

Antarafacial Mediation of Oxygen Delivery by a Phenylsulfinyl Group in the Epoxidation of Proximal Double Bonds: Intramolecular Trapping of an Early Pummerer Intermediate with Stereoelectronic Control

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 Supporting Information

ABSTRACT: Stereospecific intramolecular antarafacial epoxidation of a double bond via an early Pummerer reaction intermediate has been demonstrated. The intermediate is presumably generated via trifluoroacetylation of a sulfoxide precursor. Ionization of trifluoroacetate would formally generate a dipositive “sulfenium” equivalent. This species attacks an otherwise unactivated, proximal olefinic linkage in an antiperiplanar fashion, with trifluoroacetate serving as the nucleophile. Proposed mechanistic intermediates were characterized structurally (in several cases by crystallographic means) and shown to serve as precursors en route to the final antarafacial epoxides. The sense of the cyclization seems to be driven by principles inherent in Markovnikov's rule.

Recently, we described a simple two-step sequence for generating what we have termed “*trans*-Diels–Alder” (*trans*-DA) motifs containing angular functionality.¹ Of course, many issues remain to be addressed before this capability can be fully exploited. We have already come upon a remarkable observation in the course of an attempted Pummerer rearrangement² of sulfoxide **2** (derived from the “*trans*-DA” product **1** in Scheme 1). Treatment of **2** with trifluoroacetic anhydride (TFAA)³ led, not unexpectedly, to the disappearance of the starting material. However, subsequent treatment with aqueous sodium bicarbonate failed to produce the anticipated aldehyde **3**. Instead, a compound in which the erstwhile angular sulfoxide function in **2** had given way to a sulfide was obtained. Correspondingly, the double bond had become an epoxide. It is clear that the oxygen of the oxido linkage had not arisen by direct transfer from the sulfoxide because the epoxide (see compound **4**)⁴ had emerged at the α -face of the double bond, i.e., *anti* to the β -face phenylsulfinyl precursor. In this paper, we establish an interesting mechanistic pathway to account for the formation of **4**. Follow-up studies served to generalize the scope of this novel intramolecular *yet antarafacial* sulfoxide-induced overall oxidation of an otherwise unactivated double bond and to identify its limitations.

To initiate our study, we began by trying to understand the $2 \rightarrow 4$ conversion at a more rigorous level. Compound **2** was

subjected to the action of TFAA in dichloromethane from 0 °C to room temperature over 1 h. The resultant product was treated with aqueous sodium bicarbonate (in a two-phase setting). Compound **4** was produced in 94% yield. In another experiment, following the TFAA step but before the workup with aqueous sodium bicarbonate, evaporation of the solvent gave rise to a semisolid residue. However, exchange of trifluoroacetate by tetrafluoroborate⁵ gave rise to a new salt that fortunately could be coaxed into a state of crystallinity. X-ray analysis of this new salt revealed it to be structure **9**. As shown in Scheme 1, the double bond had apparently been attacked in an electrophilic sense by the TFAA-activated sulfoxide, giving rise to the bridged sulfonium trifluoroacetate **8** and subsequently to the corresponding sulfenium tetrafluoroborate **9**. Moreover, the formal carbenium-like entity at C₈ in **7** had been discharged by trifluoroacetate. The precise timing of these steps with respect to level of concertedness could not be established on the basis of our data set. However, since the covalent trifluoroacetate in **9** is trans-periplanar with respect to the “C–S⁺” bond, the two bond formations (C₇–S⁺ and C₈–O) may well correspond to orchestrated *trans*-diaxial attacks upon the resident C₇–C₈ olefin in precursor **5**.

Treatment of **9** with aqueous sodium bicarbonate indeed afforded epoxide **4**. In summary, then, the activated sulfonium salt⁶ had attacked C₇ of the double bond, giving rise to a stable but unprecedented bicyclic [2.2.2] sulfonium-containing substructure with neutralization by trifluoroacetate having occurred at C₈. Treatment of this salt with sodium bicarbonate apparently accomplished deacylation of the covalent trifluoroacetate at C₈, leading to the formation of the oxido linkage with concurrent release of the neutral thiophenyl function, as shown in **4**.^{6–8}

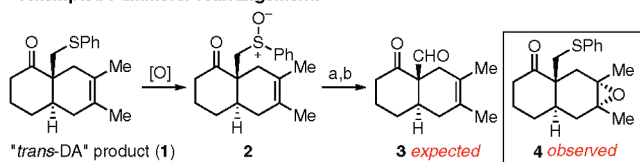
Of course, the dipositive “sulfenium” (early Pummerer⁹) species formalized as **6**, which arose from heterolysis of the presumed trifluoroacetoxysulfenium species (of intermediate **5**), could in principle have attacked the proximal double bond at either C₇ or C₈ (presteroid numbering), generating in either case tertiary carbenium ion character at the alternate carbon. The fact that the reaction produces apparently only the bicyclo [2.2.2] “sulfonium” substructure, as in **7**, may reflect either kinetic or thermodynamic preferences regarding the optimal size of the sulfonium-containing ring system

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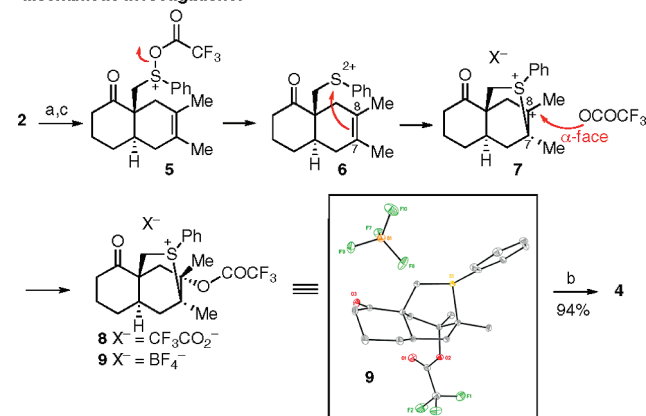
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Scheme 1^a

• Attempted Pummerer rearrangement.



• Mechanistic investigations.



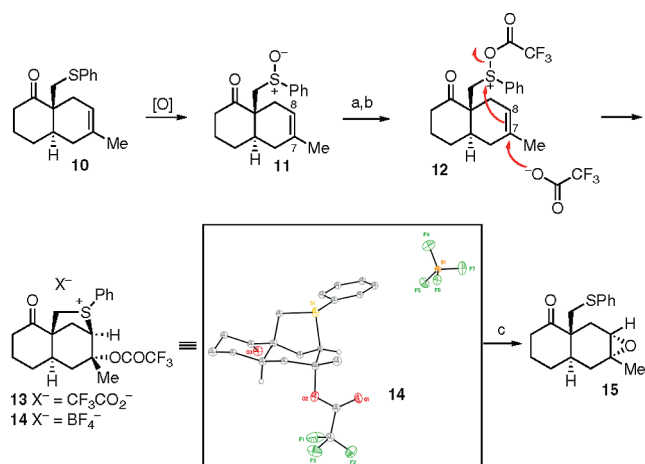
^a Key: (a) TFAA, CH₂Cl₂, 0 °C → rt; (b) NaHCO₃(aq); (c) HBF₄OEt₂, CH₂Cl₂, rt.

and the optimal point for neutralization of the carbenium ion character by the weakly nucleophilic trifluoroacetate counterion.

In view of these results and uncertainties, it was of interest to examine this novel type of epoxidation sequence in the context of sulfoxide **11** obtained from sulfide **10** (Scheme 2). Here, too, we were asking several questions. First, at this stage there was an unaddressed issue as to whether the less substituted olefin would even be sufficiently nucleophilic to interdict what must be a highly reactive formally “dipositive” sulfenium species, **12**, before it could progress to the normal Pummerer rearrangement. Moreover, in the case at hand, the sense of trapping by cyclization raised the question as to whether trapping would occur, as above, at C₇, which would generate secondary carbenium ion character at C₈. Alternatively, cyclization might now occur at C₈, thus delivering tertiary carbenium ion character at C₇.

In the event, reaction was conducted as before. TFAA treatment left a sulfonium trifluoroacetate intermediate (now known to be **13**), which was, as above, converted to the crystalline tetrafluoroborate. The structure of this compound was shown by X-ray crystallographic analysis to be **14**. Apparently, the formally “dipositive” sulfenium equivalent arising from heterolysis of **12** (in sharp contrast to **5**) attacks the proximal C₇–C₈ double bond in a *trans*-diaxial Markovnikov¹⁰ sense, with trifluoroacetate acting as the nucleophile at C₇. Treatment of **12** with aqueous sodium bicarbonate afforded epoxide **15** (70% overall yield from **11**). Thus, in the case of trisubstituted olefin **11**, cyclization either kinetically or thermodynamically leads to the bridged [3.2.1] Markovnikov substructure shown in **14**, in contrast to the bridged [2.2.2] sulfonium-containing substructure of **9** en route to **4**.

We studied the scope and limitations of this stereospecific, overall “anti-orchestrated” delivery of oxygen to the proximal double bond, and the results are presented in Table 1. Entry 1 shows that the reaction is applicable even to a disubstituted double bond, albeit in sharply diminished yield. Entry 2 shows

Scheme 2^a

^a Key: (a) TFAA, CH₂Cl₂, 0 °C → rt; (b) HBF₄OEt₂, CH₂Cl₂, rt; (c) NaHCO₃(aq), 70% from **11**.

the reaction to be operative even with a particularly congested tetrasubstituted double bond. Entry 3 demonstrates the capacity to incorporate functionality in each of the rings of the Diels–Alder-derived bicycle. Entry 4 shows the extendability of the epoxidation to the *trans*-hydrindanoid series, while entry 5 demonstrates its applicability to the corresponding *cis* junction, albeit in somewhat diminished yield.¹¹ Entry 6 shows the reaction sequence also to be applicable to a more conformationally flexible monocyclic system.

It should be noted that the reaction conditions employed in Schemes 1 and 2 as well as Table 1 do not include pyridine, which could be used in effecting a Pummerer rearrangement.¹² Interestingly, under Pummerer rearrangement conditions where pyridine was added, aldehyde products were observed along with the epoxides. In some instances, the Pummerer-derived aldehydes appeared to be the more predominant products, but the formation of mixtures of epoxides and aldehydes compromises the value of such reactions from the standpoint of synthesis.

We also studied the possible applications of this reaction to olefins in acyclic contexts. Accordingly, the reactions using sulfoxides **28** and **31** as substrates were examined. In the case of **28**, the reaction did indeed produce compound **29** bearing the thiophenyl and oxido linkages. However, the yield was only 22%. The major product of the reaction was **30**, which contains the allylic trifluoroacetate as well as the phenylthio functions. Since we do not know the precise structure of the intermediate sulfonium species arising from cyclization, we cannot rigorously assert the mechanism of formation of either **29** or **30** in detail. However, the formation of **30** as the major product can clearly be accommodated in various obvious ways via the chemistry described above.

Attempts to apply the reaction to sulfoxide **31** led at best to very low levels of epoxide **32** (Scheme 3). This compound was produced in less than 5% yield. While its presence could be inferred from analysis of the NMR spectrum of the crude reaction mixture, the presumed product **32** could not be obtained in homogeneous form. Hence, the reaction seemed to break down when the resident olefin was housed in a setting of an acyclic terminal vinyl group, which is presumably a less activated intramolecular nucleophilic trapping agent.

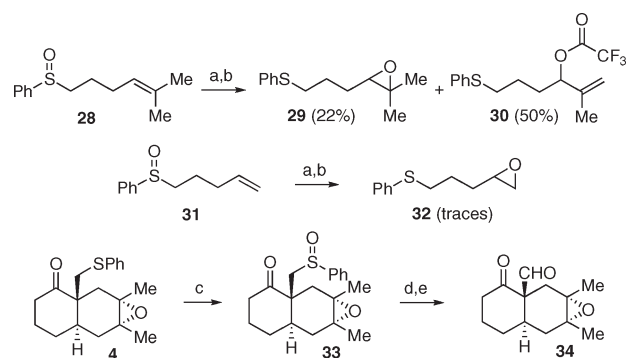
Table 1

entry	sulfoxide	product	Temp.	yield
1			-78 °C → rt ^b	35%
2			0 °C → rt ^a	59%
3			0 °C → rt ^a	86%
4			0 °C → rt ^a	93%
5			-78 °C → rt ^b	40%
6			0 °C → rt ^a	77%

^a General procedure: The mixture of sulfoxide (0.1 mmol) and TFAA (0.3 mmol) in CH₂Cl₂ was stirred at 0 °C (0.5 h) and then warmed to rt (0.5 h). Aqueous NaHCO₃(sat.) was then added, and the biphasic mixture was stirred for 4 h prior to standard workup. ^b The reaction was run at -78 °C and warmed to rt for up to 12 h prior to addition of NaHCO₃(aq).

Finally, we were able to demonstrate that the chemistry described above could be used to generate an angular aldehyde function. For this purpose, we returned to epoxide **4**. Treatment of this compound with *m*-CPBA gave rise to sulfoxide **33**. Exposure of **33** to standard Pummerer conditions¹³ gave the hitherto-unknown compound **34** containing keto, aldehyde, and oxido functions, as shown in Scheme 3.

In summary, we have discovered, admittedly with considerable happenstance, an unexpected but interesting and potentially valuable line of chemistry arising from the ability of a properly placed olefinic linkage to interdict the course of the normal Pummerer reaction at an early stage. Aside from the novel structural chemistry associated with the now-characterized complex sulfonium salts **9** and **14**, the reaction raises interesting issues of mechanism that have been addressed. In addition to its

Scheme 3^a

^a Key: (a) TFAA, -78 °C → rt; (b) NaHCO₃(aq); (c) *m*-CPBA, CH₂Cl₂, -78 → -20 °C; (d) TFAA, Py, 0 °C → rt; (e) NaHCO₃(aq), 47% over two steps.

potential value in building diversity libraries, this chemistry raises the possibility of applications directed toward the synthesis of complex target systems of natural origin. Such studies are in fact underway.

■ ASSOCIATED CONTENT

S Supporting Information. General experimental procedures, spectroscopic and analytical data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (2) De Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157–405.
- (3) See: Sharma, A. K.; Swern, D. *Tetrahedron Lett.* **1974**, *15*, 1503–1506.
- (4) The stereochemistry of this epoxide was rigorously proven by crystallographic determination of the structure of the corresponding sulfone.
- (5) Brajeul, S.; Delpech, B.; Marazano, C. *Tetrahedron Lett.* **2007**, *48*, 5597–5600.
- (6) For a general review of activated sulfenium ions as electrophiles, see: (a) Nenajdenko, V. G.; Balenkova, E. S. *Russ. J. Org. Chem.* **2003**, *39*, 291–330. For an example of a cyclization reaction that is quite different but somewhat related, see: (b) Nenajdenko, V. G.; Verteletzkiy, P. V.; Gridnev, I. D.; Shevchenko, N. E.; Balenkova, E. S. *Tetrahedron* **1997**, *53*, 8173–8180.

(7) The precise mechanism of epoxide formation remains to be determined. The simplest conceptual possibility involves hydrolytic conversion of the trifluoroacetate to —OH , which then would cyclize to afford the epoxide. This pathway involves cleavage of a neopentyl trifluoroacetate to generate the required C_8 hydroxyl. Another possibility envisions the potential of participation by the ester-like oxygen in **9** to generate a “high-energy” trifluoroacetylated oxirane, which would cleave instantaneously to provide **4**. Finally, one can consider displacement of trifluoroacetate by the resident thionium species to generate the formally dipositive sulfonium, which would be hydrolytically displaced to generate the required β -hydroxysulfonium intermediate en route to the epoxide.

(8) For a related epoxide formation from an intermediate generated in a totally different fashion, see: (a) Corey, E. J.; Su, W. G. *Tetrahedron Lett.* **1990**, 31, 2677–2680. Indeed, the famous Corey methylenation of carbonyl compounds to generate oxiranes also anticipated, in its last step, a related epoxide formation. See: (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, 87, 1353–1364.

(9) Trapping of carbon after deprotonation is a well-known cyclization method associated with the Pummerer reaction. We refer to this process as trapping a late Pummerer intermediate. The intermediates in the present work, where trapping occurs at sulfur, are described as early Pummerer intermediates.

(10) Markovnikov, V. *Justus Liebigs Ann. Chem.* **1870**, 153, 228–259.

(11) The byproducts obtained in this reaction arise as a mixture of species in which the six-membered ring appears as the homoannular cyclohexadiene or one of the two isomeric conjugated methylenecyclohexenes. The formation of these products is readily accommodated in the mechanistic framework described above.

(12) For a valuable review of the traditional Pummerer reaction, see: Padwa, A.; Gunn, D. E.; Osterhout, M. H. *Synthesis* **1997**, 1353–1377.

(13) Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, 43, 4172–4177.