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An Efficient Enantioselective Synthesis of (2*R*)-Hydroxymethyl Glutamic Acid and an Approach to the (2*R*)-Hydroxymethyl-Substituted Sphingofungins

Christopher J. Hayes,*[,†] Daniel M. Bradley,[†] and Nicholas M. Thomson[‡]

The School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, United Kingdom, and Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom

chris.hayes@nottingham.ac.uk

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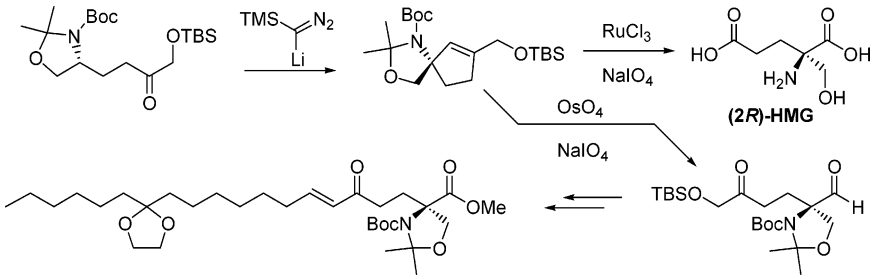

We have developed a short enantioselective synthesis of (2*R*)-hydroxymethyl glutamic acid (HMG) starting from Garner's aldehyde using an alkylidene carbene 1,5-CH insertion as a method to construct the quaternary stereocenter. A variety of conditions were examined for the oxidative cleavage of the key cyclopentene intermediate and we found that $RuCl_3/NaIO_4$ led directly to the desired amino bis-acid product. We were also able to show that oxidative cleavage of the cyclopentene 1,5-CH insertion product could be used to produce the amino acid-containing skeleton of the sphingofungin family of natural products.

Introduction

The novel α,α-dialkyl-α-amino acid (2*R*)-hydroxymethyl glutamic acid (HMG) **2** was first synthesized by Kozikowski et al. as part of an ongoing program to produce more specific glutamate receptor agonists and antagonists.[1] During this study it was found that **2** was a potent mGluR3 agonist and a weak mGluR2 antagonist and since this initial report, Langlois,[2] Ohfune,[3] Park and Jew,[4] Battistini and Casiraghi,[5] and Ma[6] have also disclosed syntheses of enantiopure HMG **2**. These publications highlight a variety of contemporary synthetic methods available for the enantioselective construction of α-alkylserine derivatives, and we now wish to report our own initial work in this area.

During a research program examining the use of alkylidene carbene 1,5-CH insertion reactions in asymmetric synthesis,[7a−f] we were able to complete an enantioselective total synthesis of

† University of Nottingham.

‡ Pfizer Global Research and Development.

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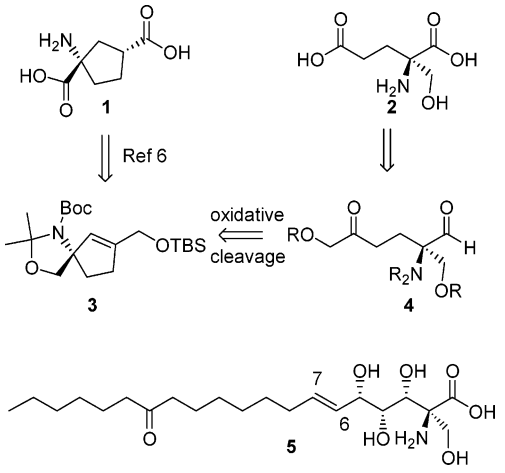


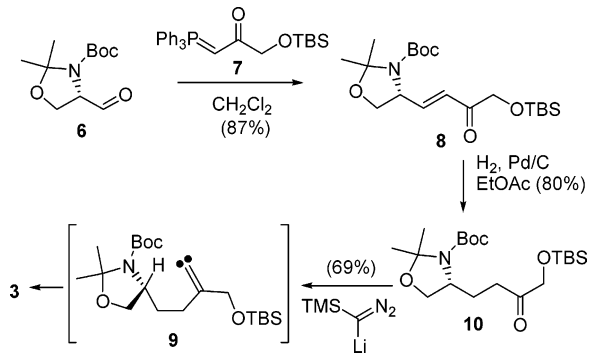
FIGURE 1.

the mGluR agonist (1*S*,3*R*)-1-aminocyclopentane-1,3-diarboxylic acid (ACPD) **1**.[7a] This synthesis relied upon the exquisite 1,5-insertion selectivity of alkylidene carbenes to form an advanced cyclopentene synthetic intermediate **3**. We were then able to convert this material into the desired target **1** using standard functional group interconversions. The 1,5-CH insertion reaction is obviously well suited to the synthesis of cyclopentene and cyclopentane-containing targets, but we wished to broaden the scope of this synthetic strategy to allow access to acyclic target molecules. During our recent total synthesis of the natural product (−)-TAN1251 A we were able to utilize an alkylidene carbene 1,5-CH insertion to form a key quaternary center,[8] but we needed to perform a ring expansion reaction on a key cyclopentene CH-insertion product to provide the cyclohexane ring present in the natural product. This was readily accomplished by an oxidative cleavage−aldol condensation strategy.[9] Due to the success of this synthetic approach, we wondered whether similar oxidative cleavage reactions could be applied to the synthesis of other acyclic target structures. In particular we saw that the cyclopentene **3** used in our ACPD **1** synthesis gave us the opportunity to prepare a range of α-alkylserine derivatives. Oxidative cleavage of the olefin in **3**, using ozonolysis for example, should afford the acyclic keto-aldehyde product **4**. We felt that this material would be an ideal precursor to HMG **2**, with the synthesis being completed using a few relatively straightforward synthetic steps. We also noted that the keto-aldehyde **4** had a substitution and oxidation pattern similar to that of the polar headgroup of the sphingofungins[10] (e.g. sphingofungin E **5**), and wondered whether we could use this 1,5-CH insertion−oxidative cleavage approach to access this important class of biologically active natural products.

Results and Discussion

To achieve a synthesis of **2** our first task was to prepare multigram quantities of the key cyclopentene intermediate **3**, and this was readily achieved using our previously published procedure.[7a] The 1,5-CH insertion precursor **10** was prepared from (*S*)-Garner's aldehyde[11] **6** via the enone **8**, and then exposed to lithio-TMS-diazomethane at low temperature (−78 °C).[12] Upon warming to 0 °C, the desired cyclopentene product **3** was formed in good yield and in excellent enantiomeric excess (>97% ee)[7a] (Scheme 1).

SCHEME 1



Having secured a reliable route to **3** we were now in a position to explore the oxidative cleavage conditions required to produce the keto-aldehyde **4**. Ozonolysis was initially explored, and the desired keto-aldehyde **12** could be isolated in a modest 32% yield. Unfortunately, we were not able to optimize this reaction and we therefore turned our attention to alternative conditions. As we had already successfully prepared the diol **11** from **3** during our synthesis of ACPD **1,** we wondered whether **11** could be cleaved with sodium periodate to produce **12**. The diol **11** was therefore prepared in high yield via an Upjohn dihydroxylation,[13] and upon treatment with 1 equiv of $NaIO_4$ the desired keto-aldehyde **12** was produced in 80% yield (Scheme 2). When the diol **11** was exposed to an excess of $NaIO_4$ (4 equiv) we were pleased to find that the carboxylic acid **13** was produced in excellent yield (96%). We believe that this product is being produced in situ via oxidative cleavage of the protected acyloin moiety of **12**, and this discovery is to our considerable advantage as cleavage of this C−C bond is required in our proposed synthesis of **2**. As $NaIO_4$ can be used as the co-oxidant in OsO_4-mediated dihydroxylations, we explored the possibility of accessing the acid **13** from **3** in a one-pot procedure.[14] After some initial optimization, we were pleased to find that oxidation of **3** with $K_2OsO_4 \cdot H_2O$ (0.03 equiv) and $NaIO_4$ (4 equiv) provided the desired acid **13** in 63% yield (Scheme 2). To complete a synthesis of HMG **2** from **13** all that remained was

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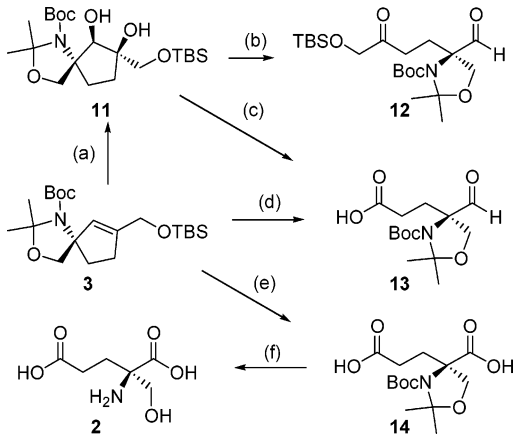
SCHEME 2 [a]



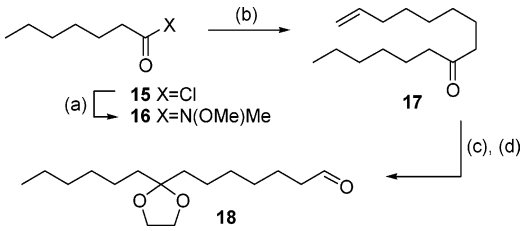
[a] Reagents and conditions: (a) K_2OsO_4, NMO, acetone/H_2O (94%); (b) $NaIO_4$ (1 equiv), THF/H_2O (80%); (c) $NaIO_4$ (4 equiv), THF/H_2O (96%); (d) K_2OsO_4, $NaIO_4$ (4 equiv), THF/H_2O (63%); (e) $RuCl_3$, $NaIO_4$ (5.8 equiv), CCl_4/MeCN/H_2O (88%); (f) $HCl_{(conc)}$, EtOAc then Dowex 50W×8-200, 2 M $NH_{3\ (aq)}$ (85%).

oxidation of the aldehyde to a carboxylic acid and removal of the Boc and aminal protecting groups.

Although a wide variety of conditions were potentially available for oxidation of the aldehyde **13** to the acid **14**, we were particularly attracted to methods that were compatible with our tandem olefin/acyloin oxidative cleavage conditions, as this opened up the possibility of developing a one-pot procedure for the synthesis of the diacid **14** from the cyclopenetene **3**. The $RuCl_3$/$NaIO_4$-mediated oxidation procedure of Sharpless[15] seemed ideally suited to our needs as this reagent combination not only provides a mild method of accessing carboxylic acids from aldehydes, but is also capable of performing oxidative cleavage of olefins to provide carboxylic acid products. We reasoned that replacing OsO_4 with RuO_4 (generated in situ from $RuCl_3$) would allow us to access the desired diacid **14** from **3** in one synthetic operation, thus removing the need to perform several individual oxidations. To our delight, we found that exposure of the cyclopentene **3** to $RuCl_3$ (0.06 equiv) and $NaIO_4$ (5.8 equiv) in CCl_4/MeCN/H_2O afforded the desired dicarboxylic acid **14** in excellent yield (88%). Deprotection of the diacid **14** with HCl (conc) in EtOAc followed by ion exchange chromatography (Dowex 50W×8-200, 2 M $NH_{3\ aq}$) finally afforded (2*R*)-HMG **2** as a white solid (Scheme 2).

Having successfully completed a synthesis of (2*R*)-HMG **2** from **3** we were keen to see if we could use the keto-aldehyde **12** to access the polar headgroup of the (2*R*)-hydroxymethyl-substituted sphingofungins (e.g. **5**).[16] We envisaged that the C5-ketone in **12** could become the C5-carbinol in a target molecule such as **5** and that the C6−C7 double bond could be constructed using a Wittig olefination. A Wittig reaction has been used previously for this bond construction;[16a] however, the reaction was performed using a non-stabilized ylide leading to the formation of the undesired *Z*-alkene and a subsequent equilibration step was then required to obtain the correct geometry. In our approach we planned to react a stabilized ylide (e.g. **21**) in a Wittig reaction with the aldehyde **18**, which should furnish the desired *E*-olefin geometry directly.

SCHEME 3 [a]



[a] Reagents and conditions: (a) NH(Me)OMe·HCl, Pyr, 100%; (b) $H_2C{=}CH(CH_2)_6MgBr$, 74%; (c) $HO(CH_2)_2OH$, PTSA; (d) $K_2OsO_4.2H_2O$, NMO, acetone/H_2O, then $NaIO_4$/SiO_2, DCM, 87% (3 steps).

As we had already prepared the keto-aldehyde **12**, our first task was to prepare the aldehyde **18** and this was readily accomplished by using the approach shown in Scheme 3. Formation of the Weinreb amide **16** from heptanoyl chloride **15** proceeded without problem.[17] Addition of 7-octenylmagnesium bromide to the crude amide, followed by acidic workup then gave the ketone **17** in high yield.[18] Protection of the ketone with ethylene glycol under Dean−Stark conditions and oxidative cleavage (OsO_4/$NaIO_4$ on SiO_2[19]) then gave the aldehyde **18** for use in the subsequent Wittig reaction.

Our next task was to develop a suitable procedure for oxidizing the aldehyde **12** to the corresponding carboxylic acid without cleaving the protected acyloin moiety. We had already shown that $NaIO_4$ mediates cleavage of this functionality, so we were particularly careful to avoid conditions incorporating this, or any other glycol-cleaving oxidants. Pleasingly we found that sodium chlorite was an excellent reagent for this oxidation and the resulting acid was converted to its methyl ester **19** by treatment with TMS-diazomethane (75%, 2 steps). Deprotection of the TBS-ether **19** with buffered TBAF then gave the corresponding alcohol **20** in good yield. Having constructed the protected α,α-dialkyl-α-amino acid **20**, we then needed to develop a Wittig olefination procedure for its connection to the aldehyde **18**. Fortunately, elaboration of the acyloin moiety present in **20** into the required phosphorane **21** was relatively straightforward and was accomplished as shown in Scheme 4. Thus, activation of the alcohol **20** as its mesylate **22** and subsequent treatment with triphenylphosphine first provided a phosphonium salt. Deprotonation with Et_3N then afforded the phosphorane **21**, which was reacted in situ with the previously prepared aldehyde **18** to afford the desired enone **23** as the required *E*-geometric isomer. After extensive optimization of this procedure we were able to develop a one-pot procedure, giving 61% of **23** starting from the alcohol **20**, which removes the need to handle any of the sensitive and/or polar intermediates involved. To achieve a total synthesis of sphingofungin E **5** we next need to develop a protocol for introducing the required oxygenation at C3 and C4 of the enone **23** and these studies are currently underway in our laboratory, and progress will be reported in due course.

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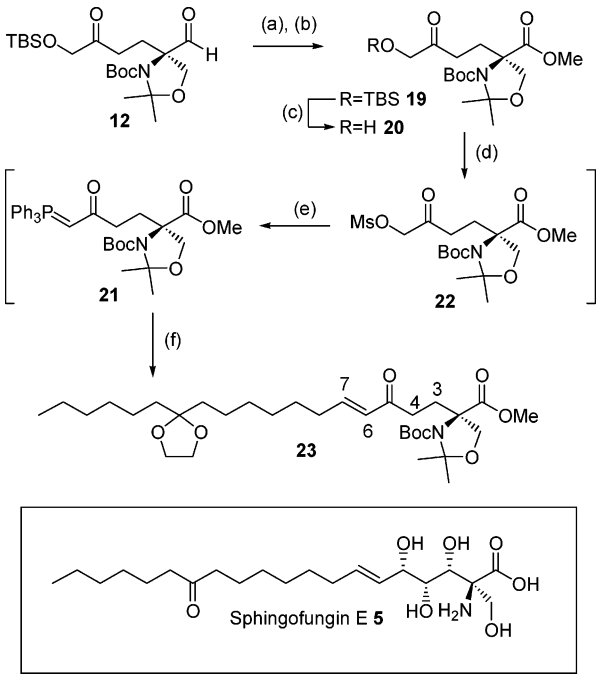
(17) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(18) The synthesis of the ketone **17** followed a similar route to that used by Trost for a homologous compound (see refs 15d and 15e).

(19) $NaIO_4$ on silica was prepared according to the procedure given in the following: Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.

SCHEME 4 [a]



[a] Reagents and conditions: (a) $NaClO_2$, $H_2C{=}CMe_2$, NaH_2PO_4, ^tBuOH; (b) $TMSCHN_2$, MeOH, PhH (75%, 2 steps); (c) TBAF, THF/H_2O/HOAc (77%); (d) MsCl, Et_3N, CH_2Cl_2; (e) PPh_3, Et_3N, CH_2Cl_2; (f) **18**, CH_2Cl_2 (61%, 3 steps).

In conclusion, we have shown that an alkylidene carbene 1,5-CH insertion reaction can be used to effect an efficient total synthesis of the potent mGluR3 agonist (*2R*)-hydroxymethyl glutamic acid (HMG) **2**. The synthesis is accomplished in an overall yield of 36%, over 5 steps from (*S*)-Garner's aldehyde, and represents one of the most efficient enantioselective syntheses of this important compound to date. We have also shown that oxidative cleavage of the spirocycle **3** can also provide hydroxymethyl-substituted amino acid fragments (e.g. **20**) for future use in the synthesis of a variety of sphingofungin natural products (e.g **5**) and their analogues.

Experimental Section

(5*S*,6*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxymethyl)-6,7-dihydroxy-2,2-dimethyl-3-oxa-1-azaspiro[4.4]nonane-1-carboxylic Acid *tert*-Butyl Ester (11). *N*-Methylmorpholine *N*-oxide (1.34 g; 9.91 mmol) was added in one portion to a stirring solution of cyclopentene **3** (1.31 g; 3.30 mmol) in acetone/water (10:1; 143 mL). $K_2OsO_4 \cdot 2H_2O$ (121 mg; 0.33 mmol) was then added in one portion, and the resulting mixture was stirred at room temperature for a further 4.5 days. The reaction was quenched with Na_2SO_3 (1.26 g; 10.0 mmol) and concentrated in vacuo (water removed by azeotrope with ethyl acetate) onto silica. The free flowing 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 diol **11** (1.34 g; 94%) as a colorless oil $[\alpha]^{25}_D$ 41 (*c* 3.27, $CHCl_3$), 97% ee (Chiralpak AD, 8:92 IPA/Hexane, 1 mL/min) (found: C 58.6, H 9.4, N 3.3; $C_{21}H_{41}NO_6Si$ requires C 58.4, H 9.6, N 3.2); ν_{max}/cm^{-1} (film) 3454 br (OH), 1694 (CO); δ_H (400 MHz, $CD_3C_6D_5$, 368 K) 4.80 (1H, br s), 4.51 (1H, d, $J = 9.2$ Hz), 3.72 (1H, d, $J = 9.2$ Hz), 3.59 (1H, d, $J = 9.8$ Hz), 3.55 (1H, d, $J = 9.8$ Hz), 2.49 (1H, s), 2.43−2.33 (1H, m), 2.22 (1H, br d, $J = 5.5$ Hz), 2.06−1.96 (1H, m), 1.83−1.73 (1H, m), 1.67 (3H, s), 1.67−1.56 (1H, m(obscured)), 1.61 (3H, s), 1.47 (9H, s), 0.95 (9H, s), 0.07 (6H, s); δ_C (101 MHz, $CD_3C_6D_5$, 368 K) 152.2, 94.6, 80.0, 78.8, 76.1, 71.9, 71.5, 70.0, 31.8, 31.1, 29.0, 26.8, 26.5, 18.9, −4.3; *m*/*z* (ES+) 454.2629 (M + Na; $C_{21}H_{41}NNaO_6Si$ requires 454.2601).

(4*R*)-4-[4-(*tert*-Butyldimethylsilyloxy)-3-oxobutyl]-4-formyl-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (12). $NaIO_4$ (770 mg; 3.60 mmol) was added in one portion to a stirring solution of diol **11** (1.56 g; 3.60 mmol) in THF/water (2:1, 17 mL). The mixture was stirred for 2.5 days, adsorbed onto silica (ethyl acetate used to azeotrope water), and filtered through a plug of silica. Concentration in vacuo gave a slightly yellow oil (1.46 g) that was purified by column chromatography (4:1, petrol/Et_2O), yielding aldehyde **12** (1.24 g; 80%) as a colorless oil $[\alpha]^{27}_D$ −8.56 (*c* 1.92, $CHCl_3$) (found: C 59.15, H 8.9, N 3.0. $C_{21}H_{39}NO_6Si$ requires C 58.7, H 9.2, N 3.3); ν_{max}/cm^{-1} (film) 1740 (CO), 1709 (CO), 1689 (CO); δ_H (500 MHz; $CDCl_3$, 1.5:1 mixture of rotamers) 9.48/9.42 (1H, s), 4.16 (2H, app s), $3.92_{maj}/3.91_{min}$ (1H, d, $J_{maj} = 9.7$ Hz, $J_{min} = 9.5$ Hz), $3.79_{maj}/3.73_{min}$ (1H, d, $J_{maj} = 9.7$ Hz, $J_{min} = 9.5$ Hz), 2.79−2.67 (1H, m), 2.65−2.55 (1H, m), 2.34−2.15 (2H, m), 1.66/1.603 (3H, s), 1.595/1.57 (3H, s), 1.48/1.41 (9H, s), 0.91 (9H, s), 0.08 (6H, s); δ_C (126 MHz; $CDCl_3$, 1.5:1 mixture of rotamers) 210.1, 197.9/197.7, 152.2/150.9, 96.4/95.4, 81.8/81.5, 71.1/70.1, 69.4/69.3, 67.7, 33.4/33.0, 28.4/28.2, 26.7, 25.9, 25.6/25.4, 24.7, 24.2, 18.4, −5.4; *m*/*z* (ES+) 452.2461 (M + Na; $C_{21}H_{39}NNaO_6Si$ requires 452.2444).

(4*R*)-4-(2-Carboxyethyl)-4-formyl-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester 13 (via oxidative cleavage of cyclopentene 3). $K_2OsO_4 \cdot 2H_2O$ (4.70 mg; 12.8 μmol) was added in one portion to a stirring solution of cyclopentene **3** (173 mg; 0.44 mmol) and $NaIO_4$ (378 mg; 1.77 mmol) in THF (1.2 mL) and water (0.6 mL). The mixture was stirred for 6 days, quenched with Na_2SO_3 (206 mg; 1.63 mmol) and water (1 mL), and stirred for a further 30 min. The mixture was adsorbed onto silica (ethyl acetate used to azeotrope water), filtered through a plug of silica/Celite/sand, and concentrated in vacuo, giving a brown oil (261 mg). This was purified by column chromatography (petrol/ethyl acetate/glacial acetic acid 8/4/0.1), giving the air sensitive (the aldehyde readily oxidizes to a carboxylic acid upon standing in air) acid **13** (83.4 mg; 63%) as a colorless oil $[\alpha]^{28}_D$ −6.6 (*c* 3.47, $CHCl_3$); ν_{max}/cm^{-1} 3458br (OH), 3203 br (OH), 1739 (CO), 1712 (CO) 1683 (CO); δ_H (500 MHz, $CDCl_3$, 1.6:1 mixture of rotamers) 9.45/9.38 (1H, s), $3.92_{maj}/3.91_{min}$ (1H, d, $J_{maj} = 9.7$ Hz, $J_{min} = 9.5$ Hz), $3.90_{maj}/3.75_{min}$ (1H, d, $J_{maj} = 9.7$ Hz, $J_{min} = 9.5$ Hz), 2.57−2.13 (4H, m), 1.65/1.60 (3H, s), 1.59/1.57 (3H, s), 1.47/1.40 (9H, s); δ_C (126 MHz, $CDCl_3$, 1.6:1 mixture of rotamers) 197.5/197.3, 197.4/179.3, 152.2/150.8, 96.6/95.5, 82.2/81.9, 70.9/70.5, 67.5/67.4, 29.1/28.9, 28.3/28.2, 26.7, 26.4/26.3, 25.6, 25.2, 24.0; *m*/*z* (ES+) 324.1387 (M + Na; $C_{14}H_{23}NNaO_6$ requires 324.1423).

(4R)-4-(2-Carboxyethyl)-4-formyl-2,2-dimethyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester 13 (via oxidative cleavage of diol 11). $NaIO_4$ (291 mg; 1.36 mmol) was added in one portion to a stirring solution of diol **11** (146 mg; 0.34 mmol) in THF/water (2:1; 2 mL). The resulting mixture was stirred at room temperature for a further 17.5 h. The reaction was quenched with Na_2SO_3 (180 mg; 1.42 mmol) in water (2 mL). The organic solvent was removed in vacuo, and the remaining aquoeus was extracted with *i*-PrOH/$CHCl_3$ (1:1; 20 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo, giving acid **13** as a yellow oil (98.1 mg; 96%), which was used without further purification . The data recorded were identical with those reported above.

(4*R*)-4-(2-Carboxyethyl)-2,2-dimethyloxazolidine-3,4-dicarboxylic Acid 3-*tert*-Butyl Ester (14). $RuCl_3$ (anhydrous; 5.0 mg; 24.1 μmol) was added in one portion to a stirring solution of cyclopentene **3** (156 mg; 0.39 mmol) and $NaIO_4$ (484 mg; 2.26 mmol) in CCl_4 (0.75 mL), CH_3CN (0.75 mL), and H_2O (1.13 mL). The mixture was stirred at room temperature for 12 days. Diethyl ether (2 mL) was added and the mixture was stirred for a further 30 min (the RuO_4 oxidizes the diethyl ether). The mixture was adsorbed onto silica (ethyl acetate used to azeotrope water), filtered through a silica/Celite/sand plug, and concentrated in vacuo, giving

diacid **14** as a dark green oil (109 mg; 88% crude). The crude diacid was judged pure enough by ^{1}H NMR spectroscopy to be used without purification in further transformations. An aliquot (61 mg) of the crude product was purified by column chromatography (column acidified by washing with petrolr (20 mL) containing glacial acetic acid (10 drops); eluent 1:1 petrol/ethyl acetate), giving a colorless oil (44 mg; 56%). $[\alpha]^{25}_D$ 4.4 (*c* 1.64, $CHCl_3$); ν_{max}/cm^{-1} 3473 br (OH), 3176 br (OH), 1712 br (CO); δ_H (500 MHz; $CDCl_3$; 1.2:1 mixture of rotamers) 8.38 (2H, br s), 4.25/4.16 (1H, d, J = 9.2 Hz), 3.96/3.91 (1H, d, J = 9.2 Hz), 2.56−2.17 (4H, m), 1.63/1.58 (3H, s), 1.61/1.57 (3H, s), 1.48/1.41 (9H, s); δ_C (126 MHz; $CDCl_3$, 1.2:1 mixture of rotamers) 179.3/179.1/178.5/176.4, 152.8/151.1, 97.1/96.2, 82.1/81.6, 72.0/71.3, 68.2/67.4, 29.3/29.2, 29.8/28.1, 28.5/28.4, 26.5/25.9, 24.6/22.9; *m*/*z* (ES+) 340.1346 ($C_{14}H_{23}NNaO_7$ requires 340.1372).

(2*R*)-2-Hydroxymethylglutamic Acid (HMG) 2. Concentrated HCl in ethyl acetate (3 M, 2.5 mL) was added to the crude diacid **14** (36.0 mg) and the mixture was stirred for 19 h. The reaction was was concentrated in vacuo and purified twice by ion exchange column chromatography (Dowex 50W×8-200; 2 M NH_3 aq) giving HMG **2** (21.8 mg; 85% (2 steps)) as a white solid: mp 217 °C dec; $[\alpha]^{28}_D$ −6.9 (*c* 2.86, H_2O); δ_H (500 MHz; D_2O) 7.22 (2H, br s), 3.98 (1H, d, J = 12.0 Hz), 3.79 (1H, d, J = 12.0 Hz), 2.45−2.32 (2H, m), 2.05 (2H, app t, J = 7.7 Hz); δ_C (126 MHz; D_2O) 180.3, 174.4, 66.2, 64.9, 31.5, 28.7; *m*/*z* (ES−) 176.0547 (M − H; $C_6H_{10}NO_5$ requires 176.0559). The HCl salt of HMG **2** was also prepared for comparison to literature data[1] (21.8 mg; 186 μmol), thus HMG **2** was dissolved in 2 N HCl (10 mL) and stirred for 5 min. The solvent was removed in vacuo giving HMG·HCl (30.6 mg) as an off-white solid: mp 266 °C dec; δ_H (400 MHz; D_2O) 4.10 (1H, d, J = 12.2 Hz), 3.85 (1H, d, J = 12.2 Hz), 2.72−2.50 (2H, m), 2.30−2.16 (2H, m); δ_C (126 MHz; D_2O) 176.1, 171.9, 64.4, 63.5, 28.1, 26.8; *m*/*z* (ES−) 176 (M − 2H).

(4*R*)-4-[4-(*tert*-Butyldimethylsilyloxy)-3-oxobutyl]-2,2-dimethyloxazolidine-3,4-dicarboxylic Acid 3-*tert*-Butyl Ester 4-Methyl Ester (19). A solution of sodium chlorite (80%; 7.56 g; 67.5 mmol) and sodium hydrogen orthophosphate (8.04 g; 51.5 mmol) in water (23.8 mL) was added dropwise over 1 min to a cool (0 °C) stirring solution of the aldehyde **12** (1.21 g; 2.82 mmol) in 2-methyl-2-butene (12.0 mL; 0.11 mol) and *tert*-butyl alcohol (26.0 mL). The resulting solution was stirred at room temperature for 16 h. The organic solvent was removed in vacuo, and the remaining mixture was partitioned between water (50 mL) and ethyl acetate (125 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 125 mL) and the combined organic phase dried ($MgSO_4$). Concentration in vacuo gave the acid as a colorless oil (1.32 g), which was used without further purification. An aliquot (46.8 mg) was purified by column chromatography (1:1 petrol/acetic acid (0.1 M in ethyl acetate)), giving pure acid (38.3 mg; 93%) as a colorless oil: $[\alpha]^{25}_D$ 14.8 (*c* 0.76, $CHCl_3$) (found: C 56.3, H 8.8, N 3.0.; $C_{21}H_{39}NO_7Si$ requires C 56.6, H 8.8, N 3.1); ν_{max}/cm^{-1} (film) 3202 br (OH), 1738 (CO), 1707 (CO), 1682 (CO); δ_H (500 MHz; $CDCl_3$, 1.2:1 mixture of rotamers) 4.41 (1H, d, J = 9.4 Hz), 4.20−4.10 (3H, m), 3.92_{min}/3.81_{maj} (1H, d, J_{min} = 9.0 Hz, J_{maj} = 9.2 Hz), 2.80−2.16 (4H, m), 1.64/1.62 (3H, s), 1.564/1.558 (3H, s), 1.50/1.41 (9H, s), 0.92 (9H, s), 0.08 (6H, s); δ_C (126 MHz; $CDCl_3$, 1.2:1 mixture of rotamers) 210.4/210.0, 177.9/174.4, 154.1/151.2, 97.0/96.3, 82.9/81.4, 71.9/70.9, 69.5/69.3, 69.0/67.6, 33.6/33.4, 28.5/28.4, 27.1/26.4, 25.9, 25.5, 23.1, 18.4, −5.4; *m*/*z* (ES+) 468.2402 (M + Na; $C_{21}H_{39}NNaO_7Si$ requires 468.2394).

TMS-CHN_2 (2 M solution in hexanes, 2.30 mL; 4.6 mmol) was added dropwise over 5 min to a stirring solution of the previously prepared acid (1.04 g; 2.33 mmol) in anhydrous methanol (4.65 mL) and benzene (16.0 mL). After stirring for 23.5 h the reaction was quenched with NH_4Cl (10 mL of a saturated methanolic solution), filtered through Celite, and concentrated in vacuo giving a yellow oil (1.03 g). This was purified by column chromatography (4:1 petrol/diethyl ether) giving methyl ester **19** (812 mg; 75% (2 steps)) as a colorless oil: $[\alpha]^{26}_D$ −4.08 (*c* 1.25, $CHCl_3$) (found: C 57.7, H 9.0, N 2.9; $C_{22}H_{41}NO_7Si$ requires C 57.5, H 9.0, N 3.1); ν_{max}/cm^{-1} (film) 1746 (CO), 1705 (CO); δ_H (500 MHz; $CDCl_3$, 1.8:1 mixture of rotamers) 4.15/4.13 (2H, s), 4.02 (1H, d, J = 9.1 Hz), 3.84/3.81 (1H, d, J = 9.1 Hz), 3.71/3.70 (3H, s), 2.74−2.46 (2H, m), 2.42−2.11 (2H, m), 1.60/1.56 (3H, s), 1.58/1.54 (3H, s), 1.43/1.36 (9H, s), 0.88 (9H, s), 0.05/0.04 (6H, s); δ_H (400 MHz, C_6D_6, 340 K) 3.99 (2H, d, J = 1.4 Hz), 3.91 (1H, d, J = 9.1 Hz), 3.68 (1H, d, J = 9.1 Hz), 3.36 (3H, s), 2.74−2.36 (4H, m), 1.74 (6H, br s), 1.38 (9H, s), 0.93 (9H, s), 0.01 (6H, s); δ_C (126 MHz; $CDCl_3$, 1.8:1 mixture of rotamers) 210.3, 172.9/172.4, 151.8/151.2, 96.7/95.8, 80.81/80.76, 71.9/71.4, 69.4/69.3, 68.3/67.7, 52.6, 33.7/33.3, 28.4/28.3, 27.3/26.6, 26.8, 25.9, 24.4, 18.4, −5.4; *m*/*z* (ES+) 482.2518 (M + Na; $C_{22}H_{41}NNaO_7Si$ requires 482.2550).

(4*R*)-4-(4-Hydroxy-3-oxobutyl)-2,2-dimethyloxazolidine-3,4-dicarboxylic Acid 3-*tert*-Butyl Ester 4-Methyl Ester (20). TBAF (1 M in THF; 260 μL; 0.26 mmol) was added in one portion to a stirring solution of silyl ether **19** (101 mg; 0.22 mmol) in THF/water/acetic acid (10:1:1 v/v; 2.5 mL), and the mixture was stirred for 20 h. The reaction was concentrated in vacuo (water removed by azeotrope with ethyl acetate) and purified by column chromatography (1:1 petrol/diethyl ether to 1:1 petrol/ethyl acetate) giving the acyloin **20** (58.0 mg; 77%) as a colorless oil $[\alpha]^{31}_D$ −0.83 (*c* 1.93, $CHCl_3$) (found: C 55.5, H 8.0, N 3.8; $C_{16}H_{27}NO_7$ requires C 55.6, H,7.9, N 4.1); ν_{max}/cm^{-1} (film) 3482 br (OH), 1744 (CO), 1705 (CO); δ_H (500 MHz; C_6D_6, 1.7:1 mixture of rotamers) 3.89−3.74 (3H, m), 3.50 (1H, d, J = 9.2 Hz), 3.36/3.29 (3H, s), 2.58−2.36 (2H, m), 2.30−2.04 (2H, m), 1.73/1.60 (3H, s), 1.68/1.56 (3H, s), 1.33/1.31 (9H, s); δ_C (126 MHz; C_6D_6, 1.7:1 mixture of rotamers) 209.6/209.5, 173.1/172.5, 152.8/151.9, 97.4/96.4, 81.2/81.1, 72.4, 69.1/68.4, 68.6/68.4, 52.7/52.6, 34.3/33.8, 28.9, 28.7/28.6, 27.7/26.8, 24.8/23.5; *m*/*z* (ES+) 368.1694 (M + Na; $C_{16}H_{27}NNaO_7$ requires 368.1685).

(4*R*)-4-[11-(2-Hexyl[1,3]dioxolan-2-yl)-3-oxoundec-4-enyl]-2,2-dimethyloxazolidine-3,4-dicarboxylic Acid 3-*tert*-Butyl Ester 4-Methyl Ester (23). Methanesulfonyl chloride (15.0 μL; 0.20 mmol) was added dropwise over 10 s to a room temperature stirring solution of alcohol **20** (44.4 mg; 0.13 mmol) and triethylamine (55 μL; 0.39 mmol) in dry DCM (1.3 mL). After the solution was stirred for 60 min, triphenylphosphine (54.0 mg; 0.21 mmol) followed by *n*-Bu_4NI (7.00 mg; 19.0 μmol) were added each in one portion to the stirring solution. The mixture was stirred for 25 h, aldehyde **18** (70.0 mg; 0.26 mmol) in DCM (dry; 1 mL) was added in one portion, and the reaction was stirred for a further 6 days. The solution was loaded directly onto a silica gel column, and purified by column chromatography (3:1 petrol/diethyl ether to 2:1 petrol/diethyl ether), giving enone **23** (45.4 mg; 61%) as a colorless oil: $[\alpha]^{27}_D$ −5.85 (*c* 0.82, $CHCl_3$) (found: C 66.1, H 9.5, N 2.4; $C_{32}H_{55}NO_8$ requires C 66.1, H 9.5, N 2.4); ν_{max}/cm^{-1} 1746 (CO), 1705 (CO), 1699 (CO), 1674, 1632; δ_H (500 MHz, C_6D_6, 343K) 6.78 (1H, dt, J = 15.8, 6.9 Hz), 6.06 (1H, dt, J = 15.8, 1.4 Hz), 3.92 (1H, d, J = 9.0 Hz), 3.70 (1H, d, J = 9.0 Hz), 3.64 (4H, app s), 3.38 (3H, s), 2.76−2.40 (4H, m), 1.92−1.87 (2H, m), 1.83−1.57 (10H, m), 1.55−1.41 (4H, m), 1.38 (9H, s), 1.35−1.15 (12H, m), 0.88 (3H, t, J = 6.9 Hz); δ_C (126 MHz; C_6D_6; 343 K) 198.3, 173.4, 152.2, 146.8, 131.4, 112.7, 97.6, 80.9, 72.8, 69.1, 65.6, 52.4, 38.42, 38.35, 36.3, 33.1, 32.8, 30.69, 30.67, 30.1, 29.6, 29.1, 29.0, 26.9, 24.9, 24.8, 23.5, 14.7; *m*/*z* (ES+) 604.3806 (M + Na; $C_{32}H_{55}NNaO_8$ requires 604.3825).

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Supporting Information Available: Synthesis and characterization of **17** and **18**, and copies of the ^{1}H and ^{13}C NMR spectra of **2**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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