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Asymmetric Synthesis of the ABC-Ring System of the Antitumor Antibiotic MPC1001

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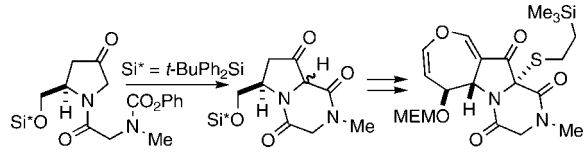
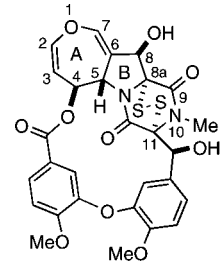


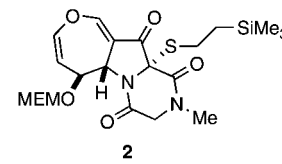
trans-4-Hydroxy-L-proline was converted into a tricyclic compound representing three contiguous rings of the anticancer antibiotic MPC1001. The tricyclic model contains the dihydrooxepin and diketopiperazine subunits, as well as one of the sulfur atoms of the natural product. The diketopiperazine unit was formed by a new method that involves cyclization of an enolate onto the carbonyl of a phenyl carbamate, and the dihydrooxepin ring was generated by using an acid-induced cyclization of an alcohol onto the β-carbon of a vinylogous amide.

Introduction

MPC1001 (**1**)[1] is a member of a group of naturally occurring dithiodiketopiperazines that incorporate a dihydrooxepin unit.[2−8] Several of these dihydrooxepins have significant biological properties,[9] and MPC1001 itself shows very strong in vitro activity against the DU145 prostate cancer cell line, with IC_{50} values for MPC1001, adriamycin, mitomycin C, and etoposide being 9.3, 20, 25, and 400 nmol/L, respectively.[1a,b] No member of the dihydrooxepin dithiodiketopiperazine family of natural products has been synthesized, and there is little published information about the pharmacophore(s) responsible for the biological activity.[1c]



MPC1001 (**1**)



2

In an earlier publication,[10] we reported a method for constructing the dihydrooxepin subunit; here, we describe the formation of the more advanced tricyclic model **2** by applying our dihydrooxepin synthesis to a suitable diketopiperazine which was itself formed by a new method.

(1) Isolation and structure of MPC1001: (a) Tsumagari, N.; Nakai, R.; Onodera, H.; Hasegawa, A.; Rahayu, E. S.; Ando, K.; Yamashita, Y. *J. Antibiot.* **2004**, *57*, 532–534. (b) Onodera, H.; Hasegawa, A.; Tsumagari, N.; Nakai, R.; Ogawa, T.; Kanda, Y. *Org. Lett.* **2004**, *6*, 4101–4104. (c) Herath, K. B.; Jayasuriya, H.; Ondeyka, J. G.; Polishook, J. D.; Bills, G. F.; Dombrowski, A. W.; Cabello, A.; Vicario, P. P.; Zweerink, H.; Guan, Z.; Singh, S. B. *J. Antibiot.* **2005**, *58*, 686–694.

(2) Seya, H.; Nozawa, K.; Nakajima, S.; Kawai, K.; Udagawa, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 109–116.

(3) (a) Ooike, M.; Nozawa, K.; Kawai, K.-I. *Phytochemistry* **1997**, *46*, 123–126. (b) Seya, H.; Nozawa, K.; Udagawa, S.; Nakajima, S.; Kawai, K. *Chem. Pharm. Bull.* **1986**, *34*, 2411–2416.

(4) (a) Nagarajan, R.; Neuss, N.; Marsh, M. M. *J. Am. Chem. Soc.* **1968**, *90*, 6518–6519. (b) Murdock, K. C. *J. Med. Chem.* **1974**, *17*, 827–835, and references quoted therein.

(5) (a) Nagarajan, R.; Huckstep, L. L.; Lively, D. H.; DeLong, D. C.; Marsh, M. M.; Neuss, N. *J. Am. Chem. Soc.* **1968**, *90*, 2980–2982. (b) Moncrief, J. W. *J. Am. Chem. Soc.* **1968**, *90*, 6517–6518. (c) Cosulich, D. B.; Nelson, N. R.; van den Hende, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 6519–6521.

(6) Hegde, V. R.; Dai, P.; Patel, M.; Das, P. R.; Puar, M. S. *Tetrahedron Lett.* **1997**, *38*, 911–914.

(7) For related compounds in which the disulfide bridge has been cleaved, see: (a) Chinworrungsee, M.; Kittakoop, P.; Saenboonrueng, J.; Kongsaeree, P.; Thebtaranonth, Y. *J. Nat. Prod.* **2006**, *69*, 1404–1410. (b) Kirby, G. W.; Robins, D. J.; Stark, W. M. *J. Chem. Res., Synop.* **1986**, 302–303.

(8) (a) Kawahara, N.; Nakajima, S.; Yamazaki, M.; Kawai, K. *Chem. Pharm. Bull.* **1989**, *37*, 2592–2595. (b) Kawahara, N.; Nozawa, K.; Yamazaki, M.; Nakajima, S.; Kawai, K. *Chem. Pharm. Bull.* **1990**, *38*, 73–78. (c) Kawahara, N.; Nozawa, K.; Yamazaki, M.; Nakajima, S.; Kawai, K. *Heterocycles* **1990**, *30*, 507–515.

(9) Chemokine receptor antagonist activity, ref 1c; antiviral activity, refs 4b and 5c; antibacterial activity, refs 1a, 3b, and 7; antifungal activity, ref 2; inhibition of epidermal growth factor, ref 6; inhibition of compound 48/80-induced histamine release, ref 8; antimalarial activity, ref 7; anticancer properties, ref 1.

(10) Peng, J.; Clive, D. L. J. *Org. Lett.* **2007**, *9*, 2939–2941.

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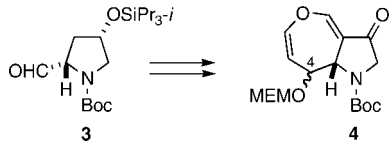
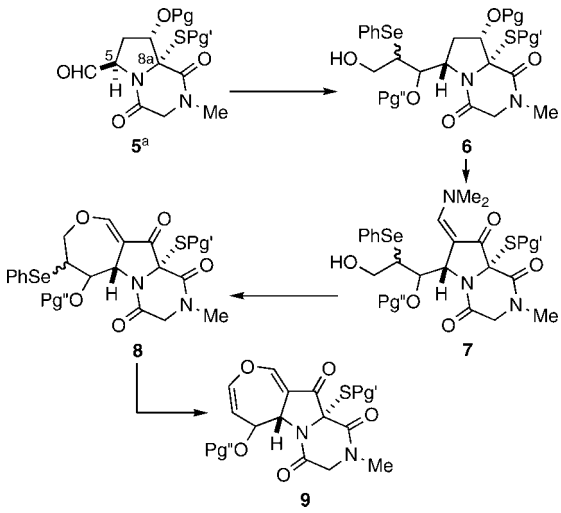
SCHEME 1. Initial Model Study

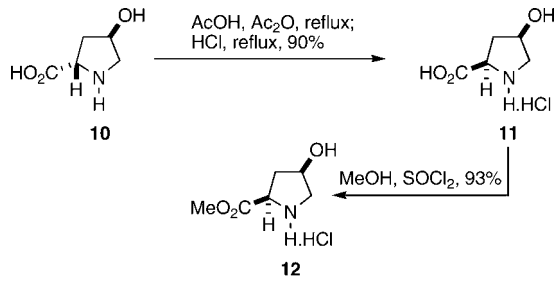


SCHEME 2. Synthetic Plan[a]



[a] Pg, Pg′, Pg″ = protecting groups.

SCHEME 3. Preparation of Amino Acid Ester 12

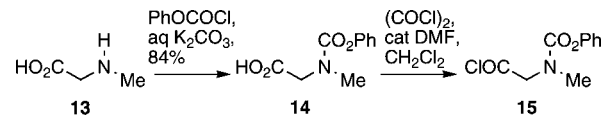


Results and Discussion

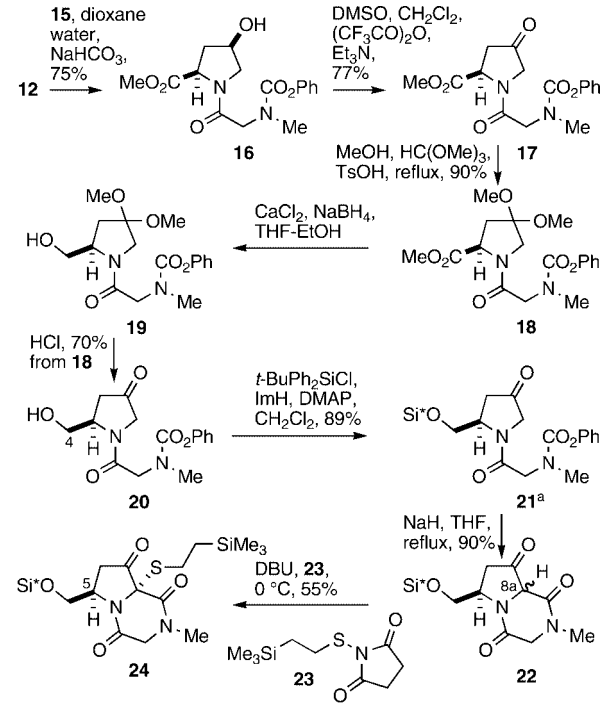
In our initial studies,[10] we had converted the aldehyde **3** into the epimeric bicyclic dihydrooxepins **4** (Scheme 1). Based on that experience, we then sought to make a tricyclic model that incorporated the diketopiperazine ring, and our approach is summarized in Scheme 2. The presence of the additional ring and stereocenter at C(8a) introduces a number of complications; in particular, in constructing intermediate **5**, a method was required to control the stereochemistry at C(8a), and this was done by a proper choice of stereochemistry at C(5), as described below.

Our starting point was *trans*-4-hydroxy-L-proline (**10**). This was converted (Scheme 3) by a literature method[11] into *cis*-4-hydroxy-D-proline hydrochloride (**11**) which was esterified in a standard way (**11** → **12**). The other required component (see **15**) was made (Scheme 4) from *N*-methylglycine (**13**) via the

SCHEME 4. Preparation of Carbamate Unit



SCHEME 5. Formation of Diketopiperazine Unit[a]



[a] Si* = *t*-BuPh$_2$Si.

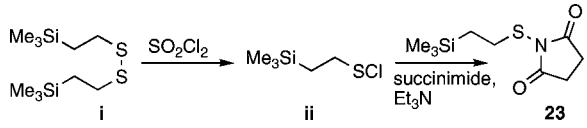
phenyl carbamate (**14**). The corresponding acid chloride **15** was then used to acylate the nitrogen of the hydroxyproline ester **12** (**12** → **16**, Scheme 5). The newly attached pendant in **16** would eventually be used to construct the diketopiperazine substructure by intramolecular attack of an enolate on the phenyl carbamate carbonyl. To prepare for that key step, several minor modifications were made to the functional groups of **16**. First, the hydroxy group was oxidized under Swern conditions and the resulting ketone was temporarily protected as a dimethyl ketal (**16** → **17** → **18**). At this point, the ester group was reduced using $NaBH_4$ in the presence of $CaCl_2$,[12] and the resulting hydroxy ketal **19** was hydrolyzed with hydrochloric acid (**19** → **20**). Finally, protection of the hydroxy group as a *t*-BuPh$_2$Si ether gave the substrate **21** for the intended cyclization. In the event, this ring closure required extensive exploratory work, but was eventually achieved in good yield (90%) by treatment of **21** with NaH in hot (70 °C) THF. The product (**22**) was obtained initially as a single compound, but it quite rapidly changed to a mixture of tautomers. In the sequence leading to **22**, the phenyl carbamate unit serves both as a nitrogen protecting group and later as a source of two of the permanent structural atoms; the cyclization **21** → **22** represents a new method for generating the diketopiperazine ring system.[13] The choice of a bulky protecting group for the C(4) hydroxy in **20** was based on our expectation that its size would direct sulfenylation of **22** at C(8a) in the correct stereochemical sense. For the sulfenylation step, we examined a number of reagents and conditions but eventually settled on the use of **23**, which

(11) (a) Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954–2960. (b) Heindl, C.; Hübner, H.; Gmeiner, P. *Tetrahedron: Asymmetry* **2003**, *14*, 3141–3152. (c) Marusawa, H.; Setoi, H.; Sawada, A.; Kuroda, A.; Seki, J.; Motoyama, Y.; Tanaka, H. *Bioorg. Med. Chem.* **2002**, *10*, 1399–1415.

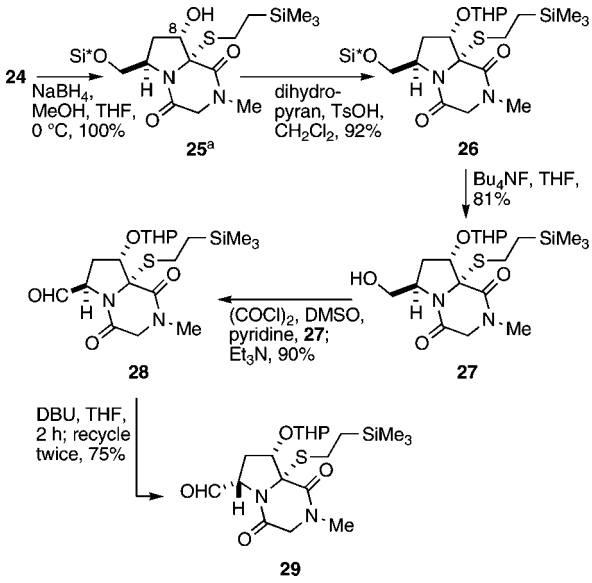
(12) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316–1323.

(13) For recent advances in the synthesis of diketopiperazines, see: Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297–3312.

SCHEME 6. Preparation of Reagent 23



SCHEME 7. Aldehyde Epimerization[a]



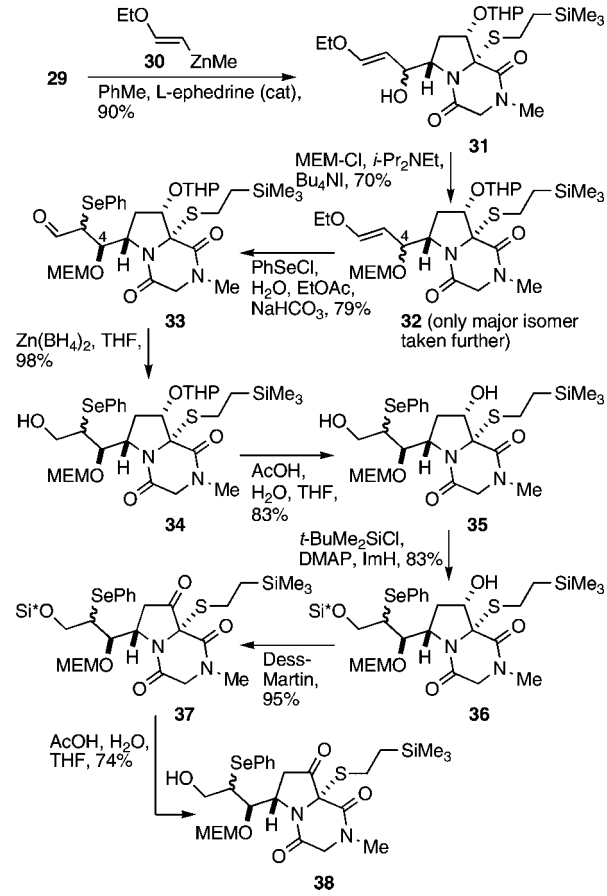
[a] Stereochemical assignment at C(8) is arbitrary.

was made as summarized in Scheme 6.[14,15] With this reagent we could isolate the protected sulfide **24** in 55% yield. A small amount (13%) of the C(8a) epimeric sulfide was also isolated. When we had protected the C(4) hydroxy of **20** as a *t*-BuMe$_2$Si or *i*-Pr$_3$Si ether, the stereoselectivity of corresponding sulfenylations was similar. At this stage (compound **24**) we were able to confirm the indicated C(8a)-stereochemistry by X-ray crystallographic analysis (see Figure 1 in the Supporting Information for ORTEP diagram).

The C(5) substituent in **24**, having served as a stereochemical directing group for introduction of the sulfur unit, now had to be modified by stereochemical inversion at C(5) and then homologation. To this end, the ketone carbonyl was reduced (Scheme 7, **24** → **25**) and the resulting alcohol [for which we show an arbitrary C(8) stereochemistry] was protected in the form of the THP ethers **26**. Use of the THP group introduced an inconvenient degree of complexity in the NMR spectra of the next few intermediates because of the additional asymmetric center of the THP unit, but this form of protection was necessary because attempts to ketalize the carbonyl group of **24** were unsuccessful and the use of 2-methoxypropene to protect alcohol **25** gave a ketal that was insufficiently stable for convenient handling. Desilylation of **26**, followed by Swern oxidation, led to aldehyde **28**. At this point, base treatment (catalytic DBU) effected the desired C(5) epimerization and, although it was necessary to recycle recovered aldehyde **28**, the desired product (**29**) could be isolated in acceptable yield (75%).

The inverted C(5) chain was now homologated (Scheme 8, **29**→**30**) by reaction with the (ethoxyvinyl)zinc reagent **30** in

SCHEME 8. Side-Chain Homologation[a]



[a] Si* = *t*-BuMe$_2$Si.

the presence of L-ephedrine.[16−18] The epimeric alcohols **31** were then masked as their MEM ethers **32**—this protecting group was used because of its satisfactory performance in our model study.[10] While the epimeric alcohols **31** were chromatographically inseparable, the derived MEM ethers **32** could be separated easily, and for the present exploration we used the major (1.3:1) epimer. Its C(4)-stereochemistry was later established as *S* (see structure **33**) on the basis of ^{1}H NMR measurements made on the final model (**2**).[20]

From **32**, the required homologation was easily achieved. Reaction with PhSeCl (**32** → **33**) simultaneously served to produce an aldehyde and to install a PhSe group that would later be used to generate an olefinic bond. Reduction of the newly formed aldehyde (**33** → **34**) was achieved with Zn-

(14) For related reagents, see, for example: Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797.

(15) Schwan, A. L.; Brillon, D.; Dufault, R. *Can. J. Chem.* **1994**, *72*, 325–333.

(16) (a) Miyaura, N.; Maeda, K.; Suginome, H. *J. Org. Chem.* **1982**, *47*, 2117–2120. (b) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170–173.

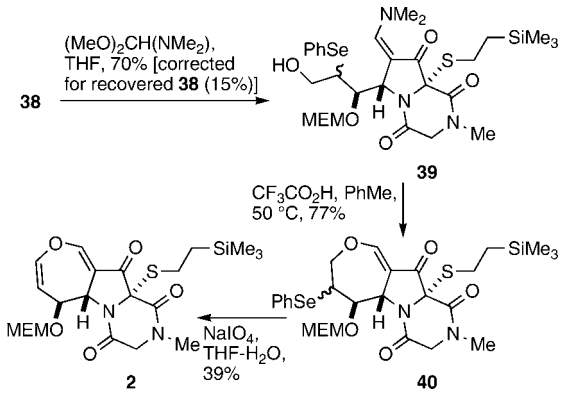
(17) Chaloner, P. A; Langadianou, E.; Perera, S. A. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2731–2735.

(18) (a) Use of *Z*-1-bromo-2-ethoxyethene/*t*-BuLi, which had been successful in our model study (ref 10), gave a complex mixture. We also tried a zinc−ate complex (cf. ref 19), but this reaction was too slow at−78 °C to be useful and gave a poor yield at a higher temperature. For related observations, see: (b) Keck, G. E.; Truong, A. P. *Org. Lett.* **2005**, *7*, 2149–2152.

(19) Wender, P. A.; Baryza, J. L.; Bennett, C. E.; Bi, F. C.; Brenner, S. E.; Clarke, M. O.; Horan, J. C.; Kan, C.; Lacote, E.; Lippa, B.; Nell, P. G.; Turner, T. M. *J. Am. Chem. Soc.* **2002**, *124*, 13648–13649.

(20) The ^{1}H NMR spectrum of **2** clearly indicated the C(4) stereochemistry because $^3J_{C(4)H-C(5)H}$ is 8.0 Hz, which corresponds closely to the value (7.7 Hz) in the natural product (ref 1b). The corresponding coupling constants for the two epimers of **4** are <3 and 7.8 Hz for cis and trans C(4) and C(5) hydrogens, respectively.

SCHEME 9. Formation of Tricyclic Model



$(BH_4)_2$[21] in very high yield (98%), and the THP ether group was then removed (aqueous AcOH). At this point, the primary hydroxy of **35** was protected (*t*-$BuMe_2SiCl$) in order to allow selective oxidation of the remaining secondary hydroxy—a process readily effected with the Dess—Martin reagent (**35** → **36** → **37**). We had initially protected the primary hydroxy of **35** as an acetate, but the subsequent oxidation proceeded poorly (under Swern conditions); moreover, hydrolysis of the resulting keto acetate was also low-yielding. The *t*-$BuMe_2Si$ group masking the primary hydroxy of **37** was removable (74%) by treatment with aqueous AcOH without disturbing either the sulfur protecting group or the MEM ether (**37** → **38**).

The hydroxy ketone **38** is a key intermediate, as it is correctly constituted for elaboration of the dihydrooxepin ring by the procedure we had developed in our earlier[10] model study. Guided by that work, we treated **38** with both Bredereck's reagent and dimethylformamide dimethyl acetal (Scheme 9). In each case, the required vinylogous amides **39** were formed (as a single geometrical isomer of unestablished stereochemistry), but on the basis of one experiment with Bredereck's reagent, the dimethylformide acetal appeared to be more efficient (70% yield corrected for recovered **38**). When the vinylogous amides were exposed to the action of CF_3CO_2H in warm PhMe (50 °C), ring closure occurred and the C(3) epimeric phenyl selenides **40** were isolated in 77% yield. Finally, oxidation of the selenium led to the desired dihydrooxepin **2** (39%), representing the ABC ring system of MPC1001. As compound **2** contains only one sulfur group, it also resembles the naturally occurring MPC1001 analog MPC1001F.[1b]

Experimental Section

Phenyl [2-[(2*R*)-2-(2-Hydroxymethyl)-4-oxopyrrolidin-1-yl]-2-oxoethyl]methylcarbamate (20). Anhydrous $CaCl_2$ (4.84 g, 43.61 mmol) was added to a stirred and cooled (0 °C) solution of methyl ester **18** (15.70 g, 39.65 mmol) in a mixture of THF (50 mL) and EtOH (50 mL), and then $NaBH_4$ (3.40 g, 87.22 mmol) was added in one portion. Stirring was continued for 3 h, the mixture was acidified with hydrochloric acid (1 M), and stirring was continued overnight. The solution was diluted with EtOAc, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using EtOAc—MeOH mixtures from pure EtOAc to 1:20 MeOH—EtOAc, gave **20** (8.45 g, 70%) as a solid: mp 65—67 °C; $[\alpha]_D = -13.6$ (CH_2Cl_2, *c* 1.30); FTIR (CH_2Cl_2, cast film microscope) 3438, 2936, 1763, 1722, 1657, 1456, 1340 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.28—2.32 (m, 1 H), 2.60—2.80 (m, 1 H), 3.05 (s, 1 H), 3.18—3.22 (m, 2 H), 3.40—3.3.52 (m, 2 H), 3.58—4.00 (m, 2 H), 4.00—4.15 (m, 2.5 H), 4.30—4.42 (m, 0.5 H), 4.65—4.75 (m, 1 H), 7.05—7.15 (m, 2 H), 7.16—7.24 (m, 1 H), 7.30—7.40 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.5, 29.3, 51.8, 53.1, 56.0, 64.1, 121.7, 125.5, 129.3, 151.2, 155.8, 167.3, 208.7; exact mass (electrospray) *m/z* calcd for $C_{15}H_{18}N_2NaO_5$ (M + Na) 329.1108, found 329.1106.

(6*R*)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]tetrahydro-2-methylpyrrolo[1,2-*a*]pyrazine-1,4,8(8a*H*)-trione (22). NaH (60% in mineral oil, 610 mg, 15.20 mmol) was added to a stirred solution of ketone **21** (4.03 g, 7.42 mmol) in THF (75 mL) (Ar atmosphere). The reaction flask was lowered into a preheated oil bath (70 °C). After 15 min, TLC analysis (silica gel, EtOAc) showed all starting material had been consumed. The reaction mixture was then cooled to 0 °C, quenched with pH 7.0 buffer, and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc—hexane to 1:20 MeOH—CH_2Cl_2, gave **22** (2.34 g, 90%) as a blue, foamy solid. The material was not stable and was used within a few hours in the next step without characterization.

(6*R*,8a*R*)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]tetrahydro-2-methyl-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-1,4,8(8a*H*)-trione (24). DBU (0.10 mL, 0.62 mmol) was added to a stirred and cooled (0 °C) solution of ketone **22** (2.78 g, 6.18 mmol) and 1-[[2-(trimethylsilyl)ethyl]thio]pyrrolidine-2,5-dione (**23**) in CH_2Cl_2 (50 mL). Stirring was continued for 8 h, at which stage TLC analysis (silica, 1:15 MeOH—CH_2Cl_2) showed no **22** remained. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 1:10 EtOAc—hexane to 1:6 EtOAc—hexane, gave **24** (2.29 g, 55%) as a solid: mp 112—114 °C; $[\alpha]_D = -38.2$ (CH_2Cl_2, *c* 0.44); FTIR (CH_2Cl_2, cast film microscope) 3072, 2953, 2859, 1765, 1688, 1473, 1427, 1409, 1397 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 9 H), 0.69—0.73 (m, 2 H), 0.97 (s, 9 H), 2.60 (dd, *J* = 18.0, 2.8 Hz, 1 H), 2.77—2.86 (m, 2 H), 3.00 (s, 3 H), 3.36 (dd, *J* = 18.0, 9.0 Hz, 1 H), 3.55 (dd, *J* = 10.6, 1.7 Hz, 1 H), 3.75 (d, *J* = 17.0 Hz, 1 H), 4.25 (dd, *J* = 10.6, 2.9 Hz, 1 H), 4.34 (apparent d, *J* = 9.6 Hz, 1 H), 4.39 (d, *J* = 16.9 Hz, 1 H), 7.34—7.45 (m, 6 H), 7.50—7.59 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.7, 15.6, 19.0, 26.6, 27.1, 33.7, 36.1, 52.5, 53.2, 62.4, 62.5, 127.7, 127.8, 129.8, 129.9, 132.62, 132.64, 135.5, 135.6, 160.8, 165.4, 194.5; exact mass (electrospray) *m/z* calcd for $C_{30}H_{42}N_2NaO_4SSi_2$ (M + Na) 605.2296, found 605.2300.

(6*R*,8*S*,8a*R*)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]hexahydro-8-hydroxy-2-methyl-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-1,4-dione (25). $NaBH_4$ (370 mg, 9.74 mmol) was added portionwise to a stirred and cooled (0 °C) solution of ketone **24** (5.66 g, 9.74 mmol) in MeOH (60 mL) and THF (20 mL). The mixture was stirred for 45 min and then quenched with saturated aqueous NH_4Cl and extract with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc—hexane, gave **25** (5.66 g, 100%) as a semisolid: $[\alpha]_D = -21.1$ (CH_2Cl_2, *c* 0.73); FTIR (CH_2Cl_2, cast film microscope) 3436, 3071, 2931, 2858, 1680, 1472, 1428 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 9 H), 0.68—0.89 (m, 2 H), 1.03 (s, 9 H), 2.27 (ddd, *J* = 12.4, 7.0, 0.9 Hz, 1 H), 2.40 (apparent q, *J* = 9.5 Hz, 1 H), 2.63 (ddd, *J* = 12.2, 11.5, 5.4 Hz, 1 H), 2.86—2.95 (m, 2 H), 3.02 (s, 3 H), 3.64 (dd, *J* = 10.4, 5.1 Hz, 1 H), 3.70 (d, *J* = 17.0 Hz, 1 H), 4.07 (apparent d, *J* = 10.0 Hz, 1 H), 4.12 (dd, *J* = 10.4, 3.9 Hz, 1 H), 4.36 (d, *J* = 17.1 Hz, 1 H), 4.95 (ddd, *J* = 11.0, 7.0, 4.1 Hz, 1 H), 7.35—7.47 (m, 6 H), 7.55—7.63 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.8, 17.0, 19.1, 26.6, 26.7, 31.7, 33.1, 53.6, 55.3, 62.5, 72.3, 74.1, 127.6, 127.7, 129.6, 129.7, 132.7, 133.0, 135.4, 135.5, 164.6, 166.2; exact mass (electrospray) *m/z* calcd for $C_{30}H_{44}N_2NaO_4SSi_2$ (M + Na) 607.2453, found 607.2457.

(6*R*,8*S*,8a*R*)-6-[[(*tert*-Butyldimethylsilyl)oxy]methyl]hexahydro-2-methyl-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-1,4-dione (26). TsOH·H_2O

(21) Uemura, S.; Ohe, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 907–910.

(16 mg, 0.082 mmol) was added to a stirred solution of alcohol **25** (2.40 g, 4.11 mmol) and 2,3-dihydropyran (1.10 mL, 12.33 mmol) in CH_2Cl_2. After 30 min, powered K_2CO_3 was added, and stirring was continued for 2 h. The mixture was filtered through Celite, using CH_2Cl_2 as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel, using 1:4 EtOAc−hexane, gave **26** (2.48 g, 92%) as an oil: $[\alpha]_D = -17.8$ (CH_2Cl_2, *c* 0.47); FTIR (CH_2Cl_2, cast film microscope) 3072, 2951, 2858, 1681, 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9 H), 0.60−0.81 (m, 2 H), 1.02 (s, 9 H), 1.51−1.90 (m, 6 H), 2.24−2.40 (m, 1 H), 2.49−2.79 (m, 2 H), 3.02 (s, 3 H), 2.96−3.16 (m, 1 H), 3.44−3.55 (m, 2 H), 3.69 (d, $J = 16.7$ Hz, 1 H), 3.90−3.98 (m, 1 H), 4.00−4.15 (m, 2 H), 4.46 (d, $J = 16.8$ Hz, 0.5 H), 4.49 (d, $J = 16.8$ Hz, 0.5 H), 4.95−5.16 (m, 2 H), 7.33−7.44 (m, 6 H), 7.57−7.65 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.84, −1.81, 16.9, 17.0, 18.2, 20.0, 25.2, 25.4, 26.52, 26.54, 26.8, 27.0, 29.5, 30.1, 30.5, 32.4, 33.4, 33.6, 53.5, 53.6, 55.1, 55.6, 60.7, 62.6, 62.7, 63.1, 71.0, 71.1, 74.7, 79.8, 94.3, 100.5, 127.55, 127.59, 129.5, 129.6, 132.7, 133.0, 135.48, 135.52, 165.0, 165.2, 165.3, 165.5; exact mass (electrospray) *m*/*z* calcd for $C_{35}H_{52}N_2NaO_5SSi_2$ (M + Na) 691.3028, found 691.3034.

(6*R*,8*S*,8a*R*)-Octahydro-2-methyl-1,4-dioxo-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-6-carbaldehyde (28). DMSO (0.63 mL, 8.72 mmol) was added at a fast dropwise rate to a stirred and cooled (−78 °C) solution of $(COCl)_2$ (0.40 mL, 4.36 mmol) in CH_2Cl_2 (20 mL). After the addition, stirring was continued for 15 min and then a solution of alcohol **27** (1.25 g. 2.91 mmol) and pyridine (0.35 mL, 4.36 mmol) in CH_2Cl_2 (10 mL) was added. Stirring at −78 °C was continued for 40 min and then Et_3N (1.21 mL, 8.72 mmol) was added dropwise. The cold bath was left in place but not recharged and stirring was continued for 4 h, by which time the mixture had reached ca. −30 °C. The mixture was diluted with CH_2Cl_2 and saturated aqueous $NaHCO_3$ was added. The organic layer was separated and washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 1:1 EtOAc-hexane to pure EtOAc and finally 1:4 acetone-EtOAc, gave aldehyde **28** (1.11 g, 90%) as an oil: $[\alpha]_D = -34.6$ (CH_2Cl_2, *c* 0.49); FTIR (CH_2Cl_2, cast film microscope) 2950, 1737, 1678, 1418 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 9 H), 0.62−0.81 (m, 2 H), 1.45−1.90 (m, 6 H), 2.25−2.44 (m, 1.5 H), 2.58−2.80 (m, 1.5 H), 2.98−3.18 (m, 4 H), 3.50−3.62 (m, 1 H), 3.80−3.88 (m, 1.5 H), 4.20−4.28 (m, 0.5 H), 4.40−4.64 (m, 3 H), 4.83 (apparent s, 0.5 H), 5.05 (apparent s, 0.5 H), 9.46−9.52 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.87, −1.85, 16.6, 16.8, 18.0, 19.3, 25.1, 25.2, 26.7, 26.9, 29.0, 29.9, 30.2, 33.7, 33.9, 45.7, 52.9, 59.9, 60.4, 61.0, 62.7, 70.3, 74.2, 78.8, 94.6, 100.1, 164.3, 164.82, 164.84, 165.1, 195.5, 195.7; exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{32}N_2NaO_5SSi$ (M + Na) 451.1693, found 451.1699.

(6*S*,8*S*,8a*R*)-Octahydro-2-methyl-1,4-dioxo-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-6-carbaldehyde (29). DBU (50 μL, 0.32 mmol) was added to a stirred solution of aldehyde **28** (2.70 g, 6.31 mmol) in THF (50 mL). Stirring was continued for 1 h, and then the solvent was evaporated. Flash chromatography of the residue over silica gel, using 1:3 EtOAc−CH_2Cl_2 to 1:10 acetone−EtOAc, gave **29** (1.41 g) and recovered **28** (0.97 g). The recovered aldehyde was subjected twice more to the above conditions to provide the epimerized aldehyde **29** (2.02 g, 75% in all) as an oil: $[\alpha]_D = -68.0$ (CH_2Cl_2, *c* 0.17); FTIR (CH_2Cl_2, cast film microscope) 2950, 1737, 1678, 1418 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 9 H), 0.68−0.81 (m, 2 H), 1.55−1.88 (m, 6 H), 2.05−2.38 (m, 1 H), 2.52−2.80 (m, 2 H), 3.00−3.20 (m, 4 H), 3.55−3.62 (m, 1 H), 3.80−3.88 (m, 2 H), 4.19−4.30 (m, 1 H), 4.48−4.60 (m, 1.5 H), 4.70−4.75 (m, 0.5 H), 4.90 (apparent s, 0.5 H), 5.14 (s, 0.5 H), 9.48−9.52 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.78, −1.77, 16.6, 16.7, 18.1, 19.1, 25.28, 25.33, 26.8, 27.1, 29.2, 30.0, 30.1, 33.9, 34.0, 52.8, 60.3, 60.8, 61.2, 62.4, 70.2, 75.7, 80.3, 94.8, 99.9, 164.3, 164.5, 164.8, 164.9, 196.98, 197.05; exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{32}N_2NaO_5SSi$ (M + Na) 451.1693, found 451.1697.

(6*S*,8*S*,8a*R*)-6-[(2*E*)-3-Ethoxy-1-hydroxy-2-propenyl)]hexahydro-2-methyl-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-1,4-dione (31). $BH_3 \cdot SMe_2$ (10.0 M, 10.0 μL, 0.10 mmol) was added dropwise to a stirred and cooled (0 °C) solution of ethyl ethynyl ether (40% w/v in hexanes, 72.0 μL, 0.30 mmol) in PhMe (1.0 mL). After the addition, the cold bath was removed, and stirring was continued for 5.5 h. The mixture was recooled to 0 °C and Me_2Zn (2.0 M in PhMe, 0.19 mL, 0.38 mmol) was added. Stirring was continued for 30 min, and then a solution of aldehyde **29** (64.0 mg, 0.15 mmol) in PhMe (1.2 mL) was added to the resulting zinc reagent.

A solution of L-ephedrine (180 mg, 1.09 mmol) in dry PhMe (6 mL) was prepared during the above operations, an aliquot [58 μL, corresponding to 0.01 mmol L-ephedrine] was added dropwise to the reaction mixture, and stirring was continued for 30 min at 0 °C and for 40 h at room temperature. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:60 MeOH−CH_2Cl_2 to 1:40 MeOH−CH_2Cl_2, gave alcohols **31** (67.3 mg, 90%) as an oil: FTIR (CH_2Cl_2, cast film microscope) 3363, 2950, 1674, 1422, 1401 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9 H), 0.62−0.80 (m, 2 H), 1.29 (apparent t, $J = 7.1$ Hz, 3 H), 1.52−1.88 (m, 6 H), 2.06−2.80 (m, 3 H), 2.95−3.16 (m, 4 H), 3.52−3.60 (m, 1 H), 3.72−4.02 (m, 6 H), 4.10−4.31 (m, 1 H), 4.40−4.75 (m, 2 H), 4.88−4.92 (m, 0.3 H), 5.05−5.15 (m, 0.7 H), 5.60 (d, $J = 17.0$ Hz, 0.3 H), 6.51−6.59 (m, 0.7 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.84, −1.82, 0.92, 14.6, 16.3, 16.5, 16.7, 18.0, 19.3, 19.4, 25.2, 25.3, 25.5, 26.8, 27.0, 27.2, 27.3, 28.5, 30.0, 30.06, 30.10, 30.19, 30.24, 32.6, 33.51, 33.62, 33.69, 33.81, 52.8, 53.0, 61.00, 61.07, 62.48, 62.51, 62.8, 63.1, 63.3, 63.8, 64.3, 64.76, 64.79, 67.9, 70.49, 70.54, 70.95, 71.15, 74.2, 74.9, 76.1, 76.2, 79.2, 79.8, 94.46, 94.48, 100.1, 100.3, 102.3, 102.4, 149.97, 150.04, 164.14, 164.72, 164.79, 165.25, 166.37, 166.48, 166.89, 167.05; exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{40}N_2NaO_6SSi$ (M + Na) 523.6629, found 523.6628.

(6*S*,8*S*,8a*R*)-6-[3-Ethoxy-1-[(2-methoxyethoxy)methoxy]-2-propenyl]hexahydro-2-methyl-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-1,4-dione (32). MEM-Cl (1.19 mL, 10.44 mmol) was added to a stirred solution of alcohols **31** (1.74 g, 3.48 mmol), *i*-Pr_2NEt (3.03 mL, 17.41 mmol), and Bu_4NI (1.28 g, 3.48 mmol) in THF (40 mL). The mixture was refluxed for 24 h and cooled to (0 °C). Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 3:1 EtOAc-hexane to pure EtOAc, gave the major isomer **32** (more polar, 0.79 g, 39%) and the minor isomer **32** (less polar, 0.63 g, 31%) as oils.

The less polar isomer had: FTIR (CH_2Cl_2, cast film microscope) 2949, 1738, 1679, 1597, 1556 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.02 (s, 9 H), 0.60−0.80 (m, 2 H), 1.24 (apparent t, $J = 7.1$ Hz, 3 H), 1.42−1.88 (m, 6 H), 2.20−2.38 (m, 1.5 H), 2.46−2.68 (m, 1.5 H), 2.88−3.08 (m, 4 H), 3.30−3.40 (m, 3 H), 3.42−3.64 (m, 5 H), 3.68−3.90 (m, 5 H), 4.22−4.60 (m, 3 H), 4.72−4.80 (m, 2 H), 4.86−5.10 (m, 2 H), 6.49 (dd, $J = 12.6$, 2.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.76, −1.74, 14.6, 16.6, 16.7, 18.8, 19.3, 25.36, 25.42, 26.9, 27.0, 30.1, 30.3, 33.9, 53.39, 53.41, 58.93, 58.94, 59.5, 60.2, 61.0, 62.4, 65.16, 65.22, 66.7, 66.8, 67.4, 70.4, 70.6, 71.65, 71.72, 71.82, 71.91, 75.2, 80.0, 91.77, 91.86, 92.3, 94.5, 95.6, 99.5, 99.6, 99.9, 151.38, 151.42, 164.3, 164.5; exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{48}N_2NaO_8SSi$ (M + Na) 611.2793, found 611.2794.

The more polar isomer had: FTIR (CH_2Cl_2, cast film microscope) 2949, 2882, 1679, 1419, 1400 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9 H), 0.60−0.80 (m, 2 H), 1.27 (t, $J = 7.0$ Hz, 3 H),

1.48−1.88 (m, 6 H), 2.25−2.70 (m, 3 H), 2.90−3.04 (m, 4 H), 3.40 (s, 3 H), 3.52−3.65 (m, 5 H), 3.70−3.84 (m, 2 H), 5.85−3.96 (m, 2 H), 4.00−4.09 (m, 1 H), 4.20−4.30 (m, 1.5 H), 4.58−4.65 (m, 1.5 H), 4.70−4.82 (m, 2 H), 4.90−5.15 (m, 2 H), 6.40 (d, J = 12.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.76, 15.0, 16.5, 16.7, 18.0, 19.2, 25.35, 25.41, 26.8, 26.9, 27.0, 29.5, 30.1, 30.3, 33.7, 33.9, 53.3, 53.4, 57.7, 58.3, 59.0, 61.0, 62.3, 64.4, 64.5, 66.8, 66.9, 71.6, 71.7, 71.8, 72.8, 75.2, 76.7, 77.1, 77.4, 80.0, 92.4, 92.5, 94.6, 97.0, 97.1, 99.8, 151.6, 151.7, 164.3, 164.5; exact mass (electrospray) m/z calcd for $C_{27}H_{48}N_2NaO_8SSi$ (M + Na) 611.2793, found 611.2793. This major and more polar isomer was used for the following steps.

(3*R*)-3-[(2-Methoxyethoxy)methoxy]-3-[(6*S*,8*S*,8a*R*)-octahydro-2-methyl-1,4-dioxo-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazin-6-yl]-2-(phenylseleno)propionaldehyde (33). PhSeCl (153 mg, 0.80 mmol) in EtOAc (0.5 mL) was added over 4 min to a stirred biphasic mixture of the more polar ethyl vinyl ether **32** (0.47 g, 0.80 mmol), $NaHCO_3$ (200 mg, 2.40 mmol), EtOAc (6 mL), and water (3 mL). Stirring was continued for 40 min, and the mixture was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel using EtOAc gave aldehydes **33** (450 mg, 79%) as an oil: FTIR (CH_2Cl_2, cast film microscope) 2926, 1677, 1401 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.00 (s, 9 H), 0.60−0.80 (m, 2 H), 1.42−1.88 (m, 6 H), 2.20−2.80 (m, 3 H), 2.92−3.16 (m, 4 H), 3.28−3.40 (m, 3 H), 3.40−3.88 (m, 9 H), 4.26−4.50 (m, 2 H), 4.60−5.00 (m, 3 H), 5.00−5.18 (m, 1 H), 7.22−7.20 (m, 3 H), 7.52−7.64 (m, 2 H), 9.30−9.48 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.82, −1.82, 16.6, 18.7, 19.6, 25.2, 27.1, 30.1, 33.7, 53.2, 53.4, 57.5, 58.0, 58.9, 61.0, 62.4, 67.8, 71.3, 71.6, 72.5, 75.0, 79.7, 79.9, 94.4, 97.6, 99.9, 125.2, 128.6, 129.4, 131.4, 135.0, 135.6, 165.1, 191.4; exact mass (electrospray) m/z calcd for $C_{31}H_{48}N_2NaO_8S^{80}SeSi$ (M + Na) 739.1958, found 739.1958.

(6*S*,8*S*,8a*R*)-Hexahydro-6-[(1*R*)-3-hydroxy-1-[(2-methoxyethoxy)methoxy]-2-(phenylseleno)propyl]-2-methyl-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-1,4-dione (34). $Zn(BH_4)_2$ (0.16 M in Et_2O, 5.8 mL, 0.91 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of aldehydes **33** (0.44 g, 0.61 mmol) in THF (5 mL). Stirring was continued for 4 h. Then the mixture was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:20 MeOH−EtOAc, gave the primary alcohols **34** (0.43 g, 98%) as an oil: FTIR (CH_2Cl_2, cast film microscope) 3124, 3044, 2947, 2700, 1673, 1437, 1418 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 9 H), 0.52−0.70 (m, 2 H), 1.42−1.82 (m, 6 H), 2.20−2.40 (m, 1.5 H), 2.50−2.60 (m, 1.5 H), 2.92−3.02 (m, 4 H), 3.05−4.20 (m, 1 H), 3.30−3.40 (m, 3 H), 3.43−3.60 (m, 4 H), 3.60−3.75 (m, 3 H), 3.78−3.83 (m, 3 H), 4.18−4.28 (m, 0.5 H), 4.32−4.50 (m, 2 H), 4.57−4.70 (m, 2 H), 4.72−4.88 (m, 2 H), 5.00−5.08 (m, 0.5 H), 7.18−7.28 (m, 3 H), 7.62−7.68 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.79, −1.74, 16.4, 16.6, 18.5, 19.1, 25.35, 25.40, 26.9, 27.0, 28.9, 30.2, 31.5, 33.8, 34.0, 45.8, 48.4, 53.2, 53.3, 57.0, 58.5, 59.0, 59.4, 62.2, 63.8, 67.8, 68.1, 71.6, 75.6, 77.2, 78.0, 80.6, 94.9, 96.5, 96.8, 99.9, 127.4, 127.6, 128.9, 129.0, 129.2, 134.3, 135.4, 164.4, 164.6; exact mass (electrospray) m/z calcd for $C_{31}H_{50}N_2NaO_8S^{80}SeSi$ (M + Na) 741.2115, found 741.2115.

(6*S*,8*S*,8a*R*)-Hexahydro-8-hydroxy-6-[(1*R*)-3-hydroxy-1-[(2-methoxyethoxy)methoxy]-2-(phenylseleno)propyl]-2-methyl-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-1,4-dione (35). A solution of the primary alcohols **34** (336 mg, 0.47 mmol) in AcOH (4 mL) and water (1 mL) was stirred for 40 h. The mixture was diluted with EtOAc and water and then basified with solid $NaHCO_3$. The organic layer was separated, washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:20 MeOH−EtOAc, gave diols **35** (245 mg, 83%) as an oil: FTIR (CH_2Cl_2, cast film) 3451, 2950, 2890, 1661, 1400 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.02 (s, 9 H), 0.52−0.80 (m, 2 H), 2.20−2.35 (m, 2 H), 2.55−2.66 (m, 1 H), 2.70−2.82 (m, 1 H), 2.97 (s, 3 H), 3.20−3.40 (m, 4 H), 3.40−3.52 (m, 3 H), 3.55−3.62 (m, 2 H), 3.62−3.72 (m, 2 H), 3.75−3.88 (m, 2 H), 4.19−4.25 (m, 1 H), 4.30−4.45 (m, 2 H), 4.50−4.70 (m, 2 H), 4.75−4.80 (m, 1 H), 7.18−7.25 (m, 3 H), 7.55−7.76 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.92, −1.86, 16.1, 16.2, 25.4, 25.8, 30.7, 31.0, 33.40, 33.44, 46.8, 48.5, 53.1, 57.2, 58.4, 58.8, 62.8, 63.3, 67.7, 68.1, 71.4, 71.6, 73.3, 75.2, 75.4, 76.8, 77.1, 77.4, 78.5, 82.2, 96.4, 97.5, 127.4, 127.8, 128.0, 129.0, 129.1, 134.0, 134.9, 163.6, 163.7, 166.1; exact mass (electrospray) m/z calcd for $C_{26}H_{42}N_2NaO_7S^{80}SeSi$ (M + Na) 657.1539, found 657.1539.

(6*S*,8*S*,8a*R*)-6-[3-(*tert*-Butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-2-(phenylseleno)propyl]hexahydro-8-hydroxy-2-methyl-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-1,4-dione (36). *t*-$BuMe_2SiCl$ (88 mg, 0.58 mmol) was added to a stirred solution of diols **35** (245 mg, 0.39 mmol), imidazole (53 mg, 0.78 mmol), and DMAP (3 mg) in CH_2Cl_2 (5 mL). Stirring was continued for 48 h, and then water was added. The mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:3 EtOAc−hexane to EtOAc, gave protected alcohols **36** (240 mg, 83%) as an oil: FTIR (CH_2Cl_2, cast film) 3448, 2953, 2929, 2886, 2857, 1770, 1681, 1472, 1398 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00−0.02 (m, 15 H), 0.65−0.80 (m, 2 H), 0.82−0.86 (m, 9 H), 1.60 (br s, 1 H), 2.30−2.40 (m, 2 H), 2.65−2.82 (m, 2 H), 3.00−3.02 (m, 3 H), 3.38−3.42 (m, 4 H), 3.52−3.60 (m, 2 H), 3.70−3.80 (m, 4 H), 3.88 (t, J = 10.2 Hz, 1 H), 4.20−4.42 (m, 2 H), 4.58−4.78 (m, 2 H), 4.82 (AB q, J = 16.8 Hz, $\Delta\nu_{AB}$ = 23.5 Hz, 2 H), 7.22−7.30 (m, 3 H), 7.60−7.62 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −1.8, 16.3, 16.5, 25.2, 25.5, 25.92, 25.93, 30.5, 31.8, 33.5, 48.9, 49.1, 53.3, 57.6, 57.9, 58.9, 62.7, 64.1, 68.1, 68.2, 71.8, 73.4, 74.0, 75.7, 76.1, 79.8, 84.2, 97.4, 97.6, 127.2, 127.6, 129.0, 129.1, 129.6, 129.9, 133.7, 134.5, 162.9, 166.6; exact mass (electrospray) m/z calcd for $C_{32}H_{56}N_2NaO_7S^{80}SeSi_2$ (M + Na) 771.2404, found 771.2404.

(6*S*,8a*R*)-6-[3-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2-methoxyethoxy)methoxy]-2-(phenylseleno)propyl]tetrahydro-2-methyl-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-1,4,8(8a*H*)-trione (37). Dess−Martin periodinane (169 mg, 0.40 mmol) was added to a stirred solution of secondary alcohols **36** (199 mg, 0.27 mmol) in CH_2Cl_2 (6.7 mL). Stirring was continued for 5 h, and then saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc−hexane to 2:1 EtOAc−hexane, gave ketones **37** (189 mg, 95%) as an oil: FTIR (CH_2Cl_2, cast film) 2953, 2929, 2886, 2857, 1771, 1690, 1397 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00−0.05 (m, 15 H), 0.62−0.70 (m, 2 H), 0.80−0.92 (m, 9 H), 2.72−2.85 (m, 2 H), 3.00−3.10 (m, 5 H), 3.36−3.44 (m, 4 H), 3.57 (t, J = 5.0 Hz, 2 H), 3.68−3.82 (m, 4 H), 3.92 (t, J = 10.1 Hz, 1 H), 4.39 (dd, J = 6.9, 1.2 Hz, 1 H), 4.43 (d, J = 15.7 Hz, 1 H), 4.83 (AB q, J = 7.1 Hz, $\Delta\nu_{AB}$ = 36.1 Hz, 2 H), 4.98−5.04 (m, 1 H), 7.20−7.28 (m, 3 H), 7.55−7.60 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −1.72, −1.69, 16.0, 16.1, 25.8, 25.9, 27.0, 27.1, 34.4, 39.4, 49.1, 49.3, 52.8, 52.9, 54.1, 54.7, 59.0, 62.9, 63.7, 63.9, 64.4, 68.2, 68.3, 71.6, 71.7, 78.9, 81.7, 96.9, 97.4, 127.3, 129.0, 129.1, 129.6, 133.7, 134.4, 160.6, 160.7, 164.3, 164.4, 199.0, 199.6; exact mass (electrospray) m/z calcd for $C_{32}H_{54}N_2NaO_7S^{80}SeSi_2$ (M + Na) 769.2248, found 769.2247.

(6*S*,8a*R*)-Tetrahydro-6-[3-hydroxy-1-[(2-methoxyethoxy)methoxy]-2-(phenylseleno)propyl]-2-methyl-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-1,4,8-trione (38). A solution of the silyl-protected alcohols **37** (19.8 mg, 0.027 mmol) in AcOH (0.4 mL), water (0.13 mL), and THF (0.13 mL) was stirred for 2 days, and then saturated aqueous $NaHCO_3$ was added. The

mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:1 EtOAc−hexane, gave primary alcohols **38** (12.4 mg, 74%) as an oil: FTIR (CH_2Cl_2, cast film microscope) 3465, 2951, 2928, 2893, 1769, 1682, 1478, 1340 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 0.63−0.73 (m, 2 H), 2.60−2.88 (m, 3 H), 3.00−3.04 (m, 4 H), 3.40 (s, 3 H), 3.41−3.48 (m, 1 H), 3.50−3.62 (m, 3 H), 3.70−3.92 (m, 4 H), 4.34 (d, J = 7.4 Hz, 1 H), 4.40−4.50 (m, 1 H), 4.85 (AB q, J = 6.8 Hz, $\Delta\nu_{AB}$ = 50.7 Hz, 2 H), 5.14 (apparent t, J = 7.4 Hz, 1 H), 7.20−7.30 (m, 3 H), 7.52−7.63 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.73, −1.71, 16.0, 16.2, 27.2, 27.3, 34.3, 38.1, 38.9, 48.0, 49.8, 52.7, 52.8, 54.7, 55.2, 58.96, 58.99, 62.4, 62.88, 62.94, 63.7, 68.0, 68.8, 71.5, 71.7, 78.6, 82.8, 96.7, 97.5, 127.6, 128.3, 129.0, 129.2, 129.3, 134.0, 135.4, 160.3, 160.6, 164.4, 165.3, 198.6, 199.2; exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{40}N_2NaO_7S^{80}SeSi$ (M + Na) 655.1383, found 655.1374.

(6*S*,8a*R*)-7-[(Dimethylamino)methylene]tetrahydro-6-[3-hydroxy-1-[(2-methoxyethoxy)methoxy]-2-(phenylseleno)propyl]-2-methyl-8a-[[2-(trimethylsilyl)ethyl]thio]pyrrolo[1,2-*a*]pyrazine-1,4,8-trione (39). A solution of ketones **38** (20.0 mg, 0.032 mmol) and *N,N*-dimethylformamide dimethyl acetal (9.8 μL, 0.073 mmol) in THF (0.8 mL) was refluxed for 44 h (Ar atmosphere). Evaporation of the solvent and flash chromatography of the residue over silica gel, using pure EtOAc to 1:20 MeOH−EtOAc, and finally 1:10 MeOH−CH_2Cl_2, gave recovered ketones **38** (3.0 mg) and vinylogous amides **39** (13.0 mg, 70% corrected for recovered starting material) as a yellow oil: FTIR (CH_2Cl_2, cast film microscope) 3384, 2919, 1671, 1591 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 0.60−0.80 (m, 2 H), 1.80−1.90 (m, 1 H), 2.71−2.82 (m, 1 H), 2.90−3.05 (m, 4 H), 3.10 (s, 2 H), 3.15 (s, 4 H), 3.30−3.42 (m, 5 H), 3.51−3.61 (m, 2 H), 3.62−3.80 (m, 5 H), 3.82−4.98 (m, 2 H), 4.35 (apparent s, 0.5 H), 4.45−4.60 (m, 0.5 H), 4.70−4.85 (m, 1.5 H), 5.10−5.18 (m, 0.5 H), 5.35 (s, 0.7 H), 5.75 (s, 0.3 H), 7.20−7.30 (m, 3 H), 7.52−7.88 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.6, 16.8, 25.6, 26.8, 27.0, 27.2, 34.4, 49.4, 49.6, 52.8, 52.9, 59.0, 59.4, 60.0, 61.9, 62.1, 64.2, 67.9, 68.0, 68.6, 71.6, 71.69, 71.74, 77.4, 83.3, 95.6, 95.7, 97.9, 98.2, 127.1, 127.9, 128.2, 129.0, 129.1, 129.6, 133.6, 135.1, 147.7, 150.4, 162.2, 164.9, 166.0; exact mass (electrospray) *m*/*z* calcd for $C_{29}H_{45}N_3NaO_7S^{80}SeSi$ (M + Na) 710.1805, found 710.1804.

(5a*S*,6*S*,11a*R*)-2,3,5a,6,7,8-Hexahydro-6-[(2-methoxyethoxy)-methoxy]-2-methyl-7-(phenylseleno)-11a-[[2-(trimethylsilyl)ethyl]thio]oxepino[3′,4′:4,5]pyrrolo[1,2-*a*]pyrazine-1,4,11(11a*H*)-trione (40). CF_3CO_2H (2.2 μL, 0.029 mmol) was added to a stirred solution of vinylogous amides **39** (18.0 mg, 0.026 mmol) in PhMe (1.5 mL) and the mixture was heated and stirred for 50 h at 50 °C. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 1:1 EtOAc−hexane to pure EtOAc, and then 1:20 MeOH−EtOAc, gave the recovered amides **39** (3.0 mg) and cyclized products **40** (10.8 mg, 77% corrected for recovered starting material) as an oil: FTIR (CH_2Cl_2, microscope) 3057, 2925, 1731, 1692, 1621, 1462, 1400 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02−0.10 (m, 9 H), 0.72−0.88 (m, 2 H), 2.96−3.08 (m, 5 H), 3.40 (s, 2.1 H), 3.42 (s, 0.9 H), 3.55−3.65 (m, 2 H), 3.68−3.75 (m, 2 H), 3.82−3.90 (m, 1 H), 4.06−4.10 (m, 0.3 H), 4.10 (AB q, J = 15.8 Hz, $\Delta\nu_{AB}$ = 237.7 Hz, 2 H), 4.14 (dd, J = 13.5, 4.0 Hz, 0.7 H), 4.30 (dd, J = 10.0, 4.0 Hz, 0.7 H), 4.49 (dd, J = 9.6, 6.6 Hz, 0.3 H), 4.88 (AB q, J = 7.0 Hz, $\Delta\nu_{AB}$ = 24.6 Hz, 2 H), 4.96 (d, J = 7.4 Hz, 0.3 H), 5.00 (d, J = 13.3 Hz, 0.7 H), 5.65 (dd, J = 10.2, 1.7 Hz, 0.7 H), 5.69 (dd, J = 9.4, 1.7 Hz, 0.3 H), 7.25−7.40 (m, 3 H), 7.47 (d, J = 1.7 Hz, 0.3 H), 7.50 (d, J = 1.7 Hz, 0.7 H), 7.63−7.67 (m, 0.6 H), 7.68−7.72 (m, 1.4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.7, 15.8, 27.2, 34.2, 47.0, 48.7, 52.3, 52.4, 55.1, 56.1, 59.0, 63.2, 67.7, 68.6, 68.9, 71.6, 71.7, 80.4, 83.2, 106.8, 109.0, 127.5, 127.6, 128.3, 128.7, 129.3, 129.4, 135.0, 136.0, 157.4, 157.7, 160.5, 163.2, 163.6, 185.9; exact mass (electrospray) *m*/*z* calcd for $C_{27}H_{38}N_2NaO_7S^{80}SeSi$ (M + Na) 665.1226, found 665.1228.

(5a*S*,6*S*,11a*R*)-2,3,5a,6-Tetrahydro-6-[(2-methoxyethoxy)methoxy]-2-methyl-11a-[[2-(trimethylsilyl)ethyl]thio]oxepino[3′,4′:4,5]pyrrolo[1,2-*a*]pyrazine-1,4,11(11a*H*)-trione (2). $NaIO_4$ (0.10 M in H_2O, 0.14 mL, 0.014 mmol) was added dropwise to a stirred and cooled (0 °C) solution of selenides **40** (9.0 mg, 0.014 mmol) in a mixture of THF (0.3 mL) and water (0.2 mL). The cold bath was removed after 30 min, and stirring was continued overnight. The mixture was then diluted with CH_2Cl_2 and basified with saturated aqueous $NaHCO_3$. The organic phase was washed with brine, dried (Mg_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:1 EtOAc−hexane to 8:3 EtOAc−hexane, and finally pure EtOAc, gave the dihydrooxepin **2** (2.6 mg, 39%) as an oil: FTIR (CH_2Cl_2, microscope) 2917, 1731, 1692, 1621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 0.65−0.75 (m, 2 H), 2.80−2.90 (m, 2 H), 3.04 (s, 3 H), 3.40 (s, 3 H), 3.55−3.60 (m, 2 H), 3.70−3.78 (m, 2 H), 4.08 (AB q, J = 16.0 Hz, $\Delta\nu_{AB}$ = 228.9 Hz, 2 H), 4.49 (ddd, J = 8.0, 2.2, 2.2 Hz, 1 H), 4.90 (AB q, J = 7.2 Hz, $\Delta\nu_{AB}$ = 38.3 Hz, 2 H), 5.02 (dd, J = 8.0, 2.2 Hz, 1 H), 5.22 (dd, J = 8.3, 2.0 Hz, 1 H), 6.36 (dd, J = 8.4, 2.3 Hz, 1 H), 7.62 (d, J = 2.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.7, 15.6, 26.9, 29.7, 34.2, 52.4, 57.6, 59.1, 67.5, 71.6, 76.4, 95.7, 110.1, 112.2, 138.4, 151.4, 160.3, 163.3, 185.4; exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{32}N_2NaO_7SSi$ (M + Na) 507.1592, found 507.1593.

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Supporting Information Available: Experimental procedures for **11**, **12**, **14**–**18**, **21**, **23**, and **27** X-ray structure data for **24**, and spectral data, as well as copies of NMR spectra, for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. The X-ray data has been deposited with the Cambridge Crystallographic Data Centre and assigned the registry no. 699177.

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