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Intramolecular Conjugate Addition Reactions of Amines and Carbamates to 2,5-Cyclohexadien-1-ones: Stereoselective Synthesis of Perhydroindoles

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Abstract: *Intramolecular conjugate addition reactions of 4,4-disubstituted-2,5-cyclohexadien-1-ones are described within the context of possible approaches to manzamine A. Amine* ***4*** *provided tricycle* ***6****, with improper relative stereochemistry for use in an approach to manzamine A. Carbamates* ***25*** *and* ***38*** *gave perhydroindoles* ***26*** *and* ***28b*** *under conditions of thermodynamic control, respectively, with the proper relative stereochemistry required for manzamine A. Carbamate* ***25*** *gave diastereomeric perhydroindole* ***27*** *under conditions of thermodynamic control.*
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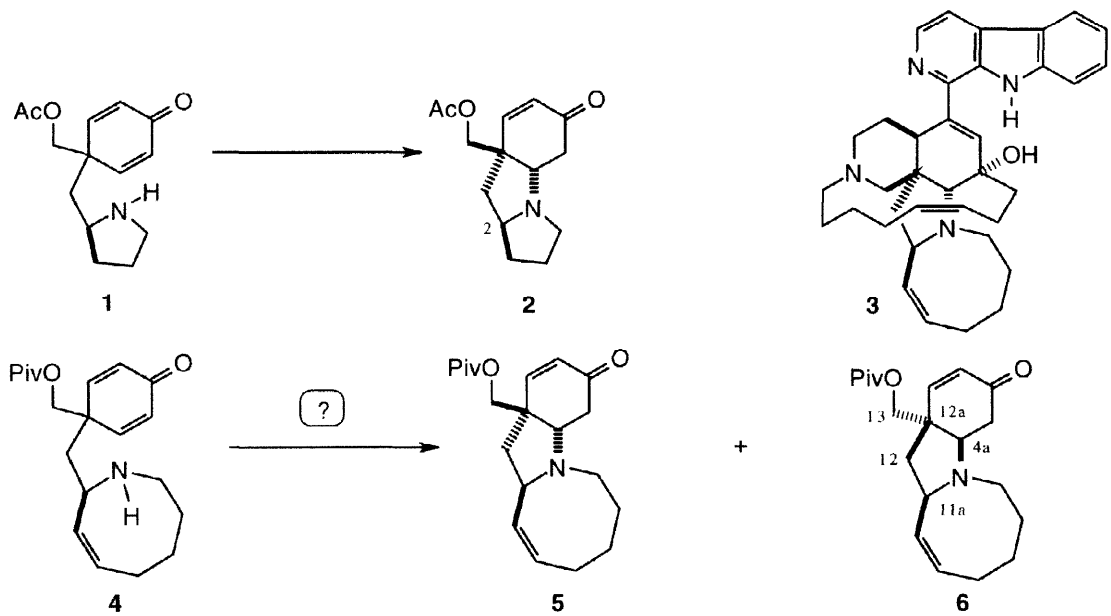
A number of stereoselective 1,4-cyclohexadiene desymmetrization reactions have been reported in which a stereogenic center in the cyclization substrate determines the stereochemical course of the reaction. For example, the Curran group has provided a nice example of such diastereoselectivity in a free radical cyclization and the Wipf group has reported a diastereoselective intramolecular conjugate addition of a carbamate to a 2,5-cyclohexadien-1-one.[1-3] We recently reported that amino cyclohexadienone **1** undergoes a diasteroselective intramolecular conjugate addition reaction to provide perhydropyrrolo[1,2-*a*]indole **2**, another example of this process.[4] This article describes an attempt to extend this process to an approach to the marine alkaloid manzamine A (**3**), and delineates some of the scope and limitations of this process.[5]



Our approach called for the synthesis of amino cyclohexadienone **4** and examination of the stereochemical course of its intramolcular conjugate addition reaction. Of course it was hoped that this process would afford the desired tricyclic manzamine A substructure **5** rather than its diastereomer **6**. The synthesis of a precursor of **4** was accomplished as shown in Scheme 1.[6] Reductive alkylation of benzoic acid (**7**) with 2-bromoethyl *tert*-butyl ether gave crude dihydrobenzoic acid **8** in 98% yield.[7] Treatment of crude **8** with ethyl chloroformate in the presence of triethylamine, followed by reduction of the intermediate mixed anhydride with sodium borohydride, afforded alcohol **9** in 94% yield after purification. Esterification of **9** using pivaolyl chloride provided **10** (87%). Deprotection of the *tert*-butyl ether using a catalytic amount of ferric chloride in acetic anhydride,[8] followed by hydrolysis of the intermediate acetate with sodium hydroxide, gave alcohol **11** (90%). Swern oxidation of **11** provided aldehyde **12** in 96% yield.[9] Reaction of **12** with the organolithium reagent derived from *tert*-butyl 5-

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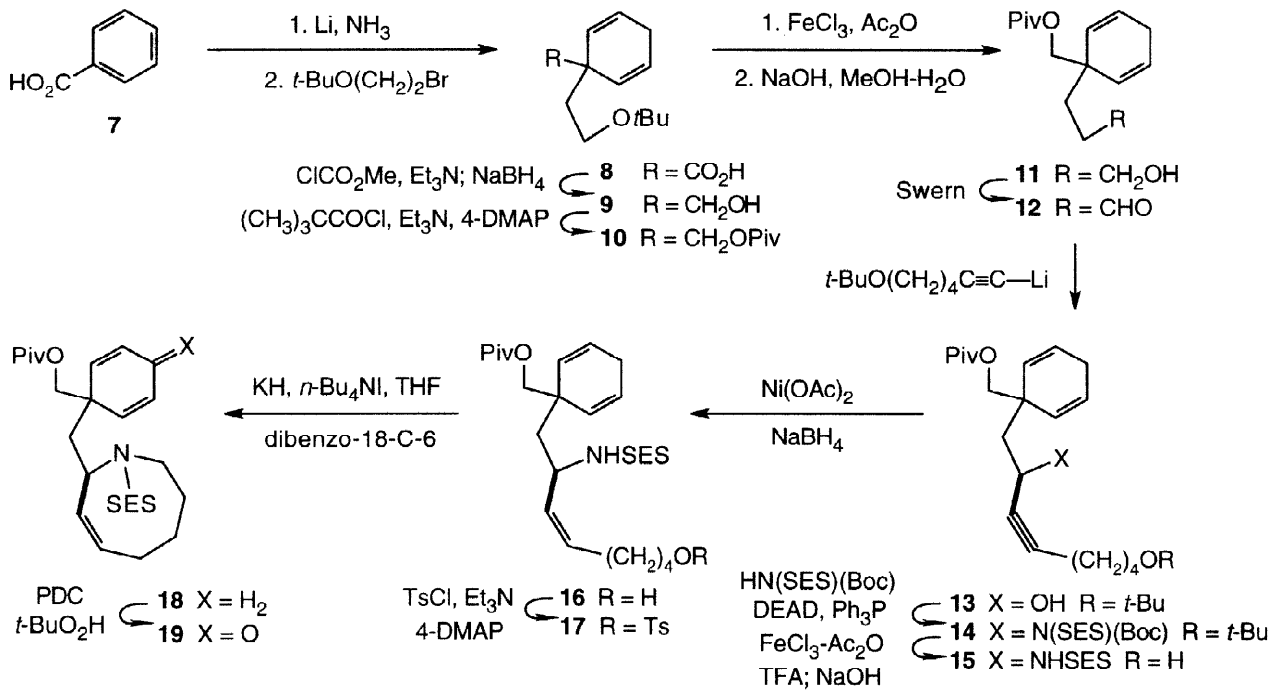
hexynyl ether gave a 90% yield of alcohol **13**, which reacted with *tert*-butyl 2-[(trimethylsilyl)ethyl]-sulfonylcarbamate under Mitsunobu conditions to afford **14** (73%).[10-12] The *tert*-butyl ether protecting group was once again replaced by an acetate using ferric chloride-acetic anhydride, followed by removal of the Boc-group using trifluoroacetic acid, and acetate hydrolysis to give hydroxy sulfonamide **15** (93%). Reduction of the triple bond using nickel boride[13] provided *cis*-olefin **16** (90%), which was converted to tosylate **17** (93%) using *p*-toluenesulfonyl chloride and triethylamine in the presence of 4-(dimethylamino)pyridine. Treatment of **17** (0.01 M in toluene) with potassium hydride in the presence of tetra-*n*-butylammonium iodide (1.1 equiv) and dibenzo-18-crown-6 (0.2 equiv) gave azocine **18** in 80% yield. Oxidation of **18** using pyridinium dichromate and *tert*-butyl hydroperoxide in benzene gave dienone **19** as a crystalline material in 73% yield.[14]

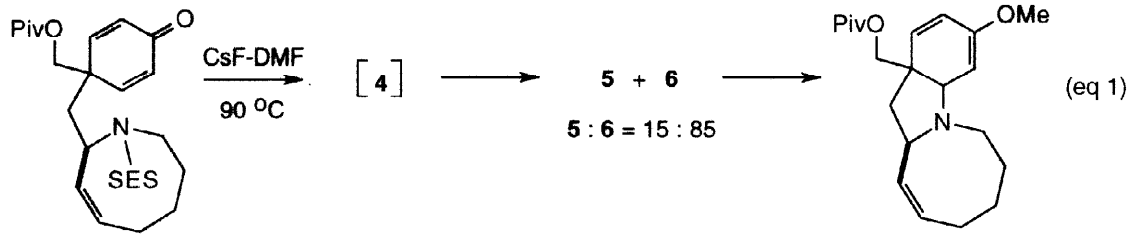
Scheme 1



Generation of amino cyclohexadienone **4** was accomplished by deprotection of **19** with cesium fluoride in *N,N*-dimethylformamide at 90 °C.[11] This gave an 88% crude yield of tricyclic enones **6** and **5** in approximately an 85:15 ratio, respectively (equation 1). The major isomer was isolated from this mixture in 70-80% yield in reasonably pure form by column chromatography over alumina. The presence of the minor isomer in the crude mixture was inferred from signals that appeared in the ^{1}H NMR spectrum, as delineated in the experimental section. The stereochemical assignment for the major isomer was based on difference nOe experiments.[15] Thus, by a combination of ^{1}H-^{1}H and ^{1}H-^{13}C COSY experiments, it was possible to locate the diastereotopic protons of the C_{13} (δ 3.97 and 4.26) and C_{12} (δ 1.60 and 2.16) methylene groups, the vinylic signal due to the proton on C_1 (δ 6.44), and the methine signals at C_{4a} (δ 2.78) and C_{11a} (δ 3.30) in $CDCl_3$. The critical difference nOe experiments involved irradiation of H_{11a} which showed enhancement of the signals due to H_{4a} (2%) and $H_{12\alpha}$ (5% at δ 2.16 and 0% at δ 1.60), and independent irradiation of the H_{13} signals which also showed enhancement of signals due to H_{4a} (2-3%) and $H_{12\alpha}$ (2-3% at δ 2.16 and 0% at δ 1.60). These experiments indicate a *cis*-relationship between H_{4a} and H_{11a} on the pyrrolidine ring, consistent with structure **6** and inconsistent with structure **5**. Other nOe experiments were also consistent with this assignment.

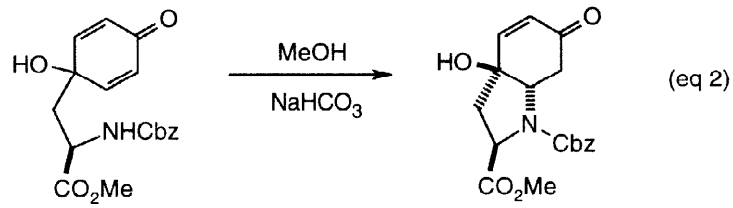
The stereochemical outcome of the cyclization shown in equation 1 was discouraging from the standpoint of a projected synthesis of manzamine A because **6** has the wrong stereochemistry at C_{4a} and C_{12a} relative to C_{11a}. It was unclear whether or not the partitioning of **4** between **5** and **6** was dictated by thermodynamics or kinetics and thus, some epimerization experiments were conducted. It was possible to convert **6** to the corresponding hydrochloride salt, but warming this material in chloroform or acetonitrile lead only to slow formation of a myriad of products. Warming this salt in methanol did provide enol ether **20** (40%) whose relative stereochemistry at the three stereogenic centers was not proven. The most successful epimerization experiment involved treatment of **6**

with boron trifluoride etherate in toluene at 80 °C for 17 h, which afforded modest recovery of a 7:3 mixture of **6** and **5**, respectively, after a basic work-up. Although these experiments were not definitive in regard to the question of thermodynamic versus kinetic control of the cyclization, they did indicate that this route was unlikely to be useful, in terms of stereochemistry, as an approach to manzamine A.



19 **20**

The Wipf group had reported that the cyclization of carbamate **21** gave perhydroindole **22** with excellent diastereoselectivity (equation 2).[2] Based on this result, our attention turned to **25**, a substrate that could be converted to a tricyclic manzamine substructure if the cyclization proceeded with the required stereochemistry. The cyclization substrate was prepared from alkyne **14**. Catalytic hydrogenation of **14** over palladium on barium sulfate in the presence of pyridine gave *cis*-olefin **23** (equation 3) in 60% yield.[16] Oxidation of **23** provided dienone **24** (60%).[14] We initially examined *in situ* generation and cyclization of **25** under conditions similar to those used to generate **1** and **4**. These conditions (CsF, DMF, 85 °C, 18 h) gave a good yield of an 85:15 mixture of **27** and **26**, respectively, from which pure **27** could be isolated in 45% yield by chromatography. The course of the reaction, however, could be altered by lowering the reaction temperature. For example, treatment of **24** with CsF-DMF at room temperature for 3.5 h gave dienone **25** (81%) as the major product. Resubjecting **25** to CsF-DMF at room temperature for 3 h now provided a 77% yield of **26** contaminated with a trace of **27**, from which pure **26** could be isolated by column chromatography. Finally, treatment of either **26** or **27** with CsF-DMF at 94 °C for 21-41 h gave an 85:15 mixture of **27** and **26**, respectively (50-85% recovery). These experiments indicate that **27** is thermodynamically more stable than **26**, but **26** is the cyclization product of kinetic control. It is notable that treatment of dienone **25** with $NaHCO_3$-MeOH (Wipf cyclization conditions) also gave **26** as the major product (36%) accompanied by only a trace of **27**.[17]



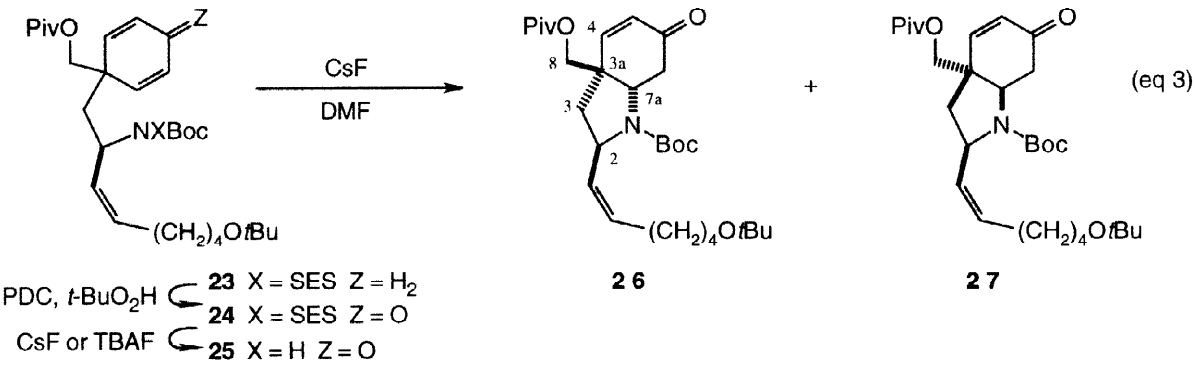
21 **22**

The stereochemical assignment for **26** was based on difference nOe experiments. Thus, irradiation of H_2 (δ 4.54 in $CDCl_3$) resulted in a 7.5% enhancement of the signal due to $H_{3\beta}$ (δ 2.2). Irradiation of $H_{3\beta}$ gave 25%, 9% and 6% enhancements of signals due to $H_{3\alpha}$ (δ 1.80), H_2 and H_4 (δ 6.55), respectively. Irradiation of $H_{3\alpha}$ resulted in a 26% nOe at $H_{3\beta}$ and 2-3% enhancement of signals due to the diasterotopic H_8 methylenes (δ 4.25 and 4.05) and H_{7a} (δ 4.20). Irradiation of the H_8 methylene at δ 4.25 also gave a 4% enhancement of the H_{7a} methine. These experiments (and others) clearly established the stereochemical relationship of substituents around the pyrrolidine ring. The stereochemistry for **27** was assigned by inference from the aforementioned experiments.

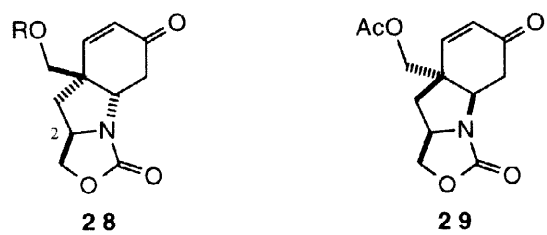
In addition to the stereochemical features described above, there is one other interesting aspect to the chemistry described in equation 3. As noted above, it was observed that treatment of **24** with CsF-DMF at room temperature gave **25**, but treatment of **25** with the identical reactions conditions used to deprotect **24** gave **26**. This suggests that an intermediate which cannot undergo an intramolecular conjugate addition reaction is initially formed in the deprotection of **24**, and that **25** is only produced upon workup. Although we have no direct evidence, it seems reasonable that this intermediate be an amine-sulfur dioxide adduct ($RNSO_2^-$ Cs^+) that only loses SO_2 upon

either warming or protonation. This suggests that deprotection reactions of *N*–SES amines and amides most likely involve two sequential fragmentations rather than a single fragmentation.

The results shown in equation 3 indicated that application of this desymmetrization strategy to manzamine A might be complicated by thermodynamic problems. In otherwords, any stereocontrol gained in a cyclization step might be lost later due to a retro-Michael-Michael process. In an attempt to guide future studies, some model molecular mechanics calculations were performed.[18, 19] In agreement with the experimental observations, the calculations indicated that carbamate **27** was lower in energy than carbamate **26**. The calculations also agreed with the suggestion that the stereochemistry observed in the cyclizations of **1** and **4** might be a function of relative product stability. For example, calculations suggested that both **2** and **6** are more stable than 2-epi-**2** and **5**, respectively. Since these examples suggested that fusion of a 5-membered ring to the 1,2-position of a perhydroindole would provide the thermodynamic bias needed to establish the stereochemistry required by manzamine A, a carbamate of type **28** was set as our next target. Indeed, calculations indicated that **28a** would be more stable than the diastereomeric carbamate **29**.[18] Carbamate **28b** was selected as the actual target for synthesis. It was imagined that the C_{3a} substituent would provide a functional handle for construction of the azocine ring and the malonyl group would provide a handle for construction of the A-ring of the manzamine alkaloids.



The synthesis of **28b** is shown in Scheme 2. Reductive alkylation of benzoic acid with allyl bromide gave **30** in 92% yield. Conversion of **30** to the corresponding acid chloride followed by ammonolysis provided amide **31** (91%). Application of the Knapp lactamization process gave **32** (57%).[20] *N*-Acylation of **32** using di-*tert*-butyl dicarbonate and 4-(dimethylamino)pyridine provided **33** in 65% yield. Methanolysis of **33** gave ester **34** (54%).[21] Treatment of **34** with pyridine in toluene at reflux resulted in cyclization to carbamate **35** (63%). Reduction of **35** with lithium borohydride gave **36** in 57% yield and esterification of this alcohol with monobenzyl malonate, using dicyclohexylcarbodiimide and 4-dimethylaminopyridine, provided **37** in 96% yield. Oxidation of **37** with pyridnium dichromate and *tert*-butyl hydroperoxide completed gave dienone **38** (44%).[14]



28

a R = $COCH_3$

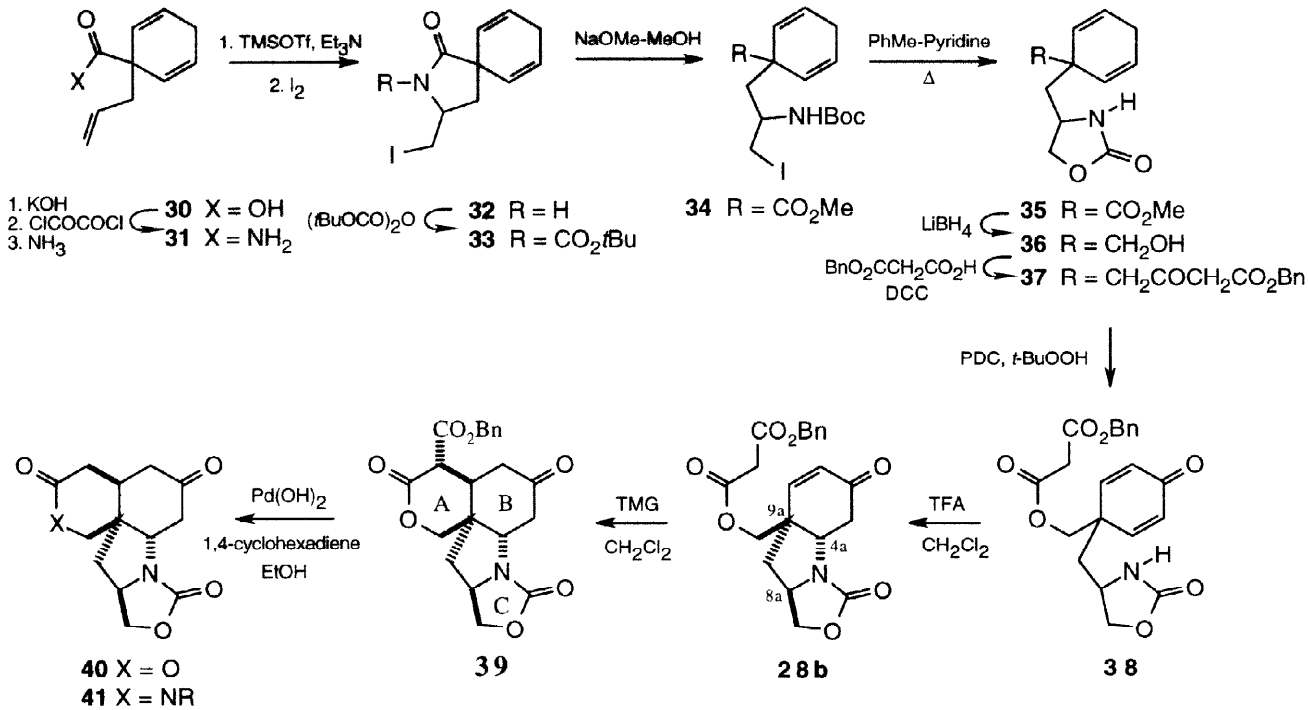
b R = $COCH_2CO_2Bn$

29

The next objective was to convert dienone **38** to tetracycle **39** via **28b** using two sequential intramolecular conjugate addition reactions. To achieve stereoselectivity in this overall transformation, it was necessary to trigger the carbamate cyclization first. This was accomplished under acidic conditions as treatment of **38** with trifluoroacetic acid in dichloromethane at room temperature for 7 h gave an 88% yield of **28b** as the major diastereomer.[22, 23] The stereochemistry of **28b** was assigned on the basis of difference nOe experiments that established the relationship of substituents on the pyrrolidine ring. Cyclization of **28b** to **39** was accomplished in

70% yield using tetramethylguanidine as the base. The structure of **39**, including stereochemistry, was consistent with ^{1}H-NMR spectroscopic data and was established by X-ray crystallography.[24] Transfer hydrogenolysis of **39** provided keto lactone **40** in 78% yield.[25]

Scheme 2



Whereas it was gratifying to see the cyclization of **38** give **28b** as a single diastereomer, conversion of the A-ring lactone oxygen to an A-ring lactam (for example **41**) has been problematic to date. We are hopeful, however, that the stereoselectivity patterns that have been uncovered in the course of this research, will extend the use of cyclohexadienone cyclizations in complex molecule synthesis.

Experimental Section[26]

1-(2-*tert*-Butoxyethyl)-2,5-cyclohexadiene-1-carboxylic acid (8). To a solution of 20.0 g (0.164 mol) of benzoic acid in 200 mL of THF in a 2-L round bottom flask equipped with a dry ice-acetone condenser and cooled in a dry ice-acetone bath was condensed 600 mL of ammonia. To the resulting mixture was added 2.84 g (0.409 mol) of Li metal in approximately 0.2 g portions over 15 min. The reaction held a dark blue color for 2.5 h, and then 47.5 mL (0.328 mol) of 2-bromoethyl *tert*-butyl ether was added over a period of 10 min. The ammonia was allowed to evaporate overnight, and the residue was partitioned between 400 mL of water and 100 mL of pentane. The aqueous layer was extracted with two 100-mL portions of ether, cooled in an ice-water bath and the pH was adjusted to 1 by addition of 50 mL of concentrated aqueous HCl. The resulting mixture was saturated with sodium chloride and extracted with three 100-mL portions of CH_2Cl_2. The combined extracts were dried ($MgSO_4$), and concentrated under reduced pressure to yield 36.1 g (98%) of carboxylic acid **8** as a pale yellow oil suitable for use in the next reaction: IR (neat) 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 9H), 1.93 (t, J = 7.0, 2H), 2.61 (m, 2H), 3.34 (t, J = 7.0, 2H), 5.7-5.9 (m, 4H), the acidic proton was not recorded; ^{13}C NMR ($CDCl_3$) δ 25.9, 27.2, 39.8, 46.0, 57.5, 73.1, 125.6, 126.8, 180.4; exact mass calcd. for $C_{13}H_{20}O_3$ *m/z* 224.1412, found *m/z* 224.1405.

1-(2-*tert*-Butoxyethyl)-2,5-cyclohexadiene-1-methanol (9). To a vigorously stirred solution of 20.2 g (90.1 mmol) of acid **8** in 25.1 mL of triethylamine and 450 mL of THF was added 15.5 mL (162 mmol) of ethyl chloroformate over 30 min maintaining the temperature at -5-10 °C. A freshly prepared solution of 13.7 g (361 mmol) of sodium borohydride in 20 mL of water was then added over a period of 10 min. The resulting mixture was stirred at rt for 1 h, THF was removed in vacuo, and the residue was partitioned between 200 mL of ether and

100 mL of brine. The aqueous layer was extracted with two 100-mL portions of ether, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed over 200 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 3:7) to provide 17.8 g (94%) of alcohol **9**, 1.23 g of which was distilled at 124 °C/1 torr to give 0.92 g of the alcohol as a colorless liquid: IR (neat) 3424 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.61 (t, *J* = 6.7, 2H), 2.65 (m, 2H), 3.38 (t, *J* = 6.7, 2H), 5.55 (dt, *J* = 10.5, 2.0, 2H), 5.89 (dt, *J* = 10.5, 3.3, 2H), the hydroxyl proton was not detected; ^{13}C NMR ($CDCl_3$) δ 26.5 (t), 27.3 (q), 38.3 (t), 41.1 (s), 57.7 (t), 70.0 (t), 73.0 (s), 125.8 (d), 129.9 (d); exact mass calcd. for $C_{13}H_{23}O_2$ (M^++H) *m/z* 211.1698, found *m/z* 211.1692.

[1-(2-*tert*-Butoxyethyl)-2,5-cyclohexadiene-1-yl]methyl pivalate (10). To a solution of 14.1 g (67.1 mmol) of alcohol **9** and 0.82 g (6.7 mmol) of 4-DMAP in 28.0 mL of triethylamine and 140 mL of CH_2Cl_2 was added 12.4 mL (101 mmol) of pivaloyl chloride in one portion with cooling in an ice bath. The resulting mixture was stirred at rt for 54 h, then diluted with 150 mL of ether, followed by addition of 50 mL of brine and 21 mL of concentrated aqueous HCl with cooling in an ice bath. The organic layer was washed with 100 mL of 1N aqueous HCl and 100 mL of brine. The combined aqueous layer was extracted with 150 mL of ether. The obtained extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The remaining pivaloyl chloride was removed from the residue by evaporation at 40-50 °C/1 torr for 4 h and the crude product was chromatographed over 200 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 1:9) to provide 17.2 g (87%) of pivaloate **10** as a colorless oil, and 0.9 g (6%) of starting alcohol: IR (neat) 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (s, 9H), 1.11 (s, 9H), 1.57 (t, *J* = 7.8, 2H), 2.55 (m, 2H), 3.24 (t, *J* = 7.8, 2H), 3.81 (s, 2H), 5.40 (dt, *J* = 10.5, 2.0, 2H), 5.76 (dt, *J* = 10.5, 3.4, 2H); ^{13}C NMR ($CDCl_3$) δ 26.4 (t), 27.1 (q), 27.4 (q), 37.9 (t), 38.7 (s), 39.4 (s), 58.3 (t), 70.7 (t), 72.6 (s), 125.7 (d), 129.1 (d), 178.1 (s); exact mass calcd. for $C_{18}H_{31}O_3$ (M^++H) *m/z* 295.2272, found *m/z* 295.2276.

[1-(2-hydroxyethyl)-2,5-cyclohexadiene-1-yl]methyl pivalate (11). To a solution of 17.2 g (58.4 mmol) of ether **10** in 130 mL of acetic anhydride was added 0.66 g (4.1 mmol) of ferric chloride in one portion with cooling in an ice bath. After 15 min, 100 g of sodium bicarbonate was added. The resulting mixture was diluted with 150 mL of ether, stirred for 20 min at rt and then filtered through a 50 g pad of silica gel. Solvents were removed under reduced pressure (40 °C/1 torr). The residue was dissolved in 150 mL of methanol and warmed with 6.7 g of 40% aqueous sodium hydroxide at 15 °C for 30 min. To the mixture was added 100 mL of EtOAc and 10 mL of brine. Solvents were removed in vacuo and the residue was partitioned between 150 mL of ether and 100 mL of brine. The aqueous layer was extracted with 100 mL of ether. Combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed over 200 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 3:7) to provide 12.5 g (90%) of hydroxyester **11** as a colorless oil: IR (neat) 3386, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 9H), 1.62 (t, *J* = 6.8, 2H), 1.95 (s, 1H), 2.59 (m, 2H), 3.59 (t, *J* = 6.8, 2H), 3.82 (s, 2H), 5.45 (dt, *J* = 10.5, 2.0, 2H), 5.83 (dt, *J* = 10.5, 3.4, 2H); ^{13}C NMR ($CDCl_3$) δ 26.3 (t), 27.1 (q), 38.8 (s), 39.7 (t), 59.9 (t), 70.6 (t), 126.4 (d), 129.1 (d), 178.2 (s), one upfield singlet was not observed; exact mass calcd. for $C_{14}O_{23}O_3$ (M^++H) *m/z* 239.1647, found *m/z* 239.1641.

[1-(Formylethyl)-2,5-cyclohexadiene-1-yl]methyl pivalate (12). To a solution of 5.03 mL (57.7 mmol) of oxalyl chloride in 280 mL of CH_2Cl_2 cooled in a dry ice-acetone bath was added 8.18 mL (115.3 mL) of dimethylsulfoxide. The solution was stirred for 10 min followed by addition of 12.4 g (51.9 mmol) of alcohol **11** in 70 mL of CH_2Cl_2. The resulting white suspension was stirred for additional 10 min and 36.2 mL (260 mmol) of triethylamine was added. The cooling bath was replaced with an ice bath. The mixture was stirred for 1 h, quenched with 100 mL of brine and 15 mL concentrated aqueous HCl, and extracted with 200 mL of heptane and 100 mL of ether. The aqueous layer was extracted with 50 mL of ether, the organic layers were combined and dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed over 200 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 1:9) to provide 11.8 g (96%) of aldehyde **12** as a colorless oil: IR (neat) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 9H), 2.34 (d, *J* = 3.0, 2H), 2.60 (m, 2H), 3.87 (s, 2H), 5.54 (br d, *J* = 9.5, 2H), 5.87 (br d, *J* = 9.5, 2H), 9.57 (t, *J* = 3.0, 1H); ^{13}C NMR ($CDCl_3$) δ 26.3 (t), 27.0 (q), 38.7 (s), 38.8 (s), 50.0 (t), 70.0 (t), 127.1 (d), 127.4 (d), 177.8 (s), 202.0; exact mass calcd. for $C_9H_{10}O$ [M^+-$(CH_3)_3CCO_2H$] *m/z* 134.0732, found *m/z* 134.0746.

(±)-[1-(8-*tert*-Butoxy-2-hydroxy-3-octynyl)-2,5-cyclohexadiene-1-yl]methyl pivalate (13). To a solution of 3.46 g (22.4 mmol) of *tert*-butyl 5-hexynyl ether[27] in 50 mL of THF was added 8.8 mL of a 2.5 M solution of *n*-BuLi in hexanes in one portion with cooling in a dry ice-acetone bath. The resulting mixture was then stirred for 30 min with cooling in an ice-water bath and then cannulated over a period of 1 h into a solution of 5.04 g (21.3 mmol) of aldehyde **12** in 50 mL of THF cooled in dry ice-acetone bath. The mixture was stirred for 10 more min with cooling in an ice-water bath, followed by addition of 10 mL of aqueous saturated sodium bicarbonate and 100 mL of pentane. The organic layer was washed with 10 mL of brine. The combined

aqueous phases were extracted with 20 mL of ether. The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed over 150 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 2:8) to provide 7.49 g (90%) of alcohol **13** as a colorless oil: IR (neat) 3430, 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 18H), 1.53 (m, 4H), 1.76 (dd, J = 14.1, 4.3, 1H), 1.87 (dd, J = 14.1, 7.9, 1H), 2.16 (m, 2H), 2.62 (m, 2H), 3.29 (t, J = 6.1, 2H), 3.83 (s, 2H), 4.44 (m, 1H), 5.44 (dd, J = 10.6, 2.1, 1H), 5.60 (dd, J = 10.6, 2.1, 1H), 5.86 (dt, J = 10.6, 3.3, 2H); ^{13}C NMR ($CDCl_3$) δ 18.5 (t), 25.3 (t), 26.3 (t), 27.1 (q), 27.5 (q), 29.7 (t), 38.8 (s), 40.0 (s), 46.0 (t), 60.2 (d), 60.8 (t), 70.4 (t), 72.4 (s), 81.5 (s), 85.1 (s), 126.66 (d), 126.72 (d), 128.5 (d), 129.6 (d), 178.1 (s); exact mass calcd. for $C_{24}H_{37}O_4$ (M^+-H) *m/z* 389.2692, found *m/z* 389.2325.

***tert*-Butyl-(±)-[7-*tert*-butoxy-1-[[1-(hydroxymethyl)-2,5-cyclohexadiene-1-yl]methyl]-2-heptynyl][[2-(trimethylsilyl)ethyl]sulfonyl]carbamate, pivalate (ester) (14)**. To a solution of 5.96 g (15.3 mmol) of alcohol **13**, 6.01 g (21.4 mmol) of SESNHBoc, and 4.98 g (18.5 mmol) of Ph_3P in 65 mL of THF was added 3.07 mL (18.3 mmol) of 94% solution of diethyl azodicarboxylate in CH_2Cl_2 in one portion with cooling in an ice-water bath. The mixture was allowed to warm to 15 °C for 4 h, 10 g of silica gel and 150 mL of hexanes was added, and the mixture was filtered through 50 g of silica gel. The filtrate was concentrated and chromatographed over 200 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 2:8) to provide 7.34 g (73%) of sulfonamide **14** as a pale yellow oil: IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H), 1.02 (m, 2H), 1.15 (s, 9H), 1.16 (s, 9H), 1.4-1.6 (m with underlying singlet, 13H), 1.99 (dd, J = 14.0, 4.2, 1H), 2.14 (m, 2H), 2.29 (dd, J = 14.0, 8.2, 1H), 2.58 (A of ABq, J = 23.0, 1H), 2.68 (B of ABq, J = 23.0, 1H), 3.26 (m, 1H), 3.31 (t, J = 6.0, 2H), 3.45 (m, 1H), 3.81 (A of ABq, J = 10.6, 1H), 3.86 (B of ABq, J = 10.6, 1H), 5.00 (m, 1H), 5.47 (brt, J = 10.8, 2H), 5.88 (m, 2H); ^{13}C NMR ($CDCl_3$) δ -2.1 (q), 10.0 (t), 18.5 (t), 25.5 (t), 26.5 (t), 27.1 (q), 27.5 (q), 28.0 (q), 29.8 (t), 38.8 (s), 40.4 (s), 44.4 (t), 47.3 (d), 50.5 (t), 60.7 (t), 70.6 (t), 72.3 (s), 79.0 (s), 83.8 (s), 84.2 (s), 126.7 (d), 127.6 (d), 127.8 (d), 128.2 (d), 151.1 (s), 178.1 (s); exact mass calcd. for $C_{34}H_{61}NO_7SSi$ (M^++2H) *m/z* 655.3938, found *m/z* 655.0248.

(±)-[1-[8-hydroxy-2-[2-(trimethylsilyl)ethanesulfonamido]-3-octynyl]-2,5-cyclohexadiene-1-yl]methyl pivalate (15). As described for the preparation of **11**, 6.90 g (10.6 mmol) of ether **14** was reacted with 0.12 followed by filtration through 20 g of silica gel gave 7.11 g of crude product. This material was dissolved in 100 mL of CH_2Cl_2 and treated with 4.65 mL (63.3 mmol) of dimethylsulfide and 24.4 mL (317 mmol) of trifluoroacetic acid. The mixture was stirred for 9 h at rt and quenched with 40 mL of saturated aqueous sodium bicarbonate and 23 g of solid sodium bicarbonate with cooling in an ice-water bath. The heterogenous mixture was stirred for additional 2 h at rt, and diluted with 100 mL of ether. The aqueous layer was extracted with 50 mL of ether. The combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in 50 mL of methanol and 1.08 mL of 40% aqueous sodium hydroxide was added. The solution was stirred for 30 min at rt following by addition of 10 mL of brine. Solvents were removed in vacuo and residue was partitioned between 100 mL of ether and 20 mL of brine. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and the residue was chromatographed over 200 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 1:1) to afford 4.91 g (93%) of hydroxysulfonamide **15** as a pale yellow oil: IR (neat) 3500, 3275, 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (s, 9H), 1.02 (m, 2H), 1.16 (s, 9H), 1.5-1.7 (m, 5H), 1.83 (d, J = 6.6, 2H), 2.17 (td, J = 6.7, 2.0, 2H), 2.60 (A of ABq, J = 24.0, 1H), 2.73 (B of ABq, J = 24.0, 1H), 3.01 (m, 2H), 3.63 (t, J = 6.2, 2H), 3.84 (A of ABq, J = 10.7, 1H), 3.86 (B of ABq, J = 10.7, 1H), 4.19 (m, 1H), 4.61 (m, 1H), 5.49 (br t, J = 12.4, 2H), 5.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ -2.0 (q), 10.3 (t), 18.5 (t), 24.8 (t), 25.9 (t), 26.4 (t), 27.3 (q), 31.8 (t), 38.9 (s), 40.0 (s), 43.1 (d), 44.1 (t), 49.8 (t), 62.1 (t), 70.4 (t), 80.2 (s), 84.6 (s), 127.4 (d), 128.4 (d), 176.3 (s), one sp2-hybridized carbon was not observed due to overlap; exact mass calcd. for $C_{25}H_{44}NO_5SSi$ (M^++H) *m/z* 498.2709, found *m/z* 498.2737.

(±)-[1-[(Z)-8-hydroxy-2-[2-(trimethylsilyl)ethanesulfonamido]-3-octenyl]-2,5-cyclohexadiene-1-yl]methyl pivalate (16). To a mixture of 98 mg (2.60 mmol) of sodium borohydride and 648 mg (2.60 mmol) of nickel diacetate tetrahydrate was added 30 mL of 96% aqueous ethanol, accompanied by hydrogen evolution. The solution was stirred for 5 min at rt, 2.17 mL (15.6 mmol) of triethylamine was added followed by 5 min of stirring and then addition of 5.18 g (10.4 mmol) of sulfonamide **15** in 20 mL of ethanol. The resulting black suspension was evacuated and filled with hydrogen three times, and stirred under an atmosphere of hydrogen for a period of 7 h during which 279 mL (11.4 mmol) of hydrogen was absorbed. The reaction mixture was diluted with 100 mL of ether, filtered through 25 g of silica gel, and the filtrate was concentrated in vacuo. The residue was chromatographed over 150 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 1:1) to provide 4.68 g (90%) of olefin **16** as a colorless oil: IR (neat) 3552, 3298, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.01 (s, 9H), 0.94 (m, 2H), 1.15 (s, 9H), 1.4-1.8 (m, 7H), 2.09 (m, 2H), 2.67 (A of br ABq, J = 24.0, 1H), 2.75 (B of br ABq, 1H), 2.82 (m, 2H), 3.62 (t, J = 6.5, 2H), 3.81 (A of ABq, J = 10.6, 1H), 3.83 (B of ABq, J = 10.6, 1H),

4.34 (m, 1H), 4.54 (m, 1H), 5.21 (t, J = 10.2, 1H), 5.41 (m, 2H), 5.55 (dd, J = 10.2, 2.2, 1H), 5.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ -2.0 (q), 10.4 (t), 25.4 (t), 26.5 (t), 27.1 (t), 27.1 (q), 32.1 (t), 38.9 (s), 40.1 (s), 42.4 (t), 48.7 (d), 50.1 (t), 62.3 (t), 70.7 (t), 127.4 (d), 127.6 (d), 128.1 (d), 128.9 (d), 130.9 (d), 131.8 (d), 178.2 (s); exact mass calcd. for $C_{20}H_{32}NO_3$ (M^+-$SO_2CH_2CH_2SiMe_3$) m/z 334.2382, found m/z 334.2383.

(±)-[1-[(*Z*)-8-hydroxy-2-[2-(trimethylsilyl)ethanesulfonamido]-3-octenyl]-2,5-cyclohexadiene-1-yl]methyl pivalate, *p*-toluenesulfonate (ester) (17). To a solution of 4.68 g (9.36 mmol) of alcohol **16**, 0.10 g (0.82 mmol) of 4-DMAP, and 5.80 mL (41.6 mmol) of triethylamine in 100 mL of CH_2Cl_2 was added 3.01 g (15.8 mmol) of *p*-toluenesulfonyl chloride in one portion with cooling in an ice-water bath. The resulting mixture was stirred at rt for 4.5 h, diluted with 150 mL of ether, and washed sequentially with 50 mL of brine (adjusting acidity of aqueous phase to pH 1 with aqueous HCl), and 40 mL of saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and chromatographed over 200 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 3:7) to give 5.70 g (93%) of tosylate **17** as a pale yellow oil: IR (neat) 3296, 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ -0.01 (s, 9H), 0.93 (m, 2H), 1.15 (s, 9H), 1.3-1.7 (m, 6H), 2.04 (m, 2H), 2.42 (s, 3H), 2.64 (A of br ABq, J = 23.0, 1H), 2.73 (B of br ABq, 1H), 2.80 (m, 2H), 3.81 (br s, 2H), 4.00 (t, J = 6.4, 2H), 4.29 (m, 1H), 4.53 (m, 1H), 5.20 (t, J = 9.6, 1H), 5.31 (t, J = 7.1, 1H), 5.40 (dd, J = 10.2, 2.1, 1H), 5.53 (dd, J = 10.2, 2.0, 1H), 5.93 (m, 2H), 7.33 (d, J = 8, 2H), 7.75 (d, J = 8, 2H); ^{13}C NMR ($CDCl_3$) δ -2.1 (q), 10.4 (t), 21.6 (q), 25.2 (t), 26.5 (t), 26.8 (t), 27.1 (q), 28.5 (t), 38.9 (s), 40.1 (s), 42.3 (t), 48.6 (d), 50.1 (t), 70.2 (t), 70.6 (t), 127.3 (d), 127.5 (d), 127.8 (d), 128.2 (d), 128.9 (d), 129.8 (d), 131.0 (d), 131.3 (d), 133.1 (s), 144.7 (s), 178.1 (s); exact mass calcd. for $C_{27}H_{38}O_5S$ (M^+-$SO_2CH_2CH_2SiMe_3$) m/z 488.2451, found m/z 488.2538.

(±)-[1-[[1,2,5,6,7,8-Hexahydro-1-[[2-(trimethylsilyl)ethyl]sulfonyl]-2-azocinyl]methyl]-2,5-cyclohexadiene-1-yl]methyl pivalate (18). To a solution of 3.54 g (5.41 mmol) of tosylate **17**, 2.20 g (5.96 mmol) of tetrabutylammonium iodide, and 0.40 g (1.11 mmol) of dibenzo-18-crown-6 in 550 mL of toluene was added 1.41 g (7.03 mmol) of a 20% suspension of potassium hydride in mineral oil. The mixture was heated under reflux for 1 h, cooled to the temperature of an ice-water bath, and quenched with 100 mL of brine containing 6 mmol of HCl. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and chromatographed over 100 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 2:8) to give 2.09 g (80%) of azocine **18** as a white solid: mp 93-94 °C (from hexanes-ether); IR (KBr) 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 9H), 1.01 (m, 2H), 1.17 (s, 9H), 1.4-2.1 (m, 8H), 2.65 (m, 2H), 2.7-3.0 (m, 2H), 3.24 (br d, J = 16.8, 1H), 3.69 (td, J = 11.0, 2.8, 1H), 3.83 (A of ABq, J = 10.6, 1H), 3.89 (B of ABq, J = 10.6, 1H), 4.44 (br d, J = 8.6, 1H), 5.45 (m, 3H), 5.50 (br t, J = 12.0, 1H), 5.88 (br d, J = 10.2, 1H), 5.98 (br d, J = 10.2, 1H); ^{13}C NMR ($CDCl_3$) δ -2.0 (q), 10.2 (t), 23.6 (t), 24.5 (t), 25.6 (t), 26.5 (t), 27.2 (q), 38.9 (s), 40.6 (s), 41.8 (t), 45.9 (t), 49.2 (t), 54.2 (d), 70.8 (t), 126.4 (d), 126.7 (d), 128.1 (d), 128.3 (d), 128.9 (d), 132.9 (d), 178.1 s); Anal. calcd. for $C_{25}H_{43}NO_4SSi$: C, 62.33; H, 8.99. Found: C 62.39; H 9.04.

(±)-[1-[[1,2,5,6,7,8-Hexahydro-1-[[2-(trimethylsilyl)ethyl]sulfonyl]-2-azocinyl]methyl]-4-oxo-2,5-cyclohexadiene-1-yl]methyl pivalate (19). To a suspension of 1.48 g (3.07 mmol) of sulfonamide **18**, 1.36 mL (12.3 mmol) of *tert*-butyl hydroperoxide (90%), and 3.7 g of Celite in 38 mL of benzene was added 4.62 g (12.3 mmol) of pyridinium dichromate over 10 min 10 °C. The resulting mixture was stirred at rt for 6 h, diluted with 150 mL of ether, and filtered through 25 g of basic alumina (Brockman activity III). The filtrate was concentrated in vacuo and the residue was chromatographed over 60 g of basic alumina (Brockman activity III, eluted in gradient mode from hexanes to EtOAc-hexanes, 1:1) to provide 1.11 g (73%) of dienone **19** as a white crystalline material: mp 127 °C (from ether): IR (KBr) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 9H), 0.99 (m, 2H), 1.09 (s, 9H), 1.47 (m, 1H), 1.70 (m, 3H), 2.03 (m, 1H), 2.15 (dd, J = 13.6, 9.3, 1H), 2.23 (dd, J = 13.6, 3.2, 1H), 2.45 (m, 1H), 2.84 (t, J = 9.0, 2H), 3.23 (m, 1H), 3.43 (m, 1H), 4.06 (m, 1H), 4.08 (A of ABq, J = 10.7, 1H), 4.11 (B of ABq, J = 10.7, 1H), 5.30 (ddd, J = 11.6, 4.4, 1.4, 1H), 5.57 (m, 1H), 6.34 (dd, J = 10.1, 1.9, 1H), 6.43 (dd, J = 10.1, 1.9, 1H), 6.76 (dd, J = 10.1, 3.0, 1H), 6.94 (dd, J = 10.1, 3.0, 1H); ^{13}C NMR ($CDCl_3$) δ -2.0 (q), 10.1 (t), 25.3 (t), 25.6 (t), 26.6 (t), 27.0 (q), 38.8 (s), 41.5 (t), 46.0 (s), 46.2 (t), 50.7 (t), 54.2 (d), 67.4 (t), 130.3 (d), 130.5 (d), 131.3 (d), 131.6 (d), 150.6 (d), 150.3 (d), 177.7 (s), 185.7 (s); Anal. calcd. for $C_{25}H_{41}NO_5SSi$: C, 60.57; H, 8.34. Found: C 60.65; H 8.36.

(±)-[(4a*R,11a*R**,12a*R**)-4,4a,6,7,8,9,11a,12-Octahydro-3-oxoazocino[1,2-*a*]indol-12a(3*H*)-yl]methyl pivalate (6).** A suspension of 1.90 g (3.83 mmol) of sulfonamide **19**, and 2.33 g (15.3 mmol) of cesium fluoride in 9 mL of DMF was heated at 90 °C for 15 h, was cooled to rt, and diluted with 4 mL of methanol. Low boiling components were evaporated at 40 °C/1 torr and the residue was chromatographed over 120 g of basic alumina (Brockman activity III, eluted in gradient mode from hexanes to EtOAc-hexanes, 2:8) to provide 1.01 g (80%) of amine **6** as a pale yellow thick oil: IR (neat) 1732, 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 9H), 1.47 (m, 3H), 1.59 (dd, J = 13.1, 6.4, 1H), 1.80 (m, 2H), 2.15 (dd, J = 13.1, 9.9, 1H), 2.24 (br d, J = 11.8,

1H), 2.6-2.9 (m, 4H), 2.87 (td, J = 11.9, 2.8, 1H), 3.28 (m, 1H), 3.94 (A of ABq, J = 11.2, 1H), 4.25 (B of ABq, J = 11.2, 1H), 5.40 (m, 2H), 5.95 (d, J = 10.1, 1H), 6.43 (dd, J = 10.1, 2.0, 1H); ^{13}C NMR ($CDCl_3$) δ 24.0 (t), 24.5 (t), 26.2 (t), 27.1 (q), 38.1 (t), 38.8 (s), 41.3 (t), 45.9 (s), 52.3 (t), 63.0 (d), 67.4 (t), 67.6 (t), 126.7 (d), 127.9 (d), 133.0 (d), 151.2 (d), 178.0 (s), 197.7 (s); exact mass calcd. for $C_{20}H_{29}NO_3$ *m/z* 331.2147, found *m/z* 331.2140. Signals attributed to the minor isomer **5** were visible in the ^{1}H NMR spectrum of the crude product ($CDCl_3$) at δ 4.1 (d, J = 11 Hz), 4.3 (d, J = 11 Hz), 5.93 (d, J = 10), 6.55 (d, J = 10, 2).

***tert*-Butyl-(±)-[(*Z*)-7-*tert*-butoxy-1-[[1-(hydroxymethyl)-2,5-cyclohexadiene-1-yl]methyl]-2-heptenyl][[2-(trimethylsilyl)ethyl]sulfonyl]carbamate, pivalate (ester) (23).** To a solution of 1.06 g (1.62 mmol) of alkyne **14**, 0.113 mL (0.81 mmol) of triethylamine in 10 mL of 96% ethanol was added 86 mg of 5% palladium on barium sulfate. The resulting black suspension was placed under an atmosphere of hydrogen and stirred for a period of 40 min while 44 mL (1.80 mmol) of hydrogen was absorbed. The reaction mixture was diluted with 20 mL of ether, filtered through 25 g of silica gel, and filtrate was concentrated in vacuo. The residue was chromatographed over 60 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 1:9) to provide 0.64 g (60%) of olefin **23** and 0.15 g (14%) of starting alkyne **14**. Olefin **23** is a colorless oil: IR (neat) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 9H), 0.93 (m, 2H), 1.14 (s, 18H), 1.35 (m, 2H), 1.4-1.6 (m, 2H), 1.49 (s, 9H), 1.8-2.2 (m, 4H), 2.60 (m, 2H), 3.28 (m, 4H), 3.79 (s, 2H), 5.10 (m, 1H), 5.2-6.1 (m, 6H); ^{13}C NMR ($CDCl_3$) δ -1.9 (q), 10.2 (t), 26.2 (t), 26.7 (t), 27.3 (q), 27.7 (q), 27.9 (t), 28.2 (q), 30.6 (t), 39.0 (s), 40.7 (s), 43.4 (t), 51.5 (t), 52.5 (d), 61.4 (t), 71.0 (t), 72.5 (s), 84.1 (s), 126.7 (d), 127.1 (d), 128.7 (d), 128.8 (d), 129.7 (d), 133.3 (d), 151.6 (s), 178.2 (s); exact mass calcd. for $C_{34}H_{62}NO_7SSi$ (M^++H) *m/z* 656.4016, found *m/z* 656.4046.

***tert*-Butyl-(±)-[(*Z*)-7-*tert*-butoxy-1-[[1-(hydroxymethyl)-4-oxo-2,5-cyclohexadiene-1-yl]methyl]-2-heptenyl][[2-(trimethylsilyl)ethyl]sulfonyl]carbamate, pivalate (ester) (24).** To a suspension of 1.10 g (1.68 mmol) of diene **23**, 0.67 mL (6.71 mmol) of *tert*-butyl hydroperoxide (90%), and 2.0 g of Celite in 20 mL of benzene was added 2.52 g (6.71 mmol) of pyridinium dichromate over 10 min at 10 °C. The resulting mixture was stirred at rt for 12 h, diluted with 100 mL of ether, and filtered through 20 g of basic alumina (Brockman activity III). The filtrate was concentrated and the residue was chromatographed over 50 g of basic alumina (Brockman activity III, eluted in gradient mode from hexanes to EtOAc-hexanes, 2:8) to provide 0.68 g (60%) of dienone **24** as a colorless oil: IR (neat) 1732, 1669 cm-1; ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 9H), 0.93 (dd, J = 11.2, 7.0, 2H), 1.11 (s, 9H), 1.17 (s, 9H), 1.33 (m, 2H), 1.45 (m, 2H), 1.51 (s, 9H), 1.92 (m, 2H), 2.40 (br d, J = 6.6, 2H), 3.2-3.4 (m, 4H), 4.10 (s, 2H), 4.91 (m, 1H), 5.46 (m, 1H), 5.67 (t, J = 9.2, 1H), 6.30 (dd, J = 10.1, 1.8, 1H), 6.40 (dd, J = 10.1, 1.8, 1H), 6.71 (dd, J = 10.1, 3.0, 1H), 6.91 (dd, J = 10.1, 3.0, 1H); ^{13}C NMR ($CDCl_3$) δ -1.9 (q), 10.2 (t), 26.0 (t), 27.2 (q), 27.7 (q), 28.2 (q), 28.2 (t), 30.6 (t), 39.0 (s), 41.9 (t), 46.2 (s), 52.0 (d), 52.0 (t), 61.3 (t), 67.5 (t), 72.6 (s), 85.0 (s), 128.4 (d), 131.7 (d), 131.9 (d), 135.3 (d), 150.2 (d, 2C based on intensity), 151.4 (s), 177.9 (s), 185.9 (s); exact mass calcd. for $C_{34}H_{60}NO_8SSi$ (M^++H) *m/z* 670.3808, found *m/z* 670.3779.

***tert*-Butyl-(±)-[(*Z*)-7-*tert*-butoxy-1-[[1-(hydroxymethyl)-4-oxo-2,5-cyclohexadiene-1-yl]methyl]-2-heptenyl]carbamate, pivalate (ester) (25).** To a solution of 172 mg (0.257 mmol) of sulfonamide **24** in 1.5 mL of dimethylformamide was added 156 mg of CsF (1.03 mmol) in one portion. The reaction mixture was stirred for 3.5 h at rt, diluted with 10 mL of ether, washed with two portions of brine (4 + 2 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 2:8) to provide, in order of elution, 6 mg (4%) of starting sulfonamide **24**, 9 mg (7%) of bicyclic ketone **26**, and 105 mg (81%) of dienone **25** as a colorless thick oil: IR (neat) 3340, 1732, 1668 cm^{-1}; ^{1}H NMR (C_6D_6, 50 °C) δ 1.08 (s, 9H), 1.14 (s, 9H), 1.3-1.6 (m, 4H), 1.41 (s, 9H), 1.67 (m, 1H), 1.9-2.1 (m, 3H), 3.27 (t, J = 6.1, 2H), 3.64 (br s, 2H), 3.99 (br d, J = 7.5, 1H), 4.31 (br quintet, J = 7.2, 1H), 4.94 (br t, J = 9.2, 1H), 5.28 (dt, J = 10.7, 7.2, 1H), 6.2-6.4 (m, 3H), 6.50 (br d, J = 10.2, 1H); ^{13}C NMR (C_6D_6, 50 °C) δ 27.0 (t), 27.6 (q), 28.2 (q), 28.5 (t), 29.0 (q), 31.2 (t), 39.3 (s), 43.0 (t), 45.8 (s), 46.1 (d), 61.8 (t), 68.2 (t), 72.6 (s), 79.6 (s), 131.2 (d), 131.6 (d), 132.2 (d), 133.4 (d), 149.4 (d), 149.8 (d), 154.9 (s), 177.5 (s), 185.0 (s); exact mass calcd. for $C_{24}H_{37}NO_6$ (M^+–*t*-Bu+H) *m/z* 449.2777, found *m/z* 449.2687. The ratio of **24**:**25** varied from one run to another but **26** was never formed in more than trace amounts. Cyclization of **25** to **26** did occur if an acidic workup was used or if **25** was exposed to $CDCl_3$.

***tert*-Butyl-(±)-[(2*R**,3a*S**,7a*S**)-2-[(*Z*)-6-*tert*-butoxy-1-hexenyl]-3a,6,7,7a-tetrahydro-3a-(hydroxymethyl)-6-oxo-1-indolinecarboxylate, pivalate ester (26).** To a solution of 26 mg (0.05 mmol) of dienone **25** in 0.25 mL of dimethylformamide was added 31 mg (0.2 mmol) of cesium fluoride. The resulting mixture was stirred at rt for 3 h and then filtered through a 0.5 x 5.0 cm plug of basic activity I alumina, rinsing with copius amounts of CH_2Cl_2. The eluent was concentrated in vacuo to provide 20 mg (77%) of **26** as a

colorless oil, contaminated with trace amounts of **27** by ^{1}H NMR: IR (neat) 1732, 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 75 °C) δ 1.1-1.6 (m with three s at 1.18, 1.21 and 1.44, 31H), 1.82 (dd, *J* = 13.2, 6.4, 1H), 2.09 (m, 2H), 2.21 (dd, *J* = 13.2, 8.3, 1H), 2.84 (dd, *J* = 16.6, 5.1, 1H), 2.97 (dd, *J* = 16.6, 6.9, 1H), 3.35 (t, *J* = 6.1, 2H), 4.10 (A of ABq, *J* = 11.3, 1H), 4.23 (t, *J* = 6.4, 1H), 4.27 (B of ABq, *J* = 11.3, 1H), 4.54 (m, 1H), 5.40 (m, 2H), 6.07 (d, *J* = 10.3, 1H), 6.55 (d, *J* = 10.3, 1H), the signal at δ 6.55 was broad rt; ^{13}C NMR ($CDCl_3$, 55 °C) δ 26.7 (t), 27.5 (q), 27.9 (q), 28.7 (q), 30.8 (t), 38.9 (t), 39.2 (s), 40.9 (t), 46.6 (s), 54.6 (d), 59.8 (d), 61.6 (t), 67.3 (t), 72.6 (s), 80.5 (s), 130.1 (d), 130.3 (d), 133.2 (d), 148.5 (d), 153.8 (s), 178.0 (s), 196.5 (s), one upfield triplet was not observed; exact mass calcd. for $C_{29}H_{47}NO_6$ *m/z* 505.3403, found *m/z* 505.3355.

***tert*-butyl-(±)-[(2*R**,3a*R**,7a*R**)-2-[(*Z*)-6-*tert*-butoxy-1-hexenyl]-3a,6,7,7a-tetrahydro-3a-(hydroxymethyl)-6-oxo-1-indolinecarboxylate, pivalate ester (27).** To a solution of 60 mg (0.09 mmol) of dienone **24** in 1 mL of dimethylformamide was added 109 mg (0.71 mmol) of cesium fluoride. The resulting mixture was stirred at 85 °C for 18 h, and diluted with 3.0 mL of CH_2Cl_2 and 3 mL of ether. The resulting mixture was filtered through 5 g of silica gel using EtOAc-hexanes as eluant. The filtrate was concentrated in vacuo to give 43 mg of crude product. ^{1}H NMR analysis of this residue indicated the presence of **26** and **27** in a 15:85 ratio. The residue was chromatographed over 14 g of silica gel (eluted in gradient mode from hexanes to EtOAc-hexanes, 3:7) to provide 20 mg (45%) of perhydroindole **27** as a colorless oil: IR (neat) 1732, 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 9H), 1.18 (s, 9H), 1.3-1.6 (m, 4H), 1.41 (s, 9H), 1.82 (dd, *J* = 13.3, 7.1, 1H), 2.10 (m, 2H), 2.25 (dd, *J* = 13.3, 8.2, 1H), 2.69 (dd, *J* = 16.6, 8.8, 1H), 2.89 (dd, *J* = 16.6, 5.8, 1H), 3.31 (t, *J* = 6.3, 2H), 3.93 (A of ABq, *J* = 11, 1H), 4.25 (m overlapping with d, *J* = 11, 2H), 4.66 (q, *J* = 7.6, 1H), 5.35 (m, 2H), 6.05 (d, *J* = 10.3, 1H), 6.64 (d, *J* = 10.3, 1H); ^{13}C NMR ($CDCl_3$) δ 26.6 (t), 27.4 (q), 27.7 (t), 27.8 (q), 28.6 (q), 30.6 (t), 39.1 (s), 40.0 (t), 41.3 (t), 46.6 (s), 54.9 (d), 59.5 (d), 61.5 (t), 67.1 (t), 72.7 (s), 80.5 (s), 129.9 (d), 131.0 (d), 132.5 (d), 149.7 (d), 154.4 (s), 178.2 (s), 197.3 (s); exact mass calcd. for $C_{29}H_{48}NO_6$ (M^++H) *m/z* 506.3482, found *m/z* 506.3480. Similar treatment of **24** or pure **26** or pure **27** provided a 15:85 mixture of **26** and **27**, respectively.

1-Allyl-2,5-cyclohexadiene-1-carboxylic acid (30). To a stirred solution of 25.95 g (0.21 mol) of benzoic acid in 170 mL of dry THF in a 2-L round bottom flask equipped with a dry ice-acetone condenser and cooled in a dry ice-acetone bath was condensed 900 mL of ammonia. To this solution was added 3.40 g (0.49 mol) of lithium wire in small portions over a 40 min period. The solution maintained a dark blue color for 30 min, and then 48.4 g (0.40 mol) of allyl bromide was added dropwise via syringe over a 10 min period. The solution was stirred for an additional 2 h, and then 28.0 g (0.52 mol) of solid ammonium chloride was added slowly over a 2 min period. The ammonia was allowed to evaporate overnight. The yellow residue was dissolved in 400 mL of water and then extracted with four 110-mL portions of ethyl ether. The aqueous layer was cooled in an ice-water bath and acidified to pH 1 with 175 mL of concentrated aqueous HCl. The solution was extracted with three 175-mL portions of CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 32.11 g (92%) of acid **30** as a light pink oil, suitable for use in the next reaction: IR (neat) 3460-2367, 1698, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45-2.47 (d, *J* = 7.3 Hz, 2H), 2.62-2.72 (m, 2H), 5.03-5.09 (dm, *J* = 9.4 Hz, 2H), 5.62-5.78 (m, 3H), 5.88-5.94 (m, 2H), 11.2-11.8 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 26.0 (t), 44.0 (t), 47.5 (s), 118.3 (t), 126.1 (d), 126.3 (d), 132.8 (d), 180.7 (s), exact mass calcd for $C_{10}H_{12}O_2$ *m/z* 164.0838, found *m/z* 164.0857.

1-Allyl-2,5-cyclohexadiene-1-carboxamide (31). To a slurry of 31.98 g (0.195 mol) of acid **30** in 348 mL of methanol was added 10.9 g (0.195 mol) of solid KOH in one portion. The solution was stirred until the KOH dissolved and was then concentrated in vacuo. The resulting white solid was suspended in 500 mL of dry benzene cooled in an ice-water bath, and 23.0 g (0.182 mol) of neat oxalyl chloride was added dropwise via syringe over a 5 min period. The solution was stirred for 19 h and then 105 mL of a 30% aqueous NH_4OH was added dropwise over a 30 min period. The cold bath was removed, the solution was stirred for an additional 2 h, and was then extracted with 500 mL of CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 27.1 g (91%) of amide **31** as a light yellow oil, suitable for use in the next reaction: IR (neat) 3470-3201, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45-2.48 (dt, *J* = 5.1, 1.1 Hz, 2H), 2.65-2.69 (m, 2H), 4.98-5.05 (dm, *J* = 8.1 Hz, 2H), 5.58-5.70 (m, 3H), 5.80 (bs, 1H), 5.88-5.94 (m, 2H), 6.22 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 26.0 (t), 42.2 (t), 48.0 (s), 117.6 (t), 126.4 (d), 128.2 (d), 134.0 (d), 176.7 (s); exact mass calcd for $C_{10}H_{13}NO$ *m/z* 163.0998, found *m/z* 163.0978.

(±)-3-(Iodomethyl)-2-azaspiro[4.5]deca-6,9-dien-1-one (32). To a solution of 11.9 g (72.6 mmol) of amide **31** and 16.16 g (0.16 mol) of triethylamine in 90 mL of pentane, cooled in an ice water bath, was added 35.5 g (0.16 mol) of neat trimethylsilyl trifluoromethanesulfonate dropwise via syringe over a 5 min period. The solution was stirred for 1 h. The pentane was removed in vacuo and the solid residue was dissolved in 90 mL of dry THF and cooled in an ice-water bath. To this solution was added 18.4 g (72.60 mmol) of iodine in one

portion and the solution was then stirred for 18 h. The solution was partitioned between 400 mL of ethyl ether and 620 mL of a saturated aqueous solution of sodium bicarbonate/sodium sulfite (1:1). The aqueous layer was extracted with 200 mL of CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was recrystallized from 300 mL acetone/methanol (4:1) to give 12.1 g (57%) of iodolactam **32** as a light tan solid: mp 173.5-176.5 °C; IR ($CDCl_3$) 3235, 1697, 1652 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.61-1.68 (dd, J = 13.0, 7.3 Hz, 1H), 2.06-2.13 (dd, J = 13.0, 6.9 Hz, 1H), 2.58-2.62 (bs, 2H), 3.27-3.37 (m, 2H), 3.55-3.63 (m, 1H), 5.46-5.51 (dm, J = 3.9 Hz, 1H), 5.58-5.62 (dm, J = 5.9 Hz, 1H), 5.75-5.85 (m, 2H), 7.93 (bs, 1H); ^{13}C NMR (DMSO-d_6) δ 14.9 (t), 25.7 (t), 43.4 (t), 47.3 (s), 50.5 (d), 124.9 (d), 125.9 (d), 127.3 (d), 128.3 (d), 176.5 (s); Anal. calcd. for $C_{10}H_{12}INO$: C, 41.52; H, 4.19. Found: C, 41.58; H, 4.17.

***tert*-Butyl (±)-3-(iodomethyl)-1-oxo-2-azaspiro[4.5]deca-6,9-diene-2-carboxylate (33).** To a stirred solution of 822 mg (2.84 mmol) of iodide **32** and 621 mg (2.84 mmol) of di-*tert*-butyl dicarbonate in 35 mL of dry THF cooled in an ice-water bath was added 69 mg (0.57 mmol) of solid 4-dimethylaminopyridine in one portion. The solution was stirred for 10 min, the cold bath was removed, and the solution was stirred an additional 48 h. The solution was suction filtered through a 100 g pad of silica gel (11 x 3 cm) and the silica gel was washed with copious amounts of ethyl ether. The filtrate was concentrated in vacuo to give 717 mg (65%) of lactam **33** as a white solid, suitable for use in the next reaction: mp 85-90 °C; IR ($CDCl_3$) 1786, 1751, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H), 1.84-1.91 (dd, J = 13.6, 6.8 Hz, 1H), 2.18-2.25 (dd, J = 13.6, 7.9 Hz, 1H), 2.59-2.71 (dm, J = 23.2 Hz, 1H), 2.74-2.85 (dm, J = 23.2 Hz, 1H), 3.50-3.62 (m, 2H), 3.97-4.05 (m, 1H), 5.50-5.59 (m, 2H), 5.89-6.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.3 (t), 25.8 (t), 27.9 (q), 39.3 (t), 47.9 (s), 54.1 (d), 83.3 (s), 125.6 (d), 126.1 (d), 126.9 (d), 127.5 (d), 150.2 (s), 174.4 (s); Anal. Calcd. for $C_{15}H_{20}INO_3$: C, 46.29; H, 5.18. Found: C, 46.35; H, 5.16.

Methyl (±)-1-[2-[(*tert*-butoxycarbonyl)amino]-3-iodopropyl]-2,5-cyclohexadiene-1-carboxylate (34). To a stirred solution of 5.95 g (15.29 mmol) of lactam **33** in 100 mL of absolute methanol cooled in an ice-water bath was added a solution of 387 mg (16.90 mmol) of sodium metal in 30 mL of methanol dropwise via an additional funnel over a 3 min period. The solution was stirred an additional 1.5 h and poured into 200 mL of saturated brine. The solution was extracted with two 125-mL portions of ether and four 75-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give 3.48 g (54%) of amide **34** as a light yellow solid, suitable for use in the next reaction: mp 84-87 °C; IR ($CDCl_3$) 3366, 1712 cm^{-1}; ^1H NMR (C_6D_6) δ 1.37 (s, 9H), 1.64-1.70 (dd, J = 14.1, 3.6 Hz, 1H), 1.87-1.94 (dd, J = 14.1, 9.5 Hz, 1H), 2.20-2.41 (m, 2H), 2.78-2.83 (dd, J = 10.0, 4.4 Hz, 1H), 2.98-3.03 (dd, J = 10.0, 5.0 Hz, 1H), 3.30 (s, 3H), 3.62-3.69 (m, 1H), 4.38-4.41 (d, J = 8.7 Hz, 1H), 5.56-5.62 (m, 2H), 5.68-5.73 (dm, J = 10.2 Hz, 1H), 5.81-5.86 (dm, J = 10.2 Hz, 1H); ^{13}C NMR (C_6D_6) δ 15.6 (t), 26.1 (t), 28.4 (q), 44.7 (t), 46.8 (s), 47.4 (d), 51.9 (q), 79.0 (s), 125.8 (d), 126.5 (d), 126.6 (d), 127.5 (d), 154.6 (s), 174.5 (s); Anal. calcd. for $C_{16}H_{24}INO_4$: C, 45.62; H, 5.74. Found: C, 46.14; H, 5.79.

Methyl (±)-1-[2-oxo-4-oxazolidinyl)methyl]-2,5-cyclohexadiene-1-carboxylate (35). A solution of 5.02 g (11.87 mmol) of amide **34** and 1.41 g (17.81 mmol) of pyridine in 63 mL of dry toluene was stirred at reflux for 24 h. The hot solution was suction filtered and the filtrate was cooled to -15 °C for 15 h. The resulting solid was collected to give 1.78 g (63%) of oxazolidinone **35** as light yellow crystals (mp 117.5-120 °C) suitable for use in the next reaction. Recrystallization of a sample from EtOAc/hexanes (1:1) gave an analytically pure sample as white platelets: mp 120-123 °C; IR ($CDCl_3$) 3268, 1758, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91-1.97 (dd, J = 14.3, 3.8 Hz, 1H), 2.04-2.11 (dd, J = 14.2, 7.5 Hz, 1H), 2.68-2.72 (m, 2H), 3.70 (s, 3H), 3.91-3.98 (m, 2H), 4.38-4.47 (m, 1H), 5.51 (bs, 1H), 5.62-5.67 (dm, J = 8.3 Hz, 1H), 5.77-5.82 (dm, J = 8.1 Hz, 1H), 5.96-6.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.8 (t), 44.1 (t), 46.8 (s), 49.6 (d), 52.5 (q), 70.5 (t), 125.8 (d), 126.7 (d), 127.3 (d), 127.4 (d), 158.9 (s), 173.8 (s); Anal. calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37. Found: C, 60.75; H, 6.39.

(±)-4-[[1-(Hydroxymethyl)-2,5-cyclohexadienyl]methyl]-2-oxazolidinone (36). To a stirred solution of 900 mg (3.80 mmol) of ester **35** in 6 mL of dry THF at rt was added 166 mg (7.62 mmol) of lithium borohydride in one portion. The solution was stirred for 48 h, then cooled in an ice-water bath, and quenched with 2.5 mL of concentrated aqueous HCl. The solution was saturated with solid sodium chloride and diluted with 30 mL of ether. The organic layer was washed with 10 mL of saturated brine. The combined aqueous layers were extracted with 30 mL of CH_2Cl_2. The combined ether and CH_2Cl_2 layers were dried ($MgSO_4$) and concentrated in vacuo to give 581 mg (73%) of a light yellow solid. The crude residue was purified by chromatography over 12 g of silica gel (eluted with hexanes-EtOAc, 1:1 to EtOAc) to give 449 mg (57%) of alcohol **36** as light yellow crystals: mp 92.5-94.5 °C; IR ($CDCl_3$) 3334, 1747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54-1.60 (dd, J = 13.8, 2.6 Hz, 1H), 1.65-1.72 (dd, J = 13.9, 7.7 Hz, 1H), 1.81 (bs, 1H), 2.68-2.72 (m, 2H), 3.32-3.39 (AB

quartet, J = 11.8, 10.5 Hz, 2H), 3.90-3.98 (m, 2H), 4.38-4.46 (m, 1H), 5.36-5.41 (dm, J = 8.1 Hz, 1H), 5.52-5.57 (m, 2H), 5.99-6.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 26.3 (t), 42.1 (s), 42.6 (t), 50.2 (d), 70.3 (t), 70.8 (t), 128.2 (d), 128.4 (d), 129.4 (d), 159.3 (s), one olefin doublet was missing, but probably appears at 128.2 based on signal intensity; Anal. calcd. for $C_{11}H_{15}NO_3$: C, 63.13; H, 7.23. Found: C, 63.06; H, 7.22.

(±)-Benzyl [1-[(2-oxo-4-oxazolidinyl)methyl]-2,5-cyclohexadien-1-yl]methyl malonate (37) To a stirred solution of 241 mg (1.09 mmol) of alcohol **36**, 212 mg (1.09 mmol) of monobenzyl malonate, and 13 mg (0.11 mmol) of 4-dimethylaminopyridine in 10 mL of dry CH_2Cl_2 cooled in an ice-water bath was added a solution of 226 mg (1.09 mmol) of dicyclohexylcarbodimide in 5 mL of dry CH_2Cl_2 dropwise via syringe over a 5 min period. The solution was stirred for 10 min, the cold bath was removed, and the solution was allowed to stir for an additional 20 h. The solution was suction filtered and the filter cake was washed with copious amounts of CH_2Cl_2. The filtrate was concentrated in vacuo and the residue was purified by chromatography over 12 g of silica gel (eluted with hexanes-EtOAc, 1:1 to EtOAc) to give 428 mg (96%) of ester **37**, suitable for use in the next reaction, as a thick colorless oil: IR (neat) 3319, 1748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.52-1.58 (dd, J = 14.1, 4.7 Hz, 1H), 1.65-1.72 (dd, J = 14.1, 6.5 Hz, 1H), 2.58-2.62 (m, 2H), 3.37-3.38 (s, 2H), 3.79-3.86 (m, 2H), 3.88 (s, 2H), 4.27-4.35 (m, 1H), 5.12 (s, 2H), 5.28-5.33 (dm, J = 10.3 Hz, 1H), 5.41-5.46 (dm, J = 12.5 Hz, 1H), 5.83-5.91 (m, 3H), 7.26-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.2 (t), 39.6 (s), 41.3 (t), 42.5 (t), 49.9 (d), 67.1 (t), 70.8 (t), 71.5 (t), 127.4 (d), 127.8 (d), 128.12 (d), 128.14 (d), 128.4 (d), 128.5 (d), 135.1 (s), 159.3 (s), 166.05 (s), 166.07 (s), one olefinic carbon was not observed due to magnetic equivalence; exact mass calcd. for $C_{21}H_{23}NO_6$ *m/z* 385.1525, found *m/z* 385.1538.

(±)-Benzyl [4-oxo-1-[(2-oxo-4-oxazolidinyl)methyl]-2,5-cyclohexadien-1-yl]methyl malonate (38). A stirred slurry of 2.00 g (5.19 mmol) of ester **37** and 5.74 g of Celite in 100 mL of dry benzene was cooled in an ice-water bath for 15 min. To this slurry was added in sequence 5.86 g (15.58 mmol) of pyridinium dichromate in one portion and 1.40 g (15.53 mmol) of *tert*-butyl hydroperoxide in one portion via syringe. The solution was stirred for 30 min, the cold bath was removed, and the solution was allowed to stir an additional 3 h. The solution was suction filtered and the filter cake was washed with copious amounts of CH_2Cl_2. The filtrate was concentrated in vacuo and the residual oil was chromatographed over 50 g of silica gel (eluted with EtOAc) to give 917 mg (44%) of dienone **38** as a thick colorless oil: IR (neat) 3290, 1754, 1666, 1627 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.93 (dd, J = 14.1, 5.6 Hz, 1H), 2.06 (dd, J = 14.1, 6.8 Hz, 1H), 3.41 (d, J = 3.3 Hz, 2H), 3.59-3.67 (m, 1H), 3.84 (t, J = 8.7 Hz, 1H), 4.08-4.17 (m, 2H), 4.31 (t, J = 8.6 Hz, 1H), 5.14 (s, 2H), 6.09 (bs, 1H), 6.36-6.43 (m, 2H), 6.70 (dd, J = 10.1, 2.9 Hz, 1H), 6.81 (dd, J = 9.7, 2.9 Hz, 1H), 7.25-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 41.1 (t), 41.3 (t), 44.6 (s), 49.2 (d), 67.4 (t), 68.3 (t), 70.4 (t), 128.3 (d), 128.5 (d), 128.6 (d), 132.2 (d), 134.9 (s), 148.4 (d), 148.8 (d), 159.1 (s), 165.7 (s) 165.8 (s), 184.7 (s), one olefinic carbon was not observed due to magnetic equivalence; exact mass calcd. for $C_{21}H_{21}NO_7$ *m/z* 399.1318, found *m/z* 399.1335.

(±)-Benzyl [(4a*R,8a*R**,9a*S**)-5,6,9,9a-tetrahydro-3,6-dioxo-1*H*,3*H*-oxozolo[3,4-*a*]indol-8a(4a*H*)-yl]methyl malonate (28b).** To a stirred solution of 1.18 g (2.96 mmol) of dienone **38** in 50 mL of dry CH_2Cl_2 at rt was added 17.8 g (0.156 mol) of trifluoroacetic acid in one portion via syringe. The solution was allowed to stir for 7 h. The solution was washed with two 30-mL portions of saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 1.03 g (88%) of enone **28b** as a thick colorless oil, suitable for use in the next reaction: IR (neat) 1754, 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.83 (dd, J = 12.2, 11.1 Hz, 1H), 1.98 (dd, J = 12.2, 5.1 Hz, 1H), 2.65 (dd, J = 17.0, 4.7 Hz, 1H), 2.87 (dd, J = 17.0, 2.9 Hz, 1H), 3.44 (s, 2H), 3.91-4.00 (m, 1H), 4.09-4.17 (m, 2H), 4.23 (d, J = 11.4 Hz, 1H), 4.37-4.46 (m, 2H), 5.15 (s, 2H), 6.17 (dd, J = 10.5, 0.4 Hz, 1H), 6.44 (dd, J = 10.4, 1.6 Hz, 1H), 7.29-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 39.7 (t), 40.6 (t), 41.2 (t), 50.0 (s), 57.1 (d), 59.9 (d), 67.2 (t), 67.4 (t), 128.4 (d), 128.53 (d), 128.56 (d), 131.9 (d), 134.9 (s), 146.7 (d), 161.1 (s), 165.70 (s), 165.78 (s), 195.7 (s); exact mass calcd. for $C_{21}H_{21}NO_7$ *m/z* 399.1318, found *m/z* 399.1309.

Benzyl (±)-(4*R,4a*S**,7a*R**,11a*S**,12a*R**)-octahydro-3,6,9-trioxo-1*H*,3*H*,9*H*,11*H*-oxazolo[3,4-*a*]pyrano[3,4-*d*]-indole-4-carboxylate (39).** To a stirred solution of 996 mg (2.58 mmol) of enone **28b** in 25 mL of dry CH_2Cl_2 at rt was added 594 mg (5.16 mmol) of tetramethylguanidine via syringe in one portion. The solution was allowed to stir at rt for 3.5 h and then concentrated in vacuo. The crude residue was purified by chromatography over 12 g of silica gel (eluted with CH_2Cl_2-methanol, 9:1) to give 696 mg (70%) of lactone **39** as a light tan solid: mp 194-197 °C; IR (DMSO) 1751 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.01 (dd, J = 13.2, 7.9 Hz, 1H), 2.20 (dd, J = 13.1, 7.4 Hz, 1H), 2.29-2.71 (m, 5H), 3.84 (d, J = 11.7 Hz, 1H), 3.98-4.06 (m, 2H), 4.20 (dd, J = 8.7, 4.3 Hz, 1H), 4.34-4.40 (m, 1H), 4.51 (t, J = 8.4 Hz, 1H), 4.56 (d, J = 11.7 Hz, 1H), 5.22 (s, 2H), 7.32-7.39 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 37.7 (d), 40.8 (t), 42.1 (t), 42.5 (t), 47.2 (s), 51.0 (t), 56.5 (t), 57.9 (t), 67.0 (d), 69.2 (d), 70.8 (d), 128.1 (d), 128.4 (d), 128.6 (d), 135.7 (s), 160.7 (s), 168.1 (s),

169.0 (s), 206.9 (s); Anal. calcd. for $C_{21}H_{21}NO_7$: C, 63.14; H, 5.30. Found: C, 63.19; H, 5.32. A sample suitable for X-ray crystallographic analysis was grown from DMSO-d_6.

(±)-(4'a*R,7'a*S**,11'a*R**,12'a*S**)-Hexahydro-1*H*,3*H*,9*H*,11*H*-oxazolo[3,4-*a*]pyrano-[3,4-*d*]indole-3,6,9(4*H*)-trione (40).** A slurry of 768 mg (1.92 mmol) of benzyl ester **39**, 847 mg (1.06 mmol) of 1,4-cyclohexadiene, and 350 mg of 10% palladium hydroxide on carbon in 40 mL of absolute ethanol was stirred at reflux for 45 min. The hot solution was suction filtered through a thin 4 cm diameter pad of Celite, and then the filtrate was concentrated in vacuo to give 400 mg (78%) of slightly impure ketone **40** as a white solid. Recrystallization of a sample from methanol-acetone provided pure material: mp 178-180 °C; IR (DMSO) 1732, 1650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.91 (dd, J = 10.9, 9.1 Hz, 1H), 2.22 (dd, J = 12.8, 7.3 Hz, 1H), 2.35-2.42 (m, 2H), 2.43-2.52 (m, 3H), 2.55 (m, 1H), 2.61-2.74 (m, 1H), 3.88-3.98 (m, 2H), 4.18 (dd, J = 9.1, 3.6 Hz, 1H), 4.28-4.40 (m, 1H), 4.40-4.55 (m, 2H); ^{13}C NMR (C_6D_6-DMSO-d_6) δ 34.3 (d), 34.8 (t), 41.7 (t), 43.0 (t), 43.5 (t), 47.2 (s), 57.1 (d), 59.2 (d), 68.9 (t), 71.7 (t), 161.2 (s), 171.2 (s), 207.1 (s); exact mass calcd. for $C_{13}H_{15}NO_5$ *m/z* 265.0950, found *m/z* 265.0952.

References and Notes

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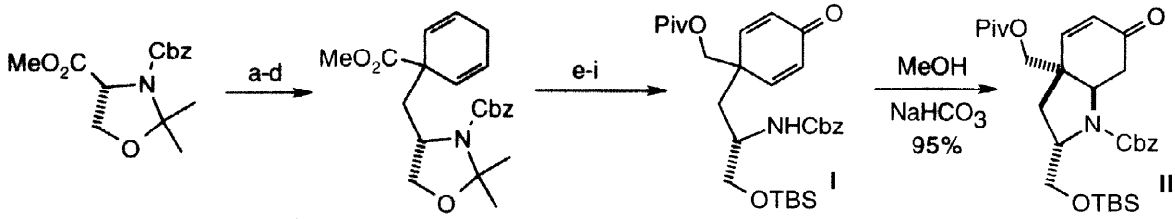
17. In ancilliary studies, we have also shown that carbamate **I** is converted to perhydroindole **II** in 95% yield upon treatment with $NaHCO_3$-MeOH. Cyclization of **I** using CsF and epimerization studies with **II** were not performed. The synthesis of **I** from a known ester [Garner, P.; Park, J. M. *Organic Syntheses* **1992**, *70*, 18] is outlined near the top of the next page. Details appear in the PhD Thesis of Gilles Chambournier, The Ohio State University, 1998.
18. Calculations were performed using SPARTAN using a molecular mechanics minimization (SYBIL)/conformer search (OSAWA) procedure. This process suggested approximately a 3 kcal mol^{-1} energy difference between **4** (lower energy) and 2-epi-**4**, a 1.6 kcal mol^{-1} energy difference between **5** and **6** (lower), and a 0.5 kcal mol^{-1} energy difference between **28a** (lower) and 2-epi-**28a**.
19. Whereas calculations are in agreement with the thermodynamic preference for **27** observed in the cyclization of **25**, we are not in a position to rationalize the kinetic preference for **26**. If one assumes that the cyclization occurs via a face-to-face approach of the dienone and carbamate π-systems, an explaination emerges that involves $A^{1,3}$ strain as a controlling feature.[2] It is not clear to us, however, that this approach should be prefered. It is also possible that the dienone and carbamate approach one another such that the π-system of the enone interacts with a lone pair in an sp^2-hybridized orbital on the carbamate nitrogen (either in the anion or an imidate tautomer). This requires a different analysis of the problem that does not lead us to an obvious

explaination for our experimental observations. This problem does seem to be a good candidate for computational analysis and such studies are planned.



(a) $NaBH_4$, LiCl, MeOH, 99% (b) MsCl, Et_3N, 4-DMAP, 86% (c) LiBr, acetone, 78% (d) 1,4-dihydrobenzoic acid, LDA (2.1 equiv), THF; then K_2CO_3, MeI, DMF, 58% (e) 10-CSA, MeOH, 86% (f) TBS-Cl, 4-DMAP, CH_2Cl_2, 90% (g) $NaBH_4$, THF, EtOH, 55% (h) Pivaloyl chloride, 4-DMAP, CH_2Cl_2, 84% (i) PDC, Celite, *t*-BuO_2H, PhH, 77%

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22. Under basic conditions the malonate group in **38** underwent cyclization prior to the carbamate to provide a mixture of diastereomeric products. Thus, the use of acid-first and base-second is important to the timing of the two conjugate addition reactions.
23. On one occasion, the Cr^{6+} oxidation of **37** provided a 2:1 mixture of **28b** (minor) and its C_{8a}-diastereomer (major) rather than dienone **38**. The presence of the C_{8a}-diastereomer was based on the appearance of vinylic signals at δ 6.08 (d, J = 11) and 6.47 (dd, J = 11, 2) as well as other ^{1}H NMR signals ($CDCl_3$). Treatment of this mixture with trifluoracetic acid (0.5 M in CH_2Cl_2) for 2 h resulted in partial isomerization of the C_{8a}-diastereomer to **28b**, while treatment of the mixture with trifluoroacetic acid (3.0 M in CH_2Cl_2) resulted in complete isomerization of the C_{8a}-diastereomer to **28b**. These results suggest that the stereochemical course of the transformation shown Scheme 2 (**38**→**28b**) is governed by thermodynamics.
24. X-ray crystallography was performed by Dr. Judith C. Gallucci at The Ohio State University.
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26. All melting points are uncorrected. ^{1}H NMR spectra were taken on 200-500 MHz instruments in the indicated solvent and at rt unless stated otherwise and are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet), coupling constants in hertz, integration]. ^{13}C NMR were taken at 50-125 MHz in the indicated solvent and are reported as follows: chemical shift (multiplicity determined by DEPT). Chromatography was performed using either gravity or flash chromatography techniques as required. Solvents and reagents were dried and purified prior to use when deemed necessary using standard procedures. Reactions requiring an inert atmosphere were run under a blanket of argon.
27. This reagent was prepared by reaction of isobutylene with 5-hexyn-1-ol in hexanes in the presence of Amberlyst DV265 (Alexakis, A.; Gardette, M.; Colin, S. *Tetrahedron Lett.* **1988**, *29*, 2951).

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Dedication: This paper is dedicated to Professor David A. Evans and Professor Teruaki Mukaiyama on the occasion of their receipt of the 1999 Tetrahedron Prize.