Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 3170–3174

Synthetic studies of neoclerodane diterpenes from *Salvia divinorum*: Selective modification of the furan ring

Wayne W. Harding,[a] Matthew Schmidt,[a] Kevin Tidgewell,[a] Pavitra Kannan,[a] Kenneth G. Holden,[b] Christina M. Dersch,[c] Richard B. Rothman[c] and Thomas E. Prisinzano[a,*]

[a]*Division of Medicinal and Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, IA 52242, USA*
[b]*Holden Laboratories, Carmel, CA 93923, USA*
[c]*Clinical Psychopharmacology Section, IRP, NIDA, NIH, DHHS, Baltimore, MD 21224, USA*

Received 23 February 2006; revised 15 March 2006; accepted 16 March 2006
Available online 18 April 2006

Abstract—A synthetic sequence has been developed to selectively functionalize the furan ring of the natural product salvinorin A (**2a**). The synthetic routes described convert the furan ring in **2a** into an *N*-sulfonylpyrrole, oxazole or an oxadiazole. In addition, a procedure has been found to remove the furan skeleton completely. Biological results indicate that replacement of the furan ring with an *N*-sulfonylpyrrole leads to reduced affinity and efficacy at κ opioid receptors.

G-protein coupled, seven transmembrane segment receptors (GPCRs or 7TM receptors) are the largest superfamily of proteins in the body.[1,2] Currently, more than 60% of drugs target GPCRs.[3] One class of GPCRs are opioid receptors. These receptors are particularly intriguing members of this family in that they are activated both by endogenously produced opioid peptides and by exogenously administered opioid drugs, such as morphine (**1**) (Fig. 1).[4] There are at least three opioid receptor subtypes, μ, δ, and κ.[4] Opioid receptor ligands are among the most effective analgesics known but are also highly addictive drugs of abuse.[5] New opioid receptor ligands are needed to gain a greater understanding of the mechanisms of opioid tolerance and dependence, as well as, to provide new insight into the design of more effective treatments for pain.

Previous work has shown salvinorin A (**2a**), a neoclerodane diterpene from *Salvia divinorum*, to be a potent and selective κ opioid receptor agonist.[6,7] This is unique given that virtually all opioid ligands feature a basic nitrogen, which is protonated at physiological pH and is thought to interact with a conserved aspartate residue, located inside the receptor transmembrane domain and conserved among all the opioid receptors.[8,9] Several recent reports have begun to explore the structure–activity relationships of **2a** at opioid receptors.[10,11,7,12–15]

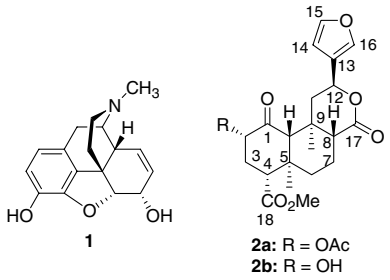


Figure 1. Structures of morphine (**1**), salvinorin A (**2a**), and salvinorin B (**2b**).

As part of our program to develop novel analgesics with a potential for reduced tolerance and dependence, we initiated studies to prepare several heterocyclic replacements for the furan ring present in **2a**. This was based on the activities of salvinicin A and B, as well as, our goal to reduce the potential for hepatotoxicity seen with furan containing natural products.[16–19] There are few reported methods for the functionalization of 3-substi-

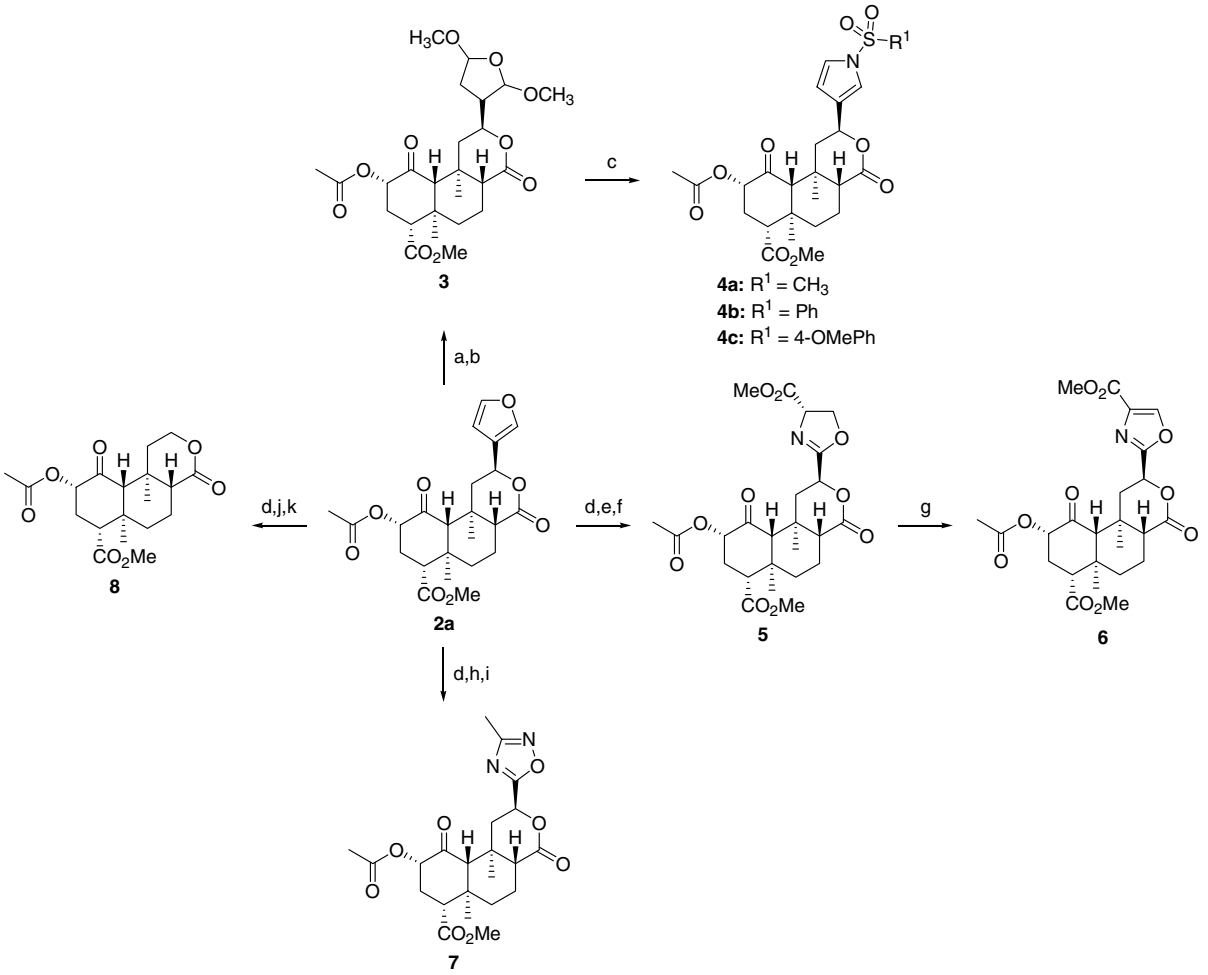
Keywords: Salvinorin A; Kappa; Opioid; *Salvia divinorum*; Heterocycle.
* Corresponding author. Tel.: +1 319 335 6920; fax: +1 319 335 8766; e-mail: thomas-prisinzano@uiowa.edu

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.03.062

tuted furans.[20–23] Previously described methods have detailed the photooxidation of the furan moeity under basic conditions to form a γ-hydroxybutenolide. However, there are few reports of converting the furan ring to other heterocycles such as an *N*-sulfonylpyrrole, oxazole, or oxadiazole. Thus, we set out to develop the methodologies to alter **2a** to help further define our understanding of the elements important to molecular recognition at opioid receptors.

Salvinorin A (**2a**) was isolated from *S. divinorum* as described previously.[24] With **2a** in hand, we sought to convert the furan ring to a pyrrole (Scheme 1). The treatment of **2a** with bromine in a mixture of CH_2Cl_2 and methanol at −30 °C gave the corresponding 2,5-dimethoxydihydrofuran derivative in 93% yield as a mixture of *cis* and *trans* isomers.[15] This alkene was reduced with hydrogen and 5% rhodium on carbon as catalyst to afford dimethoxytetrahydrofuran **3** in 92% yield. The reduction of **3** leads to a mixture of compounds, presumably containing the 2,5-dimethoxy *cis* and *trans* isomers and appearing as two spots on TLC, that were not separated. The reaction of dimethoxytetrahydrofuran **3** (as a mixture of compounds) with methanesulfonamide at 95 °C in acetic acid afforded a mixture of methanesulfonylpyrrole **4a** (30%) and its C-8 epimer (25%).[25] These compounds, however, were readily separated by column chromatography. Using similar methodology, benzenesulfonamides **4b** and **4c** were prepared in 30% and 23% yield, respectively. As seen with **4a**, significant amounts of the C-8 epimers were also formed (20% and 18%, respectively). Attempts to remove the benzenesulfonyl group in **4b** using Mg and MeOH,[26] and tetrabutylammonium fluoride[27] were unsuccessful.

Upon first glance, the epimerization of the C-8 position was not without precedent. Koreeda and co-workers have previously proposed a complex mechanism for this epimerization under basic conditions, involving cleavage of the C-8/9 bond.[28,29] Recently, Rizzacasa and co-workers proposed that this epimerization seen is the result of enolate formation, followed by protonation from the opposite face.[10] The exact mechanism of this transformation is currently unresolved. However, it was interesting to note that unlike the previously described conditions this epimerization occurs under acidic conditions.



Scheme 1. Reagents and conditions: (a) Br_2, MeOH, CH_2Cl_2; (b) H_2, 5% Rh/C, MeOH; (c) appropriate sulfonamide, HOAc, 95 °C; (d) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$; (e) EDCI, HOBt, L-serine methyl ester hydrochloride, NEt_3, CH_2Cl_2; (f) Deoxo-Fluor, CH_2Cl_2; (g) $BrCCl_3$, DBU, CH_2Cl_2; (h) EDCI, $CH_3C(NH_2)$=NOH, CH_2Cl_2; (i) toluene, heat; (j) $PhOPOCl_2$, C_6H_5SeH, NEt_3, THF; (k) Bu_3SnH, AIBN, toluene.

Given the mixture of compounds formed in the hydrogenation step, it was thought that perhaps this reaction leads to C-8 epimerization. The two spots of **3** on TLC were reminiscent of **2b** and its C-8 epimer formed upon hydrolysis of **2a**, and thus it was presumed that one spot corresponded to the C-8 epimer of **3** and the other to the desired epimer. Subsequently, both spots were isolated and purified. ^{1}H NMR of the separated spots indicated that neither compound contained any C-8 epimer. Interestingly, the reaction of either spot of **3** with benzenesulfonamide in acetic acid afforded a mixture of **4b** and its C-8 epimer. This suggested that C-8 epimerization was occurring during the pyrrole formation step.

To test if the C-8 proton was labile under acidic conditions, **2a** was heated in acetic acid at 95 °C overnight. As expected, this led to a mixture of **2b** and its C-8 epimer. Interestingly, further heating did not increase the amount of the C-8 epimer of **2b**. Energy calculations indicate that the C-8 epimer of **2a** is lower in energy than **2a** by approximately 2.2 kcal/mol. Similar calculations showed that the C-8 epimer of **4a** is lower in energy than **4a** by approximately 1.7 kcal/mol.

Having successfully converted the furan ring in **2a** to an *N*-sulfonylpyrrole, we focused on preparing other heterocyclic derivatives of **2a**. The reaction of **2a** with $NaIO_4$ and a catalytic amount of $RuCl_3{\cdot}3H_2O$ in a mixture of CCl_4, acetonitrile, and water afforded the C-13 acid in 74% yield.[15] The C-13 acid was then coupled with L-serine methyl ester hydrochloride using *N*-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole hydrate (HOBT) to give the corresponding β-hydroxy amide in 75% yield. Cyclization of the β-hydroxy amide using bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) afforded oxazoline **5** in 74% yield.[30] The conversion of oxazoline **5** to oxazole **6** was accomplished in 80% yield by treatment with bromotrichloromethane and 1,8-diazabicyclo[5.4.0]undec-7-en (DBU).[30] It is interesting to note that these conditions did not result in epimerization at the C-8 position. This is presumably due to the low temperature, short reaction time, and bulky nature of DBU. The coupling of C-13 acid with acetamide oxime followed by heating in toluene afforded oxadiazole **7** in 56% yield.[31] Unfortunately, these conditions lead to the formation of the corresponding C-8 epimer (11% yield). Finally, we focused on removing the furan skeleton completely from **2a**. The coupling of the C-13 acid derivative of **2a** with selenophenol was accomplished via the mixed anhydride using phenyl dichlorophosphate to give the corresponding phenyl seleno ester in 64% yield.[32] Decarbonylation of the phenyl seleno ester with tri-*n*-butyltin hydride and 2,2′-azobis(2-methylpropionitrile) (AIBN) in toluene afforded **8** in 70% yield.[32]

Diterpenes **4a**–**4c** and **6** were then evaluated for opioid receptor affinity (Table 1).[35] Generally, replacement of the furan ring led to decreased affinity at κ receptors compared to **2a**. The replacement of the furan ring with an *N*-sulfonylpyrrole (**4a**–**4c**) was found to be better tolerated than a 4-carbomethoxyoxazole (**6**). Diterpenes **4a**–**4c** were then tested for functional activity at κ receptors using a [^{35}S]GTP-γ-S assay (Table 2).[35] As a group, pyrroles **4a**–**4c** were found to be less active at κ receptors compared to **2a**. Interestingly, **4a**–**4c** were found to be partial agonists compared to (−)-U50,488 and **2a**. *N*-Methylsulfonylpyrrole **4a** was found to be the most active in the series (ED_{50} = 3600 nM) but was 90-fold less active than **2a**. These results indicate that replacement of the furan ring with an *N*-sulfonylpyrrole leads to reduced affinity and efficacy at κ opioid receptors compared to **2a**.

Table 1. Binding affinities of **4a**–**4c** and **6** at opioid receptors using [^{125}I]IOXY as radioligand[33,34]

Compound	K_i ± SD (nM)		
	μ	δ	κ
2a[a]	>1000[b]	>1000[b]	1.9 ± 0.2
4a	>10,000	>10,000	840 ± 90
4b	>10,000	>10,000	410 ± 30
4c	>10,000	>10,000	1620 ± 110
6	>10,000	>10,000	8530 ± 550

[a] Data from Ref. 7.
[b] Partial inhibitor.

Table 2. Results from [^{35}S]GTP-γ-S functional assay carried out in stably transfected CHO cells containing DNA for human κ receptors

Compound	κ Agonism	
	E_{max}[b]	ED_{50} ± SD (nM)
2a[a]	120 ± 2	40 ± 10
4a	70 ± 3	3600 ± 580
4b	60 ± 3	9160 ± 1900
4c	60 ± 5	15190 ± 3590

[a] Data from Ref. 7.
[b] E_{max} is the percentage at which compound stimulates binding compared to (−)-U50,488 (500 nM) at κ receptors.

In conclusion, we have provided methodology to selectively functionalize the furan containing natural product salvinorin A.[36–41] In particular, we have shown it is possible to convert the furan to either an *N*-sulfonylpyrrole, oxazoline, oxazole or oxadiazole. Finally, we have described a method to remove the furan skeleton altogether. Biological results indicate that replacement of the furan ring with an *N*-sulfonylpyrrole leads to reduced affinity and efficacy at κ opioid receptors compared to **2a**. Further exploration of these findings is underway and will be reported in due course.

Acknowledgments

This work was supported by National Institutes of Health, National Institute on Drug Abuse Grant DA18151 (to TEP), and in part by the Intramural Research Program of the NIH, NIDA. The authors also thank Vic Parcell and Lynn Teesch of the High Resolution Mass Spectrometry Facility, University of Iowa, for mass spectral analysis.

References and notes

1. Gether, U. *Endocr. Rev.* **2000**, *21*, 90.
2. Lundstrom, K. *Trends Biotechnol.* **2005**, *23*, 103.
3. Lundstrom, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3654.
4. Waldhoer, M.; Bartlett, S. E.; Whistler, J. L. *Annu. Rev. Biochem.* **2004**, *73*, 953.
5. Stein, C.; Schafer, M.; Machelska, H. *Nat. Med.* **2003**, *9*, 1003.
6. Roth, B. L.; Baner, K.; Westkaemper, R.; Siebert, D.; Rice, K. C.; Steinberg, S.; Ernsberger, P.; Rothman, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11934.
7. Harding, W. W.; Tidgewell, K.; Byrd, N.; Cobb, H.; Dersch, C. M.; Butelman, E. R.; Rothman, R. B.; Prisinzano, T. E. *J. Med. Chem.* **2005**, *48*, 4765.
8. Le Bourdonnec, B.; Goodman, A. J.; Michaut, M.; Ye, H.-F.; Graczyk, T. M.; Belanger, S.; DeHaven, R. N.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 864.
9. Aldrich, J. V. In *Burger's Medicinal Chemistry and Drug Discovery*; Wolff, M. E., Ed., 5th ed.; John Wiley: New York, 1996; p 321.
10. Munro, T. A.; Rizzacasa, M. A.; Roth, B. L.; Toth, B. A.; Yan, F. *J. Med. Chem.* **2005**, *48*, 345.
11. Beguin, C.; Richards, M. R.; Wang, Y.; Chen, Y.; Liu-Chen, L. Y.; Ma, Z.; Lee, D. Y.; Carlezon, W. A., Jr.; Cohen, B. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2761.
12. Lee, D. Y.; He, M.; Kondaveti, L.; Liu-Chen, L. Y.; Ma, Z.; Wang, Y.; Chen, Y.; Li, J. G.; Beguin, C.; Carlezon, W. A., Jr.; Cohen, B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4169.
13. Lee, D. Y. W.; Karnati, V. V. R.; He, M.; Liu-Chen, L.-Y.; Kondaveti, L.; Ma, Z.; Wang, Y.; Chen, Y.; Beguin, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3744.
14. Munro, T. A.; Goetchius, G. W.; Roth, B. L.; Vortherms, T. A.; Rizzacasa, M. A. *J. Org. Chem.* **2005**, *70*, 10057.
15. Harding, W. W.; Schmidt, M.; Tidgewell, K.; Kannan, P.; Holden, K. G.; Gilmour, B.; Navarro, H.; Rothman, R. B.; Prisinzano, T. E. *J. Nat. Prod.* **2006**, *69*, 107.
16. Dalvie, D. K.; Kalgutkar, A. S.; Khojasteh-Bakht, S. C.; Obach, R. S.; O'Donnell, J. P. *Chem. Res. Toxicol.* **2002**, *15*, 269.
17. Harding, W. W.; Tidgewell, K.; Schmidt, M.; Shah, K.; Dersch, C. M.; Snyder, J.; Parrish, D.; Deschamps, J. R.; Rothman, R. B.; Prisinzano, T. E. *Org. Lett.* **2005**, *7*, 3017.
18. Kouzi, S. A.; McMurtry, R. J.; Nelson, S. D. *Chem. Res. Toxicol.* **1994**, *7*, 850.
19. Zhou, S.; Koh, H.-L.; Gao, Y.; Gong, Z.-y.; Lee, E. J. D. *Life Sci.* **2004**, *74*, 935.
20. Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773.
21. Held, C.; Frohlich, R.; Metz, P. *Adv. Synth. Catal.* **2002**, *344*, 720.
22. Demeke, D.; Forsyth, C. J. *Org. Lett.* **2003**, *5*, 991.
23. Cheung, A. K.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 11584.
24. Tidgewell, K.; Harding, W. W.; Schmidt, M.; Holden, K. G.; Murry, D. J.; Prisinzano, T. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5099.
25. Wasley, J. W. F.; Chan, K. *Syn. Commun.* **1973**, *3*, 303.
26. Yokoyama, Y.; Matsumoto, T.; Murakami, Y. *J. Org. Chem.* **1995**, *60*, 1486.
27. Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595.
28. Koreeda, M.; Brown, L.; Valdes, L. J. ., III *Chem. Lett.* **1990**, 2015.
29. Valdes, L. J., III; Butler, W. M.; Hatfield, G. M.; Paul, A. G.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 4716.
30. Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.
31. Gu, X.; Dragovic, J.; Koo, G. C.; Koprak, S. L.; LeGrand, C.; Mundt, S. S.; Shah, K.; Springer, M. S.; Tan, E. Y.; Thieringer, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5266.
32. Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285.
33. Ni, Q.; Xu, H.; Partilla, J. S.; de Costa, B. R.; Rice, K. C.; Rothman, R. B. *Peptides* **1993**, *14*, 1279.
34. de Costa, B. R.; Iadarola, M. J.; Rothman, R. B.; Berman, K. F.; George, C.; Newman, A. H.; Mahboubi, A.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **1992**, *35*, 2826.
35. Xu, H.; Hashimoto, A.; Rice, K. C.; Jacobson, A. E.; Thomas, J. B.; Carroll, F. I.; Lai, J.; Rothman, R. B. *Synapse* **2001**, *39*, 64.
36. Satisfactory ^{1}H and ^{13}C NMR and mass spectral data were obtained for all final products. Elemental analyses were with in ±0.4%.
37. General procedure: A mixture of **3** (0.20 mg, 0.40 mmol) and methanesulfonamide (0.08 g, 0.80 mmol) in glacial acetic acid (4 mL) was heated at 95 °C for 3 h. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (2× 30 mL). The combined organic extract was washed with 1 N NaOH (2× 25 mL) and water (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude product as an oil. The oil was purified by column chromatography (eluent: EtOAc/hexanes, 50%) to give 0.06 g (30%) of **4a** and 0.05 g (25%) of 8-*epi*-**4a** as colorless oils. Compound **4a**: ^{1}H NMR ($CDCl_3$): δ 1.12 (3H, s); 1.46 (3H, s); 1.60 (3H, m); 1.81 (1H, dd, J = 3.0, 9.6); 2.09 (1H, dd, J = 2.4, 11.1); 2.18 (3H, s); 2.19 (2H, m); 2.30 (2H, m); 2.52 (1H, dd, J = 5.1, 13.5); 2.76 (1H, m); 3.16 (3H, s); 3.74 (3H, s); 5.14 (1H, dd, J = 9.3, 10.8); 5.50 (1H, dd, J = 5.1, 12); 6.34 (1H, dd, J = 1.5, 3.0); 7.09 (1H, dd, J = 1.2, 1.5); 7.11 (1H, m); ^{13}C NMR ($CDCl_3$): δ 15.1, 16.4, 18.1, 20.5, 30.8, 35.5, 38.1, 42.1, 42.9, 43.5, 51.4, 52.9, 53.6, 64.0, 73.0, 75.0, 111.7, 117.5, 121.3, 128.4, 170.0, 171.0, 171.5, 202.0; HRESIMS *m/z* $[M+H]^+$ 510.1803, (calcd for $C_{24}H_{32}NO_9S$, 510.1798); 8-*epi*-**4a**: ^{1}H NMR ($CDCl_3$): δ 1.07 (3H, s); 1.38 (3H, s); 1.62 (3H, m); 1.82 (2H, m); 2.00 (1H, m); 2.17 (3H, s); 2.31 (3H, m); 2.44 (1H, dd, J = 3.6, 11.1); 2.79 (1H, dd, J = 7.4, 8.8); 3.15 (3H, s); 3.74 (3H, s); 5.16 (1H, dd, J = 9.6, 10.2); 5.27 (1H, dd, J = 6.1, 11.6); 6.37 (1H, dd, J = 1.6, 3.3); 7.09 (1H, dd, J = 2.3, 3.2); 7.13 (1H, dd, J = 2.0, 2.0); ^{13}C NMR ($CDCl_3$): δ 16.1, 18.2, 20.6, 21.2, 30.6, 35.2, 37.7, 42.4, 43.0, 44.9, 47.4, 52.0, 53.5, 65.9, 71.3, 75.0, 112.1, 117.9, 121.3, 127.0, 170.0, 171.5, 173.0, 201.8; HRESIMS *m/z* $[M+H]^+$ 510.1798, (calcd for $C_{24}H_{32}NO_9S$, 510.1798).
38. Preparation of **5**: A mixture of the C-13 acid[15] (0.03 g, 0.73 mmol), EDCI (0.03 g, 1.93 mmol), HOBT (0.02 g, 1.55 mmol), L-serine methyl ester hydrochloride (0.03 g, 1.45 mmol), and NEt_3 (0.3 mL, 2.15 mmol) in CH_2Cl_2 (30 mL) was stirred at rt for 6 h. The mixture was then washed sequentially with 2 N HCl (40 mL) and water (40 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude product as an oil. The oil was purified by flash chromatography (eluent: MeOH/CH_2Cl_2, 2%) to afford the β-hydroxy amide (0.03 g, 75%) as a white foam. Deoxo-Fluor (0.12 mL) was added dropwise with stirring to a solution of the β-hydroxy amide (0.02 g, 0.39 mmol) in CH_2Cl_2 (40 mL) at −30 °C. The reaction mixture was stirred at −30 °C for 2 h and was quenched with saturated $NaHCO_3$ (20 mL). The organic layer was collected and washed with water (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give a brown oil. The oil was purified by flash chromatography (eluent: EtOAc/hexanes, 80%) to afford

0.01 g (74%) of **5** as a white foam. ^{1}H NMR ($CDCl_3$): δ 1.06 (3H, s); 1.35 (3H, s); 1.55 (3H, m); 1.75 (2H, m); 2.08 (1H, m); 2.14 (3H, s); 2.19 (1H, m); 2.27 (2H, m); 2.50 (1H, dd, J = 6.6, 13.5); 2.71 (1H, dd, J = 7.2, 9.6); 3.70 (3H, s); 3.78 (3H, s); 4.47 (1H, dd, J = 9.0, 10.8); 4.56 (1H, dd, J = 8.1, 8.7); 4.76 (1H, ddd, J = 0.6, 7.8, 10.8); 5.14 (2H, m); ^{13}C NMR ($CDCl_3$): δ 15.9, 16.4, 18.3, 20.8, 30.9, 35.4, 38.1, 39.3, 42.2, 50.6, 52.2, 53.0, 53.7, 64.3, 68.1, 70.5, 71.1, 75.1, 167.6, 170.1, 170.2, 171.0, 171.7, 201.9; Anal. ($C_{24}H_{31}NO_{10}\cdot 1.25H_2O$): C, H, N.

39. Preparation of **6**: $BrCCl_3$ (0.14 g, 0.71 mmol) and DBU (110 μL, 0.71 mmol) were added sequentially to a solution of **5** (0.10 g, 0.20 mmol) in CH_2Cl_2 (30 mL) at 5 °C. The reaction mixture was stirred for 1.5 h and then quenched by the addition of saturated $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined CH_2Cl_2 portion was dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford a crude residue. The residue was purified by flash chromatography (eluent: EtOAc/hexanes, 40–50%) to afford 0.08 g (80%) of **6** as a white solid, mp 201–203 °C: ^{1}H NMR ($CDCl_3$): δ 1.13 (3H, s); 1.47 (3H, s); 1.62 (3H, m); 1.82 (1H, dd, J = 2.7, 9.9); 2.06 (1H, s); 2.17 (3H, s); 2.24 (1H, dd, J = 2.7, 11.4); 2.29 (3H, m); 2.60 (1H, dd, J = 6.0, 13.5); 2.77 (1H, dd, J = 5.7, 11.1); 3.75 (3H, s); 3.94 (3H, s); 5.15 (1H, dd, J = 8.4, 11.4); 5.65 (1H, dd, J = 6.3, 11.4); 8.25 (1H, s); ^{13}C NMR ($CDCl_3$): δ 15.5, 16.5, 18.3, 20.7, 30.9, 35.5, 38.2, 39.4, 42.2, 51.1, 52.2, 52.6, 53.7, 64.0, 70.8, 75.2, 133.8, 145.1, 161.8, 161.3, 169.9, 170.0, 171.7, 202.0; Anal. ($C_{24}H_{29}NO_{10}$): C, H, N.

40. Preparation of **7**: A mixture of the C-13 acid[15] (0.05 g, 0.12 mmol), EDCI (0.05 g, 0.32 mmol), HOBT (0.04 g, 0.26 mmol), acetamide oxime (0.04 g, 0.28 mmol), and NEt_3 (0.3 mL, 2.15 mmol) in CH_2Cl_2 (30 mL) was stirred at rt for 6 h. The mixture was then washed sequentially with 2 N HCl (40 mL) and water (40 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude ester. A solution of the ester in toluene (30 mL) was then heated at reflux overnight. The solvent was removed under reduced pressure to afford a crude residue. The crude residue was purified by column chromatography (eluent: EtOAc/hexanes, 40%) to afford 0.03 g (56%) of **7** as an oil: ^{1}H NMR ($CDCl_3$): δ 1.12 (3H, s); 1.48 (3H, s); 1.64 (3H, m); 1.83 (1H, dd, J = 2.7, 9.9); 1.92 (1H, dd, J = 11.1, 13.5); 2.18 (3H, s); 2.29 (4H, m); 2.42 (3H, s); 2.66 (1H, dd J = 6.6, 13.5); 2.74 (1H, dd, J = 7.2, 9.9); 3.74 (3H, s); 5.15 (1H, dd, J = 9.6, 10.2); 5.74 (1H, dd, J = 6.6, 10.5); ^{13}C NMR ($CDCl_3$): δ 11.7, 15.7, 16.5, 18.3, 20.8, 30.9, 35.6, 38.1, 40.1, 42.2, 51.0, 52.2, 53.7, 64.1, 69.7, 75.1, 167.6, 169.4, 170.1, 171.6, 176.0, 201.9; HRESIMS m/z $[M+H]^+$ 449.1924, (calcd for $C_{22}H_{29}N_2O_8$, 449.1940).

41. Preparation of **8**: NEt_3 (71 μL, 0.5 mmol) and phenyl dichlorophosphate (50.3 μL, 0.34 mmol) were added to a solution of C-13 acid[15] (0.07 g, 0.17 mmol) in THF (20 mL) at 0 °C. After 30 min, NEt_3 (117 μL, 0.84 mmol) and selenophenol (71 μL, 0.68 mmol) were added and the solution was warmed to room temperature. Et_2O (100 mL) was added and the mixture was washed with saturated NaCl (50 mL). The organic portion was dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford a crude oil. The oil was purified by column chromatography (eluent: EtOAc/hexanes, 40%) to afford 0.06 g of the phenyl seleno ester. A solution of the phenyl seleno ester (0.06 g, 0.11 mmol), tri-*n*-butyltin hydride (87 μL, 0.33 mmol), and a catalytic amount of AIBN (0.007 g) in toluene (20 mL) was heated at reflux for 3 h. The solvent was then removed under reduced pressure to afford a crude residue. The crude residue was purified by column chromatography (eluent: EtOAc/hexanes, 40%) to afford 0.03 g (70%) of **8** as a white solid, mp 203–206 °C: ^{1}H NMR ($CDCl_3$): δ 1.09 (3H, s); 1.29 (1H, m); 1.36 (3H, s); 1.57 (2H, m); 1.61 (1H, s); 1.71 (1H, m); 1.80 (1H, dd, J = 3.3, 12.0); 2.07 (1H, m); 2.19 (3H, s); 2.30 (3H, m); 2.77 (1H, dd, J = 6.9, 9.9); 3.74 (3H, s); 4.31 (1H, dd, J = 6.0, 12.0); 4.41 (1H, m); 5.15 (1H, dd, J = 9.6, 10.5); ^{13}C NMR ($CDCl_3$): δ 16.4, 17.7, 18.4, 20.8, 30.9, 35.1, 37.0, 38.2, 42.4, 49.9, 52.2, 53.8, 65.2, 65.5, 75.3, 170.2, 171.8, 172.6, 202.1; Anal ($C_{19}H_{26}O_7$): C, H, O.