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The Versatile Steroid Nucleus: Design and Synthesis of a Peptidomimetic Employing this Novel Scaffold.

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Abstract: The design and synthesis of peptidomimetic **1** employing the novel cyclopentanoperhydrophenanthrene skeleton is described. The large body of steroid literature allows for the introduction of diverse peptidal side chains with precise regio- and stereoselective control. Compound **1** binds to the fibrinogen receptor on blood platelets (GP IIb/IIIa), for which it was designed, with an IC_{50} of ca. 100 μM.

Elsewhere,[1] we have recently described the basis for a program to design mimetics of β-turns in which the relevant amino acid sidechains of peptidal hormones and neurotransmitters are attached to novel scaffoldings. We refer to such structures as nonpeptidal peptidomimetics to distinguish them from the more widely explored peptidal peptidomimetics.

Peptidomimetics have emerged as an active field at the interface of bioorganic, organic, and medicinal chemistry.[2] This interest derives from the expectation that such molecules will have both better biostability and oral bioavailability than their peptide counterparts. Progress to date has come from three distinct approaches: (1) the systematic replacement of amide bonds with isosteres (e.g., ketomethylene or reduced amide isosteres) resulting in structures closely resembling peptides, (2) broad screening of sample collections, microbial broths, fungal metabolites, etc., generating molecules which have no obvious structural relationship with the natural ligands and which have been termed limetics (ligand mimetics) by Veber,[3] and, (3) the design and synthesis of novel scaffoldings with retention of peptidal sidechains, bridging the huge gap between the two categories, but more closely resembling the former. The screening leads may or may not recognize the same binding site as the natural ligands.

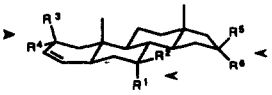
Several groups have reported on the design and synthesis of novel scaffolds.[4] These early compounds were not designed for specific receptors, as they lacked relevant peptidal sidechains that would permit biological testing; their conformations were therefore probed solely by physical measurements. One of our fundamental goals has been the design of scaffolds with sufficient sidechain functionality to allow our compounds to be tested at least in vitro, which we consider to be a more critical assessment of design. To our knowledge, bicyclo[2.2.2]octane[5] and β-D-glucose[6] were the first scaffolds successfully employed in the development of peptidomimetics which were recognized by the endocrine receptors for which they were designed.[7]

In the design of nonpeptidal peptidomimetics, knowledge of the bioactive conformation of peptidal ligands is required for the design process. However, when little is known about the shape of ligands that bind to a receptor, constrained peptidal and nonpeptidal peptidomimetics can be used as a probe. Our program continues to implement this convergent approach in the investigation of the bioactive geometry of peptidal ligands, and ultimately, in the development of more highly active, orally bioavailable compounds. Here, we wish to report the use of the cyclopentanoperhydrophenanthrene skeleton to probe the bioactive conformations of small peptide ligands which bind to the fibrinogen receptor.[8]

Of the host of potential rigid frameworks that could be used as scaffolds, the steroid nucleus was of interest for several reasons: (1) its volume closely matches that of the backbone of a cyclic hexapeptide *(vide infra)*,[9] (2) many steroids are drugs with excellent oral bioavailability, (3) the rigid steroid nucleus can reduce the tendency for hydrophobic collapse[10] of appended peptide sidechains, (4) the enormous body of steroid

literature allows for the introduction of diverse peptidal sidechains with precise regio- and stereoselective control, and finally, (5) steroids offer multiple possibilities for sidechain trajectories i.e., axial, equatorial, quasi-axial and equatorial, as well as pseudo axial and equatorial (Figure 1).

Figure 1.



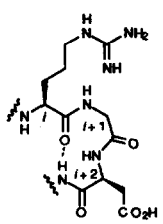
➢ axial and equatorial (R^1 and R^2)
➢ quasi-axial and equatorial (R^3 and R^4)
➢ pseudo axial and equatorial (R^5 and R^6)

The integrins are a family of cell surface adhesion receptors which include the fibrinogen receptor on blood platelets,[11] a membrane linked heterodimer (GP IIb/IIIa). This receptor, when activated, initiates platelet aggregation. There are several adhesive proteins which bind to platelet GP-IIb/IIIa including vitronectin, type I collagen, von Willebrand factor, and fibrinogen; however, because of its abundance, fibrinogen appears to be the most important of these with regard to platelet aggregation in blood circulation.[12] Because platelet aggregation is a key step in thrombus formation, the development of antagonists of fibrinogen binding to its receptor are of potential value in the treatment or prevention of stroke and heart attacks. Many potent peptidal fibrinogen receptor antagonists have been reported. Antagonists found in nature and those obtained by design and synthesis contain the peptide sequence Arg-Gly-Asp (RGD), thought to be sufficient for binding, provided that it is able to assume the bioactive conformation.[13] Although conformational studies had been conducted on two snake venom proteins and several small peptides, at the outset of this project little was known about the bioactive conformation of the RGD peptides which bind to the fibrinogen receptor.

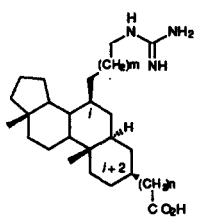
Echistatin,[14] a 49 residue snake venom protein, and kistrin,[15-18] a 68 amino acid protein also isolated from snake venom, bind with high affinity to GP IIb/IIIa. The solution structure of both were determined by NMR and both were found to contain the RGD sequence in highly flexible loop regions of the molecules. Structural studies with small peptides suggested[19-23] that RGD is part of a β-turn in its bioactive conformation. Reed *et al.* proposed, based on NMR and CD studies coupled with energy calculations, that the linear peptide GRGDSP adopts a nested set of β-turns initiated at Gly-1 and Arg-2 with Gly-3 occupying the *i + 1* position of the second β-turn.[19] Similarly, studies with c-(GRGDSPA) by Mizutani using NMR suggested that cyclization enforces a β-turn conformation of the RGDS sequence, in which the Gly of RGD also occupies the *i+1* position.[22] In view of these results, and because glycine frequently occupies the *i+1* position of turns in peptides,[24] we undertook the design of a rigid steroidal structure to mimic the presentation of the Arg and Asp sidechains found in a β-turn with glycine as the *i+1* residue.

Comparing the trajectories of the *i* and *i+2* positions of a type 1 β-turn with various positions on a steroid skeleton, we determined that equatorial substituents at the 3β and 7β positions of an allopregnane have spacing and geometry similar to the *i* and *i+2* amino acid sidechains respectively (Figure 2). We also compared the steroid skeleton to a cyclic hexapeptide containing a β-turn and found that the volume and geometry matched quite well (Figure 2). Through modeling studies, we determined that steroid **1** (n = m = 1) provides the proper length sidechains for best overlap. Nevertheless, we selected a synthetic plan which would permit construction of chain-extended versions of **1** (i.e., **2-4**, Figure 2).

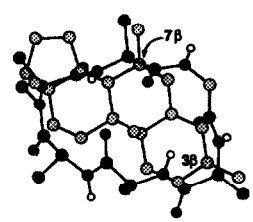
Figure 2.



Type 1 β-turn



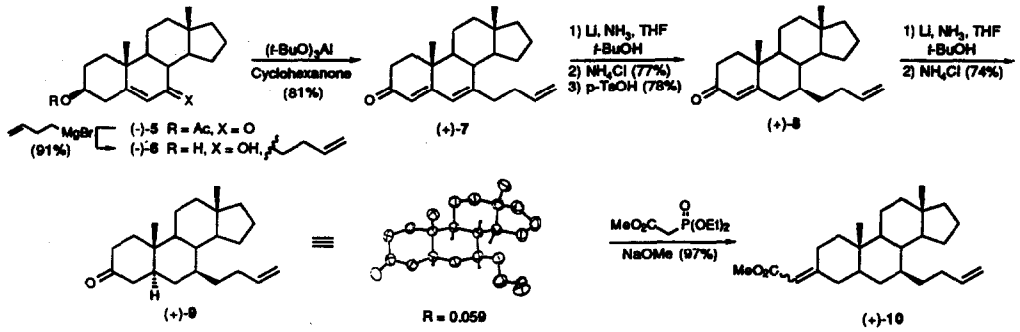
1 n = m = 1 IC_{50} = 100 μM
2 n = 1, m = 2
3 n = 2, m = 1 } inactive
4 n = m = 2



Overlay of a cyclic hexapeptide (black carbon atoms) and the steroid nucleus (white carbon atoms). The sidechains have been omitted for clarity.

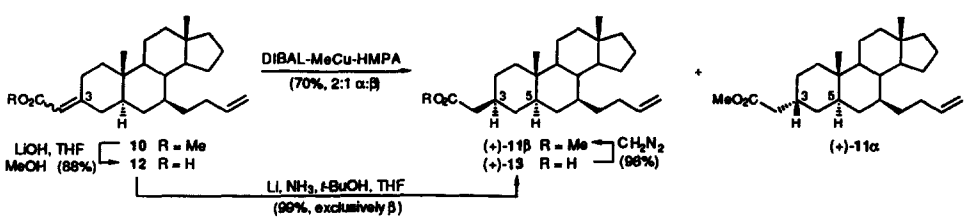
Δ^5-Androsten-7-one-3β-ol acetate [(-)-**5**][25] served as the starting point for the syntheses of **1**. Addition of the Grignard reagent derived from 4-bromobutene to **5** effected 1,2 addition at the 7-keto position as well as liberation of the 3-hydroxyl group (Scheme 1).[26] Oppenauer oxidation of the resulting diastereomeric mixture afforded dieneone (+)-**7** in 81% yield.[27] Reduction with lithium in ammonia[28] followed by reconjugation with *p*-toluenesulfonic acid smoothly led to α,β unsaturated ketone (+)-**8**. A second reduction with lithium in ammonia[29] gave ketone (+)-**9** whose stereochemistry was unequivocally assigned by X-ray crystallography.[30] Horner-Emmons olefination of **9** with methyl diethyl-phosphonoacetate then gave ester **10** as a 1:1 mixture of the olefinic isomers.[31]

Scheme 1



Attempts to convert **10** into the desired β-isomer (+)-**13** employing dissolving metal conditions led only to decomposition. Reduction of **10**, using a protocol described by Tsuda (DIBAL-MeCu-HMPA),[32] resulted in a 70% yield of **11** as a 2:1 (α:β) mixture of diastereomers at C(3) (Scheme 2). Assignment of the 3α configuration to the major isomer was based on comparison with empirically derived ^{13}C data for a series of substituted decalins.[33] It is well known that axially oriented substituents on decalins shift both the α and γ carbon resonances upfield relative to their equatorially disposed counterparts, due in part to steric crowding. The observed C(3) and C(5) carbons of the major diastereomer are shifted upfield 5.1 and 6.1 ppm respectively relative to the desired minor isomer. Fortunately, reduction of the corresponding free acid (+)-**12** with lithium in ammonia yielded only the desired β-isomer (+)-**13** in nearly quantitative yield.[34] Esterification with diazomethane provided (+)-**11**, which was identical in all respects to the minor isomer obtained previously.

Scheme 2

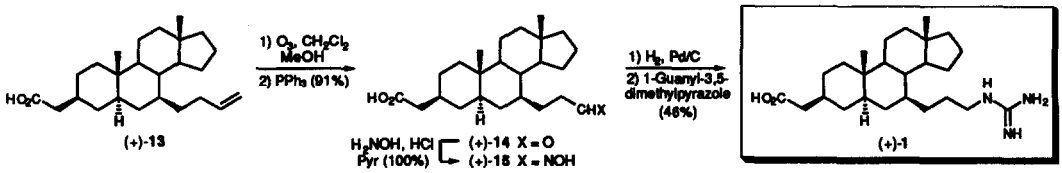


Completion of **1** was achieved by ozonolysis of acid **13** followed by condensation with hydroxylamine to furnish oxime **15** (Scheme 3). Hydrogenation[35] followed by guanylation of the resultant amino sidechain with 1-guanyl-3,5-dimethylpyrazole nitrate[36] yielded the first of our desired synthetic targets. In this final transformation, separation of **1** from byproducts proved difficult, requiring an initial purification through a short column of RP C-18 coated silica, followed by reverse phase HPLC.

Steroid mimetic **1** was tested in an ELISA GP IIb/IIIa fibrinogen receptor assay. It was found to bind to the GP IIb/IIIa receptor with an IC_{50} of ca. 100 μM using fibrinogen as a ligand. The dose response curve of **1** resembled that of members of a series of RGD-containing acyclic peptide analogs; moreover, **1** completely

displaced the ligand. Although the binding affinity is far less than that for a variety of RGD-containing peptides, the fact that **1** bound to the receptor for which it was designed supports the notion that the steroid nucleus can function as a scaffold for the development of peptidomimetics.

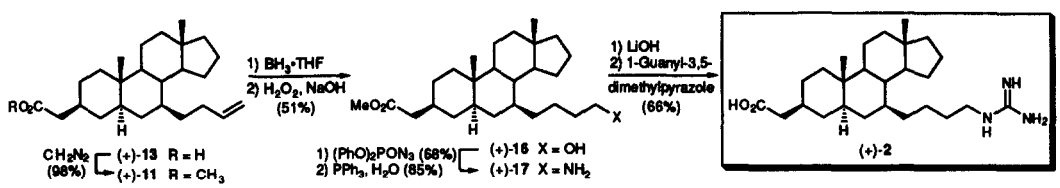
Scheme 3



Because we were uncertain as to what the optimal length sidechains should be, we undertook the synthesis of the chain extended homologs **2-4**. We first examined extension of the arginine sidechain because in a series of linear peptides containing the RGD sequence, Samanen *et al.* had found that substitution of homoArg for Arg resulted in about a 30% increase in potency.[37] Therefore, if the poor binding of **1** was simply a question of improper length, we would expect **2** to have a higher affinity for the receptor. However, a decrease in affinity might suggest that the initial assumptions regarding the placement of amino acids in the β-turn were incorrect. Likewise, it has been recognized that replacement of aspartic acid for glutamic acid in the RGD sequence is accompanied by a marked decrease in binding affinity.[37] Therefore, by a similar analogy, homologation of the 3β sidechain (a glutamic acid mimic) would be expected to result in a lower binding affinity should this compound truly be a mimic. The common intermediate for the synthesis of all three chain extended homologs was acid **13**.

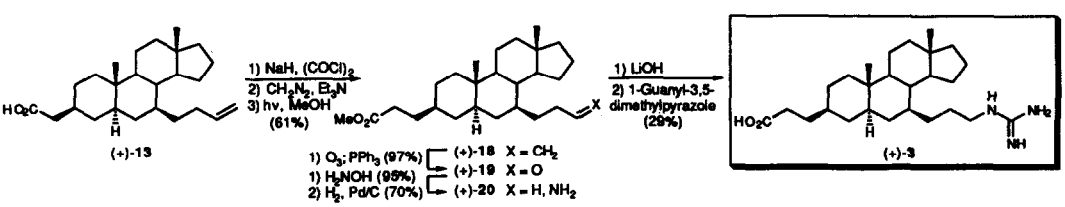
Extension of the arginine sidechain mimic was accomplished by esterification of **13** with diazomethane followed by hydroboration of the terminal olefin to yield the primary alcohol (+)-**16**. Conversion to the primary azide with diphenylphosphoryl azide[38] and reduction with triphenylphosphine[39] and water gave (+)-**17**. Again, guanylation of the free carboxylic acid with 1-guanyl-3,5-dimethylpyrazole nitrate gave the 7β-homologated target (+)-**2** in 66% yield (Scheme 4).

Scheme 4



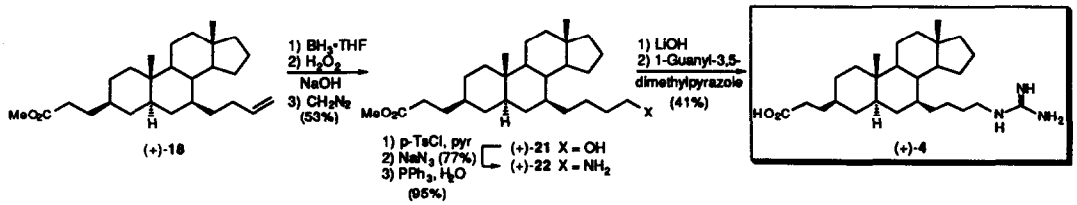
Homologation of the C(3) carboxylic acid sidechain was next effected exploiting the photochemical Arndt-Eister protocol as illustrated in Scheme 5. Toward this end, generation of the α-diazoketone was achieved by treatment of the acid chloride derived from **13** with excess diazomethane. Irradiation of the diazoketone in methanol through pyrex gave the homologated methyl ester (+)-**18**.[40] The amino sidechain was then elaborated as previously described (ozone, hydroxylamine, and H_2); liberation of the carboxylic acid followed by guanylation of the free amine gave homologated target (+)-**3**.

Scheme 5



The bis-homologated peptidomimetic (+)-4 was constructed in an analogous manner starting with (+)-18 (Scheme 6). In this instance the primary azide was formed in better overall yield (e.g. 77%) by a two-step protocol involving tosylation and displacement with sodium azide. Liberation of the acid and guanylation of the free amine yielded compound (+)-4.

Scheme 6



Compounds 2-4 did not bind to the fibrinogen receptor at 100 μM, thus serving as negative controls. Extension of either sidechain independently (2 and 3) or simultaneously (4) resulted in a total loss of affinity for the receptor. We interpret these results, in conjunction with the low binding affinity of 1, as suggesting that although a type 1 β-turn may be involved, glycine probably does not occupy the *i+1* position in the bioactive conformation of peptides which bind to the GP IIb/IIIa receptor. Binding studies with a series of cyclic hexapeptides (one of which had an IC_{50} of 19 nM), designed and synthesized by us in concert with the steroids described herein, reinforce this conclusion.[41] Recent NMR and molecular modeling studies carried out at Genentech on thioether-bridged cyclic peptides,[42] and in other laboratories,[43,44] on similarly constrained peptides, have suggested alternative conformations which may more closely resemble the bioactive geometry.

The fact that 1 bound at all encourages the notion that the steroid nucleus is a viable scaffold for the design and synthesis of peptidomimetics. Indeed, shortly after the completion of this work, Venapalli *et al.* described the isolation of a steroidal natural product which is a substance P antagonist,[45] thereby providing additional justification for this novel scaffold.

We are continuing our effort to exploit the steroidal nucleus and other rigid polycyclic scaffolds in the design and synthesis of a more potent RGD mimic using both the information about the bioactive conformation described herein, and that obtained recently with cyclic peptides synthesized in our laboratories and elsewhere.

Acknowledgements. We are grateful to Dr. Robert McDowell and Dr. Michael Venuti of the Bioorganic Chemistry Department at Genentech, Inc., South San Francisco, California, for making the results of their ongoing modeling studies of RGD peptides available to us. We thank Mr. Craig Muir and Mr. Chip Allee of the Biochemical Pharmacology group of the Cell Biology Department at Genentech, Inc. for carrying out the ELISA GP IIb/IIIa-fibrinogen binding assay. In addition, we thank Drs. George Furst, Patrick J. Carroll, and Mr. John Dykins of the University of Pennsylvania Spectroscopic Service Centers for assistance in securing and interpreting high-field NMR, X-ray crystallographic, and mass spectral data. Financial support was provided by the National Institutes of Health (Institute of General Medical Sciences) through grant GM-41821, and by Bachem, Inc. (CA).

EXPERIMENTAL

7-(3-Butenyl)-3,7-dihydroxyandrost-5-ene (-)-6. A solution of 3-butenylmagnesium bromide (generated from 4-bromobutene and magnesium dust) in THF (300 mL, 1.9 M, 0.59 mol) was added via canula to a solution of 3β-acetoxyandrost-5-en-7-one[24] (19.38 g, 0.059 mol) in THF (250 mL) at -60 °C. The mixture was stirred at -60 °C for 1 h, then allowed to warm to room temperature for 2 h. The mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated to give a yellow oil. Flash column chromatography (hexane/EtOAc, 2:1) afforded 6 as a mixture (1:1.5) of diastereomers (18.39 g, 91% yield). Analytical samples of the two diastereomers were obtained by additional flash column chromatography. 6β-OH: white solid; mp 80-82 °C (pentane/Et_2O); $[\alpha]_D^{25}$ -75.0° (*c* 0.66, $CHCl_3$); IR ($CHCl_3$) 3620 (m), 3460 (br, w), 3090 (w), 3020 (m), 2900 (s), 2880 (m), 1650 (w), 1470 (w), 1445 (w), 1385 (w), 1155 (m), 1145 (m), 1000 (w), 975 (w), 920 (w), 865 (w), 620 (w) cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 0.70 (s, 3 H), 1.04 (s, 3 H), 1.00-2.10 (m, 21 H), 2.12 (m, 1 H), 2.22-2.29 (m, 3 H), 3.53 (m, 1 H), 4.94 (apparent d, *J* = 10.0 Hz, 1 H), 5.02 (d, *J* = 16.9 Hz, 1 H), 5.28 (s, 1 H), 5.83 (m, 1 H); ^{13}C NMR (62.9

MHz, $CDCl_3$) δ 16.8, 19.2, 20.6, 21.1, 28.2, 31.5, 36.5, 37.2, 37.3, 38.2, 39.5, 41.1, 42.0, 44.5, 46.2, 71.1, 74.2, 114.3, 128.3, 139.6, 141.3; high resolution mass spectrum (CI, NH_3) *m/z* 344.2701 [M^+; calcd for $C_{23}H_{36}O_2$: 344.2717].

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.06; H, 10.42.

6α-OH: white solid; mp 117-118 °C (pentane/Et_2O); $[\alpha]_D^{25}$ -75.0° (*c* 0.70, $CHCl_3$); IR ($CHCl_3$) 3620 (m), 3480 (br, w), 3090 (w), 3020 (m), 2960 (s), 2890 (m), 1650 (w), 1465 (w), 1445 (w), 1385 (w), 1135 (m), 1000 (w), 980 (w), 950 (w), 920 (w), 640 (w) cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 0.73 (s, 3 H), 0.95 (s, 3 H), 1.04-2.10 (m, 23 H), 2.23 (ddd, *J* = 13.3, 11.5, 2.0 Hz, 1 H), 2.33 (ddd, *J* = 13.3, 5.0, 2.2 Hz, 1 H), 4.91 (apparent d, *J* = 10.2 Hz, 1 H), 4.98 (dd, *J* = 17.1, 1.4 Hz, 1 H), 5.17 (d, *J* = 1.9 Hz, 1 H), 5.28 (m, 1 H), 5.78 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 17.4, 18.0, 20.6, 21.3, 28.6, 29.2, 31.5, 36.5, 37.1, 38.4, 39.6, 40.7, 41.5, 41.7, 46.1, 48.2, 70.9, 72.6, 114.2, 128.8, 138.7, 144.5; high resolution mass spectrum (CI, NH_3) *m/z* 344.2731 [M^+; calcd for $C_{23}H_{36}O_2$: 344.2717].

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.86; H, 10.35.

Dienone (+)-7. A mixture of diastereomeric diols **6** (2.21 g, 6.40 mmol), aluminum tri-t-butoxide (6.93 g, 28.1 mmol) and cyclohexanone (19 mL, 180 mmol) in toluene (110 mL) was heated at reflux for 5 h. The solvent was removed under reduced pressure and the residue extracted with methylene chloride. The combined extracts were washed with 10% aqueous sodium hydroxide and water, dried ($MgSO_4$), and concentrated. Flash column chromatography (hexane/EtOAc, 6:1) gave **7** as a yellow oil (1.69 g, 81% yield); $[\alpha]_D^{25}$ +255.0° (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 3100 (w), 3020 (w), 2960 (s), 2880 (m), 1655 (s), 1625 (s), 1460 (w), 1425 (m), 1390 (m), 1375 (m), 1240 (m), 1140 (m), 1000 (w), 950 (w), 920 (w), 900 (w), 620 (w) cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 0.75 (s, 3 H), 0.98 (s, 3 H), 0.97-1.75 (m, 12 H), 1.89-2.48 (m, 9 H), 4.90 (apparent d, *J* = 9.2 Hz, 1 H), 4.95 (dt, *J* = 17.2, 1.7 Hz, 1 H), 5.52 (s, 1 H), 5.71 (m, 1H), 5.89 (s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 16.2, 17.7, 20.5, 20.7, 28.6, 33.1, 33.9, 34.2, 35.5, 36.2, 38.5, 39.3, 41.0, 43.0, 51.1, 51.5, 115.0, 121.5, 125.3, 137.5, 155.0, 164.4, 199.3; high resolution mass spectrum (CI, NH_3) *m/z* 325.2556 [$(M+H)^+$; calcd for $C_{23}H_{33}O$: 325.2531].

Enone (+)-8. A solution of (+)-**7** (2.35 g, 7.25 mmol) in *t*-butanol (0.85 mL) and THF (110 mL) was added in one portion to a blue solution of lithium (0.39 g, 55.70 mmol) in THF (110 mL) and NH_3 (380 mL) at -75 °C. The mixture was stirred at -75 °C for 8 min, then quenched with saturated ammonium chloride. The ammonia was allowed to evaporate, and the residue was extracted with ether. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Flash column chromatography (hexane/EtOAc, 6:1) provided the β,γ enone as a colorless oil (1.82 g, 77% yield): $[\alpha]_D^{25}$ +67.0° (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 3095 (w), 3020 (w), 2980 (s), 2900 (m), 1745 (s), 1650 (w), 1460 (m), 1420 (w), 1390 (m), 1240 (w), 1140 (m), 1000 (w), 920 (w), 615 (w) cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 0.74 (s, 3 H), 1.13 (s superimposed on a m, 3 H), 1.00-1.77 (m, 15 H), 1.84 (m, 1 H), 1.91-1.98 (m, 2 H), 2.09 (m, 1 H), 2.26 (apparent dt, *J* = 15.5, 5.3 Hz, 1 H), 2.42 (ddd, *J* = 15.6, 12.0, 5.4 Hz, 1 H), 2.82 (dd, *J* = 16.6, 1.8 Hz, 1 H), 3.24 (apparent dt, *J* = 16.6, 2.8 Hz, 1 H), 3.24 (app. dt, *J* = 16.6, 3.1 Hz, 1 H), 4.91 (app. dd, *J* = 10.2, 3.3 Hz, 1 H), 4.98 (apparent dd, *J* = 17.0, 3.3 Hz, 1 H), 5.24 (apparent t, *J* = 2.5 Hz, 1 H), 5.78 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 17.7, 19.3, 20.5, 22.0, 27.6, 30.6, 34.4, 35.8, 36.2, 36.8, 37.3, 39.0, 39.6, 40.4, 41.4, 47.7, 49.6, 55.6, 114.3, 127.4, 138.0, 138.8, 210.3; high resolution mass spectrum (CI, NH_3) *m/z* 344.2979 [$(M+NH_4)^+$; calcd for $C_{23}H_{38}NO$: 344.2953].

A solution of the above β,γ enone (1.82 g, 5.60 mmol) in acetonitrile (65 mL) was cooled to 0 °C, and *p*-toluenesulfonic acid (0.52 g, 3.3 mmol) was added. The mixture was stirred at 0 °C for 1 h, then concentrated and the residue was extracted with ether. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Flash column chromatography (hexane/EtOAc, 6:1) furnished **8** as a colorless oil (1.42 g, 78%); $[\alpha]_D^{25}$ +65.0° (*c* 0.49, $CHCl_3$); IR ($CHCl_3$) 3100 (w), 3020 (m), 2980 (s), 2900 (m), 1670 (s), 1625 (m), 1460 (m), 1440 (w), 1420 (w), 1390 (m), 1370 (m), 1280 (w), 1240 (m), 1135 (m), 1000 (w), 940 (m), 865 (w), 615 (w) cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 0.75 (s, 3 H), 1.14 (s, 3 H), 0.96-2.03 (m, 19 H), 2.09-2.19 (m, 2 H), 2.27-2.42 (m, 3 H), 4.93 (apparent d, *J* = 10.2 Hz, 1 H), 4.99 (apparent d, *J* = 17.1 Hz, 1 H), 5.70 (d, *J* = 1.3 Hz, 1 H), 5.77 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 17.6, 17.9, 20.8, 21.7, 29.0, 30.7, 34.0, 34.5, 35.8, 38.4, 38.9, 39.0, 39.5, 40.2, 42.0, 42.5, 54.4, 54.5, 114.5, 122.8, 138.6, 171.3, 199.5; high resolution mass spectrum (CI, NH_3) *m/z* 327.2722 [$(M+H)^+$; calcd for $C_{23}H_{35}O$: 327.2688].

Ketone (+)-9. A solution of (+)-**8** (0.17 g, 0.51 mmol) in *t*-butanol (0.06 mL) and THF (12 mL) was added in one portion to a blue solution of lithium (21 mg, 3 mmol) in THF (18 mL) and NH_3 (30 mL) at -70 °C. The mixture was stirred at -70 °C for 5 min, then quenched with saturated ammonium chloride. The ammonia was allowed to evaporate, and the residue was extracted with ether. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Flash column chromatography (hexane/EtOAc, 6:1) afforded **9** as a white solid (0.12 g, 74% yield); mp 81-82.5 °C (MeOH); $[\alpha]_D^{25}$ +65.0° (*c* 0.49, $CHCl_3$); IR ($CHCl_3$) 3095 (w), 2980 (s), 2900 (s), 1720 (s), 1650 (m), 1460 (m), 1425 (m), 1390 (m), 1365 (w), 1350 (w), 1310 (w), 1240 (m), 1135 (m), 1000

(m), 920 (m), 620 (w) cm-1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.69 (s, 3 H), 0.92 (s, 3 H), 0.68-2.36 (m, 27 H), 4.86 (apparent d, J = 10.1 Hz, 1 H), 4.93 (apparent d, J = 17.1 Hz, 1 H), 5.72 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.5, 18.2, 20.7, 22.2, 28.9, 31.0, 34.8, 35.1, 35.7, 38.2, 39.1, 39.4, 39.7, 40.1, 40.5, 42.1, 44.5, 45.4, 55.1, 55.3, 114.1, 139.0, 211.9; high resolution mass spectrum (CI, NH_3) m/z 328.2794 [M^+; calcd for $C_{23}H_{36}O$: 328.2767].

Methyl ester 10. A suspension of sodium methoxide (0.36 g, 6.75 mmol) in DMF (1.7 mL) was cooled to 0 °C, and methyl diethylphosphonoacetate (1.42 g, 6.75 mmol) was added. The mixture was warmed to room temperature for 1 h, then cooled to 0 °C and a solution of (+)-**9** (0.36 g, 1.35 mmol) in DMF (4.1 mL) was added. The mixture was allowed to warm to room temperature overnight, poured into water, and extracted with ether. The combined extracts were washed with 10% aqueous HCl and water, dried ($MgSO_4$), and concentrated. Flash column chromatography (hexane/EtOAc, 20:1) gave **10** as a mixture (1:1) of isomers (0.501 g, 97% yield); IR ($CHCl_3$) 3090 (w), 2970 (s), 2950 (s), 2895 (s), 2880 (s), 1720 (s), 1650 (m), 1460 (m), 1445 (m), 1395 (m), 1385 (m), 1295 (w), 1255 (m), 1240 (m), 1195 (m), 1170 (s), 1030 (w), 1000 (w), 920 (w), 870 (w), 610 (w) cm-1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70 (s, 6 H), 0.85 (s, 6 H), 0.96-1.98 (m, 47 H), 2.07-2.13 (m, 4 H), 2.29 (dt, J = 14.2, 4.5 Hz, 1 H), 3.45 (apparent d, J = 14.2 Hz, 1 H), 3.65 (s, 3H), 3.65 (s, 3 H), 3.71 (apparent d, J = 17.9 Hz, 1 H), 4.89 (apparent d, J = 10.1 Hz, 2 H), 4.96 (apparent d, J = 17.2 Hz, 2 H), 5.55 (s, 1 H), 5.56 (s, 1 H), 5.77 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 18.3, 20.8, 21.9, 22.0, 25.6, 29.0, 31.1, 31.2, 32.2, 33.7, 35.0, 35.1, 35.6, 35.7, 35.9, 39.5, 39.7, 40.0, 40.2, 40.3, 40.5, 40.7, 42.1, 46.1, 46.9, 50.7, 55.5, 55.6, 55.7, 112.0, 112.2, 113.9, 139.2, 139.3, 163.7, 167.2; high resolution mass spectrum (CI, NH_3) m/z 385.3119 [$(M+H)^+$; calcd for $C_{26}H_{41}O_2$: 385.3106].

Carboxylic acid (+)-12. A suspension of **10** (0.62 g, 1.61 mmol) in 10% aqueous lithium hydroxide (12 mL), methanol (12 mL) and THF (17 mL) was heated at reflux for 2 h. The mixture was concentrated, quenched with 10% aqueous hydrochloric acid and extracted with methylene chloride. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Flash column chromatography (hexane/EtOAc, 4:1) provided the α,β-unsaturated acid as a mixture (1:1) of isomers (0.52 g, 88% yield). Analytical samples of the two isomers were obtained by additional flash column chromatography (hexane/ EtOAc, 6:1); *E*-isomer: white foam; IR ($CHCl_3$) 3450-2450 (br, m), 2960 (s), 1695 (s), 1645 (s), 1455 (m), 1420 (m), 1390 (m), 1300 (m), 1275 (m), 1260 (m), 1185 (m), 1110 (m), 1000 (w), 910 (m), 870 (m) cm-1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.71 (s, 3 H), 0.84 (s, 3 H), 0.83-2.18 (m, 26 H), 2.32 (dt, J = 13.7, 4.7 Hz, 1 H), 3.45 (d, J = 13.5 Hz, 1 H), 4.97 (apparent d, J = 17.1 Hz, 1 H), 4.99 (apparent d, J = 10.1 Hz, 1 H), 5.60 (s, 1 H), 5.78 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.0, 18.3, 20.8, 21.9, 29.0, 31.2, 32.4, 34.0, 35.1, 35.5, 35.9, 39.5, 39.7, 40.2, 40.5, 40.8, 42.1, 46.1, 55.4, 55.6, 112.0, 113.9, 139.4, 166.5, 172.5; high resolution mass spectrum (CI, NH_3) m/z 388.3267 [$(M+NH_4)^+$; calcd for $C_{25}H_{42}NO_2$: 388.3215].

Z-**isomer**: Colorless oil; IR ($CHCl_3$) 3450-2450 (br, m), 2970 (s), 2945 (s), 2935 (s), 1695 (s), 1645 (s), 1455 (m), 1420 (m), 1390 (m), 1380 (m), 1330 (w), 1295 (m), 1280 (m), 1265 (m), 1240 (m), 1200 (w), 1170 (w), 1155 (w), 995 (w), 940 (w), 910 (m), 870 (m) cm-1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70 (s, 3 H), 0.85 (s, 3 H), 0.97-2.10 (m, 25 H), 2.11-2.15 (m, 2 H), 3.71 (apparent d, J = 13.5 Hz, 1 H), 4.89 (apparent dd, J = 10.1, 1.8 Hz, 1 H), 4.97 (apparent dd, J = 17.1, 3.3 Hz, 1 H), 5.58 (s, 1 H), 5.77 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.0, 18.3, 20.8, 22.0, 25.9, 29.0, 29.7, 31.2, 35.0, 35.7, 39.6, 39.8, 40.0, 40.2, 40.6, 40.7, 42.2, 46.9, 55.5, 55.6, 112.2, 114.0, 139.3, 166.7, 172.4; high resolution mass spectrum (CI, NH_3) m/z 388.3245 [$(M+NH_4)^+$; calcd for $C_{25}H_{42}NO_2$: 388.3215].

A solution of the mixture of α,β–unsaturated carboxylic acids (1.60 g, 4.32 mmol) in THF (15 mL) was added in one portion to a blue solution of lithium (0.35 g, 50 mmol) in *t*-butanol (0.36 mL), THF (12 mL) and NH_3 (60 mL) at -75 °C. The mixture was stirred at -75 °C for 45 min, then quenched with saturated ammonium chloride. The ammonia was allowed to evaporate, and the residue was acidified with 10% aqueous HCl and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Flash column chromatography (hexane/EtOAc, 4:1) gave **13** as a white solid (1.59 g, 99% yield); mp 105-106 °C (MeCN/Et_2O); $[\alpha]_D^{25}$ +36.0° (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) 3400-2500 (br, m), 2940 (s), 2890 (s), 2870 (s), 1715 (s), 1645 (w), 1465 (w), 1455 (m), 1415 (w), 1390 (w), 1380 (w), 1300 (m), 1270 (w), 1165 (w), 1000 (w), 940 (w), 910 (m) cm-1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.69 (s, 3 H), 0.70 (s, 3 H), 0.88-1.82 (m, 27 H), 1.94 (m, 1 H), 2.09 (m, 1 H), 2.22 (apparent d, J = 7.0 Hz, 2 H), 4.89 (apparent d, J = 10.2 Hz, 1 H), 4.96 (apparent d, J = 17.0 Hz, 1 H), 5.78 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.4, 18.3, 20.8, 21.7, 28.7, 29.0, 31.2, 34.8, 35.1, 35.2, 35.3, 35.7, 38.6, 39.6, 39.8, 40.3, 40.7, 41.8, 42.1, 44.7, 55.6, 56.0, 113.9, 139.5, 179.8; high resolution mass spectrum (CI, NH_3) m/z 390.3370 [$(M+NH_4)$+; calcd for $C_{25}H_{44}NO_2$: 390.3371].

Anal. Calcd for $C_{25}H_{40}O_2$: C, 80.59; H, 10.82. Found: C, 80.27; H, 10.53.

Aldehyde (+)-14. A solution of (+)-**13** (0.41 g, 1.09 mmol) in methylene chloride (30 mL) and methanol (3 mL) was cooled to -78 °C, and ozone was bubbled into the mixture until a blue color persisted. The excess ozone

was purged with argon, and triphenylphosphine (0.31 g, 1.20 mmol) was added. The mixture was allowed to warm to room temperature overnight, and then concentrated under reduced pressure. Flash column chromatography (hexane/EtOAc, 2:1) furnished **14** as a white foam (0.37 g, 91% yield); $[\alpha]_D^{25}$ +0.32° (*c* 0.85, $CHCl_3$); IR ($CHCl_3$) 3400-2400 (br, m), 2940 (s), 2860 (s), 1725 (s), 1715 (s), 1450 (m), 1410 (w), 1390 (w), 1380 (w), 1300 (w), 1150 (w), 940 (w) cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 0.68-0.75 (m, 2 H), 0.70 (s, superimposed on m, 6 H), 0.85-1.83 (m, 24 H), 2.02 (m, 1 H), 2.19-2.24 (m, 2 H), 2.35 (m, 1 H), 2.44 (m, 1 H), 9.73 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4, 18.2, 20.8, 21.7, 28.0, 28.7, 29.2, 34.8, 35.2, 35.2, 35.4, 38.6, 39.5, 39.8, 40.4, 40.6, 41.6, 41.6, 42.2, 44.7, 55.4, 55.9, 179.0, 203.1; high resolution mass spectrum (CI, NH_3) *m/z* 392.3156 $[(M+NH_4)^+$; calcd for $C_{24}H_{42}NO_3$: 392.3164].

Oxime 15. A solution of (+)-**14** (0.12 g, 0.32 mmol) and hydroxylamine hydrochloride (0.027 g, 0.38 mmol) in pyridine (1 mL) was stirred at room temperature overnight. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (hexane/EtOAc, 2:1) to give **15** as a mixture of isomers (0.12 g, 100% yield); 2:3 syn/anti mixture; mp 170-174 °C (MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.74 (s, 6 H), 0.76 (s, 6 H), 0.70-2.45 (m, 64 H), 6.62 (t, *J* = 5.4 Hz, 1 H), 7.32 (t, *J* = 6.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 12.9, 18.7, 21.7, 22.7, 22.9, 23.4, 26.7, 27.9, 29.8, 30.2, 31.4, 33.2, 34.0, 34.6, 36.4, 36.4, 36.5, 36.7, 36.8, 36.9, 38.2, 40.0, 40.9, 40.9, 41.6, 41.6, 42.0, 42.4, 42.9, 43.3, 46.2, 46.3, 57.0, 57.6, 152.7, 153.3. 177.0; high resolution mass spectrum (CI, NH_3) *m/z* 407.3201 $[(M+NH_4)^+$; calcd for $C_{24}H_{43}N_2O_3$: 407.3273].

Guanidine (+)-1. A suspension of **15** (1.00 g, 2.58 mmol) and 10% palladium on carbon (0.11 g) in acetic acid (15 mL) was shaken on a Parr hydrogenator (100 psi) for 20 h. The catalyst was removed by filtration and the solution was concentrated under reduced pressure. The residue was washed with ether and methanol to give the amino acid as a white powder (0.797 g) that was used without further purification.

A suspension of the amino acid (0.12 g, 0.31 mmol) and 1-guanyl-3,5-dimethylpyrazole nitrate (0.08 g, 0.4 mmol) in pyridine (2 mL) was heated at reflux for 6 h. The mixture was concentrated under reduced pressure, and the residue washed with ether and purified by reverse phase HPLC (MeCN/H_2O) to afford **1** as a white foam (0.072 g, 46% yield from **15**); $[\alpha]_D^{25}$ +26.4° (*c* 0.67, MeOH); IR (KBr) 3600-2500 (br, m), 2940 (s), 2860 (s), 1675 (s), 1450 (w), 1380 (w), 1200 (s), 1140 (s), 935 (w), 845 (w), 800 (w), 720 (w) cm-1; ^1H NMR (500 MHz, CD_3OD) δ 0.74 (s, 3 H), 0.75 (s, 3 H), 0.90-1.90 (m, 33 H), 2.14 (m, 2 H), 3.12 (m, 2 H); ^{13}C NMR (62.9 MHz, CD_3OD) δ 12.8, 18.7, 21.7, 22.9, 27.3, 29.8, 31.5, 33.9, 36.3, 36.4, 36.5, 37.1, 40.0, 40.8, 40.9, 41.6, 42.3, 42.7, 42.8, 43.3, 46.2, 57.0, 57.5, 158.6, 177.0; high resolution mass spectrum (CI, NH_3) *m/z* 418.3418 $[(M+H)^+$; calcd for $C_{25}H_{44}N_3O_2$: 418.3433].

Hydroxy ester (+)-16. A solution of (+)-**13** (0.23 g, 0.62 mmol) in ether (10 mL) was cooled to 0 °C, and a solution of excess diazomethane (generated from N-methyl-N-nitrosourea and potassium hydroxide) in ether (25 mL) at 0 °C was added. The mixture was allowed to warm to room temperature overnight, then purged with argon. The residue was concentrated under reduced pressure and purified by flash column chromatography (hexane/EtOAc, 9:1) to give the ester as a colorless oil (0.24 g, 98% yield): IR ($CHCl_3$) 3090 (w), 2940 (s), 2880 (s), 1740 (s), 1645 (w), 1460 (m), 1445 (m), 1380 (m), 1300 (m), 1250 (m), 1170 (m), 1020 (w), 1000 (w), 920 (m), 610 (w) cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 0.69 (s, 3 H), 0.72 (s, 3 H), 0.85-1.80 (m, 25 H), 1.92 (m, 1 H), 2.08 (m, 1 H), 2,17 (m, 1 H), 2.26 (m, 1 H), 2.37 (m, 1 H), 3.64 (s, 3 H), 4.94 (apparent d, *J* = 9.3 Hz, 1 H), 4.99 (apparent d, *J* = 17.0 Hz, 1 H), 5.77 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4, 18.3, 20.8, 21.5, 25.7, 29.0, 30.1, 31.2, 32.9, 33.4, 35.2, 35.7, 35.8, 37.2, 38.9, 39.7, 39.8, 40.3, 40.9, 42.2, 51.4, 55.7, 56.2, 113.8, 139.6, 174.1; high resolution mass spectrum (CI, NH_3) *m/z* 404.3488 $[(M+NH_4)^+$; calcd for $C_{26}H_{46}NO_2$: 404.3528].

A solution of the ester **11** (0.27 g, 0.66 mmol) in THF (3 mL) was cooled to 0 °C and borane-tetrahydrofuran (0.70 mL, 0.70 mmol) was added dropwise. The mixture was allowed to warm to room temperature for 3 h, then cooled to 0 °C and a solution of 30% hydrogen peroxide (1.8 mL) and 5% sodium hydroxide (2.8 mL) was added dropwise. The mixture was warmed to room temperature for 3 h and extracted with ethyl acetate. The combined extracts were washed with 5% hydrochloric acid and saturated brine, dried (Na_2SO_4), and concentrated. Flash column chromatography (hexane/EtOAc, 3:1) furnished **16** as a colorless oil (0.14 g, 51% yield); $[\alpha]_D^{25}$ +30.0° (*c* 0.42, MeOH); IR ($CHCl_3$) 3620 (w), 3460 (br, w), 2940 (s), 2860 (s), 1730 (s), 1465 (m), 1450 (m), 1440 (m), 1380 (m), 1370 (m), 1295 (m), 1260 (m), 1150 (m), 1015 (m), 910 (s) cm-1; ^1H NMR (500 MHz, CD_3OD) δ 0.67 (s, 6 H), 0.80-1.82 (m, 31 H), 2.15 (apparent d, *J* = 7.0 Hz, 2 H), 3.59 (t, *J* = 6.6 Hz, 2 H), 3.62 (s, 3 H); ^{13}C NMR (62.9 MHz, CD_3OD) δ 12.4, 18.3, 20.8, 21.7, 23.0, 28.7, 29.0, 33.2, 35.0, 35.2, 35.3, 35.7, 35.9, 38.6, 39.6, 39.8, 40.3, 41.2, 41.8, 42.1, 44.8, 51.3, 55.6, 56.0, 63.0, 173.6; high resolution mass spectrum (CI, NH_3) *m/z* 422.3638 $[(M+NH_4)^+$; calcd for $C_{26}H_{48}NO_3$: 422.3633].

Amine (+)-17. A solution of (+)-**16** (0.12 g, 0.30 mmol) in THF (2 mL) was stirred at room temperature and triphenylphosphine (0.16 g, 0.61 mmol) was added, followed by a solution diethyl azodicarboxylate (0.093 g, 0.54

mmol) in THF (0.5 mL). A solution of diphenylphosphoryl azide (0.095 g, 0.35 mmol) was then added dropwise, and the reaction was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and purified by flash column chromatography (hexane/EtOAc, 9:1) to give the azide as a colorless oil (0.086 g, 68% yield): $[\alpha]_D^{25}$ +31.0° (*c* 0.64, $CHCl_3$); IR ($CHCl_3$) 2960 (s), 2940 (s), 2875 (s), 2110 (s), 1735 (s), 1465 (m), 1455 (m), 1440 (m), 1380 (w), 1355 (w), 1300 (m), 1260 (m), 1150 (m), 1015 (w), 910 (w) cm-1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (s, 6 H), 0.80-1.82 (m, 30 H), 2.16 (apparent d, *J* = 7.0 Hz, 2 H), 3.22 (t, *J* = 7.0 Hz, 2 H), 3.63 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4, 18.3, 20.8, 21.7, 24.0, 28.8, 29.0, 29.3, 35.0, 35.2, 35.3, 35.4, 35.9, 38.7, 39.6, 39.8, 40.3, 41.2, 41.8, 42.1, 44.8, 51.3, 51.5, 55.6, 56.0, 173.5; high resolution mass spectrum (CI, NH_3) *m/z* 447.3750 $[(M+NH_4)^+$; calcd for $C_{26}H_{47}N_4O_2$: 447.3698].

A solution of the azide (0.035 g, 0.081 mmol) and triphenylphosphine (0.024 g, 0.09 mmol) in THF (1 mL) and water (0.04 mL) was stirred at room temperature 24 h, then heated at 50 °C for 10 h. The solution was concentrated under reduced pressure and purified by flash column chromatography (CH_2Cl_2/MeOH, 10:1) to afford **17** as a colorless oil (0.027 g, 85% yield); $[\alpha]_D^{25}$ +35.0° (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) 3500-2500 (br, w), 2930 (s), 2860 (s), 1735 (s), 1590 (w), 1455 (m), 1440 (m), 1380 (m), 1300 (m), 1260 (m), 1150 (m), 1110 (w), 940 (w), 855 (w), 640 (w) cm-1; ^{1}H NMR (500 MHz, CD_3OD) δ 0.66 (s, 6 H), 0.80-1.80 (m, 30 H), 2.04 (br s, 2 H), 2.15 (apparent d, *J* = 7.0 Hz, 2 H), 2.67 (br s, 2 H), 3.62 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 12.4, 18.3, 20.8, 21.7, 24.2, 28.8, 29.0, 29.7, 33.8, 35:0, 35.2, 35.3, 35.7, 35.9, 38.7, 39.6, 39.8, 40.4, 41.2, 41.8, 42.1, 44.8, 51.3, 55.6, 56.0, 173.5; high resolution mass spectrum (CI, NH_3) *m/z* 404.3519 $[(M+H)^+$; calcd for $C_{26}H_{46}NO_2$: 404.3528].

Guanidine (+)-2. A solution of (+)-**17** (0.014 g, 0.033 mmol) in 10% aqueous lithium hydroxide (0.15 mL), THF (0.3 mL) and methanol (0.5 mL) was stirred at room temperature for 1 h and acidified with 10% acetic acid. The mixture was concentrated under reduced pressure and the residue dissolved in pyridine (0.5 mL). To the solution was added 1-guanyl-3,5-dimethylpyrazole nitrate (0.023 g, 0.11 mmol) and the mixture was heated at reflux for 12 h. The solvent was then removed under reduced pressure and the residue purified by preparative thin layer chromatography ($CHCl_3$/MeOH/H_2O, 6:4:1) to give **2** as a tan solid (0.0092 g, 66% yield); $[\alpha]_D^{25}$ +23.0° (*c* 0.34, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 0.67 (s, 6 H), 0.75-1.85 (m, 27 H), 1.89 (d, *J* = 2.2 Hz, 2 H), 3.14 (m, 2 H), 3.30 (m, 2 H), 3.33 (m, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 12.9, 18.7, 21.7, 22.9, 25.1, 30.3, 30.3, 30.4, 36.5, 36.8, 36.9, 37.3, 37.5, 40.3, 41.0, 41.9, 42.5, 42.6, 43.3, 46.4, 49.6, 50.0, 57.2, 57.8, 158.7, 180.3; high resolution mass spectrum (CI, NH_3) *m/z* 432.3632 $[(M+H)^+$; calcd for $C_{26}H_{46}N_3O_2$: 432.3590].

Methyl ester (+)-18. A solution of (+)-**13** (0.15 g, 0.40 mmol) in THF (2 mL) was cooled to 0 °C, and sodium hydride (10.9 mg, 0.44 mmol) was added. The mixture was warmed to room temperature for 1 h, then cooled to 0 °C and oxalyl chloride (0.090 mL, 0.94 mmol) was added. The mixture was then warmed to room temperature for 3 h, concentrated, and diluted with ether (4 mL). The mixture was added to a solution of triethylamine (0.04 g, 0.4 mmol) and excess diazomethane (generated from N-methyl-N-nitrosourea and potassium hydroxide) in ether (4 mL) at 0 °C. The solution was allowed to warm to room temperature for 90 min, then filtered and purged with argon. The residue was concentrated under reduced pressure, dissolved in methanol (2 mL) and ether (1.5 mL), and irradiated with a mercury medium-pressure lamp (450 W) at 0 °C for 4 h. The mixture was concentrated and the residue purified by flash column chromatography (hexane/Et_2O, 20:1) to give **18** as a colorless oil (0.098 g, 61% yield); $[\alpha]_D^{25}$ +37.1° (*c* 0.80, $CHCl_3$); IR ($CHCl_3$) 3070 (w), 2920 (s), 2850 (s), 1730 (s), 1640 (w), 1450 (m), 1440 (m), 1375 (m), 1320 (w), 1300 (w), 1270 (m), 1245 (m), 1190 (m), 1170 (m), 1120 (w), 990 (w), 910 (m) cm-1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (s, 3 H), 0.69 (s, 3 H), 0.80-1.80 (m, 28 H), 1.93 (m, 1 H), 2.10 (m, 1 H), 2.29 (apparent t, *J* = 7.8 Hz, 2 H), 3.64 (s, 3 H), 4.88 (apparent ddd, *J* = 10.1, 3.2, 1.1 Hz, 1 H), 4.97 (apparent ddd, *J* = 17.1, 3.5, 1.6 Hz, 1 H), 5.78 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.4, 18.3, 20.8, 21.7, 28.7, 29.0, 31.2, 31.7, 32.2, 35.1, 35.4, 35.5, 35.9, 37.3, 38.8, 39.7, 39.8, 40.3, 40.7, 42.1, 44.8, 51.4, 55.6, 56.1, 113.8, 139.5, 174.5; high resolution mass spectrum (CI, NH_3) *m/z* 418.3724 $[(M+NH_4)^+$; calcd for $C_{27}H_{48}NO_2$: 418.3685].

Aldehyde (+)-19. A solution of (+)-**18** (0.08 g, 0.20 mmol) in methylene chloride (7 mL) and methanol (0.6 mL) was cooled to -78 °C, and ozone was bubbled into the reaction until a blue color persisted. The excess ozone was purged with argon, and triphenlphosphine (0.058 g, 0.22 mmol) was added. The mixture was allowed to warm to room temperature overnight, and then concentrated under reduced pressure. Flash column chromatography (hexane/Et_2O, 5:1) afforded **19** as a colorless oil (0.078 g, 97% yield): $[\alpha]_D^{25}$ +33.8° (*c* 0.80, $CHCl_3$); IR ($CHCl_3$) 3030 (w), 2920 (s), 2850 (s), 1725 (s), 1450 (m), 1435 (m), 1380 (w), 1270 (w), 1170 (w), 1010 (w) cm-1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.65 (s, 3 H), 0.66 (s, 3 H), 0.79-1.69 (m, 26 H), 1.78 (m, 1 H), 2.00 (m, 1 H), 2.26 (apparent t, *J* = 7.8 Hz, 1 H), 2.32 (m, 1 H), 2.42 (m, 1 H), 3.61 (s, 3 H), 9.71 (t, *J* = 1.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 18.2, 21.7, 27.9, 28.6, 29.1, 31.6, 32.1, 35.2, 35.4, 35.5, 37.2, 38.7, 39.5, 39.7, 40.3, 41.6, 42.1, 44.7, 51.4, 55.3, 55.9, 174.4, 202.9; high resolution mass spectrum (CI, NH_3) *m/z* 420.3470 $[(M+NH_4)^+$; calcd for $C_{26}H_{46}NO_3$: 420.3477].

Amine (+)-20. Aldehyde (+)-**19** was converted to its hydroxyl amine as for **14** (95%): IR ($CHCl_3$) 3595 (w), 3300 (br, w), 2930 (s), 2880 (s), 1735 (s), 1455 (m), 1440 (m), 1380 (w), 1305 (w), 1275 (w), 1180 (w), 1010 (w), 890 (w) cm-1; ^1H NMR [500 MHz, $CDCl_3$ (mixture of isomers)] δ 0.67 (s, 3 H), 0.68 (s, 3 H), 0.76 (s, 3 H), 0.80-1.89 (m, 56 H), 2.09 (m, 1 H), 2.29 (t, J = 7.8 Hz, 4 H), 2.20-2.42 (m, 3 H), 3.63 (s, 6 H), 6.66 (t, J = 5.5 Hz, 1 H), 7.37 (t, J = 6.0 Hz, 1 H), 8.00 (br, 1 H), 8.40 (br, 1 H); ^{13}C NMR [125 MHz, $CDCl_3$ (mixture of isomers)] δ 12.4, 12.4, 20.8, 21.7, 22.5, 27.0, 28.7, 29.1, 31.7, 32.0, 32.2, 32.5, 35.3, 35.5, 35.6, 35.6, 37.3, 38.8, 39.6, 39.8, 40.3, 40.3, 40.7, 41.0, 42.2, 44.8, 51.4, 55.5, 55.5, 56.1, 152.4, 153.2, 174.8; high resolution mass spectrum (CI, NH_3) *m/z* 418.3257 [$(M+H)^+$; calcd for $C_{26}H_{44}NO_3$: 418.3321].

The oxime of **19** was hydrogenated as for **15** to give **20** (70%); $[\alpha]_D^{25}$ +31.0° (*c* 0.30, $CHCl_3$); IR ($CHCl_3$) 3500-2400 (br, w), 3020 (w), 2960 (s), 2940 (s), 2860 (s), 1735 (s), 1625 (w), 1526 (w), 1475 (m), 1450 (m), 1440 (m), 1390 (m), 1380 (m), 1240 (m), 1175 (m), 1130 (w), 1010 (w), 880 (w), 640 (w), 590 (w) cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 0.65 (s, 3 H), 0.66 (s, 3 H), 0.71-1.90 (m, 30 H), 2.27 (apparent t, J = 7.7 Hz, 2 H), 2.88 (br s, 2 H), 3.62 (s, 3 H), 8.21 (br s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4, 18.3, 20.8, 21.7, 25.3, 28.6, 29.2, 31.7, 32.2, 32.8, 35.3, 35.5, 35.9, 37.3, 38.8, 39.5, 39.7, 40.3, 40.4, 40.8, 42.1, 44.8, 51.4, 55.5, 56.0, 174.5; high resolution mass spectrum (CI, NH_3) *m/z* 404.3594 [$(M+H)^+$; calcd for $C_{26}H_{46}NO_2$: 404.3529].

Guanidine (+)-3. Amine (+)-**20** was converted to guanidine **3** as for **2** and purified by reverse phase HPLC ($MeCN/H_2O$) in, 29% yield; $[\alpha]_D^{25}$ +15.0° (*c* 0.29, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 0.66 (s, 3 H), 0.70 (s, 3 H), 0.80-1.85 (m, 31 H), 2.24 (t, J = 7.7 Hz, 2 H), 3.26 (m, 2 H); ^{13}C NMR (62.9 MHz, CD_3OD) δ 12.9, 18.7, 21.7, 22.9, 27.3, 29.8, 30.1, 30.8, 32.6, 33.5, 33.9, 36.7, 37.2, 38.7, 40.1, 40.8, 40.9, 41.6, 42.3, 42.9, 43.3, 46.3, 57.0, 57.6, 158.6, 178.0; high resolution mass spectrum (CI, NH_3) *m/z* 432.3562 [$(M+H)^+$; calcd for $C_{26}H_{46}N_3O_2$: 432.3589].

Hydroxyester (+)-21. A solution of borane-tetrahydrofuran (1M, 0.71 mL, 0.71 mmol) was added to a solution of ester (+)-**18** (0.29 g, 0.71 mmol) in THF (5 mL) at 0 °C. After stirring at room temperature for 4 h, 30% hydrogen peroxide (1.5 mL) and 5% NaOH (2.5 mL) were added to the mixture at 0 °C. The mixture was stirred at room temperature overnight and extracted with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Purification by flash column chromatography (hexane/EtOAc, 3:1) gave **21** (0.072 g, 24% yield) and the hydroxy acid (0.131 g, 45% yield); $[\alpha]_D^{25}$ +30.0° (*c* 0.85, $CHCl_3$); IR ($CHCl_3$) 3620 (w), 3460 (br, w), 2930 (s), 2860 (s), 1735 (s), 1455 (m), 1440 (m), 1390 (m), 1380 (m) 1275 (m), 1240 (m), 1190 (w), 1175 (m), 1010 (w), 890 (w), 590 (w) cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 0.65 (s, 3 H), 0.67 (s, 3 H), 0.75-1.90 (m, 33 H), 2.27 (t, J = 7.6 Hz, 2 H), 3.58 (t, J = 6.6 Hz, 2 H), 3.62 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.4, 18.3, 20.8, 21.7, 23.0, 28.7, 29.0, 31.7, 32.2, 33.3, 35.2, 35.5, 35.7, 36.0, 37.3, 38.8, 39.7, 39.8, 40.3, 41.3, 42.1, 44.9, 51.4, 55.6, 56.1, 63.0, 174.6; high resolution mass spectrum (CI, NH_3) *m/z* 436.3822 [$(M+NH_4)^+$; calcd for $C_{27}H_{50}NO_3$: 436.3790].

Hydroxy acid: $[\alpha]_D^{25}$ +33.0° (*c* 0.22, $CHCl_3$); IR ($CHCl_3$) 3620 (w), 3600-2400 (br, w), 2940 (s), 2860 (s), 1715 (s), 1465 (m), 1455 (m), 1410 (m), 1390 (m) 1280 (m), 1245 (m), 1165 (w), 1125 (w), 1040 (w), 1015 (w), 940 (w), 630 (w), 590 (w) cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 0.66 (s, 3 H), 0.67 (s, 3 H), 0.75-1.80 (m, 33 H), 2.31 (t, J = 7.6 Hz, 2 H), 3.61 (t, J = 7.7 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.4, 18.3, 20.8, 21.7, 23.0, 28.7, 29.0, 31.6, 32.0, 32.9, 35.4, 35.5, 35.7, 36.0, 37.2, 38.8, 39.7, 39.8, 40.3, 41.3, 42.1, 44.9, 55.6, 56.1, 63.1, 179.3; high resolution mass spectrum (CI, NH_3) *m/z* 422.3657 [$(M+NH_4)^+$; calcd for $C_{26}H_{48}NO_3$: 422.3633].

A solution of diazomethane in ether (4 mL), which was generated from N-methyl-N-nitrosourea and potassium hydroxide, was added to a solution of the hydroxy acid (0.128 g, 0.31 mmol) in ether (4 mL) at 0 °C. After 20 min, excess diazomethane was removed by purging argon into the resulting solution at room temperature. The solution was concentrated to give a residue which was purified by flash column chromatography (hexane/EtOAc, 3:1) to afford **21** (0.083 g, 63% yield).

Amine (+)-22. A solution of ester (+)-**21** (0.15 g, 0.35 mmol) and *p*-toluenesulfonyl chloride (0.11 g, 0.55 mmol) in pyridine (1.2 mL) was stirred at 0 °C for 5 h, then poured into ice water and extracted with methylene chloride. The combined extracts were washed with 10% HCl, dilute aqueous sodium carbonate and saturated brine, dried ($MgSO_4$), and concentrated. The residue was dissolved in acetone (1.8 mL) and methanol (0.6 mL), and 5 M aqueous sodium azide (1 mL) was added to the solution. The mixture was heated at reflux for 14 h, concentrated, and extracted with ether. The combined extracts were dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (hexane/Et_2O, 15:1) gave the azide as a colorless oil (0.12 g, 77% yield): $[\alpha]_D^{25}$ +33.0° (*c* 0.38, $CHCl_3$); IR ($CHCl_3$) 2940 (s), 2865 (s), 2110 (s), 1735 (s), 1465 (m), 1455 (m), 1440 (m), 1380 (m), 1355 (m) 1270 (m), 1200 (m), 1180 (m), 1130 (w), 1110 (w), 910 (w) cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 0.65 (s, 3 H), 0.66 (s, 3 H), 0.60-1.80 (m, 32 H), 2.26 (t, J = 7.7 Hz, 2 H), 3.20 (t, J = 6.9 Hz, 2 H), 3.61 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 18.2, 20.7, 21.7, 24.0, 28.6, 29.0, 29.3, 31.6, 32.1, 35.3, 35.4, 35.4, 36.0, 37.3, 38.8, 39.6, 39.8, 40.2, 41.1, 42.1, 44.8, 51.3, 51.4, 55.6, 56.1, 174.3.

The azide of **21** was reduced as for **17** to give **22** (95%) as a colorless oil; $[\alpha]_D^{25}$ +30.0 (*c* 0.18, $CHCl_3$); IR ($CHCl_3$) 3500-2500 (br, w), 2940 (s), 2865 (s), 1735 (s), 1665 (w), 1590 (w), 1470 (m), 1460 (m), 1445 (m), 1390 (m), 1380 (m), 1325 (w), 1310 (w), 1280 (m), 1255 (m), 1200 (m), 1180 (m), 1130 (w), 860 (w), 650 (w) cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 0.65 (s, 3 H), 0.66 (s, 3H), 0.70-1.80 (m, 34 H), 2.27 (t, *J* = 7.7 Hz, 2 H), 2.65 (br s, 2 H), 3.62 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4, 18.3, 20.8, 21.7, 24.2, 28.7, 29.0, 31.7, 32.2, 34.2, 35.4, 35.5, 35.7, 36.1, 37.3, 38.8, 39.7, 39.8, 40.2, 41.3, 42.1, 44.9, 51.4, 55.7, 56.1, 174.5; high resolution mass spectrum (CI, NH_3) *m/z* 418.3661 $[(M+H)^+$; calcd for $C_{27}H_{48}NO_2$: 418.3685).

Guanidine (+)-4. Amine **22** was converted to guanidine **4** as for **3** (41%); $[\alpha]_D^{25}$ +27.0 (*c* 0.67, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.66 (s, 6 H), 0.80-1.80 (m, 32 H), 2.21 (t, *J* = 7.7 Hz, 2 H), 3.08 (t, *J* = 6.9 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.9, 18.7, 21.7, 22.9, 25.0, 29.9, 30.2, 30.4, 32.6, 33.5, 36.7, 37.4, 38.7, 40.1, 40.9, 40.9, 41.6, 42.5, 42.7, 43.3, 46.4, 57.1, 57.7, 158.7, 178.0; high resolution mass spectrum (CI, NH_3) *m/z* 446.3748 $[(M+H)^+$; calcd for $C_{27}H_{48}N_3O_2$: 446.3746).

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