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Silyl-Substituted Spirodiepoxides: Stereoselective Formation and Regioselective Opening

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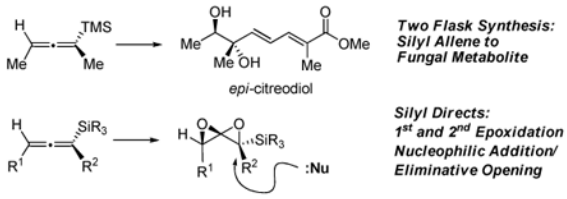
Abstract



A short synthesis of the natural product *epi*-citreodiol and the method developed to gain access to this target are described. Key advances focus on silyl substituted allenes. Upon exposure to dimethyldioxirane, spirodiepoxides form with high face selectivity and subsequently react at the silyl terminus.

Here we report direct entry to enantioenriched α′-hydroxy enones and its derivative enediols. These motifs are widely distributed among natural products, especially polyketides, such as gabosine A,[1] hypothemycin,[2] picromycin,[3] incednine,[4] and *epi*-citreodiol,[5] among others. In principle, spirodiepoxide methodology offers a means by which to access such motifs.[6] The efficiency of the transformation from allene to derivatized spirodiepoxide has been limited by the selectivity of allene epoxidation. In other studies we described the challenges associated with epoxidation of 1,3 disubstituted allenes.[7] As briefly shown in Scheme 1, the stereoselectivity of the first epoxidation of an allene of type **I** ($R^1 = R^2$) is excellent [**I**→**II** (major) and **III** (minor), dr > 20:1]. Epoxidation of allene oxides (e.g. **II** and **III**) is usually less selective. For example, linear, unfunctionalized substituents lead to low ratios of spirodiepoxide products [**II**→**IV** (major) and **V** (minor), dr ~ 2:1]. The situation is complicated by issues of site selectivity as well. In cases for **I** where $R^1 \neq R^2$ two different allene oxides could form, each with high facial selectively, and thereby lead to a total of three spirodiepoxides (**I**→**IV-VI**).[7] Moreover, there is an additional problem: subsequent nucleophilic or eliminative opening would generate two regioisomeric products from each spirodiepoxide (e.g. **IV**→**VII** and **VIII**). We wondered whether the presence of a silyl substituent would address each of these issues simultaneously and in so doing achieve the selective conversion of allenes to substituted ketone derivatives.

It was not clear at the outset that the presence of a silyl substituent would successfully address the issues of regio and stereoselective allene epoxidation (Scheme 1). The concern

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Supporting Information Available Synthetic methods and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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was that the first oxidation of an allene of type **IX** might take place at the double bond distal to the silyl group (**IX→X**). Since face selectivity in these systems is governed by steric factors of the non-reacting terminus, the bulk of the silyl substituent could well render the oxidation face-selective. However, the second oxidation of the resulting allene oxide would be expected to be low (**X→XII** and **XIII**), in analogy to the conversion of **II** to **IV** and **V** – compare this with the alternative scenario wherein the first oxidation takes place on the double bond bearing the silyl group (**IX→XI**). This oxidation should be highly selective in analogy to **I → II**, and the second oxidation, **XI→XII**, could well be selective due to the bulk of the silyl substituent.

The electronic effects of silyl substitution are well documented.[8] In the context of allene epoxidation, the α-effect favors the desired outcome (**IX→XI**), whereas the β-effect does not. We evaluated the possibilities computationally. Density functional calculations[9] of silyl substituted allenes **1–4** indicate that the position of the HOMO depends upon the substitution pattern (Figure 1). For trisubstituted silyl allene **3**, the HOMO resides at the double bond adjacent to the silyl group and suggests that in the absence of overriding factors epoxide formation for this type of allene will be selective for this site as desired.

A preliminary assessment of silyl substituted allenes and the resultant spirodiepoxides is presented in Scheme 2 and Table 1. Consistent with the above computational and stereochemical analysis, exposure of silyl substituted allene **5** to DMDO/chloroform solutions[7] gave spirodiepoxide **6** along with a minor diastereomer (dr = 10:1) as indicated by 400 mHz ^{1}H NMR analysis. This highly selective formation of a spirodiepoxide strongly suggests that the silyl group dictates site-selective epoxidation of the proximal allene double bond (dr > 20:1) and the stereoselective epoxidation of the resultant allene oxide (dr ≈ 10:1). Such spirodiepoxides appear stable towards many nucleophiles that are known to react readily with non-silyl spirodiepoxides, such as water, alcohol, and azide (data not shown). Interestingly, treatment of **6** with benzoic acid resulted in the selective formation of α-hydroxy-α′-benzoyl ketone **7** in an overall yield of 82%. The efficiency of this reaction was unexpected, since acids effect decomposition of non-silyl spirodiepoxides to many products.[6f,10] Structural analysis (^{1}H NMR) supports the assignment shown and indicates that benzoate added to the carbon bearing the silyl substituent. Recently, we reported a method for synthesizing carbinol-functionalized azoles from spirodiepoxides.[6e] Accordingly, treatment of the epoxidation product derived from allene **5** with thiobenzamide in chloroform gave a 1:1 ratio of carbinol-functionalized thiazolines **8a** and **8b**. Under these conditions the silyl group migrated to the adjacent oxygen. Use of methanol instead of chloroform gave a 1:1 ratio of non-silyl thiazolines **9a** and **9b**. Dehydrative aromatization of thiazolines **8** and **9** gave a single thiazole (**10**). Crystallographic analysis of **8a** confirmed the structure of the thioamide and by analogy **6-10**, **12**, and **13** (Table 1). Thus, silyl substitution dictates both regio- and stereoselective allene epoxidation and subsequent regioselective opening of the spirodiepoxide intermediate.

Table 1 catalogs data related to the behavior of enantioentriched allenes **5** and **11** and their stereoselective, single flask conversion to azoles of type **10**, **12**, and **13**. The enantiomeric ratios of the products are excellent and reflect the stereoselectivity of spirodiepoxide formation. Addition of thiobenzamide and benzamidine gave good yields of thiazole and imidazole. Benzamide reacted, albeit slowly, with the spirodiepoxide derived from **5** to give oxazole **12** in modest yield but did not react under these conditions with the spirodiepoxide derived from **11**. The addition is slow in comparison to addition to non-silyl spirodiepoxides. This is despite the presense of methanol, an additive known to facilitate spirodiepoxide opening.[6b,d,11]

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In all cases studied, silyl migration occurred rapidly, and the use of methanol promoted the loss of silyl altogether. The conditions for migration leading to **8** and **9** are remarkably mild. Regardless of solvent, there was no evidence of the formation of intermediate structures. Although silyl migration is known,[12] in this case it appears to be facilitated by the combination of the geminally positioned sulfur, nitrogen, or oxygen and the vicinal hydroxyl.

Encouraged by the above results, we set out to realize the eliminative opening of spirodiepoxides (**XIV→XVII**, Scheme 3). Proteodesilylation of α-hydroxy silylenones[12,13] and site-selective eliminative opening of silyl substituted epoxides are known.[14,15] We examined this type of elimination for spirodiepoxides derived from **5**, **14** and **15** (Table 2). Brønsted and Lewis acids in polar solvent were found to effect enone formation (entries 1-3). Interestingly, so did cyclopentadienyl titanium (IV) chloride in combination with zinc dust, (compare entries 1-3 with 4-6).[16,17]

In contrast to the titanium mediated reaction, which favors the α′-hydroxy-*Z*-enone product (**16–18**), the organolithium and Grignard reagents gave α,β-dihydroxy olefins directly (**19–21** entries 7–12). Athough difficult to rationalize, the *E/Z* selectivity appears to depend on both the substrate structure and the reagents employed. When methyllithium was used **21** was isolated in excellent yield (entry 9). The *E/Z* geometry strongly favored the *E* product. No evidence of the isomeric tertiary alcohol was obtained as only the chelation controlled addition product was observed. Crystallographic analysis of this product established the relative stereochemistry and confirmed the olefin geometry assignment. Methyl magnesium bromide, however, gave **21** favoring *Z* enone albeit in lower yield.

Lastly, we used silyl-substituted allenes to the first total synthesis of *epi*-citreodiol (**22**, Scheme 4). This natural product was isolated, along with citreodiol, from the mycelium of *Penicillium citreo-viride B.* (IFO 6050)[5] and is related to the potent inhibitor of ATP-synthesis and ATP-hydrolysis, citreoviridin (**23**).[18] Our synthesis began with known allene **24**.[19] Exposure of **24** to DMDO in chloroform, treatment with methyllithium in ether, and then proteodesilation[13] in acetonitrile gave **25** as a single isomer in 69% yield. This sequence was run in a single flask. Although direct olefin cross metathesis of **25** with **28** failed to give the desired product, the synthesis was nevertheless completed in a second single flask procedure. Olefin metathesis with acrolein and catalyst **26**[20] (→**27**) followed by Wittig olefination[21] gave **22** as a single isomer in excellent overall yield. The structural characteristics of synthetic **22** were identical to the published NMR and optical rotation data for natural *epi*-citreodiol, e.g. $[\alpha]_D^{23}$ -7.5° (c = 2.3, $CHCl_3$), lit[5]: $[\alpha]_D^{21}$ -7.1° (c = 2.3, $CHCl_3$). Thus direct entry to this natural product was realized without recourse to protecting group strategies with high efficiency and selectively via the silyl subsituted spirodiepoxide.

In summary, preliminary assessment of silyl substituted allenes reveals that this arrangement is an excellent means by which to control regio and stereoselective spirodiepoxide formation. Moreover, silyl-substituted spirodiepoxides are shown to undergo subsequent site-selective nucleophilic and eliminative opening. Further studies are ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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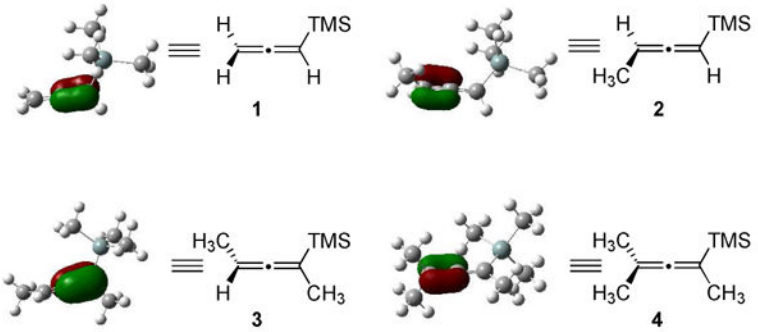

Figure 1.
DFT calculated position of the HOMO of silyl substituted allenes.

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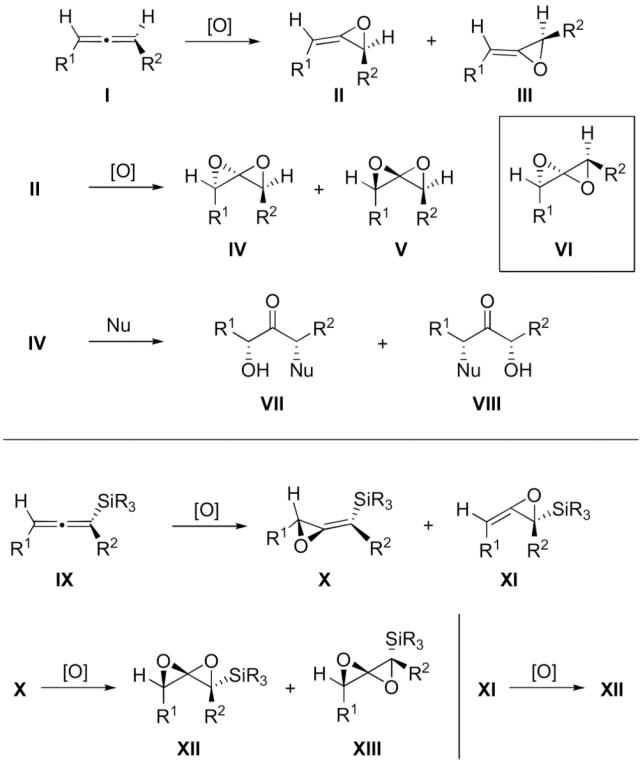
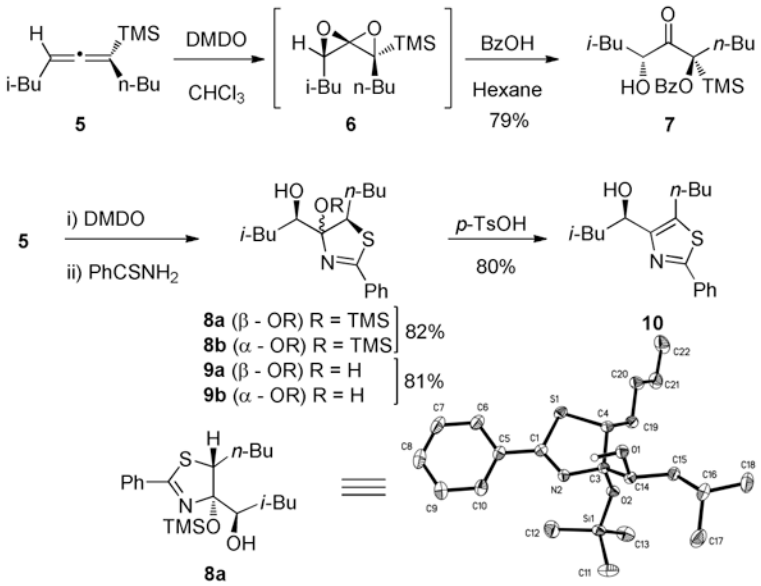


Scheme 1.
Model for stereoselective spirodiepoxidation.



Scheme 2.
Silyl-directed spirodiepoxidation.

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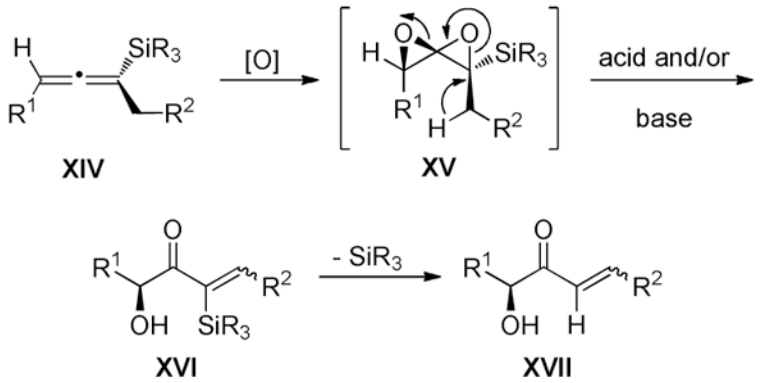
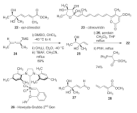


Scheme 3.
Silyl-directed eliminative opening



Scheme 4.
Synthesis of epi-citreodiol

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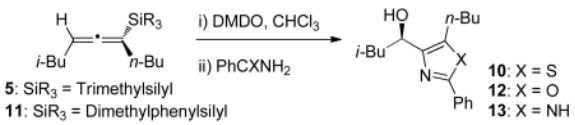
Table 1

Single flask preparation of functionalized azoles.



entry	allene	amide	product	time (h)	condition	yield (%)	er[a]
1	**5**	$C_6H_6CSNH_2$	**10**	12	A	80	97%
2	**5**	$C_6H_6CONH_2$	**12**	48	A	52	95%
3	**5**	$C_6H_6CNHNH_2$	**13**	48	B	72	>95%
4	**11**	$C_6H_6CSNH_2$	**10**	24	A	76	98%
5	**11**	$C_6H_6CNHNH_2$	**13**	48	B	78	>95%

Condition A: DMDO/$CHCl_3$, -40 °C to rt, 2 h; 3 equiv amide, MeOH, rt, then 10 mol % *p*-TSOH, reflux. *Conditon B:* DMDO/$CHCl_3$, -40 °C to rt, 2 h; 5 equiv amide, MeOH, rt. a) er (enantiomeric ratio) was determined by chiral HPLC except for entries 3 and 5, which were based on the dr (diastereomeric ratio) assessed by Mosher ester analysis.

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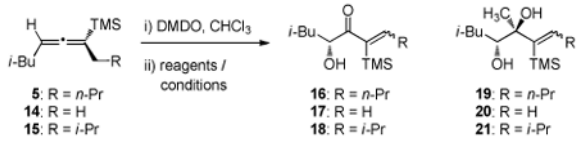
Table 2

Spirodiepoxide eliminative opening.



entry	allene	reagent	conditions	product (*E*:*Z*)	yield (%)
1	**14**	PTSA	$CHCl_3$, -78 °C, 1 h	**17**	58
2	**14**	$MgBr_2$, Et_3N	DCM, -40 °C, 2 h	**17**	54
3	**14**	SiO_2	$CHCl_3$, rt, 6 h	**17**	60
4	**14**	Cp_2TiCI_2, Zn	THF, -60 °C, 10 min	**17**	66
5	**5**	Cp_2TiCI_2, Zn	THF, -60 °C, 10 min	**16** (*1*:*1*)	72
6	**15**	Cp_2TiCI_2, Zn	THF, -60 °C, 10 min	1**8** (*1*:*5*)	74
7	**14**	CH_3Li	Et_2O, -40 °C to rt, 2 h	**20**	85
8	**5**	CH_3Li	Et_2O, -40 °C to rt, 2 h	**19** (*2.2*:*1*)	83
9	**15**	CH_3Li	Et_2O, -40 °C to rt, 2 h	**21** (*16*:*1*)	86
10	**14**	CH_3MgBr	Et_2O, -78 °C to 0 °C, 2 h	**20**	48
11	**5**	CH_3MgBr	Et_2O, -78 °C to 0 °C, 2 h	**19** (*1*:*3.4*)	40
12	**15**	CH_3MgBr	Et_2O, -78 °C to 0 °C, 2 h	**21** (*1*:*12*)	38