Chirospecific Syntheses of Precursors of Cyclopentane and Cyclopentene Carbocyclic Nucleosides by [3 + 3]-Coupling and Transannular Alkylation

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A new method is reported for the preparation of enantiomerically pure (1*R*,2*S*,4*S*)-1-amino-2-hydroxy-4-(hydroxymethyl)cyclopentane, (1*R*,2*R*,4*S*)-1-amino-2-fluoro-4-(hydroxymethyl)cyclopentane, and (1*R*,4*S*)-1-amino-4-(hydroxymethyl)-2-cyclopentene, advanced precursors to carbocyclic nucleosides. The method involves initial conversion of D-serine into an aldehyde with 9-phenylfluorenyl protection at nitrogen and *O*-benzyl protection at oxygen. A [3 + 3]-coupling of this aldehyde with a titanium homoenolate derived from *tert*-butyl 3-iodopropionate gave the corresponding *anti*-lactone in high yield. Regioselective hydrogenolysis of the amine protecting group, accompanied by intramolecular *O*- to *N*-cyclization formed a lactam. After suitable nitrogen protection and functional group manipulation, transannular alkylation afforded the corresponding 2-benzyl- or 2-(*p*-methoxybenzyl)-6-hydroxy-2-azabicyclo[2.2.1]-3-heptanone. Functional group modification of the 2-benzyl analogue gave the resulting 6(*S*)-hydroxy and 6(*R*)-fluoro *N*-BOC imides; alternatively, the 2-(*p*-methoxybenzyl) analogue was converted to an *N*-BOC imide containing an olefinic linkage at C-5 and C-6 of the bicycle. Subjecting each of the *N*-BOC imides to a reduction–deprotection sequence then afforded the desired carbocyclic analogues. The [3 + 3]-coupling method also allowed improved and expedient access to an advanced tribenzylated lactam previously used in the racemic syntheses of the hydroxylated alkaloids D-mannonolactam, deoxymannojirimycin, and prosopinone, providing a formal asymmetric synthesis of these alkaloids.

Introduction

Carbocyclic nucleosides, in which the furanose oxygen has been substituted by a carbon atom, are pharmacologically important isosteres of nucleosides possessing a wide variety of antineoplastic[1] and antiviral activities.[2] The potential advantages in the therapeutic use of these compounds are numerous, as carbocyclic nucleosides are chemically and enzymatically more stable than nucleosides.[3] For example, carbovir (**1**) has shown great promise in clinical trials as a possible alternative to anti-HIV agent 3′-azido-3′-deoxythymidine, AZT.[4,5]

Strategic precursors in the synthesis of carbocyclic nucleosides are substituted 1-amino-3-(hydroxymethyl)-cyclopentanes, a subject which has been reviewed recently.[6] These compounds can be converted to carbocyclic nucleosides via standard methods.[7–9] Present routes to the synthesis of this carbocyclic moiety, including utilization of the bicyclo[2.2.1]heptene[10] and azabicyclo[2.2.1]-heptene[11] systems, overcome the problem of diastereoselectivity, but still have the disadvantage of being nonenantioselective. Usually, in order to prepare the necessary chiral precursors, chemical or enzymatic resolution methods must be utilized.[12,13] Preparation of these materials from substrates available from the chiral pool is an alternative solution to this problem. We have recently reported enantioselective routes to (1*R*,4*S*)-1-amino-4-(hydroxymethyl)-2-cyclopentene and (1*R*,4*S*)-1-amino-4-(hydroxymethyl)-2-cyclopentane from D-gluconono-δ-lactone and (*S*)-aspartic acid, respectively, using a Dieckmann cyclization as the key cyclopentane bond-forming step.[14–16]

We now report an enantiospecific synthesis of (1*R*,4*S*)-1-amino-4-(hydroxymethyl)-2-cyclopentene (**12**), a carbocyclic precursor of antiviral agents carbovir[5] (**1**) and

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1995.

(1) (a) Vince, R.; Brownell, J.; Daluge, S. *J. Med. Chem.* **1984**, *27*, 1358. (b) MacCoss, M.; Robins, M. J. In *Chemistry of Antitumor Agents*; Wilman, D. E. V., Ed.; Blackie and Sons: U. K., 1990; p 261.

(2) (a) Suhadolnik, R. J. *Nucleosides as Biological Probe*; Wiley: New York, 1979; p 147. (b) Marquez, V. E.; Lim, M.-I. *Med. Res. Rev.* **1986**, *6*, 1. (c) Robins, R. K; Revanker, G. R. In *Antiviral Drug Development*; De Clercq, E., Walker, R. T., Plenum: New York, 1988; p 11.

(3) Wolfe, M. S.; Borchardt, R. T. *J. Med. Chem.* **1991**, *34*, 1521.

(4) (a) Richman, D. D.; Fischl, M. A.; Grieco, M. H. *N. Engl. J. Med.* **1987**, *317*, 192. (b) Larder, B. A.; Sharon, D. K. *Science* **1989**, *246*, 1155.

(5) (a) Handa, S.; Earlam, G. J.; Geary, P. J.; Hawes, J. E.; Philips, G. T.; Pryce R. J *J. Chem. Soc. Perkin Trans. 1* **1994**, 1885. (b) Nokami, J.; Matsuura, H.; Nakasima, K.; Shibata, S. *Chem. Lett.* **1994**, 1071. (c) Trost, B. M.; Li, L.; Guile, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 8745 (see ref 9 of this article for syntheses from 1992–1990). Some recent racemic syntheses are presented in (d) Legraverand, M.; Aubertin, A.-M.; Obert, G.; Huel, C.; Bisagni, E. *Nucleosides Nucleotides* **1994**, *13*, 915. (e) Jung, M. E.; Rhee, H. *J. Org. Chem.* **1994**, *59*, 4719.

(6) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571.

(7) Lister, J. H. In *Fused Pyrimidines*; Brown, D. W., Ed.; Wiley: New York, 1971; Part II, p 31.

(8) (a) Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958**, 153. (b) Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1958**, 157.

(9) Birkett, P. R.; King, H.; Chapleo, C. B.; Ewing, D. F.; Mackenzie, G. *Tetrahedron* **1993**, *49*, 11029.

(10) (a) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 3075. (b) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885.

(11) (a) Cermak, R. C.; Vince, R. *Tetrahedron Lett.* **1981**, *22*, 2331. (b) Kam, B. L.; Oppenheimer, N. J. *J. Org. Chem.* **1981**, *46*, 3268. (c) Daluge, S.; Vince, R. *J. Org. Chem.* **1978**, *43*, 2311. (d) Daluge, S.; Vince, R. *Tetrahedron Lett.* **1976**, 3005.

(12) Roberts, S. M.; Shoberu, K. A. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2605.

(13) The enzymatic and chemical resolution of various racemic carbocyclic nucleosides are described in Daluge, S. M. Eur. Pat. Appl. 434450, June 26, 1991.

(14) Park, K. H.; Rapoport, H. *J. Org. Chem.* **1994**, *58*, 394.

(15) Bergmeier, S. C.; Cobas, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369. For the HPLC doping study, 2% of the *R*,*S*-carbamate adduct was added to the *R*-carbamate adduct of **43** showing a 1% increase in the minor diastereomer.

(16) (a) Chang, H. S.; Bergmeier, S. C.; Frick, J. A; Bathe, A.; Rapoport, H. *J. Org. Chem.* **1994**, *58*, 5336. (b) Bergmeier, S. C.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 5019.

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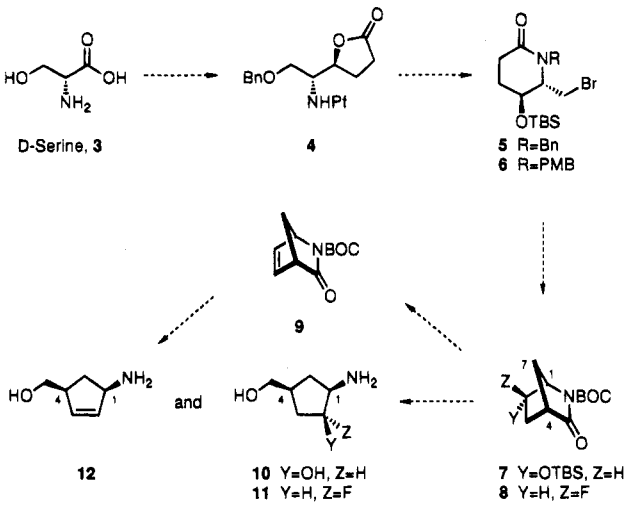
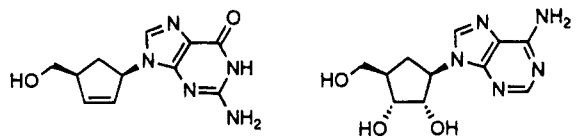
Scheme 1. Projected Syntheses of Carbocyclic Nucleosides



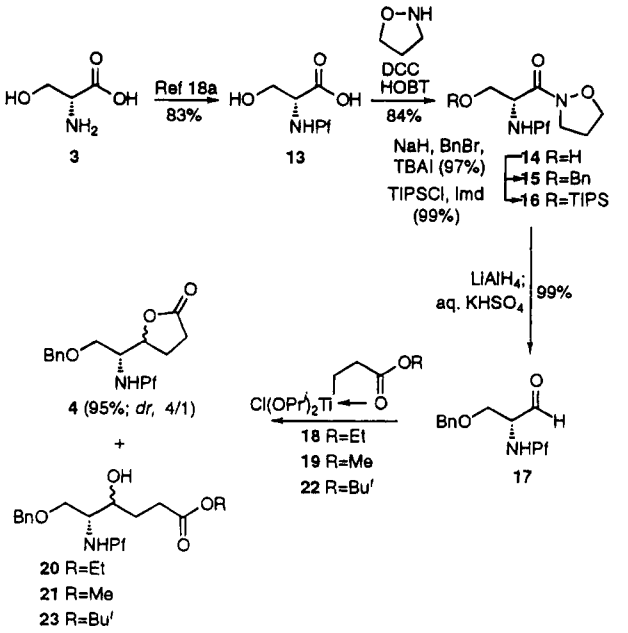
aristeromycin[17] (**2**), starting from D-serine (**3**). This route



is amenable to the production of enantiomerically pure cyclopentane analogues, as shown by the syntheses of (1*R*,2*S*,4*S*)-1-amino-2-hydroxy-4-(hydroxymethyl)cyclopentane (**10**) and (1*R*,2*R*,4*S*)-1-amino-2-fluoro-4-(hydroxymethyl)cyclopentane (**11**), which also have been accomplished in high yield. A variation in the synthetic pathway to the carbocyclic precursors can provide access to a tribenzylated lactam, an advanced intermediate used in the racemic syntheses of the hydroxylated alkaloids D-mannonolactam, deoxymannojirimycin, and prosopinone, thus constituting a formal asymmetric synthesis of these alkaloids. Since the biological activity of carbocyclic nucleosides and bioactive alkaloids often is unique to a specific enantiomer, the use of serine as the starting point in the synthesis is clearly advantageous, as both of its antipodes are readily available.

The projected synthesis of cyclopentanes **10**–**12** is outlined in Scheme 1. The plan begins with conversion of D-serine (**3**) into aldehyde **17** containing 9-phenylfluorenyl protection at nitrogen and *O*-benzyl protection at oxygen.[18] It was envisioned that the [3 + 3]-coupling of this aldehyde with a titanium homoenolate derived from 3-iodopropionate would afford the corresponding enantiomerically pure lactone, dihydrofuran-2(3*H*)-one (**4**). The 9-phenylfluorenyl group was chosen as the *N*-protecting group of the serinal as this group inhibits racemization at the α-position of the aldehyde during the [3 + 3]-coupling reaction. Regioselective hydrogenolytic removal of the amine protecting group of **4**, accompanied by intramolecular *O*- to *N*-cyclization of the resulting amino lactone was expected to produce a lactam, which after suitable protection and functional group manipulation, could be converted to bromides **5** or **6**. Transannular alkylation of either bromolactam would give the corresponding 2-benzyl- or 2-(*p*-methoxybenzyl)-2-azabicyclo[2.2.1]-3-heptanone. This cyclization is critical as it would create an amide linkage at positions C-1 and C-4 of the resulting azabicyclo[2.2.1]-3-heptanone product and also set the requisite 1,3-cis relationship of the amino and hydroxymethyl moieties of **10**–**12**, positions C-1 and C-4, respectively, of the cyclopentane rings. Reduction and amine deprotection of **7**, **8**, and **9** would then afford the desired cyclopentylamines **10**, **11**, and **12**.

Scheme 2. Stereoselective [3 + 3] Coupling Reaction of Propionate Homoenolates to Aldehyde 17



Results and Discussion

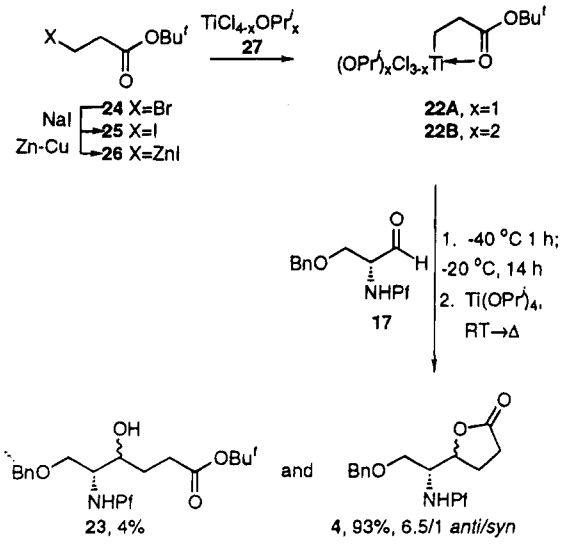
Preparation of *N*-(9-Phenyl-9-fluorenyl)-D-serinal *O*-Benzyl Ether (17). Previously,[18a] it was shown that L-serine (*ent*-**3**) can be converted to *N*-(9-phenyl-9-fluorenyl)-L-serine isoxazolidide (*ent*-**14**) in two steps and 66% overall yield through initial selective 9-phenyl-9-fluorenyl (Pf) protection of the amino group of L-serine and DCC-coupling of the acid moiety of the resulting product, *N*-(9-phenyl-9-fluorenyl)-L-serine (*ent*-**13**), with isoxazolidine in the presence of hydroxybenzotriazole (HOBT), as shown in Scheme 2. Repetition of the second step in this procedure using D-serine (**3**) on scales larger than 100 mmol and crystallization of the crude product from EtOAc afforded **14** in 70% overall yield from D-serine (**3**).

Alkylation of the sodium salt of **14** with benzyl bromide in the presence of TBAI gave benzyl ether analogue **15** in 97% yield.[19] Another analogue, **16**, was prepared through silylation of **14** with TIPSCl in the presence of imidazole.[20] Although reduction of **16** with LAH and hydrolysis using aqueous $KHSO_4$ gave only moderate yields (~50%) of the corresponding aldehyde, the analogous reaction with benzyl ether **15** gave serinal **17** in 99% yield. It is of interest to note that **17** is stable to chromatography without loss of enantiomeric purity.

[3 + 3]-Coupling Studies. In order to elaborate the three-carbon framework of aldehyde **17** into lactone **4**,

(17) Kusaka, T.; Tamamoto, H.; Shibaata, M.; Muroi, M.; Hicki, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255.
(18) (a) Lubell, W. D.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3824. (b) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.
(19) (a) Kanai, K.; Sakamoto, I.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1529. (b) Czernecki, S.; Georgoulis, C.; Provelenghio, U. C. *Tetrahedron Lett.* **1976**, 3535.
(20) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797.

Scheme 3. Titanium Homoenolate [3 + 3]-Coupling Reaction of *tert*-Butyl Propionate with Aldehyde 17



the proposed six carbon precursor of cyclopentanes **10**, **11** and **12**, a [3 + 3]-coupling method was required. Initially, a modification of the reported[21] titanium homoenolate method was attempted. Thus, treatment of aldehyde **17** with a 2-fold excess of the titanium homoenolate of ethyl or methyl ester, **18** or **19**, gave 32–52% yields of lactone **4** as a 4/1 mixture of diastereomers (Scheme 2). None of the expected hydroxy esters, **20** or **21**, was isolated. Presumably, each of the initially formed alkoxy esters had lactonized to **4** during the course of the reaction. The low yield of lactone **4** prompted investigation of the analogous titanium homoenolate derived from *tert*-butyl 3-iodopropionate.[22] Treatment of **17** with homoenolate **22** under similar reaction conditions afforded lactone **4** in 95% yield, but again as a 4/1 diastereomeric mixture.

In order to improve the diasteroselectivity of the reaction, control of temperature and variation of the titanium species were investigated (Scheme 3). Organozinc reagent **26** was prepared as reported for the ethyl ester.[21b] Thus, the *tert*-butyl 3-bromopropionate was converted to the corresponding iodide **25**, and warming of the iodide[22] with activated zinc–copper in toluene/dimethylacetamide (DMA) gave organozinc homoenolate reagent **26**. The appropriate organotitanium reagent **22** utilized in the coupling reaction with **17** was generated by transmetalation of iodozinc reagent **27** with the corresponding chlorotitanium isopropoxide species. All coupling reactions were initially conducted at −40 °C for 1 h and −20 °C for 14 h, the minimum temperature range and time determined for complete consumption of aldehyde **17**.

The coupling of **22A** (**22**, where $x = 1$) with serinal **17** (2-fold excess of **22A** relative to **17**) gave almost exclusively hydroxy ester **23**, as observed by TLC and ^{1}H NMR. Surprisingly, appreciable cyclization of **23** to lactone **4** did not occur either under the reaction conditions or upon warming to room temperature. Addition of titanium isopropoxide until equimolar to the titanium tetrachloride, followed by warming of the mixture to 40 °C for 2 h, however, gave 71% of lactone **4** as a 6.5/1 mixture of diastereomers. In addition, approximately an 8% yield of hydroxy ester **23** was also isolated.[23]

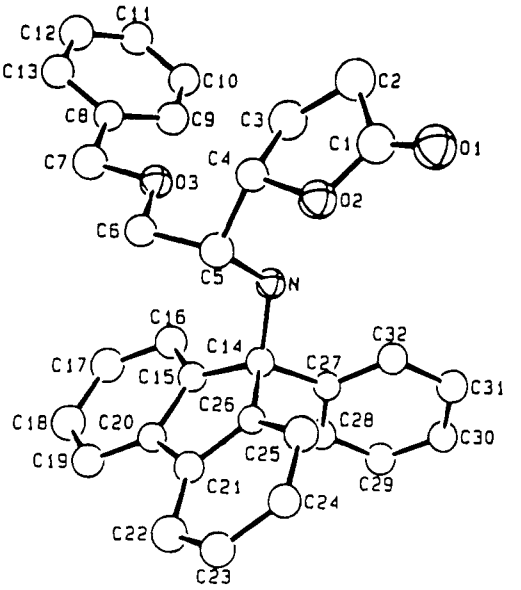


Figure 1. Structure of (5*S*)-5-[(1*R*)-1-[(phenylfluoren-9-yl)-amino]-2-(benzyloxy)ethyl]dihydrofuran-2(3*H*)-one (*anti*-**4**) as determined by X-ray crystallography (arbitrary numbering system).

Treatment of zinc reagent **26** (200 mol % relative to **17**) with a 1.5/1 mixture of $TiCl_3(OPr^i)$/$TiCl_2(OPr^i)_2$ (combined 150 mol % relative to **17**) produced, presumably, a 1/3/2 mixture of **26**/**22A**/**22B**. Coupling of this homoenolate mixture with serinal **17** under the standard initial reaction conditions gave only **23**. Again, appreciable cyclization of **23** to **4** did not occur upon warming of the mixture to room temperature. Addition of titanium isopropoxide until equimolar to titanium tetrachloride, followed by warming of the mixture to 40 °C for 3 h, however, gave a 93% yield of lactone **4** as a 6.5/1 mixture of isomers and 4% of **23**.[23] As expected, the coupling reaction of **17** with titanium species **22B** (**22**, where $x = 2$; 200 mol % relative to **17**) under the initial reaction conditions and stirring at room temperature for 13 h gave a 93% yield of **4** as a 6.5/1 mixture of diastereomers. In addition, approximately a 4% yield of **23** was also isolated.[23]

The major *anti*-diastereomer, as elucidated by X-ray crystallography (Figure 1), was crystallized from the crude mixture in 68% yield with a diastereomeric ratio (dr) > 98/2. Such diastereoselectivity is consistent with the reported model rationalizing the high anti selectivity of *N*,*N*-dibenzyl protected serinals toward nucleophiles.[24,25]

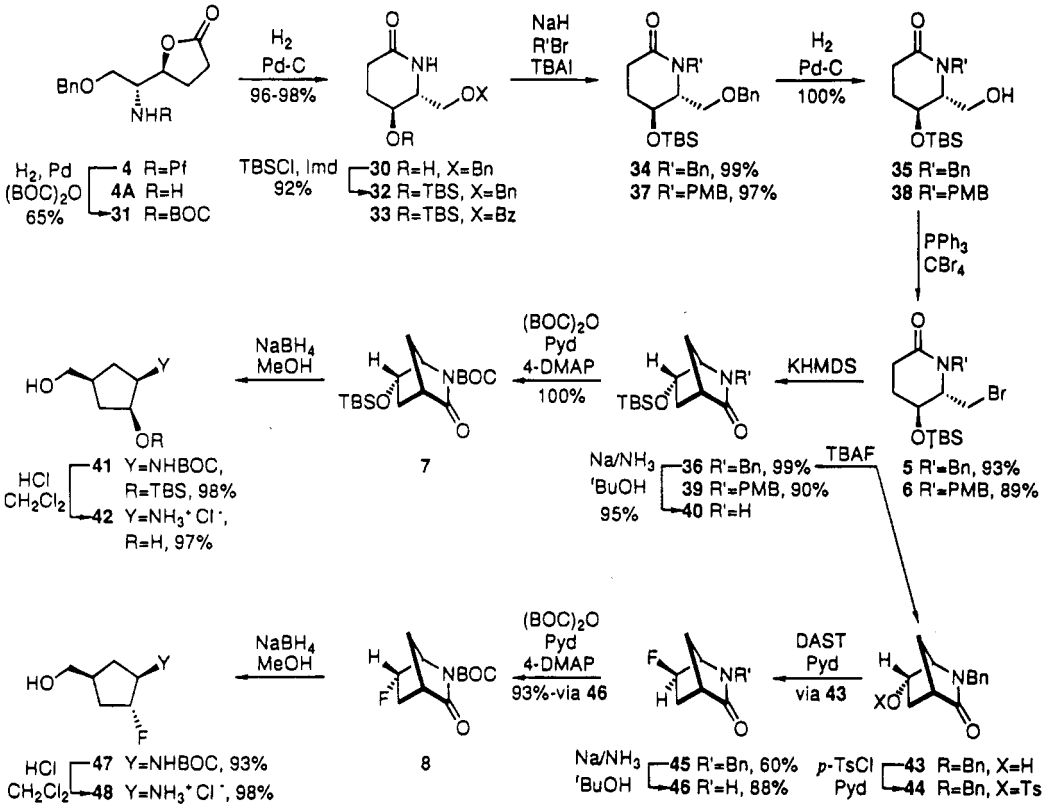
(21) (a) Armstrong, J. D., III; Hartner, F. W.; DeCamp, A. E.;Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1992**, *33*, 6599. (b) DeCamp, A. E.; Kawaguchi, A. T.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867.

(22) *tert*-Butyl 3-iodopropionate was prepared by esterification of 3-bromopropionic acid (Mathias, L. J. *Synthesis* **1979**, 561) and iodide exchange of the resulting bromo ester. An alternative esterification method is presented by McCloskey, A. L.; Fonken, G. S.; Kluiber, R. W.; Johnson, W. S. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 261.

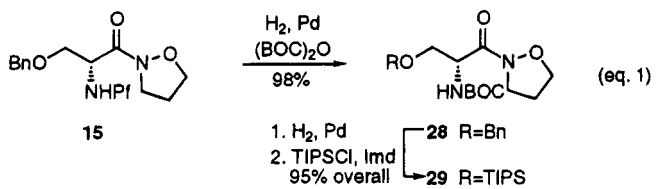
(23) Determination of the diastereomeric ratio (dr) of lactone **4** on the Bruker AM-400 with either use of a (i) a normal ^{1}H NMR pulse width (PW = 4.9), (ii) a PW = P1 = 11 (90° pulse); where NS = 1, or (iii) normal pulse width with a 10 s delay between scans, gave identical results. The dr of hydroxy ester **23** was not determined.

(24) (a) Anh, N. T. *Top. Current Chem.* **1980**, *88*, 145. (b) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.

Scheme 4. Synthesis of Cyclopentanes 42 and 48 (Hydrochloride Salts of 10 and 11)



Regioselective Hydrogenolysis of Lactone 4. The synthesis of **42**, the hydrochloride of **10**, is shown in Scheme 4. Key to this synthesis was the successful regioselective hydrogenolysis of **4**. In order to immediately address this issue, a model study was conducted using isoxazolidine **15** (eq 1). To simplify the



(eq. 1)

interpretation of the spectral data, the *N*-BOC analogue **28** was prepared. Hydrogenolysis of **15** in methanol containing $(BOC)_2O$ gave **28** in 98% yield. Thus, complete regioselectivity was achieved in the hydrogenolysis of the 9-phenylfluorenyl moiety over the benzyl ether. In contrast to **15**, removal of the benzyl moiety of **28** under identical conditions is slower (12 vs 3 h). For characterization purposes, the primary hydroxyl of the resulting hydrogenation product was protected as the TIPS-analogue **29**.[20]

In the synthetic sequence, the next objective was the preparation of **30** (Scheme 4). Hydrogenolysis of *anti*-**4** in THF/MeOH gave **30** in yields of 96–98%. A room temperature cyclization of the primary amine intermediate **4A** is appreciably slower, as evidenced by the formation of *N*-BOC-analogue **31** in 65% yield through hydrogenolysis of **4** in the presence of $(BOC)_2O$. Silylation of the secondary hydroxyl moiety of **30** with TBDMSCl[26] gave *anti*-**32** in 92% yield (62% overall from **4**). Alternatively, the chromatographic separation of the anti and syn isomers of **32**, after performing the identical hydrogenation–silylation sequence with **4**, now a 6.5/1 mixture of anti and syn diastereomers, gave a much higher 77% overall yield of *anti*-**32**. Silyl ether **32** was unstable upon prolonged storage as it slowly converted to *O*-benzoyl analogue **33**, presumably due to a base catalyzed aerobic oxidation of **32**.[27] Alkylation of the sodium salt of lactam **32** using benzyl bromide in the presence of catalytic TBAI,[19a] followed by selective reduction of the resulting dibenzylated product **34**, afforded primary alcohol **35** (100% yield) which was treated with carbon tetrabromide and triphenylphosphine.[28] Transannular alkylation of the resulting bromo amide **5** using KHMDS, gave *N*-benzyl azabicyclo[2.2.1]heptan-3-one (**36**) in a notable 88% overall yield from **35**.

As an alternative intermediate, the *p*-methoxybenzyl analogue of **36** was prepared. Alkylation of the sodium salt of **32** using *p*-methoxybenzyl bromide in the presence of a catalytic amount of TBAI,[19a] followed by selective reduction of the resulting dibenzylated product **37**, afforded alcohol **38** in 97% overall yield. Treatment of alcohol **38** with carbon tetrabromide and triphenylphosphine,[28] followed by intramolecular cyclization of the resulting bromo amide **6** using KHMDS gave *N*-PMB analogue **39** in 81% overall yield. Thus, either one of the strategic azabicyclo[2.2.1]heptan-3-one precursors **36** or **39** could potentially be used to prepare **10**.

Preparation of 42, the HCl Salt of Aminocyclopentane 10. Debenzylation of bicycle **36** using Li/NH_3,

(25) (a) Hormuth, S.; Reissig H.-U. *J. Org. Chem.* **1994**, *59*, 67 (see also reference 1a cited within). (b) Grieco, P. A.; Moher, E. D. *Tetrahedron Lett.* **1993**, 5567.

(26) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(27) Gigg, R.; Conant, R. *J. Chem. Soc., Chem. Commun.* **1983**, 465.

(28) Falorni, M.; Lardicci, L. *J. Org. Chem.* **1986**, *51*, 5291.

followed by NH_4Cl neutralization and aqueous treatment, gave moderate yields of secondary lactam **40**[29] due to concomitant base cleavage of the strained amide moiety of both **36** or **40**. Debenzylation of **36** using Na/NH_3[30] in the presence of *tert*-BuOH, followed by quenching of the reaction mixture with AcOH, gave **40** reproducibly in yields of 95−100% without the need of an aqueous treatment.[31] Bicycle **40**, with $(BOC)_2O$ and 4-DMAP in pyridine[32] followed by methanolic $NaBH_4$ reduction of the resulting *N*-BOC imide **7**,[33] gave (hydroxymethyl)cyclopentane **41** in 92% overall yield. Removal of the *N*-BOC moiety of **41** with saturated HCl in CH_2Cl_2, gave the hydrochloride salt of **10**, aminocyclopentane **42**, in 97% yield. Thus, the preparation of the first analogue **42** was accomplished in 37% overall yield from D-serine (**3**).

Preparation of 48, the HCl Salt of Aminocyclopentane 11. Preparation of the hydrochloride **48**, beginning from bicycle **36**, is shown in Scheme 4. Treatment of **36** with 1 M TBAF in THF,[26] followed by conversion of the resulting alcohol **43** to tosylate[34] **44** proceeded uneventfully in 96% overall yield from **36**. All attempts to invert the 6-(*S*)-configuration of tosylate **44** through the use of S_N2-type displacement reactions (F^-, I^-, MeS^-, etc.), however, gave only unreacted **44**.[35]

The failure of this approach was attributed to steric hindrance by the hydrogens of the single carbon bridge on the *exo*-face of the azabicyclo[2.2.1]heptane ring moiety of **44**. Since an S_N2-transition state requires an *anti*-relationship between nucleophile and leaving group, the trajectory required for attack by the fluoride ion would be greatly hindered by the single carbon bridge of **44**. Potentially, a possible solution could be in control of the proximity of the fluoride ion to the hydroxyl-derived leaving group through a close ion pair association in the transition state structure. In support of this hypothesis, treatment of **43** with DAST in the presence of pyridine gave **45** in 60% yield as the only isolable product.[36] Again, debenzylation using Na/NH_3 in the presence of *tert*-BuOH, followed by an AcOH quench, afforded **46** in 88% yield.[30,31]

The ^1H, ^{19}F, and ^{13}C NMR data matched those reported[37] for the racemate of **46**, for which stereochemistry had been assigned by comparison of $^{13}C-^{19}F$ coupling constants of a 7-*anti*-bromo-2-*exo*-fluoroazabicyclo[2.2.1]-heptane precursor in agreement with those reported for the analogous deazabicyclo[2.2.1]heptane system.[38] A more rigorous proof of stereochemistry was provided by the magnitude of $^{19}F-^1H$ coupling constants and the use $^{19}F-^1H$ NOE difference experiments as shown in Figure 2. The assignment of geminal and vicinal protons to the fluoro group at C-6 and C-5, respectively, was based on the magnitude of $^{19}F-^1H$ coupling constant ($J_{F,H6}$ = 54 Hz, $J_{F,H5exo}$ = 34 Hz, and $J_{F,H5endo}$ = 17 Hz). Assignment of the *exo*-fluoro configuration, as well as the stereochemical assignments of the protons at C-5 and C-7, then were determined unambiguously through $^{19}F-^1H$ NOE difference experiments. The fluorine produced no NOE enhancement to H-7anti though it displayed NOEs of approximately 2% to H-7syn, 1.9% to H-5exo, 2.1% to H-1, and 14.2% to H-6endo. With ample quantities of **46** in hand, completion of the synthesis was straightforward. Treatment of **46** with $(BOC)_2O$/4-DMAP/pyridine,[32] followed by reduction[33] of the resulting imide **8** gave (hydroxymethyl)cyclopentane derivative **47** in 81% overall yield from **45**. Removal of the *N*-BOC protecting group of carbamate **47** using HCl in CH_2Cl_2 gave the hydrochloride **48** of (1*R*,2*R*,4*S*)-1-amino-2-fluoro-4-(hydroxymethyl)cyclopentane (**11**), in 98% yield. Thus, the preparation of the fluoro analogue **48** was accomplished in 18% overall yield from D-serine (**3**).

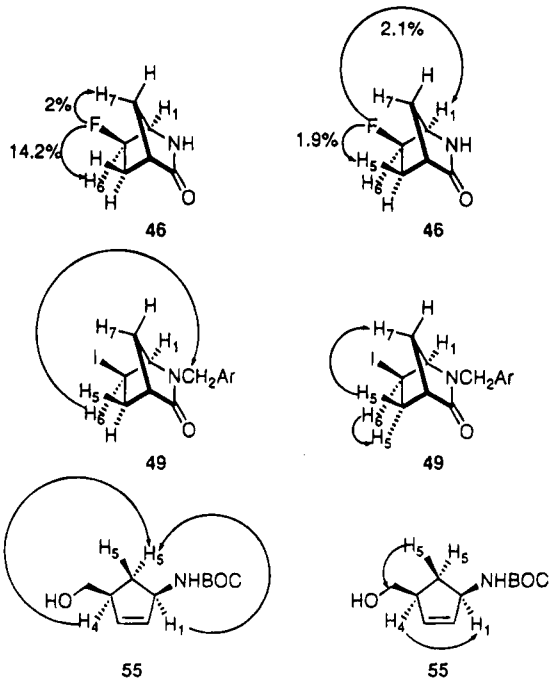


Figure 2. $F^{19}-^1H$ NOE difference experiments (**46**) and NOE interactions derived from NOESY experiments on **49** and **55**.

Preparation of Aminocyclopentene 55. The preparation of the cyclopentene analogue **55** is outlined in Scheme 5. Our initial attempt began with tosylate **44**. Although the dehydrohalogenation of the C-6 epimer of tosylate **44** has been reported,[34] a similar attempt with **44** failed. All efforts at elimination from **44** were unsuccessful. Reversal of the configuration at C-6, however, was possible by treatment of alcohol **43** with diiodotriphenylphosphorane in refluxing toluene to afford iodide **49** in 93% yield.[39] The stereochemical assignment of **49** was corroborated through $^1H-^1H$ decoupling and 2-D NOESY experiments (Figure 2). For example, the ^1H NMR spectrum of **49** demonstrated H-6 as a ddd with $J_{6,5endo}$ = 7.6 Hz, $J_{6,5exo}$ = 3.8 Hz, and $J_{6,7anti}$ = 1.8 Hz (w-

(29) Kim, M. Y.; Starrett, J. E., Jr.; Weinreb, S. M. *J. Org. Chem.* **1981**, *46*, 5383.
(30) Sisko, J.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4945.
(31) The only modification of this experimental protocol was that excess acetic acid was used in place of ammonium chloride to quench the reaction, and no aqueous treatment was used. The crude mixture was filtered through Celite (see Experimental Section).
(32) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 23.
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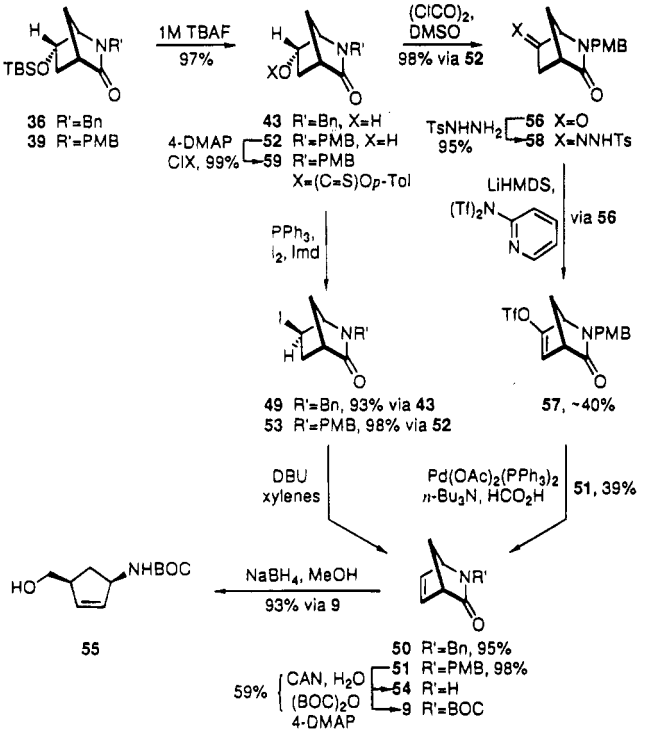
(38) Alvernhe, G.; Laurent, A.; Haufe, G. *Synthesis*, **1987**, 562.
(39) (a) Sardina, F. J.; Howard, M. H.; Morningstar, M.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5025. A mechanistic study on this reaction is presented in (b) Garegg, P. J.; Regberg, T.; Stawinski, J.; Stromberg, R. *J. Chem. Soc. Perkin Trans. 2* **1987**, 271.

Scheme 5. Preparation of Cyclopentane 22



coupling). The assignment was strengthened further by 2-D NOESY experiments demonstrating that H-6endo showed significant cross peaks to the benzyl methylene and aromatic CH moieties; whereas H-5exo showed a cross peak to H-7syn. The lack of a cross peak of H-6endo to either H-7endo or H-7syn was also supportive. As expected, the dehydrohalogenation of iodide **49** with DBU in refluxing xylenes gave olefin **50** in a notable 98% yield.[40] Reductive debenzylation of the amide moiety of **49** using Na/NH_3 in the presence of *tert*-BuOH, however, produced a multitude of products.[30,31]

Since *N*-benzyl olefin **50** appeared unsuitable, the *p*-methoxybenzyl (PMB) olefin analogue **51** was prepared from silyl ether **39**, as the PMB-amide moiety can be removed under a variety of mild oxidative conditions.[41] Alkylation of the sodium salt of **40** with *p*-methoxybenzyl bromide in the presence of TBAI provided an alternative preparation of **39** in 98% yield. Desilylation of **39** using TBAF,[26] treatment of the resulting alcohol **52** with diiodotriphenylphosphorane in refluxing toluene,[39] and dehydrohalogenation[40] of the iodide **53** afforded olefin **51** in a 93% overall yield from **39**. Although standard hydride abstraction methods failed to remove the PMB-protecting moiety of **51**,[37,41] success was realized through an oxidation–hydrolysis sequence using CAN in 2/1, CH_3CN-H_2O,[42] and a following treatment of the product mixture containing **53** with $(BOC)_2O$ in pyridine/4-DMAP[32] gave pure **9** in 59% overall yield from **51**.

Reduction of imide **9** with methanolic sodium borohydride afforded alcohol **55** in 93% yield.[33] No epimerization of the intermediate aldehyde had occurred under these reaction conditions. Corroboration of the *cis*-1,4-relationship between the C-1 carbamate and C-4 hydroxymethyl substituents of **55** was provided through the use of a 2-D NOESY experiments (Figure 2). Significant NOESY cross peaks were observed between H1-H5a, H4-H5a, and H-5b to the protons of the hydroxymethyl substituent at C-4; whereas, no correlation was observed between H-5b and H-1. In addition a small cross peak was observed between H-1 and H-4. Thus, the desired *cis*-relationship of the carbamate and alcohol moiety of **55** was maintained through the reduction sequence.

An additional route to **55** allows the possibility of preparing numerous olefin-substituted analogues, though the overall yield of this sequence was substantially lower (Scheme 5). This sequence uses alcohol **52** as the starting point. Oxidation of alcohol **52** gave ketone **56** in 98% yield. Conversion of this ketone to vinyl triflate analogue **57** proved most problematic, however, due to the instability of the triflate moiety. Trapping of the lithium enolate of **56** with *N*-(2-pyridyl)triflamide gave the best results with the formation of enol triflate **57** in ~40% yield. Trapping of the lithium or potassium enolate of **56** with $PhN(Tf)_2$ gave only a 20% yield of **57**. Reduction of **57** under standard conditions [$Pd(PPh_3)_2(OAc)_2/HCO_2H/n$-$Bu_3N$/DMF] gave olefin **51** in 39% yield.[43]

Presumably, this alternative route could provide new olefin-substituted analogues through standard vinyl triflate coupling processes;[44] however, this avenue was left unexplored. More obvious paths to olefin **52** proceeding through the base induced[45] elimination of tosylhydrazone **58** (prepared in ~100% yield by condensation of (*p*-tosylsulfonyl)hydrazine with **56** in the presence of catalytic mineral acid) or pyrolysis[46] of thionocarbonate analogue **59** (prepared in 98% yield by treatment of **56** with *p*-cresol thionoformate in the presence of 4-DMAP) were unsuccessful.

Formation of a Symmetrical Intermediate and Determination of Enantiomeric Ratios. In order to determine whether any racemization had occurred during the titanium homoenolate [3 + 3]-coupling reaction, the enantiomeric purity of alcohol **43** was determined. To minimize the possibility of enantiomeric enrichment during purification after the [3 + 3]-coupling reaction, recrystallization was not used as a purification method in the preparation of **43**. The enantiomeric ratio (er) of alcohol **43** was determined by derivatization of **43** with (*R*)-1-phenethyl isocyanate and racemic (*R/S*)-1-phenethyl isocyanate.[15] The corresponding carbamates were then each subjected to HPLC analysis to establish detection limits; the er was determined to be >100/1. Thus, no racemization had occurred during manipulation of serinal **17** or the [3 + 3]-coupling reaction.

In the synthesis leading to olefin **55**, another potential racemization pathway is through formation of a symmetrical charged intermediate due to the equilibration of iodides **49/53** during the iodination and/or dehydrohalogenation reactions as shown in Figure 3. Determination of the er of olefin **55** should demonstrate whether stereochemical integrity was maintained during these crucial reactions. Although treatment of **55** with (*R*)-1-phenethyl isocyanate and racemic (*R/S*)-1-phenethyl iso-

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(41) Greene, T. W.; Wuts, P. G. In *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; p 401.
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(43) (a) Paquette, L. A.; Meister, P. G.; Friedrich, D.; Saurer, D. R. *J. Am. Chem. Soc.* **1993**, *115*, 49. (b) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
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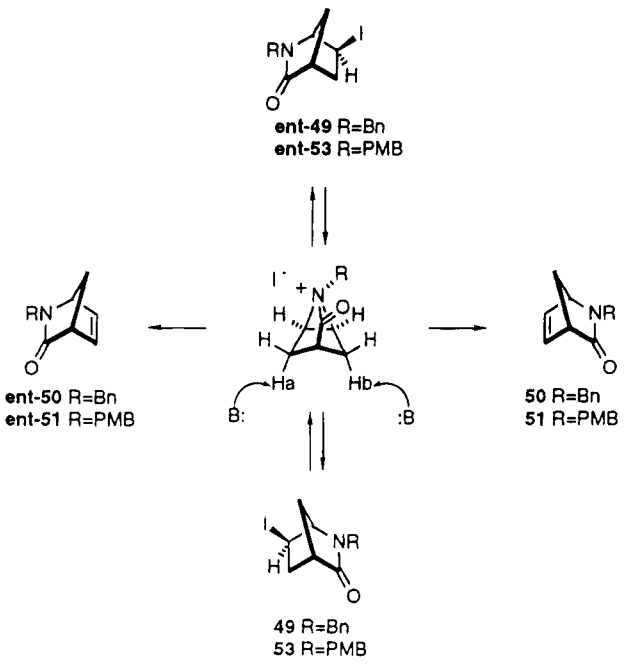


Figure 3. Postulated symmetrical intermediate.

cyanate gave the corresponding carbamates which proved inseparable by HPLC analysis,[15] the reaction of **55** with Mosher's acid (MTPA), EDC, and 4-DMAP allowed determination of an er of 72/28 through ^{1}H NMR analyses of the resulting olefinic ester resonances.[47] This result was confirmed by (a) derivatization of alcohol **55** with (*R*) and (*R,S*)-*N*-(phenylsulfonyl)proline,[48] and (b) through chiral GC assay of *N*-BOC imide **9**.[49]

A final piece of supporting evidence for the existence of the symmetrical intermediate came through determination of the enantiomeric composition of olefin **52**, emanating from the vinyl triflate route. Chiral GC assay of *N*-BOC imide **9** derived from this olefin revealed only a single enantiomer (er > 100/1). Evidently, the formation of a symmetrical intermediate via the iodides plays a signifiant, though not exclusive, role.

Also, it has been reported[34] that the C-6 epimer of tosylate **44** undergoes substitution with phenoxide ion under solvolytic conditions with complete retention of configuration. Although in this case it was hypothesized that the symmetrically charged intermediate shown in Figure 3 may have played an exclusive role, neither the racemic nature of the starting material nor the low mass balance was considered. The loss of enantiomeric purity in the present study provides more credible support for involvement of this achiral intermediate in this reaction type.

The EDC-coupling reaction of MTPA with olefin **55** required multiple treatments, although the ester was afforded cleanly.[47] The reaction of fluoro analogue **47** (prepared in 90% yield by treatment of HCl salt **48** with $(BOC)_2O$/DIEA), however, was even more sluggish and did not proceed to completion even after multiple treatments. This lack of reactivity was overcome by using the pentafluorophenyl ester of MTPA. This C_6F_5-ester was prepared conveniently in approximately 80–85% overall yield through the coupling of MTPA in the presence of a 3-fold excess of pentafluorophenol,[50] followed by standard extractive isolation, filtration through silica gel (eluting with hexanes), and recrystallization from hexanes. Coupling of the highly crystalline *R*- and *S*-form of the MTPA-C_6F_5 ester (150–170 mol %) with **47** and *dl*-**55** in the presence of 340 mol % of 4-DMAP in acetonitrile gave the corresponding MTPA esters rapidly in essentially quanitative yield. The isolation from these reactions was simple and consisted of washing with mild base to remove pentafluorophenol, removing excess reagent by a hexane filtration through silica gel, and eluting the products from the silica gel with ethyl acetate.

Integration of the ^{1}H and ^{19}F NMR resonances of the reaction of the MTPA-C_6F_5 ester (*R*-form) with *dl*-**55** produced, as expected, a 1/1 mixture of diastereomeric esters. Analysis of the ^{1}H decoupled ^{19}F NMR resonances of the 2-trifluoromethyl group of the esters, resulting from the coupling of the *R*- and *S*-MTPA-C_6F_5 esters with **47**, established an er >100/1, after a doping study.[51] Thus, the enantiomeric integrity of the fluoro analogue had been maintained during and after this crucial inversion sequence in sharp contrast to iodides **49/53**. Whether the stronger C–F bond and/or the lower reaction temperature prevented the formation of a symmetrical intermediate, is unknown.

Synthesis of Cyclopentene 68, HCl Salt of 12. Since the vinyl triflate route produced cyclopentene **12** in unacceptable yield, an alternative synthetic route (Scheme 6) was examined in which incorporation of the $\Delta^{2,3}$-olefinic moiety would be postponed until after the reductive ring opening of the *N*-BOC-azabicyclo[2.2.1]-heptane function of **10**. An elimination sequence involving the secondary hydroxyl of an analogue of **42** was chosen that should completely preclude the formation of a symmetrical intermediate through avoidance of inversion of the 2-(*S*) configuration of **60**.

Treatment of primary alcohol **41** with MOMCl in the presence of DIEA gave **60** with differentially protected primary- and secondary-alcohols in 94% yield, setting the stage for incorporation of the $\Delta^{2,3}$-double bond. Fluoride mediated cleavage of the silyl ether of **60**, followed by mesylation of the resulting alcohol **61**, gave **62** in quantitative yield. Attempts at elimination from mesylate **62** using sodium methoxyethoxide in DMF at 0 °C produced three olefins: a 4/1 mixture of the $\Delta^{1,2}/\Delta^{1,5}$ (1/1 mixture) and $\Delta^{2,3}$-olefinic products, **63** and **64**, respectively. Since a 9-Pf analogue of **62** has been shown to eliminate only to the $\Delta^{2,3}$-olefin under identical conditions, this result further confirms the profound directing influence of the 9-Pf moiety.[14] A KOBu^t induced elimination of the mesylate **62** in DMSO at room temperature produced solely **63**.

An initial attempt to promote a syn-elimination of the secondary hydroxyl of **61** through use of the Burgess

(47) Use of a long relaxation delay or normal PW (RD = 0) in acquiring the ^{1}H NMR spectra gave identical results. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

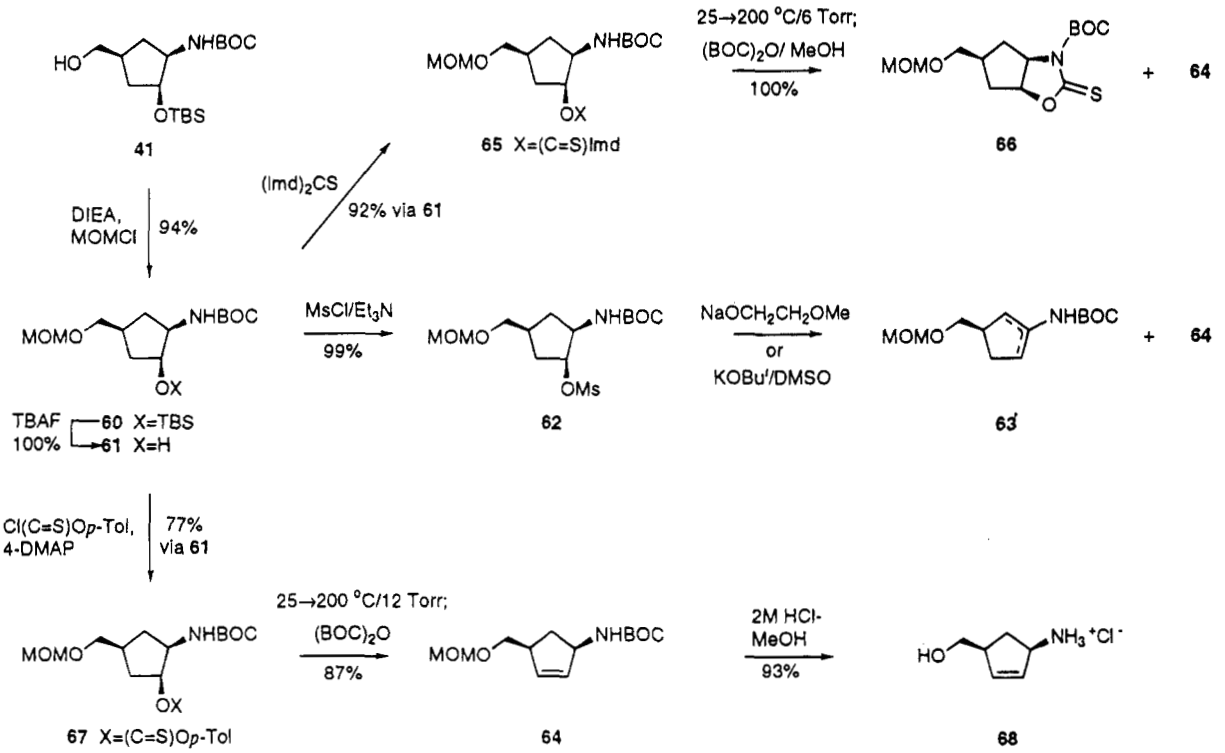
(48) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.

(49) Chiral GC analyses were performed with a J&W Cyclodex-B cyclodextrin column by comparison of **rac-9** [prepared from treatment of **rac-54** (Aldrich) with $(BOC)_2O$/4-DMAP/pyridine] and imide **9** prepared through our method. Thermal cleavage of the *N*-BOC moiety was a major event; however, the measured er, 72/28, was identical with the MTPA and proline ester analogues of alcohol **55**.

(50) Bodansky, M.; Bodansky, A. *The Practice of Peptide Synthesis; Reactivity and Structure Concepts in Organic Chemistry*; Springer-Verlag: New York, 1984; Vol. 21, p 122.

(51) Use of a long relaxation delay, normal PW (RD = 0) or ^{1}H decoupling in acquiring ^{19}F NMR spectra gave identical results. For the doping study, a 1% dope of the (*S*)-MTPA ester of **47** added to the *R*-ester of **47** gave a 1% increase in the integration of the minor diastereomer demonstrating the sensitivity of the method.

Scheme 6. Preparation of 68, the HCl Salt of 12



reagent[52] failed. Also, although the reaction of **61** with thiocarbonyl diimidazole proceeded uneventfully to afford imidazolide **65** in 91% yield, distillative pyrolysis (25 → 200 °C; 12 mmHg) produced a 4.5/1 mixture of cyclic thiocarbamate **66** and desired olefin **64** with no detection of **63**.

We then turned to the thiocresol carbonate analogue **67**, which was prepared using *p*-cresyl chlorothionoformate in CH_3CN/4-DMAP in 77% yield, along with 15% of **66**. Distillative pyrolysis (25 → 200 °C; 12 mmHg) afforded the desired olefin **64** isolated as its *N*-BOC derivative in 87% yield. Hydrolysis of **64** with 2 M HCl/MeOH gave pure hydrochloride salt **68** in quanitative yield (95% based on a single recrystallization from Et_2O–MeOH). A vapor diffusion recrystallization of a small portion of this material produced crystals of X-ray quality (Figure 4), providing proof not only of the structure, but also the absolute configuration.[53] This hydrochloride salt exists in a H-bonded network with two molecules per unit cell and shows a 22° puckering of the cyclopentene ring from planarity. When stored free of moisture at 24 °C, it is stable for long periods, in contrast with the noted instability of the free base form.[11c,13]

In order to assess the enantiomeric purity of crude **68**, it was converted to *N*-BOC derivative **55** and treated with the *R*-MTPA-C_6F_5 ester. The MTPA ester of **55** was formed in quantitative yield and showed an er >100/1, using a doping study.[54] Thus, the HCl salt of **12**, alcohol **68**, has been prepared enantiomerically pure, constituting a formal chirospecific synthesis of carbovir (**1**).[55]

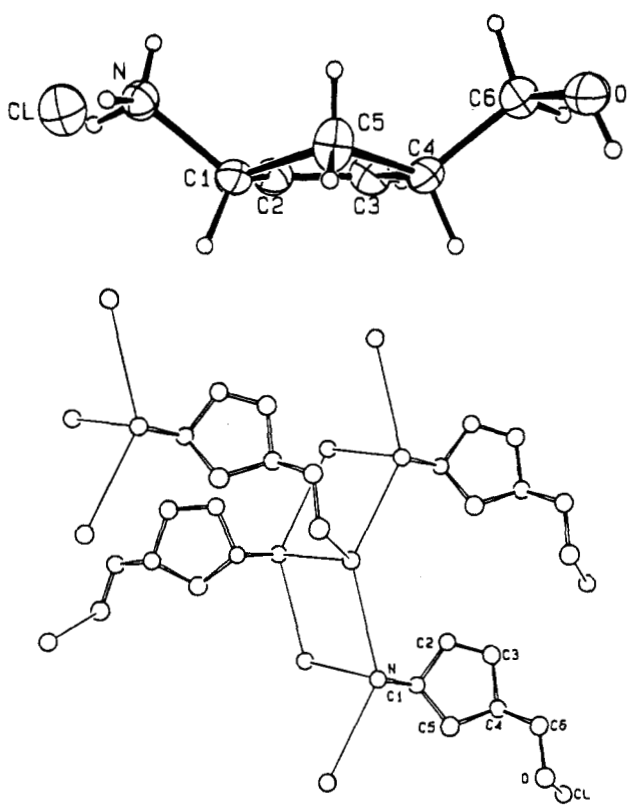


Figure 4. Structure of **68**, the HCl salt of (1*R*,4*S*)-1-amino-4-(hydroxymethyl)-2-cyclopentene (**12**), as determined by X-ray crystallography.

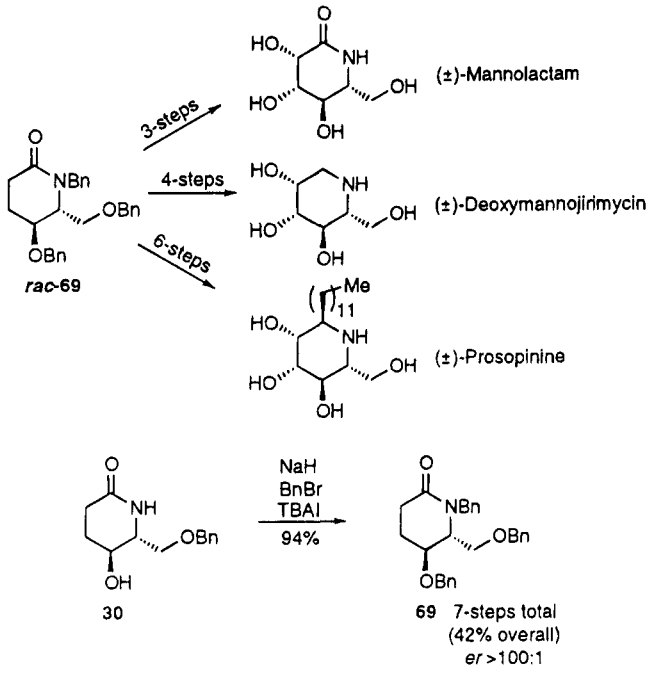
Formal Chirospecific Syntheses of Mannonolactam, Deoxymannojirimycin, and Prosopinone through Tribenzyl Lactam 69. A variation in the synthetic pathway to the carbocyclic nucleosides precursors allowed improved and expedient access to **69** used in the racemic syntheses[55] of D-mannonolactam, deoxymannojirimycin, and prosopinone, providing a formal

(52) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(53) The authors have deposited atomic coordinates for **4** and **12**·HCl with the Cambridge Crystallographic Data Centre. The Coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, U. K.

(54) The doping experiment consisted of adding 1% of the mixture resulting from the reaction of *d,l*-**55** with (*R*)-MTPA-C_6F_5 ester to the crude ester derived from the reaction with **55**, formed via the pyrolysis–hydrolysis–$(BOC)_2O$ sequence. Analysis of the ^1H coupled ^{19}F NMR signals were used to determine an er > 200/1.

Scheme 7. Formal Asymmetric Syntheses of d-Mannonolactam, Deoxymannojirimycin, and Prosopinone via Tribenzyl Lactam 69



chirospecific synthesis of these polyhydroxylated piperidines (Scheme 7). The strategic intermediate **69** for the target molecules was prepared in 94% yield simply through *N,O*-dibenzylation of the corresponding lactam alcohol **30**, resulting from the hydrogenation–cyclization sequence of lactone **4**. In this way, intermediate **75** was prepared enantioselectively (er >100/1) in seven steps and 42% overall yield from D-serine (**3**).[56]

Conclusion

We report a titanium homoenolate [3 + 3]-coupling method for the preparation of the HCl salts of enantiomerically pure (1*R*,2*S*,4*S*)-1-amino-2-hydroxy-4-(hydroxymethyl)cyclopentane (**10**), (1*R*,2*R*,4*S*)-1-amino-2-fluoro-4-(hydroxymethyl)cyclopentane (**11**), and (1*R*,4*S*)-1-amino-4-(hydroxymethyl)-2-cyclopentene (**12**), precursors to carbocyclic nucleosides. In the determination of the enantiomeric ratios of the target molecules, the highly lipophilic crystalline pentafluorophenyl ester of MTPA was used and had the major advantages over the acid chloride of purity, high reactivity, and simple removal of excess reagent. The titanium homoenolate coupling methodology developed also can be applied to the formal chirospecific syntheses of three polyhydroxylated alkaloids, D-mannonolactam, deoxymannojirimycin, and prosopinone.

Experimental Section

General. All melting points are uncorrected. NMR spectra were taken in $CDCl_3$ and are referenced to TMS unless otherwise noted. ^{13}C NMR data are recorded as chemical shift (multiplicity determined from DEPT). ^{19}F spectra were referenced to the racemate of compound **45** as reported.[37] Solvents were dried and purified prior to use: THF and xylenes were distilled from sodium metal; CH_2Cl_2, DMF, DMA, toluene, hexanes, and pyridine were distilled from CaH_2. Reactions requiring an inert solvent were conducted under Ar or N_2. After extractive isolation, the organic phase was dried over $MgSO_4$ unless otherwise noted and evaporated under reduced pressure. Chromatography was carried out using 230–400 mesh silica gel. The width of the column corresponded to the amount of of silica gel used in the separation: (a) 1.6 cm width, 0–20 g silica; (b) 3 cm width, 20–90 g; (c) 5-cm width, 90–360 g; (d) 8-cm width, 360–500 g. HPLC analyses were conducted on a 4.6 × 250 mm-5 μm Microsorb SI normal-phase silica column, monitoring at 254 nm. Elemental analyses were determined by Microanalytical Laboratories, University of California at Berkeley.

***N*-(9-Phenyl-9-fluorenyl)-D-serine Isoxazolidide *O*-Benzyl Ether (15).** A solution of 41.9 g (104 mmol) of alcohol **14**[18a] in 350 mL of THF was treated with NaH (3.96 g, 157 mmol) at rt and the resulting suspension stirred for 5 min. To this mixture was added 386 mg (1.04 mmol) of TBAI, followed by 12.8 mL (108 mmol) of benzyl bromide. The suspension was stirred for 24 h, and 12 mL of glacial AcOH was added slowly, followed by 180 mL of water. The aqueous solution was extracted with EtOAc (2 × 300 mL), and the organic layers were combined, washed with 100 mL of saturated aqueous $NaHCO_3$ solution, dried, and evaporated. The residue was chromatographed (300 g of silica gel, eluting with 30% EtOAc/hexane) to afford 49.8 g (97%) of benzyl ether **15** as a white solid. A portion was recrystallized from 30% EtOAc/hexane to provide an analytical sample: mp 94 °C; $[\alpha]^{20}_D$ +169° (*c* 1.5, $CHCl_3$); IR (CH_2Cl_2) 3035, 1640 cm^{-1}; ^1H NMR δ 1.82 (s, 1H), 1.95 (s, 1H), 2.70 (s, 1H), 3.23 (s, 1H), 3.34 (s, 1H), 3.51 (s, 1H), 3.53 (m_c, 3H), 4.4 (m_c, 2H), 7.15–7.38 (m, 13H), 7.38 (d, *J* = 7.1, 3H), 7.66 (t, *J* = 7.8, 2H); ^{13}C NMR (two doublets of ArH obscured) δ 26.69 (t), 42.71 (t), 52.45 (d), 68.12 (t), 72.83 (t), 73.02 (s), 73.30 (t), 119.38 (d), 119.60 (d), 125.45 (d), 126.00 (d), 126.83 (d), 126.99 (d), 127.25 (d), 127.35 (d), 127.91 (d), 128.07 (d), 128.10 (d), 128.17 (d), 138.36 (s), 139.63 (s), 141.27 (s), 144.61 (s), 149.42 (s), 149.77 (s), 173.17 (s). Anal. Calcd for $C_{32}H_{30}N_2O_3$: C, 78.3; H, 6.2; N, 5.7. Found: C, 78.4; H, 6.4; N, 5.8.

2(*R*)-[(9-Phenyl-9-fluorenyl)amino]-3-(benzyloxy)propanal (17). To a rapidly stirring suspension of 787 mg (20.7 mmol) of $LiAlH_4$ in 120 mL of THF cooled to −5 °C was added a solution of 9.60 g (19.6 mmol) of acylisoxazolidide **15** in 80 mL of THF cooled to 0 °C over a 5 min period. The slurry was stirred for 40 min, 2.5 mL of water was added dropwise, 9.6 g of $KHSO_4$ dissolved in 48 mL of water was then added, and the mixture was warmed to rt. The mixture was stirred for an additional 10 min and partitioned between 600 mL of Et_2O and 125 mL of 1 M NaH_2PO_4, and the aqueous layer was washed with Et_2O (100 mL). The organic layers were combined, washed with 125 mL of water and 125 mL of brine, dried, and evaporated. The residue was chromatographed (300 g of silica gel, eluting with 20% EtOAc/hexane) to afford 8.18 g (99%) of the aldehyde **17** as a colorless oil: IR (CH_2Cl_2) 3038 (br), 1725 cm^{-1}; ^1H NMR δ 2.79 (t, *J* = 5.1, 1H, CHN), 3.24 (dd, *J* = 9.6, 5.6, 1H), 3.39 (s, 1H), 3.55 (dd, *J* = 9.7, 5.1, 1H), 4.34 (s, 2H), 7.10–7.34 (m, 14H), 7.48 (dd, *J* = 7.9, 6.5, 2H), 9.48 (d, *J* = 1.0, 1H); ^{13}C NMR δ 61.72 (d), 69.95 (t), 72.77 (s), 72.97 (t), 119.92 (d), 119.98 (d), 125.13 (d), 125.36 (d), 126.12 (d), 127.27 (d), 127.56 (d), 127.69 (d), 127.95 (d), 127.98 (d), 128.29 (d), 128.34 (d), 128.47 (d), 128.68 (d), 137.64 (s), 140.43 (s), 140.56 (s), 144.27 (s), 148.84 (s), 149.36 (s), 203.01 (s). HRFABMS Calcd for $C_{29}H_{26}NO_2$ (M + H)$^+$: 420.1968. Found: 420.1964.

Preparation of (5*S*)-5-[(1*R*)-1-[(9-Phenyl-9-fluorenyl)amino]-2-(benzyloxy)ethyl]dihydrofuran-2(3*H*)-one (*anti*-Lactone 4) from Titanium Homoenolate 22B. The iodozinc-homoenolate **26** was prepared by stirring 9.60 g (37.5 mmol) of *tert*-butyl 3-iodopropionate, 3.82 g (58.7 mmol) of freshly prepared Zn–Cu couple, 62 mL of toluene, and 6 mL of DMA under a nitrogen atmosphere (1 h at rt, 4 h at 80 °C). The mixture was cooled to rt and the excess Zn–Cu couple allowed

(55) Although **12** has been reported as a free base (refs 11c, 13, and citations in ref 14), it was described as unstable and was not characterized. The only reported salts are the dibenzoyltartrate (ref 13) and the trifluoroacetate (ref 14), precluding direct comparison. The NMR data reported in ref 14, however, are in close agreement with those of **68**.

(56) The synthesis of *rac*-**69** in seven steps and 12% overall yield has been reported by Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575.

to settle. To another reaction vessel were added 11 mL of toluene, 56 mL of CH_2Cl_2, and 5.53 mL (18.59 mmol) of Ti(O*i*Pr)$_4$. The solution was cooled to −40 °C, and 2.04 mL (18.59 mmol) of $TiCl_4$ was added dropwise. The resulting yellow solution was warmed to rt, vigorously stirred for 15 min, and then recooled to −40 °C. To this solution was added the iodozinc-homoenolate solution via cannula (leaving solids behind), producing a dark red solution containing titanium homoenolate **22B**. The resulting solution was stirred at −20 °C for 5 min and then cooled to −40 °C. To this mixture was added a solution of 7.80 g (18.6 mmol) of aldehyde **17** in 10 mL of CH_2Cl_2 at −50 °C via cannula, and the mixture stirred for 1 h, warmed to −20 °C over a 1 h period, stirred for 14 h, and then slowly warmed to rt over 3 h. The red solution was stirred 15 h, poured into a mixture of 50 mL of water, and extracted with 200 mL of EtOAc. A small amount of insoluble residue in the reaction mixture was dissolved in 10 mL of CH_2Cl_2 and added to the aqueous layer, which was extracted with EtOAc (3 × 100 mL). The organic layers were combined, washed with brine (2 × 50 mL), dried, and evaporated. The resulting residue was chromatographed (350 g of silica gel, eluting with 30% EtOAc/hexane) to afford 400 mg (4%) of hydroxy ester **23** and 8.20 g (93%) of lactone **4** existing as a 6.5/1 mixture of anti/syn diastereomers.

A solution of 2.05 g of lactone **4** (6.5/1 *anti/syn*) in 22.5 mL of MeOH/petroleum ether/CH_2Cl_2 10/1/0.5 was gradually cooled to 0 °C over 6 h. The resulting slurry was filtered to afford 1.50 g (69%) of *anti*-**4** (>98% pure). A similar recrystallization from the mother liquor afforded 300 mg (14%) of a 3/1 mixture of *anti*/*syn* lactone **4**. A solution of 10 mg of *anti*-**4** dissolved in 2 mL of 12% benzene/hexane was left to slowly evaporate over 24 h to produce crystals of *anti*-**4** suitable for X-ray analysis.

Data for 6.7/1 mix of *anti/syn*-23: IR (CH_2Cl_2) 3500 (s), 3410, 1723 cm^{-1}; ^{1}H NMR δ 1.42 (s, 9H); 1.55−1.60 (m, 2H), 1.60−1.70 (m, 1H), 2.08 (m, 1.18H), 2.15−2.30 (m, 2H), 2.59 (dd, *J* = 9.5, 4.0, 0.82H), 3.00 (d, *J* = 9.5, 1H), 3.10 (m, 0.82H), 3.29 (dd, *J* = 9.6, 4.8, 0.18H), 3.50−3.57 (m, 1H), 4.14 (s, 1.72H), 4.26 (s, 0.28H), 7.17−7.41 (m, 16H), 7.67 (dd, *J* = 7.5, 1H), 7.71 (dd, *J* = 7.5, 1H); ^{13}C NMR (some ArH doublets obscured) δ 28.03 (q), 28.52 (t), 28.68 (t), 31.83 (t), 32.53 (t), 55.54 (d), 56.15 (d), 69.16 (t), 69.23 (t), 71.16 (d), 71.99 (s), 72.29 (d), 72.70 (t), 72.91 (t), 79.84 (s), 79.91 (s), 119.75 (d), 119.89 (d), 119.91 (d), 124.76 (d), 125.27 (d), 125.65 (d), 125.92 (d), 125.96 (d), 127.09 (d), 127.56 (d), 127.59 (d), 127.62 (d), 127.69 (d), 127.92 (d), 128.15 (d), 128.23 (d), 128.29 (d), 128.31 (d), 128.35 (d), 137.85 (s), 137.94 (s), 139.86 (s), 139.91 (s), 140.53 (s), 140.66 (s), 144.92 (s), 145.14 (s), 148.45 (s), 149.23 (s), 150.36 (s), 151.35 (s), 173.12 (s), 173.23 (s). Anal. Calcd for $C_{36}H_{39}NO_4$: C, 78.6; H, 7.1; N, 2.6. Found: C, 78.2; H, 7.1; N, 2.5.

Selected Data for *syn*-4: ^{1}H NMR (C_6D_6) δ 2.78 (dd, *J* = 9.5, 7.2, 1H, BnOCH), 4.26 (dt, *J* = 6.6, 3.8, 1H, lactone CH). **Data for *anti*-4:** mp 130 °C; $[\alpha]^{20}_D$ −247.3° (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) 3313, 1770 cm^{-1}; ^{1}H NMR (C_6D_6) δ 1.58−1.84 (m, 3H), 1.88−1.96 (m, 1H), 2.20 (m, 1H), 2.37 (dd, *J* = 9.4, 4.0, 1H), 2.64 (s, 1H), 3.14 (dd, *J* = 9.4, 1.5, 1H), 3.86 (d, *J* = 11.6, 1H), 3.90 (d, *J* = 11.6, 1H), 4.08 (q, *J* = 7.1, 1H), 6.91−7.20 (m, 13H), 7.29 (d, *J* = 7.3, 1H), 7.37 (d, *J* = 7.4, 1H), 7.41−7.45 (m, 3H); ^{1}H NMR ($CDCl_3$) δ 2.18−2.30 (m, 2H), 2.36−2.48 (m, 3H), 2.54 (dd, *J* = 9.4, 3.9, 1H), 2.83 (s, 1H), 3.17 (dd, *J* = 9.4, 1.4, 1H), 4.16 (d, *J* = 11.5, 1H), 4.24 (d, *J* = 11.5, 1H), 4.49−4.53 (m, 1H), 7.20−7.28 (m, 8H), 7.31−7.38 (m, 5H), 7.41−7.47 (m, 3H), 7.68 (d, *J* = 7.5, 1H), 7.73 (d, *J* = 7.6, 1H); ^{13}C NMR (1 ArH doublet obscured) δ 25.16 (t), 28.62 (t), 55.19 (d), 68.18 (t), 72.33 (s), 72.73 (t), 80.59 (d), 119.99 (d), 124.87 (d), 125.90 (d), 126.07 (d), 127.20 (d), 127.64 (d), 127.68 (d), 127.74 (d), 127.90 (d), 128.22 (d), 128.32 (d), 128.43 (d), 128.48 (d), 138.03 (s), 140.03 (s), 144.94 (s), 148.35 (s), 151.13 (s), 177.48 (s). Anal. Calcd for $C_{32}H_{29}NO_3$: C, 80.8; H, 6.1; N, 3.0. Found: C, 81.1; H, 6.0; N, 3.1.

(5*S*,6*R*)-5-Hydroxy-6-benzyloxymethyl-2-piperidinone (6.5/1, *anti/syn*-30 from 6.5/1, *anti/syn*-4). To a solution of **4** (6.5/1, *anti*/*syn*, 7.83 g, 16.5 mmol) in 350 mL of 40% THF/MeOH, was added 1.65 g of 10% Pd−C. The resulting slurry was degassed and then stirred under a balloon of hydrogen for 26 h. The slurry was degassed under nitrogen and filtered through Celite, and the Celite pad was washed with an additional 400 mL of MeOH and 50 mL of CH_2Cl_2. The solvent was removed through distillation at atmospheric pressure at which time all of the intermediate amino lactone **4A** was no longer present. The residue was chromatographed (100 g of silica gel, eluting with CH_2Cl_2 → 2.5% MeOH/CH_2Cl_2) to afford 3.79 g (98%) of 6.5/1, *anti*/*syn*-**30** as a colorless oil. Selected data for *syn*-**30**: ^{1}H NMR (C_6D_6) δ 1.07−1.18 (m, 1H), 2.07−2.17 (m, 1H), 2.47−2.57 (m, 1H), 6.32 (s, 1H).

(5*S*,6*R*)-5-Hydroxy-6-[(benzyloxy)methyl]-2-piperidinone (*anti*-30 from *anti*-4). Applying the procedure described above for preparing alcohol **30**, 3.20 g (6.73 mmol) of *anti*-**4** afforded 1.52 g (96%) of pure *anti*-**30**: mp 76−77 °C; $[\alpha]^{20}_D$ +23.8° (*c* 1.2, $CHCl_3$); IR (CH_2Cl_2) 3588, 3378, 1658 cm^{-1}; ^{1}H NMR δ 1.79−1.90 (m, 1H), 1.93−2.01 (m, 1H), 2.30 (ddd, *J* = 17.7, 10.1, 6.3, 1H), 2.46 (dt, *J* = 17.7, 5.5, 1H), 3.40 (t, *J* = 8.8, 1H), 3.48 (q, *J* = 7.4, 1H), 3.63 (s, 1H, OH), 3.68 (dd, *J* = 8.9, 4.5, 1H), 3.69−3.75 (m, 1H), 4.52 (s, 2H), 6.35 (s, 1H), 7.27−7.36 (m, 5H); ^{13}C NMR δ 28.06 (t), 28.40 (t), 58.02 (d), 66.30 (d), 71.92 (t), 73.44 (t), 127.69 (d), 1227.93 (d), 128.47 (d), 137.28 (s), 171.60 (s). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.4; H, 7.3; N, 6.0. Found: C, 66.0; H, 7.3; N, 5.8.

(5*S*,6*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-[(benzyloxy)methyl]-2-piperidinone (*anti*-32 from *anti*-30). To a solution of 1.48 g (6.27 mmol) of *anti*-**4** in 37 mL of DMF was added 2.99 g (43.9 mmol) of imidazole, followed by 3.78 g (25.1 mmol) of TBDMSCl. The solution was stirred for 15 h and partitioned between 200 mL of 1/1 Et_2O/petroleum ether and 50 mL of water. The water layer was washed with Et_2O/petroleum ether (1/1, 3 × 100 mL). The combined organic layers were washed with 200 mL of brine, dried, and evaporated. The residue was chromatographed over 75 g of silica gel (eluting with 45% EtOAc/hexane) to afford 2.01 g (92%) of *anti*-**32** as a colorless oil: $[\alpha]^{20}_D$ +38.7° (*c* 1.3, $CHCl_3$); IR (CH_2Cl_2) 3385, 1663 cm^{-1}; ^{1}H NMR δ 0.04 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.77−1.84 (m, 1H), 1.86−1.92 (m, 1H), 2.30 (ddd, *J* = 17.8, 9.5, 6.2, 1H), 2.51 (dt, *J* = 17.8, 5.8, 1H), 3.32 (t, *J* = 8.7, 1H), 3.47 (m, 1H), 3.61 (dd, *J* = 9.0, 3.9, 1H), 3.72, (ddd, *J* = 10.3, 6.5, 3.6, 1H), 4.49 (d, *J* = 11.8, 1H), 4.53 (d, *J* = 11.8, 1H), 6.21 (s, 1H), 7.27−7.36 (m, 5H); ^{13}C NMR δ −5.03 (q), −4.44 (q), 17.79 (s), 25.57 (q), 28.27 (t), 28.45 (t), 58.70 (d), 66.53 (d), 71.36 (t), 73.31 (t), 127.65 (d), 127.80 (d), 128.39 (d), 137.41 (s), 171.02 (s). Anal. Calcd for $C_{19}H_{31}SiNO_3$: C, 65.3; H, 8.9; N, 4.0. Found: C, 65.1; H, 9.1; N, 4.1.

(5*S*,6*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-[(benzyloxy)methyl]-2-piperidinone (*anti*-32 from 6.7/1 *anti/syn*-30). Applying the procedure described above for the preparation of *anti*-**32**, 3.77 g (16.0 mmol) of a mixture of *anti*/*syn*-**30**, 6.5/1, was converted to *anti*-**32**. Chromatography of the crude reaction mixture over 450 g of silica gel (eluting with 50% EtOAc/hexane) afforded 4.32 g (77%) of *anti*-**32** as a colorless oil, followed by 650 mg (12%) of 1.5/1 *syn*/*anti*-**32**.

(5*S*,6*R*)-1-Benzyl-5-[(*tert*-butyldimethylsilyl)oxy]-6-[(benzyloxy)methyl]-2-piperidinone (34). To a solution of 4.29 g (12.3 mmol) of **32** in 45 mL of THF was added 486 mg (20.25 mmol) of NaH. The slurry was stirred for 15 min and a solution of 1.57 mL (13.3 mmol) of neat benzyl bromide was added, followed by 72 mg (0.19 mmol) of TBAI. The mixture was stirred for 42 h, 1 mL of *tert*-BuOH added, followed by the slow dropwise addition of 1.5 mL of water. The aqueous solution was extracted with CH_2Cl_2 (4 × 80 mL). The organic extracts were combined, washed with 75 mL of brine, dried, and evaporated. The residue was chromatographed (250 g of silica gel, eluted with 35% EtOAc/hexanes) to afford 5.32 g (99%) of benzyl amide **34** as a pale yellow oil: $[\alpha]^{20}_D$ +28.6° (*c* 1.3, $CHCl_3$); IR (CH_2Cl_2) 1645 cm^{-1}; ^{1}H NMR δ −0.07 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.72−1.80 (m, 1H), 1.94−2.04 (m, 1H), 2.39 (ddd, *J* = 17.8, 6.4, 2.4, 1H), 2.73 (ddd, *J* = 17.8, 11.6, 7.0, 1H), 3.38 (dd, *J* = 14.5, 7.5), 3.38−3.43 (m, 1H), 3.56 (dd, *J* = 14.5, 8.2, 1H), 3.93 (d, *J* = 15.3, 1H), 4.18 (m, 1H), 4.43 (d, *J* = 12.1, 1H), 4.50 (d, *J* = 12.1, 1H), 5.40 (d, *J* = 15.3, 1H), 7.21−7.44 (m, 10H); ^{13}C NMR δ −5.03 (q), 17.88 (s), 25.16 (t), 25.65 (q), 27.04 (t), 47.66 (t), 62.29 (d), 65.67 (d), 69.20 (t), 73.18 (t), 126.96 (d), 127.47 (d), 127.75 (d), 127.80 (d), 128.37

(d), 128.41 (d), 137.13 (s), 137.58 (s), 170.08 (s). Anal. Calcd for $C_{26}H_{37}NO_3Si$: C, 71.0; H, 8.5; N, 3.2. Found: C, 71.3; H, 8.5; N, 3.4.

(5*S*,6*R*)-1-Benzyl-5-[(*tert*-butyldimethylsilyl)oxy]-6-(hydroxymethyl)-2-piperidinone (35). A solution of 4.40 g (10.0 mmol) of **34** in 48 mL of absolute ethanol was degassed under a nitrogen atmosphere, and 1.30 g of 10% Pd–C was added. The resulting slurry was degassed once more and then stirred under a balloon of hydrogen over 23 h. The slurry was degassed under a nitrogen atmosphere and filtered through Celite, and the Celite pad washed with 500 mL of CH_2Cl_2. The filtrate was evaporated to afford 3.50 g (100%) of the primary alcohol **35** as a white solid which was taken directly into the next reaction without further purification. A small portion of alcohol **35** was chromatographed over a plug of silica gel (eluting with 2% MeOH/CH_2Cl_2): mp 99–100 °C; $[\alpha]^{20}_D$ +49.6° (*c* 3.6, $CHCl_3$); IR (CH_2Cl_2) 3605, 3200–500 (br), 1635 cm^{-1}; ^1H NMR δ −0.08 (s, 3H), 0.02 (s, 3H), 0.82 (s, 9H), 1.75–1.81 (m, 1H), 2.10–2.20 (m, 1H), 2.35 (ddd, J = 17.9, 6.7, 2.4, 1H), 2.69 (ddd, J = 17.8, 11.6, 6.9, 1H), 3.23–3.30 (m, 1H), 3.47 (s, 1H), 3.58–3.70 (m, 2H), 4.00 (d, J = 15.4, 1H), 4.16 (p, J = 1.7, 1H), 5.37 (d, J = 15.4, 1H), 7.20–7.33 (m, 5H); ^{13}C NMR δ −4.99 (q), −4.97 (q), 17.91 (s), 25.56 (t), 25.68 (q), 27.12 (t), 47.63 (t), 61.19 (t), 64.30 (d), 66.06 (d), 127.13 (d), 127.62 (d), 128.53 (d), 137.02 (s), 170.99 (s). Anal. Calcd for $C_{19}H_{31}NO_3Si$: C, 65.3; H, 8.9; N, 4.0. Found: C, 65.1; H, 9.0; N, 4.0.

(5*S*,6*R*)-1-(*p*-Methoxybenzyl)-5-[(*tert*-butyldimethylsilyl)oxy]-6-[(benzyloxy)methyl]-2-piperidinone (37). To a solution of 330 mg (0.0440 mmol) of **32** in 3.5 mL of THF was added 45.0 mg (1.89 mmol) of NaH. The slurry was stirred for 15 min, and a solution of 168 μL (1.18 mmol) of neat *p*-methoxybenzyl bromide[42] was added, followed by 72 mg (0.016 mmol) of TBAI. The mixture was stirred for 21 h, and 1 mL of *tert*-BuOH was added, followed by 100 mL of AcOH. After 5–10 min, water was added slowly dropwise and the mixture partitioned between 75 mL of CH_2Cl_2 and 10 mL of water. The aqueous solution was extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were combined, washed with 30 mL of brine, dried, and evaporated. The residue was chromatographed (75 g of silica gel, eluted with 30% → 50% EtOAc/hexanes) to afford 430.3 mg (97%) of *p*-methoxybenzylamide **37** as a pale yellow oil: $[\alpha]^{20}_D$ +33.1° (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 1638 cm^{-1}; ^1H NMR δ −0.11 (s, 3H), −0.01 (s, 3H), 0.78 (s, 9H), 1.67–1.75 (m, 1H), 1.89–1.99 (m, 1H), 2.34 (ddd, J = 17.8, 6.5, 2.3, 1H), 2.65 (ddd, J = 17.8, 11.7, 7.0, 1H), 3.35 (dd, J = 14.1, 7.5), 3.34–3.39 (m, 1H), 3.52 (dd, J = 14.1, 8.0, 1H), 3.75 (s, 3H), 3.80 (d, J = 15.0, 1H), 4.10–4.14 (m, 1H), 4.41 (d, J = 12.1, 1H), 4.47 (d, J = 12.1, 1H), 5.30 (d, J = 15.0, 1H),6.78 (d, J = 8.6, 2H), 7.12 (d, J = 8.6, 2H), 7.23–7.37 (m, 5H); ^{13}C NMR δ −5.03 (q), −4.96 (q), 17.90 (s), 25.15 (t), 25.66 (q), 27.12 (t), 47.12 (t), 55.25 (q), 62.01 (d), 65.62 (d), 69.25 (t), 73.22 (t), 113.88 (d), 127.52 (d), 127.84 (d), 128.46 (d), 129.24 (d), 129.34 (s), 137.66 (s), 158.76 (s), 170.04 (s). Anal. Calcd for $C_{27}H_{39}NO_4Si$: C, 69.0; H, 8.4; N, 3.0. Found: C, 68.8; H, 8.4; N, 3.3.

(5*S*,6*R*)-1-(*p*-Methoxybenzyl)-5-[(*tert*-butyldimethylsilyl)oxy]-6-(hydroxymethyl)-2-piperidinone (38). Applying the procedure for preparing alcohol **35**, 560 mg (1.19 mmol) of benzyl ether **37** was converted to 453 mg (100%) of alcohol **38** as a white solid which was taken directly into the next reaction without further purification: mp 87–88 °C; $[\alpha]^{20}_D$ +62.8° (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 3620, 3100–3500 (br),1640 cm^{-1}; ^1H NMR δ −0.10 (s, 3H), −0.01 (s, 3H), 0.78 (s, 9H), 1.69–1.75 (m, 1H), 2.12 (ddd, J = 16.1, 11.5, 6.5, 1H), 2.31 (ddd, J = 17.8, 6.3, 2.6, 1H), 2.64 (ddd, J = 17.8, 11.6, 6.9, 1H), 3.23–3.27 (m, 1H), 3.56 (s, 1H), 3.47 (s, 1H), 3.64 (t, J = 6.0, 2H), 3.75 (s, 3H), 3.93 (d, J = 15.1, 1H), 4.12–4.14 (m, 1H), 5.27 (d, J = 15.1, 1H), 6.79 (d, J = 8.6, 2H), 7.16 (d, J = 8.5, 2H); ^{13}C NMR δ −5.03 (q), −4.93 (q), 17.88 (s), 25.60 (t), 25.65 (q), 27.19 (t), 47.04 (t), 55.24 (q), 61.15 (t), 63.99 (d), 66.06 (d), 114.00 (d), 129.08 (d), 129.18 (s), 158.83 (s), 170.85 (s). Anal. Calcd for $C_{20}H_{33}NO_4Si$: C, 63.2; H, 8.8; N, 3.7. Found: C, 62.9; H, 8.6; N, 3.6.

(5*S*,6*R*)-1-Benzyl-5-[(*tert*-butyldimethylsilyl)oxy]-6-(bromomethyl)-2-piperidinone (5). To a solution of 3.40 g (9.73 mmol) of primary alcohol **35** and 4.52 g (13.6 mmol) of CBr_4 in 52 mL of CH_2Cl_2 at 0 °C was added a solution of 3.06 g (11.67 mmol) of PPh_3 in 26 mL of CH_2Cl_2 dropwise over a 5 min period. The solution was warmed to rt over a 1 h period, stirred for an additional 13 h, and then evaporated. The residue was chromatographed (150 g of silica gel, eluted with 25% EtOAc/hexane) to afford 3.73 g (93%) of bromide **5** as a white solid: $[\alpha]^{20}_D$ +27.7° (*c* 2.2, $CHCl_3$); mp 78–79 °C; IR (CH_2Cl_2) 1641 cm^{-1}; ^1H NMR δ −0.04 (s, 3H), 0.05 (s, 3H), 0.83 (s, 9H), 1.78–1.87 (m, 1H), 1.93–2.04 (m, 1H), 2.42 (ddd, J = 17.9, 6.3, 3.8, 1H), 2.74 (ddd, J = 17.7, 10.7, 6.8, 1H), 3.21 (dd, J = 10.8, 9.7, 1H), 3.44 (dt, J = 9.3, 2.5, 1H), 3.55 (dd, J = 10.8, 2.8, 1H), 3.89 (d, J = 15.3, 1H), 4.30 (p, J = 2.7, 1H), 5.46 (d, J = 15.3, 1H), 7.23–7.33 (m, 5H); ^{13}C NMR δ −4.92 (q), −4.89 (q), 17.86 (s), 24.87 (t), 25.66 (q), 27.31 (t), 30.65 (t), 47.45 (t), 63.27 (d), 65.36 (d), 127.39 (d), 127.85 (d), 128.65 (d), 136.51 (s), 169.75 (s). Anal. Calcd for $C_{19}H_{30}NO_2BrSi$: C, 55.3; H, 7.3; N, 3.4. Found: C, 55.5; H, 7.2; N, 3.5.

(5*S*,6*R*)-1-(*p*-Methoxybenzyl)-5-[(*tert*-butyldimethylsilyl)oxy]-6-(bromomethyl)-2-piperidinone (6). Applying the procedure for preparing alcohol **35**, except that the reaction mixture was stirred for 22 h instead of 13 h, 425 mg (1.12 mmol) of alcohol **38** was converted to 440 mg (89%) of bromide **6**: $[\alpha]^{20}_D$ +32.0° (*c* 1.3, $CHCl_3$); mp 71–72 °C; IR (CH_2Cl_2) 1639 cm^{-1}; ^1H NMR δ −0.08 (s, 3H), 0.01 (s, 3H), 0.77 (s, 9H), 1.71–1.80 (m, 1H), 1.88–1.98 (m, 1H), 2.36 (ddd, J = 17.8, 6.2, 3.8, 1H), 2.66 (ddd, J = 17.8, 10.6, 6.9, 1H), 3.17 (dd, J = 10.6, 9.8, 1H), 3.38 (dt, J = 9.4, 2.5, 1H), 3.50 (dd, J = 10.9, 2.7, 1H), 3.75 (s, 3H), 3.78 (d, J = 15.1, 1H), 4.25 (p, J = 2.6, 1H), 5.35 (d, J = 15.1, 1H), 6.80 (d, J = 8.6, 2H), 7.16 (d, J = 8.5, 2H); ^{13}C NMR δ −5.00 (q), −4.97 (q), 17.75 (s), 24.73 (t), 25.55 (q), 27.26 (t), 30.61 (t), 46.74 (t), 55.15 (q), 62.85 (d), 65.17 (d), 113.99 (d), 128.53 (s), 129.21 (d), 158.91 (s), 169.57 (s). Anal. Calcd for $C_{20}H_{32}SiNO_3Br$: C, 54.3; H, 7.3; N, 3.2. Found: C, 54.6; H, 7.2; N, 3.2.

(1*R*,4*S*,6*S*)-6-(*tert*-Butyldimethylsiloxy)-2-benzyl-2-azabicyclo[2.2.1]-3-heptanone (36). To a solution of KHMDS (27.80 mL of a 0.92 M solution in THF, 25.58 mmol) in 480 mL of THF cooled to −55 °C was added a solution of 5.26 g (12.75 mmol) of bromide **5** in 190 mL of THF at rt at a rate such that the internal temperature stayed below −50 °C during the addition (15–20 min). The dark pink solution was warmed to −35 °C gradually over 15 min, stirred 40 min, and warmed to rt over a 15 min period. The resulting cloudy pink solution was stirred for an additional 5 min, and then 745 μL (13.0 mmol) of glacial AcOH was added. The mixture was concentrated to 15 mL under reduced pressure, diluted with 50 mL of water, and extracted with EtOAc (4 × 100 mL). The organic layers were combined, washed with 100 mL of brine, dried, and evaporated. The resulting residue was chromatographed (350 g of silica gel, eluted with 25% EtOAc/hexane) to afford 4.17 g (99%) of bicyclic amide **36** as a colorless oil which slowly crystallized over several days to a white solid: mp 65–66 °C; $[\alpha]^{20}_D$ −81.3° (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 1693 cm^{-1}; ^1H NMR δ 0.05 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.37 (dt, J = 12.7, 3.1, 1H), 1.39 (d, J = 9.8, 1H), 1.74 (dddd, J = 9.8, 1.5, 1.5, 1.5, 1H), 2.15 (ddd, J = 12.8, 8.2, 4.4, 1H), 2.73–2.77 (m, 1H), 3.55 (s, 1H), 4.02 (d, J = 15.3, 1H), 4.51 (dt, J = 8.2, 2.6, 1H), 5.12 (d, J = 15.3, 1H), 7.22–7.33 (m, 5H); ^{13}C NMR δ −4.93 (q), −4.73 (q), 17.94 (s), 25.77 (q), 35.08 (t), 38.43 (t), 45.96 (d), 46.87 (t), 62.06 (d), 75.04 (d), 127.15 (d), 127.82 (d), 128.50 (d), 137.85 (s), 177.12 (s). Anal. Calcd for $C_{19}H_{29}NO_2Si$: C, 68.8; H, 8.8; N, 4.2. Found: C, 68.4; H, 9.0; N, 4.3.

(1*R*,4*S*,6*S*)-6-(*tert*-Butyldimethylsiloxy)-2-(*p*-methoxybenzyl)-2-azabicyclo[2.2.1]-3-heptanone (39). Procedure A. Applying the procedure for preparing bicyclic amide **36**, 418 mg (0.946 mmol) of bromide **6** was converted to 308 mg (90%) of bicyclic amide **39**.

Procedure B. Applying the procedure for preparing **37**, 878 mg (3.64 mmol) of secondary amide **40** was converted to 1.29 g (98%) of PMB-amide **39** as a pale yellow oil: $[\alpha]^{20}_D$ −78.5° (*c* 2.0, $CHCl_3$); IR (CH_2Cl_2) 1693 cm^{-1}; ^1H NMR δ 0.04 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.30–1.36 (m, 2H), 1.70 (dm, J = 9.8, 1H), 2.13 (ddd, J = 12.8, 8.2, 4.4, 1H), 2.72–2.74 (m, 1H), 3.52 (s, 1H), 3.77 (s, 3H), 3.94 (d, J = 15.1, 1H), 4.49 (dt, J = 8.2, 2.6, 1H), 5.04 (d, J = 15.0, 1H), 6.83 (d, J = 8.6, 2H), 7.14 (d, J = 8.5, 2H); ^{13}C NMR δ −4.91 (q), −4.72 (q), 17.95

(s), 25.79 (q), 35.08 (t), 38.51 (t), 46.03 (d), 46.24 (t), 55.20 (q), 61.84 (d), 75.05 (d), 113.94 (d), 129.15 (d), 128.50 (d), 129.82 (s), 177.02 (s). Anal. Calcd for $C_{20}H_{31}NO_3Si$: C, 66.4; H, 8.6; N, 3.9. Found: C, 66.4; H, 8.6; N, 3.8.

(1*R*,4*S*,6*S*)-6-(*tert*-Butyldimethylsiloxy)-2-azabicyclo-[2.2.1]-3-heptanone (40). Into a solution of 1.0 mL (10.6 mmol) of *tert*-BuOH and 12 mL of THF cooled to −78 °C was condensed in 5 mL of ammonia. Sodium metal was added in several pieces (200 mg, 8.66 mmol), producing a dark blue solution. To this mixture was added a solution of 624 mg (1.88 mmol) of *N*-benzyl amide **36** in 12 mL of THF at −78 °C. The solution was stirred for 6 min, warmed to −33 °C for 2 min, and recooled to −78 °C, and 207 μL (3.62 mmol) of glacial AcOH was added. The ammonia was then allowed to quickly evaporate, the residue diluted with 50 mL of THF, and the resulting slurry filtered through a pad of Celite. The reaction flask was washed with dry THF (4 × 50 mL), and the washings in turn were transferred and filtered through the Celite pad. The combined filtrate was evaporated and the resulting residue chromatographed (30 g of silica gel, eluted with 50% EtOAc/hexane → 2% MeOH−50% EtOAc/hexane) to afford 450 mg (99%) of **40** as a pale yellow glassy solid. Using this procedure, 2.32 g of **36** was converted to 1.60 g (94.5%) of **40**: mp 76−77 °C; $[\alpha]^{20}_D$ −170.4° (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 3433, 1722 cm^{-1}; ^1H NMR δ 0.01 (s, 3H), 0.01 (s, 3H), 0.82 (s, 9H), 1.23 (dt, *J* = 12.9, 2.9, 1H), 1.45 (d, *J* = 9.9, 1H), 1.87 (dddd, *J* = 9.8, 1.6, 1.6, 1.6, 1H), 2.11 (ddd, *J* = 12.9, 8.4, 4.4, 1H), 2.58−2.62 (m, 1H), 3.61 (s, 1H), 4.51 (dt, *J* = 8.3, 2.6, 1H), 5.71 (s, 1H); ^{13}C NMR δ −4.81 (q), −4.76 (q), 17.90 (s), 25.70 (q), 35.66 (t), 38.31 (t), 45.91 (d), 59.73 (d), 73.31 (d), 181.66 (s). Anal. Calcd for $C_{12}H_{23}NO_2Si$: C, 59.7; H, 9.6; N, 5.8. Found: C, 60.0; H, 9.7; N, 5.6.

(1*R*,4*S*,6*S*)-*N*-(*tert*-Butyloxycarbonyl)-6-(*tert*-butyldimethylsiloxy)-2-azabicyclo[2.2.1]-3-heptanone (7). To a mixture of 1.57 g (6.50 mmol) of amide **40** and 849 mg (6.95 mmol) of DMAP dissolved in 41 mL of anhydrous pyridine was added 3.62 g (16.59 mmol) of $(BOC)_2O$. The solution was stirred for 36 h and then evaporated, and the residue was chromatographed (45 g of silica gel, eluted with 10% EtOAc/hexane → 25% EtOAc/hexane) to afford 2.22 g (100%) of imide **7**: $[\alpha]^{20}_D$ −24.5° (*c* 1.1, $CHCl_3$); mp 67−68 °C (soften), 69−70 °C (melt); IR (CH_2Cl_2) 1781, 1752, 1714 cm^{-1}; ^1H NMR δ 0.05 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.39 (dt, *J* = 12.9, 2.9, 1H), 1.45−1.51 (m with s at 1.51, 10H), 1.91 (dddd, *J* = 9.8, 1.6, 1.6, 1.6, 1H), 2.18 (ddd, *J* = 13.1, 8.5, 4.5, 1H), 2.74 (dm, *J* = 3.1, 1H), 4.43−4.49 (m, 2H); ^{13}C NMR δ −5.01 (q), −4.86 (q), 18.13 (s), 25.80 (q), 28.05 (q), 34.58 (t), 36.61 (t), 47.32 (d), 62.14 (d), 72.46 (d), 82.17 (s), 150.20 (s), 174.97 (s). Anal. Calcd for $C_{17}H_{31}NO_4Si$: C, 59.8; H, 9.2; N, 4.1. Found: C, 59.8; H, 9.3; N, 4.1.

(1*R*,2*S*,4*S*)-1-[(*tert*-Butyloxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-4-(hydroxymethyl)cyclopentane (41). To a solution of 2.22 g (6.50 mmol) of imide **7** in 85 mL of MeOH was added $NaBH_4$ (3 × 1.23 g, 32.5 mmol) over 1 h. The mixture was stirred for 30 min, an additional 1.23 g portion of $NaBH_4$ was added, and the mixture was stirred 2 h more. The mixture was concentrated to one-fifth volume and diluted with 100 mL of saturated aqueous NH_4Cl, and the resulting aqueous solution was extracted with EtOAc (4 × 150 mL). The organic layers were combined, washed with 50 mL of brine, dried, and evaporated. The residue was chromatographed (70 g of silica gel, eluted with 35% EtOAc/hexane) to afford 2.19 g (98%) of alcohol **41** as a colorless oil: $[\alpha]^{20}_D$ +41.1° (*c* 1.4, $CHCl_3$); IR (CH_2Cl_2) 3620, 3427, 1720 cm^{-1}; ^1H NMR δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.40−1.50 (m with s at 1.43, 10H), 1.97−2.10 (m, 2H), 2.20−2.32 (m, 2H), 3.52 (dd, *J* = 10.2, 5.2, 1H), 3.57 (dd, *J* = 10.2, 5.1, 1H), 3.80−3.90 (m, 1H), 4.07−4.13 (m, 1H), 4.74 (d, *J* = 5.7, 1H); ^{13}C NMR δ −5.00 (q), −4.80 (q), 18.11 (s), 25.80 (q), 28.39 (q), 31.51 (t), 36.60 (t), 36.70 (d), 55.30 (d), 66.79 (t), 73.32 (d), 79.16 (s), 155.38 (s). Anal. Calcd for $C_{17}H_{35}NO_4Si$: C, 59.1; H, 10.2; N, 4.1. Found: C, 59.3; H, 9.8; N, 4.2.

(1*R*,2*S*,4*S*)-1-Amino-2-hydroxy-4-(hydroxymethyl)cyclopentane Hydrochloride (42). To a solution of 220 mg (0.637 mmol) of **41** in 0.5 mL of CH_2Cl_2 cooled to 0 °C was added 6 mL of saturated HCl in CH_2Cl_2. The solution was warmed to rt, stirred for 16 h, and evaporated. The residue was digested in 4 mL of MeOH and filtered, and the filtrate was evaporated to afford 103.5 mg (97%) of hydrochloride salt **42** as an amber oil. ^1H and ^{13}C NMR analyses indicated only the desired product to be present. The oil was dissolved in 1.5 mL of MeOH and was added dropwise to a rapidly stirring solution of 23 mL of Et_2O to produce an off-white solid. The supernatant was decanted and the solid dried at 80 °C (0.3 torr) for 2 days to afford 90 mg (84%) of **42**: mp 107−108 °C; $[\alpha]^{20}_D$ +20.6° (*c* 1.3, $CHCl_3$); IR (Nujol) 3250−3600 (br), 1900−2000 cm^{-1}; ^1H NMR (CD_3OD) δ 1.50−1.62 (m, 2H), 2.08−2.24 (m, 2H), 2.23−2.31 (m, 1H), 3.42 (td, *J* = 7.7, 5.0, 1H), 3.51 (dd, *J* = 9.4, 5.5, 1H), 3.54 (dd, *J* = 9.4, 5.1, 1H), 4.19 (q, *J* = 5.0, 1H); ^{13}C NMR (CD_3OD) δ 32.04 (t), 36.20 (t), 38.32 (d), 55.60 (d), 66.27 (t), 71.62 (d). Anal. Calcd for $C_6H_{14}NO_2Cl$: C, 43.0; H, 8.4; N, 8.4. Found: C, 43.1; H, 8.1; N, 8.5.

(1*R*,4*S*,6*S*)-6-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]-3-heptanone (43). To a solution of 343 mg (1.03 mmol) of silyl ether **36** in 10 mL of THF was added 2.0 mL (2.0 mmol) of 1 M TBAF in THF. The resulting yellow solution was stirred for 20 min and concentrated to approximately one-half volume, and 1 mL of glacial AcOH was added. The mixture was chromatographed (30 g of silica gel, eluting with EtOAc → 1% MeOH/EtOAc) to afford 225 mg (100%) of alcohol **43**: $[\alpha]^{20}_D$ −135° (*c* 1.2, $CHCl_3$); mp 135−136 °C; IR (CH_2Cl_2) 3605, 1693 cm^{-1}; ^1H NMR δ 1.37 (dt, *J* = 13.2, 2.9, 1H), 1.41 (d, *J* = 9.9, 1H), 1.80 (dm, *J* = 9.8, 1H), 2.25 (ddd, *J* = 13.2, 8.5, 4.3, 1H), 2.71−2.85 (m, 1H), 2.95 (s, 1H), 3.60−3.69 (m, 1H), 4.12 (d, *J* = 15.2, 1H), 4.55 (dm, *J* = 8.4, 1H), 5.05 (d, *J* = 15.2, 1H), 7.18−7.42 (m, 5H); ^{13}C NMR δ 34.83 (t), 39.43 (t), 45.94 (t), 47.05 (t), 62.28 (d), 74.29 (d), 127.38 (d), 128.00 (d), 128.63 (d), 137.60 (s), 177.42 (s). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0; N, 6.4. Found: C, 71.5; H, 7.1; N, 6.3.

(1*R*,4*S*,6*R*)-6-Fluoro-2-azabicyclo[2.2.1]-3-heptanone (46). To a solution of 652 mL (5.12 mmol) of DAST in 1.12 mL of pyridine was added a solution of 163 mg (0.750 mmol) of alcohol **43** in 3.9 mL of CH_2Cl_2. The mixture was stirred for 30 h, cooled to 0 °C, and quenched by the dropwise addition of 1 mL of water. The solution was partitioned between 100 mL of CH_2Cl_2 and 20 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was washed with of CH_2Cl_2 (2 × 40 mL), and the combined organic extracts were washed with 40 mL of 2 M aqueous HCl and 10 mL of brine, dried, and evaporated. The residue was chromatographed (15 g of silica gel, eluted with 30% EtOAc/hexanes) to afford 99 mg (60%) of intermediate *N*-benzyl fluoro compound **45** as a glass which was taken directly into the next reaction without further purification.

Applying the procedure for preparing secondary amide **40**, 98 mg (0.450 mmol) of benzyl amide **45** was converted to 51 mg (88%) of fluoro amide **46**, recrystallized from the minimum amount of 75% EtOAc/hexanes (75% recovery), followed by sublimation at 50−60 °C, 0.1 torr.

Selected Data for 45: IR (CH_2Cl_2) 1710 cm^{-1}; ^1H NMR δ 1.73−2.00 (m, 3H), 2.12 (dddd, *J* = 17, 14.0, 6.4, 2.6, 1H), 2.79 (dm, *J* = 2.2, 1H), 3.76 (br s, 1H), 4.07 (d, *J* = 14.9, 1H), 4.49 (d, *J* = 14.9, 1H), 4.62 (ddd, *J* = 54.1, 6.3, 1.3, 1H), 7.22−7.45 (m, 5H); ^{19}F NMR δ −5.41 (ddd, J_{F-H} = 54, 35, 17); ^{13}C NMR δ 33.90 (t, J_{C-F} = 20.7), 37.03 (t, J_{C-F} = 1.9), 43.35 (d, J_{C-F} = 1.5), 44.91 (t), 61.18 (d, J_{C-F} = 26.8), 90.70 (d, J_{C-F} = 191.9), 127.81 (d), 127.98 (d, 2C), 128.81 (d, 2C), 136.73 (s), 177.27 (s).

46: mp 131−132 °C; $[\alpha]^{20}_D$ −95.4 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2) 3438, 1715 cm^{-1}; ^1H NMR δ 1.85 (ddd, *J* = 33_{H-F}, 13.9, 3.5, 1H, $H\text{-}5_{exo}$), 1.91 (dm, *J* = 10.2, 1.6, 1H, $H\text{-}7_{syn}$), 2.07 (dm, *J* = 10.0, 1H, $H\text{-}7_{anti}$), 2.12 (dddd, *J* = 16.7_{H-F}, 14.0, 6.4, 2.6, 1H, $H\text{-}5_{endo}$), 2.68 (dm, *J* = 3.0, 1H, H-4), 3.94 (br s, 1H, H-1), 4.89 (dddd, *J* = 54.1_{H-F}, 5.6, 3.0, 1.5, 1H, H-6), 5.90 (s, 1H, NH); ^{19}F NMR δ −7.85 (ddd, J_{F-H} = 54.3, 34.0, 16.7); ^{13}C NMR δ 32.93 (t, J_{C-F} = 20.8, C-5), 37.97 (t, J_{C-F} = 1.6, C-7), 42.50 (d, C-4), 57.45 (d, J_{C-F} = 27.1, C-1), 92.05 (d, J_{C-F} = 192.0, C-6), 180.97 (s, C-3). Anal. Calcd for C_6H_8FNO: C, 55.8; H, 6.2; N, 10.8. Found: C, 56.1; H, 6.2; N, 10.8.

(1*R*,4*S*,6*R*)-*N*-(*tert*-Butyloxycarbonyl)-6-fluoro-2-azabicyclo[2.2.1]-3-heptanone (8). Applying the procedure for preparing imide **7**, 112 mg (0.870 mmol) of amide **46** was

converted to 185 mg (93%) of imide **8**, sublimed at 60–70 °C, 0.1 torr: mp 100–101 °C; $[\alpha]^{20}_D$ −18.7° (*c* 1.4, $CHCl_3$); IR (CH_2Cl_2) 1793, 1769, 1718 cm^{-1}; ^1H NMR δ 1.52 (s, 9H), 1.85–2.07 (m, 3H), 2.26 (dddd, *J* = 17_{H-F}, 14.7, 6.4, 1.5, 1H), 2.82 (dm, *J* = 2.5, 1H), 4.58 (apparent br s, 1H), 4.97 (ddd, *J* = 53_{H-F}, 6.3, 1.4, 1H); ^{19}F NMR δ −6.90 (ddd, J_{F-H} = 53, 34, 17); ^{13}C NMR δ 27.99 (q), 33.42 (t, J_{C-F} = 21.7), 34.32 (t, J_{C-F} = 1.3), 44.58 (d, J_{C-F} = 1.4), 60.57 (d, J_{C-F} = 28.9), 83.44 (s), 90.48 (d, J_{C-F} = 191.0), 149.03 (s), 174.42 (s). Anal. Calcd for $C_{11}H_{16}NO_3$: C, 57.6; H, 7.0; N, 6.1. Found: C, 57.8; H, 7.0; N, 6.2.

(1*R*,2*R*,4*S*)-1-[(*tert*-Butyloxycarbonyl)amino]-2-fluoro-4-(hydroxymethyl)cyclopentane (47). Applying the procedure for preparing alcohol **41**, 173 mg (0.760 mmol) of imide **8** was converted to 164 mg (93%) of alcohol **47**: mp 98–99 °C; $[\alpha]^{20}_D$ +10.6° (*c* 1.6, $CHCl_3$); IR (CH_2Cl_2) 3625, 3445, 3375, 1715 cm^{-1}; ^1H NMR (two different N-H forms) δ 1.44 (s, 9H), 1.74–2.25 (m, 3H, OH, 2 × H-3), 2.30–2.40 (m, 1H, H-5), 2.42–2.47 (m, 1H, H-5), 3.61–3.68 (m, 2H), 4.07–4.12 (m, 1H), 4.89 (dm, J_{H-F} = 59, 1H, H-2), 5.23–5.41 (s, 0.77 H, NH), 5.52–5.64 (s, 0.23H, NH); selected data (C_6D_5N, 298 K) 3.63–3.76 (m, 2H, OCH_2), 5.20 (dm, *J* = 52.4, 1H, H-2), 7.42 (s, 0.13H, NH), 7.62 (m, 0.87H, NH); selected data (C_6D_5N, 398 K) δ 3.68 (d, *J* = 4.7, 2H, OCH_2), 5.13 (dp, *J* = 52.4, 2.7, 1H, H-2); ^{19}F NMR (^1H decoupled, 298 K, $CDCl_3$) δ −1.07 (0.77F), −1.44 (0.23F); (1H decoupled; C_6D_5N, 298 K) δ −2.68 (0.87F), −3.40 (0.13F), (^1H decoupled, C_6D_5N, 398 K) δ −2.50 (1F); ^1H coupled ^{19}F signals appear as a ddd, *J* = 52, 36, 21; ^{13}C NMR δ 28.37 (q, Me × 3), 32.73 (t, J_{C-F} = 20.3, C-3), 32.73 (t, C-5), 56.51 (d, J_{C-F} = 19.8, C-1), 64.59 (t, HO*C*H_2 at C-4), 79.48 (s, *C*$(CH_3)_3$), 98.98 (d, J_{C-F} = 173.4, C-2), 155.20 (s, C=O). Anal. Calcd for $C_{11}H_{20}NO_3F$: C, 56.6; H, 8.6; N, 6.0. Found: C, 56.9; H, 8.4; N, 6.1.

(1*R*,2*R*,4*S*)-1-Amino-2-fluoro-4-(hydroxymethyl)cyclopentane Hydrochloride (48). To a solution of 162 mg (0.690 mmol) of carbamate **47** dissolved in 0.5 mL of CH_2Cl_2 at 0 °C was added 7 mL of saturated HCl in CH_2Cl_2, and the solution warmed to rt. The resulting slurry was stirred 16 h, the liquor decanted, and the solid triturated with 10 mL of 80% CH_2Cl_2/hexanes. The solid was dried at 70 °C, 0.3 torr for 2 days to afford 115.6 mg (98%) of hydrochloride **48**: $[\alpha]^{20}_D$ −10° (*c* 1.7, CH_3OH); mp 159–160 °C; IR (Nujol) 3200–3400 (br), 2040–2140 (br) cm^{-1}; ^1H NMR (CD_3OD) δ 1.50 (dt, *J* = 13.1, 8.1, 1H), 1.87–2.12 (m, 2H), 2.33–2.52 (m, 2H), 3.53 (d, *J* = 4.9, 2H), 3.69 (dtd, *J* = 20.6_{H-F}, 7.6, 3.4), 5.10 (ddt, *J* = 52.4_{H-F}, 6.4, 3.2, 1H); ^{19}F NMR (CD_3OD) δ 0.59 (m); ^{13}C NMR (CD_3OD) δ 33.11 (t, J_{C-F} = 2.5, C-5), 34.85 (t, J_{C-F} = 21.8, C-3), 39.23 (d, C-4), 58.02 (d, J_{C-F} = 27.9, C-1), 65.09 (t, HO*C*H_2 at C-4), 97.50 (d, J_{C-F} = 179.3, C-2). Anal. Calcd for $C_6H_{13}NOClF$: C, 42.5; H, 7.7; N, 8.3. Found: C, 42.5; H, 7.7; N, 8.2.

(1*R*,4*S*,6*R*)-6-Iodo-2-benzyl-2-azabicyclo[2.2.1]-3-heptanone (49). Applying the procedure for preparing PMB-iodo amide **53**, except that the reaction mixture was heated to reflux for only 2.5 h instead of 3.75 h, 241 mg (1.11 mmol) of alcohol **43** was converted to 164 mg (93%) of iodide **49**: mp 63–64 °C; $[\alpha]^{20}_D$ −58.1° (*c* 1.6, $CHCl_3$); IR (CH_2Cl_2) 1703 cm^{-1}; ^1H NMR δ 2.03 (dddd, *J* = 10.0, 1.8, 1.8, 1.8, 1H, $H\text{-}7_{anti}$), 2.20 (d, *J* = 10.0, 1H, $H\text{-}7_{syn}$), 2.34 (ddd, *J* = 14.1, 3.9, 3.9, 1H, $H\text{-}5_{exo}$), 2.45 (ddd, *J* = 14.1, 7.6, 1.8, 1H, $H\text{-}5_{endo}$), 2.83 (dd, *J* = 3.7, 1.9, 1H, H-4), 3.73 (ddd, *J* = 7.6, 3.8, 1.8, 1H, H-6), 3.88 (m, 1H, H-1), 4.03 (d, *J* = 15.0, 1H, ArCHN), 4.59 (d, *J* = 15.0, 1H, ArCHN), 7.25–7.42 (m, 5H, ArH); ^{13}C NMR δ 18.47 (d), 37.28 (t), 38.14 (t), 44.42 (t), 46.56 (d), 66.27 (d), 127.80 (d), 127.85 (d), 128.83 (d), 136.57 (s), 176.34 (s). Anal. Calcd for $C_{13}H_{14}NOI$: C, 47.7; H, 4.3; N, 4.3. Found: C, 47.9; H, 4.4; N, 4.1.

(1*R*,4*S*)-2-Benzyl-2-azabicyclo[2.2.1]-5-hepten-3-one (50). To a solution of 330 mg (1.01 mmol) of iodide **49** in 8 mL of xylenes was added 760 mL (5.05 mmol) of DBU and the solution heated to reflux for 16.5 h. The mixture was cooled to rt, diluted with 80 mL of CH_2Cl_2, and extracted with 3 M aqueous HCl (2 × 20 mL). The organic layer was washed with 20 mL of saturated aqueous $NaHCO_3$, 25 mL of brine, dried, and evaporated. The residue was chromatographed (15 g of silica gel, eluted with 22% EtOAc/hexane) to afford 191 mg (95%) of olefin **50** as a colorless oil: IR and NMR data identical with those reported.[34] HRMS calcd for $C_{13}H_{13}NO$ (M^+): 199.0993. Found: 199.0997. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.4; H, 6.6; N, 7.0. Found: C, 77.9; H, 6.7; N, 7.1.

(1*R*,4*S*)-2-(*p*-Methoxybenzyl)-2-azabicyclo[2.2.1]-5-hepten-3-one (51). Applying the procedure described above for preparing olefin **50**, 1.42 g (3.98 mmol) of iodide **53** was converted to 0.895 g (98%) of olefin **51** as a low melting glass.

Vinyl Triflate Reduction. Alternative Preparation of 51. To a solution of 1.4 mg (5.3 μmol) of PPh_3 in 0.4 mL of DMF was added 0.60 mg (2.6 μmol) of $Pd(OAc)_2$ and the resulting mixture stirred for 10 min. To this solution was added 38.6 mg (0.101 mmol) of vinyl triflate **57** in three 0.5-mL portions of DMF, followed by 74.3 μL (0.312 mmol) of Bu_3N and 8 μL (0.2 mmol) of anhydrous HCO_2H. The mixture was stirred 6 h and then partitioned between 50 mL of 50% Et_2O/petroleum Et_2O and 10 mL of 1 M aqueous H_3PO_4 solution. The organic layer was dried then evaporated, and the resulting residue chromatographed (17 g of silica gel, 20% → 55% EtOAc/hexanes) to afford 9 mg of olefin **51** (39%): mp 33–35 °C; $[\alpha]^{20}_D$ −40.0° (*c* 2.2, $CHCl_3$); IR and NMR data identical with those reported.[37] Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.3; H, 6.6; N, 6.1. Found: C, 73.1; H, 6.7; N, 6.1.

(1*R*,4*S*,6*S*)-6-Hydroxy-2-(*p*-methoxybenzyl)-2-azabicyclo[2.2.1]-3-heptanone (52). Applying the procedure for preparing alcohol **43**, 1.587 g (4.390 mmol) of TBS ether **39** was converted to 1.048 g (97%) of alcohol **52**: mp 139.3–140 °C; $[\alpha]^{20}_D$ −129° (*c* 1.0; $CHCl_3$); IR (CH_2Cl_2) 3610, 3100–3600 (br), 1689 cm^{-1}; ^1H NMR δ 1.33–1.42 (m, 2H), 1.74 (dm, *J* = 9.6, 1H), 2.22 (ddd, *J* = 13.0, 8.6, 4.3, 1H), 2.70–2.74 (m, 1H), 3.57–3.63 (m, 2H), 3.76 (s, 3H), 4.05 (d, *J* = 15.0, 1H), 4.51–4.59 (m, 1H), 4.97 (d, *J* = 15.0, 1H), 6.82 (d, *J* = 8.4, 2H), 7.17 (d, *J* = 8.4, 2H); ^{13}C NMR δ 34.56 (t), 39.38 (t), 45.92 (d), 46.34 (t), 55.15 (q), 62.03 (d), 74.02 (d), 113.94 (d), 129.27 (d), 129.53 (s), 158.85 (s), 177.35 (s). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9; N, 5.7. Found: C, 67.7; H, 6.9; N, 5.7.

(1*R*,4*S*,6*R*)-6-Iodo-2-(*p*-methoxybenzyl)-2-azabicyclo-[2.2.1]-3-heptanone (53). To a suspension of 1.98 g (7.53 mmol) of PPh_3 and 1.37 g (20.1 mmol) of imidazole in 20.4 mL of toluene was added 1.91 g (7.53 mmol) of iodine, forming a brown slurry which was heated to 60 °C for 10 min. To this mixture was added 1.01 g (4.12 mmol) of alcohol **43** in one portion, followed by 49 mL of toluene at 60 °C. The heterogeneous mixture was heated to reflux for 3.75 h, cooled to rt, and partitioned with 15 mL of water. The aqueous solution was extracted with CH_2Cl_2 (5 × 70 mL), and the combined organic extracts were washed with 100 mL of saturated aqueous $NaHCO_3$ and 100 mL of brine, dried, and evaporated. The residue was chromatographed (45 g of silica gel, eluted with 25% EtOAc/hexane) to afford 1.46 g (97%) of iodide **53** as a colorless oil which slowly solidified into a white solid: mp 88–94 °C; $[\alpha]^{20}_D$ −43.6° (*c* 1.4, $CHCl_3$); IR (CH_2Cl_2) 1703 cm^{-1}; ^1H NMR δ 2.01 (dm, *J* = 10.0, 1H), 2.19 (d, *J* = 10.0, 1H), 2.34 (ddd, *J* = 14.1, 3.9, 3.9, 1H), 2.44 (ddd, *J* = 14.1, 7.6, 1.8, 1H), 2.83 (dd, *J* = 3.7, 1.9, 1H), 3.68–3.73 (m, 1H), 3.81 (s, 3H), 3.87–4.0 (m, 1H), 4.03 (d, *J* = 14.9, 1H), 4.49 (d, *J* = 15.0, 1H), 6.88 (d, *J* = 8.6, 2H), 7.17 (d, *J* = 8.6, 2H); ^{13}C NMR δ 18.69 (d), 37.31 (t), 38.07 (t), 43.88 (t), 46.61 (d), 55.20 (q), 66.17 (d), 114.20 (d), 128.56 (s), 129.18 (d), 159.19 (s), 176.22 (s). Anal. Calcd for $C_{14}H_{16}NIO_2$: C, 47.1; H, 4.5; N, 3.9. Found: C, 47.4; H, 4.6; N, 3.9.

(1*R*,4*S*)-*N*-(*tert*-Butyloxycarbonyl)-2-azabicyclo[2.2.1]-5-hepten-3-one (9). To a rapidly stirring solution of 95 mg (0.415 mmol) of amide **51** dissolved in 3.3 mL of 67% CH_3CN/H_2O cooled to 0 °C was added 636 mg (1.16 mmol) of CAN. The mixture was stirred for 17 min and diluted with 8 mL of ice-cold water, and the resulting aqueous solution was poured into a solution of 65 mL of rapidly stirring EtOAc. The aqueous layer was separated and extracted with EtOAc (2 × 60 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (2 × 15 mL), dried, and evaporated to afford 32.6 mg of products. The residue was chromatographed (20 g of silica gel, eluted with 60% EtOAc/hexane → 10% MeOH–50% EtOAc/hexane) to afford 33 mg of crude secondary lactam **54**. This residue was dissolved in 1.9 mL of anhydrous pyridine, and 39 mg (0.32 mmol) of DMAP was added, followed by 163 mg (0.75 mmol) of $(BOC)_2O$. The

solution was stirred for 22 h, the resulting orange solution evaporated, and the residue chromatographed (15 g of silica gel, eluted with 15% EtOAc/hexane → 22% EtOAc/hexane) to afford 51.6 mg (59% overall from olefin **51**) of imide **9** as a white solid. This solid and *rac*-**9**[44] were analyzed by chiral GC on a J&W Cyclodex-B cyclodextrin column using T_0inj = 200; t_0 = 1 min; T_0 = 80 °C; rate = 0.70 °C/min; [t_r ((1*R*,4*S*)-**9**), 20.04 min; t_r ((1*S*,4*R*)-**9**), 20.90 min; er of ((1*R*,4*S*)-**9**)/((1*S*,4*R*)-**9**) = 72/28]: mp 68–71 °C; $[\alpha]^{20}_D$ −94.6° (*c* 1.2, $CHCl_3$); IR (CH_2Cl_2) 1780, 1755, 1708 cm^{-1}; ^1H NMR δ 1.50 (s, 9H), 2.14 (dm, *J* = 8.5, 1H), 2.34 (dm, *J* = 8.5, 1H), 3.37–3.40 (m, 1H), 4.95 (q, *J* = 1.8, 1H), 6.65 (dt, *J* = 5.3, 3.5, 1H), 6.89 (dd, *J* = 5.3, 2.2, 1H); ^{13}C NMR δ 27.99 (q), 54.39 (d), 54.87 (t), 62.35 (d), 82.54 (s), 138.16 (d), 139.97 (s), 150.34 (s), 176.18 (s). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.2; H, 7.2; N, 6.7. Found: C, 63.5; H, 7.3; N, 6.7.

(1*R*,4*S*)-*N*-(*tert*-Butyloxycarbonyl)-1-amino-4-(hydroxymethyl)-2-cyclopentene (55). Applying the procedure for preparing alcohol **41**, 52 mg (0.250 mmol) of imide **9** was converted to 48.1 mg (93%) of alcohol **55**: mp 51–56 °C (soften), 56–59 °C; $[\alpha]^{20}_D$ +8.9 (*c* 1.7, $CHCl_3$); IR (CH_2Cl_2) 3627, 3443, 1706 cm^{-1}; ^1H NMR δ 1.41 (dt, *J* = 13.9, 4.3, 1H, H-5b), 1.44 (s, 9H, $OC(CH_3)_3$), 1.83–2.05 (s, 1H, OH), 2.49 (dt, 1H, *J* = 13.7, 8.7, H-5a), 2.80–2.85 (m, 1H, H-4), 3.57 (dd, *J* = 10.5, 4.5, 1H, HOC*H* at C-4), 3.65 (dd, *J* = 10.5, 4.2, 1H, HOC*H* at C-4), 4.64–4.70 (m, 1H, H-1), 4.85 (s, 1H, NH), 5.76 (dt, *J* = 5.6, 2.2, 1H, H-3), 5.80 (dm, *J* = 5.6, 1H, H-2); ^{13}C NMR δ −25.43 (q), 34.58 (t), 46.87 (d), 55.95 (d), 65.03 (t), 79.19 (s), 133.90 (d), 134.01 (d), 155.27 (s). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.9; H, 9.0; N, 6.6. Found: C, 61.9; H, 9.0; N, 6.5.

(1*R*,4*S*)-2-(*p*-Methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (56). To a solution of 332 μL (3.80 mmol) of oxalyl chloride in 3.8 mL of CH_2Cl_2 at −78 °C was added dropwise a solution of 540 μL (7.60 mmol) of DMSO. The pale yellow solution was stirred for 20 min at −78 °C, and a solution of 465 mg (1.88 mmol) of alcohol **52** in 6.6 mL of CH_2Cl_2 was added over a 10 min period. The mixture was stirred for an additional 1 h to produce a white slurry, 1.88 mL (13.5 mmol) of Et_3N was added over 5 min, and the mixture warmed to rt over 20 min. The mixture was stirred for an additional 40 min and then partitioned between 150 mL of CH_2Cl_2 and 30 mL of water. The organic layer was washed with 2 M aqueous H_3PO_4 (2 × 50 mL) and 50 mL of brine, dried, and evaporated. The residue was chromatographed (30 g of silica gel, eluting with 60% EtOAc/hexane) to afford 452 mg (98%) of ketone **56**: mp 85.5–86.5 °C; $[\alpha]^{20}_D$ −247° (*c* 1.1; $CHCl_3$); IR (CH_2Cl_2) 1764, 1710 cm^{-1}; ^1H NMR δ 1.85 (d, *J* = 10.5, 1H), 2.11–2.18 (m, 2H), 2.22 (ddd, *J* = 10.3, 5.5, 4.0, 1H), 3.01–3.02 (m, 1H), 3.55 (t, *J* = 1.5, 1H), 3.78 (s, 3H), 3.87 (d, *J* = 14.9, 1H), 4.68 (d, *J* = 14.9, 1H), 6.84 (dm, *J* = 8.7, 2H), 7.17 (d, *J* = 8.6, 2H); ^{13}C NMR δ 35.09 (t), 39.02 (t), 42.41 (d), 45.06 (t), 55.18 (q), 64.58 (d), 114.11 (d), 127.88 (s), 129.57 (d), 159.29 (s), 176.48 (s), 206.05 (s). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.2; N, 5.7. Found: C, 68.5; H, 6.2; N, 5.6.

(1*R*,4*S*,6*S*)-6-[[(*p*-Methylphenoxy)thiocarbonyl]oxy]-2-(*p*-methoxybenzyl)-2-azabicyclo[2.2.1]-3-heptanone (59). To a solution of 50 mg (0.20 mmol) of alcohol **52** dissolved in 2.1 mL of CH_3CN was added 60 mg (0.5 mmol) of 4-DMAP, followed by 50 μL (0.32 mmoL) of *p*-cresyl chlorothionoformate. The mixture was stirred for 15 h and then dissolved in 80 mL of EtOAc which was washed vigorously with 40 mL of 1 M aqueous NaOH, 40 mL of aqueous 2 M HCl, and 40 mL of brine. The solution was dried and evaporated and the resulting residue chromatographed (15 g of silica gel, eluting with 65% EtOAc/hexane) to afford 80 mg (99%) of **59** as a colorless oil: $[\alpha]^{20}_D$ −4.7° (*c* 1.1, $CHCl_3$); IR (CH_2Cl_2) 1702 cm^{-1}; ^1H NMR δ 1.54 (d, *J* = 10.1, 1H), 1.75 (dt, *J* = 13.9, 3.1, 1H), 1.89 (dm, *J* = 10.1, 1H), 2.52 (ddd, *J* = 13.9, 8.7, 4.3, 1H), 2.38 (s, 3H), 2.89–2.91 (m, 1H), 3.76 (d, *J* = 15.0, 1H), 3.80 (s, 3H), 4.02 (m, 1H), 5.05 (d, *J* = 15.0, 1H), 5.69 (dt, *J* = 8.5, 2.5, 1H), 6.88 (d, *J* = 8.6, 2H), 7.00 (d, *J* = 8.4, 2H), 7.19 (d, *J* = 8.5, 2H), 7.24 (d, *J* = 8.4, 2H); ^{13}C NMR δ 20.89 (q), 32.49 (t), 38.92 (t), 45.49 (d), 45.81 (t), 55.22 (q), 55.29 (d), 85.60 (d), 114.07 (d), 121.31 (d), 128.89 (s), 129.42 (d), 130.16 (d), 136.50 (s), 151.15 (s), 159.07 (s), 176.40 (s), 194.58 (s). Anal. Calcd for $C_{22}H_{23}NSO_4$: C, 66.5; H, 5.8; N, 3.5. Found: C, 66.5; H, 6.1; N, 3.5.

General Procedure for Preparation of (*R*)- or (*S*)-MTPA-C_6F_5 Esters. To a solution of 441 mg (2.14 mmol) of DCC in 2.5 mL of EtOAc cooled to 0 °C was added 1.18 g (6.41 mmol) of pentafluorophenol. The solution was stirred 30 min, 500 mg (2.14 mmol) of (*R*)-(+)-MTPA (99% *ee*) or (*S*)-(−)-MTPA (95% *ee*) were added, and the solution was stirred an additional 1.5 h. The mixture was warmed to rt, stirred 8 h, and cooled to −10 °C and 2 mL of hexane added. The urea precipitate was collected by filtration (450 mg), the solid washed with 1.5 mL of cold hexane, and the mother liquor evaporated. The residue was dissolved in 50 mL of CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution (2 × 40 mL), 40-mL of saturated aqueous $NaHCO_3$ containing 0.30 g of dissolved sodium hydroxide, and 40 mL of water, dried, and evaporated. The residue was chromatographed over 20 g of silica gel (eluting with 500 mL of hexane) to afford 806 mg (94%) of the (*R*)- or (*S*)-MTPA-C_6F_5 ester. The solid could be recrystallized by dissolving 191 mg of the crude MTPA-C_6F_5 ester in 1 mL of hexane, cooling to −4 °C for 1 h to form a slurry, removing the liquor by pipette while cold, and immediately placing the solid under vacuum to afford 154–172 mg (85–90% recovery) of the MTPA-C_6F_5 esters as a white crystalline solid.

(*R*)-MTPA-C_6F_5 ester: mp 45 °C; $[\alpha]^{20}_D$ +45.1° (*c* 1.0, $CHCl_3$); ^1H NMR δ 3.72 (d, *J* = 1.2, 3H, OCH_3), 7.47–7.51 (m, 3H, ArH), 7.62–7.64 (m, 2H, ArH); ^{19}F NMR (TFA) δ −88.34 (t, *J* = 20.5, 2F), −83.07 (dd, *J* = 22.3, 21.5, 1F), −78.55 (d, *J* = 18.2, 2F), 1.12 (s, 3F); ^{13}C NMR δ 56.02, 85.29 (q, J_{C-F} = 20.9), 122.82 (q, J_{C-F} = 289, CF_3), 127.16, 128.70, 130.00, 130.98, 136.73–136.87 (m), 138.85–138.89 (m), 139.17–139.46 (m), 139.66–139.83 (m), 141.29–141.49 (m), 142.18–142.35 (m), 163.29. Anal. Calcd for $C_{16}H_8F_8O_3$: C, 48.0; H, 2.0. Found: C, 48.0; H, 2.0.

(*S*)-MTPA-C_6F_5 ester: mp 45 °C; $[\alpha]^{20}_D$ −43.5 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_8F_8O_3$: C, 48.0; H, 2.0. Found: C, 47.9; H, 2.2.

Formation of Carbamates 47 and 55. To a 0.45 M solution of HCl salt **48** or **68** in MeOH was added 200 mol % of $(BOC)_2O$ and 300 mol % of DIEA. The solution was stirred for 4 h and evaporated, and the residue was chromatographed over 10 g of silica gel (eluting with 30% EtOAc/hexanes) to afford 99–100% of carbamate **47** or **55**.

General Procedure for the Preparation of Derivatives from MTPA-C_6F_5 Esters. To a 0.15 M solution of alcohol *dl*-**55**, **55** (1*R*,4*S*, from pyrolysis), or **47** in dry CH_3CN was added 320 mol % of 4-DMAP, followed by 160 mol % of (*R*)-(+)- or (*S*)-(−)-MTPA-C_6F_5 ester. The mixture was stirred until the alcohol was consumed as determined by TLC (ca. <24 h). The solution was diluted with 50 mL of CH_2Cl_2, washed with 1 M aqueous NaOH (2 × 40 mL) and 2 M aqueous HCl (2 × 40 mL), dried, and evaporated. The residue was chromatographed over 10 g of silica gel (eluting with 300 mL of hexanes to recover unreacted MTPA-C_6F_5 ester then 200 mL of EtOAc to afford the corresponding olefinic or fluoro MTPA ester. Selected data for *dl*-**55**-(*R*)-MTPA ester: ^1H NMR δ 5.71 (dm, *J* = 8.3, 2H, CH=CH for *ent*-ester), 5.56 (dm, *J* = 8.3, 2H, CH=CH for ester); ^{19}F NMR δ 75.13 (s, 3F), 75.38 (s, 3F). Selected data for (1*R*,4*S*)-**55**-(*R*)-MTPA ester: ^{19}F NMR (^1H coupled) δ 75.39 (0.0101F, CF_3 for *ent*-ester), 75.39 (2.989F, CF_3 for ester); Selected data for **47**-(*R*)-MTPA ester: ^1H NMR δ 4.59 (dm, *J* = 52.9, 1H, CHF); ^{19}F NMR (^1H decoupled) δ −30.08 (0.0095H, C-2F for *ent*-ester), −29.44 (0.9905H, C-2F for ester). **47**-(*S*)-MTPA ester: ^1H NMR δ 4.67 (dm, *J* = 52.7, 1H, CHF).

(1*R*,2*S*,4*S*)-1-[(*tert*-Butyloxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-4-[(methoxymethoxy)methyl]cyclopentane (60). To a solution of 700 mg (2.025 mmol) of alcohol **41** in 12 mL of CH_2Cl_2 was added 2.47 mL (14.18 mmol) of DIEA followed by 616 μL (8.11 mmol) of chloromethyl methyl ether. The mixture was stirred for 6 h and then partitioned between 10 mL of water and 70 mL of CH_2Cl_2. The organic layer was washed with 40 mL of 2 M aqueous HCl, 40 mL of saturated aqueous $NaHCO_3$, and 10 mL of brine, dried, and evaporated. The residue was chromatographed (70 g of silica gel, eluting with 25% EtOAc/hexane) to afford 740 mg (94%) of acetal **60** as a colorless oil: $[\alpha]^{20}_D$ +36.5° (*c* 1.5, $CHCl_3$); IR (CH_2Cl_2) 3445, 1709 cm^{-1}; ^1H NMR δ 0.03 (s, 6H),

0.88 (s, 9H), 1.23–1.57 (m with s at 1.41, 11H), 1.95 (ddd, J = 18.9, 9.6, 4.9, 1H), 2.05 (dt, J = 12.2, 7.6, 1H), 2.12–2.22 (m, 1H), 3.32 (s, 3H), 3.35–3.47 (m, 2H), 3.77–3.85 (m, 1H), 4.04–4.08 (m, 1H), 4.58 (s, 2H), 4.78 (d, J = 8.1, 1H); ^{13}C NMR δ −5.10 (q), −4.72 (q), 18.01 (s), 25.78 (q), 28.36 (q), 33.26 (t), 34.58 (d), 36.52 (t), 54.90 (q), 55.04 (d), 73.11 (t), 73.11 (d), 78.90 (s), 96.40 (t), 155.43 (s). Anal. Calcd for $C_{19}H_{39}NO_5Si$: C, 58.6; H, 10.1; N, 3.6. Found: C, 58.3; H, 9.8; N, 3.5.

(1*R*,2*S*,4*S*)-1-[(*tert*-Butyloxycarbonyl)amino]-2-hydroxy-4-[(methoxymethoxy)methyl]cyclopentane (61). Applying the procedure for preparing alcohol **43**, over 24 h, 740 mg (1.90 mmol) of TBS ether **60** was converted to 523 mg (100%) of alcohol **61** as a colorless oil: $[\alpha]^{20}_D$ +0.8° (c 2.1, $CHCl_3$); IR (CH_2Cl_2) 3610, 3440, 1706 cm^{-1}; ^{1}H NMR δ 1.34–1.47 (m with s at 1.42, 10H), 1.55 (ddd, J = 14.5, 2.0, 1.6, 1H), 2.03–2.18 (m, 2H), 2.27–2.38 (m, 1H), 3.19 (d, J = 6.9, 1H), 3.36 (s, 3H), 3.43–3.50 (m, 2H), 3.77–3.88 (m, 1H), 3.93–3.97 (m, 1H), 4.64 (s, 2H), 5.16 (d, J = 8.1, 1H); ^{13}C NMR δ 28.34 (q), 31.58 (t), 34.30 (d), 35.62 (t), 55.49 (q), 55.62 (d), 70.92 (t), 72.65 (d), 79.07 (s), 96.45 (t), 155.72 (s). Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.7; H, 9.1; N, 5.1. Found: C, 56.4; H, 9.1; N, 5.0.

(1*R*,4*S*)-1-[(*tert*-Butyloxycarbonyl)amino]-4-(hydroxymethyl)-2-cyclopentene (64). A 25 mL round bottom flask containing 592 mg (1.39 mmol) of **67** was connected to a Kugelrohr apparatus under a vacuum of 12 Torr and was heated from 24 → 200 °C over a 15 min period. The apparatus was cooled to rt, and the resulting distillate was washed back into the distilling flask using 17 mL of MeOH. To this solution were added 610 mg (2.78 mmol) of $(BOC)_2O$ and 725 μL (4.17 mmol) of DIEA, followed by stirring for 2 h. The solution was evaporated and the residue diluted with 50 mL of CH_2Cl_2 which was washed with 2 M aqueous HCl (2 × 20 mL), 1 M aqueous NaOH (2 × 20 mL), and 20 mL of saturated aqueous $NaHCO_3$, dried, and evaporated. The residue was chromatographed (35 g of silica gel, eluted with 10 → 25% EtOAc/hexane) to afford 312 mg (87%) of olefin **64** as a colorless oil: $[\alpha]^{20}_D$ −12.8° (c 2.3, $CHCl_3$); IR (CH_2Cl_2) 3440, 1705 cm^{-1}; ^{1}H NMR δ 1.31 (dt, J = 13.6, 4.6, 1H), 1.42 (s, 9H), 2.49 (dt, J = 13.4, 8.3, 1H), 2.83–2.92 (m, 1H), 3.34 (s, 3H), 3.45–3.53 (m, 2H), 4.61 (s, 2H), 4.65–4.72 (m, 1H), 4.73–4.83 (m, 1H), 5.72–5.77 (m, 1H), 5.78–5.81 (m); ^{13}C NMR δ 28.42 (q), 35.41 (t), 44.76 (d), 55.27 (q), 55.89 (d), 70.52 (t), 79.03 (s), 95.53 (t), 133.08 (d), 134.56 (d), 155.19 (s). Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.7; H, 9.0; N, 5.4. Found: C, 60.4; H, 8.9; N, 5.5.

(1*R*,2*S*,4*S*)-1-[(*tert*-Butyloxycarbonyl)amino]-2-[[(*p*-methylphenoxy)thiocarbonyl]oxy]-4-[(methoxymethoxy)methyl]cyclopentane (67). The procedure for preparing thionocarbonate **59** was applied, except 402 mol % of 4-DMAP and 225 mol % of *p*-cresyl chlorothionoformate were reacted in 9 mL of CH_3CN over 11.5 h with 116 mg (0.42 mmol) of alcohol **61** which was converted to 124 mg (69%) of **67** as a colorless oil. In addition, 13 mg (9.7%) of **66** was isolated and 20 mg (17%) of **61** was recovered after chromatography (17 g of silica gel, eluting with 10% → 50% EtOAc/hexanes). **67:** $[\alpha]^{20}_D$ +31.7° (c 1.3, $CHCl_3$); IR (CH_2Cl_2) 3450, 1715 cm^{-1}; ^{1}H NMR δ 1.39–1.50 (m), 1.47 (s, 9H), 1.83–1.90 (m, 1H), 2.20–2.37 (m, 3H), 2.38 (s, 3H), 3.38 (s, 3H), 3.43–3.50 (m, 2H), 4.17–4.28 (m, 1H), 4.64 (s, 2H), 4.93 (d, J = 7.9, 1H), 5.48–5.53 (m, 1H), 7.01 (d, J = 8.4, 2H), 7.22 (d, J = 8.3, 2H); ^{13}C NMR δ 20.89 (q), 28.34 (q), 32.89 (t), 33.65 (t), 34.28 (d), 53.29 (d), 55.26 (q), 71.57 (t), 79.54 (s), 85.18 (d), 96.45 (t), 121.43 (d), 130.01 (d), 136.25 (s), 151.16 (s), 155.10 (s), 194.23 (s). Anal. Calcd for $C_{21}H_{31}NSO_6$: C, 59.3; H, 7.3; N, 3.3. Found: C, 59.3; H, 7.5; N, 3.4.

(1*R*,4*S*)-1-Amino-4-(hydroxymethyl)-2-cyclopentene Hydrochloride (68). A solution of 312 mg (1.21 mmol) of carbamate **67** in 20 mL of 20% 2 N HCl/MeOH was heated at reflux for 23 h, cooled to rt, and evaporated and the residue dried under high vacuum to afford 181 mg (100%) of crystalline **68**, pure by ^{1}H and ^{13}C NMR. The solid was recrystallized from 2 mL of MeOH by slowly adding Et_2O until the solution was turbid, then sitting 3 h, and filtering to give 153 mg after drying. The procedure was repeated to afford an additional 16 mg of **68** which was combined with the first crop; total yield, 169 mg (93%) of the HCl salt **68** as pale brown crystals. A second recrystallization of 10 mg in the same solvent system (vapor diffusion method) afforded colorless needles: mp 129–130 °C; $[\alpha]^{20}_D$ −28.8° (c 1.2; $CHCl_3$); ^{1}H NMR δ 1.65 (dt, J = 14.2, 4.3, 1H), 2.49 (dt, J = 14.2, 8.4, 1H), 2.94–3.03 (m, 1H), 3.56 (dd, J = 10.4, 4.4, 1H), 3.65 (dd, J = 10.4, 4.0, 1H), 4.20 (dm, J = 7.4, 1H), 5.76 (dt, J = 4.5, 2.0, 1H), 5.80 (dm, J = 4.5, 1H); ^{13}C NMR (MeOH-d_4) δ 33.24 (t), 48.37 (d), 57.04 (d), 63.40 (d), 129.36 (d), 141.19 (d). Anal. Calcd for $C_6H_{12}NOCl$: C, 48.2; H, 8.1; N, 9.4. Found: C, 48.3; H, 8.1; N, 9.2.

(5*S*,6*R*)-1-Benzyl-5-(benzyloxy)-6-[(benzyloxy)methyl]-2-piperidinone (69). To a solution of 118 mg (0.50 mmol) of *anti*-**30** in 2.9 mL of mechanically stirred THF was added 31 mg (1.28 mmol) of NaH. The slurry was stirred for 15 min, and 127 μL (1.1 mmol) of benzyl bromide was added, followed by 3 mg (8 μmol) of TBAI. The mixture was stirred for 24 h, and 1 mL of water was added slowly, followed by dilution with 15 mL of water and 50 mL of CH_2Cl_2. The organic layer was separated, and the aqueous solution was extracted with CH_2Cl_2 (2 × 50 mL). The organic extracts were combined, dried, and evaporated, and the residue was chromatographed (17 g of silica gel, eluting with 40% EtOAc/hexanes) to afford 196 mg (94%) of tribenzyl amide **69**: $[\alpha]^{20}_D$ +48.6° (c 1.2, $CHCl_3$); IR (CH_2Cl_2) 1640 cm^{-1}; ^{1}H NMR δ 1.95–2.09 (m, 2H), 2.43 (ddd, J = 18.7, 6.0, 4.0, 1H), 2.71 (ddd, J = 18.6, 10.2, 8.1, 1H), 3.44 (dd, J = 9.9, 7.1), 3.56 (dd, J = 9.9, 4.0, 1H), 3.68 (m, 1H), 3.87 (dd, J = 6.6, 3.0, 1H), 4.01 (d, J = 15.3, 1H), 4.31 (d, J = 11.7, 1H), 4.39 (d, J = 11.7, 1H), 4.41 (d, J = 11.9, 1H), 4.46 (d, J = 11.9, 1H), 5.38 (d, J = 15.3, 1H), 7.18–7.42 (m, 15H); ^{13}C NMR δ 22.35 (t), 27.37 (t), 47.87 (t), 58.54 (d), 69.31 (t), 69.96 (t), 71.95 (d), 73.22 (t), 127.04 (d), 127.25 (d), 127.46 (d), 127.54 (d), 127.74 (d), 127.83 (d), 128.22 (d), 128.38 (d), 128.43 (d), 137.20 (s), 137.49 (s), 138.00 (s), 170.15 (s). Anal. Calcd for $C_{27}H_{29}NO_3$: C, 78.0; H, 7.0; N, 3.4. Found: C, 77.7; H, 7.3; N, 3.4.

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Supporting Information Available: Experimental procedures and full characterization of compounds **16**, **28**, **29**, **31**, **33**, **44**, **57**, **58**, **62**, and **63** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm verison of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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