An Asymmetric Approach to Spirocylic Systems: A Formal Synthesis of Zizaene†

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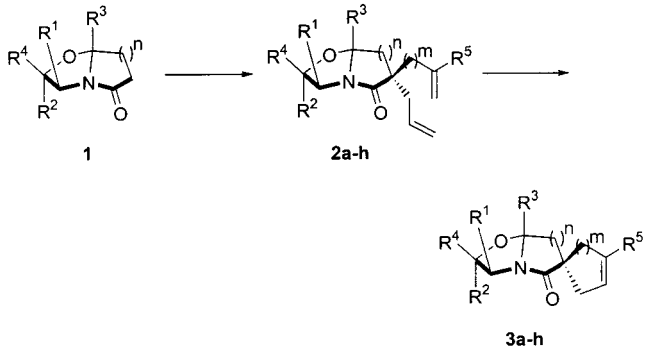
A general route to enantiopure spirocarbocycles is described. The use of various chiral bicyclic lactams **1** that have been doubly alkylated with olefinic halides gives good yields of α,α-disubstituted chiral lactams **2** which were cyclized to spiro-olefins using ring closure metathesis methodology (Grubbs' catalyst). These spirolactams **3**, formed in generally excellent yields, were shown to be smoothly transformed into spirocyclopentenone **6**, spirocyclohexenone, **7**, and spirolactams **8**. Further demonstration of this spirocyclization methodology was featured in a formal synthesis of zizaene, by preparing in enantiomeric form the Coates' intermediate **21**. This synthetic effort provided additional examples of the synthetic versatility of chiral bicyclic lactams **2a**,**b**.

The creation of quaternary centers, especially those representing stereogenic centers, continues to be a challenging task for the synthetic organic chemist. One solution to this problem has been developed in these laboratories through the ongoing successful evaluation of the bicyclic lactam **1** as a chiral template in the synthesis of a variety of molecules of quaternary stereocenters (Scheme 1).[1] An even more difficult problem is the assemblage of chiral spirocyclic centers, a structural array found in many natural products. At the center of the chiral spirocycle center resides a quaternary carbon (e.g., **3**), which can be readily accessed utilizing the abovementioned lactam template. We describe herein the use of chiral bicyclic lactams, doubly substituted with olefinic appendages **2** followed by ring-closing metathesis[2,3] to furnish **3**. The chiral nonracemic spirocyclic compounds **3** resulting from this sequence can serve as useful intermediates in a variety of synthetic endeavors.

We have previously reported that a wide variety of bicyclic lactams **1** can be dialkylated at the α-carbon with very high diastereoselectivity.[1,4] Therefore, it was envisioned that alkylation with two different unsaturated electrophiles would provide suitable precursors for ring-closing metathesis remote from the newly formed chiral center to furnish **2**. This could be followed by cyclization using the ruthenium catalyst[2] resulting in the creation of a new spiroappended ring adjacent to the lactam carbonyl (**3**). The spiro systems are then poised to be transformed into a variety of useful intermediates, including cyclic enones and substituted piperidines (vide supra). It should be noted that early attempts to effect the ring-closing methathesis on the corresponding thiolactams failed,[1b] presumably due to the interaction of the sulfur atom with the ruthenium catalyst.

Scheme 1



Various bicyclic lactams **1** were doubly alkylated following previously described conditions[4] (LDA or *s*-BuLi, THF, −78 °C), thus providing the dialkyl derivatives **2a**−**h** listed in Table 1. The alkylations leading to the quaternary center in **2** were all highly diastereoselective (>95% de) in the second alkylation step except for entries 1 and 6 (**2a** and **2f**). In both of these cases, the two diastereomers proved to be inseparable by flash chromatography and the mixtures were thus utilized as such for the ring-closing metathesis that followed. In all other entries, the crude dialkylated diastereomers **2b**−**e**,**g**,**h** (>98% de) were subjected to the ring-closing metathesis (RCM) conditions.[2] With monosubstituted terminal olefins, the cyclization proceeded smoothly using 5 mol % of $Cl_2(PCy_3)_2RuCHPh$ catalyst at room temperature, producing the corresponding spirocyclic lactams **3** in excellent yields with various appended ring sizes. However, if a geminally substituted olefin was present in the starting material (entries 1, 4, and 5), the metathesis appeared to be considerably slower using the semistable commercially available ruthenium benzylidene catalyst. However, it was later found that significantly improved yields were obtained when the reaction mixture was heated along with slow addition of the catalyst (method C, Table 1).

† This paper is dedicated to the memory of Professor Arthur G. Schultz.

(1) For reviews on this subject, see: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (b) Groaning, M. H.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843. (c) Meyers, A. I.; Brengel, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1.

(2) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(3) Fu, G.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.

(4) (a) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A. *J. Org. Chem.* **1996**, *61*, 5712. (b) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F.; Williard, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 7429.

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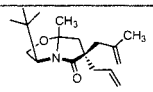
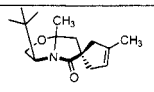
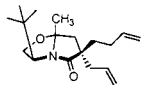
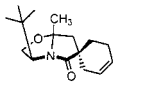
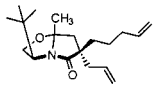
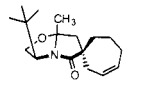
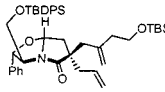
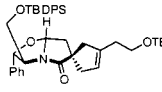
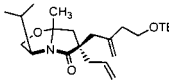
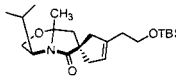
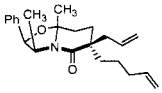
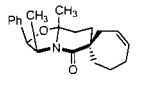
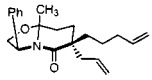
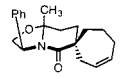
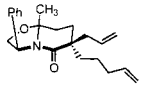
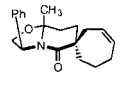
Table 1

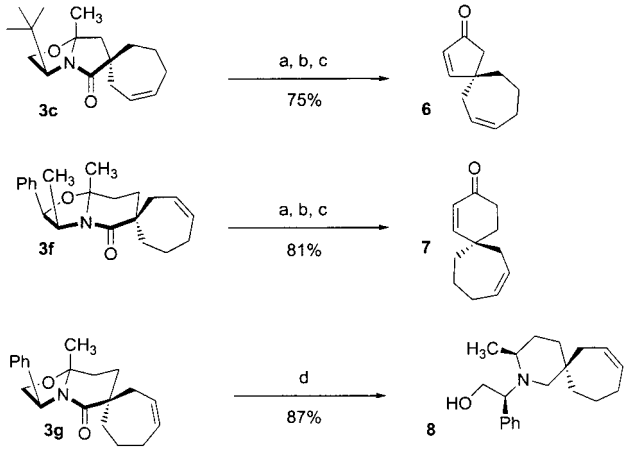
Entry	Lactam **2**	**2**, % de[a] (ratio)	Conditions[b] for RCM	Product **3**	Yield (%) **3**
(1)	 **2a**	71 (85:15)	B	 **3a**	91
(2)	 **2b**	95 (>97:3)	A	 **3b**	97
(3)	 **2c**	95 (>97:3)	A	 **3c**	90
(4)	 **2d**	95 (>97:3)	B	 **3d**	89
(5)	 **2e**	95 (>97:3)	C	 **3e**	95
(6)	 **2f**	33 (67:33)	A	 **3f**	82
(7)	 **2g**	95 (>97:3)	B	 **3g**	85
(8)	 **2h**	95 (>97:3)	A	 **3h**	93

[a] The substituent from the first alkylation is present on the exo face (except for **2d** where the allyl group was introduced first). The endo substituent was introduced in the second alkylation step (except for **2d**). The yields for the purified double alkylation products, **2**, are given in the Experimental. [b] Conditions: (A) substrate was stirred in dichloromethane (0.007 M) at ambient temperature with 5 mol % of $Cl_2(PCy_3)_2RuCHPh$ for 18−24 h; (B) substrate was stirred in dichloromethane (0.007 M) heated at reflux with 15 mol % of $Cl_2(PCy_3)_2RuCHPh$ (added in three equal portions every 4−6 h) for 18−24 h; (C) substrate was heated in toluene (100 °C) and $Cl_2(PCy_3)_2RuCHPh$ (5 mol %) added via syringe pump over 3 h.

The nature of the substituents on bicyclic lactams **1** appeared to have little effect on the outcome of the spiro cyclization leading to **3**. Furthermore, lactam **2d** (entry 4) was chosen for further study due to the earlier observation that [3.3.0] bicyclic lactams bearing an angular hydrogen (i.e. **1**, $n = 1$, $R^3 = H$, Scheme 1) generally gave poor selectivity during the second alkylation step. The presence of the *endo* phenyl group in **2d** (Table 1) resulted in exclusive alkylation on the *exo*-face of the lactam. This is in contrast to the generally observed alkylation pathway, which almost invariably gave endo alkylation.[4a] In the absence of any substituent on the endo face (**1**, $R^2 = H$), the alkylation of bicyclic lactam enolate almost exclusively furnished the *endo* alkylation product. As Table 1 illustrates, both [3.3.0] and [4.3.0] bicyclic lactams (**2f**, **2g**, **2h**) with various substitution patterns can be utilized in conjunction with the metathesis cyclization to create a wide variety of useful synthetic intermediates.

With the metathesis products **3** in hand, an effort was made to determine whether the remote chirality of the quaternary center, as well as lactam carbonyl, could affect the stereochemistry of reduction of the double bond present in **3**. In other words, a new stereogenic center could potentially be set in place via the selective hydrogenation. In this regard, spiro lactam **3d** was exposed to the iridium catalyst[5] under an atmosphere of hydrogen,

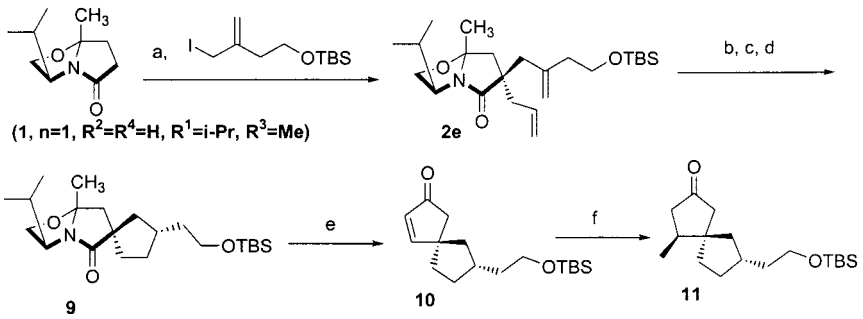
Scheme 2[a]



[a] Conditions: (a) Red-Al, THF, 0 °C; (b) EtOH, 1 M $Bu_4NH_2PO_4$, rt; (c) EtOH, KOH, rt; (d) DIBAL-H, THF −78 °C to room temperature.

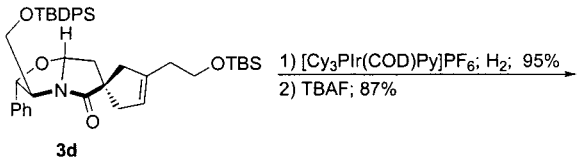
(5) Crabtree, R. H.; Felkin, H.; Fellebeen-Kahn, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.

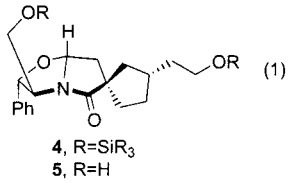
Scheme 3[a]



[a] Conditions: (a) LDA, THF −78 °C, 72%; (b) LDA, THF −78 °C, allyl bromide, 98%, (c) $Cl_2(PCy_3)_2Ru$=CHPh (method C) 95%; (d) $[PCy_3Ir(COD)Py]Pf_6$ (1%) H_2, CH_2Cl_2, 85%; (e) i. Red-Al, THF, 0 °C, ii. EtOH, 1 M $Bu_4NH_2PO_4$, rt; iii. EtOH, KOH, rt 85%; (f) $LiCuMe_2(CN)$, THF −78 °C, 97%.

which afforded **4** as a single diastereomer in excellent yield. The stereochemistry was initially assigned on the





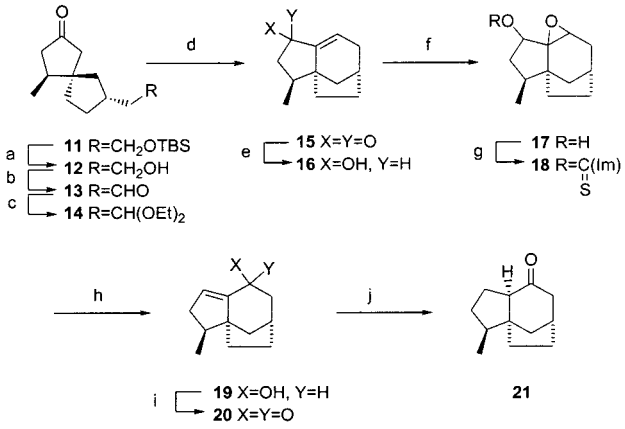
(1)

basis of the assumption that the lactam carbonyl should facilitate the delivery of hydrogen on the same face of the molecule due to the oxygen lone pairs coordinating with the catalyst metal center. This latter effect has been previously observed by the late professor Schultz.[6]It was therefore necessary to unambiguously confirm the stereochemistry of the reduction, and this was accomplished by removing the silicon protecting groups in **4**, which afforded the crystalline diol **5**. Single-crystal X-ray analysis (Supporting Information) revealed that the assignment of the newly formed stereogenic center in **5** was as predicted. Thus, the notion of the lactam carbonyl acting as a remote director of stereochemical reduction appeared to be verified.

To afford more generally useful products, the amino alcohol portions of lactams **3c**, **3f**, and **3g** were removed by utilizing methods previously described[1] to furnish various spirocyclic enones **6** and **7** as well as piperidine **8** shown in Scheme 2.

To demonstrate the further synthetic utility of this method, a sequence leading to the key intermediate **21** in the synthesis of zizaene[7] was investigated. Commercially available lactam **1** (Scheme 3) was alkylated with the allylic iodide $ICH_2C(CH_2)CH_2CH_2OTBS$ (readily available from dimethyl itaconate, see Experimental). This was followed directly by a second alkylation with allyl bromide to furnish the 2,2-disubstituted lactam **2e** as an initial 6:1 mixture of diastereomers. After separation (to >97:3) by flash column chromatography, the ring-closing metathesis generated the expected spirocyclopentene **3e** (Table 1) in 95% yield. The resulting olefin in **3e** was reduced with Crabtree's iridium catalyst[5] to **9** in greater than >97% de, thus setting the remote stereogenic center needed in the tricyclic framework of the zizaene family of natural products. Removal of the chiral auxiliary was accomplished by treatment of **9** with Red-Al to reduce the lactam carbonyl to the carbonolamine, which was then hydrolyzed using a 1 M $Bu_4NH_2PO_4$ buffer. The resulting keto-aldehyde was treated with KOH to effect the aldol cyclization affording spiroenone **10** in good overall yield. The addition of the requisite methyl group was accomplished by conjugate addition of the higher order cuprate $(Me_2Cu(CN)Li)$[8] to enone **10** to produce the corresponding cyclopentanone **11**. As expected, the addition of the methyl group was highly stereoselective as judged by ^1H NMR.

Scheme 4[a]



[a] Conditions: (a) TBAF, 83%; (b) Swern oxidation, 99%; (c) EtOH, TsOH(cat.); (d) TsOH(cat.), toluene reflux, 63%; (e) Dibal-H, 62%; (f) MCPBA, 48%; (g) Im_2CS, DMAP, 84%; (h) Bu_3SnH, AIBN, 64%; (i) PDC, 67%; (j) Pd−C, H_2, 99%.

Scheme 4 describes the final sequence wherein **11** was transformed into the known advanced zizaene intermediate **21**. With the final methyl group in place, the TBS protecting group in **11** was removed using TBAF followed by Swern oxidation of the resulting alcohol **12** which afforded the pivotal aldehyde **13**. An intramolecular aldol reaction on aldehyde **13** was now required to form the desired tricyclic system **15** found in zizaene. Basic catalysis (KOH, EtOH) failed to produce the desired

(6) Schultz, A. G.; McCloskey, P. J. *J. Org. Chem.* **1985**, *50*, 5905.
(7) Coates, R. M.; Sowerby, R. L. *J. Am. Chem. Soc.* **1972**, *94*, 5386.
(8) (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* (b) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.

tricycle, leading only to unidentifiable products with complete consumption of starting material. However, it was observed that acid catalysis on **13** (TsOH, toluene reflux) did produce the desired tricycle in modest yields with recovered starting material. In addition, the corresponding diethyl acetal **14** also underwent an acid-catalyzed intramolecular aldol reaction with reduced reaction times and greater conversion to the aldol tricyclic product **15**.

To complete the synthesis of the Coates' intermediate[7] **21**, a 1,3-carbonyl transposition was carried out as follows: Dibal reduction of the aldol enone **15** gave a diastereomeric mixture of allylic alcohols **16**. Epoxidation of the alcohol mixture with MCPBA to epoxide **17** was followed by conversion to the xanthate esters **18** using thiocarbonyldiimidazole (TCDI). Exposure of the xanthate mixture to standard radical conditions (Barton deoxygenation[9]) resulted in the epoxycarbinyl radical rearrangement, which cleaved the epoxide, thus furnishing the two diastereomerically transposed allylic alcohols **19** in excellent yield. Oxidation of the mixture of alcohols to the ketone followed by hydrogenation of the remaining double bond gave tricycle **21** which was identical in all respects to the key intermediate reported by Coates in his synthesis of zizaene.[7]

In conclusion, we have demonstrated that [3.3.0]- and [4.3.0]bicyclic lactams with various substitution patterns can be utilized in conjunction with the RCM to create a wide variety of useful spirocyclic synthetic intermediates which can be used in the synthesis of complex natural products.

Experimental Section

General Experimental for Alkylations of Lactams 1. (A) General First Alkylation Step. To a stirred solution of diisopropylamine (1.1 equiv) in THF (0.71 M) was added *n*-BuLi (1.1 equiv) at 0 °C. The resulting solution was stirred for 5 min at 0 °C and transferred via cannula to a precooled (−78 °C) solution of the lactam **1** (1.0 equiv) in THF (0.28 M). The resulting solution was stirred 1 h at −78 °C, at which time a solution of the olefinic halide (1.2 equiv) in THF (1.5 M) was added dropwise. The reaction mixture was stirred for 2 h at −78 °C and warmed to room temperature, and saturated NH_4Cl was added. The mixture was extracted with diethyl ether (4 × 25 mL), and the combined organic layers were washed with brine (25 mL) and dried over anhydrous magnesium sulfate. Flash chromatography (silica gel, hexanes/EtOAc) provided the monoalkylated lactam that was used immediately in the second alkylation step.

(B) Second Alkylation Step. The previous procedure was used except that a different olefinic halide was employed.

Lactam 2a from methallyl chloride, followed by allyl bromide. Flash chromatography (silica gel, hexanes/ethyl acetate, 20:1) afforded 229 mg (51% after both alkylations) of a diastereomeric mixture (6:1) of **2a** as a colorless oil. Major diastereomer: IR (NaCl) ν 2958, 1711, 1317 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.45 (s, 3H), 1.76 (m, 3H), 2.09 and 2.25 (Ab_q, J_{gem} = 14.1 Hz, 2H), 2.15−2.41 (m, 4H), 3.69 (dd, J = 4.5, 9.3 Hz, 1H), 3.81 (dd, J = 9.9, 3 Hz, 1H), 4.07 (dd, J = 8.1, 9 Hz, 1H), 4.76 (m, 1H), 4.91 (m, 1H), 5.02−5.10 (m, 2H), 5.57−5.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 25.7, 27.3, 33.0, 42.1, 42.8, 46.5, 50.8, 66.2, 66.9, 97.3, 115.8, 118.8, 133.9, 142.2, 185.2; mass spectrum (FAB), *m*/*z* (rel intensity) 292 (M + 1, 100), 291 (M^+, 14), 276 (6), 234 (11); HRMS, calcd for $C_{18}H_{29}NO_2$ + 1 292.2198, found 292.2268.

Lactam 2b from 4-iodo-1-butene, followed by allyl bromide. Flash chromatography (silica gel, hexanes/ethyl acetate, 25:1) afforded 283 mg (65% after both alkylations) of **2b** as a colorless oil: IR (NaCl) ν 2962, 1710, 1322 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.51 (s, 3H), 1.65−1.72 (m, 2H), 1.98 and 2.30 (Ab_q, J_{gem} = 14.1 Hz, 2H), 2.08 (m, 2H), 2.29 (m, 2H), 3.69 (dd, J = 7.8, 9 Hz, 1H), 3.84 (dd, J = 9, 9.3 Hz, 1H), 4.10 (dd, J = 8.1, 9 Hz, 1H), 4.94−5.11 (m, 4H), 5.11 (m, 1H), 5.66 (m, 1H), 5.80 (ddt, J = 17.1, 10.1, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 27.2, 28.8, 32.8, 37.6, 40.9, 44.3, 50.8, 65.8, 67.1, 97.2, 114.8, 118.6, 133.8, 137.9, 184.6; mass spectrum (FAB), *m*/*z* (rel intensity) 292 (M + 1, 100), 290 (13), 276 (7), 234 (10); HRMS, calcd for $C_{18}H_{29}NO_2$ + 1 292.2198, found 292.2281.

Lactam 2c from 5-iodo-1-pentene, followed by allylbromide. Flash chromatography (silica gel, hexanes/ethyl acetate, 25:1) afforded 503 mg (66% after both alkylations) of **2c** as a colorless oil: IR (NaCl) ν 2964, 1712, 1319 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.40−1.48 (m, 2H), 1.50 (s, 3H), 1.57−1.63 (m, 2H), 1.95 and 2.28 (Ab_q, J_{gem} = 14.1 Hz, 2H), 2.08 (m, 2H), 2.27 (m, 2H), 3.69 (dd, J = 8.2, 9.3 Hz, 1H), 3.83 (dd, J = 9, 9.3 Hz, 1H), 4.10 (dd, J = 8.3, 9.2 Hz, 1H), 4.94−5.07 (m, 3H), 5.09 (m, 1H), 5.65 (m, 1H), 5.78 (ddt, J = 17.1, 10.2, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 26.2, 27.2, 32.9, 33.8, 37.8, 40.9, 44.3, 51.0, 65.7, 67.1, 97.3, 114.9, 118.4, 137.9134.0, 138.3, 184.9; mass spectrum (FAB), *m*/*z* (rel intensity) 306 (M + 1, 100), 290 (7.5), 248 (10); HRMS, calcd for $C_{19}H_{31}NO_2$ + 1 306.2355, found 306.2420.

Lactam 2d from allyl bromide, followed by *tert*-butylsiloxyethalyl iodide. Flash chromatography (silica gel, hexanes/ethyl acetate, 15:1) afforded 671 mg (68% after both alkylations) of **2d** as a pale yellow oil: IR (NaCl) ν 1710, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 1.08 (s, 9H), 2.20−2.32 (m, 5H), 2.41−2.53 (m, 3H), 3.68 (m, 2H), 3.76 (m, 1H), 3.94 (m, 2H), 4.93 (m, 1H), 4.99 (m, 1H), 5.15 (m, 3H), 5.31 (dd, J = 6.3, 2.4 Hz, 1H), 5.78 (m, 1H), 7.17 (m, 2H), 7.28 (m, 3H), 7.24 (m, 6H), 7.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, −5.3, 15.3, 18.3, 19.3, 25.9, 26.9, 33.8, 40.2, 43.0, 44.2, 51.5, 62.3, 63.2, 63.7, 65.8, 82.3, 90.5, 116.2, 119.2, 127.8, 128.2, 128.5, 129.8, 129.9, 132.8, 133.0, 133.9, 135.6, 135.6, 139.1, 143.1, 181.3. Anal. Calcd for $C_{43}H_{59}NSi_2O_4$: C, 72.73; H, 8.37; N, 1.97. Found: C, 72.83; H, 8.46; N, 1.85.

Lactam 2e from *tert*-butylsiloxyethalyl iodide, followed by allyl bromide. Flash chromatography (silica gel, hexanes/ethyl acetate, 20:1) afforded 1.28 g (83% after both alkylations) of **2e** as a colorless oil: $[\alpha]_D$ +20° (*c*, 1.39, $CHCl_3$); IR (NaCl) ν 2930, 1713, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.86 (s, 9H), 1.03 (d, J = 6.6 Hz, 3H), 1.41 (s, 3H), 1.62 (m, 1H), 2.07−2.26 (m, 6H), 2.33 (dd, J = 8.8, 13.2 Hz, 1H), 2.44 (d, J = 13.2 Hz, 1H), 3.56 (m, 1H), 3.59 (dd, J = 6.6, 10.2 Hz, 1H), 3.68 (m, 3H), 4.12 (t, J = 8.0 Hz, 1H), 4.85 (s, 1H), 4.96 (s, 1H), 5.06 (m, 2H), 5.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 18.3, 19.1, 20.9, 25.1, 25.9, 34.4, 39.7, 40.3, 43.4, 50.9, 62.1, 62.6, 70.1, 96.9, 116.1, 118.7, 133.7, 143.2, 183.5.

Lactam 2f from allyl bromide, followed by 5-iodo-1-pentene. Flash chromatography (silica gel, hexanes/ethyl acetate, 15:1) afforded 118 mg (50% after both alkylations) of a diastereomeric mixture (2:1) of **2f** as a colorless oil: (major diastereomer) ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J = 7.1 Hz, 3H), 1.39−1.48 (m, 3H), 1.59 (s, 3H), 1.66−2.07 (m, 8H), 2.47 (ddt, J = 5.7, 13.2, 1.2 Hz, 1H), 4.77 (m, 1H), 4.87−5.09 (m, 5H), 5.58−5.82 (m, 2H), 7.21−7.34 (m, 5H).

Lactams 2g and **2h** from 5-iodopentene, followed by allyl bromide. Flash chromatography (silica gel, hexanes/ethyl acetate, 25:1) afforded 177 mg (38% after both alkylations) of **2g** and 73 mg (15%) of **2h** as colorless oils. **2g**: $[\alpha]_D$ = +95° (*c*, 1.10); IR (NaCl) ν 2939, 1644, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41−1.45 (m, 1H), 1.49 (s, 3H), 1.69−1.89 (m, 3H), 1.99−2.11 (m, 3H), 2.30 (dd, J = 7.3, 13.9 Hz, 1H), 2.51 (dd, J = 7.3, 13.9 Hz, 1H) 3.90 (t, J = 8.8 Hz, 1H), 4.49 (t, J = 8.8 Hz, 1H), 4.95−5.12 (m, 4H), 5.35 (t, J = 8.8 Hz, 1H) 5.72−5.88 (m, 2H), 7.17−7.34 (m, 5H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 26.2, 32.9, 33.9, 39.1, 43.6, 45.2, 59.2, 69.9, 93.9, 114.6, 118.1, 125.3, 127.1, 128.6, 134.5, 138.4, 140.1, 174.1; mass spectrum (EI), *m*/*z* (rel intensity) 339 (M^+, 9.7), 324 (26.9), 298 (48.8), 271 (100); HRMS, calcd for $C_{22}H_{29}NO_2$ 339.2198, found

(9) Barton, P. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

339.2186. **2h**: IR (NaCl) ν 2941, 1645, 1388 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30−1.42 (m, 1H), 1.46 (s, 3H), 1.51−1.63 (m, 2H), 1.72−1.86 (m, 3H), 1.94−2.15 (m, 5H), 2.53 (dd, J = 5.8, 13.2 Hz, 1H), 3.90 (t, J = 8.8 Hz, 1H), 4.48 (t, J = 8.8 Hz, 1H), 4.93−5.21 (m, 4H), 5.31 (t, J = 8.1 Hz, 1H) 5.71−5.86 (m, 2H), 7.18−7.34 (m, 5H); mass spectrum (EI), *m*/*z* (rel intensity) 339 (M^+, 10.7), 324 (34.0), 298 (34.3), 271 (100); HRMS, calcd for $C_{22}H_{29}NO_2$ 339.2198, found 339.2192.

Spiro Lactam 3a. Lactam **2a** (96 mg, 0.33 mmol) was treated with $Cl_2(PCy_3)_2RhCHPh$ (14 mg, 0.017 mmol) in 1,2-dichloroethane (47 mL) according to method B. Flash chromatography (silica gel, hexanes/ethyl acetate, 20:1) furnished 79 mg (91%) of **3a** as a colorless oil: IR (NaCl) ν 2953, 1714, 1338 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.53 (s, 3H), 1.69 (m, 3H), 2.16 (m, 1H), 2.18 and 2.34 (Ab_q, J_{gem} = 12.9 Hz, 2H), 2.44 (m, 1H), 2.71 (m, 1H), 3.05 (m, 1H), 3.70 (dd, J = 8.1, 9.3 Hz, 1H), 3.92 (dd, J = 9, 9.3 Hz, 1H), 4.17 (dd, J = 8.1, 9.3 Hz, 1H), 5.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 25.8, 27.1, 33.0, 43.2, 50.6, 51.7, 53.6, 64.7, 68.0, 97.2, 123.1, 118.8, 136.3,184.4; mass spectrum (FAB), *m*/*z* (rel intensity) 264 (M + 1, 100), 248 (4.7), 206 (5); HRMS, calcd for $C_{16}H_{25}NO_2$ + 1 264.1885, found 264.1968.

Spiro Lactam 3b. Lactam **2b** (112 mg, 0.384 mmol) was treated with $Cl_2(PCy_3)_2RhCHPh$ (15.8 mg, 0.0192 mmol) in 1,2-dichloroethane (55 m) according to method A. Flash chromatography (silica gel, hexanes/ethyl acetate, 25:1) furnished 98 mg (97%) of **3b** as a colorless solid: mp = 79.5−80 °C (hexanes); $[\alpha]_D$ +117 (*c*, 0.54, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.52 (s, 3H), 1.69−1.93 (m, 3H), 2.01 and 2.25 (Ab_q, J_{gem} = 13.8 Hz, 2H), 2.17 (m, 2H), 2.56 (m, 1H), 3.71 (dd, J = 8.1, 9.3 Hz, 1H), 3.88 (dd, J = 9, 9.3 Hz, 1H), 4.14 (dd, J = 8.1, 9 Hz, 1H), 5.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 26.2, 27.1, 30.4, 32.8, 34.3, 46.2, 46.3, 65.3, 67.4, 97.0, 124.8, 125.5, 185.3. Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found: C, 72.90; H, 9.58; N, 5.36.

Spiro Lactam 3c. Lactam **2c** (119 mg, 0.390 mmol) was treated with $Cl_2(PCy_3)_2RhCHPh$ (16.0 mg, 0.0194 mmol) in 1,2-dichloroethane (56 mL) according to method A. Flash chromatography (silica gel, hexanes/ethyl acetate, 20:1) furnished 97 mg (90%) of **3c** as a colorless solid: mp = 100−101 °C (hexanes); $[\alpha]_D$ +195 (*c*, 1.12, $CHCl_3$); IR (NaCl) ν 2929, 1710, 1322 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.47 (s, 3H), 1.43 (m, 1H), 1.47 (s, 3H), 1.72 (m, 1H), 1.95−2.05 (m, 4H), 2.13−2.23 (m, 3H), 2.56 (m, 1H), 3.69 (dd, J = 8.1, 9.3 Hz, 1H), 3.86 (dd, J = 9, 9.3 Hz, 1H), 4.26 (dd, J = 8.1, 9.3 Hz, 1H), 5.63 (m, 1H), 5.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 26.2, 27.2, 28.3, 32.9, 35.9, 40.2, 44.6, 49.0, 65.6, 67.5, 97.4, 127.6, 133.8, 186.3. Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81; N, 5.05. Found: C, 73.51; H, 9.81; N, 5.06.

Spiro Lactam 3d. Lactam **2d** (671 mg, 0.945 mmol) was treated with $Cl_2(PCy_3)_2RhCHPh$ (39.0 mg, 0.0473 mmol) in 1,2-dichloroethane (100 mL) according to method B. Flash chromatography (silica gel, hexanes/ethyl acetate, 20:1) furnished 573 mg (89%) of **3d** as a pale yellow oil: $[\alpha]_D$ +31.3 (*c*, 1.95, $CHCl_3$); IR (NaCl) ν 1713, 1107 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.91 (s, 9H), 1.10 (s, 9H), 2.23 (dd, J = 14.1, 3 Hz, 1H), 2.31−2.42 (m, 4H), 2.50 (dd, J = 13.8, 5.7 Hz, 1H), 2.86 (m, 1H), 3.08 (m, 1H), 3.74 (m, 2H), 3.82 (m, 1H), 4.00 (m, 2H), 5.24 (d, J = 6.3 Hz, 2H), 5.36 (m, 1H), 5.41 (dd, J = 5.7, 2.7 Hz, 1H), 7.23−7.46 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 18.3, 19.2, 25.9, 26.9, 34.3, 43.2, 45.0, 49.1, 52.6, 61.9, 63.3, 63.8, 82.9, 90.5, 123.1, 126.4, 127.8, 127.8, 128.3, 128.6, 129.8, 133.0, 133.1, 135.6, 138.6, 139.1, 182.8; mass spectrum (FAB), *m*/*z* (rel intensity) 682 (M + 1, 24), 624 (100), 604 (75); HRMS, calcd for $C_{41}H_{55}Si_2NO_4$ + 1 682.3670, found 682.3765.

Spiro Lactam 3e. Lactam **2e** (244 mg, 1.57 mmol) was treated with $Cl_2(PCy_3)_2RhCHPh$ (51.2 mg, 0.0622 mmol) in toluene (100 mL) according to method C. Flash chromatography (silica gel, hexanes/ethyl acetate, 20:1) furnished 223 mg (94%) of **3e** as a colorless oil: $[\alpha]_D$ +65 (*c*, 1.67, $CHCl_3$); IR (NaCl) ν 2929, 1714, 1359 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.89 (s, 9H), 1.04 (d, J = 6.6 Hz, 3H), 1.50 (s, 3H), 1.66 (m, 1H), 2.13−2.32 (m, 4H), 2.15 (d, J = 13.2, 1H), 2.29 (d, J = 13.2, 1H), 2.46 (br d, J = 16.1 Hz, 1H), 2.76 (br dd, J = 2.2, 16.1 Hz, 1H), 3.05 (m, 1H), 3.66 (m, 1H), 3.68 (t, J = 6.8 Hz, 2H), 4.12 (t, J = 8 Hz, 1H), 3.81 (dd, J = 6.6, 8.8 Hz, 1H), 4.20 (dd, J = 7.3, 8.8 Hz, 1H), 5.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, 18.3, 19.0, 20.6, 25.9, 34.1, 43.7, 46.4, 49.5, 51.2, 61.3, 61.9, 70.9, 96.8, 116.1, 123.4, 138.0, 182.9.

Spiro Lactam 3f. Lactam **2f** (112 mg, 0.317 mmol) was treated with $Cl_2(PCy_3)_2RhCHPh$ (13.1 mg, 0.0159 mmol) in 1,2-dichlororethane (45 mL) according to method A. Flash chromatography (silica gel, hexanes/ethyl acetate, 20:1) furnished 85 mg (82%) of **3f** as a colorless solid: mp = 139.5−141 °C (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 7.3 Hz, 3H), 1.34−1.48 (m, 2H), 1.63 (s, 3H), 1.65−2.27 (m, 7H), 2.82 (m, 1H), 4.72 (dd, J = 5.7, 7.5 Hz, 1H), 5.02 (dd, J = 6.9, 6.3 Hz, 1H), 5.57 (m, 1H), 5.87 (m, 1H), 7.21−7.33 (m, 5H). Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.66; H, 8.30; N, 4.29.

Spiro Lactam 3g. Lactam **2g** (51.5 mg, 0.158 mmol) was treated with $Cl_2(PCy_3)_2RhCHPh$ (8.9 mg, 0.0108 mmol) according to method A. Flash chromatography (silica gel, hexanes/ethyl acetate, 9:1) furnished 44.5 mg (95%) of **3g** as a colorless oil: $[\alpha]_D$ +154° (*c*, 1.11, $CHCl_3$); IR (NaCl) ν 2928, 1641, 1386 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.51−1.89 (m, 4H), 2.05 (m, 1H), 2.12−2.35 (m, 6H), 2.74 (d(br), J = 15.4 Hz, 1H), 3.94 (dd, J = 8.1, 8.8 Hz, 1H), 4.52 (t, J = 8.8 Hz, 1H), 5.36 (t, J = 8.1 Hz, 1H), 5.60 (m, 1H), 5.94 (m, 1H), 7.12−7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.2, 26.5, 28.9, 32.1, 34.1, 42.9, 58.4, 69.7, 93.7, 125.1, 126.9, 127.7, 128.5, 133.8, 140.2, 176.2; mass spectrum (EI), *m*/*z* (rel intensity) 311 (M^+, 83), 244 (100), 231 (21), 91 (52); HRMS, calcd for $C_{20}H_{25}NO_2$ 311.1885, found 311.1876.

Spiro Lactam 3h. Lactam **2h** (44.9 mg, 0.132 mmol) was treated with $Cl_2(PCy_3)_2RhCHPh$ (6.9 mg, 0.0083 mmol) according to method A. Flash chromatography (silica gel, hexanes/ethyl acetate,9:1) furnished 39.0 mg (93%) of **3h** as a colorless oil: $[\alpha]_D$ +27 (*c*, 1.47, $CHCl_3$); IR (NaCl) ν 2928, 1641, 1386 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 3H), 1.52−1.78 (m, 4H), 1.89 (m, 1H), 2.01−2.28 (m, 6H), 2.90 (d(br), J = 13.9 Hz, 1H), 3.95 (dd, J = 8.1, 8.8 Hz, 1H), 4.52 (t, J = 8.8 Hz, 1H), 5.36 (t, J = 8.1 Hz, 1H), 5.66 (m, 1H), 5.92 (m, 1H), 7.12−7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 23.3, 26.0, 28.5, 32.3, 36.9, 42.6, 58.3, 69.7, 93.7, 125.3, 126.9, 128.5, 128.6, 133.9, 140.3, 176.2; mass spectrum (EI), *m*/*z* (rel intensity) 311 (M^+, 40), 244 (100), 231 (32), 120 (27); HRMS, calcd for $C_{20}H_{25}NO_2$ 311.1885, found 311.1881.

Spiro Lactam 4. To a stirred solution of **3d** (573 mg, 0.840 mmol) in CH_2Cl_2 (4.7 mL) was added $[Cy_3PIr(COD)Py]PF_6$ (34.0 mg, 0.042 mmol). A balloon of hydrogen with a needle inlet was inserted through the rubber septum. Hydrogen was bubbled through the solution for ∼5 min, and the reaction mixture was stirred under a positive pressure of hydrogen for 16 h. The solvent was removed in vacuo, and the residue was subjected to flash chromatography (silica gel, hexanes/ethyl acetate, 6:1), affording 544 mg (95%) of **4** as a pale yellow oil: $[\alpha]_D$ +22.2 (*c*, 0.86, $CHCl_3$); IR (NaCl) ν 1714, 1113 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.91 (s, 9H), 1.09 (s, 9H), 1.27−1.42 (m, 2H), 1.62 (m, 2H), 1.72 (m, 1H), 2.00−2.40 (m, 6H), 3.64 (m, 2H), 3.81 (dd, J = 12.3, 5.1 Hz, 1H), 3.98 (m, 2H), 5.20 (d, J = 5.7 Hz, 1H), 5.36 (dd, J = 5.7, 2.7 Hz, 1H), 7.22−7.46 (m, 11H), 7.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 18.3, 19.3, 26.0, 26.9, 32.8, 36.5, 38.1, 39.4, 41.8, 46.2, 52.8, 62.5, 63.5, 64.0, 126.4, 127.7, 127.8, 128.3, 128.6, 129.8, 129.9, 135.6, 135.6, 139.2, 176.2; HRMS, calcd for $C_{41}H_{57}NSi_2O_4$ 684.3826, found 684.3911.

Diol 5. To a stirred solution of **4** (695 mg, 1.02 mmol) in THF (5 mL) at 0 °C was added a 1.0 M solution of tetrabutylammonium fluoride in THF (2.55 mmol). The reaction mixture was slowly warmed to room temperature and stirred for 3 h. Water was added, and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. Flash chromatography (silica gel, ethyl acetate) afforded 294 mg (87%) of **5** as a colorless solid: mp = 106.5−108 °C (hexanes, ethyl acetate); $[\alpha]_D$ +51.6 (*c*, 0.73, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (m, 2H), 1.67 (m, 3H), 2.00−2.44 (m, 6H), 2.56 (bs, 2H), 3.64 (t, J = 6.6 Hz, 2H), 3.70 (m, 1H), 3.84 (dd, J =

4.8, 15 Hz, 2H), 4.92 (d, J = 6.9 Hz, 1H), 5.32 (m, 1H), 7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.7, 36.5, 37.6, 38.8, 42.0, 46.0, 53.2, 62.0, 62.3, 65.0, 83.2, 83.2, 90.0, 126.4, 128.6, 128.7, 138.1, 185.0. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.83; H, 7.62; N, 4.21. This sample was submitted for single-crystal X-ray determination. Data may be found in the Supporting Information.

Spirocyclopentenone 6. To a stirred solution of spiro lactam **3c** (41.3 mg, 0.0148 mmol) in THF (1.0 mL) at 0 °C was added Red-Al (0.4 mL, 3.3 M). After stirring for 3 h at 0 °C, the reaction was quenched with methanol (0.5 mL) and stirred for 1 h. The resulting mixture was partitioned between diethyl ether and water. The organic layer was concentrated in vacuo, the residue was dissolved in ethanol (2 mL), and $Bu_4NH_2PO_4$ (2.0 mL, 1 M) was added. After stirring at room temperature for 24 h, the reaction mixture was diluted with diethyl ether (75 mL) and washed with water (3 × 20 mL). Diethyl ether was removed in vacuo, the crude keto aldehyde was dissolved in ethanol (3.5 mL), and aqueous potassium hydroxide (0.2 mL, 1 M) was added. The reaction mixture was stirred at room temperature for 16 h and diluted with diethyl ether (75 mL). The solution was washed with water (3 × 10 mL) and brine and dried over anhydrous magnesium sulfate. Flash chromatography (silica gel, hexanes/ethyl acetate 19:1) afforded 18.1 mg (75%) of **6** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (m, 3H), 1.96 (m, 1H), 2.12−2.26 (m, 6H), 5.69 (m, 1H), 5.78 (m, 1H), 6.08 (d, J = 5.1 Hz, 1H), 5.57 (d, J = 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 32.1, 36.1, 43.7, 47.7, 124.7, 126.9, 132.0, 149.7, 171.8; mass spectrum (EI), m/z (rel intensity) 148 (M^+, 49), 94 (53), 66 (100).

Spirocyclohexenone 7. To a stirred solution of **3f** (35.0 mg, 0.108 mmol) at 0 °C was added Red-Al (0.216 mmol, 3.4 M). The reaction mixture was warmed to room temperature and stirred for 15 h, at which time it was quenched by cautious addition of methanol (0.5 mL). The mixture was diluted with water (10 mL) and extracted with diethyl ether (3 × 25 mL). The ethereal solution was dried over anhydrous magnesium sulfate. After removing diethyl ether in vacuo, the residue was dissolved in ethanol (2.2 mL) and 1.0 M $Bu_4NH_2PO_4$ (2.2 mL) and the mixture was heated at reflux with stirring for 16 h. The contents were cooled to room temperature, and diethyl ether was added until a biphasic mixture was observed. The biphasic mixture was stirred vigorously for 1 h, and the layers were separated. The aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. Flash chromatography (silica gel, hexanes/ethyl acetate, 10:1) furnished 15.3 mg (81%) of **7** as a colorless oil: IR (NaCl) ν 2921, 1680, 1445 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53−1.63 (m, 2H), 1.80 (dd, J = 5.1, 6.6 Hz, 2H), 1.89 (dd, J = 6.6, 13.9 Hz, 2H), 2.14−2.34 (m, 4H), 2.40 (t, J = 6.6 Hz, 2H), 5.62 (m, 1H), 5.86 (d, J = 10.2 Hz, 1H), 5.94 (m, 1H), 6.83 (d, J = 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 28.6, 34.7, 34.3, 36.8, 37.2, 42.3, 126.6, 126.8, 134.2, 158.5, 200.4; mass spectrum (EI), m/z (rel intensity) 176 (M^+, 68), 109 (71), 91 (77), 79 (100); HRMS, calcd for $C_{12}H_{16}O$ 176.1201, found 176.1203.

Spiro Piperidine 8. To a cooled (−78 °C) solution of **3g** (18.3 mg, 0.062 mmol) in THF (4 mL) was added DIBAL-H (0.5 mL, 1.5 M/toluene). The resulting solution was stirred at −78 °C for 1 h and then warmed to room temperature and stirred for an additional 2 h. The reaction mixture was quenched with aqueous NaOH (1.5 mL, 2 M) and stirred for 3 h. Water was added (40 mL), and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were concentrated in vacuo and dried over anhydrous magnesium sulfate. Flash chromatography (silica gel, hexanes/ethyl acetate 4:1) furnished 16.0 mg (87%) of **8** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (m, 1H), 1.30 (d, J = 6.6 Hz, 3H), 1.35−1.51 (m, 5H), 1.60 (m, 1H), 2.10 (m, 2H), 2.27 (t, J = 6.6 Hz, 2H), 2.36 (m, 1H), 2.69 (dd, J = 2.2, 11.7 Hz, 1H), 3.32 (d, J = 10.2 Hz, 1H), 3.53 (dt, J = 5.1, 10.2 Hz, 1H), 3.69 (t, J = 10.2 Hz, 1H), 4.30 (dd, J = 5.1, 10.2 Hz, 1H), 5.72 (m, 1H), 5.92 (m, 1H), 7.14 (m, 2H), 7.28−7.37 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 21.5, 28.7, 31.9, 33.3, 34.1, 34.5, 45.3, 54.1, 54.9, 59.2, 60.7, 127.5, 128.0, 128.5, 128.9, 133.5.

2-(*tert*-Butylsiloxyethyl)allyl Iodide. To a solution of methyl itaconate (4.24 g, 26.8 mmol) in THF (250 mL) cooled to −78 °C was added neat DIBAL-H (21.0 mL, 117 mmol) dropwise over 15 min. The mixture was stirred for 30 min at −78 °C and then warmed to room temperature. After 1 h the reaction mixture was cooled to 0 °C and water (15 mL) was added (caution!) slowly over 30 min. The reaction mixture slowly gelled. Aqueous NaOH (15 mL, 2.0 M) was added over 30 min followed by an additional 30 mL of water. After 3 h, solid Na_2SO_4 was added (∼40 g) and the mixture was stirred for 12 h. The solids were filtered away and the filter cake washed with THF (300 mL). The solvent was removed to afford a yellow oil that was subjected to flash chromatography (hexanes/ethyl acetate, 4:1) to furnish 2.50 g (91%) of 2-methylenebutane-1,4-diol as a yellow oil that was used in the next step without further purification. Dimethyl sulfide was added (3.0 mL, 40.7 mmol) to a white suspension of *N*-chlorosuccinimide (5.03 g, 37.7 mmol) in dichloromethane (100 mL) and cooled to 0 °C. The resulting milky suspension was stirred for 10 min, and a solution of 2-methylenebutane-1,4-diol (2.50 g, 24.5 mmol) in dichloromethane (10 mL) was added. After 30 min the mixture turned homogeneous, and then the mixture was stirred for 12 h and *tert*-butyldimethylsilyl chloride (4.60 g, 30.5 mmol) and imidazole (3.23 g, 47.4 mmol) were added. The mixture was stirred for an additional 12 h, and the reaction was quenched with aqueous bicarbonate (50 mL). The layers were separated, and the dichloromethane layer was washed with water (3 × 20 mL). The combined aqueous washings were extracted with dichloromethane (2 × 15 mL), and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the crude material was subjected to flash chromatography (hexanes) to afford 4.42 g (77%) of a clear oil that was added to a suspension of K_2CO_3 (5.24 g, 37.9 mmol) and NaI (5.18 g, 34.5 mmol) in acetone (25 mL). This mixture was stirred in the dark for 24 h at ambient temperature. The mixture was then diluted with water (900 mL) and the product extracted with hexanes (3 × 200 mL). The combined organic layers were washed with brine (150 mL) and dried over anhydrous magnesium sulfate. The solvent was removed to furnish 2.47 g (97%) of a light yellow unstable oil that was immediately used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 2.44 (t, J = 6.6 Hz, 2H), 3.76 (t, J = 6. Hz, 2H), 3.97 (s, 2H), 4.94 (d, J = 1.1 Hz, 1H), 5.27 (s, 1H).

Spiro Lactam 9. To a solution of spirocyclo lactam **3e** (1.09 g, 2.74 mmol) in dichloromethane (25 mL) was added [PCy_3-Ir(COD)Py]PF_6 (18.4 mg). The solution was then placed under an atmosphere of hydrogen (balloon) and stirred at ambient temperature. After stirring at room temperature for 36 h, the solvent was removed, and flash chromatography (silica gel, hexanes/ethyl acetate, 4:1) afforded 1.04 g (96%) of spirocyclo lactam **9** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.87 (d, J = 6.6, 3H), 0.88 (s, 9H), 1.02 (d, J = 6.6, 3H), 1.21 (m, 1H), 1.37 (dd, J = 8.8, 12.5, 1H), 1.47 (s, 3H), 1.50−1.71 (m, 4H),1.96 (m, 1H), 2.13−2.32 (m, 5H), 3.51−3.63 (m, 3H), 3.80 (dd, J = 7.3, 8.8, 1H), 4.16 (dd, J = 8.0, 8.8, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, 19.1, 20.7, 25.5, 26.0, 32.7, 33.9, 36.3, 37.1, 39.1, 46.8, 50.5, 53.9, 61.4, 62.6, 70.8, 96.8, 183.8; IR (neat) 2930, 1714, 1471, 1352, 1254, 1101, 1030, 899, 836, 775, 662 cm^{-1}; $[\alpha]_D$ +44 (*c*, 1.41, $CHCl_3$).

Spirocyclopentenone 10. A solution of lactam **9** (239 mg, 0.60 mmol) in THF (6 mL) was cooled to 0 °C, and Red-Al was added (0.3 mL, 1.0 mmol). The resulting mixture was stirred for 1 h at 0 °C and then quenched with MeOH (0.8 mL). The reaction mixture was concentrated in vacuo, the residue was dissolved in EtOH (4 mL), and $Bu_4NH_2PO_4$ (3 mmol) and water (3 mL) were added. The mixture was stirred at room temperature for 17 h and then heated at a gentle reflux for 5 h. The mixture was diluted with water and extracted with ethyl ether. The solvents were removed in vacuo, and the residue was dissolved in EtOH (3 mL) and treated with 1 M NaOH (10 drops). The resulting solution was stirred at room temperature

for 24 h. The solvent was removed in vacuo, and the crude material was partitioned between ethyl ether and water. The aqueous layer was extracted with ethyl ether, and the combined organics were washed with brine and dried over anhydrous magnesium sulfate. Flash chromatography furnished 147 mg (83%) of **10** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.39 (m, 2H), 1.6 (dd, J = 6.6, 13.9, 2H), 1.70 (m, 2H), 2.01 (m, 2H), 2.21 (m, 1H), 2.34 (d, J = 1.5, 2H), 3.61 (t, J = 6.6, 2H), 5.99 (d, J = 5.9, 1H), 7.49 (d, J = 5.9, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, 18.4, 26.0, 32.6, 39.8, 39.3, 39,7, 45.0, 50.2, 62.2, 130.9, 171.9, 209.9; IR (neat) 3420, 2926, 2739, 1713, 1681, 1586, 1471, 1446, 1407, 1387, 1360, 1254, 1177, 1101, 1005, 939, 835, 775, 662 cm^{-1}; $[\alpha]_D$ +34 (*c*, 1.11, $CHCl_3$).

Methyl Spirocyclopentene 11. A slurry of CuCN (290 g, 3.3 mmol) in THF (2 mL) was cooled to −78 °C, and MeLi was added (4.5 mL, 1.4 M). This mixture was warmed to 0 °C for 15 min and then cooled back to −78 °C and stirred for 20 min. Spirocyclopentenone **10** was then added, and the mixture was stirred at −78 °C for 6 h and then warmed to room temperature and stirred for 12 h. The reaction mixture was quenched with NH_4Cl and diluted with water. The aqueous solution was extracted with ethyl ether, and the combined organic layers were concentrated in vacuo. Flash chromatography afforded 184 mg (94%) of **11** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.02 (d, J = 7.4, 3H), 1.13−1.38 (m, 2H), 1.50−1.70 (m, 4H), 1.80−2.20 (m, 6H), 2.24−2.41 (m, 2H), 3.61 (t, J = 6.6, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, 15.0, 18.4, 26.0, 31.9, 32.5, 38.2, 39.2, 39.6, 39.9, 44.3, 218.7 IR (neat) 2928, 2857, 2738, 1746, 1471, 1405, 1386, 1360, 1255, 1160, 1098, 1006, 939, 836, 775, 662 cm^{-1}; $[\alpha]_D$ −2 (*c*, 1.13, $CHCl_3$).

Hydroxy Spirocyclopentene 12. To a solution of silyl ether **11** (184 mg) was added tetrabutylammonium fluoride (0.7 mmol) in THF (4.5 mL). After stirring at room temperature for 2 h, the solvent was removed in vacuo and the residue purified on SiO_2 to furnish 96.2 mg (83%): ^{1}H NMR (300 MHz, CDCl3) δ 0.99 (d, J = 7.4, 3H), 1.13−1.38 (m, 2H), 1.50−1.70 (m, 4H), 1.80−2.20 (m, 6H), 2.24−2.41 (m, 2H), 3.60 (t, J = 6.6, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 15.0, 31.9, 32.3, 36.0, 36.4, 38.1, 39.1, 39.4, 39.6, 44.2, 46.0, 49.7, 53.1, 61.2, 218.9, 219.0; IR (neat) 3417 (br), 2931, 2862, 1745, 1462, 1453, 1404, 1380, 1240, 1203, 1162, 1050 cm^{-1}.

Aldehyde 13. To a cooled (−78 °C) solution of DMSO (0.1 mL) in dichloromethane (5 mL) was added a solution of oxalyl chloride (0.4 mL, 0.8 mmol). This mixture was stirred for 5 min, and alcohol **12** (0.1034 g) was added. After 20 min, triethylamine (0.7 mL) was added and the resulting mixture was stirred for 5 min at −78 °C and then warmed to ambient temperature. The reaction mixture was diluted with ether (100 mL), washed with water (3 × 20 mL) and brine (20 mL), and dried over anhyudrous magnesium sulfate. Flash chromatography (silica gel, hexanes/ethyl acetate, 3:1) furnished 102.6 mg (99%) of aldehyde **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, J = 7.4, 3H), 1.17−1.43 (m, 3H), 1.57−1.75 (m, 2H), 1.83−2.54 (m, 9H), 9.74 (t, J = 1.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 15.1, 31.8, 32.2, 33.4, 33.8, 37.9, 39.1, 39.5, 43.8, 45.9, 50.5, 52.9, 53.4, 201.6, 218.2.

Epoxy Xanthate 18. A solution of aldehyde **13** (45 mg) and TsOH (12.6 mg) in absolute ethanol (10 mL) was stirred for 24 h. The solvent was removed in vacuo, and the residue was filtered though SiO_2. The crude diethyl acetal was then taken up in toluene (10 mL), and TsOH was added (19.2 mg). The resulting solution was heated at reflux for 1.5 h. The solvent was removed in vacuo and the residue purified on SiO_2 to afford 25.1 mg (61%) of the tricycle as a mixture of diastereomers that were used without further purification. Enone **15** (19 mg) was dissolved in THF (2 mL) at −78 °C, and DIBAL-H (0.1 mL, 1.5 M) was added to the solution. The mixture was stirred for 1 h at −78 °C and quenched by the addition of methanol (0.5 mL). The mixture was warmed to room temperature and the solvent removed in vacuo. The residue was partitioned between ethyl ether and 1 M NaOH and purified on SiO_2 to furnish 11.9 mg (62%) of a colorless oil as a mixture of diastereomers that were immediately dissolved in CH_2Cl_2 (2 mL). MCPBA (40.2 mg) was added to the solution and stirred at room temperature for 24 h. The reaction was quenched by adding sodium thiosulfate (3 mL, 5%) and diluted with water (20 mL). The aqueous solution was extracted with ethyl ether, and the combined organic layers were washed with 1 M NaOH and brine and dried over anhydrous magnesium sulfate. The crude diastereomeric epoxides were dissolved in CH_2Cl_2 (1 mL), and thiocarbonyl diimidazole (10.2 mg), followed by 4,4-dimethylamino pyridine (3.0 mg), was added. After 24 h the reaction mixture was filtered through SiO_2 and purified to afford 8.0 mg (84%) of the diastereomeric xanthate esters: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (d, J = 7.3 Hz), 1.14 (d, J = 7.3 Hz), 1.22−2.2 (m), 2.4 (m), 2.7 (m), 3.26 (m), 3.30 (m), 5.87 (t, J = 5.8), 6.09 (dd, J = 3.6, 8.8), 7.02 (s), 7.61 (m), 8.34 (m).

Tricycle 21. A mixture of xanthate ester **18** (8.0 mg), Bu_3SnH (25 μL), and AIBN (1 mg) in benzene (3 mL) was heated to reflux for 4 h. The mixture was cooled, and 3 M NH_4OH (5 mL) was added. The resulting mixture was stirred at room temperature for 3 h, extracted with ethyl ether, washed with brine, and dried over anhydrous magnesium sulfate. The solution was filtered through a plug of SiO_2 to afford 3 mg (64%) of **19** as a colorless solid. The alcohol was taken up in CH_2Cl_2, and a mixture of PDC (30 mg) and Celite (30 mg) was added. The resulting mixture was stirred for 14 h, filtered through SiO_2, and purified to afford 1.5 mg (67%) of enone **20** that was dissolved in EtOH (1.5 mL), and Pd−C (5.2 mg, 10%) was added. The mixture was placed under an atmosphere of hydrogen (balloon). After 12 h, the reaction mixture was filtered through Celite to afford, after solvent evaporation, 1 mg (66%) of the tricyclic ketone **21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, J = 7.3 Hz), 1.07−1.72 (m), 1.81 (m), 1.96 (m), 2.38 (d, J = 8.1 Hz), 2.45 (d, J = 8.1) which agreed with the spectrum of previously prepared material; GC-MS 178 (M^+), 136 (100).

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Supporting Information Available: Spectral data for compounds including X-ray for diol **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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