Asymmetric Synthesis of Substituted 2-Azaspiro[3.5]nonan-1-ones: An Enantioselective Synthesis of the Cholesterol Absorption Inhibitor (+)-SCH 54016

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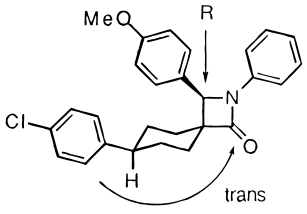
Substituted 2-azaspiro[3.5]nonan-1-ones are potent cholesterol absorption inhibitors.[1] Structure-activity studies identified (+)-SCH 54016 (**1**) as one of the most potent compounds in this series.[2] In order to generate multigram quantities of (+)-SCH 54016 for continuing biological evaluation, an efficient synthetic route for this class of compounds had to be developed. An optimal pathway would not only afford stereochemical control at C-4 of the 2-azetidinone ring, but also lend itself amenable to a dissymmetric spiroannulation at C-3 providing a *trans* relationship between the 4-chlorophenyl moiety and the carbonyl group, as this is critical for activity.[2] Herein, we report a general highly enantioselective synthetic route to substituted 2-azaspiro[3.5]nonan-1-ones such as (+)-SCH 54016 **(1)**.



(+)-SCH 54016 (**1**)
Hamster ED_{50} = 0.66 mpk
Rhesus Monkey ED_{50} = 0.01 mpk

Several synthetic routes to substituted 2-azaspiro[3.5]-nonan-1-ones have been reported.[3] However, none of these provide control of the stereochemistry of substituents at the cyclohexyl ring. Due to steric constraints, C-4 substituted 2-azetidinone enolates predominantly yield the C-3,4-*trans*-diastereomer upon reaction with electrophiles.[4] This propensity of 2-azetidinone enolates could be exploited to achieve the diastereomeric control of substituents on the cyclohexyl ring of 2-azaspiro[3.5]-nonan-1-ones. Thus, the intramolecular alkylation of **C**, Figure 1, should result in the formation of **D**, with the electrophilic center **Y** approaching the enolate of **C** *trans* to the C-4 substituent. **C** should be readily available by

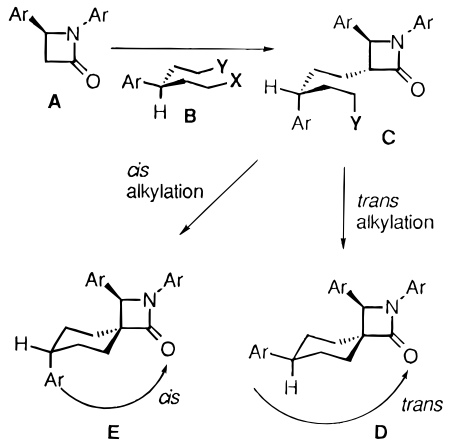
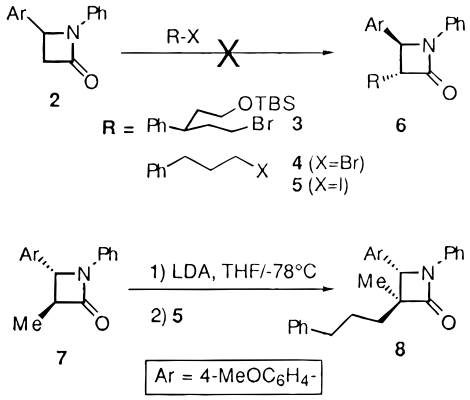


Figure 1.

Scheme 1



the alkylation of a chiral C-3 unsubstituted 2-azetidinone **A** with a chiral bis-electrophile **B**, where the electrophilic center **X** reacts first. The selectivity of this intramolecular spiro-alkylation would determine the ratio of the *cis*- and *trans*-cyclohexyl diastereomers **D** and **E**. By analogy, reversing the chirality of **B** or by altering the reactivity of the centers **X** and **Y** should yield the corresponding diastereomer **E**, thereby allowing for the synthesis of either diastereomer. This methodology should also provide a route for the diastereoselective synthesis of various regioisomers of **D** or **E** with the use of the appropriate bis-electrophile.

The synthesis of a 2-azaspiro[3.4]octan-1-one, by the bis-alkylation of a C-3 unsubstituted 2-azetidinone with 1,5-diiodopentane, has been reported before.[3f] All attempts at the synthesis of **6** *via* the alkylation of **2** with **3** were unsuccessful (Scheme 1).[5] Subsequent attempts at alkylation of **2** with **4** or **5** were also unsuccessful; however, the enolate of **2** could be methylated with iodomethane.[6] Further investigation revealed that at temperatures below −30 °C the electrophiles **3**−**5** were unreactive; warming the reaction above −30 °C, however, resulted in the decomposition of the enolate of **2**.[6] In contrast, the alkylation of monosubstituted 2-azetidinone **7** with **5** proceeded smoothly to yield the disubstituted 2-azetidinone **8** as a single diastereomer where the phenylpropyl side chain was *trans* to the C-4 aryl moiety.[7]

(1) Dugar, S.; Clader, J.; Chan, T.-M; Davis, H., Jr. *J. Med. Chem.* **1995**, *38*, 4875.
(2) Dugar, S. *et al.* Manuscript to be submitted to *J. Med. Chem.*
(3) (a) Mullen, G. B.; Georgiev, V. S. *Heterocycles* **1986**, *24*, 3441. (b) Ishibashi, H; Nakamura, N.; Tatsunori, S.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* **1991**, *32*, 1725. (c) Ikeda, M.; Uchino, T.; Ishibashi, H.; Tamura, Y.; Kido M. *J. Chem. Soc., Chem. Commun.* **1984**, 758. (d) Spurr, P. R.; Hamon, D. P. G. *J. Amer. Chem. Soc.* **1983**, *105*, 4734. (e) Wittig, G.; Hesse, A. *Liebigs Ann. Chem.* **1976**, 500. (f) Fujisawa, T.; Ukaji, Y.; Noro, T.; Date. K.; Shimizu, M. *Tetrahedron* **1992**, *48*, 5629. (g) Le Blanc, S.; Pete, J.-P.; Piva, O. *Tetrahedron Lett.* **1992**, *33*, 1993. (h) Toda, F.; Miyamoto, H.; Takeda, K.; Matsugawa, R.; Maruyama, N. *J. Org. Chem.* **1993**, *58*, 6208.
(4) Gabe, E.; Lee, F. *J. Org. Chem.* **1990**, *55*, 5525. (b) Mash, E. A.; Sharma, M. K. *Tetrahedron* **1987**, *43*, 679.
(5) The alkylation was investigated using the bases LDA, LICA, or LHMDS in the presence or absence of HMPA.
(6) Browne, M. E.; Burnett, D. A.; Caplen, M. A.; Chen, L.-Y.; Clader, J. W.; Domalski, M.; Dugar, S.; Pushpavanam, P.; Sher, R.; Vaccaro, W.; Viziano, M.; Zhao, H. *Tetrahedron Lett.* **1995**, *36*, 2555.

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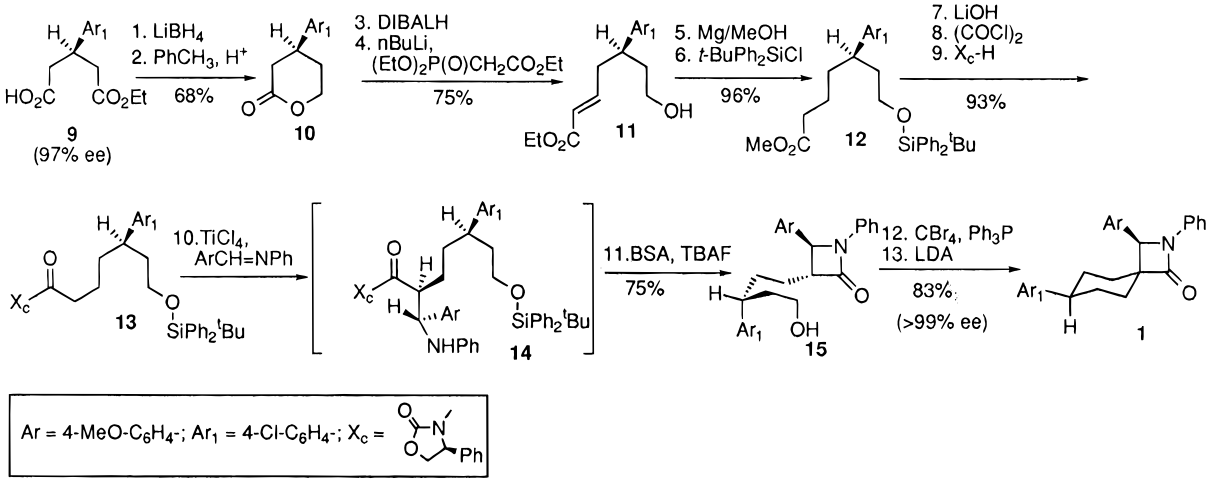
Scheme 2



Since the synthesis of the C-3 monoalkylated 2-azetidinone **6** was not accessible *via* direct alkylation of **2** an alternate route, outlined in Scheme 2, was employed.

(*R*)-3-(4-Chlorophenyl)glutarate monoethyl ester (**9**), obtained by α-chymotrypsin-catalyzed hydrolysis of the corresponding diethyl glutarate (ee = 97%),[8] was selectively reduced.[9] The resulting hydroxy acid was cyclized without purification to give lactone **10** in 68% yield (two steps). A one-pot process involving first the reduction of lactone **10** with diisobutylaluminum hydride to the lactol followed by Horner−Emmons reaction with triethyl phosphonoacetate gave the hydroxy ester **11** in 75% yield.[10] The alcohol was protected as a silyl ether and the double bond in **11** reduced with magnesium powder in methanol to give methyl ester **12**.[11] Subsequent hydrolysis to the acid and condensation of the acid chloride with Evans's chiral auxiliary (*R*)-4-phenyl-2-oxazolidinone gave **13** in 97% yield. Condensation of the titanium enolate[12] of **13** with *N*-(4-methoxybenzylidene)-aniline gave **14** which was used without purification.[13] Silylation of the aniline with *N*,*O*-bis(trimethylsilyl)-acetamide followed by treatment with tetrabutylammonium fluoride resulted in the cyclization to form the 2-azetidinone ring and simultaneous hydrolysis of the silyl ether to give **15** in 75% yield.[13] The enolate−imine condensation proceeded with the predicted stereoselectivity as the corresponding *cis* diastereomer of **15** was not detectable by 400 MHz ^{1}H-NMR. Azetidinone **15** was then converted to the corresponding bromide, which underwent smooth intramolecular alkylation when treated with lithium diisopropylamide in tetrahydrofuran to give **1** in 83% yield (28% overall from **9**) and >99% ee (as determined by HPLC) after purification on a silica gel column.[14] As expected, the approach of the bromide side chain occurred *trans* to the C-4 aryl substituent translating into a *trans* relationship between the 4-chlorophenyl moiety and the 2-azetidinone carbonyl group.

In summary, this investigation has led to an efficient and highly enantioselective synthesis of (+)-SCH 54016 (**1**). Though the intermolecular diastereoselective *trans* alkylation of C-4 substituted 2-azetidinones is well documented, to our knowledge this is the first instance of an unambiguous intramolecular *trans*alkylation of a 2-azetidinone. This route should also serve as a general method for the asymmetric synthesis of various azaspiro-[3.5]nonan-1-ones for structure−activity relationship studies.

Experimental Section

Synthesis of (3*R*)-(4-Chlorophenyl)pentanedioic Acid Monoethyl Ester (9). Diethyl 3-(4-chlorophenyl)glutarate (19.2 g, 64.4 mmol) was added to a 5 L round-bottomed flask containing aqueous solution of potassium chloride (2.5 L of a 50 mM solution) and vigorously stirred with an overhead stirrer. To this mixture was added α-chymotrypsin (7.5 g, from bovine pancreas, Sigma, type II), and the reaction was maintained at rt and pH 7.8 by automatic titration with 0.2 M NaOH solution. After 120 h (at which point 70.8 mmol of NaOH was consumed), the reaction was stopped by adjusting the pH to 2.25 with 6 N HCl. The solution was lyophilized, and the residue was extracted with ethyl acetate (750 mL). The enzyme was removed by filtration and the ethyl acetate removed under reduced pressure to give **9** (16.0 g, 97% ee, 92% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) 7.26 (2H, d, J = 9.8 Hz), 7.16 (2H, d, J = 9.8 Hz), 4.03 (2H, q, J = 7 Hz), 3.61 (1H, qt, J = 7 Hz), 2.80−2.56 (4H, m), 1.15 (3H, t, J = 7 Hz). Anal. Calcd for $C_{13}H_{15}ClO_4$: C, 57.68; H, 5.59. Found: C, 57.65; H, 6.06.

Synthesis of (4*S*)-(4-Chlorophenyl)tetrahydro-2*H*-pyran-2-one (10). To a stirred suspension of $LiBH_4$ (802 mg, 35 mmol) in anhyd DME (20 mL) was added a solution containing the monoacid ester **9** (4.72 g, 20 mmol) and methanol (1.42 mL, 35 mmol) in DME (60 mL). The reaction mixture was heated at reflux for 1 h and then allowed to reach rt. The reaction was quenched with 1 N HCl at 0 °C. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concd to give a crude product which was used in the next step without further purification.

The crude product from the previous step was taken up into toluene (80 mL) and was heated at reflux for 3.5 h in the presence of *p*-toluenesulfonic acid (20 mg) with azeotropic removal of water. After cooling to rt, the mixture was concd to dryness to leave a solid. Purification by silica gel chromatography (2:1 ethyl acetate/hexane, R_f 0.35) afforded **10** (2.8 g, 76%) as a white solid. Mp: 81−83 °C. ^{1}H NMR (400 MHZ, $CDCl_3$) 7.33 (2H, J = 7.5 Hz, d), 7.15 (2H, J = 7.5 Hz, d), 4.52 (1H, J = 11.5, 4.9, 3.8 Hz, ddd), 4.39 (1H, J = 11.6, 3.7 Hz, dt), 3.23 (1H, m), 2.91 (1H, J = 17.3, 5.9, 1.6 Hz, ddd,), 2.59 (1H, J = 17.3, 10.6 Hz, dd), 2.17 (1H, m), 2.02 (1H, m); HRMS (M^+ + H) calcd for $C_{11}H_{11}ClO_2$ 210.0448, found: 210.0457. Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.53; H, 5.20.

(7) Structure was confirmed by NOE experiments.
(8) Chênevert, R.; Desjardins M. *Tetrahedron Lett.* **1991**, *32*, 4249.
(9) Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000.
(10) Takacs, J.; Helle, M.; Seely, F. *Tetrahedron Lett.* **1986**, *27*, 1257.
(11) Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409.
(12) Evans, D. A.; Reiger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.
(13) Thiruvengadam, T. K.; Tann, C.-H.; Lee, J.; McAllister, T.; Sudhakar, A. U.S. Patent 5,306,817, 1994. Thiruvengadam, T. K.; McAllister, T.; Tann, C.-H. PCT Intl. Appl. WO 95 01,961 (*Chem. Abstr.* **1995**, *123*, 9326b).
(14) The %ee was determined on a Chiralcel OD column (95:5, hexane/2-propanol).

Synthesis of Ethyl (5*S*)-(4-Chlorophenyl)-7-hydroxy-2-heptenoate (11). To a stirred solution of triethyl phosphonoacetate (2.15 mL, 10.6 mmol) in 50 mL anhyd THF was added a solution of *n*-butyllithium (6.9 mL, 11.0 mmol; 1.6 M in hexane) at −78 °C. The mixture was stirred at this temperature for 30 min, and then the lactone **10** (2.1 g, 10.0 mmol) dissolved in anhyd THF (10 mL) was added dropwise. The resulting mixture was stirred at −78 °C for 10 min. DIBALH (10.0 mL, 10.0 mmol; 1.0 M in toluene) was added at the rate of 1 mL/min by a syringe pump. The cooling bath was removed, and the mixture was stirred at rt overnight. The mixture was quenched with aqueous 10% $KHSO_4$ solution (70 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concd to give the crude product. The crude product was purified by silica gel chromatography (1:1 ethyl acetate/hexane, R_f 0.25) to afford **11** (2.2 g, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.09−7.30 (4H, m), 6.79 (1H, J = 15.4, 6.9 Hz, td), 5.78 (1H, J = 15.4 Hz, d), 4.15 (2H, J = 7.2 Hz, q), 3.57 (1H, m), 3.42(1H, m), 2.93 (1H, m), 2.50 (2H, m), 1.98 and 1.79 (2H, m), 1.70 (1H,bs), 1.26 (3H, t). $[\alpha]^{23.1}_D$ = +30.7° (c = 0.54, MeOH). HRMS (M^+ + H) calcd for $C_{15}H_{19}ClO_3$ 282.1023, found 282.1031. Anal. Calcd for $C_{15}H_{19}ClO_3 \cdot {}^1/_4H_2O$: C, 62.72; H, 6.84. Found: C, 62.85; H, 6.99.

Synthesis of Methyl (5*R*)-7-[2-[[(1,1-Dimethylethyl)-diphenylsilyl]oxy]ethyl]-5-(4-chlorophenyl)heptanoate (12). The alcohol ester **11** (2.1 g, 7.4 mmol), *tert*-butyldiphenylsilyl chloride (2.3 g, 8.1 mmol), triethylamine (1.3 mL, 8.9 mmol), and DMAP (catalytic) were dissolved in 50 mL of anhyd CH_2Cl_2 and stirred at rt for 15 h (precipitation observed after 15 min). The mixture was quenched with 10% $KHSO_4$ (40 mL), and the aqueous phase was extracted with of CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concd to leave 3.9 g (100%) of crude product as a clear oil which was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$) 7.00−7.60 (14H, m), 6.79 (1H, J = 15.4, 6.9 Hz, td), 5.74 (1H, J = 15.4 Hz, d), 4.15 (2H, J = 7.2 Hz, q), 3.55 (1H, m), 3.42 (1H, m), 3.00 (1H, m), 2.45 (2H, m), 1.98 and 1.71 (2H, m), 1.26 (3H, t), 1.01 (9H, s).

To a solution of the crude α,β-unsaturated ester (3.8 g, 7.3 mmol) in methanol (100 mL) was added magnesium powder (1.8 g, 73 mmol) in portions over a period of 1.5 h. The mixture was stirred at rt for an additional 0.5 h and then concd. The residue was taken up into ethyl acetate (200 mL), filtered, and concd. Purification of the crude product mixture by silica gel chromatography (9:1 ethyl acetate/hexane, R_f 0.5) afforded **12** (3.7 g, 97%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.00−7.60 (14H, m), 3.61 (3H, s), 3.51 (1H, m), 3.42 (1H, m), 2.79 (1H, m), 2.22 (2H, J = 7.2 Hz, t), 1.90 and 1.69 (2H, m), 1.40−1.60 (4H, m), 1.01 (9H, s). $[\alpha]^{23.1}_D$ = +4.5° (c = 0.60, MeOH).

Synthesis of (4*R*,5*S*)-3-[5-(4-Chlorophenyl)-7-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-oxoheptyl]-4-phenyl-2-oxazolidinone (13). To a stirred solution of ester **12** (6.0 g, 11.8 mmol) in THF (40 mL) was added a solution of LiOH (21 mL of a 1 M solution). The mixture was stirred vigorously at rt for 2 days and then acidified at 0 °C with 1 N HCl. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over magnesium sulfate, filtered, and concd. The residue was taken up into anhyd toluene (70 mL), and oxalyl chloride (5.2 mL, 60 mmol) was added. The mixture was stirred at rt overnight and then was concd to dryness. The crude acid chloride was dissolved in anhyd CH_2Cl_2 (40 mL) and was added dropwise to a stirred solution consisting of *(R)*-4-phenyl-2-oxazolidinone (1.87 g, 12 mmol), triethylamine (3.5 mL, 24 mmol), and 4-(dimethylamino)pyridine (catalytic) in CH_2Cl_2 (60 mL) at −5 °C. After the addition was completed, the mixture was stirred at rt for 3 h and quenched with 1 N HCl (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The organic phase was dried over Na_2SO_4, filtered, and concd. Purification by silica gel chromatography (1:4 ethyl acetate/hexane, R_f 0.4) afforded **13** (7.0 g, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.60 (2H, d, J = 6.6 Hz), 7.55 (2H, d, J = 6.6 Hz), 7.29−7.42 (11H, m), 7.20 (2H, d, J = 8.3 Hz), 6.99 (2H, d, J = 8.3 Hz), 5.37 (1H, dd, J = 1.7, 8.9 Hz), 4.66 (1H, t, J = 8.9 Hz), 4.27 (1H, dd, J = 3.6, 8.9 Hz), 3.50 (1H, m), 3.40 (1H, m), 2.88 (2H, m), 2.75 (1H, m), 1.89 (2H, m), 1.35−1.70 (4H, m), 1.01 (9H, s).

Synthesis of (3*R*,4*S*)-3-[3-(4-Chlorophenyl)-5-hydroxypentyl]-4-(4-methoxyphenyl)-1-phenyl-2-azetidinone (15). To a stirred solution of **13** (5.5 g, 8.6 mmol) in CH_2Cl_2 (40 mL), cooled to −25 °C, was added a solution of titanium tetrachloride (9.5 mL/1.0 M in CH_2Cl_2, 9.5 mmol). After the mixture was stirred at this temperature for 10 min, diisopropylethylamine (3.0 mL, 17.2 mmol) was added and the mixture was stirred at −25 °C for another 30 min followed by slow addition of a solution of *N*-(4-methoxybenzylidene)aniline (3.7 g, 17.2 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at −25 °C for an additional 1 h and quenched with 2 N sulfuric acid (150 mL) at 0 °C. The mixture was diluted with ethyl acetate (400 mL) and stirred at 0 °C until a clear separation of the two phases resulted. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 80 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concd to give **14** as a greenish solid.

The crude product mixture was dissolved in hot toluene (70 mL) at 90 °C. *N*,*O*-bis(trimethylsilyl)acetamide (5.1 g, 6.5 mmol) was added to this solution and the reaction mixture stirred at 90 °C for 1 h followed by addition of tetra-*n*-butylammonium fluoride (5.0 g, 19.1 mmol). The mixture was heated at 90 °C for an additional 2 h and then allowed to cool to rt. The reaction mixture was quenched with 10% $KHSO_4$ and extracted with ethyl acetate (3 × 70 mL). The organic phase was dried over Na_2SO_4 , filtered, and concd. Purification by silica gel chromatography (1:1 ethyl acetate/hexane, R_f 0.25) afforded **15** (1.8 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) 6.99−7.45 (13H, m), 5.20 (1H, bs), 4.51(1H, d, J = 2.3 Hz), 3.80 (3H, s), 3.56 (1H, m), 3.42 (1H, m), 2.99 (1H, dt, J = 2.3, 8.3 Hz), 2.77 (1H, m), 1.70−1.97 (6H, m). HRMS (M^+ + H) calcd for $C_{27}H_{29}ClNO_3$ 450.1836, found 450.1826.

Synthesis of (3*R*)-7-(4-Chlorophenyl)-4-(4-methoxyphenyl)-2-phenyl-2-azaspiro[3.5]nonan-1-one (1). To a mixture of alcohol **15** (218 mg,0.4 mmol) and carbon tetrabromide (380 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triphenylphosphine (300 mg, 1.1 mmol). The cooling bath was removed, and the mixture was stirred for 1.5 h as it warmed to rt. It was then diluted with hexane (10 mL, and the precipitate was filtered through Celite. The filtrate was concd and the crude product mixture was purified on a silica gel column (1:3 ethyl acetate/hexane, R_f 0.30) to give 3-[5-bromo-3-(4-chlorophenyl)pentyl]-4-(4-methoxyphenyl)-1-phenyl-2-azetidinone (256 mg, 100%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) 6.99−7.30 (13H, m), 4.52 (1H, d, J = 2.4 Hz), 3.80 (3H, s), 3.30 (1H, m), 3.05 (1H, m), 3.00 (1H, dt, J = 2.4, 8.3 Hz), 2.80 (1H, m), 1.65−1.20 (6H, m).

To a solution of diisopropylamine (0.34 mL, 2.6 mmol) in anhyd THF (15 mL) cooled in an acetone/dry ice bath was added *n*-butyllithium (1.6 mL/1.6 M in hexane, 2.6 mmol). The reaction mixture was stirred at −78 °C for 0.5 h followed by the addition of 3-[5-bromo-3-(4-chlorophenyl)pentyl]-4-(4-methoxyphenyl)-1-phenyl-2-azetidinone (740 mg, 1.3 mmol) as a solution in anhyd THF (20 mL). The mixture was stirred at −78 °C for an additional 0.5 h, and the cooling bath was removed. The progress of cyclization was monitored by silica gel TLC (1:9, ethyl acetate/hexane, R_f 0.35) until completion (1.5−3.5 h.). The mixture was quenched with 10% $KHSO_4$ (50 mL) and extracted with ethyl acetate (3 × 60 mL). The organic phase was dried over magnesium sulfate, filtered, and concd. Purification by silica gel chromatography (1:9 ethyl acetate/hexane) afforded 420 mg (83%) **1** as a white solid: mp 174−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 6.99−7.30 (13H, m), 4.52 (1H, d, J = 2.4 Hz), 3.80 (3H, s), 3.30 (1H, m), 3.05 (1H, m), 3.00 (1H, dt, J = 2.4, 8.3 Hz), 2.80 (1H, m), 1.65−1.20 (6H, m). HRMS (M^+ + H) calcd for $C_{27}H_{27}NO_2Cl$ 432.1730, found 432.1734. Anal. Calcd for $C_{27}H_{26}ClNO_2$: C, 75.08; H, 6.07; N, 3.24. Found: C, 75.37; H, 5.94; N, 3.39. $[\alpha]^{25}_D$ = +60.7° (c = 0.54, MeOH).

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Supporting Information Available: ^{1}H-NMR spectra for compounds **12**, **13**, and **15** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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