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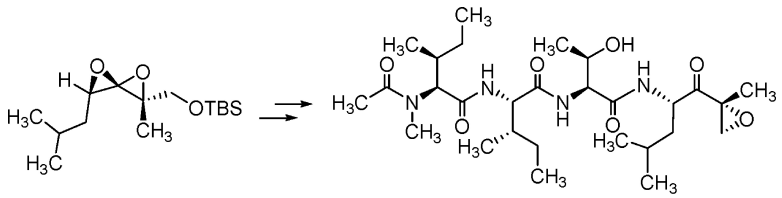

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Spirodiepoxides in Total Synthesis: Epoxomicin

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Substrate-directed and reagent-controlled asymmetric alkene epoxidation and subsequent nucleophilic epoxide opening are among the most widely used strategies for introducing molecular complexity in target-oriented synthesis.[1] Yet the analogous oxidation/nucleophilic opening of the intrinsically stereogenic allene remains unexplored in synthesis.[2] The oxidation products, spirodiepoxides (e.g., **3**), can in principle serve as synthetically useful three-carbon units of bond formation and stereochemistry and provide direct access to highly functionalized and highly enantioenriched ketones and ketone derivatives. Here we present an efficient route to the potent and selective proteasome inhibitor epoxomicin[3] (**1**) and thus establish the first use of the spirodiepoxide functional group in total synthesis.

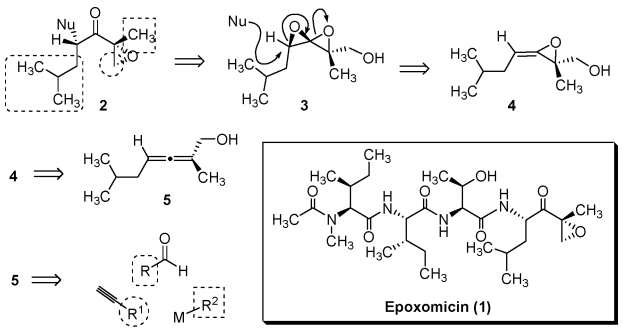
Proteasome targeting has emerged as a new modality for the potential treatment of diseases ranging from malaria to cancer.[4] The importance of understanding and controlling proteasome function led us to design new approaches to epoxomicin (**1**).[5] In the most concise approach, the functionality and stereochemical arrangement of simplified structure **2**, present in **1**, would be orchestrated simultaneously (Scheme 1), and modifications in the peripheral highlighted portions of **2** would not encumber the synthetic route. Spirodiepoxides of type **3** could serve as precursors to such target systems. In the presence of a suitable nucleophile such species should undergo regioselective S_N2 reactions. Enantiomerically pure spirodiepoxide would be derived from oxidation of optically pure, and appropriately protected, allene (e.g., **5**), which would arise in turn from aldehyde, alkyne, and organometallic precursors. The highlighted substituents of these precursors correspond to those indicated in **2**. Oxidation of **5**, first at the less hindered face of the more substituted π-bond, would give rise to **3** as the major isomer. This approach would require identification of a hydroxyl protecting group for **5** and a nitrogen nucleophile suitable for spirodiepoxide opening.

The pioneering work of Crandall stands as the only reported systematic analysis of spirodiepoxides.[6] Thus, simple allenes may be oxidized to spirodiepoxides, which rearrange in the presence of acid. A number of nucleophiles have been successfully added to spirodiepoxides, and consistent with S_N2 substitution, the ratio of products corresponds to the ratio of oxidation products.

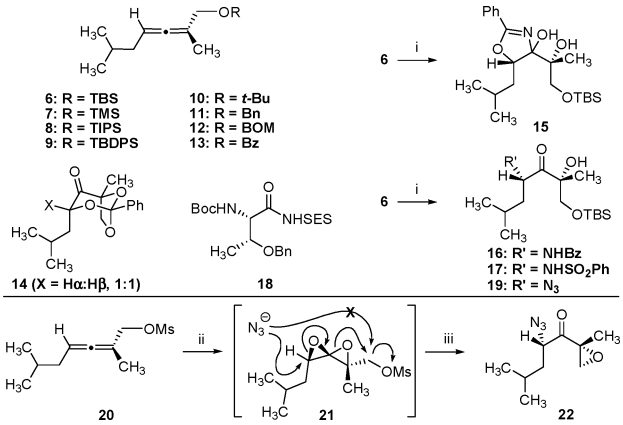
To initiate our studies, a series of *O*-protected hydroxy allenes (**6**−**13**) was prepared and oxidized with dimethyldioxirane (DMDO), as shown in Scheme 2. Functional group compatibility and approximate ratios of oxidation products were determined by ^{1}H NMR analysis of the crude spirodiepoxides.[7] While benzoate **13** led to ortho ester **14**, silyl and alkyl ether protection is compatible with the spirodiepoxide functionality and gave the corresponding spirodiepoxides in ratios of approximately 2:1.

To proceed toward **1**, suitable nitrogen nucleophiles were identified by exposure to spirodiepoxides derived from allene **6**.[7] Addition of benzamide under neutral conditions led to *O*-alkylation/cyclization and gave oxazolines **15** in 44% yield, whereas the

Scheme 1



Scheme 2 [a]



[a] Reagents and conditions: (i) DMDO, acetone, −40 to 23 °C, 2 h; then nucleophile (see Supporting Information); (ii) DMDO, acetone, −50 to 23 °C, 2 h; (iii) Bu_4NN_3, $CHCl_3$, −30 °C, 2 h; 30%. Major isomers shown. SES = $SO_2CH_2CH_2Si(CH_3)_3$.

N-alkylated product **16** predominated, albeit in modest yield (30%), when benzamide was first treated with *n*-BuLi. Benzenesulfonamide in the presence of base[8] gave adduct **17** (75%), but under neutral conditions no product was observed. In hopes of inducing *N*-alkylation of an amide precursor, we prepared *N*-acyl sulfonamide **18** by using our thio acid/azide amidation.[9] Under a variety of conditions (DIEA, K_2CO_3, LiHMDS, NaHMDS, or KHMDS), no reaction with the spirodiepoxide took place. In the absence of base, however, an unstable adduct formed and then decomposed upon treatment with fluoride. While sodium azide added slowly to spirodiepoxides derived from **6**, tetrabutylammonium azide added rapidly even at low temperature to give **19** in 73% yield.

When the spirodiepoxide derived from allenyl mesylate **20** was exposed to tetrabutylammonium azide, epoxide **22** was formed in 30% yield. Azide appears to preferentially open the spirodiepoxide rather than displace the neopentyl-like mesylate (see **21**). The nascent vicinal alkoxide displaces the mesylate to form a new epoxide, which resists subsequent azide opening. Azide **22** and the amine derived by reduction proved unstable and therefore were not

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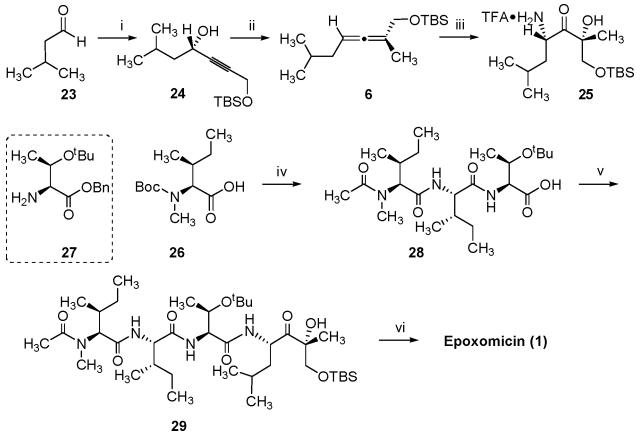
Scheme 3 [a]



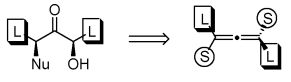
[a] Reagents and conditions: (i) (−)-*N*-methylephedrine, $Zn(OTf)_2$, Et_3N, toluene, rt, 2 h, $TBSOCH_2CCH$ then **23** 14 h, 93%, >95% ee; (ii) a. MsCl, Et_3N, DCM, −65 to 23 °C, 2 h; b. MeMgBr, CuBr, LiBr, THF/*tert*-butyl ether, −65 to 23 °C, 2 h, 91%; (iii) a. DMDO, −40 to 23 °C, 1.5 h; b. Bu_4NN_3, $CHCl_3$, −20 to 23 °C, 1 h, 73% (3:1 dr); c. 10% Pd/C, H_2, $(Boc)_2O{\cdot}K_2CO_3$, EtOAc, rt, 12 h, 91%; d. TFA, 0 °C, 13 min; (iv) a. **26**, HCl·Ile-OMe, DCC, HOBT, Et_3N, DMF, 0 to 23 °C, 12 h, 93%; b. 25% TFA−DCM, 10 to 23 °C, 40 min; c. TEA, Ac_2O, DMAP, DCM, 0 to 23 °C, 3 h, 95%; d. 5% NaOH, MeOH−H_2O, rt, 2 h, 99%; e. **27**, DCC, HOBT, DCM−DMF, rt, 3 h, 92%; f. 10% Pd/C, H_2, MeOH, rt, 2 h, 100%; (v) **25**, DIEA, DCC, HOBT, DCM−DMF, rt, 4 h, 86%; (vi) a. TBAF, THF, 0 to 23 °C, 1 h, 89%; b. MsCl, DIEA, DCM, −40 to 23 °C, 1 h; c. K_2CO_3, THF−H_2O, rt, 3 h, 93%; d. TFA, 0 to 23 °C, 20 min, 88%.

advanced. Amines related to **19**, however, were stable to manipulation leading to **1**, as described below.

The optimized synthesis of epoxomicin is presented in Scheme 3. Isovaleraldehyde was subjected to asymmetric alkynylation[10] to form **24** (93% yield, >95% ee). The alcohol was converted to the mesylate and subsequently transformed into allene **6** upon copper-mediated[11] S_N2' displacement (91%). As described above, treatment of **6** with DMDO[12] followed by exposure to azide smoothly produced **19** (>95% er) in 73% yield (3:1 ratio of separable diastereomers). In situ reduction/protection (91%) and then treatment with acid converted the major azido alcohol to the stable crude amine salt (**25**) ready for peptide coupling. DCC-promoted coupling of **26** with methyl isoleucinate (93%), Boc removal and acetylation (95%), saponification (99%), coupling to threonine **27**[7] (see inset), and then hydrogenolysis gave **28** (92%, two steps), which smoothly coupled with **25** to furnish **29** (86%, **19** → **29**). Exposure of **29** to fluoride cleaved the silyl ether-protecting group (89%). The resultant primary alcohol was converted to the mesylate and cyclized to give the epoxide (93%), and then the *tert*-butyl ether was removed (88%) to produce **1**.

Spectral data for synthetic **1** proved identical to published data for natural **1**, including $[\alpha]_D^{25}$ −64.0 (*c* 0.47, MeOH), lit[3a] −66.1 (*c* 0.50, MeOH), and confirms the stereochemical assignments in Scheme 3. Chemical correlation secured the syn stereochemistry of the major isomers of **15**−**17**, **19**, and **22** as shown in Scheme 2.

Nucleophilic opening of a spirodiepoxide effectively establishes specific stereochemical communication across a carbonyl. As depicted in eq 1, oxidation/nucleophilic opening installs three



(Eq 1)

L = large substituent; S = small substituent

functional groups, nucleophile, ketone, and alcohol, with syn selectivity. Importantly, this transformation is achieved in the absence of other stereodirecting functionalities. This report also establishes that chiral spirodiepoxides can be prepared and manipulated on gram scale.[13] Coupled with the two-step assembly of all the carbon atoms of the targeted substructure, this method is a highly efficient, flexible, and modular synthesis of highly functionalized ketones and their derivatives. In addition to disclosing the selective reaction of a spirodiepoxide in the presence of a mesylate and several new and diverse reactions of spirodiepoxides (e.g. formation of ortho ester **14**, oxazoline **15**, and azido epoxide **22**), we have completed the synthesis of epoxomicin in an overall yield of 26% from **23** (20% including all steps). This route should also provide new epoxomicin analogues with improved activity and selectivity. Issues such as the scope of compatible functional groups and nucleophiles, control of regioselective nucleophilic addition, stereoselective oxidation of the allene precursors, and elucidation and exploitation of the mechanisms of spirodiepoxide opening are under investigation.

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

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