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Further Uses of Pyrrole-Based Dienoxysilane Synthons: A Full Aldol Approach to Azabicyclo[*x*.2.1]alkane Systems

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Two racemic 2-azabicyclo[2.2.1]heptane structures, **15** and **21**, and two chiral non-racemic 6-azabicyclo[3.2.1]octane representatives, **28** and **36**, have been synthesized starting from 1-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsilyloxy)-pyrrole (TBSOP, **5**) and suitable ketones, **9**, **16**, **22** and **29**. 2-Azabicycle **15** was then elaborated to racemic cyclopentane amino acid **38**, while 6-azabicycle **36** served to access the enantiomerically pure normorphan-type structure **40**. For all substrates, a uniform synthetic scheme was implemented based on the combination of two diastereoselective aldol-type carbon–carbon bond-forming reactions, the efficiencies of which were secured by appropriate aldol-stabilizing steps. A mechanistic rationale accounting for the markedly diastereoselective character of the key Mukaiyama aldol reactions between TBSOP and the ketone acceptors has been postulated that involves hetero-Diels–Alder transition-state structures in which the preference for *endo* versus *exo* addition is governed by the electronic nature of the substituents in the ketone substrates.

Introduction

The vinylogous Mukaiyama aldol addition of pyrrole-based dienoxysilane compounds to carbonyl substrates, typically aldehydes, has now evolved into an established methodology[1] with a wide range of densely functionalized heterocyclic and carbocyclic molecules and other useful fragments in the portfolio.[1,2] Recent notable achievements in this area include, for example, the enantioselective synthesis of the (20*S*) proteasome inhibitor (+)-lactacystin (**1**) developed by Baldwin and co-workers,[2a] the discovery of the potent influenza virus neuraminidase inhibitor A-315675 (**2**) by researchers at the Abbott group,[2b,2e] the stereoselective access to the pentacyclic alkaloid (–)-cephalotaxine (**3**) by Royer and co-workers[2c] and the stereocontrolled entry to a collection of hydroxylated carbocyclic amines and amino acids, as exemplified by structure **4**, developed by us (Figure 1).[2d,2f–2i]

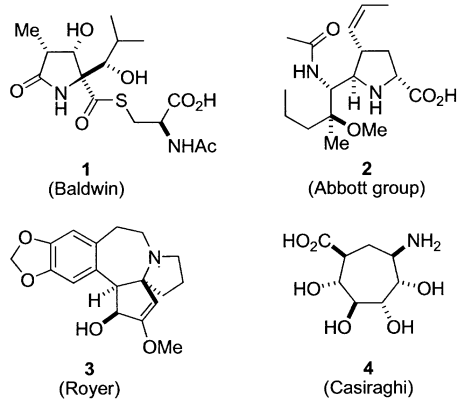

Figure 1. Notable targets whose synthesis capitalized on the pyrrole-based dienoxysilane chemistry.

In keeping with our longstanding interest in the development of reliable procedures for the synthesis of highly substituted alicyclic and heterocyclic structures using furan-, pyrrole- and thiophene-based dienoxysilane synthons,[1] we now report a flexible approach to decorated azabicyclo-[*x*.2.1]alkane systems[3] from 1-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsilyloxy)pyrrole (TBSOP, **5**)[4] and suitable ketones using a combination of two highly diastereoselective, aldol-based carbon–carbon bond-forming strategies: a crossed vinylogous Mukaiyama aldol reaction (VMAR)[5] followed by an intramolecular silylative Mukaiyama aldol reaction (ISMAR).

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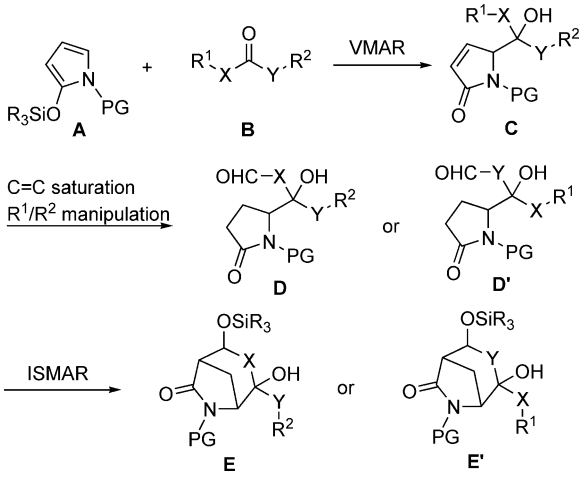
Unlike aldehydes, the use of ketone acceptors in simple and vinylogous Mukaiyama aldol-type addition reactions[6] is still hampered by the intrinsically sluggish nature of the ketone component and the competing retrograde fragmentation of the tertiary aldolate adducts formed. Notably, this obstacle was pleasingly surmounted here by adopting procedures that stabilize the emerging α,β-unsaturated ketols by in situ silylation or reduction.

Results and Discussion

Scheme 1 depicts the general concept for the construction of the targeted bicyclic entities formulated on the basis of our own precedents.[1,2d,2h,2i] Thus, a given aldol adduct of generic formula **C** is first assembled by connecting pyrrole **A** and ketone **B** through a crossed vinylogous Mukaiyama aldol reaction (VMAR). Then, in preparation of the second carbon–carbon bond juncture, **C** is elaborated to aldehydes **D/D′** by double-bond saturation followed by manipulation of either the R^1 or R^2 ketone end groups. Finally, intermediates **D/D′** are subjected to an intramolecular silylative Mukaiyama aldol reaction (ISMAR), a step that completes the construction of the targeted bicyclic systems **E/E′**.



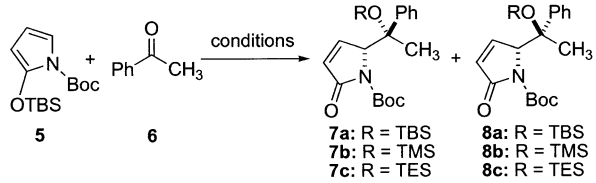
Scheme 1. Synthetic route to the azabicyclo[*x*.2.1]alkanes (X, Y = 0–*n* carbon atoms; PG = protecting group; VMAR = vinylogous Mukaiyama aldol reaction; ISMAR = intramolecular silylative Mukaiyama aldol reaction).

In principle, the scope of the proposed strategy was expected to be quite large because by utilizing various types of ketones **B** (X, Y = 0–*n* carbon atoms) one would be able to assemble the azabicycloalkane scaffolds with a high degree of skeletal and stereochemical variation.

Preparative Work

We set about investigating this project by identifying useful conditions for the vinylogous Mukaiyama aldol addition between TBSOP (**5**) and acetophenone (**6**). Several Lewis acid/solvent systems (Table 1) promoted the reaction effectively, giving the expected silylated adducts **7** and **8** in high isolated yields and with good margins of diastereoselectivity, invariably favouring the *N*,*O*-*syn*-configured (5*R**,1′*S**) isomers **7**. Two reaction modes were especially productive: the use of $SnCl_4$ in diethyl ether (Entry 2, 85% yield, 85:15 *dr*) and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (Entry 3, 91% yield, 94:6 *dr*). Remarkably, when non-silicon Lewis acid promoters were employed, the reactions proceeded in a fully silylative manner, with the TBS group from the donor installed on the aldol hydroxy group. However, with silicon promoters (e.g., TMSOTf or TESOTf), *O*-trimethylsilyl- or *O*-triethylsilylcarbinols emerged with only traces of the *O*-TBS congeners (Entries 8 and 9). This suggests that minimal silicon scrambling occurred between the donor and promoter silicon atoms during the silylative Mukaiyama aldol coupling reaction. The relative stereochemistry of the major racemic adduct **7a** (and hence **7b** and **7c** by analogy) was firmly established as (5*R**,1′*S**) (*N*,*O*-*syn*) by single-crystal X-ray analysis, as shown in Figure 2.

Table 1. Optimization of the addition reaction between silyloxypyrrole **5** and acetophenone **6**, giving unsaturated lactams **7** and **8**.[a]



Entry	Lewis acid	Solvent	Products	Yield [%][b]	*syn*/*anti* ratio[c]
1	$SnCl_4$	CH_2Cl_2	**7a**, **8a**	70	75:25
2	$SnCl_4$	Et_2O	**7a**, **8a**	85	85:15
3	$BF_3{\cdot}OEt_2$	CH_2Cl_2	**7a**, **8a**	91	94:6
4	$BF_3{\cdot}OEt_2$	THF	**7a**, **8a**	52	81:19
5	$BF_3{\cdot}OEt_2$	Hex/THF	**7a**, **8a**	46	82:18
6	$TiCl_4$	CH_2Cl_2	[d]	–	–
7	$ScOTf_3$	CH_2Cl_2	**7a**, **8a**	trace	–
8	TMSOTf	CH_2Cl_2	**7b**, **8b**	50	70:30
9	TESOTf	CH_2Cl_2	**7c**, **8c**	56	65:35
10	TBSOTf	CH_2Cl_2	**7a**, **8a**	60	60:40

[a] Unless otherwise noted, all reactions were carried out at –80 °C with **5** (200 mg, 0.67 mmol), **6** (0.87 mmol), Lewis acid promoter (0.87 mmol), and solvent (3 mL). [b] Isolated combined yield. [c] Determined by ^1H NMR analysis of the unpurified reaction mixtures. [d] A complex reaction mixture was observed.

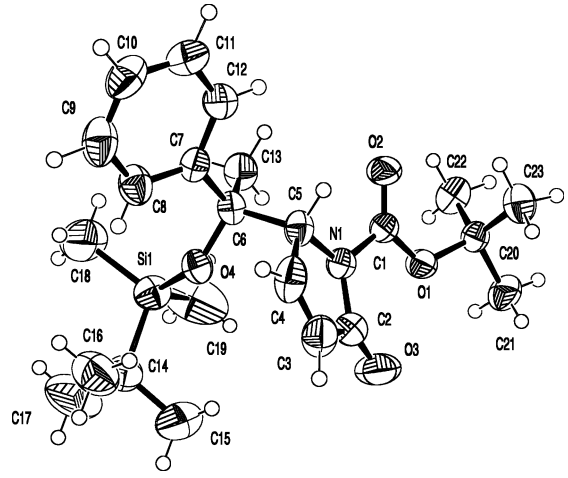


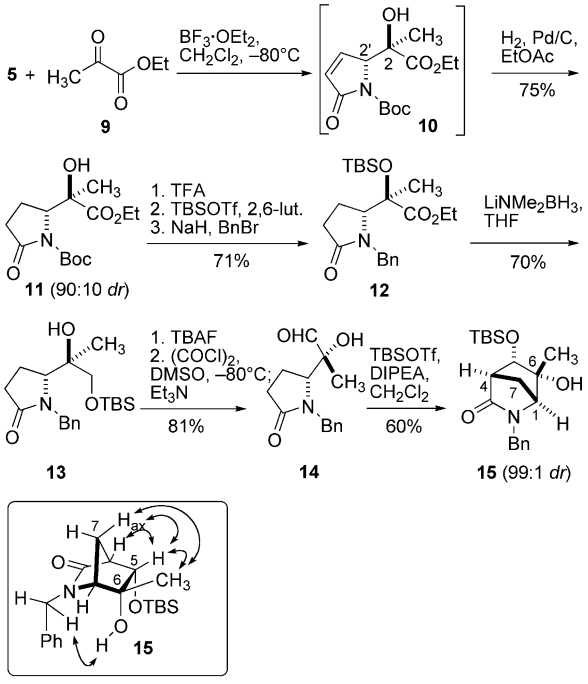
Figure 2. X-ray structure of the adduct **7a** showing the N,O-*syn* stereodisposition (50% thermal ellipsoids).

The conditions employed for pyrrole **5** and acetophenone (**6**) were also applicable to a variety of other simple ketone substrates.[7] However, as our targets were the azabicyclo[*x*.2.1]alkane scaffolds, we explored the reactions of two achiral (**9** and **16**) and two chiral non-racemic substrates (**22** and **29**) which embodied at least one manipulatable ketone substituent.

Synthesis of 2-Azabicyclo[2.2.1]heptanes 15 and 21

Pyruvic ester **9** and oxo(phenyl)acetate **16**, the ketone components of these syntheses, both possess a carboxylate functional unit that can be easily manipulated to give an aldehyde group, as demanded by the planned aldol carbocyclization.

Targeting bicycle **15** (Scheme 2), the opening move was the crossed aldol coupling between pyrrole **5** and pyruvate **9**, which was examined with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at –80 °C, one of the best protocols found with acetophenone in the preparatory work described above. Unfortunately, the conversion was unacceptable, with only marginal amounts of unsaturated and non-silylated[8] tertiary carbinol **10** isolated by column chromatography (25% yield). Realizing that a retro-aldolization process was responsible for this sterile attempt,[6a] we opted not to isolate the unstable unsaturated adduct **10**, but to prepare the corresponding saturated adduct **11** by directly exposing the crude reaction product to catalytic hydrogen. Indeed, this dual addition–reduction protocol proved successful, allowing the expedient synthesis of the saturated 2,2′-*anti* compound **11**, which was isolated in a preparatively useful yield (75%, two steps) and with a good margin of diastereoselectivity (90:10 *dr*) (Scheme 2).



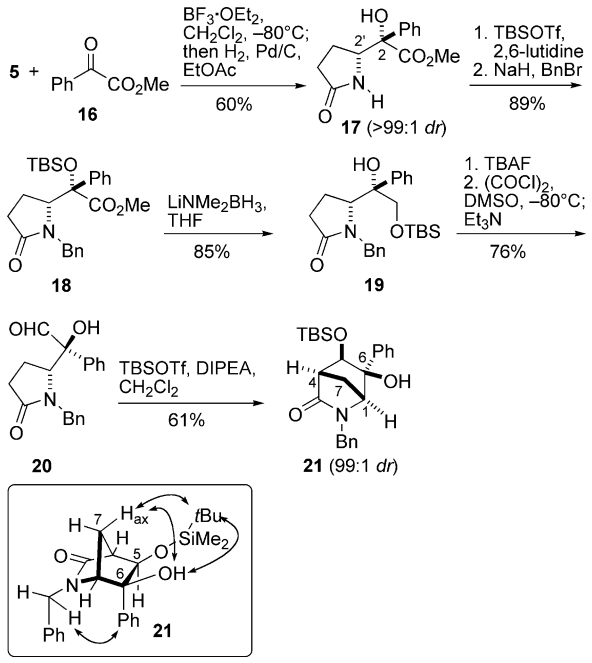
Scheme 2. Synthesis of 2-azabicyclo[2.2.1]heptane **15** (relative configuration of racemic compounds). Double-headed arrows indicate diagnostic NOE contacts.

Having surmounted this initial obstacle, the synthesis of **15** then proceeded by manipulation of the ethyl carboxylate portion within **11** to a carbaldehyde. Thus, protection of the tertiary hydroxy group as a TBS ether and swapping the *N*-Boc protecting group for the acid-tolerant benzyl moiety afforded ethyl ester **12** in a 71% isolated yield (three steps). Reduction of the ester functionality within **12** in the presence of a lactam carbonyl group was quite problematic. However, after exploring several possibilities, we found that the chemoselective reduction of the ester group to a primary alcohol could be carried out by employing $LiNMe_2BH_3$ in THF, conditions that caused the simultaneous transmigration of the tertiary carbinol TBS protecting group to the newly formed primary hydroxy group to give rise to carbinol **13** in a 70% isolated yield. Pleasingly, this silyl transfer, albeit unexpected, proved inconsequential for the synthesis overall.

After desilylation, oxidation of the primary hydroxy group by a conventional Swern protocol (oxalyl chloride, DMSO, Et_3N) was clean and productive, and returned the aldehyde **14** in 81% yield. The way was now clear for the second intramolecular aldol reaction which led to the five-membered carbocycle of the 2-azabicycle skeleton. According to our precedent that smooth carbocyclization occurs in a silylative and irreversible manner by exposing similar aldehydo-lactams to the TBSOTf/DIPEA couple,[2d,2h,2i] we treated aldehyde **14** with this Lewis acid/Lewis base system. As we had hoped, azacycle **15** was formed as a single diastereoisomer with a *cis* relationship between the C-5 and C-6 hydroxy substituents (60% isolated yield). The 2,2′-*anti* relative stereochemistry of the first aldol construct **10**, and of all the intermediates, was not proved directly, but emerged from a correlation with azabicycle **15**, the product of the second diastereoselective aldol construction. Strong NOE contacts were observed between the axially disposed 7-H_{ax} and the C-6 methyl protons, between 5-H and the methyl protons themselves, as well as between 7-H_{ax} and 5-H, all consistent with their *cis* relationship. In addition, the presence of a medium NOE contact between the C-6 hydroxy group and the benzyl CH_2 group validated the assignment.

The synthesis of azabicycle **21** commenced with oxo(phenyl)acetate **16** (Scheme 3), paralleling almost exactly the chemistry exploited with pyruvate **9**. The initial aldol addition, promoted by $BF_3{\cdot}OEt_2$, produced an unstable unsaturated and non-silylated[8] adduct (not isolated) which was promptly hydrogenated and deprotected to give saturated lactam **17** in >99:1 *dr* (by ^1H NMR) and 60% yield over two steps. Remarkably, the stereochemistry of **17**, which was conclusively confirmed at a later stage in the synthesis, indicated a *syn* relationship of the N,O substituents at the two newly generated stereocentres C-2 and C-2′, opposite to that observed in the pyruvate-derived congener **11**. This point will be addressed later.

Prior to the decisive aldol carbocyclization, **17** was next converted into aldehyde **20** by a clean five-step sequence that involved the protection of certain functionalities to give **18**, ester reduction to **19**, desilylation and Swern oxidation



Scheme 3. Synthesis of 2-azabicyclo[2.2.1]heptane **21** (relative configuration of racemic compounds). Double-headed arrows indicate diagnostic NOE contacts.

(58% overall yield). Finally, exposure of aldehyde **20** to TBSOTf/DIPEA (1:1, 3.0 equiv.) revealed bicycle **21** as a single diastereoisomer with the C-5 and C-6 hydroxy groups in a *cis* disposition (61% yield). Thus, the basic structure of the planned 2-azabicyclo[2.2.1]heptane system was assembled.

As for the pyruvate-derived bicycle **15**, the stereochemistry of racemic **21** was certified by two-dimensional ^{1}H–^{1}H NOESY analysis which highlighted diagnostic correlations between 7-H_{ax} and the C-6 hydroxy proton, between 7-H_{ax} (as well as the C-6 OH proton) and the C-5 silyloxy protecting group, and finally between the *ortho* protons of the C-6 phenyl group and the benzyl CH_2 group. Furthermore, the presence of long-range W coupling constants 7-H_{eq}–5-H and 1-H–4-H corroborated the given structure. With this assignment, the stereochemistries of the initial *syn*-configured adduct **17** and the intermediary compounds in this synthesis were also confirmed as shown.

Perhaps the most intriguing result in this section is the substrate-dependent stereodifferentiation of the first intermolecular aldol coupling reactions of ketones **9** and **16** which give rise to *anti*-configured **11** and *syn*-configured **17**, respectively. Figure 3 delineates a rationale that accounts for this divergence based on hetero-Diels–Alder-like mechanistic models.[1b,9]

For **9**, the best orbital alignment in the approach via **TS1** requires the electron-withdrawing ethoxycarbonyl component of the ketone to be oriented *endo* (methyl *exo*) with respect to the diene, generating the *anti*-disposed adduct **11**. However, for **16**, one envisions the phenyl ring prevailing in the *endo* disposition, as in the approach via **TS2**, which dictates a strong preference for the *syn*-disposed aldol product **17**.

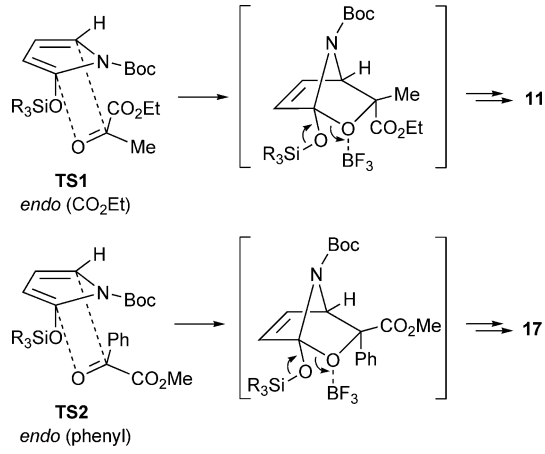


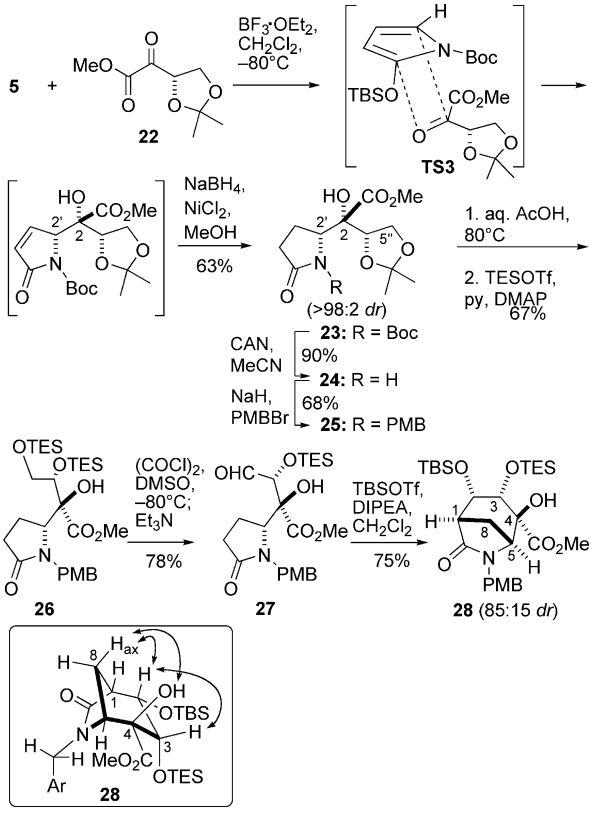
Figure 3. Proposed mechanism for the diastereo-divergent vinylogous Mukaiyama aldol addition reaction between silyloxypyrrole **5** and ketones **9** and **16** (only one enantiomer shown).

Synthesis of 6-Azabicyclo[3.2.1]octane Systems 28 and 36

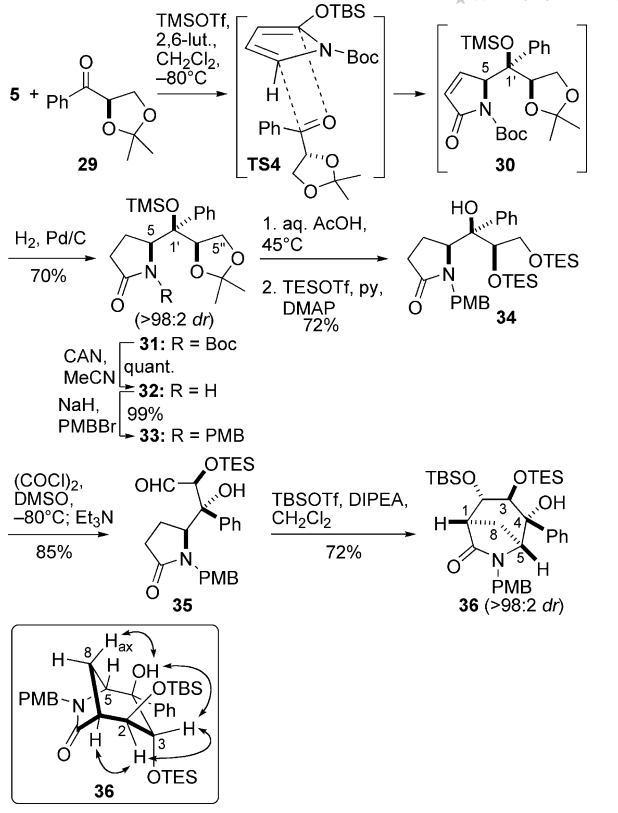
Here, the task was to translate in a chiral environment the concepts and results of the reactions with achiral ketones **9** and **16**. To this end, attention was focused on readily available (*S*)-configured oxo ester **22** (ex L-ascorbic acid)[10] and (*R*)-configured phenyl ketone **29** (ex D-glyceraldehyde),[11] both of which bear a stereocentre α to the reacting carbonyl group.

To access azabicyclooctane **28**, we first realized the aldol reaction between **5** and **22** by employing BF_3·OEt_2 as the promoter (Scheme 4). Pleasingly, by a sequential addition–reduction protocol, the saturated, non-silylated[8] *syn–syn* aldol adduct **23** was obtained in a virtually pure state (63% yield over two steps) with high levels (>98:2 *dr*) of simple and facial stereoselectivities, presumably via transition-state **TS3**. The stereochemistry of **23** was not discernible at this point, so the adduct was advanced through the synthetic sequence. At a later stage (see below) it was determined that **23** was 2,2′-*syn*;2,4′′-*syn*-configured, as shown.

To convert the C-5′′ hydroxymethyl terminus within **23** into an aldehyde, a multi-step manipulation was required. This included nitrogen deprotection to **24** (CAN, MeCN), reprotection to **25** (NaH, PMBBr), acidic fission of the acetonide moiety (80% aq. AcOH, 80 °C), double silylation to **26** (TESOTf, pyridine) and Swern oxidation[12] to aldehydolactam **27** (32% yield over five steps). Irrespective of the redundant functionalization of the aldehyde substrate, with a free tertiary alcohol and a methoxycarbonyl functionality, the silylative Mukaiyama-type cycloaldolization of **27** was productive (TBSOTf, DIPEA), predominantly affording the azabicycle **28** (85:15 *dr*) in a good yield of 75% after silica gel chromatography. This suggested that enolate silylation occurred completely and retro-aldolization was totally suppressed. The rigid nature of azabicycle **28** strongly facilitated its structural assignment by ^{1}H and ^{13}C NMR analysis. In particular, the high-field ^{1}H–^{1}H NOESY spectrum of **28** revealed medium/strong correlations between 2-H and



Scheme 4. Synthesis of 6-azabicyclo[3.2.1]octane **28**. Double-headed arrows indicate diagnostic NOE contacts.



Scheme 5. Synthesis of 6-azabicyclo[3.2.1]octane **36**. Double-headed arrows indicate diagnostic NOE contacts.

8-H_{ax}, and between *cis*-disposed 2-H and 3-H, as well as between 8-H_{ax} and the C-4 hydroxy proton. In addition, long-range W coupling constants between equatorially disposed 1-H and 3-H and between 3-H and 5-H corroborated this assignment. From this analysis, the structures of all the intermediates shown in Scheme 4, which correlate with **28** by synthesis, were also ascertained with confidence.

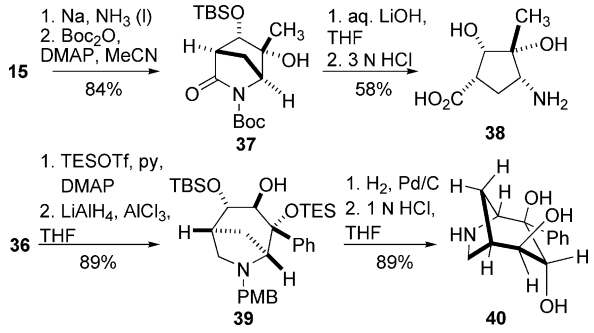
Next, bicycle **36** was targeted starting from isopropylidene-protected phenyl ketone **29** (Scheme 5). Quite unexpectedly, however, neither $BF_3{\cdot}OEt_2$ nor any of the other conditions tested during the preparative work with acetophenone (see above) promoted the aldol addition of silyloxydiene **5** to this chiral ketone. To overcome this problem, a revised, amine-buffered silylative strategy was adopted in which the retrograde addition was hampered by in situ aldolate silylation.[6a,13]

After considerable experimentation, effective coupling was best achieved by employing TMSOTf as the Lewis acid (3.0 equiv.) combined with 2,6-lutidine (2.0 equiv.). In this case, the silylative addition proceeded via **TS4**, which provided the *O*-trimethylsilyl-protected aldol product **30** after aqueous workup (brine, pyridine). As partial desilylation and fragmentation occurred during chromatographic purification on silica, it was best to sequestrate the unsaturated intermediate **30** promptly by catalytic H_2, arriving at the more robust saturated lactam **31** (H_2, Pd/C; 70% yield over two steps, >98:2 *dr*).

After exchanging Boc for PMB to give **33**, dismantling of the acid-sensitive protecting groups (aq. AcOH) afforded a triol intermediate which was directly converted into silylated lactam **34** in 71% yield over four steps. Aldehyde **35** was then obtained in a further step by a modified Swern oxidative protocol[12] in 85% isolated yield. The second decisive aldol reaction also proceeded uneventfully using our proven silylative methodology (TBSOTf/DIPEA) to give the six-membered carbocyclic frame of the azabicyclooctane **36** (72% yield, >98:2 *dr*). The stereochemistry of bicycle **36** was analyzed by extensive ^1H NMR measurements and provided the structure shown in Scheme 5.

Elaboration of Azabicycles 15 and 36

With a clean entry to azabicyclo[*x*.2.1]alkane structures in hand, we finally addressed their elaboration to densely functionalized carbo- and heterocyclic entities. 2-Aza- and 6-azabicycles **15** and **36** were selected to access racemic cyclopentane amino acid **38** and enantiopure normorphan **40**, respectively (Scheme 6). For **38**, bicycle **15** was first debenzylated by exposure to sodium in liquid ammonia and reprotected to give the *N*-Boc derivative **37** in order to facilitate the hydrolytic lactam fission (84% yield, two steps). The desired opening proceeded cleanly by exposure to LiOH in wet THF to afford a protected amino acid which was fully deprotected (3 N HCl) to furnish racemic amino acid **38** (hydrochloride salt, 58% yield over two steps).[14]



Scheme 6. Elaboration of azabicycles **15** and **36**.

For the conversion of the 6-azabicycle **36** into the normorphan structure **40**, the stereochemistry and substituents of the target molecule were already in place, and elaboration of the lactam carbonyl group plus global deprotection were solely required. Thus, after protection of the tertiary carbinol within **36** as the *O*-TES ether, the carbonyl group was reduced with in situ generated AlH_3 ($LiAlH_4/AlCl_3$) to provide amine **39** (89%, two steps) which was subjected to hydrogenolytic removal of PMB and subsequent acidic desilylation. This led to normorphan triol **40** in 89% yield over two steps. The relative/absolute stereochemistries of both **38** and **40** were confirmed, as indicated, by chemical correlation with the corresponding parent compounds **15** and **36**, and by the usual NMR techniques.

Conclusions

The stereocontrolled synthesis of four azabicycloalkane systems, **15** and **21** (chiral racemic), and **28** and **36** (chiral non-racemic), all of which embodied one quaternary stereocentre, has been realized. 2-Aza- and 6-azabicycles **15** and **36** were then elaborated into densely functionalized cyclopentane amino acid **38** (racemic) and normorphan alkaloid **40** (enantiopure), respectively. The constructions shared a common synthetic route that featured two highly diastereoselective, yet problematic aldol-based carbon–carbon bond formations. The problem of retro-addition that plagues these processes was surmounted here by implementing dual addition–reduction techniques or, better, silylative aldol-stabilizing protocols.

The substrate-driven diastereoselectivity of the vinylogous Mukaiyama aldol addition between pyrrolic diene **5** and ketones **9**, **16**, **22** and **29** was rationalized based on the participation of hetero-Diels–Alder transition-state structures in which the *endo* versus *exo* paradigm is influenced, as expected, by the electronic character of the substituents in the ketone dienophile.

With these achievements emerging as a firm testament to the vitality of the heterocyclic dienoxysilane scaffolds, we anticipate their utility in organic synthesis to be enhanced even more.

Experimental Section

General Experimental Procedures: All organic solvents were dried and freshly distilled before use according to literature procedures. All moisture-sensitive reactions were carried out under a positive pressure of nitrogen or argon. TLC analysis was performed on silica gel 60 F_{254} plates with visualization under short-wavelength UV light or by dipping the plates into molybdate reagent (aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate) followed by heating. Flash chromatography was performed on 40–63 μm silica gel using the indicated solvent mixtures. Melting points were determined with an optical thermo-microscope and are uncorrected. Optical rotations were measured at ambient temperature using a 100-mm cell with a 1-mL capacity and are given in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra were recorded at 300/75 MHz (Bruker Avance 300), 400/100 MHz (Varian Mercury Plus MP400), or 600/150 MHz (Varian Inova SB-600). Chemical shifts (δ) are given in parts per million (ppm) using [D]chloroform ($CHCl_3$: δ_H = 7.26 ppm; $CDCl_3$: δ_C = 77.0 ppm), [D_4]methanol (CD_2HOD: δ_H = 3.31 ppm; CD_3OD: δ_C = 49.0 ppm), or deuterium oxide (DOH: δ_H = 4.75 ppm) as the internal reference. High-resolution mass spectrometry (HRMS) measurements were performed with a mass spectrometer equipped with an external electrospray ion source.

Materials: 1-(*tert*-Butoxycarbonyl)-2-(*tert*-butyldimethylsilyloxy)-pyrrole (**5**) was prepared from pyrrole according to a previously described protocol.[15] Acetophenone (**6**), ethyl pyruvate (**9**) and methyl oxo(phenyl)acetate (**16**) were purchased from Sigma Aldrich and used without further purification.

Methyl 2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxoacetate (**22**) was prepared from 5,6-isopropylidene-L-ascorbic acid (Aldrich) according to the following three-step procedure.[10] 5,6-Isopropylidene-L-ascorbic acid (5.0 g, 23.13 mmol) was added to a stirred solution of K_2CO_3 (6.8 g, 49.20 mmol) in H_2O (26 mL) at room temperature. H_2O_2 (30% v/v, 5.5 mL, 53.85 mmol) was slowly added to the resulting yellowish solution, cooled to 0 °C. The colourless reaction mixture was stirred at room temperature for 24 h, and then it was concentrated under vacuum to give a white solid which was treated with EtOH (125 mL) and heated at reflux for 30 min. The reaction mixture was filtered, while the solid residue was treated again with EtOH (125 mL) and heated at reflux for 30 min (twice). The collected filtrates were concentrated under vacuum to furnish (*R*)-2-hydroxy-2-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]acetic acid as a white solid (3.9 g, 96% yield). MeI (1.8 mL, 28.78 mmol) was slowly added to a solution of the above acid (3.9 g, 22.14 mmol) in MeCN (24.4 mL) at room temperature. The resulting mixture was heated at reflux at 80 °C for 3 h, filtered through a Büchner funnel and concentrated under vacuum to give a yellow oily residue which was purified by silica gel flash chromatography (EtOAc/hexane, 80:20) to furnish methyl (*R*)-2-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyacetate (4.0 g, 95% yield) as a colourless oil. $[a]_D^{20}$ = +16.8 (*c* = 1.92, $CHCl_3$) {ref.[10b] $[a]_D^{20}$ = +16.2 (*c* = 3.7, CH_2Cl_2)}. Freshly activated molecular sieves (4 Å, 38.45 g) and pyridinium chlorochromate (18.24 g, 84.56 mmol) were sequentially added to a solution of the above methyl ester (4.0 g, 21.14 mmol) in dry CH_2Cl_2 (250 mL) at room temperature. The resulting reaction mixture was vigorously stirred for 16 h, filtered through a short pad of silica gel and purified by silica gel flash chromatography (EtOAc/hexane, 40:60) to give ketone **22** (2.59 g, 65% yield) as a colourless oil. $[a]_D^{20}$ = –8.0 (*c* = 0.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.07 (dd, *J* = 7.6, 4.8 Hz, 1 H), 4.36 (dd, *J* = 8.8, 7.6 Hz, 1 H), 4.18 (dd, *J* = 8.8, 4.8 Hz, 1 H), 3.91 (s, 3 H), 1.48 (s, 3 H), 1.44 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 191.3 (C_q), 161.5 (C_q), 111.7 (C_q), 78.2 (CH), 65.7 (CH_2), 53.1 (CH_3), 25.8 (CH_3), 25.2 (CH_3) ppm.

[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]phenylmethanone (**29**) was prepared from 2,3-*O*-isopropylidene-D-glyceraldehyde (ex D-mannitol)[16] according to the following procedure. *tert*-Butyllithium (1.7 M solution in pentane, 13.5 mL, 23.05 mmol) was added to a stirred solution of bromobenzene (2.32 mL, 23.05 mmol) in anhydrous Et_2O (50 mL) under argon at –80 °C over a period of 20 min. After 40 min, a diethyl ether solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (1.0 g, 7.68 mmol dissolved in 10 mL of Et_2O) was slowly added at –80 °C. After 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and brine (30 mL) while the temperature was allowed to reach an ambient value (20 °C). The organic fraction was extracted with EtOAc (three times), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The resulting oily residue was purified by silica gel flash chromatography (hexane/EtOAc, 80:20) to furnish [(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]phenylmethanol (1.36 g, 85% yield) as a 4:1 mixture of diastereoisomers. Dess–Martin periodinane (3.04 g, 7.18 mmol) was added to a stirred solution of the above carbinol mixture (1.36 g, 6.53 mmol) in dry CH_2Cl_2 (30 mL) under argon at room temperature, and the resulting white slurry was stirred for 1 h. Saturated aqueous $NaHCO_3$ (about 20 mL) was then added until neutralization, and saturated aqueous $Na_2S_2O_3$ (10 mL) was added. The resulting mixture was extracted with hexane (three times), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The resulting residue was purified by silica gel flash chromatography (hexane/EtOAc, 60:40) to furnish ketone **29** (1.32 g, 98%) as white crystals. M.p. 50–52 °C. $[\alpha]_D^{20}$ = +11.82 (*c* = 0.99, $CHCl_3$) {ref.[11] m.p. 61–62 °C, $[\alpha]_D^{23}$ = +15.3 (*c* = 3.6, MeOH)}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.99 (m, 2 H), 7.56 (tt, *J* = 7.4, 1.4 Hz, 1 H), 7.45 (m, 2 H), 5.27 (dd, *J* = 7.2, 5.9 Hz, 1 H), 4.31 (dd, *J* = 8.5, 7.3 Hz, 1 H), 4.24 (dd, *J* = 8.5, 5.9 Hz, 1 H), 1.46 (s, 3 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 196.5 (C_q), 135.0 (C_q), 133.6 (CH), 128.7 (2 C, CH), 128.6 (2 C, CH), 111.0 (C_q), 77.8 (CH), 66.2 (CH_2), 25.9 (CH_3), 25.6 (CH_3) ppm.

(*R)-1-(*tert*-Butoxycarbonyl)-5-[(*S**)-1-(*tert*-butyldimethylsilyloxy)-1-phenylethyl]-1*H*-pyrrol-2(5*H*)-one (7a) and (*R**)-5-[(*R**)-1-(*tert*-Butyldimethylsilyloxy)-1-phenylethyl]-1-(*tert*-butoxycarbonyl)-1*H*-pyrrol-2(5*H*)-one (8a):** See Table 1, Entry 3. To a solution of silyloxypyrrole **5** (200 mg, 0.67 mmol) in anhydrous CH_2Cl_2 (3.0 mL) under argon at –80 °C was added acetophenone (**6**) (105 mg, 0.87 mmol). After 10 min, $BF_3{\cdot}OEt_2$ (110 μL, 0.87 mmol) was slowly added, and the resulting mixture was stirred at –80 °C for 3 h. The reaction mixture was quenched at –80 °C with saturated aqueous $NaHCO_3$ (5 mL) and solid $NaHCO_3$ (150 mg) while the temperature was allowed to reach an ambient value. Further portions of $NaHCO_3$ were added until a neutral pH was achieved. The mixture was extracted with CH_2Cl_2 (three times). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give an oily residue which was purified by silica gel flash chromatography (hexane/Et_2O, 85:15) to furnish pure lactams **7a** (241 mg) and **8a** (14 mg) in 86 and 5% yields, respectively.

Compound 7a: Colourless crystals. M.p. 89–91 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.48 (m, 2 H), 7.34 (m, 3 H), 6.81 (dd, *J* = 6.1, 2.2 Hz, 1 H), 6.01 (dd, *J* = 6.1, 1.6 Hz, 1 H), 5.0 (t, *J* = 1.9 Hz, 1 H), 1.70 (s, 3 H), 1.50 (s, 9 H), 0.94 (s, 9 H), 0.12 (s, 3 H), –0.03 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 170.3 (C_q), 150.4 (C_q), 150.1 (CH), 146.0 (C_q), 128.2 (2 C, CH), 127.3 (CH), 126.8 (CH), 125.2 (2 C, CH), 82.8 (C_q), 78.8 (C_q), 70.9 (CH), 27.9 (3 C, CH_3), 27.0 (CH_3), 26.2 (3 C, CH_3), 18.7 (C_q), –1.8 (CH_3), –2.2 (CH_3) ppm. $C_{23}H_{35}NO_4Si$ (417.61): calcd. C 66.15, H 8.45, N 3.35; found C 65.98, H 8.56, N 3.23. Crystal data: see below. ORTEP plot: see Figure 2.

Compound 8a: Colourless resin. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.29 (m, 5 H), 7.09 (dd, *J* = 6.1, 2.1 Hz, 1 H), 5.74 (dd, *J* = 6.0, 1.2 Hz, 1 H), 5.0 (t, *J* = 1.6 Hz, 1 H), 1.70 (s, 3 H), 1.63 (s, 9 H), 0.99 (s, 9 H), 0.12 (s, 3 H), –0.02 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 169.9 (C_q), 150.5 (C_q), 150.3 (CH), 143.2 (C_q), 127.7 (2 C, CH), 127.3 (CH), 126.4 (CH), 125.4 (2 C, CH), 83.1 (C_q), 79.8 (C_q), 70.1 (CH), 28.1 (3 C, CH_3), 27.7 (CH_3), 26.1 (3 C, CH_3), 18.6 (C_q), –1.6 (CH_3), –2.2 (CH_3) ppm. $C_{23}H_{35}NO_4Si$ (417.61): calcd. C 66.15, H 8.45, N 3.35; found C 66.00, H 8.59, N 3.29.

Ethyl (*R)-2-[(*R**)-1-(*tert*-Butoxycarbonyl)-5-oxopyrrolidin-2-yl]-2-hydroxypropanoate (11):** $BF_3{\cdot}OEt_2$ (0.55 mL, 4.37 mmol) was added to a solution of ethyl pyruvate (**9**) (0.48 mL, 4.37 mmol) in dry CH_2Cl_2 (10 mL) under argon at –80 °C. After 5 min, a solution of silyloxypyrrole **5** (1.0 g, 3.36 mmol, dissolved in 3 mL of dry CH_2Cl_2) was added. After stirring at –80 °C for 4 h, pyridine (0.53 mL, 6.55 mmol) was added, and the reaction mixture was stirred for an additional 15 min. Water (10 mL) was added, and the temperature was allowed to reach an ambient value. The reaction mixture was extracted with CH_2Cl_2 (three times), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give an oily residue which was almost entirely used as such in the subsequent reductive reaction. A small portion of this crude residue, however, was purified by silica gel flash chromatography (hexane/EtOAc, 50:50) to furnish unsaturated lactam **10** as a colourless resin. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.21 (dd, *J* = 6.1, 2.2 Hz, 1 H), 6.18 (dd, *J* = 6.1, 1.6 Hz, 1 H), 5.02 (t, *J* = 2.1 Hz, 1 H), 4.2–4.4 (m, 2 H), 3.83 (s, 1 H), 1.55 (s, 9 H), 1.47 (s, 3 H), 1.30–1.40 (m, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 173.8 (C_q), 168.3 (C_q), 150.6 (C_q), 146.3 (CH), 128.2 (CH), 83.5 (C_q), 74.2 (C_q), 66.6 (CH), 62.3 (CH_2), 27.8 (3 C, CH_3), 22.2 (CH_3), 13.7 (CH_3) ppm.

Palladium on carbon (60 mg) was added to a solution of the above crude residue in anhydrous EtOAc (50 mL) at room temperature. The reaction vessel was degassed under vacuum and thoroughly purged with hydrogen (three times). The resulting heterogeneous mixture was stirred under hydrogen for 12 h, after which time the hydrogen was evacuated, the catalyst filtered off and the filtrate concentrated under vacuum to give a crude residue which was purified by silica gel flash chromatography (hexane/EtOAc, 1:1) to furnish pure lactam **11** (987 mg, 75% for two steps) as a white solid. M.p. 101–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.59 (d, *J* = 8.8 Hz, 1 H), 4.22 (br. q, *J* = 7.1 Hz, 2 H), 3.50 (br. s, 1 H), 2.76 (ddd, *J* = 17.7, 10.9, 9.5 Hz, 1 H), 2.27 (ddd, *J* = 17.6, 10.0, 1.0 Hz, 1 H), 2.03 (m, 1 H), 1.72 (br. dd, *J* = 12.9, 9.4 Hz, 1 H), 1.49 (s, 9 H), 1.35 (s, 3 H), 1.20 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 174.8 (2 C, 2Cq), 150.5 (C_q), 82.8 (C_q), 78.0 (C_q), 62.1 (CH_2), 61.3 (CH), 32.2 (CH_2), 27.6 (3 C, CH_3), 23.5 (CH_3), 21.0 (CH_2), 13.8 (CH_3) ppm. $C_{14}H_{23}NO_6$ (301.34): calcd. C 55.80, H 7.69, N 4.65; found C 55.98, H 7.75, N 4.59.

Ethyl (*R)-2-[(*R**)-1-Benzyl-5-oxopyrrolidin-2-yl]-2-(*tert*-butyldimethylsilyloxy)propanoate (12):** Trifluoroacetic acid (TFA, 3.0 mL) was added dropwise to a stirred solution of lactam **11** (0.98 g, 3.27 mmol) in dry CH_2Cl_2 (20 mL) at room temperature. After 2 h, the solvent was evaporated under vacuum, and the resulting oily residue was purified by silica gel flash chromatography (hexane/EtOAc, 90:10) to furnish an *N*-deprotected lactam intermediate (0.65 g, 99%) as a white solid. M.p. 120–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.45 (br. s, 1 H), 4.26 (q, *J* = 7.1 Hz,

2 H), 4.00 (br. s, 1 H), 3.89 (dd, J = 8.5, 4.3 Hz, 1 H), 2.43 (ddd, J = 17.1, 10.1, 7.4 Hz, 1 H), 2.29 (m, 1 H), 2.14 (m, 1 H), 2.06 (m, 1 H), 1.45 (s, 3 H), 1.30 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 179.8 (C_q), 174.8 (C_q), 76.3 (C_q), 62.3 (CH_2), 60.7 (CH), 30.0 (CH_2), 22.4 (CH_3), 21.8 (CH_2), 14.1 (CH_3) ppm.

The above lactam intermediate (0.65 g, 3.23 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) at room temperature under argon, and 2,6-lutidine (0.73 mL, 6.26 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 1.44 mL, 6.26 mmol) were sequentially added whilst stirring. After 2 h, additional portions of TBSOTf (2 × 1.44 mL, 2 × 6.26 mmol) were added to the reaction mixture. The reaction mixture was quenched with brine (50 mL) and extracted with CH_2Cl_2 (three times) 2 h after the last addition. The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give a crude residue which was purified by silica gel flash chromatography (hexane/EtOAc, 70:30 to 0:100). This protected lactam intermediate was obtained (0.86 g, 85%) as a white solid. M.p. 97–99 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18 (br. s, 1 H), 4.21 (q, J = 7.1 Hz, 2 H), 3.85 (dd, J = 8.0, 4.7 Hz, 1 H), 2.38 (ddd, J = 17.3, 10.3, 7.2 Hz, 1 H), 2.25 (ddd, J = 17.2, 9.8, 6.0 Hz, 1 H), 1.90–2.15 (m, 2 H), 1.45 (s, 3 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.90 (s, 9 H), 0.15 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 179.0 (C_q), 173.8 (C_q), 79.0 (C_q), 61.6 (CH), 61.3 (CH_2), 30.0 (CH_2), 25.6 (3 C, CH_3), 22.8 (CH_3), 21.6 (CH_2), 18.3 (C_q), 14.1 (CH_3), –2.9 (CH_3), –3.2 (CH_3) ppm.

NaH (60% dispersion in mineral oil, 164 mg, 4.09 mmol) and benzyl bromide (486 μL, 4.09 mmol) were sequentially added to a solution of the above lactam (860 mg, 2.73 mmol) in anhydrous THF (50 mL) at room temperature. After being heated at reflux whilst stirring for 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) at room temperature until neutralization. The mixture was extracted with EtOAc (three times) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The resulting residue was purified by silica gel flash chromatography (hexane/EtOAc, 70:30) to furnish *N*-benzyllactam **12** (0.941 g, 85%, corresponding to a 71% yield over three steps) as a glassy solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.2–7.4 (m, 5 H), 5.24 (1/2 ABq, J = 15.4 Hz, 1 H), 4.18 (m, 2 H), 4.15 (1/2 ABq, J = 15.2 Hz, 1 H), 3.79 (dd, J = 6.7, 3.8 Hz, 1 H), 2.54 (dt, J = 17.1, 9.6 Hz, 1 H), 2.31 (m, 1 H), 2.00 (m, 2 H), 1.49 (s, 3 H), 1.25 (t, J = 7.2 Hz, 3 H), 0.89 (s, 9 H), 0.18 (s, 3 H), 0.11 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 176.7 (C_q), 173.9 (C_q), 136.7 (C_q), 128.7 (2 C, CH), 127.6 (2 C, CH), 127.3 (CH), 80.6 (C_q), 64.1 (CH), 61.5 (CH_2), 46.1 (CH_2), 30.0 (CH_2), 25.8 (3 C, CH_3), 23.9 (CH_3), 21.5 (CH_2), 18.3 (C_q), 14.0 (CH_3), –3.0 (CH_3), –3.2 (CH_3) ppm. $C_{22}H_{35}NO_4Si$ (405.60): calcd. C 65.15, H 8.70, N 3.45; found C 64.98, H 8.77, N 3.38.

(*R)-1-Benzyl-5-[(*R**)-1-(*tert*-butyldimethylsilyloxy)-2-hydroxypropan-2-yl]pyrrolidin-2-one (13):** *n*-BuLi (1.6 M solution in hexane, 14.5 mL, 23.20 mmol) was added dropwise to a solution of $Me_2NH{\cdot}BH_3$ (1.37 g, 23.20 mmol) in dry THF (25 mL) at 0 °C. After stirring at 0 °C for 1 h, a portion of this reaction mixture (5 mL, 4.64 mmol) was added dropwise to a solution of lactam **12** (941 mg, 2.32 mmol) in dry THF (150 mL) precooled to –15 °C. Further portions of the reducing solution (4 × 5 mL, 4 × 4.64 mmol) were sequentially added to the reaction mixture over a period of 4 h. After 15 h, the reaction mixture was quenched with H_2O (130 mL) and 1 M citric acid solution until the pH was 3–4 and then was extracted with EtOAc (three times). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give a residue which was purified by silica gel flash chromatography (CH_2Cl_2/hexane, 65:35, to hexane/EtOAc, 60:40) to furnish lactam **13** (0.59 g, 70% yield) as a white solid. M.p. 87–89 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.2–7.4 (m, 5 H), 5.11 (1/2 ABq, J = 14.7 Hz, 1 H), 4.34 (1/2 ABq, J = 14.7 Hz, 1 H), 3.61 (dd, J = 8.7, 3.4 Hz, 1 H), 3.49 (ABq, $\Delta\nu$ = 11.5 Hz, 2 H), 2.6 (br. s, 1 H), 2.49 (dt, J = 17.5, 9.4 Hz, 1 H), 2.35 (ddd, J = 17.2, 9.5, 4.6 Hz, 1 H), 1.9–2.1 (m, 2 H), 1.16 (s, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 176.7 (C_q), 137.2 (C_q), 128.5 (2 C, CH), 128.2 (2 C, CH), 127.2 (CH), 75.9 (C_q), 66.6 (CH_2), 61.2 (CH), 46.6 (CH_2), 30.3 (CH_2), 25.8 (3 C, CH_3), 22.2 (CH_3), 20.8 (CH_2), 18.2 (C_q), –5.5 (CH_3), –5.6 (CH_3) ppm. $C_{20}H_{33}NO_3Si$ (363.57): calcd. C 66.07, H 9.15, N 3.85; found C 66.20, H 9.21, N 3.80.

(*R)-2-[(*R**)-1-Benzyl-5-oxopyrrolidin-2-yl]-2-hydroxypropanal (14):** Tetrabutylammonium fluoride (TBAF, 635 mg, 2.43 mmol) was slowly added to a stirred solution of lactam **13** (590 mg, 1.62 mmol) in anhydrous THF (25 mL) under argon at room temperature. After 1 h, the reaction mixture was quenched with H_2O (50 mL) and saturated aqueous NH_4Cl (20 mL) at room temperature until neutralization. The mixture was extracted with EtOAc (three times) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The resulting residue was purified by silica gel flash chromatography (EtOAc/MeOH, 95:5) to furnish an *O*-deprotected diol intermediate (0.38 g, 95% yield) as a colourless resin. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.30 (m, 5 H), 5.14 (1/2 ABq, J = 14.7 Hz, 1 H), 4.33 (1/2 ABq, J = 14.7 Hz, 1 H), 3.61 (dd, J = 8.5, 3.5 Hz, 1 H), 3.54 (ABq, $\Delta\nu$ = 27.6 Hz, 2 H), 2.85 (br. s, 2 H), 2.52 (dt, J = 17.3, 9.6 Hz, 1 H), 2.35 (ddd, J = 17.3, 9.5, 4.2 Hz, 1 H), 1.9–2.1 (m, 2 H), 1.19 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 177.0 (C_q), 137.0 (C_q), 128.6 (2 C, CH), 128.2 (2 C, CH), 127.4 (CH), 76.1 (C_q), 66.1 (CH_2), 62.3 (CH), 46.6 (CH_2), 30.3 (CH_2), 21.9 (CH_3), 20.9 (CH_2) ppm.

Dimethyl sulfoxide (DMSO, 382 μL, 5.39 mmol) was added dropwise to a stirred solution of oxalyl chloride (2.0 M in CH_2Cl_2, 1.54 mL, 3.08 mmol) in dry CH_2Cl_2 (15 mL) at –80 °C under argon,. After 10 min, a solution of the previous diol intermediate (0.38 g, 1.54 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise over a period of 15 min. After 1 h, Et_3N (1.30 mL, 9.24 mmol) was added and the reaction mixture was stirred at –80 °C for 10 min and then warmed to 25 °C over a period of 2 h. Distilled water (50 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3×). The collected organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (EtOAc/hexane, 75:25) to furnish aldehyde **14** (0.32 g, 85% yield) as a colourless resin. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.65 (s, 1 H), 7.1–7.4 (m, 5 H), 5.16 (1/2 ABq, J = 15.1 Hz, 1 H), 4.21 (1/2 ABq, J = 15.0 Hz, 1 H), 4.69 (dd, J = 8.5, 3.6 Hz, 1 H), 2.3–2.7 (m, 3 H), 2.10 (m, 1 H), 1.35 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 202.4 (CH), 176.3 (C_q), 136.0 (C_q), 128.4 (2 C, CH), 127.8 (2 C, CH), 127.3 (CH), 80.7 (C_q), 62.0 (CH), 46.5 (CH_2), 29.9 (CH_2), 20.9 (CH_2), 20.6 (CH_3) ppm. $C_{14}H_{17}NO_3$ (247.29): calcd. C 68.00, H 6.93, N 5.66; found C 67.87, H 7.01, N 5.59.

(1*R,4*S**,5*S**,6*R**)-2-Benzyl-5-(*tert*-butyldimethylsilyloxy)-6-hydroxy-6-methyl-2-azabicyclo[2.2.1]heptan-3-one (15):** TBSOTf (0.90 mL, 3.93 mmol) was added dropwise to a solution of diisopropyl(ethyl)amine (DIPEA, 0.68 mL, 3.93 mmol) in dry CH_2Cl_2 (150 mL) at room temperature. After stirring for 5 min, a preformed solution of aldehyde **14** (323 mg, 1.31 mmol) in dry CH_2Cl_2 (25 mL) was slowly added over a period of 15 min. After 2 h, a

further portion of the DIPEA/TBSOTf solution (15 mL, 3.93 mmol) was added to the reaction mixture. After 5 h from the beginning of the reaction, the mixture was quenched with brine (150 mL) and extracted with CH_2Cl_2 (three times). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give a residue which was purified by silica gel flash chromatography (hexane/EtOAc, 80:20) to furnish lactam **15** (0.28 g, 60% yield) as a glassy solid. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 7.29 (m, 2 H, Ph), 7.23 (m, 3 H, Ph), 5.04 (1/2 ABq, J = 15.0 Hz, 1 H, CH_2Ph), 4.01 (1/2 ABq, J = 15.6 Hz, 1 H, CH_2Ph), 3.89 (d, J = 4.2 Hz, 1 H, 5-H), 3.48 (s, 1 H, OH), 3.30 (m, 1 H, 1-H), 2.81 (dd, J = 4.2, 1.8 Hz, 1 H, 4-H), 1.81 (dt, J = 10.8, 1.8 Hz, 1 H, 7-H_{eq}), 1.46 (br. d, J = 10.8 Hz, 1 H, 7-H_{ax}), 1.31 (s, 3 H, Me on C-6), 0.92 (s, 9 H, *t*Bu), 0.18 (s, 3 H, Me), 0.14 (s, 3 H, Me) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 173.1 (C_q, C-3), 138.0 (C_q, Ph), 128.8 (2 C, CH, Ph), 128.3 (2 C, CH, Ph), 127.4 (CH, Ph), 76.4 (CH, C-5), 75.5 (C_q, C-6), 65.4 (CH, C-1), 52.1 (CH, C-4), 46.9 (CH_2, *C*H_2Ph), 35.2 (CH_2, C-7), 26.6 (CH_3, Me on C-6), 26.0 (3 C, CH_3, *t*Bu), 18.4 (C_q, *t*Bu), –4.5 (CH_3, Me), –4.9 (CH_3, Me) ppm. $C_{20}H_{31}NO_3Si$ (361.55): calcd. C 66.44, H 8.64, N 3.87; found C 66.31, H 8.70, N 3.79.

Methyl (*S)-2-Hydroxy-2-[(*R**)-5-oxopyrrolidin-2-yl]-2-phenylacetate (17):** $BF_3{\cdot}OEt_2$ (0.55 mL, 4.36 mmol) was added to a solution of methyl oxo(phenyl)acetate (**16**) (0.62 mL, 4.36 mmol) in dry CH_2Cl_2 (8.0 mL) under argon at –80 °C. After 5 min, a solution of silyloxypyrrole **5** (1.0 g, 3.36 mmol, dissolved in 3.0 mL of dry CH_2Cl_2) was added. After stirring at –80 °C for 4 h, anhydrous EtOAc (8.0 mL) and palladium on carbon (70 mg) were added to the reaction mixture. The reaction vessel was degassed under vacuum and thoroughly purged with hydrogen (three times). The resulting heterogeneous mixture was stirred under hydrogen while the temperature was allowed to rise to room temperature over a period of 2 h. After 12 h, the hydrogen was evacuated, pyridine (0.35 mL, 4.36 mmol) was added and the catalyst filtered off. The mixture was quenched with H_2O (30 mL) and extracted with EtOAc (four times). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give a residue which was purified by silica gel flash chromatography (pure EtOAc to EtOAc/MeOH, 95:5) to furnish the *N*-deprotected lactam **17** (0.5 g, 60% yield) as white crystals. M.p. 145–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.80 (s, 1 H), 7.68 (m, 2 H), 7.36 (m, 3 H), 4.56 (s, 1 H), 4.51 (dd, J = 8.5, 2.0 Hz, 1 H), 3.86 (s, 3 H), 2.53 (dt, J = 16.9, 9.3 Hz, 1 H), 2.18 (ddd, J = 17.1, 9.8, 3.9 Hz, 1 H), 1.8–2.0 (m, 2 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 180.7 (C_q), 173.9 (C_q), 137.6 (C_q), 128.2 (2 C, CH), 127.9 (CH), 125.6 (2 C, CH), 80.7 (C_q), 60.7 (CH), 53.5 (CH_3), 30.0 (CH_2), 21.0 (CH_2) ppm. $C_{13}H_{15}NO_4$ (249.26): calcd. C 62.64, H 6.07, N 5.62; found C 62.51, H 6.15, N 55.

Methyl (*S)-2-[(*R**)-1-Benzyl-5-oxopyrrolidin-2-yl]-2-(*tert*-butyldimethylsilyloxy)-2-phenylacetate (18):** 2,6-Lutidine (0.47 mL, 4.02 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 0.92 mL, 4.02 mmol) were sequentially added to a stirred solution of lactam **17** (0.5 g, 2.01 mmol) dissolved in anhydrous CH_2Cl_2 (15 mL) at room temperature under argon. After 2 h, additional portions of TBSOTf (2 × 0.92 mL, 2 × 4.02 mmol) were added to the reaction mixture. After 12 h from the beginning of the reaction, the mixture was quenched with brine (50 mL) and extracted with CH_2Cl_2 (three times). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give a crude residue which was purified by silica gel flash chromatography (hexane/EtOAc, 70:30 to 0:100). An *O*-protected lactam intermediate was obtained (0.71 g, 97%) as a white solid. M.p. 94.0–94.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.35 (m, 5 H), 6.12 (br. s, 1 H), 4.36 (t, J = 7.2 Hz, 1 H), 3.76 (s, 3 H), 2.15–2.30 (m, 2 H), 1.95 (m, 1 H), 1.59 (m, 1 H), 1.00 (s, 9 H), 0.15 (s, 3 H), 0.10 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 178.3 (C_q), 172.6 (C_q), 138.9 (C_q), 128.1 (2 C, CH), 127.8 (CH), 124.5 (2 C, CH), 82.1 (C_q), 61.0 (CH), 52.1 (CH_3), 29.3 (CH_2), 25.8 (3 C, CH_3), 19.7 (CH_2), 18.8 (C_q), –3.7 (2 C, CH_3) ppm.

NaH (60% dispersion in mineral oil, 117 mg, 2.92 mmol) and benzyl bromide (0.35 mL, 2.98 mmol) were sequentially added to a solution of the previous lactam (710 mg, 1.95 mmol) in anhydrous THF (50 mL) at room temperature. After being heated at reflux whilst stirring for 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (40 mL) at room temperature until neutralization. The mixture was extracted with EtOAc (three times), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The resulting residue was purified by silica gel flash chromatography (hexane/EtOAc, 70:30) to furnish *N*-benzyllactam **18** (0.81 g, 92%, corresponding to a 89% yield over two steps) as a white solid. M.p. 128.5–129.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.47 (m, 2 H), 7.34 (m, 6 H), 7.12 (d, J = 6.9 Hz, 2 H), 5.30 (1/2 ABq, J = 15.9 Hz, 1 H), 4.53 (t, J = 6.4 Hz, 1 H), 3.69 (s, 3 H), 3.67 (1/2 ABq, J = 15.9 Hz, 1 H), 2.25 (m, 2 H), 1.76 (m, 2 H), 1.00 (s, 9 H), 0.18 (s, 6 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 176.9 (C_q), 172.6 (C_q), 139.6 (C_q), 136.7 (C_q), 128.5 (2 C, CH), 128.2 (2 C, CH), 128.1 (CH), 127.1 (CH), 126.9 (2 C, CH), 126.1 (2 C, CH), 82.7 (C_q), 63.6 (CH), 52.5 (CH_3), 44.7 (CH_2), 29.8 (CH_2), 26.5 (3 C, CH_3), 20.5 (CH_2), 19.4 (C_q), –2.3 (CH_3), –2.5 (CH_3) ppm. $C_{26}H_{35}NO_4Si$ (453.65): calcd. C 68.84, H 7.78, N 3.09; found C 69.01, H 7.91, N 3.01.

(*R)-1-Benzyl-5-[(*S**)-2-(*tert*-butyldimethylsilyloxy)-1-hydroxy-1-phenylethyl]pyrrolidin-2-one (19):** The title compound was prepared from lactam **18** (810 mg, 1.79 mmol) according to the procedure described for the synthesis of compound **13**. Purification by silica gel flash chromatography (CH_2Cl_2/hexane, 70:30, to hexane/EtOAc, 60:40) furnished lactam **19** (0.65 g, 85% yield) as a white solid. M.p. 123.8–124.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.33 (m, 10 H), 5.35 (1/2 ABq, J = 14.6 Hz, 1 H), 4.51 (1/2 ABq, J = 14.6 Hz, 1 H), 4.01 (1/2 ABq, J = 9.8 Hz, 1 H), 3.88 (1/2 ABq, J = 9.8 Hz, 1 H), 3.82 (dd, J = 8.6, 1.4 Hz, 1 H), 3.23 (s, 1 H), 1.98 (m, 1 H), 1.7–1.9 (m, 2 H), 1.42 (m, 1 H), 0.80 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 176.5 (C_q), 139.6 (C_q), 137.2 (C_q), 128.5 (2 C, CH), 128.2 (2 C, CH), 128.1 (2 C, CH), 127.7 (CH), 127.2 (CH), 125.8 (2 C, CH), 79.0 (C_q), 66.5 (CH_2), 60.9 (CH), 46.8 (CH_2), 29.5 (CH_2), 25.5 (3 C, CH_3), 21.4 (CH_2), 17.9 (C_q), –5.6 (CH_3), –5.8 (CH_3) ppm. $C_{25}H_{35}NO_3Si$ (425.64): calcd. C 70.55, H 8.29, N 3.29; found C 70.43, H 8.34, N 3.35.

(*S)-2-[(*R**)-1-Benzyl-5-oxopyrrolidin-2-yl]-2-hydroxy-2-phenylacetaldehyde (20):** The title compound was prepared from lactam **19** (650 mg, 1.52 mmol) according to the two-step procedure described for the synthesis of compound **14**. After the first desilylative reaction, purification by silica gel flash chromatography (EtOAc/hexane, 70:30) furnished a diol intermediate (0.44 g, 94% yield) as a white solid. M.p. 190.0–191.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.2–7.5 (m, 10 H), 5.30 (1/2 ABq, J = 14.6 Hz, 1 H), 4.46 (1/2 ABq, J = 14.6 Hz, 1 H), 4.08 (br. d, J = 11.9 Hz, 1 H), 3.89 (dd, J = 11.1, 7.3 Hz, 1 H), 3.80 (dd, J = 8.7, 1.5 Hz, 1 H), 3.15 (br. s, 1 H), 2.21 (br. s, 1 H), 1.95 (m, 1 H), 1.5–1.9 (m, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 176.7 (C_q), 139.6 (C_q), 137.0 (C_q), 128.6 (2 C, CH), 128.5 (2 C, CH), 128.2 (2 C, CH), 128.1 (CH), 127.3 (CH), 126.1 (2 C, CH), 80.2 (C_q), 66.6 (CH_2), 61.2 (CH), 46.8 (CH_2), 29.5 (CH_2), 21.4 (CH_2) ppm.

After the second oxidative step, purification by silica gel flash chromatography (EtOAc/hexane, 50:50) furnished aldehyde **20** (0.36 g, 81% yield) as a colourless resin. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.62 (d, J = 1.1 Hz, 1 H), 7.3–7.5 (m, 8 H), 7.23 (d, J = 6.8 Hz, 2 H), 5.22 (1/2 ABq, J = 15.8 Hz, 1 H), 4.32 (t, J = 6.0 Hz, 1 H), 4.05 (d, J = 0.6 Hz, 1 H), 3.73 (1/2 ABq, J = 15.6 Hz, 1 H), 2.71 (dt, J = 16.9, 9.6 Hz, 1 H), 2.31 (dt, J = 16.9, 6.8 Hz, 1 H), 2.2–2.4 (m, 2 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 201.0 (CH), 177.0 (C_q), 135.5 (C_q), 135.4 (C_q), 129.1 (2 C, CH), 129.0 (2 C, CH), 128.4 (CH), 127.9 (CH), 127.8 (2 C, CH), 125.6 (2 C, CH), 84.3 (C_q), 60.8 (CH), 45.2 (CH_2), 29.7 (CH_2), 20.4 (CH_2) ppm. $C_{19}H_{19}NO_3$ (309.36): calcd. C 73.77, H 6.19, N 4.53; found C 73.90, H 6.25, N 4.48.

(1*R,4*S**,5*R**,6*S**)-2-Benzyl-5-(*tert*-butyldimethylsilyloxy)-6-hydroxy-6-phenyl-2-azabicyclo[2.2.1]heptan-3-one (21):** The title compound was prepared from aldehyde **20** (360 mg, 1.16 mmol) according to the procedure described for the synthesis of compound **15**. Purification by silica gel flash chromatography (hexane/EtOAc, 85:15) furnished bicycle **21** (300 mg, 61% yield) as a colourless resin. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 7.40 (dd, J = 7.8, 6.0 Hz, 2 H, Ph), 7.38 (dd, J = 7.8, 7.2 Hz, 2 H, Ph), 7.32 (t, J = 7.2 Hz, 1 H, Ph), 7.20 (m, 3 H, CH_2-*Ph*), 6.87 (d, J = 7.2 Hz, 2 H, CH_2-*Ph*), 4.59 (1/2 ABq, J = 15.0 Hz, 1 H, C*H*$_2$-Ph), 4.58 (m, 1 H, 5-H), 4.20 (s, 1 H, OH), 3.36 (q, J = 1.7 Hz, 1 H, 1-H), 2.76 (q, J = 1.3 Hz, 1 H, 4-H), 2.36 (br. d, J = 10.2 Hz, 1 H, 7-H$_{ax}$), 2.35 (1/2 ABq, J = 15.0 Hz, 1 H, C*H*$_2$-Ph), 1.96 (dq, J = 10.1, 1.7 Hz, 1 H, 7-H$_{eq}$), 0.87 (s, 9 H, *t*Bu), 0.15 (s, 3 H, Me), 0.04 (s, 3 H, Me) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 173.8 (C_q, C-3), 142.2 (C_q, Ph), 136.3 (C_q, Ph), 128.6 (2 C, CH, Ph), 128.5 (2 C, CH, Ph), 128.0 (2 C, CH, Ph), 127.8 (CH, Ph), 127.5 (CH, Ph), 126.2 (2 C, CH, Ph), 79.2 (C_q, C-6), 74.6 (CH, C-5), 67.7 (CH, C-1), 53.7 (CH, C-4), 45.5 (CH_2, *C*H$_2$Ph), 38.6 (CH_2, C-7), 25.7 (3 C, CH_3, *t*Bu), 18.0 (C_q, *t*Bu), –4.6 (CH_3, Me), –5.0 (CH_3, Me) ppm. $C_{25}H_{33}NO_3Si$ (423.62): calcd. C 70.88, H 7.85, N 3.31; found C 70.71, H 7.91, N 3.24.

Methyl (*S*)-2-[(*R*)-1-*tert*-Butoxycarbonyl-5-oxopyrrolidin-2-yl]-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyacetate (23): $BF_3{\cdot}OEt_2$ (2.6 mL, 20.64 mmol) was added to a solution of ketone **22** (2.59 g, 13.76 mmol) in dry CH_2Cl_2 (58 mL) under argon at –80 °C. After 15 min, a solution of silyloxypyrrole **5** (4.07 g, 13.76 mmol, dissolved in 5 mL of dry CH_2Cl_2) was added. After stirring at –80 °C for 24 h, pyridine (3.3 mL, 41.28 mmol) was added, and the reaction mixture was stirred for an additional 15 min. Water (50 mL) was added, and the temperature was allowed to reach an ambient value. The reaction mixture was extracted with CH_2Cl_2 (three times), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give an oily residue which was almost entirely used as such in the subsequent reductive reaction. A small portion of this crude residue, however, was purified by silica gel flash chromatography (hexane/EtOAc, 60:40) to furnish an unsaturated lactam intermediate as a colourless oil. $[\alpha]_D^{20}$ = +67.5 (c = 4.43, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.33 (dd, J = 6.4, 2.4 Hz, 1 H), 6.13 (dd, J = 6.0, 2.0 Hz, 1 H), 4.97 (t, J = 2.0 Hz, 1 H), 4.34 (dd, J = 6.8, 5.2 Hz, 1 H), 4.15 (dd, J = 8.4, 6.8 Hz, 1 H), 4.06 (dd, J = 9.2, 5.2 Hz, 1 H), 3.80 (s, 3 H), 3.64 (s, 1 H), 1.55 (s, 9 H), 1.43 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.2 (C_q), 168.3 (C_q), 150.9 (C_q), 147.7 (CH), 128.0 (CH), 109.8 (C_q), 83.8 (C_q), 78.5 (C_q), 78.1 (CH), 65.2 (CH_2), 64.1 (CH), 53.4 (CH_3), 27.9 (3 C, CH_3), 25.9 (CH_3), 24.4 (CH_3) ppm.

$NiCl_2{\cdot}6H_2O$ (408 mg, 1.72 mmol) was added to a stirred solution of the previous unsaturated intermediate (3.27 g, 8.80 mmol) dissolved in dry methanol (70 mL) at 0 °C whilst stirring. After 15 min, $NaBH_4$ (130 mg, 3.43 mmol) was added at the same temperature. After 30 min, two additional portions of $NaBH_4$ (2 × 65 mg, 2 × 1.72 mmol) were sequentially added to the reaction mixture over a period of 1 h. After 1 h, the mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with CH_2Cl_2 (three times). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give a crude residue which was purified by silica gel flash chromatography (hexane/EtOAc, 60:40). Pure lactam **23** was obtained (3.23 g, 63% over two steps) as a colourless oil. $[\alpha]_D^{20}$ = +32.6 (c = 3.21, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.52 (dd, J = 8.0, 1.2 Hz, 1 H), 4.37 (dd, J = 6.4, 5.2 Hz, 1 H), 4.15 (dd, J = 8.4, 7.2 Hz, 1 H), 4.00 (dd, J = 8.8, 5.2 Hz, 1 H), 3.82 (s, 3 H), 3.61 (s, 1 H), 2.47 (ddd, J = 18.4, 12.4, 8.8 Hz, 1 H), 2.35 (ddd, J = 17.6, 9.2, 2.0 Hz, 1 H), 2.13 (m, 2 H), 1.53 (s, 9 H), 1.41 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.0 (C_q), 173.9 (C_q), 151.1 (C_q), 109.5 (C_q), 83.6 (C_q), 78.7 (C_q), 77.5 (CH), 65.2 (CH_2), 59.7 (CH), 53.6 (CH_3), 31.8 (CH_2), 27.9 (3 C, CH_3), 25.9 (CH_3), 24.4 (CH_3), 20.1 (CH_2) ppm. $C_{17}H_{27}NO_8$ (373.40): calcd. C 54.68, H 7.29, N 3.75; found C 54.78, H 7.33, N 3.67.

Methyl (*S*)-2-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxy-2-[(*R*)-5-oxopyrrolidin-2-yl]acetate (24): Cerium(IV) ammonium nitrate (CAN) (525 mg, 0.96 mmol) was added in small portions to a stirred solution of lactam **23** (1.79 g, 4.79 mmol) in CH_3CN (200 mL) warmed to 80 °C. After stirring at 80 °C for 4 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ until complete neutralization and extracted with EtOAc (three times). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give a crude residue which was purified by silica gel flash chromatography (EtOAc/MeOH, 95:5) to furnish *N*-deprotected lactam **24** (1.45 g, 90%) as a white glassy solid. $[\alpha]_D^{20}$ = +22.1 (c = 2.22, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.94 (br. s, 1 H), 4.24 (t, J = 6.0 Hz, 1 H), 4.14 (br. dd, J = 7.2, 4.8 Hz, 1 H), 4.07 (dd, J = 8.8, 6.8 Hz, 1 H), 3.96 (dd, J = 8.8, 6.0 Hz, 1 H), 3.86 (s, 3 H), 3.85 (s, 1 H), 2.43 (m, 1 H), 2.3–2.1 (m, 3 H), 1.38 (s, 3 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 180.0 (C_q), 173.5 (C_q), 109.8 (C_q), 79.8 (C_q), 77.2 (CH), 65.0 (CH_2), 57.6 (CH), 53.4 (CH_3), 30.0 (CH_2), 25.8 (CH_3), 24.8 (CH_3), 21.0 (CH_2) ppm. $C_{12}H_{19}NO_6$ (273.28): calcd. C 52.74, H 7.01, N 5.13; found C 52.85, H 7.13, N 5.09.

Methyl (*S*)-2-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-hydroxy-2-[(*R*)-1-(4-methoxybenzyl)-5-oxopyrrolidin-2-yl]acetate (25): NaH (60% dispersion in mineral oil, 318 mg, 7.96 mmol) was added to a stirred solution of the *N*-deprotected lactam **24** (1.45 g, 5.30 mmol) in anhydrous THF (150 mL) under argon at room temperature. After 30 min, *p*-methoxybenzyl bromide (PMBBr, 0.92 mL, 6.36 mmol) was added. After being warmed at 45 °C for 3 h, the reaction mixture was quenched with saturated aqueous NH_4Cl at room temperature until neutralization. The mixture was diluted with H_2O and extracted with EtOAc (three times). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to leave a residue which was purified by silica gel flash chromatography (EtOAc/MeOH, 90:10) to furnish lactam **25** (1.42 g, 68%) as a colourless oil. $[\alpha]_D^{20}$ = –20.0 (c = 7.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.06 (d, J = 8.8 Hz, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 5.12 (1/2 ABq, J = 15.6 Hz, 1 H), 4.31 (t, J = 6.4 Hz, 1 H), 4.00 (dd, J = 8.8, 7.2 Hz, 1 H), 3.94 (dd, J = 8.4, 2.0 Hz, 1 H), 3.89 (dd, J = 8.8, 6.4 Hz, 1 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.67 (1/2 ABq, J = 15.6 Hz, 1 H), 3.48 (s, 1 H), 2.58 (dt, J = 16.8, 9.6 Hz, 1 H), 2.30 (ddd, J = 16.8, 9.6, 2.4 Hz, 1 H), 2.13 (m, 1 H), 1.99 (dq, J = 13.6, 10.8 Hz, 1 H), 1.36 (s, 3 H), 1.30 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 176.8 (C_q),

173.6 (C_q), 158.9 (C_q), 129.0 (C_q), 128.5 (2 C, CH), 113.9 (2 C, CH), 109.4 (C_q), 78.9 (C_q), 77.5 (CH), 64.8 (CH_2), 59.7 (CH), 55.2 (CH_3), 53.2 (CH_3), 44.6 (CH_2), 29.9 (CH_2), 25.8 (CH_3), 24.8 (CH_3), 21.2 (CH_2) ppm. $C_{20}H_{27}NO_7$ (393.43): calcd. C 61.06, H 6.92, N 3.56; found C 60.90, H 7.00, N 3.49.

Methyl (2*S*,3*S*)-2-Hydroxy-2-[(*R*)-1-(4-methoxybenzyl)-5-oxopyrrolidin-2-yl]-3,4-bis(triethylsilyloxy)butanoate (26): Lactam **25** (1.25 g, 3.18 mmol) was dissolved in 80% aqueous acetic acid (13.6 mL), and the resulting mixture was warmed to 80 °C whilst stirring. After 3 h, the reaction mixture was concentrated under vacuum to leave a crude residue which was purified by silica gel flash chromatography (EtOAc/MeOH, 90:10) to furnish a triol intermediate (876 mg, 78%) as a glassy solid. $[\alpha]_D^{20}$ = –43.3 (*c* = 4.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.05 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 5.11 (1/2 ABq, *J* = 15.6 Hz, 1 H), 4.19 (dd, *J* = 8.4, 2.0 Hz, 1 H), 3.90–3.84 (m, 2 H), 3.79 (s, 6 H), 3.74 (t, *J* = 3.2 Hz, 1 H), 3.48 (1/2 ABq, *J* = 15.6 Hz, 1 H), 3.18 (br. s, 1 H), 2.63 (dt, *J* = 16.4, 10.0 Hz, 1 H), 2.42 (br. s, 1 H), 2.29 (ddd, *J* = 16.8, 10.0, 2.4 Hz, 1 H), 2.22 (m, 1 H), 2.06 (m, 1 H), 1.78 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 177.6 (C_q), 175.06 (C_q), 159.0 (C_q), 128.5 (2 C, CH), 128.3 (C_q), 114.0 (2 C, CH), 79.3 (C_q), 73.8 (CH), 61.9 (CH_2), 60.3 (CH), 55.2 (CH_3), 53.3 (CH_3), 44.4 (CH_2), 30.1 (CH_2), 21.1 (CH_2) ppm.

The above triol intermediate (876 mg, 2.48 mmol) was dissolved in anhydrous pyridine (8.1 mL) at room temperature under argon, and triethylsilyl trifluoromethanesulfonate (TESOTf, 1.68 mL, 7.44 mmol) and 4-(dimethylamino)pyridine (DMAP, 46 mg, 0.37 mmol) were sequentially added whilst stirring. After 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl until neutralization and extracted with CH_2Cl_2 (twice) and EtOAc (twice). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give a crude residue which was purified by silica gel flash chromatography (hexane/EtOAc, 70:30). Pure lactam **26** was obtained (1.24 g, 86% yield) as a colourless oil. $[\alpha]_D^{20}$ = –19.8 (*c* = 6.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.08 (d, *J* = 8.4 Hz, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 5.07 (1/2 ABq, *J* = 15.2 Hz, 1 H), 4.20 (br. d, *J* = 8.8 Hz, 1 H), 3.97 (dd, *J* = 5.6, 5.2 Hz, 1 H), 3.79 (s, 3 H), 3.73 (s, 3 H), 3.72 (s, 1 H), 3.61 (dd, *J* = 10.4, 4.4 Hz, 1 H), 3.56 (1/2 ABq, *J* = 15.2 Hz, 1 H), 3.43 (dd, *J* = 10.0, 6.0 Hz, 1 H), 2.65 (dt, *J* = 17.2, 9.2 Hz, 1 H), 2.26 (m, 2 H), 1.93 (m, 1 H), 1.0–0.8 (m, 18 H), 0.56 (m, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 177.4 (C_q), 174.5 (C_q), 158.8 (C_q), 129.0 (C_q), 128.5 (2 C, CH), 113.8 (2 C, CH), 80.1 (C_q), 75.7 (CH), 64.0 (CH_2), 59.8 (CH), 55.2 (CH_3), 52.5 (CH_3), 44.5 (CH_2), 30.2 (CH_2), 21.6 (CH_2), 6.7 (3 C, CH_3), 6.6 (3 C, CH_3), 5.2 (3 C, CH_2), 4.1 (3 C, CH_2) ppm. $C_{29}H_{51}NO_7Si_2$ (581.89): calcd. C 59.86, H 8.83, N 2.41; found C 59.78, H 8.90, N 2.43.

Methyl (2*S*,3*R*)-3-Formyl-2-hydroxy-2-[(*R*)-1-(4-methoxybenzyl)-5-oxopyrrolidin-2-yl]-3-(triethylsilyloxy)propanoate (27): Dimethyl sulfoxide (DMSO, 1.51 mL, 21.30 mmol) was added dropwise to a stirred solution of oxalyl chloride (2.0 M in CH_2Cl_2, 5.3 mL, 10.65 mmol) in dry CH_2Cl_2 (45 mL) at –80 °C under argon. After 1 h, a solution of the lactam **26** (1.24 g, 2.13 mmol) in dry CH_2Cl_2 (45 mL) was added dropwise at the same temperature. After 2.5 h, the reaction mixture was warmed to –35 °C and stirred for an additional 1.5 h. The reaction mixture was cooled again to –80 °C, and Et_3N (4.45 mL, 31.95 mmol) was slowly added. After 40 min at –80 °C, the reaction mixture was warmed to 25 °C, quenched with brine (100 mL) and extracted with EtOAc (three times). The collected organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude residue which was purified by silica gel flash chromatography (hexane/EtOAc, 70:30) to furnish aldehyde **27** (0.77 g, 78% yield) as a glassy solid. $[\alpha]_D^{20}$ = –5.8 (*c* = 1.85, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.55 (d, *J* = 2.4 Hz, 1 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 4.97 (1/2 ABq, *J* = 15.2 Hz, 1 H), 4.20 (d, *J* = 2.0 Hz, 1 H), 3.96 (1/2 ABq, *J* = 14.8 Hz, 1 H), 3.94 (d, *J* = 4.8 Hz, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.75 (s, 1 H), 2.45 (dt, *J* = 17.2, 10.4 Hz, 1 H), 2.54 (ddd, *J* = 16.8, 10.0, 1.2 Hz, 1 H), 2.17 (m, 1 H), 2.00 (m, 1 H), 0.88 (t, *J* = 8.0 Hz, 9 H), 0.53 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 201.0 (C_q), 177.4 (C_q), 172.5 (C_q), 158.9 (C_q), 130.0 (C_q), 129.0 (2 C, CH), 113.9 (2 C, CH), 81.5 (C_q), 78.3 (CH), 60.0 (CH), 55.2 (CH_3), 53.3 (CH_3), 45.6 (CH_2), 29.6 (CH_2), 21.5 (CH_2), 6.5 (3 C, CH_3), 4.6 (3 C, CH_2) ppm. $C_{23}H_{35}NO_7Si$ (465.61): calcd. C 59.33, H 7.58, N 3.01; found C 59.45, H 7.62, N 2.93.

Methyl (1*S*,2*S*,3*S*,4*S*,5*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-6-(4-methoxybenzyl)-7-oxo-3-(triethylsilyloxy)-6-azabicyclo[3.2.1]-octane-4-carboxylate (28): The title compound was prepared from aldehyde **27** (704 mg, 1.51 mmol) according to the procedure described for the synthesis of compound **15**. Purification by silica gel flash chromatography (hexane/EtOAc, 70:30) furnished bicycle **28** (613 mg, 75% yield) as a white solid. M.p. 57–60 °C. $[\alpha]_D^{20}$ = –26.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 7.18 (d, *J* = 8.4 Hz, 2 H, Ar), 6.81 (d, *J* = 8.4 Hz, 2 H, Ar), 5.01 (1/2 ABq, *J* = 15.0 Hz, 1 H, CH_2Ar), 4.43 (m, 1 H, 3-H), 4.15 (t, *J* = 2.4 Hz, 1 H, 2-H), 3.88 (1/2 ABq, *J* = 14.4 Hz, 1 H, CH_2Ar), 3.77 (s, 3 H, OMe), 3.76 (s, 3 H, CO_2Me), 3.67 (s, 1 H, OH), 3.59 (dd, *J* = 5.4 Hz, 1 H, 5-H), 2.44 (m, 1 H, 1-H), 1.97 (dt, *J* = 12.0, 5.4 Hz, 1 H, 8-H_{eq}), 1.40 (d, *J* = 12.0 Hz, 1 H, 8-H_{ax}), 0.97 (m, 9 H, $SiCH_2CH_3$), 0.96 (s, 9 H, *t*Bu), 0.70 (m, 6 H, $SiCH_2CH_3$), 0.15 (s, 6 H, Me) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 173.5 (C_q, C-7), 170.9 (C_q, CO_2Me), 158.6 (C_q, Ar), 129.4 (2 C, CH, Ar), 129.1 (C_q, Ar), 113.6 (2 C, CH, Ar), 77.4 (C_q, C-4), 74.8 (CH, C-3), 71.1 (CH, C-2), 58.9 (CH, C-5), 54.9 (CH_3, OMe), 52.4 (CH_3, CO_2Me), 45.8 (CH_2, CH_2Ar), 44.6 (CH, C-1), 31.9 (CH_2, C8), 26.0 (3 C, CH_3, *t*Bu), 18.3 (C_q, *t*Bu), 6.5 (3 C, CH_3, $SiCH_2CH_3$), 4.6 (3 C, CH_2, $SiCH_2CH_3$), –4.2 (CH_3, Me), –4.0 (CH_3, Me) ppm. $C_{29}H_{49}NO_7Si_2$ (579.87): calcd. C 60.07, H 8.52, N 2.42; found C 59.91, H 8.59, N 2.37.

(*S*)-1-(*tert*-Butoxycarbonyl)-5-{(*R*)-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl](phenyl)(trimethylsilyloxy)methyl}pyrrolidin-2-one (31): Trimethylsilyl trifluoromethanesulfonate (TMSOTf, 2.63 mL, 14.55 mmol) was added to a solution of ketone **29** (1.0 g, 4.85 mmol) in dry CH_2Cl_2 (30 mL) under argon at –80 °C. After 5 min, a solution of silyloxypyrrole **5** (2.88 g, 9.70 mmol, dissolved in 10 mL of dry CH_2Cl_2) and 2,6-lutidine (1.13 mL, 9.70 mmol) were sequentially added. After stirring at –80 °C for 4 h, pyridine (9.70 mL, 0.78 mmol) was added, and the reaction mixture was stirred for an additional 15 min. Brine (100 mL) was added, and the temperature was allowed to reach an ambient value. The reaction mixture was extracted with CH_2Cl_2 (three times), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give an oily residue which was almost entirely used as such in the subsequent reductive reaction. A small portion of this crude residue, however, was purified by silica gel flash chromatography (hexane/EtOAc, 80:20) to furnish unsaturated lactam **30** as white crystals. M.p. 118–122 °C. $[\alpha]_D^{20}$ = –132.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.49 (m, 2 H), 7.30 (m, 3 H), 6.77 (dd, *J* = 6.1, 2.1 Hz, 1 H), 5.68 (dd, *J* = 6.1, 1.2 Hz, 1 H), 5.32 (t, *J* = 1.8 Hz, 1 H), 4.72 (dd, *J* = 7.4, 5.9 Hz, 1 H), 4.33 (dd, *J* = 9.0, 5.9 Hz, 1 H), 4.10 (dd, *J* = 9.0, 7.6 Hz, 1 H), 1.63 (s, 9 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 0.04 (s, 9 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 170.0 (C_q), 150.7 (C_q), 150.2 (CH), 141.2 (C_q), 128.6 (CH), 127.8 (2 C, CH), 127.7 (2 C, CH), 125.6 (2 C, CH),

110.0 (C_q), 82.5 (C_q), 80.6 (C_q), 79.4 (CH), 65.9 (CH_2), 65.6 (CH), 27.9 (3 C, CH_3), 25.4 (CH_3), 23.7 (CH_3), 1.83 (3 C, CH_3) ppm.

Palladium on carbon (30 mg) was added to a solution of the above crude residue in anhydrous EtOAc (30 mL) at room temperature. The reaction vessel was degassed under vacuum and thoroughly purged with hydrogen (three times). The resulting heterogeneous mixture was stirred under hydrogen for 12 h, after which time the hydrogen was evacuated, the catalyst filtered off and the filtrate concentrated under vacuum to give a crude residue which was purified by silica gel flash chromatography (hexane/EtOAc, 70:30) to furnish pure lactam **31** (1.57 g, 70% for two steps) as a colourless oil. $[\alpha]_D^{20}$ = –64.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.52 (m, 2 H), 7.33 (m, 3 H), 4.80 (br. d, *J* = 8.5 Hz, 1 H), 4.49 (dd, *J* = 7.0, 5.7 Hz, 1 H), 4.19 (dd, *J* = 9.3, 5.7 Hz, 1 H), 4.12 (dd, *J* = 9.2, 7.5 Hz, 1 H), 1.7–2.1 (m, 4 H), 1.61 (s, 9 H), 1.34 (s, 3 H), 1.17 (s, 3 H), 0.12 (s, 9 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 175.0 (C_q), 151.1 (C_q), 141.0 (C_q), 127.5 (2 C, CH), 127.4 (CH), 127.1 (2 C, CH), 109.4 (C_q), 82.9 (C_q), 82.4 (C_q), 79.2 (CH), 65.9 (CH_2), 60.3 (CH), 31.6 (CH_2), 27.8 (3 C, CH_3), 25.3 (CH_3), 23.8 (CH_3), 21.3 (CH_2), 2.14 (3 C, CH_3) ppm. $C_{24}H_{37}NO_6Si$ (463.64): calcd. C 62.17, H 8.04, N 3.02; found C 62.09, H 8.11, N 2.95.

(*S*)-5-{(*R*)-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl](phenyl)(trimethylsilyloxy)methyl}pyrrolidin-2-one (32): The title compound was prepared from lactam **31** (1.50 g, 3.23 mmol) according to the procedure described for the synthesis of compound **24**. Purification by silica gel flash chromatography (hexane/EtOAc, 20:80) furnished lactam **32** (1.17 g, quantitative) as a colourless oil. $[\alpha]_D^{20}$ = –23.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.33 (m, 5 H), 6.45 (br. s, 1 H), 4.57 (t, *J* = 7.8 Hz, 1 H), 4.24 (t, *J* = 7.5 Hz, 1 H), 3.68 (t, *J* = 8.1 Hz, 1 H), 3.54 (dd, *J* = 8.1, 7.0 Hz, 1 H), 2.18 (dt, *J* = 17.2, 9.3 Hz, 1 H), 2.00 (ddd, *J* = 17.2, 8.0, 5.8 Hz, 1 H), 1.67 (m, 2 H), 1.52 (s, 3 H), 1.38 (s, 3 H), 0.25 (s, 9 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 177.6 (C_q), 140.5 (C_q), 128.1 (2 C, CH), 127.5 (CH), 125.3 (2 C, CH), 110.0 (C_q), 81.6 (CH), 79.5 (C_q), 65.0 (CH_2), 61.3 (CH), 29.2 (CH_2), 26.0 (CH_3), 24.6 (CH_3), 22.1 (CH_2), 2.69 (3 C, CH_3) ppm. $C_{19}H_{29}NO_4Si$ (363.52): calcd. C 62.78, H 8.04, N 3.85; found C 62.85, H 7.99, N 3.77.

(*S*)-5-{(*R*)-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl](phenyl)(trimethylsilyloxy)methyl}-1-(4-methoxybenzyl)pyrrolidin-2-one (33): The title compound was prepared from lactam **32** (1.00 g, 2.75 mmol) according to the procedure described for the synthesis of compound **25**. Purification by silica gel flash chromatography (hexane/EtOAc, 80:20) furnished lactam **33** (1.31 g, 99% yield) as white crystals. M.p. 85–87 °C. $[\alpha]_D^{20}$ = +34.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.61 (m, 2 H), 7.35 (m, 3 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 5.35 (1/2 ABq, *J* = 14.4 Hz, 1 H), 4.66 (t, *J* = 6.6 Hz, 1 H), 4.50 (1/2 ABq, *J* = 14.4 Hz, 1 H), 4.07 (dd, *J* = 9.0, 7.2 Hz, 1 H), 3.99 (dd, *J* = 9.0, 6.3 Hz, 1 H), 3.88 (br. d, *J* = 8.7 Hz, 1 H), 3.84 (s, 3 H), 1.97 (m, 1 H), 1.73 (m, 2 H), 1.41 (s, 3 H), 1.37 (s, 3 H), 0.92 (m, 1 H), 0.27 (s, 9 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 177.2 (C_q), 158.6 (C_q), 141.0 (C_q), 129.3 (2 C, CH), 129.2 (C_q), 127.8 (CH), 127.6 (2 C, CH), 127.0 (2 C, CH), 113.7 (2 C, CH), 109.9 (C_q), 82.6 (C_q), 79.8 (CH), 66.1 (CH_2), 59.3 (CH), 54.9 (CH_3), 46.1 (CH_2), 29.0 (CH_2), 25.5 (CH_3), 23.7 (CH_3), 22.6 (CH_2), 2.13 (3 C, CH_3) ppm. $C_{27}H_{37}NO_5Si$ (483.67): calcd. C 67.05, H 7.71, N 2.90; found C 66.89, H 7.80, N 2.85.

(*S*)-5-[(1*R*,2*R*)-1-Hydroxy-1-phenyl-2,3-bis(triethylsilyloxy)propyl]-1-(4-methoxybenzyl)pyrrolidin-2-one (34): The title compound was prepared from lactam **33** (1.20 g, 2.48 mmol) according to the two-step procedure described for the synthesis of compound **26**. After the first acidic deprotection, purification by silica gel flash chromatography (EtOAc/MeOH, 98:2) furnished a triol intermediate (0.73 g, 80% yield) as a white foam. $[\alpha]_D^{20}$ = +42.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.30 (m, 5 H), 7.17 (d, *J* = 8.6 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 5.05 (1/2 ABq, *J* = 14.5 Hz, 1 H), 4.50 (1/2 ABq, *J* = 14.5 Hz, 1 H), 4.23 (m, 1 H), 4.08 (dd, *J* = 5.9, 2.1 Hz, 1 H), 4.07–3.90 (br. s, 3 H), 3.78 (s, 3 H), 3.54 (m, 2 H), 1.84 (m, 3 H), 1.44 (m, 1 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 176.9 (C_q), 158.5 (C_q), 138.8 (C_q), 129.2 (2 C, CH), 128.8 (C_q), 127.9 (2 C, CH), 127.5 (CH), 125.7 (2 C, CH), 113.7 (2 C, CH), 81.6 (C_q), 71.9 (CH), 63.0 (CH_2), 62.3 (CH), 54.9 (CH_3), 45.9 (CH_2), 29.4 (CH_2), 20.7 (CH_2) ppm.

After the second silylative step, purification by silica gel flash chromatography (hexane/EtOAc, 60:40) furnished lactam **34** (1.07 g, 90% yield) as a colourless oil. $[\alpha]_D^{20}$ = +21.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.37 (m, 5 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 5.23 (1/2 ABq, *J* = 14.2 Hz, 1 H), 4.48 (1/2 ABq, *J* = 14.1 Hz, 1 H), 4.39 (dd, *J* = 6.0, 1.7 Hz, 1 H), 4.00 (m, 1 H), 3.80 (s, 3 H), 3.67 (dd, *J* = 11.0, 1.7 Hz, 1 H), 3.53 (dd, *J* = 11.0, 6.0 Hz, 1 H), 3.33 (s, 1 H), 2.00–1.75 (m, 3 H), 1.24 (m, 1 H), 0.85 (m, 18 H), 0.7–0.4 (m, 12 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 175.7 (C_q), 158.6 (C_q), 137.9 (C_q), 129.2 (2 C, CH), 129.1 (C_q), 127.7 (2 C, CH), 127.5 (CH), 126.1 (2 C, CH), 113.7 (2 C, CH), 82.0 (C_q), 75.9 (CH), 65.0 (CH_2), 60.8 (CH), 54.8 (CH_3), 46.1 (CH_2), 28.9 (CH_2), 20.6 (CH_2), 6.4 (3 C, CH_3), 6.2 (3 C, CH_3), 5.5 (3 C, CH_2), 3.6 (3 C, CH_2) ppm. $C_{33}H_{53}NO_5Si_2$ (599.95): calcd. C 66.06, H 8.90, N 2.33; found C 66.00, H 8.96, N 2.37.

(2*S*,3*R*)-3-Hydroxy-3-[(*S*)-1-(4-methoxybenzyl)-5-oxopyrrolidin-2-yl]-3-phenyl-2-(triethylsilyloxy)propanal (35): The title compound was prepared from lactam **34** (1.0 g, 1.66 mmol) according to the procedure described for the synthesis of compound **27**. Purification by silica gel flash chromatography (hexane/EtOAc, 60:40) furnished aldehyde **35** (0.68 g, 85% yield) as a colourless oil. $[\alpha]_D^{20}$ = +2.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.38 (d, *J* = 2.6 Hz, 1 H), 7.45 (m, 5 H), 7.19 (d, *J* = 8.5 Hz, 2 H), 6.90 (d, *J* = 8.5 Hz, 2 H), 5.30 (1/2 ABq, *J* = 14.2 Hz, 1 H), 4.61 (d, *J* = 2.6 Hz, 1 H), 4.43 (1/2 ABq, *J* = 14.3 Hz, 1 H), 3.92 (dd, *J* = 5.6, 1.6 Hz, 1 H), 3.82 (s, 3 H), 3.21 (s, 1 H), 1.93 (m, 2 H), 1.42 (m, 2 H), 0.84 (m, 9 H), 0.7–0.3 (m, 6 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 198.7 (CH), 175.9 (C_q), 158.7 (C_q), 135.1 (C_q), 129.1 (2 C, CH), 128.6 (CH), 128.3 (C_q), 128.1 (2 C, CH), 126.3 (2 C, CH), 113.9 (2 C, CH), 80.8 (C_q), 78.1 (CH), 60.2 (CH), 54.9 (CH_3), 46.3 (CH_2), 28.8 (CH_2), 20.9 (CH_2), 6.1 (3 C, CH_3), 4.3 (3 C, CH_2) ppm. $C_{27}H_{37}NO_5Si$ (483.67): calcd. C 67.05, H 7.71, N 2.90; found C 67.19, H 7.79, N 2.83.

(1*R*,2*S*,3*R*,4*R*,5*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-hydroxy-6-(4-methoxybenzyl)-4-phenyl-3-(triethylsilyloxy)-6-azabicyclo[3.2.1]-octan-7-one (36): The title compound was prepared from aldehyde **35** (650 mg, 1.34 mmol) according to the procedure described for the synthesis of compound **15**. Purification by silica gel flash chromatography (hexane/EtOAc, 90:10 to 60:40) furnished bicycle **36** (570 mg, 72% yield) as white crystals. M.p. 140–142 °C. $[\alpha]_D^{20}$ = +35.2 (*c* = 1.0, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 7.49 (m, 2 H, Ph), 7.37 (m, 2 H, Ph), 7.34 (m, 1 H, Ph), 7.01 (d, *J* = 8.4 Hz, 2 H, Ar), 6.88 (d, *J* = 8.4 Hz, 2 H, Ar), 4.97 (1/2 ABq, *J* = 15.6 Hz, 1 H, CH_2Ar), 4.36 (m, 1 H, 3-H), 4.22 (m, 1 H, 2-H), 4.10 (m, 2 H, 5-H, OH), 3.83 (s, 3 H, OMe), 3.32 (1/2 ABq, *J* = 15.6 Hz, 1 H, CH_2Ar), 2.80 (d, *J* = 12.0 Hz, 1 H, 8-H_{ax}), 2.76 (t, *J* = 4.2 Hz, 1 H, 1-H), 2.09 (dt, *J* = 12.0, 4.8 Hz, 1 H, 8-H_{eq}), 0.96 (s, 9 H, *t*Bu), 0.85 (m, 9 H, $SiCH_2CH_3$), 0.57 (m, 6 H, $SiCH_2CH_3$), 0.24 (s, 3 H, CH_3), 0.21 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz,

$CDCl_3$, 25 °C): δ = 173.8 (C_q, C-7), 158.5 (C_q, Ar), 141.9 (C_q, Ph), 128.9 (C_q, Ar), 128.4 (2 C, CH, Ph), 127.6 (2 C, CH, Ar), 127.5 (CH, Ph), 126.8 (2 C, CH, Ph), 113.7 (2 C, CH, Ar), 77.7 (CH, C-3), 73.4 (C_q, C-4), 71.5 (CH, C-2), 59.3 (CH, C-5), 54.9 (CH_3, OMe), 45.9 (CH, C-1), 44.0 (CH_2, *C*H_2Ar), 28.5 (CH_2, C-8), 25.3 (3 C, CH_3, *t*Bu), 17.5 (C_q, *t*Bu), 6.43 (3 C, CH_3, SiCH_2*C*H_3), 4.70 (3 C, CH_2, Si*C*H_2CH$_3$), –4.6 (CH_3, Me), –4.8 (CH_3, Me) ppm. $C_{33}H_{51}NO_5Si_2$ (597.93): calcd. C 66.29, H 8.60, N 2.34; found C 66.15, H 8.68, N 2.30.

(1*R,4*S**,5*S**,6*R**)-2-(*tert*-Butoxycarbonyl)-5-(*tert*-butyldimethylsilyloxy)-6-hydroxy-6-methyl-2-azabicyclo[2.2.1]heptan-3-one (37):** Anhydrous ammonia (10 mL) was condensed into a two-necked flask containing a solution of bicycle **15** (250 mg, 0.69 mmol) in anhydrous THF (20 mL) maintained at –78 °C. Sodium metal was added to the mixture until a blue colour persisted. The reaction mixture was stirred at –78 °C for 1 h and quenched by addition of solid NH_4Cl (300 mg). The ammonia was evaporated, the mixture was warmed to room temperature and the residue treated with MeOH and a saturated aqueous NH_4Cl solution (until complete neutralization), and extracted with EtOAc (three times). The organic extracts were dried ($MgSO_4$), filtered and concentrated under vacuum to give an *N*-deprotected bicyclic intermediate (180 mg, 98%) as a colourless resin. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 5.69 (br. s, 1 H), 3.96 (d, *J* = 4.2 Hz, 1 H), 3.61 (br. s, 1 H), 3.49 (m, 1 H), 2.75 (m, 1 H), 2.0 (dt, *J* = 10.8, 1.9 Hz, 1 H), 1.61 (dq, *J* = 10.8, 0.9 Hz, 1 H), 1.27 (s, 3 H), 0.95 (s, 9 H), 0.20 (s, 3 H), 0.17 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 176.7 (C_q), 84.8 (C_q), 73.6 (CH), 62.4 (CH), 51.8 (CH), 34.5 (CH_2), 26.0 (CH_3), 25.7 (3 C, CH_3), 18.1 (C_q), –4.7 (CH_3), –5.1 (CH_3) ppm.

Di-*tert*-butyl dicarbonate (240 mg, 1.10 mmol) and 4-(dimethylamino)pyridine (DMAP, 13.4 mg, 0.11 mmol) were sequentially added to a solution of the previous *N*-deprotected bicyclic intermediate (150 mg, 0.55 mmol) in dry MeCN (20 mL) at room temperature under argon. After stirring at room temperature for 12 h, the solvent was evaporated under reduced pressure, and the crude residue was purified by silica gel flash chromatography (hexanes/EtOAc, 70:30) to furnish bicyclic compound **37** (170 mg, 86%) as a glassy solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.24 (m, 1 H), 3.89 (d, *J* = 4.0 Hz, 1 H), 3.54 (s, 1 H), 2.84 (m, 1 H), 1.96 (dt, *J* = 11.1, 2.1 Hz, 1 H), 1.59 (s, 3 H), 1.52 (dt, *J* = 11.0, 0.6 Hz, 1 H), 1.50 (s, 9 H), 0.92 (s, 9 H), 0.18 (s, 3 H), 0.14 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 173.0 (C_q), 153.8 (C_q), 82.2 (C_q), 75.6 (C_q), 73.3 (CH), 65.3 (CH), 53.5 (CH), 31.9 (CH_2), 28.0 (3 C, CH_3), 26.1 (CH_3), 25.7 (3 C, CH_3), 17.8 (C_q), –4.7 (CH_3), –5.1 (CH_3) ppm. $C_{18}H_{33}NO_5Si$ (371.54): calcd. C 58.19, H 8.95, N 3.77; found C 58.03, H 9.01, N 3.70.

(1*S,2*S**,3*R**,4*R**)-4-Amino-2,3-dihydroxy-3-methylcyclopentanecarboxylic Acid (38):** Bicyclic lactam **37** (150 mg, 0.40 mmol) was dissolved in THF (8 mL) and H_2O (4 mL), and the resulting mixture was treated with LiOH (57.6 mg, 2.40 mmol). After 3 h, the reaction mixture was quenched with a 1 N aqueous HCl solution (until pH = 2) and extracted with EtOAc (five times). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give an oily residue which was purified by silica gel flash chromatography (EtOAc/MeOH/AcOH, 8:2:1) to furnish a protected cyclopentanecarboxylic acid intermediate (99 mg, 90% yield) as a colourless resin. ^{1}H NMR (300 MHz, D_2O, 25 °C): δ = 4.01 (d, *J* = 8.3 Hz, 1 H), 3.60 (m, 1 H), 3.06 (q, *J* = 8.5 Hz, 1 H), 2.13 (m, 1 H), 1.85 (dt, *J* = 13.4, 8.9 Hz, 1 H), 1.33 (s, 9 H), 1.13 (s, 3 H) ppm.

The above cyclopentanecarboxylic acid intermediate (95 mg, 0.34 mmol) was treated with a 3 N aqueous HCl solution (5 mL) at room temperature. After stirring at this temperature for 2 h, the reaction mixture was concentrated under reduced pressure to give a mixture (67 mg, glassy solid) of amino acid **38** (64%, corresponding to a 58% yield for two steps, as the hydrochloride salt) and its γ-lactone form (**38**-γ-lactone) (32%, as the hydrochloride salt). ^{1}H NMR (300 MHz, D_2O, 25 °C): δ = 4.07 (d, *J* = 5.7 Hz, 1 H, 2-H-γ-lactone), 4.01 (d, *J* = 6.2 Hz, 1 H, 2-H), 3.2–3.4 (m, 2 H, 4-H, 4-H-γ-lactone), 3.11 (td, *J* = 8.9, 6.2 Hz, 1 H, 1-H), 2.70 (td, *J* = 8.8, 5.6 Hz, 1 H, 1-H-γ-lactone), 2.34 (dt, *J* = 14.0, 8.6 Hz, 1 H, 5a-H-γ-lactone), 2.27 (dt, *J* = 14.6, 8.3 Hz, 1 H, 5a-H), 2.10 (ddd, *J* = 14.4, 8.7, 6.4 Hz, 1 H, 5b-H), 1.92 (dt, *J* = 13.8, 8.6 Hz, 1 H, 5b-H-γ-lactone), 1.21 (s, 3 H, Me), 1.20 (s, 3 H, Me-γ-lactone) ppm. ^{13}C NMR (75.4 MHz, D_2O, 25 °C): δ = 180.2 (C_q, COOH), 178.1 (C_q, CO-γ-lactone), 83.9 (CH, C-2-γ-lactone), 80.5 (CH, C-2), 79.3 (C_q, C-3-γ-lactone), 77.2 (C_q, C-3), 59.5 (CH, C-4), 59.0 (CH, C-4-γ-lactone), 50.9 (CH, C-1-γ-lactone), 48.4 (CH, C-1), 31.5 (CH_2, C-5), 31.3 (CH_2, C-5-γ-lactone), 25.9 (CH_3, Me), 22.5 (CH_3, Me-γ-lactone) ppm. HRMS (positive ESI): calcd. for $C_7H_{14}NO_4$ [M + H]$^+$ 176.0923; found 176.0907 (158.0815 for the γ-lactone form).

(1*S*,2*S*,3*R*,4*R*,5*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-6-(4-methoxybenzyl)-4-phenyl-4-(triethylsilyloxy)-6-azabicyclo[3.2.1]-octane (39): Bicyclic lactam **36** (500 mg, 0.83 mmol) was dissolved in anhydrous pyridine (20 mL) at room temperature under argon, and triethylsilyl trifluoromethanesulfonate (TESOTf, 0.94 mL, 4.15 mmol) and 4-(dimethylamino)pyridine (DMAP, 20.3 mg, 0.16 mmol) were sequentially added whilst stirring. After 24 h, the reaction mixture was concentrated under vacuum, and toluene (50 mL) was added. The solution was concentrated, and the resulting crude residue was purified by silica gel flash chromatography (hexane/EtOAc, 95:5). A fully protected bicyclic lactam was obtained (530 mg, 90% yield) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.30 (m, 5 H), 7.12 (d, *J* = 8.3 Hz, 2 H), 6.95 (d, *J* = 8.6 Hz, 2 H), 5.00 (1/2 ABq, *J* = 16.4 Hz, 1 H), 4.43 (m, 1 H), 4.18 (br. d, *J* = 4.7 Hz, 1 H), 4.12 (m, 1 H), 3.84 (s, 3 H), 3.35 (1/2 ABq, *J* = 16.1 Hz, 1 H), 3.10 (d, *J* = 11.0 Hz, 1 H), 2.66 (m, 1 H), 2.01 (dt, *J* = 9.9, 4.3 Hz, 1 H), 1.01 (s, 9 H), 0.77 (m, 18 H), 0.56 (m, 6 H), 0.21 (s, 3 H), 0.19 (s, 3 H), 0.11 (m, 6 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 174.8 (C_q), 158.3 (C_q), 142.0 (C_q), 129.4 (C_q), 127.9 (2 C, CH), 127.6 (2 C, CH), 127.5 (CH), 127.2 (2 C, CH), 113.7 (2 C, CH), 78.8 (CH), 75.0 (C_q), 71.9 (CH), 57.8 (CH), 54.9 (CH_3), 46.4 (CH), 43.4 (CH_2), 27.5 (CH_2), 25.5 (3 C, CH_3), 17.7 (C_q), 6.7 (3 C, CH_3), 6.4 (3 C, CH_3), 5.5 (3 C, CH_2), 4.9 (3 C, CH_2), –4.7 (CH_3), –4.8 (CH_3) ppm.

Dry THF (30 mL) was added to a reaction vessel containing anhydrous $AlCl_3$ (0.93 g, 7.0 mmol) cooled to 0 °C under argon, and the resulting colourless solution was stirred at the same temperature for 10 min. Lithium aluminium hydride ($LiAlH_4$, 21.0 mL of a 1.0 M solution in THF, 21.0 mmol) was added, and vigorous bubbling was observed. The colourless AlH_3 solution so obtained was warmed to room temperature and stirred for 30 min, after which time it was cooled again to –80 °C. The alane solution (10 mL, 1.4 mmol) was added by syringe to a precooled (–80 °C) solution of the above bicyclic lactam intermediate (500 mg, 0.70 mmol) in dry THF (30 mL), and the resulting colourless mixture was stirred at –80 °C for 1 h, warmed to 20 °C and stirred for an additional 1 h. The reaction mixture was quenched with MeOH (10 mL), a 5% aqueous citric acid solution (5 mL) and water (50 mL), and the resulting slurry was thoroughly extracted with EtOAc (five times). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum to give a crude residue which was purified by silica gel flash chromatography (hexane/EtOAc, 95:5 to 80:20) to provide amine **39** (480 mg, 99% yield, corresponding to 89% yield for two steps) as a white resin. $[a]_D^{20}$ = +1.8 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.64 (m, 2 H), 7.36 (m, 3 H), 6.98 (m, 2 H), 6.76 (m, 2 H), 4.82 (br. s, 1 H), 4.25 (d, J = 12.8 Hz, 1 H), 4.00 (m, 3 H), 3.77 (s, 3 H), 3.57 (br. d, J = 11.7 Hz, 1 H), 2.92 (br. d, J = 11.7 Hz, 1 H), 2.86 (m, 1 H), 2.40 (m, 2 H), 1.62 (m, 1 H), 0.95 (s, 9 H), 0.81 (t, J = 8.4 Hz, 9 H), 0.22 (m, 6 H), 0.13 (s, 3 H), 0.11 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 158.9 (C_q), 129.8 (2 C, Cq), 128.4 (2 C, CH), 127.9 (4 C, CH), 127.5 (CH), 113.8 (2 C, CH), 77.4 (2 C, CH), 76.9 (C_q), 66.8 (CH), 61.3 (CH_2), 56.8 (CH_2), 55.2 (CH_3), 42.7 (CH), 26.0 (3 C, CH_3), 25.4 (CH_2), 18.3 (C_q), 7.1 (3 C, CH_3), 5.9 (3 C, CH_2), –4.6 (CH_3), –4.9 (CH_3) ppm. $C_{33}H_{53}NO_4Si_2$ (583.95): calcd. C 67.87, H 9.15, N 2.40; found C 67.98, H 9.29, N 2.37.

(1*S*,2*S*,3*R*,4*R*,5*S*)-4-Phenyl-6-azabicyclo[3.2.1]octane-2,3,4-triol (40): Palladium on carbon (30 mg) was added to a solution of amine **39** (450 mg, 0.64 mmol) in absolute EtOH (20 mL) at room temperature. The reaction vessel was degassed under vacuum and thoroughly purged with hydrogen (three times). The resulting heterogeneous mixture was stirred under hydrogen for 3 h, after which time the hydrogen was evacuated, the catalyst filtered off and the filtrate concentrated under vacuum to give a crude residue which was purified by silica gel flash chromatography (EtOAc/MeOH/NH_3, 98:1:1) to furnish an *N*-deprotected amine intermediate (270 mg, 91%) as a white solid. M.p. 120–122 °C. $[\alpha]_D^{20}$ = +11.6 (c = 0.5, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.51 (br. d, J = 7.4 Hz, 2 H), 7.39 (br. t, J = 7.0 Hz, 2 H), 7.31 (br. d, J = 7.2 Hz, 1 H), 4.25 (br. d, J = 5.4 Hz, 1 H), 4.03 (m, 1 H), 3.94 (m, 1 H), 3.79 (br. s, 2 H), 3.08 (m, 2 H), 2.99 (d, J = 11.8 Hz, 1 H), 2.40 (m, 1 H), 1.62 (m, 1 H), 0.96 (s, 9 H), 0.79 (t, J = 8.0 Hz, 9 H), 0.22 (m, 6 H), 0.15 (s, 3 H), 0.13 (s, 3 H) ppm. ^{13}C NMR (75.4 MHz, CD_3OD, 25 °C): δ = 143.7 (C_q), 129.4 (2 C, CH), 128.9 (CH), 128.5 (2 C, CH), 78.7 (CH), 78.3 (CH), 77.6 (C_q), 61.2 (CH), 48.5 (CH_2), 42.9 (CH), 27.7 (CH_2), 26.5 (3 C, CH_3), 19.1 (C_q), 7.4 (3 C, CH_3), 7.0 (3 C, CH_2), –4.5 (CH_3), –4.7 (CH_3) ppm.

The above *N*-deprotected amine intermediate (270 mg, 0.58 mmol) was dissolved in THF (10 mL) and treated with a 1 N aqueous HCl solution (3.0 mL) at room temperature. After stirring at this temperature for 3 h, the reaction mixture was concentrated under reduced pressure to give azabicycle **40** (134 mg, 98%, corresponding to 89% yield for two steps) as a glassy solid as the hydrochloride salt. $[\alpha]_D^{20}$ = +10.43 (c = 0.23, MeOH). ^{1}H NMR (600 MHz, CD_3OD, 25 °C): δ = 7.49 (dd, J = 8.4, 1.2 Hz, 2 H, Ph), 7.44 (t, J = 7.2 Hz, 2 H, Ph), 7.35 (tt, J = 7.2, 1.2 Hz, 1 H, Ph), 4.48 (dd, J = 5.4, 1.2 Hz, 1 H, 5-H), 4.11 (br. d, J = 1.2 Hz, 1 H, 3-H), 3.98 (dt, J = 4.2, 1.8 Hz, 1 H, 2-H), 3.71 (dd, J = 11.4, 1.8 Hz, 1 H, 7-H_{endo}), 3.32 (dd, J = 11.4, 5.4 Hz, 1 H, 7-H_{exo}), 3.16 (br. d, J = 12.6 Hz, 1 H, 8-H_{ax}), 2.72 (dt, J = 4.8, 4.0 Hz, 1 H, 1-H), 1.83 (dtd, J = 12.6, 4.8, 1.2 Hz, 1 H, 8-H_{eq}) ppm. ^{13}C NMR (75.4 MHz, CD_3OD, 25 °C): δ = 145.8 (C_q, Ph), 129.4 (2 C, CH, Ph), 128.4 (CH, Ph), 128.1 (2 C, CH, Ph), 78.2 (CH, C-3), 76.4 (CH, C-2), 74.7 (C_q, C-4), 61.8 (CH, C-5), 49.7 (CH_2, C-7), 42.6 (CH, C-1), 28.3 (CH_2, C8) ppm. $C_{13}H_{18}ClNO_3$ (271.74): calcd. C 57.46, H 6.68, N 5.15; found C 57.29, H 6.74, N 5.10.

X-ray Crystallography: X-ray diffraction was carried out with a Bruker-Siemens SMART AXS 1000 diffractometer equipped with a CCD detector: Mo-K_α radiation (λ = 0.71069 Å), μ = 0.1226 mm^{-1}. Data-collection details for the Bruker-Siemens SMART AXS 1000 diffractometer are: crystal-to-detector distance = 5.0 cm, 2424 frames collected (complete sphere mode), time per frame = 20 s, oscillation $\Delta\Phi$ = 0.300°. Data were corrected for absorption effects by the SADABS[17] procedure. Crystal decay was negligible in all cases. The phase problem was solved by direct methods and the structures were refined by full-matrix least squares on all F^2 performed using SHELXL97,[18] as implemented in the WINGX program.[19] Anisotropic displacement parameters were refined for all non-hydrogen atoms, whereas hydrogen atoms were located from Fourier maps and refined isotropically. Nine hydrogen atoms, more exactly those on the terminal methyl groups, were introduced into calculated positions. Analytical expressions of neutral atom scattering factors were employed according to the *International Tables for X-ray Crystallography*.[20] Structure drawing was carried out by using ORTEPIII.[21] CCDC-673479 contains 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.

Crystal Data for 7a: M.p. 89–91 °C. $C_{23}H_{35}NO_4Si$, M_r = 417.62, orthorhombic, space group *Pcab*, a = 10.774(1), b = 11.646(1), c = 38.777(4) Å, V = 4865.5(8) Å^3, Z = 8, $\rho_{calcd.}$ = 1.140 Mg m^{-3}, T = 298.15 K, $F(000)$ = 1808, crystal size = 0.40 × 0.30 × 0.30 mm, θ range for data collection = 1.05–26.52°, index ranges = $-12 \le h \le 12$, $-14 \le k \le 14$, $-48 \le l \le 32$, reflections collected = 25981, independent reflections = 4857, completeness to θ (26.52°) = 96.0%, refinement method = full-matrix least squares on F^2, parameters = 342, goodness-of-fit on F^2 = 1.035, final R indices $[I > 2\sigma(I)] = R_1$ = 0.0564, wR_2 = 0.1485, largest difference peak and hole = 0.26 and –0.37 e Å^{-3}.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds **7a**, **8a**, **10**–**15**, **17**–**21**, **23**–**28** and **31**–**40**.

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