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Enantioselective Synthesis of the Excitatory Amino Acid (1*S*,3*R*)-1-Aminocyclopentane-1,3-dicarboxylic Acid

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An enantioselective synthesis of the α,α-dialkyl-α-amino acid (1*S*,3*R*)-ACPD has been achieved using an alkylidene carbene 1,5-CH insertion reaction as a key step. The ketone cyclization precursor was synthesized from Garner's aldehyde in high yield via a Wittig homologation and subsequent catalytic hydrogenation. Treatment of the ketone with 1.2 equiv of lithio(trimethylsilyl)diazomethane in THF resulted in the formation of the corresponding cyclopentene-containing CH-insertion product in 62−69% yield in high enantiomeric excess. Subsequent functional group manipulation allowed the synthesis of the amino acid (1*S*,3*R*)-ACPD to be completed.

Introduction

(1*S*,3*R*)-1-Aminocyclopentane-1,3-dicarboxylic acid (ACPD, **1**) is a conformationally restricted analogue of L-glutamic acid, which is the major neurotransmitter in the mammalian central nervous system (CNS). Glutamate receptors can be divided into two major classes: (1) the ionotropic (iGluRs) and (2) the metabotropic (mGluRs) glutamate receptors. Compound **1** selectively agonizes the latter.[1] The use of **1** as a tool in the study of glutamate receptor function and its potential use as a therapeutic agent for neurodegenerative disorders have led a number of research groups to develop stereoselective syntheses of this material (Figure 1).

On the basis of the previously reported route of Connors and Ross,[2a] and then later Meister et al.,[2b] Curry et al. synthesized all four stereoisomers of **1** from (±)-3-oxocyclopentanecarboxylic acid **3** by brucine salt mediated resolution, followed by construction of the α,α-dialkyl-α-amino acid moiety using a Bucherer−Bergs/Strecker-type transformation.[2c] Azerad et al. subsequently showed that esters of the key oxocyclopentanecarboxylic acid **3** could be resolved using a microbial reduction of the cyclopentanone, followed by separation and oxidation of the resulting cyclopentanol.[2d] Using a conceptually different approach, Ma et al. completed an enantioselective synthesis of **1** starting from L-malic acid **4**.[2e] In this synthesis, the (1*S*)-stereocenter was introduced via a Curtius rearrangement and the 3-carboxylic acid substituent was installed via a displacement of the mesylate **2** with cyanide, followed by hydrolysis. The fact that the cyanide displacement only proceeded with 40% de seemed to indicate that some S_N1 substitution or subsequent epimerization was occurring during this transformation. Recently, Hodgson et al. used an asymmetric carbamate-directed hydroboration of **5** to synthesize **2** in moderate enantiomeric excess[2f,g] and were able to complete a synthesis of **1** via a route similar to that described by Ma.

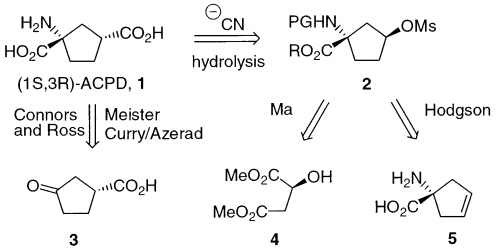

FIGURE 1. Previous syntheses of (1*S*,3*R*)-ACPD **1**.

We have previously reported a method for the construction of the cyclopentane-containing α,α-dialkyl-α-amino acid (1*S*,3*R*)-2,5-methanoleucine based upon an alkylidene carbene 1,5-CH insertion reaction,[3] and we now wish to report a full account of our studies on the application of this methodology to a short and novel enantioselective synthesis of (1*S*,3*R*)-ACPD **1**.

Results and Discussion

Our retrosynthetic analysis of **1** is shown in Scheme 1. Based upon our previous studies, we planned to access

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(1) (a) Knöpfel, T.; Kuhn, R.; Allgeier, H. *J. Med. Chem.* **1995**, *38*, 1417. (b) Knöpfel, T.; Gasparini, F. *Drug Discovery Today* **1996**, *1*, 103.

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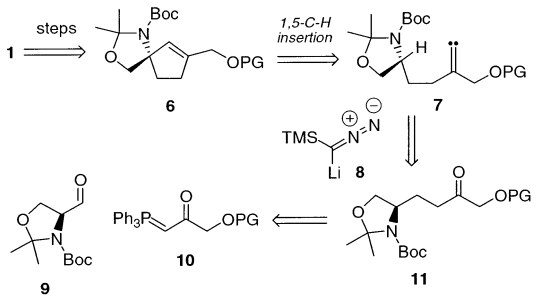
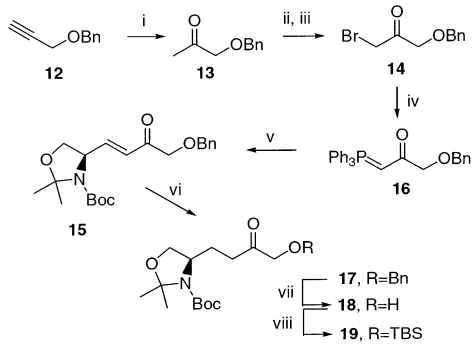
SCHEME 1



SCHEME 2[a]



[a] Reagents: (i) $HgSO_4$, H_2SO_4, MeOH/H_2O (65%); (ii) Br_2, MeOH; (iii) TFA/H_2O (90%, two steps); (iv) PPh_3, PhMe, then KOH, H_2O (60%); (v) **9**, CH_2Cl_2 (91%); (vi) Pd/C, H_2, EtOAc, 2 h (95%); (vii) Pd/C, H_2, 18 h (82%); (viii) TBSOTf, Et_3N, DMAP, DMF (83%).

the dicarboxylic acid from the protected diol **6** using standard functional group interconversions. The desired (3*R*)-stereochemistry in **1** could be introduced by catalytic hydrogenation of **6**, with the bulky Boc protecting group blocking one face of the cyclic olefin. We anticipated that the key cyclopentene **6** could be accessed via a 1,5-CH insertion reaction of a suitably functionalized alkylidene carbene **7**, which in turn could be generated from the corresponding ketone **11** by treatment with lithio(trimethylsilyl)diazomethane **8**.[4] The cyclization precursor **11** was further disconnected to reveal Garner's aldehyde **9** and the phosphorane **10** as possible starting materials.

As multigram quantities of Garner's aldehyde **9**[5a] were readily available using the modified procedure as described by Taylor et al.,[5b] our synthetic attention first turned to the elaboration of the alkoxy-substituted phosphorane **10**. Following literature precedent,[6] alkylation of benzyl alcohol with propargyl bromide gave the desired ether **12**, and mercuric ion-mediated hydrolysis of the alkyne then afforded the corresponding methyl ketone **13** in acceptable yield (Scheme 2). Bromination of **13** afforded the desired bromomethyl ketone **14** along with significant amounts of its dimethoxy ketal derivative, but acid-mediated hydrolysis of the crude reaction mixture allowed **14** to be isolated in good overall yield. With multigram quantities of **14** in hand, the synthesis of the phosphorane **16** was completed using a standard two-step procedure involving displacement of the bromide with triphenylphosphine, followed by generation of the ylide with KOH.[7]

Pleasingly, the phosphorane **16** underwent smooth Wittig-type olefination with Garner's aldehyde to afford the unsaturated ketone **15** (>20:1, *E*/*Z*) in excellent yield. Catalytic hydrogenation over palladium on carbon then afforded the hydroxymethyl ketone **18**. We found that reduction of the olefin in **15** was much faster than hydrogenolysis of the benzyloxy group, and the intermediate saturated benzyloxymethyl ketone **17** could be isolated if desired. For the synthesis of ACPD, exchange of the benzyl protecting group was deemed necessary as the benzylic methylene present in **17** would provide a competitive site for 1,5-CH insertion of the alkylidene carbene intermediate. To complete the synthesis of the cyclization precursor **19**, all that remained was TBS-protection of the hydroxymethyl ketone **18**. To our chagrin, TBS-protection of **18** proved to be a nontrivial operation and a number of alternative procedures had to be examined before suitable conditions were found. For example, treatment of a solution of **18** in DMF with TBSCl in the presence of imidazole followed by aqueous workup resulted in the isolation of only small amounts of **19**, with the starting material **18** accounting for the mass balance. Deprotonation of the α-hydroxy ketone **18** with LDA in THF or DMF before addition of TBS-Cl and aqueous workup resulted in the same low yield of **19**. Fortunately, the desired cyclization precursor **19** could be accessed conveniently by using TBSOTf in the presence of Et_3N and DMAP. We found that after stirring for 1 h at room temperature, the crude reaction mixture could be loaded directly onto a SiO_2 gel flash column, and the desired product **19** could be isolated in high yield and purity by elution with petroleum ether/Et_2O (6:1). Subsequent investigations revealed that the silyloxymethyl ketone **19** was very susceptible to mildly basic hydrolysis, and the nature of this reactivity is currently being investigated.

Although we were able to access the desired cyclization precursor **19** using the chemistry described above, we were somewhat unhappy with several aspects of the route and we decided to address these by developing a more efficient second-generation synthesis. Upon examination of the synthesis of **19** (vide supra), it was clear that both the effort required to synthesize the phosphorane **16** on large scale, and a rather frustrating benzyl to TBS protecting group swap, were making it difficult to access multigram quantities of **19**. We felt it would be much better if we could synthesize an ylide (e.g., **21**) with the desired TBS protecting group already in place and to do this in a much more convergent manner. We therefore decided to examine methods for the synthesis of the revised ylide **21**. We felt that the route used to synthesize the phosphorane **16** would be unsuitable, as it was quite lengthy and the TBS-protecting group required was unlikely to survive the harshly acidic conditions used. In principle we felt it should be possible to access **21** directly by acylation of methylenetriphenylphosphorane

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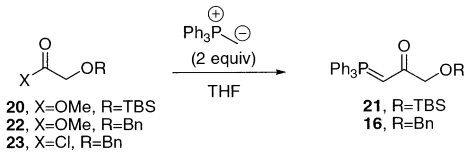
(7) For details of the synthesis of **16** see the Supporting Information.

SCHEME 3

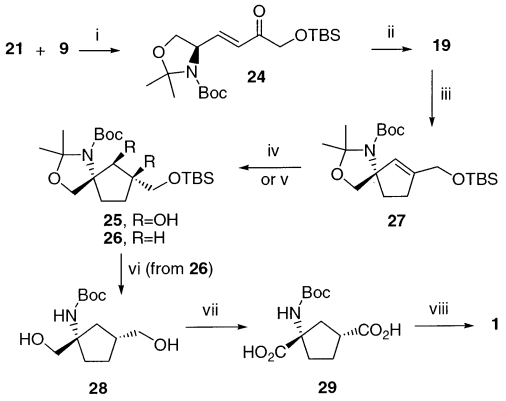


with methyl glycolate **20**.[8] To test this new route, methyl glycolate was first protected (TBSCl, imidazole, DMF) to afford **20**.[9] Pleasingly, we found that the desired stabilized ylide **21** could be accessed in good yield (50−69%) on a 60−70 g scale, by the dropwise addition of **20** to 2 equiv of a cool (0 °C) solution of methylenetriphenylphosphorane in THF. The ylide **21** could be purified by flash column chromatography if required, but we found that on a large scale, washing the solid product with EtOAc was sufficient to provide material of adequate purity for further transformations. We also found that the benzyloxy-substituted phosphorane **16** could be accessed in a similar manner by treatment of methylenetriphenylphosphorane with the commercially available acid chloride **23** or the methyl ester derivative **22** (Scheme 3).

Gratifyingly, the new phosphorane **21** underwent smooth Wittig reaction with Garner's aldehyde to afford the corresponding enone **24**, and catalytic hydrogenation proceeded cleanly to complete the new route to the desired cyclization precursor **19**. To our pleasure, and in accord with our previously reported model study,[3] reaction of **19** with lithio(trimethylsilyl)diazomethane in THF (−78 → 0 °C) gave the desired cyclopentene product **27** in 62−69% yield. We were unable to determine the enantiomeric excess of **27** directly and further derivatization was required. Thus dihydroxylation of **27** using the Upjohn conditions[10] afforded the corresponding diol (+)-**25** (94%) in high diasteromeric excess (>95% de by ^{1}HNMR of the crude reaction mixture). A racemic sample of **25** was prepared from (±)-Garner's aldehyde **9** using an identical synthetic route to that described above, and this was used as a reference sample for subsequent % ee determinations. Using this sample, the diol (+)-**25** was shown to have >95% ee by chiral HPLC analysis (Chiralpak AD, 8:92 IPA/hexane), thus confirming the stereochemical integrity of the quaternary stereocenter in the insertion product **27**. Having installed the (1*S*)-quaternary center, the remaining (3*R*)-stereochemistry was then introduced via catalytic hydrogenation (Pd, 10% on carbon) to afford **26** as the predominant diastereoisomer (10:1, 3*R*/3*S*) (Scheme 4). Unfortunately we were unable to separate the minor diasteroisomer from this mixture, and the 10:1 mixture of (3*R*/3*S*) isomers was carried through the remaining transformations.

With all of the C−C bond formations completed, all that remained to finish the synthesis of **1** was a series of standard functional group interconversions. First of all,

SCHEME 4[a]



[a] Reagents: (i) CH_2Cl_2, rt (87%); (ii) Pd/C, H_2, EtOAc (80%); (iii) $TMSCHN_2$, BuLi, THF (−78 °C), then **19** (−78 → 0 °C) (69%); (iv) OsO_4, NMO, Me_2CO/H_2O (94%); (v) Pd/C, H_2, EtOAc; (vi) HF/MeCN (81%, two steps); (vii) $RuCl_3$, $NaIO_4$, CCl_4, MeCN, H_2O; (viii) HCl, EtOAc (49%, two steps).

selective deprotection of **26** with HF/MeCN afforded the corresponding diol **28** in good yield. Oxidation of this diol with $RuCl_3/NaIO_4$[11] next afforded *N*-Boc-protected ACPD **29**, which was sufficiently pure to use in the final deprotection step without further purification. Exposure of **29** to HCl in EtOAc effected removal of the Boc protecting group, and evaporation of the volatiles resulted in the production of (1*S*,3*R*)-ACPD as its HCl salt (49%, from **28**). Ion exchange chromatography (Dowex 50 × 8−200, 2 M $NH_{3(aq)}$), of this salt then afforded (1*S*,3*R*)-ACPD **1** as a white solid. The data recorded (mp, ^{1}H NMR, ^{13}C NMR) for our synthetic material matched that previously reported for ACPD **1**, and copies of the ^{1}H and ^{13}C NMR data are provided in the Supporting Information.[12]

In summary, we have shown that the excitatory amino acid (1*S*,3*R*)-ACPD **1** can be synthesized from Garner's aldehyde **9** in seven steps using a conceptually novel approach. An alkylidene carbene 1,5-CH insertion reaction was used as a key step to introduce the (1*R*)-quaternary center with a high degree of stereocontrol, and the cyclopentene-containing CH-insertion product **27** should prove to be a valuable building block in the synthesis of other glutamate analogues. These and other studies in this area will be reported in due course.

Experimental Section

Starting materials were obtained from commercial suppliers and used without further purification unless otherwise stated. All reactions were performed in flame-dried apparatus under an atmosphere of nitrogen at room temperature unless otherwise stated. CH_2Cl_2 was distilled from CaH_2, and THF from Na/benzophenone ketyl under nitrogen. Flash chromatography

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(12) For NMR data of an authentic sample of **1**, see: Larue, V.; Gharbi-Benarous, J.; Acher, F.; Valle, G.; Crisma, M.; Toniolo, C.; Azerad, R.; Girault, J.-P. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1111. We believe that the slight difference between our observed optical rotation for **1** ($[\alpha]^{29}_D$ −5.6 (c 1.3, H_2O)) and that previously reported in the literature[2c] ($[\alpha]^{29}_D$ −6.9 (*c* 1.0, H_2O)) is due to the presence of 5−10% of the (1*S*,3*S*)-diasteroisomer of **1** ($[\alpha]^{20}_D$ +8.4 (*c* 1.0, H_2O)).

was carried out using Merck silica gel 60, 35−70μ as the stationary phase and the solvents used were either of analytical grades or were distilled before use. Chiral HPLC was carried out using a Chiralpak AD column with appropriate mixtures of HPLC grade 2-propanol and hexane being used as eluent. Unless otherwise stated, Infrared spectra were obtained of dilute chloroform solutions. NMR spectra were obtained at the indicated spectrometer frequency as dilute solutions in $CDCl_3$ at room temperature unless is otherwise stated. All coupling constants are reported in hertz (Hz). High-resolution mass spectra were obtained using either chemical ionization (CI, methane), fast atom bombardment (FAB), electron ionization (EI), or electrospray (ES) techniques.

1-(*tert*-Butyldimethylsilanyloxy)-3-(triphenylphosphanylidene)propan-2-one 21. *n*-Butyllithium (172 mL; 2.5 M in hexanes; 431 mmol) was added dropwise in four portions (3 × 50 mL and 1 × 22 mL), each over 5 min (with a 10 min interval between each addition), to a cool (0 °C) stirring suspension of Ph_3PCH_3·Br (156 g; 437 mmol) in THF (1 L), and the resulting yellow/orange solution was stirred at 0 °C for a further 40 min. (*O*-TBS)methyl glycolate **20**[9] (39.7 g 194 mmol) was added dropwise over 1 min, and the resulting mixture was then warmed to room temperature and stirred for a further 2 h. Water (600 mL) was added, and the mixture was stirred for 10 min before removal of the THF in vacuo. The resulting aqueous residue was partitioned between ethyl acetate (1.2 L) and water (600 mL), and the separated organic phase was dried ($MgSO_4$) and concentrated in vacuo, giving a pale yellow solid. This material was purified by trituration with minimal ethyl acetate (×4), giving **21** as a white solid (61.0 g; 69%): mp 118−122 °C; δ_H (400 MHz) 0.14 (6H, s), 0.95 (9H, s), 4.14 (2H, s), 4.34 (1H, d, *J* 26.0), 7.42−7.46 (6H, m), 7.51−7.55 (3H, m), 7.65−7.70 (6H, m); δ_C (101 MHz, 303K) 192.1 (d, *J* 4.0), 133.0 (d, *J* 10.1), 132.0 (d, *J* 3.0), 128.7 (d, *J* 13.1), 127.1 (d, *J* 90.5), 68.2 (d, *J* 13.1), 49.0 (d, *J* 109.6), 26.3, 18.7, −4.9; δ_P (162 MHz, 303K) 17.5; *m*/*z* (ES+) 449.2070 (M + H, $C_{27}H_{34}O_2PSi$ requires 449.2066). Anal. Calcd for $C_{27}H_{33}O_2PSi$: C, 72.3; H, 7.4. Found: C, 72.4; H, 7.3.

(4*R*)-4-[4-(*tert*-Butyldimethylsilanyloxy)-3-oxobut-1-enyl]-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester 24. (*S*)-Garner's aldehyde **9** (2.16 g; 9.42 mmol) was added dropwise over 2 min to a stirring solution of the ylide **21** (8.6 g; 19.2 mmol) in dichloromethane (20 mL), and the mixture was stirred at room temperature for 3 days. Removal of the solvent in vacuo left the crude product, which was purified by column chromatography (4:1 pentane/diethyl ether) to give the enone **24** as a colorless oil (3.28 g; 87%): $[\alpha]_D$ −60 (*c* 1.04, $CHCl_3$) >95% ee (Chiralpak AD, hexane/*i*-PrOH (95:5), 1 mL/min); ν_{max}(film)/cm^{-1} 1698, 1631; δ_H (400 MHz, C_6D_6, 343K) 0.15 (6H, s), 0.92 (9H, s), 1.36 (9H, s), 1.47 (3H, s), 1.61 (3H, s), 3.42 (1H, dd, *J* 9.0, 2.7), 3.65 (1H, dd, *J* 9.0, 6.5), 4.09−4.26 (1H, m), 4.13 (2H, app s), 6.46 (1H, d, *J* 15.8), 6.83 (1H, dd, *J* 15.8, 6.8); δ_C (101 MHz, C_6D_6, 343K) 197.6, 152.4, 145.6, 126.5, 95.2, 80.6, 69.8, 68.1, 59.3, 29.1, 27.6, 26.7, 24.9, 19.1, −4.7; *m*/*z* (ES+) 422.2357 (M + Na, $C_{20}H_{37}NNaO_5Si$ requires 422.2339). Anal. Calcd for $C_{20}H_{37}NO_5Si$: C, 60.11; H, 9.33; N, 3.51. Found: C, 60.03; H, 9.36; N, 3.49.

(4*R*)-4-[4-(*tert*-Butyldimethylsilanyloxy)-3-oxobutyl]-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester 19. Palladium (341 mg, 10% on carbon) was added in one portion to a stirring solution of the enone **24** (301 mg; 0.75 mmol) in ethyl acetate (126 mL). The reaction vessel was purged with hydrogen by four evacuate/fill cycles, and the resulting mixture was stirred under an atmosphere of hydrogen (balloon) for 17 h. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated in vacuo to afford a yellow oil (2.17 g), which was purified by column chromatography (3:1 pentane/diethyl ether) to give **19** as a colorless oil (2.03 g; 80%): $[\alpha]_D$ −18.1 (c 4.55, $CHCl_3$) >95% ee (Chiralpak AD, hexane/*i*-PrOH (99:1), 0.5 mL/min); ν_{max}/cm^{-1} 1713, 1682; δ_H (400 MHz, C_6D_6, 340 K) 0.03 (6H, s), 0.94 (9H, s), 1.42 (9H, s), 1.46 (3H, s), 1.65 (3H, s), 1.85−1.94 (1H, m), 1.96−2.04 (1H, m), 2.27−2.42 (2H, m), 3.44 (1H, d, *J* 8.8), 3.62 (1H, dd, *J* 8.8, 6.0), 3.81 (1H, br s), 4.00 (2H, app s); δ_C (125 MHz, 1:1 mixture of rotamers) 210.0, 152.5, 151.9, 93.9, 93.4, 80.0, 79.7, 69.2, 67.0, 56.6, 34.9, 34.6, 28.4, 27.0, 25.8, 24.4, 23.1, 18.3, −5.5; *m*/*z* (FAB positive ion) 402.2646 (MH^+, $C_{20}H_{40}NO_5Si$ requires 402.2676). Anal. Calcd for $C_{20}H_{39}NO_5Si$: C, 59.8; H 9.8; N, 3.5. Found: C, 59.5; H, 9.5; N, 3.2.

(4*S*)-2,2-Dimethyl-7-(*tert*-butyldimethylsilanyloxymethyl)-1-oxa-3-azaspiro[4.4]non-6-ene-3-carboxylic Acid *tert*-Butyl Ester 27. *n*-Butyllithium (6.17 mL, of a 2.1 M solution in hexanes, 13.0 mmol) was added dropwise over 11 min to a cold (−78 °C) stirring solution of trimethylsilyldiazomethane (7.50 mL of a 2 M solution in hexanes, 15.0 mmol) in THF (20 mL), and the resulting mixture was stirred for 1 h at −78 °C. The ketone **19** (3.92 g, 13.6 mmol) in THF (13 mL) was then added, dropwise over 20 min, and the mixture was stirred for another 70 min. The reaction mixture was warmed to 0 °C and stirred for 15 min. The reaction was quenched with NH_4Cl (20 mL of a saturated solution diluted with water (25 mL)), extracted with ether (250 mL), dried ($MgSO_4$), and concentrated in vacuo to give the crude product. Column chromatography [petroleum ether (40−60 °C)/Et_2O (10:1)] afforded the pure product **27** (2.68 g, 69%) as a colorless oil: $[\alpha]_D$ −49.0 (*c* 1.24, $CHCl_3$); ν_{max}/cm^{-1} 1682; δ_H (400 MHz, C_6D_6, 340K) 0.28 (6H, s), 1.17 (9H, s), 1.62 (9H, s), 1.83 (3H, s), 1.87 (3H, s), 2.15 (1H, ddd, *J* 12, 8.7, 3.0), 2.30−2.40 (1H, m), 2.50−2.70 (2H, m), 3.83 (1H, d, *J* 8.7), 3.87 (1H, d, *J* 8.7), 4.31 (1H, d, *J* 13.8), 4.36 (1H, d, *J* 13.8), 5.63 (1H, s); δ_C (125 MHz, 2.3:1 mixture of rotamers) 152.1, 151.1, 146.3, 145.3, 126.6, 125.8, 94.8, 94.1, 79.4, 79.1, 74.3, 73.9, 73.7, 73.2, 62.4, 62.2, 35.0, 33.3, 30.7, 28.5, 26.9, 25.9, 24.5, 18.4, −5.3; *m*/*z* (ES+) 420.2523 (M + Na, $C_{12}H_{39}NNaO_4Si$ requires 420.2546). Anal. Calcd for $C_{21}H_{39}NO_4Si$: C, 63.43; H, 9.89; N, 3.52. Found: C, 63.31; H, 9.82; N, 3.45.

(4*S*,6*R*,7*R*)-6,7-Dihydroxy-2,2-Dimethyl-7-(*tert*-butyldimethylsilanyloxymethyl)-1-oxa-3-azaspiro[4.4]nonane-3-carboxylic Acid *tert*-Butyl Ester 25. *N*-Methylmorpholine-*N*-oxide (1.34 g; 9.91 mmol) was added in one portion to a room temperature stirring solution of the alkene **27** (1.31 g; 3.30 mmol) in acetone/water (10:1; 143 mL). K_2OsO_4·$2H_2O$ (121 mg; 0.33 mmol) was added in one portion to the stirring mixture, and the resulting stirred at room temperature for a further 4.5 days. The reaction was quenched with Na_2SO_3 (1.26 g) and concentrated in vacuo, and the residue was adsorbed onto silica gel by evaporation from ethyl acetate (~500 mL) to form a free-flowing powder. The dry powder was slurried in ethyl acetate and filtered through Celite, and the eluent was concentrated in vacuo, giving a dark yellow oil (1.47 g). This was purified by column chromatography (3:1 petrol/ethyl acetate), giving **25** as a colorless oil (1.34 g; 94%): $[\alpha]^{25}_D$ 41 (*c* 3.3, $CHCl_3$) (97% ee, Chiralpak AD, 8:92 IPA/hexane); ν_{max}(film)/cm^{-1} 3454, 1694; δ_H (400 MHz, $CD_3C_6D_5$, 368K) 0.07 (6H, s), 0.95 (9H, s), 1.47 (9H, s), 1.61 (3H, s), 1.67−1.56 (1H, m (obscured)), 1.67 (3H, s), 1.73−1.83 (1H, m), 1.96−2.06 (1H, m), 2.22 (1H, d (br), *J* 5.5 Hz), 2.33−2.43 (1H, m), 2.49 (1H, s), 3.55 (1H, d, *J* 9.8 Hz), 3.59 (1H, d, *J* 9.8 Hz), 3.72 (1H, d, *J* 9.2 Hz), 4.51 (1H, d, *J* 9.2 Hz), 4.80 (1H, s (br)); δ_C (126 MHz, C_6D_6, 340 K) 151.9, 94.3, 79.7, 78.5, 75.8, 71.2, 69.7, 31.4, 30.7, 30.2, 28.7, 26.5, 26.1, 18.5, −4.3; *m*/*z* (ES+) 454.2629 (M + Na, $C_{21}H_{41}NNaO_6Si$ requires 454.2601).

(1*S*,3*R*)-1-*tert*-Butoxycarbonylamino-1,3-dihydroxymethylcyclopentane 28. Palladium (109 mg, 10% on carbon) was added to a solution of the unsaturated spirocycle **27** (870 mg, 2.19 mmol) in EtOAc (44 mL). The reaction vessel was purged with hydrogen by three evacuate/fill cycles, and the resulting mixture was stirred under an atmosphere of hydrogen (balloon) for 19 h. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated in vacuo to afford **26** (928 mg), which was used in the following reaction without further purification. HF (0.57 mL of 48% aqueous solution) was added in one portion to a stirring solution of crude **26** (927 mg) in CH_3CN (23 mL), and the

resulting solution was stirred for 15 min at room temperature before being quenched with excess $NaHCO_3$ (30 mL of a saturated solution). The aqueous layer was extracted with Et_2O (3 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography [petroleum (40−60 °C)/Et_2O/MeOH gradient; (30:5:2)−(8:15:1)] afforded the diol **28** (451 mg; 81%) as a colorless oil: $[\alpha]_D$ +6.9 (c 1.78, $CHCl_3$); ν_{max} /cm^{-1} 3625, 3439, 1693; δ_H (400 MHz, C_6D_6, 343 K) 1.30−1.42 (2H, m), 1.39 (9H, s), 1.43−1.52 (1H, m), 1.54−1.63 (1H, m), 1.68−1.76 (1H, m), 1.78−1.89 (2H, m), 3.05 (1H, br s, O*H*), 3.21 (2H, app s), 3.47−3.60 (2H, m), 4.79 (1H, br s); δ_C (100 MHz) 156.0, 79.9, 68.8, 66.3, 64.9, 40.2, 38.5, 34.9, 28.4, 27.0; *m*/*z* (EI positive ion) 246.1688 (MH^+, $C_{12}H_{24}NO_4$ requires 246.1705). Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.33; H, 9.56; N, 5.57.

(1*R*,3*S*)-1-Aminocyclopentane-1,3-dicarboxylic Acid 1. CCl_4 (0.48 mL), CH_3CN (0.72 mL), and H_2O (0.48 mL) were added successively to a mixture of $NaIO_4$ (240 mg, 1.12 mmol) and $RuCl_3 \cdot xH_2O$ (62 mg, 0.30 mmol). After being stirred for 35 min, the mixture was added dropwise over 30 s to a cool (0 °C) stirring solution of the diol **28** (118 mg). After the mixture was stirred at 0 °C for 45 min, $NaIO_4$ (534 mg, 2.54 mmol) was added in one portion, and the resulting mixture stirred at 0 °C for a further 3 h. The mixture was adsorbed onto silica, filtered through a pad of silica (EtOAc as eluent), and concentrated in vacuo giving the *N*-Boc-bis-carboxylic acid **29** as a colorless oil (111 mg) in crude form. HCl (concd, 2.5 mL) was added in one portion to a stirring solution of the crude *N*-Boc bis-carboxylic acid **29** in EtOAc (7.5 mL) and after 7 h at room temperature, the solution was concentrated in vacuo giving a yellow oil (106 mg). The crude material was dissolved in methanol (0.6 mL), and ethyl acetate (24 mL) and the mixture was concentrated in vacuo until a white precipitate formed. The solid was removed by filtration and washed with cold (0 °C) EtOAc, giving a white powder (49 mg; 49%, 2 steps); δ_H (500 MHz, MeOH) 2.04−2.14 (2H, m), 2.19 (1H, dd, *J* 14.3, 8.3), 2.37−2.43 (1H, m), 2.61 (1H, dd, *J* 14.3, 8.3); δ_C (126 MHz; MeOH) 176.6, 174.0, 65.5, 45.1, 40.1, 36.7, 30.3. The hydrochloride salt was dissolved in NaOH (2M; 5 mL), washed with diethyl ether (4 mL, then 8 mL), and the aqueous acidified (HCl, 1M) to pH 5. Concentration in vacuo gave a white solid, which was purified by ion exchange chromatography (Dowex 50X8 200; 2M NH_3 aq), giving ACPD **1** (24.9 mg; 30%, 2 steps from **28**) as a white solid: mp 248 °C dec (lit.[2c] mp 246−250 °C dec); $[\alpha]^{29}_D$ −5.6 (c 1.3, H_2O) (lit.[2c] $[\alpha]^{29}_D$ −6.9 (*c* 1.0, H_2O)); δ_H (400 MHz, D_2O) 1.93−2.07 (2H, m), 2.14 (1H, dd, *J* 14.5, 4.7), 2.21−2.36 (2H, m), 2.42 (1H, dd, *J* 14.5, 8.6), 3.03−3.11 (1H, m); δ_C (101 MHz, D_2O) 186.7, 180.1, 69.7, 49.3, 42.5, 38.5, 32.8.

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Supporting Information Available: Experimental procedures for the preparation of **15**, **16**, **18**, and **19**. Copies of the ^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra for our synthetic sample of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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