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Katsuki–Jacobsen oxidation–epoxidation of α-silyloxy sulfinyl dienes: application to the formal synthesis of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol

Roberto Fernández de la Pradilla* and Alejandro Castellanos

Instituto de Química Orgánica, CSIC, Juan de la Cierva, 3, 28006 Madrid, Spain

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Abstract—The 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 synthesis of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol is reported.

Substituted tetrahydrofurans are commonly occurring substructures found in a broad array of natural products and biologically active molecules like, for instance, *Laurencia* sesquiterpenes ((−)-*kumausalene*), polyether antibiotics (*pamamycin*-607) or *Annonaceous* acetogenins (*muricatetrocin C*).[1] Due to the biological relevance of these molecules and their unique structural features, considerable effort has been devoted toward the development of methods for the stereoselective construction of substituted tetrahydrofurans.[2]

In recent years, we have been studying in depth the nucleophilic and electrophilic epoxidation of α-hydroxy dienyl sulfoxides as versatile routes to highly functionalized sulfinyl and sulfonyl tetrahydrofurans.[3] Scheme 1 shows an outline of our strategy that entails lithiation of the mixture of dienes **1*E*/*Z***,[4] and condensation with freshly distilled aldehydes followed by chromatographic separation to afford dienols **2** and **3**.[5] These diastereomers were interconverted by a Mitsunobu protocol. The treatment of the chosen diastereomers **3a–d**, prepared as described above, with *m*-CPBA in toluene resulted in a fast oxidation at sulfur to produce 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 TBDMSCl in the presence of imidazol allowed for a straightforward separation of both diastereomers by column chromatography.

In view of the low selectivities associated with the use of *m*-CPBA, we decided to explore other alternatives. Thus, epoxidation of substrate **3a** under Payne conditions occurred with no changes in selectivity (60:40) and lower yield.[6] Similarly, the reaction of diene **3a** with CF_3CO_3H,[7] led just to sulfonyl diene **4a**. After these disappointing results we chose to explore enantioselective epoxidation conditions with our α-hydroxy dienyl sulfoxides. Unfortunately Shi's epoxidation using commercially available D-Epoxone resulted in recovered starting material.[8] Katsuki–Jacobsen epoxidation,[9] 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 dienyl sulfones.[11] It should be mentioned that acyclic dienyl sulfones were not good substrates for this chemistry.[11a]

Despite the fact that terminal olefins have led to worse selectivities than substituted olefins in Katsuki–Jacobsen epoxidations, we decided to explore the Jacobsen epoxidation of α-hydroxy dienyl sulfoxides **3a–d** (Scheme 1)

Keywords: Sulfoxides; Katsuki–Jacobsen epoxidation; Tetrahydrofurans.
* Corresponding author. Tel.: +34 91 562 29 00; fax: +34 91 564 48 53; e-mail: iqofp19@iqog.csic.es

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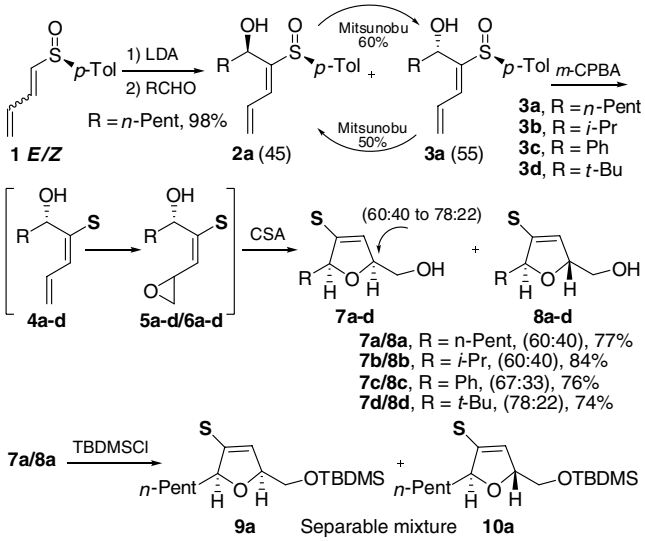
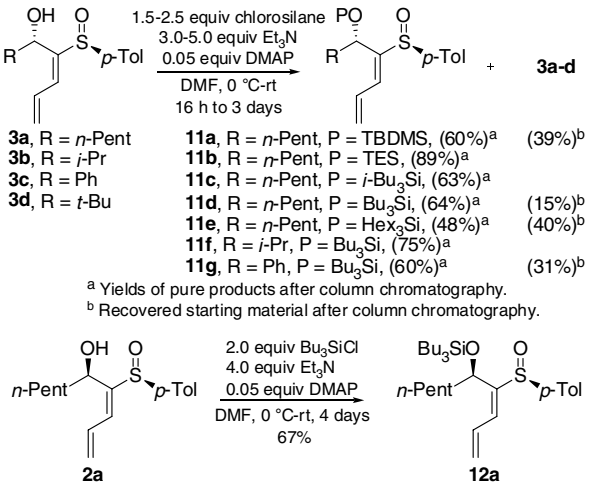


Scheme 1. Preparation of starting materials and sulfonyl dihydrofurans (**S** = SO_2*p*-Tol).



Scheme 2. Silylation reactions.

and sulfone **4a**,[12] under the conditions reported by Fuchs, hoping that the combined effects of the allylic stereocenter and the chiral catalyst would lead to a useful stereocontrol. These experiments resulted in a fast oxidation at sulfur to their corresponding α-hydroxy dienyl sulfones, followed by a slow distal epoxidation. Subsequent treatment of the intermediate monoepoxides with catalytic CSA afforded the expected sulfonyl dihydrofurans with a modest increase of 2,5-*trans* selectivity (ca 60:40). Details on these experiments will be included in a forthcoming full account on this chemistry.

With these preliminary results in hand, we decided to modify our substrates seeking 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.[13] 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, DMAP in DMF to render silyl ethers **11a**–**g** from hydroxy dienyl sulfoxides **3a**–**c** (Scheme 2). It should be pointed out that TIPS and TBDPS derivatives could not be prepared under these conditions leading to recovered starting materials. The unoptimized yields of these protections ranged from moderate (60–63%) to good (89%), with recovery of starting material in some cases. With substrate **3d** (R = *t*-Bu), no reaction was observed perhaps due to its considerable steric hindrance. The protection of alcohol **2a** with *R* configuration in the allylic center to afford silyl ether **12a** is also shown in Scheme 2.

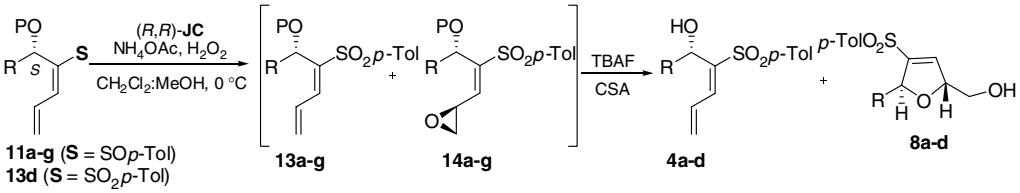
Table 1 summarizes the results for the epoxidation and cyclization of silyloxy derivatives **11a**–**g**. The crude mixtures were filtered through silica gel, treated with TBAF in THF to cleave the silyl ether and then cyclized in the presence of CSA. In the early experiments that did not reach completion, silyloxy sulfonyl dienes **13** were present in the crude mixtures; these led to dienes **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 TBDMS group (entry 1, substrate **11a**) supposed an increase in *trans* selectivity producing after desilylation and cyclization 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 catalyst (*R*,*R*)-**JC**. In contrast, the treatment of **11a** with *m*-CPBA in toluene led to an equimolar mixture of diastereomeric vinyl oxiranes.

The use of a TES group (entry 2, substrate **11b**) increased slightly the selectivity (77:23) with catalyst (*R*,*R*)-**JC**. Similarly, the *i*-Bu_3Si group (entry 3) led to a 90:10 ratio of dihydrofurans. With Bu_3Si derivative, **11d**, and (*R*,*R*)-**JC** catalyst, a 90:10 selectivity was observed (entry 4) with excellent yield. To clarify the role of the sulfoxide in the process, this protocol was applied to sulfone **13d** (entry 5) 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 Hex_3Si group and the selectivity was again found to be 90:10 (entry 6). Finally, the scope of the methodology was tested with substrates **11f** (R = *i*-Pr), and **11g** (R = Ph), (Table 1, entries 7 and 8) bearing a Bu_3Si protecting group. In both cases the selectivity measured was 90:10.

These results suggest that bulky silyl ethers at the allylic position are acting like directing groups increasing the *anti* selectivity in the epoxidation presumably due to their steric hindrance that blocks a face of the diene (see Scheme 3). The enhanced selectivity found for silyl ethers bearing longer alkyl chains is noteworthy (compare entries 4 and 2).

Table 2 shows the experiments carried out with substrate **12a** with *R* configuration at the allylic position. Catalyst (*R*,*R*)-**JC** gave a 60:40 selectivity favoring epoxidation by the face that produces 2,5-*trans* dihydrofurans after cyclization. With catalyst (*S*,*S*)-**JC**,

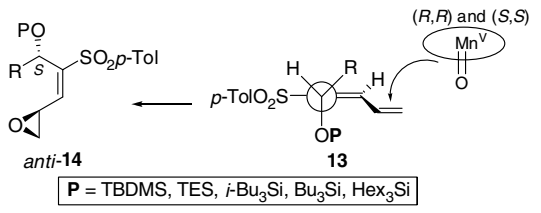
Table 1. Jacobsen epoxidation of (*S*)-silyloxy sulfinyl and sulfonyl dienes



Entry	Substrate	P	Sulfur oxidation state	Conditions	Yield[a]
1	**11a** R = *n*-Pent	TBDMS	SO*p*-Tol	5% (*R*,*R*)-**JC** 1.0 equiv NH_4OAc 8.0 equiv H_2O_2 2 days	30% **4a** + 60% **8a** (71:29)
2	**11b** R = *n*-Pent	TES	SO*p*-Tol	5% (*R*,*R*)-**JC** 1.0 equiv NH_4OAc 8.0 equiv H_2O_2 2 days	35% **4a** + 60% **8a** (77:23)
3	**11c** R = *n*-Pent	*i*-Bu_3Si	SO*p*-Tol	10% (*R*,*R*)-**JC** 2.0 equiv NH_4OAc 16.0 equiv H_2O_2 3 days	24% **4a** + 73% **8a** (90:10)
4	**11d** R = *n*-Pent	Bu_3Si	SO*p*-Tol	20% (*R*,*R*)-**JC** 4.0 equiv NH_4OAc 32.0 equiv H_2O_2 6 days	89% **8a** (90:10)
5	**13d** R = *n*-Pent	Bu_3Si	SO_2*p*-Tol[c]	15% (*R*,*R*)-**JC** 3.0 equiv NH_4OAc 24.0 equiv H_2O_2 6 days	97% **14a** (90:10)[b]
6	**11e** R = *n*-Pent	Hex_3Si	SO*p*-Tol	25% (*R*,*R*)-**JC** 5.0 equiv NH_4OAc 40.0 equiv H_2O_2 6 days	90% **8a** (90:10)
7	**11f** R = *i*-Pr	Bu_3Si	SO*p*-Tol	15% (*R*,*R*)-**JC** 3.0 equiv NH_4OAc 24.0 equiv H_2O_2 6 days	95% **8b** (90:10)
8	**11g** R = Ph	Bu_3Si	SO*p*-Tol	20% (*R*,*R*)-**JC** 4.0 equiv NH_4OAc 32.0 equiv H_2O_2 5 days	95% **8c** (90:10)

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

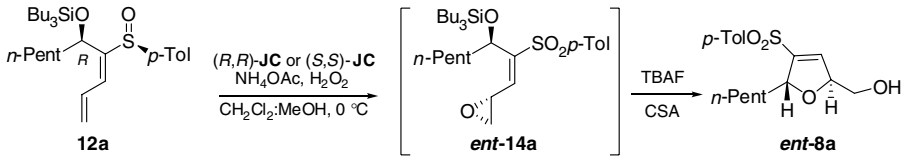
the selectivity increased to 86:14. In both cases, yields of the final product ***ent*-8a** were good after four additions of reagents. Thus, it appears that the stereochemical outcome of the process is primarily controlled by the substrate. The optical purity of dihydrofurans **8a** and ***ent*-8a** was secured by formation of their TBDMS ethers, separation and comparison of their optical rotation data with data measured for samples obtained with *m*-CPBA.



Scheme 3. Proposed favored approximation of the oxo-complex to the diene system.

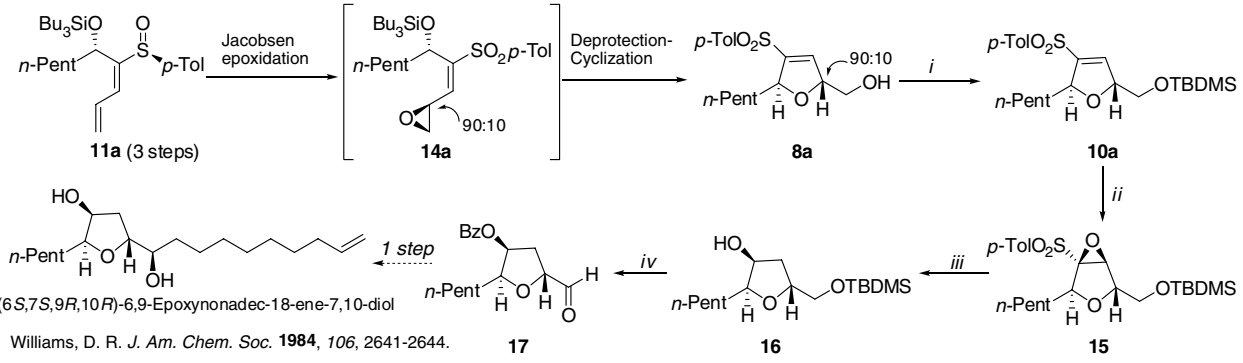
As an application of this study and following the interest of the group in the synthesis of natural products containing substituted THF rings, we report here the formal synthesis of the marine epoxy lipid (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol and our approach is

Table 2. Jacobsen epoxidation of (*R*)-silyloxy sulfinyl dienes



Entry	Substrate	Conditions	Yield[a]
1	**12a**	20% (*R*,*R*)-**JC** 4.0 equiv NH_4OAc 32.0 equiv H_2O_2 11 days	98% ***ent*-8a** (60:40)
2	**12a**	20% (*S*,*S*)-**JC** 4.0 equiv NH_4OAc 32.0 equiv H_2O_2 11 days	89% ***ent*-8a** (86:14)

[a] Yields of pure products after column chromatography.



Scheme 4. Formal synthesis of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol. Key: (i) TBDMSCl, ImH, DMAP, CH_2Cl_2, 0 °C to rt, 90%; (ii) KO*t*-Bu, THF, −40 to 0 °C, 97%; (iii) (a) MgI_2, Et_2O, 0 °C to rt, 97%; (b) L-Selectride, THF, −78 °C, 100% (85:15); (iv) (a) $PhCO_2H$, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 92%; (b) Dowex, MeOH, rt, 96%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −70 °C, 80%.

shown in Scheme 4.[14] Since its isolation and because of its peculiar substitution this natural product has been studied in depth and it has been the target of several synthetic efforts.[15]

As described above, Jacobsen epoxidation of silyloxy sulfinyl diene **11a** gave a 90:10 mixture of monoepoxides **14a** that after deprotection/cyclization afforded an inseparable mixture of sulfonyl dihydrofurans **8a** that was transformed into the readily separable *tert*-butyl dimethyl silyl ethers. Nucleophilic epoxidation of 2,5-*trans* diastereomer **10a** with KO*t*-Bu,[3] gave sulfonyl oxirane **15** as a single isomer and in excellent yield.[16] Reductive cleavage of the sulfonyl oxirane with freshly prepared MgI_2,[17] followed by reduction of the resulting ketone with L-Selectride afforded alcohol **16** with good stereoselectivity (85:15). After separation by chromatography, the secondary alcohol was protected as a benzoate and then the silyl ether was cleaved with Dowex resin in good yield for the two steps. Swern oxidation of the primary alcohol afforded aldehyde **17**, that had identical spectral data to that in the literature.[15a] This intermediate has been transformed into the natural product in one step by Williams, by addition of the appropriate Grignard reagent.

In conclusion, silylation of α-hydroxy dienyl sulfoxides allows for a selective Katsuki–Jacobsen oxidation and distal epoxidation. Subsequent deprotection and cyclization leads to 2,5-*trans* substituted sulfonyl dihydrofurans with good yield and selectivity. The optimization and extension of this protocol to more substituted dienes is currently being investigated in our laboratories. In addition, this process has been applied to a formal synthesis of a marine natural product that illustrates also the usefulness of our reductive cleavage of sulfonyl oxiranes with MgI_2.

Acknowledgments

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