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Spirodiepoxides: Synthesis of Epoxomicinoids

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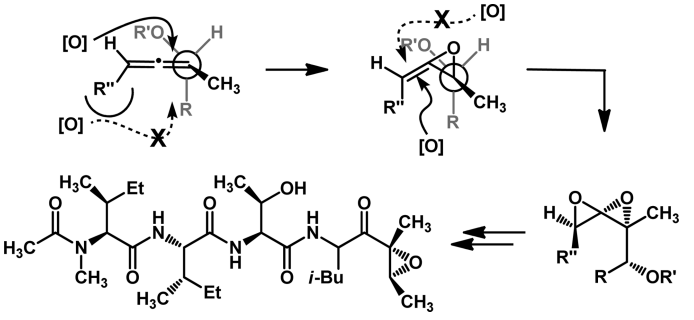

Three closely related analogues of epoxomicin have been synthesized. Allene-derived spirodiepoxides were key intermediates. Spirodiepoxide formation and stereochemical dependence on solvent, oxidant, and allene structure were cataloged. The facial selectivity of the first epoxidation of 1,3-disubstituted and trisubstituted allenes was found to be >20:1 with dimethyldioxirane in chloroform. For stereogenic allenes, the facial selectivity of the second oxidation is dependent primarily on allene structure and secondarily on solvent and oxidant. For the acyclic systems evaluated this ratio was as high as 8:1. A conformational model is advanced to account for these observations.

Introduction

Spirodiepoxide-based transformations offer new routes of entry to highly enantioenriched and densely functionalized motifs (e.g., **1**→**2**, Scheme 1). Recently, we disclosed the first application of spirodiepoxides in total synthesis and have made progress in understanding the structure and reactivity of this group.[1] Necessarily, the focus has been on stereoselective allene oxidation, spirodiepoxide transformations, and development of a mechanistic framework to rationalize and predict the behavior of this functionality. Our studies are advanced in the context of target-driven syntheses. Here we disclose findings on solvent, oxidant, and substrate-dependent allene epoxidation and the application of these findings to the synthesis of analogues of the proteasome inhibitor epoxomicin (**3**).

Scheme 2 shows a simple steric model for allene to spirodiepoxide conversion (**I** → **II** → **III**).[2] This model assumes that the site of first oxidation is selective, e.g., the R_S/R_L terminus in the case of **I**. The preferred approach of oxidant occurs on the same side as the small substituent on the nonreacting terminus of the allene, or allene oxide (see arrows). Prior studies support the above model and suggest that the first oxidation is selective (**I** → **II**, ∼10:1) and that the second is not (**II** → **III**, ∼1:1).[2] It is noteworthy that these foundational studies focused exclusively on achiral and racemic allenic hydrocarbons, where the allene was the sole stereogenic moiety and the substituents were simple linear or branched alkanes. These observations are consistent with the notion that allene epoxidation (i.e., allene oxide formation) is slower and more selective than allene oxide epoxidation.[3]

(1) (a) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348. (b) Lotesta, S. D.; Hou, Y.; Williams, L. J. *Org. Lett.* **2007**, *9*, 869. (c) Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2007**, *129*, 2438. (d) Shangguan, N.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093. (e) Lotesta, S. D.; Kiren, S.; Williams, L. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7108. (f) Wang, Z.; Shangguan, N.; Cusick, J. R.; Williams, L. J. *Synlett* **2008**, *2*, 213. (g) Ghosh, P.; Zhang, Y.; Emge, T. J.; Williams, L. J. *Org. Lett.* **2009**, *11*, 4402. (h) Ghosh, P.; Cusick, J. R.; Inghrim, J.; Williams, L. J. Submitted for publication. (i) Duffy, R. J.; Morris, K. A.; Romo, D. *Tetrahedron* **2009**, *65*, 5879.

(2) Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153.

(3) Although the rationale that allene oxide epoxidation is faster than allene epoxidation appears compelling, unambiguous exceptions are known; see, for example: (a) Camp, R. L.; Green, F. D. *J. Am. Chem. Soc.* **1968**, *90*, 7349. (b) Crandall, J. K.; Machleder, W. H. *J. Heterocycl. Chem.* **1969**, *6*, 777. (c) Marshall, J. A.; Tang, Y. *J. Org. Chem.* **1994**, *59*, 1457.

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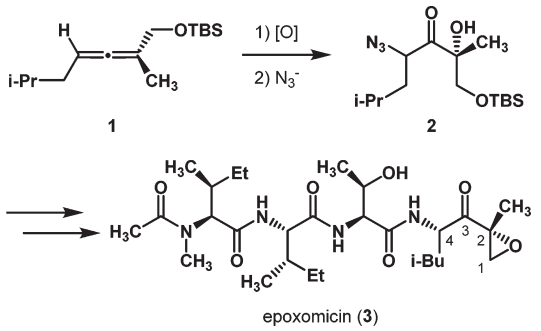
SCHEME 1



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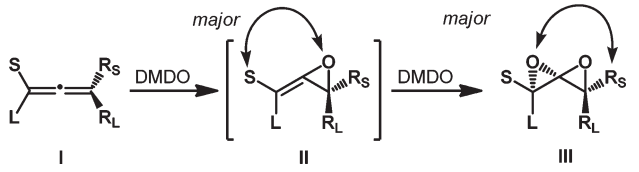

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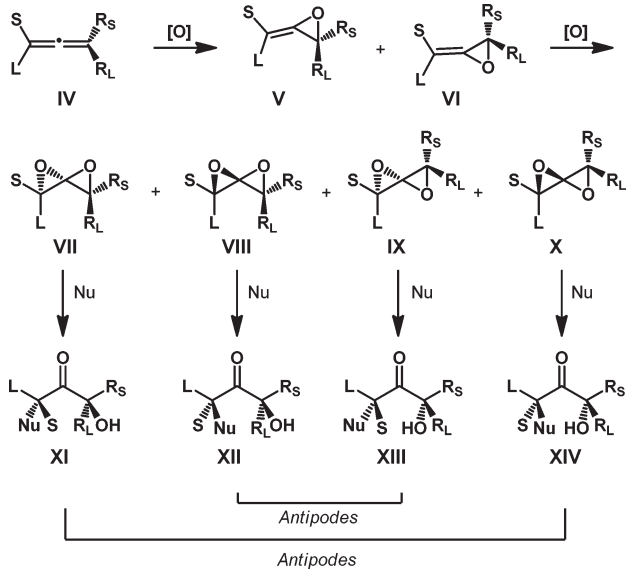


Spirodiepoxide formation represents an unusually complex set of stereochemical possibilities.[4] Although many interesting outcomes are possible, we focus on the complexities related to epoxidation of stereogenic allenes. In principle, an enatiopure allene can give as many as four diastereomeric spirodiepoxides, even in instances where the first oxidation is regioselective (**IV** → **V** + **VI** → **VII**−**X**), Scheme 3). Upon substitution, which for simplicity we will assume occurs regioselectively and with inversion of configuration, the minor isomers **IX** and **X** give rise to the antipodal isomers of the products derived from the major spirodiepoxide products **VII** and **VIII**. Hence, *high enantiopurity of the allene precursor will not ensure high enantiopurity of the spirodiepoxide substitution products*.

(4) Note that the central spirodiepoxide carbon will be stereogenic in all but the most symmetric of structures.

TABLE 1. Stereoselective Spirodiepoxide Formation: Influence of Dioxirane and Solvent

4a R^1 = *i*-Bu, R^2,R^3 = *n*-Bu
4b R^1,R^2 = *n*-Bu, R^3 = H
4c R^1,R^2 = *i*-Pr, R^3 = H

			selectivity[a]	
entry	allene	conditions	r_1	r_2
1	**4a**	DMDO/DME	5:1	na
2	**4a**	DMDO/hexane	9:1	na
3	**4a**	DMDO/acetone	10:1	na
4	**4a**	DMDO/CH_2Cl_2	> 20:1	na
5	**4a**	DMDO/$CHCl_3$	> 20:1	na
6	**4a**	DMDO/CCl_4	> 20:1	na
7	**4a**	DMDO/*t*-BuOH	> 20:1	na
8	**4b**	DMDO/acetone	10:1	1.1:1
9	**4b**	DMDO/CH_2Cl_2	> 20:1	1.8:1
10	**4b**	DMDO/$CHCl_3$	> 20:1	2.0:1
11[b]	**4b**	DMDO/CCl_4	> 20:1	1.4:1
12[c]	**4b**	MEDO/MEK	14:1	1.3:1
13	**4b**	DEDO/DEK	16:1	1.5:1
14	**4c**	DMDO/acetone	10:1	2.5:1
15	**4c**	DMDO/CH_2Cl_2	> 20:1	3.3:1
16	**4c**	DMDO/$CHCl_3$	> 20:1	5.0:1
17	**4c**	DMDO/CCl_4	> 20:1	2.0:1
18	**4c**	DMDO/*t*-BuOH	> 20:1	4.6:1

[a]Ratios determined by ^{1}H NMR. [b]MEDO: methylethyldioxirane, MEK: methyl ethyl ketone. [c]DEDO: diethyldioxirane, DEK: diethyl ketone. The allenes used here were racemic.

In order for a single spirodiepoxide to be formed both the first and second oxidations must be fully face selective (e.g., **IV**→**V**→**VII**). The intrinsic reactivity of the allene and allene oxide will tend to favor selective first epoxidation and less selective second epoxidation.[5] For instance, oxidation of a stereogenic trisubstituted allene will likely give a preponderance of two spirodiepoxides owing to the high site and stereoselectivity expected for the first epoxidation (S = H, Scheme 3). Clearly, allene epoxidation must be selective for spirodiepoxides to be efficiently applied to the synthesis of stereochemically elaborate products.

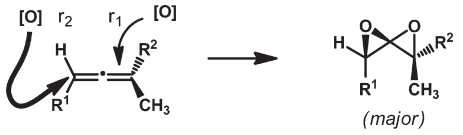
Results and Discussion

Our work on functionalized allenes indicates that spirodiepoxide formation may be highly stereoselective. Tables 1 and 2 summarize solvent and oxidant dependence as well as the effect of a chiral center adjacent to a stereogenic allene. These results are described along with a stereochemical model that accounts for these findings (Figure 1).

We focused on the use of dioxirane oxidants in this study. Dimethyldioxirane (DMDO) was prepared as a dilute solution

(5) (a) Although symmetric 1,3-disubstituted allenes will give two spirodiepoxides in instances where the first oxidation is highly selective and the second oxidation is not, 1,3-disubstituted allenes that lack symmetry will give three spirodiepoxides. (b) The possible outcomes of substitution for the major spirodiepoxides derived from enantiopure C_2-symmetric allenes constitute another interesting scenario. The expected product for the C_2-symmetric spirodiepoxide is an α-hydroxy-α′-substituted ketone as a single enantiomer (unless the α′-substituent is hydroxyl!). Substitution of the non-C_2-symmetric spirodiepoxide product will give a racemic mixture, unless only one of the enatiotopic termini is opened in the process.

TABLE 2. Stereoselective Spirodiepoxide Formation: Influence of Allene Structure



(major)

entry	allene	R^1	R^2	product	selectivity[a] r_1	r_2
1	**1**	*i*-Bu	CH_2OTBS	**10**	>20:1	2:1
2	**6**	*i*-Pr	*i*-Pr	**11**	>20:1	3.3:1
3	**7a**	*i*-Bu		**12a**	>20:1	5:1
4	**7b**	*i*-Bu		**12b**	>20:1	1:1
5	**8**	*i*-Bu		**13**	>20:1	6:1
6	**9**	CH_2OTBS		**14**	>20:1	8:1

in acetone ($\sim$ 0.10 M)[6] and extracted into halogenated solvent. The resultant comparatively concentrated solutions ($\sim$ 0.3 M) contained only trace quantities of residual acetone ($< 3\%$).[7] These solutions were diluted to 0.1 M by addition of the solvents indicated in Table 1. Methylethyldioxirane (MEDO) and diethyldioxirane (DEDO) were prepared as solutions in their parent ketones. In contrast to acetone solutions of DMDO, these other dioxiranes are not readily extracted into halogenated solvent, and consequently, solvent studies were not conducted for these oxidants.[8]

Consistent with the analysis outlined above, achiral allenes such as **4a**[1c] give two diastereoisomeric spirodiepoxides (Table 1, entries 1−7). Such oxidations enable the direct determination of face selectivity for the first epoxidation of an allene. For electron-rich allenes where $R_L = R_S$ (Scheme 3), the first oxidation should take place at the more substituted terminus.[9] Since $R_L = R_S$ the two faces of the second π-bond are equivalent and only two diastereomeric spirodiepoxides are formed. The ratio is apparent upon inspection of the ^{1}H NMR of the mixture. Although

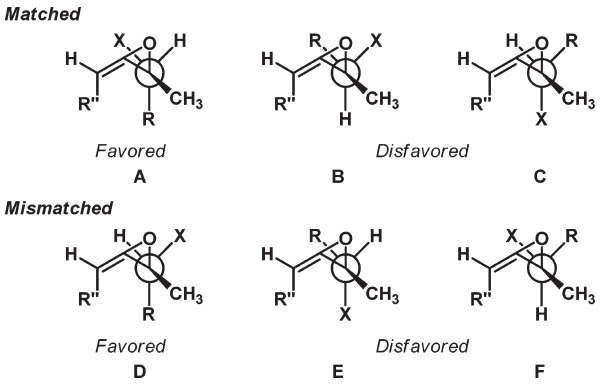


FIGURE 1. Model for diastereoselectivity.

DMDO/acetone solutions give good selectivity for the first oxidation (r_1 = 10:1) and is superior to solvents such as DME and hexanes (entries 1−3), DMDO in chlorinated solvents and *tert*-butyl alcohol gives excellent selectivity for the first oxidation ($r_1 >$ 20:1).

Oxidation of allene **4b** with DMDO in acetone gave four products in an approximate ratio of 11:10:1.1:1. This is understood as reflecting a selective first oxidation for which $r_1 \approx$ 10:1 and an unselective second oxidation for which $r_2 \approx$ 1.1:1 (entry 8, Table 1). Again acetone was found to be inferior to halogenated solvents for these oxidations. Interestingly, chloroform is slightly superior to the other halogenated solvent combinations examined (entries 8−11). MEDO and DEDO are also superior to acetone but less selective than DMDO/chloroform (entries 12 and 13). For these oxidants, the selectivity of the first epoxidation is improved significantly and that of the second oxidation is improved slightly relative to acetone. These data may reflect subtle solvent effects and are consistent with the increased steric bulk of MEDO and DEDO in comparison to DMDO. We also examined branched allene **4c**. Similar trends were observed, albeit with generally higher selectivity (entries 14−18). Although only modestly improved, the face selectivity of the second oxidation of unfunctionalized alkyl allenes is superior in halogenated solvent (entries 15−17). Branching improves the face selectivity of the second oxidation,[2,10] which is further enhanced in halogenated solvent and *tert*-butyl alcohol (e.g., compare entries 10 and 16). DMDO in chlorinated solvent, however, is the most selective and convenient dioxirane system studied to date.[11]

The face selectivity of chiral trisubstituted allenes is shown in Table 2. The first oxidation is outstanding for each substrate ($r_1 >$ 20:1). In our synthesis of epoxomicin, low-temperature oxidation of silyl ethers of type **1** gave four spirodiepoxides with two major isomers in modest ratio in

(6) The Supporting Information in ref 1b describes in detail the method used to prepare DMDO.

(7) Ferrer, M.; Gibert, M.; Sánchez-Baeza, F.; Messeguer, A. *Tetrahedron Lett*. **1996**, *37*, 3585.

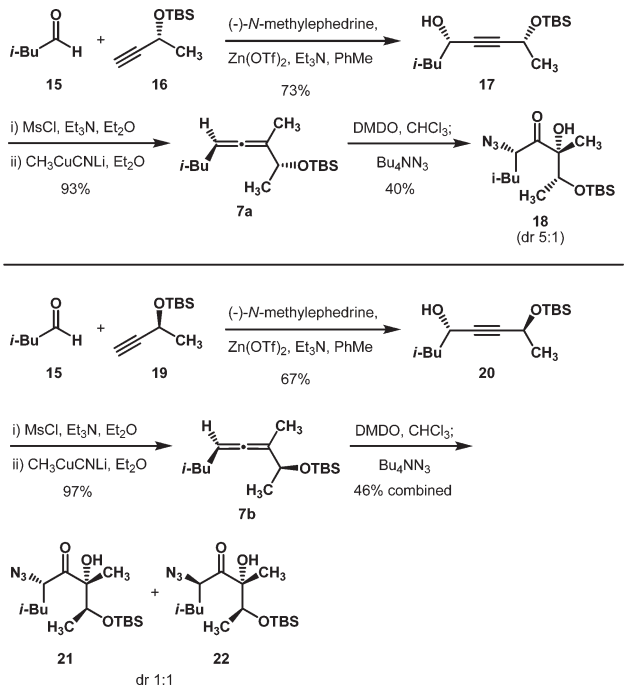
(8) For the synthesis of MEDO and DEDO, see: (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem*. **1985**, *50*, 2847. Other methods of oxidation were also evaluated, such as the use of Shi's fructose-derived catalyst, Jacobsen's (salen)manganese(III) catalyst, as well as trifluoromethyl methyl dioxirane (TFDO). Oxidation with these reagents was difficult to reproduce and led to the formation of several products. For the Shi oxidation, see: (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc*. **1997**, *119*, 11224. (c) Zhu, Y.; Tu, Y.; Shi, Y. *Tetrahedron Lett*. **1998**, *39*, 7819. For the Jacobsen epoxidation, see: (d) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1990**, *112*, 2801. (e) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc*. **1991**, *113*, 7063. For the original preparation of TFDO and its use as an oxidant, see: (f) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc*. **1989**, *111*, 6749.

(9) This was first pointed out in ref 2.

(10) Spirodiepoxide formation from di-*tert*-butylallene is high ($\sim$9:1), even in acetone.

(11) Structure assignments of the diastereomeric spirodiepoxides described in Table 1 are based on analogy to other spirodiepoxides. There is strong evidence to support these assignments. Although Crandal and coworkers (ref 2) provided rigorous proof of structure of a spirodiepoxide derivative in only one instance, all of that work was supported by compelling, albeit circumstantial, spectroscopic evidence and the logical force of the steric model itself. Our work (ref 1), especially the communication related to the present work (ref 1a), provides numerous unambiguous structural proofs of spirodiepoxide derivatives, including both major and minor isomers, by chemical correlation, total synthesis, or crystallographic analysis. Without exception, these data support the steric models presented here.

SCHEME 4



DMDO/acetone along with minor isomers.[12] DMDO/chloroform oxidation gave only two spirodiepoxides (2:1). This ratio was higher for allene bearing branched substituents (**6**, 3.3:1). However, divergent results were observed for the related stereoisomeric allenes **7a**[1c] and **7b**. One isomer showed enhanced selectivity upon epoxidation (**7a**, 5:1), whereas a 1:1 mixture was obtained from the epimer (**7b**). Replacement of the methyl group on the stereogenic carbon of **7a** with ethyl further improved selectivity (**8**, 6:1) as did replacement of the electron donating alkyl group R_1 with heterofunctionality[1c] (**13**, 8:1). Thus, selectivity of the second oxidation depends on the allene substitution pattern and relative stereochemistry of proximal substituents.[11,13]

In contrast to the data in Table 1, the stereoselective oxidations shown in Table 2 are not well rationalized by the earlier model (Scheme 2). The observed selectivities are modest but follow distinct trends. Consequently, we suggest a refined model for stereoselectivity (Figure 1). Oxygen atom transfer to the more substituted terminus of the allene would give the expected allene oxide, based on steric considerations. The presence and nature of branching combined with intrinsic conformational preferences gives rise to the possibility of cooperative (matched) or competitive (mismatched) diastereoselectivity in the second oxidation. In light of the data we favor a rationale based on (1) the allene oxide

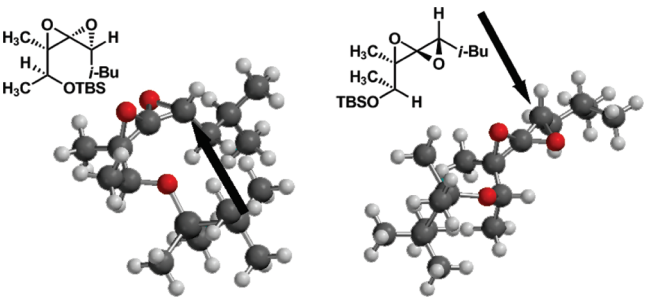


FIGURE 2. Steric influence on major vs minor spirodiepoxide reactivity.

$O-C_{sp^3}$ bond as highly polarized,[3,14] (2) arrangements that represent electronically stabilized conformations as preferred, and (3) these ground-state conformational and stereoelectronic considerations as relevant to low energy transition states.

In the absence of overriding factors, the best vicinal electron-donating substituent (R) will be oriented antiperiplanar to the highly polarized allene oxide $O-C_{sp^3}$ (A, Figure 1). Conversely, the conformation should be relatively destabilized with an electron-withdrawing substituent (X) arranged antiperiplanar to the allene oxide $O-C_{sp^3}$ bond (C). The presence of an alkyl substituent on the allene oxide C_{sp^3} terminus may provide a secondary conformational bias; however, the steric bulk of this group, relative to a hydrogen substituent, should reduce face selectivity in addition to any conformational bias it might otherwise induce (compare Table 1, entry 16 with Table 2, entry 2). The apparent matched and mismatched cases of **7a** and **7b** are consistent with this model. In both cases, the methyl substituent attached to the allene will project only the methyl hydrogen near one face of the reacting double bond. Compound **7a** would project a methyl group near the opposite face of the allene oxide double bond. In contrast, **7b** would project only the methine hydrogen near the double bond. Thus, the two faces of the double bond for **7b** would be nearly indistinguishable, whereas **7a** would be comparatively biased. The introduction of R with greater bulk could well increase selectivity, as observed (compare entries 3 and 5, Table 2). In addition to these steric and stereoelectronic factors, the intrinsic reactivity of the double bond contributes to epoxidation face selectivity. Since the reactivity of the allene oxide is high, selectivity is often low. Introduction of flanking heterofunctionality, as in **9** (entry 6), gives rise to higher selectivity (cf. entry 5).

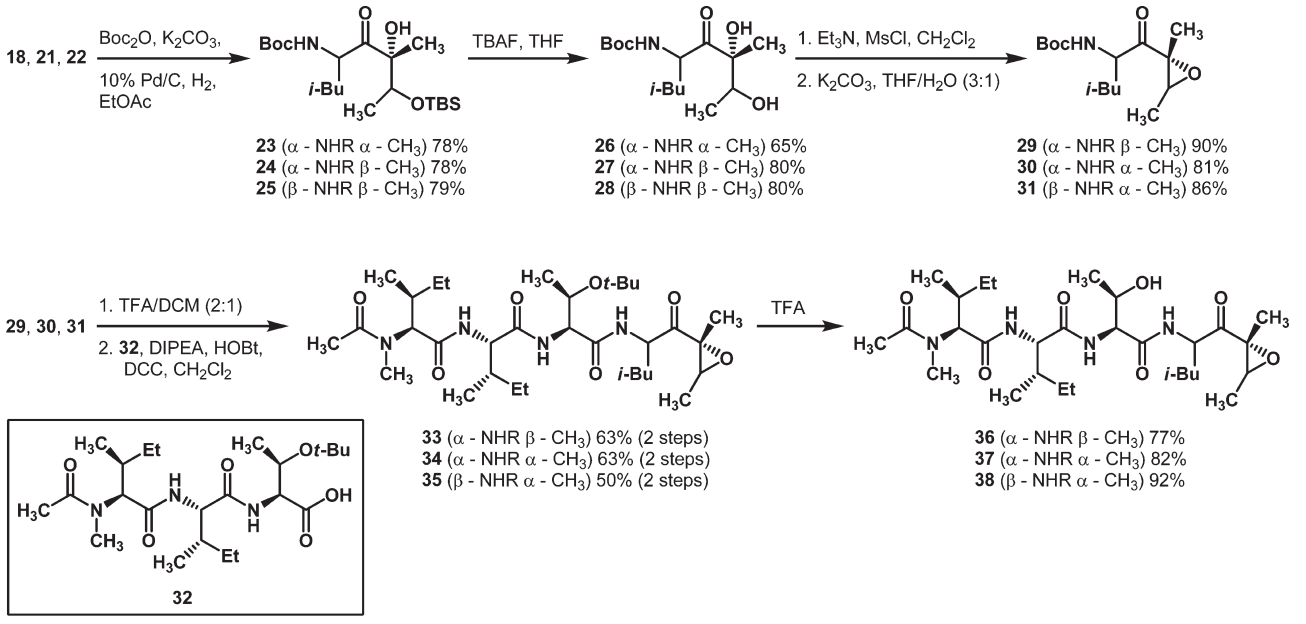
Scheme 4 summarizes the route employed to prepare elaborated epoxomicin analogues. Asymmetric zinc-mediated alkynylation of isovaleryl aldehyde with **16** or **19** gave a single diastereomeric product as assessed by Mosher ester analysis, even though this aldehyde is not α-branched. We have found that to obtain good yields in Carreira alkynylations it is essential to use high-purity aldehyde. In this case, distillation is adequate and the aldehyde so obtained can be stored for months at low temperature. Without distillation, isovaleryl aldehyde gave

(12) Structures for the major isomers listed in Table 2 were assigned as follows: A derivative of **10** was correlated to the natural product epoxomicin (ref 1). Spectral data for compound **11** matched reported data for this material (ref 2). The major isomer of compound **14** was derivatized and thence correlated to the natural product erythromycin (ref 1c). One of the two azide derivatives obtained from the mixture of spirodiepoxides **12b** (compound **22**) was crystallized and subjected to single-crystal X-ray analysis. Spirodiepoxides **12a**, the other isomer of **12b**, and **13** were based on close analogy to the major isomer of **14**.

(13) ^{1}H NMR analysis of the mixture derived from DMDO/acetone gave an approximate ratio of 2:1 for the major isomers. The major and minor isomer signals were not baseline resolved. There was no evidence of minor products formed in DMDO/chloroform.

(14) The high degree of polarization in the allene oxide C−O bond is consistent with facile formation of the oxyallyl zwitterions from this functionality. See: (a) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (b) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773.

SCHEME 5



aldol-related products under Carreira alkynylation conditions.[15]

Conversion of the propargyl alcohol to the allene gave **7a** and **7b**. Spirodiepoxidation of these allenes, as described above, was followed by azide opening to give **18** from **7a**, which was readily isolated from the minor diastereomer (dr = 5:1). In contrast, **7b** gave two separable isomers in a 1:1 ratio. Crystallographic analysis established the relative stereochemistry of **21** and **22**. Interestingly, the diastereomeric spirodiepoxides derived from **7a**, as well as the spirodiepoxides derived from **7b**, convert to the azide products at significantly different rates. This is consistent with the relative accessibility of the reactive terminus of the spirodiepoxide. As illustrated for the major and minor isomeric spirodiepoxides derived from **7a** in Figure 2, the major isomer is less accessible to an external nucleophile than the minor isomer (see arrows). In our total synthesis of epoxomicin (Scheme 1) both spirodiepoxide isomers reacted completely and both azide products decomposed slowly upon silica gel chromatography, with the minor isomer being lost at a greater rate than the major isomer.[1a] In contrast, spirodiepoxides derived from congeners **7a** and **7b** reacted slowly with azide, probably due to steric considerations, and the reaction did not reach completion. This is reflected in the isolated yields of the products. The azides products, however, were well behaved on silica gel and did not decompose upon chromatography.

Azides **18**, **21** and **22** were taken through the following sequence (Scheme 5). Reduction of the azide with concomitant Boc protection (→ **23**−**25**), removal of the silyl group (→ **26**−**28**), and then epoxide formation by mesylation of the secondary alcohol followed by cyclization gave the modified warheads (**29**−**31**). Boc group removal was followed by coupling to known tripetide **32** (→ **33**−**35**). The targets **36**−**38** were arrived at via deprotection of the *tert*-butyl ether using TFA.[16]

Conclusions

In summary, we have evaluated substrate-dependent formation of spirodiepoxides by way of dioxirane epoxidation. A framework for understanding and predicting face selectivity was outlined. To date, the most convenient dioxirane method for spirodiepoxidation is exposure to DMDO/chloroform solutions. The first oxidation proceeds with excellent face selectivity (>20:1). The second oxidation may proceed with good selectivity (up to 8:1) depending on substrate. These methods were applied to the preparation of three epoxomicin analogues. In addition to providing a simple procedure for improved allene epoxidation, the present work provides a foundation for the systematic evaluation of substrate- and reagent-directed methods for spirodiepoxide formation. Work in these areas is ongoing and will be reported in due course.

Experimental Section

General Procedure for Preparation of Spirodiepoxides from Allenes. Dimethyldioxirane (DMDO) was prepared[6] (~0.10 M) or extracted into halogenated solvent[7] ($CHCl_3$ ~0.30 M, CH_2Cl_2 ~0.38 M, CCl_4 ~0.25 M). This solution (3 equiv) was added dropwise to a solution of the allene cooled to −40 °C and dissolved in the same solvent such that the final concentration of DMDO was ~0.10 M. The reaction was stirred under nitrogen and allowed to warm to room temperature (21 °C) over 2 h. The solvent was evaporated, and the resulting epoxide was dried under vacuum and used without further purification.

Propargyl Alcohol 20. A suspension of $Zn(OTf)_2$ (600 mg, 1.65 mmol), (−)-*N*-methylephedrine (355 mg, 1.98 mmol), and Et_3N (0.20 mL, 2.01 mmol) in toluene (5 mL) was stirred at room temperature for 30 min. TBS-protected (*S*)-3-butyn-2-ol

(15) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Anand, N. K.; Carreira, E. M *J. Am. Chem. Soc.* **2001**, *123*, 9687. (c) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605. (d) Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 964. See also: (e) Kirkham, J. E. D.; Courtney, T. D. L.; Lee, V.; Baldwin, J. E. *Tetrahedron* **2005**, *61*, 7219.

(16) Growth inhibition studies of these and related compounds will be reported separately.

19 (360 mg, 1.95 mmol) was added in one portion and the reaction stirred for 2 h. Isovaleraldehyde (130 mg, 1.51 mmol) was added in one portion, and the reaction was stirred overnight at room temperature. The reaction was diluted with EtOAc (50 mL), washed with saturated aqueous NH_4Cl (4 × 5 mL), dried over anhydrous $MgSO_4$, and then evaporated to give the crude product. FCC with 5% ethyl acetate−hexane gave 271 mg of propargyl alcohol **20** (1.00 mmol, 67%) as a clear colorless oil: $[\alpha]_D$ −64 (c = 3.6, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3352, 1468, 1252; δ_H (400 MHz, $CDCl_3$) 4.54 (1H, qd, J = 6.5, 1.5 Hz), 4.46−4.38 (1H, m), 1.91−1.77 (1H, m), 1.76 (1H, d, J = 5.5 Hz), 1.66−1.49 (2H, m), 1.40 (3H, d, J = 6.5 Hz), 0.94 (3H, d, J = 6.7 Hz), 0.92 (3H, d, J = 6.7 Hz), 0.90 (9H, s), 0.13 (3H, s), 0.12 (3H, s); δ_C (100 MHz, $CDCl_3$) 87.4, 84.4, 61.0, 59.0, 46.8, 25.8, 25.4, 24.7, 22.5 (2), 18.2, −4.3, −4.9; MS (ESI) m/z calcd for $C_{15}H_{30}O_2SiNa$ $[MNa]^+$ 293.2, found 293.2.

Allene 7b. To a solution of propargyl alcohol **20** (195 mg, 0.721 mmol) in Et_2O (5 mL) was added Et_3N (0.2 mL, 1.44 mmol) dropwise. The solution was cooled to 0 °C, MsCl (0.11 mL, 1.42 mmol) was added dropwise, and the reaction stirred for 1 h from 0 °C to room temperature. After the reaction was completed, as judged by TLC, the solution was cooled to 0 °C. CuCN (269 mg, 3.00 mmol) in Et_2O (5 mL) was cooled to 0 °C, and a solution of 1.6 M MeLi in Et_2O (1.9 mL, 3.04 mmol) was then added. The cuprate was then added dropwise via syringe to the above mesylate. The resultant mixture was allowed to warm to room temperature over 1 h and was then quenched with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (3 × 10 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, and then concentrated. FCC purification of the crude product with pentane gave 187 mg of allene **7b** (0.696 mmol, 97%) as a colorless oil: $[\alpha]_D$ +32 (c = 3.3, $CHCl_3$); IR ν_{max} (neat) /cm^{-1} 1967, 1255, 1085; δ_H (500 MHz, $CDCl_3$) 5.05−5.00 (1H, m), 4.29 (1H, qd, J = 6.3, 1.2 Hz), 1.85 (2H, dd, J = 7, 7 Hz), 1.65 (3H, d, J = 2.9 Hz), 1.70−1.58 (1H, m), 1.24 (3H, d, J = 6.3 Hz), 0.91 (6H, d, J = 6.6 Hz), 0.89 (9H, s), 0.05 (3H, s), 0.04 (3H, s); δ_C (125 MHz, $CDCl_3$) 200.9, 102.6, 89.4, 70.5, 38.6, 28.4, 25.9 (3), 23.0, 22.2, 22.2, 18.2, 13.6, −4.7, −5.0; MS (ESI) m/z calcd for $C_{16}H_{32}OSiH$ $[MH]^+$ 269.2, found 269.2.

Allene 8. This allene was prepared following the procedure for **20** and **7b** above, except as noted below. For alkynylation: $Zn(OTf)_2$ (170 mg, 0.458 mmol), (−)-*N*-methylephedrine (101 mg, 0.561 mmol), Et_3N (0.08 mL, 0.571 mmol), TBS-protected (*R*)-1-pentyn-3-ol (110 mg, 0.554 mmol), and isovaleraldehyde (37 mg, 0.426 mmol). The crude propargyl alcohol was taken on without purification (79 mg, 0.277 mmol). For mesylation: Et_3N (0.05 mL, 0.360 mmol), MsCl (25 μL, 0.316 mmol). Allene formation: CuCN (95 mg, 1.061 mmol), 1.6 M MeLi in Et_2O (0.69 mL, 1.108 mmol). FCC purification using pentane gave 75 mg of allene **8** (0.266 mmol, 62%, two steps) as a colorless oil: $[\alpha]_D$ +35 (c = 3.1, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 1967, 1255, 1085; δ_H (500 MHz, $CDCl_3$) 4.93−4.86 (1H, m), 3.95 (1H, t, J = 6.6 Hz), 1.85 (2H, t, J = 7.2 Hz), 1.65−1.53 (1H, m), 1.56 (3H, d, J = 3 Hz), 1.53−1.40 (2H, dq, J = 6.6, 7.2 Hz), 0.87 (6H, d, J = 6.6 Hz), 0.85 (9H, s), 0.80 (3H, t, J = 7.5 Hz), 0.00 (6H, s); δ_C (125 MHz, $CDCl_3$) 201.9, 101.0, 89.1, 76.4, 38.7, 29.5, 26.1 (3), 22.5, 22.4, 18.5, 13.3, 10.5, −4.4, −4.8; MS (ESI) m/z calcd for $C_{17}H_{34}OSiH$ $[MH]^+$ 283.2, found 283.2.

Azide 18. DMDO in $CHCl_3$ (0.2 M, 14 mL, 2.80 mmol) was added to the known allene **7a** (290 mg, 1.08 mmol) at −40 °C. The reaction mixture was allowed to stir from −40 °C to room temperature over 2 h. Solvent was dried under vacuum, and the crude spirodiepoxide was dissolved in dry $CDCl_3$ (5 mL) and cooled to −20 °C. A solution of tetrabutylammonium azide (313 mg, 1.10 mmol) in dry $CHCl_3$ (5 mL) was added and stirred for 1 h from −20 °C to room temperature. Solvent was evaporated to about 1 mL. The crude product in $CHCl_3$ was purified by FCC using 50% DCM−hexane to give 150 mg of azide **18** (0.437 mmol, 40%) as a colorless oil: $[\alpha]_D$ −17 (c = 0.96, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3487, 2107, 1682; δ_H (400 MHz, $CDCl_3$) 4.36 (1H, dd, J = 10.7, 2.9 Hz), 3.86 (1H, q, J = 6.3 Hz), 2.83 (1H, s), 1.94−1.78 (1H, m), 1.79−1.68 (1H, m), 1.60−1.46 (1H, m), 1.33 (3H, s), 1.09 (3H, d, J = 6.3 Hz), 1.01 (3H, d, J = 1.9 Hz), 0.99 (3H, d, J = 1.8 Hz), 0.92 (9H, s), 0.12 (3H, s), 0.11 (3H, s); δ_C (100 MHz, $CDCl_3$) 212.2, 81.9, 73.8, 62.7, 38.7, 25.8 (3), 25.6, 24.6, 23.3, 21.1, 18.3, 18.1, −4.0, −4.8; MALDI-TOF-MS m/z calcd for $C_{16}H_{33}N_3O_3SiNa$ $[MNa]^+$ 366.2189, found 366.2201.

Azides 21 and 22. Azides **21** and **22** (294 mg, 0.856 mmol, dr 1:1, 44% combined yield) were obtained as a colorless oil from 522 mg of **7b** (1.94 mmol) using the same procedure as for allene **7a**. Azides **21** and **22** were separated by FCC using 50% DCM−hexane. **21**: $[\alpha]_D$ +82 (c = 0.50, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3533, 2112, 1724; δ_H (500 MHz, $CDCl_3$) 4.23 (1H, dd, J = 10.8, 3.3 Hz) 4.17 (1H, q, J = 6.3 Hz), 3.32 (1H, s), 1.90−1.80 (1H, m), 1.80−1.73 (1H, m), 1.66−1.58 (1H, m), 1.20 (3H, s), 1.12 (3H, d, J = 6.3 Hz), 1.01 (3H, d, J = 6.6 Hz), 0.99 (3H, d, J = 6.5 Hz), 0.88 (9H, s), 0.09 (3H, s), 0.04 (3H, s); δ_C (125 MHz, $CDCl_3$) 213.3, 82.0, 72.5, 61.8, 38.4, 25.7 (3), 25.5, 23.2, 21.4, 21.1, 17.8, 17.0, −4.2, −5.0; MALDI-TOF-MS m/z calcd for $C_{16}H_{33}N_3O_3SiNa$ $[MNa]^+$ 366.2189, found 366.2177. **22**: $[\alpha]_D$ −16 (c = 0.44, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3527, 2108, 1724; δ_H (500 MHz, $CDCl_3$) 4.41 (1H, dd, J = 10.9, 2.9 Hz), 4.22 (1H, q, J = 6.3 Hz), 3.36 (1H, s), 1.92−1.80, (1H, m), 1.64−1.56 (1H, m), 1.46−1.38 (1H, m), 1.23 (3H, s), 1.13 (3H, d, J = 6.3 Hz), 0.99 (3H, d, J = 6.7 Hz), 0.97(3H, d, J = 6.6 Hz), 0.88 (9H, s), 0.11 (3H, d), 0.03 (3H, d); δ_C (125 MHz, $CDCl_3$) 212.3, 81.8, 71.6, 60.0, 38.8, 25.8 (3), 25.3, 23.2, 21.4, 21.2, 17.8, 17.2, −4.4, −4.7; MALDI-TOF-MS m/z calcd for $C_{16}H_{33}N_3O_3SiNa$ $[MNa]^+$ 366.2189, found 366.2194. Slow evaporation of a sample of **22** dissolved in hexanes and a minimum amount of EtOAc gave crystals suitable for single-crystal X-ray analysis.

***tert*-Butyl Carbamate 23.** To a solution of azide **18** (293 mg, 0.853 mmol) in EtOAc were added K_2CO_3 (354 mg, 2.561 mmol), $(Boc)_2O$ (1.16 mg, 5.32 mmol), and 10% Pd/C (54 mg). The resultant suspension was then hydrogenated under 1 atm of pressure overnight. The reaction mixture was filtered through a pad of silica gel, and the solvent was evaporated. FCC purification using 4% EtOAc−hexane gave 278 mg of *tert*-butyl carbamate **23** (0.666 mmol, 78%) as a clear oil: $[\alpha]_D$ +34 (c = 0.70, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3543, 3438, 3390, 1712; δ_H (500 MHz, $CDCl_3$) 4.98 (2H, bs), 3.85 (1H, q, J = 6.2 Hz), 2.85 (1H, s), 1.83−1.68 (2H, m), 1.41 (9H, s), 1.33(3H, s), 1.20−1.10 (1H, m), 1.07 (3H, d, J = 6.2 Hz), 1.02 (3H, d, J = 6.2 Hz), 0.92 (3H, d, J = 6.5 Hz), 0.90 (9H, s), 0.089 (3H, s), 0.085 (3H, s); δ_C (100 MHz, $CDCl_3$) 214.9, 155.3, 81.9, 79.3, 73.5, 55.6, 41.2, 28.3 (3), 25.8 (3), 25.2, 23.6, 23.3, 21.2, 18.3, 18.0, −4.2, −4.8; MALDI-TOF-MS m/z calcd for $C_{21}H_{43}NO_5SiNa$ $[MNa]^+$ 440.2808, found 440.2821.

***tert*-Butyl Carbamate 24.** *tert*-Butyl carbamate **24** (42 mg, 0.101 mmol, 84%) was obtained as a white crystalline solid from 41 mg of **21** (0.119 mmol) using the same procedure as for azide **18**: $[\alpha]_D$ +43 (c = 0.60, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3539, 3434, 3382, 1708; δ_H (500 MHz, $CDCl_3$) 5.17 (1H, d, J = 9.1 Hz), 4.94−4.88 (1H, m), 4.19 (1H, q, J = 6.3 Hz), 3.34 (1H, s), 1.80−1.70 (2H, m), 1.41 (9H, s), 1.23−1.16 (1H, m), 1.19(3H, s), 1.11 (1H, d, J = 6.3 Hz), 1.04 (3H, d, J = 5.9 Hz), 0.91 (3H, d, J = 6.3 Hz), 0.84 (9H, s), 0.06 (3H, s), −0.04 (3H, s); δ_C (125 MHz, $CDCl_3$) 216.1, 155.0, 82.0, 79.1, 72.7, 55.2, 42.4, 28.3 (3), 25.8 (3), 25.0, 23.8, 21.6, 21.4, 17.8, 16.7, −4.5, −4.9; MALDI-TOF-MS m/z calcd for $C_{21}H_{43}NO_5SiNa$ $[MNa]^+$ 440.2808, found 440.2817.

***tert*-Butyl Carbamate 25.** *tert*-Butyl carbamate **25** (47 mg, 0.113 mmol, 79%) was obtained as a white crystalline solid from 49 mg of **22** (0.143 mmol) using the same procedure as for azide

18: $[\alpha]_D$ +7 (c = 0.44, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3441, 3396, 1713; δ_H (500 MHz, $CDCl_3$) 5.05−4.94 (1H, m), 4.88 (1H, d, J = 9.2 Hz) 4.33 (1H, q, J = 6.3 Hz), 3.13 (1H, s), 1.42 (9H, s), 1.18 (3H, s), 1.16−1.04 (2H, m), 1.13 (3H, d, J = 6.3 Hz), 1.00 (3H, d, J = 6.5 Hz), 0.91 (3H, d, J = 6.7 Hz), 0.86 (9H, s), 0.09 (3H, s), −0.02 (3H, s); δ_C (125 MHz, $CDCl_3$) 214.8, 155.3, 82.2, 79.4, 70.5, 52.8, 41.0, 28.3 (3), 25.8 (3), 25.1, 23.6, 21.3, 21.1, 17.8, 16.9, −4.5, −4.55; MALDI-TOF-MS m/z calcd for $C_{21}H_{43}NO_5$-SiNa $[MNa]^+$ 440.2808, found 440.2825.

Diol 26. To a solution of *tert*-butyl carbamate **23** (82 mg, 0.20 mmol) in THF (2 mL) was added TBAF (0.4 mL, 1 M solution in THF) at 0 °C and the mixture stirred for 1 h from 0 °C to room temperature. The reaction mixture was quenched by NH_4Cl (4 mL) and extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated to give the crude product. FCC purification using 20% EtOAc−hexane gave 39 mg of diol **26** (0.13 mmol, 65%) as a white crystal: $[\alpha]_D$ +8 (c = 0.16, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3323, 1714, 1674; δ_H (500 MHz, $CDCl_3$) 4.99 (1H, d, J = 7.6 Hz), 4.75−4.69 (1H, m), 4.47(1H, d, J = 11.3 Hz), 4.16 (1H, s), 3.58 (1H, dq, J = 11.3, 6.6 Hz), 1.81−1.71 (1H, m), 1.73−1.65 (1H, m), 1.41 (9H, s), 1.28 (3H, s), 1.22−1.15 (1H, m), 1.13 (3H, d, J = 6.7 Hz), 0.98 (3H, d, J = 6.4 Hz), 0.93 (3H, d, J = 6.5 Hz); δ_C (125 MHz, $CDCl_3$) 215.7, 157.2, 82.7, 80.8, 74.6, 55.7, 39.3, 28.2 (3), 25.2, 23.4, 21.9, 21.0, 16.1; MALDI-TOF-MS m/z calcd for $C_{15}H_{29}NO_5Na$ $[MNa]^+$ 326.1943, found 326.1957.

Diol 27. Diol **27** (31 mg, 0.102 mmol, 80%) was obtained as a white crystalline solid from 53 mg of **24** (0.127 mmol) using the same procedure as for *tert*-butyl carbamate **23**: $[\alpha]_D$ +1.9 (c = 0.13, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3363, 1716, 1683; δ_H (500 MHz, $CDCl_3$) 4.84 (1H, d, J = 7.1 Hz), 4.76−4.70 (1H, m), 4.41(1H, d, J = 3.9 Hz), 3.98 (1H, qd, J = 6.4, 3.9 Hz), 3.71 (1H, s), 1.82−1.71 (1H, m), 1.74−1.67 (1H, m), 1.41 (9H, s), 1.26−1.18 (1H, m), 1.22 (3H, s), 1.17 (3H, d, J = 6.4 Hz), 1.00 (3H, d, J = 6.3 Hz), 0.96 (3H, d, J = 6.5 Hz); δ_C (125 MHz, $CDCl_3$) 217.9, 157.0, 82.2, 80.8, 71.7, 55.3, 38.9, 28.2 (3), 25.2, 23.4, 21.5, 20.9, 15.5; MALDI-TOF-MS m/z calcd for $C_{15}H_{29}NO_5Na$ $[MNa]^+$ 326.1943, found 326.1965.

Diol 28. Diol **28** (50 mg, 0.165 mmol, 80%) was obtained as a white crystalline solid from 86 mg of **25** (0.206 mmol) using the same procedure as for *tert*-butyl carbamate **23**: $[\alpha]_D$ +1 (c = 0.10, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3370, 1708, 1692; δ_H (500 MHz, $CDCl_3$) 5.02 (1H, d, J = 8.4 Hz), 4.83−4.76 (1H, m), 4.09−4.02 (1H, qd, J = 6.9, 6.9 Hz), 3.89 (1H, s), 3.47 (1H, d, J = 7.6 Hz), 1.81−1.71 (1H, m), 1.48−1.30 (2H, m), 1.41 (9H, s), 1.37 (3H, s), 1.18 (3H, d, J = 6.5 Hz), 0.96 (3H, d, J = 6.5 Hz), 0.93 (3H, d, J = 6.7 Hz); δ_C (125 MHz, $CDCl_3$) 214.8, 156.4, 82.0, 80.8, 71.7, 52.4, 40.4, 28.2 (3), 24.9, 23.4, 21.5, 21.1, 16.3; MALDI-TOF-MS m/z calcd for $C_{15}H_{29}NO_5Na$ $[MNa]^+$ 326.1943, found 326.1959.

Epoxide 29. To a solution of diol **26** (26 mg, 0.086 mmol) in DCM (1 mL) was added Et_3N (24 μL, 0.17 mmol) and the mixture cooled to 0 °C. Methanesulfonyl chloride (13 μL, 0.17 mmol) was added dropwise and the mixture stirred under argon from 0 °C to room temperature for 1 h. The reaction mixture was extracted with DCM (2 × 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated to give the crude mesylate. The crude mesylate and K_2CO_3 (100 mg, 0.724 mmol) in THF−water (3:1, 4 mL) was stirred at room temperature for 4 h. The reaction mixture was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated. FCC purification using 10% EtOAc−hexane gave 22 mg of epoxide **29** (0.077 mmol, 90%, two steps) as a colorless oil: $[\alpha]_D$ +5.8 (c = 0.56, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3379, 1709; δ_H (500 MHz, $CDCl_3$) 4.83 (1H, d, J = 8.8 Hz), 3.42 (1H, q, J = 5.3 Hz), 1.88−1.67 (1H, m), 1.52−1.45 (1H, m), 1.45 (3H, s), 1.41 (9H, s), 1.37 (3H, d, J = 5.4 Hz), 1.16−1.09 (1H, m), 0.97 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.7 Hz); δ_C (125 MHz, $CDCl_3$) 210.5, 155.6, 79.6, 62.8, 56.9, 51.7, 40.3, 28.3 (3), 25.1, 23.4, 21.3, 13.6, 12.8; MALDI-TOF-MS m/z calcd for $C_{15}H_{27}NO_4Na$ $[MNa]^+$ 308.1838, found 308.1847.

Epoxide 30. Epoxide **30** (22 mg, 0.077 mmol, 81%, two steps) was obtained as a crystalline solid from 29 mg of **27** (0.096 mmol) using the same procedure as for diol **26**: $[\alpha]_D$ +25 (c = 0.12, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3376, 1707; δ_H (500 MHz, $CDCl_3$) 4.88 (1H, d, J = 8.9 Hz), 4.88−4.71 (1H, m), 3.09 (1H, q, J = 5.7 Hz), 1.85−1.72 (1H, m), 1.70−1.60 (1H, m), 1.51 (3H, s), 1.43 (9H, s), 1.35 (3H, d, J = 5.5 Hz), 1.18−1.11 (1H, m), 1.04 (3H, d, J = 6.5 Hz), 0.96 (3H, d, J = 6.7 Hz); δ_C (125 MHz, $CDCl_3$) 209.3, 155.5, 79.6, 64.0, 56.1, 51.7, 39.7, 28.2(3), 25.1, 23.4, 21.2, 19.8, 13.9; MALDI-TOF-MS m/z calcd for $C_{15}H_{27}NO_4Na$ $[MNa]^+$ 308.1838, found 308.1843.

Epoxide 31. Epoxide **31** (29 mg, 0.102 mmol, 86% 2 steps) was obtained as a white crystalline solid from 36 mg of **28** (0.119 mmol) using the same procedure as for diol **26**: $[\alpha]_D$ +11 (c = 0.11, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3358, 1707; δ_H (500 MHz, $CDCl_3$) 4.85 (1H, d, J = 8.6 Hz), 4.63−4.56 (1H, m), 3.06 (1H, q, J = 5.5 Hz), 1.78−1.67 (1H, m), 1.60 (3H, s), 1.57−1.52 (1H, m), 1.42 (9H, s), 1.41−1.34 (1H, m), 1.19 (3H, d, J = 5.5 Hz), 0.97 (3H, d, J = 6.5 Hz), 0.94 (3H, d, J = 6.7 Hz); δ_C (125 MHz, $CDCl_3$) 207.1, 155.3, 79.9, 64.9, 61.2, 54.7, 39.7, 28.3 (3), 24.7, 23.3, 21.5, 19.2, 14.2; MALDI-TOF-MS m/z calcd for $C_{15}H_{27}NO_4Na$ $[MNa]^+$ 308.1838, found 308.1832.

Tetrapeptide 33. To epoxide **29** (18 mg, 0.063 mmol) at 0 °C was added DCM/TFA (2:1, 0.3 mL) and the mixture stirred under argon for 25 min. Solvent was evaporated at 0 °C under vacuum, and the residue was azeotroped with benzene and dried to give the amine salt. To the amine salt and tripeptide acid **32** (32 mg, 0.070 mmol) in DCM (2 mL) was added diisopropylethylamine (37 μL, 0.21 mmol) at 0 °C and the mixture stirred. After 2 min, 1-hydroxybenzotriazole (HOBt) (19 mg, 0.141 mmol) was added at room temperature. Dicyclohexylcabrodiimide (DCC) (15 mg, 0.073 mmol) was added and the mixture stirred at room temperature under argon for 5 h. The reaction was diluted with EtOAc (50 mL), and the precipitated urea byproduct was filtered off. The filtrate was washed with saturated aqueous $NaHCO_3$, water, and brine, dried over anhydrous Na_2SO_4, and then evaporated. FCC purification using 60% EtOAc−hexane gave 25 mg of tetrapeptide **33** (0.040 mmol, 63%, two steps) as a white solid: $[\alpha]_D$ −3 (c = 0.30, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3295, 1721, 1633, 1538; δ_H (500 MHz, $CDCl_3$) 7.60 (1H, d, J = 7.5 Hz), 6.96 (1H, d, J = 5.6 Hz) 6.68 (1H, d, J = 6.7 Hz), 4.62 (1H, d, J = 11.4 Hz), 4.55−4.50 (1H, m), 4.28 (1H, dd, J = 5.5, 3.9 Hz), 4.24 (1H, dd, J = 8.1, 6.0 Hz), 4.21 (1H, dd, J = 6.5, 3.9 Hz), 3.52 (1H, q, J = 5.4 Hz), 2.93 (3H, s), 2.18−2.10 (1H, m), 2.10 (3H, s), 2.03−1.95 (1H, m), 1.72−1.64 (1H, m), 1.57−1.49 (1H, m), 1.45 (3H, s), 1.38 (3H, d, J = 5.4 Hz), 1.38−1.32 (2H, m), 1.28 (9H, s), 1.30−1.20 (1H, m), 1.16−0.90 (2H, m), 1.07 (3H, d, J = 6.4 Hz), 0.97−0.92 (9H, m), 0.91−0.84 (9H, m); δ_C (125 MHz, $CDCl_3$) 209.1, 172.2, 170.7, 170.4, 169.6, 75.4, 65.9, 63.2, 61.6, 58.0, 57.1, 57.0, 50.9, 39.6, 36.2, 32.0, 31.3, 28.1(3), 25.4, 24.6, 24.3, 23.4, 21.9, 21.3, 16.6, 15.7, 15.6, 13.6, 12.8, 11.3, 10.4; MALDI-TOF-MS m/z calcd for $C_{33}H_{60}N_4O_7Na$ $[MNa]^+$ 647.4360, found 647.4379.

Tetrapeptide 34. Tetrapeptide **34** (27 mg, 0.043 mmol, 62% 2 steps) was obtained as a white crystalline solid from 20 mg of **30** (0.070 mmol) using the same procedure as for epoxide **29**: $[\alpha]_D$ −10 (c = 0.60, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3296, 1722, 1633, 1538; δ_H (500 MHz, $CDCl_3$) 7.58 (1H, d, J = 8.3 Hz), 7.04 (1H, d, J = 5.5 Hz) 6.68 (1H, br. s), 4.97−4.87 (1H, m), 4.58 (1H, d, J = 11.2 Hz), 4.32 (1H, dd, J = 5.5, 5.4 Hz), 4.26 (1H, dd, J = 8.2 Hz, 5.9 Hz), 4.22 (1H, dd, J = 6.5, 3.9 Hz), 3.09 (1H, q, J = 5.7 Hz), 2.95 (3H, s), 2.18−2.10 (1H, m), 2.11 (3H, s), 2.08−1.99 (1H, m), 1.72−1.64 (2H, m), 1.51 (3H, s), 1.41 (3H, d, J = 5.7 Hz),

1.38−1.32 (2H, m), 1.30 (9H, s), 1.30−1.20 (1H, m), 1.16−0.90 (2H, m), 1.08 (3H, d, J = 6.4 Hz), 0.97−0.84 (18H, m); δ_C (125 MHz, $CDCl_3$) 207.8, 172.2, 170.7, 170.4, 169.3, 75.3, 65.7, 64.1, 62.0, 61.2, 58.0, 57.3, 55.2, 39.1, 36.1, 32.2, 31.3, 28.1 (3), 25.3, 24.6, 24.2, 23.4, 22.0, 21.1, 19.9, 16.6, 15.7, 15.5, 13.8, 11.3, 10.3; MALDI-TOF-MS m/z calcd for $C_{33}H_{60}N_4O_7Na$ $[MNa]^+$ 647.4360, found 647.4353.

Tetrapeptide 35. Tetrapeptide **35** (24 mg, 0.038 mmol, 50% 2 steps) was obtained as a white crystalline solid from 22 mg of **31** (0.077 mmol) using the same procedure as for epoxide **29**: $[\alpha]_D$ −8 (c = 0.29, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3303, 1724, 1632, 1537; δ_H (500 MHz, $CDCl_3$) 7.29 (1H, d, J = 7.4 Hz), 7.01 (1H, d, J = 5.7 Hz) 6.74 (1H, br. s), 4.88−4.82 (1H, m), 4.62 (1H, d, J = 11.4 Hz), 4.29−4.21 (3H, m), 3.05 (1H, q, J = 5.5 Hz), 2.94 (3H, s), 2.18−2.10 (1H, m), 2.12 (3H, s), 2.05−1.95 (1H, m), 1.84−1.67 (1H, m), 1.62−1.56 (1H, m), 1.57 (3H, s), 1.50−1.30 (2H, m), 1.30−1.20 (1H, m), 1.24 (9H, s), 1.20−0.90 (2H, m), 1.20 (3H, d, J = 5.5 Hz), 0.99 (3H, d, J = 6.3 Hz), 0.97−0.93 (9H, m), 0.91−0.84 (9H, m); δ_C (125 MHz, $CDCl_3$) 205.9, 172.3, 170.72, 170.71, 168.8, 75.4, 65.6, 65.2, 61.7, 61.1, 58.3, 57.5, 53.9, 39.4, 36.2, 32.0, 31.3, 28.2 (3), 24.63, 24.58, 24.4, 23.4, 22.0, 21.0, 19.4, 17.6, 15.8, 15.7, 14.5, 11.3, 10.3; MALDI-TOF-MS m/z calcd for $C_{33}H_{60}N_4O_7Na$ $[MNa]^+$ 647.4360, found 647.4348.

Epoxomicinoid 36. To tetrapeptide **33** (20 mg, 0.032 mmol) was added TFA (0.3 mL). The solution was allowed to stir at 0 °C for 10 min and then was stirred for another 10 min without the ice bath. Solvent was evaporated at room temperature and azeotroped with benzene. FCC purification using EtOAc gave 14 mg of **36** (0.025 mmol, 77%) as a white solid: $[\alpha]_D$ −36 (c = 0.60, $CHCl_3$); IR ν_{max}(neat)/cm^{-1} 3295, 1716, 1643, 1538; δ_H (500 MHz, $CDCl_3$) 7.18 (1H, d, J = 7.7 Hz), 7.14 (1H, d, J = 8.0 Hz), 6.92 (1H, d, J = 7.0 Hz), 4.68−4.56 (2H, m), 4.43 (1H, dd, J = 7.7, 2.7 Hz), 4.30−4.20 (2H, m), 3.52 (1H, d, J = 3.4 Hz), 3.46 (1H, q, J = 5.4 Hz), 2.97 (3H, s), 2.16−2.07 (1H, m), 2.11 (3H, s), 2.05−1.95 (1H, m), 1.70−1.60 (1H, m), 1.56−1.48 (1H, m), 1.45 (3H, s), 1.38 (3H, d, J = 5.4 Hz), 1.40−1.20 (2H, m), 1.15−1.05 (1H, m), 1.11 (3H, d, J = 6.5 Hz), 1.02−0.88 (2H, m), 0.94−0.84 (18H, m); δ_C (125 MHz, $CDCl_3$) 209.2, 172.2, 171.7, 170.7, 170.6, 66.5, 63.1, 61.7, 58.0, 57.1, 56.5, 51.0, 39.3, 36.1, 32.2, 31.8, 29.7, 25.1, 24.7, 24.6, 23.4, 22.0, 21.1, 17.8, 15.5, 13.6, 12.8, 11.1, 10.5; MALDI-TOF-MS m/z calcd for $C_{29}H_{52}N_4O_7Na$ $[MNa]^+$ 591.3734, found 591.3721.

Epoxomicinoid 37. Compound **37** (15 mg, 0.026 mmol, 82%) was obtained as white crystalline solid from 20 mg of **34** (0.032 mmol) using the same procedure as for tetrapeptide **33**: $[\alpha]_D$ −16 (c = 0.35, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3293, 1716, 1633, 1538; δ_H (500 MHz, $CDCl_3$) 7.14 (1H, d, J = 8.0 Hz), 7.10 (1H, d, J = 8.8 Hz), 6.92 (1H, d, J = 7.6 Hz), 5.00−4.93 (1H, m), 4.62 (1H, d, J = 11.4, 2.7 Hz), 4.33−4.24 (2H, m), 4.27 (1H, dd, J = 8.1, 6.6 Hz), 3.61 (1H, br. s), 3.09 (1H, q, J = 5.7 Hz), 2.98 (3H, s), 2.17−2.06 (1H, m), 2.11 (3H, s), 2.05−1.95 (1H, m), 1.75−1.60 (2H, m), 1.50 (3H, s), 1.44−1.20 (2H, m), 1.37 (3H, d, J = 5.7 Hz), 1.15−1.06 (1H, m), 1.13 (3H, d, J = 6.5 Hz), 1.04−0.88 (2H, m), 0.98 (3H, d, J = 6.2 Hz), 0.94 (3H, d, J = 6.3 Hz), 0.90−0.84 (12H, m), δ_C (125 MHz, $CDCl_3$) 208.2, 172.2, 171.6, 170.7, 170.6, 66.5, 64.1, 62.0, 61.3, 58.0, 56.7, 55.3, 38.6, 36.1, 32.3, 31.8, 25.2, 24.7, 24.5, 23.4, 22.1, 20.9, 19.9, 17.8, 15.6, 15.5, 13.9, 11.2, 10.5; MALDI-TOF-MS m/z calcd for $C_{29}H_{52}N_4O_7Na$ $[MNa]^+$ 591.3734, found 591.3737.

Epoxomicinoid 38. Compound **38** (7 mg, 0.012 mmol, 92%) was obtained as a white crystalline solid from 8.2 mg of **35** (0.013 mmol) using the same procedure as in tetrapeptide **33**: $[\alpha]_D$ −10 (c = 0.11, $CHCl_3$); IR ν_{max} (neat)/cm^{-1} 3294, 1719, 1638, 1532; δ_H (500 MHz, $CDCl_3$) 7.23 (1H, d, J = 7.1 Hz), 7.05 (1H, d, J = 5.1 Hz), 6.88 (1H, d, J = 7.8 Hz), 4.82−4.74 (1H, m), 4.49 (1H, d, J = 11.5 Hz), 4.40 (1H, qd, J = 6.5, 1.6 Hz), 4.25 (1H, dd, J = 7.8, 1.6 Hz), 4.11 (1H, dd, J = 5.6, 4.8 Hz), 3.14 (1H, br. s), 3.06 (1H, q, J = 5.5 Hz), 2.96 (3H, s), 2.21−2.06 (2H, m), 2.15 (3H, s), 1.87−1.77 (1H, m), 1.70−1.62 (1H, m), 1.59 (3H, s), 1.60−1.32 (2H, m), 1.30−1.06 (1H, m), 1.21 (3H, d, J = 5.5 Hz), 1.17 (3H, d, J = 6.5 Hz), 1.08−0.92 (2H, m), 1.00−0.85 (18H, m), δ_C (125 MHz, $CDCl_3$) 207.4, 172.7, 172.1, 171.1, 171.07, 67.1, 65.0, 63.1, 61.4, 59.9, 58.0, 55.6, 38.6, 35.7, 33.1, 31.3, 25.0, 24.7, 24.4, 23.4, 22.1, 21.0, 19.6, 18.9, 16.0, 15.8, 14.3, 11.6, 10.3; MALDI-TOF-MS m/z calcd for $C_{29}H_{52}N_4O_7Na$ $[MNa]^+$ 591.3734, found 591.3753.

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