Combinatorial Synthesis of Natural Product-like Molecules Using a First-Generation Spiroketal Scaffold

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Received July 23, 2001

Recently, significant attention has been focused on the synthesis small-molecule libraries based on natural product or natural product-like structures. In this paper, we report our initial studies on the use of the 1,7-dioxaspiro[5,5]undecane (spiroketal) moiety as a rigid-core template for elaboration using parallel synthesis techniques. The synthesis of a spiroketal scaffold that is reminiscent of the spiroketal subunits found in the spiroketal macrolide antibiotics will be described. Elaboration of three independently addressable functional groups on the scaffold using solution-phase parallel synthesis techniques led to the preparation of a small library of natural product-like compounds. These studies pave the way for evaluation of highly functionalized spiroketals in phenotypic assays and as prospective antagonists of protein−protein interactions.

Introduction

The synthesis of novel and rigid scaffolds for diversification using combinatorial chemistry techniques has been an important goal in the discovery of new biologically active molecules.[1] A number of literature examples have been reported wherein rigid architectures have been employed, including substituted glycouril compounds,[2] calix[4]arene derivatives,[3] spirodiamino acid scaffolds,[4] tri- and tetracarboxylate cores,[5] cyclopeptides,[6] carbohydrate scaffolds,[7] and steroid nuclei.[8] Recently, significant attention has also been focused on the synthesis of small-molecule libraries based on natural product or natural product-like structures.[9] We have initiated studies in this area, employing the 1,7-dioxaspiro[5,5]undecane moiety as a rigid-core template for elaboration using parallel synthesis techniques. The spiroketal moiety is a prevalent structure in a wide number of biologically important natural products[10] and has also been employed as a scaffold in the synthesis of conformationally restrained glycomimetics[11] and gyrase inhibitors[12] (parts a and b of Figure 1, respectively). The use of spiroketals as lead structures is a potentially promising area for investigation because recent literature reports have shown that simplified compounds exhibit interesting pharmacological effects, such as tubulin modulation and cytotoxicity against tumor cell lines (cf. parts c and d of Figure 1).[13] Herein, we report our studies on the synthesis of a spiroketal scaffold containing three independently addressable functional groups and the use of parallel solution-phase synthesis[14] methods (extractive workups, polymer reagent, scavenger techniques, and column-based extractions) for elaboration of the scaffold. We have focused our initial efforts on the preparation of highly functionalized spiroketals with general structure **1** (Figure 2), using a scaffold that is reminiscent of spiroketal subunits found in the spiroketal macrolide antibiotics cytovaricin,[15] spongistatins (altohyrtins),[16] and the rutamycins/oligomycins.[17] In addition to further development of methodologies for streamlined synthesis (a descriptor for methodology that lends itself to efficient application to parallel organic synthesis), our motivation to prepare libraries of spiroketals is also based on planned evaluation of these molecules in phenotypic assays[18] and as antagonists of protein−protein interactions.[19] Functionalized spiroketals **1** are ultimately derived from spiroketal ketone **2**, which may be prepared from condensation of chiral ketone **3** and aldehyde **4** using established reaction sequences.[20]

Results and Discussion

The synthesis of protected hydroxy ketone fragment **3** (Scheme 1) was initiated by hydrolytic kinetic resolution (HKR)[21] of (±)-1,2-epoxy-5-hexene to afford *S*-epoxide **5** (85%). Epoxide ring opening using 2-methyl-1,3-dithiane[22] provided hydroxydithiane **6**, which was silylated to afford **7**. Although treatment of **7** with mercury(II) perchlorate afforded low yields of **3**, presumably due to competitive oxymercuration of the terminal olefin, dithiane cleavage using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)[23] afforded methyl ketone **3** in high yield.[24] Preparation of the requisite aldehyde fragment **4** was initiated by protection of commercially available 5-hexen-1-ol as a *p*-methoxybenzyl ether to afford **8** (Scheme 2). Sharpless asymmetric dihydroxylation[25] of **8** using AD-mix-β provided diol **9** (80% ee), which was converted to acetonide **10**. PMB deprotection

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10.1021/cc010047w CCC: $22.00
Published on Web 10/20/2001

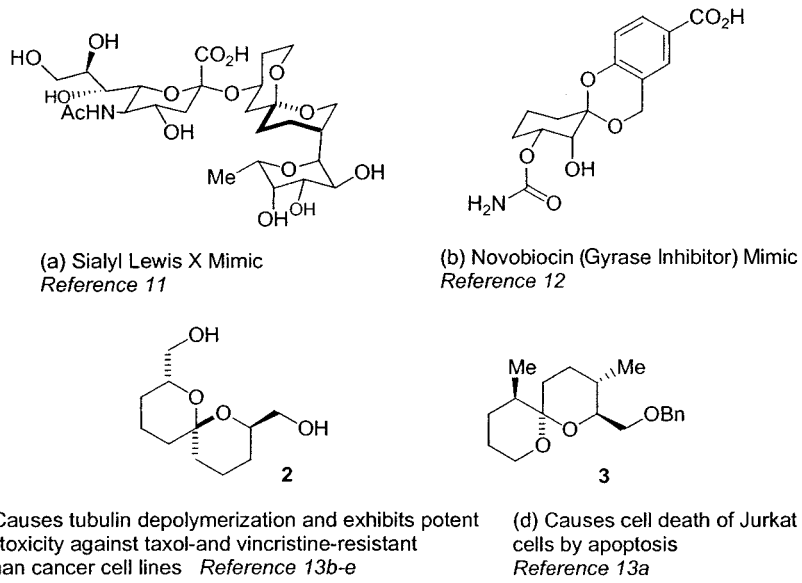


Figure 1. Non-natural spiroketal derivatives.

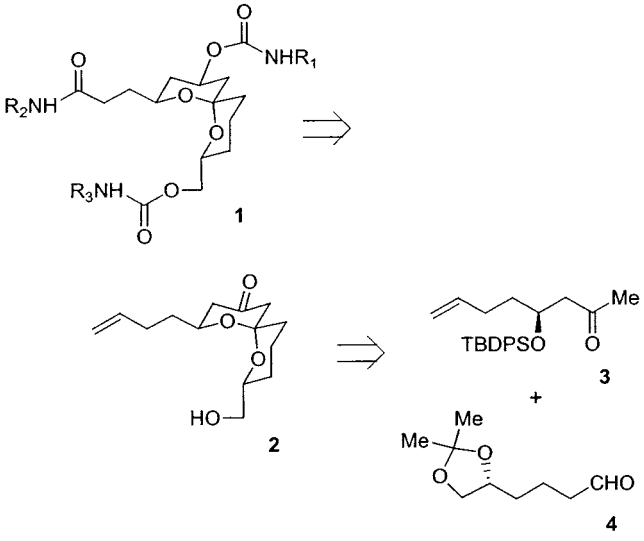


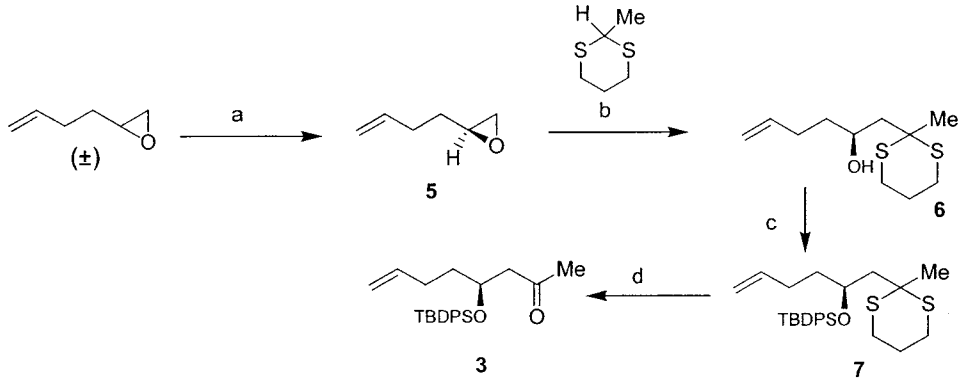
Figure 2. General structure and retrosynthesis of spiroketals derived from elaboration of a three-vector scaffold.

(DDQ)[26] of **10** followed by Swern oxidation[27] provided aldehyde **4** (83%, two steps). Union of **3** with aldehyde **4** was effected using the Mukaiyama reaction[28] of the derived silyl enol ether **11** to afford **12** as a 1:1 mixture of diastereomers (Scheme 3). Oxidation of **12** with Collin's reagent[16a] afforded β-diketone **13** (64%). Global deprotection−spiroketalization of **13** was accomplished by treatment with 48% aqueous HF/CH_3CN/CH_2Cl_2 (6:9:50)[29] to produce the target spiroketal scaffold **2** as a single diastereomer (80%). Stereochemical assignment of scaffold **2** was supported by nuclear Overhauser effect (NOE) experiments (Scheme 3, 5% NOE between H_1 and H_2) and subsequently confirmed by X-ray crystallographic analysis of a functionalized spiroketal (cf. Figure 4).

Initial studies for scaffold modification focused on oximation of the spiroketal ketone functionality (Scheme 4).[9g,30] Treatment of **2** with methoxylamine hydrochloride (NaOAc, 2:1 EtOH/H_2O) provided oxime **14** in quantitative yield. Reaction of **14** with 1,1′-carbonyldiimidazole (CDI) in THF followed by treatment of the intermediate imidazolide[31] with excess L-phenylalanine ethyl ester afforded a carbamate ethyl ester, which after hydrolysis gave spiroketal acid **15**. To evaluate the possible use of a "catch and release"[32] protocol for product purification, **15** was incubated with PS-Trisamine resin[33] in CH_2Cl_2, the resin was washed, and products were released by treatment with 20% AcOH in CH_2Cl_2. Unfortunately, the released product **15** was contaminated with elimination product **16**, which suggested the need for reduction of the spiroketal ketone to permit more robust elaboration chemistries (Scheme 5). Silyl protection of **2** afforded silyl ether **17**, which was selectively reduced ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C)[34] to equatorial alcohol **18**. We next implemented a plan to convert the secondary alcohol into a series of carbamates for the first diversity step. Hydroxyspiroketal **18** was converted to *p*-nitrophenyl carbonate **19** (4-nitrochloroformate, pyridine), which was treated with 1-naphthalenemethylamine to produce carbamate **20** in near-quantitative yield. For library synthesis, three primary amines were employed for the R_1 diversity step (cf. Figure 3). Terminal olefin **20** was converted to acid **21** in three steps by osmylation, oxidative cleavage using $Pb(OAc)_4$, and chlorite oxidation.[35] In these reactions, only extractive workups were required for product purification.

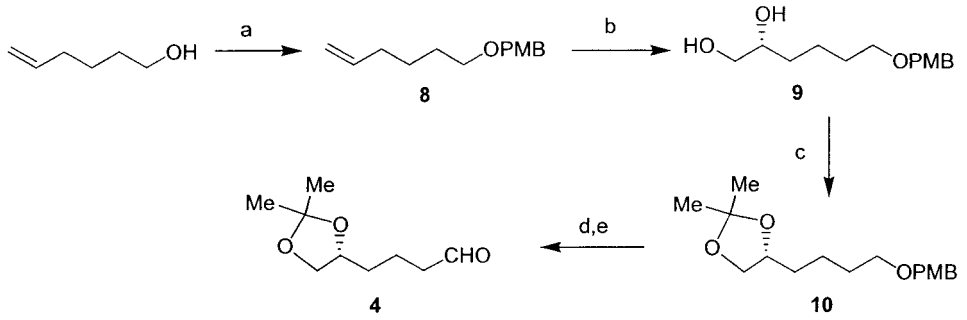
R_2 and R_3 diversity elements were next incorporated onto the spiroketal scaffold using a series of streamlined solution-phase reactions. The R_2 diversity step was accomplished using amide bond formation (Scheme 6). Coupling of acid **21** with L-phenylalanine ethyl ester hydrochloride (EDC, HOBt, DIEA, CH_2Cl_2) gave amide **22** in near-quantitative yield (99%) after liquid−liquid extraction.[14b,c] For library synthesis, three amino acid ethyl esters were employed (cf., Figure 3), in which case nine parallel reactions were effectively conducted on the Quest 210 (Argonaut Technologies) using 10 mL Teflon reaction vessels to facilitate reactions and subsequent liquid−liquid extractions directly in the same vessel. Introduction of the R_3 diversity element required silyl deprotection and carbamate formation of the pendant hydroxymethyl group. For example, treatment of **22** with excess HF·pyridine in THF effected cleavage of the

Scheme 1[a]



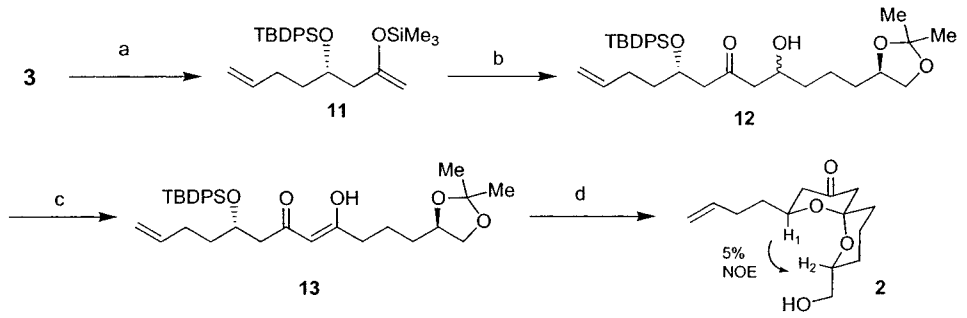
[a] Reagents and conditions: (a) (*S*,*S*)-salen-Co, H_2O (0.55 equiv), AcOH (5 mol %), THF, 0 °C to room temp, 85%; (b) *n*-BuLi, THF, HMPA, −35 °C, 2h, −78 °C, **5**, 73%; (c) TBDPSCl, imidazole, room temp, 24 h, 90%; (d) DDQ, CH_3CN/H_2O (9:1), room temp, 4 h, 81%.

Scheme 2[a]



[a] Reagents and conditions: (a) NaH, DMF, 0 °C to room temp, 3 h, *p*-$MeOC_6H_4CH_2Br$, 0 °C to room temp, 12 h, 98%; (b) AD-mix-β, *t*-$BuOH/H_2O$ (1:1), 0 °C, 18 h, 90%; (c) acetone, TsOH, room temp, 30 min, 92%; (d) DDQ, CH_2Cl_2/H_2O (18:1), 0 °C, 5 h, 86%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −70 °C, 96%.

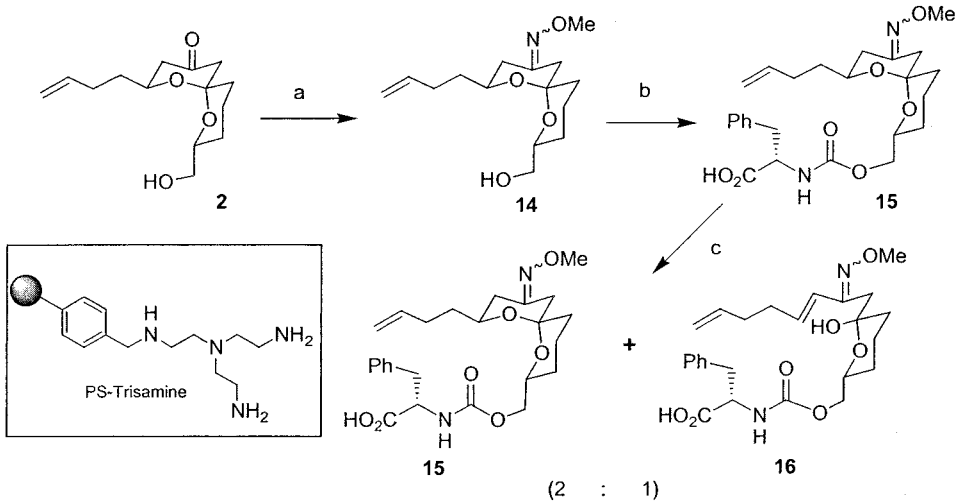
Scheme 3[a]



[a] Reagents and conditions: (a) (i) KHMDS, THF, −78 °C, 1.5 h, (ii) TMSCl, −78 °C, 2 h, 98%; (b) **4**, −78 °C, BF_3OEt_2, 1.5 h, 65%; (c) CrO_3, Celite, pyridine, CH_2Cl_2, 3.5 h, 64%; (d) $HF/CH_3CN/CH_2Cl_2$ (6:9:50), 24 h, 80%.

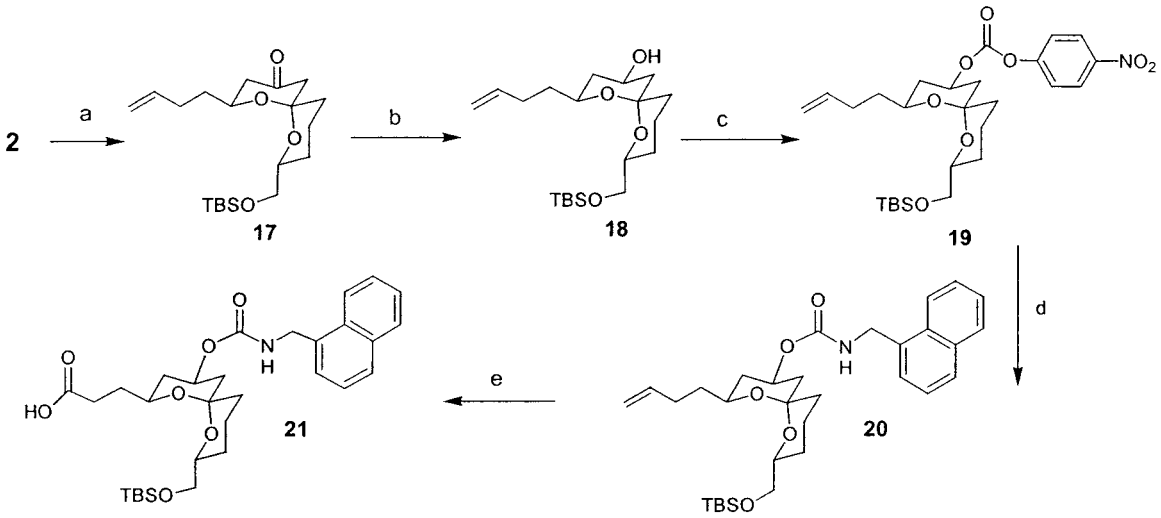
TBS ether. After completion of the reaction, residual HF was neutralized using a liquid scavenger, methoxytrimethylsilane ($MeOSiMe_3$), which affords volatile side products.[36] Pyridine was removed by directly passing reaction mixtures through a Waters Oasis MCX (mixed-mode cation exchange) cartridge (6 cm^3) attached to Luer fittings below the reaction vessels to afford alcohol **23**. Nine such parallel TBS deprotection reactions were carried out in this manner on the Quest 210. **23** was further converted to imidazolide **24** using a slight excess of CDI in CH_2Cl_2. After completion of the reaction, excess CDI and the byproduct imidazole were removed from the reaction mixture using solid-supported liquid extraction (SLE)[37] (1 M aqueous NaH_2PO_4[38] preloaded onto ChemElut Plus liquid−liquid extraction cartridges).[33] For carbamate formation, imidazolide **24** was reacted with isoamylamine (9.0 equiv) in toluene (50 °C, 12 h) to yield fully functionalized spiroketal **25** (98% yield, 88% HPLC purity). Excess amine and imidazole byproducts were removed by gravity elution of the reaction mixtures through a ChemElut Plus liquid−liquid extraction cartridge pretreated with 10% HCl. The choice of toluene for carbamate formation is derived from the requirement for use of water-immiscible solvents in the SLE procedure.[37] For the R_3 diversity step, parallel carbamate formation reactions were carried out in 10 mL (13 mm × 150 mm) reactors on the Argonaut FirstMate synthesizer. Using the methodology described in Scheme 6, we synthesized a small library of 90 highly functionalized spiroketals (3 × 3 × 10) in yields ranging from 77 to 97% with HPLC purities from 80 to 96% (Table 1). Figure 4 also shows a single X-ray crystal structure analysis[39] of a representative highly functionalized spiroketal (**33**), which both confirms the absolute stereochemistry of

Scheme 4[a]



[a] Reagents and conditions: (a) methoxylamine hydrochloride, EtOH/H_2O (2:1), room temp, 2 h, 100%; (b) (i) CDI, THF, room temp, 5h, (ii) L-phenylalanine ethyl ester hydrochloride, pyridine, 55 °C, 12 h, (iii) LiOH, H_2O, THF, room temp, 5 h, 95% (three steps); (c) (i) PS-Trisamine (4.0 equiv), CH_2Cl_2, (ii) 20% AcOH/CH_2Cl_2.

Scheme 5[a]



[a] Reagents and conditions: (a) TBSCl, imidazole, DMF, room temp, 12 h, 90%; (b) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C, 70%; (c) 4-nitrophenylchloroformate, pyridine, THF, room temp, 20 min, 100%; (d) 1-naphthalenemethylamine, DMF, room temp, 4 h, 98%; (e) (i) OsO_4, NMO, *t*-BuOH/H_2O (2:1), (ii) $Pb(OAc)_4$, THF, (iii) $NaClO_2$, NaH_2PO_4, *t*-BuOH/2-methyl-2-butene (2:1), 97% (three steps).

the spiroketal scaffold and illustrates the interesting projection of functionality from the spiroketal core.

As an alternative to extractive workups, we have also investigated use of polymer reagent and scavengers for R_2 and R_3 diversity steps (Scheme 7). For example, treatment of spiroketal acid **21** (1.0 equiv) with PS-HOBt resin (DIC, catalyst DMAP, DMF/CH_2Cl_2 (1:2)) followed by resin washing led to the resin-bound HOBt ester **42**. Release of product from resin with L-leucine ethyl ester hydrochloride (1.5 equiv, DIEA, CH_2Cl_2) afforded amide **43**, in which case excess amino acid ester was removed by passing the reaction mixture through 12 mL ChemElut Plus cartridges pretreated with 10% HCl. Conversion of **43** to imidazolide **44** followed the earlier sequence (cf. **22** → **24**, Scheme 6). Further conversion of **44** to carbamate **45** was accomplished by treatment of **44** with 4-(aminomethyl)pyridine (9 equiv, 50 °C, toluene). In this and other cases involving use of primary amines containing basic sites for carbamate formation, consecutive amine scavenging using PS-isocyanate resin[33,40] and removal of imidazole using SLE (ChemElut Plus cartridge, 1 M aqueous NaH_2PO_4) were found to produce spiroketal products in high yield and purities (cf. **45**: 81% yield, 90% HPLC purity).

Spiroketal functionalization was also extended to a fourth diversity element as described in Scheme 8. Reaction of imidazolide **44** with benzylamine as previously described and workup using SLE afforded spiroketal **46**. Ester hydrolysis of **46** (LiOH, THF) followed by acidification and extraction led to acid **47**. Coupling of acid **47** with 2-diphenylethylamine (EDC, HOBt, DIEA, CH_2Cl_2) gave functionalized spiroketal product **48** in 95% overall yield and 86% HPLC purity after liquid−liquid extraction.

Finally, we have briefly examined an alternative method for spiroketal scaffold diversification involving direct reaction of the pendant alkene (Scheme 9). Nitrophenyl carbonate **19** was converted to carbamate **49** using previously described methods. Nitrile oxide 1,3-dipolar cycloaddition of **49** (1-nitropropane, PhNCO, catalyst Et_3N, benzene, reflux)[41]

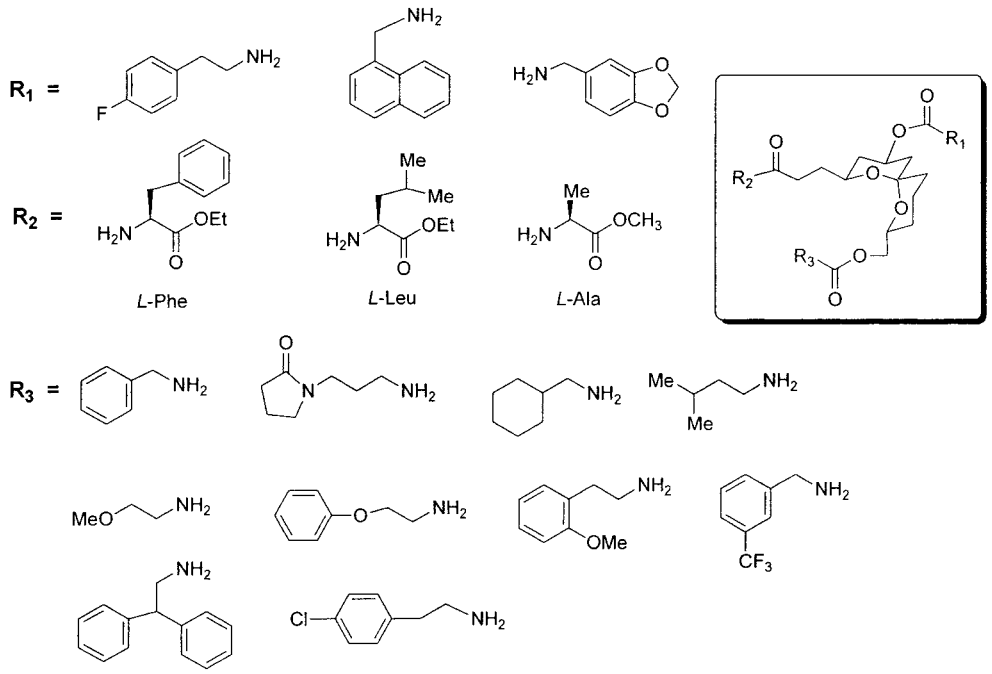
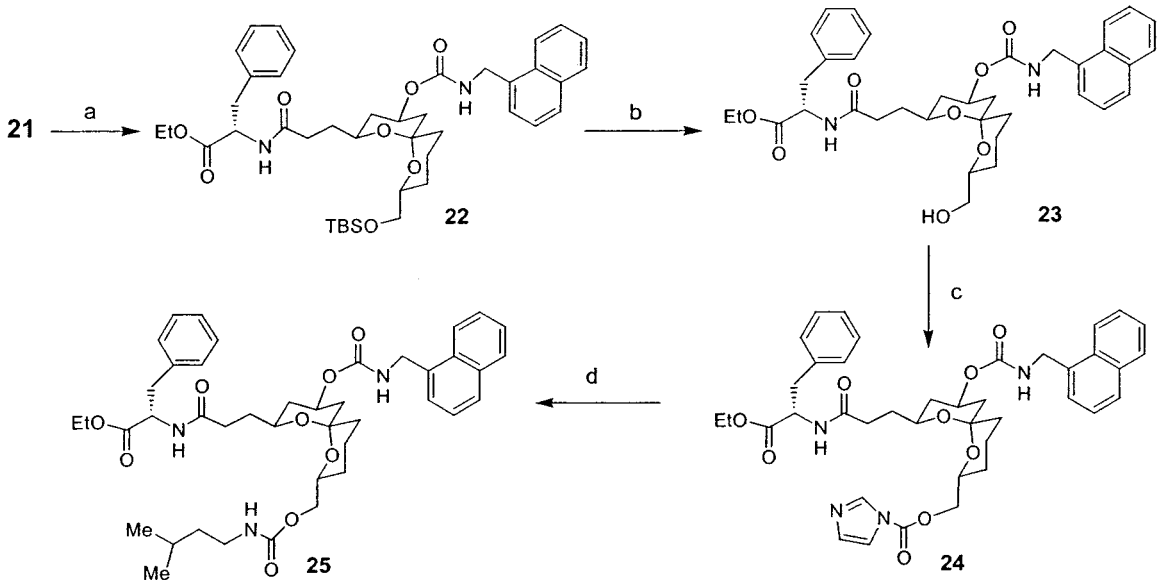


Figure 3. Building blocks used for the spiroketal library.

Scheme 6[a]



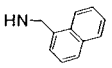
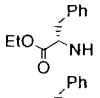
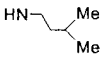
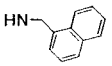
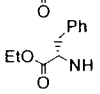
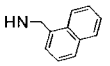
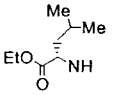
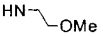
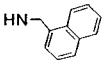
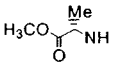
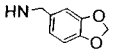
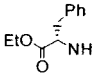
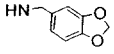
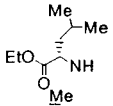
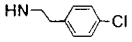
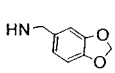
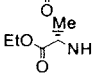
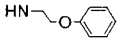
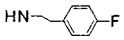
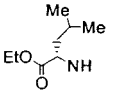
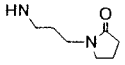
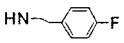
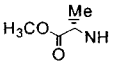
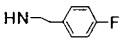
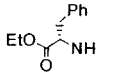
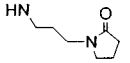
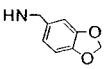
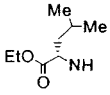
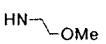
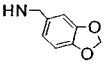
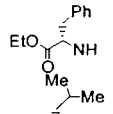
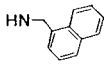
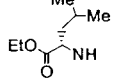
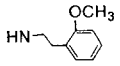
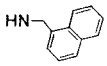
[a] Reagents and conditions: (a) L-phenylalanine ethyl ester hydrochloride, EDC, HOBt, DIEA, CH_2Cl_2, room temp, 12 h, 99%; (b) (i) HF·pyridine, THF, room temp, 4 h, (ii) $MeOSiMe_3$ (2 equiv), room temp, 2 h, (iii) Waters MCX cartridge, 100%; (c) (i) CDI (1.1 equiv), CH_2Cl_2, room temp, 4 h, (ii) ChemElut Plus cartridge (1 M NaH_2PO_4), 100%; (d) (i) isoamylamine, toluene, 50 °C, (ii) ChemElut Plus cartridge (10% HCl), 98%.

afforded spiroketal isoxazole **50** as a mixture of diastereomers. Streamlined removal of the TBS protecting group of **50** and imidazolide formation as described previously gave spiroketal imidazolide **51** in 71% (three steps) yield. Fully functionalized spiroketal **52** was obtained in 95% yield (96% HPLC purity) by reaction of **51** with 2-methoxyphenylamine and reaction workup using solid-supported liquid extraction. Such alternative functionalization protocols illustrate the versatility of the spiroketal scaffold and the possibility for preparation of a number of diverse structures.

Conclusion

We have synthesized a rigid spiroketal scaffold containing three independently addressable vectors for the functionalization and have used the scaffold to generate a small combinatorial library of natural product-like molecules. Synthesis of the compounds employed streamlined solution-phase synthesis methods including polymer-supported reagents and scavengers and solid-supported liquid extraction cartridges. Preliminary studies have shown that up to four diversity elements may be installed on the spiroketal scaffold to produce highly functionalized molecules. Additional and diverse functionalization reactions of the spiroketal scaffold may be performed to prepare other spiroketal chemotypes. We are currently examining the biological activity of these compounds as prospective antagonists of protein−protein interactions, as well as the preparation of alternative spiroketal scaffolds in an effort to produce larger and more diverse

Table 1. Representative Fully Functionalized Spiroketals

compound	R_1	R_2	R_3	yield (%)[a]	purity (%)[b]
25				97	88
26				98	88
27				92	94
28				93	89
29				77	86
30				82	87
31				74	87
32				96	84
33				79	85
34				89	80
35				80	92
36				95	90
37				93	89
38				87	83
39				86	89
40				84	96
41				82	94

[a] Chemical yield based on weight of crude product obtained from purified spiroketal carbamates (cf. compound **20**). [b] HPLC analysis: 20% CH_3CN/H_2O (integral at 230 nm).

libraries. The results of these and related studies will be reported in due course.

Experimental Section

General Information. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded on a 75.0 MHz spectrometer at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ 7.24; ^{13}C, δ 77.0). Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), and coupling constants. All ^{13}C NMR spectra were recorded with complete proton decou-

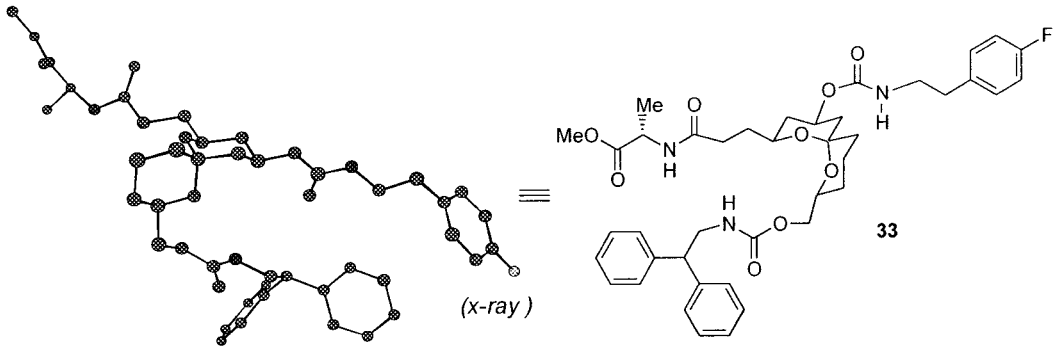
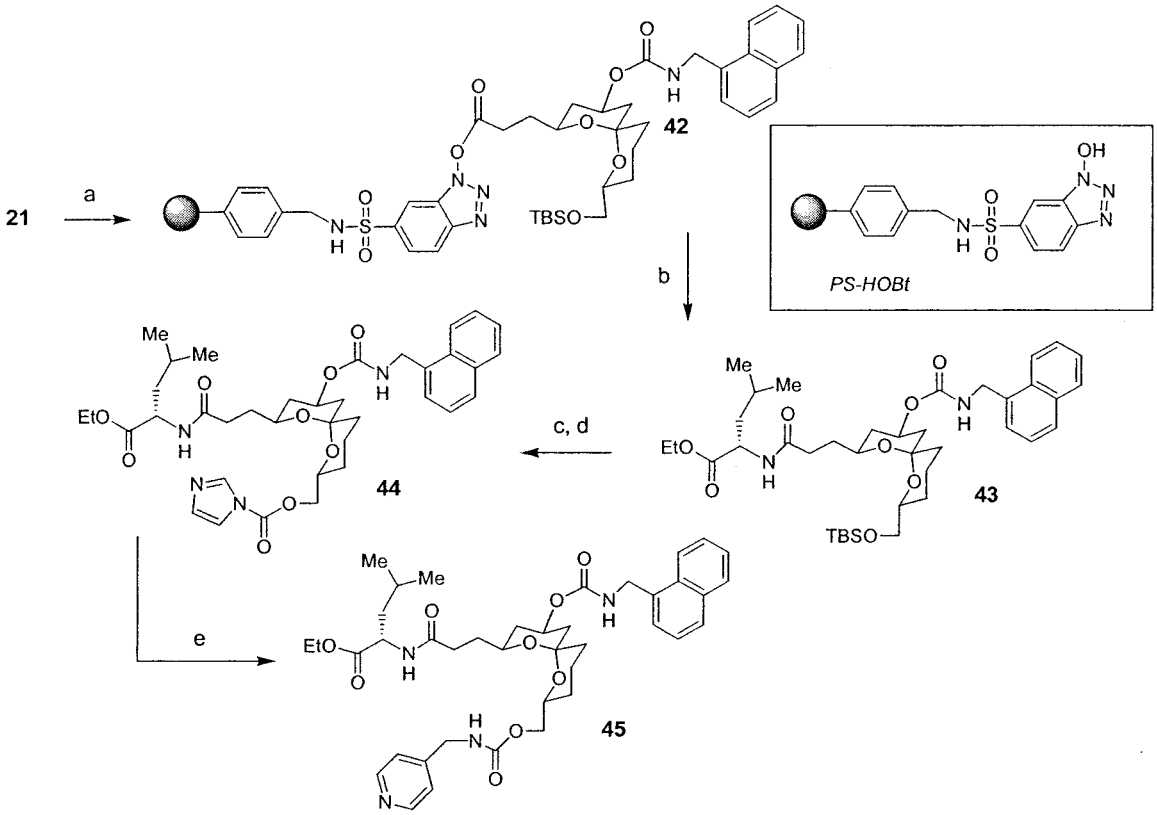


Figure 4. Chem3D representation of the X-ray structure of spiroketal **33**.

Scheme 7[a]

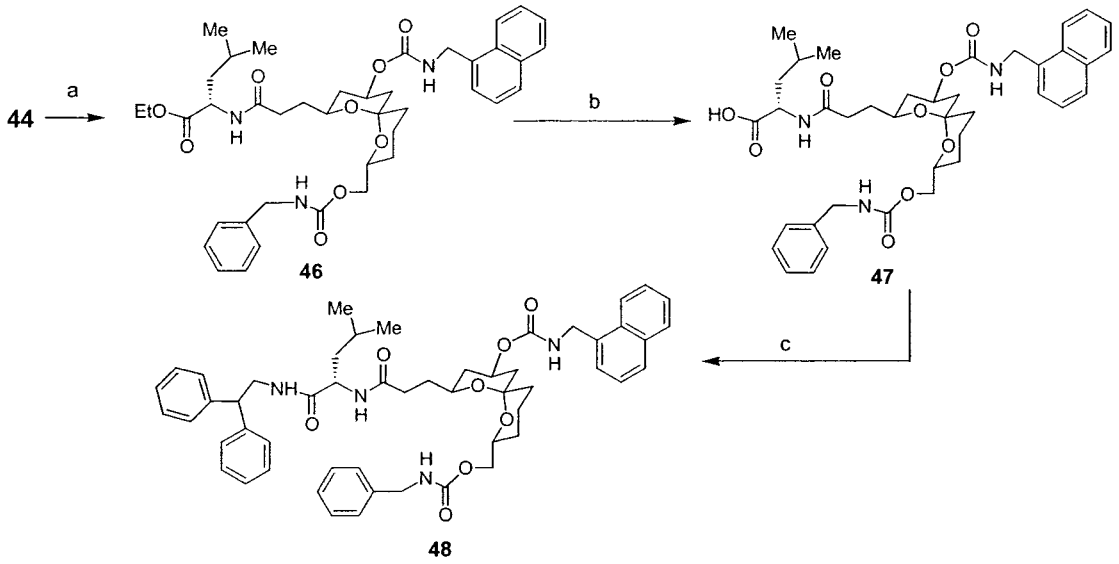


[a] Reagents and conditions: (a) PS-HOBt resin, DIC (1.0 equiv), DMAP (0.1 equiv), DMF/CH_2Cl_2 (1:3), 7 h; (b) (i) L-leucine ethyl ester hydrochloride (1.5 equiv), DIEA (3.0 equiv), CH_2Cl_2, 5 h, (ii) Chem-Elut cartridge (10% HCl), 78% (two steps); (c) (i) HF·pyridine, room temp, 4 h, (ii) $MeOSiMe_3$ (2 equiv), room temp, 2 h, (iii) Waters MCX cartridge; (d) (i) CDI, CH_2Cl_2, room temp, 4 h, (ii) ChemElut Plus cartridge (1 M NaH_2PO_4) (98%, two steps); (e) (i) 4-(aminomethyl)pyridine, toluene, 50 °C, 12 h, (ii) PS-isocyanate resin, (iii) ChemElut Plus cartridge (1 M NaH_2PO_4), 81%.

pling. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR. Chiral HPLC analysis was performed on an Agilent 1100 series (CHIRALCEL OD, column no. OD00CE-AI015). Achiral HPLC analysis was performed on an Agilent 1100 series (reverse-phase C-18 column) using water and CH_3CN as eluents. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm and are reported as $[\alpha]^{22}_D$ (concentration in grams per 100 mL of solvent). High-resolution mass spectra were obtained in the Boston University mass spectrometry laboratory using a Finnegan MAT-90 spectrometer. Methylene chloride (CH_2Cl_2) and toluene were distilled from calcium hydride. Tetrahydrofuran was distilled from sodium and benzophenone. Analytical thin-layer chromatography was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200−400 mesh silica gel (Natland International Corporation). All other reagents were used as supplied by Sigma-Aldrich, Lancaster, TCI, and Alfa Aesar unless otherwise noted. ChemElut Plus cartridges (3.0 mL aqueous capacity (12 mL)) were obtained from Argonaut Technologies (part no. 900252). Waters Oasis MCX 6 cm^3 cartridges (part no. 186000776) were obtained from Waters, Inc. PS-HOBt and PS-isocyanate resins were obtained from Argonaut Technologies (San Carlos, CA). Parallel reactions were carried out using the Quest-210 and FirstMate synthesizers (Argonaut Technologies, San Carlos, CA).

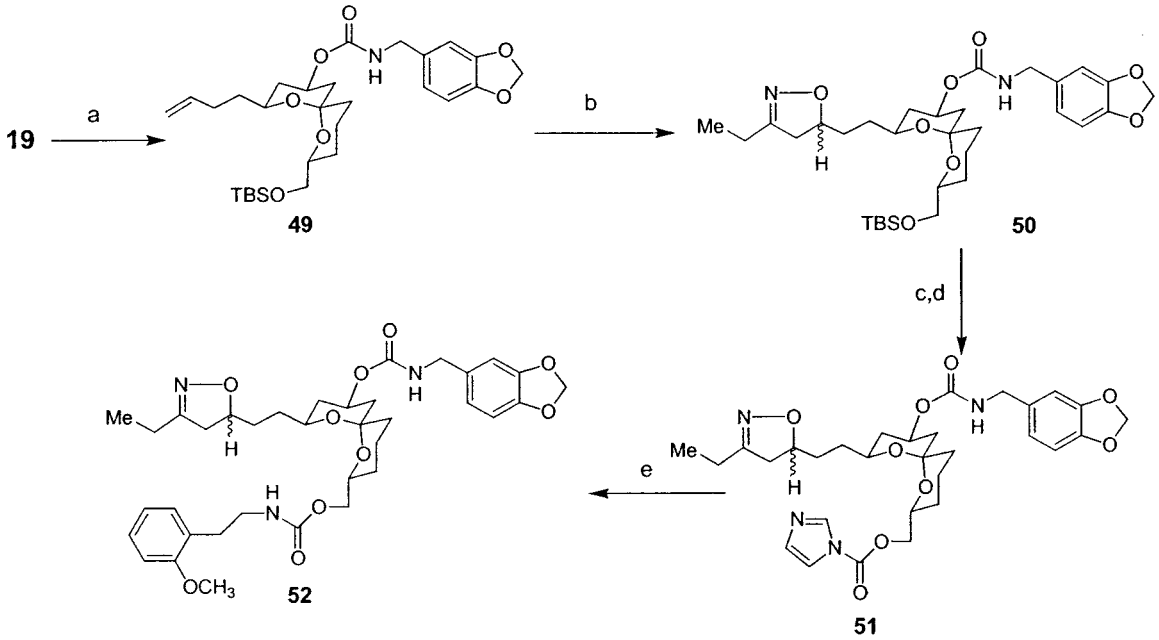
***(S)*-1,2-Epoxy-5-Hexene (5).** To a stirred solution of (±)-1,2-epoxy-5-hexene (20 g, 0.20408 mol) and *S,S*-salen-Co catalyst (489 mg, 5 mol %) at 0 °C were added consecutively THF (1.5 mL), AcOH (175 μL, 2.0 mol %), and water (1.5 mL, 0.55 equiv) at the same temperature. The reaction was warmed to room temperature and stirred for 16 h, at which

Scheme 8[a]



[a] Reagents and conditions: (a) (i) benzylamine, toluene, 50 °C, 12 h, (ii) ChemElut Plus cartridge (10% HCl), 98%; (b) (i) 1M aqueous LiOH, THF, room temp, 5 h, (ii) 5% HCl, 98%; (c) 2-diphenylethylamine, EDC, HOBt, DIEA, CH_2Cl_2, room temp,12 h, 95%.

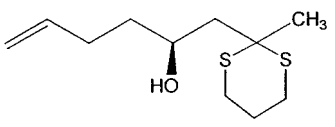
Scheme 9[a]



[a] Reagents and conditions: (a) piperonylamine, DMF, 98%; (b) 1-nitropropane, phenyl isocyanate, Et_3N, benzene, reflux, 24 h; (c) (i) HF·pyridine, room temp, 4 h, (ii) $MeOSiMe_3$ (2 equiv), room temp, 2 h, (iii) Waters MCX cartridge; (d) (i) CDI, THF, room temp, 5 h, (ii) Chem-Elut cartridge (1 M NaH_2PO_4), 71% (three steps); (e) (i) 2-methoxyphenethylamine, toluene, 50 °C, 12 h, (ii) Chem-Elut cartridge (10% HCl), 95%.

time volatiles (epoxide) were vacuum-transferred (0.025 Torr) into a cooled (−78 °C) receiving flask. The recovered epoxide was passed through a small pad of silica gel to remove the residual water, and THF was removed using distillation at ambient pressure to afford (*S*)-1,2-epoxy-5-hexene **5** (8.5 g, 85%) as a clear oil. For enantiomeric excess determination, the epoxide was ring-opened with 2-naphthalenethiol. To a stirred solution of epoxide (50 mg, 0.51 mmol) in MeOH (1.0 mL) were added at 0 °C 2-naphthalenethiol (90 mg, 0.56 mmol, 1.1 equiv) and Et_3N (57 mg, 0.56 mmol). After the solution was stirred for 2 h, water was added. The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (10−20% EtOAc/hexanes) to yield the 2-naphthylsulfide derivative (125 mg, 95%) as a clear oil, 90% ee [chiral HPLC, 10% 2-propanol/hexane, Rt = 14.18 min (major), 15.45 min (minor)].

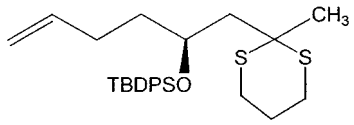
Hydroxydithiane (6).



A solution of 2-methyl-1,3-dithiane (8.2 g, 0.061 mol) in THF (30.0 mL) and HMPA (3.0 mL) was cooled to −30 °C, and a solution of *n*-BuLi (2.6 M solution in hexane 25.90

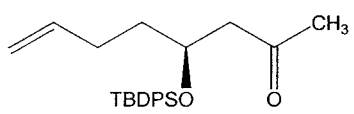
mL, 0.0674 mol) was added slowly. The reaction mixture was stirred at −30 °C for 2 h. A solution of epoxide **5** (6.0 g, 0.061 mol) in THF (10 mL) was added dropwise to the reaction mixture at −78 °C. After the solution was stirred for 2 h at −78 °C, the reaction mixture was warmed to −40 °C and stirred for a further 1 h. The reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (2−10% EtOAc/hexanes) to yield compound **6** (9.6 g, 73%) as a clear oil. $[\alpha]^{22}_D$ −41.7° (*c* 2.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3440, 3074, 1639, 1276, 995 cm^{-1}. ^1H NMR: δ 5.85−5.75 (m, 1H), 5.04−4.92 (m, 2H), 3.94−3.89 (m, 1H), 3.41 (s, 1H), 3.02−2.93 (m, 2H), 2.78−2.73 (m, 2H), 2.36 (dd, J = 9.2, 14.8 Hz, 1H), 2.22−1.99 (m, 3H), 1.90−1.80 (m, 2H), 1.64−1.55 (m, 5H), 1.50−1.41 (m, 1H) ppm. ^{13}C NMR: δ 138.6, 115.0, 68.42, 47.9, 47.7, 37.1, 30.0, 28.7, 27.0, 26.8, 24.8 ppm. HR-MS (CI) calcd for $C_{11}H_{20}OS_2$ $[M + H]^+$, 233.0956; found, 233.1018.

TBDPS Dithiane (7).



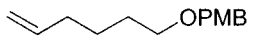
To a solution of alcohol **6** (17. 0 g, 0.0787 mol) in DMF (17.0 mL) were added imidazole (13.4 g, 0.197 mol) and TBDPSCl (24.96 g, 0.094 mol). After being stirred for 16 h at 25 °C, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (0−5% EtOAc/hexanes) to yield **7** (32.2 g, 90%) as a clear oil. $[\alpha]^{22}_D$ −4.0° (*c* 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3074, 3048, 1639, 1276, 997 cm^{-1}. ^1H NMR: δ 7.73−7.69 (m, 4H), 7.42−7.34 (m, 6H), 5.59−5.49 (m, 1H), 4.86−4.80 (m, 2H), 4.13−4.03 (m, 1H), 2.70−2.48 (m, 4H), 2.32−2.17 (m, 2H), 2.09−1.97 (m, 2H), 1.87−1.77 (m, 2H), 1.75−1.53 (m, 4H), 1.02 (bs, 9H) ppm. ^{13}C NMR: δ 138.7, 136.3, 136.2, 134.8, 134.5, 129.8, 129.7, 127.8 114.5, 71.2, 47.8, 37.3, 29.2, 28.8, 27.3, 26.8, 25.2, 19.6 ppm. HR-MS (CI) calcd for $C_{27}H_{38}OS_2Si$ $[M + H]^+$, 471.2133; found, 471.2208.

Methyl Ketone (3).



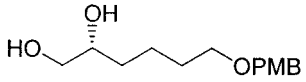
To a stirred solution of compound **7** (20 g, 0.044 mol) in CH_3CN/H_2O (9:1) (150 mL) was added DDQ (15.0 g, 0.066 mol, 1.5 equiv) dissolved in CH_3CN/H_2O (9:1) (150 mL) dropwise. After the mixture was stirred for 3 h, saturated $NaHCO_3$ was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The product was purified by silica gel chromatography (0−5% EtOAc/hexanes) to yield compound **3** (13.6 g, 81%) as a clear oil. $[\alpha]^{22}_D$ +17.0° (*c* 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3071, 1715, 1640, 998 cm^{-1}. ^1H NMR: δ 7.69−7.66 (m, 4H), 7.44−7.36 (m, 6H), 5.64−5.54 (m, 1H), 4.90−4.83 (m, 2H), 4.26−4.20 (m, 1H), 2.53 (ABq, J = 6.0, 15.6 Hz, 2H), 2.04−2.00 (m, 2H), 1.97 (s, 3H), 1.56−1.51 (m, 2H), 1.04 (bs, 9H) ppm. ^{13}C NMR: δ 207.3, 138.3, 136.1, 134.3, 134.2, 129.9, 127.8, 114.8, 69.8, 50.9, 36.5, 31.1, 29.4, 27.2, 19.6 ppm. HR-MS (CI) calcd for $C_{24}H_{32}O_2Si$ $[M^+]$, 380.2172; found, 380.2197.

1-[(4-Methoxyphenyl)methoxy]hex-5-ene (8).



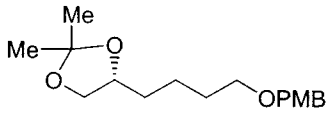
5-Hexenol (10.0 g, 0.1 mol, 1.0 equiv) was added at 0 °C to a flask containing NaH [5.28 g, 0.11 mol, 1.1 equiv (60% in mineral oil, prewashed with 3 × 40 mL hexane)] and DMF (40 mL). The mixture was brought to room temperature, stirred for 1 h, and recooled to 0 °C. 4-Methoxybenzyl chloride (13.56 mL, 2.85 mmol, 1.0 equiv) was then added dropwise. After the mixture was stirred at room temperature for 12 h, the reaction was quenched with saturated NH_4Cl, diluted with water, and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (2−5% EtOAc/hexanes) to yield compound **8** (21.8 g, 99%) as a clear oil. IR (neat): $\tilde{\nu}_{max}$ = 3075, 3048, 1036, 994 cm^{-1}. ^1H NMR: δ 7.25 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 5.85−5.71 (m, 1H), 5.02−4.93 (m, 2H), 4.42 (s, 2H), 3.76 (s, 3H), 3.44 (t, J = 6.8 Hz, 2H), 2.09−2.03 (m, 2H), 1.65−1.58 (m, 2H), 1.50−1.43 (m, 2H) ppm. ^{13}C NMR: δ 159.2, 138.8, 130.9, 129.2, 128.4, 114.5, 113.8, 113.6, 72.5, 70.0, 55.2, 33.6, 29.3, 25.6 ppm. HR-MS (CI) calcd for $C_{14}H_{20}O_2$ $[M^+]$, 220.1463; found, 220.1471.

Diol (9).



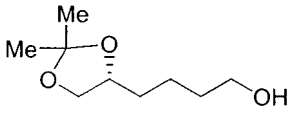
To a stirred and cooled (0 °C) solution of AD-mix-β (50.0 g,) in *t*-BuOH/H_2O (1:1) (360 mL) was added compound **8** (12.0 g, 0.0545 mol), and the reaction mixture was stirred at 0 °C for 24 h. The reaction mixture was brought to room temperature and filtered, and the residue was washed with *t*-BuOH. The combined organic layers were concentrated in vacuo. After extraction of concentrated residue with EtOAc, the organic layer was dried over $MgSO_4$, and filtered and concentrated in vacuo. The product was purified by silica gel chromatography (60−100% EtOAc/hexanes) to afford compound **9** (14.0 g, 90%) as a white solid. $[\alpha]^{22}_D$ −1.8° (*c* 1.0, $CHCl_3$); 80% ee [chiral HPLC 20% 2-propanol/hexane, Rt = 17.79 min (major), 19.29 min (minor)]. IR (neat): $\tilde{\nu}_{max}$ = 327, 3074, 1652, 1170 cm^{-1}. ^1H NMR: δ 7.25 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.42 (s, 2H), 3.79 (s, 3H), 3.68−3.52 (m, 2H), 3.46−3.36 (m, 5H), 1.68−1.33 (m, 6H) ppm. ^{13}C NMR: δ 159.3, 130.7, 129.4, 113.9, 72.7, 72.2, 70.1, 66.8, 55.4, 33.0, 29.7, 22.4 ppm. HR-MS (CI) calcd for $C_{14}H_{22}O_4$ $[M^+]$, 254.1518; found, 254.1496.

Acetonide (10).



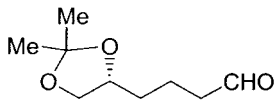
To a stirred solution of compound **9** (14.0 g, 0.055 mol) in acetone (30 mL) was added *p*-toluenesulfonic acid monohydrate (100 mg, 0.525 mmol). After the mixture was stirred for 2 h at 25 °C, the solvent was concentrated in vacuo. The product was directly purified by silica gel chromatography (20% EtOAc/hexanes) to yield compound **10** (14.9 g, 92%) as a clear oil. $[\alpha]^{22}_D$ −8.3° (*c* 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3075, 1715, 1612, 1171 cm^{-1}. ^1H NMR: δ 7.26−7.23 (m, 2H), 6.88−6.85 (m, 2H), 4.42 (s, 2H), 4.09−4.00 (m, 2H), 3.78 (s, 3H), 3.50−3.42 (m, 2H), 1.67−1.60 (m, 4H), 1.51−1.45 (m, 2H), 1.40 (s, 3H), 1.38−1.37 (m, 1H), 1.35 (S, 3H) ppm. ^{13}C NMR: δ 159.2, 130.8, 129.2, 113.8, 108.6, 76.1, 72.6, 69.9, 69.5, 55.2, 33.5, 29.8, 27.0, 25.8, 22.6 ppm. HR-MS (CI) calcd for $C_{17}H_{26}O_4$ $[M + H]^+$, 295.1831; found, 295.1873.

Acetonide Alcohol (53).



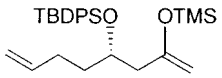
To a stirred and cooled (0 °C) solution of compound **10** (13.4 g, 0.046 mol) in CH_2Cl_2/H_2O (18:1) (304 mL), DDQ (11.4 g, 0.050 mol, 1.1 equiv) was added. After stirring for 4 h at 0 °C, the reaction was quenched with saturated $NaHCO_3$, diluted with water, and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The product was purified by silica gel chromatography (30−80% EtOAc/hexanes) to afford compound **53** (6.8 g, 90%) as a clear oil. $[\alpha]^{22}_D$ −12.3° (*c* 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3411 cm^{-1}. ^1H NMR: δ 4.05−3.95 (m, 2H), 3.56 (t, *J* = 6.4 Hz, 2H), 3.44 (t, *J* = 7.2 Hz, 1H), 2.16 (bs, 1H), 1.65−1.38 (m, 5H), 1.36 (s, 3H), 1.32−1.31 (m, 1H), 1.35 (S, 3H) ppm. ^{13}C NMR: δ 108.9, 76.8, 76.2, 69.6, 62.6, 33.4, 32.8, 27.1, 25.9, 22.2 ppm. HR-MS (CI) calcd for $C_9H_{18}O_3$ $[M^+]$, 174.1256; found, 174.1237.

Acetonide Aldehyde (4).



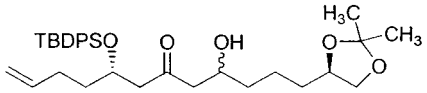
To a solution of oxalyl chloride (2.65 g, 0.021 mol, 1.4 equiv) in CH_2Cl_2 (30 mL) was added dropwise DMSO (3.73 g, 0.048 mol, 3.2 equiv) in CH_2Cl_2 (10 mL) at −70 °C. After the mixture was stirred for 10 min, a solution of alcohol **53** (2.6 g, 0.015 mol) in CH_2Cl_2 (10 mL) was added. After the mixture was stirred for 30 min, Et_3N (7.5 g, 0.075 mol, 5.0 equiv) was added. After 10 min, the cooling bath was removed and reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The product was purified by silica gel chromatography (30% EtOAc/hexanes) to afford aldehyde **4** (2.47 g, 96%) as a clear oil. IR (neat): $\tilde{\nu}_{max}$ = 2723, 1724 cm^{-1}. ^1H NMR: δ 9.54 (d, *J* = 4.8 Hz, 1H), 3.88−3.79 (m, 2H), 3.31−3.26 (m, 1H), 2.31−2.26 (m, 2H), 1.56−1.32 (m, 4H), 1.32−1.10 (m, 6H) ppm. ^{13}C NMR: δ 201.6, 108.6, 75.5, 69.1, 43.4, 32.8, 26.8, 25.5, 18.3 ppm.

Silyl Enol Ether (11).



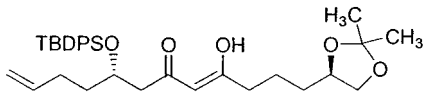
To a stirred and cooled (−78 °C) solution of methyl ketone **3** (2.8 g, of 7.34 mmol) in THF (25 mL) was added KHMDS (0.66 M solution in toluene (15.7 mL, 10.315 mmol) dropwise over 15 min. After the mixture was stirred for 1.5 h at −78 °C, TMSCl (1.04 g, 9.5789 mmol) was added and stirring was continued for an additional 2 h at −78 °C. The reaction was quenched with saturated $NaHCO_3$ and extracted with ethyl acetate, and the organic layer was washed with brine, dried over Na_2SO_4, and filtered and concentrated in vacuo. The product was passed through a small pad of silica gel pretreated with 2% Et_3N + 2% ethyl acetate/hexanes to yield silyl enol ether **11** (2.2 g, 93%) as a clear oil, which was used without further purification.

Aldol Product (12).



To a stirred and cooled (−78 °C) solution of silyl enol ether **11** (2.2 g, 4.87 mmol) in CH_2Cl_2 (2.5 mL) aldehyde **4** (0.837 g, 4.87 mmol) in CH_2Cl_2 (2.5 mL) was added and stirred for 5 min. $BF_3{\cdot}OEt_2$ (0.829 g, 5.84 mmol, 1.2 equiv) was added dropwise, and stirring continued at −78 °C for an additional 1.5 h. The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2, the organic layer was washed with water and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The product was purified by silica gel chromatography (10−35% EtOAc/hexanes) to yield aldol product **12** (1.7 g, 65%) as a clear oil. $[\alpha]^{22}_D$ +7.0° (*c* 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3467, 3071, 1708, 1640, 998 cm^{-1}. ^1H NMR: δ 7.67−7.63 (m, 4H), 7.43−7.35 (m, 6H), 5.62−5.52 (m, 1H), 4.88−4.83 (m, 2H), 4.26−4.17 (m, 1H), 4.10−3.99 (m, 2H), 3.95−3.80 (m, 1H), 3.50−3.46 (m, 1H), 2.93−2.91 (m, 1H), 2.59−2.34 (m, 4H), 2.15−1.95 (m, 2H), 1.62−1.47 (m, 6H), 1.43−1.39 (m, 4H), 1.33−1.27 (m, 4H), 1.01 (bs, 9H) ppm. ^{13}C NMR: δ 210.5, 138.2, 136.1, 134.1, 130.0, 127.8, 114.9, 108.9, 76.8, 76.2, 76.1, 69.7, 69.6, 69.5, 67.4, 67.2, 50.7, 50.4, 50.1, 36.6, 36.5, 36.3, 33.7, 33.6, 29.4, 27.2, 26.0, 22.1, 21.8, 19.6 ppm. HR-MS (CI) calcd for $C_{33}H_{48}O_5Si$ $[M + H]^+$, 553.3271; found, 553.3415.

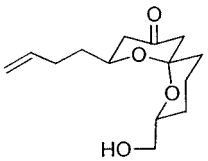
***β*-Diketone (13).**



To a slurry of Celite (30 g) in CH_2Cl_2 (150 mL) was added pyridine (8.8 mL, 108.9 mmol, 21 equiv) followed by CrO_3

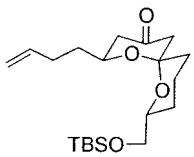
(4.2 g, 41.5 mmol, 10 equiv, dried in vacuo prior to use for 12 h). The resulting heterogeneous mixture was stirred for 2 h at room temperature. Aldol product **12** (2.8 g, 5.2 mmol) in CH_2Cl_2 (50 mL) was added slowly, and the reaction mixture was stirred vigorously for an additional 1.5 h. The dark-red reaction mixture was poured into saturated aqueous NH_4Cl and filtered, the residue was washed with ethyl acetate, and the filtrate was extracted with ethyl acetate. The combined reddish organic layer was passed through a small pad of Florisil, and the crude product was further eluted with EtOAc (200 mL). The resulting colorless filtrate was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by silica gel chromatography (15−30% EtOAc/hexanes) to yield β-diketone **13** (1.78 g, 64%) as a clear oil. $[\alpha]^{22}_D$ +8.9° (*c* 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3071, 1652, 1616, 997 cm^{-1}. ^1H NMR: δ 7.71−7.63 (m, 4H), 7.44−7.34 (m, 6H), 5.63−5.53 (m, 1H), 5.31 (s, 1H), 4.88−4.82 (m, 2H), 4.17−4.00 (m, 3H), 3.48 (t, J = 7.2 Hz, 1H), 2.43−2.33 (m, 2H), 2.24 (t, J = 7.2 Hz,1H), 2.03−1.97 (m, 2H), 1.71−1.47 (m, 6H), 1.39 (s, 3H), 1.34 (s, 3H), 1.02 (bs, 9H) ppm. ^{13}C NMR: δ 194.5, 191.0, 138.3, 136.1, 135.0, 134.3, 134.1, 129.9, 127.8, 114.9, 114.8, 109.0, 100.9, 75.9, 70.8, 69.6, 57.7, 50.7, 45.8, 43.6, 38.4, 36.4, 33.3, 29.25, 27.2, 26.8, 25.9, 22.0, 19.6 ppm. HR-MS (CI) calcd for $C_{33}H_{46}O_5Si$ $[M + H]^+$, 551.3115; found, 551.3189.

Spiroketal (2).



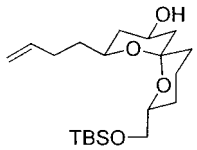
To a mixture of 48% aqueous HF/CH_3CN/CH_2Cl_2 (6:9:50) (72 mL) was added β-diketone **13** (2.4 g, 4.45 mmol), and the reaction was stirred at room temperature for 24 h. The mixture was poured carefully into an ice-cold saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The product was purified by silica gel chromatography (10−35% EtOAc/hexanes) to yield spiroketal **2** (0.9 g, 80%) as a clear oil. IR (neat): $\tilde{\nu}_{max}$ = 3445, 3076, 1717, 981 cm^{-1}. ^1H NMR: δ 5.85−5.75 (m, 1H), 5.03−4.94 (m, 2H), 3.92−3.85 (m, 1H), 3.66−3.61 (m, 1H), 3.51−3.39 (m, 2H), 2.41−2.24 (m, 4H), 2.21−2.08 (m, 3H), 2.00−1.54 (m, 5H), 1.49−1.39 (m, 2H), 1.31−1.21 (m, 1H) ppm. ^{13}C NMR: δ 206.1, 138.1, 115.2, 99.5, 71.2, 68.6, 66.0, 52.0, 47.2, 35.6, 34.9, 30.0, 25.9, 18.6 ppm. HR-MS (CI) calcd for $C_{14}H_{22}O_4$ $[M + H]^+$: 255.1518; found, 255.1587.

Spiroketal TBS Ether (17).



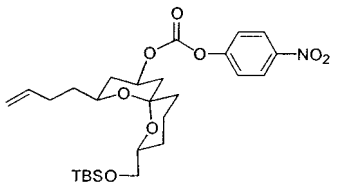
To a stirred solution of spiroketal **2** (2.1 g, 8.77 mmol) in DMF (4.0 mL) were added consecutively imidazole (1.6 g, 23.2 mmol) and TBSCl (1.6 g, 10.8 mmol). After being stirred for 24 h, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The product was purified by silica gel chromatography (5−20% EtOAc/hexanes) to yield spiroketal **17** (2.7 g, 90%) as a light-yellow oil. IR (neat): $\tilde{\nu}_{max}$ = 3077, 1726, 1641, 983 cm^{-1}. ^1H NMR: δ 5.88−5.78 (m, 1H), 5.05−4.95 (m, 2H), 3.97−3.91 (m, 1H), 3.62−3.56 (m, 1H), 3.50 (dd, J = 6.4, 10.4 Hz, 1H), 3.42 (dd, J = 4.8, 10.8 Hz, 1H), 2.40−2.24 (m, 4H), 2.18−2.10 (m, 2H), 1.95−1.57 (m, 6H), 1.42 (ddd, J = 4.0, 4.4, 13.2 Hz, 1H), 1.20−1.11 (m, 1H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm. ^{13}C NMR: δ 205.9, 138.2, 115.2, 99.3, 71.6, 68.1, 66.6, 52.1, 47.2, 35.7, 34.9, 30.1, 26.6, 26.1, 18.9, 18.5, −5.1, −5.2 ppm. HR-MS (CI) calcd for $C_{20}H_{36}O_4Si$ $[M + H]^+$, 369.2383; found, 369.2439.

Spiroketal Alcohol (18).



To a stirred and cooled (0 °C) solution of spiroketal **17** (1.9 g, 5.1630 mmol) in MeOH (10 mL) was added $CeCl_3 \cdot 7H_2O$ (2.3 g, 6.2 mmol, 1.2 equiv), and the reaction mixture was stirred for 10 min. To the resulting clear solution was added $NaBH_4$ (235 mg, 6.2 mmol, 1.2 equiv). After being stirred for 20 min, the reaction mixture was diluted with water and extracted with EtOAc, and the organic layer washed with water and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The product was purified by silica gel chromatography (10−30% EtOAc/hexanes) to afford alcohol **18** (1.34 g, 70%) as a clear oil. IR (neat): $\tilde{\nu}_{max}$ = 3354, 3077, 1652, 977 cm^{-1}. ^1H NMR: δ 5.88−5.78 (m, 1H), 5.03−4.92 (m, 2H), 4.16−4.08 (m, 1H), 3.67−3.50 (m, 3H), 3.46−3.42 (m, 1H), 2.31−2.22 (m, 1H), 2.14−2.05 (m, 1H), 2.01−1.96 (m, 1H), 1.92−1.81 (m, 2H), 1.68−1.37 (m, 7H), 1.26−1.07 (m, 3H), 0.86 (s, 9H), 0.02 (s, 6H) ppm. ^{13}C NMR: δ 138.9, 114.7, 97.7, 70.7, 67.5, 66.9, 65.0, 45.2, 41.2, 35.6, 35.5, 30.4, 27.3, 26.1, 18.9, 18.5, −5.0, −5.1 ppm. HR-MS (CI) calcd for $C_{20}H_{38}O_4Si$ $[M^+]$, 370.2539; found, 370.2494.

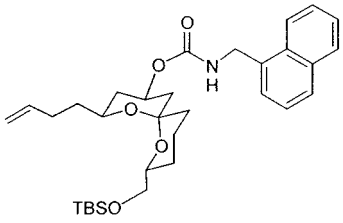
Spiroketal Nitrophenyl Carbamate (19).



4-Nitrophenyl chloroformate (1.06 g, 5.270 mmol, 1.5 equiv) was added to a stirred solution of alcohol **18** (1.3 g, 3.51 mmol) in THF (10 mL) and pyridine (0.89 g, 11.24 mmol, 3.2 equiv). After the mixture was stirred for 20 min, water was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with 5% HCl, water, saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The product was purified

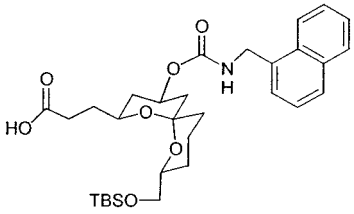
by silica gel chromatography (10% EtOAc/hexanes) to yield **19** (1.78 g, 100%) as a clear oil. ^{1}H NMR: δ 8.25 (d, J = 9.2 Hz, 2H), 7.35 (d, J = 9.2 Hz, 2H), 5.87−5.79 (m, 1H), 5.23−5.17 (m, 1H), 5.05−4.94 (m, 2H), 3.80−3.68 (m, 1H), 3.63−3.51 (m, 2H), 3.50−3.44 (m, 1H), 2.30−2.23 (m, 1H), 2.18−2.09 (m, 2H), 1.94−1.82 (m, 1H), 1.70−1.30 (m, 10H), 0.87 (s, 9H), 0.04 (s, 6H) ppm.

Representative Procedure for Carbamate Preparation: Spiroketal Carbamate (20).



To a stirred solution of **19** (480 mg, 0.943 mmol) in DMF (2.0 mL) was added 1-naphthalenemethylamine (222 mg, 1.42 mmol, 1.5 equiv). After being stirred for 4 h, the reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with 5% HCl, water, saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The product was purified by silica gel chromatography (10−15% EtOAc/hexanes) to yield carbamate **20** (515 mg, 98%) as a clear oil. IR (neat): $\tilde{\nu}_{max}$ = 3336, 3077, 1716, 1652, 978 cm^{-1}. ^{1}H NMR: δ 8.02 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.80−7.77 (m, 1H), 7.55−7.48 (m, 2H), 7.41−7.38 (m, 2H), 5.88−5.78 (m, 1H), 5.18−5.12 (m, 1H), 5.04−4.93 (m, 2H), 4.85−4.75 (m, 3H), 3.72−3.68 (m, 1H), 3.61−3.56 (m, 2H), 3.47−3.42 (m, 1H), 2.29−2.22 (m, 1H), 2.15−2.00 (m, 3H), 1.95−1.79 (m, 1H), 1.65−1.11 (m, 9H), 0.89 (s, 9H), 0.07(s, 6H) ppm. ^{13}C NMR: δ 155.9, 38.8, 134.1, 131.6, 129.0, 128.7, 126.4, 126.1, 125.6, 123.6, 114.8, 97.7, 70.7, 68.8, 67.2, 66.9, 43.4, 41.6, 37.9, 35.5, 35.4, 30.3, 27.5, 26.2, 18.8, −5.0, −5.1 ppm.

Representative Procedure for Carboxylic Acid Formation: Spiroketal Carbamate Acid (21).

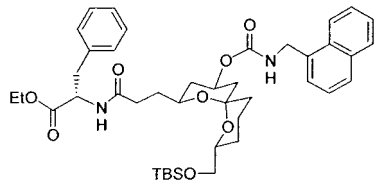


To a stirred solution of carbamate **20** (515 mg, 0.93 mmol) in *t*-BuOH/H_2O (2:1) (3.0 mL) was added 4-methylmorpholine *N*-oxide (120 mg, 1.02 mmol, 1.1 equiv) followed by OsO_4 (4 wt % solution in water, 50 μL). After the mixture was stirred for 12 h, the solvent was evaporated in vacuo, brine was added, and the reaction mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and filtered and concentrated in vacuo to yield the diol intermediate (546 mg, 100%) as a light-brown oil, which was used without further purification.

To a stirred solution of the above diol (540 mg, 0.9199 mmol) in THF (10 mL) was added at room temperature $Pb(OAc)_4$ (530 mg, 1.1959 mmol, 1.3 equiv). After the mixture was stirred for 30 min, water was added and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo to yield the spiroketal aldehyde (509 mg, 100%) as a light-yellow oil that was used without further purification.

To a solution of the above aldehyde (500 mg, 0.9 mmol) in *tert*-butyl alcohol (3.0 mL) was added 2-methyl-2-butene (1.5 mL). A solution of sodium chlorite (162 mg, 1.8 mmol, 2.0 equiv, 80% $NaClO_2$) and sodium dihydrogen phosphate (216 mg, 1.8 mmol, 2.0 equiv) in H_2O (1.5 mL) was added slowly to the solution, and the resulting solution was stirred for 5 h at room temperature. The solvent was concentrated in vacuo, water (10 mL) was added, and the reaction acidified to pH 4.0 with 5% HCl. The reaction was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and filtered and concentrated in vacuo to yield **21** (500 mg, 97%) as a white solid. IR (neat): $\tilde{\nu}_{max}$ = 3338, 3077, 1711, 1649, 997 cm^{-1}. ^{1}H NMR: δ 8.00 (d, J = 7.2. Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.79−7.77 (m, 1H), 7.54−7.47 (m, 2H), 7.40−7.39 (m, 2H), 5.22−5.09 (m, 1H), 4.88−4.70 (m, 3H), 3.79−3.62 (m, 1H), 3.50−3.44 (m, 3H), 2.62−2.54 (m, 1H), 2.45−2.37 (m, 1H), 2.07−1.97 (m, 2H), 1.88−1.72 (m, 3H), 1.68−1.50 (m, 3H), 1.44−1.15 (m, 5H), 0.89 (s, 9H), 0.0(s, 6H) ppm. ^{13}C NMR: δ 179.4, 156.7, 134.9, 134.8, 132.4, 129.8, 129.5, 127.5, 127.2, 127.0, 126.4, 124.4, 98.7, 71.6, 69.3, 67.8, 67.7, 44.1, 42.3, 38.4, 36.0, 31.7, 28.0, 27.0, 19.5, 19.4, −4.1, −4.2 ppm. HR-MS (CI) calcd for $C_{31}H_{45}NO_7Si$ $[M + H]^+$, 572.2965; found, 572.3049.

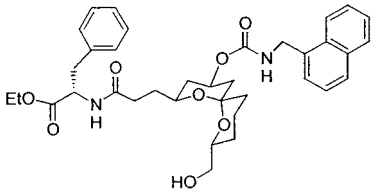
Representative Procedure for Amide Formation: Spiroketal Amide (22).



To a 10 mL Quest 210 Teflon reaction vessel was added a solution of acid **21** (100 mg, 0.175 mmol) in CH_2Cl_2 (2.0 mL). To the above acid were added consecutively L-phenylalanine ethyl ester hydrochloride (56.0 mg, 0.25 mmol), 1-hydroxybenzotriazole (HOBt) (33.0 mg, 0.25 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (47 mg, 0.25 mmol), and diisopropylethylamine (DIEA) (91 mg, 0.77 mmol). After the mixture was agitated for 12 h, water was added and the reaction mixture was extracted with EtOAc. The organic layer was washed consecutively with 5% HCl, water, and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo to afford amide **22** (129 mg, 99%) as a white solid that was used without further purification. IR (neat): $\tilde{\nu}_{max}$ = 3326, 3076, 1733, 1711, 1635 cm^{-1}. ^{1}H NMR: δ 7.84 (d, J = 8.0. Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.62−7.60 (m, 1H), 7.39−7.30 (m, 2H), 7.24−7.21 (m, 2H), 7.12−7.03 (m, 3H), 6.93−6.91 (m, 2H), 5.82 (d, J = 8.0 Hz, 1H), 5.01−4.95 (m, 1H), 4.76−4.58 (m, 4H), 3.96 (q, J = 7.2, 14.0 Hz, 2H), 3.54−3.44 (m, 1H), 3.44−3.40 (m, 1H), 3.35−3.26 (m, 2H), 2.98−

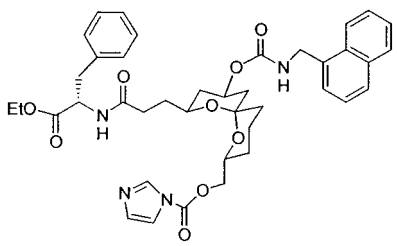
2.89 (m, 2H), 2.33−2.25 (m, 1H), 2.07−1.99 (m, 1H), 1.90−1.80 (m, 2H), 1.64−1.56 (m, 3H), 1.46−1.33 (m, 3H), 1.26−0.95 (m, 7H), 0.73 (s, 9H), −0.09 (s, 3H), −0.1 (s, 3H) ppm. ^{13}C NMR: δ 172.4, 171.9, 155.8, 136.2, 134.1, 131.5, 129.5, 129.0, 128.7, 127.2, 126.7, 126.4, 126.1, 125.6, 123.6, 97.7, 70.8, 68.5, 67.1, 66.9, 61.6, 53.3, 43.3, 41.5, 38.2, 37.6, 35.2, 33.0, 31.6, 27.3, 26.1, 18.7, 18.6, 14.3, −5.0, −5.1 ppm. HR-MS (CI) calcd for $C_{42}H_{58}N_2O_8Si$ $[M + H]^+$, 747.3962; found, 747.4073.

Representative Procedure for TBS Group Deprotection: Spiroketal Alcohol (23).



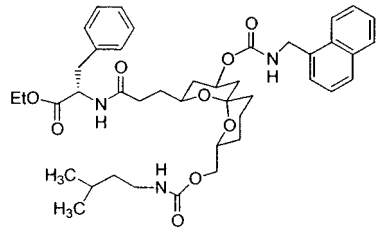
To a 10 mL Quest 210 Teflon reaction vessel was added amide **22** (129 mg, 0.173 mmol) dissolved in THF (0.5 mL) followed by 1.0 M solution of HF/pyridine (3.5 mL, 20 equiv) in THF. After the mixture was agitated for 4 h, $MeOSiMe_3$ (962 μL, 7.0 mmol, 2.0 equiv) was added to neutralize HF and the reaction mixture was agitated for a further 2 h. The reaction mixture was directly passed through a Waters MCX cartridge attached to the Quest 210 lower Luer manifold into a collection vial. The cartridge was washed further with THF, and the combined filtrate was concentrated in vacuo to afford alcohol **23** (109 mg, 100%) as a white solid, which was used without further purification. IR (neat): $\tilde{\nu}_{max}$ = 3400, 3330, 3061, 1710, 1659 cm^{-1}. ^{1}H NMR: δ 7.98 (d, J = 8.0. Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.78−7.76 (m, 1H), 7.54−7.46 (m, 2H), 7.42−7.37 (m, 2H), 7.28−7.19 (m, 3H), 7.08−7.07 (m, 2H), 6.0 (d, J = 7.6 Hz, 1H), 5.19−5.07 (m, 1H), 4.99−4.87 (m, 1H), 4.85−4.66 (m, 3H), 4.12 (q, J = 7.2, 14.0 Hz, 2H), 3.70−3.40 (m, 4H), 3.12−3.04 (m, 2H), 2.45−2.37 (m, 1H), 2.27−2.19 (m, 1H), 2.06−1.99 (m, 3H), 1.99−1.72 (m, 4H), 1.64−1.50 (m, 2H), 1.49−1.24 (m, 4H), 1.21 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR: δ 172.4, 172.0, 155.9, 136.2, 134.1, 133.9, 131.5, 129.5, 129.0, 128.7, 127.3, 126.8, 126.5, 126.1, 125.6, 123.5, 97.9, 70.7, 68.4, 67.2, 66.3, 61.7, 53.4, 43.3, 41.5, 38.2, 37.6, 35.2, 32.9, 31.6, 26.4, 18.5, 14.4, 14.3 ppm. HR-MS (CI) calcd for $C_{36}H_{44}N_2O_8$ $[M^+]$, 632.3098; found, 632.3040.

Representative Procedure for Imidazolide Formation: Spiroketal Imidazolide (24).



To a 10 mL (13 mm × 150 mm) reactor on the FirstMate synthesizer, a solution of alcohol **23** (109 mg, 0.17 mmol) in CH_2Cl_2 (2.0 mL) and 1,1′-carbonyldiimidazole (CDI) (31 mg, 0.19 mmol, 1.1 equiv) were added. After being stirred for 4 h, the reaction mixture was eluted through a 12 mL ChemElut Plus cartridge pretreated with 3.0 mL of 1 M NaH_2PO_4. The cartridge was washed with 1.0 mL of CH_2Cl_2, and the combined organic layers were concentrated in vacuo to afford imidazolide **24** (125 mg, 100%) as a white solid. IR (neat): $\tilde{\nu}_{max}$ = 3317, 3061, 1765, 1719 1665 cm^{-1}. ^{1}H NMR: δ 8.15 (bs, 1H), 7.98 (d, J = 8.0. Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.80−7.77 (m, 1H), 7.57−7.47 (m, 2H), 7.44−7.38 (m, 3H), 7.28−7.21 (m, 3H), 7.10−7.02 (m, 3H), 5.96 (d, J = 7.6 Hz, 1H), 5.16−5.02 (m, 1H), 4.92−4.86 (m, 1H), 4.85−4.70 (m, 3H), 4.35−4.26 (m, 2H), 4.12 (q, J = 7.2, 14.0 Hz, 2H), 3.90−3.80 (m, 1H), 3.68−3.60 (m, 1H), 3.15−3.04 (m, 2H), 2.38−2.32 (m, 1H), 2.25−2.17 (m, 1H), 2.06−1.99 (m, 2H), 1.99−1.74 (m, 3H), 1.66−1.54 (m, 3H), 1.47−1.40 (m, 1H), 1.36−1.16 (m, 6H) ppm. ^{13}C NMR: δ 172.1, 171.9, 155.8, 148.9, 136.2, 134.1, 133.9, 131.5, 131.0, 129.5, 129.0, 128.7, 127.3, 126.8, 126.5, 126.2, 125.6, 123.5, 98.1, 70.6, 68.2, 67.6, 67.5, 61.7, 53.3, 43.3, 41.3, 38.2, 37.5, 34.9, 32.7, 31.5, 29.9, 26.8, 18.4, 14.3 ppm. HR-MS (CI) calcd for $C_{40}H_{46}N_4O_9$ $[M^+]$, 726.3265; found, 726.3227.

Representative Procedure for Imidazolide Formation: Trifunctional Spiroketal (25).

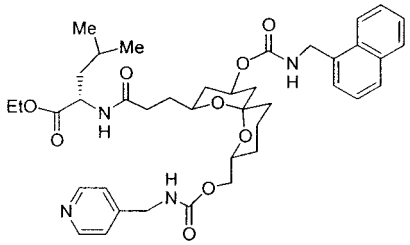


To a 10 mL 13 mm × 150 mm reactor on the FirstMate synthesizer, a solution of imidazolide **24** (10.0 mg, 0.014 mmol) in toluene (0.5 mL) was added followed by isoamylamine (11.0 mg, 0.124 mmol, 9.0 equiv), and the reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was brought to room temperature and eluted through a 12 mL ChemElut Plus cartridge pretreated with 3.0 mL of 10% HCl. The cartridge was further washed with toluene (2.5 mL), and the combined organic layers were concentrated to afford compound **25** (10.1 mg, 98%) as a waxy solid. ^{1}H NMR: δ 7.98 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.80−7.78 (m, 1H), 7.59−7.47 (m, 2H), 7.44−7.38 (m, 2H), 7.29−7.20 (m, 3H), 7.14−7.06 (m, 2H), 5.96 (d, J = 6.4 Hz, 1H), 5.20−5.05 (m, 1H), 4.90−4.70 (m, 4H), 4.12 (q, J = 7.2, 14.0 Hz, 2H), 4.02−3.89 (m, 2H), 3.71−3.59 (m, 2H), 3.25−3.05 (m, 4H), 2.48−2.36 (m, 1H), 2.32−2.22 (m, 1H), 2.12−1.94 (m, 2H), 1.84−1.72 (m, 3H), 1.68−1.11 (m, 14H), 0.96 (d, J = 6.4 Hz, 6H) ppm. ^{13}C NMR: δ 172.4, 172.0, 156.8, 155.8, 136.2, 134.1, 134.0, 131.5, 129.5, 129.0, 128.7, 127.3, 126.8, 126.5, 126.2, 125.6, 123.6, 97.9, 68.6, 68.5, 67.7, 67.2, 61.7, 53.4, 43.4, 41.4, 39.6, 39.1, 38.3, 37.7, 35.0, 32.7, 31.4, 29.9, 26.9, 25.9, 22.7, 18.7, 14.3 ppm. HR-MS (CI) calcd for $C_{42}H_{55}N_3O_9$ $[M + H]^+$, 746.3938; found, 746.4019.

Procedure for Amide Formation Using PS-HOBt Resin: Spiroketal Amide (43). To a 10 mL Quest 210 reaction vessel was added PS-HOBt resin (1.12 mmol/g, 110

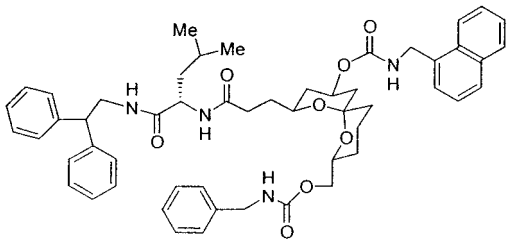
mg, 0.123 mmol) and a mixture of DMF/CH_2Cl_2 (1:3) (1.2 mL). To the above resin were added consecutively acid **21** (70 mg, 0.123 mmol 1.0 equiv), DMAP (1.5 mg, 10 mol %), and 1,3-diisopropylcarbodiimide (DIC) (16.0 mg, 0.123 mmol 1.0 equiv). After the mixture was agitated for 7 h, the resin was filtered, washed with DMF, THF, DMF, CH_2Cl_2 (3 × 5 mL each), and dried under high vacuum for 2 h to yield PS-HOBt ester resin **42**. To a 10 mL Quest 210 reaction vessel was added dried PS-HOBt ester resin **42** (110 mg, 0.123 mmol) and CH_2Cl_2 (1.0 mL). To the above resin were added consecutively L-leucine ethyl ester hydrochloride (36.0 mg, 0.185 mmol, 1.5 equiv) and diisopropylethylamine (DIEA) (48 mg, 0.77 mmol). After the mixture was agitated for 6 h, the solvent was removed and the resin was washed with CH_2Cl_2 (2 × 2 mL). The combined organic solvents were directly eluted through a 12 mL ChemElut Plus cartridge pretreated with 3.0 mL of 10% HCl. The cartridge was washed with a further 1.0 mL of CH_2Cl_2, and the combined organic layers were concentrated in vacuo to afford amide **43** (68.2 mg, 78%) as a waxy solid. ^{1}H NMR: δ 8.0 (d, J = 8.0. Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.99−7.78 (m, 1H), 7.53−7.48 (m, 2H), 7.42−7.40 (m, 1H), 5.92 (d, J = 8.8 Hz, 1H), 5.21−5.09 (m, 1H), 4.89−4.68 (m, 3H), 4.64−4.49 (m, 1H), 4.14 (q, J = 6.8, 14.0 Hz, 2H), 3.73−3.65 (m, 1H), 3.62−3.56 (m, 1H), 3.54−3.42 (m, 2H), 2.54−2.45 (m, 1H), 2.28−2.19 (m, 1H), 2.10−1.90 (m, 2H), 1.89−1.74 (m, 2H), 1.50−1.40 (m, 8H), 1.39−1.10 (m, 7H), 0.98−0.90 (m, 6H), 0.089 (s, 9H), 0.07 (s, 6H) ppm.

Trifunctional Spiroketal (45).



To a 10 mL (13 mm × 150 mm) reactor on the FirstMate synthesizer containing a solution of imidazolide **44** (10.0 mg, 0.014 mmol) in toluene (0.5 mL) was added 4-(aminomethyl)pyridine (14.0 mg, 0.043 mmol, 9.0 equiv), and the reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was brought to room temperature, PS-isocyanate resin (1.25 mmol/g, 0.220 g, 0.275 mmol, 2.1 equiv) and toluene (1.5 mL) were added, and the mixture was agitated for 5 h. The reaction mixture was added directly to a 12 mL ChemElut cartridge was pretreated with 3.0 mL of 1 M NaH_2PO_4 and was gravity-eluted. The cartridge was further washed with toluene (1.0 mL), and the combined organic layers were concentrated to afford compound **45** (8.5 mg, 81%). ^{1}H NMR: δ 8.60−8.53 (m, 2H), 8.01 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.80−7.77 (m, 1H), 7.56−7.48 (m, 2H), 7.42−7.38 (m, 2H), 5.90 (d, J = 8.0 Hz, 1H) 5.70−5.62 (m, 1H), 5.55−5.38 (m, 1H), 4.92−4.86 (m, 1H), 4.82−4.70 (m, 2H), 4.61−4.52 (m, 1H), 4.41 (t, J = 6.8 Hz, 2H), 4.15 (q, J = 6.8, 14.0 Hz, 2H), 4.10−4.07 (m, 1H), 3.99−3.94 (m, 1H), 3.76−3.45 (m, 2H), 2.56−2.37 (m, 1H), 2.32−2.20 (m, 1H), 2.14−1.95 (m, 2H), 1.86−1.75 (m, 2H), 1.53−1.40 (m, 4H), 1.38−1.15 (m, 10H), 0.96−0.53 (m, 8H) ppm. HR-MS (CI) calcd for $C_{40}H_{52}N_4O_9$ [M + H]$^+$, 733.3734; found, 733.3767.

Compound (48).



To a stirred solution of ester **46** (17.0 mg, 0.0237 mmol) in THF (1.0 mL) was added 1.0 M aqueous solution of LiOH (236 μL, 10 equiv). After being stirred for 5 h, the reaction mixture was acidified with 10% HCl to pH 3.0 and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford acid **47** (15 mg, 92%) as a waxy solid.

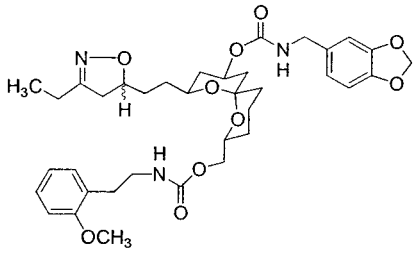
To a stirred solution of the above acid **47** (14.0 mg, 0.0203 mmol) in CH_2Cl_2 (1.0 mL) were added consecutively 2,2-diphenylethylamine (6.0 mg, 0.029 mmol), 1-hydroxybenzotriazole (HOBt) (4.0 mg, 0.029 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (6.0 mg, 0.029 mmol), and diisopropylethylamine (DIEA) (8.0 mg, 0.061 mmol). After the mixture was stirred for 12 h, water was added and the reaction mixture was extracted with EtOAc. The organic layer was washed with 5% HCl, water, and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo to afford amide **48** (17.2 mg, 96%) as a waxy solid. ^{1}H NMR: δ 8.01 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.80−7.77 (m, 1H), 7.55−7.47 (m, 2H), 7.43−7.39 (m, 2H), 7.34−7.19 (m, 15H), 6.02−5.86 (m, 2H), 5.34 (bs, 1H), 5.18−5.05 (m, 1H), 4.90−470 (m, 3H), 4.42−4.28 (m, 2H), 4.18−4.12 (m, 2H), 4.02−3.90 (m, 3H), 3.79−3.59 (m, 3H), 2.34−2.24 (m, 2H), 2.14−1.92 (m, 3H), 1.90−1.78 (m, 2H), 1.74−1.38 (m, 6H), 1.33−1.13 (m, 4H), 1.01−0.72 (m, 6H) ppm. HR-MS (CI) calcd for $C_{53}H_{62}N_4O_8$ [M + H]$^+$, 883.4568; found, 883.4584.

Spiroketal Isoxazole (52). To a stirred solution of alkene **49** (30.0 mg, 0.055 mmol) in benzene were added consecutively 1-nitropropane (7.0 mg, 0.083 mmol, 1.5 equiv), phenyl isocyanate (20.0 mg, 0.166 mmol, 3.0 equiv), and Et_3N (20 μL, catalytic amount), and the reaction mixture was stirred at 25 °C for 30 min. The resultant white solid suspension was refluxed for 24 h. After the mixture was cooled, water was added and the mixture was extracted with ethyl acetate, the organic layer was washed with water and brine, dried over $MgSO_4$, and filtered and concentrated in vacuo. The product was passed through small pad of silica gel, eluting with EtOAc to yield isoxazole **50** (34 mg, 100%), which was used without further purification.

To a 10 mL Quest 210 reaction vessel was added the above isoxazole **50** (34 mg, 0.0552 mmol) dissolved in THF (0.5 mL), followed by HF·pyridine (1.0 M in THF, 2.76 mL, 2.76 mmol, 50 equiv). After the mixture was mixed for 4 h, MeOSiMe_3 (760 μL, 5.52 mmol, 2.0 equiv) was added to neutralize the HF and the reaction mixture wasagitated for a

further 2 h. The reaction mixture was directly passed through a Waters MCX cartridge attached to the Quest 210 lower Luer manifold and collected directly into a scintillation vial. The cartridge was washed further with THF, and the combined filtrates were concentrated in vacuo to afford an alcohol (28.0 mg, 100%), which was used without further purification.

To a 10 mL (13 mm × 150 mm) reactor on the FirstMate synthesizer, a solution of the above alcohol (28 mg, 0.056 mmol) in CH_2Cl_2 (1.5 mL) was added followed by 1,1′-carbonyldiimidazole (CDI) (140 mg, 0.084 mmol, 1.5 equiv). After the mixture was stirred for 4 h, the reaction mixture was eluted through a 12 mL ChemElut Plus cartridge pretreated with 3.0 mL of 1 M NaH_2PO_4. The cartridge was washed with 1.0 mL of CH_2Cl_2, and the combined organic layers were concentrated in vacuo. The product was purified by silica gel chromatography (50−80% EtOAc/hexanes) to yield imidazolide **51** (23.8 mg, 71%). ^{1}H NMR: δ 8.12 (s, 1H), 7.42 (s, 1H), 7.06 (s, 1H), 6.75−6.68 (m, 3H), 5.92 (s, 2H), 5.07−5.02 (m, 1H), 4.90−4.80 (m, 1H), 4.56−4.45 (m, 1H), 4.32−4.31 (m, 2H), 4.21−4.20 (m, 2H), 3.86−3.82 (m, 1H), 3.62−3.50 (m, 1H), 2.95 (dd, J = 10.0, 16.4 Hz, 1H), 2.52 (dd, J = 8.0, 16.8 Hz, 1H), 2.36−2.29 (m, 2H), 2.19−1.99 (m, 2H), 1.92−1.80 (m, 2H), 1.73−1.55 (m, 5H), 1.50−1.40 (m, 2H), 1.39−1.11 (m, 6H) ppm.



To a stirred solution of imidazolide **51** (14.0 mg, 0.023 mmol) in toluene (0.5 mL) was added 2-methoxyphenethylamine (32.0 mg, 0.211 mmol, 9.0 equiv), and the reaction mixture was stirred at 50 °C for 12 h. The reaction was brought to room temperature and eluted through a 12 mL ChemElut Plus cartridge pretreated with 3.0 mL of 10% HCl. The cartridge was further washed with toluene (2.5 mL), and the combined organic layers were concentrated to afford **52** (14.0 mg 95%) as a waxy solid. ^{1}H NMR: δ 7.20−7.16 (m, 1H), 7.12−7.11 (m, 1H), 6.89−6.83 (m, 2H), 6.76−6.69 (m, 3H), 5.92 (s, 2H), 5.17−5.02 (m, 1H), 4.98−4.92 (m, 1H), 4.90−4.80 (m, 1H), 4.58−4.46 (m, 1H), 4.28−4.10 (m, 2H), 4.09−3.98 (m, 1H), 3.93−3.88 (m, 1H), 3.82 (s, 3H), 3.72−3.52 (m, 2H), 3.44−3.32 (m, 2H), 2.95 (dd, J = 10.4, 16.8 Hz, 1H), 2.80 (t, J = 6.8 Hz, 2H), 2.52 (dd, J = 7.6, 16.8 Hz, 1H), 2.32 (q, J = 7.2, 14.8 Hz, 2H), 2.10−1.98 (m, 2H), 1.87−1.71 (m, 2H), 1.70−1.38 (m, 7H), 1.34−1.11 (m, 6H). HR-MS (CI) calcd for $C_{36}H_{47}N_3O_{10}$ $[M + H]^+$, 682.3261; found, 682.3271.

Acknowledgment. We thank Boehringer-Ingelheim, Inc. (Ridgefield, CT) for financial support, Argonaut Technologies, Waters, ThermoSavant, and Genevac for their generous support of the Center for Streamlined Synthesis, and Rhodia ChiRex for supplying salen-Co catalysts.

Note Added in Proof. An approach to the synthesis of symmetrically substituted spiroketals using a polyethylene glycol-based ketal protecting group was recently reported. See: Haag, R.; Leach, A. G.; Ley, S. V.; Nettekoven, M.; Schnaubelt, J. *Synth. Commun.* **2001**, *31*, 2965−2977.

Supporting Information Available. ^{1}H NMR and mass spectral data for spiroketal compounds, X-ray structure coordinates of **33**, and X-ray crystallographic data for **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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