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A Biogenetically Based Strategy Towards the Polycyclic Core Skeleton of Sarain A

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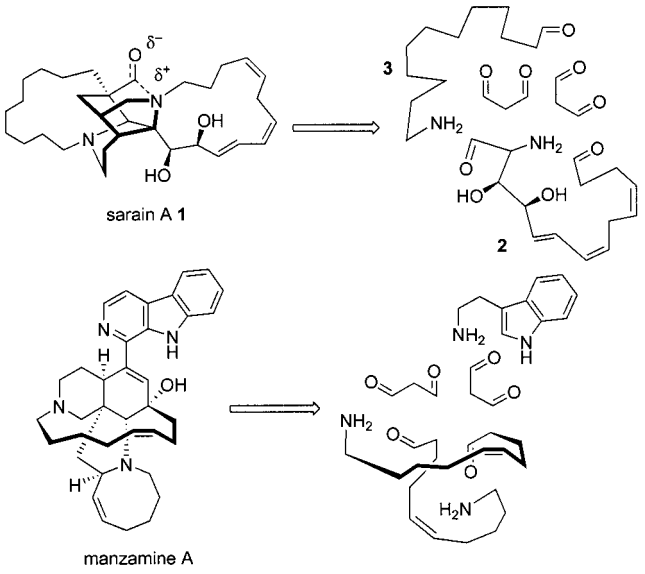
An approach to the polycyclic core of sarain A, based upon a proposed biogenetic route, is presented. Condensation of a protected amino acid with a bromoacrylamide and subsequent addition of malonaldehyde sodium salt and methyl iodide afforded, after stereoselective hydrogenation, a highly functionalized diazabicyclo[4.3.0]nonane system **16**. This intermediate possesses the stereochemistry required for the synthesis of the core skeleton of sarain A, a model of which (**31**) was obtained by an allylsilane strategy previously described by Weinreb and co-workers.

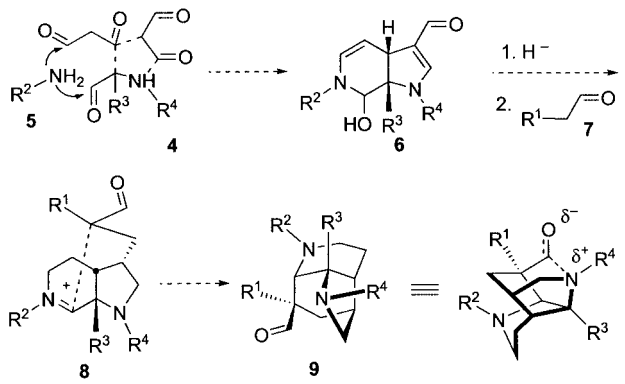
Introduction

Since its discovery,[1] sarain A (**1**), a complex polycyclic alkaloid extracted from the sponge *Reniera sarai*, has become one of the most challenging targets in natural products synthesis (Scheme 1),[2–5] as a result of which the first total synthesis has very recently been achieved.[6] We have suggested[7] that the biogenetic origin of sarain A (**1**) could possibly be the result of the condensation, in a multistep reductive process, of four intermediates: a sphingolipid **2** and an amino aldehyde **3** with two malonaldehyde units. One advantage of such a hypothesis is that it closely links the origin of sarain A to that, also proposed by us,[8] of manzamine A, an alkaloid extracted from sponges of the same order (*Haplosclerida*). Such considerations are also consistent with recent observations suggesting that these alkaloids are in fact produced by sponge-associated bacteria.[9]



Scheme 1. Proposed biogenetic pathway.

While these proposals are still speculative, as no biosynthetic studies are yet available, they offer valuable bases for the design of new synthetic strategies for sarain A. From the point of view of the proposed biogenetic pathway depicted in Scheme 1, there are many different ways to assemble the hypothetical starting units. In addition, aldehydes and malonaldehyde are unstable compounds, so the question of whether to use more stable synthetic equivalents arises. We chose to study the route summarized in Scheme 2, as a result of which a first study of this model



Scheme 2. General strategy.

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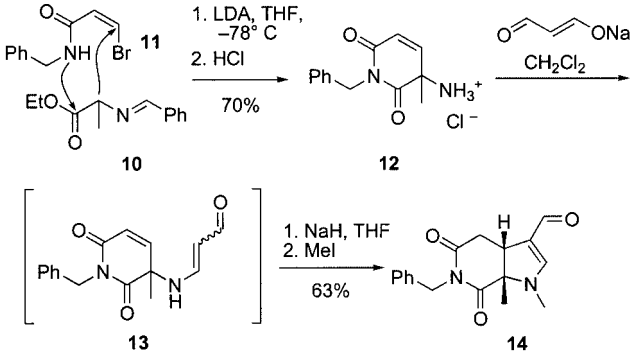
based on Knoevenagel chemistry was recently published.[7] We now report a new and efficient approach to highly functionalized diazabicyclo[4.3.0]nonane analogues of **6**, together with some observations concerning their regio- and stereoselective reduction, which is strongly influenced by proximity effects, and lastly the synthesis of an analogue of the core skeleton of sarain A.

Results and Discussion

As shown in Scheme 2, four molecules (**4**, **5**, and two malonaldehyde units) need to be condensed to afford intermediates such as **6**. Selective reduction and side-chain elongation with aldehyde **7** should then afford iminium salt **8**, Mannich cyclization of which would be likely to produce sarain A core skeleton **9**.

We first tried to mimic the first sequence of the projected synthesis leading to intermediates **6**, and accordingly to highly functionalized diazabicyclo[4.3.0]nonane systems (Scheme 3). L-Alanine imino derivative **10** was deprotonated and treated with bromoacrylamide derivative **11** to provide salt **12** in 70% yield after acidic imine hydrolysis.[10] This crude hydrochloride was then treated with malonaldehyde sodium salt, affording enaminal **13**. This intermediate was not isolated, but was directly treated with sodium hydride, followed by methyl iodide, ultimately to provide



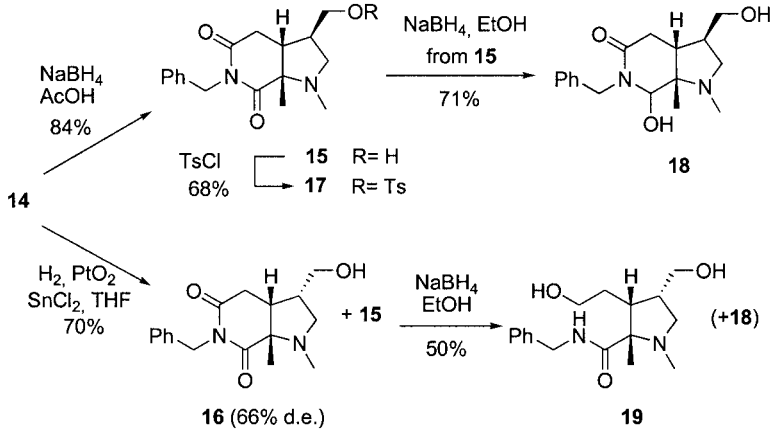
Scheme 3. Short route to a diazabicyclo[4.3.0]nonane system.

the highly functionalized diazabicyclo[4.3.0]nonane **14** with complete *cis* ring junction stereoselectively in an overall yield of 44%. This sequence, which does not required purification of any intermediate, is of particular interest since it consists of the condensation of four different molecules with formation of two C–C and three C–N bonds in a very short process. The stereospecificity of the ring closure reaction can be explained by the nearly planar shape of the five sp^2 atoms in **13**. The enaminal anion can only add to the double bond from the same side as the nitrogen atom.

The direct functionalization of vinylogous amide **14** by organometallic species proved to be difficult, but possible. The best alternative was the reduction of enaminal **14** in order to introduce the third stereocenter (Scheme 4) by using sodium borohydride in acetic acid which fully reduced the enaminal function but stereospecifically delivered the undesired alcohol isomer **15**. We had shown in our previous paper[7] that such a configuration is the thermodynamic one, as was further confirmed when alcohol **16** was oxidized to the corresponding aldehyde. Under enolization conditions, this aldehyde was completely epimerized at C-3 (results not shown). Hydrogenation of **14** in the presence of platinum oxide resulted in the formation of the desired *endo* isomer **16**, though with poor selectivity (1.6:1 mixture with **15**), but isomer **16** could eventually be obtained as a 4.7:1 mixture with **15** through the use of a catalytic amount of tin dichloride as catalyst activator.[11] The two diastereoisomers proved to be difficult to separate and were used as a mixture in the next steps.

Tosylate **17** could be crystallized and subjected to X-ray analysis (Figure 1),[12] which established the stereochemistry at C-3 in tosylate **17** and, as a consequence, in its precursor alcohol **15**.

A brief investigation of borohydride reduction of the imide moiety revealed some interesting features. Imide **15** was reduced to give **18** as a single diastereoisomer, but NOESY experiments and molecular modeling did not allow conclusive determination of the relative configuration at the hemiaminal center. Selective reduction at the more hindered sites of imides by $NaBH_4$ is already known, and ring opening can be prevented by continuously lowering the pH of



Scheme 4. Reduction studies on intermediate **14**.

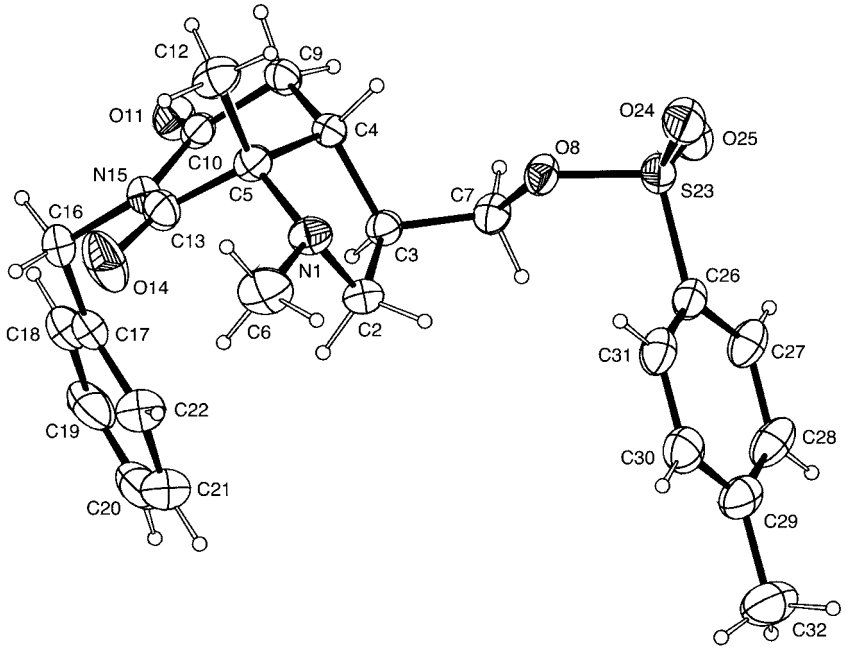


Figure 1. ORTEP plot of tosylate **17**.[13] Ellipsoids are drawn at 30% probability level.

the reaction mixture.[14] In contrast, imide **16** gave the diol **19** as the result of a double reduction process. It is very likely that the hydroxy moiety in **16** allowed intramolecular delivery of the reagent and enforced the double reduction. X-ray analysis of diol **19** unambiguously confirmed the structure found by NMR spectroscopy (Figure 2).

Reduction of the crude mixture of imides **15** and **16** (1:4.7 ratio, Scheme 5) with DIBAH gave two products **20** (from **16**, 72% yield) and **21** (from **15**, 12% yield). Since no other isomer could be detected, this reduction can be regarded as highly, if not totally, regioselective.

The sequence was followed by transformation into cyclic *N*-acylenamine **22**, allowing reduction of the double bond by hydrogenation in the presence of Raney nickel to give alcohol **23** (Scheme 5). Removal of the benzyl group with sodium in ammonia delivered alcohol **24** in 71% overall yield from aminal **20**. In order to elongate the side chain as in model **8** (see Scheme 2), alcohol **24** was activated as a tosylate. However, attempts to introduce aldehyde enolates (see **7**) or their equivalents (imine or malonate anions) invariably failed at this point. This can be interpreted in terms of S_N2 substitution of the tosylate group being disfavored because of the bulkiness and concave shape of the bicyclic core.

In contrast, introduction of a small nucleophile such as cyanide anion could be performed at 100 °C, affording nitrile **26** in good yield (Scheme 6), DIBAH reduction and hydrolysis then affording aldehyde **27**. This aldehyde allowed us to validate our strategy towards the sarain A core skeleton quickly with the aid of an allylsilane methodology previously developed by Weinreb and co-workers.[2] Allylsilane **28** [mixture of (*E*) and (*Z*) isomers] was obtained from

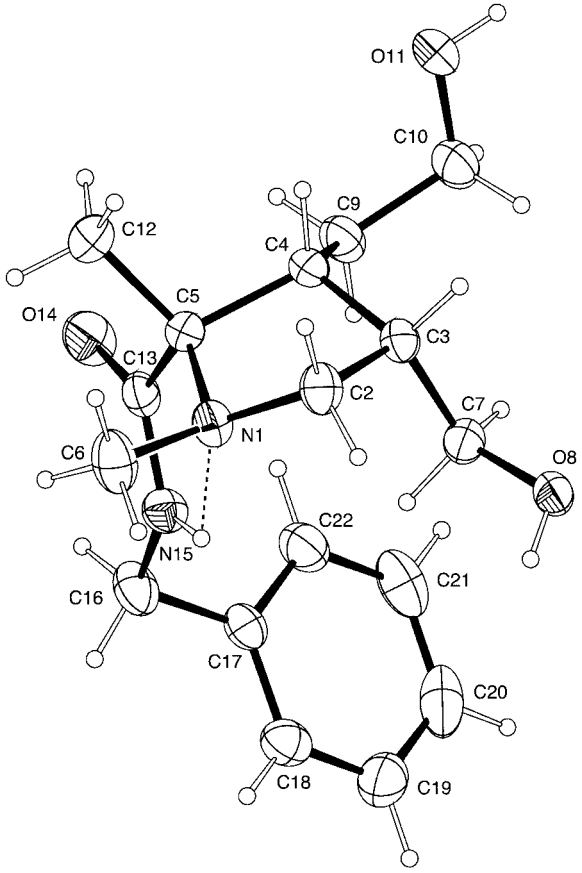
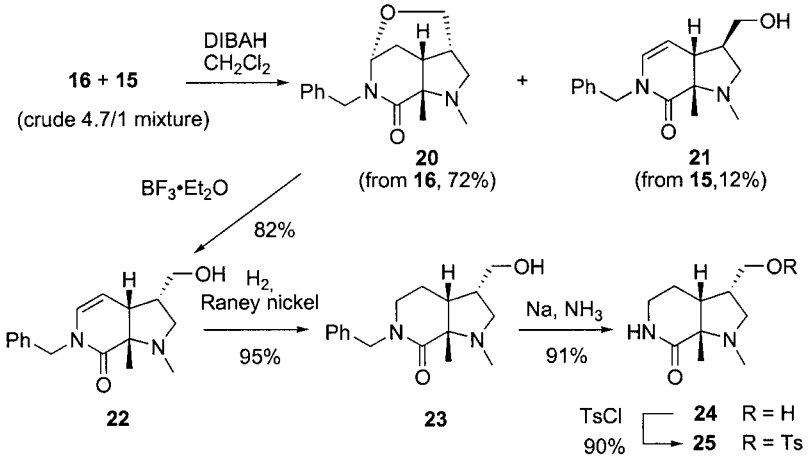
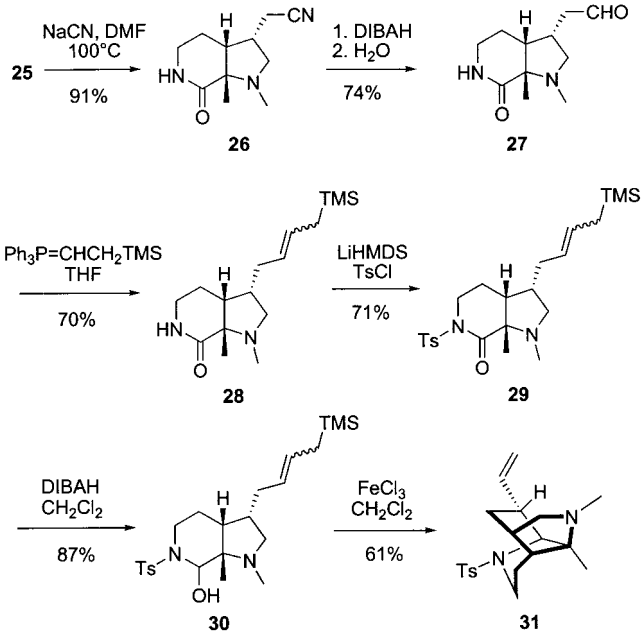


Figure 2. ORTEP plot of alcohol **19**. Ellipsoids are drawn at 30% probability level.



Scheme 5. Selective imide **16** reduction.

aldehyde **27** in 70% yield, tosylation gave a mixture of isomers **29**, which was reduced with DIBAH to afford the targeted iminium ion precursors **30**, and cyclization with ferric chloride finally delivered the sarain A core skeleton analogue **31**.



Scheme 6. Synthesis of sarain A model **31** by an allylsilane strategy.[2]

Conclusions

We have shown that it is possible to obtain the sarain A core skeleton analogue **31** by a route based on the proposed biogenetic pathway depicted in Scheme 2. The reported strategy has some advantages over our previous approach. Of particular interest is the short, stereoselective route to highly functionalized diazabicyclo[4.3.0]nonane systems such as **14**, achieved by successive condensations of four different molecules. Reduction studies of these intermediates also gave encouraging results. Firstly, a hydrogenation procedure allowed the desired *endo* isomer to be obtained, while the regioselectivity can be also controlled for imide reduction. These results open the way to further developments of this strategy, which are underway in our laboratory.

Experimental Section

General Remarks: NMR spectra were recorded with the following Bruker spectrometers: AC 250 (250 MHz), AC 300 (300 MHz), Avance 300 (300 MHz), DPX 400 (400 MHz), Avance 500 (500 MHz). FT-IR spectra were recorded as films on NaCl or in a diamond (SensIR DurasampIR II) cell with a Perkin–Elmer Spectrum BX FT-IR spectrophotometer. Mass spectra were recorded by electrospray ionization with a Micromass LCT instrument (ESI-TOF). Melting points were measured with a Büchi Melting Point B-540 apparatus.

***N*-Benzylidene-L-alanine Ethyl Ester (10):** TEA (7.8 mL, 56.3 mmol) and benzaldehyde (5.7 mL, 56.07 mmol) were added to a stirred solution of L-alanine ethyl ester hydrochloride (8.6 g, 56 mmol) in MeCN (100 mL). The reaction mixture was stirred overnight and filtered through Celite, and the solvents were evaporated. The residue was diluted with Et_2O and filtered through Celite again, and the organic layer was concentrated to give imine **10** (11.5 g, 100% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.1 Hz, 3 H,), 1.52 (d, J = 6.9 Hz, 3 H), 4.09–4.23 (m, 3 H), 7.35 (m, 5 H), 8.30 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 19.2, 60.8, 67.8, 128.3, 128.4, 130.8, 135.6, 162.6, 172.3 ppm. IR (neat): $\tilde{\nu}$ = 2981, 1730, 1641, 1449, 1369, 1184, 1124, 1046, 1021, 752 cm^{-1}. HRMS (ESI$^+$, MeOH): m/z = 206.1186 [M + H]$^+$ (calcd. for $C_{12}H_{16}NO_2$ 206.1181).

(*Z*)-*N*-Benzyl-3-bromoacrylamide (11): Propiolic acid (9.0 g, 128.5 mmol) was added to a solution of LiBr (11.16 g, 128.5 mmol) in MeCN (125 mL).[15] The mixture was heated at reflux overnight, filtered through Celite, and washed with Et_2O (3 × 50 mL) to give lithium (*Z*)-3-bromoacrylate (17.73 g, 88% yield). Isobutyl chloroformate (6.8 mL, 51.7 mmol) was added at 0 °C to a stirred suspension of this acrylate salt (8.08 g, 51.5 mmol) in THF (250 mL). The reaction mixture was allowed to warm to room temp. and stirred until it turned clear and the solution was cooled to 0 °C, after which benzylamine (5.9 mL, 54.0 mmol) was added and the mix-

ture was stirred overnight. AcOEt (500 mL) was added, the organic phase was washed with H_2O (2 × 500 mL) and dried with $MgSO_4$, and the solvents were evaporated. The resulting oil was dissolved in a mixture of AcOEt and Et_2O (1:1) and crystallized at –20 °C to give (*Z*)-*N*-benzyl-3-bromoacrylamide (6.18 g, 50% yield): m.p. 75–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.44 (d, *J* = 6.0 Hz, 2 H), 6.54 (d, *J* = 8.1 Hz, 1 H), 6.62 (d, *J* = 8.1 Hz, 1 H), 7.26 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.5, 114.1, 127.5, 127.8, 128.7, 128.3, 137.6, 163.7 ppm. IR (neat): $\tilde{\nu}$ = 3276, 1606, 1537, 1494, 1450, 1351, 1247, 1184, 1028 cm^{-1}. MS (ESI$^+$, MeOH): *m*/*z* = 262.264 $[M+Na]^+$. $C_{10}H_{10}BrNO$ (240.10): calcd. C 50.02, H 4.20, N 5.83; found C 50.09, H 4.32, N 5.54.

5-Amino-1-benzyl-5-methyl-3,4-dehydroglutarimide Hydrochloride (12·HCl): Ethyl *N*-benzylidene-L-alanate **10** (6.5 g, 31.6 mmol) in THF (80 mL) was added at –78 °C under argon to a stirred solution of LDA (63 mmol) in dry THF (160 mL). The reaction mixture was maintained at –78 °C for an additional 20 min, after which a solution of (*Z*)-*N*-benzyl-3-bromoacrylamide (**11**) (7.6 g, 31.6 mmol) in THF (80 mL) was added. The mixture was allowed to warm to room temp. and stirred for 14 h, after which H_2O (200 mL) was added. The reaction mixture was then diluted with Et_2O (200 mL) and the organic layer was separated, washed with H_2O (5 × 200 mL), and dried with $MgSO_4$. The organic layer was concentrated to dryness to give the imine, which was dissolved in Et_2O (220 mL). An aqueous HCl solution (0.2 N, 162 mL) was added and the resulting mixture was vigorously stirred for 3 h. The organic phase was decanted and the aqueous phase was washed with Et_2O (5 × 100 mL) and concentrated to give **12**·HCl (5.79 g, 69% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (s, 3 H), 5.01 (d, *J* = 14.7 Hz, 1 H), 5.07 (d, *J* = 14.7 Hz, 1 H), 6.47 (d, *J* = 10.2 Hz, 1 H), 6.94 (d, *J* = 10.2 Hz, 1 H), 7.31 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1, 44.2, 56.7, 124.7, 128.6, 129.3, 129.5, 137.6, 142.3, 163.9, 172.3 ppm. IR (neat): $\tilde{\nu}$ = 3385, 2848, 1728, 1687, 1643, 1196, 1145 cm^{-1}. HRMS (ESI$^+$, MeOH): *m*/*z* = 231.1128 $[M-Cl^-]^+$ (calcd. for $C_{13}H_{15}N_2O_2$ 231.1134).

Enaminal 14: Amine **12**·HCl (1.85 g, 6.93 mmol) was added under argon to a stirred solution of malonaldehyde sodium salt[16] (1 g, 8.93 mmol) in dry CH_2Cl_2 (30 mL). The reaction mixture was stirred for 3 h and filtered through Celite, and the solvents were evaporated. The resulting orange solid (intermediate vinylogous amide **13**, 2.03 g, 90% purity by ^{1}H NMR) was dissolved in dry THF (15 mL), and sodium hydride (60% in mineral oil, 332 mg, 8.32 mmol) was added. After 3 h, the mixture was cooled to 0 °C, after which methyl iodide (1.3 mL, 20 mmol) was added. The reaction mixture was stirred at 0 °C for 2 h and then at room temp. for 1 h, the solvent was evaporated, and the residue was diluted with CH_2Cl_2 (50 mL), the mixture filtered through Celite, and the filtrate concentrated to afford an orange solid (1.49 g). Column chromatography of the residue on silica gel (AcOEt/CH_2Cl_2, 40:60) gave enaminal **14** (1.31 g, 63% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 3 H), 2.72 (dd, *J* = 16.0, 6.1 Hz, 1 H), 2.79 (s, 3 H), 3.34 (dd, *J* = 16.0, 4.6 Hz, 1 H), 3.47 (t, *J* = 5.3 Hz, 1 H), 4.80 (d, *J* = 14.0 Hz, 1 H), 5.04 (d, *J* = 14.0 Hz, 1 H), 6.82 (s, 1 H), 7.30 (m, 5 H), 9.24 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 32.3, 32.7, 41.5, 43.7, 70.4, 115.0, 127.6, 128.4, 128.6, 136.7, 157.0, 168.8, 170.3, 181.8 ppm. IR (neat): $\tilde{\nu}$ = 2923, 2777, 1729, 1678, 1626, 1578, 1438, 1408, 1356, 1266, 1162 cm^{-1}. HRMS (ESI$^+$, MeOH): *m*/*z* = 299.1429 $[M+H]^+$ (calcd. for $C_{17}H_{19}N_2O_3$ 299.1395).

Alcohol 15: $NaBH_4$ (480 mg, 12.7 mmol) was slowly added at 0 °C to enaminal **14** (175 mg, 0.59 mmol) in glacial acetic acid (12 mL). The reaction mixture was stirred at room temp. for 15 min, and was then cooled to 0 °C. H_2O (10 mL) was added to the reaction mixture, which was neutralized with a 50% aqueous NaOH solution. The mixture was extracted with CH_2Cl_2 (3 × 200 mL), the combined organic extracts were dried with $MgSO_4$, and the solvents were evaporated. Column chromatography of the residue on silica gel (CH_2Cl_2/MeOH, 97:3) gave alcohol **15** as a colorless oil (148 mg, 84% yield): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 3 H), 1.90 (m, 1 H), 1.95 (s, 1 H), 2.09 (ddd, *J* = 7.6, 5.0, 2.9 Hz, 1 H), 2.32 (dd, *J* = 9.9, 8.7 Hz, 1 H), 2.42 (s, 3 H), 2.65 (dd, *J* = 9.9, 3.3 Hz, 1 H), 2.72 (dd, *J* = 16.7, 5.0 Hz, 1 H), 2.86 (dd, *J* = 16.7, 2.9 Hz, 1 H), 3.60 (dd, *J* = 14.9, 0.7 Hz, 1 H), 3.64 (dd, *J* = 14.9, 0.7 Hz, 1 H), 4.88 (d, *J* = 13.8 Hz, 1 H), 4.93 (d, *J* = 13.8 Hz, 1 H), 7.20–7.40 (m, 5 H) ppm. ^{13}C NMR (75 MHz,$CDCl_3$): δ = 19.9, 34.2, 35.3, 42.5, 43.0, 43.5, 55.5, 65.7, 66.2, 127.4, 128.4, 128.8, 137.5, 171.4, 173.9 ppm. IR (neat): $\tilde{\nu}$ = 3439, 2968, 2927, 2801, 1722, 1672, 1447, 1378, 1353, 1335, 1162 cm^{-1}. HRMS (ESI$^+$, MeOH): *m*/*z* = 303.1696 $[M+H]^+$ (calcd. for $C_{17}H_{23}N_2O_3$ 303.1709).

Alcohol 16: A pressure reaction vessel was charged with enaminal **14** (200 mg, 0.67 mmol), THF (25 mL), PtO_2 (33 mg), and $SnCl_2$ (2.3 mg). The reaction mixture was then hydrogenated in a Parr apparatus under pressure (4 bar) overnight. After filtration through Celite, the solvent was evaporated. Column chromatography of the residue on deactivated silica gel (eluent AcOEt/acetone, 4:1; silica gel was shaken in a mixture of AcOEt/acetone/TEA, 20:5:1.25 before use) afforded a mixture of alcohols **15** and **16** (168 mg, 83% yield, 4.7:1 diastereoselectivity). An analytically pure sample of alcohol **16** was obtained, but the mixture was usually used as it was. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 3 H), 2.33 (s, 3 H), 2.33–2.82 (m, 6 H), 3.46 (d, *J* = 6.6 Hz, 2 H), 4.83 (s, 2 H), 7.13–7.26 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.0, 31.1, 35.1, 40.5, 41.6, 43.1, 55.2, 61.6, 65.4, 127.3, 128.3, 128.5, 137.1, 171.9, 173.6 ppm. IR (neat): $\tilde{\nu}$ = 3368, 1671, 1603, 1383, 1094 cm^{-1}. HRMS (ESI$^+$, MeOH): *m*/*z* = 325.1514 $[M+Na]^+$ (calcd. for $C_{17}H_{22}N_2NaO_3$ 325.1528).

Tosylate 17: TsCl (156 mg, 0.82 mmol), DMAP (10 mg, 0.08 mmol), and freshly distilled TEA (0.114 mL, 0.82 mmol) were added at 0 °C to a solution of alcohol **15** (124 mg, 0.41 mmol) in dry CH_2Cl_2 (4 mL). The reaction mixture was stirred at room temp. overnight, a saturated solution of aqueous $NaHCO_3$ was added, the system was extracted three times with CH_2Cl_2, the combined organic extracts were dried with $MgSO_4$, and the solvents were evaporated. Column chromatography of the residue on silica gel (heptanes/AcOEt, 1:1) afforded tosylate **13** as a white solid (128 mg, 68% yield); m.p. 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 3 H), 1.89–2.04 (m, 2 H), 2.25 (dd, *J* = 10.2, 8.2 Hz, 1 H), 2.37 (s, 3 H), 2.45 (s, 3 H), 2.50 (dd, *J* = 10.2, 3.2 Hz, 1 H), 2.67 (dd, *J* = 16.7, 4.8 Hz, 1 H), 2.78 (dd, *J* = 16.7, 2.7 Hz, 1 H), 3.93 (dd, *J* = 9.6, 7.2 Hz, 1 H), 3.99 (dd, *J* = 9.4, 6.6 Hz, 1 H), 4.84 (d, *J* = 13.8 Hz, 1 H), 4.91 (d, *J* = 13.8 Hz, 1 H), 7.25–7.40 (m, 5 H), 7.41 (d, *J* = 8.2 Hz, 2 H), 7.75 (d, *J* = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9, 27.1, 33.8, 35.1, 39.7, 43.0, 43.8, 54.5, 65.9, 72.2, 127.5, 127.9, 128.4, 128.8, 130.0, 132.7, 137.4, 145.1, 170.7, 173.6 ppm. IR (neat): $\tilde{\nu}$ = 2928, 2803, 1724, 1673, 1356, 1176, 963, 814, 701 cm^{-1}. HRMS (ESI$^+$, MeOH): *m*/*z* = 457.1755 $[M+H]^+$ (calcd. for $C_{24}H_{29}N_2O_5S$ 457.1752).

Derivative 18: $NaBH_4$ (200 mg, 5.23 mmol) was added at 0 °C to a solution of alcohol **15** (150 mg, 0.49 mmol) in absolute EtOH (15 mL). The resulting mixture was stirred at 0 °C for 5 h with addition of 3 drops of a solution of HCl gas in EtOH (2 N) every 15 min. The mixture was then acidified until pH = 3, stirred for an additional 20 h, and made alkaline with 10% KOH in EtOH solu-

tion until pH = 9, the organic solvent was evaporated, and the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL). After three extractions with CH_2Cl_2, the combined organic layers were dried with $MgSO_4$ and the solvents were evaporated. Column chromatography of the residue on alumina (eluent CH_2Cl_2/TEA, 98:2) gave amide **18** as a colorless oil (107 mg, 71% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.70 (s, 3 H), 1.83 (q, J = 8.9 Hz, 1 H), 2.00 (m, 1 H), 2.15 (s, 3 H), 2.47 (dd, J = 10.5, 9.4 Hz, 1 H), 2.60 (d, J = 9.5 Hz, 2 H), 3.16 (dd, J = 9.4, 7.0 Hz, 1 H), 3.58 (d, J = 5.9 Hz, 2 H), 3.87 (d, J = 14.5 Hz, 1 H), 4.49 (s, 1 H), 5.00 (d, J = 14.5 Hz, 1 H), 7.31 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7, 34.4, 37.4, 45.8, 47.8, 50.2, 57.1, 63.5, 65.3, 84.1, 127.4, 128.4, 128.6, 137.5, 171.8 ppm. IR (neat): $\tilde{\nu}$ = 3385, 2923, 1651, 1482, 1454, 1385, 1176, 1044, 705 cm^{-1}. HRMS (ESI^+, MeOH): m/z = 305.1863 $[M+H]^+$ (calcd. for $C_{17}H_{25}N_2O_3$ 305.1865).

Diol 19: $NaBH_4$ (93 mg, 2.4 mmol) was added at 0 °C to a solution of alcohol **16** (74 mg, 0.24 mmol) in absolute EtOH (7 mL). After 1 h, H_2O (4.5 mL) was added and the reaction mixture was stirred at 55 °C for 1 h. Acetic acid was added dropwise to adjust the pH to ca. 4, and then the aqueous layer was made alkaline with a saturated aqueous $NaHCO_3$ solution. After three extractions with CH_2Cl_2, the combined organic layers were dried with $MgSO_4$ and the solvents were evaporated. Column chromatography of the residue on alumina (AcOEt/acetone, 1:1) gave diol **19** as a white solid (38 mg, 50% yield); m.p. 155–156 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 3 H), 1.41–1.52 (m, 1 H), 1.70–1.81 (m, 1 H), 2.03–2.25 (m, 2 H), 2.17 (s, 3 H), 2.58 (dd, J = 5.7, 9.6 Hz, 1 H), 2.95 (d, J = 9.0 Hz, 1 H), 3.41 (dd, J = 8.4, 11.4 Hz, 1 H), 3.55–3.69 (m, 3 H), 4.33 (qd, J = 12.3, 5.7 Hz, 2 H), 7.18–7.30 (m, 5 H), 8.13 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 29.7, 35.7, 42.9, 43.4, 52.2, 56.5, 61.9, 62.6, 69.0, 127.5, 127.9, 128.8, 138.5, 175.1 ppm. IR (neat): $\tilde{\nu}$ = 3327, 2934, 1651, 1512, 1030 cm^{-1}. MS (ESI^+, MeOH): m/z = 457 $[M+H]^+$. $C_{17}H_{26}N_2O_3$ (306.40): calcd. C 66.64, H 8.55, N 9.40; found C 66.48, H 8.54, N 9.10.

Tricyclic Derivative 20: DIBAH (1 M in CH_2Cl_2, 10 mL, 10 mmol) was added dropwise at –78 °C to a solution of alcohol **16** (crude mixture with isomeric **15** in a 4.7:1 ratio, 1.54 g, 5 mmol) in dry CH_2Cl_2 (15 mL). The mixture was stirred for 1.5 h and trifluoroacetic acid (2 mL) was then added. The reaction mixture was allowed to warm to room temp. and stirred for an additional 0.5 h. An aqueous NaOH solution (5 N) was added to the reaction mixture to ensure an alkaline pH of 8–9, the reaction mixture was diluted with H_2O and extracted three times with CH_2Cl_2, the combined organic extracts were dried with $MgSO_4$ and the solvents evaporated. Column chromatography of the residue on silica gel (eluent AcOEt/acetone, 4:1) gave the tricyclic derivative **20** as a white solid (1.02 g, 72% yield) and the unsaturated alcohol **21** (from **15**) as a colorless liquid (0.18 g, 12% yield).

Tricyclic Derivative 20: M.p. 82–84 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.75 (dt, J = 13.8, 2.4 Hz, 1 H), 2.15 (dt, J = 13.8, 3.0 Hz, 1 H), 2.34 (m, 1 H), 2.49 (m, 1 H), 2.57 (s, 3 H), 2.95 (dd, J = 9.0, 6.3 Hz, 1 H), 3.63 (dd, J = 7, 12.0, 6.3 Hz, 1 H), 3.85 (dd, J = 12.0, 6.0 Hz, 1 H), 3.90 (d, J = 15 Hz, 1 H), 4.89 (m, 1 H), 5.15 (d, J = 15 Hz, 1 H), 7.25–7.34 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1, 25.0, 34.5, 35.6, 40.6, 47.9, 57.2, 61.4, 64.8, 79.7, 127.2, 128.2, 128.4, 137.5, 172.6 ppm. IR (neat): $\tilde{\nu}$ = 2790, 2360, 1647, 1493, 1448, 1411, 1362, 1328, 1211, 1175, 1041, 725 cm^{-1}. HRMS (ESI^+, MeOH): m/z = 287.1777 $[M+H]^+$ (calcd. for $C_{17}H_{23}N_2O_2$ 287.1760). $C_{17}H_{22}N_2O_2$ (286.37): calcd. C 71.30, H 7.74, N, 9.78; found C 70.88, H 7.79, N 9.52.

Derivative 21: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 3 H), 2.02–2.07 (m, 1 H), 2.21 (dd, J = 8.1, 5.7 Hz, 1 H), 2.61 (dd, J = 5.7, 9.9 Hz, 1 H), 2.65 (s, 3 H), 2.86 (t, J = 9.3 Hz, 2 H), 3.60 (d, J = 5.7 Hz, 2 H), 4.53 (d, J = 15 Hz, 1 H), 4.61 (d, J = 15 Hz, 1 H), 5.09 (dd, J = 7.8, 6 Hz, 1 H), 5.84 (d, J = 8.1 Hz, 1 H), 7.12–7.27 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 35.8, 46.2, 48.3, 49.1, 55.0, 65.0, 65.6, 108.0, 126.8, 127.4, 127.4, 128.6, 137.2, 173.0 ppm. IR (neat): $\tilde{\nu}$ = 3361, 2923, 1650, 1495, 1453, 1384, 1253, 1218, 1172, 1028, 725, 697 cm^{-1}. HRMS (ESI^+, MeOH): m/z = 287.1767 $[M+H]^+$ (calcd. for $C_{17}H_{23}N_2O_2$ 287.1760).

Enaminone 22: $BF_3{\cdot}Et_2O$ (0.28 mL, 2.24 mmol) was added to a solution of tricyclic derivative **20** (128 mg, 0.44 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was heated at reflux overnight and was then diluted with 1 N aqueous NaOH solution and extracted three times with $CHCl_3$. The combined organic extracts were dried with $MgSO_4$ and the solvents evaporated. Column chromatography of the residue on silica gel (eluent AcOEt/acetone, 2:1) gave unsaturated enaminone **22** as a colorless oil (105 mg, 82% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 3 H), 2.41–2.45 (m, 1 H), 2.68 (s, 3 H), 2.74–2.77 (m, 1 H), 2.78–2.92 (m, 3 H), 3.55 (dd, J = 5.1, 10.2 Hz, 1 H), 3.64 (dd, J = 5.1, 10.2 Hz, 1 H), 4.55 (d, J = 15.3 Hz, 1 H), 4.78 (d, J = 15.3 Hz, 1 H), 5.00 (dd, J = 8.7, 5.1 Hz, 1 H), 6.03 (dd, J = 8.7, 1.5 Hz, 1 H), 7.24–7.36 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 36.3, 41.8, 48.1, 49.3, 56.4, 63.3, 64.3, 103.6, 127.5, 127.6, 128.2, 128.6, 137.0, 172.5 ppm. IR (neat): $\tilde{\nu}$ = 3383, 2928, 1658, 1650, 1644, 1453, 1392, 1028, 728, 697 cm^{-1}. HRMS (ESI^+, MeOH): m/z = 287.1743 $[M+H]^+$ (calcd. for $C_{17}H_{23}N_2O_2$ 287.1760). $C_{17}H_{22}N_2O_2$ (286.37): calcd. C 71.30, H 7.74, N 9.78; found C 70.83, H 7.95, N 9.54.

Amide 23: A solution of unsaturated alcohol **22** (100 mg, 0.34 mmol) in MeOH (20 mL) was hydrogenated at atmospheric pressure in the presence of Raney nickel in H_2O (4 mL). After stirring overnight, the reaction mixture was filtered through Celite and the solvent evaporated. The residue was diluted with $CHCl_3$, dried with $MgSO_4$, and concentrated to give amide **2** as a colorless oil (95 mg, 95% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 3 H), 1.72–1.79 (m, 1 H), 1.89–1.98 (m, 1 H), 2.25–2.40 (m, 2 H), 2.62 (s, 3 H), 2.79 (dd, J = 7.5, 9.9 Hz, 1 H), 2.97 (dd, J = 3.6, 9.9 Hz, 1 H), 3.23 (dd, J = 3.3, 8.1 Hz, 2 H), 3.64 (dd, J = 4.2, 10.5 Hz, 1 H), 3.74 (dd, J = 4.8, 10.5 Hz, 1 H), 4.59 (s, 2 H), 7.23–7.35 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 23.0, 36.5, 39.5, 46.1, 47.1, 50.3, 57.1, 62.9, 65.0, 127.3, 127.8, 128.6, 137.2, 172.9 ppm. IR (neat): $\tilde{\nu}$ = 3385, 2925, 2847, 1620, 1491, 1451, 1354, 1169, 1029, 909, 726, 698 cm^{-1}. HRMS (ESI^+, MeOH): m/z = 289.1918 $[M+H]^+$ (calcd. for $C_{17}H_{25}N_2O_2$ 289.1916).

Amide 24: A flask containing *tert*-butyl alcohol (0.58 mL) and THF (7 mL) was cooled to –78 °C and NH_3 gas was condensed into the mixture (approximately 12 mL). Sodium metal (101 mg, 4.4 mmol) was added in small portions, producing a deep blue solution, and benzylamide **23** (87 mg, 0.3 mmol), dissolved in THF (2 mL), was added. The mixture was stirred for 6 min, the dry ice bath was removed, and the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL). After the NH_3 had been allowed to evaporate, the mixture was extracted with $CHCl_3$, and the organic phase was dried with $MgSO_4$ and concentrated. Column chromatography of the residue on silica gel with CH_2Cl_2/MeOH (2:1) as the eluent gave amide **24** as a white solid (54 mg, 91% yield). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 3 H), 1.81–1.85 (m, 1 H), 1.92 (dq, J = 4.5, 12.0 Hz, 1 H), 2.24–2.29 (m, 1 H), 2.37–2.40 (m, 1 H), 2.53 (s, 3 H), 2.74 (t, J = 9.0 Hz, 1 H), 2.89 (dd, J = 2.5, 9.5 Hz, 1 H), 3.22–3.28 (m, 1 H), 3.33–3.37 (m, 1 H), 3.68 (dd, J = 4.0, 10.0 Hz, 1 H), 3.75 (dd, J = 4.0, 10.0 Hz, 1 H),

6.02 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 23.5, 36.3, 39.7, 40.9, 47.0, 56.8, 63.1, 64.1, 175.5 ppm. IR (neat): $\tilde{\nu}$ = 3299, 1643, 1493, 1461, 1346, 1178, 1098, 1057, 1029 cm^{-1}. HRMS (ESI$^+$, MeOH): *m*/*z* = 199.1440 $[M+H]^+$ (calcd. for $C_{10}H_{19}N_2O_2$ 199.1447).

Tosylate 25: TsCl (136 mg, 0.70 mmol), DMAP (8.7 mg, 0.07 mmol), and TEA (0.075 mL, 0.54 mmol) were added at 0 °C to a solution of alcohol **19** (70 mg, 0.35 mmol) in dry CH_2Cl_2 (4 mL). The reaction mixture was allowed to warm to room temperature and stirred for 2 h and was then diluted with a saturated aqueous $NaHCO_3$ solution and extracted three times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and the solvents evaporated. Column chromatography of the residue on silica gel, with acetone as eluent, gave tosylate **25** as a white solid (111 mg, 90% yield); m.p. 149–150 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (s, 3 H), 1.58–1.61 (m, 1 H), 1.79 (dq, *J* = 5.0, 12.5 Hz, 1 H), 2.16–2.21 (m, 1 H), 2.43 (s, 3 H), 2.47 (s, 3 H), 2.61 (t, *J* = 10 Hz, 1 H), 2.73–2.81 (m, 2 H), 3.18–3.29 (m, 2 H), 4.01 (dd, *J* = 7.0, 9.5 Hz, 1 H), 4.10 (t, *J* = 9 Hz, 1 H), 6.09 (br. s, 1 H), 7.37 (d, *J* = 8.5 Hz, 2 H), 7.80 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 21.4, 21.5, 21.6, 35.9, 37.4, 40.9, 41.1, 45.4, 54.2, 65.4, 69.6, 127.9, 129.9, 132.7, 145.0, 173.0 ppm. IR (neat): $\tilde{\nu}$ = 3369, 2929, 1737, 1659, 1353, 1216, 1188, 1174, 961 cm^{-1}. HRMS (ESI$^+$, MeOH): *m*/*z* = 353.1520 $[M+H]^+$ (calcd. for $C_{17}H_{24}N_2O_4S$ 353.1535).

Cyanide 26: NaCN (512 mg, 10.4 mmol) was added to a solution of tosylate **25** (368 mg, 1.04 mmol) in DMF (10 mL). The reaction mixture was stirred at 100 °C for 3 h, diluted with a saturated aqueous $NaHCO_3$ solution, and extracted three times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and the solvents evaporated. Column chromatography of the residue on silica gel with CH_2Cl_2/MeOH (20:1) as eluent gave cyanide **21** as a white solid (196 mg, 91% yield); m.p. 129–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 3 H), 1.58–1.61 (m, 1 H), 1.70–1.88 (m, 1 H), 2.22–2.30 (m, 1 H), 2.39–2.46 (m, 2 H), 2.50 (s, 3 H), 2.78–2.90 (m, 3 H), 3.23–3.39 (m, 2 H), 6.47 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1, 18.0, 21.9, 35.2, 35.9, 40.7, 46.6, 57.2, 64.8, 118.9, 174.0 ppm. IR (neat): $\tilde{\nu}$ = 3197, 2936, 2879, 2827, 2244 (CN), 1659, 1494, 1448, 1212, 1363, 1348, 1184, 1094, 979 cm^{-1}. HRMS (ESI$^+$, MeOH): *m*/*z* = 230.1275 $[M+Na]^+$ (calcd. for $C_{11}H_{17}N_3ONa$ 230.1269).

Aldehyde 27: DIBAH (1 M in CH_2Cl_2, 0.57 mL, 0.57 mmol) was added dropwise at –78 °C to a solution of nitrile **26** (57 mg, 0.27 mmol) in dry THF (0.5 mL), and the mixture was kept at –78 °C for 1 h. DIBAH (1 M in CH_2Cl_2, 0.57 mL, 0.57 mmol) was added again, and the mixture was then stirred at –78 °C for an additional 1 h. MeOH and saturated aqueous NH_4Cl solution were added to the mixture, which was allowed to warm to room temp., diluted with H_2O, and extracted three times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and the solvents evaporated. Crude aldehyde **27** (42 mg, 74% yield) was obtained as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (s, 3 H), 1.44–1.49 (m, 1 H), 1.64–1.78 (m, 2 H), 2.07–2.15 (m, 1 H), 2.39 (s, 3 H), 2.50–2.55 (m, 2 H), 2.66–2.88 (m, 3 H), 3.13–3.26 (m, 2 H), 6.20 (br. s, 1 H), 9.74 (t, *J* = 1.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0, 21.3, 31.1, 35.0, 40.1, 43.8, 45.5, 56.9, 64.1, 172.8, 200.1 ppm. IR (neat): $\tilde{\nu}$ = 3295, 2930, 2852, 1716, 1650, 1492, 1454, 1345, 1161, 1096 cm^{-1}. HRMS (ESI$^+$, MeOH): *m*/*z* = 211.1424 $[M+H]^+$ (calcd. for $C_{11}H_{19}N_2O_2$ 211.1447).

Derivatives 28 (Mixture of Isomers): *n*-Butyllithium (1.6 M in hexane, 0.37 mL, 0.59 mmol) was added at 0 °C to a suspension of methyltriphenylphosphonium bromide (206 mg, 0.57 mmol) in dry THF (2.5 mL). The mixture was allowed to warm to room temp., stirred for 1 h, and cooled to 0 °C. (Iodomethyl)trimethylsilane (0.085 mL, 0.57 mmol) was added, and the solution was allowed to warm to room temp. After 2 h, the reaction mixture was treated at –78 °C with methyllithium (0.37 mL, 1.6 M in Et_2O). The mixture immediately turned red. After the mixture had been stirred at room temp. for 1 h, a homogeneous red solution had formed, and aldehyde **27** (38 mg, 0.18 mmol) in THF (1.8 mL) was added to this at –78 °C. The mixture was allowed to warm to room temp. and stirred overnight, and was then diluted with a saturated aqueous ammonium chloride solution and extracted three times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and the solvents evaporated. Column chromatography of the residue on silica gel with CH_2Cl_2/MeOH (50:1) as eluent gave a mixture of isomers **28** as a colorless oil (37 mg, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 9 H), 1.21 (s, 3 H), 1.48 (d, *J* = 7.8 Hz, 2 H), 1.62–1.97 (m, 3 H), 2.01–2.09 (m, 3 H), 2.45 (s, 3 H), 2.68 (t, *J* = 9.6 Hz, 1 H), 2.82 (dd, *J* = 9.3, 7.8 Hz, 1 H), 3.24–3.33 (m, 2 H), 5.18–5.26 (m, 1 H), 5.40–5.46 (m, 1 H), 5.89 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.7, 18.7, 21.5, 27.4, 36.1, 38.5, 41.4, 46.8, 53.4, 58.3, 65.3, 125.3, 126.7, 174.0 ppm. IR (neat): $\tilde{\nu}$ = 3326, 2950, 1655, 1624, 1492, 1341, 1245, 1153, 1099 cm^{-1}. HRMS (ESI$^+$, MeOH): *m*/*z* = 295.220 $[M+H]^+$ (calcd. for $C_{16}H_{31}N_2OSi$ 295.2206).

Tosylamides 29: Amides **28** (37 mg, 0.12 mmol) were dissolved in dry THF (1.2 mL) and the mixture was cooled to 0 °C. LiHMDS (0.25 mL, 1 M in hexane, 0.25 mmol) was added to the resulting solution, and the mixture was stirred for 15 min. *p*-Toluenesulfonyl chloride (60 mg, 0.31 mmol) and DMAP (4.6 mg, 0.04 mmol) were added in one portion, and the solution was allowed to warm slowly to room temp. over 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution and extracted three times with CH_2Cl_2, the combined organic extracts were dried with $MgSO_4$ and the solvents evaporated. Column chromatography of the residue on silica gel (heptanes/ethyl acetate, 5:1) gave tosylamides **29** as a colorless oil (40 mg, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 9 H), 1.12 (s, 3 H), 1.47 (d, *J* = 8.7 Hz, 2 H), 1.72–1.80 (m, 1 H), 1.88–1.98 (m, 1 H), 2.03–2.23 (m, 3 H), 2.15 (s, 3 H), 2.36–2.50 (m, 1 H), 2.42 (s, 3 H), 2.64–2.78 (m, 2 H), 3.74–3.82 (m, 1 H), 4.10–4.16 (m, 1 H), 5.03–5.24 (m, 1 H), 5.39–5.53 (m, 1 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.90 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.8, 16.2, 18.8, 21.6, 23.4, 27.5, 35.0, 38.8, 45.6, 47.1, 58.6, 68.7, 125.0, 127.1, 128.3, 129.2, 136.4, 144.3, 172.8 ppm. IR (neat): $\tilde{\nu}$ = 2950, 1693, 1595, 1352, 1246, 1165, 1089 cm^{-1}. HRMS (ESI$^+$, MeOH): *m*/*z* = 449.2287 $[M+H]^+$ (calcd. for $C_{23}H_{37}N_2O_3SSi$ 449.2294).

Iminium Precursor 30: DIBAH (1 M in CH_2Cl_2, 0.36 mL, 0.36 mmol) was added at –78 °C to a solution of lactam **29** (40 mg, 0.09 mmol) in dry CH_2Cl_2 (1 mL). The solution was allowed to warm slowly to room temp. over 3 h, and H_2O (0.5 mL) was added. The solution was filtered through Celite, which was washed with CH_2Cl_2, the filtrate was concentrated, and the crude product (35 mg, 87% yield) was obtained, ^{1}H NMR (300 MHz, $CDCl_3$; major isomer): δ = 0.00 (s, 9 H), 1.14 (s, 3 H), 1.42 (d, *J* = 9 Hz, 2 H), 1.59–1.63 (m, 3 H), 1.83–1.98 (m, 3 H), 2.24 (s, 3 H), 2.43 (s, 3 H), 2.72–2.76 (m, 1 H), 2.87–2.90 (m, 1 H), 3.13–3.16 (m, 1 H), 3.29–3.35 (1 H), 5.07–5.25 (m, 3 H), 5.37–5.47 (m, 1 H), 7.31 (d, *J* = 8.5 Hz, 2 H), 7.85 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$; characteristic signals): δ = –1.8, 80.3, 125.6, 126.9, 127.9, 129.4, 136.0, 143.2 ppm. IR (neat): $\tilde{\nu}$ = 3350, 2954, 1736, 1336, 1259, 1162, 1092, 1015, 853, 799 cm^{-1}. HRMS (ESI$^+$, MeOH): *m*/*z* = 451.2461 $[M+H]^+$ (calcd. for $C_{23}H_{39}N_2O_3SSi$ 451.2451).

Sarain A Core Skeleton Analogue 31: The above crude aminal was dissolved in dry CH_2Cl_2 (15 mL) and the mixture was cooled to –78 °C. Anhydrous ferric chloride (126 mg, 0.3 mmol) was added in one portion, and the resulting solution was warmed to room temp. After 30 min, the solution was diluted with 1 N aqueous NaOH (2 mL) and stirred for 1 h, the mixture was extracted three times with CH_2Cl_2, the combined organic extracts were dried with $MgSO_4$ and the solvents evaporated. Column chromatography of the residue on silica gel (acetone/ethyl acetate, 1:4) gave tricyclic product **31** as a colorless oil (17 mg, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (s, 3 H), 1.44–1.52 (m, 1 H), 1.76–1.88 (m, 4 H), 2.00–2.14 (m, 2 H), 2.22–2.45 (m, 1 H), 2.41 (s, 3 H), 2.47 (s, 3 H), 3.16 (ddd, J = 5.4, 12.9, 13.2 Hz, 1 H), 3.31–3.36 (m, 1 H), 3.62 (dd, J = 8.7, 13.5 Hz, 1 H), 3.93 (d, J = 4.5 Hz, 1 H), 4.74 (dt, J = 10.5, 1.5 Hz, 1 H), 4.97 (dt, J = 16.8, 1.5 Hz, 1 H), 5.54–5.65 (m, 1 H), 7.26 (d, J = 8.7 Hz, 2 H), 7.66 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 21.4, 22.5, 32.5, 33.6, 38.1, 38.9, 40.3, 41.6, 58.4, 59.5, 60.7, 114.5, 127.2, 129.2, 138.5, 139.7, 142.5 ppm. IR (neat): $\tilde{\nu}$ = 2924, 1681, 1453, 1327, 1155, 1093, 997 cm^{-1}. HRMS (ESI$^+$, MeOH): m/z = 361.1968 $[M+H]^+$ (calcd. for $C_{20}H_{29}N_2O_2S$ 361.1950).

X-ray Crystallography of Tosylate 17: Small prismatic colorless crystal (0.55 × 0.35 × 0.35 mm). Empirical formula $C_{24}H_{28}N_2O_5S$, M = 456.54, T = 293 K. Monoclinic system, space group $C2$, chiral. The unit cell [parameters: a = 22.973(9), b = 7.806(3), c = 12.919(4) Å, β = 91.33(2)°, V = 2316 Å^3] contains four molecules (Z = 4), d_C = 1.309 g cm^{-3}, F(000) = 968, μ = 0.177 mm^{-1}, λ(Mo-K_α) = 0.71073 Å. Intensity data were measured with a Nonius Kappa-CCD area detector diffractometer with use of graphite-monochromated Mo-K_α radiation, in φ- and ω-scans, up to θ = 28.71°. 11528 data were collected, giving 5793 unique monoclinic (*hkl* and *–h–k–l*) reflections. The structure was solved by direct methods with the *SHELXS86*[17] program and refined by full-matrix least squares based upon unique F^2 with the *SHELXL97* program.[18] All the hydrogen atoms, located on difference Fourier maps, were fitted at theoretical positions and treated as riding. They were assigned an isotropic displacement parameter equivalent to 1.12 × that of the bonded atom (1.15 for those of the methyl groups). Refinement of 292 parameters on F^2 gave $R_1(F)$ = 0.0405 calculated with the 4899 observed reflections with $I \geq 2\sigma(I)$ and $wR_2(F^2)$ = 0.1032 considering all the 5793 data. Goodness of fit = 1.014. The residual density was found between –0.19 and 0.16 e·Å^{-3}. In the enantiomer drawn in Figure 1, the *cis* ring junction along C4–C5 appears clearly. Torsion angle values show that the pyrrolidine ring exhibits an envelope conformation, with atom C5 deviating by –0.627(2) Å from the mean plane of the other four atoms, whilst the six-membered ring also adopts an envelope conformation with atom C4 situated at –0.586(2) Å from the mean plane of the other five atoms. The dihedral angle of these two rings is 100.3°, whilst that of the two phenyl planes is 137.4°. It is noteworthy that the crystal from a racemic solution belongs to the chiral monoclinic space group $C2$. Analysis of Bijvoet pair differences through the sulfur anomalous contribution (also measured with Cu-K_α radiation on the same crystal) revealed random dispersion between positive and negative differences corroborating the high value of the Flack parameter (0.56), pointing to a case of racemic lamellar twinning, so the two enantiomers are present in the crystals. Such behavior prompted us to check whether tosylate **17** was actually a racemic mixture. The rotatory power proved to be zero ($[\alpha]_D$ = 0 ± 0.06) and chiral HPLC (column OJ, hexane/*i*PrOH, 65:35, 1 mL/min) on individual crystals showed that the compositions of each crystal were between 52:48 to 48:52 in ratio. As a conclusion, tosylate **17** is definitely a racemic mixture but it crystallizes in achiral space group $C2$ as described above. However, individual crystals can exhibit a very slight enrichment of one enantiomer over the other.

X-ray Crystallography of Diol 19: Colorless prismatic crystal (0.60 × 0.35 × 0.30 mm). Empirical formula $C_{17}H_{26}N_2O_3$, M = 306.40, T = 293 K. Monoclinic system, space group $P2_1/n$, racemic. The unit cell [parameters: a = 8.033(4), b = 12.395(5), c = 16.817(7) Å, β = 94.98(2)°, V = 1668 Å^3] contains four molecules (Z = 4), d_C = 1.220 g cm^{-3}, F(000) = 664, μ = 0.084 mm^{-1}, λ(Mo-K_α) = 0.71073 Å. Intensity data were measured with a Nonius Kappa-CCD area detector diffractometer with use of graphite-monochromated Mo-K_α radiation, in φ- and ω-scans, up to θ = 29.1°. 17243 data were collected giving 7835 monoclinic (*hkl* and *–h–k–l*) reflections, of which 4444 were unique. The structure was solved with the *SHELXS86* program and refined by full-matrix least squares based upon unique F^2 with the *SHELXL97* program. The hydrogen atoms, located on difference Fourier maps, were fitted at theoretical positions and treated as riding, except for the H–N15 atom (refined). They were assigned an isotropic displacement parameter equivalent to 1.15 × that of the bonded atom (1.20 × for those of the methyl and hydroxy groups). Refinement of 206 parameters on F^2 gave $R_1(F)$ = 0.0497 calculated with the 3022 observed reflections with $I \geq 2\sigma(I)$ and $wR_2(F^2)$ = 0.1352 considering all the 4444 data. Goodness of fit = 1.006. The residual density was found between –0.20 and 0.19 e Å^{-3}. One of the two enantiomers appears in Figure 2, showing all the pyrrolidine ring substituents fixed in an axial position. The pyrrolidine ring exhibits an envelope conformation in C2, this atom deviating by 0.549(2) Å from the mean plane of the other four atoms. An intramolecular hydrogen bond is observed between the N15–H atoms and the nitrogen atom N1 [distances N15···N1 2.612(2) Å, H_{N15}···N1 2.01 Å, angle N–H···N 117.3°]. The crystal packing study shows that all the hydroxy groups are engaged in intermolecular hydrogen bonds, so the molecules are assembled in dimers through centosymmetric centers, by hydrogen bonds formed between the O11–H hydroxy groups towards the O8 oxygen atoms according to the following scheme: distances O11–H(x, y, z)···O8(2 – x, –y, 1 – z) 2.801(3) Å, H_{O11}···O8 1.99 Å, angle O–H···O 168.5° and reciprocally; same enantiomeric molecules of these dimers are linked together through hydrogen bonds formed between the O8–H hydroxy groups and the nearest O14 oxygen atoms; according to a second scheme: distances O8–H(x, y, z)···O14(1.5 – x, 0.5 + y, 1.5 – z) 2.716 (3) Å, H_{O8}···O14 1.91 Å, angle O–H···O 169.3° and reciprocally, between O14(x, y, z) and O8–H(1.5 – x, –0.5 + y, 1.5 – z).

CCDC-601385 (**17**) and -601386 (**19**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra for compounds **14**–**20**, **22**–**23**, **25**–**27**, **31**.

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