Modification of C-Terminal Peptides to Form Peptide Enamides: Synthesis of Chondriamides A and C

Xiang Wang and John A. Porco, Jr.*

Department of Chemistry and Center for Streamlined Synthesis, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

porco@chem.bu.edu

Received May 29, 2001

Introduction

Enamides have been studied extensively as synthons in organic synthesis and have been used prominently in the preparation of heterocycles[1] and in asymmetric synthesis.[2] These functional groups are stable under neutral or basic conditions, but with Brønsted acids, they undergo protonation to form *N*-acyliminium ions that may react with oxygen, sulfur, or π-based nucleophiles.[3] Recently, there has been renewed interest in the synthesis of enamides due to the isolation and potent antitumor activity of the salicylate antitumor macrolides (cf. oximidine II[4] (**1**) and salicylihalamides A[5] (**2**) and B (**3**), Figure 1), which contain highly unsaturated enamide side chains. As part of a general program toward the synthesis of enamide-containing natural products, we recently reported the synthesis of enamides related to the salicylate antitumor macrolides lobatamides[6] and oximidines[4] using copper(I)-carboxylate-catalyzed substitution of vinyl iodides and amides.[7] An additional class of bioactive enamide natural products that has attracted our attention are the linear and cyclic peptide enamides, representative members of which are shown in Figure 1. Frangufoline (**4**) is a cyclopeptide alkaloid[8] with sedative and antiinflammatory properties that has been reported to bind to multiple sites on calmodulin.[9] Chondriamide A (**5**) shows cytotoxicity against KB and LOVO cells and antiviral activity against HSV II.[10] Chondriamide C (**6**) is a bis-indole-containing marine natural product that shows both cytotoxicity and anthelmintic activity.[11] Terpeptin (**7**) is a novel peptide recently isolated from *Aspergillus terreus* that inhibits the cell cycle at the G2/M phase.[12] Due to the presence of numerous amide functional groups in these molecules, we considered alternatives to vinyl halide amidation[7] developed in our laboratories to access natural and unnatural compounds in this class. Since all of the compounds contain unsaturated enamides derived from aromatic amino acid residues, we reasoned that modification of C-terminal peptides by an oxidative decarboxylation-elimination process could be implemented to produce natural and unnatural peptide enamides from readily available peptide precursors (Figure 2). The overall (and possibly biomimetic) process is analogous to known enzymatic posttranslational, oxidative decarboxylation reactions such as the EpiD flavoprotein-catalyzed oxidative decarboxylation of peptidyl cysteines.[13] Although decarboxylation of dehydroamino acids has been utilized to prepare enamides[14] and β-elimination reactions have been used to produce enamides and related compounds,[15] synthesis of peptide enamides from tandem oxidative decarboxylation-elimination of C-terminal amino acids is underdeveloped.[16] Herein, we report general protocols for the synthesis of peptide enamides from C-terminal peptides and application of this methodology to the synthesis of the cytotoxic indole-enamide natural products chondriamides A and C.

Results and Discussion

Our first plan was to examine the elimination chemistry of *O*-acetyl-*N*-acyl-*N*,*O*-acetals, which are readily available from oxidative decarboxylation of *N*-acyl-α-

(1) (a) Ninomiya, I. *Heterocycles* **1980**, *14*, 1567. (b) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron* **2000**, *56*, 3941. (c) Baker, S. R.; Burton, K. I.; Parsons, A. F.; Pons, J.; Wilson, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 427. (d) Brodney, M. A.; Padwa, A. *J. Org. Chem.* **1999**, *64*, 556. (e) Okano, T.; Sakaida, T.; Eguchi, S. *J. Org. Chem.* **1996**, *61*, 8826. (f) Schultz, A. G.; Guzzo, P. R.; Nowak, D. M. *J. Org. Chem.* **1995**, *60*, 8044.

(2) (a) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *95*, 6429. (b) Becker, Y.; Eisenstadt, A.; Stille, J. K. *J. Org. Chem.* **1980**, *45*, 2145. (c) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125. (d) Gilbertson, S. R.; Chang, C. T. *J. Org. Chem.* **1995**, *60*, 6226. (e) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 9590.

(3) For reviews on *N*-acyliminium ion chemistry, see: (a) Zaugg, H. E. *Synthesis* **1984**, 85 and 181. (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (c) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(4) (a) Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153. (b) For recent synthetic studies regarding the enamide side chain, see: Kuramochi, K.; Kouji, W.; Watanabe, H.; Kitahara, T. *Synlett* **2000**, 397. (c) Raw, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 10357.

(5) (a) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188. (b) For revision of the absolute configuration of salicylihalamide, see: Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 4308.

(6) McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, J. H., II; Laakso, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805.

(7) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333.

(8) "*Cyclopeptide Alkaloids*" *in Progress in the Chemistry of Organic Natural Products*; Gournelis, D. C., Laskaris, G. G., Verpoorte, R., Eds.; Springer: New York, 1998; p 1.

(9) Han, Y. N.; Kim, G.-Y.; Hwang, K. H.; Han, B. H. *Arch. Pharm. Res.* **1993**, *16*, 289.

(10) Palermo, J. A.; Flower, P. B.; Seldes, A. M. *Tetrahedron Lett.* **1992**, *33*, 3097.

(11) Davyt, D.; Entz, W.; Fernandez, R.; Mariezcurrena, R.; Mombru, A. W.; Saldana, J.; Dominguez, L.; Coll, J.; Manta, E. *J. Nat. Prod.* **1998**, *61*, 1560.

(12) Kagamizono, T.; Sakai, N.; Arai, K.; Kobinata, K.; Osada, H. *Tetrahedron Lett.* **1997**, *38*, 1223.

(13) Kempter, C.; Kupke, T.; Kaiser, D.; Metzger, J. W.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2104.

(14) (a) Schmidt, U.; Lieberknecht, A. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 550. (b) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Bokens, H. *Liebigs Ann. Chem.* **1985**, 785.

(15) (a) Schmidt, U.; Lieberknecht, A.; Bokens, H.; Griesser, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1026. (b) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Boekens, H. *Tetrahedron Lett.* **1982**, *23*, 4911. (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697. (d) Schmidt, U.; Lieberknecht, A.; Boekens, H.; Griesser, H. *J. Org. Chem.* **1983**, *48*, 2680. (e) Schmidt, U.; Schanbacher, U. *Liebigs Ann. Chem.* **1984**, 1205. (f) Schmidt, U.; Schanbacher, U. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 152. (g) Berthon, L.; Uguen, D. *Tetrahedron Lett.* **1985**, *26*, 3975. (h) Schmidt, U.; Zaeh, M.; Lieberknecht, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1002. (i) Katritzky, A. R.; Ignatchenko, A. V.; Lang, H. *Synth. Commun.* **1995**, *25*, 1197. (j) Johnson, A. P.; Luke, R. W. A.; Boa, A. N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 895. (k) Xiao, D.; Stephen, P.; Joullie, M. M. *Tetrahedron Lett.* **1998**, *39*, 9631. (l) Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem.* **1999**, *64*, 6646. (m) Laib, T.; Bois-Choussy, M.; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 7645. (n) Labrecque, D.; Charron, S.; Rej, R.; Blais, C.; Lamothe, S. *Tetrahedron Lett.* **2001**, *42*, 2645.

(16) For an example, see: Harding, K. E.; Liu, L. T.; Farrar, D. G.; Coleman, M. T.; Tansey, S. K. *Synth. Commun.* **1991**, *21*, 1409.

10.1021/jo0158027 CCC: $20.00
Published on Web 10/31/2001

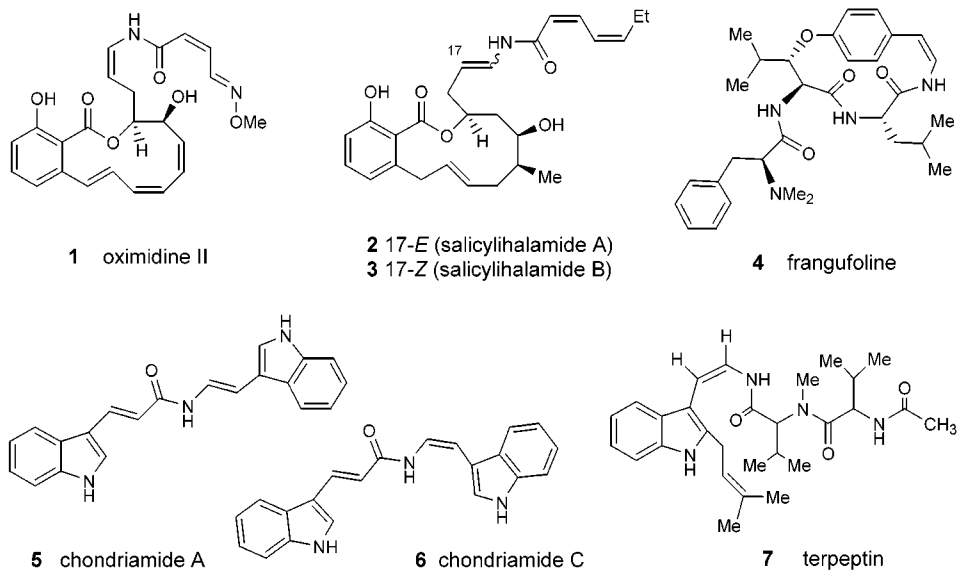


Figure 1. Representative enamide natural products.

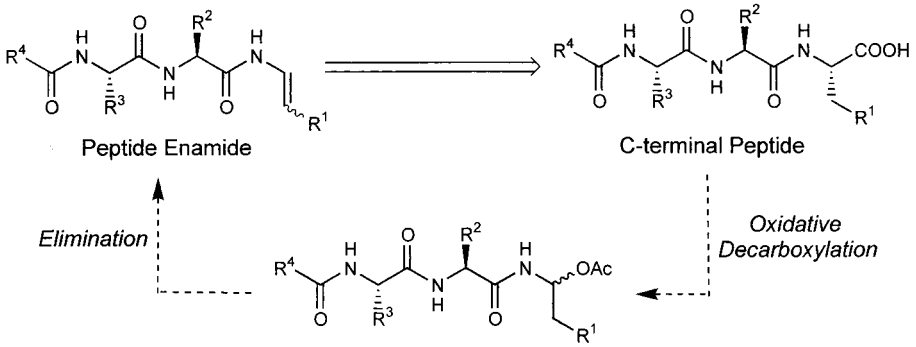
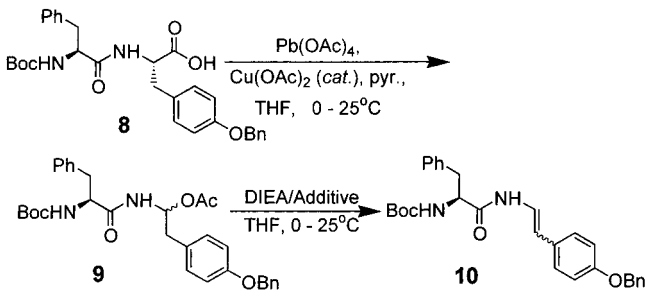


Figure 2. Chemical modification of C-terminal peptides to form peptide enamides.

amino acids.[17] In preliminary experiments, dipeptide substrates related to natural products **4**−**7** containing C-terminal tyrosine and tryptophan moieties were evaluated. Treatment of C-terminal dipeptide **8** with lead tetraacetate led to efficient formation of **9** as a 1:1 mixture of acetal diastereomers (Scheme in Table 1).[16] Using the Argonaut FirstMate synthesizer,[18] we evaluated the effect of Lewis acid additives on the elimination of **9** using diisopropylethylamine (DIEA) as a base (Table 1). Using $La(OTf)_3$, $ZnBr_2$, and $LiClO_4$ as additives, we identified $LiClO_4$ (1.2 equiv, entry 4) as a useful additive for high conversion to enamide **10**.[19] Using this general condition, we found that a number of crude *N*,*O*-acetals **12** may be cleanly eliminated to form enamides **13** by sequential addition of lithium perchlorate ($LiClO_4$) and DIEA (THF, 0−25 °C). In the case of C-terminal tryptophan derivatives, protection of the indole with the *p*-toluenesulfonamide protecting group[20] (entries 3 and 4, Table 2) was found to be optimal for protection against oxidative degradation[21] relative to *Nin*-Boc protection (entry 2, Table 2).[22] Interestingly, protected tryptophan

Table 1. Parallel Evaluation of Additives in Elimination of *N*,*O*-Acetal 9



entry	additive	ratio (Z:E)[a]	yield (%)[b]
1	none	1.1:1	24
2	$ZnBr_2$ (1.2 equiv)	1:3	23
3	$La(OTf)_3$ (1.2 equiv)	1:11	14
4	$LiClO_4$ (1.2 equiv)	1:1.1	87
5	$LiClO_4$ (10 equiv)	1:−	45

[a] Determined by ^1H NMR integration. [b] Isolated yield.

(17) (a) Gledhill, A. P.; McCall, C. J.; Threadgill, M. D. *J. Org. Chem.* **1986**, *51*, 3196. (b) Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P.; Berner, H.; Schneider, H. *Helv. Chim. Acta* **1989**, *72*, 401. (c) Corcoran, R. C.; Green, J. M. *Tetrahedron Lett.* **1990**, *31*, 6827. (d) Apitz, G.; Steglich, W. *Tetrahedron Lett.* **1991**, *32*, 3163. (e) Apitz, G.; Jäger, M.; Jaroch, S.; Kratzel, M.; Schäeffeler, L.; Steglich, W. *Tetrahedron* **1993**, *49*, 8223. (f) Steglich, W.; Jäger, M.; Jaroch, S.; Zistler, P. *Pure Appl. Chem.* **1994**, *66*, 2167. (g) Osada, S.; Fumoto, T.; Kodama, H.; Kondo, M. *Chem. Lett.* **1998**, 675. (h) Boto, A.; Hernandez, R.; Suarez, E. *J. Org. Chem.* **2000**, *65*, 4930.

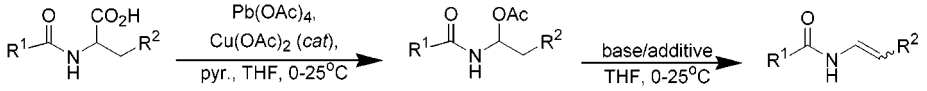
(18) Argonaut Technologies FirstMate. http://www.argotech.com/firstmate (accessed Oct 18, 2001).

(19) For the use of DBU/$LiClO_4$ to prepare dehydroalanine-containing peptides by elimination of acetic acid from *O*-acetylserine residues, see: Sommerfeld, T. L.; Seebach, D. *Helv. Chim. Acta.* **1993**, *76*, 1702.

(20) For a review of sulfonamide protection of indoles, see: Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915.

(21) For related use of the *Nin*-diphenylphosphinothioyl protecting group to prevent oxidative destruction of the indole nucleus, see: Kiso, Y.; Kimura, T.; Shimokura, M.; Narukami, T. *J. Chem. Soc., Chem. Commun.* **1988**, 287.

Table 2. Synthesis of Peptide Enamides from C-Terminal Tyrosine and Tryptophan Substrates

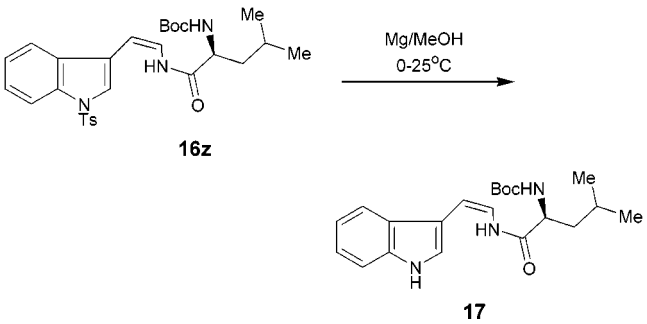


11 12 13

entry	substrate	base/additive	ratio (Z:E)	product	yield (%)[a]
1	Boc-L-Leu-L-Tyr(OBn)-OH	DIEA/$LiClO_4$	0.9:1	**14**	80
2	Boc-L-Leu-L-Trp(*Nin*-Boc)-OH	DIEA/$LiClO_4$	7:1	**15**	33
3	Boc-L-Leu-L-Trp(*Nin*-Ts)-OH	DIEA/$LiClO_4$	12:1	**16**	64
4	Boc-L-Leu-L-Trp(*Nin*-Ts)-OH	DBU/---	8:1	**16**	55

[a] Isolated yield, average of two runs.

Scheme 1. Reductive Detosylation of Indole Enamide 16Z



16z 17

substrates (entries 2−4, Table 2) afforded high *Z*-enamide selectivity (7−12:1 Z:E). Similar selectivity was found using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base (entry 4, Table 2) indicating that the enamide stereoselectivity was not related to the use of lithium salt additives. Treatment of **16Z** with excess Mg in methanol[23] (25 °C, 0.5 h) led to efficient formation of **17** (100% yield) (Scheme 1) verifying the chemical and configurational stabilities of the enamide product to reductive detosylation conditions that are required for syntheses of linear peptide enamide natural products such as **5**−**7**.

To further define the scope of the method, a number of other peptide and non-peptide substrates were evaluated (Table 3). In addition to C-terminal tyrosine- and tryptophan-containing peptides, and C-terminal phenylalanine-containing peptides, both dipeptide (entry 1) and tripeptide substrates (entry 2), undergo oxidative decarboxylation-elimination to form the corresponding enamides **18** and **19** (approximately 1:1 E:Z mixtures) in good yield. Entry 4 demonstrates efficient syntheses of the unsaturated *Z*-enamide natural product lansiumamide A (**21Z**) and its *E*-enamide stereoisomer (**21E**), which are fully separable by silica gel chromatography.[24] Enamides derived from C-terminal leucine (entry 5) were found to require both a stronger base and a higher reaction temperature (45 °C) to produce enamides **22** and were shown to favor the Z isomer (2.2:1 Z:E) under these conditions. To check for epimerization of the stereogenic center using this procedure, we prepared the enantiomers of both **22Z** and **22E** from Boc-D-phenylalanine. Chiral HPLC analysis indicated that all enamides are greater than 99% optically pure.[25] Finally, we prepared model compounds (entries 6 and 7) to illustrate potential

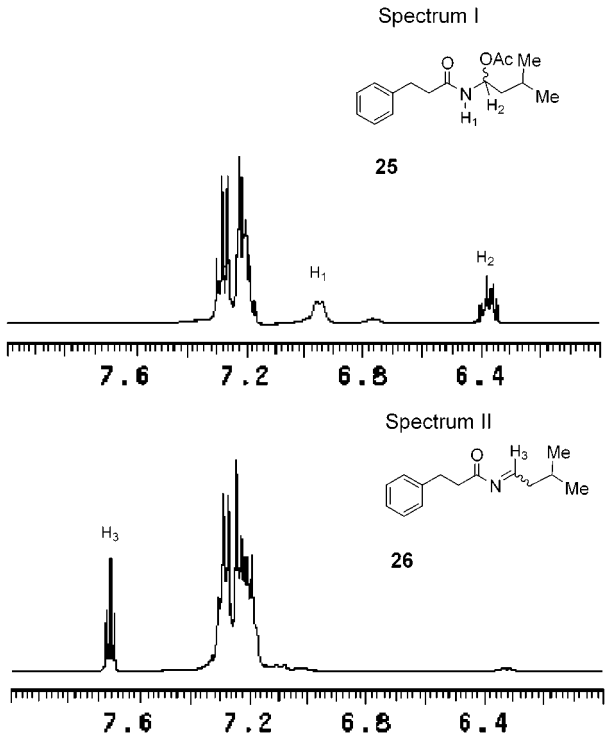


Figure 3. Spectra of an *O*-acetyl-*N*-acyl-*N*,*O*-acetal (Spectrum I) and an *N*-acyl imine intermediate (Spectrum II).

application of this method to prepare the enamide side chains of the salicylate antitumor macrolides. It is also noteworthy that the *Z*-*O*-methyloxime enamide of products **24Z**/**24E** were found to be configurationally stable under the reaction conditions. In the latter two cases, copper(II) acetate (30 mol %) was a required additive for oxidative decarboxylation reactions for optimal yield and reproducibility.[26]

To determine the mechanism for elimination of *O*-acetyl-*N*-acyl-*N*,*O*-acetals and clarify the *Z*-enamide selectivity observed for C-terminal tryptophan substrates, we conducted mechanistic studies using ^{1}H NMR spectroscopy. Our initial mechanistic hypothesis was that treatment of *O*-acetyl-*N*-acyl-*N*,*O*-acetal substrates with $LiClO_4$ would lead to the generation of *N*-acyliminium ion intermediates. However, addition of $LiClO_4$ (1 equiv) to representative *N*,*O*-acetals in [D_8]THF showed little change in the ^{1}H NMR and no evidence for characteristic absorptions for these reactive intermediates.[27] However, treatment of substrate **25** (Spectrum I, Figure 3) with

(22) For preparation of *Nin*-Boc tryptophan derivatives, see: Moody, C. J.; Doyle, K. J.; Elliott, M. C.; Mowlem, T. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, *16*, 2413.

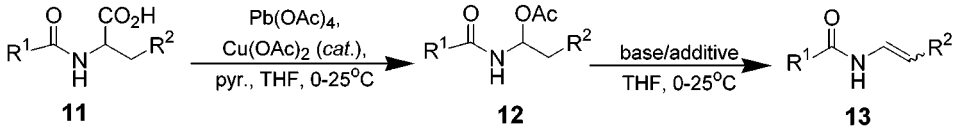
(23) For example, see: Hikawa, H.; Yokoyama, Y.; Murakami, Y. *Synthesis* **2000**, *2*, 214.

(24) (a) Lin, J. *Phytochemistry* **1989**, *28*, 621. (b) For recent synthetic studies, see: Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735.

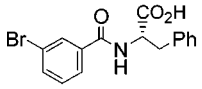
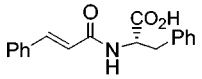
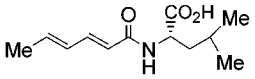
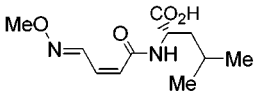
(25) HPLC analyses of **22Z**, **22E**, *ent*-**22Z**, and *ent*-**22E**: CHIRACEL OD, 95/5 hexane/2-propanol, t_R = 16.1, 12.8, 8.8, and 8.8 min, respectively.

(26) Kochi, J. K.; Bacha, J. D. *J. Org. Chem.* **1968**, *33*, 2746.

Table 3. Application to Other Peptide and Nonpeptide Enamides



11 **12** **13**

entry	substrate	base/additive	ratio (Z:E)	product	yield (%)[a]
1	Boc-L-Leu-L-Phe-OH	DIEA/$LiClO_4$	0.7:1	**18**	83
2	Boc-L-Leu-L-Leu-L-Phe-OH	DIEA/$LiClO_4$	0.8:1	**19**	75
3		DIEA/$LiClO_4$	1.4:1	**20**	65
4		DIEA/$LiClO_4$	1:1	**21**	75
5	Boc-L-Phe-L-Leu-OH	DBU[b]	2.2:1	**22**	60
6		DBU[c]	1.7:1	**23**	41
7		DBU[b]	2.1:1	**24**	58

[a] Isolated yield, average of two runs. [b] Reaction temperature = 45 °C. [c] Reaction temperature = 60 °C.

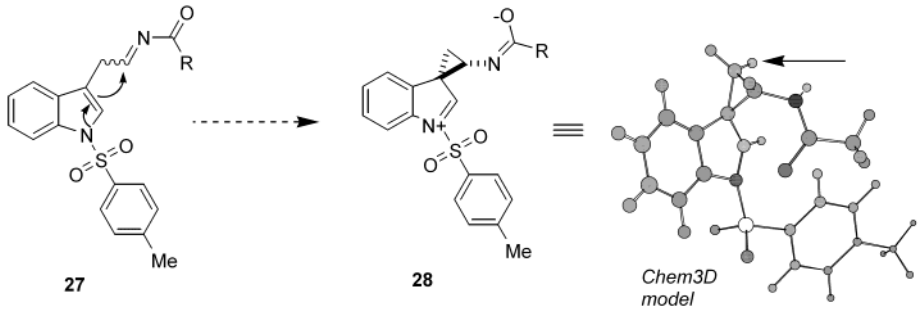


Figure 4. Possible involvement of spiroindolenine intermediates for trytophan substrates.

DIEA (2.0 equiv) in the presence of lithium perchlorate (1.2 equiv) in [D_3]acetonitrile led to a loss of signals for the NH (H_1 = δ 6.96) and *N*,*O*-acetal methine (H_2 = δ 6.37) protons and the appearance of a characteristic proton (H_3 = δ 7.66, J = 5.2 Hz) for *N*-acylimine **26** (Spectrum II, Figure 3).[28] Further isomerization to enamide products does not occur in this instance due to the aliphatic substitution where we have found DBU to be required (cf. entries 5−7, Table 3). For indole-containing substrates (cf. entries 3−5, Table 2), the high Z-selectivities are clearly distinct from other C-terminal peptides. One possible explanation for this distinction would be the transformation of an *N*-acylimine **27** to a spirocyclopropylindolenine intermediate **28** (Figure 4) that subsequently opens to the *Z*-enamide by preferential elimination of the indicated hydrogen (Chem3D model, Figure 4). Spiroindolenines have been proposed as intermediates in electrophilic substitution of indoles,[29] including both three-[30] and four-membered[31] intermediates. Support for this mechanistic hypothesis awaits further experimentation involving evaluation of indole modifications or trapping of the spiro-intermediate.[32]

Finally, we applied the oxidative decarboxylation-elimination methodology to short syntheses of the indole-enamide natural products chondriamides A and C.[33] Both

(27) There have been a few literature reports where ^1H and ^{13}C NMR spectroscopy have been employed to detect *N*-acyliminium ion intermediates, see: (a) Yamamoto, Y.; Nakada, T.; Nemoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 121. (b) Heaney, H.; Taha, M. O. *Tetrahedron Lett.* **1998**, *39*, 3341.

(28) (a) Jendrzejewski, S.; Steglich, W. *Chem. Ber.* **1981**, *114*, 1337. (b) Steglich, W.; Jager, M.; Jaroch, S.; Zistler, P. *Pure Appl. Chem.* **1994**, *66*, 2167. (c) Bretschneider, T.; Miltz, W.; Munster, P.; Steglich, W. *Tetrahedron* **1988**, *44*, 5403.

(29) (a) Jackson, A. H.; Smith, P. *J. Chem. Soc., Chem. Commun.* **1967**, 264. (b) Jackson, A. H.; Naidoo, B.; Smith, P. *Tetrahedron* **1968**, *24*, 6119. (c) Jackson, A. H.; Naidoo, B. *J. Chem. Soc., Perkin Trans. 2* **1973**, 548. (d) Jackson, A. H.; Lynch, P. P. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1215.

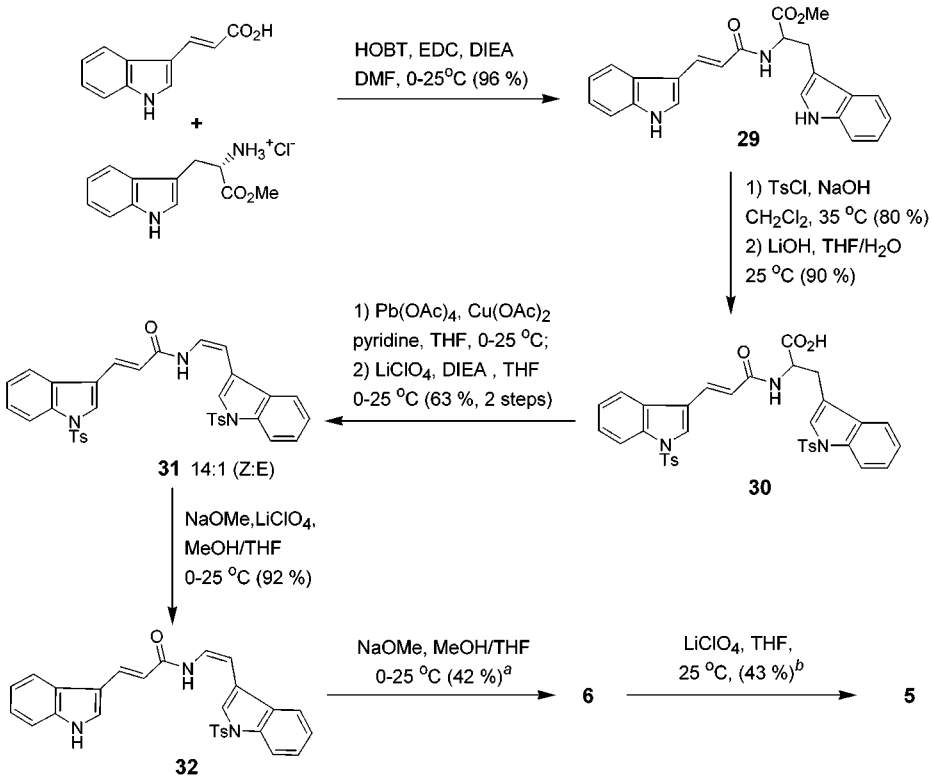
(30) Decodts, G.; Wakselman, M. *Bull. Soc. Chim. Fr.* **1972**, 4586.

(31) Ganesan, A.; Heathcock, C. H. *Tetrahedron Lett.* **1993**, *34*, 439.

(32) For examples, see: (a) Nakagawa, M.; Liu, J.; Ogata, K.; Hino, T. *J. Chem. Soc., Chem. Commun.* **1988**, 463. (b) Biswas, K. M.; Jackson, A. H.; Kobaisy, M. M.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 461.

(33) For efforts to produce *Z*-indole enamides, see: Brettle, R. A.; Mosedale, J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2185.

Scheme 2. Synthesis of Chondriamides A and C



[a] 70 % yield based on recovered starting material. [b] 75 % yield based on recovered starting material.

compounds were isolated from the red alga *Chondria* sp. and are *E*- and *Z*-enamide stereoisomers, respectively. Their highly unsaturated structures include two 3-substituted indoles that are unstable to acidic, oxidative, and reductive conditions, thus requiring mild reaction conditions for both enamide formation and final deprotection. To prepare a substrate for oxidative decarboxylation-elimination, tryptophan methyl ester hydrochloride was acylated with *trans*-3-indoleacrylic acid (EDC/HOBT, DIEA, DMF) to afford 3-indole-acryltryptophan methyl ester **29** (Scheme 2). Interestingly, the ethyl ester of **29** was isolated as a minor compound during the isolation of chondriamide A, indicating that the free acid, 3-indoleacryltryptophan, may be a biosynthetic precursor.[10] Bis-tosylation of the indole nitrogens of **29** (NaOH/TsCl/CH_2Cl_2)[34] was followed by ester hydrolysis (LiOH) to produce enamide precursor **30** (70% overall yield). Oxidative decarboxylation of **30** followed by elimination furnished bis-*Nin*-Ts-protected chondriamide C **31** with high *Z*-enamide stereoselectivity (14:1 Z:E) and good yield (63% for two steps). Unfortunately, attempted deprotection of **31** using the aforementioned reductive detosylation conditions (Mg, MeOH, 25 °C) was not suitable for this substrate and led to overreduction of the 3-indoleacrylamide functionality. We therefore focused on the use of nucleophilic protocols for detosylation. After considerable experimentation and screening of reaction conditions, we found that use of NaOMe[35] and $LiClO_4$ as additive selectively removed the tosyl group associated with the 3-indoleacrylamide moiety to furnish monotosyl enamide **32** (92%). Further treatment of **32** with NaOMe (MeOH/THF) (0.01 M) provided the natural product chondriamide C (**6**) in 42% yield (70% based on recovered starting material) whose spectral data matched those reported for the natural product.[11] Enamide isomerization was effected by treatment of **6** with $LiClO_4$ (20 mol %, THF, 24 h) to produce chondriamide A (**5**) in 43% yield (75% yield based on recovered starting material). Attempted isomerization of other *Z*-enamide substrates containing either conjugated acrylamide (**21Z**) or tryptophan-containing substrates (**17**) was unsuccessful indicating the requirement of both functionalities for isomerization using $LiClO_4$.

Conclusion

We have described protocols for the synthesis of peptide enamides based on tandem oxidative decarboxylation-elimination of C-terminal peptides. Substrates containing C-terminal tryptophans have been found to form *Z*-enamides with high selectivity, which has been exploited in expeditious syntheses of the cytotoxic indole-enamide natural products chondriamides A and C. In preliminary studies, synthetic peptide enamides have also shown useful levels of cytotoxicity in tumor cell lines. For example, in an ATP-based cell viability assay, compounds **14E** and **17** showed cytotoxicity in a human acute T-cell leukemia (Jurkat) cell line (IC_{50} ca. 7 and 20 μM, respectively). Other related compounds (e.g., **18E**) did not show cytotoxicity indicating significant levels of specificity. Further biological evaluation of peptide enamides, mechanistic studies, and applications of this methodology to the synthesis of additional natural product targets are in progress and will be reported in due course.

(34) Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915.
(35) (a) Dekhane, M.; Potier, P.; Dodd, R. H. *Tetrahedron* **1993**, *49*, 8139. (b) Lin, C.; Ennis, M. D.; Hoffman, R. L.; Phillips, G.; Haadsma-Svensson, S. R.; Ghazal, N. B.; Chidester, C. G. *J. Heterocycl. Chem.* **1994**, *31*, 129.

Experimental Section

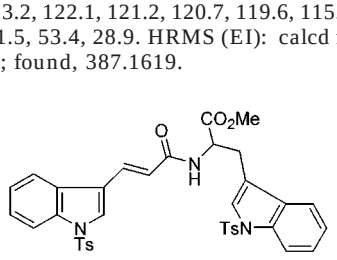
General Methods. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded on a 75.0 MHz spectrometer at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ 7.24; ^{13}C, δ 77.0). Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), and coupling constants. All ^{13}C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR instrument. Chiral HPLC analysis was performed on an Agilent 1100 series HPLC (CHIRALCEL OD, Column No. OD00CE-AI015). Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm and are reported as $[\alpha]_D^{22}$ (concentration in grams/100 mL of solvent). High-resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory using a Finnegan MAT-90 spectrometer. Methylene chloride (CH_2Cl_2) and toluene were distilled from calcium hydride. Tetrahydrofuran was distilled from sodium and benzophenone. Analytical thin-layer chromatography was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200−400 mesh silica gel (Natland International Corporation). All other reagents were used as supplied by Sigma-Aldrich, Fluka, Lancaster, and Strem Chemicals unless otherwise noted.

Representative Procedure for Oxidative Decarboxylation-Elimination of Aromatic *N*-Acyl Amino Acids: Peptide Enamide (18). To a flask containing Boc-L-Leu-L-Phe-OH (227 mg, 0.60 mmol), $Cu(OAc)_2$ (32.7 mg, 0.18 mmol), and pyridine (97.2 μL, 1.20 mmol) in distilled THF (2.4 mL) at 0 °C under N_2 was added $Pb(OAc)_4$ (292.6 mg, 0.66 mmol). The resulting solution was allowed to warm to room temperature and stirred for 2 h. The reaction was then quenched by saturated $NaHCO_3$, and the solution was extracted with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude *N*,*O*-acetal was used directly without further purification in the next step. The crude product was dissolved in distilled THF (2.4 mL) and treated with $LiClO_4$ (76.5 mg, 0.72 mmol). The reaction mixture was cooled to 0 °C, treated with DIEA (208.8 μL, 1.20 mmol), and stirred for 10 min before it was warmed to room temperature. After the starting material was no longer detected by TLC, the reaction was quenched with saturated $NaHCO_3$ and the solution was extracted with EtOAc. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification on silica gel (20% EtOAc, 3% Et_3N/hexanes) provided 65 mg (33%) of **18Z** as a white solid and 99 mg (50%) of **18E** as a white solid. **18Z**. Mp: 77−80 °C. $[\alpha]_D^{22} = -7.1°$ ($c = 0.59$, $CHCl_3$). IR (neat) $\tilde{\nu}_{max}$: 1674, 1652, 1507, 1485, 1165 cm^{-1}. ^{1}H NMR δ: 8.49 (d, J = 9.6 Hz, 1H), 7.36 (t, J = 7.2 Hz, 2H), 7.21−7.28 (m, 4H), 6.91 (dd, J = 11.2, 9.2 Hz, 1H), 5.76 (d, J = 9.2 Hz, 1H), 4.73 (bs, 1H), 4.12 (m, 1H), 1.64−1.78 (m, 2H), 1.43−1.50 (m, 1H), 1.40 (s, 9H), 0.92 (t, J = 6.8 Hz, 6H). ^{13}C NMR δ: 170.2, 155.8, 135.5, 129.0, 127.8, 126.9, 121.5, 110.7, 80.6, 53.2, 40.3, 28.2, 24.8, 22.9, 21.8. HR-MS (EI): calcd for $C_{19}H_{28}N_2O_3$ [M$^+$], 332.2100; found, 332.2094. Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.87; H, 8.80; N, 8.29. **18E**. Mp: 118−122 °C. $[\alpha]_D^{22} = -51°$ (c = 0.56, $CHCl_3$). IR (neat) $\tilde{\nu}_{max}$: 1669, 1650, 1532, 1167 cm^{-1}. ^{1}H NMR δ: 8.75 (d, J = 8.8 Hz, 1H), 7.40 (t, J = 12.4 Hz, 1H), 7.12−7.21 (m, 5H), 6.08 (d, J = 14.8 Hz, 1H), 5.13 (d, J = 6.0 Hz, 1H), 4.24 (bs, 1H), 1.69 (m, 2H), 1.55 (m, 1H), 1.44 (s, 9H), 0.94 (d, J = 6.4 Hz, 3H), 0.92 (d, J = 6.4 Hz, 3H). ^{13}C NMR δ: 170.4, 156.2, 136.1, 128.6, 126.6, 125.6, 122.6, 80.6, 53.2, 40.9, 28.4, 24.8, 23.0, 21.9. HR-MS (EI): calcd for $C_{19}H_{28}N_2O_3$ [M$^+$], 332.2100; found, 332.2089. Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.54; H, 8.70; N, 8.21.

Indole Enamide (17). A mixture of Mg turnings (184 mg, 7.6 mmol) and distilled MeOH (1 mL) was stirred at room temperature for 5 min under argon. After this time, the mixture was cooled to 0 °C and a solution of **16Z** (105 mg, 0.2 mmol) in MeOH (0.5 mL) was added. The resulting mixture was warmed to room temperature and vigorously stirred for 30 min. The reaction was quenched by saturated NH_4Cl, and the solution was extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide **17** (75 mg, 100% yield) as a yellow solid. Mp: 68−72 °C. $[\alpha]_D^{22} = +38°$ ($c = 0.62$, $CHCl_3$). IR (neat) $\tilde{\nu}_{max}$: 1695, 1655, 1539, 1499, 1163 cm^{-1}. ^{1}H NMR δ: 8.43 (s, 1H), 8.35 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.20 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.87 (t, J = 9.6 Hz, 1H), 5.95 (d, J = 9.2 Hz, 1H), 4.89 (bs, 1H), 4.20 (bs, 1H), 1.67 (m, 2H), 1.49 (m, 1H), 1.31 (s, 9H), 0.89 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H). ^{13}C NMR δ: 171.2, 157.0, 137.0, 127.7, 123.8, 123.2, 121.2, 121.0, 120.1, 112.3, 112.2, 81.5, 54.2, 41.6, 30.8, 29.3, 25.8, 24.0, 22.9. HR-MS (EI): calcd for $C_{21}H_{29}N_3O_3$ [M$^+$], 371.2209; found, 371.2235.

General Procedure for Oxidative Decarboxylation of Aliphatic *N*-Acyl Amino Acids: Enamide (24). To a flask containing *N*-((2*Z*)-4-(methoxyimino)-2-butenamido)-leucine[36] (223 mg, 0.92 mmol), $Cu(OAc)_2$ (50 mg, 0.28 mmol), and pyridine (149 μL, 1.84 mmol) in distilled THF (4.0 mL) at 0 °C under N_2 was added $Pb(OAc)_4$ (449 mg, 1.012 mmol). The resulting solution was allowed to warm to room temperature and stirred for 2 h and then diluted with 3% Et_3N/EtOAc (10 mL). The mixture was eluted through a cartridge containing silica gel (6 mL), washed with 3% Et_3N/EtOAc (20 mL), and concentrated in vacuo. The crude acetate was used directly without further purification in the next step. The crude product was dissolved in distilled THF (10.0 mL) and then treated with DBU (203.6 μL, 1.38 mmol). The mixture was heated to 45 °C for 2.5 h and cooled to room temperature. The reaction was quenched with saturated $NaHCO_3$, and the solution was extracted with EtOAc. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification on silica gel (20% EtOAc, 3% Et_3N/hexanes) provided of **24Z** (70 mg, 39% yield) as a white solid and **24E** (34 mg 19% yield) as a white solid. **24Z**. Mp: 109−111 °C. IR (neat) $\tilde{\nu}_{max}$: 1645, 1618, 1518, 1045 cm^{-1}. ^{1}H NMR δ: 8.99 (d, J = 10.4 Hz, 1H), 7.39 (bd, J = 10.4 Hz, 1H), 6.60 (t, J = 10.8 Hz, 1H), 6.48 (dd, J = 11.6, 10.0 Hz, 1H), 5.97 (d, J = 11.6 Hz, 1H), 4.66 (t, J = 9.6 Hz, 1H), 2.44 (m, 1H), 0.97 (d, J = 7.2 Hz, 6H). ^{13}C NMR δ: 163.0, 148.7, 136.3, 125.6, 121.6, 119.4, 63.4, 26.9, 23.9. HR-MS (EI): calcd for $C_{10}H_{16}N_2O_2$ [M$^+$], 196.1212; found, 196.1221. **24E**. Mp: 121−123 °C. IR (neat) $\tilde{\nu}_{max}$: 1637, 1618, 1533, 1044 cm^{-1}. ^{1}H NMR δ: 9.00 (d, J = 10.0 Hz, 1H), 7.29 (bd, J = 9.6 Hz, 1H), 6.74 (dd, J = 14.4, 10.4 Hz, 1H), 6.46 (dd, J = 11.6, 10.8 Hz, 1H), 5.86 (d, J = 11.6 Hz, 1H), 5.19 (dd, J = 14.0, 6.8 Hz, 1H), 2.32 (m, 1H), 0.98 (d, J = 6.4 Hz, 6H). ^{13}C NMR δ: 161.8, 147.7, 135.0, 124.6, 122.1, 120.1, 62.3, 29.0, 22.7. HR-MS (EI): calcd for $C_{10}H_{16}N_2O_2$ [M$^+$], 196.1212; found, 196.1217.

3-Indole-acryltryptophan Methyl Ester (29). To a mixture of *trans*-3-indole-acrylic acid (225 mg, 1.20 mmol), tryptophan methyl ester hydrochloride (255 mg, 1.0 mmol), HOBt (149 mg, 1.1 mmol), EDC (211 mg, 1.1 mmol), and DMF (3 mL) at 0 °C under N_2 was added DIEA (627 μL, 3.6 mmol). The resulting solution was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was diluted with EtOAc, washed with 1 N $NaHCO_3$, brine, dried, filtered, and concentrated to provide **29** (373 mg, 96% yield) as a yellow solid. Mp: 70−73 °C. IR (neat) $\tilde{\nu}_{max}$: 3405, 1736, 1653, 1604, 1436, 1213 cm^{-1}. ^{1}H NMR δ: 9.04 (s, 1H), 8.43 (s, 1H), 7.79 (d, J = 16.0 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 9.2 Hz, 2H), 7.05−7.18 (m, 5H), 6.95 (s, 1H), 6.26−6.30 (m, 2H), 5.11 (dd, J = 9.2, 5.2 Hz, 1H), 3.64 (s, 3H), 3.37 (m, 2H). ^{13}C NMR δ: 173.9, 168.4, 138.3, 137.3, 136.6, 130.0, 128.7, 126.4, 124.2, 124.0, 123.2, 122.1, 121.2, 120.7, 119.6, 115.9, 114.1, 113.0, 112.5, 110.9, 61.5, 53.4, 28.9. HRMS (EI): calcd for $C_{23}H_{21}N_3O_3$ [M$^+$], 387.1583; found, 387.1619.



33

(36) Prepared from (2*Z*)-4-methoxyimino-2-butenoic acid (ref 7) using the following procedure: (1) L-leucine methyl ester hydrochloride, EDC, HOBt, and DMF and (2) LiOH, aqueous THF, (85%, two steps).

Bis-sulfonamide (33). A mixture of **29** (218 mg, 0.56 mmol), NaOH (56.0 mg, 1.40 mmol), and distilled CH_2Cl_2 (3.0 mL) was stirred for 15 min, and then toluenesulfonyl chloride (191 mg, 1.68 mmol) was added. The reaction mixture was heated to 35 °C and stirred for 30 min and then diluted with EtOAc. The organic layer was washed exhaustively with water, dried with Na_2SO_4, filtered, and concentrated in vacuo. Purification on silica gel (45% EtOAc/hexanes) provided bis-sulfonamide **30** (317 mg, 81% yield) as a yellow solid. Mp: 114−117 °C. IR (neat) $\tilde{\nu}_{max}$: 1742, 1624, 1447, 1368, 1174, 1126 cm^{-1}. ^1H NMR δ: 7.98 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.0 Hz, 2H), 7.67−7.78 (m, 5H), 7.45 (d, J = 8.0 Hz, 2H), 7.37 (s, 1H), 7.10−7.36 (m, 7H), 7.44 (d, J = 15.6 Hz, 1H), 6.29 (s, 1H), 5.08 (d, J = 5.6 Hz, 1H), 3.68 (s, 3H), 3.29 (m, 2H), 2.30 (s, 3H), 2.19 (s, 3H). ^{13}C NMR δ: 173.0, 166.7, 146.5, 145.9, 136.6, 136.3, 136.2, 135.9, 133.8, 131.9, 131.1, 130.9, 129.3, 128.9, 128.0, 127.8, 126.4, 126.0, 125.6, 125.0, 124.3, 121.6, 121.2, 120.5, 119.4, 118.2, 114.9, 114.8, 61.4, 53.6, 28.7, 22.6, 22.4. HR-MS (EI): calcd for $C_{37}H_{33}N_3O_7S_2$ [M^+], 695.1760; found, 695.1825.

Carboxylic Acid (30). To a solution of **33** (317 mg, 0.456 mmol) in distilled THF (2 mL) and distilled water (1 mL) at room temperature was added lithium hydroxide monohydrate (32.8 mg, 0.781 mmol). The resulting solution was stirred for 3 h at 25 °C. The pH of the aqueous layer was adjusted to 2 with 1 N HCl solution. The mixture was extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford acid **30** (282 mg, 90% yield) as a yellow solid. Mp: 125−128 °C. IR (neat) $\tilde{\nu}_{max}$: 3379, 1734, 1654, 1447, 1372, 1125, 1077 cm^{-1}. ^1H NMR δ: 7.86 (t, J = 9.2 Hz, 2H), 7.77 (s, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.52−7.56 (m, 2H), 7.46 (d, J = 8.0 Hz, 1H), 7.07−7.20 (m, 7H), 6.94 (m, 1H), 6.89 (d, J = 8.0 Hz, 2H), 6.52 (d, J = 15.6 Hz, 1H), 5.10 (dd, J = 12.4, 6.4 Hz, 1H), 3.30 (m, 2H), 2.20 (s, 3H), 1.85 (s, 3H). ^{13}C NMR δ: 175.3, 168.2, 146.5, 145.8, 136.4, 136.1, 135.9, 135.8, 131.8, 131.1, 130.8, 129.2, 128.0, 127.7, 126.3, 125.9, 125.8, 125.0, 124.4, 121.4, 120.8, 120.6, 119.2, 118.5, 114.6, 53.8, 28.3, 22.5, 22.2. HR-MS (EI): calcd for $C_{36}H_{31}N_3O_7S_2$ [M^+], 681.1603; found, 681.1594.

Bis-Ts Chondriamide C (31). To a flask containing acid (**30**) (68.2 mg, 0.10 mmol), $Cu(OAc)_2$ (5.4 mg, 0.03 mmol), and pyridine (16.2 μL, 0.20 mmol) in 0.4 mL of distilled THF at 0 °C under N_2 was added $Pb(OAc)_4$ (48.8 mg, 0.11 mmol). The resulting solution was warmed to room temperature and stirred for 1 h. The reaction was quenched with saturated $NaHCO_3$, and the solution was extracted with EtOAc. The organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude *N*,*O*-acetal was used directly without further purification in the next step. The crude product was dissolved in distilled THF (2.0 mL), treated with $LiClO_4$ (32 mg, 0.72 mmol), and cooled to 0 °C. To this solution was added DIEA (209 μL, 0.30 mmol). After being stirred for 10 min, the reaction mixture was warmed to room temperature. After the starting material was no longer detected by TLC (ca. 15 min), the reaction was quenched with saturated $NaHCO_3$ and the solution was extracted with EtOAc. The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give **31** (40 mg, 63% yield, 14:1 Z:E as determined by ^1H NMR integration) as a yellow powder. Mp: 248−249 °C. IR (neat) $\tilde{\nu}_{max}$: 1642, 1612, 1445, 1366, 1267, 1171, 1138, 1088 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone) δ: 9.19 (d, J = 10.4 Hz, 1H), 8.19 (s, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 7.85−7.96 (m, 7H), 7.63 (d, J = 8.0 Hz, 1H), 7.36−7.46 (m, 8H), 7.30 (t, J = 8.4 Hz, 1H), 7.23 (d, J = 10.0 Hz, 1H), 7.08 (d, J = 16.0 Hz, 1H), 5.82 (d, J = 9.6 Hz, 1H), 2.36 (s, 3H), 2.33 (s, 3H). HR-MS (EI): calcd for $C_{35}H_{29}N_3O_5S_2$ [M^+], 635.1549; found, 635.1504.

***Nin*-Ts Chondriamide C (32).** To a flask containing **31** (320 mg, 0.503 mmol), $LiClO_4$ (134 mg, 1.258 mmol), and freshly distilled THF (60 mL) at 0 °C under N_2 was added NaOMe (1 M in MeOH, 4.02 mL) dropwise. The resulting solution was warmed to room temperature and stirred for 40 min. The reaction was quenched with 1 N $NaHCO_3$, and the solution was extracted with EtOAc. The organic extracts were washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification on silica gel (35% acetone/hexanes) provided **32** (223 mg, 92% yield) as a yellow powder. Mp: 183−185 °C. IR (neat) $\tilde{\nu}_{max}$: 3280, 1696, 1644, 1605, 1491, 1249, 1174 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone) δ: 10.83 (bs, 1H), 9.14 (d, J = 11.2 Hz, 1H), 7.93−8.04 (m, 6H), 7.91(s, 1H), 7.80 (d, J = 2.8 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 11.6 Hz, 1H), 7.18−7.41 (m, 7H), 7.94 (d, J = 15.6 Hz, 1H), 5.76 (d, J = 9.6 Hz, 1H). ^{13}C NMR (75 MHz, [D_6]acetone) δ: 166.5, 147.4, 139.7, 138.1, 136.9, 136,5, 132.6, 132.4, 131.9, 128.8, 127.2, 126.8, 126.4, 125.3, 124.5, 122.6, 122.1, 121.7, 119.6, 116.6, 115.3, 115.1, 114.1, 99.0, 22.4. HR-MS (EI): calcd for $C_{28}H_{23}N_3O_3S$ [M^+], 481.1460; found, 481.1466.

Chondriamide C (6). To a solution of **32** (60 mg, 0.125 mmol) in freshly distilled THF (10 mL) at 0 °C under argon was added NaOMe (1 M solution in MeOH, 1.12 mmol) dropwise. The resulting solution was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with 1 N $NaHCO_3$ solution, and the solution was extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification on silica gel (35% acetone/hexanes) afforded recovered starting material (23.4 mg, 39%) and the desired product chondriamide C (**6**) (17.4 mg, 42% yield; 75% yield based on recovered starting material) as a yellow solid. Mp: 223−225 °C. IR (neat) $\tilde{\nu}_{max}$: 3396, 3262, 1704, 1644, 1606, 1484, 1272 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone) δ: 10.76 (bs, 1H), 10.42 (bs, 1H), 8.75 (d, J = 10.8 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 15.6 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.63−7.77 (m, 2H), 7.50 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.06−7.23 (m, 5H), 7.96 (d, J = 15.2 Hz, 1H), 5.94 (d, J = 9.2 Hz, 1H). ^{13}C NMR (75 MHz, [D_6]acetone) δ: 166.2, 139.7, 138.1, 137.2, 132.2, 129.0, 127.2, 125.0, 124.4, 123.7, 122.4, 122.2, 121.1, 120.5, 117.3, 115.2, 113.9, 113.2, 112.8, 102.9. HR-MS (EI): calcd for $C_{21}H_{17}N_3O$ [M^+], 327.1372; found, 327.1361.

Chondriamide A (5). To the solution of chondriamide C (44 mg, 0.134 mmol) in freshly distilled THF (3 mL) under argon was added $LiClO_4$ (2.9 mg, 0.027 mmol). The resulting solution was stirred at room temperature for 20 h before it was diluted with EtOAc, washed with brine, dried, and concentrated in vacuo. Purification on silica gel (40% acetone/hexanes) afforded recovered starting material (19 mg, 43%) and the desired product chondriamide A (**5**) (19 mg, 43% yield; 75% yield based on recovered starting material) as a yellow solid. Mp: 235−238 °C. IR (neat) $\tilde{\nu}_{max}$: 3421, 3193, 1666, 1636, 1589, 1420, 1249 cm^{-1}. ^1H NMR (400 MHz, [D_6]acetone) δ: 10.75 (bs, 1H), 10.25 (bs, 1H), 9.29 (d, J = 10.4 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 16.0 Hz, 1H), 7.77−7.80 (m, 2H), 7.72 (dd, J = 14.8, 10.4 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.40−7.43 (m, 2H), 7.10−7.25 (m, 4H), 6.79 (d, J = 15.2 Hz, 1H), 6.46 (d, J = 15.2 Hz, 1H). ^{13}C NMR (75 MHz, [D_6]acetone) δ: 165.3, 139.7, 139.2, 136.5, 131.8, 127.4, 124.4, 123.5, 122.9, 122.4, 122.0, 121.2, 117.5, 115.1, 114.9, 114.0, 113.4, 106.8. HR-MS (EI): calcd for $C_{21}H_{17}N_3O$ [M^+], 327.1372; found, 327.1413. Synthetic and natural chondriamide A gave the same R_f value in the following three solvent systems: R_f = 0.31 (silica gel, 1/1 acetone/hexanes), R_f = 0.76 (3/2 EtOAc/acetone), R_f = 0.50 (3/1 EtOAc/CH_2Cl_2).

Acknowledgment. We thank Profs. John Snyder (Boston University) and Scott J. Miller (Boston College) for helpful discussions, Prof. Eduardo Manta (Universidad de la Republica, Uruguay) for samples and spectral data for the chondriamides, and Prof. Junying Yuan and Dr. Alexei Degterev (Harvard Medical School) for conducting preliminary cytotoxicity assays.

Supporting Information Available: Characterization for E and Z isomers of enamides **10**, **14**−**16**, and **19**−**23**, and NMR data comparison of natural and synthetic chondriamides A and C. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0158027