Stereocontrolled Syntheses of C-Aryl Taxanes by Intramolecular Heck Olefination. Novel Instances of Diastereofacial Guidance By Proximal Coordination

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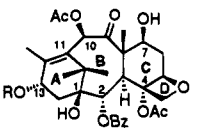
Abstract: Stereospecific syntheses of baccatin III constructs bearing an aromatic C-ring (**2a** and **2b**) have been demonstrated. A key step involves the use of an intramolecular Heck olefination reaction to form the C_{10}−C_{11} bond (see transformations **15** → **16** and **27** → **28**). Novel stereospecific reactions en route to **2a** and **2b** were also discovered (see **8** → **10**, **8** → **23**, **13** → **14**, and **25** → **26**).

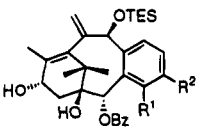
Background

The tetracyclic diterpenoid taxol (**1a**) has recently been approved for clinical application as an anticancer drug for the treatment of ovarian cancer.[1] It is also being evaluated as to its effectiveness against other carcinomas. Its mode of action seems to be associated with acceleration of tubulin polymerization and the blocking of its depolymerization.[2] Though the supply of taxol itself from its main natural source, the Pacific yew tree (*Taxus brevifolia*) is limited, the core structure baccatin III (**1b**), is more available, and viable protocols for conversion of baccatin III to taxol have been developed.[3]

We have been exploring strategies and methods that could be utilized toward the synthesis of baccatin III as well as deep structural variants thereof.[3b,4] In this connection we initiated a program to prepare analogs in which the C,D-sector of baccatin III is replaced with an aromatic construct.[5] In the context of this project, we also hoped to synthesize derivatives in which oxygenation would be included in the aromatic sector to mimic (albeit in a rough way) the oxetane D-ring of taxol. Below, we document our results on the stereospecific formation of such totally synthetic taxane constructs (**2a,b**).[5,6] We further describe the derivatization of **2a,b** by attachment of the *N*-benzoyl-β-phenylisoserine side chain[3] and the biological evaluations of these products.



1a taxol, R=N-benzoyl-β-phenylisoserine
1b baccatin III, R=H



2a $R^1 = R^2 = H$
2b $R^1 \wedge R^2 = -OCH_2O-$

Discussion of Results

Our starting material was ketal **4** which was prepared from 2,2,6-trimethylcyclohexane-1,3-dione (**3**) as previously described (Scheme 1).[7] Acidic deketalization and treatment of the resulting ketone **5** with trimethylsilyl cyanide gave **6**. Reduction of the nitrile function of the protected cyanohydrin **6** with diisobutylaluminum hydride afforded aldehyde **7** in 93% yield. Earlier,[5] we had reported on the reaction of various aryllithium reagents with siloxy aldehyde **7**. For example, reductive metalation of *o*-bromostyrene (**9**) with *n*-BuLi followed by addition of **7** afforded a 1:2 epimeric mixture of carbinols **10** and **11** in 79% yield. While these diastereomers were separated and the required **10** was carried forward to a successful conclusion, a selective route to the desired coupling product would obviously be helpful for the synthesis. Toward this goal, we examined the consequences of adding metallostyrene derivatives to hydroxy aldehyde **8** rather than **7**. The hydroxy aldehyde was readily secured by deprotection of **7** with potassium carbonate in methanol.

Addition of 2-lithiostyrene to **8** was highly stereoselective. Racemic **10** was obtained in 88% yield. Only trace amounts of **11** were noted. The relative stereochemistry of **10** at C_1 and C_2[8] had been rigorously established[5] by crystallographic determination of one of its subsequent transformation products. The high stereoselectivity in the reaction of **8**, in contrast to **7**, with the lithiated styryl reagent **9** is likely to be the consequence of a powerful metal chelation effect of the vicinal lithioalkoxide generated from deprotonation of the hydroxyl group.[9] This chelation effect results in the formation of the desired "anti-

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(1) For a recent review on the preclinical and clinical development of taxol and taxotere, see: Rothenbery, M. *Curr. Opin. Invest. Drugs* **1993**, *2*, 1269−1277.

(2) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.

(3) For the first conversion of baccatin III to taxol, see: (a) Denis, J.-N.; Greene, A. E.; Guenard, D.; Gueritte−Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917. For other approaches, see: (b) Nicolaou, K. C.; Guy, R. K.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.

(4) For a recent review, see: Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. The Taxane Dipertenoids. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1−188.

(5) Masters, J. J.; Jung, D. K.; Bornmann, W. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1993**, *34*, 7253−7256.

(6) For total syntheses of taxol, see: (a) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulyannan, K.; Sorenson, E. J. *Nature* **1994**, *367*, 630. (b) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597−1598, 1599−1560.

(7) Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989.

(8) The numbering utilized is analogous to that of the taxol system.

(9) Cf. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569.

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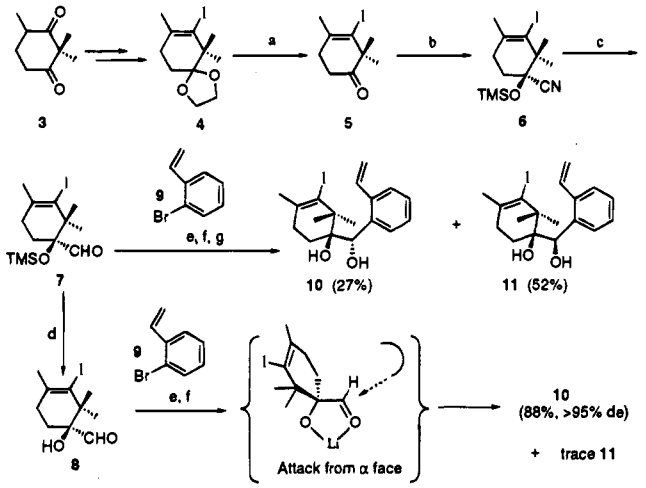
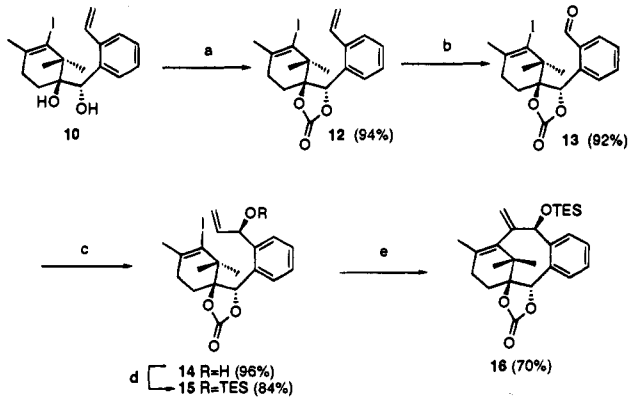
Scheme 1[a]



[a] Reagents: (a) 1:13 N HCl/THF, 70 °C, 96%; (b) (TMS) CN, KCN-(cat), 18-crown-6, CH_2Cl_2, 0 °C, 98%; (c) DIBAL-H, hexane, −78 °C, 93%; (d) K_2CO_3, MeOH, 25 °C, 60%; (e) *n*-BuLi, THF/Et_2O, −78 °C; (f) THF, −78 °C; (g) TBAF, THF, 25 °C.

Scheme 2[a]

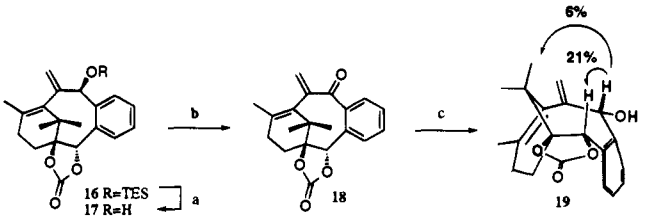


[a] Reagents: (a) $COCl_2$, pyridine, CH_2Cl_2, 25 °C; (b) O_3 CH_2Cl_2, −78 °C, PPh_3; (c) vinylmagnesium bromide, THF, −78 °C; (d) (TES)-OTf, NEt_3, DMAP, CH_2Cl_2, 0−25 °C; (e) $Pd(PPh_3)_4$, K_2CO_3, MeCN, reflux.

Cram" [10] addition product as depicted. The use of α-metallooxido aldehydes arising from deprotonation of the free alcohol has been recognized only very recently as being helpful in realizing high margins of stereoselectivity.[11]

At this juncture, the diol **10** was protected as its cyclic carbonate **12** using phosgene and pyridine[12] (Scheme 2). It was hoped that constraint of the C_1-C_2 bond would favor the projected closure of the $C_{10}-C_{11}$ bond (*vide infra*).[8] Ozonolysis of **12** afforded the aldehyde **13**. Subsequent treatment of **13** with vinylmagnesium bromide in THF resulted in the formation of the carbinol **14** *as a single diastereomer*. Silylation of **14** with triethylsilyl trifluoromethanesulfonate afforded **15**. At this

Scheme 3[a]



[a] Reagents: (a) TBAF, THF, 25 °C, 90%; (b) PDC, Celite, 25 °C, 81%; (c) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 83%.

stage, the configuration at C_9 was unknown.[8] Subsequently the stereochemistry was shown to be of the *R* configuration (*vide infra*).[13]

The stage was now set for the critical cyclization attempt. Toward this end we explored the possibility of a Heck olefination reaction to fashion the $C_{10}-C_{11}$ bond.[5,14-16] In the event, closure was accomplished from the reaction of **15** with tetrakis(triphenylphosphine)palladium(0) and potassium carbonate in refluxing acetonitrile. The desired "C-aryl taxane" **16** was formed in 70% yield. That cyclization had in fact occurred in the indicated sense was demonstrated by NMR spectral analysis which revealed the presence of the *exo*-methylene arrangement, in conjunction with mass spectral corroboration of the molecular formula (see Experimental Section).

Much effort was expended investigating this key intramolecular Heck olefination reaction. It was found that temperatures above 60 °C were required for cyclization to occur. However, even at higher temperatures, the reaction was sluggish and reaction times of 2−7 days were necessary to ensure total consumption of starting material. Furthermore, it was also evident that the catalyst was becoming inactivated and the rate of reaction was decaying over time. Periodic addition of 10 mol% palladium(0) to the reaction proved to be helpful in achieving consumption of starting material. When conducted in this way, the reaction was generally complete in 36 h, and yields of 70% of **16** could be routinely obtained.

At this stage, the configuration of C_9 relative to the C_1-C_2 stereogenic centers was not known. Deprotection of **16** with tetrabutylammonium fluoride provided the β-carbinol **17** in 90% yield. Oxidation of **17** using PDC in CH_2Cl_2 afforded ketone **18** (Scheme 3). The latter was reduced with sodium borohydride using the Luche[17] protocol to afford a carbinol which was not the same as **17**. The stereochemistry of C_9 of **17** and the new carbinol **19** were determined by NOE experiments. Thus, irradiation of the C_9 methine of **19** showed a 6% enhancement to the C_{17}-methyl and a 21% enhancement to the C_2-methine. No corresponding enhancements were observed from **17**. These results serve to define the configurations of **17** and **19** to be as shown and therefore establish structures of **14**, **15**, and **16** to be as previously assigned. Furthermore, these results are in agreement with compound **17** existing as the endo atropisomer.[18]

With the configuration at C_9 in **17** and **19** assigned with confidence, we return to the remarkable stereoselectivity manifested in the vinylation of aldehyde **13** leading to alcohol **14**. The issue is potentially of wide-ranging scope. In its

(10) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245.

(11) During preparation of this paper, a stereoselective addition of an aryllithium species to a taxol A-ring hydroxy aldehyde intermediate has surfaced; see: Nakamura, T.; Waizumi, N.; Tsuruta, K.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1994**, 584−586.

(12) (a) In an earlier communication[5] we had used an acetal as a constraining device. Subsequent to that in a steroid model (Masters, J. J.; Jung, D. K.; Danishefsky, S. J.; Snyder, L. B.; Park, T. K.; Isaacs, R. C.; Alaimo, C. A.; Young, W. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 452−455), we had switched to a cyclic carbonate for ease of deprotection. In their total synthesis of taxol[6a] and in a subsequent disclosure, Nicolaou and colleagues have elegantly demonstrated this value of the cyclic carbonate; see: (b) Nicolaou, K. C.; Claiborne, C. F.; Nantermet, P. G.; Couladouros, E. A.; Sorenson, E. J. *J. Am. Chem. Soc.* **1994**, *116*, 1591−1592.

(13) The material is racemic, but the stereochemistry is assigned relative to the absolute congiguration at C_1 and C_2 of baccatin III (**1b**) in its natural configuration.

(14) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: New York, 1985; p 179.

(15) Cf. Overman, L. *Pure Appl. Chem.* **1992**, *64*, 1813.

(16) For a recent example of an intramolecular Heck reaction in a difficult synthetic context, see: McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 6094.

(17) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(18) Cf. Shea, K. J.; Gilman, J. W. *Tetrahedron Lett.* **1984**, *25*, 2451.

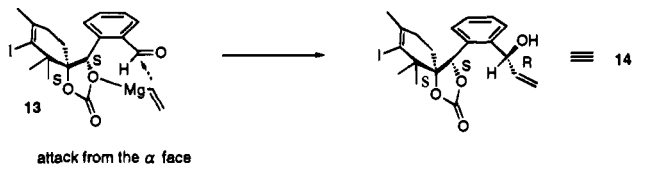
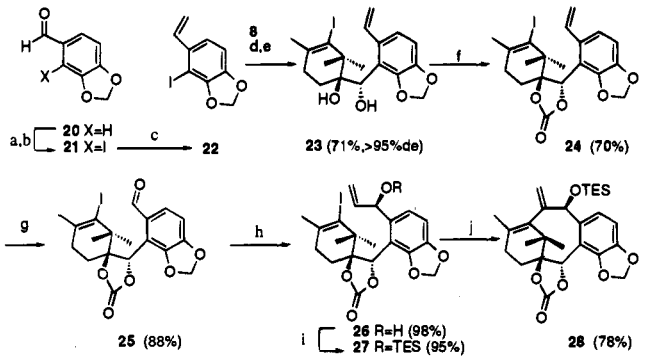


Figure 1.

Scheme 4[a]



[a] Reagents: (a) *n*-BuLi, $(CH_3)_2NCH_2CH_2NCH_3H$, 0 °C; (b) *n*-BuLi, I_2, −78 °C; (c) CH_3Ph_3PBr, KO-*t*-Bu, 25 °C; (d) *n*-BuLi, THF/Et_2O, −78 °C; (e) THF, −78 °C; (f) $COCl_2$, pyridine, DMAP, CH_2Cl_2, 0 °C; (g) O_3, CH_2Cl_2, −78 °C, PPh_3; (h) vinylmagnesium bromide, THF, −78 °C; (i) (TES)OTf, NEt_3, DMAP, 0 °C; (j) $Pd(PPh_3)_4$, K_2CO_3, MeCN, reflux.

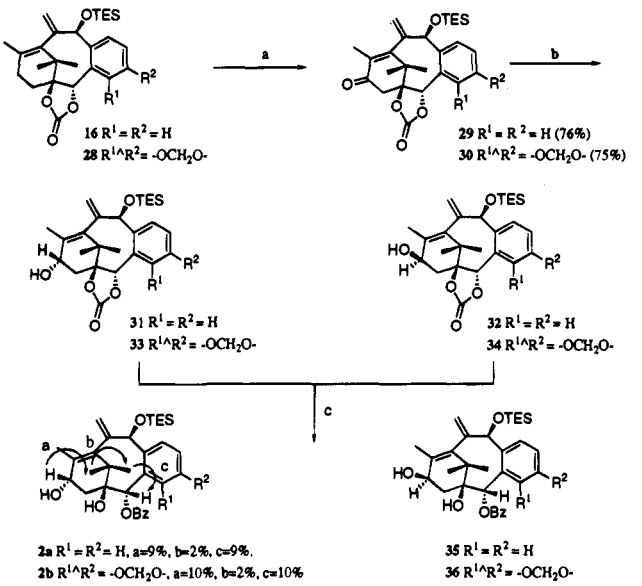
broadest sense, the stereochemical question which such a case poses is that of diastereofacial control by an ortho stereogenic center in a nucleophilic addition reaction to a proximal conjugated π system. Obviously, each instance has to be evaluated on its own merit. In Figure 1 a model to account for this particular reaction is offered for consideration. In this rationalization, the aldehyde oxygen is positioned anti to the ortho aryl−substituent bond. In the likely rotamers about the aryl−ethylene carbonate bond, delivery of the nucleophile to the α face involves less hindrance than would be encountered if attack occurred in the alternate sense. Furthermore, nucleophilic attack by a Lewis acidic Grignard reagent in the indicated *re* (α) sense may also be favored by guidance from the benzylic oxygen of the carbonate linkage. Clearly alternative models where the reactive aldehyde rotamer and the sense of the nucleophilic addition are reversed can be entertained. Since the single data point (*i.e.*, the configuration at C_9 of **14**) cannot resolve the two unknowns (pertinent rotamer and sense of nucleophilic attack), the actual basis for the remarkable stereoselectivity is still a matter of conjecture. Nonetheless, the finding is remarkable, and it suggests new ways for transmitting chiral information across benzo structures.[19]

In an analogous fashion, the oxygenated C-aryl structure compound **28** was prepared as shown in Scheme 4. The initially required aryl iodide **22** was prepared from piperonal (**20**). A key feature of this route involved the applicability of the *in situ* aldehyde protection strategy of Comins[20] to allow for the conversion of **20** to **21**. Wittig olefination of the latter led to **22**. Coupling of lithiated **22** with the previously described **8** gave **23**. The latter was converted to **27** as practiced in the simple benzo series. Heck cyclization of **27** gave **28** in 78% yield. The assignments of the configurations at C_1 and C_2 shown throughout the series follow from the eventual cyclization

(19) For a discussion of the effects of resident chirality in the ortho position on Grignard additions to a benzaldehyde, see: (a) Alexakis, A.; Sedrani, R.; Normant, J. F.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 283. (b) Sedrani, M. R. Ph.D. Thesis, L'Universite Paris, 1990. We thank Professor Scott Denmark for bringing this work to our attention.

(20) Comins, D. L. Int. Patent PCT/US91/09598, 1991.

Scheme 5[a]



[a] Reagents: (a) PCC, NaOAc, Celite, 25 °C; (b) $NaBH_4$, $CeCl_3$, MeOH, 0 °C; (c) PhLi, THF, −78 °C.

at the stage of **27**. The configuration at C_9 was first assigned by analogy with the benzo series and was demonstrated to be as shown by subsequent experiments (*vide infra*).

Two routes were envisioned to transform C-aryl systems **16** and **28** into the desired baccatin III constructs **2a** and **2b** . The most straightforward method contemplated the generation of a carbonyl group at C_{13}. The latter would be expected to suffer selective reduction from the less hindered (*i.e.*, β) face to form the desired C_{13}-α-alcohols. Final treatment of such products with phenyllithium[12b] would generate **2a** and **2b**.

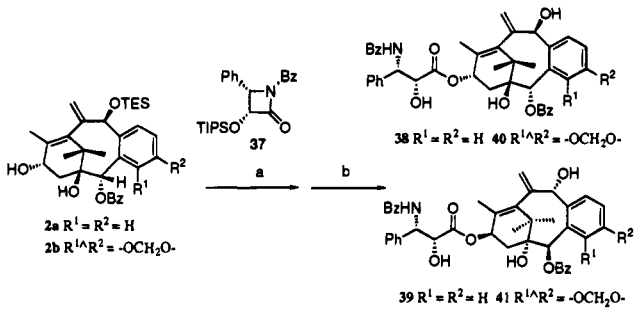
An alternative route would start with cleavage of the C_1−C_2-carbonate. This conversion would be followed by oxidation and reduction at C_{13}. There was concern that release of the carbonate constraint, engaging C_1 and C_2, could allow for the formation of the exo atropisomer.[18] In such a setting, selectivity in the critical reduction of the intermediate enone might be compromised.

In practice, oxidation of **16** using excess PCC and sodium acetate[12b] in refluxing benzene proceeded smoothly (Scheme 5). Reduction of the resulting enone **29** under Luche conditions provided the α- and β-alcohols **31** and **32** in a 10:1 ratio. These compounds were not separated. Subsequent treatment of the mixture with phenyllithium allowed for purification of the desired α-alcohol **2a**. Only trace amounts (*ca.* 5−10%) of β-alcohol **35** were detected. Not surprisingly, reduction of enone **29** in the absence of $CeCl_3$ led to a mixture of the desired α-alcohol **31** as well as to 1,4 reduction material. No β-alcohol **32** was observed.

In a similar way, allylic oxidation of the piperonal-derived compound **28** proceeded smoothly to afford **30**. Surprisingly, reduction of **30** using Luche conditions resulted in an inseparable 1:1 mixture of diastereomeric alcohols **33** and **34**. Thus, competitive delivery of the hydride from the α face of the molecule was occurring. Conceivably, the lack of selectivity in this methylenedioxy series may result from competing complexation of the reducing agent with the dioxolane linkage. This contact might tend to direct hydride delivery toward the otherwise more hindered α face at C_{13}. In this way the striking difference in the stereochemical outcome between the benzo and piperonal series can be rationalized.

Treatment of the mixture of **33** and **34** with phenylithium afforded **2b** and **36**. These stereoisomers were readily separated

Scheme 6[a]



[a] Reagents: (a) NaHMDS; (b) TBAF.

by column chromatography on SiO_2. Interestingly, reduction of the enone **30** without the use of $CeCl_3$ enhanced the ratio of α- to β-alcohol formation (>95:5, 58%). However, this improved selectivity was hardly helpful since, in this protocol, substantial amounts of 1,4 reduction material (23%) were also generated.

The stereochemistry of the C_{13}-α-alcohols **2a** and **2b** was confirmed by NOE experiments. Compounds **2a** and **2b** each showed NOE enhancements between the C_{13}-methine and C_{16}-methine as well between the C_{17}-methyl and C_2-methine. Additionally, the C_9-methine of **2a** and **2b** showed no correlation to C_{17}-methyl or C_2-methine.

The above described methodology illustrates a concise route by which C-aryl taxol analogues can be generated. Alternative methods to produce these constructs have recently appeared.[3b] Accordingly, we were interested in evaluating the biological consequences of these derivatives. Toward this end, we investigated the incorporation of the "taxol side chain" (*N*-benzoyl-β-phenylisoserine) utilizing the Ojima–Holton protocol.[6b,21] Reaction of racemic **2a** with β-lactam **37** using sodium hexamethyldisilazide in tetrahydrofuran at −78 °C and subsequent treatment with tetrabutylammonium fluoride gave a 1:1 mixture of diastereomers[22] **38** and **39** as depicted in Scheme 6. Similarly **2b** was transformed into diastereomers **40** and **41**. The mixture of diastereomers **38/39** and **40/41** were each evaluated in tubulin polymerization assays as well as for cytotoxicity (cell line HCT116). Both mixtures were found to be completely inactive.[23] In the light of a recent disclosure[12b] reporting that similar C-aryl taxanes are significantly active, it appears that the structural requirements for biological activity are rather strict.

In summary, a novel strategy for the synthesis of a baccatin III construct bearing an aromatic C-ring has been demonstrated. The key step is the formation of the C_{10}–C_{11} bond by an intramolecular Heck olefination reaction. The synthesis of **2a** is stereospecific and regiospecific at each stage. A particularly intriguing instance of asymmetric induction under the control of an ortho stereogenic center (see **13** → **14** and **25** → **26**) has been demonstrated.

The application of the intramolecular Heck reaction to provide access to other baccatin constructs, and possibly to baccatin III itself, is a major subject of research in our laboratory. Results of our progress will be described in due course.

(21) Ojima, I.; Sun, C. M.; Zucco, M.; Park, Y. H.; Duclos, O.; Kuduk, S. *Tetrahedron Lett.* **1993**, *34*, 4149. Ojima, I.; Habus, I.; Zucco, M.; Park, Y. M.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985.

(22) We subsequently determined that the β-lactam which we utilized to be of 85% enantiomeric excess. Thus, compounds **38–41** contain minor amounts of the corresponding antipodes.

(23) Cell line HCT-116: taxol, $IC_{50} = 0.004$ μM; **38/39** and **40/41**, $IC_{50} > 11.3$ μM. Tubulin polymerization assay: taxol, $EC_{0.01}$ (μM) = 3.8 ± 1; **38/39** and **40/41**, $EC_{0.01}$ (μM) > 1000.

Experimental Section

General Procedures. Melting points are uncorrected and were measured using a digital melting point Electrothermal IA 9100 apparatus. Infrared spectra (IR) were obtained with a Perkin-Elmer 1600 Series Fourier Transform spectrometer. NMR spectra were recorded using a Bruker AMX-400 spectrometer. High-resolution mass spectra (HRMS) were recorded at the Department of Chemistry of Columbia University. Flash chromatography was performed using EM Science silica gel 60 (230–400 mesh). Reactions were conducted under a nitrogen atmosphere unless otherwise noted.

Preparation of Vinyl Iodide 5. A solution of **4** (2.05 g, 6.65 mmol) in 25 mL of THF and 25 mL of 3 N HCl was heated at reflux for 0.75 h. The mixture was cooled and diluted with Et_2O/H_2O. The aqueous phase was washed with Et_2O, and the combined extracts were dried with $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 and 10% EtOAc/hexane to give 1.68 g (96%) of **5**: clear oil; ^1H NMR ($CDCl_3$) δ 2.56 (m, 4 H), 2.01 (s, 3 H), 1.27 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 208.9, 137.8, 112.5, 52.1, 35.5, 31.8, 30.3, 28.0; IR (neat) 1720, 1631, 1460, 1343, 1254 cm^{-1}; HRMS for $C_9H_{13}OI$, calcd 264.0010, found 264.0017.

Preparation of Protected Cyanohydrin 6. A solution of **5** (1.62 g, 6.13 mmol) in 40 mL of CH_2Cl_2 was cooled to 0 °C and treated with trimethylsilyl cyanide (1.23 g, 9.20 mmol) followed by potassium cyanide (40 mg, 0.61 mmol) and 18-crown-6 (40 mg, 0.15 mmol). The mixture was stirred for 0.5 h and quenched by addition of 5 mL of H_2O. The mixture was washed with CH_2Cl_2, and the combined extracts were dried with $MgSO_4$. The dried extracts were then filtered through a bed of Florisil using CH_2Cl_2 as the eluent, and the solvent was removed under reduced pressure to afford 2.19 g (98%) of **6**: clear oil; ^1H NMR ($CDCl_3$) δ 2.46 (dt, 1 H, J = 18.2, 7.7 Hz), 2.32 (dt, 1 H, J = 18.2, 5.3 Hz), 2.06 (dd, 2 H, J = 7.7, 5.4 Hz), 1.91 (s, 3 H), 1.37 (s, 3), 1.14 (s, 3 H), 0.27 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 136.6, 120.7, 110.8, 74.0, 47.1, 30.9, 30.6, 30.3, 28.7, 24.4, 1.2; IR (neat) 1631, 1461, 1253, 1134 cm^{-1}; HRMS for $C_{13}H_{22}OSiI$, calcd 363.0515, found 363.0527.

Preparation of Aldehyde 7. A solution of **6** (2.13 g, 5.86 mmol) in 120 mL of hexanes was cooled to −78 °C and treated dropwise with DIBAL-H (8.8 mL, 1 M solution in hexanes, 8.8 mmol). The mixture was allowed to stir at −78 °C for 6.5 h. The mixture was then diluted with Et_2O (120 mL), treated with SiO_2 (27 g), and slowly allowed to warm to room temperature (rt) over 10 h. The mixture was poured into H_2O (150 mL), and the organic layer was removed. The aqueous phase was washed with Et_2O (2 × 100 mL), and the combined organic layers were dried with $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 with 10% EtOAc/hexane to give 1.99 g (93%) of **7**: clear oil; ^1H NMR ($CDCl_3$) δ 9.75 (s, 1 H), 2.34 (m, 2 H), 1.96 (m, 1 H), 1.92 (s, 3 H), 1.85 (m, 1 H), 1.15 (s, 3 H), 1.10 (s, 3 H), 0.15 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 203.6, 136.8, 114.0, 82.0, 45.8, 30.7, 30.4, 27.3, 27.1, 26.3, 2.3; IR (neat) 1734, 1632, 1248 cm^{-1}; HRMS for $C_{13}H_{23}O_2SiI$, calcd 366.0512, found 366.0531.

Preparation of α-Hydroxy Aldehyde 8. A solution of **7** (2.5 g, 6.84 mmol) in 50 mL of MeOH was cooled to 0 °C and treated with K_2CO_3 (15 mg). After 1 h, the mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography on SiO_2 with 5–10% EtOAc/hexane as the eluent to give 1.2 g (60%) of **8**: clear oil; ^1H NMR ($CDCl_3$) δ 9.79 (s, 1 H), 3.60 (s, 1 H), 2.54–2.48 (m, 1 H), 2.35–2.28 (m, 1 H), 1.97 (s, 3 H), 1.93–1.89 (m, 2 H), 1.14 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 204.63, 137.15, 113.80, 78.89, 45.10, 30.90, 30.03, 27.24, 25.95; IR (neat) 3916, 2971, 1717, 1575, 1457, 907 cm^{-1}; HRMS for $C_{10}H_{15}O_2I$, calcd 294.0117, found 294.0106.

Conversion of 7 to Diols 10 and 11. A solution of 2-bromostyrene (**9**; 0.57 g, 3.1 mmol) in 6 mL of Et_2O and 26 mL of THF at −78 °C was treated with *n*-butyllithium (1.9 mL, 1.6 M solution in hexanes, 3.1 mmol). After 10 min, the mixture was rapidly added via cannula to a solution of **7** (0.96 g, 2.6 mmol) in 10 mL of THF at −78 °C. The mixture was stirred for 10 min at −78 °C and quenched by addition of NH_4Cl(satd). The mixture was diluted with H_2O and washed with EtOAc (2 × 20 mL). The combined extracts were dried with $MgSO_4$,

and the solvent was removed under reduced pressure. The residue was dissolved in 50 mL of THF and treated dropwise with TBAF (2.7 mL, 1 M solution in THF, 2.7 mmol). After 10 min, the solvent was removed under reduced pressure and the residue was purified by column chromatography on SiO_2 with 60% CH_2Cl_2/petroleum ether to give 0.28 g (27%) of **10** and 0.54 g (52%) of **11**. **10**: white solid; mp 140−141 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (br s, 1 H), 7.44 (d, 1 H, J = 7.3 Hz), 7.32 (t, 1 H, J = 7.5 Hz), 6.98 (br s, 1 H), 5.62 (d, 1 H, J = 17.2 Hz), 5.35 (d, 1 H, J = 11.0 Hz), 5.26 (br s, 1 H), 3.21 (s, 1 H), 2.42 (br s, 1 H), 2.10 (dt, 1 H, J = 7.1, 17.9 Hz), 1.86 (s, 3 H), 1.79 (dt, 1 H, J = 18.0, 6.2 Hz), 1.39 (m, 2 H), 1.37 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.4, 137.8, 136.9, 134.3, 128.2, 128.1, 127.8, 126.3, 117.5, 117.0, 76.0, 70.3, 48.3, 31.1, 29.8, 28.1, 27.6, 27.0; IR (film) 3495, 3323, 1654, 1406, 1323 cm^{-1}; HRMS for $C_{18}H_{23}O_2I$, calcd 398.0743, found 398.0735. **11**: white film; ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 1H, J = 7.6 Hz), 7.47 (d, 1H, J = 7.1 Hz), 7.33 (m, 2H), 7.19 (dd, 1H, J = 17.4, 11.0 Hz), 5.58 (d, 1H, J = 17.4 Hz), 5.44 (d, 1H, J = 3.0 Hz), 5.35 (d, 1H, J = 11.0 Hz), 2.25 (dd, 2H, J = 8.0, 4.9 Hz), 2.10 (dt, 1H, J = 13.8, 8.2 Hz), 1.94 (d, 1H, J = 3.1 Hz), 1.92 (s, 3H), 1.79 (dt, 1H, J = 13.9, 4.8 Hz), 1.35 (s, 3H), 1.32 (s, 3H), 1.26 (s, 1H): ^{13}C NMR ($CDCl_3$) δ 138.7, 138.3, 137.9, 135.8, 128.0, 127.6, 127.5, 126.5, 117.0, 76.7, 72.3, 47.3, 31.3, 29.9, 27.5, 27.2, 23.8; IR (film) 3540, 3462, 1714, 1625 cm^{-1}; HRMS for $C_{18}H_{23}O_2I$, calcd 398.0743, found 398.0750.

Conversion of 8 to Diol 10. A solution of 2-bromostyrene (**9**; 6.0 g, 32 mmol) in 10 mL of Et_2O and 40 mL of THF at −78 °C was treated dropwise with *n*-butyllithium (11.8 mL, 2.5 M solution in hexanes, 29.5 mmol). After 10 min, the mixture was rapidly added via cannula to a solution of **8** (0.97 g, 3.3 mmol) in 5 mL of THF at −78 °C. The mixture was stirred for 30 min at −78 °C and quenched with NH_4Cl(satd). The mixture was diluted with H_2O and washed with EtOAc (2 × 20 mL). The combined extracts were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on SiO_2 with 15% EtOAc/hexane to give 1.15 g (88%) of **10**.

Preparation of Cyclic Carbonate 12. A solution of **10** (23 mg, 0.060 mmol) in 1 mL of CH_2Cl_2 was treated with pyridine (134 μL, 0.180 mmol) followed by phosgene (150 μL, 1.9 M solution in toluene, 0.300 mmol). After 12 h, the mixture was diluted with $NaHCO_3$(satd) and the aqueous phase was washed with EtOAc (2 × 20 mL). The combined extracts were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on SiO_2 with 15−20% EtOAc/hexane to give 23 mg (94%) of **12**: white solid; mp 163−164 °C; ^{1}H NMR ($CDCl_3$) δ 7.43 (1 H, AA′BB′), 7.33 (2 H, AA′BB′), 7.23 (1 H, AA′BB′), 6.82 (dd, 1 H, J = 17.2, 10.0 Hz), 5.88 (s, 1 H), 5.99 (dd, 1 H, J = 17.2, 0.85 Hz), 5.33 (dd, 1 H, J = 10.0, 0.85 Hz), 2.17−2.11 (m, 1 H), 1.76 (s, 3 H), 1.68−1.57 (m, 2 H), 1.50−1.43 (m, 1 H), 1.33 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.32, 138.41, 136.97, 133.25, 131.96, 129.43, 128.03, 127.21, 126.87, 118.64, 110.58, 88.41, 79.00, 46.79, 30.61, 29.75, 26.89, 25.85, 25.05; IR (film) 2907, 1797, 1259, 1163, 1048, 777 cm^{-1}; HRMS for $C_{19}H_{21}O_3I$, calcd 424.0536, found 424.0547.

Preparation of Aldehyde 13. A solution of **12** (0.26 g, 0.61 mmol) in 40 mL of CH_2Cl_2 at −78 °C was treated with O_3 until a blue solution resulted. After 1 min, excess O_3 was removed by passing N_2 through the solution. The mixture was then treated with triphenylphosphine (0.19 g, 0.73 mmol) and allowed to warm to rt over 1 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 with 10% EtOAc/hexane to give 0.24 g (92%) of **13**: white solid; mp 150−151 °C; ^{1}H NMR ($CDCl_3$) δ 10.04 (s, 1H), 7.85 (1H, AA′BB′), 7.71 (1 H, AA′BB′), 7.64 (1 H, AA′BB′), 7.52 (1 H, AA′BB′), 6.84 (s, 1 H), 2.24−2.16 (m, 1 H), 1.77 (s, 3 H), 1.64−1.49 (m, 3 H), 1.42 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 192.02, 154.46, 137.52, 136.25, 135.01, 133.95, 133.48, 129.73, 128.60, 111.21, 89.01, 76.62, 60.21, 46.72, 30.46, 29.69, 26.66, 26.17, 25.01; IR (film) 2982, 1801, 1704, 1168, 1048, 905, 732 cm^{-1}; HRMS for $C_{18}H_{19}O_4I$, calcd 426.0328, found 426.0341.

Preparation of Carbinol 14. A solution of **13** (0.60 g, 1.4 mmol) in 15 mL of THF at −78 °C was treated dropwise with vinylmagnesium bromide (2.1 mL, 1 M solution in THF, 2.1 mmol). After 1 h, the reaction was quenched by addition of NH_4Cl (satd). The aqueous phase was washed with EtOAc (2 × 10 mL), and the combined extracts were dried with $MgSO_4$. The solvent was removed under reduced pressure to give 0.61 g (96%) of **14**: clear oil; ^{1}H NMR ($CDCl_3$) δ 7.60 (1 H, AA′BB′), 7.34 (2 H, AA′BB′), 7.30 (1 H, AA′BB′), 6.04−5.96 (m, 1 H), 5.92 (1 H), 5.36−5.24 (m, 3 H), 3.03 (br s, 1 H), 2.17−2.13 (m, 1 H), 1.85 (s, 3 H), 1.85−1.67 (m, 3 H), 1.37 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.81, 140.25, 139.73, 139.28, 132.02, 129.78, 129.98, 127.31, 126.63, 116.61, 110.47, 88.67, 78.33, 70.75, 47.19, 30.66, 29.90, 27.07, 25.96, 25.54, 24.99; IR (neat) 3470, 2965, 1789, 1462, 1261, 1169, 1048 cm^{-1}; HRMS for $C_{20}H_{23}O_4I$, calcd 472.0985, found 472.0978.

Preparation of Silyl Ether 15. A solution of **14** (0.61 g, 1.3 mmol) in 40 mL of CH_2Cl_2 at 0 °C was treated sequentially with triethylamine (0.24 mL, 1.73 mmol), 4-(*N*,*N*-dimethylamino)pyridine (20 mg, 0.16 mmol), and triethylsilyl trifluoromethanesulfonate (0.42 g, 1.6 mmol). After 12 h, the reaction was quenched by addition of $NaHCO_3$(satd). The aqueous phase was washed with EtOAc (2 × 20 mL), and the combined extracts were dried with $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 with 5% EtOAc/hexane to give 0.64 g (84%) of **15**: clear oil; ^{1}H NMR ($CDCl_3$) δ 7.52 (2 H, AA′BB′), 7.36 (2 H, AA′BB′), 6.22 (s, 1 H), 5.92−5.86 (m, 1 H), 5.28 (m, 1 H), 5.14−5.06 (m, 2 H), 2.30−2.25 (m, 1 H), 1.85 (s, 3 H), 1.85−1.77 (m, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 0.90 (t, 9 H, J = 7.9 Hz), 0.59 (q, 6 H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 154.65, 140.96, 140.36, 138.20, 131.91, 129.37, 128.16, 127.49, 127.31, 115.66, 111.19, 88.20, 77.87, 73.97, 47.31, 30.67, 29.95, 26.85, 25.93, 25.03, 6.62, 4.78; IR (neat) 2954, 1804, 1461, 1165, 1043 cm^{-1}; HRMS for $C_{26}H_{37}O_4SiI$, calcd 568.1506, found 568.1523.

Cyclization of 15. Preparation of Diene 16. A mixture of **15** (0.37 g, 0.65 mmol), K_2CO_3 (0.28 g, 2.0 mmol), and $Pd(PPh_3)_4$ (75 mg, 0.065 mmol) in 6.5 mL of MeCN was heated to reflux. After 12 h, additional $Pd(PPh_3)_4$ (80 mg, 0.069 mmol) was introduced. After 24 h, additional $Pd(PPh_3)_4$ (60 mg, 0.052 mmol) was introduced. After 36 h, the mixture was allowed to cool, diluted with EtOAc, and filtered through a pad of SiO_2. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 with 5% EtOAc/hexane to give 0.2 g (70%) of **16**: clear film; ^{1}H NMR ($CDCl_3$) δ 7.53 (1 H, AA′BB′), 7.27 (1 H, AA′BB′), 7.13 (2 H, AA′BB′), 6.61 (s, 1 H), 5.49 (d, 1 H, J = 1.3 Hz), 5.28 (s, 1 H), 5.05 (d, 1 H, J = 1.3 Hz), 2.31−2.21 (m, 2 H), 1.97−1.94 (m, 1 H), 1.44 (s, 3 H), 1.21−1.17 (m, 1 H), 1.21 (s, 3 H), 1.60 (t, 9 H, J = 7.8 Hz), 0.64 (s, 3 H), 0.50 (q, 6 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 154.47, 149.35, 140.19, 136.52, 135.00, 134.74, 130.28, 127.60, 127.41, 125.18, 119.76, 82.58, 82.55, 77.89, 39.40, 27.44, 24.89, 23.04, 21.99, 21.98 6.49, 4.57; IR (neat) 2955, 1806, 1037, 846, 745 cm^{-1}; HRMS for $C_{26}H_{36}O_4Si$, calcd 440.2383, found 440.2393.

Desilylation of 16. Preparation of Carbinol 17. A solution **16** (25 mg, 0.057 mmol) in 500 μL of THF was treated with TBAF (0.11 mL, 1 M solution on THF, 0.11 mmol). After 1 h, the solvent was removed under reduced pressure and the residue was purified by column chromatography on SiO_2 and 10% EtOAc/hexane to give 17 mg (90%) of **17**: clear film; ^{1}H NMR ($CDCl_3$) δ 7.58 (1 H, AA′BB′), 7.34 (1 H, AA′BB′), 7.20 (2 H, AA′BB′), 6.62 (s, 1 H), 5.66 (d, 1 H, J = 1.0 Hz), 5.44 (s, 1 H), 5.16 (d, 1 H, J = 1.0 Hz), 2.39−2.35 (m, 1 H), 2.27−2.22 (m, 1 H), 1.45 (s, 3 H), 1.39−1.35 (m, 1 H), 1.25 (s, 3 H), 1.24−1.21 (m, 1 H), 0.68 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.2, 148.9, 138.9, 136.8, 134.7, 134.4, 130.9, 127.9, 127.7, 125.3, 120.5, 92.7, 82.5, 77.8, 39.3, 27.3, 24.7, 22.9, 22.1, 21.9; IR (neat) 3555, 2918, 1790, 1290, 1200, 1038, 748 cm^{-1}; HRMS for $C_{20}H_{22}O_4$, calcd 326.1513, found 326.1518.

Oxidation of 17. Preparation of Enone 18. A mixture of **17** (16 mg, 0.050 mmol), PDC (92 mg, 0.25 mmol), and Celite (92 mg) in 2 mL of CH_2Cl_2 was stirred at rt for 48 h. The mixture was filtered through a pad of SiO_2, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on SiO_2 with 20% EtOAc/hexane to give 13 mg (81%) of **18**: clear film; ^{1}H NMR ($CDCl_3$) δ 7.48 (2 H, AA′BB′), 7.37 (2 H, AA′BB′), 6.59 (d, 1 H, J = 1.7 Hz), 5.57 (s, 1 H), 5.44 (d, 1 H, J = 1.7 Hz), 2.49−2.36 (m, 1 H), 2.32−2.28 (m, 1 H), 2.13−2.05 (m, 1 H), 1.46−1.38 (m, 1 H), 1.32 (s, 3 H), 1.22 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.36, 153.36, 145.62, 140.23, 139,87, 132.20, 131.77, 130.18, 129.33, 128.78, 126.63, 123.76, 92.20, 79.67, 40.17, 27.50, 24.250, 23.20, 22.30,

22.29; IR (neat) 2952, 1807, 1673, 1594, 1201 cm^{-1}; HRMS for $C_{20}H_{20}O_4$, calcd 324.1362, found 324.1360.

Reduction of Enone 18. Preparation of Carbinol 19. A mixture of **18** (16 mg, 19 μmol) and anhydrous $CeCl_3$ (9.0 mg, 37 μmol) in 1 mL of MeOH and 500 μL of THF at 0 °C was treated with $NaBH_4$ (7.0 mg, 0.19 mmol). The solution was stirred for 30 min and quenched by addition of 0.3 N HCl. The aqueous phase was washed with EtOAc (2 × 10 mL), and the combined extracts were dried with $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 with 20% EtOAc/hexane to give 5 mg (83%) of **19**: clear film; ^1H NMR ($CDCl_3$) δ 7.71 (1 H, AA'BB'), 7.50 (1 H, AA'BB'), 7.30 (2 H, AA'BB'), 5.75 (dd, 1 H, J = 2.3, 1.6 Hz), 5.60 (s, 1 H), 5.40 (m, 1 H), 4.97 (dd, 1 H, J = 1.6, 1.2 Hz), 2.42 (d, 1 H, J = 5.2 Hz), 2.33−2.25 (m, 2 H), 1.98−1.94 (m, 1 H), 1.36 (s, 3 H), 1.34−1.29 (m, 1 H), 1.23 (s, 3 H), 0.67 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.01, 147.74, 140.79, 138.05, 131.96, 133.51, 127.92, 126.98, 124.93, 123.49, 112.56, 92.70, 78.70, 72.92, 39.22, 27.51, 24.78, 23.02, 21.72, 20.49; IR (neat) 3461, 2919, 1789, 1290, 1204, 1038, 748 cm^{-1}; HRMS for $C_{20}H_{22}O$, calcd 327.1596, found 327.1593.

Preparation of 2-Iodopiperonal (21). A solution of *N,N,N'*-trimethylethylenediamine (16.3 g, 0.160 mmol) in 100 mL of 1,2-dimethoxyethane at 0 °C was treated with *n*-butylithium (64 mL, 2.5 M solution in hexanes, 0.16 mmol). After 0.5 h, the mixture was added via cannula to a solution of piperonal (20 g, 0.13 mmol) in 300 mL of 1,2-dimethoxyethane at 0 °C. After 1 h, the mixture was diluted with 200 mL of THF and treated with *n*-butyllithium (78 mL, 2.5 M solution in hexanes, 0.20 mmol). The mixture was allowed to warm to rt over 4 h, and then cooled to −78 °C and treated with iodine (60 g, 0.24 mmol) in portions. The resulting mixture was slowly allowed to warm to rt over 12 h. The mixture was diluted with $Na_2S_2O_4$(satd) and the aqueous phase washed with EtOAc. The combined extracts were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on SiO_2 with 10% EtOAc/hexane to give **21** which was contaminated with piperonal. Crystallization from 10% EtOAc/hexanes afforded 16.2 g (44%) of **21**: off-white solid; mp 127−128 °C; ^1H NMR ($CDCl_3$) δ 9.89 (s, 1 H), 7.52 (d, 1 H, J = 8.3 Hz), 6.84 (d, 1 H, J = 8.3 Hz), 6.14 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 192.79, 150.93, 150.28, 128.82, 127.50, 108.34, 101.48, 76.02; IR (film) 2914, 1682, 1595, 1456, 1233 cm^{-1}; HRMS for $C_8H_5O_3I$, calcd 275.9283, found 275.9279.

Preparation of Iodostyrene 22. A solution of methyltriphenylphosphonium bromide (9.2 g, 26 mmol) in 200 mL of THF at rt was treated with potassium *tert*-butoxide (24 mL, 1 M solution in THF, 24 mmol). After 1 h, the mixture was allowed to settle and the supernatant was added via cannula to a solution of **21** (2.80 g, 10.11 mmol) in 50 mL of THF at rt. The solution was stirred at rt for 1 h and diluted with H_2O, and the aqueous phase was washed with CH_2Cl_2. The combined extracts were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on SiO_2 with 10% EtOAc/hexane to given 2.53 g (91%) of **22**: off-white solid; mp 63−64 °C; ^1H NMR ($CDCl_3$) δ 7.05 (d, 1 H, J = 8.1 Hz), 6.79 (m, 1 H), 6.73 (d, 1 H, J = 8.1 Hz), 6.02 (s, 2 H), 5.52 (dd, 1 H, J = 0.9, 17.3 Hz), 5.20 (dd, 1 H, J = 0.9, 10.7 Hz); ^{13}C NMR ($CDCl_3$) δ 149.50, 145.49, 138.92, 134.25, 119.56, 115.43, 108.28, 100.69, 76.66; IR (film) 2912, 1455, 1233, 1033 cm^{-1}; HRMS for $C_9H_7O_2$, calcd 273.9505, found 273.9491.

Preparation of Diol 23. A solution of **22** (0.58 g, 2.1 mmol) in 5 mL of THF at −78 °C was treated with *n*-butyllithium (1.05 mL, 2 M solution in hexanes, 2.10 mmol). After 10 min, the mixture was rapidly added via cannula to a solution of **8** (0.20 g, 0.70 mmol) in 2 mL of THF at −78 °C. After 30 min, the reaction was quenched by addition of NH_4Cl(satd) and the aqueous phase was washed with EtOAc (2 × 20 mL). The combined extracts were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on SiO_2 with 15% EtOAc/hexane to give 0.22 g (71%) of **23**: white film; ^1H NMR ($CDCl_3$) δ 6.97 (d, 1 H, J = 8.1 Hz), 6.80 (d, 1 H, J = 8.1 Hz), 6.79 (m, 1 H), 6.03 (s, 1 H), 5.94 (s, 1 H), 5.46 (d, 1 H, J = 17.1 Hz), 5.23 (d, 1 H, J = 10.8 Hz), 5.13 (d, 1 H, J = 7.8 Hz), 3.34 (d, 1 H, J = 7.8 Hz), 2.90 (s, 1 H), 2.13−2.04 (m, 1 H), 1.83 (s, 3 H), 1.83−1.60 (m, 1 H), 1.58−1.50 (m, 1 H), 1.49 (s, 3 H), 1.43−1.38 (m, 1 H), 1.35 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.21, 144.47, 137.32, 133.73, 132.00, 122.32, 120.86, 116.84, 108.46, 100.83, 77.00, 71.10, 47.65, 31.04, 30.01, 28.73, 28.18, 26.79; IR (neat) 3526, 2977, 1470, 1249, 1068, 904, 815, 732 cm^{-1}; HRMS for $C_{19}H_{23}O_4I$, calcd 442.0641, found 442.0637.

Preparation of Cyclic Carbonate 24. A solution of **23** (0.18 g, 0.41 mmol) in 2 mL of CH_2Cl_2 was treated sequentially with pyridine (200 μL, 2.40 mmol), 4-(*N,N*-dimethylamino)pyridine (10 mg, 0.08 mmol), and phosgene (400 μL, 1.9 M solution in toluene, 0.80 mmol). After 12 h, the reaction was quenched by addition of $NaHCO_3$(satd) and the aqueous phase was washed with EtOAc (2 × 20 mL). The combined extracts were dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on SiO_2 with 15% EtOAc/hexane to give 0.14 g (70%) of **24**: white solid; mp 140−141 °C; ^1H NMR ($CDCl_3$) δ 6.96 (d, 1 H, J = 8.1 Hz), 6.83 (d, 1 H, J = 8.1 Hz), 6.67 (dd, 1 H, J = 11.0, 16.5 Hz), 6.04 (s, 1 H), 6.00 (s, 1 H), 5.78 (s, 1 H), 5.50 (dd, 1 H, J = 16.5, 1.1 Hz), 5.28 (dd, 1 H, J = 11.0, 1.1 Hz), 2.24−2.15 (m, 1 H), 2.04−1.98 (m, 1 H), 1.79 (s, 3 H), 1.68−1.62 (m, 2 H), 1.33 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.20, 146.05, 138.54, 132.15, 120.58, 117.77, 114.61, 110.07, 109.62, 101.75, 87.08, 77.02, 76.50, 46.80, 30.52, 29.99, 26.87, 25.50, 24.68; IR (neat) 2980, 1800, 1472, 1335, 1251, 1168, 1061 cm^{-1}; HRMS (NH_3) for $C_{20}H_{25}NO_5I$, calcd 486.0778, found 486.0779.

Preparation of Aldehyde 25. A solution of **24** (0.36 g, 0.74 mmol) in 100 mL of CH_2Cl_2 at −78 °C was treated with O_3 until a blue solution resulted. After 1 min, excess O_3 was removed by passing N_2 through the solution. The mixture was then treated with triphenylphosphine (0.22 g, 0.84 mmol) and allowed to warm to rt over 1 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 with 20% EtOAc/hexane to give 0.32 g (88%) of **25**: white film; ^1H NMR ($CDCl_3$) δ 9.80 (s, 1 H), 7.40 (d, 1 H, J = 8.0 Hz), 7.08 (br s, 1 H), 7.04 (d, 1 H, J = 8.0 Hz), 6.21 (s, 1 H), 6.15 (s, 1 H), 2.33−2.27 (m, 1 H), 1.88−1.79 (m, 2 H), 1.82 (s, 3 H), 1.63−1.59 (m, 1 H), 1.37 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.06, 154.39, 152.67, 148.03, 137.13, 134.15, 128.31, 116.97, 111.15, 109.01, 102.97, 87.74, 75.04, 46.76, 30.38, 30.01, 26.27, 25.68, 24.74; IR (neat) 2981, 1797, 1688, 1454, 1263, 1170, 1061, 730 cm^{-1}; HRMS (NH_3) for $C_{19}H_{23}NO_6I$, calcd 488.0570, found 488.0596.

Preparation of Carbinol 26. A solution of **25** (0.32 g, 0.68 mmol) in 50 mL of THF at −78 °C was treated dropwise with vinylmagnesium bromide (1.36 mL, 1 M solution in THF, 1.36 mmol). After 1 h, the reaction was quenched by addition of NH_4Cl(satd). The aqueous phase was washed with EtOAc (2 × 10 mL), and the combined extracts were dried with $MgSO_4$. The solvent was removed under reduced pressure to give 0.33 g (98%) of **26**: clear oil; ^1H NMR ($CDCl_3$) δ 7.08 (d, 1 H, J = 8.2 Hz), 6.87 (d, 1 H, J = 8.2 Hz), 6.07 (d, 1 H, J = 1.3 Hz), 6.01 (d, 1 H, J = 1.3 Hz), 6.01−5.93 (m, 1 H), 5.77 (s, 1 H), 5.34−5.26 (m, 2 H), 5.11 (m, 1 H), 2.23−2.21 (m, 1 H), 2.09−2.05 (m, 1 H), 1.87 (s, 3 H), 1.85−1.77 (m, 2 H), 1.41 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.36, 147.37, 146.31, 139.67, 139.17, 133.51, 119.60, 116.97, 114.76, 110.14, 109.50, 101.71, 86.99, 76.85, 70.94, 47.06, 30.43, 30.14, 26.97, 25.48, 24.44; IR (neat) 3453, 2918, 1787, 1453, 1265, 1170, 1058, 731 cm^{-1}; LRMS for $C_{21}H_{23}O_6I$, calcd 520, found 521 [$(M + 1)^+$].

Preparation of Silyl Ether 27. A solution of **26** (95 mg, 0.20 mmol) in 3 mL of CH_2Cl_2 at 0 °C was treated sequentially with pyridine (0.5 mL, 0.9 mmol), 4-(*N,N*-dimethylamino)pyridine (5 mg, 0.04 mmol), and triethylsilyl trifluoromethanesulfonate (0.10 mL, 0.44 mmol). After 12 h, the reaction was quenched by addition of $NaHCO_3$(satd). The aqueous phase was washed with EtOAc (2 × 20 mL), and the combined extracts were dried with $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 with 5% EtOAc/hexane to give 0.11 g (95%) of **27**: white oil; ^1H NMR ($CDCl_3$) δ 6.96 (d, 1 H, J = 8.2 Hz), 6.82 (d, 1 H, J = 8.2 Hz), 6.28 (s, 1 H), 6.03 (s, 1 H), 5.97 (s, 1 H), 5.93−5.85 (m, 1 H), 5.18 (d, 1 H J = 5.5 Hz), 5.11 (d, 1 H, J = 10.2 Hz), 5.03 (d, 1 H, J = 17.2 Hz), 2.39−2.33 (m, 1 H), 1.96−1.88 (m, 2 H), 1.86 (s, 3 H), 1.73−1.67 (m, 1 H), 1.31 (s, 3 H), 1.30 (s, 3 H), 0.90 (t, 9 H, J = 7.8 Hz), 0.58 (q, 6 H, J = 7.8 Hz); ^{1c} NMR ($CDCl_3$) δ 154.54, 147.07, 46.75, 141.04, 138.06, 134.39, 120.84, 115.68, 114.97, 111.31, 109.15, 101.58, 86.89, 76.77, 74.39, 47.27, 30.63, 30.35, 26.80, 25.79,

24.51, 6.61, 4.71; IR (neat) 2953, 1805, 1452, 1246, 1166, 1058, 727, 672 cm^{-1}; HRMS for $C_{27}H_{37}O_6SiI$, calcd 612.1404, found 612.1401.

Cyclization of 27. Preparation of Diene 28. A mixture of **27** (108 mg, 0.170 mmol), K_2CO_3 (108 mg, 0.780 mmol), and $Pd(PPh_3)_4$ (10 mg, 8.6 μmol) in 3 mL of MeCN was heated to reflux. After 8 h, additional $Pd(PPh_3)_4$ (10 mg, 8.6 μmol) was introduced. After 20 h, additional $Pd(PPh_3)_4$ (10 mg, 8.6 μmol) was introduced. After 32 h, the mixture was allowed to cool, diluted with EtOAc, and filtered through a pad of SiO_2. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 with 5% EtOAc/hexane to give 67 mg (78%) of **28**: clear film; ^1H NMR ($CDCl_3$) δ 6.62 (d, 1 H, J = 8.0 Hz), 6.59 (s, 1 H), 6.58 (d, 1 H, J = 8.0 Hz), 6.00 (s, 1 H), 5.98 (s, 1 H), 5.46 (s, 1 H), 5.26 (s, 1 H), 5.05 (s, 1 H), 2.59–2.42 (m, 2 H), 2.00–1.94 (m, 1 H), 1.52–1.50 (m, 1 H), 1.40 (s, 3 H), 1.23 (s, 3 H), 0.86 (t, 9 H, J = 7.9 Hz), 0.75 (s, 3 H), 0.55 (q, 6 H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 154.38, 149.43, 147.72, 145.36, 136.94, 135.40, 134.10, 124.12, 119.67, 117.13, 106.78, 101.31, 93.63, 82.41, 77.17, 39.93, 28.13, 24.59, 23.93, 22.08, 22.04, 6.63, 4.69; IR (neat) 2956, 1805, 1460, 1233, 1033, 850, 747 cm^{-1}; HRMS for $C_{27}H_{36}O_6Si$, calcd 484.2281, found 484.2277.

Allylic Oxidation of 16. Preparation of Enone 29. A mixture of **16** (33 mg, 0.075 mmol), PCC (0.48 g, 2.2 mmol), and NaOAc (0.12 g, 1.5 mmol) in 2 mL of benzene was heated at reflux for 12 h. The mixture was cooled, diluted with EtOAc, and filtered through a pad of SiO_2. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 with 10–15% EtOAc/hexane to give 26 mg (76%) of **29**: clear film; ^1H NMR ($CDCl_3$) δ 7.52 (1 H, AA'BB'), 7.27 (1 H, AA'BB'), 7.19 (1 H, AA'BB'), 7.14 (1 H, AA'BB'), 6.80 (s, 1 H), 5.61 (s, 1 H), 5.39 (s, 1 H), 5.17 (s, 1 H), 2.87 (d, 2 H, J = 3.8 Hz), 1.55 (s, 3 H), 1.34 (s, 3 H), 0.82 (s, 3 H), 0.76 (t, 9 H, J = 7.8 Hz), 0.56 (q, 6 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 195.91, 156.55, 153.37, 147.23, 139.04, 138.15, 132.97, 130.18, 128.62, 128.37, 125.38, 119.37, 88.19, 82.59, 77.65, 41.01, 39.74, 30.34, 21.36, 14.74, 6.50, 4.57; IR (neat) 2956, 1812, 1682, 1039, 749 cm^{-1}; HRMS for $C_{26}H_{34}O_5Si$, calcd 454.2176, found 454.2191.

Allylic Oxidation of 28. Preparation of Enone 30. A mixture of **29** (85 mg, 0.18 mmol), PCC (1.10 g, 5.2 mmol), and NaOAc (0.290 g, 3.52 mmol) in 4 mL of benzene was heated at reflux for 12 h. The mixture was cooled, diluted with EtOAc, and filtered through a pad of SiO_2. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 with 10% EtOAc/hexane to give 67 mg (75%) of **30**: white film; ^1H NMR ($CDCl_3$) δ 6.80 (s, 1 H), 6.65 (d, 1 H, J = 8.0 Hz), 6.57 (d, 1 H, J = 8.0 Hz), 6.00 (d, 1 H, J = 1.2 Hz), 5.95 (d, 1 H, J = 1.2 Hz), 5.59 (s, 1 H), 5.30 (s, 1 H), 5.16 (s, 1 H), 3.24 (d, 1 H, J = 19 Hz), 2.90 (d, 1 H, J = 19 Hz), 1.52 (s, 3 H), 1.34 (s, 3 H), 0.95 (s, 3 H), 0.86 (t, 9 H, J = 7.8 Hz), 0.57 (q, 6 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 196.89, 156.66, 153.33, 148.37, 147.31, 145.50, 138.14, 132.53, 124.16, 119.31, 115.37, 107.51, 101.74, 88.98, 76.78, 41.44, 40.77, 29.95, 21.41, 14.64, 6.62, 4.64; IR (neat) 2956, 1812, 1682, 1457, 1230, 1038, 855 cm^{-1}; HRMS for $C_{27}H_{34}O_7Si$, calcd 498.2074, found 498.2066.

Reduction of Enone 29. Preparation of 2a. A mixture of **29** (33.0 mg, 0.072 mmol) and anhydrous $CeCl_3$ (36 mg, 0.15 mmol) in 1 mL of MeOH and 0.5 mL of THF at 0 °C was treated with $NaBH_4$ (8.0 mg, 0.21 mmol). After 20 min, the reaction was quenched by addition of NH_4Cl(satd) and the aqueous phase was washed with EtOAc (2 × 10 mL). The combined extracts were dried with $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on SiO_2 with 20% EtOAc/hexanes to give 14 mg of a 10:1 mixture of **31** and **32**. A solution of this mixture (14 mg, 0.030 mmol) in 3 mL of THF at −78 °C was treated with phenyllithium (0.15 mL, 2 M solution in hexanes, 0.30 mmol). After 0.5 h, the reaction was quenched by addition of NH_4Cl(satd) and the aqueous phase was washed with EtOAc (2 × 10 mL). The combined extracts were dried with $MgSO_4$, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography on SiO_2 with 20% EtOAc/hexane afforded 12 mg (31%) of **2a**: white film; ^1H NMR ($CDCl_3$) δ 8.10 (2 H, aryl), 7.78 (1 H, aryl), 7.56 (1 H, aryl), 7.47 (2 H, aryl), 7.29 (1 H, aryl), 7.22 (s, 1 H), 7.18 (1 H, aryl), 7.15 (1 H, aryl), 5.52 (d, 1 H, J = 1.4 Hz), 5.33 (s, 1 H), 5.04 (d, 1 H, J = 1.4 Hz), 4.40 (m, 1 H), 2.55 (dd, 1 H, J = 10.0, 15.4 Hz), 2.46 (s, 1 H), 2.37 (dd, 1 H, J = 15.4, 3.8 Hz), 1.53 (s, 3 H), 1.08 (s, 3 H), 0.86 (t, 9 H, J = 7.8 Hz), 0.72 (s, 3 H), 0.65 (q, 6 H, J = 7.8 Hz), 0.68 (d, 1 H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 166.23, 149.46, 142.73, 140.77, 137.85, 137.47, 133.03, 130.39, 129.69, 128.43, 127.15, 125.92, 118.31, 82.85, 78.95, 73.51, 67.97, 42.02, 39.76, 26.14, 22.14, 15.64, 6.63, 4.58; IR (neat) 3500, 2953, 1731, 1270, 1068 cm^{-1}; HRMS for $C_{32}H_{42}O_5Si$, calcd 534.2802, found 534.2795.

Reduction of Enone 30. Preparation of Epimers 2b and 36. A mixture of **30** (24 mg, 0.048 mmol) and anhydrous $CeCl_3$ (26 mg, 0.11 mmol) in 1 mL of MeOH and 0.5 mL of THF at 0 °C was treated with $NaBH_4$ (20 mg, 0.53 mmol). After 20 min, the reaction was quenched by addition of NH_4Cl(satd) and the aqueous phase was washed with EtOAc (2 × 10 mL). The combined extracts were dried with $MgSO_4$, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography on SiO_2 with 20% EtOAc/hexane afforded 12 mg of a 1:1 mixture of **33** and **34**. A solution of this mixture in 2 mL of THF at −78 °C was treated with phenyllithium (1.2 mL, 0.44 M solution in hexanes, 0.53 mmol). After 30 min, the reaction was quenched by addition of NH_4Cl(satd) and the aqueous phase was washed with EtOAc (1 × 10 mL) and CH_2Cl_2 (1 × 10 mL). The combined extracts were dried with $MgSO_4$, and the solvent was removed under reduced pressure. Purification of the residue by column chromatography on SiO_2 with 30% EtOAc/hexane afforded 6 mg (22%) of **2b** and 6 mg (22%) of **36**. **2b**: ^1H NMR ($CDCl_3$) δ 8.16 (2 H, aryl), 7.54 (1 H, aryl), 7.43 (2 H, aryl), 7.17 (s, 1 H), 6.64 (d, 1 H, J = 7.8 Hz), 6.54 (d, 1 H, J = 7.8 Hz), 5.97 (d, 1 H, J = 1.2 Hz), 5.96 (d, 1 H, J = 1.2 Hz), 5.45 (s, 1 H), 5.30 (s, 1 H), 5.00 (s, 1 H), 4.63 (m, 1 H), 2.77 (dd, 1 H, J = 4.0, 15.1 Hz), 2.50 (s, 1 H), 2.44 (dd, 1 H, J = 10.0, 15.0 Hz), 1.49 (s, 3 H), 1.04 (s, 3 H), 0.88 (t, 9 H, J = 7.9 Hz), 0.80 (s, 3 H), 0.62 (q, 6 H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 166.46, 155.70, 149.48, 147.61, 144.78, 137.68, 137.15, 133.62, 132.63, 130.28, 129.86, 128.03, 124.30, 123.56, 105.80, 100.06, 81.97, 79.18, 73.45, 67.83, 42.18, 39.12, 25.11, 22.24, 15.10, 6.52, 4.44; IR (neat) 3452, 2954, 2876, 1725, 1710, 1444, 1280, 1234, 1049, 990, 861 cm^{-1}; HRMS for $C_{33}H_{42}O_7Si + NH_4$, calcd 596.3044, found 596.3075. **36**: ^1H NMR ($CDCl_3$) δ 8.15 (2 H, aryl), 7.54 (1 H, aryl), 7.43 (2 H, aryl), 7.17 (s, 1 H), 6.60 (d, 1 H, J = 7.9 Hz), 6.50 (d, 1 H, J = 7.9 Hz), 5.99 (d, 1 H, J = 1.3 Hz), 5.94 (d, 1 H, J = 1.3 Hz), 5.47 (d, 1 H, J = 1.2 Hz), 5.28 (s, 1 H), 5.05 (d, 1 H, J = 1.3 Hz), 3.64 (m, 1 H), 3.17 (dd, 1 H, J = 9.8, 14.5 Hz), 2.54 (s, 1 H), 1.99 (dd, 1 H, J = 15.0, 4.0 Hz), 1.72 (d, 1 H, J = 6.0 Hz) 1.45 (s, 3 H), 1.33 (s, 3 H), 0.88 (t, 9 H, J = 7.9 Hz), 0.76 (s, 3 H), 0.65 (q, 6 H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 166.16, 149.01, 147.29, 144.83, 143.03, 135.31, 133.63, 132.64, 130.23, 129.80, 128.05, 123.92, 123.52, 117.87, 105.80, 100.36, 83.83, 82.75, 72.45, 70.83, 41.60, 37.62, 29.97, 21.35, 19.30, 6.54, 4.42; IR (neat) 3452, 2954, 2876, 1725, 1710, 1444, 1280, 1234, 1049, 990, 861 cm^{-1}; LRMS for $C_{33}H_{42}O_7Si$, calcd 578, found 579 $[(M + 1)^+]$.

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Supplementary Material Available: Figures showing the ^1H NMR spectra of compounds **2a, 2b, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 36,** and "less" and "more" polar diastereomers and text describing exemplary experimental procedures for **38** and **39**) (31 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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