

Highly stereoselective metal-catalyzed epoxidation of hydroxy vinyl sulfones¹

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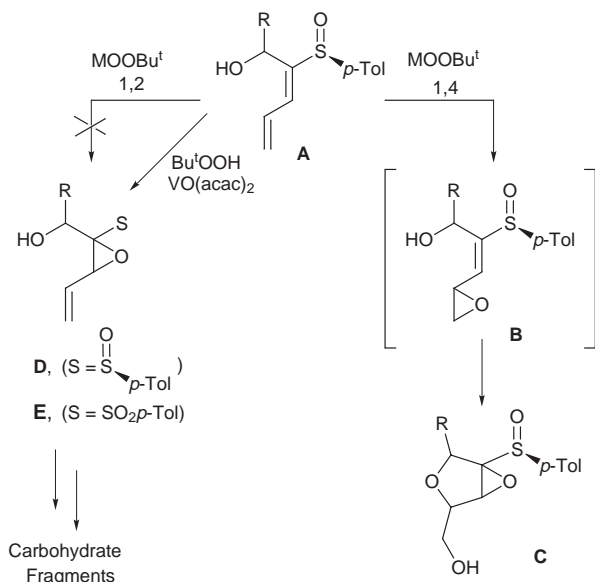
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Acyclic α -hydroxyalkyl α,β -unsaturated sulfoxides undergo oxidation at sulfur followed by a highly regio- and stereoselective epoxidation at the electron deficient alkene by treatment with Bu^tOOH–VO(acac)₂; this methodology allows for an expedient entry into unusual carbohydrate fragments.

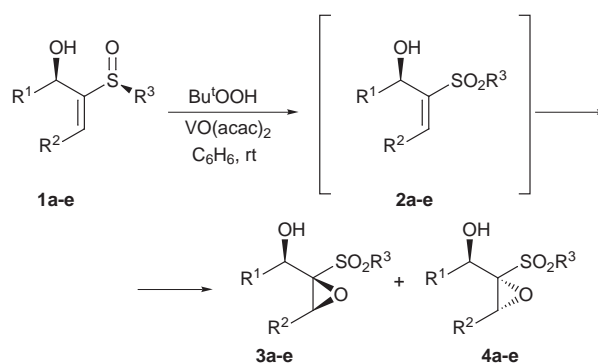
In the course of our efforts to develop synthetic applications of the nucleophilic epoxidation of vinyl sulfoxides,² the reactivity of dienyl substrates **A** (Scheme 1) with metalated hydro-



Scheme 1

peroxides was explored. In this fashion, tetrahydrofuran derivatives **C** were obtained, presumably by remote nucleophilic epoxidation to produce **B**, followed by ring closure and a second epoxidation. This finding was subsequently applied to expedient formal syntheses of the marine natural products *trans*-kumausyne and kumausallene.³ Nonetheless, we remained interested in developing a swift entry to carbohydrate derivatives by straightforward manipulations of monoepoxides **D** or **E**.⁴ The metal-catalyzed electrophilic epoxidation of α -hydroxyalkyl α,β -unsaturated esters and ketones developed by Markó appeared as a viable and simple option to prepare the elusive 1,2-epoxides.⁵ In this paper we report the facile and highly stereo- and regioselective epoxidation of hydroxy vinyl and dienyl sulfones to produce sulfonyloxiranes **E**, as well as preliminary studies on the transformation of these intermediates into carbohydrate derivatives.

To establish the viability of the process and to gain insight into the stereochemical outcome of the proposed epoxidation, our initial efforts were focused on the simple substrate **1a**,⁶ (Scheme 2) which underwent a very fast (5–10 min) oxidation



1a , R ¹ = Et, R ² = Bu, R ³ = <i>p</i> -Tol	2a	3a (76%)	4a (-)
1b , R ¹ = (CH ₂) ₂ Ph, R ² = Bu, R ³ = Bu ^t	2b	3b (54%)	4b (-)
1c , R ¹ = Et, R ² = Ph, R ³ = <i>p</i> -Tol	2c	3c (-)	4c (60%)
1d , R ¹ = Ph, R ² = vinyl, R ³ = <i>p</i> -Tol	2d	3d (67%)	4d (-)
1e , R ¹ = R ² = vinyl, R ³ = <i>p</i> -Tol	2e (70%)	3e (65%)	4e (-)

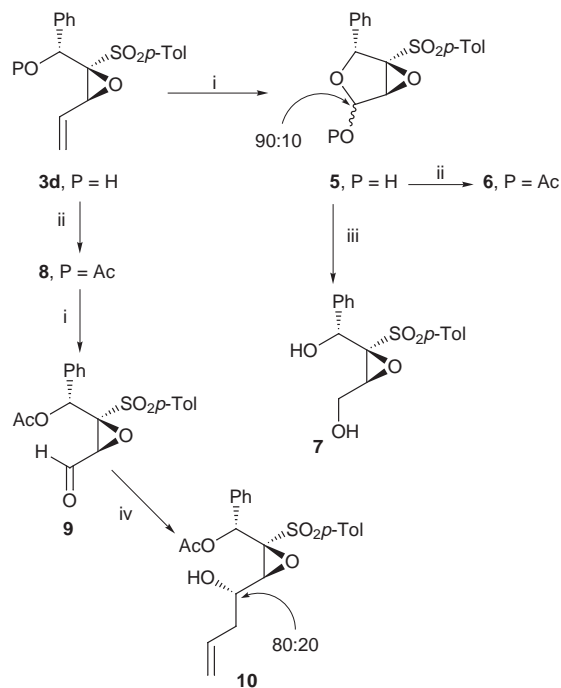
Scheme 2

to vinyl sulfone **2a** upon treatment with 5% VO(acac)₂ and 1.5 equiv. of Bu^tOOH in benzene. Subsequent addition of 5% of catalyst and 1 equiv. of Bu^tOOH gave the known sulfonyloxirane **3a**,⁷ as a single isomer and in good overall yield (76%). It should be pointed out that this finding nicely complements our highly selective route to diastereomer **4a** by nucleophilic epoxidation of **1a** with LiOOBu^t in Et₂O.⁷ Similarly, *tert*-butylsulfinyl substrate **1b** produced a fair yield of oxirane **3b** in a very comparable process.

To probe the reactivity and selectivity of a substrate with a strong 1,3-allylic strain, phenyl substituted vinyl sulfoxide **1c** was submitted to the above conditions and a good yield of diastereomer **4c** was obtained as a single isomer.⁸ To test the viability of our proposed approach to carbohydrates, the electrophilic epoxidation of sulfinyl diene **1d** was examined and a fair yield of the sensitive vinyloxirane **3d** was obtained as a single isomer.†

Encouraged by these results we studied an even more challenging substrate, trienol **1e** which has an additional allylic alcohol moiety, also susceptible to epoxidation under these reaction conditions. To our delight **1e** rapidly afforded a good yield of vinyl substituted 1-sulfonyldiene **2e** (1.3 equiv. Bu^tOOH, 5% VO(acac)₂, 15 min, 70%).⁹ In a separate experiment (5 equiv. Bu^tOOH, 10% VO(acac)₂, 4 h, 65%), formation of dienyl sulfone **2e** was monitored by TLC and a good overall yield of monoepoxide **3e** was obtained as a single isomer.‡

Our investigation into the transformation of our hydroxy epoxy sulfones into carbohydrate-like fragments is shown in Scheme 3. At this stage of the project we selected ozonolysis as our key reaction; thus, under standard conditions, an excellent yield of lactol **5** was obtained. To explore the reactivity of **5**, and seeking additional structural evidence, lactol **5** was acetylated to produce the furanose derivative **6** in good yield



Scheme 3 Reagents and conditions: i, O_3 (7 min), CH_2Cl_2 , $-78^\circ C$; then Me_2S , rt, 2 h, 88% for **5**, 53% for **9**. ii, 3–6 equiv. Ac_2O , 3–6 equiv. Et_3N , DMAP, CH_2Cl_2 , rt, 14 h, 80% for **6**, 91% for **8**. iii, 6 equiv. $NaBH_4$, $EtOH$, $0^\circ C$, 1 h, 70%. iv, 3 equiv. allyltributyltin, 4 equiv. $BF_3 \cdot OEt_2$, CH_2Cl_2 , $-78^\circ C$, 5 h, 69%.

and was also reduced with $NaBH_4$ to give epoxy diol **7**. On the other hand, acetylation of **3d** gave **8** which led to a fair yield of epoxy aldehyde **9** upon ozonolysis; subsequent allylation of **9** under standard conditions produced a good yield of a separable 80:20 mixture of homoallylic alcohols **10**,¹⁰ which, for instance, should be immediate precursors of unusual 2-deoxyhexoses by ozonolysis.

In conclusion, a novel methodology to carry out highly selective catalytic epoxidations of hydroxy vinyl sulfones has been developed. In this manner, a simple change of reaction conditions gives rise to either diastereomeric sulfonyloxirane **3a** or **4a** for sterically “unbiased” substrates. The straightforward preparation of enantiopure hydroxy-1-sulfonyl diene 1,2-monoepoxides is remarkable and allows for a swift entry (4 steps) into densely functionalized unusual carbohydrate derivatives such as **5**. We are currently exploring the scope and limitations of this epoxidation as well as additional applications of the methodology to the synthesis of tetrahydrofurans and carbohydrate derivatives.¹¹

Experimental

Synthesis of (+)-($\alpha R,2S,3S$)-2-(α -hydroxybenzyl)-2-(p -tolylsulfonyl)-3-vinyloxirane, **3d**

A 25 mL round-bottomed flask was charged with 1-phenyl-2-(p -tolylsulfinyl)penta-2,4-dien-1-ol (300 mg, 1.01 mmol) in 4 mL of dry C_6H_6 . To the above solution, $VO(acac)_2$ (13 mg, 0.05 mmol) was added, and the resulting mixture was stirred at room temperature for 5 min. A solution of 2.5 equiv. of Bu^tOOH (5.0–6.0 M in decane, 0.45 mL, 2.5 mmol) in 1.3 mL of benzene, was then added dropwise to produce a red solution. After 2 h 30 min the addition of 5% $VO(acac)_2$ and 2.5 equiv. Bu^tOOH was repeated. After about 4 h an additional 5% $VO(acac)_2$ was added. After 6 h, the reaction mixture was quenched with a solution of $Na_2S_2O_4$ (0.23 M, 5 mL, 1.15 mmol) diluted with $EtOAc$ (8 mL), the layers were separated and the organic layer was washed with a saturated solution of $NaCl$ (2×4 mL). The aqueous layer was extracted with $EtOAc$ (2×8 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a crude product which was purified by chromatography on silica gel

(5–30% $EtOAc$ –hexane) to give epoxy sulfone **3d**, 221 mg (67%) as a white solid.

Data of **3d**: mp: 132 – $134^\circ C$ (hexane); $R_f = 0.34$ (30% $EtOAc$ –hexane); $[a]_D^{20} = +10.8$ ($c = 0.60$, $CHCl_3$); 1H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3 H, CH_3 p -Tol), 3.80 (d, 1 H, $J = 10.6$ Hz, OH), 4.56 (d, 1 H, $J = 6.2$ Hz, H-3), 4.94 (d, 1 H, $J = 10.6$ Hz, H-2'), 5.58 (d, 1 H, $J = 10.6$ Hz, H-3''), 5.71 (d, 1 H, $J = 17.1$ Hz, H-3'''), 5.97 (ddd, 1 H, $J = 17.1, 10.7, 6.2$ Hz, H-3'), 6.96–7.24 (m, 9 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.6, 62.1, 70.6, 78.0, 124.1, 125.8 (2 C), 127.7, 128.0 (2 C), 128.8, 128.9 (2 C), 129.1 (2 C), 133.9, 137.9, 144.6; IR (KBr): 3530, 3480, 2930, 1600, 1500, 1490, 1460, 1315, 1300, 1180, 1160, 1150, 1090, 1060, 1000, 940, 810, 780, 750, 710, 670 cm^{-1} ; MS (EI/70 eV): 174, 157, 146, 139, 129, 118, 107, 91 (100%), 77, 65, 57, 39; MS (Atmospheric Pressure Chemical Ionization): 329 ($M - 1$)⁻, 155 (100%); Anal. calcd for $C_{18}H_{18}O_4S$: C, 65.44; H, 5.49; S, 9.70. Found: C, 65.48; H, 5.45; S, 9.65%.

Synthesis of (–)-($3S,4S,5R$)-3,4-epoxy-5-phenyl-4-(p -tolylsulfonyl)tetrahydrofuran-2-ol, **5**

A 25 mL round-bottomed flask was charged with (+)-($\alpha R,2S,3S$)-2-(α -hydroxybenzyl)-2-(p -tolylsulfonyl)-3-vinyloxirane (54 mg, 0.16 mmol) in 3 mL of dry CH_2Cl_2 , and cooled to $-78^\circ C$. Oxygen was then bubbled through the mixture (10 min), followed by ozone (7 min). Then, 5 equiv. of Me_2S (0.06 mL, 0.82 mmol) was added dropwise and the resulting colorless solution was stirred at room temperature for 1 h 30 min. The solvent was removed under reduced pressure to give a crude product which was purified by chromatography on silica gel (20–40% $EtOAc$ –hexane) to give 48 mg (88%) of lactol **5**, as a colorless oil (90:10 mixture of anomers).

Data of **5**: $R_f = 0.12$ (2% CH_2Cl_2 – $EtOAc$); $[a]_D^{20} = -14.6$ ($c = 0.25$, $CHCl_3$); 1H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3 H, CH_3 p -Tol major), 2.43 (s, 3 H, CH_3 p -Tol minor), 3.30 (br s, 1 H, OH major), 4.33 (s, 1 H, H-3 major), 4.34 (s, 1 H, H-3 minor), 5.05 (s, 1 H, H-5 major), 5.20 (s, 1 H, H-5 minor), 5.58 (s, 1 H, H-2 major), 5.78 (s, 1 H, H-2 minor), 7.10–7.49 (m, 9 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.7, 65.0, 77.0, 82.0, 95.1, 128.2 (2 C major), 128.5, 129.1 (2 C major), 129.1, 129.2, 129.6 (2 C major), 129.7 (2 C major), 129.8, 134.1, 135.0, 145.6; IR ($CHCl_3$): 3420 (br), 3020, 2990, 2880, 1580, 1480, 1440, 1310, 1140, 1120, 1070, 1020, 770, 730 cm^{-1} ; MS (EI/70 eV): 332 (M), 303, 211, 176, 157, 147, 139, 131, 107 (100%), 91, 79, 71, 63, 51, 43.

Acknowledgements

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Notes and references

† While these procedures have not been optimized, consistently higher yields were obtained, particularly for vinyloxiranes, if 5 equiv. of Bu^tOOH were employed to enhance the reaction rate and if purification of the crude material was carried out as soon as possible. The stereochemistry of **3d** was assigned by comparison of key signals of the 1H NMR spectrum of lactol **5** (Scheme 3) with that of a related compound reported by us (see ref. 2). In addition, a derivative of **5** had NOE data fully compatible with the proposed structure.

‡ Preliminary experiments using larger loads of catalyst (20%) and prolonged reaction times (24 h) gave rise to monoepoxide **3e** (20–30%) along with variable amounts (30–40%) of a single isomer of a very sensitive bis-oxirane arising by “normal” epoxidation of the allylic alcohol moiety of **3e**.

- 1 Taken in part from the M. S. Theses of P. M. and J. P.
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- 4 For reviews on the synthesis of carbohydrate derivatives from acyclic precursors, see: (a) D. J. Ager and M. B. East, *Tetrahedron*, 1993, **49**, 5683; (b) D. J. Ager and M. B. East, *Tetrahedron*, 1992, **48**, 2803.
- 5 M. Bailey, I. Staton, P. R. Ashton, I. E. Markó and W. D. Ollis, *Tetrahedron: Asymmetry*, 1991, **2**, 495.
- 6 Substrates **1** were prepared by lithiation of the corresponding vinyl or dienyl sulfoxides and trapping with an aldehyde. In turn, most vinyl sulfoxide precursors are available in one step by the method of Craig: D. Craig, K. Daniels and A. R. MacKenzie, *Tetrahedron*, 1993, **49**, 11263.
- 7 R. Fernández de la Pradilla, P. Manzano, J. Priego, A. Viso, M. Martínez-Ripoll and A. Rodríguez, *Tetrahedron Lett.*, 1996, **37**, 6793.
- 8 The structure of **4c** was assigned by comparison of its spectral data with those of very closely related compounds described by Jackson in a thorough study of the nucleophilic epoxidation of hydroxy vinyl sulfones. See: R. F. W. Jackson, S. P. Standen, W. Clegg and A. McCamley, *J. Chem. Soc., Perkin Trans. 1*, 1995, 141.
- 9 For an excellent review on sulfonyl-1,3-dienes, see: J.-E. Bäckvall, R. Chinchilla, C. Nájera and M. Yus, *Chem. Rev.*, 1998, **98**, 2291. For very recent reports somewhat complementary to our own results, see: (a) J. G. Urones, I. S. Marcos, N. M. Garrido, P. Basabe, A. J. Bastida, S. G. San Feliciano, D. Díez and J. M. Goodman, *Synlett*, 1998, 1361; (b) J. G. Urones, I. S. Marcos, N. M. Garrido, P. Basabe, S. G. San Feliciano, R. Coca and D. Díez, *Synlett*, 1998, 1364.
- 10 The stereochemistry of the newly created center is tentatively assigned in analogy with the results of Procter for nucleophilic additions to α,β -epoxy aldehydes. See: G. P. Howe, S. Wang and G. Procter, *Tetrahedron Lett.*, 1987, **28**, 2629. For a leading reference on reagent controlled allylation of α,β -epoxy aldehydes, see: W. R. Roush, J. A. Straub and M. S. VanNieuwenhze, *J. Org. Chem.*, 1991, **56**, 1636.
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