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Studies on a Total Synthesis of the Microbial Immunosuppressive Agent FR901483

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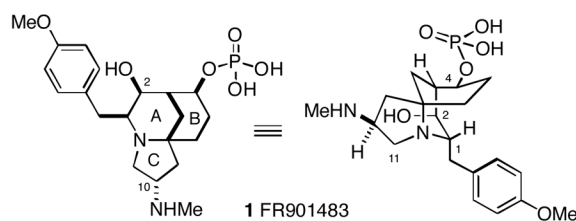
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Abstract

A strategy is outlined for construction of the fungal immunosuppressant FR901483 (**1**). It was possible to convert 1,4-cyclohexanedione monoethylene ketal in five simple steps to iodoacetamide ketone **10**, which was cyclized in good yield to the key bridged keto lactam **11** containing the A/B 2-azabicyclo[3.3.1]nonane ring system of the natural product. This intermediate could be transformed to *N*-Boc lactam **16**, whose derived enolate underwent stereoselective hydroxylation with the Davis oxaziridine to produce alcohol **17** having the desired C-2 configuration. Compound **17** was then converted in three steps to alkoxy carbamate **20**. The *N*-acyliminium ion derived from intermediate **20** could be alkylated in good overall yield with *p*-methoxybenzylmagnesium chloride to afford a 5:4 mixture of the desired PMB product **21** and the epimer **23**. In an attempt to improve the stereoselectivity in this alkylation, the inverted C-4 protected alcohol *N*-Boc lactam **33** was prepared and its enolate was hydroxylated. Inexplicably, the product of this reaction was the undesired equatorial alcohol **34**. Some model systems were investigated towards annulation of the C-ring of the natural product. It was found that homoallylic amine **40** could be cyclized with PhSCl in the presence of silica gel to generate the desired 5-endo tetracyclic product **42** in moderate yield. This cyclization protocol was also successfully applied to the actual FR901483 system **22**, leading to the requisite tricycle **43**.

Introduction and Background

The fungal metabolite FR901483 (**1**), which was isolated in 1996 from a *Cladobotryum* species, has a unique constitution unprecedented in natural products chemistry.¹ The structure and relative stereochemistry of **1** were originally determined by X-ray crystallography, and its absolute configuration was later established by total synthesis.² The crystal structure of FR901483 shows some interesting conformational features. For example, the B-ring of the molecule exists in a boat, perhaps due to the large C-4 phosphate group (which would be axial in the A/B chair-chair form). It is not clear from published data, however, if the molecule assumes the same conformation in solution. Furthermore, the pyrrolidine nitrogen has an equatorial lone pair, giving a *cis* fusion of the [6,5]-A/C-rings, but at the same time creating a 1,3-diaxial interaction between C-11 and the C-2 hydroxyl group. FR901483 shows immunosuppressive activity both *in vitro* and *in vivo*. Interestingly, the dephosphorylated compound is completely inactive. It was suggested that the compound acts by inhibiting purine nucleotide biosynthesis.¹



Several successful total syntheses of FR901483 have appeared in the past few years.² The first synthesis of this metabolite, reported by Snider in 1999, was biogenetically inspired starting from (*S*)-tyrosine, and established the absolute stereochemistry of **1**, but was not highly stereoselective.^{2a} Subsequent enantioselective total syntheses described by Sorensen^{2b} and Ciufolini^{2c,e} are also closely patterned after the putative biogenesis of FR901483 originating from two molecules of tyrosine. In 2001 Funk reported an elegant synthesis of racemic **1**,^{2d} and more recently syntheses have been described by the Fukuyama^{2f} and Brummond^{2g} groups. This continues to be an active area of research, and a number of other strategies leading toward this natural product have appeared in the literature.³

Retrosynthetic Plan

We have been investigating a new strategy for the construction of FR901483 and in this paper we report our progress to date.⁴ Retrosynthetically, our strategy for synthesis of **1** involved forming the third and final C-ring from a bridged bicyclic intermediate **2** containing the azabicyclo[3.3.1]nonane A/B-ring system (Scheme 1). This strategy is different from the previous total syntheses, where an azaspirocyclic core containing the [6,5]-B/Crings is generally formed first, and subsequently the A-ring is generated via an intramolecular aldol reaction. This latter process in general seems to produce either mixtures of stereoisomeric products or the incorrect isomer at C-2. We envisioned that the C-1 (FR901483 numbering used throughout) *p*-methoxybenzyl group of bicycle **2** could be installed via attack of a PMB organometallic reagent from the least hindered face of an *N*-acyliminium ion **3** generated from the α -alkoxycarbamate **4**. We also anticipated that the C-4 hydroxyl group stereochemistry, initially set as shown in **4**, would have to be inverted at some point (*vide infra*). The plan was to prepare intermediate **4** from the simple 2-azabicyclo[3.3.1]nonanone **5**.

Results and Discussion

Construction of the A/B Ring System

The first challenge in the synthesis of FR901483 was to efficiently prepare the key A/B bicyclic ketolactam **11** (Scheme 2). The route began by condensing commercially available 1,4-cyclohexanedione monoethylene ketal with benzylamine to give imine **6**, which without purification was treated with allylmagnesium bromide to form homoallylic amine **7**. *N*-Acylation of amine **7** with chloroacetyl chloride then afforded chloroacetamide **8**. α -Iodoamidoketone **10** was then formed from α -chloroamide **8** following ketal hydrolysis to **9** and Finkelstein halogen exchange.

A few examples have been reported of intramolecular cyclizations involving alkylation of an enolate of an α -/ α' -unsubstituted cyclohexanone and a tethered 4-alkyl electrophile to form bicyclo[3.3.1]nonane ring systems, but these annulations often occur in poor to mediocre yields.^{5,6} Indeed, we found initially that cyclization could be achieved if iodoketone **10** is treated with KO*t*-Bu in *t*-BuOH/THF (1:1) at room temperature, furnishing the desired bicyclo[3.3.1]nonanone **11**, but only in moderate 46–58% yields, depending upon the reaction scale. However, we were pleased to find that the cyclization to **11** could be effected in a much

improved 79% yield from ketone **10** if K_2CO_3 (2 equiv.) is used as the base in acetone/ H_2O at room temperature.⁷

Reduction of ketone **11** with sodium borohydride was completely stereoselective, cleanly affording the equatorial alcohol **12** which was then protected as the triisopropylsilyl ether **13** (Scheme 3). We next investigated the introduction of oxygen at C-2. Thus, bicyclic lactam **13** was first deprotonated with LDA, followed by treatment of the resulting enolate with the Davis oxaziridine reagent⁸ led to a single α -hydroxylation product **14** in good yield. X-ray analysis of this compound indicated that it did indeed have the correct C-2 stereochemistry for FR901483. However, since dissolving metal reductive removal of the *N*-benzyl substituent of **14** (and *O*-protected derivatives) led to loss of the C-2 oxygen, an alternative sequence of reactions was explored.

It was possible to first remove the *N*-benzyl group of **13** using sodium in liquid ammonia to generate lactam **15** (Scheme 4). A Boc group could then be installed on **15** to produce the *N*-acyl lactam **16**. This intermediate was converted to the corresponding enolate with sodium hexamethyldisilazide, followed by exposure to the Davis oxaziridine reagent to produce hydroxy lactam **17**. The stereochemistry of this alcohol was established by analysis of a later intermediate (*vide infra*). Subsequent chemoselective partial reduction of *N*-Boc lactam **17** with lithium aluminum hydride afforded α -hydroxycarbamate **18**, which without purification was converted to methoxy compound **19** with scandium triflate in methanol.⁹ We had hoped that the hydroxyl group in **19** would promote alkylation at C-1 from the desired direction via chelation-controlled delivery of an organometallic reagent. Unfortunately, all attempts to directly couple alcohol **19** with excess *p*-methoxybenzylmagnesium chloride in the presence of a variety of Lewis acids were unsuccessful.¹⁰

Since we were concerned that deprotonation of the alcohol moiety in **19** by the Grignard reagent might possibly be interfering with the coupling step, a protected compound, benzyl ether **20**, was prepared (Scheme 5). Addition of *p*-methoxybenzylmagnesium chloride (3.5 equiv.) and $TiCl_4$ to the *O*-protected system **20** did in fact produce coupled product in good total yield, but as a mixture of epimers **21** and **23** which was not easily separated. However, removal of the Boc protecting group led to a chromatographically separable 5:4 mixture of the desired PMB product **22** along with the undesired epimer **24**. The configurations of amines **22** and **24** were established by 1H NMR nOe experiments (key enhancements indicated). Interestingly, these nOe studies indicate that the A-ring in the minor isomer **24** appears to exist in a boat as shown in conformer **24b**. This latter conformation avoids the non-bonded interactions between the axial PMB group and the B-ring in conformer **24a**. These structural and stereochemical assignments were also supported by the coupling constants between the protons at C-1,2 (i.e. 2.8 Hz for **22**, and 9.2 Hz for the diaxial arrangement in **24b**).

In view of the disappointingly low level of stereoselectivity in the introduction of the PMB group, we turned to the alternative strategy outlined in Scheme 6. The plan was to first invert the stereochemistry at C-4 to produce a synthon like **25**, which has the correct FR901483 configuration at this position. Addition of *p*-methoxybenzylmagnesium chloride to **25** would then afford **26**. The expectation was that this intermediate would have the B-ring in a boat conformation with the large OTIPS group equatorial, similar to the case in the natural product (Cf. **1**). Compound **26** would subsequently be converted to the desired PMB product **28** via hydride reduction which we believed should occur from the less hindered axial face of intermediate acyliminium ion **27**.

In order to test this approach, equatorial alcohol **12** was first inverted via a Mitsunobu procedure to afford the C-4 epimeric axial alcohol **29** (Scheme 7).¹¹ The alcohol functionality was then protected as the TIPS ether **30**. This lactam could be hydroxylated stereoselectively in 60%

yield using LDA, followed by the Davis oxaziridine, to produce the axial C-2 alcohol **31**. The configuration of this product was confirmed by its conversion to diol **32**, whose structure was established by X-ray crystallography. Interestingly, the B-ring of this compound in the crystal was observed to be a chair, with the C-4 hydroxyl group axial. As we had experienced earlier, attempted removal of the *N*-benzyl group of **31** with sodium/liquid ammonia led to only a low yield (~20%) of the desired NH lactam.

It was therefore necessary to again revise the sequence of steps here, which in this case led to some unexpected results. Removal of the *N*-benzyl group from lactam **30** proceeded uneventfully, and the resulting product was converted to *N*-Boc compound **33** (Scheme 8). However, we were surprised to find that hydroxylation of **33** as previously done with *N*-Boc lactam **16** (Cf. Scheme 4) led exclusively to the incorrect equatorial C-2 alcohol **34**, whose structure was unambiguously determined by X-ray crystallography.¹² Moreover, the crystal structure shows that like alcohol **32**, hydroxylation product **34** exists with the B-ring in a chair, putting the large OTIPS group axial. At this point we are unable to offer a compelling rationale as to why the enolate of *N*-benzyl lactam **30** leads to the desired axial hydroxylation product **31**, whereas the corresponding *N*-Boc system undergoes hydroxylation to produce the undesired equatorial product **34**.

Prior to becoming aware that alcohol **34** in fact had the incorrect C-2 stereochemistry, we continued to explore the strategy outlined in Scheme 6 for introduction of the PMB group. After alcohol protection, benzyl ether **35** underwent clean addition of *p*-methoxybenzylmagnesium chloride to afford adduct **36** which appears to be one stereoisomer, although its configuration was not established (Scheme 9). This intermediate could be reduced with sodium cyanoborohydride in acetic acid to give a single stereoisomeric product **37** which was deacylated to amine **38**. Based on the large observed coupling constant for H₁/H₂ of 9.0 Hz, we have tentatively assigned the stereochemistry to **38** as shown with an equatorial PMB group.

Studies on Annulation of the C-ring

The plan for construction of the C-ring of FR901483 was to effect a 5-*endo trig* cyclization of a suitable homoallylic amine to produce a properly C-10 functionalized pyrrolidine system. Initial experiments on formation of the C-ring were conducted with simple model bicyclic amino alkenes **39** and **40** (Scheme 10). There are a number of examples in the literature of this type of cyclization process starting from both homoallylic amines (as well as *N*-acylated amine derivatives) and homoallylic alcohols.^{13–15} Table 1 indicates some of the results of the cyclizations which were tested. Promising results were obtained using the selenium-induced cyclization methodology of Paulmier et al. (entries 3 and 4).¹³ Thus, tricyclic selenide **41** (X = SePh) could be prepared as a mixture of stereoisomers from homoallylic amine **39** in moderate yields. The cyclization of **39** using phenylsulfenyl chloride,¹⁵ however, proceeded in an improved 52% yield to afford tricyclic sulfide **41** (X = SPh, entry 5). With TIPS-protected substrate **40**, tricycle **42** (X = SPh, entry 9) could be formed in 61% yield as a 3:2 mixture of stereoisomers. In this latter case, silica gel proved to be an effective additive.¹⁴ In none of these cases did we observe any azetidine formation via a 4-*exo trig* cyclization mode.¹³

Using the best reaction conditions found for the simple homoallylic amine **40**, we have examined cyclization of the actual FR901483 substrate **22** (Scheme 11). The cyclization conditions involved initial addition of phenylsulfenyl chloride to amine **22** which was premixed with the mild acid pyridinium trifluoromethanesulfonate (PPTS). The cyclized product **43** then was produced upon addition of K₂CO₃ and silica gel. Tricyclic sulfide **43** was formed in 51% yield as a chromatographically separable 3:2 mixture of C-10 stereoisomers whose configurations were not established. In order to confirm that this process had led to products of 5-*endo trig* cyclization, the mixture of sulfides was desulfurized with Raney nickel to afford

tricyclic **44** in good yield. If the cyclization had in fact produced the 4-*exo trig* products, an NMR-detectable methyl group would have been produced in this reduction step. The sulfide functionality in tricyclics **43** should provide a convenient handle for eventual introduction of the methylamino group of the natural product.

Conclusion

In this report we have described a new approach to the synthesis of the tricyclic framework of FR901483 (**1**). We have shown that bicyclic keto lactam **11** can be efficiently prepared in five steps from 1,4-cyclohexanedione monoethylene ketal. This key A/B-ring synthon can then be elaborated to the advanced intermediate **22**. A major obstacle, which will be investigated further in our future work, is the low stereoselectivity in the introduction of the C-1 *p*-methoxybenzyl group via addition to an *N*-acyliminium ion. In addition, we hope to probe the unexpected stereochemical differences in the hydroxylations of bridged lactam **30** vs *N*-Boc imide **33**. We have also found that the tricyclic sulfide **43** bearing the C-ring of the natural product can be prepared by cyclization of homoallylic amine **22** mediated by phenylsulfenyl chloride. The expectation is that compound **43** can be converted to FR901483 by a straightforward route. The results of these further studies will be reported in due course.

Experimental Section

(8-Allyl-1,4-dioxaspiro[4.5]dec-8-yl)benzylamine (**7**)

To a solution of 97% 1,4-cyclohexanedione monoethylene ketal (25.0 g, 0.16 mmol) in benzene (400 mL) in a round bottomed flask fitted with a Dean-Stark trap at rt was added benzylamine (17 mL, 0.16 mol). The mixture was refluxed for 5 h, concentrated *in vacuo* and the residual imine **6** was dissolved in Et₂O (400 mL). The solution was cooled to 0 °C and allylmagnesium bromide (200 mL, 1.0 M in Et₂O) was added dropwise. The mixture was warmed to rt, stirred for an additional 2 h, then cooled to 0 °C and quenched by the slow addition of saturated aqueous NH₄Cl followed by water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (4:1, hexanes/EtOAc) to give amine **7** (29.4 g, 64%) as an orange oil: ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.21 (m, 5H), 5.92-5.81 (m, 1H), 5.19-5.10 (m, 2H), 3.97 (s, 4H), 3.67 (s, 2H), 2.29 (d, *J* = 7.5 Hz, 2H), 2.03-1.92 (m, 2H), 1.75-1.55 (m, 6H); ¹³C NMR (90 MHz, CDCl₃) δ 141.2, 134.1, 128.2, 126.7, 117.8, 109.1, 64.1, 64.0, 53.0, 45.6, 42.0, 32.7, 30.2; IR (neat) 3063, 3029, 1637, 1372, 1112 cm⁻¹; HRMS (MALDI) calcd for C₁₈H₂₆NO₂ (MH⁺) 288.1963, found 288.1968.

2-Chloro-*N*-(8-allyl-1,4-dioxaspiro[4.5]dec-8-yl)-*N*-benzylacetamide (**8**)

To a solution of amine **7** (6.8 g, 23.5 mmol) in CH₂Cl₂ (58 mL) at 0 °C was added triethylamine (3.6 mL, 25.8 mmol). A solution of chloroacetyl chloride (2.3 mL, 28.9 mmol) in CH₂Cl₂ (19 mL) was then added dropwise via cannula and the mixture was stirred at 0 °C for 1 h before warming to rt. After stirring at rt for 2 h, the solution was cooled to 0 °C and water was added. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (4:1, hexanes/EtOAc) to give amide **8** (7.1 g, 83%) as a white solid: mp 123–124 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.17 (m, 5H), 5.78 (dddd, *J* = 17.8, 10.3, 7.5, 7.5 Hz, 1H), 5.16-5.05 (m, 2H), 4.63 (s, 2H), 3.94-3.80 (m, 6H), 2.85 (d, *J* = 7.4 Hz, 2H), 2.44 (br d, *J* = 13.0, 2H), 2.04-1.86 (m, 2H), 1.74-1.54 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 168.5, 138.5, 133.5, 129.0, 127.3, 125.2, 118.8, 107.4, 64.2 (2C), 63.2, 48.9, 44.2, 35.4, 31.3, 30.6; IR (Nujol mull) 3060, 1653, 1393 cm⁻¹; HRMS (APCI) calcd for C₂₀H₂₇ClNO₃ (MH⁺) 364.1679, found 364.1695.

***N*-(1-Allyl-4-oxocyclohexyl)-*N*-benzyl-2-chloroacetamide (9)**

To a solution of the amide **8** (29.5 g, 81 mmol) in THF (170 mL) at rt was added 5% HCl (170 mL). After stirring the mixture overnight, another portion of 5% HCl (85 mL) was added and the mixture was stirred for an additional 2 d. The mixture was then cooled to 0 °C and neutralized with saturated aqueous NaHCO₃. The aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (3:2, hexanes/EtOAc) to give ketone **9** (25.8 g, 99%) as an orange gum: ¹H NMR (360 MHz, CDCl₃) δ 7.44 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 7.4 Hz, 2H), 5.90 (dddd, *J* = 17.7, 10.3, 7.4, 7.4 Hz, 1H), 5.28-5.19 (m, 2H), 4.74 (s, 2H), 4.07 (s, 2H), 3.01 (d, *J* = 7.4 Hz, 2H), 2.63 (ddd, *J* = 17.5, 11.2, 4.8 Hz, 2H), 2.45-2.17 (m, 6H); ¹³C NMR (90 MHz, CDCl₃) δ 209.6, 168.4, 137.7, 132.6, 129.0, 127.5, 125.0, 119.3, 62.3, 49.0, 43.9, 36.9, 36.4, 32.2; IR (neat) 3065, 3031, 1713, 1651, 1396 cm⁻¹; HRMS (APCI) calcd for C₁₈H₂₃ClNO₂ (MH⁺) 320.1417, found 320.1427.

***N*-(1-Allyl-4-oxocyclohexyl)-*N*-benzyl-2-iodoacetamide (10)**

To a solution of the chloride **9** (25.8 g, 80.7 mmol) in acetone (91 mL) at rt was added sodium iodide (36 g, 240 mmol). After stirring for 3 h, the mixture was concentrated *in vacuo* and the residue was dissolved in water and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous Na₂S₂O₃ and brine, dried over MgSO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (7:3, hexanes/EtOAc) to give iodide **10** (31.0 g, 94%) as an orange solid: ¹H NMR (360 MHz, CDCl₃) δ 7.35 (t, *J* = 7.2 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 5.84 (dddd, *J* = 17.7, 10.3, 7.5, 7.5 Hz, 1H), 5.18-5.09 (m, 2H), 4.59 (s, 2H), 3.62 (s, 2H), 2.93 (d, *J* = 7.4 Hz, 2H), 2.54 (ddd, *J* = 17.9, 11.5, 5.1 Hz, 2H), 2.37-2.09 (m, 6H); ¹³C NMR (90 MHz, CDCl₃) δ 209.9, 169.9, 137.7, 132.6, 129.1, 127.6, 125.0, 119.6, 62.1, 50.6, 37.0, 36.7, 32.4; IR (neat) 3063, 3030, 1714, 1650, 1387 cm⁻¹; HRMS (APCI) calcd for C₁₈H₂₃INO₂ (MH⁺) 412.0774, found 412.0787.

1-Allyl-2-benzyl-2-azabicyclo[3.3.1]nonane-3,6-dione (11)

Method 1—To a solution of the iodide **10** (500 mg, 1.2 mmol) in *t*-BuOH/THF (1:1, 5.2 mL) at rt was added KO*t*-Bu (175 mg, 0.64 mmol) in two equal portions 5 h apart. After stirring for 2 h, the mixture was concentrated *in vacuo* and the residue was diluted with water. The solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (1:1, hexanes/EtOAc) to give ketone **11** (158 mg, 46%) as a white solid.

Method 2—To a solution of the iodide **10** (5.00 g, 12.2 mmol) in acetone (100 mL) at rt was added a solution of K₂CO₃ (3.25 g, 23.5 mmol) in water (42.5 mL). After stirring for 72 h, the mixture was concentrated *in vacuo* and the residue was diluted with water. The solution was extracted with EtOAc. The combined organic layers were washed with water, and brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (3:2, EtOAc/hexanes) to give ketone **11** (2.73 g, 79%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.16 (m, 5H), 5.54 (dddd, *J* = 16.6, 10.2, 8.1, 6.2 Hz, 1H), 5.12 (d, *J* = 10.4 Hz, 1H), 5.08 (dd, *J* = 17.1, 1.4 Hz, 1H), 4.90, 4.70 (AB_q, *J* = 15.5 Hz, Δ_vAB = 64.9 Hz, 2H), 2.83 (dd, *J* = 18.1, 7.1 Hz, 1H), 2.79 (m, 1H), 2.65-2.56 (m, 2H), 2.34-2.07 (m, 4H), 1.96 (ddd, *J* = 13.7, 3.0, 3.0 Hz, 1H), 1.85-1.77 (m, 1H), 1.66 (ddd, *J* = 13.5, 13.5, 5.3 Hz, 1H); ¹³C NMR (90 MHz, CDCl₃) δ 211.1, 170.3, 138.7, 131.7, 128.5, 127.6, 127.2, 120.0, 58.1, 44.7, 43.2, 42.6, 37.2, 35.5, 34.8, 34.5; IR (neat) 2939, 1713, 1637, 984 cm⁻¹; HRMS (APCI) calcd for C₁₈H₂₂NO₂ (MH⁺) 284.1651, found 284.1661.

1-Allyl-6-hydroxy-2-benzyl-2-azabicyclo[3.3.1]nonan-3-one (12)

To a solution of the ketone **11** (16.4 g, 57.8 mmol) in methanol (332 mL) at 0 °C was added sodium borohydride (2.70 g, 71.4 mmol). The mixture was warmed to rt and was stirred for an additional 1 h. The mixture was then concentrated *in vacuo*, diluted with Et₂O, washed with water and the aqueous layer was further extracted with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (95:5, EtOAc/MeOH) to give alcohol **12** (16.3 g, 99%) as a white foam: ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.15 (m, 5H), 5.57 (dddd, *J* = 16.8, 10.3, 8.0, 6.4 Hz, 1H), 5.07-4.98 (m, 2H), 4.68 (AB_q, *J* = 15.6 Hz, Δ*v*_{AB} = 19.1 Hz, 2H), 3.74 (ddd, *J* = 10.8, 4.6, 4.6 Hz, 1H), 2.88 (dd, *J* = 18.6, 1.8 Hz, 1H), 2.56-2.31 (m, 3H), 2.26-2.12 (m, 2H), 1.95 (ddd, *J* = 13.6, 3.4, 3.4 Hz, 1H), 1.71-1.43 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 173.3, 139.1, 132.4, 128.2, 127.3, 126.6, 118.9, 70.6, 58.0, 44.5, 43.6, 35.7, 32.7, 32.5, 31.0, 26.2; IR (film) 3378, 2936, 1615, 916 cm⁻¹; EIMS *m/z* (relative intensity) 285 (MH⁺, 7), 91 (100); HRMS calcd for C₁₈H₂₃NO₂ 285.1727, found 285.1729.

1-Allyl-2-benzyl-6-(triisopropylsilyloxy)-2-azabicyclo[3.3.1]nonan-3-one (13)

To a solution of alcohol **12** (792 mg, 2.77 mmol) in CH₂Cl₂ (11 mL) at 0 °C was added triethylamine (1.0 mL, 7.2 mmol) and triisopropylsilyl trifluoromethanesulfonate (1.0 mL, 3.7 mmol). After 2.5 h at 0 °C, the mixture was diluted with water, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (9:1, hexanes/EtOAc) to give silyl ether **13** (1.1 g, 90%) as a white solid: mp 96–97 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.31-7.17 (m, 5H), 5.47 (ddt, *J* = 16.8, 9.1, 7.7 Hz, 1H), 4.98 (d, *J* = 10.2 Hz, 1H), 4.93 (dd, *J* = 17.0, 1.3 Hz, 1H), 4.67 (AB_q, *J* = 12.4 Hz, Δ*v*_{AB} = 34.0 Hz, 2H), 3.79-3.74 (m, 1H), 2.97 (d, *J* = 18.5 Hz, 1H), 2.47 (dd, *J* = 18.5, 7.2 Hz, 1H), 2.40 (dd, *J* = 14.4, 6.3 Hz, 1H), 2.20-2.16 (m, 2H), 1.92 (ddd, *J* = 10.4, 3.2, 3.2 Hz, 1H), 1.60-1.28 (m, 5H), 1.12-0.95 (m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 173.0, 139.4, 132.6, 128.2, 127.4, 126.6, 118.9, 71.7, 57.8, 44.4, 43.8, 35.9, 33.5, 32.8, 31.0, 27.2, 17.9, 12.1; IR (neat) 3065, 3028, 1634, 1399 cm⁻¹; HRMS (MALDI) calcd for C₂₇H₄₄NO₂Si (MH⁺) 442.3141, found 442.3155.

1-Allyl-2-benzyl-4-hydroxy-6-(triisopropylsilyloxy)-2-azabicyclo[3.3.1]nonan-3-one (14)

To a solution of *N,N*-diisopropylamine (0.19 mL, 1.3 mmol) in THF (45 mL) at -78 °C was added *n*-BuLi (0.70 mL, 1.81 M in hexanes). The mixture was warmed to -30 °C and stirred for 10 min. The mixture was then cooled to -78 °C and a solution of lactam **13** (470 mg, 1.1 mmol) in THF (5 mL) was added via cannula. The mixture was slowly warmed to 0 °C and stirred for 45 min. The mixture was recooled to -78 °C and 2-(phenylsulfonyl)-3-phenyloxaziridine^{8b} (420 mg, 1.6 mmol) was then added. The resulting mixture was slowly warmed to rt while stirring for 18 h. The mixture was then carefully poured into saturated aqueous NaHCO₃. The organic layer was washed with water and brine. The combined aqueous layers were extracted with CH₂Cl₂, and the extract was dried with MgSO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1, hexanes/EtOAc) to give hydroxy lactam **14** (380 mg, 78%) as a white solid: mp 110–111 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.32-7.18 (m, 5H), 5.60 (dddd, *J* = 16.9, 10.2, 7.7, 7.7 Hz, 1H), 5.11-4.98 (m, 2H), 4.68 (AB_q, *J* = 15.6 Hz, Δ*v*_{AB} = 26.1 Hz, 2H), 4.43 (s, 1H), 3.77 (ddd, *J* = 9.5, 4.7, 4.7 Hz, 1H), 2.97 (s, 1H), 2.42 (dd, *J* = 14.3, 6.6 Hz, 1H), 2.31-2.26 (m, 1H), 2.24-2.07 (m, 2H), 1.70-1.60 (m, 1H), 1.48-1.37 (m, 2H), 1.39-1.15 (m, 2H), 1.10-0.91 (m, 21H); ¹³C NMR (90 MHz, CDCl₃) δ 174.8, 138.7, 132.4, 128.5, 127.4, 127.0, 119.5, 70.4, 66.9, 58.9, 44.9, 43.8, 40.4, 33.1, 31.9, 28.2, 18.0, 12.3; HRMS (MALDI) calcd for C₂₇H₄₄NO₃Si (MH⁺) 458.3090, found 458.3087.

1-Allyl-6-(triisopropylsilyloxy)-2-azabicyclo[3.3.1]nonan-3-one (15)

In a 1 L three-neck round bottomed flask fitted with a cold finger condenser at $-78\text{ }^{\circ}\text{C}$ was condensed ammonia (380 mL). Sodium (4.0 g, 172 mmol) followed by *t*-butanol (8.2 mL, 86 mmol) were carefully added to the ammonia, resulting in a blue mixture. After 45 min, a solution of benzyl lactam **13** (7.5 g, 17 mmol) in Et_2O (55 mL) was added to the mixture via a gastight syringe. The mixture was stirred at reflux for 75 min and then solid ammonium chloride (10 g) was carefully added until the blue color dissipated. The mixture was slowly warmed to rt while occasionally replacing the evaporating ammonia with THF. The resulting mixture was filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash chromatography (1:1, hexanes/ EtOAc) to give lactam **15** (6.0 g, 99%) as a colorless oil sufficiently pure for use in the next step: ^1H NMR (360 MHz, CDCl_3) δ 6.39 (s, 1H), 5.74 (dddd, $J = 18.8, 10.2, 8.5, 6.5$ Hz, 1H), 5.15-5.08 (m, 2H), 3.80-3.71 (m, 1H), 2.80-2.71 (m, 1H), 2.26-2.13 (m, 4H), 1.75-1.64 (m, 2H), 1.55-1.39 (m, 4H), 1.06-0.91 (m, 21H); ^{13}C NMR (90 MHz, CDCl_3) δ 173.7, 131.7, 119.9, 71.9, 52.7, 45.6, 35.8, 35.2, 34.4, 29.5, 27.5, 18.0, 12.2; IR (neat) 3192, 3076, 1651, 1401 cm^{-1} ; HRMS (APCI) calcd for $\text{C}_{20}\text{H}_{38}\text{NO}_2\text{Si}$ (MH^+) 352.2672, found 352.2688.

1-Allyl-3-oxo-6-triisopropylsilyloxy-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *t*-Butyl Ester (16)

To a solution of lactam **15** (430 mg, 1.2 mmol) in THF (60 mL) at $0\text{ }^{\circ}\text{C}$ was added 60% NaH in mineral oil (98 mg, 4.1 mmol), and the mixture was heated at reflux for 1 h. The mixture was then cooled to rt and di-*t*-butyl dicarbonate (1.4 mL, 6.1 mmol) was added, reheated to reflux and stirred for 18 h. The mixture was cooled to rt and saturated aqueous NH_4Cl (20 mL) was carefully added. The aqueous layer was extracted with Et_2O . The combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography (20:1, hexanes/ EtOAc) to give carboxy imide **16** (540 mg, 98%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 5.78 (dddd, $J = 16.6, 10.2, 8.3, 6.2$ Hz, 1H), 5.12-4.99 (m, 2H), 3.77 (ddd, $J = 9.4, 4.6, 4.6$ Hz, 1H), 2.82 (dd, $J = 18.1, 1.1$ Hz, 1H), 2.52 (dd, $J = 17.4, 9.1$ Hz, 1H), 2.34-2.18 (m, 2H), 2.17-2.04 (m, 2H), 1.94 (dd, $J = 13.6, 3.5$ Hz, 1H), 1.80-1.65 (m, 1H), 1.53-1.44 (m, 11H), 1.43-1.25 (m, 1H), 1.04-0.90 (m, 21H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.2, 153.5, 132.3, 119.1, 83.5, 71.7, 58.7, 43.0, 35.0, 34.5, 33.8, 30.9, 27.5, 17.9, 12.1; IR (neat) 2942, 1737, 1670, 1385 cm^{-1} ; HRMS (APCI) calcd for $\text{C}_{20}\text{H}_{45}\text{NO}_2\text{Si}$ ($\text{MH}^+ - \text{C}_5\text{H}_9\text{O}_2$) 352.2672, found 352.2662.

1-Allyl-4-hydroxy-3-oxo-6-(triisopropylsilyloxy)-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *t*-Butyl Ester (17)

To a solution of carboxyimide **16** (540 mg, 1.2 mmol) in THF (90 mL) at $-78\text{ }^{\circ}\text{C}$ was added sodium bis(trimethylsilyl)amide (1.8 mL, 1.0 M in THF). After the mixture was stirred for 1 h, 2-(phenylsulfonyl)-3-phenyloxaziridine^{8b} (630 mg, 2.4 mmol) was then added. After 30 min, saturated aqueous NH_4Cl was added, and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with 28% NH_4OH , water and brine, dried with MgSO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography (toluene) to give α -hydroxyimide **17** (550 mg, 98%) as a colorless oil: ^1H NMR (360 MHz, CDCl_3) δ 5.78 (dddd, $J = 14.8, 7.9, 6.5, 6.5$ Hz, 1H), 5.17-5.02 (m, 2H), 4.39-4.32 (m, 1H), 3.84-3.69 (m, 1H), 3.11 (d, $J = 1.5$ Hz, 1H), 2.71 (dd, $J = 14.2, 6.4$ Hz, 1H), 2.30-2.08 (m, 4H), 1.89-1.73 (m, 1H), 1.51 (s, 9H), 1.44-1.30 (m, 3H), 1.11-0.90 (m, 21H); ^{13}C NMR (90 MHz, CDCl_3) δ 174.7, 152.2, 132.2, 119.4, 83.9, 70.3, 67.7, 60.4, 43.1, 41.4, 32.9, 32.7, 28.6, 27.7, 18.0, 12.2; IR (Nujol mull) 3423, 3078, 1742, 1659, 1462 cm^{-1} ; HRMS (APCI) calcd for $\text{C}_{20}\text{H}_{37}\text{NO}_3\text{Si}$ ($\text{MH}^+ - \text{C}_5\text{H}_9\text{O}_2$) 368.2621, found 368.2596.

1-Allyl-4-hydroxy-3-methoxy-6-(triisopropylsilyloxy)-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *t*-Butyl Ester (19)

To a solution of α -hydroxyimide **17** (66 mg, 0.14 mmol) in THF (4.7 mL) at 0 °C was added lithium aluminum hydride (21 mg, 0.56 mmol). After stirring for 30 min at 0 °C, the mixture was carefully quenched with H₂O (0.5 mL), 15% aqueous NaOH (0.5 mL) and water (0.5 mL). This mixture was dried with Na₂SO₄ and concentrated *in vacuo*. To the crude residue was added CH₂Cl₂/MeOH (1:1, 0.3 mL) and scandium(III) trifluoromethanesulfonate (1.0 mg) at rt. After 4 h, saturated aqueous NaHCO₃ was added. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried with Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (15:1 –9:1, hexanes/EtOAc gradient) to give α -methoxyimide **19** (52 mg, 76%) as a white solid: mp 97–98 °C; ¹H NMR (300 MHz, CDCl₃) δ 5.77 (dddd, *J* = 17.5, 8.7, 6.3, 6.3 Hz, 1H), 5.67–5.24 (m, 1H), 5.09–4.99 (m, 2H), 3.93 (dd, *J* = 9.7, 6.0 Hz, 1H), 3.75–3.59 (m, 1H), 3.56 (s, 3H), 3.03–2.50 (m, 3H), 2.15 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.07–1.91 (m, 1H), 1.71–1.59 (m, 1H), 1.51 (s, 9H), 1.32–1.18 (m, 1H), 1.12–0.90 (m, 23H); HRMS (APCI) calcd for C₂₅H₄₆NO₄Si (MH⁺-MeOH) 452.3196, found 452.3166.

1-Allyl-4-benzyloxy-3-methoxy-6-triisopropylsilyloxy-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *t*-Butyl Ester (20)

To a solution of alcohol **19** (509 mg, 1.1 mmol) and 18-crown-6 (14 mg, 0.05 mmol) in THF (3 mL) at rt was added 60% NaH in mineral oil (84 mg, 3.5 mmol). After 30 min, the mixture was cooled to 0 °C and benzyl bromide (250 μ L, 2.1 mmol) was added. The mixture was warmed to rt and stirred for 18 h. Water was then carefully added to the mixture, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (30:1, hexanes/EtOAc) to give benzyl ether **20** (580 mg, 96%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.40–7.20 (m, 5H), 5.90–5.22 (m, 2H, rotamer), 5.10–4.92 (m, 2H, rotamer), 4.72–4.48 (m, 2H, rotamer), 3.82–3.62 (m, 2H), 3.46–3.22 (m, 3H, rotamer), 2.99–2.16 (m, 5H, rotamer), 1.73–1.62 (m, 1H, rotamer), 1.58–1.20 (m, 11H), 1.18–0.91 (m, 22H); ¹H NMR (300 MHz, toluene-*d*₈, 70 °C) δ 7.36–7.30 (m, 2H), 7.17–6.95 (m, 3H), 5.82 (dddd, *J* = 16.9, 10.2, 8.1, 6.7 Hz, 1H), 5.70 (br s, 1H), 5.09–4.98 (m, 2H), 4.59–4.47 (m, 2H), 3.76 (d, *J* = 5.0 Hz, 1H), 3.68 (ddd, *J* = 10.9, 5.0, 5.0 Hz, 1H), 3.30 (s, 3H), 2.97–2.81 (m, 2H), 2.63–2.50 (m, 1H), 2.30–2.18 (m, 2H), 1.70–1.57 (m, 1H), 1.49–1.32 (m, 10H), 1.11–0.88 (m, 23H); ¹³C NMR (75 MHz, toluene-*d*₈, 70 °C) δ 139.9, 135.3, 128.3, 127.9 (2C), 127.4, 117.2, 84.0, 79.9, 75.1, 72.4, 71.1, 65.8, 56.8 (2C), 42.6, 34.2, 29.5, 28.6, 18.5, 18.4, 13.0; IR (neat) 3070, 1700, 1367 cm⁻¹; HRMS (APCI) calcd for C₃₂H₅₂NO₅Si (MH⁺-MeOH) 542.3666, found 542.3617.

1-Allyl-4-benzyloxy-3-(4-methoxybenzyl)-6-triisopropylsilyloxy-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *t*-Butyl Ester (21 and 23)

To a solution of methoxyimide **20** (210 mg, 0.36 mmol) in Et₂O (5 mL) at –30 °C was added TiCl₄ (140 μ L, 1.3 mmol). After 2 min, *p*-methoxybenzylmagnesium chloride¹⁶ (1.6 mL, 0.80 M¹⁷ in THF) was added to the mixture. The mixture was slowly warmed to –10 °C over 90 min. Saturated aqueous NH₄Cl was then added to the mixture. The aqueous layer was extracted with Et₂O. The combined organics were washed with saturated aqueous NaHCO₃ and brine, dried with MgSO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (toluene) to give a mixture of carbamates **21** and **23** (210 mg, 87%) as a colorless oil. Data for the 5:4 mixture of isomers: ¹H NMR (300 MHz, CDCl₃) δ 7.35–7.11 (m, 7H), 6.84–6.72 (m, 2H), 5.90–5.72 (m, 1H \times 0.56), 5.45–5.29 (m, 1H \times 0.44), 5.14–5.04 (m, 1H), 4.94–4.85 (m, 1H), 4.68 (d, *J* = 11.2 Hz, 1H \times 0.56); 4.58 (br s, 1H \times 0.44), 4.40 (d, *J* = 11.2 Hz, 1H \times 0.56), 4.33 (br s, 1H \times 0.44), 3.99 (d, *J* = 8.4 Hz, 1H \times 0.56), 3.95–3.83 (m, 1H

× 0.44), 3.82-3.73 (m, 7H), 3.66-3.57 (m, 1H), 3.32-3.18 (m, 1H), 2.84-2.22 (m, 5H), 1.83 (dd, $J = 13.4, 8.9$ Hz, 1H × 0.56), 1.77-1.22 (m, 13H), 1.18-1.12 (m, 21H), 0.98 (ddd, $J = 7.6, 7.6, 4.6$ Hz, 1H × 0.44); ^{13}C NMR (75 MHz, CDCl_3) δ 157.7 (minor), 157.6 (major), 155.3, 138.8 (minor), 138.7 (major), 134.8 (minor), 134.3 (major), 132.2, 130.4 (minor), 130.2 (major), 128.3 (minor), 128.0 (major), 127.7 (minor), 127.5, 127.4 (major), 127.1 (minor), 127.6 (major), 118.1 (minor), 117.5 (major), 113.5 (minor), 113.1 (major), 79.3, 75.6 (minor), 74.6 (major), 72.0, 71.6 (minor), 71.1 (major), 58.8 (minor), 57.6 (major), 55.3 (minor), 55.2 (major), 44.1, 43.7 (minor), 42.3 (major), 34.8 (minor), 34.2 (major), 33.7 (major), 29.2 (minor), 28.6 (major), 28.4, 18.3 (minor), 18.2, 12.6 (minor), 12.4 (major); IR (neat) 3066, 3031, 1691, 1366 cm^{-1} ; HRMS (APCI) calcd for $\text{C}_{40}\text{H}_{62}\text{NO}_5\text{Si}$ (MH^+) 664.4397, found 664.4343.

1-Allyl-4-benzyloxy-3-(4-methoxybenzyl)-6-triisopropylsilanyloxy-2-azabicyclo[3.3.1]nonanes (**22** and **24**)

To a solution of the mixture of carbamates **21** and **23** (290 mg, 0.43 mmol) and anisole (0.5 mL, 4.3 mmol) in CH_2Cl_2 (5.7 mL) at rt was added trifluoroacetic acid (0.7 mL, 8.6 mmol). After 18 h, saturated aqueous NaHCO_3 was carefully added. The aqueous layer was extracted with CH_2Cl_2 . The combined organics were washed with saturated aqueous NaHCO_3 and brine, dried with Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 – 4:1, hexanes/EtOAc gradient) to give amines **22** (125 mg, 51%) and **24** (96 mg, 39%) as colorless oils.

22— ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.25 (m, 5H), 7.11 (d, $J = 8.6$ Hz, 2H), 6.79 (d, $J = 8.6$ Hz, 2H), 5.89-5.75 (m, 1H), 5.12-5.04 (m, 2H), 4.47 (d, $J = 11.6$ Hz, 1H), 4.21-4.08 (m, 2H), 3.78 (s, 3H), 3.76-3.69 (m, 1H), 3.50 (t, $J = 2.8$ Hz, 1H), 2.80-2.69 (m, 2H), 2.51-2.40 (m, 1H), 2.11-1.86 (m, 5H), 1.75-1.66 (m, 1H), 1.54 (ddd, $J = 7.9, 13.5, 13.5$ Hz, 1H), 1.15 (dd, $J = 12.8, 2.6$ Hz, 1H), 1.19-0.90 (m, 21H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.7, 139.2, 133.8, 131.6, 130.0, 128.2, 127.6, 127.3, 118.4, 113.6, 72.5, 71.0, 70.8, 57.0, 55.2, 50.3, 48.4, 38.4, 38.3, 35.5, 32.8, 32.4, 18.1, 18.0, 12.3; HRMS (ESI+) calcd for $\text{C}_{35}\text{H}_{54}\text{NO}_3\text{Si}$ (MH^+) 564.3873, found 564.3861.

24— ^1H NMR (300 MHz, CDCl_3) δ 7.37-7.24 (m, 5H), 7.19-7.13 (m, 2H), 6.85-6.78 (m, 2H), 5.62 (dddd, $J = 17.8, 10.2, 7.7, 7.7$ Hz, 1H), 4.87 (dd, $J = 10.1, 2.2$ Hz, 1H), 4.78 (d, $J = 11.5$ Hz, 1H), 4.71-4.62 (m, 1H), 4.42 (d, $J = 11.5$ Hz, 1H), 3.81-3.66 (m, 4H), 3.51-3.45 (m, 1H), 3.20 (dd, $J = 13.4, 2.7$ Hz, 1H), 3.06 (ddd, $J = 2.9, 9.2, 9.2$ Hz, 1H), 2.41 (dd, $J = 13.4, 9.1$ Hz, 1H), 2.28-2.20 (m, 1H), 2.10 (ddd, $J = 13.3, 3.6, 3.6$ Hz, 1H), 1.96-1.82 (m, 2H), 1.81-1.54 (m, 2H), 1.24-0.95 (m, 24H); ^{13}C NMR (75 MHz, CDCl_3) δ 157.9, 139.2, 133.7, 131.5, 130.2, 128.3, 127.7, 127.3, 117.9, 113.6, 78.6, 72.2, 70.7, 55.2, 54.5, 50.1, 47.5, 43.3, 39.3, 37.8, 31.5, 28.8, 18.4, 18.2, 12.7; IR (neat) 3067, 3030 cm^{-1} ; HRMS (ESI+) calcd for $\text{C}_{35}\text{H}_{54}\text{NO}_3\text{Si}$ (MH^+) 564.3873, found 564.3848.

1-Allyl-6-hydroxy-2-benzyl-2-azabicyclo[3.3.1]nonan-3-one (**29**)

To a solution of alcohol **12** (1.3 g, 4.4 mmol), *p*-nitrobenzoic acid (3.2 g, 19.3 mmol) and triphenylphosphine (5.7 g, 21.9 mmol) in benzene (83 mL) at rt was added diethyl azodicarboxylate (3.5 mL, 21.9 mmol) dropwise. After 1 h, the mixture was concentrated *in vacuo*. The crude residue was dissolved with MeOH/THF (5:3, 110 mL) and a solution of K_2CO_3 (1.2 g, 8.8 mmol) in H_2O (11 mL) was added at rt. The mixture was stirred for 18 h, and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography (1:2, hexanes/EtOAc) to give alcohol **29** (700 mg, 56%) as a white foam: ^1H NMR (300 MHz, CDCl_3) δ 7.30-7.11 (m, 5H), 5.54 (dddd, $J = 16.7, 10.3, 7.9, 6.4$ Hz, 1H), 5.04-4.91 (m, 2H), 4.60 (AB_q, $J = 15.6$ Hz, $\Delta\nu_{\text{AB}} = 64.5$ Hz, 2H), 3.76 (d,

$J = 2.5$ Hz, 1H), 2.93 (br s, 1H), 2.70 (dd, $J = 18.4, 7.5$ Hz, 1H), 2.36 (dd, $J = 14.4, 6.3$ Hz, 1H), 2.27 (dd, $J = 18.4, 1.8$ Hz, 1H), 2.22-2.06 (m, 2H), 2.05-1.97 (m, 1H), 1.72-1.38 (m, 4H), 1.32-1.22 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 172.3, 139.1, 132.5, 128.2, 127.3, 126.8, 118.9, 69.0, 58.9, 44.7, 44.4, 35.9, 32.8, 31.1, 28.1, 25.1; IR (film) 3388, 3064, 3027, 1611 cm^{-1} ; HRMS (ESI+) calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_2$ (MH^+) 286.1807, found 286.1802.

1-Allyl-2-benzyl-6-(triisopropylsilyloxy)-2-azabicyclo[3.3.1]nonan-3-one (30)

To a solution of alcohol **29** (860 mg, 3.0 mmol) in CH_2Cl_2 (12 mL) at 0°C was added triethylamine (1.1 mL, 7.5 mmol) and triisopropylsilyl trifluoromethanesulfonate (1.1 mL, 3.9 mmol). The mixture warmed to rt, stirred for 2 h and water (10 mL) was then added. The aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography (8:1, hexanes/EtOAc) to give silyl ether **30** (950 mg, 72%) as a colorless oil: ^1H NMR (360 MHz, CDCl_3) δ 7.32-7.16 (m, 5H), 5.57 (dddd, $J = 16.9, 10.2, 7.6, 7.6$ Hz, 1H), 5.06-4.96 (m, 2H), 4.66 (AB_q , $J = 15.5$ Hz, $\Delta\nu_{\text{AB}} = 42.0$ Hz, 2H), 3.91-3.81 (m, 1H), 2.75 (dd, $J = 18.4, 7.5$ Hz, 1H), 2.41 (dd, $J = 13.9, 5.8$ Hz, 1H), 2.36-2.28 (m, 1H), 2.21 (dd, $J = 14.3, 7.9$ Hz, 1H), 2.16-2.04 (m, 2H), 1.71 (ddd, $J = 4.7, 13.1, 13.1$ Hz, 1H), 1.64-1.57 (m, 1H), 1.55-1.39 (m, 2H), 1.30-1.19 (m, 1H), 1.11-0.96 (m, 21H); ^{13}C NMR (90 MHz, CDCl_3) δ 171.9, 139.4, 132.6, 128.1, 127.5, 126.6, 118.9, 70.0, 58.7, 44.5, 44.3, 35.8, 33.6, 31.2, 28.4, 25.7, 17.9, 12.1; IR (neat) 3063, 3027, 1623, 1398 cm^{-1} ; HRMS (ESI+) calcd for $\text{C}_{27}\text{H}_{44}\text{NO}_2\text{Si}$ (MH^+) 442.3141, found 442.3103.

1-Allyl-2-benzyl-4-hydroxy-6-triisopropylsilyloxy-2-azabicyclo[3.3.1]nonan-3-one (31)

A solution of carboxyimide **30** (1.00 g, 2.26 mmol) in THF (6.8 mL) was added dropwise via cannula to LDA (7.14 mL, 0.47 M in THF) at -78°C . The mixture was warmed to 0°C and stirred for 1 h, recooled to -78°C and 2-(phenylsulfonyl)-3-phenyloxaziridine^{8b} (886 mg, 3.39 mmol) was added. The mixture was allowed to warm to rt overnight, saturated aqueous NaHCO_3 was added and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with saturated aqueous NaHCO_3 , water and brine, dried over MgSO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography (4:1, hexanes/EtOAc) to give α -hydroxyimide **31** (628 mg, 60%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.39-7.19 (m, 5H), 5.64 (dddd, $J = 16.9, 10.3, 7.5, 6.6$ Hz, 1H), 5.12 (d, $J = 8.4$ Hz, 1H), 5.05 (dd, $J = 15.1, 1.6$ Hz, 1H), 4.78, 4.57 (AB_q , $J = 15.5$ Hz, $\Delta\nu_{\text{AB}} = 48.2$ Hz, 2H), 4.00-3.88 (m, 1H), 3.85 (s, 1H), 3.40 (s, 1H), 2.41 (dd, $J = 14.4, 6.5$ Hz, 1H), 2.24 (dd, $J = 14.2, 7.7$ Hz, 1H), 2.00 (ddd, $J = 12.1, 3.1, 1.3$ Hz, 1H), 1.88-1.65 (m, 3H), 1.57-1.46 (m, 1H), 1.22-1.14 (m, 2H), 1.10-0.89 (m, 21H).

1-Allyl-2-benzyl-4,6-dihydroxy-2-azabicyclo[3.3.1]nonan-3-one (32)

To a stirred solution of lactam alcohol **31** (200 mg, 0.437 mmol) in anhydrous THF (4.4 mL) was added tetrabutylammonium fluoride (525 μL , 1.0 M in THF, 0.525 mmol). After stirring the mixture at rt for 5 h, a further portion of tetrabutylammonium fluoride (1.0 mL, 1.0 M in THF, 1.0 mmol) was added and the mixture was stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc) to afford diol **32** (132 mg, 100%) as a white crystalline solid. Crystals suitable for X-ray crystallography were obtained by recrystallization from MeOH: ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.20 (m, 5H), 5.62 (dddd, $J = 16.9, 10.2, 7.6, 6.7$ Hz, 1H), 5.08 (d, $J = 10.7$ Hz, 1H), 5.04 (dd, $J = 16.9, 1.3$ Hz, 1H), 4.75, 4.61 (AB_q , $J = 13.4$ Hz, $\Delta\nu_{\text{AB}} = 28.1$ Hz, 2H), 3.94 (d, $J = 2.5$ Hz, 1H), 3.89 (s, 1H), 3.76 (br s, 1H), 2.41 (dd, $J = 14.4, 6.5$ Hz, 1H), 2.24 (dd, $J = 13.0, 7.3$ Hz, 2H), 1.98-1.87 (m, 3H), 1.69 (ddd, $J = 12.8, 12.8, 3.6$ Hz, 1H), 1.38-1.21 (m,

2H), 1.58-1.49 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.7, 138.4, 132.1, 128.5, 127.5, 127.1, 119.5, 70.2, 66.9, 59.9, 44.9, 44.3, 39.9, 28.1, 27.1, 25.7.

1-Allyl-3-oxo-6-triisopropylsilyloxy-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *t*-Butyl Ester (33)

In a 500 mL three-neck round bottomed flask fitted with a cold finger condenser at $-78\text{ }^\circ\text{C}$ was condensed ammonia (60 mL). Sodium (500 mg, 27.7 mmol) followed by *t*-butanol (1.0 mL, 10.9 mmol) were carefully added to the ammonia changing the color of the mixture to blue. After 45 min, a solution of *N*-benzyl lactam **30** (950 mg, 2.2 mmol) in Et_2O (17 mL) was added to the mixture dropwise via a gastight syringe. The mixture was stirred at reflux for 75 min, and then solid ammonium chloride (3 g) was carefully added until the blue color dissipated. The mixture was then slowly warmed to rt, while occasionally replacing the evaporating ammonia with THF. The resulting mixture was concentrated *in vacuo*. The crude residue was dissolved in THF (32 mL) and 60% NaH in mineral oil (170 mg, 7.2 mmol) was added at $0\text{ }^\circ\text{C}$. The mixture was heated at reflux for 1 h, was then cooled to rt and di-*t*-butyl dicarbonate (2.0 mL, 8.7 mmol) was added. The mixture was again heated at reflux and stirred for 18 h, cooled to rt and saturated aqueous NH_4Cl was carefully added. The aqueous layer was extracted with Et_2O . The combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography (20:1, hexanes/ EtOAc) to give carboxyimide **33** (660 mg, 67%) as a colorless oil: ^1H NMR (360 MHz, CDCl_3) δ 5.84-5.69 (m, 1H), 5.09-4.98 (m, 2H), 3.87-3.71 (m, 1H), 2.55 (ddd, $J = 18.1, 7.3, 4.5$ Hz, 1H), 2.50-2.41 (m, 1H), 2.16-2.03 (m, 3H), 2.01-1.90 (m, 2H), 1.73-1.49 (m, 4H), 1.48-1.40 (m, 9H), 1.08-0.86 (m, 21H); ^{13}C NMR (90 MHz, CDCl_3) δ 171.1, 153.4, 132.2, 118.8, 83.3 (2C), 69.8, 59.7 (2C), 43.4, 35.7, 34.0, 30.1, 29.8, 27.4, 25.8, 17.8 (3C), 12.0; HRMS (APCI) calcd for $\text{C}_{25}\text{H}_{46}\text{NO}_4\text{Si}$ (MH^+) 452.3196, found 452.3193.

1-Allyl-4-hydroxy-3-oxo-6-(triisopropylsilyloxy)-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *t*-Butyl Ester (34)

To a solution of carboxyimide **33** (200 mg, 0.45 mmol) in THF (27 mL) at $-78\text{ }^\circ\text{C}$ was added sodium bis(trimethylsilyl)amide (0.54 mL, 1.0 M in THF). The mixture was warmed to $-10\text{ }^\circ\text{C}$ over a 1 h period. After the mixture was cooled to $-78\text{ }^\circ\text{C}$, 2-(phenylsulfonyl)-3-phenyloxaziridine^{8b} (190 mg, 0.72 mmol) was added and the mixture was stirred for an additional 30 min. Saturated aqueous NH_4Cl was added, the mixture was warmed to rt, and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with 28% aqueous NH_4OH , water and brine, dried with MgSO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography (toluene - 25:1, toluene/ EtOAc gradient) to give α -hydroxyimide **34** (110 mg, 53%) as a white solid: mp $77\text{--}78\text{ }^\circ\text{C}$; ^1H NMR (360 MHz, CDCl_3) δ 5.78 (dddd, $J = 17.0, 10.3, 7.6, 6.8$ Hz, 1H), 5.17-5.08 (m, 2H), 4.33 (d, $J = 2.7$ Hz, 1H), 4.17 (d, $J = 6.6$ Hz, 1H), 3.47 (s, 1H), 2.64 (dd, $J = 14.6, 6.7$ Hz, 1H), 2.54-2.48 (m, 1H), 2.21-2.13 (m, 2H), 2.07 (dd, $J = 13.7, 4.0$ Hz, 1H), 1.85-1.63 (m, 3H), 1.55-1.44 (m, 10H), 1.12-0.98 (m, 21H); ^{13}C NMR (90 MHz, CDCl_3) δ 175.9, 153.0, 131.9, 119.4, 83.9, 70.0, 64.5, 62.0, 43.1, 39.7, 30.6, 27.7, 26.2, 18.1 (2C), 12.2; HRMS (ESI+) calcd for $\text{C}_{25}\text{H}_{45}\text{NNaO}_5\text{Si}$ ($\text{MH}^+ + \text{Na}$) 490.2965, found 490.2951.

1-Allyl-4-benzyloxy-3-oxo-6-triisopropylsilyloxy-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *t*-Butyl Ester (35)

To a solution of alcohol **34** (44 mg, 0.09 mmol) and 18-crown-6 (1 mg, 0.005 mmol) in THF (0.3 mL) at rt was added 60% NaH in mineral oil (7 mg, 0.30 mmol). After 30 min, the mixture was cooled to $0\text{ }^\circ\text{C}$ and benzyl bromide (22 μL , 0.18 mmol) was added. The mixture was warmed to rt and stirred for 18 h. Water was then carefully added to the mixture, and the aqueous layer was extracted with EtOAc . The combined organic layers were washed with

saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1, hexanes/EtOAc) to give benzyl ether **35** (35 mg, 69%) as a colorless oil: ¹H NMR (360 MHz, CDCl₃) δ 7.39-7.23 (m, 5H), 5.92-5.71 (m, 1H), 5.18-5.06 (m, 3H), 4.79 (d, *J* = 12.7 Hz, 1H), 4.39 (d, *J* = 2.7 Hz, 1H), 3.94 (d, *J* = 6.5 Hz, 1H), 2.54 (dd, *J* = 14.5, 6.4 Hz, 1H), 2.42-2.36 (m, 1H), 2.25-1.95 (m, 3H), 1.90-1.60 (m, 4H), 1.53 (m, 9H), 1.12-0.93 (m, 21H); ¹³C NMR (90 MHz, CDCl₃) δ 173.7, 153.4, 138.3, 132.9, 128.3, 127.7, 127.6, 119.2, 83.8, 75.8, 73.9, 65.0, 60.7, 43.4, 40.6, 30.9, 30.3, 27.7, 26.3, 18.1 (2C), 12.1 (2C); IR (neat) 3065, 3031, 1739, 1689 cm⁻¹; HRMS (APCI) calcd for C₃₂H₅₂NO₅Si (MH⁺) 558.3615, found 558.3620.

1-Allyl-4-benzyloxy-3-(4-methoxybenzyl)-6-triisopropylsilyloxy-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *t*-Butyl Ester (**36**)

To a solution of carboxyimide **35** (17 mg, 0.03 mmol) in Et₂O (0.4 mL) at -35 °C was added *p*-methoxybenzylmagnesium chloride¹⁶ (0.09 mL, 1.21 M¹⁷ in THF). The mixture was slowly warmed to rt and stirred for 18 h. Saturated aqueous NH₄Cl was then added to the mixture, and the aqueous layer was extracted with Et₂O. The combined organics were washed with brine, dried with Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (10:1, hexanes/EtOAc) to give adduct **36** (19 mg, 90%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.24 (m, 5H), 7.16-7.09 (m, 2H), 6.88-6.81 (m, 2H), 5.63 (dddd, *J* = 17.4, 10.5, 7.3, 7.3 Hz, 1H), 5.10-5.00 (m, 2H), 4.63 (d, *J* = 2.3 Hz, 1H), 4.48-4.34 (m, 2H), 4.24 (d, *J* = 10.9 Hz, 1H), 3.90-3.76 (m, 4H), 3.66 (AB_q, *J* = 15.2 Hz, Δ*v*_{AB} = 22.5 Hz, 2H), 2.71-2.53 (m, 1H), 2.39 (dd, *J* = 14.2, 7.5 Hz, 1H), 2.22-2.08 (m, 1H), 2.03-1.88 (m, 2H), 1.70-1.48 (m, 4H), 1.45-1.35 (m, 9H), 1.12-0.94 (m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 209.0, 158.7, 137.9, 133.6, 130.5, 128.2, 127.6, 125.4, 118.2, 114.1, 87.8, 82.4, 72.2, 70.6, 55.2, 53.9, 45.2, 43.5, 33.0, 32.3, 31.3, 29.7, 28.4, 18.4, 18.3, 13.0; IR (neat) 3412, 3044, 3032, 1717, 1512 cm⁻¹; HRMS (ESI⁺) calcd for C₄₀H₆₂NO₆Si (MH⁺) 680.4346, found 680.4311.

1-Allyl-4-benzyloxy-3-(4-methoxybenzyl)-6-triisopropylsilyloxy-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *t*-Butyl Ester (**37**)

To a solution of alcohol **36** (30 mg, 0.04 mmol) in AcOH (0.5 mL) at rt was added 5 portions of sodium cyanoborohydride (14 mg × 5, 0.22 mmol × 5) every 30 min for 2.5 h. After 48 h at rt, the mixture was poured into H₂O, and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine and 10% NaOH, dried with Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1, hexanes/EtOAc) to give carbamate **37** (20 mg, 69%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.25 (m, 5H), 7.20-7.13 (m, 2H), 6.89-6.83 (m, 2H), 5.82 (dddd, *J* = 16.7, 9.1, 7.3, 7.3 Hz, 1H), 5.18-5.06 (m, 2H), 4.69 (AB_q, *J* = 11.4 Hz, Δ*v*_{AB} = 19.9 Hz, 2H), 4.53-4.39 (m, 1H), 4.05-3.95 (m, 2H), 3.88 (ddd, *J* = 9.8, 9.8, 4.4 Hz, 1H), 3.80 (s, 3H), 2.91-2.78 (m, 1H), 2.77-2.62 (m, 2H), 2.55 (dd, *J* = 14.5, 7.8 Hz, 1H), 2.19-2.08 (m, 1H), 2.03-1.88 (m, 2H), 1.72-1.50 (m, 2H), 1.45-1.36 (m, 9H), 1.29-1.18 (m, 1H), 1.11-1.00 (m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 158.7, 156.6, 139.1, 134.5, 131.0, 130.7, 128.8, 128.0, 127.7, 118.7, 114.5, 80.1, 73.6, 73.3, 72.4, 55.7, 54.8, 42.6, 39.2, 37.8, 33.5, 31.9, 30.1, 28.9, 18.9 (2C), 13.7; HRMS (APCI) calcd for C₄₀H₆₂NO₅Si (MH⁺) 664.4397, found 664.4450.

1-Allyl-4-benzyloxy-3-(4-methoxybenzyl)-6-triisopropylsilyloxy-2-azabicyclo[3.3.1]nonane (**38**)

To a solution of carbamate **37** (20 mg, 0.03 mmol) and anisole (33 μL, 0.30 mmol) in CH₂Cl₂ (0.5 mL) at rt was added trifluoroacetic acid (47 μL, 0.60 mmol). After 18 h, saturated aqueous NaHCO₃ was carefully added, and the aqueous layer was extracted with CH₂Cl₂. The combined organics were washed with saturated aqueous NaHCO₃ and brine, dried with Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified by flash chromatography

(9:1, EtOAc/MeOH) to give amine **38** (17 mg, 100%) as a colorless oil: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.37-7.23 (m, 5H), 7.20-7.14 (m, 2H), 6.89-6.81 (m, 2H), 5.96-5.78 (m, 1H), 5.22-5.12 (m, 2H), 4.65 (AB_q, $J = 11.4$ Hz, $\Delta\nu = 33.4$ Hz, 2H), 4.09 (ddd, $J = 9.0, 4.7, 4.7$ Hz, 1H), 3.89 (br d, $J = 3.8$ Hz, 1H), 3.85-3.75 (m, 4H), 2.97-2.62 (m, 2H), 2.44-2.17 (m, 2H), 2.05-1.90 (m, 2H), 1.74-1.19 (m, 6H), 1.12-0.99 (m, 21H); IR (neat) 3342, 3064, 3031, 1463 cm^{-1} ; APCI m/z (relative intensity) 582.4 ($\text{MH}^+ + \text{H}_2\text{O}$, 100), 408.3 (9).

7-Benzyloxy-6-(4-methoxybenzyl)-3-phenylsulfanyl-9-triisopropylsilanyloxy-5-azatricyclo[6.3.1.0^{1,5}]dodecanes (**43a/43b**)

To a solution of amine **22** (40 mg, 0.07 mmol) in Et_2O (1 mL) at rt was added pyridinium *p*-toluenesulfonate (21 mg, 0.09 mmol). After 30 min, the mixture was concentrated *in vacuo* and the crude residue was diluted with CH_2Cl_2 (1 mL). To the mixture was then added PhSCl^{18} (12 μL , 0.11 mmol) and after 30 min, MeOH (1 mL) was added followed by K_2CO_3 (98 mg, 0.71 mmol) and silica gel (160 mg). After 18 h, the mixture was filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 – 1:1, hexanes/EtOAc gradient) to give amines **43a** (9 mg, 19%) and **43b** (15 mg, 32 %) as colorless oils.

43a— $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.32-7.15 (m, 10H), 7.02 (d, $J = 8.6$ Hz, 2H), 6.70 (d, $J = 8.6$ Hz, 2H), 4.32-4.23 (m, 1H), 4.08-3.94 (m, 2H), 3.80-3.59 (m, 6H), 3.41-3.33 (m, 1H), 2.90-2.72 (m, 2H), 2.39-2.26 (m, 1H), 2.21-1.70 (m, 5H), 1.62-1.07 (m, 3H), 0.98-0.73 (m, 21H); HRMS (ESI+) calcd for $\text{C}_{41}\text{H}_{58}\text{NO}_3\text{SSi}$ (MH^+) 672.3907, found 672.3884.

43b— $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.39-7.22 (m, 9H), 7.20-7.14 (m, 1H), 7.07 (d, $J = 8.6$ Hz, 2H), 6.76 (d, $J = 8.6$ Hz, 2H), 4.46-4.40 (m, 1H), 4.13-4.00 (m, 2H), 3.80-3.62 (m, 5H), 3.49-3.35 (m, 2H), 3.00 (dd, $J = 13.1, 10.6$ Hz, 1H), 2.89-2.80 (m, 1H), 2.46-2.28 (m, 2H), 2.12-1.49 (m, 6H), 1.34-1.19 (m, 1H), 1.12-0.81 (m, 22H); HRMS (ESI+) calcd for $\text{C}_{41}\text{H}_{58}\text{NO}_3\text{SSi}$ (MH^+) 672.3907, found 672.3884.

7-Benzyloxy-6-(4-methoxybenzyl)-9-triisopropylsilanyloxy-5-azatricyclo[6.3.1.0^{1,5}]dodecane (**44**)

To a solution of amines **43a** and **43b** (6 mg, 0.009 mmol) in EtOH (1.5 mL) at rt was added Raney-Ni (~50–70 mg) and the mixture was then heated at reflux. After 15 min, the mixture was filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash chromatography (10:1, hexanes/EtOAc) to give amine **44** (4 mg, 79%) as a colorless oil: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.38-7.24 (m, 5H), 7.14-7.08 (m, 2H), 6.82-6.75 (m, 2H), 4.41-4.32 (m, 1H), 4.15-3.99 (m, 2H), 3.78 (s, 3H), 3.73-3.61 (m, 1H), 3.51-3.29 (m, 2H), 3.02-2.71 (m, 3H), 2.45-2.32 (m, 1H), 2.18-1.92 (m, 2H), 1.90-1.11 (m, 8H), 1.01-0.79 (m, 21H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 157.8, 139.2, 130.1, 128.2, 127.5, 127.2, 113.6, 72.9, 71.5, 70.6, 61.4, 55.2, 47.8, 38.6, 38.1, 35.9, 32.4, 31.0, 29.7, 19.7, 18.1, 18.0, 12.3; HRMS (ESI+) calcd for $\text{C}_{35}\text{H}_{54}\text{NO}_3\text{Si}$ (MH^+) 564.3873, found 564.3908.

Supplementary Material

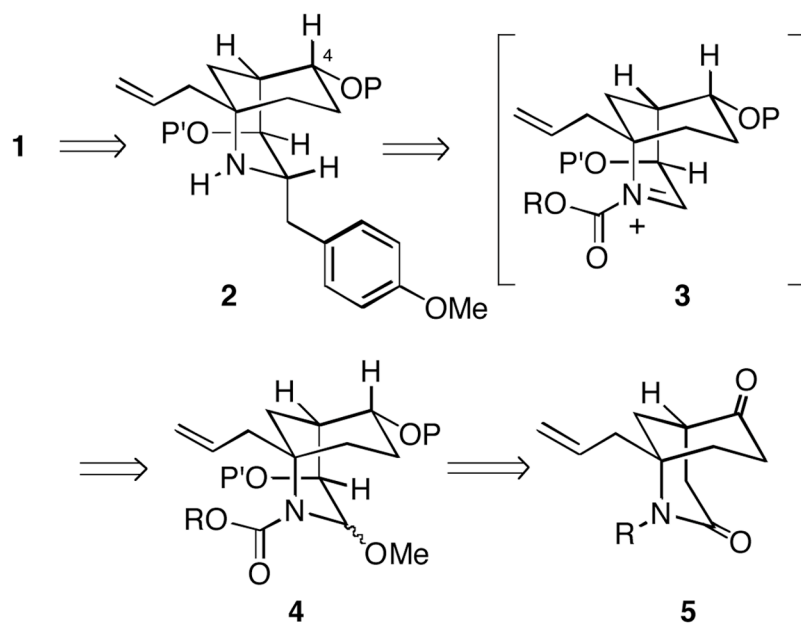
Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

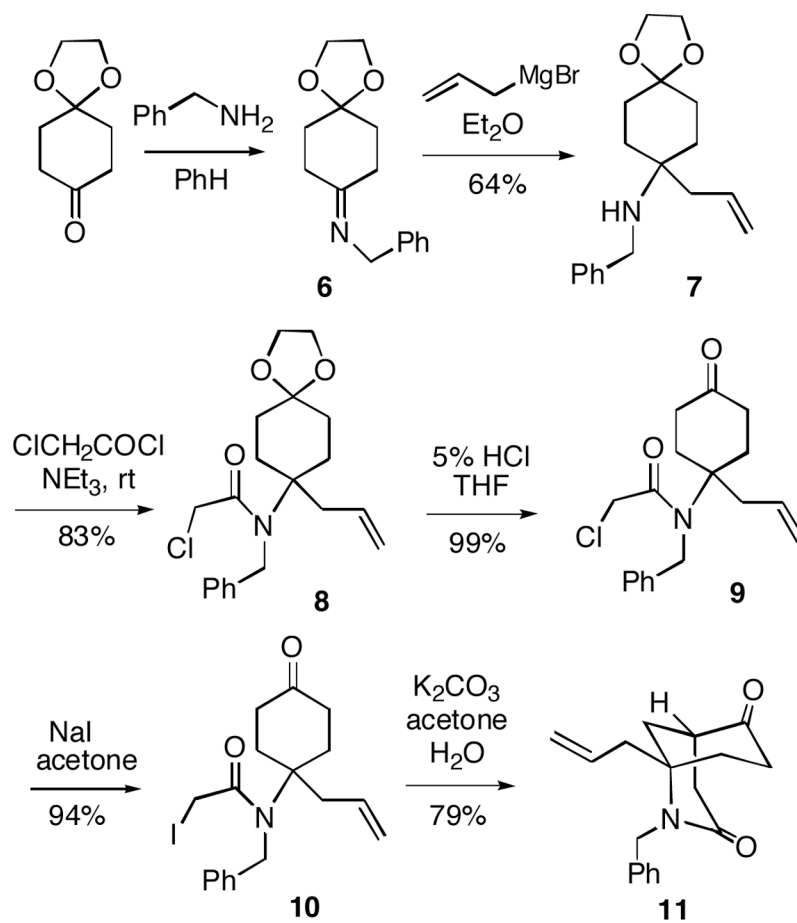
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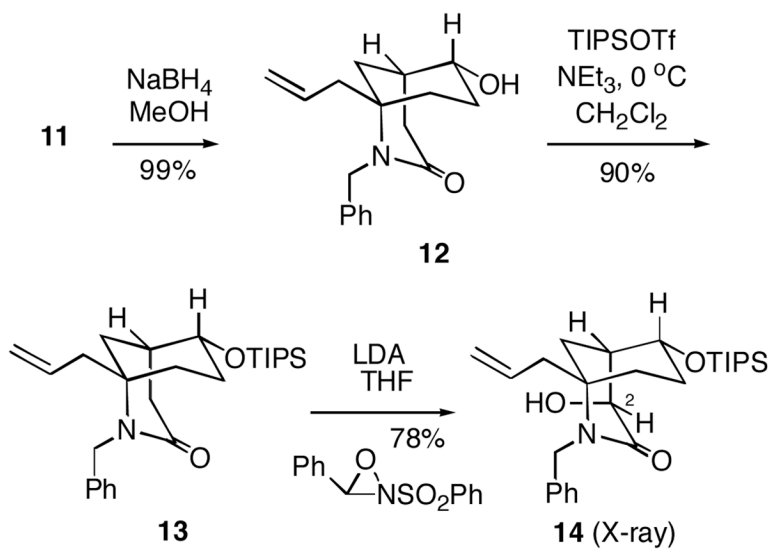
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6. For a review, see: Zefirov NS, Palyulin VA, Elieil EL, Wilen SH. *Conformational Analysis of Bicyclo[3.3.1]nonanes and Their Hetero Analogs*. Topics in Stereochemistry Wiley New York 1991:20171
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12. Exact replication of the hydroxylation conditions previously used with *N*-benzyl lactam 30 (Cf. Scheme 7), which involved the use of LDA to form the corresponding enolate in place of sodium hexamethyldisilazide, also led to the same incorrect equatorial C-2 alcohol 34, but in low yield.
13. (a) Berthe B, Outurquin F, Paulmier C. *Tetrahedron Lett* 1997;38:1393. b Pannecoucke X, Outurquin F, Paulmier C. *Eur J Org Chem* 2002:995. c Outurquin F, Pannecoucke X, Bénédicte B, Paulmier C. *Eur J Org Chem* 2002:1007.
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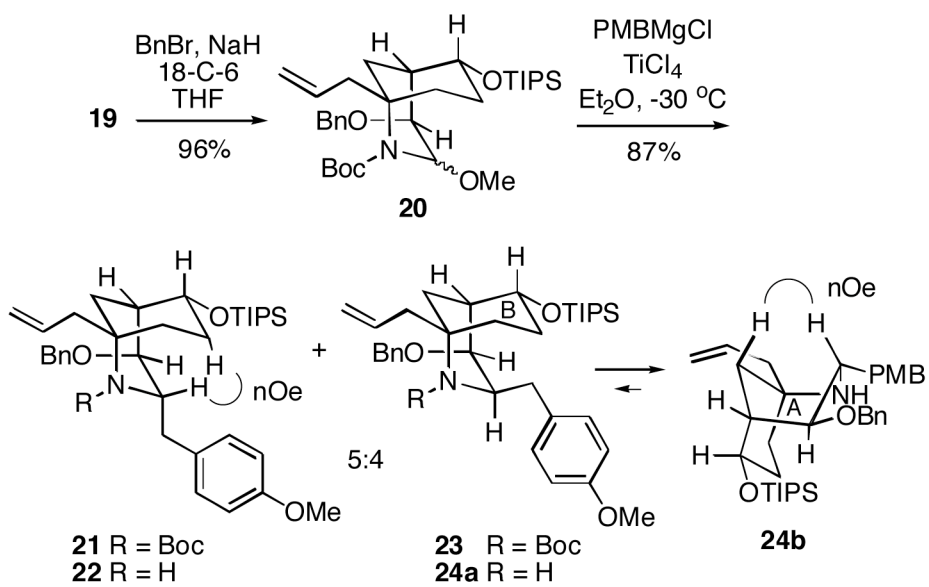
Scheme 1.



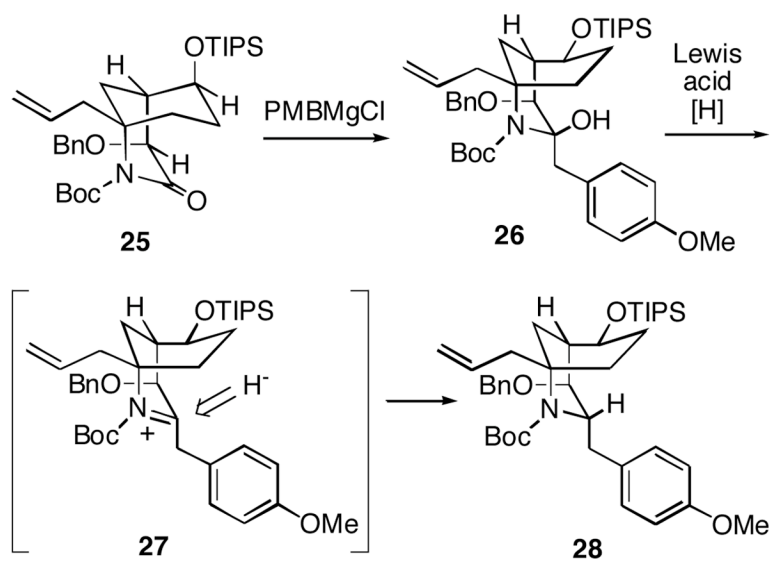
Scheme 2.



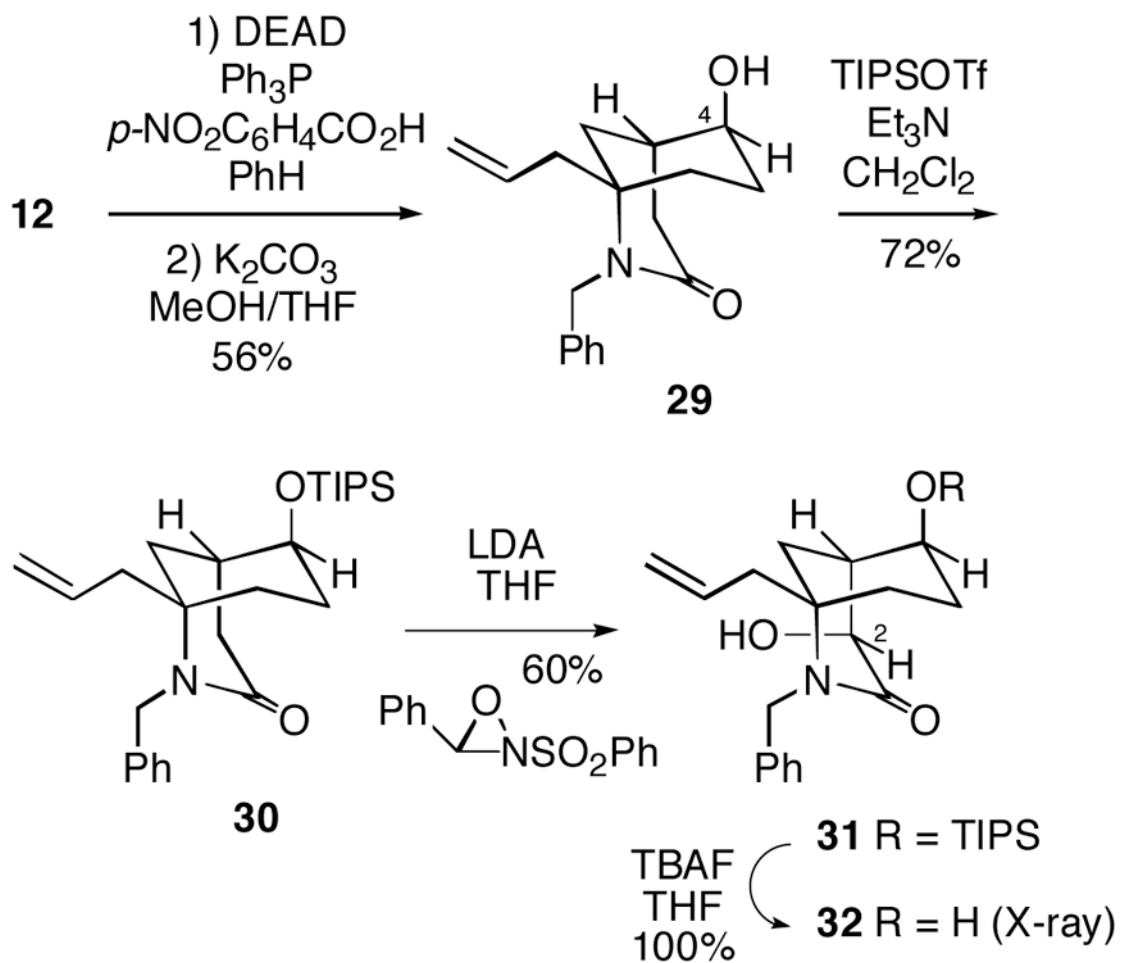
Scheme 3.



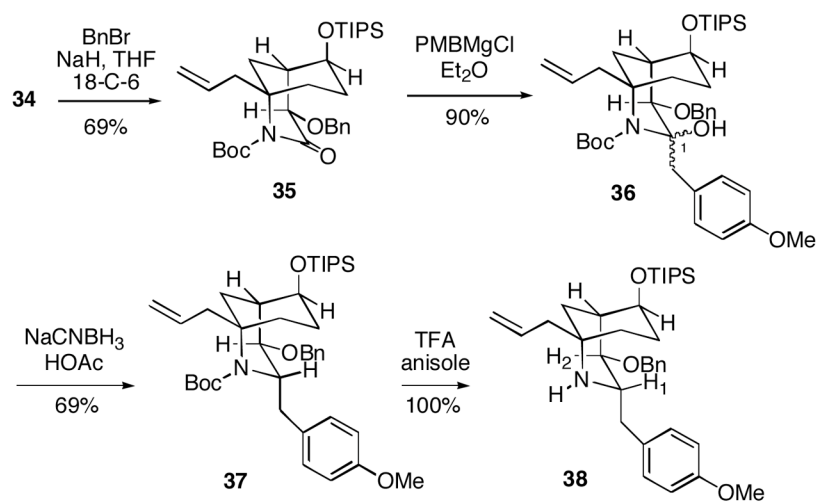
Scheme 5.



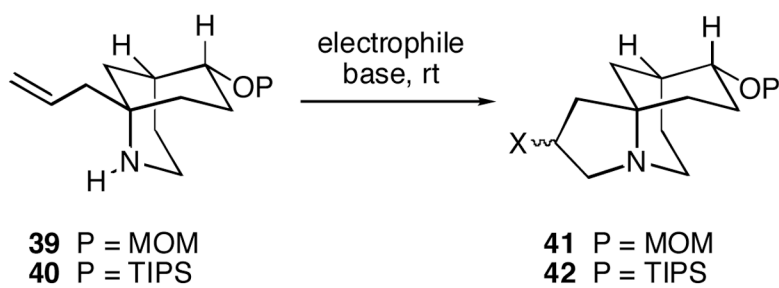
Scheme 6.



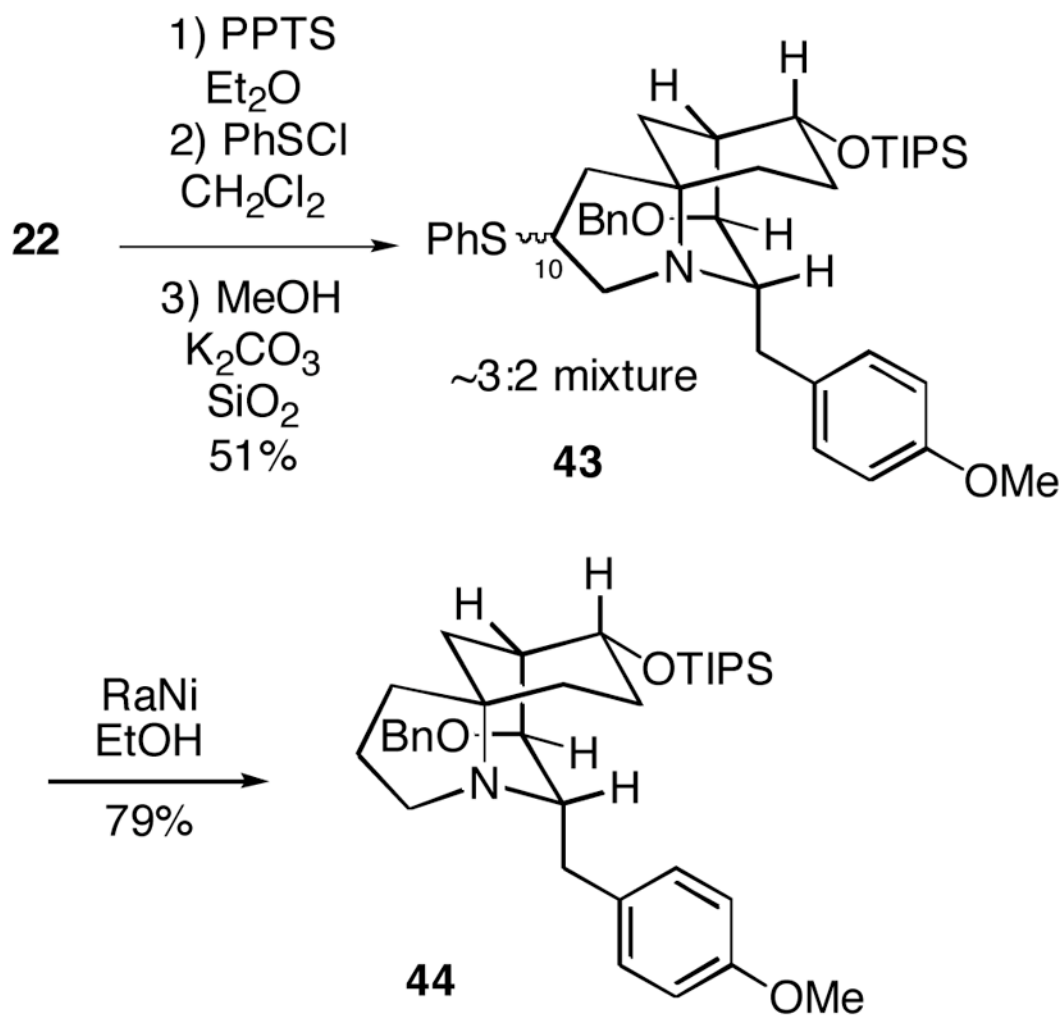
Scheme 7.



Scheme 9.



Scheme 10.



Scheme 11.

Table 1
5-Endo Trig Cyclizations of Homoallylic Amines 39 and 40.

entry	amine	electrophile (eq)	base (eq)	additive (eq)	product (%)
1	39	I ₂ (3)	NaHCO ₃ (3)	-	complex mixture
2	39	Hg(CO ₂ CF ₃) ₂ (2)	NaHCO ₃ (10)	NaCl (10)	complex mixture
3	39	PhSeBr (1.5), MeCN	Na ₂ CO ₃ (1.9)	-	41 (41) X = SePh
4	39	PhSeBr (3), MeCN	Na ₂ CO ₃ (1.9)	-	41 (37) X = SePh
5	39^a	PhSeBr (1.5), MeCN	K ₂ CO ₃ (4.5)	NaI (4)	41 (52) X = SPh
6	40	I ₂ (3)	NaHCO ₃ (3)	-	complex mixture
7	40	NIS (1.1)	-	-	complex mixture
8	40	PhSeBr (1.5), MeCN	NaHCO ₃ (1.9)	-	no reaction
9	40^a	PhSeBr (1.5), MeCN	-	SiO ₂	42 (61) X = SPh

^a pyridinium *p*-toluenesulfonate was added first to protect the amine