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Terminating Catalytic Asymmetric Heck Cyclizations by Stereoselective Intramolecular Capture of η³-Allylpalladium Intermediates: Total Synthesis of (−)-Spirotryprostatin B and Three Stereoisomers

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Abstract

A catalytic intramolecular Heck reaction, followed by capture of the resulting η^3-allylpalladium intermediate by a tethered diketopiperazine, is the central step in a concise synthetic route to (−)-spirotryprostatin B and three stereoisomers. This study demonstrates that an acyclic, chiral η^3-allylpalladium fragment generated in a catalytic asymmetric Heck cyclization can be trapped by even a weakly nucleophilic diketopiperazine more rapidly than it undergoes diastereomeric equilibration.

Keywords

palladium catalysis; total synthesis; alkaloid; mechanism; cascade reaction

1. Introduction

Small-molecule natural products play an increasingly important role in contemporary studies to understand and control cellular proliferation.1 Using temperature-sensitive mammalian tsFT210 cells and rat normal fibroblast 3Y1 cells, Osada and coworkers have identified a variety of structurally novel natural product inhibitors of the cell cycle from the marine fungus *Aspergillus*.2 Among these are the cyclotryprostatins A–C (**1**–**4**),3 tryprostatins A and B (**5** and **6**),4 and spirotryprostatins A and B (**7** and **8**), which combine diketopiperazine and prenylated indole structural motifs (Figure 1).5

Spirotryprostatin B (**8**) was initially isolated from a 400 L fermentation that yielded 11 mg of the pure natural product, allowing its constitution and the relative configuration at C3 and C18 to be determined; the relative configuration at C12 could not be directly specified, although it was assumed to be the same as in spirotryprostatin A.5 Spirotryprostatin B (**8**) inhibits G2/M-phase cell progression at low micromolar concentrations; it is more active than its saturated congener spirotryprostatin A, although considerably less active than

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several simpler compounds in this family of indole alkaloids.5 The unique structures of spirotryprostatins A and B have attracted much attention from synthetic chemists, with the first accomplishment in the area being registered by Danishefsky and Edmondson in 1998, who exploited the oxidative rearrangement of indoles to fashion the spirooxindole moiety of spirotryprostatin A (**7**).6 The first total synthesis of spirotryprostatin B was described by Williams,7 followed soon thereafter in 2000 by distinctly different constructions of this target by the Danishefsky,8 Ganesian,9 and Overman laboratories.10 The stereoselective assembly of the spiro[pyrrolidine-3,3′-oxindole] core of the spirotryprostatins continues to this day to inspire the development of imaginative synthetic chemistry.11,12 In addition, this scaffold has stimulated the discovery of cell-growth inhibitors that target the regulatory protein MDM2,13 and diversity-oriented synthesis of large bioactive compound libraries.14

The central challenge in a stereocontrolled synthesis of spirotryprostatin B (**8**) is relating the configuration of the C3 quaternary stereocenter to the adjacent secondary stereocenter of the spiropyrrolidine ring (C18). We were attracted to this problem by the considerations posed in Scheme 1, and our previous demonstration that catalytic asymmetric intramolecular Heck reactions of α,β-unsaturated 2-haloanilides can efficiently construct enantioenriched, chiral 3,3-disubstituted oxindoles.15 Controlled by an appropriate chiral ligand and the suprafacial stereospecificity of organopalladium insertions, intramolecular Heck cyclization of (2*E*)-2,4-hexadienamide **9** in a favored 5-exo sense should generate η^3-allylpalladium intermediate **10**.16 If this complex were trapped by the nitrogen of the tethered diketopiperazine at the proximal carbon of the allyl unit more rapidly than the η^3-allylpalladium fragment underwent stereomutation, spirotryprostatin B (**8**) would be produced if bond formation occurred *anti* to the metal; cyclization *syn* to the metal would lead to 18-*epi*-spirotryprostatin B (**13**).17 In a complementary scenario, cyclization of (2*Z*)-2,4-hexadienamide **11** should generate η^3-allylpalladium intermediate **12**, which if trapped in an *anti* sense would lead to C18 epimer **13**, whereas *syn* attack of nitrogen on the η^3-allylpalladium fragment would produce spirotryprostatin B (**8**).

It was of particular importance to us that pursuit of this synthetic strategy would allow the investigation of several new aspects of the use of organopalladium catalysis in synthesis: (1) catalytic asymmetric Heck cyclization onto an internal double bond of a conjugated triene, (2) the possibility of exploiting the relative configuration of an acyclic η^3-allylpalladium fragment produced in an intramolecular Heck cyclization for a further stereocontrolled bond construction,18–20 (3) trapping of η^3-allylpalladium electrophiles by a weakly nucleophilic nitrogen of a diketopiperazine, and (4) the stereoselectivity of the construction of such an allylic C–N bond.21 As the absolute configuration of spirotryprostatin B had not been established at the time our investigations began, the ability to reach reaction manifolds enantiomeric to those depicted in Scheme 1 by simply changing the chirality of the ligand was deemed an additional attractive aspect of this plan.

Herein we describe initial model studies confirming that catalytic asymmetric Heck cyclizations onto the internal double bond of a conjugated triene can take place efficiently with useful levels of enantiomeric induction, and describe in detail our investigation of the strategy outlined in Scheme 1 that culminated in total syntheses of (−)-spirotryprostatin B (**8**), (−)-18-*epi*- spirotryprostatin B (**13**), (−)-3-*epi*-spirotryprostatin B (**40**), and (−)-3,18-*epi*-spirotryprostatin B (**56**).

2. Results and discussion

2.1 Model studies

Recent investigations in our laboratories had demonstrated that intramolecular catalytic asymmetric Heck reactions were efficient transformations for preparing chiral 3,3-

disubstituted oxindoles with high levels of enantiocontrol.15 However, our previous studies had not examined such reactions of conjugated di- or trienamide precursors. As a result, we chose to study catalytic asymmetric Heck cyclizations of (*Z*)- and (*E*)-2,5-dimethyl-*N*-(2-iodophenyl)-2,4-hexadienamides **19** and **23** prior to examining the more elaborate transformations proposed in Scheme 1. The preparation of stereoisomer **19** began with a Still-Gennari olefination reaction between 3-methyl-2-butenal (**14**)and trifluoroethylphosphonate ester **15**, which provided (*Z*)-dienyl ester **16** as a single alkene stereoisomer (by ^{1}H-NMR analysis) in 86% yield (Scheme 2).22,23 Saponification of ester **16** gave acid **17**, which was converted to the corresponding acid chloride and allowed to react with 2-iodoaniline to provide anilide **18** in 90% yield. Subsequent protection of the secondary amide with (2-trimethylsilyl)ethoxymethyl chloride (SEM-Cl) delivered (*Z*)-2,4-hexadienamide **19** in high yield.

The synthesis of the corresponding *E* stereoisomer began with a Wittig reaction between aldehyde **14** and stabilized ylide **20** providing (*E*)-dienyl ester **21** in 92% yield (Scheme 3).24,25 Trimethylaluminum-mediated conversion of ester **21** to anilide **22** proceeded smoothly in 80% yield.26 Protection of the resulting amide nitrogen with SEM-Cl afforded (*E*)-2,4-hexadienamide substrate **23** in good overall yield.

Catalytic asymmetric Heck cyclizations of (*Z*)- and (*E*)-2,5-dimethyl-*N*-(2-iodophenyl)-2,4-hexadienamides **19** and **23** were conducted using conditions previously demonstrated to be optimal for similar reactions of simpler α,β-unsaturated 2-iodoanilides (Scheme 4).15 We were pleased to find that cyclization of (*Z*)-hexadienamide **19** with 10 mol % Pd-(*S*)-BINAP and 1,2,2,6,6-pentamethylpiperidine (PMP) in *N*,*N*-dimethylacetamide (DMA) at 100 °C provided oxindole **24** in 92% yield. Removal of the SEM group yielded oxindole **25**, which was found by enantioselective HPLC analysis to be highly enantioenriched (90% *ee*). Under identical conditions, cyclization of (*E*)-hexadienamide precursor **23** provided oxindole **24** in 86% yield, albeit with a somewhat lower level of enantioselection (72% *ee*). The absolute configuration of oxindole **24** was determined by its conversion to oxindole alcohol **27**, which was found to be enantiomeric to an intermediate employed to synthesize (+)-esermethole.15b,27 To this end, oxindole **24** was converted in standard fashion to its *N*-methyl derivative **26**. Dihydroxylation of the *exo*-methylene group of the diene side chain of **26**, followed by cleavage of the diol intermediate, catalytic hydrogenation of the resulting enone, Baeyer-Villiger oxidation, and ester saponification provided oxindole alcohol **27**. The yield of this sequence was low, owing largely to low selectivity in the Baeyer-Villiger oxidation. Nonetheless, sufficient quantity of oxindole **27** was obtained to establish its *S* absolute configuration.

2.2. Total synthesis of (−)-18-*epi*-spirotryprostatin B (13) and (−)-3-*epi*-spirotryprostatin B (40).

Although the catalytic asymmetric Heck cyclizations of 2,4-hexadienamides **19** and **23** were not optimized, we were sufficiently encouraged by the efficiency and enantioselectivity of these reactions to proceed ahead to investigate the plan outlined in Scheme 1. The preparation of (2*Z*)-2,4-hexadienamide **35** commenced with reductive iodination of monoprotected-propargyl alcohol **28**,28 furnishing (*Z*)-vinyl iodide **29** in 75% yield.29 Swern oxidation of allylic alcohol **29** provided a highly unstable aldehyde,30 which was immediately allowed to react with *iso*-propylidene triphenylphosphorane to afford diene **30** in near quantitative yield over the two steps. Palladium-catalyzed carbonylation of dienyl iodide **30** in the presence of methanol provided methyl ester **31**,31 and subsequent conversion to anilide alcohol **32** proceeded in 60% yield for the three steps. Swern oxidation of alcohol **32** gave aldehyde **33**. After extensive experimentation, we found that Horner–Wadsworth–Emmons coupling of aldehyde **33** with diketopiperazine phosphonate ester

3432 was best carried out with potassium *tert*-butoxide and 18-crown-6 in CH_2Cl_2, providing trienyl anilide **35** in 75% yield and >10:1 *Z*/*E* selectivity.

The pivotal catalytic asymmetric Heck cyclization/η^3-allylpalladium capture reaction of (2*Z*)-2,4-hexadienamide precursor **35** was initially carried out using 20 mol % Pd-*(S)*-BINAP and excess 1,2,2,6,6-pentamethylpiperidine in DMA at 100 °C. These conditions produced pentacyclic products **36** and **37** in a 6:1 ratio and 28% combined yield. The identical cyclization of precursor **35** using Pd-*(R)*-BINAP proceeded with similar efficiency and selectivity to provide a 6:1 mixture of pentacyclic products **37** and **36**. In each case, the major by-products were tetracyclic oxindoles **38** and **39**, resulting from elimination of palladium hydride from the intermediate η^3-allylpalladium complex. Unfortunately, efforts to increase the yield of pentacyclic products **36** and **37** having the spirotryprostatin ring system by variation of chiral ligands, solvent, base and reaction temperature met with little success. Attempts to access a potentially more electrophilic η^3-allylpalladium complex by a silver salt-mediated intramolecular Heck reaction proceeding via cationic Pd(II) intermediates led to rapid decomposition of precursor **35**.

Removing the SEM protecting group from pentacyclic products **36** and **37** proved to be extremely challenging. Numerous fluoride sources and protic acids were investigated, with all producing a complex mixture of products. After considerable experimentation, we discovered that the SEM group could be discharged from these delicate intermediates by initial exposure to dimethylaluminum chloride, followed by heating the resulting *N*-hydroxymethyl derivatives in methanol in the presence of diisopropylethylamine to remove the unit of formaldehyde. Analytically pure samples of (−)-18-*epi*-spirotryprostatin B (**13**), (−)-3-*epi*-spirotryprostatin B (**40**), and oxindoles **41** and **42** were obtained by preparative HPLC. The *trans* relationship of the aryl and 2-methylpropenyl groups in both **13** and **40** was apparent from the large nOe enhancement between H4 and H18, whereas the stereorelationship of the pyrrolidine and dihydropyrrole rings was established from long-range nOe enhancements observed between H12 and H21 of product **13** using double-pulsed field gradient spin echo (DPFGSE) nOe experiments.33† The absolute configuration of the quaternary carbon centers of **41** and **42** are logically assigned to be analogous to that of pentacyclic oxindoles **13** and **40**, respectively.

2.3. Total synthesis of (−)-spirotryprostatin B (12) and (−)-3,18-*epi*-spirotryprostatin B (56).

The Pd-(BINAP) catalyzed bis-cyclizations of (2*Z*)-2,4-hexadienamide precursor **35** demonstrated that: a) Heck insertion occurs with high regioselectivity at the internal double bond of the triene system, b) the η^3-allylpalladium intermediate is generated and captured with high stereochemical fidelity, and c) the nitrogen of the tethered diketopiperazine attacks the η^3-allylpalladium complex *anti* to the metal center. Consequently, we turned our attention to the preparation of stereoisomeric (2*E*)-2,4-hexadienamide **49**, which should serve as a precursor to spirotryprostatin B (**8**).

The synthesis of (2*E*)-*N*-(2-iodophenyl)-2,4-hexadienamide **49** began with the Baylis-Hillman adduct **43** (Scheme 7).34 Acylation of alcohol **43** under standard conditions provided the corresponding allylic acetate, which was allowed to react sequentially with $MgBr_2 \cdot Et_2O$ and *i*-Pr_2EtN/AcOH to provide primary allylic acetate **44** in 94% overall yield and high stereoselectivity (>20:1 *E*:*Z*).35 Saponification of ester **44**, followed by protection of the resulting allylic alcohol as a *tert*-butyldiphenylsilyl (TBDPS) ether gave intermediate **45** in 88% yield. For the preparation of aryl iodide precursor **49**, carboxylic acid **45** was coupled with 2-iodoaniline, providing anilide **47** in 91% yield.36 Subsequent alkylation of

†These assignments were corroborated by Danishefsky and Von Nussbaum, who independently synthesized **13** and **40**.8

the amide nitrogen with SEM-Cl, followed by removal of the TBDPS group, yielded alcohol **48** (88% over two steps). Dess-Martin oxidation37 of intermediate **48**, followed immediately by reaction of the derived aldehyde with the potassium salt of diketopiperazine phosphonate ester **34**32 gave (2*E*)-*N*-(2-iodophenyl)-2,4-hexadienamide **49** in 64% yield.

In order to examine the efficiency of bis-cyclization reactions proceeding via a cationic reaction manifold and potentially avoid the decomposition observed upon attempted cyclization of (2*Z*)-*N*-(2-iodophenyl)-2,4-hexadienamide **35** in the presence of silver salts (see above), we also prepared (2*E*)-*N*-(2-triflatophenyl)-2,4-hexadienamide **53**. In this case, carboxylic acid **45** was coupled with 2-(triisopropylsilyloxy)aniline (**46**, R^1 = OTIPS) to deliver anilide **50** in good yield.38 Protection of the amide nitrogen with SEM-Cl proceeded smoothly to furnish tertiary amide **51**. Removal of the triisopropylsilyl group with CsF and trapping of the nascent phenoxide with *N*-phenyltriflamide gave the corresponding triflate, which, after removal of the TBDPS group, provided triflate **52** in 82% yield. Dess–Martin oxidation37 of this intermediate and immediate coupling of the aldehyde product with phosphonate ester **34**32 gave (2*E*)-*N*-(2-triflatophenyl)-2,4-hexadienamide **53** in 55% yield.

Cyclization of (2*E*)-*N*-(2-iodophenyl)-2,4-hexadienamide **49** with Pd-(*S*)-BINAP under conditions identical to those employed with stereoisomer **35** unexpectedly led to the formation of oxindoles **36** and **37** as the sole pentacyclic reaction products (Scheme 8). Control experiments conducted in the absence of Pd-(*S*)-BINAP demonstrated that (2*E*)-*N*-(2-iodophenyl)-2,4-hexadienamide **49** underwent rapid isomerization of the internal double bond to give the more stable 2*Z* stereoisomer **35** when heated above 80 °C with excess PMP in DMA. As the two most likely mechanisms for isomerization of the Δ2,3 double bond of 2,4-hexadienamide **49** were base-promoted enolization followed by reprotonation, or reversible 1,4-addition of an adventitious nucleophile, we explored numerous other reaction conditions that might minimize such processes. Many HI scavengers other than PMP, including diisopropylethylamine, 2,6-di-*tert*-butylpyridine, Na_2CO_3, $NaHCO_3$, KOAc, AgOAc, Ag_2CO_3, Ag_3PO_4, and $AgBF_4$/diisopropylethylamine, were examined in various solvents (DMA, THF, PhMe, MeCN) without success. In addition, attempts to cyclize triflate congener **53** with Pd-(*S*)-BINAP using a variety of solvents and bases invariably either returned unchanged triflate **53**, or, under more forcing conditions, led to intractable mixtures of reaction products. Furthermore, extensive screening of chiral bidentate phosphine ligands other than BINAP, including 4-*tert*-butyl-2-[2-(diphenylphosphino)phenyl]oxazoline (PHOX) ligands, as well as chiral monodentate phosphines such as 2-(diphenylphosphino)-2′-alkoxy-1,1′-binapthyls (MOP ligands), failed to identify an enantioselective catalyst capable of promoting the desired conversion of precursors **49** or **53** to pentacyclic product **54**.

Although our efforts to accomplish a catalytic asymmetric bis-cyclization to prepare pentacyclic precursor **54** of spirotryprostatin B (**8**) were unsuccessful, we were able to accomplish the desired cascade cyclization of (2*E*)-*N*-(2-iodophenyl)-2,4-hexadienamide **49** with an achiral palladium catalyst. Thus, reaction of (2*E*)-2,4-hexadienamide **49** with 10 mol % Pd-2(dba)$_3$·$CHCl_3$, 40 mol % tri-*o*-tolylphosphine and excess KOAc in THF at 70 °C to give a 1:1 mixture of pentacyclic products **54** and **55** resulting from *anti*-capture of the initially produced η^3-allylpalladium intermediate. The higher catalytic activity of the Pd-(*o*-tolyl)$_3$P catalyst system relative to Pd-BINAP systems,39 and the presence of acetate in the reaction mixture, which has been shown to promote oxidative addition of Pd[0] complexes to aryl iodides,40 are likely responsible for allowing this transformation to be carried out at lower temperature under conditions that do not promote isomerization of the (2*E*)-*N*-(2-iodophenyl)-2,4-hexadienamide precursor. Removal of the SEM group from products **54** and **55**, followed by chromatographic purification provided pure (−)-spirotryprostatin B (**8**), $[\alpha]^{23}_D$ −159 (*c* 0.40, $CHCl_3$), and (−)-3,18-*epi*-spirotryprostatin B (**56**).5,7

3. Conclusion

Enantioselective total syntheses of (−)-spirotryprostatin B (**8**), (−)-18-*epi*-spirotryprostatin B (**13**), (−)-3-*epi*-spirotryprostatin B (**40**), and (−)-3,18-*epi*-spirotryprostatin B (**56**) have been accomplished in a convergent fashion. The central feature of each synthesis is a sequential Heck cyclization/η^3-allylpalladium trapping reaction that allows the pentacyclic ring system and the pivotal C3/C18 stereorelationship to be established in a single step. Moreover, these investigations demonstrate that: (a) intramolecular Heck insertions can occur with high regioselectivity at the internal double bond of triene precursors, (b) acyclic η^3-allylpalladium intermediates generated by catalytic asymmetric Heck cyclizations can captured with high stereochemical fidelity, and (c) the nitrogen of the tethered diketopiperazine attacks such η^3-allylpalladium intermediates *anti* to the metal center.

4. Experimental section

General Details

N,*N*-Dimethylacetamide and 1,2,2,6,6-pentamethylpiperidine were distilled from CaH under reduced pressure. Other general experimental details have been described.41 Experimental details for the synthesis of triflate **53** from acid **45** have been reported.42

Methyl (2*Z*)-2,5-Dimethylhexa-2,4-dienoate (16).23

A solution of KHMDS (0.5 M in PhMe, 130 mL, 65 mmol) was added dropwise to a solution of phosphonate **15** (21.7 g, 65.1 mmol) and 18-crown-6 (50 mg, 190 mmol) in THF (350 mL) at −78 °C. The resulting yellow solution was maintained at −78 °C for 1 h, then a solution of 3-methyl-2-butenal (**14**) (5.0 g, 59 mmol) in THF (20 ml) was added dropwise. The reaction was allowed to proceed for 2 h at −78 °C, then quenched with saturated aqueous NH_4Cl (100 mL) and allowed to warm to room temperature (rt). The mixture was diluted with pentane, the organic layer was separated and washed with water and brine, dried, and concentrated to a yellow oil. Purification of the residue by flash chromatography (pentane/Et_2O 95:5) gave ester **16** as a colorless oil (7.96 g, 86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, *J* = 11.7 Hz, 1H), 6.68 (d, *J* = 11.7 Hz, 1H), 3.76 (s, 3H), 1.98 (s, 3H), 1.87 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.5, 142.7, 136.4, 123.0, 122.4, 51.3, 26.8, 21.0, 18.2; IR (film) 2958, 2926, 1713, 1638, 1435, 1377, 1203 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_9H_{14}O_2$ 154.0994, found 154.0994. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.40; H, 8.99.

(2*Z*)-2,5-Dimethylhexa-2,4-dienoic acid (17)

A solution of **16** (1.0 g, 6.0 mmol), NaOH (1.2 g, 30 mmol), MeOH (40 mL), and water (10 mL) was heated at reflux for 12 h, then allowed to cool to rt. The solution was concentrated to a volume of 15 mL, then diluted with water (50 mL) and washed with hexane (2 × 30 mL). The aqueous phase was cooled to 0 °C, acidified with 2 M HCl to pH 2, and the resulting suspension was extracted with EtOAc. The combined organic extracts were washed with water, brine, dried and concentrated to provide acid **17** as a colorless crystalline solid (810 mg, 97%): mp 90–91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, *J* = 11.8 Hz, 1H), 6.82 (d, *J* = 11.8 Hz, 1H), 2.00 (s, 3H), 1.89 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 144.2, 138.9, 122.8, 122.1, 26.9, 20.8, 18.2; IR (film) 3300–2700 (br), 1684, 1663, 1624, 1591, 1408, 1260 cm^{-1}; HRMS (CI/isobutane) *m/z* calcd for $C_8H_{12}O_2$ 140.0837, found 140.0837. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.71; H, 8.57.

(2*Z*)-2,5-Dimethylhexa-2,4-dienoic acid, *N*-(2-iodophenyl)amide (18)

Oxalyl chloride (1.47 mL, 17.0 mmol) was added dropwise to a solution of **17** (0.79 g, 5.6 mmol) and CH_2Cl_2 (10 mL) at rt. After 10 min, one drop of DMF was added, and the reaction was allowed to proceed for 2 h. The solution was concentrated to a yellow oil, maintained under vacuum for 20 min, then redissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. A solution of 2-iodoaniline (1.24 g, 5.6 mmol), pyridine (0.48 g, 6.0 mmol) and CH_2Cl_2 (5 mL) was then added dropwise. The reaction mixture was then allowed to warm to rt where it was maintained for 3 h, then diluted with Et_2O (100 mL). This solution was washed with water, saturated aqueous $NaHCO_3$, water, brine, dried, and concentrated. The residue was passed through a pad of silica gel, eluting with 50:50 pentane/Et_2O, to afford amide **18** as a colorless solid (1.74 g, 90%): mp 55–56 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.78 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.71 (br s, 1H), 7.33–7.37 (m, 1H), 6.83–6.85 (m, 1H), 6.54–6.59 (m, 2H), 2.14 (s, 3H), 1.85 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 144.3, 141.1, 138.8, 138.4, 131.5, 129.2, 127.9, 125.7, 121.5, 89.6, 26.6, 21.3, 18.3; IR (film) 3248, 1641, 1522, 1431, 1304, 1262, 1014, 756 cm^{-1}; HRMS (CI/isobutane) *m/z* calcd for $C_{14}H_{16}INO$ 341.0278, found 341.0273. Anal. Calcd for $C_{14}H_{16}INO$: C, 68.55; H, 8.63. Found: C, 68.71; H, 8.57.

(2*Z*)-2,5-Dimethylhexa-2(*Z*),4-dienoic acid, *N*-(2-iodophenyl)-*N*-[(2-trimethylsilyl)ethoxymethyl]amide (19)

A stirring suspension of NaH (60% dispersion in oil, 200 mg, 5.0 mmol) in THF (20 mL) was cooled to 0 °C, then a solution of **18** (1.33 g, 3.9 mmol) and THF (20 mL) was added dropwise. The resulting slurry was allowed to warm to rt where it was maintained for 2 h, then recooled to 0 °C. Neat (2-trimethylsilyl)ethoxymethyl chloride (0.71 mL, 4.0 mmol) was added and the reaction was allowed to slowly warm to rt. After 12 h, the mixture was carefully quenched with water (1 mL), diluted with pentane, washed with water and brine, dried, and concentrated to give an orange oil. Purification of the residue by flash chromatography (hexanes/EtOAc 90:10) provided 1.56 g of amide **19** as a pale yellow oil (85%): ^{1}H NMR (500 MHz, $CDCl_3$, 2:3 mixture of amide rotamers, signals assignable to the major rotamer are noted) δ 7.94 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.24–7.35 (m, 2H), 7.03 (m, 1H), 6.16 (d, *J* = 11.6 Hz, 1H), 6.04 (d, *J* = 11.6 Hz, 1H), 5.86 (d, *J* = 10.3 Hz, 1H), 4.61 (d, *J* = 10.3 Hz, 1H), 3.85 (m, 1H), 3.74 (m 1H), 1.89 (s, 3H), 1.75 (s, 3H), 1.71 (s, 3H), 0.95–0.91 (m, 2H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 2:3 mixture of amide rotamers, signals assignable to the major rotamer are noted) δ 172.5, 142.6, 139.7, 137.4, 131.9, 129.7, 129.0, 127.8, 121.9, 99.3, 76.1, 66.8, 66.4, 26.3, 20.4, 18.2, 18.1, −1.3; IR (film) 2952, 1660, 1469, 1385, 1248, 1074, 858, 836 cm^{-1}; HRMS (CI/isobutane) *m/z* calcd for $C_{20}H_{30}IO_2NSi$ 471.1092, found 471.1088. Anal. Calcd for $C_{20}H_{30}IO_2NSi$: C, 50.95; H, 6.41; N, 2.97. Found: C, 51.14; H, 6.32; N, 2.91.

Methyl (2*E*)-2,5-Dimethylhexa-2,4-dienoate (21).[23,25]

A solution of **14** (0.76 g, 9.0 mmol), phosphorane **20**24 (2.72 g, 7.50 mmol) and CH_2Cl_2 (20 mL) was heated at reflux for 12 h, then cooled to rt and diluted with pentane. The mixture was filtered through Celite and the filtrate was concentrated to a yellow oil. The residue was distilled (bulb-to-bulb, 5 mm Hg, 105° C) to give ester **21** as a colorless oil (1.39 g, 92%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 11.8 Hz, 1H), 6.11 (dd, *J* = 11.8, 1.3 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.91 (s, 3H), 1.89 (s, 3H), 1.88 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 144.3, 143.4, 124.4, 121.2, 60.4, 26.9, 18.9, 14.4, 12.4; IR (film) 2981, 2929, 1703, 1445, 1258, 1111 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1150. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.41; H, 9.43.

(2*E*)-2,5-Dimethylhexa-2,4-dienoic acid, *N*-(2-iodophenyl)amide (22)

Trimethylaluminum (1.9 M in PhMe, 2.85 mL, 5.4 mmol) was added dropwise to a solution of 2-iodoaniline (975 mg, 4.56 mmol) and CH_2Cl_2 (15 mL) at 0 °C.26 The resulting solution was maintained at 0 °C for 20 min, then allowed to warm to rt where it was maintained for 2 h. The yellow reaction mixture was then recooled to 0 °C, and a solution of **21** (500 mg, 2.97 mmol) and CH_2Cl_2 (10 mL) was added dropwise. The solution was then allowed to warm to rt, and after 12 h was carefully poured into a stirring mixture of 1 M sodium potassium tartrate (50 mL) and ice (25 g). The mixture was extracted into Et_2O, and the combined organic extracts were washed with water and brine, dried, and concentrated to give a brown oil. Purification of the residue by flash chromatography (hexane/EtOAc 95:5 to 90:10), followed by recrystallization from hexanes provided amide **22** as colorless needles (813 mg, 80%): mp 104–105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.95 (br s, 1H), 7.78 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.42 (d, *J* = 11.5 Hz, 1H), 7.36 (m, 1H), 6.83 (m, 1H), 6.17 (d, *J* = 11.5 Hz, 1H), 2.12 (s, 3H), 1.93 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 144.3, 138.7, 138.6, 131.7, 129.4, 127.1, 125.6, 121.6, 120.9, 90.0, 27.0, 18.0, 12.9; IR (film) 3252, 1640, 1520, 1431, 1298, 1013, 755 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{14}H_{16}INO$ 341.0278, found 341.0273. Anal. Calcd for $C_{14}H_{16}INO$: C, 49.28; H, 4.73; N, 4.11. Found: C, 49.51; H, 4.83; N, 4.22.

(2*E*)-2,5-Dimethylhexa-2(*E*),4-dienoic acid, *N*-(2-iodophenyl)-*N*-[(2-trimethylsilyl)ethoxymethyl]amide (23)

Following the procedure used to prepare tertiary amide **19**, amide **22** (1.33 g, 3.90 mmol) was *N*-alkylated to yield, after chromatographic purification (hexane/EtOAc 100:0 to 85:15), tertiary amide **23** as a pale yellow oil (1.46 g, 80%): ^{1}H NMR (500 MHz, [d_6]DMSO, 60 °C) δ 7.90 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H), 7.31 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.05 (td, *J* = 7.6, 1.4 Hz, 1H), 6.36 (d, *J* = 11.2 Hz, 1H), 5.88 (d, *J* = 11.2 Hz, 1H), 5.67 (s, 2H), 3.57 (t, *J* = 7.9 Hz, 2H), 1.80 (s, 3H), 1.76 (s, 3H), 1.60 (s, 3H), 0.86 (t, *J* = 7.9 Hz, 2H), −0.03 (s, 9H); ^{13}C NMR (125 MHz, d_6-DMSO, 60 °C) δ 171.8, 144.1, 139.7, 139.2, 130.3, 128.8, 128.7, 128.6, 127.5, 119.6, 99.8, 77.4, 65.4, 25.5, 17.8, 17.3, 13.8, −1.8; IR (film) 2951, 1654, 1470, 1285, 1072, 836 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{30}INO_2Si$ 471.1092, found 471.1090. Anal. Calcd for $C_{20}H_{30}INO_2Si$: C, 50.95; H, 6.41; N, 2.97. Found: C, 51.12; H, 6.36; N, 2.96.

General Procedure for Pd-BINAP-Catalyzed Intramolecular Heck Reactions. Preparation of (*S*)-3-Methyl-3-(3-methylbuta-1(*E*),3-dienyl)-1-[(2-trimethylsilyl)ethoxymethyl]indolin-2-one (24) from (*Z*)-dimethylhexa-2,4-dienamide 19

A mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.442 g, 0.427 mmol), (*S*)-BINAP (0.745 g, 1.19 mmol) and DMA (20 mL) was stirred at rt for 4 h until a bright orange homogeneous solution was obtained. A solution of **24** (3.99 g, 8.47 mmol), 1,2,2,6,6-pentamethylpiperidine (6.2 mL, 34 mmol) and DMA (10 mL) was added, the resulting solution was degassed (three freeze-pump-thaw cycles),43 then heated at 100 °C for 16 h. After cooling to rt, the crude reaction mixture was poured into saturated $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 50 mL). The combined extracts were washed with water and brine, dried, and concentrated to give a brown oil. Purification of this residue by flash chromatography (hexanes/EtOAc 95:5) gave oxindole **24** as a pale yellow oil (2.66 g, 92%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 6.6 Hz, 1H), 7.16 (t, *J* = 6.6 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.18 (d, *J* = 15.9 Hz, 1H), 5.81 (d, *J* = 15.9 Hz, 1H), 5.20 (dd, *J* = 11.0, 6.5 Hz, 2H), 4.98 (s, 1H), 4.93 (s, 1H), 3.57 (t, *J* = 7.4 Hz, 2H), 1.85 (s, 3H), 1.58 (s, 3H), 0.93 (q, *J* = 7.4 Hz, 2H), −0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.4, 141.3, 141.2, 133.1, 132.6, 129.8, 128.2, 124.1, 122.0, 117.3, 109.9, 69.4, 65.9, 50.8, 23.5, 18.6, 17.8, −1.5; IR (film) 3056, 2952, 2894, 1725, 1614, 1488, 1341, 1081 cm^{-1}; HRMS (CI/isobutane) *m/z* calcd for $C_{20}H_{29}NO_2Si$ 343.1967, found 343.1974; $[\alpha]^{26}_D$ −27.2, $[\alpha]^{26}_{405}$ −80.5, $[\alpha]^{26}_{435}$ −63.0,

$[\alpha]^{26}_{546}$ −29.2, $[\alpha]^{26}_{577}$ −25.6 (*c* 1.0, $CHCl_3$, 90% ee). Anal. Calcd for $C_{20}H_{29}NO_2Si$: C, 69.92; H, 8.51; N, 4.08. Found: C, 69.88; H, 8.47; N, 4.06.

(*S*)-3-Methyl-3-(3-methylbuta-1(*E*),3-dienyl)indolin-2-one (25)

A solution of **24** (206 mg, 0.60 mmol), TBAF (1M in THF, 6.0 mL, 6.0 mmol) and THF (10 mL) was heated at reflux for 16 h, then cooled to rt and diluted with 30 mL of EtOAc. The solution was washed with water and brine, dried, and concentrated to give a brown oil. Purification of the residue by flash chromatography (hexanes/EtOAc 90:10 to 60:40) provided 115 mg (90%) of **25** as a colorless, crystalline solid (90% ee, HPLC, Chiralpak ASII column, 83:17 *n*-hexane/*i*-PrOH, 1 mL/min, retention time of major enantiomer = 12.3 min, retention time of minor enantiomer = 10.0 min): mp 130–131° C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.22–7.26 (m, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.24 (d, *J* = 15.9 Hz, 1H), 5.80 (d, *J* = 15.9 Hz, 1H), 4.99 (s, 1H), 4.95 (s, 1H), 1.86 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4, 141.7, 140.7, 134.1, 133.6, 129.9, 128.5, 124.6, 123.0, 117.7, 110.7, 51.4, 23.4, 19.0; IR (film) 3218, 2970, 1710, 1618, 1471, 1201, 969, 745 cm^{-1}; HRMS (CI/isobutane) *m/z* calcd for $C_{14}H_{15}NO$ 213.1154, found 213.1148; $[\alpha]^{26}_D$ +55.2, $[\alpha]^{26}_{405}$ +150.6, $[\alpha]^{26}_{435}$ +121.3, $[\alpha]^{26}_{546}$ +64.6, $[\alpha]^{26}_{577}$ +56.0 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.85; H, 7.09; N, 6.57. Found: C, 78.99; H, 7.22; N, 6.46.

(*S*)-1,3-Dimethyl-3-(3-methylbuta-1(*E*),3-dienyl)indolin-2-one (26)

A suspension of NaH (0.36 g, 60% dispersion in oil, 9.0 mmol) in THF (15 mL) was cooled to 0 °C, then a solution of **25** (1.29 g, 6.06 mmol) and THF (10 ml) was added dropwise. This mixture was allowed to warm to rt, then recooled to 0 °C. Methyl iodide (1.28 g, 9.0 mmol) was added dropwise, and the reaction was allowed to warm to rt. After 12 h, the reaction mixture was carefully poured over ice (100 g), then extracted with Et_2O. The combined organic extracts were washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography (hexanes/Et_2O 60:40) provided **26** as a pale yellow oil (1.33 g, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.16 (d, *J* = 15.9 Hz, 1H), 5.76 (d, *J* = 15.9 Hz, 1H), 4.94 (s, 1H), 4.90 (s, 1H), 3.22 (s, 3H), 1.82 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 143.0, 141.4, 133.2, 132.9, 129.9, 128.1, 124.0, 122.6, 117.1, 108.3, 50.5, 26.4, 23.2, 18.6; IR (film) 2970, 1720, 1614, 1493, 1471, 1373, 1348 cm^{-1}; $[\alpha]^{26}_D$ −59.5, $[\alpha]^{26}_{405}$ −183.5, $[\alpha]^{26}_{435}$ −142.8, $[\alpha]^{26}_{546}$ −64.7, $[\alpha]^{26}_{577}$ −64.1 (*c* 1.0, $CHCl_3$); HRMS (CI/isobutane) *m* / *z* calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1312.

(*S*)-1,3-Dimethyl-3-(2-hydroxyethyl)indolin-2-one (27)

A solution of **26** (0.50 g, 2.2 mmol), pyridine (174 μL, 2.2 mmol), *N*-methylmorpholine-*N*-oxide (0.23 g, 2.0 mmol), THF (15 mL) and water (1.5 mL) was cooled to 0 °C. A solution of osmium tetroxide (0.1 M in *t*-BuOH, 2.2 mL, 0.22 mmol) was added, and the reaction mixture was maintained at 0 °C for 12 h. Additional *N*-methylmorpholine-*N*-oxide (0.13 g, 1.1 mmol) was added, then the solution was allowed to warm to rt where it was maintained for 6 h. Solid $NaHSO_3$ (1 g), Florisil (1 g) and EtOAc (30 mL) were added, and the mixture was stirred rapidly for 30 min. This mixture was filtered and the filtrate was concentrated to a yellow oil. This crude diol was dissolved in MeOH (50 mL) and cooled to 0 °C, then a solution of $NaIO_4$ (1.2 g, 5.7 mmol) and water (15 mL) was added dropwise. The resulting mixture was maintained at 0 °C for 6 h, then allowed to warm to rt. After 12 h, the reaction mixture was diluted with Et_2O, washed with water and brine, dried and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc 80:20 to 60:40) gave the corresponding enone as a pale yellow oil (108 mg, 20%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.7

Hz, 1H), 6.79 (d, *J* = 16.1, 1H), 6.08 (d, *J* = 16.1, 1H), 3.20 (s, 3H), 2.22 (s, 3H), 1.54 (s, 3H).

A portion of this product (83 mg, 0.36 mmol) was hydrogenated in MeOH (5 mL) over 10% palladium on carbon (10 mg) under 1 atm of hydrogen for 6 h at rt. The flask was evacuated and refilled with nitrogen, then the reaction mixture was filtered through Celite and concentrated. The resulting mixture of ketone and dimethyl ketal was dissolved in THF (5 mL) and 1M HCl (0.5 mL) was added to hydrolyze the small amount of acetal produced during the hydrogenation. After 20 min at rt, the reaction was diluted with EtOAc and washed with water, brine, dried and concentrated. Purification of the residue by flash chromatography (hexanes/EtOAc 70:30 to 60:40) provided the corresponding ketone as a colorless oil (81 mg, 90%). A solution of trifluoroacetic anhydride (0.41 mL, 2.9 mmol) in $CHCl_3$ (3 mL) was cooled to 0 °C, then urea·H_2O_2 complex (226 mg, 2.90 mmol) was added in a single portion. The resulting mixture was stirred at 0 °C for 1 h, then a solution of the ketone (67 mg, 0.29 mmol) and $CHCl_3$ (1 mL) was added dropwise. The resulting solution was maintained at 0 °C for 2 h, then allowed to warm to rt. After 30 min, the solution was diluted with EtOAc and washed with 1 M $Na_2S_2O_3$, saturated $NaHCO_3$, water, brine, dried, and concentrated. Purification of the residue by flash chromatography (hexanes/EtOAc 50:50) afforded 7 mg (10%) of (*S*)-1,3-dimethyl-3-(2-acetoxyethyl)indolin-2-one as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.1 Hz, 1H), 7.07 (t, *J* = 7.5, 1H), 6.84 (d, *J* = 7.7, 1H), 3.87–3.92 (m, 1H), 3.67–3.70 (m, 1H), 3.22 (s, 3H), 2.29–2.34 (m, 1H), 2.09–2.14 (m, 1H), 1.82 (s, 3H), 1.38 (s, 3H); MS (ES) *m* / *z* calcd for $C_{14}H_{17}NO_3Na$ (M + Na) 270.3, found 270.2.

This acetate (7 mg, 0.028 mmol) was dissolved in THF (3 mL), then a solution of LiOH·H_2O (2 mg, 0.03 mmol) and water (1 mL) was added. The resulting mixture was rapidly stirred at rt for 6 h, then diluted with EtOAc and washed with water and brine (10 mL), dried, and concentrated to afford oxindole **27** as a colorless oil (4 mg, 70%): $[\alpha]^{26}_D$ −11.2 (*c* 0.40, $CHCl_3$). Spectroscopic properties of this compound were identical to those reported.15b,27 HPLC comparison to a sample of *ent*-**27**, $[\alpha]^{26}_D$ 14.0, was performed by both independent injection and co-injection: Chiralpak AS column (*n*-hexane/*i*-PrOH 90:10, 1 mL/min) **27** retention time = 18.7 min, *ent*-**27** retention time = 16.2 min.

3-Iodo-4-(*tert*-butyldiphenylsiloxy)-2(*Z*)-buten-1-ol (29)

A mechanically stirred suspension of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, 96.8 mL, 65% solution in PhMe, 320 mmol) in Et_2O (500 mL) was cooled to 0 °C, then a solution of **28**28 (50.0 g, 154 mmol) in Et_2O (100 mL) was added dropwise over 30 min. The mixture was stirred at 0 °C for 1 h, then EtOAc (15 mL, 150 mmol) was added dropwise. The resulting solution was maintained for 20 min, then solid I_2 (58.7 g, 231 mmol) was added in 5 portions at 10 min intervals with vigorous stirring. Following the final addition, the brown mixture was stirred for 10 min, then the reaction was quenched with saturated $Na_2S_2O_3$ (100 mL) and 1 M sodium potassium tartrate (100 mL). Hexanes was added and the organic layer was separated, washed with saturated $Na_2S_2O_3$ and brine, dried and concentrated to give a yellow oil. Purification of this residue by flash chromatography (hexanes/Et_2O 90:10 to 70:30), followed by recrystallization from hexanes afforded **29** as colorless plates (52.3 g, 75%): mp 49–50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 7.9, 1.4 Hz, 4H), 7.43–7.51 (m, 6H), 6.36 (m, 1H), 4.34 (d, *J* = 1.5 Hz, 2H), 4.30 (dt, *J* = 5.9, 1.3 Hz, 2H) 1.72 (s, 1H), 1.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 133.4, 132.9, 130.4, 128.3, 107.6, 71.9, 67.0, 27.3, 19.8; IR (film) 3332 (br), 3069, 2929, 2856, 1653, 1472, 1427, 1113, 701 cm^{-1}; HRMS (CI/iosbutane) *m/z* calcd for $C_{20}H_{24}IOSi$ (M–OH) 435.0641, found 435.0652. Anal. Calcd for $C_{20}H_{25}IO_2Si$: C, 53.10; H, 5.57. Found: C, 52.96; H, 5.60.

(*Z*)-2-Iodo-1-(*tert*-butyldiphenylsiloxy)-5-methylhexa-2(*Z*),4-diene (30)

A solution of DMSO (14 mL, 194 mmol) and CH_2Cl_2 (150 mL) was added dropwise over 20 min to a solution of oxalyl chloride (8.50 mL, 97.1 mmol) and CH_2Cl_2 (100 mL) at −78 °C.30 A solution of **29** (40.0 g, 88.3 mmol) and CH_2Cl_2 (150 mL) was then added dropwise over 20 min, and the reaction mixture was stirred for 20 min at −78 °C. Triethylamine (49 mL, 350 mmol) was then added, and the reaction was allowed to warm to rt. The mixture was then diluted with hexanes (1 L), washed with water and brine, dried and concentrated. The resulting oil was passed through a pad of silica gel, eluting with hexane/Et_2O 50:50, to give the crude aldehyde as a highly unstable, yellow crystalline solid, which was used without delay in the subsequent step (39.4 g, 99%): diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (d, *J* = 6.6 Hz, 1H).

A suspension of *i*-propyltriphenylphosphonium iodide (38.2 g, 88.3 mmol) in THF (400 mL) was cooled to 0 °C, then *n*-BuLi (2.5 M in hexane, 35.5 mL, 88.3 mmol) was added dropwise over 10 min. The mixture turned bright red and was rapidly stirred for 15 min at 0 °C, and then cooled to −78 °C. A solution of the crude aldehyde (39.4 g, 87.4 mmol) and THF (150 mL) was then added dropwise over 20 min. The reaction was allowed to warm to rt, then diluted with 1.5 L of hexanes and filtered through Celite. The resulting clear yellow solution was washed with water and brine, then dried and concentrated. The residue was passed through a pad of silica gel, eluting with hexanes/Et_2O 70:30, to furnish 40.7 g (98% over two steps) of diene **30** as a light yellow crystalline solid, which slowly decomposed above 0 °C: mp 58–61 °C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 6.5, 1.3 Hz, 4H), 7.43–7.51 (m, 6H), 6.83 (d, *J* = 10.2 Hz, 1H), 6.04 (d, *J* = 10.2 Hz, 1H), 4.44 (s, 2H), 1.91 (s, 3H), 1.85 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 136.0, 133.7, 130.3, 128.9, 128.2, 126.6, 104.8, 72.6, 27.3, 26.7, 20.1, 19.8; IR (film) 3071, 2929, 2856, 1421, 1112 cm^{-1}; HRMS (CI/isobutane) *m/z* calcd for $C_{23}H_{28}IOSi$ $(M - H)^+$ 475.0956, found 475.0955.

(2-*tert*-Butyldiphenylsiloxymethyl)-5-methylhexa-2(*Z*),4-dienoic acid, methyl ester (31)

A mixture of **30** (1.0 g, 2.1 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloro-palladium[II]·CH_2Cl_2 (0.17 g, 0.21 mmol), diisopropylethylamine (1.4 mL, 8.2 mmol), K_2CO_3 (0.32 g, 2.3 mmol), MeOH (4 mL) and DMF (20 mL) was stirred under an atmosphere of CO at 50 psi for 12 h. The mixture was then diluted with water (100 mL) and hexane (100 mL), then filtered through Celite. The organic phase was separated, washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography (hexanes/ether 90:10) afforded ester **31** as a colorless crystalline solid (0.763 g, 89%): mp 75–76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 6.5, 1.4 Hz, 4H), 7.41–7.48 (m, 6H), 7.25 (d, *J* = 12.0 Hz, 1H), 7.04 (d, *J* = 12.0 Hz, 1H), 4.49 (s, 2H), 3.72 (s, 3H), 1.96 (s, 3H), 1.91 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 145.3, 135.9, 135.3, 133.9, 130.1, 128.1, 125.9, 122.4, 64.2, 51.5, 27.3, 27.2, 19.7, 18.8; IR (film) 2931, 2857, 1718, 1632, 1428, 1201, 1072, 823 cm^{-1}; HRMS (CI/isobutane) *m/z* calcd for $C_{25}H_{31}O_3Si$ $(M - H)^+$ 407.2043, found 407.2047. Anal. Calcd for $C_{25}H_{32}O_3Si$: C, 73.49; H, 7.89. Found: C, 73.21; H, 7.94.

2-Hydroxymethyl-5-methylhexa-2(*Z*),4-dienoic acid, *N*-(2-iodophenyl)-*N*-[(2-trimethylsilyl)ethoxymethyl]amide (32)

Ester **31** (5.03 g, 12.3 mmol) was allowed to react with the aluminum derivative of 2-iodoaniline (5.67 g, 26.0 mmol)26 following the procedure described for the preparation of **22**. The resulting crude product was passed through a pad of silica gel (hexane/Et_2O 50:50) to provide 7.50 g of a mixture of the secondary amide and unreacted 2-iodoaniline as an oil. A solution of this crude product and THF (40 mL) was added dropwise to a stirring suspension of NaH (60% dispersion in oil, 0.740 g, 18.5 mmol) in THF (20 mL) at 0 °C.

This mixture was allowed to warm to rt where it was maintained for 2 h, then recooled to 0 °C. Neat (2-trimethylsilyl)ethoxymethyl chloride (3.27 mL, 13.0 mmol) was then added dropwise, and the reaction was allowed to warm to rt. After 12 h, the reaction mixture was carefully poured over crushed ice, and then extracted with hexanes. The combined organic extracts were washed with water and brine, then dried and concentrated. The residue was passed through a pad of silica gel, eluting with hexanes/Et_2O 50:50 to give a pale yellow oil. This material was dissolved in THF (30 mL), then TBAF (1 M in THF, 26 mL, 26 mmol) was added in one portion. The resulting dark brown solution was maintained at rt for 6 h, then diluted with Et_2O (150 mL). The solution was washed with water and brine, dried, and concentrated to yield a brown oil. Purification of this residue by flash chromatography (hexanes/EtOAc 70:30 to 50:50) gave amide **32** as a pale yellow oil (3.60 g, 60% over 3 steps): ^{1}H NMR (500 MHz, $CDCl_3$, 2:1 mixure of amide rotamers, signals assignable to the major rotamer are noted) δ 7.95 (d, *J* = 8.0 Hz, 1H), 7.28–7.46 (m, 2H), 7.04–7.12 (m, 1H), 6.62 (d, *J* = 11.7 Hz, 1H), 6.41 (d, *J* = 11.7 Hz, 1H), 5.22 (d, *J* = 10.2 Hz, 1H), 4.60 (d, *J* = 10.2 Hz, 1H), 4.36–4.53 (m, 1H), 3.69–3.89 (m, 1H), 3.29–3.51 (m, 2H), 1.88 (s, 3H), 1.86 (s, 3H), 1.28 (br s, 1H), 0.91 (m, 2H), −0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of amide rotamers, signals assignable to the major rotamer are noted) δ 171.8, 143.3, 141.3, 139.7, 132.3, 131.0, 129.6, 129.1, 126.8, 120.0, 98.1, 80.4, 66.5, 65.3, 26.3, 18.3, 17.9, −1.6; IR (neat) 3416 (br), 2952, 2921, 1651, 1470, 1408, 1249, 1075 cm^{-1}; HRMS (CI/isobutane) *m/z* calcd for $C_{20}H_{30}INO_3Si$ 487.1041, found 487.1036. Anal. Calcd for $C_{20}H_{30}INO_3Si$: C, 49.28; H, 6.20; N, 2.87. Found: C, 49.54; H, 6.33; N, 2.80.

2-Formyl-5-methylhexa-2(*Z*),4-dienoic acid, *N*-(2-iodophenyl)-*N*-[(2-trimethylsilyl)ethoxymethyl]amide (33)

Swern oxidation of **32** (1.18 g, 2.40 mmol),30 as described for the reaction of **29**, gave a crude residue that was passed through a pad of silica gel, eluting with hexane/Et_2O 50:50, to give aldehyde **33** as a colorless solid (1.14 g, 98%): mp 104–105 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 4:1 mixture of amide rotamers, signals assignable to the major rotamer are noted) δ 9.14 (s, 1H), 7.79 (d, *J* = 7.4 Hz, 1H), 7.24–7.44 (m, 2H), 7.03 (d, *J* = 12.2 Hz, 1H), 6.94–6.97 (m, 1H), 6.60 (d, *J* = 12.2 Hz, 1H), 5.84 (d, *J* = 10.6 Hz, 1H), 4.59 (d, *J* = 10.6 Hz, 1H), 3.93–3.99 (m 1H), 3.68–3.75 (m 1H), 1.95 (s, 3H), 1.87 (s, 3H), 0.81–1.06 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 167.7, 153.2, 146.3, 140.3, 140.2, 132.7, 130.4, 129.0, 123.7, 122.4, 99.9, 76.0, 66.9, 27.7, 19.7, 18.5, −0.9; IR (film) 2951, 1683, 1659, 1627, 1470, 1417, 1376, 1264, 1078, 836 cm^{-1}; HRMS (CI/isobutane) *m/z* calcd for $C_{20}H_{28}INO_3Si$ 485.0885, found 485.0886. Anal. Calcd for $C_{20}H_{28}INO_3Si$: C, 49.49; H, 5.81; N, 2.89. Found: C, 49.40; H, 5.83; N, 2.85.

(*S*)-2-(1,4-Dioxohexahydropyrrolo[1,2-*α*]pyrazin-3(*Z*)-ylidenemethyl)-5-methylhexa-2(*Z*),4-dienoic acid, *N*-(2-iodophenyl)-*N*-[2-(trimethylsilyl)ethoxy-methyl]amide (35)

A solution of diketopiperazine phosphonate **34** (1.08 g, 4.12 mmol),32 18-crown-6 (4.30 g, 16.3 mmol), and CH_2Cl_2 (10 mL) was added to a stirring suspension of potassium *tert*-butoxide (0.460 g, 4.12 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 30 min, then a solution of **33** (1.00 g, 2.06 mmol) and CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was allowed to warm to rt and stirred. After 2 h, this solution was diluted with EtOAc, washed with water and brine, dried, and concentrated to give an oil. This residue was purified by flash chromatography (hexanes/EtOAc 80:20 to 50:50) to furnish **35** as a light yellow solid (0.959 g, 75%): mp 70–72 °C; ^{1}H NMR (500 MHz, $CDCl_3$, complex because of mixture of rotamers, signals assignable to the major rotamer are noted) δ 8.64 (s, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.13–7.83 (m, 3H), 6.88 (d, *J* = 10.0 Hz, 1H), 6.34 (s, 1H), 5.91 (d, *J* = 10.0 Hz, 1H), 4.68 (s, 1H), 4.65 (s, 1H), 4.16–4.19 (m, 1H), 3.35–3.90 (m, 4H); 2.43–2.45 (m, 1H), 1.98–2.12 (m, 1H), 1.95 (s, 3H), 1.93 (s, 3H), 1.73–1.76 (m, 2H), 0.75–1.20 (m, 2H), −0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$,

complex because of mixture of rotamers, signals assignable to the major rotamer are noted) δ 165.7, 142.4, 142.2, 134.1, 132.9, 131.3, 131.0, 130.1, 129.6, 128.5, 126.3, 122.1, 114.6, 113.9, 112.6, 80.6, 67.1, 58.9, 45.6, 28.9, 26.7, 22.2, 21.8, 18.6, −1.57; IR (film) 3200, 2952, 1698, 1666, 1632, 1377, 1073 cm^{-1}; HRMS (FAB) *m* / *z* calcd for $C_{27}H_{36}IN_3O_4Si$ 621.1522, found 621.1529; $[\alpha]^{26}_D$ +118, $[\alpha]^{26}_{435}$ +401, $[\alpha]^{26}_{546}$ +154, $[\alpha]^{26}_{577}$ +126 (*c* 0.5, $CHCl_3$). Anal. Calcd. for $C_{27}H_{36}IN_3O_4Si$: C, 52.17; H, 5.84; N, 6.76. Found: C, 52.42; H, 5.84; N, 6.71.

18-*epi*-Spirotryprostatin B (13) and 3-[3-(methyl-1(*E*),3-butadienyl)indolin-2-one-3-ylmethylene]hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (41)

A mixture of $Pd_2dba_3{\cdot}CHCl_3$ (103 mg, 0.100 mmol), (*S*)-BINAP (135 mg, 0.220 mmol) and DMA (5 mL) was stirred at rt for 16 h, furnishing a bright orange homogeneous solution. A solution of (2*Z*)-2,4-hexadienamide **35** (600 mg, 0.970 mmol), PMP (0.70 mL, 3.9 mmol) and DMA (5 mL) was added, the reaction mixture was sparged with Ar for 15 min, degassed (4 freeze–pump–thaw cycles), sealed, and heated at 100 °C for 8 h. The resulting dark brown mixture was allowed to cool to rt, diluted with EtOAc (50 mL), filtered through Celite, and the filtrate was washed with water and brine, then dried and concentrated to yield a brown oil. The residue was chromatographed (hexanes/EtOAc 70:30) to give a 6:1 mixture of tetracyclic oxindole dienes **38** and **39** as a yellow solid (96 mg, 20%). Further elution (hexanes/EtOAc 50:50) provided a 6:1 mixture of pentacyclic oxindoles **36** and **37** as a light yellow foam (135 mg, 28%); **36**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.12 (m, 1H), 7.01 (m, 1H), 5.79 (s, 1H), 5.48 (d, *J* = 9.3 Hz, 1H), 5.27 (d, *J* = 9.3 Hz, 1H), 5.14 (d, *J* = 11.1 Hz, 1H), 5.03 (d, *J* = 11.1 Hz, 1H), 4.41 (m, 1H), 3.82 (m, 1H), 3.53 (m, 3H), 2.39 (m, 1H), 2.03 (m, 1H), 1.97 (m, 2H), 1.65 (s, 3H), 1.22 (s, 3H), 0.90 (m, 2H), −0.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 162.6, 154.6, 142.3, 139.5, 137.8, 129.5, 124.1, 123.7, 119.7, 118.3, 115.1, 109.8, 69.8, 66.6, 66.1, 62.4, 61.7, 45.1, 28.8, 25.9, 22.0, 18.1, 17.8, −1.3; HRMS (FAB) *m/z* calcd for $C_{27}H_{36}N_3O_4Si$ $(M+H)^+$ 494.2476, found 494.2471.

The mixture of pentacyclic oxindoles **36** and **37** was dissolved in CH_2Cl_2 (4 mL) and cooled to −78 °C. A solution of dimethylaluminum chloride (1 M in hexane, 1.5 mL, 1.5 mmol) was added dropwise, and the solution was allowed to warm to rt. After 20 min, the reaction mixture was recooled to 0 °C and a saturated aqueous solution of sodium potassium tartrate (5 mL) was carefully added, and the mixture was warmed to rt and stirred 30 min. The mixture then was diluted with EtOAc, washed with water and brine (20 mL), dried, and concentrated to a light yellow solid. This residue was dissolved in 5 mL of MeOH, 0.2 mL of diisopropylethylamine was added, the solution was heated to 45 °C for 16 h, then concentrated to yield a yellow solid. Purification of this residue by flash chromatography (CH_2Cl_2/MeOH 97:3) gave a 6:1 mixture of 18-*epi*-spirotryprostatin B (**13**) and 3-*epi*-spirotryprostatin B (**40**) as a light yellow solid (94 mg, 95%). An analytical sample of the major diastereomer, 18-*epi*-spirotryprostatin B (**13**), was isolated by preparatory HPLC (Alltech Altima C18 5μ 250 mm × 22 mm column, 50:50 water/MeOH, 10 mL/min, retention time = 37 min) as a light yellow solid: ^{1}H and ^{13}C NMR were identical to those described;[8] HRMS (CI/isobutane) *m/z* calcd for $C_{21}H_{21}N_3O_3$ 363.1609, found 363.1604; $[\alpha]^{23}_D$ −23.3 (*c* 0.15, $CHCl_3$), lit.8 $[\alpha]^{23}_D$ −24 (*c* 0.14, $CHCl_3$).

The 6:1 mixture of oxindoles **38** and **39** was deprotected in identical fashion to give a 6:1 mixture of **41** and **42** (67 mg, 95%) as a light yellow solid. An analytical sample of the major diastereomer **41** was obtained by HPLC (Alltech Altima SiO_2 10 μ 300 mm × 22 mm column, 80:20 hexanes/*i*-PrOH, retention time = 31.2 min) as a light yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.46 (s, 1H), 8.24 (s, 1H), 7.25–7.27 (m, 2H), 7.13 (td, *J* = 7.6, 1.2 Hz, 1H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.27 (d, *J* = 15.5 Hz, 1H), 6.03 (s, 1H), 5.74 (d, *J* = 15.5 Hz, 1H), 5.00 (s, 1H), 4.95 (s, 1H), 4.21–4.23 (m, 1H), 3.71–3.77 (m, 1H), 3.58–3.62 (m, 1H), 2.43–2.47 (s, 1H), 2.00–2.10 (m, 2H), 1.89–1.96 (m, 1H), 1.80 (s, 3H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 179.0, 165.9, 158.2, 140.8, 139.3, 134.5, 133.0, 132.7, 128.9, 124.9, 124.5, 123.9, 118.6, 113.2, 110.3, 59.2, 55.3, 45.8, 28.9, 21.9, 18.6; IR (film) 3182, 1693, 1632, 1444, 1384, 1228, 734 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{21}H_{22}N_3O_3$ 364.1661 (M+H), found 364.1665.

3-*epi*-Spirotryprostatin B (40)

Identical cyclization of **35** with Pd(*R*)-BINAP provided a 6:1 mixture of **37** and **36** in 26% yield. After removing the SEM-protecting group, an analytical sample of the major diastereomer **40** was isolated by preparatory HPLC (Alltech Altima C18 5 μ 250 mm × 22 mm column, 50:50 water/MeOH, 10 mL/min, retention time = 29 min) as a light yellow solid: ^1H and ^{13}C NMR were identical to those described;8 HRMS (CI/isobutane) *m/z* calcd for $C_{21}H_{21}N_3O_3$ 363.1609, found 363.1607; $[\alpha]^{23}_D$ −240.2 (*c* 0.90, $CHCl_3$), lit.8 $[\alpha]^{23}_D$ −251 (*c* 0.87, $CHCl_3$).

2-Acetoxymethyl-5-methyl-2(*E*),5-dienoic acid, methyl ester (44)

A solution of **43** (20.0 g, 23.1 mmol),34 pyridine (20 mL), acetic anhydride (40 mL) and CH_2Cl_2 (100 mL) was cooled to 0 °C, then solid *N*,*N*-dimethyl-4-aminopyridine (0.125 g, 1.03 mmol) was added in one portion and the solution was allowed to warm to rt. After 2 h, the solution was diluted with Et_2O (1 L), washed with H_2O, saturated $NaHCO_3$ and brine. This solution was then dried and concentrated to an oil, which was used without further purification (24.5 g, 98%).

Following a general procedure,35 a portion of this acetate (10.3 g, 48.5 mmol) was dissolved in THF (300 mL), then solid $MgBr_2{\cdot}Et_2O$ (22.5 g, 87.3 mmol) was added in five portions over 20 min. This solution was heated at reflux for 45 min, and then allowed to cool to rt. Hexane (600 mL) was added, and the mixture was filtered. The resulting clear filtrate was washed with water and brine, dried, and concentrated to give a pale yellow oil, which was used directly in the subsequent step (11.3 g, 100%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 12.2 Hz, 1H), 6.24 (d, *J* = 12.2 Hz, 1H), 4.36 (s, 2H), 3.80 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H). This allylic bromide (11.3 g, 48.5 mmol) was dissolved in MeCN (50 mL), then added in one portion to a stirring solution of AcOH (8.3 mL, 140 mmol), *i*-Pr_2EtN (26.2 mL, 150 mmol) and MeCN (200 mL) at rt. After 12 h, the solution was concentrated to a volume of 100 mL, hexane (300 mL) was added, the mixture was washed with 1 M citric acid (2 × 200 mL), H_2O, and saturated $NaHCO_3$. The solution was then dried and concentrated to provide allylic acetate **44** as a pale yellow oil (9.76 g, 96%), which was sufficiently pure to be used directly in the subsequent step. An analytical sample of **44** was prepared by bulb-to-bulb distillation (1.0 mm Hg, 125° C): ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 12.2 Hz, 1H), 6.25 (dd, *J* = 12.2, 1.1 Hz, 1H), 4.91 (s, 2H), 3.77 (s, 3H), 2.03 (s, 3H), 1.96 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 167.8, 149.5, 140.3, 122.1, 120.3, 58.1, 51.9, 27.2, 21.0, 19.1; IR (film) 2952, 1736, 1710, 1632, 1246, 1112 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{11}H_{16}O_4$ 212.1049, found 212.1047. Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.19; H, 7.62.

2-(*tert*-Butyldiphenylsiloxymethyl)-5-methyl-2(*E*),5-dienoic acid (45)

A solution of $LiOH{\cdot}H_2O$ (24.8 g, 590 mmol) and H_2O (150 mL) was added in one portion to a solution of **44** (12.5 g, 59 mmol) and THF (250 mL). The mixture was heated to 40 °C with rapid stirring for 18 h, allowed to cool to rt, and concentrated to a volume of 150 mL. This solution was cooled to 0 °C, acidified with concentrated HCl to pH 2, diluted with brine (50 mL), and extracted with EtOAc (5×100 mL). The combined extracts were dried and concentrated to a tan solid, which was used without further purification (9.31 g, 100%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 12.2 Hz, 1H), 6.31 (d, *J* = 12.2 Hz, 1H), 4.45 (s, 2H), 1.94 (s, 6H).

A portion of this acid (8.81 g, 56.4 mmol) and imidazole (19.2 g, 283 mmol) were dissolved in CH_2Cl_2 (100 mL), and *tert*-butyldiphenylchlorosilane (20.3 mL, 78.9 mmol) was added in one portion. The resulting solution was maintained at rt for 8 h, then Et_2O (500 mL) was added. The mixture was washed with 1 M citric acid, H_2O and brine (300 mL), dried, and concentrated to an oil. This residue was dissolved in MeOH (300 mL), then solid K_2CO_3 (5.0 g, 36 mmol) was added in one portion.‡ The resulting mixture was stirred for 30 min, filtered, 1 M aqueous solution of citric acid (100 mL) was added, and the mixture was extracted with Et_2O. The combined extracts were washed with water and brine, dried, and concentrated to yield a solid. Purification of this residue by flash chromatography (80:20 hexanes/EtOAc), provided **45** as a colorless crystalline solid (19.8 g, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dt, *J* = 6.3, 1.5 Hz, 4H), 7.69 (d, *J* = 12.1 Hz, 1H), 7.39–7.45 (m, 6H), 6.15 (dt, *J* = 12.1, 1.2 Hz, 1H), 4.54 (s, 2H), 1.92 (s, 3H), 1.86 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 148.2, 139.6, 135.8, 133.5, 129.7, 127.7, 125.9, 121.1, 58.0, 27.1, 26.8, 19.3, 19.0; IR (film) 2700–3300, 1679, 1632, 1598, 1427, 1287, 1254, 1068 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{24}H_{30}NaO_3Si$ (M+Na) 417.1867, found 147.1872. Anal. Calcd for $C_{24}H_{30}O_3Si$: C, 73.05; H, 7.66. Found: C, 73.03; H, 7.67.

2-(*tert*-Butyldiphenylsiloxymethyl)-5-methyl-2(*E*),5-dienoic acid, *N*-(2-iodophenyl)amide (47)

A mixture of **45** (344 mg, 0.872 mmol), 2-iodoaniline (229 mg, 1.04 mmol), *N*-methyl-2-chloropyridinium iodide (492 mg, 1.6 mmol), collidine (421 mg, 3.48 mmol) and PhMe (10 mL) was vigorously stirred at 80 °C for 4 h, then allowed to cool to rt.36 The mixture was diluted with EtOAc (100 mL), washed with 1M HCl and water, dried, and concentrated to give a brown oil. Purification of this residue by flash chromatography (90:10 hexanes/Et_2O) gave **47** as a pale yellow solid (472 mg, 91%): mp 73–75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 6.9 Hz, 4H), 7.45 (d, *J* = 12.1 Hz, 1H), 7.43–7.47 (m, 7H), 6.88 (t, *J* = 7.3 Hz, 1H), 5.44 (d, *J* = 12.1 Hz, 1H), 4.72 (s, 2H), 1.86 (s, 3H), 1.67 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 146.4, 139.0, 135.9, 135.3, 132.9, 129.9, 129.0, 127.8, 126.0, 123.7, 119.8, 91.3, 58.8, 27.1, 26.9, 19.2, 18.3; IR (film) 3334, 2928, 2858, 1679, 1584, 1524, 1429, 1292, 1229, 1112, 702 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{30}H_{35}INO_2Si$ 596.1482 (MH^+), found 596.1466. Anal. Calcd for $C_{30}H_{34}IO_2Si$: C, 60.50; H, 5.75; N, 2.35. Found: C, 60.73; H, 5.76; N, 2.21.

2-Hydroxymethyl-5-methylhexa-2(*E*),4-dienoic acid, *N*-(2-iodophenyl)-*N*-[(2-trimethylsilyl)ethoxymethyl]amide (48)

Following procedures analogous to those employed to prepare **32**, the sodium salt of amide **47** (9.80 g, 16.4 mmol) was *N*-alkylated with (2-trimethylsilyl)ethoxymethyl chloride (4.40 ml, 25 mmol), and the TBDPS group of the crude product was cleaved with tetrabutylammonium fluoride (1.0 M, 50 mL, 50 mmol) to provide a brown oil. Purification of this residue by flash chromatography (EtOAc/hexanes 30:70) gave **48** as a colorless solid (7.59 g, 95% over two steps): mp 114–115 °C; ^{1}H NMR (500 MHz, 75 °C, $CDCl_3$) δ 7.88 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.35 (m, 2H), 6.98 (m, 1H), 6.48 (br d, 1H), 6.02 (d, *J* = 11.5 Hz, 1H), 5.91 (br s, 1H), 4.66 (br d, 1H), 4.45 (br s, 1H), 4.33 (br s, 1H), 3.71 (br s, 1H), 3.64 (br m, 1H), 2.51 (br s, 1H), 1.79 (s, 3H), 1.61 (s, 3H), 0.85–1.00 (m, 2H), 0.01 (m, 9H); ^{13}C NMR (125 MHz, 75 °C, $CDCl_3$) δ 172.7, 145.1, 143.8, 140.2, 132.7, 131.2, 130.8, 129.2, 129.1, 119.8, 99.8, 78.3, 66.9, 59.3, 26.6, 18.6, 18.4, −1.4; IR (film) 3442, 2950, 1634, 1470, 1291, 1248, 1072, 1018, 835 cm^{-1}; HRMS (CI/isobutane) *m/z* calcd for

‡Treatment of the crude reaction mixture with MeOH/K_2CO_3 was necessary to hydrolyze the small amount (ca. 10%) of *tert*-butyldiphenylsilyl ester formed.

$C_{20}H_{30}INO_3Si$ 487.1041, found 487.1030. Anal. Calcd for $C_{20}H_{30}INO_3Si$: C, 49.28; H, 6.20; N, 2.87. Found: C, 49.50; H, 6.17; N, 2.82.

(*S*)-2-(1,4-Dioxohexahydropyrrolo[1,2-*a*]pyrazin-3(*Z*)-ylidenemethyl)-5-methylhexa-2(*E*),4-dienoic acid, *N*-(2-iodophenyl)-*N*-[2-(trimethylsilyl)ethoxy methyl]amide (49)

Alcohol **48** (609 mg, 1.25 mmol) was dissolved in CH_2Cl_2 (20 mL) at 23 °C, then Dess-Martin periodinane37 (690 mg, 1.60 mmol) was added in two equal portions with rapid stirring. The reaction mixture was stirred 20 min at rt, then a solution of saturated aqueous $Na_2S_2O_3$ (1 mL) was added, followed by saturated aqueous $NaHCO_3$ (1 mL). The resulting mixture was diluted with Et_2O, washed with water and brine, then dried and concentrated to give 604 mg of (*E*)-2-formyl-5-methylhexa-2,4-dienoic acid, *N*-(2-iodophenyl)-*N*-[2-(trimethylsilyl)ethoxy methyl]amide as a highly unstable yellow oil, which was used without delay in the subsequent step: diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (s, 1H, CHO). Potassium *tert*-butoxide (280 mg, 2.50 mmol) was suspended in CH_2Cl_2 (10 mL) with stirring, and cooled to −78 °C. A solution of diketopiperazine phosphonate **34**32 (660 mg, 2.50 mmol) and CH_2Cl_2 (5 mL) was then added dropwise with rapid stirring. The resulting mixture was stirred at −78 °C for 20 min, then a solution of the crude aldehyde (604 mg, 1.25 mmol) and CH_2Cl_2 (5 mL) was added dropwise with rapid stirring. The reaction mixture was allowed to warm to rt, diluted with EtOAc (50 mL), washed with water and brine, dried, and concentrated to give an oil. Flash chromatography of this residue (hexane/EtOAc 50:50 to 25:75) gave **49** as a light yellow foam (497 mg, 64% over two steps): ^{1}H NMR (500 MHz, 100 °C, [d_7]-*N*,*N*-dimethylformamide) δ 8.99 (br s, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.40–7.46 (br m, 2H), 7.12 (td, *J* = 7.9, 1.7 Hz, 1H), 6.76 (br d, *J* = 9.6 Hz, 1H), 6.45 (br s, 1H), 6.03 (br d, *J* = 9.6 Hz, 1H), 5.54 (br s, 1H), 4.76 (br s, 1H), 4.33 (t, *J* = 6.3 Hz, 1H), 3.64–3.78 (m, 3H), 3.45 (td, *J* = 8.8, 3.6 Hz, 1H), 2.28–2.31 (m, 1H), 1.95–2.05 (m, 3H), 1.86 (s, 3H), 1.82 (s, 3H), 0.93 (t, *J* = 8.1 Hz, 2H), −0.11 (s, 9H); ^{13}C NMR (125 MHz, 75 °C, $CDCl_3$, complex because of mixture of rotamers) δ 171.6, 171.2, 170.2, 165.1, 164.9, 157.7, 145.3, 139.8, 139.7, 133.5, 131.0, 129.3, 129.2, 128.9, 128.3, 122.2, 120.2, 113.4, 112.3, 108.1, 107.7, 99.2, 98.7, 80.7, 67.3, 67.1, 66.9, 59.1, 59.0, 58.8, 45.4, 28.9, 26.4, 21.6, 18.8, 18.1, 17.7, 13.9, −1.44, −1.64; IR (film) 3221, 2952, 1698, 1667, 1634, 1435, 1378, 1072, 835, 730 cm^{-1}; $[\alpha]^{26}_D$ +121.2, $[\alpha]^{26}_{577}$ +126.4, $[\alpha]^{26}_{546}$ +158.1, $[\alpha]^{26}_{435}$ +232.3 (*c* 0.2, $CHCl_3$); HRMS (CI/isobutane) *m/z* calcd for $C_{27}H_{36}IN_3O_4Si$ 621.1522, found 621.1530.

(−)-Spirotryprostatin B (8) and (−)-3,18-*epi*-spirotryprostatin B (56)

A mixture of $Pd_2(dba)_3$·$CHCl_3$ (23 mg, 0.023 mmol), tri-*ortho*-tolylphosphine (27 mg, 0.090 mmol) and THF (1.5 mL) was stirred at rt for 2 h, furnishing a bright red solution. This solution was added to a mixture of **49** (140 mg, 0.23 mmol) and KOAc (220 mg, 2.3 mmol) in a resealable tube. The mixture was sparged with argon for 10 min, then sealed and heated at 70 °C for 14 h. The brown reaction mixture was allowed to cool to rt and then was filtered through a pad of Celite, eluting with EtOAc. After concentration, the residue was purified by flash chromatography (EtOAc/Hexanes 75:25) to afford a mixture of **54** and **55** as a light yellow solid (80 mg, 72%). A portion of this mixture (65 mg, 0.13 mmol) was deprotected, as described for the preparation of **13**, to give a yellow solid, which was chromatographed (CH_2Cl_2/MeOH 97:3) to provide a mixture of crude (−)-spirotryprostatin B (**8**) and (−)-3,18-*epi*-spirotryprostatin B (**56**) (44 mg, 93%). These diastereomers were separated by preparatory TLC (CH_2Cl_2/MeOH 95:5) to give samples of **8** (21 mg, 33% from **49**) and **56** (19 mg, 29% from **49**).

An analytical sample of (−)-spirotryprostatin B (**8**) was obtained by preparatory HPLC (Alltech Altima C18 5μ 250 mm × 22 mm column, H_2O/MeOH 50:50, retention time = 44.0 min) to give a light yellow solid (16 mg): ^{1}H and ^{13}C NMR data were identical to those

reported;5 HRMS (CI/isobutane) calcd for $C_{21}H_{21}N_3O_3$ 363.1609, found 363.1612; $[\alpha]^{26}_D$ −159.4 (*c* 0.40, $CHCl_3$), lit. 5 $[\alpha]^{26}_D$ −162 (*c* 0.92, $CHCl_3$). An analytical sample of (−)-3,18-*epi*-spirotryprostatin B (**56)** was also obtained by preparatory HPLC (Alltech Altima C18 5μ 250 mm × 2 mm column, H_2O/MeOH 50:50, retention time = 18.6 min): a light yellow solid (5 mg); ^1H and ^{13}C NMR data were identical to those reported;7 HRMS (FAB) calcd for $C_{21}H_{22}N_3O_3$ (MH) 364.1661, found 364.1684; $[\alpha]^{26}_D$ −43.9 (*c* 0.40, CH_2Cl_2), lit.7 $[\alpha]^{26}_D$ −42.5 (*c* 0.8, CH_2Cl_2).

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18. We speculated that epimerization of this intermediate *via* bond rotation of either of the two potential η^1-allylpalladium isomers would be slow, because the C–Pd σ-bond would be either tertiary or neopentylic.

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21. Although soft nucleophiles generally react with η^3-allylpalladium complexes *anti* to the metal center, bond formation can occur by coordination to palladium followed by *syn* reductive elimination.17 No close precedent that would allow a definitive prediction of the mode of attack of a diketopiperazine nitrogen was available.

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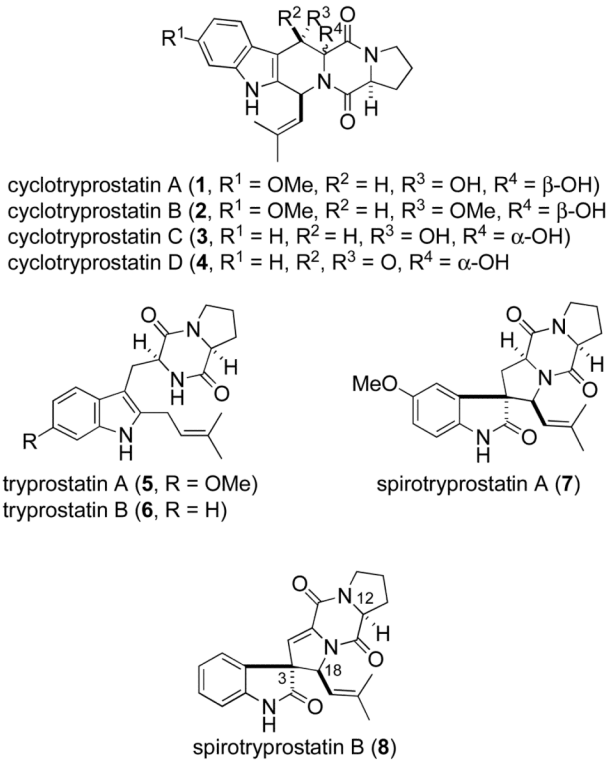
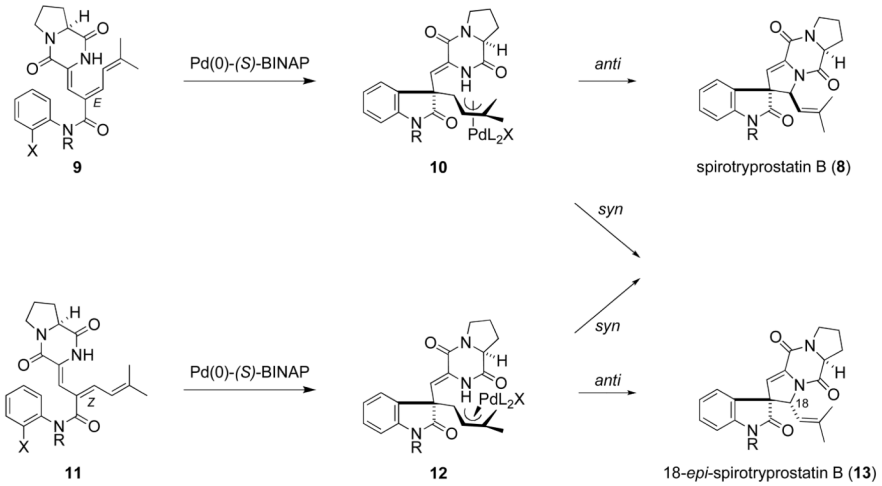
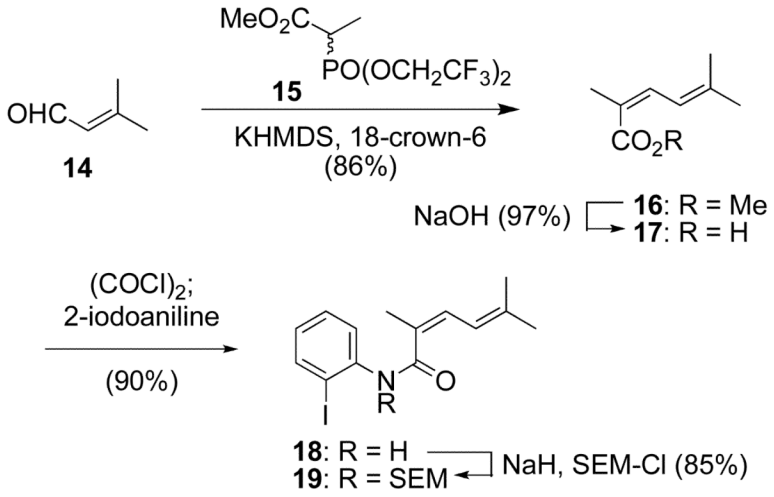


Figure 1.
Cell-cycle inhibitors from the marine fungus *Aspergillus*

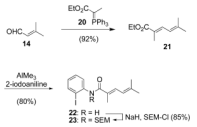


Scheme 1.

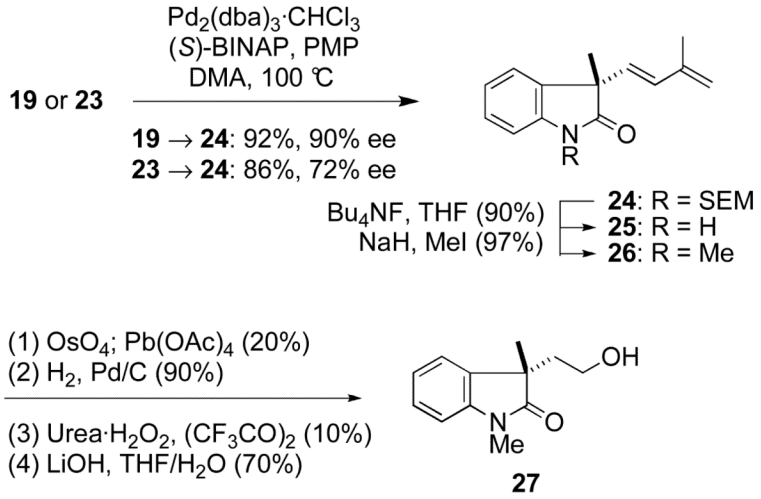
Potential construction of spirotryprostatin B by catalytic asymmetric Heck cyclization and intramolecular capture of η^3-allylpalladium intermediates.



Scheme 2.
Preparation of (*Z*)-2,5-dimethyl-*N*-(2-iodophenyl)-2,4-hexadienamide **19**.

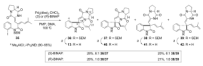


Scheme 3.
Preparation of (*E*)-2,5-dimethyl-*N*-(2-iodophenyl)-2,4-hexadienamide **23**.



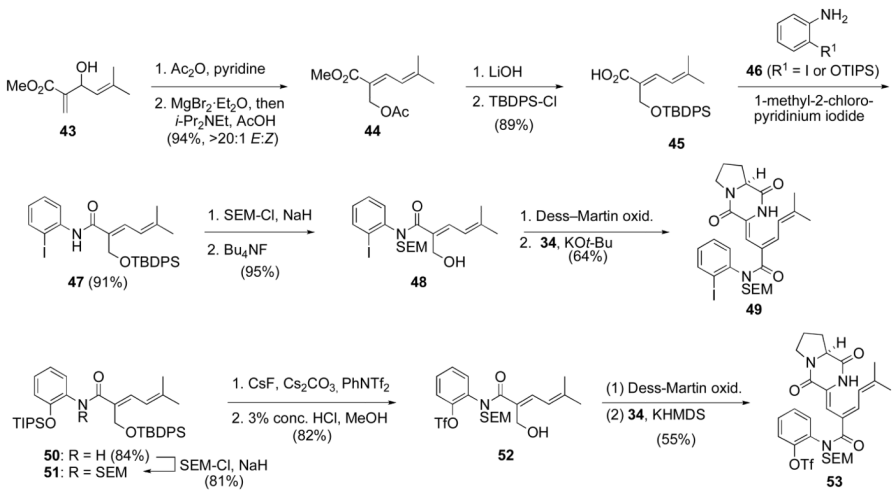
Scheme 4.
Catalytic asymmetric Heck cyclizations of (*Z*)- and (*E*)-2,4-hexadienamides **19** and **23**.

Scheme 5.
Preparation of (2*Z*)-2,4-hexadienamide cyclization precursor **35**.

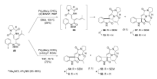


Scheme 6.

Cascade catalytic asymmetric Heck cyclization/intramolecular capture to prepare (−)-18-*epi*-spirotryprostatin B (**13**) and (−)-3-*epi*-spirotryprostatin B (**40**).



Scheme 7.
Preparation of (2*E*)-2,4-hexadienamide cyclization precursors **49** and **53**.



Scheme 8.

Cascade catalytic Heck cyclization/intramolecular capture to prepare (−)-spirotryprostatin B (**8**) and (−)-3,18-*epi*-spirotryprostatin B (**56**).