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A Stereoselective Approach to the Azaspiro[5.5]undecane Ring System Using a Conjugate Addition/Dipolar Cycloaddition Cascade: Application to the Total Synthesis of (±)-2,7,8-*epi*-Perhydrohistrionicotoxin†

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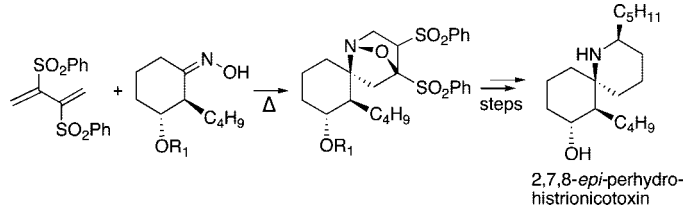
Received June 17, 2008



An efficient stereocontrolled route to the spirocyclic perhydrohistrionicotoxin derivative (±)-2,7,8-*epi*-PHTx (**4**) is described. The reaction of 2-butyl-3-(methoxymethoxy)cyclohexanone oxime with 2,3-bis(phenylsulfonyl)-1,3-butadiene gives rise to a 7-oxa-1-azanorbornane cycloadduct in high yield. The formation of the bicyclic isoxazolidine arises from conjugate addition of the oxime onto the diene to give a transient nitrone which then undergoes an intramolecular dipolar cycloaddition. Treatment of the cycloadduct with 5% Na/Hg results in reductive nitrogen−oxygen bond cleavage to furnish an azaspiro[5.5]undecane. Elaboration to the dihydropyridin-4(1*H*)-one **24** was followed by stereoselective conjugate addition using *n*-pentyl cuprate to give azaspirocycle **25**. The stereochemistry of the product was deduced from an X-ray crystal structure of the corresponding *N*-tosylhydrazone derivative. The dominant factor controlling the stereochemistry of the conjugate addition is the $A^{(1,3)}$-strain present in the planar vinylogous amide. A stereoelectronically preferred axial attack by the organocuprate at the *β*-position leads to the observed diastereoselectivity. Azaspirocycle **25** was transformed into 2,7,8-*epi*-PHTx (**4**) in five additional steps. Utilizing this tandem conjugate addition/dipolar cycloaddition cascade, we have also successfully synthesized azaspiro[5.5]undecane **36**, which had previously been converted into (±)-perhydrohistrionicotoxin (**2**), thereby completing a formal total synthesis of this alkaloid.

Introduction

The azaspirocycle alkaloid (−)-histrionicotoxin (**1**, Figure 1), isolated from skin extracts of the brightly colored neotropical frog *Dendrobates histrionicus*, is a potent noncompetitive blocker of nicotinic receptor-gated channels.[1−3] Other members of this family also contain the unique spiropiperidine structure and vary primarily in the length and degree of saturation in the side chain.[4] The significant interest in histrionicotoxin derivatives stems from their remarkable neurophysical properties,[5] their low natural abundance, and their unique structural framework containing the azaspiro[5.5]undecane ring system.[4] Thus, these alkaloids have been attractive and popular targets for synthetic chemists for many years. The majority of synthetic

† Dedicated to the memory of Albert I. Meyers, an outstanding scientist, a mentor to many, and a good friend.

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10.1021/jo801295e CCC: $40.75 © 2008 American Chemical Society
Published on Web 08/21/2008

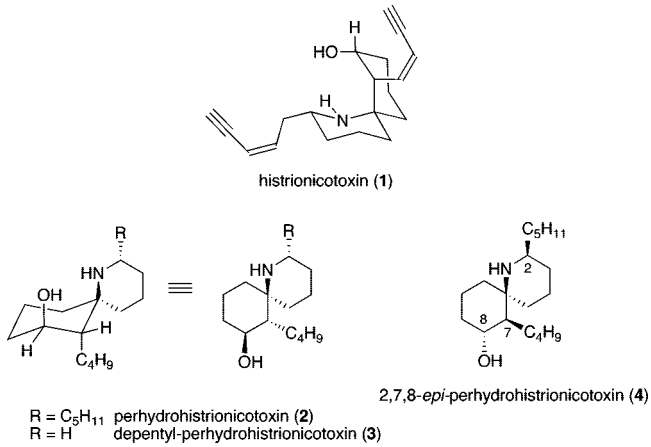
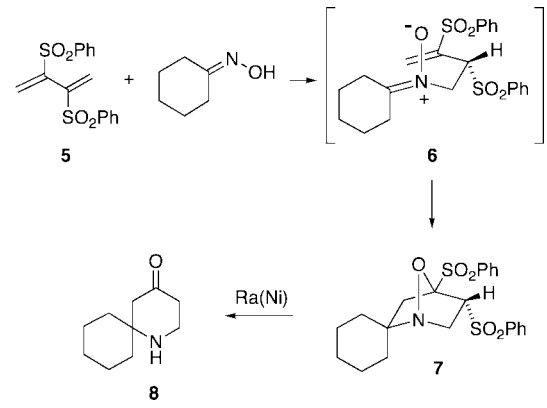


FIGURE 1

efforts have been aimed at the perhydro (**2**)- and depentylperhydrohistrionicotoxin (**3**) derivatives since these saturated materials display levels of biological activity quite similar to that of the parent alkaloid.[6−10] The first total synthesis of (±)-perhydrohistrionicotoxin (**2**) (PHTx) was described by Corey in 1975,[7] and a wide range of approaches to this compound have been reported since.[8−11] In this context, we have been interested for some time in developing new strategies for the synthesis of various piperidine alkaloids.[12] Our plan toward perhydrohistrionicotoxin is based on a [3 + 2]-annulation

SCHEME 1



strategy developed in our laboratory.[13] We report herein a new approach for the synthesis of azaspirocyclic piperidines and its application in the formal synthesis of (±)-perhydrohistrionicotoxin (**2**) and a total synthesis of (±)-2,7,8-*epi*-perhydrohistrionicotoxin (**4**)

Results and Discussion

Our synthetic strategy toward the PHTx family is founded on a renewed interest in the conjugate addition−dipolar cycloaddition cascade that we had previously used to prepare 2-substituted-4-piperidones.[13] This cascade utilizes 2,3-bis(phenylsulfonyl)-1,3-butadiene (**5**)[14] as a key reactant which functions as both a Michael acceptor and a dipolarophile. Thus, conjugate addition of an oxime to diene **5** followed by proton transfer creates a transient nitrone **6** that undergoes a 1,3-dipolar cycloaddition with the tethered vinyl sulfone (Scheme 1).[15,16] The regiochemistry of the internal cycloaddition is presumably controlled by entropic factors. N,O-Bond cleavage of the resulting cycloadduct **7** provides efficient access to the 2,2-disubstituted 4-piperidone skeleton.[13] For cycloalkanone-derived

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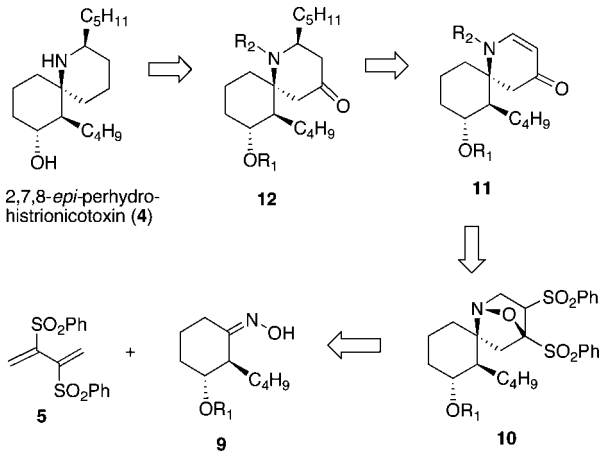
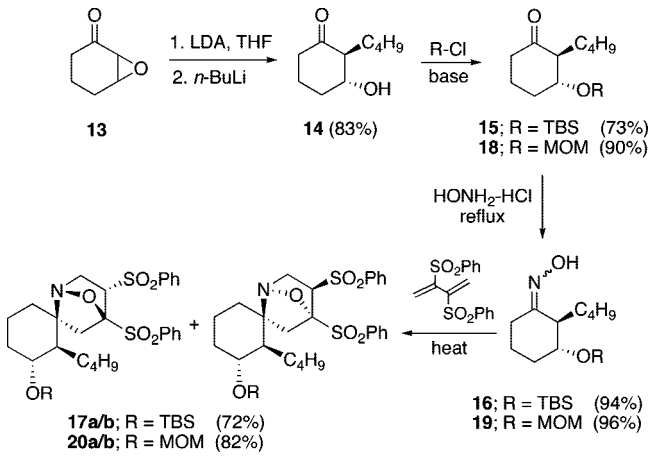
SCHEME 2



SCHEME 3

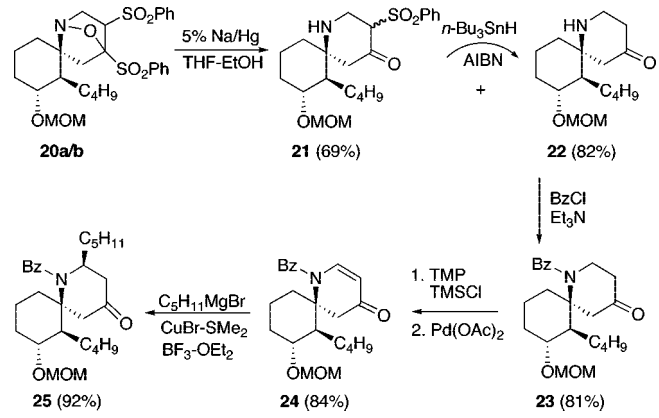


oximes, this methodology provides facile access to 2-substituted azaspirocycles with a high degree of flexibility.

Our retrosynthetic analysis (Scheme 2) reveals a potentially convenient route to (±)-7,8-*epi*-perhydrohistrionicotoxin (**4**) based on the above conjugate addition−dipolar cycloaddition cascade. Our plan involves formation of the dipolar cycloadduct **10** derived from the reaction of diene **5** with oxime **9**. This would be followed by reductive N,O-bond cleavage and a subsequent Saegusa oxidation in order to obtain azaspirocycle **11**. Conjugate addition of *n*-pentyl cuprate to the vinylogous amide should furnish **12** which, after suitable manipulation of the protecting groups and reduction of the carbonyl group, would be expected to provide (±)-*epi*-PHTx **4**.[17]

The required oxime **15** was prepared from a procedure described by Wender and co-workers.[18] This involved formation of the lithium enolate of **13**[19] using LDA followed by a regioselective ring opening of the epoxide with *n*-butyllithium. The resulting 3-hydroxy ketone **14** was immediately protected as the TBS ether **15**[20] and was then converted to the corresponding oxime **16** by condensation with hydroxylamine hydrochloride (Scheme 3). The desired cascade sequence was achieved by heating **16** with diene **5** in acetonitrile at 90 °C in a sealed tube to provide cycloadduct **17** as a 3:2 mixture of diastereomers in 72% yield.

SCHEME 4



Since the diastereomeric mixture of cycloadducts only differed in terms of the oxido bridge (and C_3 sulfone) stereochemistry, which would be subsequently destroyed upon reductive cleavage, separation of the mixture was unnecessary. Nevertheless, since the two diastereomeric cycloadducts were highly crystalline, X-ray quality crystals were easily obtained. The X-ray data showed that the overall dipolar cycloaddition had proceeded with complete stereocontrol producing the undesired relative stereochemistry about the azaspirocyclic skeleton. However, we believed that this setback could be easily overcome at a later stage of the synthesis by making use of an oxidation−epimerization−reduction sequence analogous to that used previously by Godleski and co-workers for perhydrohistrionicotoxin (**2**).[21] Unfortunately, all of our attempts to carry out a reductive N,O-cleavage of cycloadduct **17** were unsuccessful, leading only to recovered starting material and oily tars. In order to get around this difficulty, we prepared the MOM-protected oxime **19** with the hope that the diminished steric interactions would facilitate the desired reduction. Heating a sample of oxime **19** with diene **5** afforded the expected cycloadduct **20** in 82% yield as a 1:1 mixture of diastereomers. Now, the N,O reduction could be readily accomplished by using 5% Na/Hg in a 2:1 mixture of THF/ethanol which furnished piperidinone **21** (69%) along with the over-reduction product **22**. Conversion of **21** to **22** was readily accomplished in 82% yield using radical reduction conditions (Scheme 4).[22]

At this stage, we judged it prudent to protect piperidinone **22** as the corresponding benzamide in order to set the stage for the upcoming oxidation step. The desired dihydropyridin-4(1*H*)-one **24** was easily accessed via a Saegusa−Ito oxidation[23] of the corresponding silyl enol ether derived from **23**. Introduction of the final stereocenter was achieved by conjugate addition of *n*-pentyl cuprate to the vinylogous amide **24**. Thus, treatment of **24** with *n*-pentylmagnesium bromide, CuBr·SMe$_2$, and BF$_3$·OEt$_2$ provided **25** as the sole product in 92% yield (Scheme 4). The stereochemistry of the resulting piperidinone **25** was not unequivocally discernible from its spectral data. Consequently, we prepared the highly crystalline *N*-tosyl hydrazone derivative **27** (Scheme 5), and X-ray analysis of this compound confirmed the fact that the cuprate addition had proceeded with

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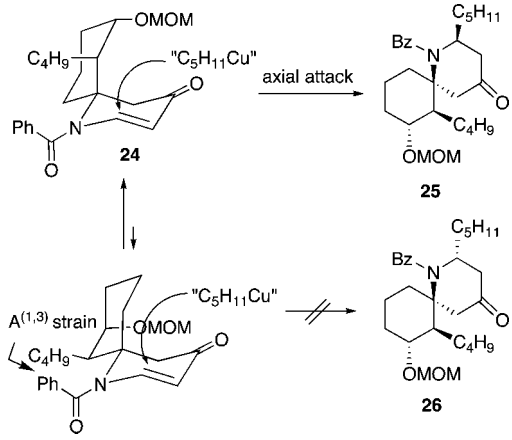
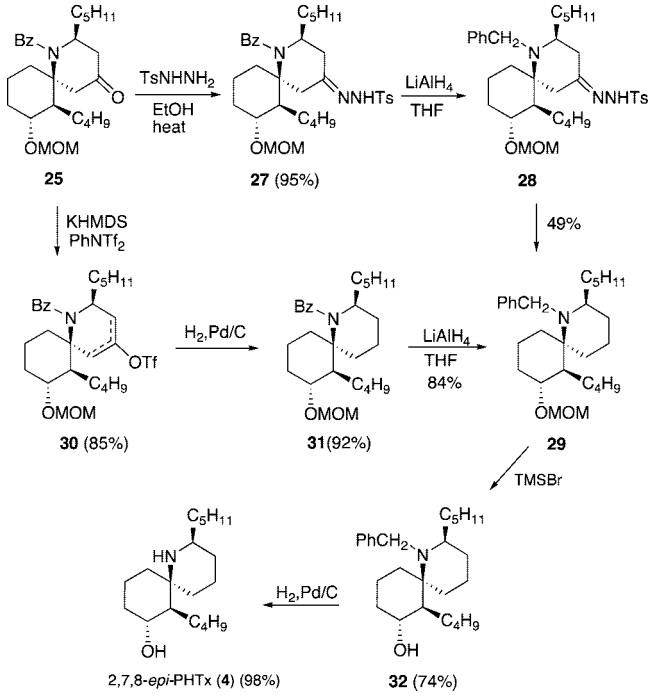


FIGURE 2. Stereoelectronically preferred axial attack.

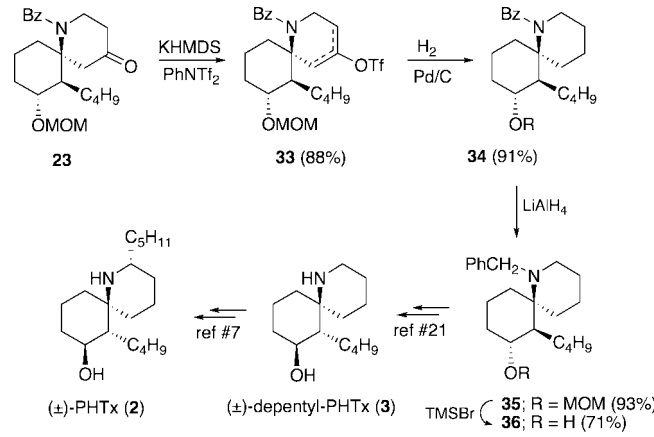
SCHEME 5



high selectivity giving rise to **25** exclusively. With this system, the overriding steric interaction corresponds to the $A^{(1,3)}$ strain associated with the vinylogous amide present in **24**. The bulkier group prefers to be in the axial position in order to avoid this interaction, thereby accounting for the high selectivity associated with the formation of **25**. Thus, a stereoelectronically preferred axial attack by the organocuprate at the β-position of **24** results in the observed diastereoselectivity (Figure 2). This outcome is perfectly consistent with previous results reported in the literature by Comins and co-workers with related *N*-acyl-2,3-dihydro-4-pyridones.[24]

The formation of piperidone **25** represents an opportunity to complete a synthesis of (±)-2,7,8-*epi*-PHTx (**4**). Non-natural perhydrohistrionicotoxin derivatives such as **4** have proven to be extremely useful for probing the mechanism of trans-synaptic transmission of neuromuscular impulses.[25] Toward this end, *N*-tosylhydrazone **27** was subjected to $LiAlH_4$ reduction. The initial product formed was the *N*-benzylazaspiro[5.5]undecane **28**, which could be further reduced to afford **29** in 49% overall yield. While this sequence was intended to increase the

SCHEME 6



efficiency of the synthesis of **29** by combining two reductive transformations into a single step, the overall reaction was somewhat capricious and the yield of **29** was found to be quite variable. An alternative method, which turned out to be much more reliable, involved the conversion of **25** into a mixture of enol triflates **30**. Hydrogenolysis of **30** afforded **31** which then furnished **29** in 84% yield upon treatment with $LiAlH_4$. Deprotection of the MOM ether in **29** with TMSBr gave **32** which was further reduced to afford (±)-2,7,8-*epi*-PHTx (**4**) in 73% yield for the two-step sequence.

An alternative route to (±)-dependylperhydrohistrionicotoxin (**3**) was also carried out starting with the readily available intermediate **23**. This compound was converted to piperidinone **34** in 80% yield by formation of a mixture of vinyl triflates **33** followed by catalytic hydrogenation. Lithium aluminum hydride reduction of the benzoyl amide present in **34** gave **35**, and this was followed by MOM deprotection to furnish alcohol **36** (Scheme 6), thereby intercepting the Godleski route toward **3**.[21]

The formation of intermediate **36** also represents a formal synthesis of (±)-perhydrohistrionicotoxin (**2**) since (±)-dependyl-PHTx (**3**) had been carried on to (±)-PHTx (**2**) by Corey and co-workers.[7]

In conclusion, a synthesis of (±)-2,7,8-*epi*-perhydrohistrionicotoxin (**4**) has been accomplished. The key element of the synthesis consists of a conjugate addition−dipolar cycloaddition of 2,3-bis(phenylsulfonyl)-1,3-butadiene with 2-butyl-3-(methoxymethoxy)cyclohexane oxime. The resulting cycloadduct was converted into (±)-2,7,8-*epi*-PHTx (**4**) by (1) reductive cleavage of the bicyclic isoxazolidine adduct, (2) oxidation followed by conjugate addition of the *n*-pentyl side chain, and (3) reduction of the carbonyl group in the piperidone ring. We have also described a formal synthesis of (±)-perhydrohistrionicotoxin (**2**) that intercepts Godleski's intermediate **36** in several steps from the starting oxime **19**. The applicability of the new methodology to other alkaloid targets is currently under study and will be the subject of future reports.

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Experimental Section

2-Butyl-3-(*tert*-butyldimethylsilyloxy)cyclohexanone (15). To a solution of 9.4 g (55 mmol) of *trans*-2-butyl-3-hydroxy-1-cyclohexanone (**14**)[9d] in 60 mL of DMF at 0 °C was added 10 g (66 mmol) of TBSCl followed by 9.2 g (135 mmol) of imidazole. The reaction mixture was slowly warmed to 25 °C over a period of 3 h. The solution was cooled to 0 °C and diluted with Et_2O, water was added, and the aqueous layer was separated and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 11.4 g (73%) of 2-butyl-3-(*tert*-butyldimethylsilyloxy)cyclohexanone (**15**) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 003 (s, 6H), 0.83−0.91 (m, 3H), 0.86 (s, 9H), 1.14−1.38 (m, 4H), 1.45−1.72 (m, 4H), 1.92−2.10 (m, 2H), 2.17−2.40 (m, 3H), and 3.78 (dt, 1H, J = 6.8 and 2.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.5, −4.9, 13.9, 17.9, 20.7, 22.8, 25.7, 27.4, 29.8, 31.5, 39.7, 59.6, 74.3, and 212.2.

2-Butyl-3-(*tert*-butyldimethylsilyloxy)cyclohexanone Oxime (16). To a solution of 10.6 g (37 mmol) of ketone **15** in 360 mL of a 1:1 EtOH/water mixture was added 7.8 g (112 mmol) of hydroxylamine hydrochloride followed by 9.2 g (112 mmol) of sodium acetate. The reaction mixture was heated at reflux at 90 °C for 6 h and cooled to 25 °C, the solvent was removed under reduced pressure, and the residue was diluted with CH_2Cl_2. The solution was washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 10.5 g (94%) of 2-butyl-3-(*t*ert-butyldimethylsilyloxy)cyclohexanone oxime (**16**) as a colorless oil: IR (neat) 3256, 1662, 1463, 1254, and 1088 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.86−0.91 (m, 3H), 0.88 (s, 9H), 1.18−1.38 (m, 4H), 1.40−1.62 (m, 4H), 1.74−1.92 (m, 2H), 2.10−2.26 (m, 2H), 2.76 (dt, 1H, J = 14.0 and 4.8 Hz), 3.75−3.82 (m, 1H), and 8.84 (brs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.8, −4.7, 13.9, 18.0, 20.0, 21.5, 22.7, 25.8, 29.0, 29.5, 30.5, 49.6, 72.9, and 160.4.

4,5-*endo*-Di(phenylsulfonyl)-2-spiro-1′-(8-butyl-9-(*tert*-butyldimethylsilyloxy)cyclohexane)-7-oxo-1-azabicyclo[2.2.1]-heptane (17). A solution of 1.05 g (3.5 mmol) of oxime **16** and 1.17 g (3.5 mmol) of 2,3-bis(phenylsulfonyl)-1,3-butadiene[14] (**5**) in 12 mL of CH_3CN was heated at 90 °C for 72 h, cooled to room temperature, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 1.61 g (72%) of a 3:2-mixture of 4,5-*endo*-di(phenylsulfonyl)-2-spiro-1′-(8-butyl-9-(*tert*-butyldimethylsilyloxy)cyclohexane)-7-oxo-1-azabicyclo[2.2.1]heptane (**17**) as a white solid. The two diastereomers were easily separated by silica gel chromatography. The major diastereomer **17a** was a white solid: mp 144−145 °C; IR (neat) 1470, 1445, 1332, and 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.10 (s, 3H), 0.20 (s, 3H), 0.83 (d, 1H, J = 12.0 Hz), 0.91 (t, 3H, J = 6.6 Hz), 0.99 (s, 9H), 1.14−1.52 (m, 10H), 1.55 (s, 2H), 2.04 (dd, 1H, J = 13.8 and 2.4 Hz), 2.26 (d, 1H, J = 10.8 Hz), 3.40 (d, 1H, J = 13.8 Hz), 3.68 (t, 1H, J = 12.0 Hz), 3.87 (dd, 1H, J = 12.0 and 4.8 Hz), 4.02 (d, 1H, J = 2.4 Hz), 4.26 (ddd, 1H, J = 11.4, 4.8 and 1.8 Hz), 7.50 (t, 2H, J = 7.5 Hz), 7.61 (t, 2H J = 7.5 Hz), 7.65 (t, 1H, J = 7.5 Hz), 7.71 (t, 1H, J = 7.5 Hz), 7.75 (d, 2H, J = 7.5 Hz), and 7.97 (d, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −5.4, −4.9, 14.0, 15.2, 18.1, 23.0, 26.0, 26.6, 27.5, 30.6, 32.4, 37.4, 44.5, 52.0, 66.3, 69.2, 74.3, 104.1, 128.7, 129.0, 129.1, 130.1, 134.3, 134.6, and 139.3. Anal. Calcd for $C_{32}H_{47}NO_6S_2Si$: C, 60.63; H, 7.47; N, 2.21. Found: C, 60.81; H, 7.41; N, 2.23.

The minor diastereomer **17b** was also a white solid: mp 150−152 °C; IR (neat) 1463, 1447, 1329, 1311, and 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.02 (s, 6H), 0.76−0.81 (m, 1H), 0.80 (t, 3H, J = 6.5 Hz), 0.94 (s, 9H), 1.15−1.04 (m, 4H), 1.32 (dt, 1H, J = 13.0 and 4.0 Hz), 1.36−1.40 (m, 1H), 1.44−1.50 (m, 1H), 1.62 (dt, 1H, J = 13.5 and 3.5 Hz), 1.73−1.80 (m, 1H), 1.80−1.90 (m, 1H), 2.18 (d, 1H, J = 12.5 Hz), 3.01−3.08 (m, 2H), 3.51 (dd, 1H, J = 13.0 and 11.0 Hz), 3.86 (d, 1H, J = 2.5 Hz), 3.97 (dd, 1H, J = 12.5 and 5.0 Hz), 4.13 (dd, 1H, J = 11.0 and 5.0 Hz), 7.48 (t, 2H, J = 7.5 Hz), 7.62 (t, 2H J = 7.5 Hz), 7.65 (t, 1H, J = 7.5 Hz), 7.71 (t, 1H, J = 7.5 Hz), 7.74 (d, 2H, J = 7.5 Hz), and 7.97 (d, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −5.1, −4.6, 14.0, 18.0, 18.1, 22.4, 26.0, 26.6, 27.5, 27.9, 31.5, 39.1, 48.7, 52.3, 67.7, 71.3, 74.1, 105.1, 128.8, 128.9, 129.2, 130.0, 134.3, 135.2, and 139.4. Anal. Calcd for $C_{32}H_{47}NO_6S_2Si$: C, 60.63; H, 7.47; N, 2.21. Found: C, 60.59; H, 7.41; N, 2.23.

2-Butyl-3-(methoxymethoxy)cyclohexanone (18). To a solution of 16 g (94 mmol) of *trans*-2-butyl-3-hydroxy-1-cyclohexanone (**14**)[9d] in 500 mL of CH_2Cl_2 at 0 °C was added 50 mL (282 mmol) of diisopropylethylamine, followed by 14 mL (188 mmol) of freshly distilled MOMCl. The reaction mixture was slowly warmed to 25 °C and was stirred overnight. The solution was cooled to 0 °C and was quenched with a saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 17.7 g (88%) of 2-butyl-3-(methoxymethoxy)cyclohexanone (**18**) as a pale yellow oil: IR (neat) 1711, 1456, 1148, 1101, and 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.44 (t, 3H, J = 6.8 Hz), 0.78−0.91 (m, 4H), 1.10−1.25 (m, 3H), 1.25−1.38 (m, 1H), 1.51−1.70 (m, 2H), 1.78−1.86 (m, 1H), 1.90−2.01 (m, 2H), 2.92 (s, 3H), 3.27 (dt, 1H, J = 6.8 and 2.9 Hz), 4.18 (d, 1H, J = 6.8 Hz), and 4.25 (d, 1H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 20.8, 22.7, 27.3, 28.2, 29.6, 39.4, 55.3, 56.8, 78.6, 94.9, and 211.3; HRMS calcd for $[(C_{12}H_{22}O_3) + H]^+$ 215.1642, found 215.1642.

2-Butyl-3-(methoxymethoxy)cyclohexanone Oxime (19). To a solution of 5.9 g (27 mmol) of ketone **18** in 140 mL of dry EtOH was added 2.0 g (29 mmol) of hydroxylamine hydrochloride followed by 6.4 mL (78 mmol) of freshly distilled pyridine. The reaction mixture was heated at reflux at 100 °C for 2 h and cooled to 25 °C, the solvent was removed under reduced pressure, and the residue was diluted with CH_2Cl_2. The residue was washed with water, dried over $MgSO_4$, filtered, concentrated under reduced pressure, and purified using flash silica gel chromatography to furnish 6.0 g (96%) of 2-butyl-3-(methoxymethoxy)cyclohexanone oxime (**19**) as a colorless oil: IR (neat) 3388, 1656, 1456, 1099, and 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, 3H), 1.22−1.37 (m, 4H), 1.41−1.54 (m, 2H), 1.55−1.65 (m, 1H), 1.68−1.87 (m, 3H), 1.92−2.05 (m, 1H), 2.37−2.45 (m, 1H), 2.97 (d, 1H, J = 14.0 Hz), 3.35 (s, 3H), 3.76 (s, 1H), 4.64 (s, 2H), and 8.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 20.0, 20.8, 22.6, 22.7, 25.7, 26.6, 27.9, 29.4, 29.7, 37.8, 46.2, 55.3, 75.6, 76.8, 94.3, 94.6, 160.3, and 160.8; HRMS calcd for $[(C_{12}H_{23}NO_3) + H]^+$ 230.1751, found 230.1751.

4,5-*endo*-(Diphenylsulfonyl)-2-spiro-1′-(8-butyl-9-(methoxymethoxy)cyclohexane)-7-oxo-1-azabicyclo[2.2.1]heptane (20). A 10 mL sealed tube was charged 0.15 g (0.65 mmol) of oxime **19**, 0.22 g (0.66 mmol) of 2,3-bis(phenylsulfonyl)-1,3-butadiene (**5**), and 2.0 mL of CH_2Cl_2. The resulting solution was heated at 100 °C for 24 h, cooled to 25 °C, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.25 g (68%) of an approximately 1:1-mixture of 4,5-*endo*-di(phenylsulfonyl)-2-spiro-1′-(8-butyl-9-(methoxymethoxy)cyclohexane)-7-oxo-1-azabicyclo[2.2.1]heptane (**20**) as a white solid in 82% yield: mp 136−140 °C; IR (neat) 1584, 1446, 1322, 1148, and 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, 3H J = 6.6 Hz), 0.96−1.14 (m, 5H), 1.19−1.50 (m, 4H), 1.56−1.80 (m, 5H), 2.15 (d, 1H, J = 12.0 Hz), 2.74 (d, 1H, J = 13.4 Hz), 3.01 (d, 1H, J = 13.4 Hz), 3.26 (d, 3H, J = 1.5 Hz), 3.58−3.70 (m, 2H), 4.00 (dd, 1H, J = 12.6 and 3.8 Hz), 4.26 (dd, 1H, J = 6.6 and 1.5 Hz), 4.42 (dd, 2H, J = 6.6 and 1.5 Hz), 7.49 (t, 2H, J = 7.5 Hz), 7.58−7.75 (m, 4H), 7.82 (d, 2H, J = 7.5 Hz), and 8.00 (d, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 18.8, 22.3, 24.5, 26.3, 27.3, 31.2, 38.6, 45.9, 52.2, 55.2, 66.9, 74.4, 74.9,

94.1, 104.3, 128.5, and 128.7. Anal. Calcd for $C_{28}H_{37}NO_7S_2$: C, 59.66; H, 6.62; N, 2.48; Found: C, 60.02; H, 6.74; N, 2.48.

3-Benzenesulfonyl-7-butyl-8-(methoxymethoxy)-1-azaspiro-[5.5]undecan-4-one (21). To a suspension of 3.4 g (24 mmol) of Na_2HPO_4 and 2.7 g (4.8 mmol) of the above mixture of cycloadducts (**20**) in 50 mL of 2:1 THF/EtOH at 0 °C was added 7.7 g (17 mmol) of 5% Na/Hg amalgam. The resulting yellow suspension was slowly warmed to 25 °C and was stirred vigorously for 19 h. The reaction mixture was filtered through a Celite plug and rinsed with Et_2O followed by CH_2Cl_2. The filtrate was concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 1.4 g (69%) of 3-benzenesulfonyl-7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]undecan-4-one (**21**) as a colorless oil along with 0.24 g (18%) of 7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]undecan-4-one (**22**). Compound **21** exhibited the following spectral properties: IR (neat) 1710, 1308, 1447, 1148, and 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) [major diastereomer] δ 0.94 (t, 3H, $J = 7.0$ Hz), 1.03−1.52 (m, 10H), 1.52−1.67 (2H), 1.67−1.81 (m, 1H), 2.01−2.11 (m, 1H), 2.21 (d, 1H, $J = 13.5$ Hz), 3.14 (d, 1H, $J = 13.5$ Hz), 3.18 (dd, 1H, $J = 15.6$ and 4.6 Hz), 3.38 (s, 3H), 3.60 (d, 1H, $J = 4.6$ Hz), 3.72 (dt, 1H, $J = 9.9$ and 4.6 Hz), 3.85 (d, 1H, $J = 15.6$ Hz) and 4.60 (d, $J = 6.9$ Hz); [minor diastereomer (distinct peaks)] δ 0.85 (t, $J = 6.9$ Hz), 2.39 (d, $J = 13.5$ Hz), and 3.31 (s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 18.6, 23.1, 27.0, 32.3, 33.0, 34.0, 41.3, 51.6, 52.2, 55.6, 62.1, 72.2, 78.4, 95.6, and 128.2; HRMS calcd for $[(C_{22}H_{33}NO_5S) + H]^+$ 424.2152, found 424.2147.

7-Butyl-8-(methoxymethoxy)-1-azaspiro[5.5]undecan-4-one (22). To a solution of 1.3 g (3.1 mmol) of sulfone **21** in 110 mL of dry toluene was added 3.4 mL (12.5 mmol) of *n*-Bu_3SnH. The reaction mixture was heated at reflux (130 °C) before 0.4 g (2.4 mmol) of AIBN was added. After the mixture was heated at reflux for 5 min, an additional 0.25 g (1.52 mmol) of AIBN was added. After a further 20 min, an additional 0.2 g (1.22 mmol) of AIBN was added. The resulting solution was heated at reflux for 3 h, cooled to 25 °C, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.72 g (82%) of 7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]undecan-4-one (**22**) as a pale yellow oil: IR (neat) 3341, 1708, 1463, 1142, and 1038 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, 3H, $J = 7.1$ Hz), 0.98−1.10 (m, 1H), 1.10−1.35 (m, 8H), 1.35−1.58 (m, 5H), 1.62 (dt, 1H, $J = 13.3$ and 4.1 Hz), 1.90−1.98 (m, 1H), 2.00 (d, 1H, $J = 13.3$ Hz), 2.25 (dd, 2H, $J = 7.1$ and 5.1 Hz), 2.64 (d, 1H, $J = 13.3$ Hz), 2.91 (dt, 1H, $J = 13.3$ and 7.1 Hz), 3.12 (dt, 1H, $J = 13.3$ and 5.1 Hz), 3.32 (s, 3H), 3.59 (dt, 1H, $J = 9.1$ and 4.1 Hz), 4.53 (d, 1H, $J = 7.1$ Hz), and 4.66 (d, 1H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 18.3, 23.2, 27.4, 31.3, 32.5, 33.6, 40.2, 42.7, 50.2, 52.8, 55.4, 60.6, 77.6, 95.2, and 210.1; HRMS calcd for $[(C_{16}H_{29}NO_3) + H]^+$ 284.2220, found 284.2220.

1-Benzoyl-7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]-undecan-4-one (23). To a solution of 0.14 g (0.49 mmol) of piperidone **22** and 280 μL (2.0 mmol) of Et_3N in 3 mL of CH_3CN at 0 °C was added 0.03 g (0.15 mmol) of DMAP followed by 170 μL (1.5 mmol) of freshly distilled benzoyl chloride. The resulting solution was slowly warmed to 25 °C and stirred for 22 h. The solution was concentrated under reduced pressure and diluted with EtOAc, and the precipitated triethylammonium salts were filtered. The filtrate was concentrated under reduced pressure, and the residue was purified using flash silica gel chromatography to furnish 0.15 g (81%) of 1-benzoyl-7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]undecan-4-one (**23**) as a colorless oil: IR (neat) 1712, 1650, 1371, 1303, and 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.76 (t, 1H, $J = 6.5$ Hz), 0.94 (t, 3H, $J = 7.1$ Hz), 1.03−1.29 (m, 3H), 1.29−1.43 (m, 3H), 1.43−1.83 (m, 5H), 2.18 (d, 1H, $J = 6.5$ Hz), 2.22 (d, 1H, $J = 19.5$ Hz), 2.30−2.48 (m, 1H), 2.61 (d, 1H, $J = 12.8$ Hz), 2.66 (d, 1H, $J = 14.2$ Hz), 3.17 (d, 1H, $J = 15.5$ Hz), 3.36 (s, 3H), 3.50 (d, 1H, $J = 15.5$ Hz), 3.58 (d, 1H, $J = 14.2$ Hz), 3.87 (dd, 1H, $J = 14.2$ and 6.5 Hz), 3.94 (d, 1H, $J = 19.5$ Hz), 4.62 (dt, 2H, $J = 15.5$ and 6.5 Hz), and 7.38−7.63 (m, 5H); [minor rotamer (distinct peaks)] δ 3.38 (s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 14.4, 17.5, 17.9, 23.5, 24.8, 25.7, 27.1, 30.3, 31.1, 31.7, 41.1, 43.3, 43.6, 43.9, 44.4, 49.0, 50.8, 53.7, 55.6, 63.3, 65.4, 73.8, 74.1, 94.6, 127.2, 128.4, 128.6, 129.0, 130.3, 130.4, 131.2, 133.7, 138.8, 174.2, 176.0, 208.3, and 209.7; HRMS calcd for $[(C_{23}H_{33}NO_4) + H]^+$ 388.2482, found 388.2480.

1-Benzoyl-7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]-undec-2-en-4-one (24). To a solution of 610 μL (3.6 mmol) of 2,2,6,6-tetramethylpiperidine in 16 mL of THF at 0 °C was added 1.5 mL (3.4 mmol) of 2.25 M *n*-BuLi. After being stirred for 1 h at 0 °C, the reaction mixture was cooled to −78 °C and 430 μL (3.4 mmol) of TMSCl and a solution of 0.93 g (2.4 mmol) of ketone **18** in 18 mL of THF was added sequentially. After being stirred for 2 h at −78 °C and then 1 h at 25 °C, the reaction mixture was cooled to 0 °C and quenched with a saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to furnish the crude silyl enol ether.

To a solution of the above compound in 6 mL of a 3:1 CH_3CN/DMSO mixture was added 0.65 g (2.9 mmol) of $Pd(OAc)_2$. The resulting solution was stirred for 41 h at 25 °C. The resulting suspension was diluted with Et_2O and filtered through a Celite plug. The filtrate was concentrated under reduced pressure and washed with a saturated $NaHCO_3$ solution. The biphasic mixture was extracted with Et_2O, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.73 g (76%) of 1-benzoyl-7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]undec-2-en-4-one (**24**) as a white solid in 84% yield: mp 113.5−115 °C; IR (neat) 1669, 1595, 1314, 1242, and 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, 3H, $J = 7.0$ Hz), 1.09−1.91 (m, 12H), 2.30 (d, 1H, $J = 12.0$ Hz), 2.54 (d, 1H, $J = 16.1$ Hz), 3.33 (s, 3H), 3.34−3.42 (m, 1H), 3.83 (d, 1H, $J = 16.1$ Hz), 3.95 (d, 1H, $J = 2.6$ Hz), 4.55 (d, 1H, $J = 7.0$ Hz), 4.58 (d, 1H, $J = 7.0$ Hz), 5.29 (d, 1H, $J = 8.1$ Hz), 7.16 (d, 1H, $J = 8.1$ Hz), and 7.42−7.63 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 18.0, 22.7, 26.0, 28.8, 31.1, 39.7, 48.5, 55.3, 69.0, 74.4, 94.4, 107.0, 128.8, 129.3, 132.2, 136.2, 146.5, 172.2, and 194.7. Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.39; H, 8.20; N, 3.57.

1-Benzoyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-azaspiro-[5.5]undecan-4-one (25). To a solution of 0.63 g (1.7 mmol) of enone **24** in 16.5 mL of dry THF was added 1.4 g (6.6 mmol) of CuBr−SMe_2. The resulting suspension was stirred for 1 h at room temperature and cooled to −78 °C, and 900 μL (6.7 mmol) of $BF_3 \cdot Et_2O$ was added. After the mixture was stirred for 1 h at −78 °C, 2.7 mL (4.9 mmol) of a solution of pentylmagnesium bromide (2.0 M in Et_2O) was slowly added. The suspension was stirred at −78 °C for an additional 3 h before being quenched with 8 mL of a 9:1 saturated aqueous NH_4Cl/concd NH_4OH solution. Upon warming to 25 °C, the biphasic mixture was diluted with a further 15 mL of a 9:1 saturated aqueous NH_4Cl/concd NH_4OH solution and then extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.68 g (92%) of 1-benzoyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-azaspiro[5.5]undecan-4-one (**25**) as a pale yellow oil: IR (neat) 1722, 1645, 1398, 1348, and 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.79 (t, 3H, $J = 7.2$ Hz), 0.94 (t, 3H, $J = 7.2$ Hz), 0.97−1.10 (m, 2H), 1.10−1.20 (m, 1H), 1.22−1.46 (m, 4H), 1.51−1.67 (m, 4H), 1.74−1.83 (m, 2H), 1.94−2.05 (m, 1H), 2.37 (dd, 1H, $J = 17.3$ and 2.4 Hz), 2.62 (d, 1H, $J = 16.3$ Hz), 2.63 (dd, 1H, $J = 19.2$ and 3.6 Hz), 2.81−2.90 (m, 1H), 3.26 (d, 1H, $J = 16.3$ Hz), 3.37 (s, 3H), 4.04−4.11 (m, 1H), 4.22−4.28 (m, 1H), 4.26 (d, 1H, $J = 6.7$ Hz), 4.68 (d, 1H, $J = 6.7$ Hz), 7.29−7.33 (m, 2H), and 7.37−7.42 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 14.1, 18.2, 22.3, 23.4, 26.6, 28.3, 29.7, 31.1, 32.5, 35.1, 37.8, 42.2, 50.7, 52.1, 55.6, 56.5, 64.9, 77.5, 95.6,

125.3, 128.7, 129.1, 139.5, 173.1, and 208.7; HRMS calcd for $[(C_{28}H_{43}NO_4) + H]^+$ 458.3265. Found: 458.3261.

1-Benzoyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-azaspiro[5.5]undecan-4-N-p-toluenesulfonylhydrazone (27). To a solution of 0.16 g (0.35 mmol) of ketone **25** in 800 μL of EtOH was added 0.9 g (0.43 mmol) of *p*-toluenesulfonyl hydrazide. The resulting suspension was heated to reflux at 90 °C and stirred for 1.5 h. The reaction mixture was cooled to 25 °C, diluted with CH_2Cl_2 and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.21 g (95%) of 1-benzoyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-azaspiro[5.5]undecan-4-*N*-*p*-toluenesulfonylhydrazone (**27**) as a white solid: mp 128−130 °C; IR (neat) 3110, 1640, 1344, 1168 and 1001 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, 3H, *J* = 7.1 Hz), 0.92 (t, 3H, *J* = 7.1 Hz), 0.96−1.47 (m, 10H), 1.51−1.80 (m, 5H), 1.91 (d, 1H, *J* = 13.5 Hz), 2.08 (d, 1H, *J* = 11.6 Hz), 2.18 (d, 1H, *J* = 12.8 Hz), 2.39 (s, 3H), 2.39−2.50 (m, 1H), 3.53 (s, 3H), 3.81 (dd, 1H, *J* = 13.5 and 1.8 Hz), 3.91 (s, 1H), 4.01−4.12 (m, 1H), 4.86 (d, 1H, *J* = 7.1 Hz), 5.16 (d, 1H, *J* = 7.1 Hz), 7.25 (d, 2H, *J* = 8.2 Hz), 7.31−7.40 (m, 5H), 7.78 (d, 2H, *J* = 8.2 Hz) and 9.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.4, 17.7, 21.6, 22.5, 23.1, 24.6, 27.1, 29.6, 31.3, 31.6, 34.2, 35.4, 37.9, 39.6, 49.6, 56.5, 59.9, 67.1, 78.3, 96.1, 126.1, 127.7, 128.6, 129.3, 129.7, 135.7, 139.9, 143.2, 152.7 and 174.4. Anal. Calcd for $C_{35}H_{51}N_3O_5S$: C, 67.17; H, 8.21; N, 6.71. Found: C, 66.96; H, 8.25; N, 6.62.

1-Benzyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-aza-spiro-[5.5]undecan-4-N-p-toluenesulfonylhydrazone (28). To a solution of 0.15 g (0.24 mmol) of tosyl hydrazone **27** in 2.5 mL of dry THF at 0 °C was added 0.06 g (1.4 mmol) of $LiAlH_4$. The reaction mixture was heated at reflux for 12 h, cooled to 0 °C and then carefully quenched with 60 μL of water, followed by 60 μL of 15% aqueous NaOH, followed by an additional 180 μL of water. The resulting suspension was warmed to 25 °C and was stirred for an additional 30 min. A portion of $MgSO_4$ was added and the suspension was stirred for an additional 30 min before being diluted with Et_2O and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.08 g (56%) of 1-benzyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-aza-spiro[5.5]-undecan-4-*N*-*p*-toluenesulfonylhydrazone (**28**) as a colorless oil: IR (neat) 1455, 1344, 1168, 1041 and 1009 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, 3H, *J* = 7.2 Hz), 0.89−1.11 (m, 10H), 1.12−1.37 (m, 8H), 1.37−1.56 (m, 5H), 1.71 (d, 1H, *J* = 13.0 Hz), 1.82 (d, 1H, *J* = 13.0 Hz), 2.01 (d, 1H, *J* = 12.3 Hz), 2.24 (d, 1H, *J* = 12.3 Hz), 2.36 (dd, 1H, *J* = 12.3 and 6.4 Hz), 2.41 (s, 3H), 2.81−2.90 (m, 1H), 3.52 (s, 3H), 3.57 (d, 1H, *J* = 12.3 Hz), 3.78 (d, 1H, *J* = 16.8 Hz), 3.81 (s, 1H), 4.31 (d, 1H, *J* = 16.8 Hz), 4.82 (d, 1H, *J* = 7.2 Hz), 5.16 (d, 1H, *J* = 7.2 Hz), 7.16−7.34 (m, 5H), 7.24 (d, 2H, *J* = 8.3 Hz), 7.80 (d, 2H, *J* = 8.3 Hz) and 9.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.3, 17.7, 21.5, 22.6, 23.2, 24.5, 27.5, 28.0, 30.1, 31.1, 31.8, 34.6, 38.2, 39.7, 50.4, 52.5, 56.4, 58.9, 62.3 78.6, 96.8, 126.3, 127.6, 128.2 and 129.2; HRMS calcd for $[(C_{35}H_{53}N_3O_4S) + H]^+$ 612.3830, found 612.3826.

1-Benzyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-azaspiro-[5.5]undecane (29). A solution of 0.042 g (0.07 mmol) of tosyl hydrazone **28** in 700 μL of dry THF at 0 °C was treated with 0.035 g (0.92 mmol) of $LiAlH_4$. The reaction mixture was heated at reflux for 15 h, cooled to 0 °C, and then carefully quenched with 50 μL of water, followed by 50 μL of 15% aqueous NaOH, and this was followed by an additional 150 μL of water. The resulting suspension was warmed to room temperature and stirred for an additional 30 min. A portion of $MgSO_4$ was added and the suspension was stirred for an additional 30 min before being diluted with Et_2O and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.014 g (49%) of 1-benzyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-azaspiro[5.5]undecane (**29**) as a colorless oil: IR (neat) 1732, 1462, 1150, 1096, and 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.68−0.87 (m, 2H), 0.85 (t, 3H, *J* = 7.6 Hz), 1.03−1.30 (m, 10H), 1.40−1.81 (m, 12H), 1.84−1.93 (m, 2H), 3.35 (s, 3H), 3.77 (s, 1H), 3.81 (d, 1H, *J* = 17.1 Hz), 4.57 (d, 1H, *J* = 6.7 Hz), 4.59 (d, 1H, *J* = 6.7 Hz), 7.14 (t, 1H, *J* = 7.6 Hz), 7.25 (t, 2H, *J* = 7.6 Hz), and 7.39 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.9, 14.0, 18.5, 22.6, 23.2, 26.3, 27.8, 29.7, 31.8, 32.1, 47.9, 55.1, 76.0, 94.9, 125.7, 127.1, 127.8, and 144.5; HRMS calcd for $[(C_{28}H_{47}NO_2) + H]^+$ 430.3680, found 430.3680.

Trifluoromethanesulfonic Acid 1-Benzoyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-azaspiro[5.5]undec-3-en-4-yl Ester (30). To a solution of 0.23 g (0.49 mmol) of ketone **25** in 5 mL of dry THF at −78 °C was added 1.2 mL (0.59 mmol) of a solution of KHMDS (0.5 M in toluene) over a period of 15 min. After the mixture was stirred for 45 min, 0.023 g (0.64 mmol) of $PhNTf_2$ was added all at once. The resulting solution was slowly warmed to 25 °C and stirred for 17 h before being diluted with CH_2Cl_2 and filtered through a plug of neutral alumina. The filtrate was concentrated under reduced pressure, and the residue was purified using flash silica gel chromatography to furnish 0.025 g (85%) of a 1.5:1 mixture of trifluoromethanesulfonic acid 1-benzoyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-azaspiro[5.5]undec-3-en-4-yl ester (**30a**) as well as trifluoromethanesulfonic acid 1-benzoyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-azaspiro[5.5]undec-4-en-4-yl ester (**30b**) as a colorless oil: IR (neat) 1657, 1418, 1211, 1143, and 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, 3H, *J* = 7.2 Hz), 0.92 (t, 3H, *J* = 7.2 Hz), 0.85−1.04 (m, 2H), 1.05−1.23 (m, 4H), 1.29−1.80 (m, 13H), 1.92 (d, 1H, *J* = 10.9 Hz), 2.44 (dt, 1H, *J* = 16.7 and 3.1 Hz), 3.20−3.34 (m, 1H), 3.35 (s, 3H), 3.88 (d, 1H, *J* = 16.7 Hz), 3.93 (s, 1H), 4.53−4.64 (m, 1H), 4.59 (s, 2H), 5.64 (t, 1H, *J* = 3.1 Hz), and 7.34−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 14.2, 18.7, 22.4, 23.4, 24.8, 26.4, 28.1, 30.8, 31.1, 33.4, 37.8, 39.1, 44.3, 55.4, 57.0, 63.8, 73.5, 94.5, 114.5, 126.7, 127.1, 128.5, 129.8, 138.9, 145.9, and 174.1; HRMS calcd for $[(C_{29}H_{42}NO_6F_3S) + H]^+$ 590.2758, found 590.2756.

7-(Butyl-8-(methoxymethoxy)-2-pentyl-1-azaspiro[5.5]-undec-1-yl)phenylmethanone (31). To a solution of 0.026 g (0.44 mmol) of the above triflate mixture in 21 mL of EtOAc was added 0.065 g (0.88 mmol) of Li_2CO_3 and 0.38 g (3.5 mmol, 40 mol%) of 5% Pd/C. The resulting suspension was stirred for 20 h under an atmosphere of hydrogen (50 psi). The reaction mixture was diluted with CH_2Cl_2 and filtered through a Celite plug. The filtrate was concentrated under reduced pressure, and the resulting residue was purified using flash silica gel chromatography to give 0.18 g (92%) of (7-butyl-8-(methoxymethoxy)-2-pentyl-1-azaspiro[5.5]undec-1-yl)phenylmethanone (**31**) as a pale yellow oil: IR (neat) 1642, 1462, 1351, 1151, and 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, 3H, *J* = 7.2 Hz), 0.94 (t, 3H, *J* = 7.2 Hz), 0.98−1.10 (m, 2H), 1.10−1.46 (m, 10H), 1.46−1.72 (m, 10H), 1.72−1.88 (m, 3H), 2.02 (d, 1H, *J* = 10.9 Hz), 2.94 (d, 1H, *J* = 13.0 Hz), 3.38 (s, 3H), 3.77−3.88 (m, 1H), 3.95 (d, 1H, *J* = 2.1 Hz), 4.60 (d, *J* = 6.6 Hz), 4.65 (d, *J* = 6.6 Hz), 7.31−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.4, 15.5, 18.5, 22.5, 23.4, 26.1, 27.5, 27.7, 29.1, 31.5, 31.9, 34.0, 36.2, 36.7, 46.5, 55.3, 57.2, 63.7, 75.3, 94.7, 125.9, 128.3, 128.6, 141.0, and 174.1; HRMS calcd for $[(C_{28}H_{45}NO_3) + H]^+$ 444.3472, found 444.3469.

Compound **31** was easily reduced to azapiro[5.5]undecane **29** using $LiAlH_4$. To a solution of 0.03 g (0.06 mmol) of amide **31** in 900 μL of dry THF at 0 °C was added 0.03 g (0.81 mmol) of $LiAlH_4$. The reaction mixture was heated at reflux overnight for 15 h, cooled to 0 °C, and then carefully quenched with 50 μL of water followed by 50 μL of 15% aqueous NaOH, and this was followed by an additional 150 μL of water. The resulting suspension was warmed to 25 °C and stirred for an additional 30 min. A portion of $MgSO_4$ was added, and the suspension was stirred for an additional 30 min before being diluted with Et_2O and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.024 g (92%) of 1-benzyl-7-butyl-8-(methoxymethoxy)-2-pentyl-1-azapiro[5.5]undecane (**29**) as a colorless

oil whose properties were identical to those of a sample of **29** prepared from the reduction of hydrazone **28**.

1-Benzyl-7-butyl-2-pentyl-1-azaspiro[5.5]undecan-8-ol (32). To a suspension of 0.02 g (0.05 mmol) of MOM ether **29** and 0.08 g of powdered 4 Å molecular sieves in 0.5 mL of dry CH_2Cl_2 at −20 °C was added 50 mL (0.39 mmol) of freshly distilled TMSBr. The resulting suspension was stirred for 3 h at −20 °C before being warmed to 0 °C. After being stirred for an additional 2 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. The biphasic mixture was diluted with CH_2Cl_2 and filtered through a Celite plug. The filtrate was extracted with CH_2Cl_2, and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.014 g (74%) of 1-benzyl-7-butyl-2-pentyl-1-azaspiro[5.5]undecan-8-ol (**32**) as a colorless oil: IR (neat) 3386, 1451, 1352, 1110, and 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.68−0.85 (m, 2H), 0.84 (t, 3H, J = 7.6 Hz), 0.86−0.98 (m, 2H), 1.11 (d, 1H, J = 3.8 Hz) 1.04−1.17 (m, 4H), 1.17−1.29 (m, 6H), 1.41−1.57 (m, 8H), 1.57−1.70 (m, 4H), 1.70−1.82 (m, 2H), 1.93 (t, 1H, J = 8.6 Hz), 3.82 (d, 1H, J = 17.1 Hz), 3.97−4.01 (m, 1H), 4.03 (brs, 1H), 7.13 (t, 1H, J = 7.6 Hz), 7.25 (t, 2H, J = 7.6 Hz), and 7.38 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.0, 14.1, 22.6, 22.7, 23.6, 25.7, 27.5, 29.3, 29.4, 29.6, 29.7, 30.3, 31.9, 32.8, 34.3, 49.9, 55.2, 63.1, 71.1, 125.5, 127.0, 127.6, and 143.9; HRMS calcd for $[(C_{26}H_{43}NO) + H]^+$ 386.3417, found 386.3419.

Another method that was used to prepare**32** involved the treatment of a solution of 0.025 g (0.05 mmol) of MOM ether **29** in 600 mL of Me_2S at −10 °C with 100 mL of $BF_3 \cdot OEt_2$. The resulting suspension was stirred for 2 h at −10 °C before being warmed to 0 °C. After being stirred for an additional 2.5 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The biphasic mixture was diluted with CH_2Cl_2 and filtered through a Celite plug. The filtrate was extracted with CH_2Cl_2, and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.017 g (74%) of **32** as a colorless oil.

7-Butyl-2-pentyl-1-azaspiro[5.5]undecan-8-ol (2,7,8-*epi*-PHTx, 4). To a solution of 0.04 g (0.0.4 mmol) of the above alcohol **32** in 7 mL of EtOH was added 0.07 g of 10% Pd/C. The reaction flask was evacuated and purged with hydrogen three times. The reaction mixture was stirred under an atmosphere of hydrogen gas for 18 h. The resulting mixture was filtered through a Celite plug and concentrated under reduced pressure to furnish 0.03 g (97%) of **4** as a colorless oil: IR (neat) 3351, 1460, 1355, 1261, 1119, and 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.76−0.92 (m, 2H), 0.878 (t, 3H, J = 7.5 Hz), 0.90 (t, 3H, J = 7.5 Hz), 1.07−1.15 (m, 1H), 1.16−1.36 (m, 16H), 1.39−1.48 (m, 2H), 1.51 (dt, 1H, J = 13.5 and 4.0 Hz), 1.54−1.61 (m, 4H), 1.67−1.75 (m, 1H), 1.93−1.99 (m, 1H), 2.22 (d, 1H, J = 13.5 Hz), 2.46−2.53 (m, 1H), and 3.60 (dt, 1H, J = 10.0 and 4.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1, 14.2, 18.9, 20.6, 22.6, 23.3, 25.7, 27.0, 29.7, 30.8, 32.0, 33.3, 34.5, 35.1, 35.9, 37.8, 49.3, 54.9, 56.4, and 72.6.; HRMS calcd for $[(C_{19}H_{37}NO) + H]^+$ 296.2953, found 296.2949.

Trifluoromethanesulfonic Acid 1-Benzoyl-7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]undec-3-en-4-yl Ester (33). To a solution of 0.44 mg (1.12 mmol) of ketone **23** in 10 mL of dry THF at −78 °C was added 3.0 mL (1.5 mmol) of a solution of KHMDS (0.5 M in toluene) over a period of 15 min. After the mixture was stirred for 45 min, 0.52 g (1.5 mmol) of $PhNTf_2$ was added all at once. The resulting solution was slowly warmed to 25 °C and stirred for 22 h before being diluted with CH_2Cl_2 and filtered through a plug of neutral alumina. The filtrate was concentrated under reduced pressure, and the residue was purified using flash silica gel chromatography to furnish 0.51 g (88%) of an approximately 3:2 mixture of trifluoromethanesulfonic acid 1-benzoyl-7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]undec-3-en-4-yl ester (**33a**) and trifluoromethanesulfonic acid 1-benzoyl-7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]undec-4-en-4-yl ester (**33b**) as a colorless oil: IR (neat) 1628, 1496, 1418, 1211, 1144, and 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75 (t, 6H, J = 7.0 Hz), 0.82−0.91 (m, 4H), 0.93−1.0 (m, 4H), 1.09−1.85 (m, 16H), 1.69 (s, 2H), 1.70 (s, 2H), 1.93−2.12 (m, 4H), 2.71−2.84 (m, 2H), 3.12 (d, 1H, J = 18.4 Hz), 3.21 (d, 1H, J = 18.4 Hz), 3.29 (d, 1H, J = 8.3 Hz), 3.34 (s, 3H), 3.40 (s, 3H), 3.59 (d, 1H, J = 17.5 Hz), 3.65 (d, 1H, J = 18.4 Hz), 3.65 (d, 1H, J = 18.4 Hz), 3.83 (d, 1H, J = 18.4 Hz), 3.94 (s, 1H), 4.01 (d, 1H, J = 18.4 Hz), 4.14 (d, 1H, J = 17.5 Hz), 4.58 (d, 1H, J = 7.6 Hz), 4.61 (d, 1H, J = 7.6 Hz), 4.63 (d, 1H, J = 7.0 Hz), 4.70 (d, 1H, J = 7.0 Hz), 5.59 (s, 1H), 5.62 (s, 1H), 7.36−7.49 (m, 8H), and 7.53 (d, 2H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 14.1, 17.3, 17.7, 22.6, 23.0, 23.3, 24.5, 24.7, 26.5, 26.7, 27.0, 30.6, 31.4, 31.6, 31.8, 34.8, 36.9, 41.3, 43.4, 44.3, 44.5, 55.5, 60.7, 62.2, 73.8, 94.6, 113.4, 114.9, 116.9, 120.0, 127.4, 128.2, 128.6, 128.7, 130.4, 131.0, 137.1, 138.2, 148.3, 149.6, 173.5, and 175.3.

7-(Butyl-8-(methoxymethoxy)-1-azaspiro[5.5]undec-1-yl)-phenylmethanone (34). To a solution of 0.51 g (0.99 mmol) of the above triflate mixture in 45 mL of EtOAc was added 0.15 g (2.0 mmol) of Li_2CO_3 and 0.85 g (0.4 mmol, 40 mol%) of 5% Pd/C. The resulting suspension was stirred for 48 h under an atmosphere of hydrogen (60 psi). The reaction mixture was diluted with CH_2Cl_2 and filtered through a Celite plug. The filtrate was concentrated, and the resulting residue was purified using flash silica gel chromatography to give 0.34 g (91%) of (7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]undec-1-yl)phenylmethanone (**34**) as a pale yellow oil: IR (neat) 1642, 1390, 1271, 1096, and 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.94 (t, 3H, J = 7.6 Hz), 1.21−1.81 (m, 15H), 1.97 (d, 1H, J = 14.3 Hz), 2.32 (d, 1H, J = 10.5 Hz), 2.76 (dt, 1H, J = 14.3 and 2.9 Hz), 2.94−3.03 (m, 2H), 3.38 (s, 3H), 3.45 (dt, 1H, J = 14.3 and 2.9 Hz), 3.95−3.98 (m, 1H), 4.61 (d, 1H, J = 6.7 Hz), 4.65 (d, J = 6.7 Hz), and 7.37−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 18.1, 20.1, 23.1, 25.6, 25.9, 27.0, 31.5, 33.3, 35.5, 40.6, 45.1, 55.2, 64.0, 74.9, 94.6, 126.3, 128.3, 128.9, 140.3, and 173.0; HRMS calcd for $[(C_{23}H_{35}NO_3) + H]^+$ 374.2690, found 374.2700.

1-Benzyl-7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]-undecane (35). To a solution of 0.13 g (0.35 mmol) of amide **34** in 5.5 mL of dry THF at 0 °C was added 0.08 g (2.1 mmol) of $LiAlH_4$. The reaction mixture was heated at reflux for 14 h, and then the suspension was cooled to 0 °C and was carefully quenched with 100 μL of water, followed by 100 μL of 15% aqueous NaOH, and this was followed by an additional 300 μL of water. The resulting suspension was warmed to 25 °C and stirred for an additional 30 min. A portion of $MgSO_4$ was added, and the suspension was stirred for an additional 30 min before being diluted with Et_2O and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.12 g (93%) of 1-benzyl-7-butyl-8-(methoxymethoxy)-1-azaspiro[5.5]undecane (**35**) as a colorless oil: IR (neat) 1465, 1450, 1216, 1152, 1098, and 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, 3H, J = 6.4 Hz), 0.95−1.09 (m, 1H), 1.19−1.79 (m, 15H), 1.89−2.10 (m, 2H), 2.10−2.23 (m, 1H), 2.44−2.58 (m, 1H), 3.37 (s, 3H), 3.66 (d, 1H, J = 14.0 Hz), 3.83−3.89 (m, 1H), 3.92 (d, 1H, J = 14.0 Hz), 4.63 (d, 1H, J = 7.0 Hz), 4.65 (d, 1H, J = 7.0 Hz), 7.20 (t, 1H, J = 7.0 Hz), 7.28 (t, 1H, J = 6.4 Hz), 7.30 (d, 1H, J = 7.0 Hz), and 7.35 (d, 2H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.0, 18.5, 20.4, 20.7, 23.4, 26.3, 27.0, 31.0, 31.6, 32.6, 44.0, 51.2, 55.2, 57.8, 76.6, 95.0, 126.2, 128.0, 128.1, and 142.8; HRMS calcd for $[(C_{23}H_{37}NO_2) + H]^+$ 360.2897, found 360.2892.

1-Benzyl-7-butyl-1-azaspiro[5.5]undecan-8-ol (36). To a suspension of 0.12 g (0.33 mmol) of MOM ether **35** and 0.55 g of powdered 4 Å molecular sieves in 2.6 mL of dry CH_2Cl_2 at −20 °C was added 400 mL (2.7 mmol) of freshly distilled TMSBr. The resulting suspension was stirred for 3 h at −20 °C before being warmed to 0 °C. After being stirred for an additional 2 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$

solution. The biphasic mixture was diluted with CH_2Cl_2 and filtered through a Celite plug. The filtrate was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.072 g (71%) of 1-benzyl-7-butyl-1-azaspiro[5.5]undecan-8-ol (**36**) as a colorless oil: IR (neat) 3386, 1451, 1352, 1110, and 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, J = 7.0 Hz), 1.02−1.18 (m, 1H), 1.18−1.95 (m, 16H), 1.95−2.13 (m, 1H), 2.17−2.28 (m, 1H), 2.42−2.56 (m, 1H), 2.56−2.69 (m, 1H), 3.61 (d, 1H, J = 14.0 Hz), 3.93 (d, 1H, J = 14.0 Hz), 4.04 (dd, 1H, J = 9.5 and 5.0 Hz), 7.21 (t, 1H, J = 7.0 Hz), 7.30 (t, 2H, J = 7.6 Hz), and 7.36 (d, 2H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.0, 19.0, 20.8, 21.4, 23.4, 27.0, 29.7, 30.9, 31.4, 33.3, 33.7, 44.3, 49.0, 52.7, 58.6, 72.5, 126.3, 128.0, 128.1, and 142.3.

Acknowledgment. The financial support provided by the National Science Foundation (CHE-0742663) is greatly appreciated.

Supporting Information Available: ^1H and ^{13}C NMR data of various key compounds lacking CHN analyses together with ORTEP drawings for compounds **17a**, **17b**, and **27** as well as the corresponding CIF files. Atomic coordinates for all three compounds will be deposited with the Cambridge Crystallographic Data Centre. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801295E