

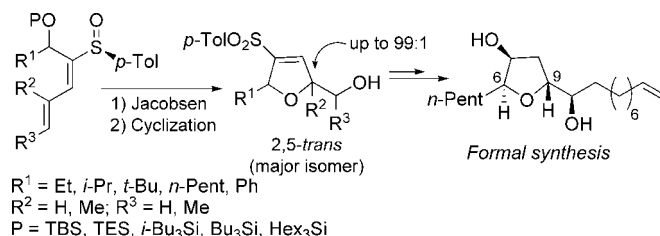
Highly Diastereoselective Katsuki–Jacobsen Oxidation–Epoxidation of α -Silyloxy Sulfinyl Dienes: Synthetic Applications

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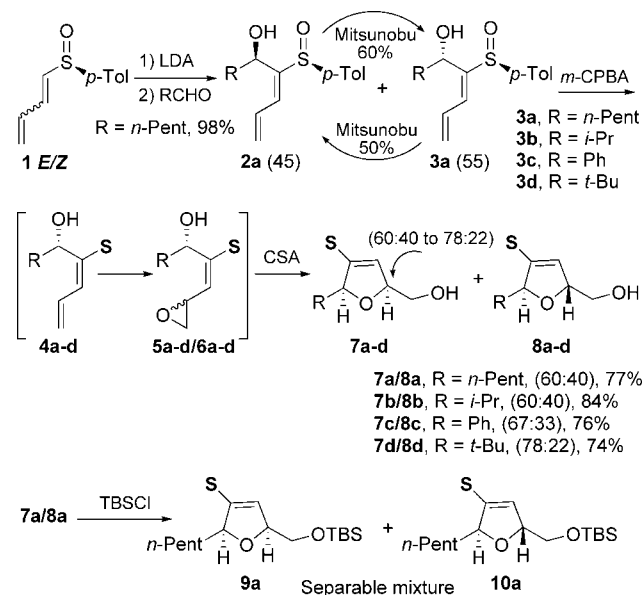
Katsuki–Jacobsen oxidation–epoxidation of acyclic α -silyloxy sulfinyl dienes, followed by acid-promoted cyclization, leads to 2,5-*trans*-sulfonyl dihydrofurans with good selectivities. As an application, the formal syntheses of (6*S*,7*S*,9*R*,10*R*)- and (6*S*,7*S*,9*S*,10*S*)-6,9-epoxynonadec-18-ene-7,10-diols is reported.

Introduction

The catalytic asymmetric epoxidation of C=C double bonds is one of the most powerful transformations known to organic chemists and plays an important role in the synthesis of optically active organic compounds. Indeed, since the invention of the Sharpless asymmetric epoxidation,¹ there has been an increasing demand for catalyst-controlled processes that allow efficient and predictable access to enantioenriched oxiranes. Katsuki and Jacobsen described in the early 1990s their efficient catalytic procedures using metal-ligated systems for the electrophilic delivery of oxygen.² Since then, the use of Mn–salen complexes has been proven to be a general and efficient method for the enantioselective epoxidation of not just unfunctionalized olefins but also more complex dienes and enynes.³ Herein, we report in full our results on the Katsuki–Jacobsen epoxidation of a variety of α -hydroxy dienyl sulfoxides and derivatives as part of our studies on the stereoselective synthesis of oxiranes and its application to the construction of densely functionalized tetrahydrofurans.

In recent years, we have been studying in depth the nucleophilic and electrophilic epoxidation of α -hydroxy dienyl sul-

SCHEME 1. Preparation of Starting Materials and Sulfonyl Dihydrofurans (S = SO₂*p*-Tol)



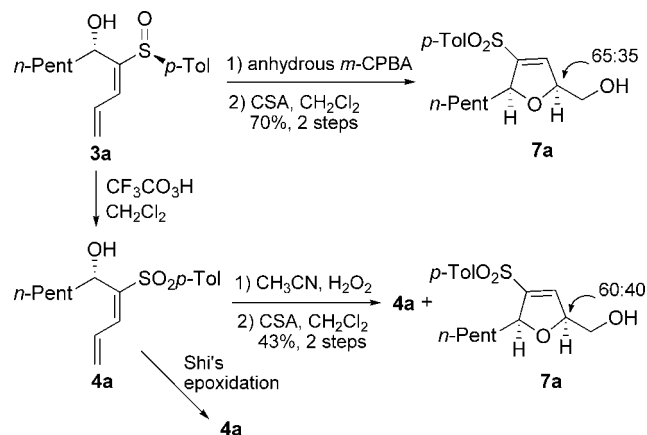
foxides as versatile routes to highly functionalized sulfinyl and sulfonyl tetrahydrofurans.⁴ Scheme 1 shows an outline of our strategy that entails lithiation of the mixture of dienes **1E/Z**⁵ and condensation with freshly distilled aldehydes, followed by chromatographic separation, to afford diastereomeric diols **2** and **3**.⁶ These diastereomers were interconverted by a Mitsunobu protocol. The

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SCHEME 2. Failed Epoxidation–Cyclization Experiments



treatment of the chosen diastereomers **3a–d**, prepared as described above, with *m*-CPBA in toluene resulted in a fast oxidation of sulfur, producing sulfones **4a–d**, followed by a slow epoxidation at the distal double bond with low stereochemical control. In a one-pot sequence, the resulting monoepoxides **5a–d/6a–d** were treated with catalytic CSA to afford good yields of predominantly 2,5-*cis* mixtures of sulfonyl dihydrofurans **7a–d/8a–d** that were difficult to separate by chromatography. Silylation of these mixtures with TBSCl in the presence of imidazole allowed for a straightforward separation of both diastereomers by column chromatography.

Results and Discussion

In view of the low selectivities associated with the use of *m*-CPBA, we decided to explore other alternatives. The use of pure anhydrous *m*-CPBA instead of the commercially available reagent did not lead to a substantial enhancement of selectivity. Similarly, the reaction of diene **3a** with $\text{CF}_3\text{CO}_3\text{H}$ ⁷ led just to sulfonyl diene **4a**. Furthermore, the epoxidation of substrate **4a** under Payne conditions occurred with no changes in selectivity (60:40) and lower yield.⁸ After these disappointing results, we chose to explore enantioselective epoxidation conditions with our α -hydroxy diene sulfoxides or derivatives. Unfortunately, Shi's epoxidation of sulfonyl diene **4a** using commercially available D-Epoxone resulted in recovered starting material (Scheme 2).⁹

Katsuki–Jacobsen epoxidation, using the commercially available catalysts developed by Jacobsen, (*R,R*)-**JC** and (*S,S*)-**JC**,¹⁰ seemed to be a good option primarily due to the excellent results obtained by Fuchs for cyclic diene sulfoxides.¹¹ Nonetheless, it

should be pointed out that acyclic diene sulfoxides were not good substrates for this chemistry.^{11a}

Despite the fact that terminal olefins have led to selectivities worse than those with substituted olefins in Katsuki–Jacobsen epoxidations, we decided to explore the Jacobsen epoxidation of α -hydroxy diene sulfoxides **3a,b,d** (Scheme 1) and sulfone **4a**, under the conditions reported by Fuchs, hoping that the combined effects of the allylic stereocenter and the chiral catalyst would lead to useful stereocontrol. These experiments resulted in a fast oxidation of sulfur to the corresponding α -hydroxy diene sulfones **4**, followed by a slow distal epoxidation. Subsequent treatment of the intermediate monoepoxides **5** and **6** with catalytic CSA afforded the expected sulfonyl dihydrofurans **8** with a modest increase of 2,5-*trans* selectivity (ca. 60:40), thus reversing the selectivity found for the *m*-CPBA protocol. In these cases, 2,5-*trans*-dihydrofurans **8a,b,d** were the major isomers in the final mixtures, with low (Table 1, entry 1) to moderate (Table 1, entry 2) conversions and fair selectivities. Longer reaction times and sequential additions of reagents were key for improving the conversion to the final products (Table 1, entries 3 and 4).

Table 2 gathers the results obtained for substrates *ent*-**4a** and **2a** with an *R* configuration at the allylic center. The use of (*R,R*)-**JC** for substrates *ent*-**4a** and **2a** (Table 2, entries 1 and 2) led to the same selectivity observed with *m*-CPBA (favoring 2,5-*cis*-dihydrofuran *ent*-**7a** after cyclization). On the other hand, using the enantiomeric catalyst (*S,S*)-**JC** (Table 2, entry 3) with diene **2a** led to an enriched mixture of 2,5-*trans*-dihydrofuran *ent*-**8a**, after cyclization with CSA.

With these preliminary results, we decided to modify our substrates to improve the selectivity of the process. The presence of bulky groups in the substrates has been shown to be important for improving the enantioselectivities in these epoxidations.¹² Therefore, introducing different silyl ethers on the hydroxyl group of our substrates seemed to be an interesting and accessible transformation. This goal was accomplished with commercially available chlorosilanes, Et_3N , and DMAP in DMF, rendering silyl ethers **11a–g** from hydroxy diene sulfoxides **3a–c** (Scheme 3). It should be pointed out that TIPS and TBDPS derivatives could not be prepared under a variety of conditions, including the use of TIPSOTf, leading instead to recovered starting materials. The unoptimized yields of these protections ranged from moderate (60–63%) to good (89%), with the recovery of starting material in some cases. With substrate **3d** (*R* = *tert*-butyl), no reaction was observed, perhaps due to its considerable steric hindrance. The protection of alcohol **2a** with an *R* configuration in the allylic center afforded silyl ether **12a** and is also shown in scheme 3.

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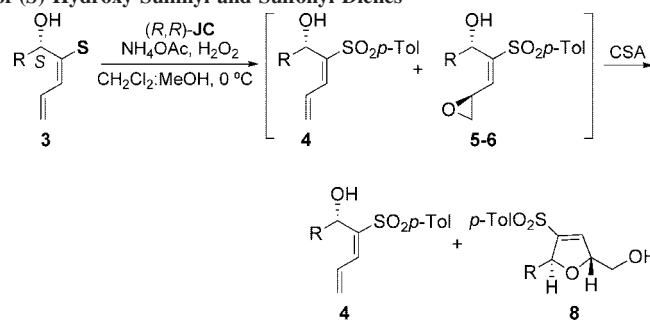
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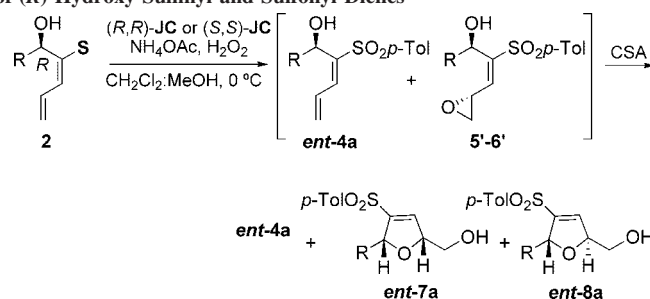
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TABLE 1. Jacobsen Epoxidation of (*S*)-Hydroxy Sulfinyl and Sulfonyl Dienes

| entry | substrate | sulfur oxidation state | conditions | yield ^b |
|-------|--------------------------------|--|---|---------------------------------------|
| 1 | 4a (R = <i>n</i> -Pent) | SO ₂ <i>p</i> -Tol ^a | 7.5% (<i>R,R</i>)- JC 1.5 equiv of NH ₄ OAc 12.0 equiv of H ₂ O ₂ , 1 day | 30% 4a + 25% 8a (64:36) |
| 2 | 3a (R = <i>n</i> -Pent) | SO <i>p</i> -Tol | 5% (<i>R,R</i>)- JC 1.0 equiv of NH ₄ OAc 8.0 equiv of H ₂ O ₂ , 16 h | 30% 4a + 60% 8a (60:40) |
| 3 | 3b (R = <i>i</i> -Pr) | SO <i>p</i> -Tol | 15% (<i>R,R</i>)- JC 3.0 equiv of NH ₄ OAc 24.0 equiv of H ₂ O ₂ , 6 days | 74% 8b (66:34) |
| 4 | 3d (R = <i>t</i> -Bu) | SO <i>p</i> -Tol | 20% (<i>R,R</i>)- JC 4.0 equiv of NH ₄ OAc 32.0 equiv of H ₂ O ₂ , 7 days | 75% 8d (65:35) ^c |

^a Sulfone **4a** was obtained by oxidation of sulfoxide **3a** with 1.5 equiv of MMPP in MeOH (2 h, 78%). ^b Yields of pure products after column chromatography. ^c The ¹H NMR spectrum of the mixture of vinyl oxiranes suggested the presence of sulfinyl monoepoxides (ca. 28%), but after cyclization with CSA, we could not isolate the corresponding sulfinyl dihydrofurans.

TABLE 2. Jacobsen Epoxidation of (*R*)-Hydroxy Sulfinyl and Sulfonyl Dienes

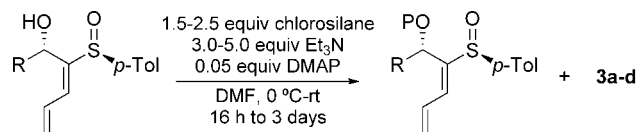
| entry | substrate | sulfur oxidation state | conditions | yield ^b |
|-------|------------------------------------|--|--|--|
| 1 | ent-4a (R = <i>n</i> -Pent) | SO ₂ <i>p</i> -Tol ^a | 7.5% (<i>R,R</i>)- JC 1.5 equiv of NH ₄ OAc 12.0 equiv of H ₂ O ₂ , 1 day | 27% ent-4a + 60% ent-8a/ent-7a (46:54) |
| 2 | 2a (R = <i>n</i> -Pent) | SO <i>p</i> -Tol | 25% (<i>R,R</i>)- JC 5.0 equiv of NH ₄ OAc 40.0 equiv of H ₂ O ₂ , 11 days | 90% ent-8a/ent-7a (40:60) |
| 3 | 2a (R = <i>n</i> -Pent) | SO <i>p</i> -Tol | 25% (<i>S,S</i>)- JC 5.0 equiv of NH ₄ OAc 40.0 equiv of H ₂ O ₂ , 11 days | 88% ent-8a/ent-7a (57:43) |

^a Sulfone **ent-4a** was obtained by oxidation of sulfoxide **2a** with 1.5 equiv of MMPP in MeOH (2 h, 78%). ^b Yields of pure products after column chromatography.

Table 3 summarizes the results for the epoxidation and cyclization of silyloxy derivatives **11a–g**. The crude mixtures were filtered through silica gel, treated with TBAF in THF to cleave the silyl ether, and then cyclized in the presence of CSA. In the early experiments that did not reach completion, silyloxy sulfonyl dienes **13** were present in the crude mixtures; these led to sulfonyl dienols **4** upon deprotection. Performing sequential additions of reagents improved the conversions and yields of these epoxidations. In spite of the moderate yield (60%), the use of a TBS group (Table 3, entry 1, substrate **11a**) produced an increase in *trans* selectivity and, after desilylation and cyclization, resulted in a 71:29 ratio favoring the 2,5-*trans*

isomer **8a**. This result represents a considerable improvement relative to the substrate, with the free OH using (*R,R*)-**JC**. In contrast, the treatment of **11a** with *m*-CPBA in toluene led to an equimolar mixture of diastereomeric vinyl oxiranes. Alternatively, the reaction of **11a** with (*S,S*)-**JC** (mismatched pair) afforded silyloxy sulfonyl diene **13a** and a (40:60) mixture of monoepoxides **14a** that were not desilylated/cyclized (Table 3, entry 2).

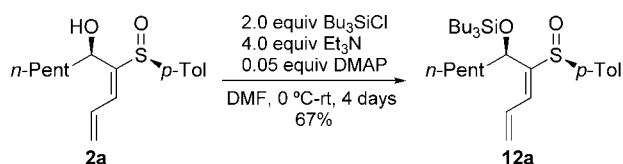
The use of a TES group (Table 3, entries 3 and 4, substrate **11b**) produced a slight increase in selectivity (77:23) with (*R,R*)-**JC** and gave a result identical to entry 2 with (*S,S*)-**JC** (Table 3, entry 4). Similarly, the use of an *i*-Bu₃Si group (Table 3,

SCHEME 3. Silylation of α -Hydroxy Sulfinyl Dienes

| | | |
|--------------------------------|---|--------------------|
| 3a , R = <i>n</i> -Pent | 11a , R = <i>n</i> -Pent, P = TBS, (60%) ^a | (39%) ^b |
| 3b , R = <i>i</i> -Pr | 11b , R = <i>n</i> -Pent, P = TES, (89%) ^a | |
| 3c , R = Ph | 11c , R = <i>n</i> -Pent, P = <i>i</i> -Bu ₃ Si, (63%) ^a | |
| 3d , R = <i>t</i> -Bu | 11d , R = <i>n</i> -Pent, P = Bu ₃ Si, (64%) ^a | (15%) ^b |
| | 11e , R = <i>n</i> -Pent, P = Hex ₃ Si, (48%) ^a | (40%) ^b |
| | 11f , R = <i>i</i> -Pr, P = Bu ₃ Si, (75%) ^a | |
| | 11g , R = Ph, P = Bu ₃ Si, (60%) ^a | (31%) ^b |

^a Yields of pure products after column chromatography.

^b Recovered starting material after column chromatography.



entry 5) led to a 90:10 ratio of dihydrofurans with (*R,R*)-**JC**, and the epoxidation with the enantiomeric catalyst (Table 3, entry 6) resulted in lower reactivity and selectivity (mismatched pair). With Bu₃Si derivative **11d** and (*R,R*)-**JC**, a 90:10 selectivity was observed (Table 3, entry 7) with excellent yield. To clarify the role of the sulfoxide in the process, this protocol was applied to sulfone **13d** (Table 3, entry 8), with comparable results. Thus, it appears that the sulfoxide moiety does not exert a significant influence on the stereochemical outcome of the process. Then we decided to check the effect of a Hex₃Si group, and the selectivity found was 90:10 again (Table 3, entry 9). Finally, the scope of the methodology was tested with substrates **11f** (R = isopropyl) and **11g** (R = Ph) (Table 3, entries 10 and 11), which bear a Bu₃Si protecting group. In both cases, the selectivity measured was 90:10.

These results suggested that bulky and ramified silyl ethers at the allylic position were effective directing groups, increasing the *anti* selectivity in the epoxidation due to their steric hindrance that blocks a face of the diene. The enhanced selectivity found for silyl ethers bearing longer alkyl chains is noteworthy (Table 3, compare entries 3 and 7).

Table 4 shows the experiments carried out with substrate **12a** with an *R* configuration at the allylic position. The use of (*R,R*)-**JC** gave a 60:40 selectivity favoring epoxidation by the face that produces 2,5-*trans*-dihydrofurans after cyclization. With (*S,S*)-**JC**, the *trans* selectivity increased to 86:14. In both cases, the yields of the final product **ent-8a** were good after four additions of reagents in the oxidation–epoxidation step. Thus, it appears that the stereochemical outcome of the process is primarily controlled by the substrate. The optical purity of dihydrofurans **8a** and **ent-8a** was secured by formation of their TBDMS ethers and by separation and comparison of their optical rotation data with data measured for samples obtained with *m*-CPBA.

Encouraged by these promising results, we decided to extend the study of this epoxidation–cyclization protocol to more substituted dienes, with the purpose of obtaining more substituted tetrahydrofurans in high diastereomeric ratios. This approach would allow us to access dihydrofurans with an additional stereocenter when starting from a diene with a substituent in the terminal position and dihydrofurans with a quaternary center when a substituent is placed in the internal

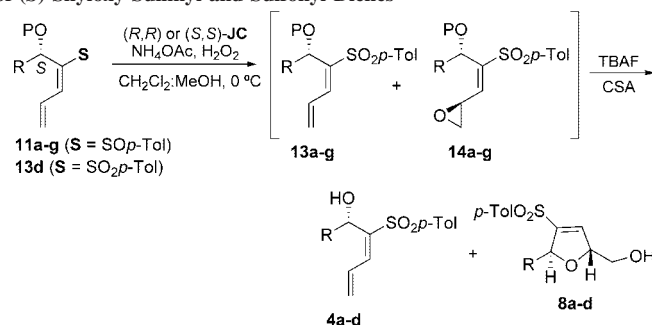
position of the diene system. Both are important moieties present in a wide range of natural products such as the *Annonaceous acetogenins*¹³ or the amphidinolides.¹⁴ Following the same methodology described before for nonsubstituted dienes, α -hydroxy dienyl sulfoxides **15a,b** and **16a,b** were prepared in good yields from the corresponding sulfinyl dienes (Scheme 4). These diastereomers could be interconverted readily by a Mitsunobu protocol. Prior to submitting our new α -hydroxy sulfinyl dienes to the Jacobsen epoxidation and cyclization, we tested the behavior of substrates **16a,b** with the *m*-CPBA/CSA protocol. Thus, hydroxy sulfinyl diene **16a** afforded an inseparable mixture of the two possible sulfonyl dihydrofurans **20** and **21** with low selectivity, with the 2,5-*cis* being the major diastereomer (Scheme 4). When substrate **16b** was treated with *m*-CPBA/CSA, the major sulfonyl dihydrofuran in the mixture was **23**. Thus, a slight reversal of the general trend was observed when a methyl substituent is located in the internal position of the diene.

In view of the good selectivities obtained before with the Bu₃Si group, we decided to use it again as a reference protecting–directing group for the new substrates. Scheme 5 summarizes the silylation and oxidation of these more substituted dienes to which afford the expected silyloxy derivatives (**24a,b**, **25**, **26a,b**, and *ent*-**26a**). It should be mentioned that sulfinyl dienol **15b** could not be protected in this manner, leading instead to the complete recovery of starting material.

Table 5 shows the results of the epoxidation under Jacobsen's conditions for substrates **16a**, **24a**, **26a**, **15a**, **25**, and *ent*-**26a**. During these experiments, we were able to isolate and partially characterize the mixtures of monoepoxides **19/27**, **28/29**, *ent*-**19a/ent-27**, and *ent*-**28/ent-29** prior to their cyclization into the corresponding dihydrofurans. As it was mentioned before for simpler substrates, the reactions were generally slow and required sequential additions of reagents over a few days to reach completion, with a fast oxidation of the sulfinyl group to the sulfone being observed. The initial experiments were carried out with **16a** and **15a** having a free hydroxyl group; these substrates afforded selectivities better for the matched pairs (Table 5, entries 1 and 3) than when the diene was not substituted, in agreement with the general rule that substituted olefins are better substrates for Jacobsen's epoxidation. Epoxidation with (*R,R*)-**JC** afforded an 87:13 mixture of monoepoxides **19a/27** when starting from hydroxy sulfinyl diene **16a** (Table 5, entry 1). Subsequent cyclization with CSA gave a mixture of sulfonyl dihydrofurans **21** and **30**. Separation of this mixture by column chromatography allowed us to identify (by NMR and NOE analysis) each diastereomer and to conclude that both products had 2,5-*trans* configuration and were epimers at the new stereocenter C-2'. The major product **21** was identical to the minor product obtained with the *m*-CPBA/CSA protocol. The minor product **30** should arise from a *cis*-monoepoxide **27** by acid-catalyzed cyclization. Reaction of **16a** with (*S,S*)-**JC** (Table 5, entry 2) resulted in an incomplete epoxidation after four additions of reagents and 5 days (mismatched pair). Cyclization mediated by CSA gave a 75:25 mixture of sulfonyl dihydrofurans **20/21** analogous to that obtained with *m*-CPBA/CSA. It is noteworthy that with hydroxy sulfinyl diene **15a** reasonable catalyst-directed diastereoselectivities were achieved

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TABLE 3. Jacobsen Epoxidation of (*S*)-Silyloxy Sulfinyl and Sulfonyl Dienes

| entry | substrate | P | sulfur oxidation state | conditions | yield ^a |
|-------|---------------------------------|------------------------------|--|---|--|
| 1 | 11a (R = <i>n</i> -Pent) | TBS | SO _{<i>p</i>} -Tol | 5% (<i>R,R</i>)- JC 1.0 equiv of NH ₄ OAc 8.0 equiv of H ₂ O ₂ , 2 days | 30% 4a + 60% 8a (71:29) |
| 2 | 11a (R = <i>n</i> -Pent) | TBS | SO _{<i>p</i>} -Tol | 5% (<i>S,S</i>)- JC 1.0 equiv of NH ₄ OAc 8.0 equiv of H ₂ O ₂ , 2 days | 13a (49) + 14a (51) (40:60) ^b |
| 3 | 11b (R = <i>n</i> -Pent) | TES | SO _{<i>p</i>} -Tol | 5% (<i>R,R</i>)- JC 1.0 equiv of NH ₄ OAc 8.0 equiv of H ₂ O ₂ , 2 days | 35% 4a + 60% 8a (77:23) |
| 4 | 11b (R = <i>n</i> -Pent) | TES | SO _{<i>p</i>} -Tol | 5% (<i>S,S</i>)- JC 1.0 equiv of NH ₄ OAc 8.0 equiv of H ₂ O ₂ , 2 days | 13c (51) + 14c (49) (40:60) ^b |
| 5 | 11c (R = <i>n</i> -Pent) | <i>i</i> -Bu ₃ Si | SO _{<i>p</i>} -Tol | 10% (<i>R,R</i>)- JC 2.0 equiv of NH ₄ OAc 16.0 equiv of H ₂ O ₂ , 3 days | 24% 4a + 73% 8a (90:10) |
| 6 | 11c (R = <i>n</i> -Pent) | <i>i</i> -Bu ₃ Si | SO _{<i>p</i>} -Tol | 20% (<i>S,S</i>)- JC 4.0 equiv of NH ₄ OAc 32.0 equiv of H ₂ O ₂ , 6 days | 21% 4a + 75% 8a (64:36) |
| 7 | 11d (R = <i>n</i> -Pent) | Bu ₃ Si | SO _{<i>p</i>} -Tol | 20% (<i>R,R</i>)- JC 4.0 equiv of NH ₄ OAc 32.0 equiv of H ₂ O ₂ , 6 days | 89% 8a (90:10) |
| 8 | 13d (R = <i>n</i> -Pent) | Bu ₃ Si | SO ₂ <i>p</i> -Tol ^c | 15% (<i>R,R</i>)- JC 3.0 equiv of NH ₄ OAc 24.0 equiv of H ₂ O ₂ , 6 days | 97% 14a (90:10) ^b |
| 9 | 11e (R = <i>n</i> -Pent) | Hex ₃ Si | SO _{<i>p</i>} -Tol | 25% (<i>R,R</i>)- JC 5.0 equiv of NH ₄ OAc 40.0 equiv of H ₂ O ₂ , 6 days | 90% 8a (90:10) |
| 10 | 11f (R = <i>i</i> -Pr) | Bu ₃ Si | SO _{<i>p</i>} -Tol | 15% (<i>R,R</i>)- JC 3.0 equiv of NH ₄ OAc 24.0 equiv of H ₂ O ₂ , 6 days | 95% 8b (90:10) |
| 11 | 11g (R = Ph) | Bu ₃ Si | SO _{<i>p</i>} -Tol | 20% (<i>R,R</i>)- JC 4.0 equiv of NH ₄ OAc 32.0 equiv of H ₂ O ₂ , 5 days | 95% 8c (90:10) |

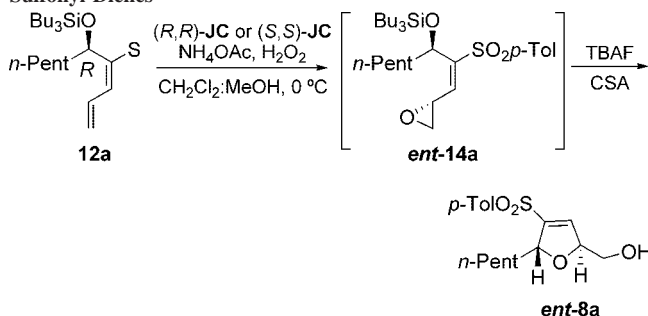
^a Yields of pure products after column chromatography. ^b Mixtures that were not desilylated/cyclized. Data taken from ¹H NMR of the crude products. ^c Sulfone **13d** was obtained from sulfoxide **11d** by oxidation with 1.5 equiv of MMPP in MeOH (2 h, 71%).

in favor of the major products 2,5-*trans*-dihydrofuran **ent-21** and 2,5-*cis*-dihydrofuran **ent-20**, respectively (Table 5, entries 3 and 4).

The Jacobsen epoxidation of silylated substrates (P = SiBu₃) led again to an important increase in the selectivity of the process. With these derivatives, it was necessary to desilylate (TBAF in THF) the mixtures of monoepoxides prior to cyclization. Although we observed variable amounts of dihydrofurans after the reaction with TBAF, we decided to maintain the treatment with CSA to ensure that cyclization was complete. The reaction of silyloxy sulfinyl diene **24a** with (*R,R*)-**JC** gave a highly selective mixture of monoepoxides **28** and **29** (96:4), which was transformed into dihydrofurans **21** and **30** in good yields after three steps (Table 5, entry 5). The mismatched pair (reaction with (*S,S*)-**JC**) for substrate **24a** afforded a mixture of dihydrofurans **20/21** comparable to that obtained with *m*-CPBA/CSA (Table 5, entry 6). On the other hand, the reaction of silyloxy derivative **25** with (*S,S*)-**JC** also showed an excellent

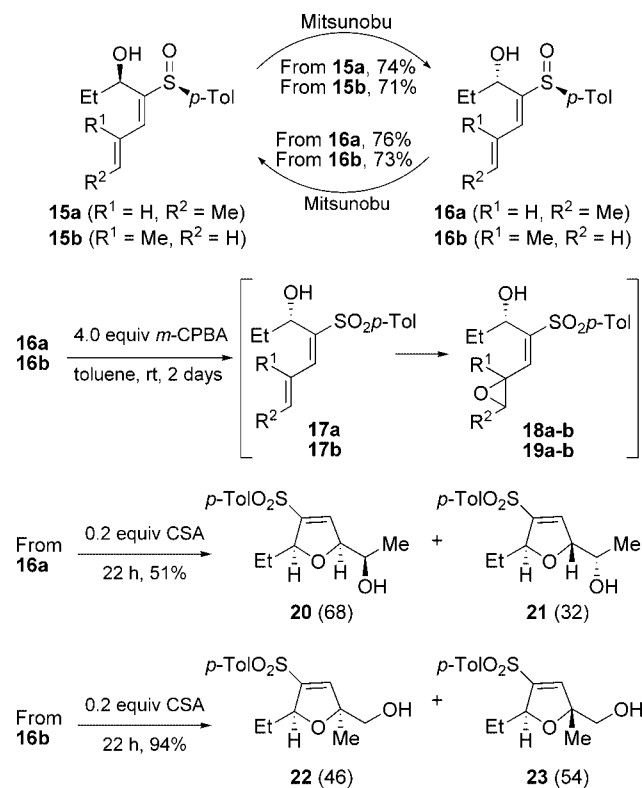
selectivity (96:4) (Table 5, entry 7). After desilylation and cyclization of the 96:4 mixture of monoepoxides **ent-28/ent-29**, only the major sulfonyl dihydrofuran **ent-21** was isolated. In a matched scenario, sulfonyl derivatives **26a** and **ent-26a** (Table 5, entries 8 and 10) produced a slight, but appreciable, drop in the formation of the minor products to almost the limit of detection (99:1 ratio) for the reaction of **ent-26a** with (*S,S*)-**JC** (Table 5, entry 10). We do not have a clear explanation for this small enhancement of selectivity found for the dienyl sulfones relative to the related sulfoxides. Finally, the epoxidation of sulfone **26a** with (*S,S*)-**JC** (Table 5, entry 9) led to a 76:24 mixture of monoepoxides **28** and **28'**, which was not cyclized.

To test the usefulness of this process for obtaining densely functionalized tetrahydrofuran derivatives, we examined the nucleophilic epoxidation of **21**, which afforded a 93:7 mixture of sulfonyl oxiranes **31** in good yield (Scheme 6).⁴ Our recently described reductive cleavage of this moiety with

TABLE 4. Jacobsen Epoxidation of (*R*)-Silyloxy Sulfinyl and Sulfonyl Dienes

| entry | substrate | sulfur oxidation state | conditions | yield ^a |
|-------|------------|------------------------|---|---------------------------|
| 1 | 12a | <i>SOp</i> -Tol | 20% (<i>R,R</i>)- JC 4.0 equiv of NH_4OAc 32.0 equiv of H_2O_2 , 11 days | 98% ent-8a (60:40) |
| 2 | 12a | <i>SOp</i> -Tol | 20% (<i>S,S</i>)- JC 4.0 equiv of NH_4OAc 32.0 equiv of H_2O_2 , 11 days | 89% 8a (86:14) |

^a Yields of pure products after column chromatography.

SCHEME 4. Substrates with Substitution in the Diene System

freshly prepared MgI_2^{15} gave cleanly the desired ketone **32**, thus opening a wide range of future synthetic applications.

Table 6 summarizes the results obtained for hydroxy and silyloxy sulfinyl dienes with internal substitution at the diene moiety, which unfortunately did not lead to useful levels of diastereoselectivity. The reaction of **16b** with (*R,R*)-**JC** occurred

with low selectivity, affording after cyclization a 39:61 mixture of sulfonyl dihydrofurans **22** and **23** (Table 6, entry 1). To our surprise, silyloxy derivative **24b** led to mixtures of sulfinyl oxiranes **33** (Table 6, entries 2 and 3). Considering that the reaction conditions were comparable to other cases studied, it is a peculiar behavior that is probably related to the conformation adopted by this diene. It is tentatively proposed that the methyl group in this position is forcing a certain arrangement of the allylic center so that the oxidant can not access readily the sulfur atom lone pair because of the presence of the bulky silyl ether. As expected, a reversal in the facial selectivity was achieved by changing to the enantiomeric catalyst. Due to the low selectivities found, these mixtures of monoepoxides were not studied any further. Finally, sulfonyl silyloxy derivative **26b** afforded a modest increase in selectivity to 23:77 (Table 6, entry 4).

We have rationalized the results of this study on the basis of a conformational analysis of the starting material, assuming an early transition state with the more stable conformer that is also the more reactive. We have also taken into account that the sulfoxide does not participate in the process because it is rapidly oxidized to the sulfone under these reaction conditions in most cases we examined. The precise balance of allylic 1,2-strain (*R* and the sulfonyl moiety) and 1,3-strain (*R* and the remote double bond) would dictate that the favored reactive conformer is **A** in all cases tested.

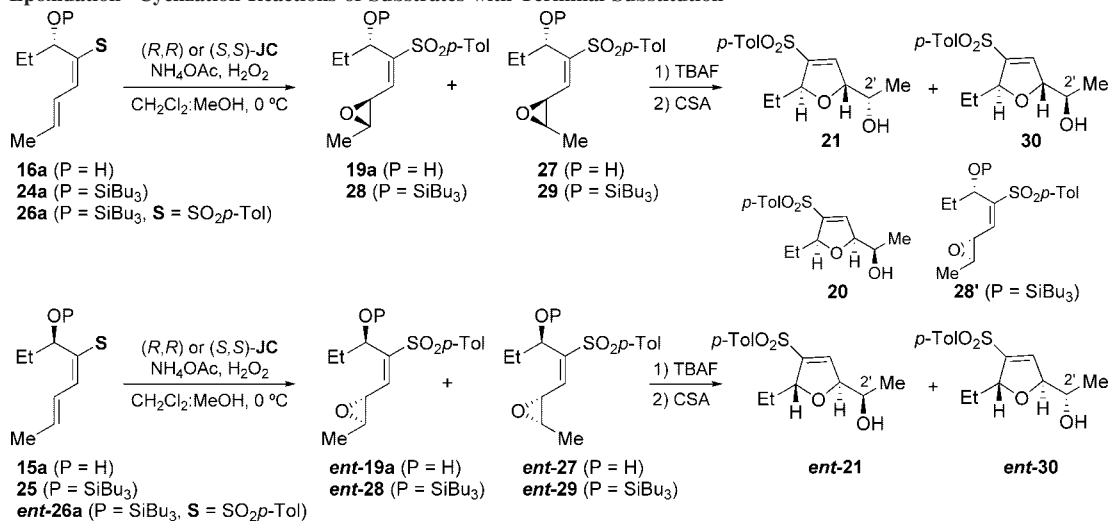
Unsubstituted Dienes. For substrates with an *S* configuration at the allylic center, the predominant approach of the oxo complex occurs by the β face of the molecule, affording an *anti*-monoepoxide (Scheme 7). This intermediate is the precursor of 2,5-*trans*-sulfonyl dihydrofurans. When P is a bulky silyl ether (such as Bu_3Si), its presence dictates the facial selectivity of the epoxidation, and it is responsible for the increased selectivities. Similarly, for substrates with an *R* configuration at the allylic center, the approach of the oxo complex by the α face of the diene on the major conformer **A** produces an *anti*-monoepoxide as the major product.

Substituted Dienes. Once the absolute stereochemistry of the sulfonyl dihydrofurans isolated was determined by careful analysis of their NMR data, including NOE experiments, and by relying on the known stereochemical outcome of the results found for *m*-CPBA, we hypothesized that the minor 2,5-*trans* products should arise from a *cis*-monoepoxide. In the case of (*S*)-hydroxy and -silyloxy sulfinyl dienes, an α attack of the oxo complex to the reactive conformer **A**, followed by evolution of the radical intermediate, leading to the *cis*-monoepoxide is proposed (Scheme 8). For the *R* series, a β attack of the oxo complex to the reactive conformer and subsequent evolution of the radical intermediate are supposed to be the key to the formation of a *cis*-monoepoxide that results in the minor sulfonyl dihydrofuran. The loss of geometry in Jacobsen epoxidations has been previously observed and generally gives rise to *trans*-oxiranes from *cis*-alkenes. In our case, it is noteworthy that we obtain *trans*-monoepoxides as major products in the epoxidation of *trans*-olefins and just small amounts of *cis*-oxiranes that are almost suppressed when P is a bulky silyl group. The precise origin of these observations is uncertain.

Synthetic Applications. Substituted tetrahydrofurans are commonly occurring substructures found in a broad array of natural products and biologically active molecules such as *Laurencia* sesquiterpenes ((-)-kumausallene), polyether antibiotics (pamamycin-607), and *Annonaceous acetogenins* (mu-

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TABLE 5. Epoxidation–Cyclization Reactions of Substrates with Terminal Substitution



| entry | substrate | conditions | monoepoxides | dihydrofurans ^c | yield ^d |
|-------|----------------|--|--|--|--------------------|
| 1 | 16a | 25% (<i>R,R</i>)- JC 5.0 equiv of NH ₄ OAc 40.0 equiv of H ₂ O ₂ , 6 days | 19a (87)/ 27 (13) ^{a,c} | 21 (87)/ 30 (13) | 70% |
| 2 | 16a | 20% (<i>S,S</i>)- JC 4.0 equiv of NH ₄ OAc 32.0 equiv of H ₂ O ₂ , 5 days | <i>b</i> | 20 (75)/ 21 (25) | 64% |
| 3 | 15a | 25% (<i>S,S</i>)- JC 5.0 equiv of NH ₄ OAc 40.0 equiv of H ₂ O ₂ , 10 days | ent-19a (83)/ ent-27 (17) ^{a,c} | ent-21 (83)/ ent-30 (17) | 71% |
| 4 | 15a | 25% (<i>R,R</i>)- JC 5.0 equiv of NH ₄ OAc 40.0 equiv of H ₂ O ₂ , 10 days | <i>b</i> | ent-20 (84)/ ent-21 (16) | 55% |
| 5 | 24a | 15% (<i>R,R</i>)- JC 3.0 equiv of NH ₄ OAc 24.0 equiv of H ₂ O ₂ , 4 days | 28 (96)/ 29 (4) ^{a,c} | 21 (96)/ 30 (4) | 77% |
| 6 | 24a | 20% (<i>S,S</i>)- JC 4.0 equiv of NH ₄ OAc 32.0 equiv of H ₂ O ₂ , 9 days | <i>b</i> | 20 (73)/ 21 (27) | 57% |
| 7 | 25 | 20% (<i>S,S</i>)- JC 4.0 equiv of NH ₄ OAc 32.0 equiv of H ₂ O ₂ , 7 days | ent-28 (96)/ ent-29 (4) ^{a,c} | ent-21 | 69% |
| 8 | 26a | 20% (<i>R,R</i>)- JC 4.0 equiv of NH ₄ OAc 32.0 equiv of H ₂ O ₂ , 5 days | 28 (97)/ 29 (3) ^{a,c} | | 81% |
| 9 | 26a | 25% (<i>S,S</i>)- JC 5.0 equiv of NH ₄ OAc 40.0 equiv of H ₂ O ₂ , 11 days | 28 (76)/ 28' (24) ^{a,c} | | |
| 10 | ent-26a | 30% (<i>S,S</i>)- JC 6.0 equiv of NH ₄ OAc 48.0 equiv of H ₂ O ₂ , 7 days | ent-28 (99)/ ent-29 (1) ^{a,c} | ent-21 | 51% |

^a Mixtures of monoepoxides isolated by filtration through silica gel. ^b Mixtures of monoepoxides that were directly desilylated/cyclized. ^c Data taken from ¹H NMR of the crude products. ^d Combined yields (two or three steps) of pure products after column chromatography.

ricatetrocin C).¹⁶ Due to the importance of these molecules and their interesting activity and unique structural characteristics, considerable effort has been devoted toward the development of methods for the stereoselective construction of substituted tetrahydrofurans.¹⁷

As an application of this study and in connection with our interest in the synthesis of natural products containing substituted THF rings, we report here the formal syntheses of the marine

epoxy lipids (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol **35**¹⁸ and (6*S*,7*S*,9*S*,10*S*)-6,9-epoxynonadec-18-ene-7,10-diol **36**.¹⁹ Since their isolation and because of their peculiar substitution, these natural products have been studied in-depth, and they have been the target of several synthetic efforts.²⁰ Our synthetic plan is shown in Scheme 9. We envisioned that we could access both natural products starting from the same α-hydroxy sulfinyl diene **3a** because the stereocenter at C-6 would be determined by the allylic center in **3a** or **11d**, and we could introduce the correct stereochemistry at C-9 by choosing

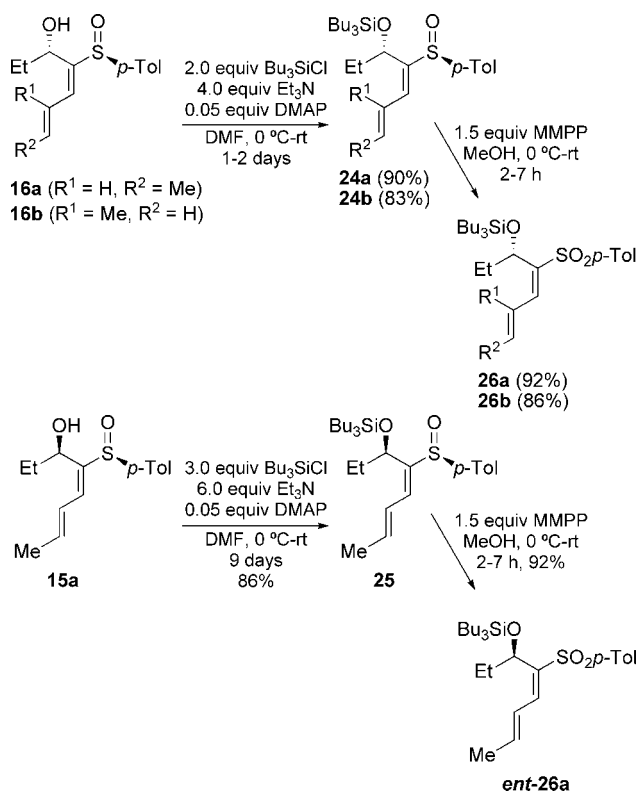
(16) (a) Suzuki, T.; Koizumi, K.; Suzuki, H.; Kurosawa, E. *Chem. Lett.* **1983**, 1639–1642. (b) Faul, M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407–2474. (c) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504–540.

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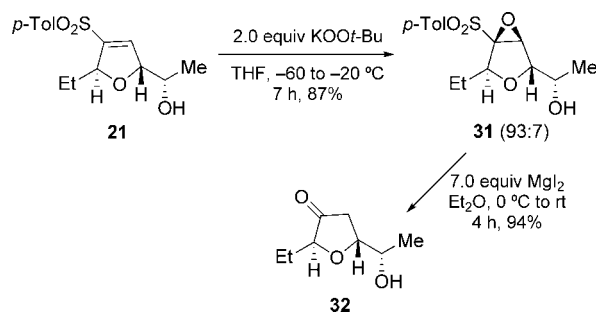
(18) Warren, R. G.; Wells, R. J.; Blount, J. F. *Aust. J. Chem.* **1980**, *33*, 891–898.

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SCHEME 5. Silylation and Oxidation of Substituted Sulfinyl Dienols



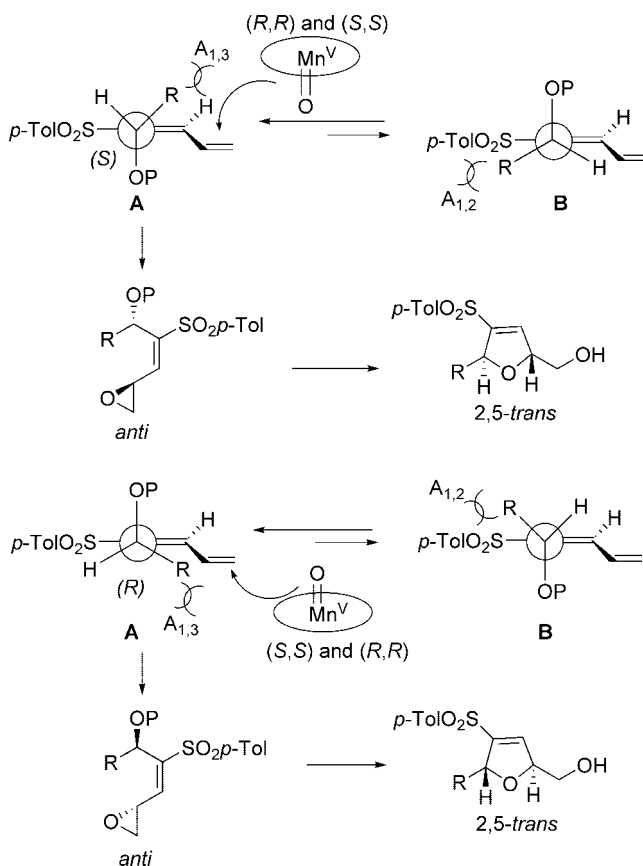
SCHEME 6. Synthesis of Tetrahydrofuran 32



the type of epoxidation. Jacobsen's epoxidation, as described in this article for **11d** ($P = \text{SiBu}_3$), would lead to a 2,5-*trans*-sulfonyl dihydrofuran that could be converted into the natural product **35**. Using the *m*-CPBA/CSA protocol on **3a** ($P = \text{H}$) would afford predominantly, but with low selectivity, the 2,5-*cis*-dihydrofuran that could be transformed into the natural product **36** in a few steps.

As described before, Jacobsen epoxidation of silyloxy sulfinyl diene **11d** gave a 90:10 mixture of monoepoxides **14d** that, after deprotection/cyclization, afforded an inseparable mixture of sulfonyl dihydrofurans **8a** (Scheme 10). Protection of the primary alcohol as a *tert*-butyldimethylsilyl ether in excellent yield allowed for the separation of diastereomers by chromatography as well as for the subsequent differentiation of the primary and secondary hydroxyls. Nucleophilic epoxidation of 2,5-*trans* diastereomer **10a** with $\text{KOO}t\text{-Bu}$ gave sulfonyl oxirane **37** as a single isomer in excellent yield.²¹ The reductive cleavage of sulfonyl oxiranes developed by our group with freshly prepared MgI_2 , followed by reduction of ketone **38** with *L*-Selectride, afforded an 85:15 mixture of alcohols **39/40**. After chromatographic separation, the secondary alcohol was protected

SCHEME 7. Stereochemical Outcome of the Process for Unsubstituted Dienes



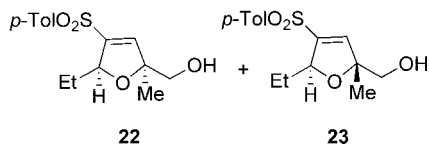
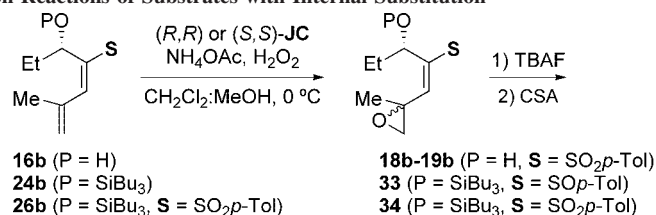
as a benzoate **41**, then the silyl ether on the primary alcohol was cleaved with Dowex in good yield for the two steps, affording **42**. Swern oxidation afforded the desired aldehyde **43** that had been transformed into **35** in one step by addition of the appropriate Grignard reagent. The spectroscopic data of **43** were identical to the reported values.^{20a}

Our synthetic approach to natural product **36** begins with the epoxidation/cyclization of hydroxy sulfinyl diene **3a** with *m*-CPBA/CSA to give a 60:40 inseparable mixture of sulfonyl dihydrofurans **8a** (Scheme 11). The silylation and separation of the mixture allowed us to access 2,5-*cis*-dihydrofuran **9a** that underwent a nucleophilic epoxidation to afford sulfonyl oxirane **44** as single isomer. The treatment of **44** with MgI_2 gave mixtures of the desired ketone **46** and a dimeric product **51** in

(20) For the synthesis of **35**, see: (a) Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'sa, A. *J. Am. Chem. Soc.* **1984**, *106*, 2641–2644. (b) Hatakeyama, S.; Sakurai, K.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 1333–1336. (c) Gurjar, M. K.; Mainkar, P. S. *Heterocycles* **1990**, *31*, 407–410. (d) Chikashita, H.; Nakamura, Y.; Uemura, H.; Itoh, K. *Chem. Lett.* **1993**, 477–480. (e) Capon, R. J.; Barrow, R. A.; Skene, C.; Rochfort, S. *Tetrahedron Lett.* **1997**, *38*, 7609–7612. (f) Wang, Z.-M.; Shen, M. *J. Org. Chem.* **1998**, *63*, 1414–1418. (g) Mori, Y.; Sawada, T.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 731–734. (h) Garcia, C.; Soler, M. A.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 4127–4130. (i) García, C.; Martín, T.; Martín, V. S. *J. Org. Chem.* **2001**, *66*, 1420–1428. For the synthesis of **36**, see refs 20e, h, i. (j) Yoda, H.; Muruyama, K.; Takabe, K. *Tetrahedron: Asymmetry* **2001**, *12*, 1403–1406. (k) Gadikota, R. R.; Callam, C.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 9046–9051.

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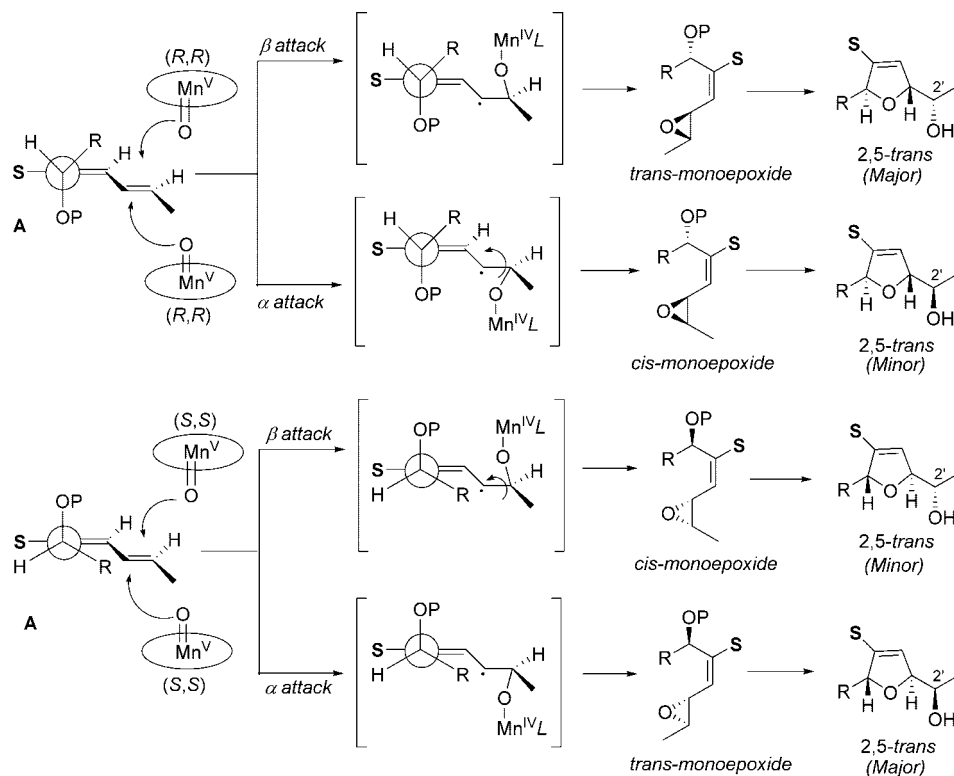
TABLE 6. Epoxidation–Cyclization Reactions of Substrates with Internal Substitution



| entry | substrate | conditions | monoepoxides ^a | dihydrofurans ^c | yield ^d |
|-------|------------|---|----------------------------------|--------------------------------|--------------------|
| 1 | 16b | 20% (<i>R,R</i>)- JC 4.0 equiv of NH ₄ OAc 32.0 equiv of H ₂ O ₂ , 6 days | | 22 (39)/ 23 (61) | 78% |
| 2 | 24b | 25% (<i>R,R</i>)- JC 5.0 equiv of NH ₄ OAc 40.0 equiv of H ₂ O ₂ , 5 days | 33 (69:31) ^{b,c} | | 75% |
| 3 | 24b | 30% (<i>S,S</i>)- JC 6.0 equiv of NH ₄ OAc 48.0 equiv of H ₂ O ₂ , 7 days | 33 (44:56) ^{b,c} | | 57% |
| 4 | 26b | 25% (<i>R,R</i>)- JC 5.0 equiv of NH ₄ OAc 40.0 equiv of H ₂ O ₂ , 6 days | 34 (23:77) ^c | 22 (23)/ 23 (77) | 53% |

^a Isolated mixtures of monoepoxides after filtration by column chromatography. ^b Mixtures of monoepoxides that were not desilylated/cyclized. ^c Data taken from ¹H NMR of the crude products. ^d Combined yields (two or three steps) of pure products after column chromatography.

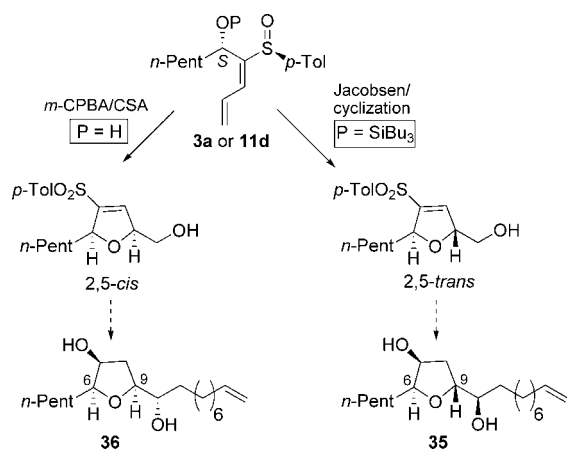
SCHEME 8. Stereochemical Outcome of the Process for Substituted Dienes



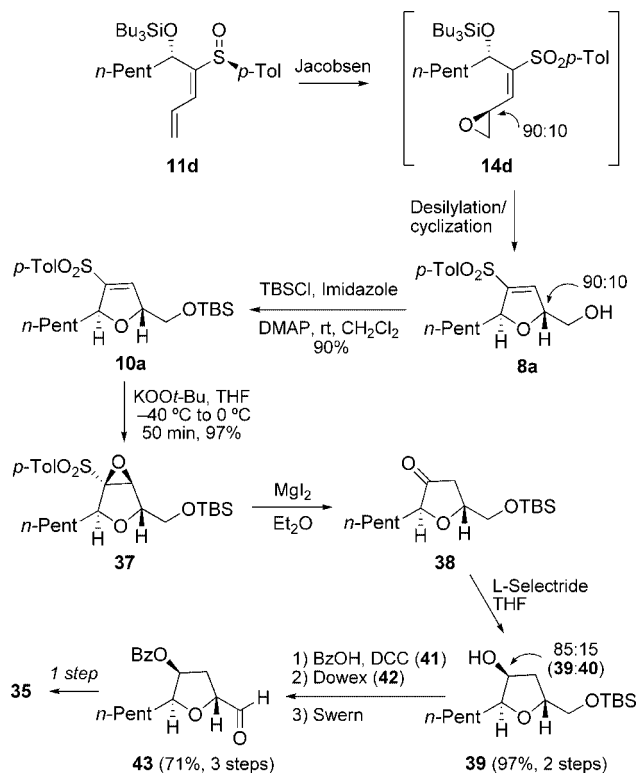
variable ratios (see Supporting Information). It should be pointed out that **51** was obtained as a single isomer that was tentatively assigned as shown in Scheme 11. In view of these unexpected results, we examined the cleavage with MgBr₂,²² which led smoothly to α -bromoketone **45** that was dehalogenated with

Al–Hg,²³ producing cleanly the desired ketone **46**. Reduction of the carbonyl group with NaBH₄ gave an 83:17 mixture of alcohols. After separation by chromatography, secondary alcohol **47** was protected as a benzoate **49**, and the silyl ether was cleaved with Dowex to give the desired alcohol **50** in good yield

SCHEME 9. Synthetic Plan for the Synthesis of Epoxy Lipids 35 and 36



SCHEME 10. Formal Synthesis of 35

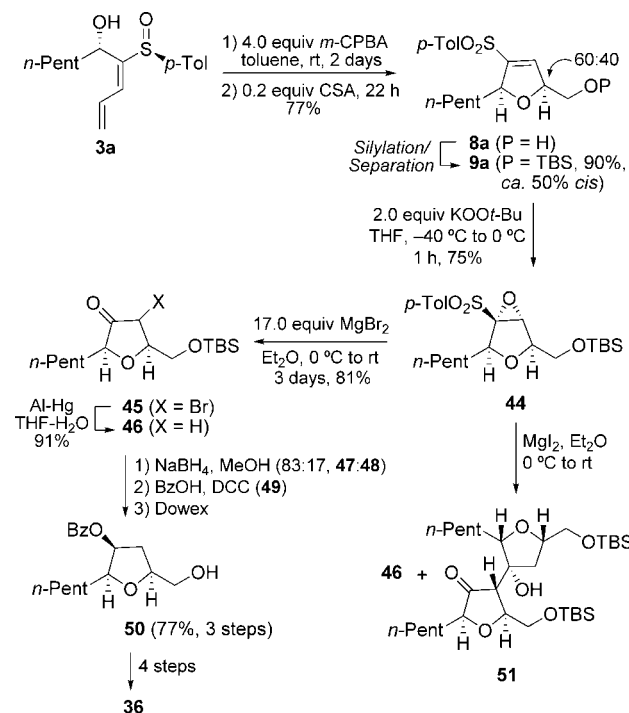


for the three steps. Alcohol **50** had been transformed into the natural product in four steps by the group of Lowary in 2001.^{20k} Our synthetic **50** showed data identical to that described in the literature.

Conclusions

The Katsuki–Jacobsen oxidation–epoxidation of α -silyloxy dienyl sulfoxides unsubstituted at the terminal position, followed by intramolecular cyclization, leads to 2,5-*trans*-substituted sulfonyl dihydrofurans with good selectivity. This methodology has been successfully extended to more substituted dienes that

SCHEME 11. Formal Synthesis of 36



ultimately lead to densely functionalized tetrahydrofurans. In addition, these methodologies have been applied to the formal syntheses of two marine natural products.

Experimental Section

Jacobsen Epoxidation of Tributylsilyloxy Sulfinyl Diene 11d: From a cold solution (0 °C) of silyloxy sulfinyl diene **11d** (60 mg, 0.122 mmol) in a 1:1 mixture of CH₂Cl₂/MeOH (1.1 mL), NH₄OAc (9.4 mg, 0.122 mmol, 1.0 equiv), (*R,R*)-**JC** (4.0 mg, 0.006 mmol, 0.05 equiv), and H₂O₂ (0.11 mL), according to the general procedure described in the Supporting Information (for 6 days), and after three additional loads of reagents, a 90:10 mixture of monoepoxides **14d** (63 mg, 98%) was obtained. Data for **14d**: *R*_f 0.23 (10% EtOAc–hexane); ¹H NMR (300 MHz) δ 0.36 (m, 6 H), 0.84 (t, 12 H, *J* = 6.8 Hz), 1.06–1.66 (m, 20 H), 2.42 (s, 3 H), 2.73 (dd, 1 H, *J* = 5.6, 2.4 Hz), 3.04 (dd, 1 H, *J* = 5.6, 4.3 Hz), 4.19 (ddd, 1 H, *J* = 9.0, 4.2, 2.4 Hz), 4.50 (dd, 1 H, *J* = 8.6, 2.7 Hz), 6.29 (d, 1 H, *J* = 9.0 Hz), 6.34 (d, 1 H, *J* = 8.8 Hz), 7.31 (d, 2 H, *J* = 8.5 Hz), 7.71 (d, 2 H, *J* = 8.1 Hz); ¹³C NMR (75 MHz) δ 13.2 (3 C), 13.8 (3 C), 14.0, 21.6, 22.4, 25.3 (3 C), 25.31, 26.5 (3 C), 31.3, 38.5, 47.9, 48.6, 69.5, 128.5 (2 C), 129.9 (2 C), 136.4, 140.3, 144.6, 150.1; IR (film) 2957, 2925, 2872, 2855, 1465, 1378, 1322, 1299, 1149, 1088, 962, 886, 835, 669 cm⁻¹; MS (ES) 545 [M + Na]⁺ (100%), 523 [M + H]⁺. Anal. Calcd for C₂₉H₅₀O₄SSi: C, 66.62; H, 9.64; S, 6.13. Found: C, 66.85; H, 9.37; S, 6.40.

Jacobsen Epoxidation of Hydroxy Sulfinyl Diene 16a: From a cold solution (0 °C) of hydroxy sulfinyl diene **16a** (20 mg, 0.08 mmol) in a 1:1 mixture of CH₂Cl₂/MeOH (0.72 mL), NH₄OAc (6 mg, 0.08 mmol, 1.0 equiv), (*R,R*)-**JC** (2.5 mg, 0.004 mmol, 0.05 equiv), and H₂O₂ (68 μ L), according to the general procedure described in the Supporting Information (for 6 days), and after four additional loads of reagents, an 87:13 inseparable mixture of monoepoxides **19a** and **27** (20 mg, 88%) was obtained as a colorless oil. Partial data for the mixture **19a/27**: *R*_f 0.26 (50% EtOAc–hexane); ¹H NMR (300 MHz) δ 0.87 (t, 3 H, *J* = 7.3 Hz), 1.37 (d, 3 H, *J* = 5.1 Hz), 1.59 (br s, 1 H), 1.71–1.81 (m, 2 H), 2.42 (s, 3 H), 3.04 (qd, 1 H, *J* = 5.1, 2.0 Hz), 3.61 (dd, 1 H, *J* = 8.3, 2.0 Hz), 4.50 (dt, 1 H, *J* = 9.4, 4.9 Hz), 6.45 (d, 1 H, *J* = 8.5 Hz), 6.55 (d, 1 H, *J* = 7.5 Hz, *min*), 7.31 (d, 2 H, *J* = 8.1 Hz), 7.72 (d, 2 H, *J*

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= 8.3 Hz); ^{13}C NMR (75 MHz) δ 10.5, 17.3, 21.6, 30.4, 54.3, 56.8, 70.5, 128.2 (2 C), 129.9 (2 C), 136.6, 140.1, 144.7, 148.2.

Cyclization with CSA of the Mixture of Monoepoxides 19a/27. Synthesis of (2*R*,2'*R*,5*S*)-1-[5-Ethyl-4-(*p*-tolylsulfonyl)-2,5-dihydrofuran-2-yl]ethanol, **30**, and (+)-(2*R*,2'*R*,5*R*)-1-[5-Ethyl-4-(*p*-tolylsulfonyl)-2,5-dihydrofuran-2-yl]ethanol, **21**: From a solution of monoepoxides **19a/27** (20 mg, 0.07 mmol) at rt in CH_2Cl_2 (0.5 mL) and CSA (7 mg, 0.03 mmol, 0.4 equiv), according to the general procedure described in the Supporting Information (12 h), and after purification by column chromatography (20–50% EtOAc–hexane), minor isomer **30** (3 mg, 13%) and major isomer **21** (19 mg, 84%) were obtained as colorless oils. Partial data for **30**: R_f 0.28 (50% EtOAc–hexane); ^1H NMR (300 MHz) δ 0.72 (t, 3 H, $J = 7.3$ Hz), 1.31 (d, 3 H, $J = 6.2$ Hz), 1.84 (m, 2 H), 2.45 (s, 3 H), 3.21 (qd, 1 H, $J = 8.3, 6.2$ Hz), 3.96 (m, 1 H), 4.34 (tdd, 1 H, $J = 6.6, 3.3, 2.0$ Hz), 6.93 (t, 1 H, $J = 1.6$ Hz), 7.33 (d, 2 H, $J = 8.1$ Hz), 7.74 (d, 2 H, $J = 8.4$ Hz); NOE H-3/H-2 (2.8%), H-5/H-2' (4.0%), H-2/H-3 (3.1%), H-2/CH₂ Et (1.7%), H-2/CH₃ (3.0%), H-2'/H-5 (4.0%), H-2'/H-2 (0.7%), H-2'/CH₃ (4.0%); ^{13}C NMR (75 MHz) δ 8.3, 17.9, 21.6, 26.1, 69.7, 73.9, 74.6, 128.0 (2 C), 129.9 (2 C), 136.9, 141.3, 143.2, 144.6. Data for **21**: R_f 0.20 (50% EtOAc–hexane); $[\alpha]_D^{20} +96.5$ ($c = 5.70$); ^1H NMR (500 MHz) δ 0.84 (t, 3 H, $J = 7.3$ Hz), 1.16 (d, 3 H, $J = 6.6$ Hz), 1.61 (ddq, 1 H, $J = 14.4, 7.3, 5.8$ Hz), 1.81 (ddq, 1 H, $J = 14.8, 7.3, 3.4$ Hz), 1.87 (d, 1 H, $J = 4.6$ Hz), 2.43 (s, 3 H), 3.86 (dq, 1 H, $J = 8.5, 6.5, 4.4$ Hz), 4.80 (ddd, 1 H, $J = 5.6, 3.8, 1.5$ Hz), 4.85 (ddd, 1 H, $J = 5.9, 3.4, 1.7$ Hz), 6.74 (t, 1 H, $J = 1.5$ Hz), 7.33 (d, 2 H, $J = 8.1$ Hz), 7.76 (d, 2 H, $J = 8.3$ Hz); NOE H-3/H-2 (3.3%), H-3/CH₃ (2.7%), H-2/H-2' (3.5%), H-2/CH₂ Et (1.7%), H-2/CH₃ (2.9%), H-2'/H-2 (3.7%), H-2'/CH₃ (4.7%); ^{13}C NMR (75 MHz) δ 8.3, 18.0, 21.7, 27.6, 69.1, 85.6, 89.0, 127.9 (2 C), 130.0 (2 C), 136.4, 138.3, 145.0, 145.2; IR (film) 3468, 3084, 2966, 2926, 2872, 1318, 1301, 1289, 1158, 1092, 1065, 815, 667 cm^{-1} ; MS (ES) 615 $[\text{M} + \text{Na}]^+$, 319 $[\text{M} + \text{Na}]^+$ (100%).

Jacobsen Epoxidation of Tributylsilyloxy Sulfinyl Diene 24a: From a cold solution (0 °C) of hydroxy sulfinyl diene **24a** (25 mg, 0.05 mmol) in a 1:1 mixture of $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (0.5 mL), NH_4OAc (4.2 mg, 0.05 mmol, 1.0 equiv), (*R,R*)-**JC** (1.7 mg, 0.003 mmol, 0.05 equiv), and H_2O_2 (49 μL), according to the general procedure described in the Supporting Information (for 4 days), and after two additional loads of reagents, an inseparable 96:4 mixture of monoepoxides **28** and **29** (21 mg, 78%) was obtained as a colorless oil. Partial data for **28** (from the mixture): R_f 0.21 (10% EtOAc–hexane); ^1H NMR (300 MHz) δ 0.33 (m, 6 H), 0.83 (t, 9 H, $J = 6.8$ Hz), 0.87 (t, 3 H, $J = 7.3$ Hz), 1.06–1.27 (m, 12 H), 1.35 (d, 3 H, $J = 5.1$ Hz), 1.49–1.72 (m, 2 H), 2.42 (s, 3 H), 2.99 (qd, 1 H, $J = 5.1, 2.0$ Hz), 3.91 (dd, 1 H, $J = 9.1, 2.0$ Hz), 4.43 (dd, 1 H, $J = 8.1, 3.7$ Hz), 6.32 (d, 1 H, $J = 9.1$ Hz), 7.31 (d, 2 H, $J = 7.8$ Hz), 7.71 (d, 2 H, $J = 8.3$ Hz); ^{13}C NMR (75 MHz) δ 10.3, 13.2 (3 C), 13.7 (3 C), 17.3, 21.6, 25.2 (3 C), 26.5 (3 C), 31.6, 54.7, 56.5, 70.7, 128.5 (2 C), 129.9 (2 C), 136.5, 140.5, 144.6, 149.2; IR (film) 2956, 2926, 2869, 1642, 1595, 1464, 1409, 1374, 1320, 1300, 1172, 1147, 1113, 1088, 1063, 1016, 886, 836, 811, 730, 668 cm^{-1} ; MS (ES) 517 $[\text{M} + \text{Na}]^+$ (100%), 495 $[\text{M} + \text{H}]^+$.

Desilylation with TBAF and Cyclization with CSA of Monoepoxides 28/29: From a cold solution (0 °C) of the mixture of monoepoxides **28** and **29** (17 mg, 0.03 mmol) in THF (0.3 mL), 1 M solution of TBAF (27 mg, 0.09 mmol, 2.5 equiv) in THF, and CSA (3.2 mg, 0.01 mmol, 0.4 equiv) in CH_2Cl_2 (0.1 mL), according to the general procedure described in the Supporting Information (for 15 h), and after purification by column chromatography (20–50% EtOAc–hexane), **30** (1 mg, 9%) and **21** (10 mg, 90%) were obtained as colorless oils.

Nucleophilic Epoxidation of Sulfonyl Dihydrofuran 21: From sulfonyl dihydrofuran **21** (57 mg, 0.19 mmol) in THF (2.0 mL) and $\text{KOO}t\text{-Bu}$ (2.0 equiv in 2.0 mL of THF), according to the general procedure described in the Supporting Information (for 7 h), a 97:3 mixture of sulfonyl oxiranes **31** was obtained. Purification by column chromatography (10–50% EtOAc–hexane) afforded

the inseparable mixture **31** (52 mg, 87%) as a colorless oil. Data for **31a** and **31b** (from the mixture): R_f 0.30 (10% EtOAc–hexane); $[\alpha]_D^{20} -23.9$ ($c = 5.0$); ^1H NMR (300 MHz) δ 0.83 (t, 3 H, $J = 7.6$ Hz), 1.00 (t, 3 H, $J = 7.3$ Hz, *min*), 1.23 (d, 3 H, $J = 6.1$ Hz), 1.24 (d, 3 H, $J = 6.3$ Hz, *min*), 1.34–1.43 (m, 2 H), 2.20 (br s, 1 H), 2.44 (s, 3 H), 3.80–3.87 (m, 2 H), 4.05 (s, 1 H), 4.16 (s, 1 H, *min*), 4.46 (dd, 1 H, $J = 6.8, 4.7$ Hz), 7.36 (d, 2 H, $J = 8.3$ Hz), 7.80 (d, 2 H, $J = 8.3$ Hz); ^{13}C NMR (75 MHz) δ 9.9, 10.2 (*min*), 19.7, 21.7, 23.3, 24.0 (*min*), 61.7 (*min*), 64.7, 66.5 (*min*), 67.8, 76.2, 77.9, 78.7 (*min*), 78.9 (*min*), 80.3, 128.9 (2 C, *min*), 129.1 (2 C), 129.9 (2 C), 130.0 (2 C, *min*), 133.6, 146.0; IR (film) 3514, 2972, 2928, 2878, 1596, 1453, 1379, 1328, 1304, 1149, 1087, 1065, 1018, 903, 813 cm^{-1} ; MS (ES) 647 $[\text{M} + \text{Na}]^+$, 335 $[\text{M} + \text{Na}]^+$ (100%), 313 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_5\text{S}$: C, 57.67; H, 6.45; S, 10.26. Found: C, 57.47; H, 6.66; S, 9.95.

Reductive Cleavage of Sulfonyl Oxirane 31 with MgI_2 , Synthesis of (–)-(2*S*,5*R*,5'*S*)-2-Ethyl-5-(1-hydroxyethyl)dihydrofuran-3-one, 32: From the mixture of oxiranes **31a** and **31b** (42 mg, 0.13 mmol) in Et_2O (0.7 mL) and MgI_2 (4.6 mL from a ca. 0.2 M solution in Et_2O , 0.94 mmol, 7.0 equiv), according to the general procedure described in the Supporting Information (for 4 h), and after chromatography (20–50% EtOAc–hexane), ketone **32** (20 mg, 94%) was obtained. Data for **32**: R_f 0.25 (10% EtOAc–hexane); $[\alpha]_D^{20} -18.7$ ($c = 1.1$); ^1H NMR (300 MHz) δ 0.96 (t, 3 H, $J = 7.3$ Hz), 1.12 (d, 3 H, $J = 6.6$ Hz), 1.54–1.69 (m, 2 H), 2.02 (br s, 1 H), 2.34 (dd, 1 H, $J = 18.2, 7.0$ Hz), 2.60 (dd, 1 H, $J = 18.2, 8.2$ Hz), 3.96 (dd, 1 H, $J = 7.6, 5.1$ Hz), 4.08 (qd, 1 H, $J = 6.4, 3.1$ Hz), 4.21 (ddd, 1 H, $J = 10.0, 7.1, 3.0$ Hz); ^{13}C NMR (75 MHz) δ 9.6, 18.2, 24.4, 35.7, 68.0, 79.2, 81.5, 215.8; IR (film) 3449, 2972, 2934, 2878, 1755, 1460, 1379, 1186, 1069 cm^{-1} ; MS (ES) 181 $[\text{M} + \text{Na}]^+$ (100%), 159 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}_3$: C, 60.74; H, 8.92. Found: C, 60.91; H, 9.08.

Synthesis of (–)-(2*S*,3*S*,4*S*,5*S*)-2-(*tert*-Butyldimethylsilyloxy-methyl)-3,4-epoxy-5-pentyl-4-(*p*-tolylsulfonyl)tetrahydrofuran, 37: From sulfonyl dihydrofuran **10a** (291 mg, 0.66 mmol) in THF (6.6 mL) and $\text{KOO}t\text{-Bu}$ (2.0 equiv in 6.6 mL of THF), according to the general procedure described in the Supporting Information (50 min), sulfonyl oxirane **37** was obtained as a single isomer. Purification by column chromatography (50–60% CH_2Cl_2 –hexane) afforded **37** (290 mg, 97%) as a colorless oil. Data for **37**: R_f 0.23 (10% EtOAc–hexane); $[\alpha]_D^{20} -9.2$ ($c = 2.02$); ^1H NMR (300 MHz) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.80 (t, 3 H, $J = 6.6$ Hz), 0.90 (s, 9 H), 1.06–1.40 (m, 8 H), 2.44 (s, 3 H), 3.66 (dd, 1 H, $J = 11.0, 5.9$ Hz), 3.71 (dd, 1 H, $J = 10.7, 3.9$ Hz), 3.95 (s, 1 H), 3.99 (dd, 1 H, $J = 5.6, 3.9$ Hz), 4.57 (t, 1 H, $J = 5.5$ Hz), 7.35 (d, 2 H, $J = 8.1$ Hz), 7.79 (d, 2 H, $J = 8.3$ Hz); ^{13}C NMR (75 MHz) δ -5.6 (2 C), 13.8, 18.2, 21.6, 22.3, 24.9, 25.8 (3 C), 26.8, 29.7, 31.5, 63.1, 65.4, 75.0, 76.5, 77.8, 129.0 (2 C), 129.7 (2 C), 133.9, 145.7; IR (film) 2952, 2930, 2857, 1597, 1494, 1464, 1382, 1334, 1303, 1256, 1161, 1091, 838, 814, 780, 705, 665 cm^{-1} ; MS (ES) 477 $[\text{M} + \text{Na}]^+$ (100%), 455 $[\text{M} + \text{H}]^+$. Anal. Calcd for $\text{C}_{23}\text{H}_{38}\text{O}_5\text{SSi}$: C, 60.75; H, 8.42; S, 7.05. Found: C, 60.51; H, 8.69; S, 6.83.

Synthesis of (–)-(2*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxymethyl)-2-pentyl-3-oxotetrahydrofuran, 38: From sulfonyl oxirane **37** (92 mg, 0.20 mmol) in Et_2O (1.0 mL) and MgI_2 (3.6 mL from a ca. 0.2 M solution in Et_2O , 0.71 mmol, 3.5 equiv), according to the general procedure described in the Supporting Information (for 3 h), and after chromatography (60–70% CH_2Cl_2 –hexane), ketone **38** (58 mg, 97%) was obtained. Data for **38**: R_f 0.31 (10% EtOAc–hexane); $[\alpha]_D^{20} -64.3$ ($c = 1.24$); ^1H NMR (300 MHz) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.84 (s, 9 H), 0.85 (t, 3 H, $J = 6.8$ Hz), 1.23–1.66 (m, 8 H), 2.42 (dd, 1 H, $J = 18.1, 4.6$ Hz), 2.51 (dd, 1 H, $J = 17.8, 7.8$ Hz), 3.64 (dd, 1 H, $J = 10.8, 2.8$ Hz), 3.86 (dd, 1 H, $J = 10.7, 3.2$ Hz), 3.99 (dd, 1 H, $J = 7.4, 4.6$ Hz), 4.41 (ddt, 1 H, $J = 7.7, 4.5, 3.1$ Hz); ^{13}C NMR (75 MHz) δ -5.7, -5.6, 14.0, 18.1, 22.4, 24.9, 25.7 (3 C), 31.6, 31.9, 38.3, 66.6, 75.4, 80.1, 216.4; IR (film) 2952, 2930, 2855, 1759, 1463, 1406, 1361, 1256, 1177, 1091, 1015, 837, 775 cm^{-1} ; MS (ES) 323 $[\text{M} + \text{Na}]^+$ (100%), 301 $[\text{M} +$

H]⁺. Anal. Calcd for C₁₆H₃₂O₃Si: C, 63.95; H, 10.73. Found: C, 64.19; H, 10.44.

Synthesis of (+)-(2*S*,3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxymethyl)-2-pentyltetrahydrofuran-3-ol, 40, and (2*S*,3*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxymethyl)-2-pentyltetrahydrofuran-3-ol, 39: From ketone **38** (97 mg, 0.32 mmol) in THF (3.2 mL) and L-Selectride (0.96 mL, 0.96 mmol, 1.0 M in THF, 3.0 equiv), according to the general procedure described in the Supporting Information, and after column chromatography (1–5% EtOAc–CH₂Cl₂), **40** (10 mg, 12%) and **39** (87 mg, 88%) were obtained as colorless oils. Data for **39**: *R*_f 0.13 (5% EtOAc–CH₂Cl₂); [α]_D²⁰ +11.1 (*c* = 1.50); ¹H NMR (300 MHz) COSY δ 0.03 (s, 6 H), 0.87 (m, 12 H), 1.23–1.64 (m, 9 H), 1.95 (dd, 1 H, *J* = 13.6, 7.2 Hz), 2.02 (ddd, 1 H, *J* = 13.5, 8.5, 4.2 Hz), 3.57 (dd, 1 H, *J* = 10.7, 4.2 Hz), 3.65 (dd, 1 H, *J* = 10.7, 4.2 Hz), 3.75 (td, 1 H, *J* = 6.8, 2.7 Hz), 4.18–4.26 (m, 2 H); ¹³C NMR (75 MHz) HSQC δ –5.4 (2 C), 14.0, 18.3, 22.6, 25.9 (3 C), 26.0, 28.9, 32.0, 37.2, 65.6, 73.5, 77.1, 82.8; IR (film) 3413, 2955, 2929, 2858, 1463, 1471, 1387, 1361, 1255, 1185, 1132, 1088, 1028, 1004, 938, 837, 813, 777, 662 cm^{–1}; MS (ES) 325 [M + Na]⁺, 303 [M + H]⁺ (100%). Anal. Calcd for C₁₆H₃₄O₃Si: C, 63.52; H, 11.33. Found: C, 63.26; H, 11.08. Data for **40**: *R*_f 0.35 (5% EtOAc–CH₂Cl₂); ¹H NMR (300 MHz) δ 0.098 (s, 6 H), 0.86 (t, 3 H, *J* = 6.5 Hz), 0.91 (s, 9 H), 1.23–1.40 (m, 8 H), 1.82 (dd, 1 H, *J* = 13.7, 2.4 Hz), 2.32 (ddd, 1 H, *J* = 13.9, 9.5, 5.6 Hz), 3.52 (dd, 1 H, *J* = 10.7, 1.7 Hz), 3.84 (dd, 1 H, *J* = 11.0, 2.2 Hz), 3.89–3.95 (m, 2 H), 4.07 (d, 1 H, *J* = 11.0 Hz), 4.20 (dd, 1 H, *J* = 9.8, 2.2 Hz); ¹³C NMR (75 MHz) δ –5.6, –5.5, 14.0, 18.5, 22.6, 25.7, 25.9 (3 C), 31.8, 33.5, 35.5, 66.0, 75.1, 77.4, 88.4; IR (film) 3433, 2955, 2930, 2854, 1462, 1361, 1254, 1092, 1042, 1004, 938, 837, 778 cm^{–1}; MS (ES) 325 [M + Na]⁺, 303 [M + H]⁺ (100%). Anal. Calcd for C₁₆H₃₄O₃Si: C, 63.52; H, 11.33. Found: C, 63.77; H, 11.66.

Synthesis of (+)-(2*S*,3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxymethyl)-3-phenylcarboxyloxy-2-pentyltetrahydrofuran, 41: From alcohol **39** (97 mg, 0.32 mmol) in CH₂Cl₂ (3.2 mL), benzoic acid (86 mg, 0.71 mmol, 2.2 equiv), DCC (132 mg, 0.64 mmol, 2.0 equiv), and DMAP (2 mg, 0.02 mmol, 0.05 equiv), according to the general procedure described in the Supporting Information, and after column chromatography (5–10% EtOAc–hexane), benzoate **41** (120 mg, 92%) was obtained as a colorless oil. Data for **41**: *R*_f 0.18 (10% EtOAc–hexane); [α]_D²⁰ +22.2 (*c* = 1.74); ¹H NMR (300 MHz) δ 0.06 (s, 6 H), 0.82 (t, 3 H, *J* = 6.9 Hz), 0.89 (s, 9 H), 1.22–1.67 (m, 8 H), 2.13 (ddd, 1 H, *J* = 14.1, 7.0, 1.0 Hz), 2.27 (ddd, 1 H, *J* = 13.8, 8.5, 5.0 Hz), 3.63 (dd, 1 H, *J* = 10.7, 3.9 Hz), 3.72 (dd, 1 H, *J* = 10.7, 4.2 Hz), 4.05 (ddd, 1 H, *J* = 9.3, 6.1, 3.4 Hz), 4.30 (ddd, 1 H, *J* = 12.5, 8.3, 4.1 Hz), 5.53 (t, 1 H, *J* = 3.7 Hz), 7.43 (t, 2 H, *J* = 7.6 Hz), 7.55 (t, 1 H, *J* = 7.5 Hz), 8.03 (dd, 2 H, *J* = 7.1, 1.5 Hz); ¹³C NMR (75 MHz) δ –5.4, –5.3, 14.0, 18.3, 22.5, 25.9 (3 C), 26.0, 29.4, 31.8, 35.1, 65.5, 76.3, 77.6, 81.8, 128.4 (2 C), 129.6 (2 C), 130.2, 133.1, 166.0; IR (film) 3064, 2952, 2929, 2858, 1722, 1603, 1469, 1463, 1452, 1315, 1273, 1114, 1094, 1027, 836, 778, 711 cm^{–1}; MS (ES) 429 [M + Na]⁺ (100%), 407 [M +

H]⁺. Anal. Calcd for C₂₃H₃₈O₄Si: C, 67.94; H, 9.42. Found: C, 68.16; H, 9.67.

Synthesis of (+)-(2*S*,3*S*,5*R*)-3-Phenylcarboxyloxy-5-hydroxymethyl-2-pentyltetrahydrofuran, 42: From benzoate **41** (114 mg, 0.28 mmol) in MeOH (2.8 mL) and Dowex resin (157 mg), according to the general procedure described in the Supporting Information, and after column chromatography (5–10% EtOAc–CH₂Cl₂), alcohol **42** (80 mg, 96%) was obtained as a colorless oil. Data for **42**: *R*_f 0.14 (10% EtOAc–CH₂Cl₂); [α]_D²⁰ +36.2 (*c* = 6.76); ¹H NMR (300 MHz) δ 0.82 (t, 3 H, *J* = 6.8 Hz), 1.22–1.72 (m, 8 H), 1.90 (t, 1 H, *J* = 6.3 Hz), 2.14 (m, 2 H), 3.53 (dt, 1 H, *J* = 11.5, 5.6 Hz), 3.75 (ddd, 1 H, *J* = 11.7, 6.1, 3.2 Hz), 4.06 (ddd, 1 H, *J* = 9.5, 6.1, 3.3 Hz), 4.37 (tdd, 1 H, *J* = 8.1, 5.6, 3.2 Hz), 5.56 (dd, 1 H, *J* = 6.1, 3.2 Hz), 7.44 (t, 2 H, *J* = 7.6 Hz), 7.56 (tt, 1 H, *J* = 7.6, 1.2 Hz), 8.03 (dd, 2 H, *J* = 8.2, 1.2 Hz); ¹³C NMR (75 MHz) δ 13.9, 22.5, 26.0, 29.4, 31.9, 34.8, 64.6, 75.9, 77.2, 77.7, 81.3, 128.5 (2 C), 129.6 (2 C), 130.1, 133.2, 165.9; IR (film) 3435, 3063, 3033, 2930, 2860, 1716, 1603, 1584, 1491, 1453, 1355, 1313, 1274, 1173, 1114, 1069, 1025, 903, 804, 711, 686, 665 cm^{–1}; MS (ES) 315 [M + Na]⁺, 293 [M + H]⁺ (100%). Anal. Calcd for C₁₇H₂₄O₄: C, 69.84; H, 8.27. Found: C, 69.65; H, 8.49.

Synthesis of (+)-(2*S*,3*S*,5*R*)-3-Phenylcarboxyloxy-5-formyl-2-pentyltetrahydrofuran, 43:^{20a} From (COCl)₂ (16 μL, 23 mg, 0.18 mmol, 3.5 equiv) in CH₂Cl₂ (0.72 mL), DMSO (18 μL, 20 mg, 0.26 mmol, 5.0 equiv) in CH₂Cl₂ (0.26 mL), alcohol **42** (15 mg, 0.05 mmol) in CH₂Cl₂ (0.4 mL), and Et₃N (46 μL, 33 mg, 0.33 mmol, 6.5 equiv), according to the general procedure described in the Supporting Information (for 1 h, 30 min), and after column chromatography (0–5% EtOAc–CH₂Cl₂), aldehyde **43** (11 mg, 80%) was obtained as a colorless oil. Data for **43**: *R*_f 0.27 (5% EtOAc–CH₂Cl₂); [α]_D²⁰ +43.7 (*c* = 1.04); ¹H NMR (300 MHz) δ 0.83 (t, 3 H, *J* = 7.1 Hz), 1.24–1.48 (m, 6 H), 1.61–1.81 (m, 2 H), 2.38 (m, 2 H), 4.03 (ddd, 1 H, *J* = 7.6, 6.0, 3.4 Hz), 4.54 (td, 1 H, *J* = 8.3, 1.5 Hz), 5.56 (q, 1 H, *J* = 3.2 Hz), 7.44 (t, 2 H, *J* = 7.8 Hz), 7.58 (t, 1 H, *J* = 7.3 Hz), 8.02 (dd, 2 H, *J* = 8.5, 1.5 Hz), 9.73 (d, 1 H, *J* = 1.7 Hz); ¹³C NMR (75 MHz) δ 13.9, 22.4, 25.9, 29.0, 31.7, 34.6, 74.5, 80.9, 83.2, 128.5 (2 C), 129.7 (3 C), 133.4, 165.8, 202.0; IR (film) 2927, 2857, 1723, 1603, 1584, 1453, 1377, 1313, 1272, 1174, 1112, 1027, 760, 711 cm^{–1}; MS (ES) 291 [M + H]⁺.

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Supporting Information Available: Experimental procedures and characterization for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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