolysis experiment was analyzed by both electrospray ionization MS and ^{13}C NMR. When the hydrolysis was performed with $H_2{}^{18}O$, MS analysis

SCHEME 7. Possible Pathways for Hydrolysis of Spiroepoxy-β-lactone 10b



of the isolated α-hydroxy ketone product **25** clearly showed an increase of 2 mass units compared to the control experiment with $H_2{}^{16}O$, suggestive of heavy water incorporation by way of cleavage of the distal epoxide C5−O6 (pathway a) rather than initial β-lactone cleavage (pathway d). However, ^{13}C NMR analysis was also used to confirm the labeled position since it is well-known that water exchanges with ketones by both acid and base catalysis,[19,20] which could also account for the increased molecular weight. ^{13}C NMR studies would reveal the actual site of ^{18}O incorporation due to the known slight shielding effect on a ^{13}C atom by an attached ^{18}O isotope versus ^{16}O,[21] and this would unequivocally distinguish incorporation of ^{18}O at the carbinol carbon (C5) by addition of $H_2{}^{18}O$ to the distal epoxide carbon or incorporation of ^{18}O into the carbonyl carbon (C2) by simple exchange. The results of the ^{13}C NMR analysis of the heavy water hydrolysis are shown in Figure 3a and clearly show an upfield shift ($\Delta\delta$ 0.014, δ 74.443 ($^{13}C-^{18}O$) vs δ 74.457 ($^{13}C-^{16}O$)) for the carbinol ^{13}C (C5) with a small downfield shoulder corresponding to residual ^{16}O incorporation. That the latter shoulder corresponds to the $^{16}O-^{13}C$ signal was confirmed by performing the hydrolysis reaction with a ~1:1 mixture of $H_2{}^{18}O/H_2{}^{16}O$ (Figure 3b). On the other hand, expansion of the carbonyl region did not show chemical shift differences expected for incorporation of ^{18}O at the carbonyl carbon again in comparison to the reaction with a ~1:1 mixture of $H_2{}^{18}O/H_2{}^{16}O$. Thus, ring cleavage of the spiroepoxy-β-lactone **10b** occurs via cleavage of the distal C5−O6 epoxide bond rather than via β-lactone cleavage, and this is consistent with expected reactivity

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(21) Diakur, J.; Nakashima, T. T.; Vederas, J. C. *Can. J. Chem.* **1980**, *58*, 1311.

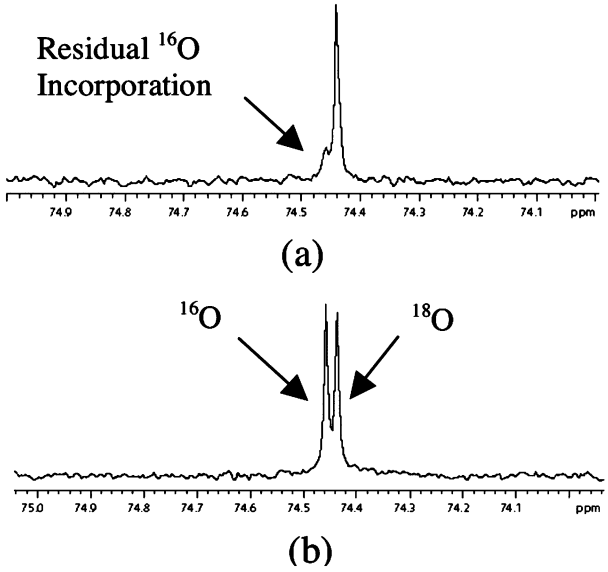
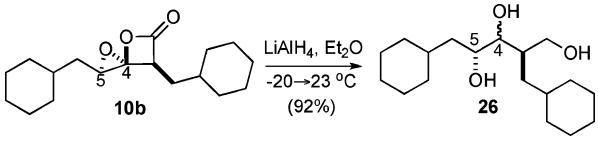


FIGURE 3. ^{13}C NMR spectral expansion of the carbinol region of α-hydroxy ketone **25** following (a) hydrolysis of spiroepoxy-β-lactone **10b** with $H_2{}^{18}O$ (90% ^{18}O atom enriched); (b) with a ~1:1 mixture of $H_2{}^{18}O/H_2{}^{16}O$ (δ 74.443 ($^{13}C-^{18}O$) vs δ 74.457 ($^{13}C-^{16}O$)).

SCHEME 8. Metal Hydride Reduction of Spiroepoxy-β-lactone 10b

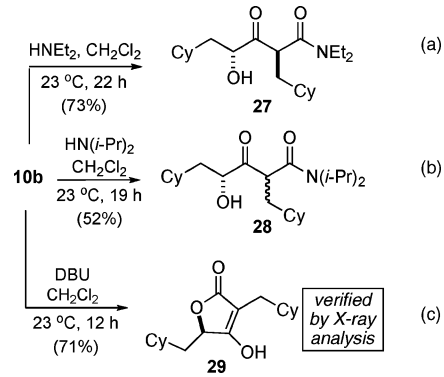


based on the relatively elongated C5−O6 bond (1.486 Å) determined by X-ray analysis. Interestingly, in hydrolysis reactions of β-propiolactone, a bifurcation of reactivity between the β-C−O bond and acyl C−O bond is observed.[22]

Metal Hydride Reductions of Spiroepoxy-β-lactones. Reduction of the spiroepoxy-β-lactone **10b** with lithium aluminum hydride gave the corresponding triol **26** in excellent yield and as a ~2:1 mixture of diastereomers, a result of initial reduction of the β-lactone carbonyl carbon (Scheme 8). Reductive C−O cleavage was not observed at C4 or C5, which is consistent with known reductions of β-lactones with metal hydrides leading to exclusive acyl versus alkyl C−O cleavage.[23] The diastereoselectivity leading to triol **26** during reduction of the presumed α-hydroxy ketone intermediate is consistent with previous reports of reduction of α-hydroxy ketones with $LiAlH_4$.[24] Other reducing agents were studied but typically led to mixtures of products. Treatment with DIBAL-H from −78 → 0 °C afforded multiple products with traces of triol **26**, and reaction with $NaBH_4$ in acetonitrile or tetrahydrofuran at 0 °C led to complex mixtures.

Reaction of Spiroepoxy-β-lactones with Amine Nucleophiles: Divergent Pathways Leading to Acyclic Amides or Tetronic Acids. Three different products were obtained when spiroepoxy-β-lactone **10b** was exposed to amines with differing nucleophilicity and basicity. Reaction of a single diastereomer of the spiroepoxy-β-lactone **10b** with diethylamine resulted in

SCHEME 9. Reaction of Spiroepoxy-β-lactone with Various Amines

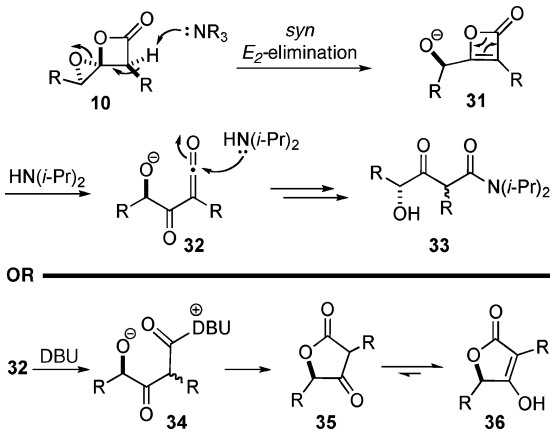


a single diastereomer of β-ketoamide **27** that presumably arises from simple nucleophilic addition to the β-lactone carbonyl (Scheme 9a). The stereochemical fidelity of α-monosubstituted-β-keto tertiary amides is due to $A^{1,3}$ strain, which severely retards the rate of epimerization,[25] and this phenomenon was employed by Calter to access optically active β-ketoamides from optically active ketene dimers.[12] Thus, the isolation of a single diastereomer of β-ketoamide **27** is expected for simple acyl substitution with $HNEt_2$ attack at the β-lactone carbonyl carbon. However, when spiroepoxy-β-lactone **10b** was exposed to the more sterically hindered amine diisopropylamine, this led to a ~1:1 mixture of diastereomeric ketoamides **28** (Scheme 9b). This result suggested that reaction with the more hindered $HN(i\text{-}Pr)_2$ must proceed through an intermediate in which the α-stereocenter is lost prior to or as a result of nucleophilic addition of the amine due to the aforementioned known stereochemical stability of tertiary amides. Exposure of diastereomerically pure diethyl amide **27** to deuterated diisopropylamine for 4 h under identical reaction conditions did not lead to epimerization nor deuterium incorporation, which suggests that epimerization of diisopropylamide **28** does not occur following amide formation but must occur at an earlier stage. Interestingly, when spiroepoxy-β-lactone **10b** was exposed to the nucleophilic, tertiary amine, diaza[5.4.0]bicycloundecane (DBU), the tetronic acid derivative **29** was obtained as the sole product and its structure was confirmed by X-ray analysis[38] (Scheme 9c). In addition, the use of *N*,*O*-dimethylhydroxylamine was studied in attempts to form the corresponding diastereomerically pure β-keto Weinreb amide cf. **27**; however, this also gave tetronic acid **29**. The use of 2-hydroxypyridine to facilitate amidation with this latter amine as employed by Calter with ketene dimers[9] also gave only tetronic acid (51%).

These disparate results with hindered amines suggest competitive pathways leading to the observed products. One possible mechanism leading to amide **33** involves an E_2 elimination of spiroepoxy-β-lactone **10**, leading to direct cleavage of the epoxide to provide the strained unsaturated β-lactone **31** (Scheme 10). The highly strained intermediate **31** then undergoes a retro-electrocyclization to form ketoketene intermediate **32**, which rationalizes the loss of stereochemistry at the α-stereocenter observed during generation of β-tertiary amide **33** upon addition of $HN(i\text{-}Pr)_2$. The use of DBU as base also raises the possibility of formation of acyl ammonium intermediate **34** from the ketoketene intermediate **32**, which can then cyclize and tautomerize to the tetronic acid **36**.

(22) Olson, A. R.; Youle, P. V. *J. Am. Chem. Soc.* **1951**, *73*, 2468.
(23) (a) Wynberg, H.; Staring, E. G. J. *J. Chem. Soc., Chem. Commun.* **1984**, 1181. (b) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6358.
(24) Fujisawa, T.; Kojima, E.; Itoh, T.; Sato, T. *Tetrahedron Lett.* **1985**, *26*, 6089.
(25) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154.

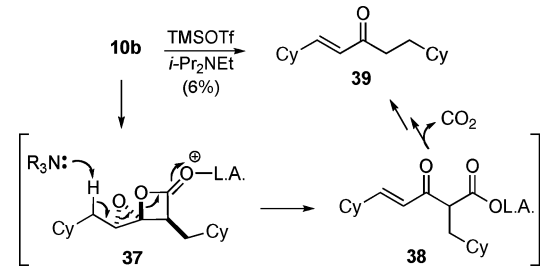
SCHEME 10. Proposed Mechanistic Pathways Leading to Disparate Products from Spiroepoxy-β-lactone 10 Induced by Amines



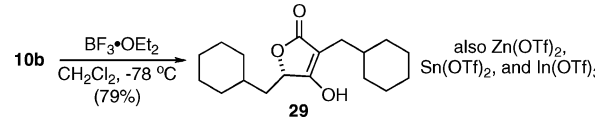
In order to provide support for the intermediacy of a ketoketene **32**, reactions leading to tetronic acid **36** were monitored by in situ infrared spectroscopy in attempts to detect the diagnostic ketene absorption at ~2100 cm^{-1}. Ketene was not detected when this reaction was run at either ambient or low temperature (−78 °C); however, this does not exclude the possibility of a short-lived ketene intermediate. An alternative method for trapping ketene intermediates was also studied involving performing the reactions in the presence of TEMPO, a reagent known to react rapidly with ketenes to provide esters containing two TEMPO molecules.[26] To compete with the intramolecular cyclization leading to tetronic acid, a large excess of TEMPO was employed. Several attempts led only to the expected rearrangement to the tetronic acid along with small quantities of the hydrolysis product, α-hydroxy ketone **25**, likely due to adventitious water.

Reactions of Spiroepoxy-β-lactone 10b with Lewis Acids. A number of conditions were studied to induce reductive cleavage via pathway b (see Scheme 3) to provide access to the desired *anti*-γ-hydroxy-*cis*-β-lactone **9** (Scheme 2). Lewis and protic acids or Lewis acid/base combinations including $ZnCl_2$, $BF_3 \cdot OEt_2$, $SmCl_3$, $LiClO_4$, TESOTf/2,6-lutidine, TIPSOTf/2,6-lutidine, $TiCl_4$/2,6-lutidine, $AlCl_3$, Amberlyst 15, silica gel, and TFA were studied in combination with excess Et_3SiH and gave either no reaction or complex mixtures of products. The only isolable product from these studies was the α,β-unsaturated ketone **39** albeit in very low yield when spiroepoxy-β-lactone **10b** was treated with trimethylsilyl triflate (TMSOTf) and Hunig's base (Scheme 11), and it formed in the presence or absence of a reductant such as Et_3SiH. This represents an alternative reaction manifold from pathways a−d (Scheme 3); however, such an E_2 elimination is known for epoxides.[27] A proposed mechanism for this process involves activation of the β-lactone carbonyl by Lewis acid complexation and E_2 elimination by the hindered amine leading to sequential opening of both rings to yield α,β-unsaturated ketone **39** following decarboxylation. On the other hand, treatment of spiroepoxylactone **10b** with TMSOTf in the presence of the more hindered base, 2,6-lutidine, gave only tetronic acid with no enone detected as might be expected for a hindered base unable to promote an E_2 elimination that solely acts as a proton scavenger.

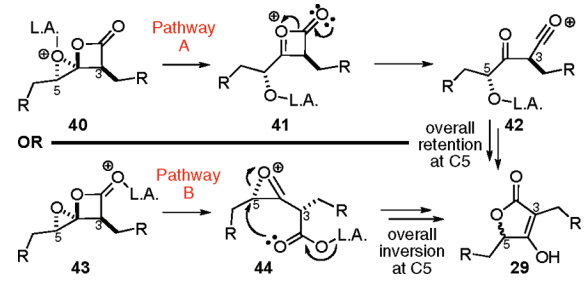
SCHEME 11. Elimination of Spiroepoxy-β-lactone 10b Leading to Enone 39



SCHEME 12. Rearrangement of Spiroepoxy-β-lactone 10b with Lewis Acids to Tetronic Acid 29



SCHEME 13. Possible Lewis Acid Mediated Rearrangement Pathways for Spiroepoxy-β-lactones



We also studied addition of sulfur nucleophiles, which might lead to a *trans*-ketalization of the ketal center of spiroepoxy-β-lactones under the influence of Lewis acids. When spiroepoxy-β-lactone **10b** was treated with benzyl thiol at low temperature (−78 → −20 °C) in CH_2Cl_2, no reaction was observed even after warming to 23 °C for extended periods. However, treatment with benzyl thiol and $BF_3 \cdot OEt_2$ at −78 °C led to rapid conversion to the previously characterized tetronic acid **29** (Scheme 12). A control experiment with only Lewis acid also gave tetronic acid **29** in good yield (79%), indicating that benzyl thiol was not involved in this process. Milder Lewis acids including $Zn(OTf)_2$, $Sn(OTf)_2$, and $In(OTf)_3$ were also studied and also led to tetronic acid but in reduced yields compared to $BF_3 \cdot OEt_2$. Furthermore, addition of Normant reagents,[28] which were expected to add to C5, instead also led to tetronic acids, consistent with the mounting results that these spiroheterocycles have a disposition to rearrange to tetronic acids under a variety of conditions (vide infra).

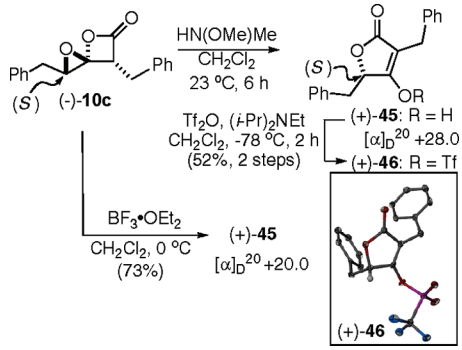
Two mechanisms leading to tetronic acid from spiroepoxy-β-lactones under Lewis acidic conditions can be envisioned (Scheme 13). Initial coordination of the Lewis acid to the epoxide oxygen could lead to complex **40** and subsequent formation of oxycarbenium ion **41** following epoxide cleavage (pathway A). Ring cleavage to the acylium ion **42** could then lead to cyclization of the pendant alkoxide to the acylium carbon leading to tetronic acid **29** with retention of configuration at

(26) Allen, A. D.; Cheng, B.; Fenwick, M. H.; Givehchi, B.; Henry-Riyad, H.; Nikolaev, V. A.; Shikhova, E. A.; Tahmassebi, D.; Tidwell, T. T.; Wang, S. *J. Org. Chem.* **2001**, *66*, 2611.

(27) For a related process leading to allylic alcohols from epoxides, see: Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738.

(28) (a) Normant, J. F.; Alexakis, A.; Cahiez, G. *Tetrahedron Lett.* **1980**, *21*, 935. (b) Zhang, W.; Matla, A. S.; Romo, D. *Org. Lett.* **2007**, *9*, 2111.

SCHEME 14. Comparison of Lewis Acid and Base-Mediated Rearrangement of Optically Active Spiroepoxy-β-lactone (−)-10c (inset, ORTEP of triflate (+)-46)

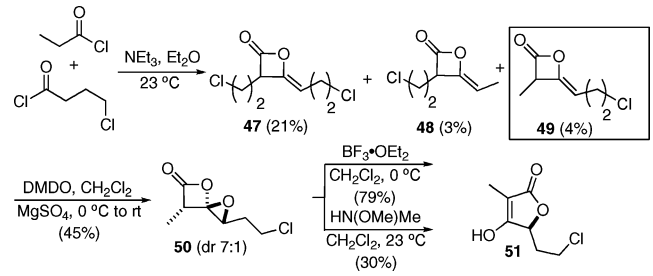


C5. Alternatively, Lewis acid coordination to the β-lactone carbonyl oxygen would give complex **43**, and ring opening would lead to carboxylate **44** that could attack the distal epoxide C−O bond leading to observed tetronic acid **29** with inversion of configuration at C5 (pathway B).

The two mechanistic scenarios in Scheme 13 were distinguished by analysis of the absolute configuration of the tetronic acids derived from Lewis acid and base-mediated rearrangement of the optically active spiroepoxy β-lactone (−)-**10c**, prepared in the context of maculalactone A synthesis (vide infra). Epoxidation of the known optically ketene dimer derived from hydrocinnamoyl chloride in the presence of *O*-TMS-quinine according to the literature procedure[9] gave the optically active spiroepoxy-β-lactone (−)-**10c**. The absolute configuration of this intermediate at C5 is assigned as *S* based on the precedents of Calter using *O*-TMS-quinine in ketene dimerizations,[29] the (*Z*)-olefin geometry,[30] and the established facial selectivity during epoxidation of ketene dimer **11b** (see Figure 2). Following rearrangement with *N*-methoxy-*N*-methylamine, tetronic acid (+)-**45** was also found to possess the *S* absolute configuration at C5 based on single-crystal X-ray analysis of the derived crystalline triflate (+)-**46** (Scheme 14), and further confirmation of retention of configuration at C5 came from conversion to (+)-maculalactone (vide infra). Rearrangement with $BF_3 \cdot OEt_2$ also afforded the tetronic acid (+)-**45** with overall retention at C5 via a putative acylium ion (pathway A, Scheme 13). In addition, the tetronic acid **45** prepared under Lewis base (e.g., HNMe(OMe)) or Lewis acid catalysis gave similar optical rotations, $[\alpha]^{20}_D$ +20.0 (c = 1.00, CH_3OH) and $[\alpha]^{20}_D$ +28.0 (c = 1.00, CH_3OH), respectively, providing support for mechanistic pathways under both reaction conditions involving retention of configuration at C5 (see Scheme 13, pathway A).

Spiroepoxy-β-lactone Derived from Heteroketene Dimer. To further expand the scope of accessible tetronic acids, functionalized heteroketene dimer **49** was prepared by dimerization of propionyl chloride and 4-chlorobutyryl chloride leading to the expected mixture of homo- and heteroketene dimers in a ratio of ∼7:1:1 (**47/48/49**), which were readily separated by flash chromatography (Scheme 15). The low yields (∼30%) appear to be due to competitive polymerization or alternative reaction

SCHEME 15. Use of a Heteroketene Dimer Leading to a Chloro-Substituted Tetronic Acid 51



manifolds during the dimerization process due to the resident alkyl chloride leading to intractable polar byproducts. Epoxidation of heteroketene dimer **49** by the usual procedure afforded the spiroepoxy-β-lactone **50** with good diastereoselectivity (7:1 mixture). Spiroepoxy-β-lactone **50** was subjected to *N*,*O*-dimethylhydroxylamine to give tetronic acid **51** in low yield (30%); however, Lewis acid catalysis proceeded more efficiently to provide tetronic acid **51** in 79% yield. Tetronic acid **51** possesses an additional functional handle (i.e., an alkyl chloride) for further elaboration. However, further efforts to optimize ketene dimerizations[31] are clearly warranted to improve the practicality of this process despite the ready availability and low cost of such simple acid chlorides.

Total Synthesis of (+)-Maculalactone A via Rearrangement of a Spiroepoxy-β-lactone to a Tetronic Acid. The facile conversion of spiroepoxy-β-lactones to tetronic acids under a variety of conditions led us to explore the application of these spiroheterocycles to tetronic acids and derivable butenolides which are common motifs found in drug candidates[32] and bioactive natural products.[33] One such example is maculalactone A, which possesses an interesting tribenzyl butenolide structure. The butenolide-containing maculalactones were isolated from the marine cyanobacterium *Kyrtuthrix maculans*, and maculalactone A (**52**) is the simplest member of this family with greater complexity found in more oxidized (**53**−**55**) and cyclized versions such as maculalactone K (**56**) (Figure 4).[34] Maculalactone A (**52**) has been synthesized in both racemic and enantioselective manner in addition to maculalactones B and C;[35,36] however, only maculalactone A (**52**) was found to possess biological activity, namely, inhibition of the growth of marine bivalves on rock surfaces (LD_{50} = 4.2 μg mL^{-1}), where *Kyrtuthrix maculans* grows, thus suggesting potential use as an antifouling agent.[37]

Our retrosynthesis of (+)-maculalactone A (**52**) began with disconnection of the C4 benzyl group, which we envisioned

(29) The absolute configuration of the dimer of methylketene prepared using quinidine was determined by conversion to a β-hydroxy ketone also derived from (*S*)-(+)-3-hydroxy-2-methyl propionate. See: Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006.

(30) The *Z* geometry of the ketene dimer was established indirectly during subsequent aldol reactions of the derived (*Z*)-lithium enolates. See: Calter, M. A.; Liao, W.; Struss, J. A. *J. Org. Chem.* **2001**, *66*, 7500, and ref 9c.

(31) For a recent report of homoketene dimerization promoted by phosphines and a lead reference to ketene dimerizations, see: Ibrahim, A. A.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2009**, *74*, 1777.

(32) (a) Sodeoka, M.; Sampe, R.; Kojima, S.; Baba, Y.; Usui, T.; Ueda, K.; Osada, H. *J. Med. Chem.* **2001**, *4*, 3216. (b) Mansour, T. S.; Caufield, C. E.; Rasmussen, B.; Chopra, R.; Krishnamurthy, G.; Morris, K. M.; Svenson, K.; Bard, J.; Smeltzer, C.; Naughton, S.; Antane, S.; Yang, Y.; Severin, A.; Quagliato, D.; Peterson, P. J.; Singh, G. *ChemMedChem* **2007**, *2*, 1414. (c) Peukert, S.; Sun, Y.; Zhang, R.; Hurley, B.; Sabio, M.; Shen, X.; Gray, C.; Dzink-Fox, J.; Tao, J.; Cebula, R.; Wattanasin, S. *Bioorg. Med. Chem.* **2008**, *18*, 1840.

(33) (a) Zografos, A. L.; Georgiadis, D. *Synthesis* **2006**, 3157. (b) Schobert, R. *Naturwissenschaften* **2006**, *94*, 1. (c) Schobert, R.; Schlenk, A. *Bioorg. Med. Chem.* **2008**, *16*, 4203.

(34) (a) Lee, S.-C.; Williams, G. A.; Brown, G. D. *J. Nat. Prod.* **1998**, *61*, 29. (b) Lee, S.-C.; Williams, G. A.; Brown, G. D. *Phytochemistry* **1999**, *52*, 537. (c) Wong, H.-F.; Williams, G. A.; Brown, G. D. *Phytochemistry* **2002**, *60*, 425. (d) Brown, G. D.; Wong, H. F.; Hutchinson, N.; Lee, S. C.; Chan, B. K. K.; Williams, G. A. *Phytochem. Rev.* **2005**, *3*, 381.

(35) Brown, G. D.; Wong, H.-F. *Tetrahedron* **2004**, *60*, 5439.

(36) Kar, A.; Gogoi, S.; Argade, N. P. *Tetrahedron* **2005**, *61*, 5297.

(37) Fusetani, N. *Nat. Prod. Rep.* **2004**, *21*, 94, and references cited therein.

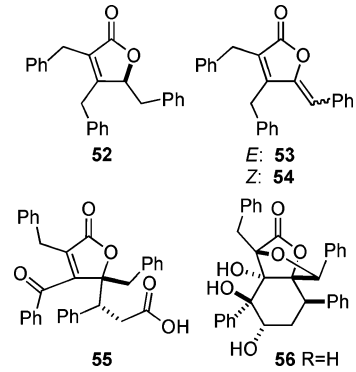
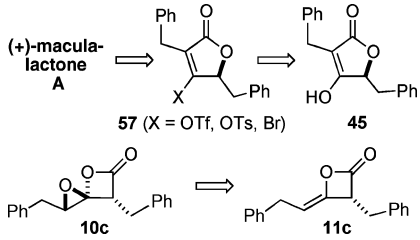
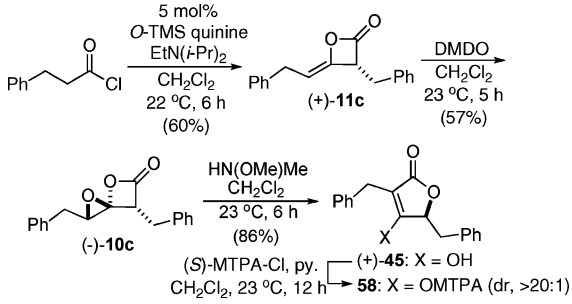


FIGURE 4. Structures of representative maculalactones.

SCHEME 16. Retrosynthesis of Maculalactone A via Spiroepoxy-β-lactone 10c



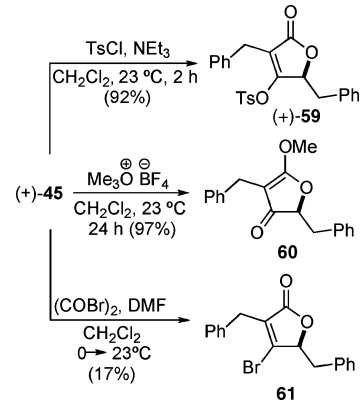
SCHEME 17. Asymmetric Synthesis of Tetronic Acid 45 via Spiroepoxy-β-lactone 10c



could be appended by a transition metal coupling or by nucleophilic organometallic reagents with an appropriate activated tetronic acid derivative **57** (Scheme 16). However, a mild procedure for addition of the final benzyl group which maintains the integrity of the potentially stereochemically labile tetronic acid derivative **57** would be required. The tetronic acid would be prepared via the described facile rearrangement of a dibenzyl spiroepoxy-β-lactone **10c**, which in turn could be derived from a facially selective epoxidation of optically active ketene dimer **11c**. The proposed synthesis would also enable us to further define reaction conditions that maintain stereochemical fidelity during conversion of the optically active diphenyl ketene dimer **11c** to tetronic acid **45**.

As described briefly above, the required optically active ketene dimer **11c** was prepared from hydrocinnamoyl chloride employing *O*-TMS-quinine (*O*-TMS-QN) as nucleophilic promoter (Scheme 17).[12] Purification of the ketene dimer was performed, as previously described,[13] and subsequent epoxidation gave spiroepoxy-β-lactone **10c** (dr, 24:1, crude reaction mixture), which following column chromatography could be obtained in 57% yield as a single diastereomer. Our previous efforts to prepare a Weinreb amide from a spiroepoxy-β-lactone using *N*,*O*-dimethylhydroxylamine (vide infra) led us to utilize this weak base ($pK_a = 4.75$, H_2O) rather than DBU to promote

SCHEME 18. Tetronic Acid Derivatives 59−61 Prepared from Tetronic Acid (+)-45



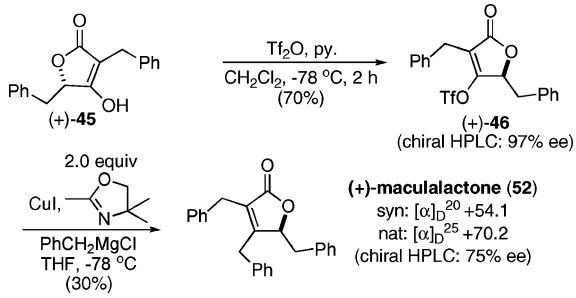
the rearrangement to the optically active tetronic acid (+)-**45** in order to minimize the potential for base-induced epimerization via furan formation following rearrangement. This provided the tetronic acid **45** in 86% yield following purification by recrystallization. The enantiomeric purity of this intermediate was determined by conversion to Mosher ester **58** and comparison to the racemic series by ^{19}F NMR, which indicated that the tetronic acid (+)-**45** was obtained in high optical purity (dr, >20:1).[38]

A number of derivatives of tetronic acid **45** were prepared and studied as possible substrates for installation of the required benzyl group at C4 (Scheme 18). Tosylation gave the tetronic acid derivative **59**, while use of Meerwein's salt gave enol ether **60**[39] in high yield (97%). The latter substrate was prepared to study direct nucleophilic addition to the ketone and subsequent elimination to provide the desired butenolide. However, treatment of these substrates with a variety of benzyl metal reagents, including lithium, magnesium, and cerium reagents led to tetronic acid likely due to competing α-deprotonation to the aromatic furan intermediate and hydrolysis during workup. Tetronic acid **45** was also converted to the corresponding vinyl bromide **61** in low yield (17%) upon treatment with oxalyl bromide.[40] However, no reaction occurred when either cuprate or boron reagents were utilized with this substrate.

Ultimately, the previously described triflate (+)-**46** (see Scheme 14) proved to be a suitable substrate for coupling; however, several initial conditions studied proved unsuccessful. Hypervalent tin reagents, which have been successfully employed in sterically hindered settings, only resulted in hydrolysis of the triflate **46**, as described previously.[41] Further coupling attempts with copper or iron catalysts also failed to provide the desired product. However, Negishi cross-coupling finally gave the first promising results by furnishing trace amounts of the natural product. An alternative benzyl cuprate addition protocol using an oxazoline ligand[42] provided (+)-maculalactone A (**52**) in 30% yield (Scheme 19).[43] The measured optical rotation of synthetic maculalactone A was lower than that of values reported for the natural product (synthetic: $[\alpha]^{20}_D$ +54.1 (c = 0.37,

(38) See Supporting Information for details including ^{19}F NMR spectra.
(39) Kapferer, T.; Brueckner, R.; Herzig, A.; Koenig, W. A. *Chem.—Eur. J.* **2005**, *11*, 2154.
(40) Le Vézouët, R.; White, A. J. P.; Burrows, J. N.; Barrett, A. G. M. *Tetrahedron* **2006**, *62*, 12252.
(41) Garcia Martinez, A.; Osio Barcina, J.; del Rosario Colorado Heras, M.; de Fresno Cerezo, A. *Organometallics* **2001**, *20*, 1020.
(42) Jalander, L.; Oksanen, L.; Rosling, A. *Acta Chem. Scand.* **1990**, *44*, 842.

SCHEME 19. Total Synthesis of (+)-Maculalactone (45)



CH_2Cl_2); natural: $[\alpha]^{25}_D$ +70.2 ($c = 0.37$, CH_2Cl_2).[44] However, the high enantiopurity of the initial dimerization and subsequent Mosher ester analysis of the tetronic acid intermediate **45** verified that the reduced enantiopurity of maculalactone was due to the triflation step when $(i\text{-Pr})_2$NEt was used (see Scheme 14). Epimerization could be avoided during triflation by use of pyridine as base to give triflate (+)-**46** in high optical purity (97% ee, chiral HPLC) and improved yield. However, epimerization during the final coupling step was not easily suppressed. Indeed, the enantiomeric excess of synthetic maculalactone was determined to be 75% ee by chiral HPLC, which is consistent with measured rotation values. Interestingly, (+)-maculalactone is isolated as a partially racemized natural product (85−95% ee), and Brown and co-workers rigorously determined that this was not due to the isolation procedure.[35]

Conclusions

Epoxidation of several functionalized ketene dimers leading to novel spiroepoxy-β-lactones, oxaspiro[2.3]hexan-5-ones, was accomplished by using the mild, neutral, and non-nucleophilic oxidizing agent DMDO in moderate to good yields. An X-ray crystal structure of a bis-cyclohexyl spiroepoxy-β-lactone revealed several interesting physical characteristics and suggested that a double anomeric effect may be operative, which may explain the unexpected stability of these spirocycles. In general, we found that cleavage of spiroepoxy-β-lactones proceeds via two principal pathways involving attack at the distal epoxide C−O bond and the β-lactone acyl C−O bond with no evidence to date for nucleophilic additions to the ketal carbon. Although the initial reaction manifold that was sought for spiroepoxy-β-lactones has remained elusive to date, we found a number of interesting reactions that reveal the unique reactivity of these novel spiroheterocycles. We demonstrated the utility of spiroepoxy-β-lactones as intermediates toward a number of functional arrays but most notably the propensity of these systems to rearrange to tetronic acids. The latter reaction was applied to the enantioselective total synthesis of (+)-maculalactone A, and this synthesis demonstrated the ability to maintain stereochemical integrity during this concise three-step sequence to a tetronic acid from an acid chloride; however, a final challenging coupling step led to erosion of enantiopurity of the final product. Given the demonstrated rich reactivity of these spiroheterocycles, further utilization of these novel intermediates will likely continue to expand in the future and even more so if practical methods for heteroketene dimer synthesis can be developed.

Experimental Section

(*R*,*Z*)-3-Benzyl-4-(2-phenylethylidene)oxetan-2-one (11c): To a solution of *O*-TMS-quinine (413 mg, 1.00 mmol) and diisopropylethylamine (3.30 mL, 20.0 mmol) in CH_2Cl_2 (185 mL, 0.1 M) at 22 °C was added hydrocinnamoyl chloride (3.52 g, 20.0 mmol) over 10 min via syringe. After stirring for 6 h, the light yellow solution was concentrated in vacuo to 35 mL (∼1/5 original volume), and 200 mL of pentane was added to precipitate the ammonium salts. After filtration through Whatmann filter paper, the solution was concentrated and purified by flash chromatography on SiO_2 elution with 1:50 EtOAc/hexanes, giving dimer **11c** (1.70 g, 60%) as a pale yellow oil: R_f 0.40 (1:9 EtOAc/hexanes); $[\alpha]^{19}_D$ +13.5 ($c = 1.2$, CH_2Cl_2); IR (thin film) ν_{max} 1859, 1723, 1353, 1217 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 7.15−7.11 (m, 2H), 7.07−6.97 (m, 6H), 6.88−6.86 (m, 2H), 4.36 (t, $J = 10$ Hz, 1H), 3.47 (t, $J = 5.0$ Hz, 1H), 3.24 (d, $J = 5.0$ Hz, 2H), 2.54 (dd, $J = 14.5$, 6.5 Hz, 1H), 2.45 (dd, $J = 14.5$, 7.5 Hz, 1H); ^{13}C NMR (125 MHz, benzene-d_6) δ 167.9, 145.8, 140.0, 136.5, 129.1 (2), 128.7 (2), 128.6 (2), 128.5, 128.2, 127.1, 126.4, 101.0, 54.8, 33.0, 31.0. LRMS calcd for $C_{18}H_{16}O_2Li$ [M + Li] 271, found 271. (Satisfactory HRMS could not be obtained for ketene dimers).

(2*S*,3*R*,6*R*)-2,6-Dibenzyl-1,4-dioxaspiro[2.3]hexan-5-one (10c): To a solution of (*R*,*Z*)-3-benzyl-4-(2-phenylethylidene)oxetan-2-one (112 mg, 0.424 mmol) in CH_2Cl_2 (30 mL) at 0 °C were added $MgSO_4$ (25.0 mg, 0.83 mmol, ∼0.50 equiv) and an acetone solution of DMDO[14] (14 mL, 0.076 M, ∼2.5 equiv) in one portion to give a pale yellow slurry which was warmed to 23 °C and stirred for 5 h. The reaction mixture was then filtered through a pad of $MgSO_4$, and the volatiles were removed by rotary evaporation. Purification by flash chromatography (1:5 Et_2O/hexanes) afforded spiroepoxy-β-lactone **10c** (68 mg, 57%, 24:1) as a clear oil: R_f 0.25 (1:5 Et_2O/hexanes); $[\alpha]^{23}_D$ −26.6 ($c = 1.0$, CH_2Cl_2); IR (thin film) ν_{max} 1854 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 7.09−7.00 (m, 3H), 6.99−6.89 (m, 5H), 6.71−6.67 (m, 2H), 3.46 (dd, $J = 6.5$, 8.0 Hz, 1H), 2.87 (app t, $J = 6.5$ Hz, 1H), 2.72 (dd, $J = 6.5$, 14.5 Hz, 1H), 2.55 (dd, $J = 6.5$, 14.5 Hz, 1H), 2.41 (dddd, $J = 6.5$, 8.0, 8.0, 15.5 Hz, 2H); ^{13}C NMR (125 MHz, benzene-d_6) δ 166.5, 136.1, 136.0, 129.1, 129.0(2), 128.8, 128.6(2), 127.2(2), 127.2(2), 90.8, 59.2, 54.3, 34.6, 31.0; HRMS (ESI) calcd for $C_{18}H_{16}O_3Li$ [M + Li] 287.1259, found 287.1262.

(*S*)-(+)-3,5-Dibenzyl-4-hydroxyfuran-2(5*H*)-one (45): To a solution of spiroepoxy-β-lactone **10c** (0.60 g, 2.1 mmol) in CH_2Cl_2 (40 mL, 0.05 M) was added *N*,*O*-dimethylhydroxylamine (0.23 mL, 3.1 mmol) and stirred at 23 °C for 6 h at which time the solution had copious amounts of white solid. The suspension was concentrated to give tetronic acid **45** as a white solid. Purification by recrystallization (1:10 EtOAc/Et_2O) provided tetronic acid **45** (86%, 0.49 g) as white crystals: mp (159−162 °C); R_f 0.10 (8:2 EtOAc/hexanes); $[\alpha]^{20}_D$ +20.0 ($c = 1.00$, CH_3OH); IR (thin film) ν_{max} 1715, 1650 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.25−7.20 (m, 5H), 7.13−7.05 (m, 3H), 6.76 (d, $J = 7.5$ Hz, 2H), 5.05 (t, $J = 4.3$ Hz, 1H), 3.43−3.28 (obs, 2H), 3.01 (dd, $J = 5.0$, 14.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.3, 175.8, 138.8, 134.8, 129.8(2), 128.1(2), 128.0(2), 127.7(2), 126.9, 125.6, 100.5, 78.3, 36.8, 26.3; HRMS (ESI) calcd for $C_{18}H_{16}O_3Na$ [M + Na] 303.0997, found 303.0989.

(*S*)-2,4-Dibenzyl-5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate (46): To a solution of tetronic acid **45** (31 mg, 0.11 mmol)

(43) Synthetic (+)-maculalactone was tested for its ability to inhibit the formation of bacterial biofilms. For Gram-positive bacteria, modest anti-biofilm activity was noted against vancomycin-resistant *Enterococcus facium* (VRE, ATCC #51559) and methicillin-resistant *Staphylococcus aureus* (MRSA, ATCC #BAA-44). A dose response study revealed IC_{50} values of 210 and 290 mM against VRE and MRSA, respectively. Growth curves of each bacterial strain grown in the presence or absence of (+)-maculalactone were identical, thus indicating that activity was driven by a non-microbicidal mechanism. Maculalactone was also screened for its ability to inhibit biofilm development of two Gram-negative strains of bacteria, *Pseudomonas aeruginosa* (PAO1) and multidrug-resistant *Acinetobacter baumannii* (ATCC #BAA-1605). However, no anti-biofilm activity was noted.

(44) Tsui, W.-Y.; Williams, G. A.; Brown, G. D. *Phytochemistry* **1996**, *43*, 1083.

in CH_2Cl_2 (1.1 mL, 0.10 M) were added pyridine (0.13 mL, 0.12 mmol) and Tf_2O (0.19 mL, 0.11 mmol) at −78 °C. After 2 h of stirring, the reaction was quenched at −78 °C with pH 7 buffer and extracted with CH_2Cl_2 (3 × 5 mL). The solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (3:10 Et_2O/hexanes) to give triflate **46** (30.0 mg, 70%) as a white solid: mp (64.2−67.7 °C); R_f 0.50 (3:7 Et_2O/hexanes); IR (thin film) ν_{max} 1779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26−7.13 (m, 8H), 6.76−6.74 (m, 2H), 5.40 (t, J = 5.0 Hz, 1H), 3.50 (s, 2H), 3.41 (dd, J = 15.0, 4.0 Hz, 1H), 3.03 (dd, J = 15.0, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, benzene-d_6) δ 167.9, 161.4, 135.3, 132.9, 129.8, 128.9, 128.8, 128.6, 128.3, 128.2, 128.1, 127.7, 127.0, 122.6, 119.9, 117.3, 77.7, 36.8, 28.3; HRMS (ESI) calcd for $C_{19}H_{16}O_5F_3S$ [M + H] 413.0671, found 413.0677.

(*S*)-(+)-Maculalactone (52). In a degassed round-bottomed flask, copper iodide-2,4,4-trimethyloxazoline complex[42] (0.09 mL, 0.03 mmol) in THF (0.18 mL) was added. To this solution was added dropwise benzyl magnesium chloride (0.10 mL, 0.22 mmol) at −78 °C. The reaction was warmed slowly from −78 to 0 °C and stirred an additional 30 min. The reaction was then cooled back to −78 °C, and then triflate **46** (23 mg, 0.05 mmol) in THF (0.18 mL) was added dropwise over 5 min. After 2.5 h of stirring at −78 °C, the reaction mixture was quenched with NH_4Cl (3 mL). After warming to ambient temperature, the mixture was extracted with ethyl acetate (3 × 5 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (3:7 EtOAc/hexanes) to yield (+)-maculalactone **52** (5.7 mg, 30%): R_f 0.53 (2:8 EtOAc/hexanes); $[\alpha]^{20}_D$ +54.1 (c = 1.0, CH_2Cl_2); IR (thin film) ν_{max} 1752, 1494 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.13 (m, 11H), 7.03 (m, 2H), 6.88 (m, 2H), 4.93 (t, J = 5.0 Hz, 1H), 3.94 (d, J = 15.5 Hz, 1H), 3.64 (d, J = 15.5 Hz, 1H), 3.56 (d, J = 15.0 Hz, 1H), 3.47 (d, J = 15.5 Hz, 1H), 3.25 (dd, J = 14.5, 4.0 Hz, 1H), 2.81 (dd, J = 14.5, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 161.8, 137.7, 136.0, 134.9, 129.62(2), 129.22(2), 128.78(2), 128.72(5), 128.31(2), 127.4, 127.2, 126.4, 81.6, 38.0, 33.3, 29.4; HRMS (ESI) calcd for $C_{25}H_{23}O_2$ [M + H] 355.1698, found 355.1693.

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Supporting Information Available: Synthetic procedures and characterization data including ^1H and ^{13}C NMR spectra for compounds **10b**,**c**, **11c**, **29**, **45**−**52**, and **58**−**61**, HPLC traces of triflate **46** and maculalactone, and X-ray crystallographic data including CIF files for spiroepoxy-β-lactone **10b**, butenolide **29**, and triflate **46**. This material is available free of charge via the Internet at http://pubs.acs.org.

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