# **Designed Rearrangement of a Spirodiepoxide**

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**Abstract:** Epoxidation of a highly functionalized aryl allene gave a rearranged enone.

Key words: spirodiepoxide, allene, oxidation, acid-induced rearrangement, MCPBA

In a series of insightful studies, Crandall and co-workers established that peracid oxidants effect the conversion of allenes to the corresponding spirodiepoxides and that the acid byproduct derived from the oxidant induces the conversion of the spirodiepoxide to a range of products (Scheme 1).<sup>1</sup> These include mixtures of stereo- and regioisomers from nucleophilic opening of the spirodiepoxide by the organic carboxylate, and rearranged products such as oxetanone,  $\alpha$ -hydroxy enone, and others (**3**–**7**), presumably by way of carbocationic intermediates. The same group reported that dimethyldioxirane (DMDO), in contrast to peracid oxidants, induces allene oxidation under conditions that enable isolation of the spirodiepoxide.<sup>2</sup>





Conversion of allenes to spirodiepoxides and thence to  $syn-\alpha$ -substituted- $\alpha'$ -hydroxy ketones is a single-flask transformation of interest in chemical synthesis ( $8 \rightarrow 9 \rightarrow 10$ , Scheme 2).<sup>2</sup> Reliable methods for epoxidation and subsequent manipulation of functionalized allenes could

SYNLETT 2008, No. 2, pp 0213–0216 Advanced online publication: 21.12.2007 DOI: 10.1055/s-2007-1000866; Art ID: S05507ST © Georg Thieme Verlag Stuttgart · New York enable concise strategies for the assembly of complex natural products. For example, the alkaloids shown in Scheme 2 each house a vicinal triad (asterisks) that could, in principle, be derived from an aryl allene by way of the corresponding spirodiepoxide. Preliminary feasibility studies, however, showed that DMDO<sup>3</sup> oxidation of aryl allene 2 did not give an isolable spirodiepoxide. Instead, a complex mixture was obtained, including reaction products possibly derived from cationic intermediates, facilitated by the aryl substituent, and traceable to the spirodiepoxide or the allene oxide precursor. We have reported on a program that aims to understand spirodiepoxide reactivity and to apply this functional group to natural product synthesis.<sup>4,5</sup> One part focuses on the manipulation of ionization pathways potentially accessible to spirodiepoxides, and includes as the context aryl substituted allenes. Presented here is the designed acid-induced rearrangement of а highly functionalized aryl spirodiepoxide.

Key elements of the experimental design are depicted in Scheme 3. Where relevant, a spirodiepoxide (II) should be polarizable at the more substituted terminus under the action of a Brønsted or Lewis acid, and the corresponding carbocation should form upon full ionization (not shown). Substrates with a suitably disposable group (X) adjacent to this site would spontaneously jettison the group and thus form a double bond (III). This process could be stepwise or concerted. Aryl-substituted allenes were selected as the context in which to evaluate these concepts, as this class of allene would be of use in synthesis. Arene 2,6-disubstitution (I, see Y) was of particular interest as a model for a range of complex natural products. Moreover, this substitution pattern ought to suppress spontaneous heterolysis of the spirodiepoxide and its precursors, a pathway that the aryl group might otherwise promote.

Allene **25** satisfies all the above criteria (Scheme 4). The substitution pattern matches that of the FR-mitomycinoids. The ether and amide groups, although potentially problematic since they are electron donating, should induce the arene to be twisted out of planarity with the allene. The trimethylsilyl group should serve as the disposable group. Moreover, the silyl cation generated in this way could also promote spirodiepoxide opening and lead to formation of the silyl ether (see below). As such, the transformation would formally be a rearrangement.

The twelve-step preparation of 25 began with commercial 5-nitrovanillin (15), as shown in Scheme 4. The aryl alcohol was converted to triflate 16. Nucleophilic aromatic substitution ( $\rightarrow$  17) and acetal formation ( $\rightarrow$  18) fol-



Scheme 2

## Scheme 3

lowed.<sup>6</sup> The original conditions of Heck for sp-sp<sup>2</sup> coupling proved superior to Sonogashira conditions and gave enyne 20 in good yield.<sup>7</sup> Direct coupling of alkyne 19 with 17 was inferior (55% yield) to coupling with iodide 18. Reduction of the nitro group to the corresponding amine 21, followed by renovation of the amino alcohol to the O,N,N-tribenzoyl derivative and then to amide 22, proved convenient and efficient. Allene 24 was prepared by epoxidation, protection, and then cuprate-promoted  $S_N 2'$  addition. Attempts to generate allenes from epoxide derivatives of **20** with the nitro group in place proved highly inefficient. Presumably, the ability of the alkyne to coordinate to copper is attenuated by the electron-withdrawing nitro group and thus coordination becomes ratelimiting. Regeneration of the aldehyde and then installation of the silyl protecting group gave 25.<sup>12</sup>

From the outset our interest was to use a peracid oxidant to achieve the conversion of the allene to the enone. Although earlier studies showed that the acid byproduct from peracid oxidation of allene initiated multiple reaction pathways, such oxidants seemed ideal for this study, since their use would obviate the need to add acid in a separate step.<sup>8</sup> Still, given the unparalleled success of DMDO, the initial focus was to induce dioxirane-mediated oxidation. The findings were discouraging: Treatment of **25** with DMDO gave several products that did not include a stable isolable spirodiepoxide; removal of the aldehyde by reduction and subsequent conversion to the benzyl ether gave an allene that, like **25**, gave several products but no isolable spirodiepoxide; protected variants of acetal **24** behaved similarly (data not shown).

It seemed likely that the electron-rich arene is not stable to DMDO oxidation or, despite our design, that the spirodiepoxide or the allene oxide precursor derived from **25** spontaneously ionizes and goes on to give several products. DMDO oxidation of benzylic ethers and arenes is known and could account for these observations.<sup>9</sup> Nevertheless, in a final attempt to channel the reactivity towards the enone structure, the DMDO oxidation was run in the presence of benzoic acid. No evidence of enone was obtained. An impasse had been reached with the dioxirane oxidant. Insofar as these experiments served as precedent, the use of peracid oxidants for this transformation seemed much less promising than in the design stage of this study.

In contrast to the DMDO oxidations described above, exposure of **25** to MCPBA effected allene oxidation and rearrangement to enones **26** (dr = 2.3:1, Scheme 5).<sup>10,12</sup>



#### Scheme 4

Importantly, there was no evidence of arene oxidation. Although the precise stereochemical assignment of the major product has not been unequivocally established, the modest apparent selectivity suggests the following sequence. Epoxidation of the disubstituted terminus occurs first, an event which would be expected to take place with high facial selectivity and lead to the predominance of a single allene oxide intermediate (27, Scheme 6). This stereocenter would be destroyed upon eventual enone formation. The expected high reactivity of the allene oxide toward epoxidation would lead to the rapid formation of spirodiepoxide. The second epoxidation would be expected to be less selective; and this stereocenter would be retained in the final enone product. The neopentyl-like TMS-methylene substituent should block approach of the oxidant to the bottom face (27b) in order to avoid severe destabilizing interactions with the arene (27a).<sup>10</sup> In contrast to the TMS-methylene, the aryl group should be able to accommodate oxidation from the top face,<sup>11</sup> and thus would lead predominantly to spirodiepoxide **28**. Once generated, the spirodiepoxide would be subject to an acid-induced reaction pathway approximated by Scheme 3 to give **26a** as the major product. Indeed, it would seem that the protic acid byproduct of oxidation, and silyl cation generated subsequently, set into motion the highly efficient overall rearrangement of the spirodiepoxide to the enone product.

In summary, this report discloses the first example of aryl allene spirodiepoxidation and the efficient conversion of an allene to an enone. This moderately complex allene ranks among the most densely functionalized substrates evaluated to date. Weakly acidic hydroxylic solvents,<sup>5c</sup> reagents that exhibit mild Lewis acid character<sup>4a</sup> or hydrogen-bonding properties,<sup>4b</sup> and now Brønsted acid reagents have been used to promote efficient spirodiepoxide open-



Scheme 5

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### Scheme 6

ing. These findings contribute to a growing body of data that demonstrate the potential of spirodiepoxides for use in complex molecule synthesis.

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- (12) Selected Analytical Data: Compound **25**: <sup>1</sup>H NMR (400 MHz, CCl<sub>3</sub>):  $\delta = -0.08$  (s, 9 H), 0.06 (d, J = 2.1 Hz, 6 H), 0.53 (q, J = 7.9 Hz, 6 H), 0.74 (t, J = 7.9 Hz, 9 H), 0.88 (s, 9 H), 1.81 (dd, J = 1.8, 5.8 Hz, 2 H), 3.56 (dd, J = 5.7, 9.9 Hz, 1 H), 3.64 (dd, J = 5.7, 10 Hz)1 H), 3.90 (s, 3 H), 4.18 (m, 1 H), 5.25 (td, *J* = 2.4, 7.8 Hz, 1 H) 7.24 (s, 1 H), 7.54 (m, 3 H), 7.89 (d, J = 7.2 Hz, 2 H), 8.68 (s, 1 H), 8.72 (br, 1 H), 10.00 (s, 1 H). IR (neat):  $v_{max} = 3403$ , 2721, 1953, 1700, 1581, 1259, 1001 cm<sup>-1</sup>. ESI-MS: *m/z* calcd for C<sub>36</sub>H<sub>57</sub>NO<sub>5</sub>Si<sub>3</sub>Na [MNa]<sup>+</sup>: 691.0; found 690.5. Compound 26: <sup>1</sup>H NMR (300 MHz, CCl<sub>3</sub>):  $\delta = 0.10$  (s, 3.8 H), 0.11 (s, 2.8 H), 0.42–0.54 (m, 6 H), 0.76–0.89 (m, 18 H), 3.44-3.52 (m, 1 H), 3.60-3.69 (m, 0.73 H), 3.73-3.78 (m, 1.13 H), 3.84 (s, 3 H), 4.02-4.08 (m, 0.48 H), 4.15-4.20 (m, 0.65 H), 4.73 (d, J = 2.4 Hz, 0.66 H), 4.75 (d, J = 2.4 Hz, 0.36 H), 5.88 (s, 0.68 H), 5.97 (s, 0.27 H), 6.54 (s, 0.71 H), 6.68 (s, 0.28 H), 7.45–7.58 (m, 4 H), 7.86 (d, J = 7.5 Hz, 2 H), 8.53 (s, 1 H), 8.73 (br, 0.31 H), 8.86 (br, 0.65 H), 10.01 (s, 1 H). IR (neat):  $v_{max}$  = 3387, 1728, 1691, 1578, 1261, 1013, 842 cm<sup>-1</sup>. ESI-MS: m/z calcd for C<sub>36</sub>H<sub>57</sub>NO<sub>7</sub>Si<sub>3</sub>Na [MNa]<sup>+</sup>: 723.0; found: 722.3.

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