



Tetrahedron report number 878

# Synthesis of unusually strained spiroheterocyclic ring systems and their exploits in synthesis

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## 1. Introduction

Small ring compounds have continually captivated physical and synthetic organic chemists because of their remarkable structures and the reactions that are feasible due to the inherent ring strain of these systems. Isolable, small, strained carbocyclic and heterocyclic rings have been known for over a century, but recently there have been a number of new spiroheterocycles described. Specifically, the

utility of oxa- and dioxaspiropentanes as well as oxa- and dioxaspirohexanes has been demonstrated in the synthesis of natural and unnatural products. The ring systems investigated to date have shown interesting and varied reactivity patterns due to the unique physical properties of these small rings. The aim of this review is to provide an overview of the synthesis and reactivity of small strained spiroheterocycles and to illustrate their applications in synthetic endeavors. This review will be restricted to spiro heterocyclic pentane and hexane systems, as other types of strained systems have been recently reviewed.<sup>1</sup>

An initial, general overview of reactivity patterns for these systems identified by various researchers will hopefully enable the reader to put the following discussion of reactions and applications in perspective. Oxaspiro[2.2]pentanes and 1,4-dioxaspiro[2.2]pentanes **I** exhibit similar reactivity patterns.<sup>2</sup> The C–O bond of the epoxide is cleaved upon either acid-mediated rearrangement or nucleophilic addition. 1-Oxaspiro[2.3]hexanes **II**, 1,4-dioxaspiro[2.3]hexanes **III**, and 4-oxaspiro[2.3]hexanes **IV** offer two primary modes of reactivity. The predominant Lewis acid promoted rearrangement through a stabilized carbocation provides cyclopentanone products, yet nucleophilic addition favors the more hindered epoxide C–O bond. However, dioxaspirohexanes **III** tend

**Abbreviations:** acac, acetylacetonate; Bz, benzoyl; cod, 1,5-cyclooctadiene; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DET, diethyl tartrate; DIBAL-H, diisobutylaluminum hydride; DMDO, dimethyl dioxirane; DMSO, dimethylsulfoxide; EtOAc, ethyl acetate; EWG, electron-withdrawing group; HMPA, hexamethylphosphoric acid triamide; LDA, lithium diisopropylamide; M.S., molecular sieves; *m*-CPBA, *meta*-chloroperbenzoic acid; Nu, nucleophile; PMB, *p*-methoxybenzyl; rt, room temperature; TBHP, *tert*-butyl hydroperoxide; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TBAN<sub>3</sub>, tetra-*n*-butylammonium azide; TFA, trifluoroacetic acid; THF, tetrahydrofuran; T.M., transition metal; TMS, trimethylsilyl; Ts, tosyl or 4-toluenesulfonyl; TsOH, *p*-toluenesulfonic acid.

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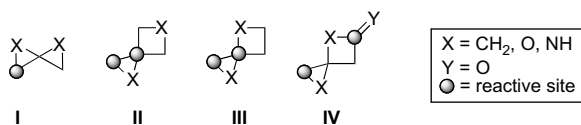
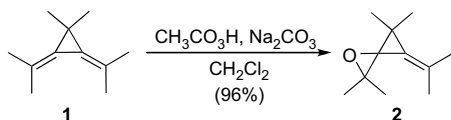


Figure 1. Structures of known small, spirocyclic ring systems.

to undergo nucleophilic substitution primarily at either of the epoxide C–O bonds. Of the four possible reactive centers in 1,4-dioxaspiro[2.3]hexan-5-ones **IV** only substitution at the less hindered epoxide C–O bond or the C=O bond has been observed under various reaction conditions (Fig. 1).

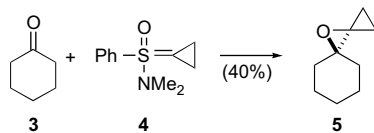
## 2. Oxaspiro[2.2]pentanes

The first confirmed example of small simple spirocyclic ring systems, oxaspiro[2.2]pentanes, appeared in 1968.<sup>3</sup> This spiro system was initially synthesized by reaction of peracetic acid and an unsaturated cyclopropane derivative **1** to give oxaspiro[2.2]pentane **2** (Scheme 1). This method proved to be quite general, as the substrate could be made by olefination of the corresponding carbonyl compounds with cyclopropyl phosphonium ylides. However, an appropriate directing group (i.e., ether) was required because of the modest diastereoselectivity observed.<sup>4</sup> After this initial report, several other methods were devised for the synthesis of oxaspiro[2.2]pentanes, which include addition of lithiated bromocyclopropanes<sup>5</sup> or diazocompounds to ketones,<sup>6</sup> reaction of singlet oxygen with bicyclopopylidene,<sup>7,8</sup> selenone additions to ketones,<sup>9</sup> and the addition of cyclopropyl sulfur ylides to carbonyl compounds.<sup>10,11</sup>



Scheme 1.

By far the most widely used and arguably the most diastereoselective synthesis of oxaspiro[2.2]pentanes remains the addition of cyclopropyl sulfoxonium ylides to carbonyl compounds.<sup>12,13</sup> A series of elegant studies revealed that ylide addition proceeds via equatorial attack at the carbonyl carbon in cyclic compounds. While this process is highly diastereoselective, an enantioselective process has not been developed. Although Johnson and co-workers reported chiral sulfoximine ylide additions to  $\alpha,\beta$ -unsaturated carbonyl compounds, the racemic counterpart performed poorly with simple carbonyl compounds as in the reaction of cyclohexanone **3** with sulfoximine ylide **4**, thus the chiral series was not attempted (Scheme 2).<sup>14</sup>



Scheme 2.

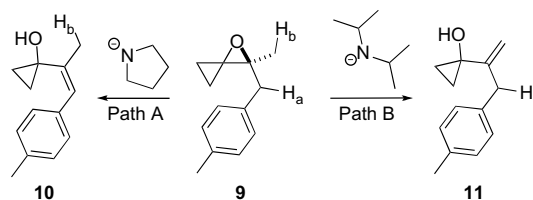
Oxaspiro[2.2]pentanes display two primary modes of reactivity. One mode, leading to a cyclobutanone, appears to be driven by the release of the strain energy of the ring system (Scheme 3).<sup>12</sup> However, as cyclobutanes possess essentially the same amount of strain energy as cyclopropanes (26 kcal/mol and 27 kcal/mol, respectively) due to the eclipsing interactions of the substituents on a cyclobutane, the rearrangement is driven not only by the release of ring strain of both the starting epoxide and the cyclopropane but also by the formation of a C=O bond.<sup>15</sup> The ring expansion of



Scheme 3.

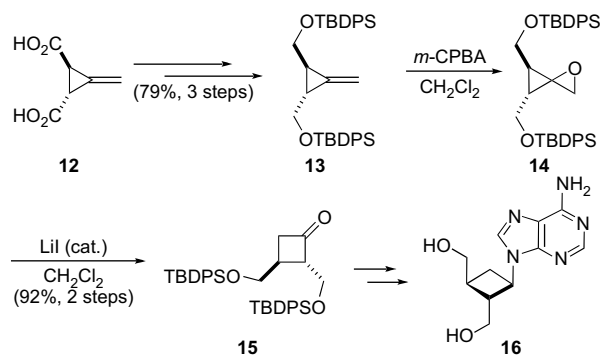
a cyclopropane to a cyclobutanone proceeds with oxaspiro[2.2]pentane **6** when appropriate stabilizing groups are present. Ionization of the epoxide, either by addition of a Lewis acid or thermal induction, yields a highly stabilized intermediate cyclopropyl carbanyl cation **7**. This type of cation is uniquely stabilized due to the enhanced  $\pi$ -character of the  $\sigma$ -bonds in cyclopropanes, which consequently permits a pinacol-like rearrangement to cyclobutanone **8**. This process is favorable due to the release of ring strain of the starting epoxide and cyclopropane in addition to the formation of a C=O bond.

The second major mode of reactivity of oxaspiro[2.2]pentanes is the base induced elimination to form vinyl cyclopropanes. The relief of ring strain upon opening of the epoxide drives this particular transformation. Trost developed conditions allowing access to both regioisomeric products **10** and **11** from spiroepoxide **9** (Scheme 4).<sup>16,17</sup> Use of the less sterically demanding lithium amide of pyrrolidine led to deprotonation of less sterically accessible H<sub>a</sub> (path A), which gave the more substituted conjugated olefin **10**. Use of the more hindered base, lithium diisopropylamide led to deprotonation of oxaspiro[2.2]pentane **9** at the more accessible H<sub>b</sub> (path B) to yield olefin **11**.



Scheme 4.

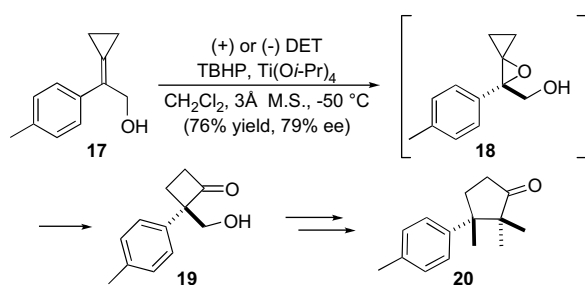
Since their last review,<sup>14</sup> oxaspiro[2.2]pentanes have continued to be valuable in the synthesis of other complex architectures. This ring system has proven to be advantageous for the synthesis of new ligands as well as natural and unnatural products. The initial application of oxaspiro[2.2]pentanes was toward the synthesis of carbocyclic analogues of oxetanocin, an antibiotic/antiviral natural product (Scheme 5).<sup>18</sup> Hsiao's synthesis hinges on the construction of an optically active cyclobutanone **15**. Their approach to this ring system depended on the preparation of oxaspiro[2.2]pentane **14** and the subsequent rearrangement to cyclobutanone **15**. The synthesis began with Feist's acid **12**, which was resolved utilizing quinine. After resolution and a series of standard manipulations, methylene cyclopropane **13** was obtained in good overall yield. The substrate was then subjected to the key oxidation/rearrangement



Scheme 5.

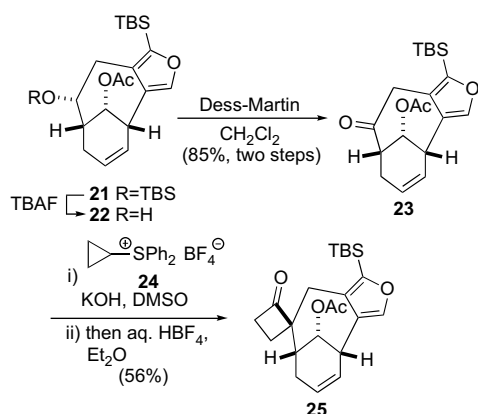
sequence. This was accomplished by exposing methylene cyclopropane **13** to *meta*-chloroperbenzoic acid and subsequent rearrangement of oxaspiro[2.2]pentane **14** with catalytic lithium iodide to give key cyclobutanone **15**. Selectivity issues were avoided in the oxidation step by the use of a  $C_2$  symmetric substrate. Cyclobutanone **15** could be further transformed into carbocyclic oxetanocin analogue **16**.<sup>19</sup>

In addition to diastereoselective methods, enantioselective epoxidation methods have also proven to be effective in yielding optically active oxaspiro[2.2]pentanes as in the synthesis of both enantiomers of  $\alpha$ -cuparenone (**20**), a sesquiterpene natural product (Scheme 6).<sup>20</sup> The synthesis of either enantiomer of  $\alpha$ -cuparenone began with epoxidation of cyclopropene **17** under Sharpless conditions resulting in an aryl substituted oxaspiro[2.2]pentane **18** that rearranged to cyclobutanone **19** in modest enantiomeric excess. Several additional steps completed the total synthesis of  $\alpha$ -cuparenone **20**.<sup>21</sup>



Scheme 6.

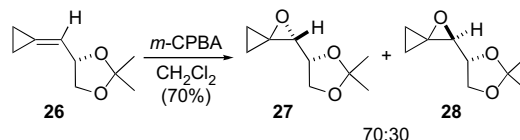
Perhaps one of the more complex settings using an oxaspiro[2.2]pentane, derived from the Trost cyclobutanone procedure, is an elegant model study toward the synthesis of the architecturally intriguing natural products CP-225,917 and CP-263,114.<sup>22,23</sup> Advanced furan intermediate **21**, derived from cyclohexenone, underwent silyl-deprotection and subsequent oxidation to give ketone **23** (Scheme 7). Addition of cyclopropyl sulfonium tetrafluoroborate **24** followed by rearrangement under acidic conditions then delivered cyclobutanone **25**.



Scheme 7.

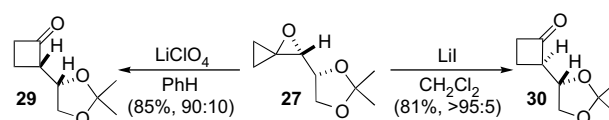
The diastereoselective synthesis of both the acetogenin natural product muricatacin and the pheromone japonilure has also been accomplished by using an oxaspiro[2.2]pentane as an intermediate.<sup>24</sup> The first key reaction was the oxidation of methylene cyclopropane **26** to the corresponding oxaspiro[2.2]pentanes **27** and **28** in modest diastereoselectivity (Scheme 8).

The key challenge was the optimization of the Lewis acid in order to achieve high diastereoselectivity from the rearrangement



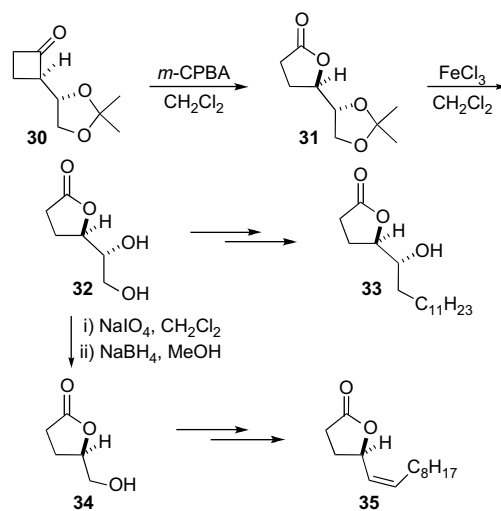
Scheme 8.

of oxaspiro[2.2]pentane **27** to cyclobutanone **30** (Scheme 9).<sup>25</sup> High selectivity for the desired diastereomer was achieved under the optimized conditions with lithium iodide in dichloromethane. Interestingly, the undesired diastereomer **29** was obtained with good diastereoselectivity by using lithium perchlorate in place of lithium iodide hinting at a change in mechanism from a halohydrin-type intermediate to a carbocationic intermediate due to the multiple coordination sites available for the lithium atoms.<sup>24</sup>



Scheme 9.

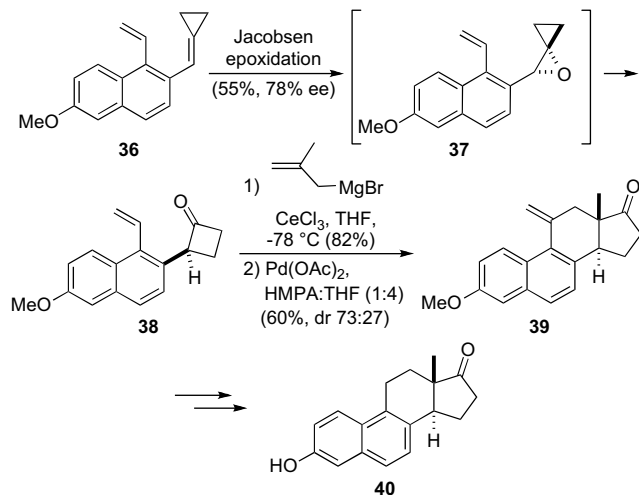
After accomplishing the key oxidation–rearrangement reaction sequence, the subsequent steps toward the formal syntheses of muricatacin and japonilure were rather straightforward (Scheme 10). Baeyer–Villiger oxidation of cyclobutanone **30** to the corresponding  $\gamma$ -lactone **31** followed by deprotection of the acetonide to diol **32** provided a common intermediate in two syntheses of muricatacin **33**.<sup>26,27</sup> Alternatively, the formal synthesis of japonilure **35** was completed after oxidative cleavage and direct reduction to alcohol **34**.<sup>28</sup>



Scheme 10.

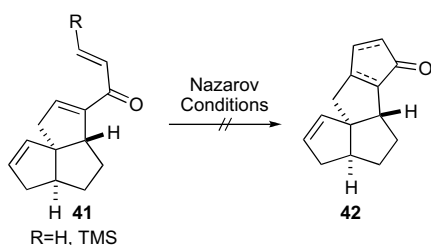
Oxaspiro[2.2]pentanes were also utilized in the total synthesis of the steroid (+)-equilenin **40**.<sup>29,30</sup> Ihara began with naphthalene derivative **36**, which was epoxidized under Jacobsen's conditions to yield cyclobutanone **38** directly due to the instability of the transient oxaspiro[2.2]pentane **37** to the reaction conditions (Scheme 11). The optical purity of the cyclobutanone **38** was not improved with other epoxidation methods. Shi epoxidation resulted in low optical purity, which could not be increased by changing either the solvent or catalyst loading. The reduction in enantioselectivity was presumably due to the stabilization of the developing benzylic cation by the methoxy substituent, which led to an unselective rearrangement to the cyclobutanone. This was supported by the

observation that optical purities increased drastically (up to 93% ee) when the methoxy substituent was replaced with hydrogen. Addition of the isoprenyl group to cyclobutanone **38** in the presence of cerium trichloride followed by treatment with stoichiometric amounts of palladium acetate gave cyclopentanone **39**, which was then transformed to (+)-equilenin **40**.



Scheme 11.

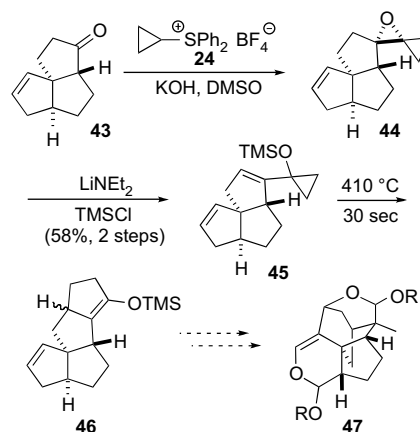
The advantage of small rings in synthesis was illustrated in Paquette's studies toward the trixikingolides since the application of a Nazarov type cyclization failed.<sup>31</sup> Divinyl ketone **41** did not lead to the desired cyclopentenone **42** in sufficient yields under a variety of reaction conditions. Assistance of a silicon atom in the  $\beta$ -position did not lead to any improvement and resulted in low yields or mixtures of stereoisomers at the newly formed ring juncture (Scheme 12).



Scheme 12.

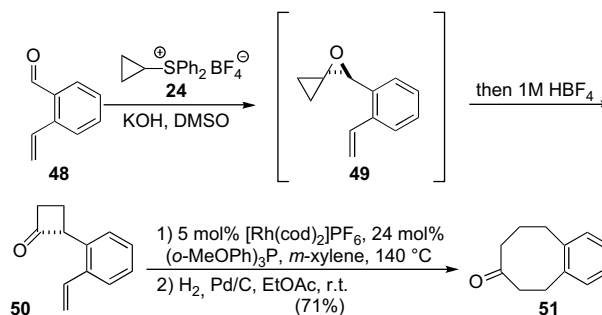
The failures of standard conditions led to the pursuit of cyclopentenone **42** via Trost's annulation procedure utilizing an oxaspiro[2.2]pentane. The sequence began with condensation of cyclopropyl sulfoxonium ylide **24** and ketone **43** leading to oxaspiro[2.2]pentane derivative **44**, which was used without purification in the elimination step to yield cyclopropane **45** (Scheme 13). To complete the annulation, cyclopropane **45** was flash-vacuum-pyrolyzed to yield the desired cyclopentanone as its silyl enol ether **46** in excellent yield. Unfortunately, attempts to utilize this strategy toward the trixikingolides **47** did not result in a complete synthesis.

In addition to enabling access to numerous natural products and several new chiral ligands, oxaspiro[2.2]pentanes have also provided access to substrates for interesting transformations. An example is the rhodium-catalyzed synthesis of an eight-membered ring developed by Murakami and co-workers (Scheme 14).<sup>32</sup> *o*-Styryl-cyclobutanone **50** was synthesized utilizing Trost's cyclopropyl sulfoxonium ylide **24** procedure to generate



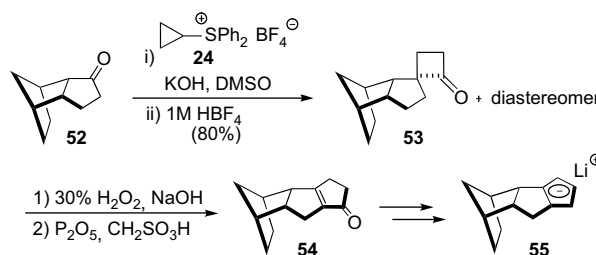
Scheme 13.

oxaspiro[2.2]pentane **49**,<sup>25</sup> which was rearranged under protic conditions to yield the desired cyclobutanone **50**. Cyclobutanone **50** was transformed to octanone **51** via olefin insertion and subsequent hydrogenation.



Scheme 14.

Not only have oxaspiro[2.2]pentanes found application in the synthesis of natural and unnatural products, but they have also found application in the synthesis of structurally interesting compounds, such as polyspiranes and ligands for catalysis. Polyspiranes have been the subject of previous reviews<sup>1d</sup> and will therefore not be discussed herein. Paquette showed that oxaspiro[2.2]pentanes could be applied in different arenas other than the total synthesis of natural products, which was exemplified in the synthesis of a new set of chiral cyclopentadienide ligands.<sup>33</sup> Ketone **52**, derived from cyclopentadiene, was subjected to the Trost cyclobutanone synthesis conditions by exposure to cyclopropyl diphenyl sulfoxonium tetrafluoroborate **24** (Scheme 15). Subsequent rearrangement with aqueous acid yielded an inconsequential mixture of cyclobutanones **53** that were oxidized to the  $\gamma$ -lactones and then exposed to phosphorous pentoxide and methane sulfonic acid to yield  $\alpha,\beta$ -unsaturated ketone **54**. Completion of the synthesis of the cyclopentadienide ligand **55** was accomplished in a three-step sequence, which included reduction of ketone **54** to the alcohol

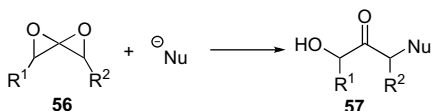


Scheme 15.

followed by elimination under acidic conditions to yield a cyclopentadiene. Subsequent deprotonation with *n*-butyl lithium gave the desired cyclopentadienide **55**.

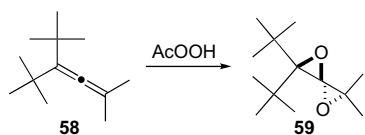
### 3. 1,4-Dioxaspiro[2.2]pentanes

In a manner similar to the oxaspiro[2.2]pentanes, the further oxidized 1,4-dioxaspiro[2.2]pentanes **56** display one primary mode of reactivity. The reactivity of the small spiroacetal hinges on the relief of strain contained in both epoxide rings to give  $\alpha$ -nucleophile substituted  $\alpha'$ -hydroxy ketones **57** as products (Scheme 16). These nucleophilic additions are broad in scope and can occur either intra- or intermolecularly.



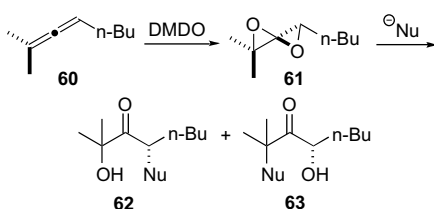
Scheme 16.

The 1,4-dioxaspiro[2.2]pentane **59** was first synthesized by Crandall in 1966 and has regained the interest of synthetic chemists in recent years.<sup>34,35</sup> Crandall found that exposure of tetramethylallene to peracetic acid resulted in the formation of several oxidized products. Although not directly detected, several of the reaction products pointed to the presence of a 1,4-dioxaspiro[2.2]pentane. However, it was not until 1968 that Crandall succeeded in isolating 1,4-dioxaspiro[2.2]pentane **59** by careful distillation of the oxidation products of allene **58** (Scheme 17).<sup>36</sup>



Scheme 17.

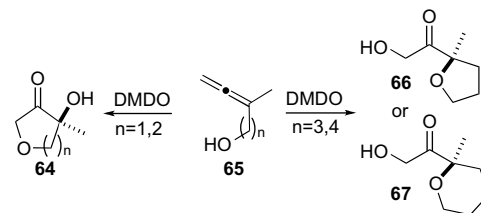
1,4-Dioxaspiro[2.2]pentanes did not find utility in more synthetically useful scenarios until two decades later primarily due to the lack of efficient, neutral, and mild oxidizing reagents.<sup>37,38</sup> The advent of dimethyl dioxirane by Murray and Jeyaraman provided a more general synthesis of the 1,4-dioxaspiro[2.2]pentanes (Scheme 18).<sup>39</sup> Exposure of diepoxide **61**, available from allene **60**, to various nucleophiles typically yielded substituted ketones of types **62** and **63** depending on the steric demands of the nucleophile and the reaction conditions. More sterically demanding nucleophiles react to form ketone **62** compared to the mixtures of substituted ketones **62** and **63** obtained with less sterically demanding nucleophiles. However, acidic conditions preferred the formation of ketone **63**.



Scheme 18.

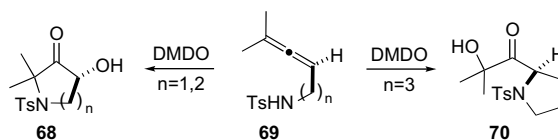
Crandall and co-workers also found that intramolecular cyclizations were possible with an appropriate pendant nucleophile (Scheme 19).<sup>40,41</sup> Thus, oxidation of allenic alcohols **65** containing a one or two-carbon atom tether yielded furanones **64** that

proceeded through attack at the distal epoxide C–O bond by the pendant alcohol. However, when the tether was extended to three or four carbon atoms, nucleophilic addition favored the proximal epoxide C–O bond to form tetrahydrofurans **66** and tetrahydropyrans **67**, respectively.



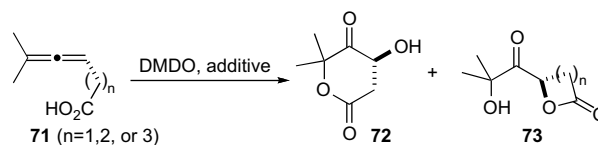
Scheme 19.

In analogy to allenyl alcohols, protected amines also give heterocyclic products (Scheme 20). Exposure of a tosyl protected allenyl amine **69** with a one or two-carbon tether yielded the corresponding pyrrolidinone or piperidinone **68**, respectively, with nucleophilic attack of the amine occurring at the distal epoxide C–O bond. Conversely, when the tether was lengthened to three carbon atoms, nucleophilic attack occurred at the proximal epoxide C–O bond yielding acylpyrrolidine **70**. Amine substrates suffered from lower yields (52% from **69** vs 87% from **65**) due to competing oxidation at the nitrogen atom to give further oxidized by-products.



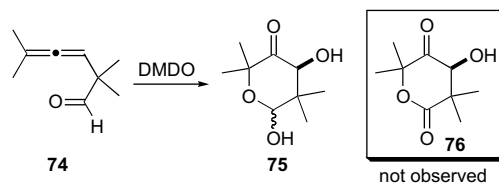
Scheme 20.

Similarly, when allenic carboxylic acids **71** were employed as substrates the corresponding lactone products were obtained (Scheme 21).<sup>42,43</sup> When the tether length was only one carbon atom,  $\delta$ -lactones **72** were obtained as major products. Interestingly, when the tether had one carbon atom and sodium bicarbonate was added to the reaction both  $\beta$ -lactone **73** and  $\delta$ -lactone **72** (major product) were observed. The  $\delta$ -lactone **72** was observed as the major product under acidic conditions.



Scheme 21.

Although it is well known that aldehydes are oxidized to carboxylic acids with DMDO,<sup>44</sup> allenyl aldehydes were also explored as substrates (Scheme 22).<sup>45</sup> Epoxidation proved to be competitive with oxidation of the aldehyde permitting intramolecular cyclization over intermolecular oxidation of aldehyde **74** resulting in the formation of the unexpected acetal **75** as a 1:1 mixture of

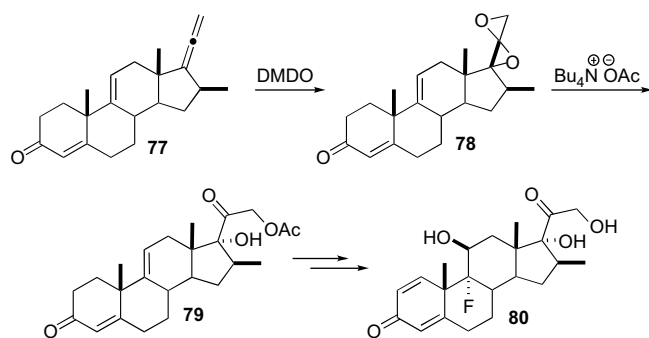


Scheme 22.



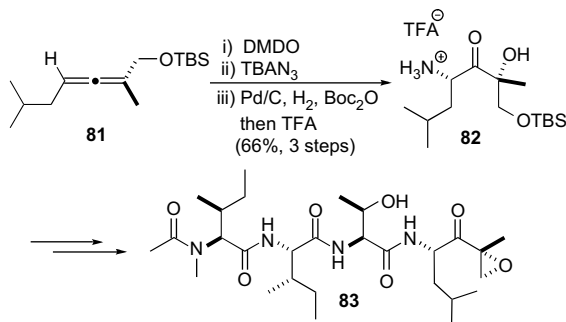
diastereomers. The *trans*-diastereomer **75** can be obtained as a single product by utilizing scrupulously dry DMDO in the presence of a suitable alcohol.

Although the 1,4-dioxaspiro[2.2]pentanes have been known and investigated since 1966, it took 30 years for this ring system to be utilized in the synthesis of a complex molecule. The betamethasone synthesis by Andrews and co-workers demonstrated the practicality of 1,4-dioxaspiro[2.2]pentanes (Scheme 23).<sup>46</sup> DMDO oxidation of allene **77**, derived from 9 $\alpha$ -hydroxyandrost-4-ene-3,17-dione, provided 1,4-dioxaspiro[2.2]pentane derivative **78**. Subjection to tetrabutylammonium acetate yielded  $\alpha$ -acetate substituted ketone **79**, which was then converted to betamethasone **80** by known reaction conditions.<sup>47</sup>



Scheme 23.

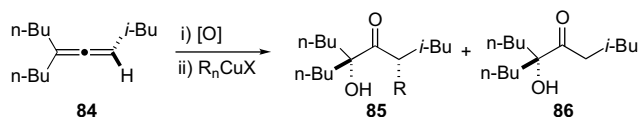
Williams' modular synthesis of the selective proteasome inhibitor epoxomicin **83** also highlights the utility of this ring system (Scheme 24).<sup>48</sup> Allene **81**, which was derived from isovaleraldehyde, underwent DMDO oxidation followed by azide addition and reduction of the unstable azidoketone to deliver the stable amino-ketone **82**. This route was pursued due to the low yield or instability of other amino-ketones derived from alternate nitrogen sources. Peptide coupling followed by transformation of the tertiary alcohol into the requisite epoxide produced epoxomicin **83**. This sequence proceeded in excellent overall yield from allene **81** (42%, nine steps).



Scheme 24.

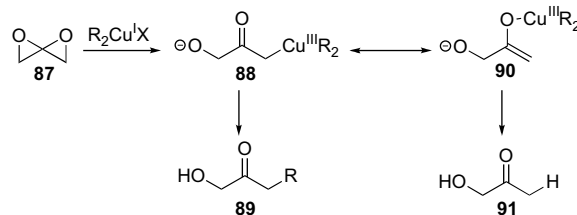
Nucleophilic additions to 1,4-dioxaspiro[2.2]pentanes are not limited to heteroatoms, carbon based nucleophiles can also provide substituted ketone products. The addition of cuprates to this ring system proved difficult at first, but was made effective with the appropriate Gilman reagent (Scheme 25).<sup>49</sup> Typical dialkyl cuprates derived from alkyl lithiums provided some of the desired addition product **85** along with undesired ketone **86** as the major product. The production of hydroxyl-ketone **86** was surprising though not unfounded.<sup>50</sup>

The reaction presumably occurred through oxidative addition of the Cu(I) species to the epoxide **87** to give intermediate **88**



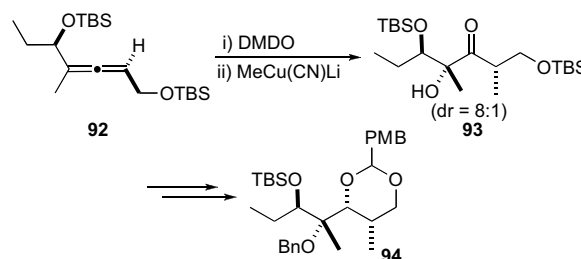
Scheme 25.

Cu(III) ketone **88**, which provided two divergent reaction pathways (Scheme 26). Expected reductive elimination yielded the desired substituted product **89**. In contrast, isomerization to the corresponding enolate **90** led to observed ketone **91**. This undesired pathway was avoided by the use of alkylcyano cuprates.



Scheme 26.

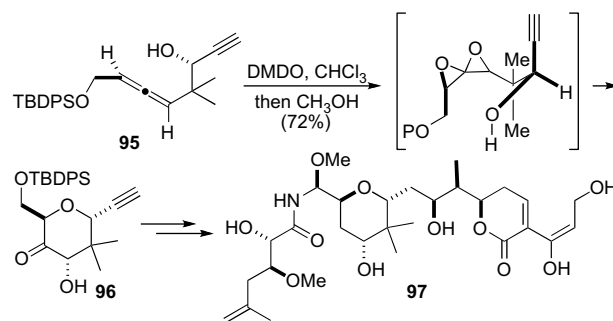
This methodology was applied to the synthesis of a precursor toward the antibiotic erythromycin (Scheme 27). Oxidation of allene **92** and subsequent exposure to methylcyanocuprate yielded ketone **93** with good diastereoselectivity. Ketone **93** was then transformed to the known protected tetrol **94** by standard methods.<sup>51</sup>



Scheme 27.

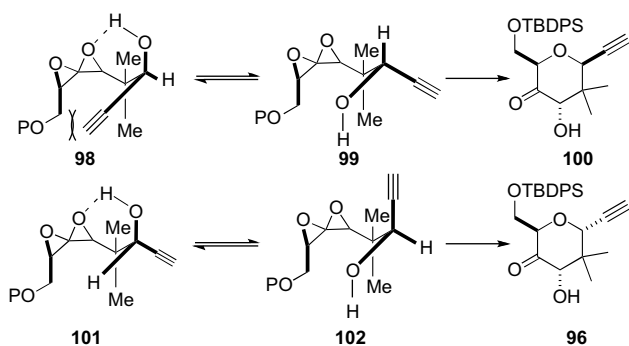
The tetrahydropyran moiety of psymberin, a selective anti-tumor agent isolated in 2004 from a sponge off the coast of Papua New Guinea,<sup>52</sup> was constructed utilizing Crandall's methodology (Scheme 28).<sup>53</sup> Advanced allene **95** was subjected to DMDO oxidation to give the intermediate 1,4-dioxaspiro[2.2]pentane, which cyclized to dihydropyranone **96** upon the addition of methanol. Dihydropyranone **96** was further transformed into a known intermediate in the synthesis of psymberin **97**.

The unusual necessity of methanol to promote cyclization can be explained by the diastereomeric conformations of the 1,4-



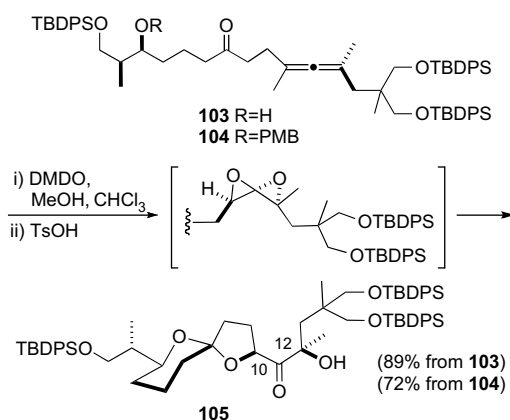
Scheme 28.

dioxaspiro[2.2]pentane (Scheme 29). Spontaneous cyclization to give the *cis*-substituted pyran **100** occurred when the epimeric alcohol was used in the oxidative cyclization. This is due to the destabilization of the unproductive hydrogen-bonded conformation **98** resulting from steric interactions, which promotes the formation of the productive conformation **99** providing *cis*-substituted pyran **100**. Conversely, the other diastereomer forms a stable hydrogen-bonded complex **101** lacking such destabilizing interactions, although interactions between the alkyne and the epoxide in the productive conformation **102** made the cyclization challenging. However, when a protic solvent was added, the stable hydrogen-bonded complex was destroyed and the reaction was driven to the formation of conformer **102** and thus the desired *trans*-substituted pyran **96**.



Scheme 29.

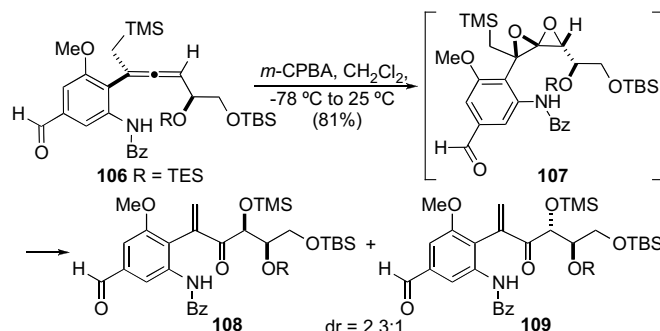
Williams also devised a synthesis of the A–B ring system of pectenotoxin **4** using a 1,4-dioxaspiro[2.2]pentane as a key intermediate (Scheme 30).<sup>54</sup> Keto-allene **103** was oxidized by DMDO to the bis-epoxide, which was then captured by the pendant ketone to generate an oxocarbenium ion. The alcohol then captured the cation to give spirocycle **105** featuring the A–B ring system of pectenotoxin **4**. Additionally, the diastereoselectivities for both oxidations were good, >20:1 for the C12 alcohol and 7:1 for the C10 center. This cascade reaction sequence was extended to reaction with the PMB protected alcohol **104** since DMDO also removes the PMB group.



Scheme 30.

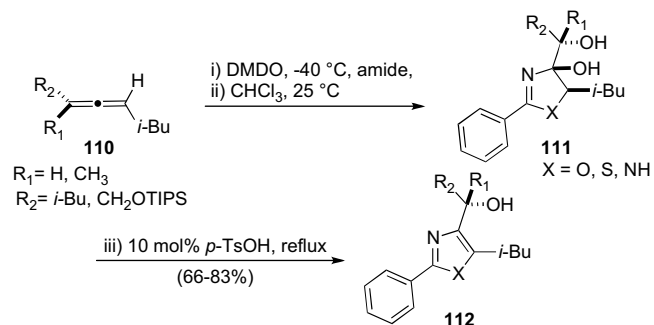
Certain alkaloids possessing a vicinal stereotriad have been envisioned as coming from aryl substituted 1,4-dioxaspiro[2.2]pentanes (Scheme 31).<sup>55</sup> Incorporation of aryl substituents particularly electron-rich aromatics pose several challenges to the preparation of the highly strained spirodiepoxides with regard to stability. After extensive investigation, Williams and co-workers

demonstrated a Brønsted acid-induced rearrangement of a presumed densely functionalized 1,4-dioxaspiro[2.2]pentane **107** intermediate to furnish enones **108** and **109** in good yield but with low diastereoselectivity. The rearrangement proceeded initially at the more substituted terminus, which led to the concomitant elimination of the TMS group. Further elaboration of enones **108** and **109** derived from the Brønsted acid-mediated rearrangement can generate precursors applicable toward the synthesis of complex natural products.



Scheme 31.

Nitrogen heterocycles have also been accessed via 1,4-dioxaspiro[2.2]pentanes through epoxidation of the corresponding allene (i.e., **110**) with DMDO and subsequent ring opening (Scheme 32).<sup>56</sup> Benzamides, thiobenzamides, and benzamidines added readily to spirodiepoxides to provide azolines **111** and azoles **112** upon successive treatment with catalytic *para* toluenesulfonic acid. Mechanistic studies revealed evidence supporting a concerted asynchronous ring opening of both epoxides rather than a stepwise process. However, a stepwise process cannot be entirely excluded especially when strong alkoxide interactions persist.



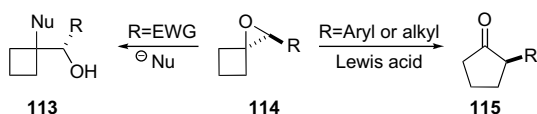
Scheme 32.

#### 4. 1-Oxaspiro[2.3]hexanes

Since the introduction of 1-oxaspiro[2.3]hexanes in the 1970s, the most prevalent method of preparation is the oxidation of methylene cyclobutanes by DMDO or peracids analogous to the previously described ring systems. Alternative methods of preparation include the addition of  $\alpha$ -lithio selenocyclobutanes to carbonyl compounds,<sup>57,58</sup> addition of sulfur ylides to cyclobutanones,<sup>59,60</sup> oxidation of methylene cyclobutanes with *N*-bromosuccinimide in water,<sup>61</sup> transition metal-mediated epoxidations of cyclobutenes,<sup>62</sup> and oxidation of methylene cyclobutanes with asymmetric versions of DMDO.<sup>63,64</sup>

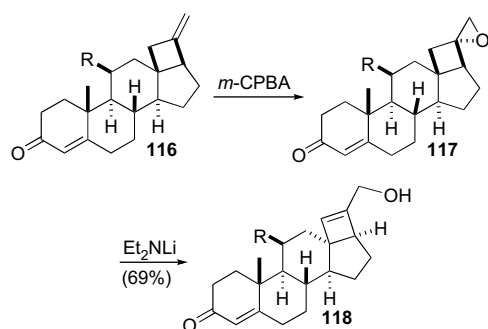
1-Oxaspiro[2.3]hexanes **114** have similar reactivity patterns to oxaspiro[2.2]pentanes upon nucleophilic addition and Lewis acid-mediated ring expansion (Scheme 33). When the ring system was functionalized with an aryl or alkyl group, a facile ring

expansion under Lewis acidic conditions to cyclopentanone **115** occurred.<sup>59,65</sup> The ring expansion was driven by the release of the strain energy of both rings, and the presence of an aryl group that likely stabilized the forming carbocation necessary for the rearrangement. Conversely, nucleophilic addition to the ring system functionalized with an electron-withdrawing group furnished substituted cyclobutanes **113** due to the destabilization of the cation.



Scheme 33.

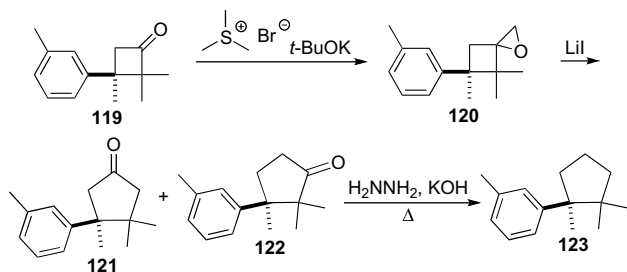
A 1-oxaspiro[2.3]hexane was initially used in synthesis during the attempted construction of an aldosterone derivative (Scheme 34).<sup>66</sup> Steroid **116**, which was obtained from pregnenolone acetate, was oxidized by *m*-CPBA to give 1-oxaspiro[2.3]hexane **117**. Subsequent elimination with lithium diethylamide gave cyclobutene **118**. The reaction sequence only worked well on unsubstituted systems (i.e., R=H) otherwise elimination did not occur. This route was later abandoned for a more productive pathway.



Scheme 34.

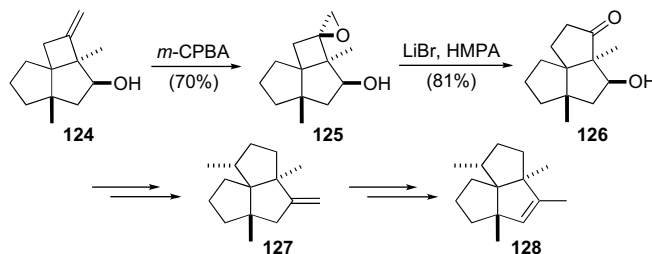
The aromatic sesquiterpene herbertene, isolated from the liverwort *Herberta adunca*, is another early example of the use of 1-oxaspiro[2.3]hexanes in natural product synthesis (Scheme 35).<sup>59,60</sup> The synthesis of the key 1-oxaspiro[2.3]hexane **120** began with cyclobutanone **119**, which was made by thermal cyclization of a toluene derivative and dimethyl ketene. Cyclobutanone **119** was then condensed with trimethylsulfonium bromide under basic conditions to yield the desired spiro system **120**. The spiro system rearranges to an inconsequential mixture of carbonyl isomers **121** and **122** upon exposure to catalytic lithium iodide. Herbertene **123** was then completed (overall yield of ~30%) after reduction of the carbonyl to the corresponding methylene using the Huang–Minlon modification of Wolff–Kischner reduction.<sup>67</sup>

1-Oxaspiro[2.3]hexanes have also been envisioned for the preparation of triquinane natural products. A common 1-oxaspiro[2.3]hexane permitted the synthesis of both isocomene and  $\beta$ -



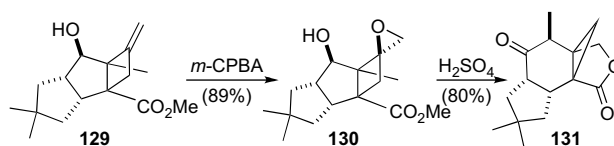
Scheme 35.

isocomene (Scheme 36).<sup>68</sup> The key 1-oxaspiro[2.3]hexane **125** was derived from cyclobutene **124** by hydroxyl directed epoxidation with *m*-CPBA to give a single epoxide **125**. Regioselective rearrangement in the presence of lithium bromide and HMPA gave cyclopentanone **126** that was then transformed into  $\beta$ -isocomene **127** and isocomene **128**, respectively.



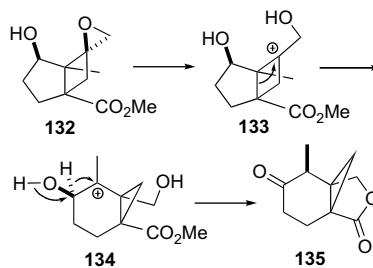
Scheme 36.

Tobe's synthesis of marasmic acid is a particularly elegant use of a 1-oxaspiro[2.3]hexane (Scheme 37).<sup>69,70</sup> In the synthesis, cyclobutene **129** was oxidized with *m*-CPBA to give epoxide **130**. A cascade rearrangement of epoxide **130** with sulfuric acid gave lactone **131**, which is a precursor to marasmic acid.



Scheme 37.

The mechanism of this cascade rearrangement is depicted in simplified version, omitting the cyclopentane for clarity (Scheme 38). Protonation of epoxide **132** led to the formation of cyclobutyl cation **133**, which then underwent a bond migration to give cyclopropyl carbanyl cation **134**. A 1,2-hydride shift gave the observed product **135** after lactonization.

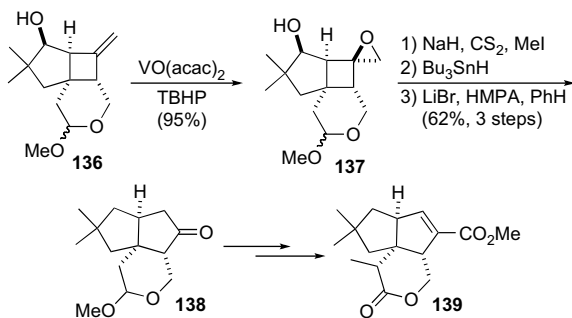


Scheme 38.

The ring expansion of a 1-oxaspiro[2.3]hexane proved to be particularly effective for the synthesis of pentalenolactone E and G methyl esters (Scheme 39).<sup>71</sup> Cyclobutene **136** was constructed by a photochemical [2+2] cycloaddition from the corresponding allene and enone. Hydroxyl directed epoxidation of alkene **136** in the presence of VO(acac)<sub>2</sub> and *tert*-butylhydroperoxide provided epoxide **137** with excellent diastereoselectivity. After Barton–McCombie deoxygenation, ring expansion gave cyclopentanone **138** as a single regioisomer. Pentalenolactone E methyl ester **139** and pentalenolactone G methyl ester were obtained after further manipulations of cyclopentanone **138**.

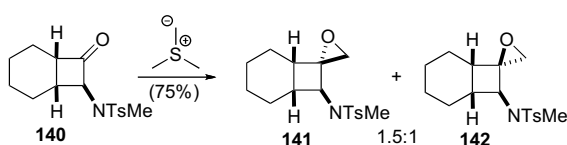
Amino-substituted 1-oxaspiro[2.3]hexanes are also accessible in good optical purity via a two-step process (Scheme 40).<sup>72,73</sup> Amino-cyclobutanone **140** was made directly from the [2+2] cycloaddition of the corresponding keteniminium salt and di-substituted olefin. Condensation of cyclobutanone **140** with a sulfur





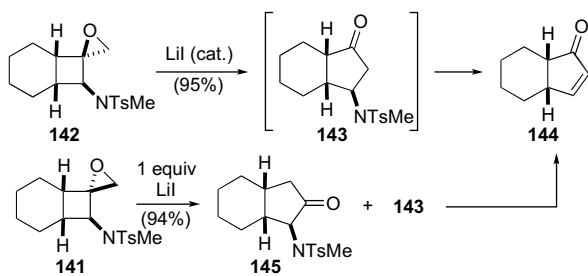
Scheme 39.

ylide gave the corresponding epoxides **141** and **142** in good yield but with poor diastereoselectivity.



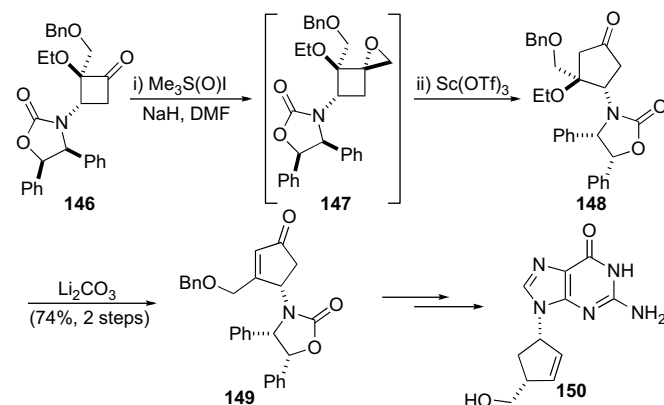
Scheme 40.

Exposure of these amino-substituted 1-oxaspiro[2.3]hexanes to either a catalytic or a stoichiometric amount of lithium iodide facilitated conversion to the subsequent cyclopentenone (Scheme 41). The *exo*-isomer **142** underwent a more facile rearrangement requiring only a catalytic amount of lithium iodide, while the *endo*-isomer **141** required a full equivalent of lithium iodide. The same  $\beta$ -aminocyclopentanone intermediate **143** was presumably formed with both isomers, but under the reaction conditions elimination occurred to give cyclopentenone **144**. The rearrangement of *endo*-isomer **141** was not as regioselective as the *exo*-isomer **142**, which resulted in the formation of  $\alpha$ -aminocyclopentanone **145** and cyclopentenone **144**. The optical purity of the starting epoxide was preserved in the products in several examples.



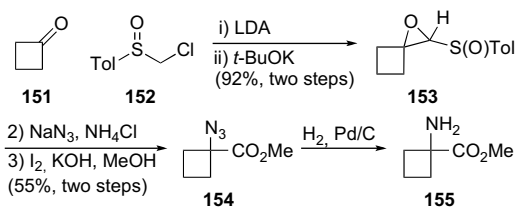
Scheme 41.

Compared to the regioisomeric mixtures obtained from diazo-methane addition to cyclobutanones, 1-oxaspiro[2.3]hexanes offer significant advantages because of their facile and highly regioselective rearrangement to the corresponding cyclopentanones. For instance, Hegedus and Brown demonstrated increased regioselectivity in the synthesis of carbovor **150** (Scheme 42).<sup>74</sup> Photolysis between a chromium carbene and an ene-carbamate constructed cyclobutanone **146**. Further reaction with dimethylsulfoxonium methylide delivered 1-oxaspiro[2.3]hexane **147**, which was then exposed to scandium triflate to trigger a rearrangement to cyclopentanone **148**. Scandium triflate provided complete conversion to the product in higher yield compared to other Lewis acids. The ethoxy group was then eliminated under basic conditions to give cyclopentenone **149**, which was then transformed after further manipulations to carbovor **150**.



Scheme 42.

Attachment of an appropriate electron-withdrawing group can suppress 1-oxaspiro[2.3]hexanes from opening to cyclobutylcarbonyl cations and subsequently rearranging under Lewis acidic conditions. These substrates were synthesized via a two-step protocol to generate a sulfoxyl substituted epoxide (Scheme 43).<sup>75,76</sup> Cyclobutanone **151** reacted with chloromethyl substituted sulfoxide **152** in the presence of LDA to give an alcohol that was cyclized to the corresponding epoxide **153**. A nucleophile was added to the distal carbon of the epoxide **153** to give an azido-aldehyde, which was directly oxidized to the methyl ester **154** by basic iodine in methanol. The azido ester **154** was then reduced to the corresponding amine **155** by catalytic hydrogenation. This procedure proved effective in the racemic series for a variety of substrates, yet the analogous process with a chiral sulfoxide was limited to a few substrates.



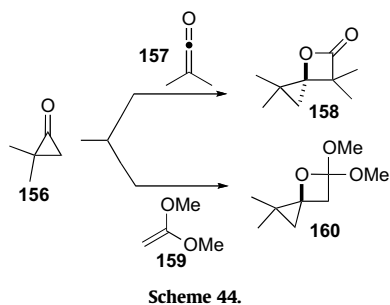
Scheme 43.

## 5. 4-Oxaspiro[2.3]hexanes

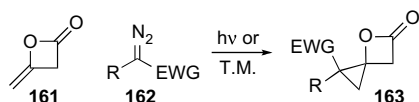
The application of 4-oxaspiro[2.3]hexanes to the synthesis of natural and unnatural products has yet to be reported, presumably due to the limited scope in their syntheses. These systems will therefore only be covered briefly. The first construction of this ring system was described by Turro and Williams in the late 1960s (Scheme 44).<sup>77,78</sup> While the cycloaddition between cyclopropanone **156** and ketene **157** proceeded to cyclopropane **158**, a higher yield (90%) was obtained with the dimethyl acetal of ketene **159** to give orthoester **160**. However, the lack of efficient syntheses of the requisite cyclopropanones hindered broad application.

One of the widely applied syntheses of 4-oxaspiro[2.3]hexanes is the decomposition of diazo compounds in the presence of diketene **161** (Scheme 45).<sup>79</sup> A variety of diazo compounds **162** bearing an electron-withdrawing group in the form of a phosphonate or ester gave the 4-oxaspiro[2.3]hexanes **163**. Although both light-mediated and transition metal-mediated decomposition of the diazo compounds gave similar results, the identity of the substituent appears to be crucial to the outcome of the reaction.

A major reaction pathway of this highly strained system is the thermal rearrangement to furanones and butenolides (Scheme

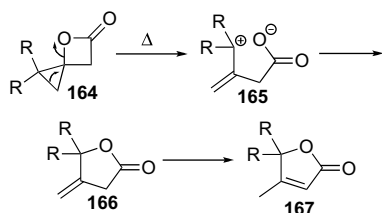


Scheme 44.



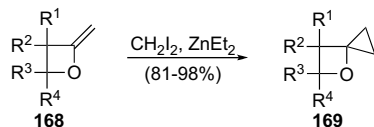
Scheme 45.

46). The reaction proceeds via cleavage of a cyclopropyl C–C bond and the C–O bond of the  $\beta$ -lactone to give zwitterionic intermediate **165**. Ring closure gave lactone **166**, which then partially or completely isomerizes to butenolide **167** under the reaction conditions.



Scheme 46.

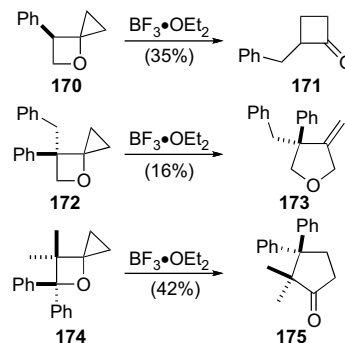
The cyclopropanation of 2-methylene oxetanes, which are available from the corresponding  $\beta$ -lactones by the method developed by Howell and Dollinger,<sup>80</sup> is the most general synthesis of 4-dioxaspiro[2.3]hexanes to date. 2-Methylene oxetanes **168**, took part in a Simmons–Smith cyclopropanation to give 4-dioxaspiro[2.3]hexanes **169** (Scheme 47).<sup>81</sup> Structural variation was limited to substrates bearing substituents on the oxetane ring, yet cyclopropanation proceeded in good yields for a variety of substrates despite the limitations.



Scheme 47.

Attention was turned to the reactivity of the ring system since a more general synthesis was in hand (Scheme 48). The 4-oxaspiro[2.3]hexanes gave a variety of different structures upon exposure to Lewis acid. Unfortunately, the yields for these reactions were moderate thus limiting their potential in synthesis.

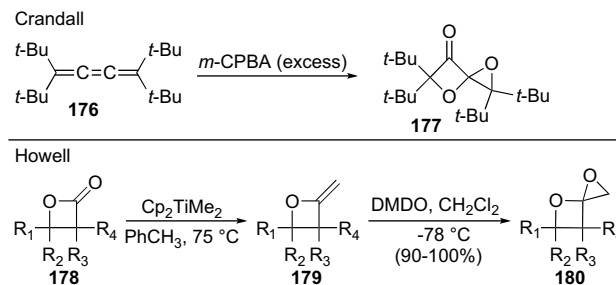
In addition to the above described procedures, 4-oxaspiro[2.3]hexanes have been observed in several other reactions. This ring system was isolated in low yields from the photochemical reaction between carbonyl compounds and olefins,<sup>82,83</sup> and by the cyclopropanation of alkylidene oxetanes with dichlorocarbene.<sup>84</sup> 4-Oxaspiro[2.3]hexanes are intermediates in the synthesis of a polyspirane,<sup>85</sup> but the most current example of their synthesis is an isolated report of the fragmentation of a benzylidene acetal.<sup>86</sup>



Scheme 48.

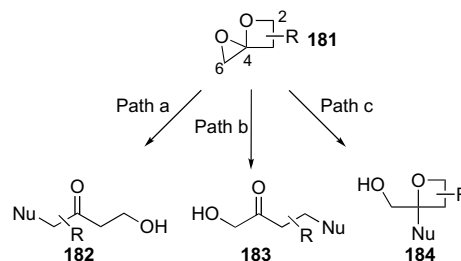
## 6. 1,4-Dioxaspiro[2.3]hexanes

1,4-Dioxaspiro[2.3]hexanes were initially synthesized fortuitously in 1987.<sup>87</sup> Crandall found that exposure of cumulene **176** to an excess of *m*-CPBA yielded several products, one of them being 1,4-dioxaspiro[2.3]hexane **177** (Scheme 49). Although this was not a synthetically practical preparation method given the starting material, a more synthetically viable route was not developed until more than a decade later. Howell and Ndakala showed that in the presence of DMDO, methyleneoxetanes **179** yielded 1,4-dioxaspiro[2.3]hexanes **180** in good yields with modest to good diastereoselectivity.<sup>88</sup> Additionally, methyleneoxetanes **179** are readily accessed from  $\beta$ -lactones **178**.<sup>80</sup> This particular method also tolerates a variety of functional groups, which should prove useful in the synthetic arena.



Scheme 49.

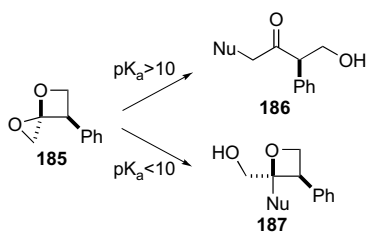
In contrast to the previously described heterocycles, 1,4-dioxaspiro[2.3]hexanes **181** display varied reactivity depending on the reaction conditions employed (Scheme 50). There are three possible modes of reactivity and the most probable is path 'a' because nucleophilic attack occurs at the least hindered C6 completely unraveling the ring system with relief of all ring strain to yield  $\alpha$ -substituted ketones **182**. The next probable pathway 'b' permits attack at C2 to relieve ring strain to yield  $\beta$ -substituted ketones **183**. Finally, the least predominant reaction pathway is 'c', in which the nucleophile adds to C4 and gives substituted oxetanes **184** as



Scheme 50.

products. Pathway 'a' seemed most likely due to the sterically unhindered attack of a nucleophile and pathway 'c' was initially precluded due to the increased basicity of the oxetane oxygen over the epoxide oxygen that increases its lability.

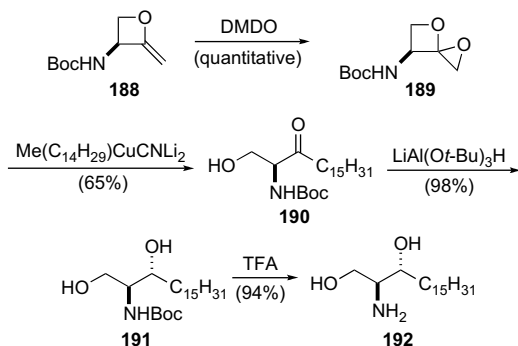
Howell and co-workers discovered interesting reactivities during their early investigations of this ring system.<sup>89,90</sup> Initially, most nucleophiles added to the least hindered C6 position following reaction pathway 'a' to yield  $\alpha$ -substituted ketones. These nucleophiles were quite diverse and included alcohols, acetate, and sodium thiophenoxide. Contrary to these results, when DIBAL-H, Me<sub>3</sub>Al, or TMSN<sub>3</sub> was utilized as nucleophiles the major products observed were substituted oxetane products resulting from addition at C4. The Lewis acidic aluminum or silicon atom may have facilitated the ring opening of the epoxide, but later this was attributed to the pK<sub>a</sub>. Heterocyclic nucleophiles, with acidic protons, that have a pK<sub>a</sub> > 10 gave  $\alpha$ -substituted ketones as products **186**, while those below a pK<sub>a</sub> of < 10 yielded substituted oxetanes **187** (Scheme 51).



Scheme 51.

Computational analysis also revealed that with anionic nucleophiles there is a small preference for attack at C6.<sup>90</sup> This mode of attack results in a highly exothermic (59.9 kcal/mol) unraveling of both rings to yield the observed product. Conversely, in acidic solution the product is driven by the stabilities of the generated oxocarbenium ions, since there is no partiality for protonation at the oxetane or the epoxide oxygen. Obviously, the preference is for opening of the epoxide ring with generation of an oxetane oxonium, which is more stable than the corresponding epoxide oxocarbenium by 18.8 kcal/mol.

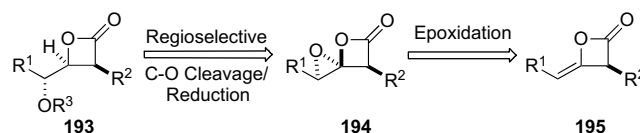
The 1,4-dioxaspiro[2.3]hexane ring system proved to be a versatile building block toward the cell signaling and immunomodulatory molecules dihydrosphingosines, sphingosines, and phytosphingosines.<sup>91</sup> Scheme 52 demonstrates this versatility in the synthesis of D-erythro-sphinganine. Methylene oxetane **188**, derived from serine, was first oxidized to the 1,4-dioxaspiro[2.3]hexane **189** by DMDO in quantitative yield. Addition of a higher order cuprate yielded ketone **190**, which was then selectively reduced with lithium tri-*tert*-butoxy aluminum hydride to give alcohol **191**. Deprotection of the Boc-group with trifluoroacetic acid afforded D-erythro-sphinganine **192**.



Scheme 52.

## 7. 1,4-Dioxaspiro[2.3]hexan-5-ones

Exploiting the potential of  $\beta$ -lactones as synthetic intermediates and in particular their application to natural product total syntheses<sup>92</sup> culminated in the first example of the novel 1,4-dioxaspiro[2.3]hexan-5-one ring system.<sup>93</sup> One endeavor required direct access to an *anti*-*cis*- $\gamma$ -hydroxy- $\beta$ -lactone (e.g.,  $\beta$ -lactone **193**). However, existing diastereoselective methods for  $\beta$ -lactone synthesis from chiral  $\alpha$ -oxy aldehydes provide only *syn*-*cis* or *syn*-*trans* selectivity.<sup>94</sup> This led us to explore the synthesis and reactivity of 1,4-dioxaspiro[2.3]hexan-5-ones (e.g., **194**) that were envisioned to be accessible via epoxidation of optically active ketene dimers.<sup>95</sup> A subsequent and likely required in situ regio- and facially selective C–O reductive bond cleavage would allow access to the desired *anti*-*cis*- $\gamma$ -hydroxy- $\beta$ -lactone **193** (Scheme 53).



Scheme 53.

Oxidation of ketene dimers with DMDO<sup>39</sup> successfully yielded 1,4-dioxaspiro[2.3]hexan-5-ones analogous with spiroepoxy oxetanes<sup>88</sup> and spirocyclopropyl- $\beta$ -lactones.<sup>79b</sup> The oxidation was applicable to a number of functionalized ketene dimers **195** to give several 1,4-dioxaspiro[2.3]hexan-5-ones **194** in modest to good yields (Table 1).

Table 1

Epoxidation of ketene dimers leading to 1,4-dioxaspiro[2.3]hexan-5-ones **194/196**<sup>a</sup>

Entry	R	Compound	dr <sup>b</sup> ( <b>194/196</b> )	Yield <sup>c</sup> (%)
1	<i>n</i> -Bu	<b>194a</b>	14:1	80
2	CyCH <sub>2</sub>	<b>194b</b>	10:1	76
3	PhCH <sub>2</sub>	<b>194c</b>	24:1	57
4	( <i>i</i> -Pr <sub>3</sub> )SiO(CH <sub>2</sub> ) <sub>4</sub>	<b>194d</b>	17:1	40
5	N <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub>	<b>194e</b>	16:1	61

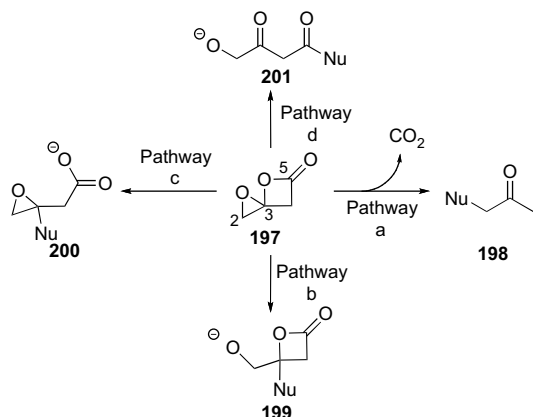
<sup>a</sup> Epoxidations were performed at ~0.1 M concentration using isolated, purified ketene dimers **195a–e** prepared by the method of Calter.<sup>95</sup>

<sup>b</sup> Ratios determined by analysis of crude reaction mixtures by <sup>1</sup>H NMR (500 MHz).

<sup>c</sup> Refers to isolated, purified (SiO<sub>2</sub>) yields.

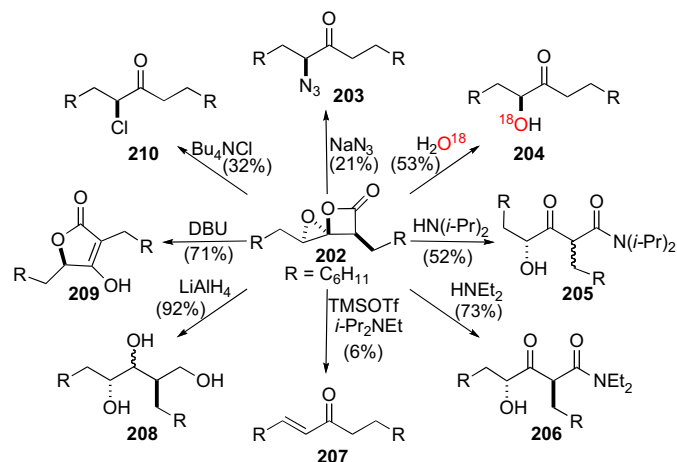
Four possible modes of reactivity with nucleophiles were envisioned upon consideration of the functionalities present in this ring system (Scheme 54). The first mode is addition to the distal epoxide C–O bond, pathway 'a', which would lead to a  $\gamma$ -substituted  $\beta$ -keto-carboxylate. Subsequent facile decarboxylation would yield  $\alpha$ -substituted ketones **198** as the final product. The second mode, pathway 'b', involves addition to an oxocarbenium derived from cleavage of the epoxide ring at the spirocenter resulting in a  $\gamma$ -hydroxy- $\beta$ -lactone **199**, which was the initially desired reaction manifold to obtain the requisite  $\beta$ -lactone for haterumalide synthesis.<sup>96</sup> Alternatively, a nucleophile could add to an oxocarbenium derived from cleavage of the  $\beta$ -lactone ring at the spirocenter instead of the epoxide (pathway 'c'), which would result in the formation of an epoxy-acid **200**. The final mode, pathway 'd', involves nucleophilic addition at the  $\beta$ -lactone carbonyl leading to acylation and cleavage of both rings to initially yield a  $\gamma$ -hydroxy- $\beta$ -keto-acid **201**.

Though four possible modes of reactivity potentially exist for 1,4-dioxaspiro[2.3]hexan-5-ones, the predominant pathways are 'a'



Scheme 54.

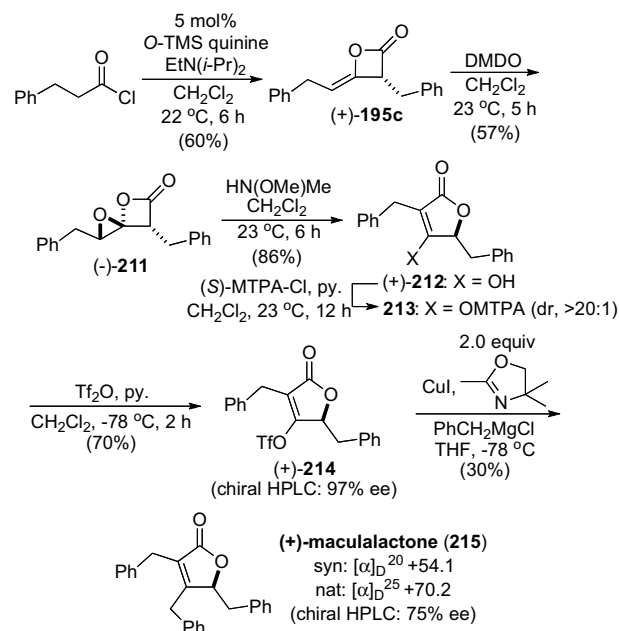
and 'd', whereas reactions proceeding through pathway 'b' or 'c' have not been observed to date. Nucleophilic addition by pathway 'a' was demonstrated by opening of spiroepoxy- $\beta$ -lactone **202** to  $\alpha$ -azidoketone **203** and  $\alpha$ -chloroketone **210**, which were obtained upon exposure to tetrabutylammonium chloride and sodium azide, respectively (Scheme 55). Two different reaction manifolds were observed by reaction of spiroepoxy- $\beta$ -lactone **202** with two different amines. Reaction with the less sterically hindered diethylamine resulted in a single diastereomer of a  $\beta$ -keto-amide **206** arising from simple nucleophilic addition through pathway 'd'. However, when spiroepoxy- $\beta$ -lactone **202** was exposed to the more sterically hindered amine, diisopropylamine, it surprisingly resulted in essentially a 1:1 mixture of diastereomeric keto-amides **205**. While this initial result was intriguing, our only viable initial hypothesis was that the reaction had to proceed through an intermediate in which the  $\alpha$ -stereocenter was lost prior to or as a result of nucleophilic addition of the amine since A<sup>1,3</sup> strain severely retards the epimerization of  $\alpha$ -substituted  $\beta$ -keto-amides.<sup>97</sup> In fact, exposure of a single diastereomer of diethyl amide **206** to deuterated diisopropylamine led to no deuterium incorporation, which is suggestive of no epimerization of that center over 4 h. The reaction of spiroepoxy- $\beta$ -lactone **202** with water over prolonged period of time led to  $\alpha$ -hydroxy ketone **204**. Mechanistically, there are two routes that could provide the same ketone product and in this instance, use of heavy water, H<sub>2</sub>O<sup>18</sup>, served to unequivocally infer the mechanism followed. The results indicate, not unexpectedly, that nucleophilic attack of water occurs exclusively at C2 leading to ketone **204** in analogy to several related systems described above. Spiroepoxy- $\beta$ -lactone **202** also reacted with base



Scheme 55.

in the presence of Lewis acid to provide a low yield of  $\alpha,\beta$ -unsaturated ketone **207** (Scheme 55). Reduction of the spiroepoxy- $\beta$ -lactone **202** with lithium aluminum hydride gave the corresponding triol **208** in excellent yield, which is a result of initial addition to the carbonyl carbon (pathway 'd'). No deoxygenation was observed at C3 or C5, which is also consistent with reduction of  $\beta$ -lactones with metal hydrides leading to acyl C–O versus C–O alkyl cleavage. Also, the product obtained from the reduction of the  $\beta$ -lactone carbonyl suggests existence of an  $\alpha$ -hydroxy ketone that is then unselectively reduced to the observed triol **208**. Interestingly, when spiroepoxy- $\beta$ -lactone **202** was exposed to the tertiary base, DBU, the tetronic acid derivative **209** was obtained as the sole product.

The utility of 1,4-dioxaspiro[2.3]hexan-5-ones was demonstrated by an enantioselective total synthesis of maculactone A **215** (Scheme 56). Maculactone A belongs to a family of  $\gamma$ -lactone containing natural products isolated from the marine cyanobacterium *Kyrtuthrix maculans* and found to inhibit growth of marine bivalves thus possessing potential use as an anti-fouling agent.<sup>98</sup> 1,4-Dioxaspiro[2.3]hexan-5-one **211** was prepared from the optically active ketene dimer **195c**,<sup>99</sup> derived from enantioselective homodimerization of hydrocinnamoyl chloride, and subsequent epoxidation with DMDO.<sup>93</sup> Rearrangement to the tetronic acid **212** with *N*-methyl-*N*-methoxy amine followed by triflation afforded tetronate (+)-**214** readied for coupling in good yield. The optical purity of the tetronic acid was determined indirectly to be >95% ee as determined by <sup>19</sup>F NMR (dr, >20:1) of the derived Mosher ester **213** and the optical purity of the derived triflate was also determined by chiral HPLC analysis (97% ee). The synthesis was completed following a challenging coupling to introduce the final benzyl group in this natural product. The best conditions found involved the use of a benzyl cuprate reagent bearing an oxazoline ligand providing (+)-maculactone A (**215**) in moderate yield.<sup>100</sup> Chiral HPLC analysis confirmed what measurement of optical rotations suggested, namely that some epimerization had occurred during coupling leading to the natural product in 75% ee. Antibacterial studies, performed by Prof. Christian Melander and Mr. Steven A. Rodgers of the Chemistry Department at North Carolina State University, revealed that synthetic (+)-maculactone exhibits IC<sub>50</sub> values of 210 and 390 nM against VRE (ATCC #51559) and MRSA (ATCC #BAA-44), respectively, and that this activity was driven by a non-microbicidal mechanism.



Scheme 56.



## 8. Conclusions

Recent advances in the synthesis of small heterocyclic rings including asymmetric routes have enabled access to several novel spiroheterocycles that serve as useful chiral synthons in organic synthesis including natural and unnatural product targets. The synthesis of these ring systems also provided access to molecules of theoretical interest for unprecedented studies of ring strain, anomeric effects, and reactivity patterns. These novel ring systems undergo various rearrangements with high stereoselectivity and thus provide efficient chirality transfer, while more traditional methods toward similar products are often less stereoselective. The combination of novel reactivity and high stereochemical control provides certainty that there will be continued interest in development of innovative transformations and continued exploitation of spiroheterocycles in synthetic endeavors.

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### Biographical sketch



**Richard J. Duffy** was born in Wilmington, Delaware. He received a B.S. degree in Chemistry and B.S. degree in Botany in 2001 from the University of Oklahoma. In December 2007, he received his Ph.D. degree in Chemistry under Professor Daniel Romo at Texas A&M University. His doctoral research focused on the synthesis and application of spiroepoxy- $\beta$ -lactones to natural product synthesis and trans-selective cross-couplings of 1,1-dichloroolefins. He began his postdoctoral studies with Professor Michael P. Doyle at the University of Maryland in November 2007.



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**Daniel Romo** received his B.A. in chemistry/biology from Texas A&M and a Ph.D. in Chemistry from Colorado State University as an NSF Minority Graduate Fellow under the tutelage of the late Professor Albert I. Meyers. Following postdoctoral studies at Harvard as an American Cancer Society Fellow, with Professor Stuart L. Schreiber he began his independent career at Texas A&M in 1993 and is currently Professor of Chemistry. Research interests in the Romo Group are at the interface of chemistry and biology focused on total synthesis and biomechanistic studies of natural products and the asymmetric synthesis and application of  $\beta$ -lactones in organic synthesis and as potential drug candidates.