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Synthesis of Isopeptide Epoxide Peptidomimetics

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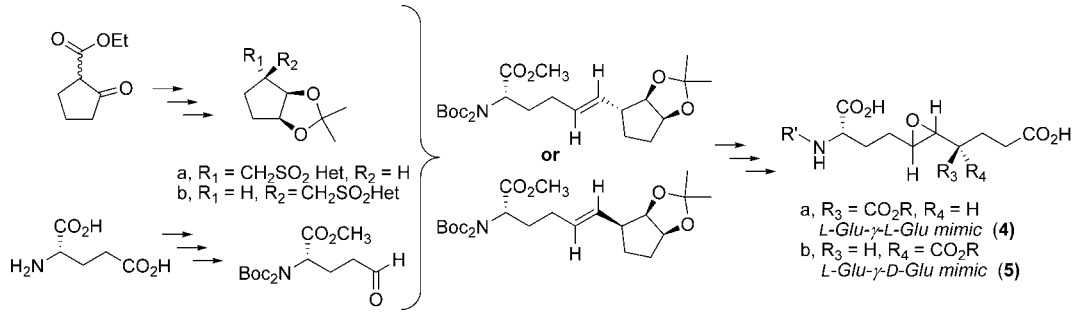

Two epoxide-containing peptidomimetics of the isopeptide, glutamyl-γ-glutamate, have been synthesized via a route that should be generally applicable to the synthesis of isopeptide analogues in which an oxirane replaces the scissile peptide bond. Enzymes that catalyze the hydrolysis of peptides and isopeptides are often susceptible to inactivation by electrophilic substrate analogues. In this research, an epoxide was installed as an electrophilic replacement of the scissile isopeptide bond. The *C*-terminal glutamyl mimic was accessed by the stereospecific synthesis of suitably substituted cyclopentenes, **8** and **10**, as surrogates for either the L- or D- enantiomer. The enantiomeric cyclopentenes were further elaborated to incorporate an appended sulfone that was reacted with a suitably protected glutamyl-γ-semialdehyde in a Julia−Kocienski olefination reaction. This olefination afforded predominantly the desired *E*-olefin isosteres of L-glutamyl-γ-D-glutamate and L-glutamyl-γ-L-glutamate, following which peracid-mediated epoxidation and deprotection provided the epoxide-containing peptidomimetics, **4** and **5**.

Introduction

Although the design and synthesis of mechanism-based inhibitors of proteases that act on proteins and peptides involving α-linked amino acids has been investigated extensively,[1] similar efforts to identify specific inhibitors of enzyme-catalyzed isopeptide hydrolysis are much less common.[2] The latter reaction, although less well studied, is of critical importance in areas such as the ubiquitination-deubiquitination cycle[3] and folate polyglutamate homeostasis involving the formation and hydrolysis of γ-glutamyl peptides.[4] The use of electrophilic substrate analogues as enzyme inactivators and probes of enzyme mechanism and structure has been at the forefront of medicinal and bioorganic chemistry research for decades. Thus, the development of "active-site-directed irreversible inhibitors"[5,6] and subsequently, "mechanism-based enzyme inhibitors"[7] has been a powerful tool in elucidating the mechanism of numerous enzyme-catalyzed reactions.

This approach has been applied to the design of selective inactivators of proteases that are postulated (and in many cases proven) to proceed via acyl enzyme intermediates, i.e., cysteine, serine, and threonine proteases.[1] In most of these inhibitors, however, the pendant electrophilic moiety (e.g., halomethylketone, acyloxymethylketone, epoxysuccinates, α,β-epoxyketones, vinyl sulfones) is incorporated in place of the *C*-terminal carboxyl group of the peptide substrate. The well-studied ubiquitination pathway of protein degradation involves ATP-dependent attachment of ubiquitin, a small protein, to a targeted protein, followed by recycling of the ubiquitin via hydrolysis

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(1) Powers, J. C.; Asgian, J. L.; Ekici, O. D.; James, K. E. *Chem. Rev.* **2002**, *102*, 4639–4750.
(2) Love, K. R.; Catic, A.; Schlieker, C.; Ploegh, H. L. *Nature Chem. Biol.* **2007**, *3*, 697–705.
(3) Wilkinson, K. D. *Cell Dev. Biol.* **2000**, *11*, 141–148.
(4) Schneider, E.; Ryan, T. J. *Clin. Chim. Acta* **2006**, *374*, 25–32.
(5) Baker, B. R. *Design of active-site-directed irreversible enzyme inhibitors; the organic chemistry of the enzymic active-site*; Wiley: New York, 1967.
(6) Baker, B. R. *Annu. Rev. Pharmacol.* **1970**, *10*, 35–50.
(7) Silverman, R. B. *Mechanism-based enzyme inactivation: chemistry and enzymology*; CRC Press: Boca Raton, FL, 1988.

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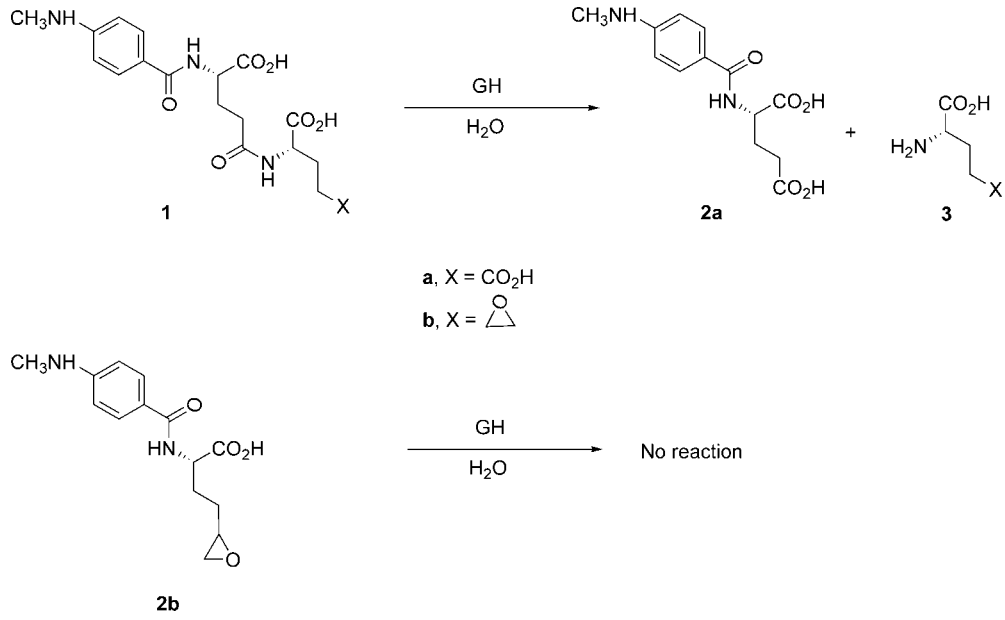
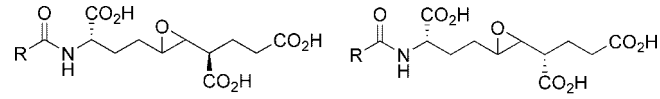


FIGURE 1. Reaction catalyzed by γ-glutamyl hydrolase.

of the isopeptide bond between the *C*-terminal glycine residue of ubiquitin and the ε-amino group of a lysine residue of the targeted protein.[3] Inhibition of the isopeptide hydrolase has been effected by the attachment of an electrophilic moiety to the *C*-terminus of ubiquitin.[2] The structure of one ubiquitin *C*-terminal hydrolase, UCH-L3, has been determined by X-ray crystallography in the absence of any ligand[8] and in the presence of ubiquitin to which an electrophilic vinyl methyl ester was attached to the *C*-terminal glycine.[9]

γ-Glutamyl hydrolase (GH, EC 3.4.19.9) is a cysteine peptidase[10] that catalyzes the hydrolysis of γ-glutamyl peptides[11] which, together with the ATP-dependent ligase, folylpolyglutamate synthetase (FPGS, EC 6.3.2.17), controls folate homeostasis in living cells. Our interest in GH led us to consider the synthesis of electrophilic substrate analogues for use in further probing the catalytic mechanism as well as for developing probes for the localization of this enzyme in complex biological environments. Our initial focus was the synthesis of *C*-terminal epoxides due to the demonstrated selectivity of the epoxide moiety for cysteine proteases, as well as the many reported syntheses of *C*-terminal epoxides and related epoxysuccinyl peptides in the literature.[1,12] The reaction catalyzed by GH is shown in Figure 1 (**1a** → **2a** + **3a**) . Evaluation of a *C*-terminal epoxide derivative, **1b**, as an inhibitor of GH revealed that **1b** inhibited the enzyme but most, if not all of the inhibition could be attributed to GH-catalyzed hydrolysis (**1b** → **2a** + **3b**), i.e., **1b** acts an alternate substrate.[13] GH does not display product inhibition and, consistent with this fact, **2b**, a compound lacking the isopeptide bond but also containing a *C*-terminal epoxide, is neither a substrate nor an inhibitor. As a result, subsequent synthetic efforts have been aimed at the synthesis of epoxide peptidomimetics in which the scissile isopeptide bond is replaced by an oxirane.

There is some precedent for the replacement of a peptide bond by an oxirane and our research builds on those initial studies.[14−18] These syntheses involved either peracid-mediated epoxidation of the corresponding *E*- or *Z*-olefins, or elaboration of the corresponding β-hydroxy selenide to the desired epoxide via an oxidative cyclization process. However, to the best of our knowledge, no such epoxide peptidomimetics of isopeptides have been synthesized. In this paper, using a peracid-mediated epoxidation of an olefin, we describe the synthesis of two diastereomeric epoxide peptidomimetics, **4** and **5**, in which the scissile isopeptide bond is replaced by an oxirane.



L-Glu-γ-L-Glu epoxide peptidomimetic

L-Glu-γ-D-Glu epoxide peptidomimetic

Results and Discussion

In previous research from our laboratory on the synthesis of phosphinic acid-containing pseudopeptide inhibitors of FPGS, the use of cyclopentene derivatives as glutarate surrogates has been described.[19] In the present work, a similar approach has been pursued. Thus, the desired oxiranes are envisioned to be accessible from the corresponding *E*-olefin, **6**, as shown in Figure 2 for the L-Glu-γ-L-Glu mimetic, **4**, with the chiral centers derived ultimately from (*N*,*N*-Boc$_2$)-L-glutamic acid γ-semial-

(8) Johnston, S. C.; Larsen, C. N.; Cook, W. J.; Wilkinson, K. D.; Hill, C. P *EMBO J.* **1997**, *16*, 3787–3796.
(9) Misaghi, S.; Galardy, P. J.; Meester, W. J. N.; Ovaa, H.; Ploegh, H. L.; Gaudet, R. *J. Biol. Chem.* **2005**, *280*, 1512–1520.
(10) Chave, K. J.; Galivan, J.; Ryan, T. J. *Biochem. J.* **1999**, *343*, 551–555.
(11) Alexander, J. P.; Ryan, T. J.; Ballou, D. P.; Coward, J. K. *Biochemistry* **2008**, *47*, 1228–1239.
(12) Albeck, A. *Drug Dev. Res.* **2000**, *50*, 425–434.
(13) Alexander, M. D. Ph.D. Thesis, The University of Michigan, 2004.
(14) Jenmalm, A.; Berts, W.; Li, Y. L.; Luthman, K.; Csoregh, I.; Hacksell, U. *J. Org. Chem.* **1994**, *59*, 1139–1148.
(15) Mann, A.; Quaranta, L.; Reginato, G.; Taddei, M. *Tetrahedron Lett.* **1996**, *37*, 2651–2654.
(16) Perlman, N.; Livneh, M.; Albeck, A. *Tetrahedron* **2000**, *56*, 1505–1516.
(17) Demarcus, M.; Ganadu, M. L.; Mura, G. M.; Porcheddu, A.; Quaranta, L.; Reginato, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 697–706.
(18) Wiktelius, D.; Berts, W.; Jensen, A. J.; Gullbo, J.; Saitton, S.; Csoregh, I.; Luthman, K. *Tetrahedron* **2006**, *62*, 3600–3609.
(19) Bartley, D. M.; Coward, J. K. *J. Org. Chem.* **2005**, *70*, 6757–6774.

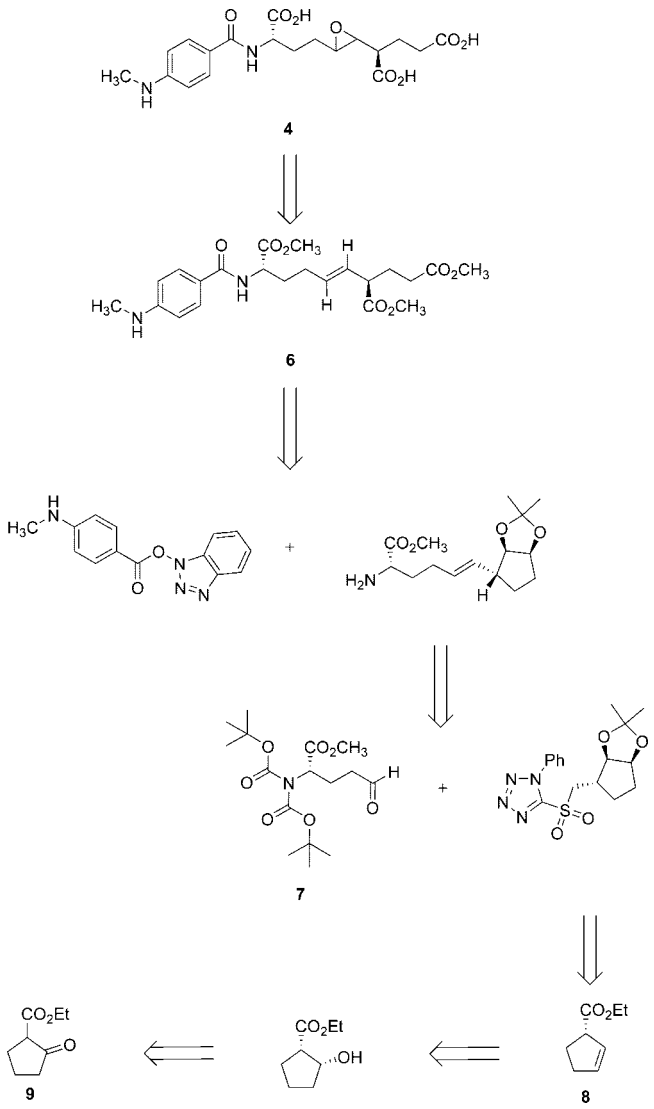
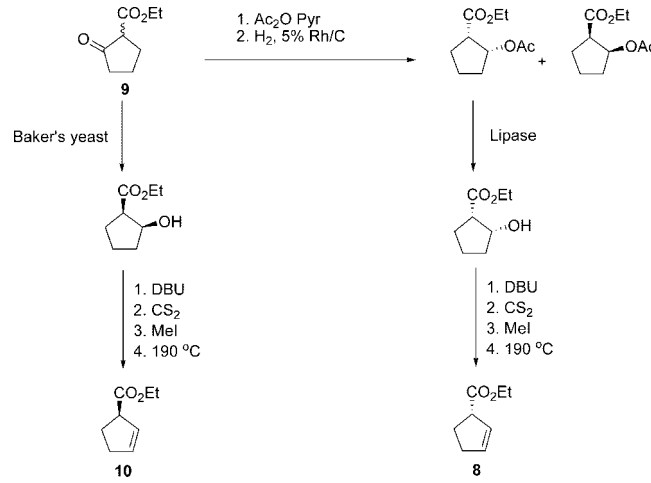


FIGURE 2. Synthesis of oxirane- and olefin-containing analogues of γ-glutamyl peptides: retrosynthetic analysis.

dehyde, **7**, and (*S*)-1-(carboethoxy)cyclopent-2-ene, **8**. The L-Glu-γ-D-Glu mimetic, **5**, also should be accessible via the same route from the enantiomer of **8** (*ent*-**8**). In developing a strategy for the synthesis of target olefin isosteres of the γ-glutamyl dipeptide (e.g., **6**), and the corresponding internal epoxide derivatives (e.g., **4**), the two important synthetic challenges that need to be addressed are (i) stereospecific generation of the chiral center which serves as a pseudo-α-carbon in the *C*-terminal glutamic acid replacement, analogous to the 2*S* or 2*R* stereochemistry in the parent isopeptide, and (ii) selective formation of the *E*-olefin during synthesis of the olefinic dipeptide isostere. Stereospecific generation of either stereoisomer at C-1 of the cyclopent-2-ene derivative, **8** or *ent*-**8** **(10)**, from ethyl 2-oxocyclopenane carboxylate, **9**, has been achieved via lipase-mediated ester hydrolysis,[13,19−21] or a dynamic kinetic resolution,[22] respectively (Scheme 1). The desired *E*-olefin is most consistently achieved by the Julia−Kocienski

SCHEME 1



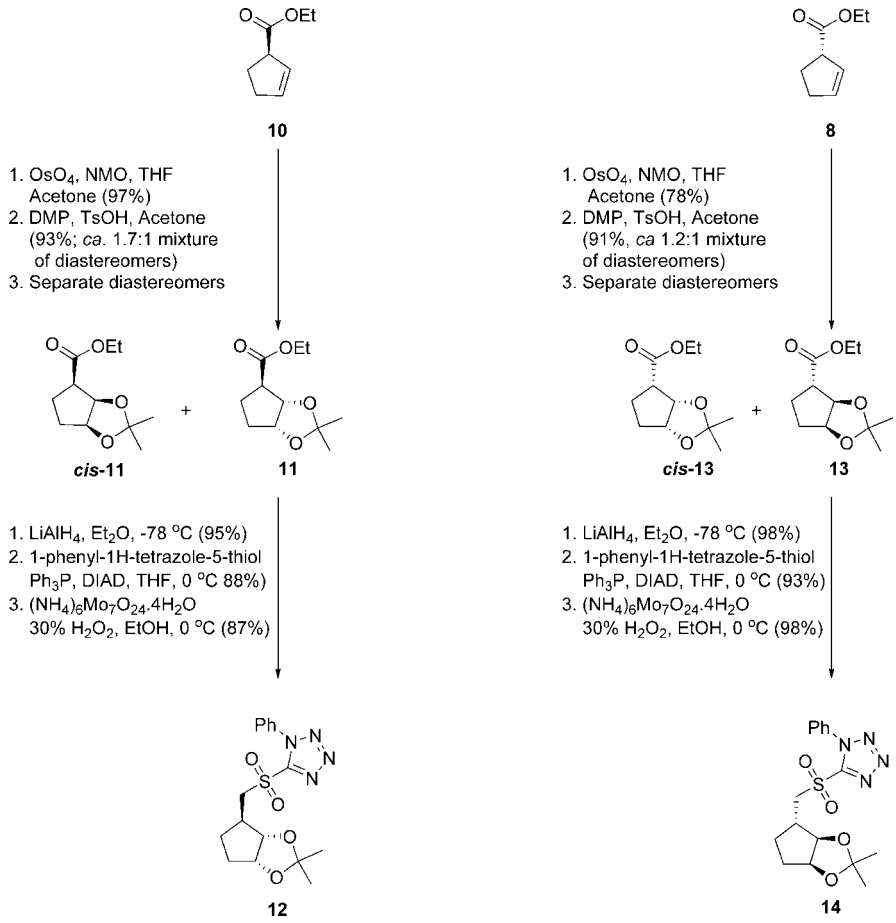
reaction through the olefination of an aldehyde (e.g., **7**).[23,24] As outlined in Scheme 1, the critical stereoselective synthesis of **10**, via sequential dynamic kinetic resolution, xanthate formation, and pyrolysis to form the desired cyclopentene derivative[25] proceeded in higher yield (65%, 5 steps)[26] than the synthesis of **8** via acetylation, hydrogenation of the enol acetate, lipase-catalyzed resolution, and pyrolysis of the enantiomeric xanthate (21%, 7 steps).[19] Accordingly, the synthesis of **5** from the more readily available enantiomer, **10**, was investigated before the synthesis of **4** from **8** (Schemes 2−5).

As shown in Scheme 2, dihydroxylation of the (1*R*)-β,γ-unsaturated ethyl ester derivative **10** was performed by using the Upjohn procedure (OsO_4/*N*-methylmorpholine *N*-oxide)[27] to afford the corresponding vicinal diols as an inseparable mixture of trans and cis diastereomers in 97% yield. To protect the free hydroxyl groups of the vicinal diols, reaction with 2,2-dimethoxypropane/acetone/TsOH afforded the corresponding isopropylidene derivatives (93% yield, diastereomeric ratio (trans:cis) = ca. 1.7:1), which were separated by flash chromatography to give **11** in 58% yield and the cis diastereomer, *cis*-**11**, in 35% yield. Stereochemistry of the diastereomers was confirmed by a nuclear Overhauser effect (NOE) between H-1 and H-2 that was observed only in the NMR spectra of the cis diastereomer. The ethyl ester functionality of the trans isomer was reduced by using $LiAlH_4$ at −78 °C to obtain the corresponding hydroxymethyl derivative in 95% yield. Mitsunobu coupling[28] of this alcohol to 1-phenyl-1*H*-tetrazole-5-thiol using PPh_3/diisopropylazodicarboxylate (DIAD) (0 °C → rt) furnished the sulfide product in 88% yield, which was followed by oxidation (H_2O_2, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 0 °C) to give sulfone **12** in 87% yield.

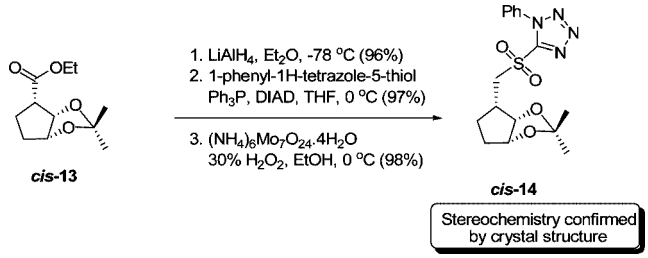
The enantiomeric sulfone, **14**, was obtained in an analogous manner from the enantiomeric cyclopentene derivative, **8**. Thus, dihydroxylation of the β,γ-unsaturated ethyl ester derivative **8** by using the Upjohn procedure[27] afforded the corresponding vicinal diols as an inseparable mixture of trans and cis diastereomers in 78% yield. Subsequent protection of the vicinal

(20) Rozzell, J. D. *Tetrahedron Lett.* **1982**, *23*, 1767–1770.
(21) Xie, Z. F.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1987**, 838–839.
(22) Wahhab, A.; Tavares, D. F.; Rauk, A. *Can. J. Chem.* **1990**, *68*, 1559–1563.
(23) Blakemore, P. R. *J. Chem. Soc., Perkin Trans 1* **2002**, 2563–2585.
(24) Plesniak, K.; Zarecki, A.; Wicha, J. *Top. Curr. Chem.* **2007**, *275*, 163–250.
(25) Maeda, K.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2880–2882.
(26) Bartley, D. M.; Coward, J. K. *J. Org. Chem.* **2006**, *71*, 372–374.
(27) Vanrheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976.
(28) Mitsunobu, O. *Synthesis* **1981**, 1–28.

SCHEME 2



SCHEME 3



diols yielded the corresponding isopropylidene derivatives (91% yield, diastereomeric ratio (trans:cis) = ca. 1.2:1). Separation of the diastereomers was accomplished by flash chromatography to give **13** in 49% yield and *cis*-**13** in 43% yield. The ethyl ester functionality of the trans isomer was reduced by using $LiAlH_4$ to obtain the corresponding hydroxymethyl derivative in 98% yield, followed by Mitsunobu coupling[28] to 1-phenyl-1*H*-tetrazole-5-thiol to give the corresponding thioether in 93% yield. This product was oxidized to sulfone **14** in 98% yield.

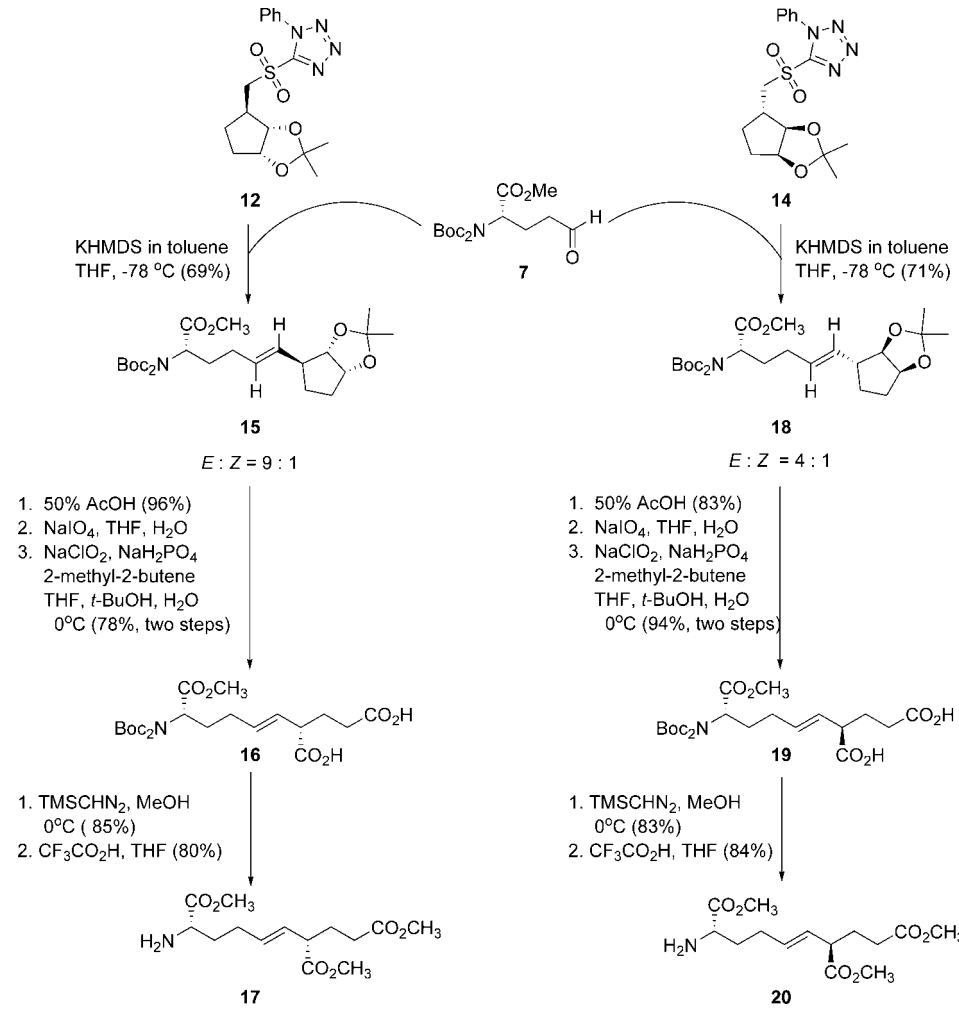
As shown in Scheme 3, the cis diastereomer, *cis*-**13**, was converted to the corresponding sulfone, *cis*-**14**, by identical chemistry to that described above for the trans diastereomer. Crystallization of *cis*-**14** enabled the determination of the absolute configuration of *cis*-**14** by X-ray crystallography and confirmed the absolute stereochemistry of all substituents in this series of compounds (**11**−**14**) originally deduced based on ^{1}H NMR spectral data (see the Supporting Information for details of the synthesis of *cis*-**14** and also the crystal structure determination).[13]

Previous research in our laboratory has shown that compounds similar to **12** and **14** with the 2,3-isopropylidene substituent trans to a bromomethyl substituent at C-1 are more reactive in S_N2 reactions than the cis diastereomers.[19] In the current research, olefination reactions of sulfone **14** or *cis*-**14** proceeded in similar yields. Since the stereochemical distinction between these diastereomers is lost in the oxidative cleavage of the masked cyclopentene moiety to the glutarate targets, it would be reasonable to proceed with the synthesis by using a mixture of diastereomeric isopropylidenes, e.g., **14** and *cis*-**14**. However, the ^{1}H NMR spectra of these mixtures are very complex, involving numerous diastereomeric and diastereotopic nuclei. In contrast, spectra of compounds derived from a single diastereomer, i.e., **12** or **14**, are considerably simplified and more readily interpreted. Therefore, we chose to explore the olefination reactions primarily with a single diastereomer, usually the more readily available trans diastereomer.[29] Subsequent investigations can be carried out with the mixture of diastereomers.

One of the important features of this reaction design is the preferred formation of a trans double bond with the Julia−Kocienski olefination.[23,24] Initial investigation of the reaction on a small scale at low temperature indicated that the reaction did not go to completion and a large proportion of unreacted sulfone **14** was recovered along with the desired product.[13] However, as depicted in Scheme 4, reaction of glutamyl semialdehyde

(29) The trans diastereomers of the isopropylidene precursors, **11** and **13**, are predicted to have a lower dipole moment, with associated decreased polarity, than the corresponding cis diastereomers. As a result, the trans diastereomers (higher R_f) were readily separated from the more polar cis diastereomers in high purity by flash chromatography.

SCHEME 4

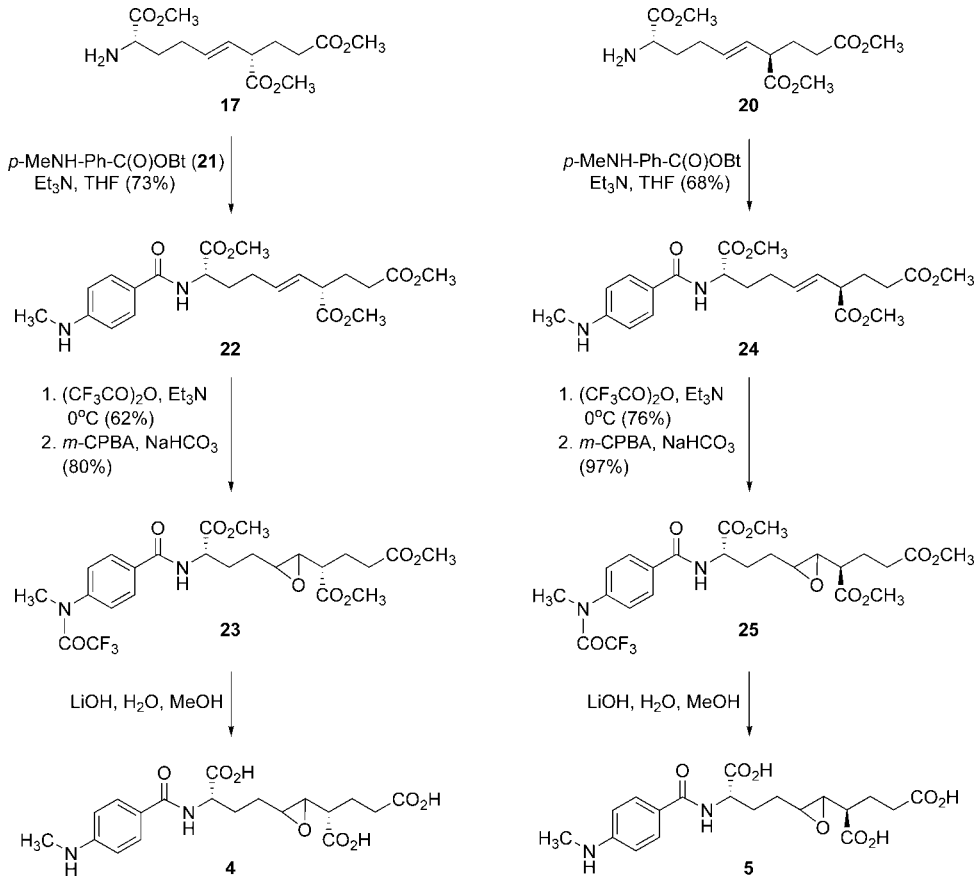


derivative **7**[30] and sulfone **12** under optimized conditions[23,24] (KHMDS, −78 °C) provided the olefin product **15** in 69% yield. Analysis of ^{1}H NMR spectral data showed predominant formation of the desired *E*-olefin (*E*:*Z* = 9:1; J_{trans} =15 Hz vs J_{cis} =11 Hz). Similarly, reaction of **7** and sulfone **14** under identical conditions provided the desired olefin product **18** in 71% yield. Analysis of the ^{1}H NMR spectral data indicated that **18** was also mostly trans (*E*:*Z* = 4:1; J_{trans} = 15 Hz vs J_{cis} =11 Hz). The Julia−Kocienski reaction is known to be readily scalable and the olefination reactions described herein are amenable to scale-up to provide adequate quantities of **15** and **18** for further elaboration to the desired target compounds. To remove the isopropylidene functionality, the Julia−Kocienski olefination product **15** was treated with 50% acetic acid to furnish the vicinal diol in 96% yield. Oxidative cleavage of the vicinal diol was performed with $NaIO_4$ to give the dialdehyde as a crude product. Without purification, the dialdehyde was oxidized under Kraus conditions ($NaClO_2$/NaH_2PO_4/2-methyl-2-butene, 0 °C)[31,32] to the diacid **16** (78% yield, two steps). Esterification of **16** ($TMSCHN_2$, 0 °C → rt) gave the corresponding triester (85% yield), which on removal of the Boc groups gave the amine **17** (80% yield). A similar series of reactions converted **18** to **20**. Thus, sequential hydrolysis to the vicinal diol (83%), oxidative cleavage to the crude dialdehyde, further oxidation to diacid **19** under Kraus conditions (94%), esterification with $TMSCHN_2$ (83%), and finally *N*-deprotection afforded **20** (84%).

Subsequent elaboration to the target epoxide peptidomimetics, **4** and **5**, is shown in Scheme 5. As described in the Supporting Information, the 1-hydroxybenzotriazole (HOBt) ester of *p*-aminobenzoic acid, **21**, was synthesized by DCC-mediated coupling of 4-(*N*-methyl)aminobenzoic acid (*N*-Me-*p*ABA) and HOBt in 84% yield. This preactivated *N*-Me-*p*ABA was coupled with olefin isostere **17** in the presence of Et_3N to give **22** (73% yield). As observed in the synthesis of terminal epoxides, **1b** and **2b** (see the Supporting Information),[13] epoxidation of **22** without prior N-protection resulted in the oxidation of the secondary amine. To avoid this problem, the amine nitrogen atom of **22** was protected as a trifluoroacetamide ($(CF_3CO)_2O$/Et_3N, 0 °C, 62% yield). Reaction of the olefinic amide with mCPBA/$NaHCO_3$ proceeded as expected, without facial selectivity, to yield the epoxide **23** (80% yield) as a mixture of trans epoxide diastereomers. TLC, NMR, and MS analysis of the product confirmed the isomeric mixture was contaminant-free. Epoxide **23** was treated with LiOH, to give, after concomitant deprotection of the acids and the amine, the corresponding target compound **4**. Formation of the desired product **4** was confirmed by NMR and MS analysis.[33,34]

(30) Padron, J. M.; Kokotos, G.; Martin, T.; Markidis, T.; Gibbons, W. A.; Martin, V. S. *Tetrahedron: Asymmetry* **1998**, *9*, 3381–3394.
(31) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175–1176.
(32) Santhanam, B.; Worfent, M. A.; Moore, J. N.; Boons, G. J. *Chem. Eur. J.* **2004**, *10*, 4798–4807.

SCHEME 5



Similarly, amine **20** was coupled with **21** to obtain **24** (68%). Formation of the *N*-Tfa derivative (76%) followed by epoxidation afforded epoxide **25** (97%) as a mixture of trans epoxide diastereomers. TLC, NMR, and MS analysis of the product confirmed the isomeric mixture contained no impurities. Epoxide **25** was treated with LiOH to give the corresponding triacid **5**, the structure of which was confirmed by NMR and mass spectral data.[35] Biochemical studies on the effect of **4** and **5** on the reaction catalyzed by GH are in progress and will be reported in due course.

Experimental Section

General Experimental Procedures. See the Supporting Information. The selectivity of the Julia−Kocienski reaction was consistent with literature precedent and provided primarily the *E* geometry for the newly formed olefin. For compounds **15** and **18**, the diastereomeric ratio (*E*:*Z*) was determined by comparing the relative integration values of corresponding methine protons, the resonances of which do not overlap with any other signals. Independent decoupling of the methine protons for both the trans and cis olefin isomers within the mixture allowed the coupling between the vinyl protons to be measured at $J = 15$ and 11 Hz for the trans and cis olefin, respectively. The *E*:*Z* ratio determined for the products of the olefination reaction, **15** (9:1) and **18** (4:1), was assumed to be maintained during subsequent chemical transformations. Compounds **7**,[30] **8**,[13,19−21] and **10**[22,25] were synthesized as described in the literature.

(3a*S*,4*R*,6a*R*)-Ethyl 2,2-Dimethyltetrahydro-3a*H*-cyclopenta[*d*]-[1,3]dioxole-4-carboxylate (11). A solution of *N*-methylmorpholine *N*-oxide (7.03 g, 60 mmol) and osmium tetroxide (3 mL of 2.5 wt % solution, 300 μmol) in water (20 mL) was added to a cooled (0 °C) stirred solution of optically pure ethyl (cyclopent-2-ene)-1-carboxylate **10** (4.22 g, 30 mmol) in acetone/THF (15 mL/15 mL). The solution was warmed to rt and stirring was continued for 22 h. TLC analysis showed the complete consumption of the starting olefin. Then the reaction mixture was diluted with DCM (70 mL) and washed with 10% Na_2SO_3 (40 mL) and saturated NH_4Cl (40 mL). The combined aqueous layers were extracted with DCM (2 × 50 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/hexane 2:3) to provide an inseparable mixture of diastereomeric diols as a colorless oil (5.08 g, 97% yield). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.24−4.05 (m, 4H), 3.52 (br s, 0.3H), 2.98−2.84 (m, 2H), 2.63 (br s, 0.6H), 2.19−1.71 (m, 4H), 1.30−1.26 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 175.2, 77.3, 74.0, 73.8, 72.9, 61.0, 60.8, 48.3, 46.2, 30.8, 29.8, 24.0, 23.8, 14.2, 14.1. R_f 0.16 (EtOAc/hexane 2:3). MS (ESI) *m*/*z* (rel intensity) 197.1 ([M + Na]$^+$, 100).

The diastereomeric mixture of cis and trans diols (6.49 g, 37 mmol) and 2,2-dimethoxypropane (100 mL) were dissolved in acetone (115 mL) and stirred for 5 min. TsOH·H_2O (704 mg, 3.7 mmol) was then added portionwise and stirring was continued at rt for 18 h. TLC analysis showed complete consumption of the starting diastereomeric diols. The reaction mixture was diluted with EtOAc (150 mL), then washed with saturated $NaHCO_3$ (50 mL)

(33) The use of a stereorandom epoxidation method was chosen to obtain the target compounds as "proof of concept" irreversible inhibitors of GH. Following biochemical evaluation of **4** and **5**, the use of chiral epoxidation methods[34] will be pursued to optimize both efficacy and selectivity.

(34) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979–2000.

(35) All of the reactions depicted in Schemes 4 and 5 were performed multiple times on less than 100 mg scale with consistent results. However, all of the chemical transformations utilized here were chosen for their generality and are known to work well on significantly larger scale. Thus, we expect the synthetic route described here to be readily amenable to gram scale without modification.

and then saturated NaCl (150 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue (7.48 g) was purified by flash chromatography (EtOAc/hexane 1:9) to give compounds *cis*-**11** (2.67 g, 35%) and **11** (4.47 g, 58%) as a colorless oil. **Cis:** ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 4.79 (t, J = 5.0 Hz, 1H), 4.66 (t, J = 5.5 Hz, 1H), 4.24−4.13 (m, 2H), 2.61−2.59 (m, 1H), 2.14−2.10 (m, 1H), 1.94−1.90 (m, 1H), 1.76−1.71 (m, 1H), 1.46−1.41 (m, 4H), 1.28−1.25 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 171.1, 109.9, 80.9, 80.4, 60.4, 50.1, 31.4, 25.8, 24.1, 24.0, 14.3. R_f 0.26 (EtOAc/hexane 1:9). MS (ESI) *m*/*z* (rel intensity) 237.1 ([M + Na]$^+$, 100). **Trans:** ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 4.83 (d, J = 5.5 Hz, 1H), 4.71 (t, J = 5.0 Hz, 1H), 4.12 (q, J = 7.5 Hz, 2H), 2.89 (d, J = 7.5 Hz, 1H), 2.11−2.08 (m, 1H), 1.92−1.75 (m, 3H), 1.45 (s, 3H), 1.32−1.24 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 174.1, 110.2, 83.2, 81.4, 60.9, 50.9, 31.8, 27.0, 26.7, 24.4, 14.5. R_f 0.41 (EtOAc/hexane 1:9). MS (ESI) *m*/*z* (rel intensity) 237.1 ([M + Na]$^+$, 100).

5-(((3a*S*,4*R*,6a*R*)-2,2-Dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]-dioxol-4 yl)methylthio)-1-phenyl-1*H*-tetrazole (12). The optically pure bicyclic ethyl ester derivative **11** (2.97 g, 13.8 mmol) was dissolved in THF (30 mL). In a separate flask, $LiAlH_4$ (0.73 g, 19.2 mmol) was suspended in THF (10 mL) in an atmosphere of argon and the mixture was cooled to 0 °C. The THF solution of the ester was added dropwise to the $LiAlH_4$ suspension at 0 °C. Vigorous bubbling was observed during the addition of the ester derivative. The reaction mixture was stirred for 4 h at 0 °C in an atmosphere of argon and then quenched by dropwise addition of 10% NH_4Cl solution (0.8 mL). The solution was allowed to warm to rt and stirring was continued for 60 min. The reaction mixture was filtered through Celite with use of EtOAc and the solvent was removed under reduced pressure to give the crude product as a clear oil (2.4 g). The crude product was purified by flash chromatography (EtOAc/hexane 3:7) to give the desired hydroxymethyl derivative as a colorless oil (2.27 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 4.65 (t, J = 5.6 Hz, 1H), 4.47 (d, J = 5.5 Hz, 1H), 3.53−3.45 (m, 2H), 2.22−2.21 (m, 1H), 1.98−1.96 (m, 1H), 1.82−1.71 (m, 3H), 1.49−1.46 (m, 3H), 1.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 110.2, 83.5, 81.1, 63.6, 48.5, 31.4, 26.8, 25.6, 24.3. R_f 0.18 (EtOAc/hexane 3:7). MS (ESI) *m*/*z* (rel intensity) 195.1 ([M + Na]$^+$, 100).

The bicyclic hydroxymethyl derivative (890 mg, 5.1 mmol) was dissolved in THF (25 mL) at 0 °C in an atmosphere of argon followed by addition of Ph_3P (2.0 g, 7.62 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (1.45 g, 8.13 mmol). In a separate flask, diisopropylazadicarboxylate, DIAD (2.08 g, 10.3 mmol), was dissolved in THF (10 mL), which gave a yellow solution. This DIAD solution was added dropwise to the reaction mixture at 0 °C. After addition of each drop of DIAD solution the reaction mixture became yellow, then the color persisted for a second and disappeared. When approximately half of the DIAD solution was added, the reaction mixture remained yellow. Stirring was continued at rt for 12 h. The TLC analysis showed the complete consumption of the starting material. The reaction mixture was diluted with Et_2O (150 mL) and washed with saturated $NaHCO_3$ solution (100 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layer was washed with saturated NaCl solution (100 mL) and dried over anhydrous Na_2SO_4, then the solvent was removed under reduced pressure to give a yellow oil that was purified by flash chromatography (EtOAc/hexane 1:9) to give the thioether precursor of **12** as a yellow oil (1.5 g, 88%). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.60−7.53 (m, 5H, Ar−H), 4.70 (t, J = 5.0 Hz, 1H), 4.43 (t, J = 5.5 Hz, 1H), 3.36 (dd, J = 13.1, 6.5 Hz, 1H), 3.27 (dd, J = 13.1, 7.0 Hz, 1H), 2.46−2.44 (m, 1H), 2.11−2.08 (m, 1H), 1.88−1.82 (m, 2H), 1.59−1.56 (m, 1H), 1.43 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 154.3, 133.9, 130.4, 130.0, 124.1, 110.4, 85.1, 80.8, 45.3, 35.1, 31.0, 28.2, 26.6, 24.3, 22.2. R_f 0.45 (EtOAc/hexane 3:7). MS (ESI) *m*/*z* (rel intensity): 355.1 ([M + Na]$^+$, 100).

$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (165 mg, 133 μmol) was dissolved in 30% H_2O_2 (1.13 mL, 10 mmol) at 0 °C to give a yellow solution that was added dropwise to the ethanolic solution of the thioether precursor (222 mg, 667 μmol) in EtOH (10 mL) at 0 °C. The yellow color of the $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ solution disappeared after addition of each drop in the reaction mixture and a white precipitate was observed. The resulting suspension was stirred at rt for 24 h, added to brine (40 mL), and extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 then filtered and the solvent was removed under reduced pressure to afford the crude product as an oil (590 mg). Purification of the crude product by flash chromatography (EtOAc/hexane 3:7) gave the pure sulfoxide **12** as a clear, colorless oil (208 mg, 87%). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.69−7.59 (m, 5H, Ar−H), 4.67 (t, J = 5.5 Hz, 1H), 4.49 (dd, J = 5.0, 2.0 Hz, 1H), 3.78 (dd, J = 15, 7.5 Hz, 1H), 3.67 (dd, J = 15.0, 7.0 Hz, 1H), 2.75−2.74 (m, 1H), 2.18−2.15 (m, 1H), 1.88−1.80 (m, 2H), 1.66−1.63 (m, 1H), 1.42 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 154.1, 133.4, 131.9, 130.1, 125.5, 111.3, 85.3, 80.5, 57.9, 40.1, 31.2, 28.9, 26.9, 24.6. R_f 0.45 (EtOAc/hHexane 3:7). MS (ESI) *m*/*z* (rel intensity) 387.1 ([M + Na]$^+$, 100).

(3a*R*,4*S*,6a*S*)-Ethyl 2,2-Dimethyltetrahydro-3a*H*-cyclopenta[*d*]-[1,3]dioxole-4-carboxylate (13). A solution of *N*-methylmorpholine *N*-oxide (1.86 g, 15.87 mmol) and osmium tetroxide (0.80 mL of 2.5 wt % solution, 79 μmol) in water (5 mL) was added to a cooled (0 °C) stirred solution of optically pure cyclopent-2-ene-ethylcarboxylate **8** (1.12 g, 7.99 mmol) in acetone/THF (3.5 mL/3 mL). Subsequent reaction conditions, workup, and purification employed identical reagents and solvents proportionately to that described in the synthesis of **11**, again providing an inseparable mixture of diastereomeric diols as a colorless oil (1.08 g, 78% yield). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.19−4.04 (m, 4H), 3.36 (br d, 0.2H), 2.90−2.80 (m, 1H), 2.26−2.10 (m, 1H), 2.00−1.90 (m, 1H), 1.82−1.68 (m, 2H), 1.30−1.26 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 175.9, 174.4, 77.2, 74.4, 74.3, 73.3, 61.2, 61.0, 48.8, 46.9, 30.6, 30.4, 24.6, 23.5, 14.5, 14.4. R_f 0.33 (EtOAc/hexane 3:2). MS (ESI) *m*/*z* (rel intensity) 197.1 ([M + Na]$^+$, 100). HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_8H_{14}O_4Na$ [M + Na]$^+$ 197.0790, found 197.0792.

The diastereomeric mixture of cis and trans diols (770 mg, 4.41 mmol) and 2,2-dimethoxypropane (15.0 mL) were dissolved in acetone (10.0 mL) and stirred for 5 min. Then $TsOH\cdot H_2O$ (22 mg, 116 μmol) was added portionwise and stirring was continued at rt for 30 min. Subsequent workup and purification employed identical reagents and solvents proportionately to that described in the synthesis of **11**, providing compounds *cis*-**13** (398 mg, 43%) and **13** (466 mg, 49%) as colorless oils. **Cis:** ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.79 (t, J = 5.7 Hz, 1H), 4.66 (t, J = 5.2 Hz, 1H), 4.25−4.11 (m, 2H), 2.63−2.57 (m, 1H), 2.18−2.06 (m, 1H), 1.94−1.89 (m, 1H), 1.77−1.70 (m, 1H), 1.49−1.41 (m, 4H), 1.28−1.25 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 171.4, 110.3, 81.2, 80.8, 60.8, 50.5, 31.8, 26.2, 24.5, 24.4, 14.6. R_f 0.25 (EtOAc/hexane 1:9). MS (ESI) *m*/*z* (rel intensity) 237.2 ([M + Na]$^+$, 100). HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{11}H_{18}NaO_4$ 237.1103, found 237.1104. **Trans:** ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 4.83 (d, J = 5.6 Hz, 1H), 4.72 (t, J = 5.2 Hz, 1H), 4.12 (q, J = 7.6 Hz, 2H), 2.90 (d, J = 7.2 Hz, 1H), 2.15−2.05 (m, 1H), 1.93−1.70 (m, 3H), 1.44 (s, 3H), 1.31−1.23 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 174.0, 110.2, 83.2, 81.4, 60.9, 50.9, 31.8, 27.0, 26.0, 24.4, 14.5. R_f 0.39 (EtOAc/hexane, 1:9). MS (ESI) *m*/*z* (rel intensity) 237.2 ([M + Na]$^+$, 100). HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{11}H_{18}O_4Na$ 237.1103, found 237.1102.

5-(((3a*R*,4*S*,6a*S*)-2,2-Dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]-dioxol-4-yl)methylthio)-1-phenyl-1*H*-tetrazole (14). The optically pure ethyl ester-containing bicycle **13** (145 mg, 0.68 mmol) was dissolved in Et_2O (1 mL). In a separate flask, $LiAlH_4$ (36 mg, 0.95 mmol) was suspended in Et_2O (4 mL) and the mixture was cooled to 0 °C. The solution of **13** was transferred to the reaction flask via syringe along with an Et_2O rinse. Vigorous bubbling was observed

upon addition. The ice bath was removed and the reaction allowed to stir at rt for 1 h, at which point TLC analysis indicated the reaction was complete (hexanes−EtOAc 2:1; **13**, R_f 0.59, HCl then $KMnO_4$, the desired hydroxymethyl derivative, R_f 0.14, HCl then $KMnO_4$). The reaction was worked up according to the Fieser and Fieser protocol.[36] The mixture was cooled to 0 °C and H_2O (36 μL), 15% NaOH (36 μL), and H_2O (105 μL) were added in that order. The mixture was stirred for 45 min during which time the gray solid turned to a white solid. Filtration through Celite with EtOAc and removal of the solvent in vacuo produced 123 mg of clear oil. Purification by flash chromatography (1 × 3 in. silica; hexanes−EtOAc 2:1 → 1:1) yielded pure hydroxymethyl derivative (114 mg, 98%) as a clear, colorless oil: $[\alpha]^{22}_D + 9.7$ (*c* 1.0, $CHCl_3$). FTIR (film, NaCl) 3425, 1041 cm^{-1}. ^1H NMR (500 MHz) δ 4.60 (t, *J* = 5.5 Hz, 1 H), 4.40 (d, *J* = 5.8 Hz, 1 H), 3.42 (dd, *J* = 7.1, 10.8 Hz, 1 H), 3.38 (dd, *J* = 8.2, 10.8 Hz, 1 H), 2.15 (m, 1 H), 2.62 (br s, 1 H), 1.91 (m, 1 H), 1.76 (m, 1 H), 1.68 (m, 1 H), 1.43 (m, 1 H), 1.40 (s, 3 H), 1.25 (s, 3 H). ^{13}C NMR (125 MHz) δ 110.0, 83.3, 81.0, 63.1, 48.2, 31.2, 26.6, 25.3, 24.2. MS (ESI) *m*/*z* (rel intensity) 227.2 ([M + Na + MeOH]$^+$, 100), 195.2 ([M + Na]$^+$, 78). HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_9H_{16}NaO_3$ 195.0997, found 195.1001.

The 1-hydroxymethyl derivative (104 mg, 0.60 mmol) was dissolved in THF (1 mL) under argon before Ph_3P (236 mg, 0.90 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (160 mg, 0.90 mmol) were added. In a separate flask, DIAD (213 μL, 1.08 mmol) was dissolved in THF (4 mL) to give a yellow solution. The reaction mixture was cooled to 0 °C and the DIAD solution was added dropwise. The yellow color persisted approximately 1 s after each drop was added before the solution returned to colorless. After approximately 75% of the DIAD had been added, the yellow color remained. After 30 min of reaction, TLC analysis (hexanes−EtOAc 1:1) indicated the alcohol (R_f 0.29) had been consumed and the sulfide (R_f 0.55) had formed. The reaction was diluted with Et_2O (50 mL) and washed with sat. $NaHCO_3$ (20 mL). The aqueous layer was repeatedly extracted with Et_2O (3 × 40 mL) and the combined organic layer was washed with brine (30 mL) and dried (Na_2SO_4). The solvent was removed by rotary evaporation to yield 816 mg of yellow oil that was purified by flash chromatography (Isco CombiFlash RETRIEVE with RediSep 10 g column; hexanes−EtOAc 5:1; R_f 0.12) to afford 184 mg of clear, colorless oil that was pure sulfide (93% yield). $[\alpha]^{24}_D$ +9.3 (*c* 1.0, $CHCl_3$). FTIR (film, NaCl) 1500, 1043 cm^{-1}. ^1H NMR (500 MHz) δ 7.51 (m, 5 H), 4.64 (t, *J* = 5.3 Hz, 1 H), 4.38 (d, *J* = 5.7 Hz, 1 H), 3.29 (dd, *J* = 13.0, 7.3 Hz, 1 H), 3.21 (dd, *J* = 13.0, 9.2 Hz, 1 H), 2.03 (m, 1 H), 2.40 (m, 1 H), 1.77 (m, 1 H), 1.51 (m, 1 H), 1.37 (s, 3 H), 1.21 (s, 3 H). ^{13}C NMR (125 MHz) δ 154.1, 133.6, 130.1, 129.8, 123.8, 110.0, 84.8, 80.5, 45.0, 34.8, 30.7, 27.7, 26.4, 24.1. MS (ESI) *m*/*z* 355.1 (MNa$^+$, 100). HRMS (ESI) calcd for $C_{16}H_{20}N_4NaO_2S$ 355.1205 (MNa$^+$), found 355.1209.

The sulfide (85 mg, 0.26 mmol) was dissolved in EtOH (95%, 1 mL) and the mixture was cooled to 0 °C. In a separate flask, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (63 mg, 0.051 mmol) was dissolved in H_2O_2 (30%, 465 μL, 4.10 mmol) at 0 °C to give a yellow solution. The oxidant solution was added to the sulfide and the reaction monitored by TLC (hexanes−EtOAc 3:1; sulfide, R_f 0.23, UV; **14**, R_f 0.23, UV; sulfoxide, R_f 0.06, UV). The starting material and product have identical R_f values. Therefore, the reaction progress was evaluated based on the appearance and then disappearance of the sulfoxide intermediate. Additionally, reaction progression was indicated by the voluminous precipitate that formed during the last 6 h of the 24 h reaction period. The mixture was diluted with brine (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) then filtered, and the solvent was removed in vacuo to afford 113 mg of clear oil. Flash chromatography (1 × 3 in. silica; hexanes−EtOAc 9:1 → 3:1) provided **14** (91 mg, 98%) as a colorless oil. $[\alpha]^{24}_D$ +13.4 (*c* 1.0, $CHCl_3$). FTIR (film, NaCl) 1498, 1340, 1153, 1044 cm^{-1}. ^1H NMR (500 MHz) δ 7.66 (m, 2 H), 7.59 (m, 3 H), 4.66 (t, *J* = 5.4 Hz, 1 H), 4.48 (dd, *J* = 5.7, 1.6 Hz, 1 H), 3.77 (dd, *J* = 7.4, 14.6 Hz, 1 H), 3.66 (dd, *J* = 7.0, 14.6 Hz, 1 H), 2.72 (m, 1 H), 2.16 (m, 1 H), 1.87 (m, 1 H), 1.79 (m, 1 H), 1.62 (m, 1 H), 1.41 (s, 3 H), 1.24 (s, 3 H). ^{13}C NMR (125 MHz) δ 153.7, 133.1, 131.6, 129.8, 125.2, 110.9, 85.0, 80.2, 57.5, 39.8, 30.9, 28.6, 26.5, 24.3. MS (ESI) *m*/*z* 387.1 (MNa$^+$, 100). HRMS (ESI) calcd for $C_{16}H_{20}N_4NaO_4S$ 387.1103 (MNa$^+$), found 387.1102.

(*S*,*E*)-Methyl 2-(Bis(*tert*-butoxycarbonyl)amino)-6-((3a*S*,4*S*,6a*R*)-2,2-dimethyltetra-hydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)hex-5-enoate (15). KHMDS in toluene (164 μL 0.5M, 82 μmol) was added dropwise to a solution of the sulfone **12** (25 mg, 68 μmol) in THF (3 mL) in an atmosphere of argon at −78 °C. The resulting yellow solution was stirred for 60 min followed by the dropwise addition of a solution of methyl (*S*)-5-oxo-2-di-*tert*-butoxycarbonylamino-pentaneoate (**7**; 43 mg, 123 μmol) in THF (2 mL). Approximately 15 min after the addition of the aldehyde, the yellow color became lighter. The reaction mixture was stirred for 1 h at −78 °C, warmed to rt, and stirred for an additional 20 h. The reaction mixture was quenched with satd. NH_4Cl solution (20 μL), stirred for 5 min, and diluted with ether (10 mL), then the layers were separated and the organic layer was washed with water (10 mL). The aqueous layer was extracted with ether (3 × 15 mL), the combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to afford a colorless oil that was purified by flash chromatography (EtOAc/hexane 1:9) to give the olefin derivative **15** as an oil (23 mg, 69%). Diastereomeric ratio (*E*:*Z*) = 9:1. ^1H NMR (500 MHz; $CDCl_3$) δ_H 5.47−5.39 (m, 1H), 5.37−5.31 (m, 0.9H), 5.23 (t, *J* = 10 Hz, 0.1H), 4.90−4.83 (m, 1H), 4.66−4.62 (m, 1H), 4.40−4.38 (m, 0.9H), 4.29−4.26 (m, 0.1H), 3.71 (s, 3H), 2.93−2.90 (m, 0.1H), 2.66−2.64 (m, 0.9H), 2.20−2.13 (m, 1H), 2.06−1.72 (m, 4H), 1.79−1.72 (m, 2H), 1.53−1.41 (m, 22H), 1.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 171.4, 152.2, 131.2, 129.3, 109.6, 85.9, 83.1, 57.5, 52.2, 47.6, 31.2, 29.8, 29.3, 28.2, 28.0, 26.4, 24.1. R_f 0.73 (EtOAc/hexane 3:7). MS (ESI) *m*/*z* (rel intensity) 506.2 ([M + Na]$^+$, 100). HRMS-ESI (*m*/*z*) calcd for $C_{25}H_{41}NO_8Na$ [M + Na]$^+$ 506.2730, found 506.2731.

(*S*)-2-((*S*,*E*)-5-(Bis(*tert*-butoxycarbonyl)amino)-6-methoxy-6-oxo-hex-1-enyl)pentanedioic Acid (16). Acetonide **15** (17 mg, 35 μmol) was dissolved in 50% AcOH (15 mL) at 0 °C and brought to rt, then the solution was stirred at rt for 15 h. The solvent was removed under reduced pressure. The crude reaction product (16 mg) was purified by flash chromatography (EtOAc/hexane 2:3) to afford the corresponding vicinal diol as a white solid (15 mg, 96%). **Diol:** ^1H NMR (500 MHz; $CDCl_3$) δ_H 5.52−5.46 (m, 1H), 5.33−5.29 (m, 1H), 4.92−4.85 (m, 1H), 4.12−4.07 (m, 1H), 3.71 (s, 3H), 3.61−3.54 (m, 1H), 3.24 (br s, 0.8H), 2.88−2.82 (m, 0.3H), 2.61−2.48 (m, 2H), 2.27−1.87 (m, 6H), 1.70−1.63 (m, 1H), 1.50 (s, 18H), 1.32−1.24 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 171.5, 152.4, 133.6, 133.1, 130.4, 130.3, 83.3, 83.2, 79.6, 78.7, 72.6, 72.4, 57.6, 56.9, 52.2, 47.2, 42.1, 30.4, 30.4, 29.8, 29.1, 28.8, 28.0, 27.4, 27.0. R_f 0.19 (EtOAc/hexane 2:3). MS (ESI) *m*/*z* (rel intensity) 466.2 ([M + Na]$^+$, 100).

The vicinal diol (19 mg, 42 μmol) was dissolved in THF/H_2O (v/v, 9/1, 3 mL) at rt and the mixture was stirred. $NaIO_4$ (47 mg, 219 μmol) was added to the above solution and stirring was continued for 20 h during which time a white precipitate was observed in the reaction mixture. TLC analysis showed the complete consumption of the starting material and formation of the desired product. The solvent was removed under reduced pressure, then the crude product was dissolved in DCM (12 mL) and washed with water (10 mL). The aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layer was dried over Na_2SO_4, then then solvent was removed under reduced pressure and dried under vacuum to obtain the desired α,γ-dialdehyde (17 mg). ^1H NMR (500 MHz; $CDCl_3$) δ_H 9.76 (br t, 1H), 9.54 (d, *J* = 1.5 Hz, 1H), 5.69−5.63 (m, 1H), 5.31−5.27 (m, 1H), 4.88−4.85 (m, 1H), 3.71

(36) Fieser, L. F.; Fieser, M. *Reagents for organic synthesis*; John Wiley & Sons, Inc.: New York, 1967; Vol. 1.

(s, 3H), 3.01−2.96 (m, 1H), 2.50 (t, $J = 7$ Hz, 2H), 2.17−1.23 (m, 24H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 201.4, 200.8, 171.2, 152.2, 152.1, 135.9, 124.3, 83.2, 57.3, 55.0, 52.2, 40.9, 29.6, 29.4, 28.0, 20.7. MS (ESI) *m/z* (rel intensity) 496.1 ([M + Na + MeOH]$^+$, 100).

The α,γ-dialdehyde (17 mg, 38 μmol) was dissolved in THF (2 mL) at 0 °C followed by addition of 2-methyl-2-butene (0.9 mL 2M). In a separate vial $NaClO_2$ (18 mg, 199 μmol), NaH_2PO_4 (5 mg, 41 μmol), and 2-methyl-2-butene (1.0 mL 2M) were dissolved in *t*-BuOH/H_2O (v/v, 7/3, 4 mL) at 0 °C. This solution was added dropwise to the reaction mixture at 0 °C, and the stirring was continued at 0 °C for 3 h. Excess $NaClO_2$ was quenched by addition of 2-propanol (1.0 mL). Solvents were removed under reduced pressure and the crude product was purified by flash chromatography (EtOAc/hexane 2:3, few drops of AcOH) to give the desired olefinated glutaric acid **16** as an oil (14 mg, 78%, two steps). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 5.63−5.57 (m, 1H), 5.50−5.39 (m, 1H), 4.88−4.84 (m, 1H), 4.04 (br s, 2H), 3.72 (br s, 3H), 3.37−3.36 (m, 1H), 3.01−2.97 (m, 1H), 2.32 (t, $J = 8$ Hz, 2H), 2.23−1.79 (m, 6H), 1.63−1.46 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 176.6, 175.9, 171.7, 152.3, 132.7, 131.8, 128.4, 83.9, 83.8, 58.0, 57.8, 52.4, 52.4, 31.7, 30.2, 29.8, 29.4, 28.0, 28.0, 27.4, 27.6, 27.4, 24.6. R_f 0.14 (EtOAC/hexane 2:3). MS (ESI) *m/z* (rel intensity) 496.1 ([M + Na]$^+$, 100).

(3*S*,8*S*,*E*)-Trimethyl 8-Aminooct-4-ene-1,3,8-tricarboxylate (17). The diacid **16** (39 mg, 82 μmol) was dissolved in MeOH (4 mL) and the mixture was cooled to 0 °C, followed by dropwise addition of Me_3SiCHN_2 (4.0 mL of a 2 M solution in diethyl ether) under continuous stirring. Initially when Me_3SiCHN_2 was added, the solution became yellow and then turned colorless. When all the Me_3SiCHN_2 was added the solution remained yellow. Stirring was continued at rt for 16 h, after which the reaction was quenched by addition of a few drops of HOAc. Solvent was removed under reduced pressure and the crude product (46 mg) was purified by flash chromatography (EtOAc/hexane 2:3) to give the corresponding trimethyl ester derivative as an oil (35 mg, 85%). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 5.60−5.55 (m, 1H), 5.45−5.34 (m, 1H), 4.87−4.83 (d, $J = 8.5$ Hz, 1H), 3.71−3.66 (m, 9H), 3.03−2.98 (m, 1H), 2.38−1.80 (m, 8H), 1.49 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 174.1, 173.4, 171.2, 152.1, 133.0, 127.6, 83.2, 83.1, 57.6, 52.2, 51.9, 51.6, 48.2, 31.4, 29.6, 29.1, 28.0, 27.2. R_f 0.66 (EtOAc/hexane 1:1). MS (ESI) *m/z* (rel intensity): 424.2 ([M − Boc + Na]$^+$, 100).

The trimethyl ester (44 mg, 87 μmol) was dissolved in THF (4 mL) and the mixture was cooled to 0 °C, followed by addition of Et_3SiH (2 mL) under stirring condition. Then CF_3COOH (6 mL) was added dropwise at 0 °C and stirring was continued at rt for 16 h. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography (EtOAc/hexane 4:1, ca. 2% Et_3N) to give the free amine derivative **17** as an oil (21 mg, 80%). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 5.59−5.53 (m, 1H), 5.46−5.35 (m, 1H), 3.72 (s, 3H), 3.66−3.64 (m, 6H), 3.45−3.43 (m, 1H), 3.04−2.99 (m, 1H), 2.33−2.29 (m, 2H), 2.17−2.02 (m, 3H), 1.88−1.78 (m, 2H), 1.65−1.59 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 176.4, 174.2, 173.4, 133.0, 133.3, 127.7, 127.5, 53.8, 52.01, 51.95, 51.91, 51.6, 48.2, 42.9, 34.2, 31.4, 31.2, 28.6, 27.4, 27.2, 23.8. R_f 0.17 (EtOAc/haxane 4:1). MS (ESI) *m/z* (rel intensity) 302.2 ([M + H]$^+$, 100), 324.2 [M + Na]$^+$.

(*S*,*E*)-Methyl 2-(Bis(*tert*-butoxycarbonyl)amino)-6-((3a*R*,4*R*,6a*S*)-2,2-dimethyltetra-hydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)hex-5-enoate (18). Sulfone **14** (11 mg, 30 μmol) was dissolved in THF (0.5 mL) under an atmosphere of argon and the mixture was cooled to −78 °C under stirring condition. KHMDS solution (80 μL, 0.5 M, 40 μmol) was added dropwise to the sulfone at −78 °C and stirring was continued for 15 min. The reaction mixture was then warmed to −50 °C and stirring was continued for 1 h, after which it was again cooled to −78 °C. A solution of methyl (*S*)-2-di-*tert*-butoxycarbonylaminopentaneoate (**7**; 20 mg, 57 μmol) in THF (1.3 mL) was added dropwise into the reaction mixture and stirring was continued at −78 °C for 3 h. The reaction solution was warmed to rt and stirring was continued for 12 h during which time a white precipitate was observed. The reaction was quenched with saturated NH_4Cl solution (200 μL). The aqueous layer was extracted with ether (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to afford a colorless oil that was purified by flash chromatography (EtOAc/hexane 1:9). Olefin derivative **18** was obtained as an oil (11 mg, 71%). Diastereomeric ratio (*E*:*Z*) = 4:1. ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 5.47−5.31 (m, 1.8H), 5.23 (t, $J =$ 11 Hz, 0.2H), 4.90−4.83 (m, 1H), 4.67−4.62 (m, 1H), 4.38 (d, J = 5.5 Hz, 0.8H), 4.28 (d, J = 5.5 Hz, 0.2H), 3.71 (s, 3H), 2.93−2.90 (m, 0.2H), 2.70−2.62 (m, 0.8H), 2.26−1.70 (m, 8H), 1.64−1.40 (m, 21H), 1.30−1.18 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.3, 152.1, 131.1, 130.7, 129.8, 129.2, 109.5, 86.6, 85.8, 83.0, 80.7, 80.6, 57.6, 57.4, 52.1, 47.4, 43.3, 31.4, 31.2, 29.9, 29.8, 29.6, 29.4, 29.3, 28.0, 27.9, 26.4, 24.3, 24.0. R_f 0.73 (EtOAc/hexane 3:7). MS (ESI) *m/z* (rel intensity) 506.2 ([M + Na]$^+$, 100). HRMS-ESI (*m/z*) calcd for $C_{25}H_{41}NO_8Na$ [M + Na]$^+$ 506.2730, found 506.2731.

(*R*)-2-((*S*,*E*)-5-(Bis(*tert*-butoxycarbonyl)amino)-6-methoxy-6-oxohex-1-enyl)pentanedioic Acid (19). Acetonide **18** (75 mg, 155 μmol) was dissolved in 50% AcOH (40 mL) at rt, and then the solution was stirred at rt for 11 h. The solvent was removed under reduced pressure. The crude reaction product (72 mg) was purified by flash chromatography (EtOAc/hexane 2:3) to afford the corresponding vicinal diol as an oil (57 mg, 83%). **Diol:** ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 5.50−5.42 (m, 1H), 5.36−5.30 (m, 1H), 4.96−4.92 (m, 0.8H), 4.84−4.81 (m, 0.2H), 4.14−4.06 (m, 1H), 3.71 (s, 3H), 3.63−3.59 (m, 1H), 3.35 (br d, 0.8H), 2.91−2.82 (m, 0.3H), 2.61 (br s, 0.7H), 2.54−2.45 (m, 1H), 2.34−1.64 (m, 7H), 1.50 (br s, 18H), 1.39−1.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.4, 152.1, 133.4, 133.3, 130.7, 130.3, 83.5, 83.4, 79.8, 78.8, 72.6, 72.6, 57.4, 57.2, 52.2, 52.2, 47.3, 42.1, 30.3, 30.3, 29.8, 29.5, 29.3, 28.0, 28.0, 27.5, 27.2, 24.4. R_f 0.19 (EtOAc/hexane 2:3). MS (ESI) *m/z* (rel intensity) 466.2 ([M + Na]$^+$, 100).

The vicinal diol (96 mg, 216 μmol) was dissolved in THF/H_2O (v/v, 9/1, 3 mL) at rt and $NaIO_4$ (232 mg, 1.08 mmol) was added with stirring. After 1 h and 30 min, additional $NaIO_4$ (231 mg, 1.07 mmol) was added and stirring was continued for 45 min during which time a white precipitate was observed in the reaction mixture. TLC analysis showed the complete consumption of the starting material and formation of the desired product. The solvent was removed under reduced pressure, then the crude product was dissolved in DCM (25 mL) and washed with water (20 mL). The aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the layer was dried under vacuum to obtain the crude α,γ-dialdehyde as an oil (93 mg). ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 9.77 (br t, 1H), 9.54 (d, $J = 1.5$ Hz, 1H), 5.68−5.60 (m, 1H), 5.32−5.21 (m, 1H), 4.88−4.81 (m, 1H), 3.71 (s, 3H), 3.40−3.30 (m, 0.2H), 3.01−2.96 (m, 0.8H), 2.60−1.23 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 201.4, 200.7, 171.2, 152.1, 135.9, 124.9, 83.2, 57.3, 55.0, 52.2, 40.8, 29.5, 29.4, 28.2, 27.9, 20.7. MS (ESI) *m/z* (rel intensity) 496.1 ([M + Na + MeOH]$^+$, 100). HRMS-ESI (*m/z*) [M + Na + MeOH]$^+$ calcd for $C_{23}H_{39}NO_9Na$ 496.2523, found 464.2260 [M + Na]$^+$.

The crude α,γ-dialdehyde (93 mg, 0.21 mmol) was dissolved in THF (4 mL) at 0 °C followed by addition of 2-methyl-2-butene (3 mL, 2 M). In a separate vial $NaClO_2$ (196 mg, 2.16 mmol), NaH_2PO_4 (52 mg, 0.43 mmol), and 2-methyl-2-butene (1.0 mL 2M) were dissolved in *t*-BuOH/H_2O (v/v, 1/1, 2 mL) at 0 °C. This solution was added dropwise to the reaction mixture at 0 °C, and the stirring was continued at 0 °C. After 2 h a solution of $NaClO_2$ (98 mg, 1.08 mmol), NaH_2PO_4 (25 mg, 0.20 mmol), and 2-methyl-2-butene (0.8 mL, 2 M) in *t*-BuOH/H_2O (v/v, 1/1, 1 mL) was added to the reaction mixture. Stirring was continued at 0 °C for an additional 1 h and 15 min. Excess $NaClO_2$ was quenched by addition of 2-propanol (4.0 mL) and stirring the reaction for 30

min. Solvents were removed under reduced pressure and the crude product was purified by flash chromatography (EtOAc/hexane 1:1, ca. 2% AcOH) to give the desired olefinated glutaric acid **19** as an oil (94 mg, 94%, two steps). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 5.63−5.58 (m, 1H), 5.53−5.44 (m, J = 15.3 Hz, 1H), 4.86−4.83 (m, 1H), 3.71 (s, 3H), 3.43−3.39 (m, 0.2H), 3.07−3.03 (m, 0.8H), 2.51−1.82 (m, 8H), 1.53 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 179.4, 178.7, 171.3, 152.2, 133.2, 127.4, 83.5, 83.3, 57.5, 52.2, 48.1, 31.6, 29.4, 29.1, 28.0, 27.4. R_f 0.14 (EtOAC/hexane 2:3). MS (ESI) m/z (rel intensity) 496.1 ([M + Na]$^+$, 100). HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{22}H_{35}NO_{10}Na$ 496.2159, found 496.2159.

(3*R*,8*S*,*E*)-Trimethyl 8-Aminooct-4-ene-1,3,8-tricarboxylate (20). The diacid **19** (91 mg, 192 μmol) was dissolved in MeOH (4 mL) and the mixture was cooled to 0 °C, followed by dropwise addition of Me_3SiCHN_2 (5.0 mL of a 2 M solution in diethyl ether) under continuous stirring. Initially when Me_3SiCHN_2 was added, the solution became yellow and then turned colorless. When all the Me_3SiCHN_2 was added the solution remained yellow. Stirring was continued at rt for 17 h, after which the reaction was quenched by addition of a few drops of HOAc. Solvent was removed under reduced pressure and the crude product (107 mg) was purified by flash chromatography (EtOAc/hexane 2:30) to give the corresponding trimethyl ester derivative as an oil (80 mg, 83%). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 5.62−5.53 (m, 1H), 5.45−5.35 (m, 1H), 4.88−4.83 (m, 1H), 3.71−3.66 (s, 9H), 3.39−3.34 (m, 0.2H), 3.03−2.98 (m, 0.8H), 2.38−1.80 (m, 8H), 1.50 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.2, 173.4, 171.3, 152.2, 133.0, 127.7, 83.2, 83.1, 57.5, 52.2, 51.9, 51.6, 48.2, 31.4, 29.6, 29.6, 29.1, 28.0, 27.2. R_f 0.66 (EtOAc/hexane 1:1). MS (ESI) (rel intensity) m/z 424.2 ([M − Boc + Na]$^+$, 100). HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{24}H_{39}NO_{10}Na$ 524.2472, found 524.2485.

The trimethyl ester (44 mg, 87 μmol) was dissolved in THF (4 mL) and the mixture was cooled to 0 °C, followed by addition of Et_3SiH (2 mL) with stirring, after which excess CF_3COOH was added dropwise at 0 °C and stirring was continued at rt for 16 h. Solvent was removed under reduced pressure and the crude product was purified by flash chromatography (EtOAc/hexane 4:1, ca. 2% Et_3N) to give the free amine derivative **20** as an oil (22 mg, 84%). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 5.59−5.53 (m, 1H), 5.46−5.5.35 (m, 1H), 3.73−3.67 (s, 9H), 3.45−3.42 (m, 1H), 3.04−2.99 (m, 1H), 2.33−2.17 (m, 2H), 2.16−2.02 (m, 3H), 1.88−1.79 (m, 2H), 1.65−1.57 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 176.4, 174.2, 173.4, 133.1, 127.7, 53.8, 52.0, 51.9, 51.6, 48.2, 42.9, 34.2, 31.4, 29.7, 28.6, 27.2, 23.8. R_f 0.17 (EtOAc/haxane 4:1). MS (ESI) m/z (rel intensity): 302.2 ([M + H]$^+$, 100).

(3*S*,8*S*,*E*)-Trimethyl 8-(4-(Methylamino)benzamido)oct-4-ene-1,3,8-tricarboxylate (22). Et_3N (0.12 mL) was added to a stirred solution of the *N*-methyl *p*-aminobenzoic acid HOBt ester (**21**; 24 mg, 86 μmol) and amine derivative **17** (26 mg, 86 μmol) in THF (4 mL) at 0 °C in an atmosphere of argon. The reaction was warmed to rt and stirring was continued for 26 h, after which time additional **21** (24 mg) and Et_3N (0.2 mL) were added and stirring continued for 24 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (EtOAc/hexane 1:1) to give pure product **22** as an oil (27 mg, 73%). ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 7.71−7.65 (m, 2H), 6.64−6.51 (m, 3H), 5.61−5.52 (m, 1H), 5.45−5.33 (m, 1H), 4.84−4.79 (m, 1H), 4.16 (br s, 1H), 3.77−3.63 (s, 9H), 3.40−3.34 (m, 0.2H), 3.03−2.97 (m, 0.8H), 2.87 (s, 3H), 2.32−1.80 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.1, 173.4, 173.3, 166.8, 152.1, 132.7, 132.6, 128.9, 128.8, 127.8, 127.6, 121.7, 111.3, 52.4, 52.4, 52.0, 52.0, 51.9, 51.6, 48.2, 43.0, 32.3, 32.2, 31.4, 31.2, 30.2, 28.3, 27.3, 27.1. R_f 0.61 (EtOAc/hexane 4:1). MS (ESI) m/z (rel intensity) 457.2 ([M + Na]$^+$, 100).

(2*S*)-Dimethyl 2-(3-((*S*)-4-Methoxy-4-oxo-3-(4-(2,2,2-trifluoro-*N*-methylacetamido)benzamido)butyl)oxiran-2-yl)pentanedioate (23). The *N*-Me-*p*AB-olefinic isostere **22** (27 mg, 62 μmol) was dissolved in THF (2 mL) in an atmosphere of argon, and the mixture was cooled to −70 °C and stirred. Then Et_3N (500 μL, 3.6 mmol) was added to the above solution followed by dropwise addition of $(CF_3CO)_2O$ (40 μL, 290 μmol) at −70 °C. Stirring was continued for 1.5 h after which the reaction temperature was allowed to rise to 0 °C. When TLC analysis showed the complete consumption of the starting material (10 h), solvent was removed and the crude product was purified by flash chromatography (EtOAc/hexane 1:1) to give pure *N*-Tfa derivative as an oil (20 mg, 62%). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.96−7.87 (m, 2H), 7.35−7.34 (m, 2H), 6.72−6.71 (br d, 0.8H), 5.61−5.54 (m, 1H), 5.47−5.35 (m, 1H), 4.85−4.79 (m, 1H), 3.80−3.79 (s, 3H), 3.67−3.62 (m, 6H), 3.37 (br s, 3H), 3.04−2.99 (m, 1H), 2.32−1.80 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 174.0, 173.3, 172.8, 165.7, 134.5, 132.3, 132.2, 131.9, 128.7, 128.6, 128.3, 128.2, 127.8, 127.7, 52.6, 52.4, 52.3, 52.2, 52.1, 52.0, 51.7, 48.13, 43.06, 39.6, 32.0, 31.7, 31.4, 31.2, 28.3, 27.3, 27.1, 23.5. R_f 0.44 (EtOAc/hexane 3:2). MS(ESI) m/z (rel intensity) 553.17 ([M + Na]$^+$, 100).

The *N*-Tfa-*N*-Me-pAB-olefin isostere, prepared as described directly above (15 mg, 11 μmol), was dissolved in DCM (2 mL), and the mixture was cooled to 0 °C under stirring condition. Then $NaHCO_3$ (7 mg, 84 μmol) was added followed by mCPBA (12 mg, 70 μmol) at 0 °C. Stirring was continued at rt for 24 h. TLC and MS analysis showed the complete consumption of the starting material and formation of the product. The reaction mixture was filtered through Celite and Na_2SO_4 with a Pasteur pipet and the crude product was purified by flash chromatography (EtOAc/hexane 7:3, 1% Et_3N) to give the desired epoxide **23** as an oil (12 mg, 80%). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.97−7.88 (m, 2H), 7.35 (br s, 2H), 4.91−4.82 (m, 1H), 3.81−3.62 (s, 9H), 3.37 (s, 3H), 3.18−2.83 (m, 3H), 2.48−1.83 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 172.9, 172.8, 172.4, 172.3, 165.8, 156.6, 143.6, 134.3, 128.65, 128.58, 127.6, 58.7, 58.5, 58.4, 57.6, 57.3, 57.1, 57.0, 56.1, 52.7, 52.2, 52.1, 51.77, 51.68, 47.18, 47.15, 39.6, 31.4, 31.3, 29.7, 29.3, 28.7, 27.6, 25.0, 23.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −67.01, −70.04, −75.68. R_f 0.51 (EtOAc/hexane 4:1). MS (ESI) m/z 569.1 (rel intensity) ([M + Na]$^+$, 100). HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{24}H_{29}F_3N_2O_9Na$ 569.1723, found 569.1723.

(3*R*,8*S*,*E*)-Trimethyl 8-(4-(Methylamino)benzamido)oct-4-ene-1,3,8-tricarboxylate (24). Et_3N (1.5 mL) was added to a stirred solution of the *N*-methyl *p*-aminobenzoic acid HOBt ester (**21**; 59 mg, 219 μmol) and amine derivative **20** (22 mg, 73 μmol) in THF (1.5 mL) at 0 °C in an atmosphere of argon. The reaction was warmed to rt and stirring was continued for 48 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (EtOAc/hexane 1:1) to give pure product **24** as an oil (21 mg, 68%). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.72−7.66 (m, 2H), 6.58−6.56 (m, 2H), 6.50−6.49 (br d, 1H), 5.57−5.50 (m, 1H), 5.50−5.30 (m, 1H), 4.90−4.80 (m, 1H), 3.77−3.66 (s, 9H), 3.42−3.40 (m, 0.2H), 3.02−2.98 (m, 0.9H), 2.88 (s, 3H), 2.33−1.80 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.1, 173.4, 173.0, 166.8, 152.1, 132.7, 132.6, 128.9, 128.8, 127.9, 127.8, 121.7, 111.4, 111.3, 52.44, 52.39, 51.97, 51.93, 51.90, 51.70, 51.63, 48.2, 32.3, 31.4, 31.1, 30.3, 30.0, 29.7, 28.3, 27.24, 27.15. R_f 0.61 (EtOAc/hexane 4:1). MS (ESI) m/z (rel intensity) 457.2 ([M + Na]$^+$, 100). HRMS-ESI m/z [M + Na]$^+$ calcd for $C_{22}H_{30}N_2O_7Na$ 457.1951, found 457.1942.

(2*R*)-Dimethyl 2-(3-((*S*)-4-methoxy-4-oxo-3-(4-(2,2,2-trifluoro-*N*-methylacetamido)benzamido)butyl)oxiran-2-yl)pentanedioate (25). The *N*-Me-*p*AB-olefinic isostere **24** (21 mg, 47 μmol) was dissolved in THF (3.5 mL) in an atmosphere of argon, and the mixture was cooled to 0 °C and stirred. Then Et_3N (68 μL, 470 μmol) was added to the above solution followed by dropwise addition of $(CF_3CO)_2O$ (67 μL, 470 μmol) at 0 °C. Stirring was continued for 10 h. TLC analysis showed the complete consumption of the starting material. Solvent was removed and the crude product was purified by flash chromatography (EtOAc/hexane 1:1) to give pure *N*-Tfa derivative as an oil (19 mg, 76%). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.97 (d, J = 8.5 Hz, 0.4H), 7.90−7.88 (m, 1.7H), 7.35 (d, J = 7.5 Hz, 2H), 7.10 (br d, 0.2H), 6.73 (br d, 0.9H), 5.64−5.54 (m, 1H), 5.48−5.36 (m, 1H), 4.85−4.75 (m, 1H), 3.80−3.63 (s, 9H), 3.37 (br s, 3H),

3.04−2.99 (m, 1H), 2.35−1.80 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.1, 173.3, 172.79, 172.76, 165.7, 132.3, 132.2, 132.1, 128.8, 128.6, 128.3, 128.2, 127.1, 127.6, 64.2, 52.7, 52.6, 52.3, 52.2, 52.05, 51.95, 51.73, 51.67, 48.1, 42.7, 39.6, 32.0, 31.7, 31.4, 31.0, 28.3, 27.24, 27.15, 23.8. R_f 0.44 (EtOAc/hexane 3:2). MS (ESI) *m*/*z* (rel intensity): 553.1 ([M + Na]$^+$, 100). HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{24}H_{29}F_3N_2O_8Na$ 553.1774, found 553.1774.

The *N*-Tfa-*N*-Me-pAB-olefin isostere, prepared as described directly above (18 mg, 33 μmol), was dissolved in DCM (3 mL), and the mixture was cooled to 0 °C under stirring condition. Then $NaHCO_3$ (18 mg, 132 μmol) was added followed by mCPBA (19 mg, 85 μmol) at 0 °C. The reaction was allowed to warm to rt. Stirring was continued at rt for 48 h. TLC and MS analysis showed the complete consumption of the starting material and formation of the product. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with $NaHCO_3$ solution (3 × 10 mL) and water (2 × 10 mL). The organic layer was dried over Na_2SO_4 and the crude product was purified by flash chromatography (EtOAc/hexane 3:2, 1% Et_3N) to give the desired epoxide **25** as an oil (18 mg, 97%). ^{1}H NMR (500 MHz; $CDCl_3$) δ_H 7.96−7.89 (m, 2H), 7.35−7.30 (m, 2H), 7.08−7.05 (m, 0.4H), 6.87 (br d, 0.7H), 6.59 (br d, 0.2H), 4.90−4.83 (m, 1H), 3.81−3.58 (s, 9H), 3.37 (s, 3H), 3.19−2.83 (m, 3H), 2.47−1.44 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.0, 172.9, 172.5, 172.4, 165.8, 128.8, 128.6, 127.7, 59.0, 58.7, 58.4, 57.7, 57.34, 57.26, 57.1, 57.0, 52.8, 52.2, 51.8, 51.7, 47.19, 47.16, 43.5, 39.6, 31.4, 31.3, 30.6, 28.8, 28.6, 27.6, 25.0, 24.3, 23.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −67.02, −70.05. R_f 0.51 (EtOAc/hexane 4:1). MS (ESI) *m*/*z* (rel intensity): 569.1 ([M + Na]$^+$, 100). HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{24}H_{29}F_3N_2O_9Na$ 569.1723, found 569.1711.

(2*S*)-2-(3-((*S*)-3-Carboxy-3-(4-(methylamino)benzamido)propyl)oxiran-2-yl)pentanetrioic Acid (4). The epoxide derivative **23** (3 mg, 5.49 μmol) was dissolved in MeOH (2 mL) under stirring condition and LiOH·H_2O (0.21 mL of a 0.1 M solution, 22 μmol) was added dropwise at rt. The reaction mixture was continuously stirred at rt, during which time additional LiOH was added in portions while the reaction progress was monitored carefully by MS analysis, which confirmed formation of the desired tricarboxylate derivative **4**. After 7 days, solvent was removed under reduced pressure and high vacuum to provide the desired product as a solid (5 mg, quantitative yield). ^{1}H NMR (600 MHz; CD_3OD) δ_H 7.69−7.66 (m, 2H), 6.59−6.57 (m, 2H), 4.47−4.40 (m, 1H), 2.80 (s, 3H), 2.65−1.59 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 182.8, 182.7, 179.64, 179.60, 176.0, 169.7, 169.6, 161.7, 154.5, 141.1, 134.0, 130.1, 122.4, 122.2, 119.4, 117.4, 115.5, 112.2, 112.0, 69.2, 56.8, 56.7, 56.5, 52.7, 50.5, 50.02, 49.98, 45.1, 39.0, 37.4, 31.0, 30.3, 30.1. HRMS-ESI (*m*/*z*) [M − H]$^-$ calcd for $C_{19}H_{23}N_2O_8$ 407.1460, found 407.1469).

(2*R*)-2-(3-((*S*)-3-Carboxy-3-(4-(methylamino)benzamido)propyl)oxiran-2-yl)pentanetrioic Acid (5). The epoxide derivative **25** (2 mg, 3.66 μmol) was dissolved in MeOH (2 mL) under stirring condition and LiOH·H_2O (0.14 mL of a 0.1 M solution, 14 μmol) was added dropwise at rt. The reaction mixture was continuously stirred at rt, during which time additional LiOH was added in portions while the reaction progress was monitored carefully by MS analysis, which confirmed formation of the desired tricarboxylate derivative **5**. After 7 days, solvent was removed under reduced pressure and high vacuum to afford the desired product as a solid (3 mg, quantitative yield). ^{1}H NMR (600 MHz; CD_3OD) δ_H 7.70−7.66 (m, 2H), 6.58 (d, J = 8.4 Hz, 2H), 4.48−4.40 (m, 1H), 2.80 (s, 3H), 2.63−1.59 (m, 8 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 182.8, 182.7, 176.9, 169.7, 161.7, 154.5, 141.1, 138.0, 130.1, 122.4, 112.2, 112.0, 69.2, 56.7, 52.8, 50.5, 50.02, 49.97, 39.0, 37.4, 34.8, 31.0, 30.3, 30.1. HRMS-ESI (*m*/*z*) [M − H]$^-$ calcd for $C_{19}H_{23}N_2O_8$ 407.1460, found 407.1454.

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Supporting Information Available: General Experimental Procedures, synthesis of 5-(((3a*S*,4*S*,6a*R*)-2,2-dimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)methylsulfonyl)-1-phenyl-1*H*-tetrazole (*cis*-**14**), ORTEP plot of compound *cis*-**14** and X-ray crystallographic data, synthesis of the HOBt ester of 4-(*N*-methyl)aminobenzoic acid (**21**), synthesis of *N*-Tfa, methyl ester precursors, **S3** and **S6**, and of terminal epoxide derivatives, **2b** and **1b**, and ^{1}H NMR and ^{13}C NMR spectra for all compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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