SYNTHESIS OF A NOVEL 6,5-BICYCLIC HEXAHYDROPYRIDAZINE DERIVATIVE

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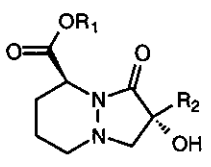
Abstract-A convergent synthesis of the 6,5-bicyclic hexahydropyridazine derivative (**3**) is described in which *(3S)*-N^1-Cbz-piperazic acid methyl ester (**4**) is coupled with the functionalized carboxylic acid fragment (**9**). The Sharpless asymmetric dihydroxylation reaction (AD) of the 1,1-disubstituted olefin (**6**) is utilized in the preparation of **9** and is observed to produce the corresponding diol with 44% enantiomeric excess and *R* stereochemistry.

In the course of the development of novel immunosuppressive agents, we required an efficient means of preparing 6,5-bicyclic hexahydropyridazine derivatives of general structure (**1**). To the best of our knowledge, molecules of class **1** have not been previously synthesized, although extensive studies have been conducted with structurally related angiotensin converting enzyme inhibitors typified by cilazapril (**2**).[2] Herein we describe a convergent synthesis of the bicyclic piperazic acid (**3**) which we believe is applicable to the preparation of a variety of molecules belonging to class **1**.



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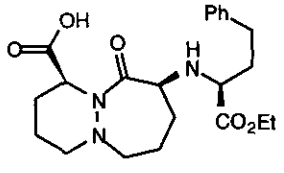

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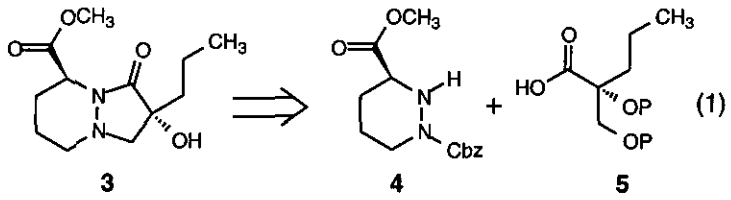
Retrosynthetic analysis suggested that the bicyclic core of **3** could be constructed from *(3S)-N*^{1}-Cbz-piperazic acid methyl ester (**4**) and a fragment which incorporated both a carboxylic acid and a protected diol moiety (**5**, eq 1, P = undetermined protecting groups). Ester (**4**) was synthesized in 58% yield by

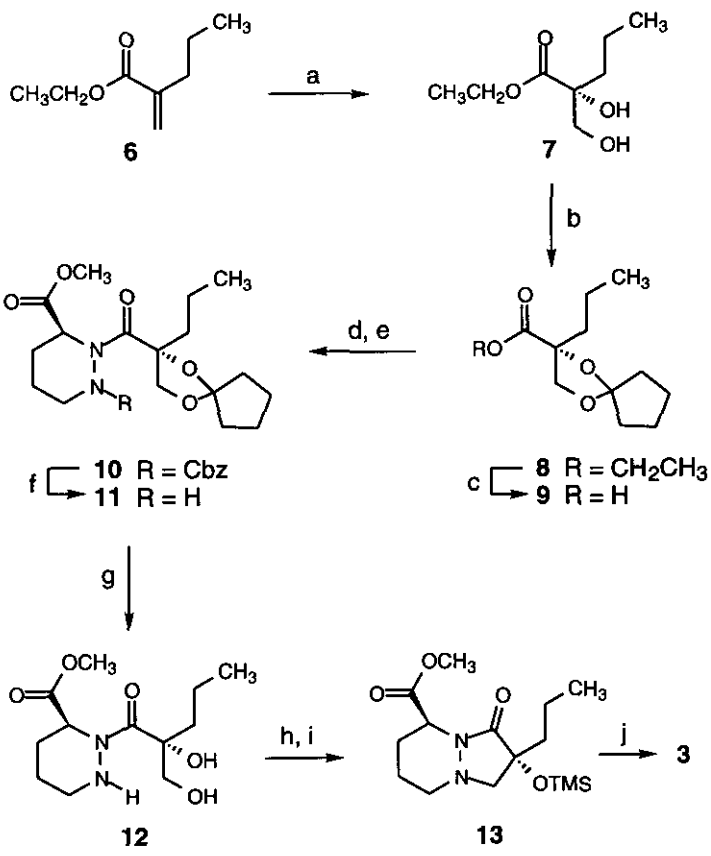


3 **4** **5**

refluxing a methanol solution of *(3S)-N*^{1}-Cbz-piperazic acid[3] (~96% ee) and *p*-toluenesulfonic acid monohydrate for 12 h. Preparation of the acid-containing fragment commenced with the osmium-catalyzed asymmetric dihydroxylation (AD) of 2-methylenepentanoic acid ethyl ester (**6**)[4] which provided diol (**7**) in 98% yield after flash column chromatography (Scheme 1).[5] As detailed below, the enantiomeric excess of **7** thus obtained was determined to be 44% with the predominant isomer depicted in Scheme 1. Previous experimentation had established the cyclopentylidene ketal as an effective 1,2-diol protecting group for utilization in the synthesis of **3**. Accordingly, diol (**7**) was treated with an excess of cyclopentanone and a catalytic amount of pyridinium *p*-toluenesulfonate in benzene at reflux with azeotropic removal of water to provide ketal (**8**) in 86% yield after purification on silica gel. The ester moiety of ketal (**8**) was hydrolyzed in near quantitative yield by exposure to methanolic sodium hydroxide at ambient temperature, and the resulting carboxylic acid (**9**) was subsequently transformed into the corresponding acid chloride by treatment with oxalyl chloride and a catalytic amount of *N,N*-dimethylformamide in benzene at 23 °C. The crude acid chloride thus obtained was coupled with *(3S)-N*^{1}-Cbz-piperazic acid methyl ester (**4**) in the presence of *N,N*-diisopropylethylamine in dichloromethane at 23 °C to provide pure amide (**10**) in 56% yield after careful flash column chromatography.[6] Interestingly, analogous reactions employing acyclic diol protecting groups (e.g., bis-OTBDMS, bis-OAc) in lieu of the cyclopentylidene ketal afforded poor yields of the desired coupling product. Amide (**10**) contained all of the carbon atoms present in the target structure (**3**), and required only the formation of a carbon-nitrogen bond to complete the 6,5-bicyclic framework.

Accordingly, the Cbz protecting group of amide (**10**) was removed by treatment with excess ammonium formate in the presence of palladium on carbon in ethanol at 45 °C to provide amine (**11**) in 84% yield.[7] Although exposure of this compound to several acidic media resulted in its decomposition, treatment of

Scheme 1[a]



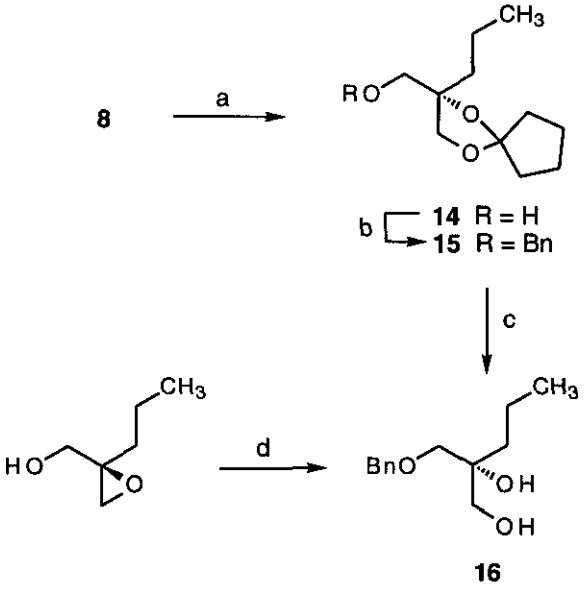
[a]Reagents and conditions (TMS = $Si(CH_3)_3$): (a) AD-mix-β, 1:1 *t*-BuOH:H_2O, 0 °C, 8 h, 98%; (b) 2.5 equiv. cyclopentanone, 0.07 equiv. PPTS, benzene, 80 °C, 10 h, 86%; (c) 3.0 equiv. NaOH, CH_3OH, 23 °C, 1 h, 92%; (d) 1.05 equiv. oxalyl chloride, 0.05 equiv. DMF, benzene, 23 °C, 1.5 h; (e) 0.67 equiv. **4**, 1.07 equiv. $(i\text{-Pr})_2NEt$, CH_2Cl_2, 23 °C, 18 h, 56% from **9**; (f) 5.0 equiv. HCO_2NH_4, 10% Pd on C, EtOH, 45 °C, 30 min, 84%; (g) 0.25 M $HClO_4$, 5:1 THF:H_2O, 23 °C, 12 h, 81%; (h) 2.0 equiv. PPh_3, 2.0 equiv. CCl_4, 1.9 equiv. Et_3N, CH_2Cl_2, 40 °C, 3 h; (i) 2.0 equiv. 2,6-lutidine, 1.5 equiv. TMSOTf, CH_2Cl_2, 0 °C, 1 h, 64% from **12**; (j) HF-pyridine, MeCN, 23 °C, 30 min, 71%.

11 with perchloric acid in aqueous tetrahydrofuran at 23 °C cleanly provided diol (**12**) in 84% yield after purification on silica gel. The described order of protecting group removal avoided problematic side reactions which occurred during attempted deketalization of amide (**10**). The bicyclic structure of the target molecule was assembled by refluxing a solution of diol (**12**) in dichloromethane in the presence of excess triphenylphosphine, carbon tetrachloride, and triethylamine.[8] The crude alcohol (**3**) thus obtained was most conveniently separated from contaminating triphenylphosphine oxide by conversion to the

corresponding trimethylsilyl ether. Thus, treatment of impure **3** with 2,6-lutidine and trimethylsilyl trifluoromethanesulfonate in dichloromethane at 0 °C afforded trimethylsilyl ether (**13**) in 64% yield from diol (**12**) after flash column chromatography. Removal of the silyl protecting group by exposure of **13** to hydrogen fluoride-pyridine in acetonitrile at 23 °C provided pure **3** in 71% yield following purification on silica gel.

The level and absolute sense of asymmetric induction obtained in the dihydroxylation of 2-methylenepentanoic acid ethyl ester (**6**) was determined as outlined below. Ketal (**8**) was reduced with diisobutylaluminum hydride to provide alcohol (**14**) in 86% yield following workup and flash column chromatography (Scheme 2). Transformation of **14** to the corresponding *(S)*-MTPA ester and ^{1}H nmr analysis revealed that the enantiomeric excess obtained in the AD reaction was 44%.[9] In addition, treatment of **14** with sodium hydride and benzyl bromide in anhydrous *N,N*-dimethylformamide afforded the corresponding benzyl ether (**15**) in good yield, which was subsequently converted to diol (**16**) in 50% yield by exposure to dilute perchloric acid in a 10:1 mixture of tetrahydrofuran and water. Alternatively, diol (**16**) was prepared from near optically pure *(2R)*-2-propyloxiranemethanol[10] by treatment with

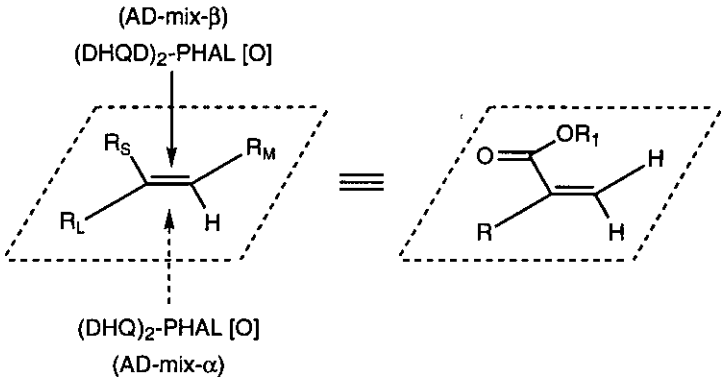
Scheme 2[a]



[a]Reagents and conditions (Bn = benzyl): (a) 2.2 equiv. DIBAL, toluene, -78→0 °C, 3 h, 86%; (b) 1.1 equiv. BnBr, 1.1 equiv. NaH, THF, 23 °C, 10 h, 78%; (c) 0.25 M $HClO_4$, 10:1 THF:H_2O, 23 °C, 40 h, 50%; (d) 2.0 equiv. Na, BnOH, 80 °C, 30 min, 37%

sodium benzyl alkoxide at 23 °C. Comparison of the optical rotations of the two diols identified the major enantiomer of **7** obtained from the AD reaction as that shown in Scheme 1 (*R* stereochemistry, see experimental section).[11] The observed asymmetric induction can be rationalized using the Sharpless mnemonic in which the alkyl group of the 1,1-disubstituted olefin substrate is considered to be larger than the ester moiety (Figure 1).[12] Such a model is consistent with the observation that 2-methylenepentanoic acid benzyl ester affords the corresponding diol in essentially 0% ee when subjected to the identical AD conditions.[13]

Figure 1



In summary, a convergent synthesis of the 6,5-bicyclic hexahydropyridazine (**3**) is described which can provide ready access to piperazic acid derivatives of general structure (**1**). In addition to the preparation of compound (**3**) reported in this work, the above procedure has been successfully applied to the synthesis of other bicyclic piperazic acids belonging to this general class.

EXPERIMENTAL SECTION

All reactions were performed in septum-sealed flasks under a slight positive pressure of argon unless otherwise noted. All commercial reagents and solvents were used as received from their respective suppliers with the following exceptions. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use. Flash column chromatography[14] was performed using silica gel 60 (Merck Art 9385). ^{1}H Nmr and ^{13}C nmr spectra were recorded at 300 and 75 MHz respectively utilizing a Varian UNITY*plus* 300

spectrometer. Chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane. Infrared absorption spectra were recorded using a Perkin-Elmer 1600 series FTIR. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

***(3S)-N*^{1}-Cbz-Piperazic Acid Methyl Ester (4).** *p*-Toluenesulfonic acid monohydrate (1.90 g, 10.0 mmol, 1.2 equiv.) was added to a solution of *(3S)-N*^{1}-Cbz-piperazic acid[3] (2.20 g, 8.32 mmol, 1 equiv.) in methanol (100 ml) at 23 °C. The reaction mixture was refluxed for 12 h, then was cooled to 23 °C and was concentrated. The brown oil thus obtained was partitioned between saturated aqueous $NaHCO_3$ (100 ml) and EtOAc (3 x 100 ml). The combined organic layers were dried over Na_2SO_4, and were concentrated. The residue was purified by flash column chromatography (gradient elution, 30%→40% EtOAc in hexanes) to afford *(3S)-N*^{1}-Cbz-piperazic acid methyl ester (**4**) (1.34 g, 58%) as a colorless oil: R_f = 0.38 (50% EtOAc in hexanes); ir (film) 3305, 1740, 1696 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.59-1.81 (m, 3 H), 2.06-2.11 (m, 1 H), 3.14 (t, 1 H, *J* = 11.2 Hz), 3.55-3.59 (m, 1 H), 3.74 (s, 3 H), 4.00-4.04 (m, 1 H), 5.19 (s, 2 H), 7.29-7.39 (m, 5 H); ^{13}C nmr ($CDCl_3$) δ 23.1, 27.2, 44.5, 51.8, 58.1, 67.3, 127.7, 127.9, 128.3, 136.2, 155.0, 171.2. Anal. Calcd for $C_{14}H_{18}N_2O_4$ C: 60.42, H: 6.52, N: 10.07. Found C: 60.44, H: 6.44, N: 10.10. $[\alpha]^{25}_D$ = -30.8° (c = 2.6, $CHCl_3$).

***(2R)*-2-Hydroxy-2-hydroxymethylpentanoic Acid Ethyl Ester (7).** 2-Methylenepentanoic acid ethyl ester[4] (2.04 g, 14.3 mmol) was added to a suspension of AD-mix-β (Aldrich, 20.0 g) in a 1:1 mixture of *tert*-butyl alcohol and water (140 ml) at 0 °C. The heterogeneous reaction mixture was stirred at 0 °C for 8 h after which sodium metabisulfite ($Na_2S_2O_5$, 16 g) was added in small portions. The dark green mixture was vigorously stirred at 23 °C for 45 min, then was partitioned between water (150 ml) and a 1:1 mixture of EtOAc and hexanes (3 x 150 ml). The combined organic layers were dried over Na_2SO_4, and were concentrated. The residue was purified by flash column chromatography (40% EtOAc in hexanes) to afford diol (**7**) (2.48 g, 98%) as a colorless oil: R_f = 0.34 (50% EtOAc in hexanes); ir (film) 3456 (br), 1731 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 0.91 (t, 3 H, *J* = 7.2 Hz), 1.08-1.28 (m, 1 H), 1.32 (t, 3 H, *J* = 7.2 Hz), 1.42-1.70 (m, 3 H), 2.13 (dd, 1 H, *J* = 9.5, 3.3 Hz), 3.54 (s, 1 H), 3.59 (dd, 1 H, *J* = 11.2, 2.3 Hz), 3.79 (t, 1 H, *J* = 10.4 Hz), 4.23-4.32 (m, 2 H); ^{13}C nmr ($CDCl_3$) δ 14.1, 16.4, 37.0, 62.2, 67.9, 78.6, 175.2. Anal. Calcd for $C_8H_{16}O_4$ C: 54.53, H: 9.15. Found C: 54.54, H: 9.11. $[\alpha]^{25}_D$ = +11.1° (c = 4.0, $CHCl_3$, 44% ee).

***(2R)*-2-Propyl-1,4-dioxaspiro[4.4]nonane-2-carboxylic Acid Ethyl Ester (8).** Diol (**7**) (2.48 g, 14.1 mmol, 1 equiv.), cyclopentanone (3.11 ml, 35.2 mmol, 2.5 equiv.) and pyridinium *p*-toluenesulfonate

(0.25 g, 1.0 mmol, 0.07 equiv.) were refluxed in benzene (60 ml) with azeotropic removal of water for 10 h. The reaction mixture was cooled to 23 °C, and was partitioned between water (100 ml) and a 1:1 mixture of EtOAc and hexanes (2 x 150 ml). The combined organic layers were dried over Na_2SO_4, and were concentrated. Purification of the residue by flash column chromatography (5% EtOAc in hexanes) afforded ketal (**8**) (2.94 g, 86%) as a colorless oil: R_f = 0.82 (30% EtOAc in hexanes); ir (film) 1755, 1729 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.92 (t, 3 H, *J* = 7.3 Hz), 1.30 (t, 3 H, *J* = 7.2 Hz), 1.39-1.52 (m, 1 H), 1.61-1.97 (m, 11 H), 3.76 (d, 1 H, *J* = 8.8 Hz), 4.17-4.29 (m, 3 H); ^{13}C nmr ($CDCl_3$) δ 14.1, 17.2, 23.3, 23.5, 36.1, 36.7, 38.5, 61.2, 71.6, 83.7, 120.6, 173.4. Anal. Calcd for $C_{13}H_{22}O_4$ C: 64.44, H: 9.15. Found C: 64.54, H: 9.04. $[\alpha]^{25}_D$ = +3.12° (c = 2.2, $CHCl_3$, 44% ee).

***(2R)*-2-Propyl-1,4-dioxaspiro[4.4]nonane-2-carboxylic Acid (9).** Powdered sodium hydroxide (1.50 g, 37.5 mmol, 3.0 equiv.) was added to a solution of ketal (**8**) (2.90 g, 12.0 mmol, 1 equiv.) in methanol (25 ml) at 23 °C. The resulting suspension was stirred for 1 h at 23 °C, then was partitioned between water (100 ml) and Et_2O (100 ml). The aqueous layer was acidified to pH = 4 with 10% aqueous $KHSO_4$ then were extracted with EtOAc (2 x 150 ml). The combined organic layers were dried over Na_2SO_4 and were concentrated to give acid (**9**) (viscous oil, 2.38 g, 92% crude yield) which was used without further purification; ir (film) 3474 (br), 3193 (br), 1729 cm^{-1}; ^1H nmr (C_6D_6) δ 0.73 (t, 3 H, *J* = 7.2 Hz), 1.23-1.30 (m, 1 H), 1.32-1.50 (m, 5 H), 1.63-1.84 (m, 6 H), 3.45 (d, 1 H, *J* = 8.9 Hz), 4.18 (d, 1 H, *J* = 8.9 Hz).

***(2'R,3S)*-N^1-(Cbz)-2-(2'-Propyl-1',4'-dioxaspiro[4.4]nonane-2'-carbonyl)hexahydropyridazine-3-carboxylic Acid Methyl Ester (10).** Oxalyl chloride (0.492 ml, 5.64 mmol, 1.05 equiv.) and *N,N*-dimethylformamide (20 μl, 0.258 mmol, 0.05 equiv.) were added sequentially to a solution of crude acid (**9**) (1.15 g, 5.37 mmol, 1 equiv.) in benzene (10 ml) at 23 °C resulting in vigorous gas evolution. The reaction mixture was stirred at 23 °C for 1.5 h after which gas evolution was not observed. Toluene (6 ml) was added and the mixture was concentrated. The resulting crude acid chloride was dissolved in CH_2Cl_2 then transferred via cannula to a 23 °C solution of *(3S)*-N^1-Cbz-piperazic acid methyl ester (**4**, 1.00 g, 3.59 mmol, 0.67 equiv.) and *N,N*-diisopropylethylamine (1.00 ml, 5.74 mmol, 1.07 equiv.) in CH_2Cl_2 (15 ml). The reaction mixture was maintained at 23 °C for 18 h, then was partitioned between water (100 ml) and a 1:1 mixture of EtOAc and hexanes (2 x 150 ml). The combined organic layers were dried over Na_2SO_4, and were concentrated. Purification of the residue by careful flash column chromatography (20% EtOAc in hexanes) afforded pure amide (**10**) (0.959 g, 56%) as a pale yellow oil: R_f = 0.45 (30% EtOAc in hexanes); ir (film) 1739, 1714, 1676 cm^{-1}; ^1H nmr (1:1 mixture of rotamers,

$CDCl_3$) δ 0.67 (t, *J* = 7.0 Hz), 0.83-1.00 (m), 1.00-1.38 (m), 1.43-1.90 (m), 1.92-2.06 (m), 2.23 (d, *J* = 13.0 Hz), 2.88-3.04 (m), 3.49 (s), 3.71-3.83 (m), 4.13-4.28 (m), 4.62 (d, *J* = 9.1 Hz), 4.97 (d, *J* = 12.1 Hz), 5.12-5.24 (m), 5.58-5.64 (m), 7.30- 7.37 (m); ^{13}C nmr (1:1 mixture of rotamers, $CDCl_3$) δ 14.0, 14.1, 16.8, 16.9, 20.1, 22.3, 23.1, 23.4, 23.5, 25.4, 31.5, 36.4, 39.9, 44.2, 51.9, 57.8, 67.8, 71.1, 84.5, 84.6, 120.3, 128.0, 128.2, 128.4, 128.5, 136.0, 154.6, 169.3, 169.6. Anal. Calcd for $C_{25}H_{34}N_2O_7$ C: 63.28, H: 7.22, N: 5.90. Found C: 63.06, H: 7.26, N: 5.81.

***(2'R,3S)*-2-(2'-Propyl-1',4'-dioxaspiro[4.4]nonane-2'-carbonyl)hexahydropyridazine-3-carboxylic Acid Methyl Ester (11).** Palladium on activated carbon (10%, 0.10 g) was added to a suspension of amide (**10**) (0.959 g, 2.02 mmol, 1 equiv.) and ammonium formate (0.637 g, 10.1 mmol, 5.0 equiv.) in ethanol (15 ml) at 23 °C. The resulting black suspension was stirred at 45 °C for 30 min, then was cooled to 23 °C and was filtered through Celite®. The clear filtrate was concentrated to ~15 ml volume, then was partitioned between saturated aqueous $NaHCO_3$ (100 ml) and EtOAc (3 x 100 ml). The combined organic layers were dried over Na_2SO_4, and were concentrated. The residue was purified by rapid flash column chromatography (50% EtOAc in hexanes) to provide amine (**11**) (0.578 g, 84%) as a colorless oil: R_f = 0.52 (50% EtOAc in hexanes); ir (film) 3263, 1740, 1668 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.92 (t, 3 H, *J* = 7.3 Hz), 1.24-1.58 (m, 3 H), 1.61-2.05 (m, 12 H), 2.26 (d, 1 H, *J* = 13.4 Hz), 2.67-2.99 (m, 1 H), 3.03 (d, 1 H, *J* = 2.0 Hz), 3.77 (s, 3 H), 4.04 (d, 1 H, *J* = 9.2 Hz), 4.11 (d, 1 H, *J* = 9.2 Hz), 4.14 (d, 1 H, *J* = 1.7 Hz), 5.31 (dd, 1 H, *J* = 5.7, 1.5 Hz); ^{13}C nmr (1:1 mixture of rotamers, $CDCl_3$) δ 14.3, 14.4, 16.9, 17.1, 22.0, 22.1, 22.9, 23.0, 23.9, 25.6, 35.2, 35.6, 36.0, 36.2, 39.5, 39.8, 46.7, 51.3, 51.4, 52.4, 71.2, 71.3, 84.8, 84.9, 119.1, 119.4, 171.7, 171.9, 173.9. Anal. Calcd for $C_{17}H_{28}N_2O_5$ C: 59.98, H: 8.29, N: 8.23. Found C: 60.06, H: 8.37, N: 8.23.

***(2'R,3S)*-2-(2'-Hydroxy-2'-hydroxymethylpentanoyl)hexahydropyridazine-3-carboxylic Acid Methyl Ester (12).** Aqueous perchloric acid (60%, 0.30 ml) was added dropwise to a solution of amine (**11**) (0.513 g, 1.51 mmol) in a 5:1 mixture of THF and water (12 ml) at 23 °C. The reaction mixture was stirred at 23 °C for 12 h, then was partitioned between saturated aqueous $NaHCO_3$ (100 ml) and EtOAc (3 x 100 ml). The combined organic layers were dried over Na_2SO_4, and were concentrated. Purification of the residue by flash column chromatography (20% hexanes in EtOAc) afforded diol (**12**) (0.337 g, 81%) as a colorless oil: R_f = 0.13 (50% EtOAc in hexanes); ir (film) 3428 (br), 3274, 1737, 1634 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.92 (t, 3 H, *J* = 7.3 Hz), 1.20-1.38 (m, 1 H), 1.39-1.70 (m, 3 H), 1.93-2.05 (m, 2 H), 2.26 (d, 1 H, *J* = 13.6 Hz), 2.47 (dd, 1 H, *J* = 9.8, 4.2 Hz), 2.83-3.09 (m, 2 H), 3.64 (dd, 1 H, *J* = 11.1, 4.1

Hz), 3.79 (s, 3 H), 4.01 (t, 1 H, J = 10.4 Hz), 4.44 (d, 1 H, J = 11.9 Hz), 5.33 (dd, 1 H, J = 5.7, 1.3 Hz), 5.55 (s, 1 H); ^{13}C nmr (major rotamer, $CDCl_3$) δ 14.3, 16.3, 21.4, 25.4, 37.4, 46.6, 52.1, 52.5, 67.9, 80.2, 171.5, 174.6. Anal. Calcd for $C_{12}H_{22}N_2O_5$ C: 52.54, H: 8.08, N: 10.21. Found C: 52.46, H: 8.15, N: 10.12.

***(2S,5S)*-3-Oxo-2-propyl-2-trimethylsilyloxyhexahydropyrazolo[1, 2-*a*]pyridazine-5-carboxylic Acid Methyl Ester (13).** Triphenylphosphine (0.574 g, 2.19 mmol, 2.0 equiv.), carbon tetrachloride, (0.211 ml, 2.19 mmol, 2.0 equiv.) and triethylamine (0.290 ml, 2.08 mmol, 1.9 equiv.) were added sequentially to a solution of diol (**12**) (0.300 g, 1.09 mmol, 1 equiv.) in CH_2Cl_2 (8 ml) at 23 °C. The reaction mixture was refluxed for 3 h, then was cooled to 23 °C. Methanol (6 ml) was added and the mixture was concentrated. The residue was passed through a short column of silica gel (eluting with 30% hexanes in EtOAc) to provide alcohol (**3**) contaminated with triphenylphosphine oxide. A -78 °C solution of crude **3** in CH_2Cl_2 (8 ml) was treated sequentially with 2,6-lutidine (0.245 ml, 2.18 mmol, 2.0 equiv.) and trimethylsilyl trifluoromethanesulfonate (0.327 ml, 1.63 mmol, 1.5 equiv.), then was maintained at 0 °C for 1 h. The reaction mixture was partitioned between 0.5 M aqueous HCl (100 ml) and a 1:1 mixture of EtOAc and hexanes (2 x 100 ml). The combined organic layers were dried over Na_2SO_4, and were concentrated. The residue was purified by flash column chromatography (gradient elution, 5→20% EtOAc in hexanes) to provide trimethylsilyl ether (**13**) (0.238 g, 64%) as a colorless oil: R_f = 0.81 (30% hexanes in EtOAc); ir (film) 1745, 1710 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 0.19 (s, 9 H), 0.96 (t, 3 H, J = 7.3 Hz), 1.40-1.84 (m, 7 H), 2.33-2.43 (m, 2 H), 2.67 (d, 1 H, J = 9.9 Hz), 3.06-3.10 (m, 1 H), 3.51 (d, 1 H, J = 9.9 Hz), 3.74 (s, 3 H), 4.85 (d, 1 H, J = 5.4 Hz); ^{13}C nmr ($CDCl_3$) δ 1.7, 14.1, 16.0, 21.4, 23.9, 37.7, 52.3, 52.4, 56.5, 63.7, 78.0, 169.6, 170.8. Anal. Calcd for $C_{15}H_{28}N_2O_4Si$ C: 54.85, H: 8.59, N: 8.53. Found C: 54.90, H: 8.63, N: 8.50.

***(2S,5S)*-2-Hydroxy-3-oxo-2-propylhexahydropyrazolo[1,2-*a*]pyridazine-5-carboxylic Acid Methyl Ester (3).** Hydrogen fluoride-pyridine (0.30 ml) was added *via* plastic pipette to a solution of trimethylsilyl ether (**13**) (0.229 g, 0.697 mmol) in CH_3CN (6 ml) in a plastic centrifuge tube at 23 °C. The reaction mixture was stirred at 23 °C for 30 min then was partitioned between 0.25 M aqueous HCl (100 ml) and EtOAc (3 x 100 ml). The combined organic layers were dried over Na_2SO_4, and were concentrated. The residue was purified by flash column chromatography (30% hexanes in EtOAc) to provide alcohol (**3**) (0.127 g, 71%) as a colorless oil: R_f = 0.23 (30% hexanes in EtOAc); ir (film) 3380 (br), 1744, 1693 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 0.98 (t, 3 H, J = 7.3 Hz), 1.44-1.80 (m, 7 H), 2.34-2.42 (m, 2

H), 2.72 (d, 1 H, J = 10.0 Hz), 2.96 (s, 1 H), 3.11-3.15 (m, 1 H), 3.57 (d, 1 H, J = 10.0 Hz), 3.76 (s, 3 H), 4.87 (d, 1 H, J = 5.1 Hz); ^{13}C nmr ($CDCl_3$) δ 14.2, 16.0, 21.4, 23.8, 37.3, 52.5, 52.6, 56.7, 62.1, 75.7, 169.4, 172.0; HRms ($C_{12}H_{20}N_2O_4$, M^+) Calcd: 256.1423, Found: 256.1430. Anal. Calcd for $C_{12}H_{20}N_2O_4$ C: 56.23, H: 7.87, N: 10.93. Found C: 56.01, H: 7.81, N: 10.65. $[\alpha]^{25}_D$ = -88.5° (c = 2.5, $CHCl_3$).

***(2S)*-(2-Propyl-1,4-dioxaspiro[4.4]non-2-yl)methanol (14).** Diisobutylaluminum hydride (13.6 ml of a 1.5 M solution in toluene, 20.4 mmol, 2.2 equiv.) was added to a solution of ketal (**8**) (2.25 g, 9.29 mmol, 1 equiv.) in toluene (60 ml) at -78 °C. The reaction mixture was stirred at -78 °C for 45 min, then was maintained at 0 °C for 3 h. The reaction mixture was partitioned between a solution of sodium/potassium tartrate (5 g) in saturated aqueous $NaHCO_3$ (150 ml) and a 1:1 mixture of EtOAc and hexanes (100 ml) and was stirred for 1 h. The resulting biphasic solution was separated and the aqueous phase was extracted with a 1:1 mixture of EtOAc and hexanes (150 ml). The combined organic layers were dried over Na_2SO_4, and were concentrated. Purification of the residue by flash column chromatography (30% EtOAc in hexanes) afforded alcohol (**14**) (1.60 g, 86%) as a colorless oil: R_f = 0.40 (30% EtOAc in hexanes); ir (film) 3450 (br) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 0.94 (t, 3 H, J = 7.3 Hz), 1.28-1.39 (m, 2 H), 1.51-1.91 (m, 10 H), 3.49 (dd, 1 H, J = 11.3, 6.6 Hz), 3.57 (dd, 1 H, J = 11.3, 6.1 Hz), 3.71 (d, 1H, J = 8.5 Hz), 3.85 (d, 1 H, J = 8.5 Hz); ^{13}C nmr ($CDCl_3$) δ 14.5, 17.1, 23.2, 23.4, 37.0, 37.1, 37.2, 65.3, 69.7, 83.0, 119.2. Anal. Calcd for $C_{11}H_{20}O_3$ C: 65.97, H: 10.06. Found C: 65.78, H: 9.99.

***(2S)*-2-Benzyloxymethyl-2-propyl-1,4-dioxaspiro[4.4]nonane (15).** Benzyl bromide (1.05 ml, 8.83 mmol, 1.1 equiv.) and sodium hydride (0.352 g of a 60% dispersion in mineral oil, 8.80 mmol, 1.1 equiv.) were added sequentially to a solution of alcohol (**14**) (1.60 g, 7.99 mmol, 1 equiv.) in THF (40 ml) at 23 °C. The reaction mixture was stirred at 23 °C for 10 h, then was partitioned between water (100 ml) and a 1:1 mixture of EtOAc and hexanes (2 x 100 ml). The combined organic layers were dried over Na_2SO_4, and were concentrated. The residue was purified by flash column chromatography (5% EtOAc in hexanes) to provide benzyl ether (**15**) (1.81 g, 78%) as a colorless oil: R_f = 0.75 (20% EtOAc in hexanes); ir (film) 2259 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 0.92 (t, 3 H, J = 7.3 Hz), 1.25-1.42 (m, 3 H), 1.57-1.81 (m, 9 H), 3.38 (s, 2 H), 3.66 (d, 1 H, J = 8.4 Hz), 3.88 (d, 1 H, J = 8.4 Hz), 4.55 (s, 2 H), 7.28-7.39 (m, 5 H); ^{13}C nmr ($CDCl_3$) δ 14.5, 16.9, 23.4, 23.5, 37.0, 37.2, 37.4, 70.7, 73.0, 73.4, 81.9, 119.1, 127.5, 128.2, 128.3, 138.2. Anal. Calcd for $C_{18}H_{26}O_3$ C: 74.45, H: 9.02. Found C: 74.24, H: 9.04.

***(2R)*-2-Benzyloxymethylpentane-1,2-diol (16).** Aqueous perchloric acid (60%, 0.30 ml) was added

dropwise to a solution of benzyl ether (**15**) (1.80 g, 6.2 mmol) in a 10:1 mixture of THF and water (20 ml) at 23 °C. The reaction mixture was stirred at 23 °C for 40 h, then was partitioned between water (100 ml) and EtOAc (2 x 100 ml). The combined organic layers were dried over Na_2SO_4, and were concentrated. Purification of the residue by flash column chromatography (40% EtOAc in hexanes) afforded diol (**16**) (0.684 g, 50%) as a colorless oil: R_f = 0.22 (30% EtOAc in hexanes); ir (film) 3407 (br) cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.91 (t, 3 H, *J* = 7.0 Hz), 1.27-1.57 (m, 4 H), 2.30-2.34 (m, 1 H), 2.71 (s, 1 H), 3.45-3.54 (m, 3 H), 3.64 (dd, 1 H, *J* = 11.2, 5.0 Hz), 4.53 (d, 1 H, *J* = 12.0 Hz), 4.57 (d, 1 H, *J* = 12.0 Hz), 7.28-7.40 (m, 5 H); ^{13}C nmr ($CDCl_3$) δ 14.6, 16.3, 37.1, 66.9, 73.5, 73.6, 74.5, 127.6, 127.8, 128.4, 137.7. Anal. Calcd for $C_{13}H_{20}O_3$ C: 69.61, H: 8.99. Found C: 69.52 H: 8.96. $[\alpha]^{25}_D$ = -5.68° (c = 1.9, $CHCl_3$).

***(2R)*-2-Benzyloxymethylpentane-1,2-diol (16)** (alternate preparation). Sodium (0.58 g, 2.58 mmol, 2.00 equiv.) was added to a solution of *(2R)*-2-propyloxiranemethanol[10] (0.150 g, 1.29 mmol, 1 equiv.) in benzyl alcohol (5 ml) at 23 °C. The resulting suspension was maintained at 80 °C for 30 min, then was cooled to 23 °C and was partitioned between water (20 ml) and Et_2O (3 x 20 ml). The combined organic layers were dried over Na_2SO_4, and were concentrated. Purification of the residue by flash column chromatography (30% EtOAc in hexanes) provided diol (**16**) (0.107 g, 37%) as a colorless oil: $[\alpha]^{27}_D$ = -8.19° (c = 1.9, $CHCl_3$).

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