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Spirodiepoxides: Synthesis of Epoxomicinoids

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Abstract

Three closely related analogs of epoxomicin have been synthesized. Allene-derived spirodiepoxides were key intermediates. Spirodiepoxide formation and stereochemical dependence on solvent, oxidant, and allene structure was 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**). 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 analogs 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 non-reacting 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

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

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Supporting Information Available: Characterization data (PDF). This material is free of charge via the Internet at <http://pubs.acs.org>.

can give as many as four diastereomeric spirodiepoxides, even in instances where the first oxidation is regioselective ($\text{IV} \rightarrow \text{V} + \text{VI} \rightarrow \text{VII-X}$), 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.

In order for a single spirodiepoxide to be formed both the first and second oxidations must be fully face selective (e.g., $\text{IV} \rightarrow \text{V} \rightarrow \text{VII}$). 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 in acetone (~ 0.10)⁶ and extracted into halogenated solvent. The resultant comparatively concentrated solutions (~ 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 (DED0) 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 ¹H-NMR of the mixture. Although 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*-butanol 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 DED0 are also superior to acetone, but less selective than DMDO/chloroform (entries 12-13). 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 DED0 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*-butanol (*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 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 R₁ 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 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 (*c.f.* entry 5).

Scheme 4 summarizes the route employed to prepare elaborated epoxomicin analogs. 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 alkynylation 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 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 ($\rightarrow$ **23-25**), removal of the silyl group ($\rightarrow$ **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 tripeptide **32** ($\rightarrow$ **33-35**). The targets **36**, **37** and **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 analogs. 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 prepared⁶ (~0.10 M) or extracted into halogenated solvent⁷ (CHCl₃ ~0.30 M, CH₂Cl₂ ~0.38 M, CCl₄ ~0.25 M). This solution (3 equiv.) was added drop-wise to a solution of the allene cooled to -40 ± 4 °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 $\text{Zn}(\text{OTf})_2$ (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 **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 $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{15}\text{H}_{30}\text{O}_2\text{SiNa}$ $[\text{MNa}]^+$ 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 $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{16}\text{H}_{32}\text{OSiH}$ $[\text{MH}]^+$ 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: $\text{Zn}(\text{OTf})_2$ (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), 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% 2 steps) as a colorless oil. $[\alpha]_D +35$ ($c = 3.1$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{17}\text{H}_{34}\text{OSiH}$ $[\text{MH}]^+$ 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. $[\alpha]_{\text{D}} -17$ ($c = 0.96$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{16}\text{H}_{33}\text{N}_3\text{O}_3\text{SiNa}$ $[\text{MNa}]^+$ 366.2189; found 366.2201.

Azides 21 and 22

294 mg of azides **21** and **22** (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 in allene **7a**. Azides **21** and **22** were separated by FCC using 50% DCM-hexane. **21**: $[\alpha]_{\text{D}} +82$ ($c = 0.50$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{16}\text{H}_{33}\text{N}_3\text{O}_3\text{SiNa}$ $[\text{MNa}]^+$ 366.2189; found 366.2177. **22**: $[\alpha]_{\text{D}} -16$ ($c = 0.44$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{16}\text{H}_{33}\text{N}_3\text{O}_3\text{SiNa}$ $[\text{MNa}]^+$ 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 was added K_2CO_3 (354 mg, 2.561 mmol), $(\text{Boc})_2\text{O}$ (1.16 mg, 5.32 mmol) and 10% Pd/C (54 mg). The resultant suspension was then hydrogenated under 1 atm 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. $[\alpha]_{\text{D}} +34$ ($c = 0.70$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{21}\text{H}_{43}\text{NO}_5\text{SiNa}$ $[\text{MNa}]^+$ 440.2808; found 440.2821.

tert-butyl-Carbamate 24

42 mg of *tert*-butyl carbamate **24** (0.101 mmol, 84%) was obtained as a white crystalline solid from 41 mg of **21** (0.119 mmol) using the same procedure as in azide **18**. $[\alpha]_D^{+43}$ ($c = 0.60$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{21}\text{H}_{43}\text{NO}_5\text{SiNa}$ $[\text{MNa}]^+$ 440.2808; found 440.2817.

tert-butyl-Carbamate 25

47 mg of *tert*-butyl carbamate **25** (0.113 mmol, 79%) was obtained as a white crystalline solid from 49 mg of **22** (0.143 mmol) using the same procedure as in azide **18**. $[\alpha]_D^{+7}$ ($c = 0.44$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{21}\text{H}_{43}\text{NO}_5\text{SiNa}$ $[\text{MNa}]^+$ 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 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 $\times$ 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 $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{15}\text{H}_{29}\text{NO}_5\text{Na}$ $[\text{MNa}]^+$ 326.1943; found 326.1957.

Diol 27

31 mg of diol **27** (0.102 mmol, 80%) was obtained as a white crystalline solid from 53 mg of **24** (0.127 mmol) using the same procedure as in *tert*-butyl carbamate **23**. $[\alpha]_D^{+1.9}$ ($c = 0.13$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{15}\text{H}_{29}\text{NO}_5\text{Na}$ $[\text{MNa}]^+$ 326.1943; found 326.1965.

Diol 28

50 mg of diol **28** (0.165 mmol, 80%) was obtained as a white crystalline solid from 86 mg of **25** (0.206 mmol) using the same procedure as in *tert*-butyl carbamate **23**. $[\alpha]_D^{+1}$ ($c = 0.10$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated 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 μ L, 0.17 mmol) and cooled to 0 °C. Methanesulfonyl chloride (13 μ L, 0.17 mmol) was added dropwise and stirred under argon from 0 °C to room temperature for 1 h. The reaction mixture was extracted with DCM (2 $\times$ 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 $\times$ 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% 2 steps) as a colorless oil. $[\alpha]_D + 5.8$ ($c = 0.56$, $CHCl_3$); IR $\nu_{max}(neat)/cm^{-1}$ 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 calculated for $C_{15}H_{27}NO_4Na$ $[MNa]^+$ 308.1838; found 308.1847.

Epoxide 30

22 mg of epoxide **30** (0.077 mmol, 81% 2 steps) was obtained as a crystalline solid from 29 mg of **27** (0.096 mmol) using the same procedure as in diol **26**. $[\alpha]_D + 25$ ($c = 0.12$, $CHCl_3$); IR $\nu_{max}(neat)/cm^{-1}$ 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 calculated for $C_{15}H_{27}NO_4Na$ $[MNa]^+$ 308.1838; found 308.1843.

Epoxide 31

29 mg of epoxide **31** (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 in diol **26**. $[\alpha]_D + 11$ ($c = 0.11$, $CHCl_3$); IR $\nu_{max}(neat)/cm^{-1}$ 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 calculated 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 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 μ L, 0.21 mmol) at 0 °C and stirred. After 2 min, 1-hydroxybenzotriazole (HOBt) (19 mg, 0.141 mmol) was added at room temperature. Dicyclohexylcarbodiimide (DCC) (15 mg, 0.073 mmol) was added and stirred at room temperature under argon for 5 h. The reaction was diluted with EtOAc (50 mL) and the precipitated urea by-product was filtered off. Filtrate was washed with saturated aqueous $NaHCO_3$, water, 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% 2 steps) as a white solid. $[\alpha]_D -3$ ($c = 0.30$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{33}\text{H}_{60}\text{N}_4\text{O}_7\text{Na}$ $[\text{MNa}]^+$ 647.4360; found 647.4379.

Tetrapeptide 34

27 mg of tetrapeptide **34** (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 in epoxide **29**. $[\alpha]_D -10$ ($c = 0.60$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{33}\text{H}_{60}\text{N}_4\text{O}_7\text{Na}$ $[\text{MNa}]^+$ 647.4360; found 647.4353.

Tetrapeptide 35

24 mg of tetrapeptide **35** (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 in epoxide **29**. $[\alpha]_D -8$ ($c = 0.29$, CHCl_3); IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $\text{C}_{33}\text{H}_{60}\text{N}_4\text{O}_7\text{Na}$ $[\text{MNa}]^+$ 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 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 $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 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 calculated for $C_{29}H_{52}N_4O_7Na$ $[MNa]^+$ 591.3734; found 591.3721.

Epoxomicinoid 37

15 mg of **37** (0.026 mmol, 82%) was obtained as white crystalline solid from 20 mg of **34** (0.032 mmol) using the same procedure as in tetrapeptide **33**. $[\alpha]_D -16$ ($c = 0.35$, $CHCl_3$); IR $\nu_{max}(neat)/cm^{-1}$ 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 calculated for $C_{29}H_{52}N_4O_7Na$ $[MNa]^+$ 591.3734; found 591.3737.

Epoxomicinoid 38

7 mg of **38** (0.012 mmol, 92%) was obtained as 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 $\nu_{max}(neat)/cm^{-1}$ 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 calculated for $C_{29}H_{52}N_4O_7Na$ $[MNa]^+$ 591.3734; found 591.3753.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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4. Note that the central spirodiepoxide carbon will be stereogenic in all but the most symmetric of structures.
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 C₂ symmetric allenes constitute another interesting scenario. The expected product for the C₂ symmetric spirodiepoxide is an α -hydroxy- α' -substituted ketone as a single enantiomer (unless the α' -substituent is hydroxyl!). Substitution of the non-C₂ symmetric spirodiepoxide product will give a racemic mixture, unless only one of the enantiotopic termini is opened in the process.
6. The supporting information in reference ^{1b} describes in detail the method used to prepare DMDO.
7. Ferrer M, Gibert M, Sánchez-Baeza F, Messegue A. Tet. Lett 1996;37:3585.
8. For the synthesis of MEDO and DEDO see: (a) Murray RW, 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. Tet. Lett 1998;39:7819. For the Jacobsen epoxidation see: (d) Zhang W, Loebach JL, Wilson SR, Jacobsen EN. J. Am. Chem. Soc 1990;112:2801. (e) Jacobsen EN, Zhang W, Muci AR, Ecker JR, 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*-butyl allene is high (~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), provide numerous unambiguous structural proof 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.
12. Structure 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 subject 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. ¹H 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 base-line 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 RP. Acc. Chem. Res 2003;36:773. [PubMed: 14567711]
- 15 (a). Frantz DE, Fässler R, Carreira EM. J. Am. Chem. Soc 2000;122:1806. (b) Anand NK, Carreira EM. J. Am. Chem. Soc 2001;123:9687. [PubMed: 11572696] (c) Boyall D, Frantz DE, Carreira EM. Org. Lett 2002;4:2605. [PubMed: 12123387] (d) Sasaki H, Boyall D, Carreira EM. Helv. Chim. Acta 2001;84:964. See also: (e) Kirkham JED, Courtney TDL, Lee V, Baldwin JE. Tetrahedron 2005;61:7219.
16. Growth inhibition studies of these and related compounds will be reported separately.

Scheme 2.

Scheme 3.

Figure 1.
Model for diastereoselectivity.

Scheme 4.

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

Scheme 5.

Table 1

Stereoselective spirodiepoxide formation: Influence of dioxirane and solvent.

entry	allene	conditions	selectivity ^a	
			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 ₂ Cl ₂	>20:1	na
5	4a	DMDO/CHCl ₃	>20:1	na
6	4a	DMDO/CCl ₄	>20:1	na
7	4a	DMDO/ <i>t</i> -BuOH	>20:1	na
8	4b	DMDO/Acetone	10:1	1.1:1
9	4b	DMDO/CH ₂ Cl 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 ₂ Cl 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/ <i>t</i> -BuOH	>20:1	4.6:1

The allenes used here were racemic.

^aRatios determined by ¹H NMR.^bMEDO: methylethylidioxirane, MEK: methyl ethyl ketone.^cDEDO: diethyldioxirane, DEK: diethyl ketone.

Table 2

Stereoselective spirodiepoxide formation: Influence of allene structure.

entry	allene	R ¹	R ²	product	selectivity ^a R ¹ R ²
1	1	<i>i</i> -Bu	CH ₂ OTBS	10	>20:1 2:1
2	6	<i>i</i> -Pr	<i>i</i> -Pr	11	>20:1 3.3:1
3	7a	<i>i</i> -Bu		12a	>20:1 5:1
4	7b	<i>i</i> -Bu		12b	>20:1 1:1
5	8	<i>i</i> -Bu		13	>20:1 6:1

entry	allene	R ¹	R ²	product	selectivity ^a	
					r ₁	r ₂
6	9	CH ₂ OTBS		14	>20:1	8:1