Studies on a Total Synthesis of the Microbial Immunosuppresive Agent FR901483
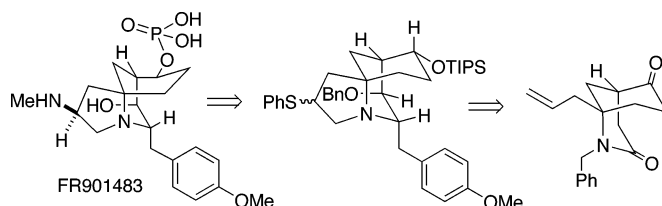
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A strategy is outlined for construction of the fungal immunosuppressant FR901483 (**1**). It was possible to convert 1,4-cyclohexanedione monoethylene ketal in five simple steps to iodoacetamide ketone **10**, which was cyclized in good yield to the 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 toward 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**.

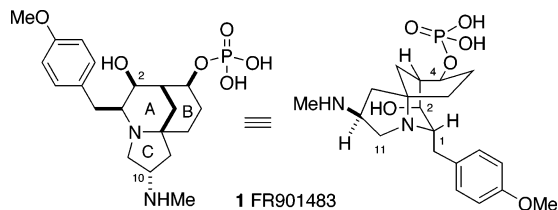## Introduction and Background

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

(1) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37.

(2) For total syntheses of FR901483, see: (a) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778. (b) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593. (c) Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765. (d) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125. (e) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534. (f) Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 2729. (g) For a formal total synthesis see: Brummond, K. M.; Hong, S. *J. Org. Chem.* **2005**, *70*, 907.

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/C-rings 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, initally 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-Iodo amidoketone **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

SCHEME 1
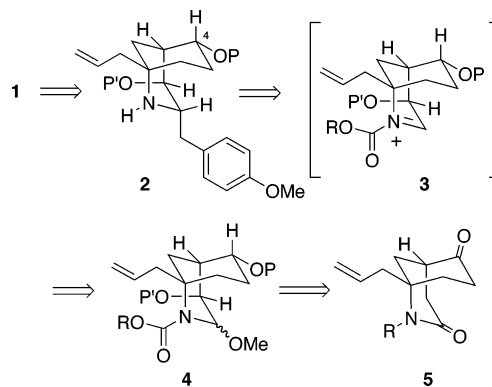
SCHEME 2
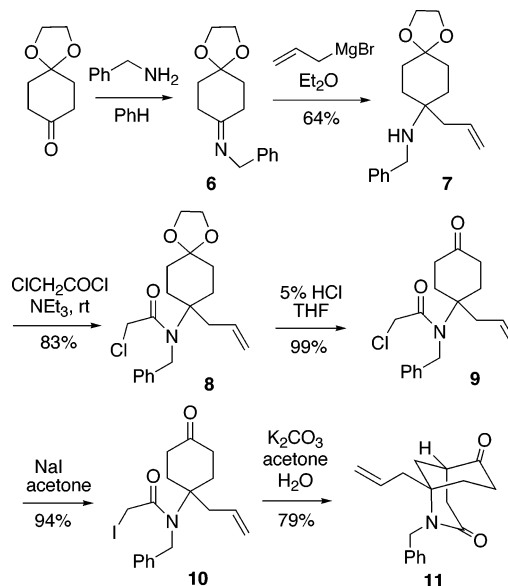
to form bicyclo[3.3.1]nonane ring systems, but these annulations often occur in poor to mediocre yields.[5,6] Indeed, we found initially that cyclization could be achieved if iodoketone **10** is treated with KO*t*-Bu in *t*-BuOH/THF (1:1) at room temperature, furnishing the desired bicyclo[3.3.1]nonanone **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

(3) For other synthetic approaches to this metabolite and some analogues, see: (a) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442. (b) Bonjoch, J.; Diaba, F.; Puigbo, G.; Sole, D.; Segarra, V.; Santamaria, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891. (c) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013. (d) Brummond, K. M.; Lu, J. *Org. Lett.* **2001**, *3*, 1347. (e) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353. (f) Bonjoch, J.; Diaba, F.; Puigbo, G.; Peidro, E.; Sole, D. *Tetrahedron Lett.* **2003**, *44*, 8387. (g) Panchaud, P.; Ollivier, C.; Renaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, *69*, 2755.

(4) Taken in part from the Ph.D. Thesis of J. E. Kropf, The Pennsylvania State University, 2002.

(5) See, for example: (a) Marvell, E. N.; Sturmer, D.; Rowell, C. *Tetrahedron* **1966**, *22*, 861. (b) Lednicer, D. *J. Med. Chem.* **1977**, *20*, 171. (c) Boger, D. L.; Patel, M.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4559. (d) Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968.

(6) For a review, see: Zefirov, N. S.; Palyulin, V. A. Conformational Analysis of Bicyclo[3.3.1]nonanes and Their Hetero Analogues. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1991; Vol. 20, p 171.

(7) In model systems, we have investigated the possibility of enantioselectively cyclizing prochiral ketones similar to **10** with chiral amide bases: Kropf, J. E.; Weinreb, S. M. *Chem. Commun.* **1998**, 2357.
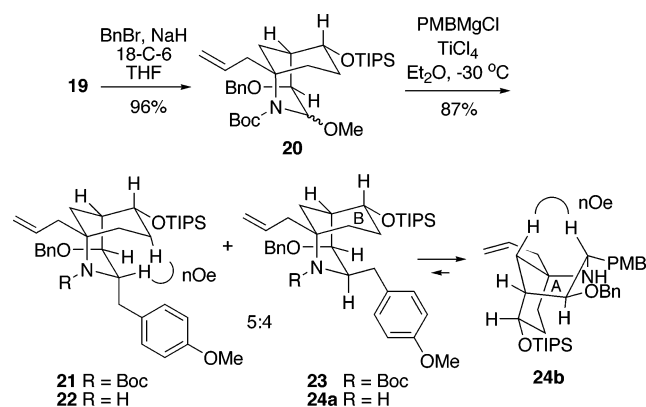
SCHEME 3
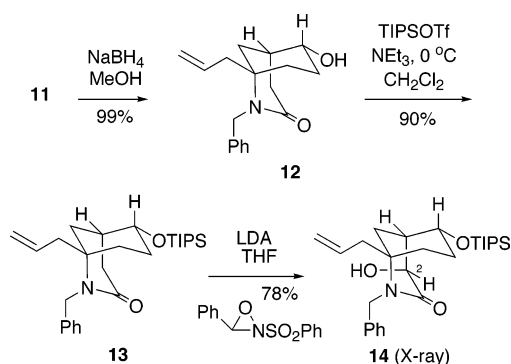
**SCHEME 4**

SCHEME 5

SCHEME 6
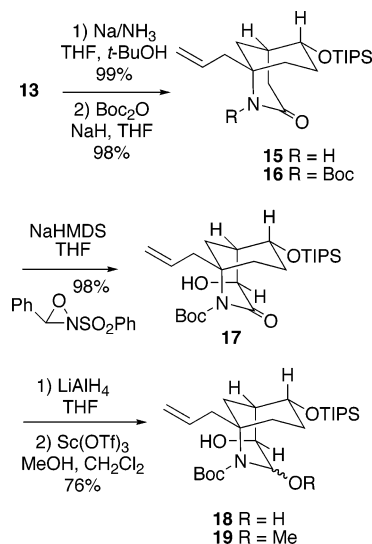
LDA, followed by treatment of the resulting enolate with the Davis oxaziridine reagent,[8] to lead to a single α-hydroxylation product **14** in good yield. X-ray analysis of this compound indicated that it did indeed have the correct C-2 stereochemistry for FR901483. However, since dissolving metal 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
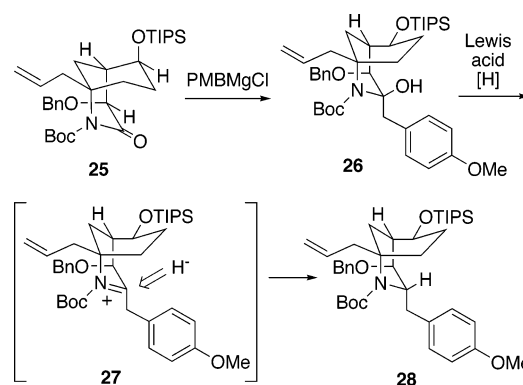
excess *p*-methoxybenzylmagnesium chloride in the presence of a variety of Lewis acids were unsuccessful.[10]

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*-methoxy-benzylmagnesium 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 ^{1}H 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 nonbonded 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

(8) (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. (b) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203.
(9) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809.

(10) Cf. Harrison, J. R.; O'Brien, P. *Tetrahedron Lett.* **2000**, *41*, 6167.

SCHEME 7

SCHEME 8

SCHEME 9

SCHEME 10

39 P = MOM
40 P = TIPS

41 P = MOM
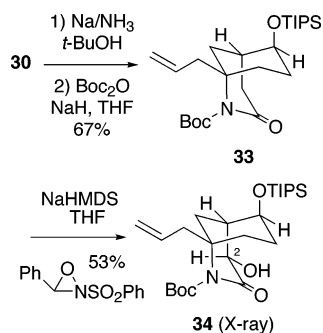42 P = TIPS
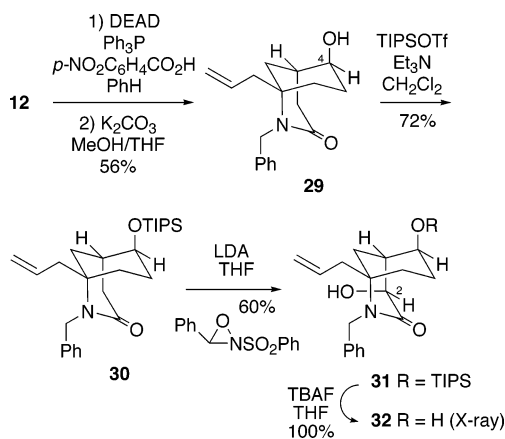
group equatorial, similar to the case in the natural product (cf. **1**). Compound **26** would subsequently be converted to the desired PMB product **28** via hydride reduction which we believed should occur from the less hindered axial face of intermediate acyliminium ion **27**.
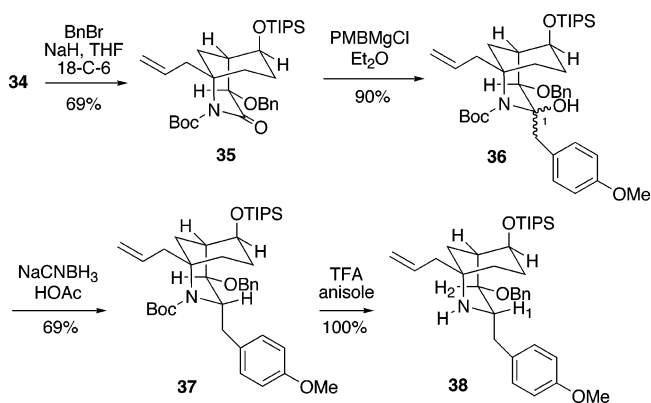
To test this approach, equatorial alcohol **12** was first inverted via a Mitsunobu procedure to afford the C-4 epimeric axial alcohol **29** (Scheme 7).[11] The alcohol functionality was then protected as the TIPS ether **30**. This lactam could be hydroxylated stereoselectively in 60% yield using LDA, 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*-benzyllactam **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 H_1/H_2 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-
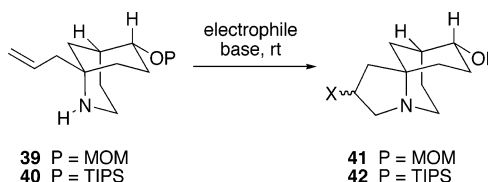
(11) (a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. (b) Mitsunobu, O. *Synthesis* **1981**, 1.

(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.

(14) (a) Cooper, M. A.; Francis, C. L.; Holman, J. W.; Kasum, B.; Taverner, T.; Tickink, E. R. T.; Word, D. A. *Aust. J. Chem.* **2000**, *53*, 123. (b) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1986**, *51*, 1724. (c) Clive, D. L. J.; Farina, V.; Singh, A.; Wong, C. K.; Kiel, W. A.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2120.

(15) Yodo, M.; Harada, H. *Chem. Pharm. Bull.* **1989**, *37*, 2361.

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

entry	amine	electrophile (equiv)	base (equiv)	additive (equiv)	product (%)
1	**39**	I_2 (3)	$NaHCO_3$ (3)		complex mixture
2	**39**	$Hg(CO_2CF_3)_2$ (2)	$NaHCO_3$ (10)	NaCl (10)	complex mixture
3	**39**	PhSeBr (1.5), MeCN	Na_2CO_3 (1.9)		**41** (41), X = SePh
4	**39**	PhSeBr (3), MeCN	Na_2CO_3 (1.9)		**41** (37), X = SePh
5	**39**[a]	PhSCl (1.4), CH_2Cl_2	K_2CO_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]	PhSCl (1.4), CH_2Cl_2		SiO_2	**42** (61), X = SPh

[a] Pyridinium *p*-toluenesulfonate was added first to protect the amine.

SCHEME 11
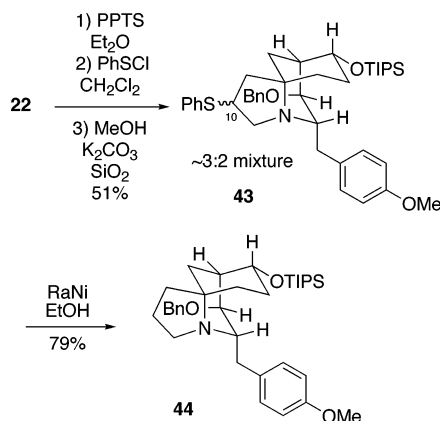
induced cyclization methodology of Paulmier et al. (entries 3 and 4).[13] Thus, tricyclic selenide **41** (X = SePh) could be prepared as a mixture of stereoisomers from homoallylic amine **39** in moderate yields. The cyclization of **39** using phenylsulfenyl chloride,[15] however, proceeded in an 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 *p*-toluenesulfonate (PPTS). The cyclized product **43** then was produced upon addition of K_2CO_3 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. 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 tricycle **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 tricycles **43** should provide a convenient handle for eventual introduction of the methylamino group of the natural product.

Conclusion

In this paper, 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 and concentrated in vacuo, and the residual imine **6** was dissolved in Et_2O (400 mL). The solution was cooled to 0 °C, and allylmagnesium bromide (200 mL, 1.0 M in Et_2O) was added dropwise. The mixture was warmed to rt, stirred for an additional 2 h, and then cooled to 0 °C and quenched by the slow addition of saturated aqueous NH_4Cl followed by water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, 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: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (90 MHz, $CDCl_3$) 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 $C_{18}H_{26}NO_2$ (MH$^+$) 288.1963, found 288.1968.

2-Chloro-*N*-(8-allyl-1,4-dioxaspiro[4.5]dec-8-yl)-*N*-benzyl-acetamide (8). To a solution of amine **7** (6.8 g, 23.5 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (19 mL) was then added dropwise via cannula, and the mixture was stirred at 0 °C for 1 h before warming to rt. After being stirred at rt for 2 h, the solution was cooled to 0 °C and water was added. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 C$_{20}$H$_{27}$ClNO$_3$ (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 the mixture was stirred 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 NaHCO$_3$. The aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with brine, dried over MgSO$_4$, 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: ^{1}H NMR (360 MHz, CDCl$_3$) 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); ^{13}C NMR (90 MHz, CDCl$_3$) 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 C$_{18}$H$_{23}$ClNO$_2$ (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 being stirred 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 Na$_2$S$_2$O$_3$ and brine, dried over MgSO$_4$, 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: ^{1}H NMR (360 MHz, CDCl$_3$) 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); ^{13}C NMR (90 MHz, CDCl$_3$) 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 C$_{18}$H$_{23}$INO$_2$ (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 being stirred 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 Na$_2$SO$_4$, 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 K$_2$CO$_3$ (3.25 g, 23.5 mmol) in water (42.5 mL). After being stirred 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 Na$_2$SO$_4$, 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: ^{1}H NMR (400 MHz, CDCl$_3$) 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, Δν$_{AB}$ = 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); ^{13}C NMR (90 MHz, CDCl$_3$) 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 C$_{18}$H$_{22}$NO$_2$ (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 Et$_2$O, and washed with water, and the aqueous layer was further extracted with Et$_2$O. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, 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: ^{1}H NMR (300 MHz, CDCl$_3$) 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, Δν$_{AB}$ = 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); ^{13}C NMR (75 MHz, CDCl$_3$) 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 C$_{18}$H$_{23}$-NO$_2$ 285.1727, found 285.1729.

1-Allyl-2-benzyl-6-(triisopropylsilanyloxy)-2-azabicyclo[3.3.1]-nonan-3-one (13). To a solution of alcohol **12** (792 mg, 2.77 mmol) in CH$_2$Cl$_2$ (11 mL) at 0 °C were 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 CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over MgSO$_4$, 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; ^{1}H NMR (300 MHz, CDCl$_3$) 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, Δν$_{AB}$ = 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); ^{13}C NMR (75 MHz, CDCl$_3$) 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 C$_{27}$H$_{44}$NO$_2$Si (MH$^+$) 442.3141, found 442.3155.

1-Allyl-2-benzyl-4-hydroxy-6-(triisopropylsilanyloxy)-2-azabicyclo[3.3.1]nonan-3-one (14). To a solution of N,N-diiso-propylamine (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 NaHCO$_3$. The organic layer was washed with water and brine. The combined aqueous layers were extracted with CH$_2$Cl$_2$, and the extract was dried with MgSO$_4$ 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; ^{1}H NMR (300 MHz, CDCl$_3$) 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, Δν$_{AB}$ = 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); ^{13}C NMR (90 MHz, CDCl$_3$) 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 C$_{27}$H$_{44}$NO$_3$Si (MH$^+$) 458.3090, found 458.3087.

1-Allyl-6-(triisopropylsilanyloxy)-2-azabicyclo[3.3.1]nonan-3-one (15). In a 1 L three-neck round-bottomed flask fitted with a coldfinger condenser at −78 °C was condensed ammonia (380 mL). Sodium (4.0 g, 172 mmol) followed by *tert*-butyl alcohol (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$_2$O (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: ^{1}H 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 C$_{20}$H$_{38}$NO$_2$Si (MH$^+$) 352.2672, found 352.2688.

1-Allyl-3-oxo-6-triisopropylsilanyloxy-2-azabicyclo[3.3.1]-nonane-2-carboxylic Acid *tert*-Butyl Ester (16). To a solution of lactam **15** (430 mg, 1.2 mmol) in THF (60 mL) at 0 °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, di-*tert*-butyl dicarbonate (1.4 mL, 6.1 mmol) was added, and the mixture was reheated to reflux and stirred for 18 h. The mixture was cooled to rt, and saturated aqueous NH$_4$Cl (20 mL) was carefully added. The aqueous layer was extracted with Et$_2$O. 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: ^{1}H 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 C$_{20}$H$_{45}$NO$_2$Si (MH$^+$ − C$_5$H$_9$O$_2$) 352.2672, found 352.2662.

1-Allyl-4-hydroxy-3-oxo-6-(triisopropylsilanyloxy)-2-azabicyclo-[3.3.1]nonane-2-carboxylic Acid *tert*-Butyl Ester (17). To a solution of carboxyimide **16** (540 mg, 1.2 mmol) in THF (90 mL) at −78 °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$_4$Cl was added, and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with 28% NH$_4$OH, 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: ^{1}H 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 C$_{20}$H$_{37}$NO$_3$Si (MH$^+$ − C$_5$H$_9$O$_2$) 368.2621, found 368.2596.

1-Allyl-4-hydroxy-3-methoxy-6-(triisopropylsilanyloxy)-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *tert*-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 being stirred for 30 min at 0 °C, the mixture

was carefully quenched with H$_2$O (0.5 mL), 15% aqueous NaOH (0.5 mL), and water (0.5 mL). This mixture was dried with Na$_2$SO$_4$ and concentrated in vacuo. To the crude residue were added CH$_2$Cl$_2$/MeOH (1:1, 0.3 mL) and scandium(III) trifluoromethanesulfonate (1.0 mg) at rt. After 4 h, saturated aqueous NaHCO$_3$ was added. The aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried with Na$_2$SO$_4$, 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; ^{1}H NMR (300 MHz, CDCl$_3$) 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 C$_{25}$H$_{46}$NO$_4$Si (MH$^+$ − MeOH) 452.3196, found 452.3166.

1-Allyl-4-benzyloxy-3-methoxy-6-triisopropylsilanyloxy-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *tert*-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 μL, 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 NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, 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: ^{1}H NMR (300 MHz, CDCl$_3$) 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); ^{1}H 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); ^{13}C 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 C$_{32}$H$_{52}$NO$_5$Si (MH$^+$ − MeOH) 542.3666, found 542.3617.

1-Allyl-4-benzyloxy-3-(4-methoxybenzyl)-6-triisopropylsilanyloxy-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *tert*-Butyl Ester (21 and 23). To a solution of methoxyimide **20** (210 mg, 0.36 mmol) in Et$_2$O (5 mL) at −30 °C was added TiCl$_4$ (140 μL, 1.3 mmol). After 2 min, *p*-methoxybenzylmagnesium chloride[16] (1.6 mL, 0.80 M[17] in THF) was added to the mixture. The mixture was slowly warmed to −10 °C over 90 min. Saturated aqueous NH$_4$Cl was then added to the mixture. The aqueous layer was extracted with Et$_2$O. The combined organics were washed with saturated aqueous NaHCO$_3$ and brine, dried with MgSO$_4$, 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: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35−7.11 (m, 7H), 6.84−6.72 (m, 2H), 5.90−5.72 (m, 1H × 0.56), 5.45−5.29 (m, 1H × 0.44), 5.14−5.04 (m, 1H), 4.94−4.85 (m, 1H), 4.68 (d, J = 11.2 Hz, 1H × 0.56); 4.58 (br s, 1H × 0.44), 4.40 (d, J = 11.2 Hz, 1H × 0.56), 4.33 (br s, 1H × 0.44), 3.99 (d, J = 8.4 Hz, 1H × 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

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(17) Titrated with salicylaldehyde phenylhydrazone: Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755.

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 C$_{40}$H$_{62}$NO$_5$Si (MH$^+$) 664.4397, found 664.4343.

1-Allyl-4-benzyloxy-3-(4-methoxybenzyl)-6-triisopropylsila-nyloxy-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$_2$Cl$_2$ (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$_2$Cl$_2$. The combined organics were washed with saturated aqueous NaHCO$_3$ and brine, dried with Na$_2$SO$_4$, 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: ^{1}H 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 C$_{35}$H$_{54}$NO$_3$Si (MH$^+$) 564.3873, found 564.3861.

24: ^{1}H 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 C$_{35}$H$_{54}$NO$_3$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$_2$CO$_3$ (1.2 g, 8.8 mmol) in H$_2$O (11 mL) was added at rt. The mixture was stirred for 18 h, and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with water and brine, dried over Na$_2$SO$_4$, 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: ^{1}H 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, $\Delta\nu_{AB}$ = 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 C$_{18}$H$_{24}$NO$_2$ (MH$^+$) 286.1807, found 286.1802.

1-Allyl-2-benzyl-6-(triisopropylsilanyloxy)-2-azabicyclo[3.3.1]-nonan-3-one (30). To a solution of alcohol **29** (860 mg, 3.0 mmol) in CH$_2$Cl$_2$ (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 and stirred for 2 h, and water (10 mL) was then added. The aqueous layer was extracted with CH$_2$Cl$_2$. 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: ^{1}H 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, $\Delta\nu_{AB}$ = 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 C$_{27}$H$_{44}$NO$_2$Si (MH$^+$) 442.3141, found 442.3103.

1-Allyl-2-benzyl-4-hydroxy-6-triisopropylsilanyloxy-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, stirred for 1 h, and 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$_2$O. 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: ^{1}H 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, $\Delta\nu_{AB}$ = 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 the mixture was stirred 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$_2$SO$_4$, 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: ^{1}H 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, $\Delta\nu_{AB}$ = 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-triisopropylsilanyloxy-2-azabicyclo[3.3.1]-nonane-2-carboxylic Acid *tert*-Butyl Ester (33). In a 500 mL three-neck round-bottomed flask fitted with a coldfinger condenser at −78 °C was condensed ammonia (60 mL). Sodium (500 mg, 27.7 mmol) followed by *tert*-butyl alcohol (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$_2$O (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 the evaporating ammonia was occasionally replaced 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 °C. The mixture was heated at reflux for 1 h and then cooled to rt, and di-*tert*-butyl dicarbonate (2.0 mL, 8.7 mmol) was added. The mixture was again heated at reflux, stirred for 18 h, and cooled to rt, and saturated aqueous NH$_4$Cl was carefully added. The aqueous layer was extracted with Et$_2$O. 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: ^{1}H 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 C$_{25}$H$_{46}$NO$_4$Si (MH$^+$) 452.3196, found 452.3193.

1-Allyl-4-hydroxy-3-oxo-6-(triisopropylsilanyloxy)-2-azabicyclo-[3.3.1]nonane-2-carboxylic Acid *tert*-Butyl Ester (34). To a solution of carboxyimide **33** (200 mg, 0.45 mmol) in THF (27 mL) at −78 °C was added sodium bis(trimethylsilyl)amide (0.54 mL, 1.0 M in THF). The mixture was warmed to −10 °C over a 1 h period. After the mixture was cooled to −78 °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$_4$Cl was added, the mixture was warmed to rt, and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with 28% aqueous NH$_4$OH, 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 77−78 °C; ^{1}H 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 C$_{25}$H$_{45}$NNaO$_5$Si (MH$^+$ + Na) 490.2965, found 490.2951.

1-Allyl-4-benzyloxy-3-oxo-6-triisopropylsilanyloxy-2-azabicyclo-[3.3.1]nonane-2-carboxylic Acid *tert*-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 °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 NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, 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: ^{1}H NMR (360 MHz, CDCl$_3$) 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); ^{13}C NMR (90 MHz, CDCl$_3$) 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 C$_{32}$H$_{52}$NO$_5$Si (MH$^+$) 558.3615, found 558.3620.

1-Allyl-4-benzyloxy-3-hydroxy-3-(4-methoxybenzyl)-6-triiso-propylsilanyloxy-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *tert*-Butyl Ester (36). To a solution of carboxyimide **35** (17 mg, 0.03 mmol) in Et$_2$O (0.4 mL) at −35 °C was added *p*-methoxy-benzylmagnesium chloride[16] (0.09 mL, 1.21 M[17] in THF). The mixture was slowly warmed to rt and stirred for 18 h. Saturated aqueous NH$_4$Cl was then added to the mixture, and the aqueous layer was extracted with Et$_2$O. The combined organics were washed with brine, dried with Na$_2$SO$_4$, 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: ^{1}H NMR (300 MHz, CDCl$_3$) 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, Δν_{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); ^{13}C NMR (75 MHz, CDCl$_3$) 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 C$_{40}$H$_{62}$NO$_6$Si (MH$^+$) 680.4346, found 680.4311.

1-Allyl-4-benzyloxy-3-(4-methoxybenzyl)-6-triisopropylsila-nyloxy-2-azabicyclo[3.3.1]nonane-2-carboxylic Acid *tert*-Butyl Ester (37). To a solution of alcohol **36** (30 mg, 0.04 mmol) in AcOH (0.5 mL) at rt was added five portions of sodium cyanoboro-hydride (14 mg × 5, 0.22 mmol × 5) every 30 min for 2.5 h. After 48 h at rt, the mixture was poured into H$_2$O, and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine and 10% NaOH, dried with Na$_2$SO$_4$, 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: ^{1}H NMR (300 MHz, CDCl$_3$) 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, Δν_{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); ^{13}C NMR (75 MHz, CDCl$_3$) 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 C$_{40}$H$_{62}$NO$_5$Si (MH$^+$) 664.4397, found 664.4450.

1-Allyl-4-benzyloxy-3-(4-methoxybenzyl)-6-triisopropylsila-nyloxy-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 CH$_2$Cl$_2$ (0.5 mL) at rt was added trifluoroacetic acid (47 μL, 0.60 mmol). After 18 h, saturated aqueous NaHCO$_3$ was carefully added, and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organics were washed with saturated aqueous NaHCO$_3$ and brine, dried with Na$_2$SO$_4$, 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}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, Δν = 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 (MH$^+$ + H$_2$O, 100), 408.3 (9).

7-Benzyloxy-6-(4-methoxybenzyl)-3-phenylsulfanyl-9-triiso-propylsilanyloxy-5-azatricyclo[6.3.1.0^{1,5}]dodecanes (43a/43b). To a solution of amine **22** (40 mg, 0.07 mmol) in Et$_2$O (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}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 C$_{41}$H$_{58}$-NO$_3$SSi (MH$^+$) 672.3907, found 672.3884.

43b: ^{1}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 C$_{41}$H$_{58}$NO$_3$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

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(18) Harpp, D. N.; Friedlander, B. T.; Smith, R. A. *Synthesis* **1979**, 181.

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

Supporting Information Available: Copies of proton and carbon NMR spectra of new compounds and X-ray data including ORTEP drawings for compounds **14**, **32**, and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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