

Application of Intramolecular Heck Reactions to the Preparation of Steroid and Terpene Intermediates Having cis A-B Ring Fusions. Model Studies for the Total Synthesis of Complex Cardenolides.

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Abstract: The cis-fused tricyclic dienone **13** is the major product formed from intramolecular Heck cyclization of the dienyl triflate **12** (Scheme 1). Similarly, the cis-hexahydrophenanthridine **22** is formed in good yield from Heck cyclization of the aryl triflate **21**. This latter conversion demonstrates that allylic ether substitution is compatible with intramolecular Heck chemistry and suggests applications of this chemistry in the synthesis of highly oxidized cardenolides.

Insertions of aryl- and alkenylpalladium intermediates into tethered alkenes and alkynes (intramolecular Heck reactions) have emerged as a broadly effective method for assembling complex polycyclic molecules.^{2,3} The excellent functional group tolerance of palladium-catalyzed reactions and the ability of intramolecularity to overcome the reluctance of substituted alkenes to participate in Heck insertion processes are major reasons for the recent explosive growth in the use of this ring-forming method. Depicted in Fig. 1 are seven natural products and one natural product congener that have recently been synthesized using intramolecular Heck insertions as the key steps.⁴ For each target molecule the bond formed by the intramolecular Heck reaction is indicated by an arrow. Of particular significance is the utility of intramolecular Heck insertions for constructing congested quaternary carbon centers,⁵ often the most challenging centers in the assembly of complex molecules. This feature is illustrated in Fig 1 in the total syntheses of (±)-6a-epipretazettine, (±)-scopadulcic acid, (-)- and (+)-morphine and (-)- and (+)-physostigmine.^{4abcf} Also notable is the recent success obtained in several laboratories in effecting asymmetric intramolecular Heck insertions using enantiopure phosphine ligands.⁶ This approach was employed in recent asymmetric syntheses of the Calabar alkaloid (-)-physostigmine and its enantiomer.^{4f}

A cis A/B ring fusion is a distinctive structural feature of several biologically important classes of steroid natural products. Examples include batrachotoxin A (**1**),⁷ an extremely toxic amphibian alkaloid

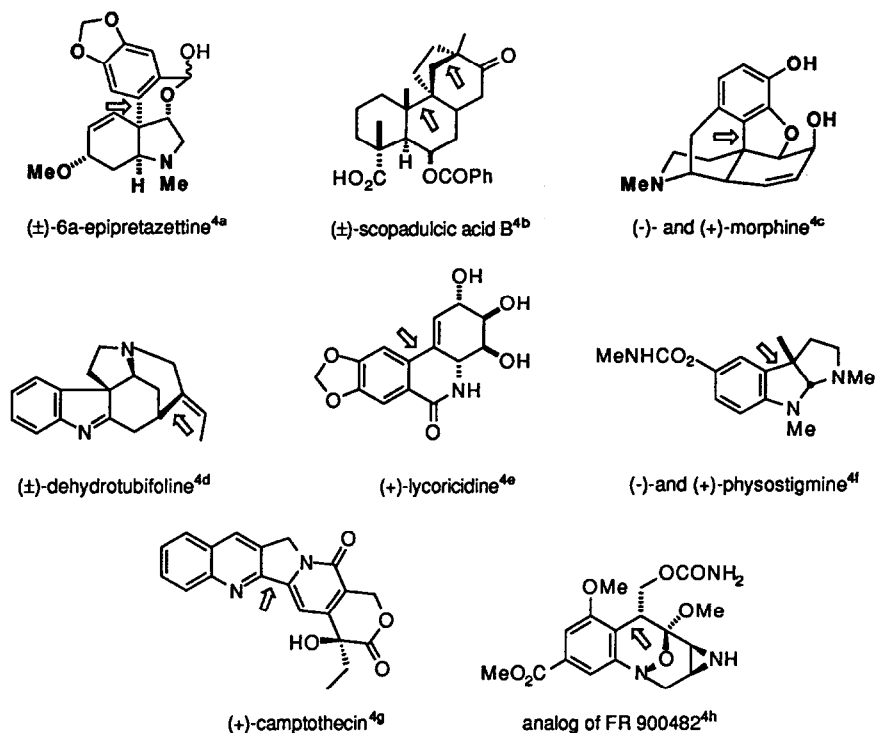
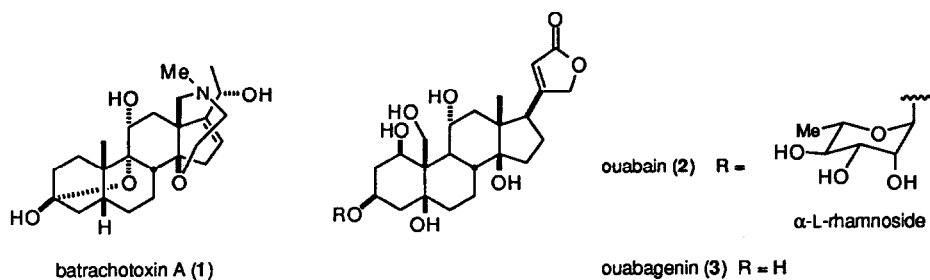


Fig 1. Polycyclic natural products prepared by intramolecular Heck strategies.

isolated from *Phyllobates aurotaenia* and the poison-dart frog *Dendrobates terribilis*, and the complex cardenolide ouabain (2), the active water-soluble extract of the ouabaio tree, which has been long used in East Africa as an arrow poison.⁸ Batrachotoxin A is an essential tool in mechanistic investigations of voltage-dependent sodium channels,^{7b} while ouabain has attracted much recent attention as the long-sought digitalis-like factor in plasma.^{8b} In this paper we present our initial findings concerning the use of intramolecular Heck insertions for constructing *cis*-fused decalin components of polycyclic ring systems. We also report that intramolecular Heck insertions are not undermined by the presence of allylic oxygen substitution, and thus hold considerable promise for the assembly of complex polyhydroxylated cardenolides such as ouabain (2).



Synthesis Strategy.

A strategy for assembling a tricyclic precursor of the A-C rings of ouabain is outlined in Fig. 2. The key step in this sequence is the projected intramolecular Heck insertion of the alkenyl aryl triflate **7** to form the *cis*-fused tricycle **6**. This latter intermediate would contain the required angular substituents at C(5) and C(10) of ouabain, as well as alkene functionality in the A ring that would plausibly allow further functionalization to reach **5** and **4** (e.g., R' = OR). Success in the critical conversion of **7** → **6** would depend on the intramolecular Heck reaction occurring faster than potentially competing π -allyl palladium chemistry arising

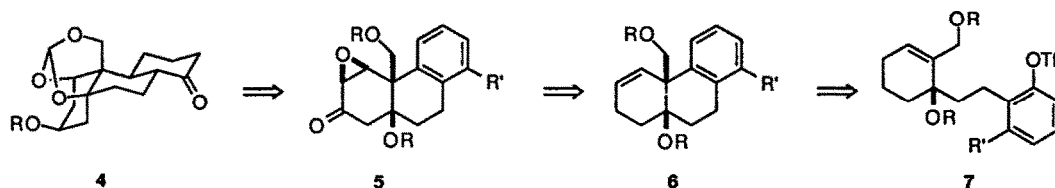


Fig. 2. One plan for the synthesis of the A, B, and C rings of ouabain.

from the two allylic oxygen substituents present in **7**.⁹ We assumed at the outset that π -allyl palladium chemistry would be minimized if the oxygen protecting groups were chosen to make OR a poor leaving group. Our expectation that cyclization of **7** would produce the *cis* tricyclic product **6** followed directly from the established preference for intramolecular Heck insertions to take place with eclipsed (rather than twisted) orientations of the Pd-C σ and alkene π bonds (Fig. 3).^{2a,4a} The eclipsed mode of insertion of **7** that would lead to **6** is illustrated in insertion conformer **8**.

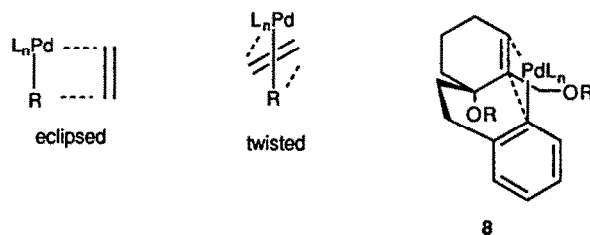
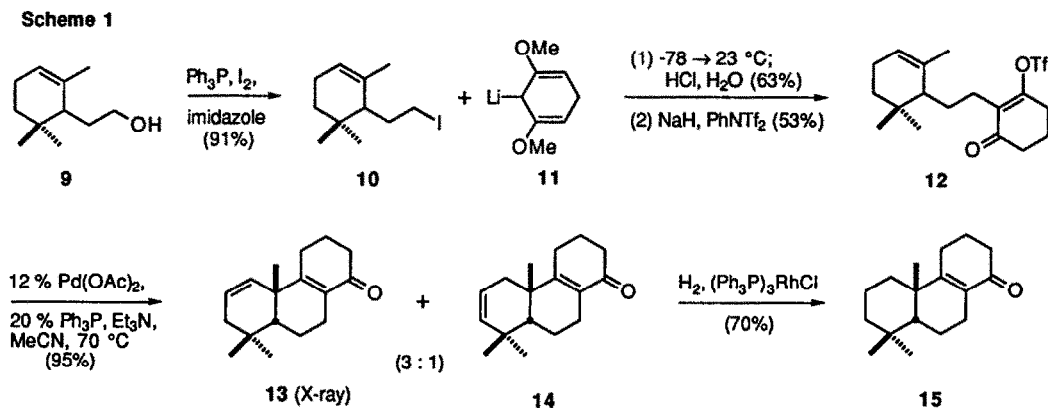


Fig. 3. Favored eclipsed topography of the insertion step.

RESULTS AND DISCUSSION

Initial Model Study. We initially examined the issue of stereoselectivity with a cyclization substrate prepared from cyclohexenylethanol **9**, a terpenoid intermediate readily available from α -ionone (Scheme 1).¹⁰ Alkylation of the derived iodide **10** with lithium reagent **11**¹¹ provided, after hydrolysis, the corresponding 1,3-cyclohexandione, which was converted to triflate **12** by treatment with NaH and PhNTf₂.¹² Intramolecular Heck cyclization of dienyl triflate **12** took place slowly upon treatment with 10-25% Pd(Ph₃P)₄ in refluxing MeCN or THF. Cyclization was much faster in the presence of 12 % of a more reactive catalyst prepared from Pd(OAc)₂ and slightly less than 2 equiv (per Pd) of Ph₃P. This latter procedure converted **12**, in essentially

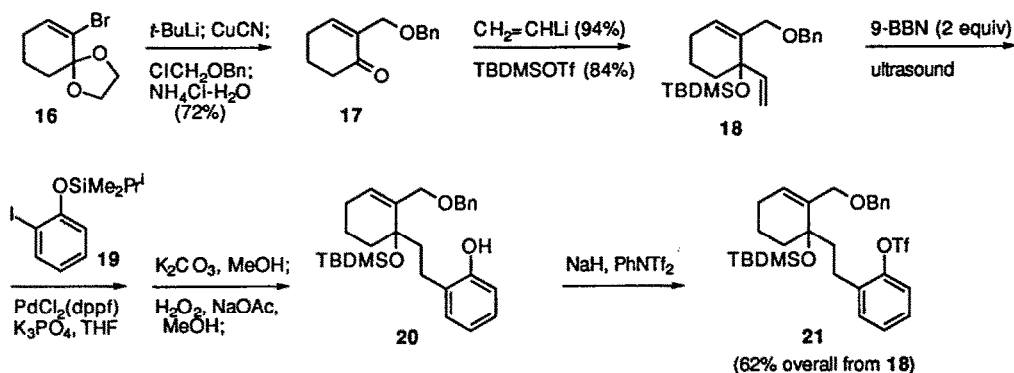
quantitative yield, into a crystalline 3:1 mixture of the two tricyclic dienones **13** and **14**. That cyclization had occurred to form the *cis*-fused tricyclic products was rigorously established by single crystal X-ray analysis of the major isomer **13** (mp 69 °C).¹³ Selective saturation of the isolated double bonds in **13** and **14** could be accomplished with Wilkinson's catalyst and gave a single tricyclic dienone **15**.¹⁴ This hydrogenation confirms the stereostructure of the minor product **14**, and establishes that palladium-catalyzed cyclization of **12** takes place exclusively to form *cis*-fused tricyclic products.



Synthesis of cis-Octahydrophenanthrenes with the Angular Functionalization of Complex Cardenolides such as Ouabain. An efficient sequence for preparing alkenyl aryl triflate **21**, a cyclization substrate containing appropriate oxidation for testing the synthesis plan proposed in Fig. 2, is summarized in Scheme 2. The sequence begins with alkylation of a cyano cuprate intermediate derived from vinyl bromide **16**¹⁵ with chloromethyl benzyl ether to provide benzyloxycyclohexenone **17**, which was easily converted to **18**. Suzuki cross coupling of this intermediate with the isopropyltrimethylsilyl ether of 2-iodophenol (**19**) then provided **20**.¹⁶ The initial step of this sequence, hydroboration of **18** with 9-BBN (9-borabicyclo[3.3.1]nonane), was problematic until it was discovered that the use of 2 equiv of 9-BBN and ultrasound was necessary to achieve clean conversion to the alkyl borane intermediate.¹⁷ Since some cleavage of the isopropyltrimethylsilyl group occurred under the basic palladium-catalyzed cross coupling conditions, the crude reaction mixture was treated with K_2CO_3 in MeOH to fully liberate the phenol moiety and then with H_2O_2 to oxidize residual boron compounds.^{16c} Conventional conversion¹² of **20** to the triflate derivative then afforded **21**. When optimized, this sequence provided the alkenyl aryl triflate **21** on gram scales in 62% overall yield from **18**.

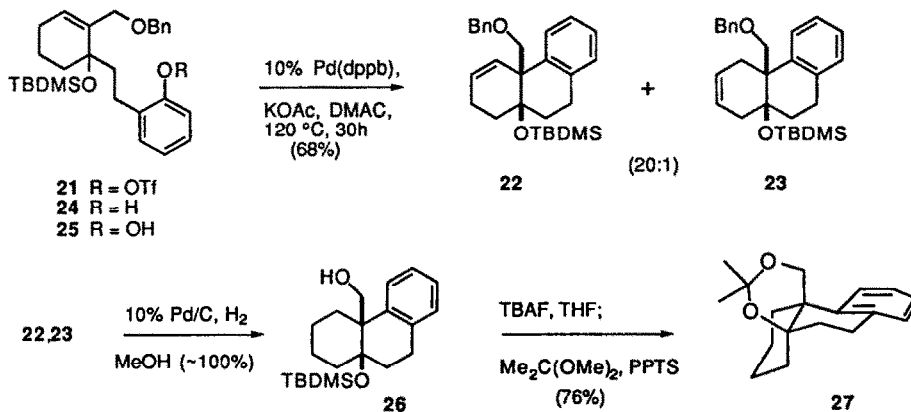
After considerable experimentation, we found that the optimum condition for promoting the desired intramolecular Heck reaction was to treat **21** in *N,N*-dimethylacetamide with 10% Pd(dppb)¹⁸ and KOAc (10 equiv) at 120 °C, which provided the hexahydrophenanthrenes **22** and **23** in a 20:1 ratio and 68% combined yield. Arene **24**, resulting from palladium-catalyzed reduction of **21**, was formed to only a minor extent (5–10%) under these conditions. Cyclizations employing monodentate phosphine ligands [$\text{Pd}(\text{Ph}_3\text{P})_4$, $\text{Pd}(o\text{-tol}_3\text{P})_4$ or $\text{Pd}(\text{Ph}_3\text{P})_2$] at 70–130 °C in several solvents provided only small amounts of products **22** and **23** and returned considerable starting triflate **21**. As observed earlier by Cabri in bimolecular Heck insertions of

Scheme 2



aryl triflates,¹⁹ cyclizations with amine bases that can function as hydride donors (Et_3N , $i\text{-Pr}_2\text{NEt}$, and 1,2,2,6,6-pentamethylpiperidine) afforded larger amounts of the reduction product **24**. Mixtures of tricyclic regioisomers were formed when amine bases were employed, pretty much irrespective of the bidentate ligand used; the highest ratios of **22**:**23**, ~2.5:1, were obtained with $\text{Pd}(\text{dppb})$. In accord with the findings of Cabri,¹⁹ replacement of amine bases with KOAc suppressed the competing reduction to form **24**. The addition of this salt, which likely alters the nature of the alkyl Pd intermediate formed after the migration step, also reduced double bond migration; **22** was the major product (**22**:**23** >6:1) with all the bidentate ligands we examined, although dppb was optimum in reducing the formation of **23**. The reaction was markedly temperature dependent and tricyclic products were not observed at reaction temperatures <100 °C. The addition of silver salts, which suppress alkene isomerizations in Heck reactions of aryl halides,^{5b} led to decomposition of **21**. Side reactions were also observed when strong inorganic bases such as K_3PO_4 or K_2CO_3 were employed, since hydrolysis of triflate **19** to give substantial amounts of **25** resulted. For example, phenol **25** was the major product when typical Jefferey conditions (NaHCO_3 and a phase transfer catalyst) were employed.²⁰

Scheme 3



That alkenes **22** and **23** were double bond regioisomers was established by catalytic hydrogenation of a 1:1.2 mixture of these compounds, which provided the octahydrophenanthridine **26** in quantitative yield. The *cis* stereochemistry of this intermediate was then rigorously established by conversion to the cyclic acetonide **27**.

CONCLUSION

This investigation demonstrates that polycyclic molecules containing *cis*-decalin subunits can be prepared efficiently, with high stereocontrol, by intramolecular Heck insertions. Particularly notable is (a) the high yield obtained in the conversion of **12** → **13** and **14**, in spite of the severe 1,3-diaxial Me-Me interaction found in these terpenoid products, and (b) the stability of the two allylic ether oxygens during the cyclization of **21** → **22**. These successful cyclizations provide further evidence of the utility of intramolecular Heck reactions in the synthesis of complex, polyfunctional target molecules and specifically suggest applications for the total synthesis of unusual terpenes and steroids.

EXPERIMENTAL SECTION

(2,6,6-Trimethyl-2-cyclohexenyl)-2-iodoethane (10). Iodine (230 mg, 0.91 mmol) was added in small portions at 0 °C to a solution of alcohol **9**¹⁰ (107 mg, 0.64 mmol), Ph₃P (217 mg, 0.83 mmol), imidazole (59 mg, 0.87 mmol), acetonitrile (6 mL) and ether (10 mL). After stirring for 1 h at 0 °C, the brown reaction mixture was diluted with ether (100 mL), washed (saturated aqueous Na₂S₂O₃, saturated aqueous CuSO₄, H₂O), dried (MgSO₄) and concentrated. The residue was purified on silica gel (2 : 1 pentane-ether) to yield 161 mg (91%) of **10** as a colorless oil (95% pure by GLC analysis): ¹H NMR (500 MHz, CDCl₃) δ 0.88 (s, 3H), 0.92 (s, 3H), 1.15 - 1.20 (m, 1H), 1.34 - 1.39 (m, 1H), 1.43 - 1.46 (m, 1H), 1.70 (d, J = 1.4 Hz, 3H), 1.87 - 1.97 (m, 3H), 2.03 - 2.10 (m, 1H), 3.23 (t, J = 8.3 Hz, 2H), 5.33 (bs, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 7.0, 22.9, 23.4, 27.2, 27.5, 31.7, 32.4, 36.3, 51.0, 121.1, 135.0; IR (film) 3044, 2972, 2924, 2852, 1456, 1448, 1374, 1350, 1218, 1170 cm⁻¹; MS(Cl) m/z 279.0578 (279.0612 calcd. for C₁₁H₂₀I, MH), 278, 222, 205, 177, 162, 151, 149, 123, 112, 109, 95, 81.

2-(2-(2,6,6-Trimethyl-2-cyclohexenyl)ethyl)-3-(trifluoromethylsulfonyl)oxy-cyclohexenone (12). Following the general procedure of Piers,¹¹ a solution of 1,5-dimethoxy-1,4-cyclohexadiene (320 mg, 2.3 mmol) and dry THF (2.3 mL) was added dropwise to a solution of *tert*-BuLi (1.5 mL, 2.5 mmol of a 1.68 M solution in pentane) and dry THF (13 mL) at -78 °C. The resulting yellow solution was stirred for 1 h at -78 °C, HMPA (530 μL, 3.05 mmol) was added and the resulting orange-red solution was stirred for 15 min at -78 °C. A solution of iodide **10** (707 mg, 2.54 mmol) and dry THF (2.3 mL) then was added dropwise at -78 °C and after 15 min the reaction was allowed to warm to 23 °C. After 2 h, the mixture was quenched with brine (25 mL) and extracted with pentane (3 x 25 mL). The combined pentane layers were washed (brine), dried (MgSO₄) and concentrated to yield 709 mg (~100%) of the alkylation product as a pale yellow oil, which was used immediately without further purification: MS(EI) m/z 290.2242 (290.2246 calcd. for C₁₉H₃₀O₂, M).

This crude material was purged with Ar, dissolved in acetone (11 mL, previously purged for 15 min with Ar), then 1N HCl (3.5 mL, 3.50 mmol, previously purged for 15 min with Ar) was added with vigorous stirring. After 4 h, the reaction was concentrated and the residue partitioned between brine (50 mL) and

CH₂Cl₂ (4 x 50 mL). The combined organic layers were washed (brine), dried (MgSO₄) and concentrated. Flash chromatography on silica gel (3:1→1:1 hexane-EtOAc) yielded 380 mg (63%) of 2-(2-(2,6,6-trimethyl-2-cyclohexenyl)ethyl)-1,3-cyclohexadione as a colorless, sticky solid: mp 148 - 150° C; MS(EI) m/z 262.1927 (262.1933 calcd. for C₁₇H₂₇O₂, M).

A solution of a portion of this dione sample (340 mg, 1.30 mmol) and dry THF (2.8 mL) was added dropwise at 0 °C to a suspension of NaH (55 mg of a 60% dispersion in mineral oil, 1.4 mmol) and dry THF (1.4 mL). After H₂-evolution ceased (~10 min), the mixture was stirred for 30 min at 23 °C and then cooled to 0 °C. A solution of *N*-phenyl-trifluoromethanesulfonylimide (509 mg, 1.42 mmol) and dry THF (1.4 mL) then was added dropwise and the resulting mixture was warmed to 23 °C and then to 60 °C. After stirring for 16 h at 60 °C, the reaction was diluted with ether (50 mL), washed (saturated aqueous NaHCO₃), dried (K₂CO₃) and concentrated. Flash chromatography on silica gel (10:1 hexane-EtOAc) yielded 434 mg (85%) of **12** as a pale yellow oil (97% pure by GLC analysis): ¹H NMR (500 MHz, CDCl₃) δ 0.86 (s, 3H), 0.97 (s, 3H), 1.11 - 1.14 (m, 1H), 1.31 - 1.36 (m, 1H), 1.37 - 1.47 (m, 3H), 1.70 (s, 3H), 1.93 (broad s, 2H), 2.03 - 2.08 (m, 2H), 2.36 - 2.40 (m, 2H), 2.45 (t, J = 6.6 Hz, 2H), 2.74 (t, J = 6.2 Hz, 2H), 5.29 (bs, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 20.6, 22.9, 23.1, 24.4, 27.2, 27.4, 28.5, 29.5, 31.4, 32.4, 36.9, 49.3, 118.2 (q, J = 319 Hz), 120.3, 132.6, 136.0, 161.6, 197.3; IR (film) 2959, 2937, 2925, 2918, 2874, 1681, 1660, 1420, 1347, 1243, 1215, 1140, 1039, 1031, 918, 796, 628 cm⁻¹; MS(CI) m/z 395.1483 (395.1504 calcd. for C₁₈H₂₆F₃O₄S, MH), 313, 261, 245, 205, 181, 137, 125, 109, 95.

Pd(0)-Catalyzed Cyclization of Vinyltriflate **12 to Form Tricyclic Dienones **13** and **14**.** A solution of **12** (100 mg, 0.25 mmol), Pd(OAc)₂ (5.7 mg, 0.03 mmol), PPh₃ (13.1 mg, 0.05 mmol), Et₃N (71 μL, 0.51 mmol) and dry acetonitrile (7.6 mL) was heated at 70 °C for 6 h. The reaction mixture then was adsorbed onto Florisil and extracted with ether. Concentration of the ether extract and purification of the residue by flash chromatography on silica gel (10:1 hexane-EtOAc) yielded 62 mg (~100%) of a pale yellow oil (a 77:23 mixture of **13** and **14** by GLC analysis), which crystallized overnight. These isomers could be separated by preparative HPLC (silica gel, 20:1 hexane-EtOAc). **Major isomer **13****: colorless plates, mp 69 °C (hexane-EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 0.78 (s, 3H), 1.00 (s, 3H), 1.23 (s, 3H), 1.49 (dd, J = 4.9, 3.6 Hz, 1H), 1.65 (dd, J = 17.4, 5.1 Hz, 1H), 1.84 - 2.00 (m, 5H), 2.24 - 2.45 (m, 6H), 5.65 (ddd, J = 10.3, 5.2, 2.1 Hz, 1H), 5.70 (d, J = 10.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 18.2, 20.4, 22.8, 23.5, 26.6, 29.5, 29.9, 32.8, 37.7, 40.1, 42.9, 47.5, 125.9, 131.4, 131.9, 162.0, 199.4; IR (film) 3020, 2950, 2938, 2897, 2867, 2833, 1665, 1622, 1464, 1456, 1436, 1378, 1366, 1325, 1296, 1197, 1188, 1131, 725 cm⁻¹; MS (EI) m/z 244.1823 (244.1827 calcd. for C₁₇H₂₄O, M, 100%), 229 (85%), 188 (46%), 162 (62%), 147 (36%), 134 (41%), 119 (16%), 105 (24%). **Minor isomer **14****: colorless plates; mp 105° C; ¹H NMR (500 MHz, CDCl₃, partial) δ 0.92 (s, 3H), 1.00 (s, 3H), 1.18 (s, 3H), 5.38 (d, J = 10.3 Hz, 1H), 5.46 (ddd, J = 10.3, 5.2, 3.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃, partial) δ 20.9, 23.0, 25.9, 26.5, 29.0, 31.8, 37.6, 39.2, 47.6, 120.0, 130.9, 138.0, 163.5, 199.8.

Hydrogenation of **13 and **14** to Form Tricyclic Enone **15**.** A solution of a ~2:1 mixture of enones **13** and **14** (24 mg, 0.10 mmol), dry benzene (5 mL) and (Ph₃P)₃RhCl (15 mg, 0.02 mmol) was shaken in a Parr-medium pressure hydrogenation apparatus at 50 psi for 9 h at 23 °C. The reaction mixture then was adsorbed

onto Florisil and was extracted with ether. Concentration of the ether extract and purification of the residue by flash chromatography (10:1 hexane-EtOAc) yielded 17 mg (70 %) of **15** as a colorless oil (97% pure by GLC), which crystallized overnight: mp 60 - 61 °C; ¹H NMR (500 MHz, CDCl₃) δ 0.78 (s, 3H), 0.95 (s, 3H), 1.09 (s, 3H), 1.15 - 1.33 (m, 4H), 1.42 - 1.48 (m, 1H), 1.86 - 1.92 (m, 2H), 1.96 - 2.00 (m, 2H), 2.05 - 2.07 (m, 2H), 2.12 - 2.19 (m, 1H), 2.31 - 2.42 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 17.3, 20.4, 20.7, 22.7, 23.2, 25.8, 31.4, 32.5, 34.6, 37.1, 37.5, 39.0, 42.6, 49.2, 132.6, 163.1, 199.5; MS(EI) *m/z* 246.1980 (246.1984 calcd. for C₁₇H₂₆O, M, 48%), 247 (100%), 231 (11%).

2-(Benzyloxymethyl)-2-cyclohexenone (17). A solution of *tert*-BuLi (31.5 mL, 53.6 mmol, 1.7 M in pentane) was added dropwise to a cold (-78 °C) solution of bromoketal **16** (5.34 g, 24.4 mmol) and THF (60 mL). After 30 min the reaction was warmed to -40 °C, maintained at that temperature for 15 min and then recooled to -78 °C. Solid CuCN (1.14 g, 12.7 mmol, dried azeotropically 2x with 2 mL of toluene) was added in one portion, and the reaction was warmed to -40 °C and stirred until the CuCN was completely dissolved (~10 min). After recooling to -78 °C, a solution of chloromethyl benzyl ether (7.45 mL, 53.6 mmol, freshly distilled and filtered through basic alumina before use) and THF (5 mL) was added dropwise and the reaction was allowed to warm to 0 °C. Water (10 mL) and saturated aqueous solution of NH₄Cl (4 mL) were added, and the resulting mixture was stirred vigorously until TLC (3:1 hexane-EtOAc) confirmed that deketalization was complete. The organic phase then was washed (2 N NH₄OH, H₂O, brine), dried (MgSO₄), filtered and concentrated, and the residue purified by flash chromatography (8:1 hexane-EtOAc) to give 3.8 g (72%) of **17** as a light yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 1.98 (m, 2H), 2.34-2.48 (m, 4H), 4.19 (d, *J* = 1.8 Hz, 1H), 4.20 (d, *J* = 1.8 Hz, 1H), 4.51 (s, 2H), 7.05 (m, 1H), 7.22-7.40 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 22.7, 25.6, 38.1, 66.8, 72.9, 127.5, 127.6, 128.3, 136.3, 138.1, 146.4, 198.5; IR (film) 3087, 3063, 3031, 1674, 1497, 1083, 1070, 737, 689 cm⁻¹; MS(CI) *m/z* 217.1234 (217.1228 calcd for C₁₄H₁₇O₂, MH), 125, 111, 110.

2-(Benzyloxymethyl)-1-*tert*-butyldimethylsiloxy-1-ethenyl-2-cyclohexene (18). To a cold (-78 °C) THF solution (25 mL) of ketone **17** (1.0 g, 4.6 mmol) was added slowly a solution of vinylolithium [prepared from tetravinyltin (2.44 g, 10.7 mmol) and *n*-BuLi (40.7 mmol)] and THF (20 mL)]. After 10 min the reaction was quenched with saturated aqueous NH₄Cl, extracted with EtOAc and the organic phase was washed (H₂O, brine) and dried (MgSO₄). After concentration the residue was purified by flash chromatography (9:1 hexane-EtOAc) to give 1.05 g (94%) of the corresponding tertiary alcohol as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 1.55-1.90 (m, 4H), 2.04 (m, 1H), 2.17 (m, 1H), 3.56 (s, 1H), 3.83 (d, *J* = 10.5 Hz, 1H), 4.22 (dt, *J* = 1.1, 10.5 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 5.14 (dd, *J* = 1.6, 10.6 Hz, 1H), 5.35 (dd, *J* = 1.7, 17.0 Hz, 1H), 5.91 (dd, *J* = 10.6, 17.0 Hz, 1H), 5.92 (bs, 1H), 7.21-7.48 (m, 5H).

To a cold (-78 °C) solution of 2,6-lutidine (3.34 mL, 28.7 mmol), *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.54 g, 17.2 mmol) and THF (30 mL) was slowly added a THF solution (8 mL) of a comparable sample of this alcohol (1.4 g, 5.73 mmol). This solution was allowed to warm to 23 °C, hexane (100 mL) was added and the resulting mixture was washed (1N HCl, saturated aqueous NH₄Cl, H₂O, brine). After drying (MgSO₄), filtration and concentration gave an oil that was purified by flash chromatography (50:1 hexane-EtOAc containing 0.2% NEt₃) to yield 1.72 g (84%) of **18** as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.86 (s, 9H), 1.68 (m, 1H), 1.72 (m, 1H), 1.85 (m, 2H), 2.11 (m,

2H), 3.98 (dd, $J = 1.7, 13.4$ Hz, 1H), 4.07 (dd, $J = 1.9, 13.4$ Hz, 1H), 4.48 (d, $J = 11.9$ Hz, 1H), 4.53 (d, $J = 11.9$ Hz, 1H), 5.06 (dd, $J = 1.5, 10.5$ Hz, 1H), 5.19 (dd, $J = 1.7, 17.2$ Hz, 1H), 5.92 (dd, $J = 10.5, 17.2$ Hz, 1H), 5.93 (bs, 1H), 7.22-7.41 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ -2.4, -1.9, 18.5, 19.6, 24.8, 25.9, 37.5, 69.0, 72.5, 76.2, 113.0, 124.2, 127.4, 127.6, 128.2, 137.5, 138.7, 143.1; IR (film) 3089, 3066, 3031, 1253, 1123, 1091, 1074, 1040, 913, 860, 836, 773 cm^{-1} ; MS (CI) m/z 359.2401 (359.2409 calcd for $\text{C}_{22}\text{H}_{35}\text{O}_2\text{Si}$, MH), 357, 302, 301, 251, 227, 209, 199, 183, 133, 121; Anal. Calcd for $\text{C}_{22}\text{H}_{34}\text{O}_2\text{Si}$: C, 73.69; H, 9.56; Found: C, 73.65; H, 9.51.

2-[(2-(Benzyloxymethyl)-1-(tert-butyldimethylsiloxy-2-cyclohexen-1-yl)ethyl]phenyl

trifluoromethanesulfonate (21). A solution of alkene **18** (308 mg, 0.856 mmol) and THF (0.5 mL) was added to a cold (0 °C) THF solution of 9-BBN (3.44 mL, 1.72 mmol, 0.5 M). The resulting solution was stirred at 23 °C for 10 min and then sonicated (micro tip, maximum output of a vibra cell sonicator) for 100 min. After cooling to 0 °C, a degassed aqueous solution of K_3PO_4 (0.57 mL, 1.7 mmol, 3 M) was added, the resulting mixture was stirred at 23 °C for 10 min (gas evolution was observed) and then $\text{PdCl}_2(\text{dppf})$ (63 mg, 0.086 mmol) and a THF solution (1 mL) of aryl iodide **19** (302 mg, 0.942 mmol) were added (the solution turned deep red). After stirring for 6.5 h at 50 °C, the resulting light brown mixture was diluted with EtOAc, washed (NH_4Cl , H_2O , brine), and dried (MgSO_4). Concentration gave a brown oil that was dissolved in MeOH-THF (5 mL, 4:1), solid K_2CO_3 (180 mg, 1.3 mmol) was added and the resulting mixture was stirred at 23 °C for 2 h. Extraction with CH_2Cl_2 , washing (brine), drying (MgSO_4) and concentration gave a brown oil, which was dissolved in THF (2 mL). An aqueous solution of NaOAc (1 mL, 3 M) was added followed by careful addition of 30% H_2O_2 (1 mL) at 0 °C and finally EtOH was added dropwise until the mixture became homogeneous. After stirring for 1.5 h at 23 °C, this solution was concentrated, the residue was dissolved in EtOAc and washed (2 N NH_4Cl , H_2O , brine), dried (MgSO_4) and concentrated to give a dark oil, which was chromatographed on silica gel (20:1 hexane-EtOAc) to give 57 mg (~15%) of **18** and 253 mg (65%) of **20** as a colorless oil (purity >90% by ^1H -NMR and GC analysis), which was directly employed in the next step: MS(CI) m/z 453.2814 (453.2825 calcd for $\text{C}_{28}\text{H}_{41}\text{O}_3\text{Si}$, MH).

A solution of phenol **20** (253 mg, 0.56 mmol) and THF (2.8 mL) was treated with NaH (16 mg, 0.67 mmol) at 0 °C and the resulting mixture was stirred at 23 °C until all the NaH had reacted (~10 min). Solid *N*-phenyl-trifluoromethanesulfonylimide (226 mg, 0.67 mmol) was added portionwise at 0 °C, the reaction was stirred for 1 h at 23 °C, EtOAc was added and the resulting solution was washed (brine), dried (MgSO_4) and concentrated. Purification of the residue by flash chromatography on silica gel (50:1 hexane-EtOAc) gave 310 mg (62% from **18**) of triflate **21** as a colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 0.04 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.69 (m, 1H), 1.78 (m, 2H), 1.92 (dt, $J = 5.1, 12.5$ Hz, 1H), 1.98-2.16 (m, 4H), 2.70-2.84 (m, 2H), 3.97 (dd, $J = 1.2, 12.1$ Hz, 1H), 4.23 (dd, $J = 1.1, 12.1$ Hz, 1H), 4.50 (d, $J = 11.7$ Hz, 1H), 4.57 (d, $J = 11.7$ Hz, 1H), 5.91 (t, $J = 3.7$ Hz, 1H), 7.21-7.39 (m, 9H); ^{13}C NMR (500 MHz, CDCl_3) δ -3.0, -1.8, 18.5, 19.9, 24.6, 25.2, 26.0, 35.1, 40.4, 69.5, 72.4, 75.2, 118.1 (q, $J = 319$ Hz), 121.1, 127.2, 127.45, 127.5, 127.8, 128.3, 128.4, 131.2, 135.7, 138.5, 139.2, 148.2; IR (film) 3060, 3033, 1418, 1250, 1216, 1142, 1069, 897, 835, 772 cm^{-1} ; MS(CI) m/z 585.2284 (585.2317 calcd for $\text{C}_{29}\text{H}_{40}\text{F}_3\text{O}_5\text{SiS}$, MH), 527, 470, 347, 345, 225, 213; Anal. Calcd for $\text{C}_{29}\text{H}_{39}\text{F}_3\text{O}_5\text{SiS}$: C, 59.56; H, 6.72; Found: C, 59.45; H, 6.67.

4a β -Benzyloxymethyl-10a β -tert-butylidimethylsilyloxy-1,2,4a,9,10,10a-hexahydrophenanthrene (22) and 4a β -Benzyloxymethyl-10a β -tert-butylidimethylsilyloxy-1,4,4a,9,10,10a-hexahydrophenanthrene (23). A mixture of **21** (42 mg, 0.072 mmol), KOAc (71 mg, 0.72 mmol), 10 mol% Pd(dppb) (prepared separately from 3.3 mg Pd₂(dba)₃ and 3.4 mg dppb in 0.2 mL of DMAC; color changed from violet to orange; catalyst was transferred with an additional 0.2 ml of DMAC) in 0.4 mL DMAC in a sealed tube was purged three times with argon and then heated to 120 °C. After 30 h the reaction was nearly complete. Workup consisted of dilution with EtOAc, washing (1 N HCl, H₂O, brine), drying (MgSO₄) and filtration. After evaporation of the solvent, isolation by preparative TLC (silica gel, 50:1 hexane-EtOAc) gave 21 mg (68%) of a mixture (>20:1 by ¹H-NMR analysis) of **22** and **23** (99% pure by GC analysis). A second fraction (2-3 mg) was a mixture of the reduction product **24** (5-10%) and starting triflate **21**. The regioisomeric tricyclic products were separated by preparative TLC, when a ~1:1-mixture was obtained with other catalysts (silica gel, 60:1 hexane-EtOAc, 2x developed). **Tricycle 22:** higher R_f; ¹H NMR (500 MHz, CDCl₃) δ 0.12 (s, 6H), 0.84 (s, 9H), 1.72-1.88 (m, 3H), 1.94 (m, 1H), 2.18-2.32 (m, 1H), 2.36-2.47 (m, 1H), 2.80 (ddd, J = 6.5, 9.5, 16.6 Hz, 1H), 2.99 (dt, J = 5.6, 17.0 Hz, 1H), 3.64 (d, J = 9.0 Hz, 1H), 3.82 (d, J = 9.0 Hz, 1H), 4.33 (d, J = 12.4 Hz, 1H), 4.45 (d, J = 12.4 Hz, 1H), 5.67 (dt, J = 3.4, 10.2 Hz, 1H), 5.89 (dt, J = 1.8, 10.2 Hz, 1H), 7.05 (d, J = 7.3 Hz, 1H), 7.08-7.18 (m, 4H), 7.21-7.32 (m, 3H), 7.48 (d, J = 7.6 Hz, 1H); ¹³C NMR (125 MHz, C₆D₆) δ -1.8, -1.5, 19.0, 23.0, 26.3, 27.6, 31.9, 33.9, 47.9, 73.4, 75.0, 77.6, 125.7, 125.8, 126.1, 127.35, 127.4, 128.4, 128.6, 129.1, 131.7, 134.5, 139.3, 142.8; IR (film) 3064, 3028, 1255, 1117, 1099, 1083, 909, 834, 772, 733 cm⁻¹; MS(Cl) m/z 435.2685 (435.2719 calcd for C₂₈H₃₉O₂Si, MH), 419, 377, 303, 285, 273, 197, 195, 181; Anal. Calcd for C₂₈H₃₈O₂Si: C, 77.37; H, 8.81; Found: C, 77.22; H, 8.89. **Tricycle 23:** lower R_f; ¹H NMR (500 MHz, CDCl₃) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.80 (s, 9H), 1.91 (ddd, J = 3.6, 9.2, 13.1 Hz, 1H), 2.08 (m, 1H), 2.10-2.19 (m, 2H), 2.47 (m, 1H), 2.65 (m, 1H), 2.89 (m, 1H), 3.04 (ddd, J = 3.6, 9.5, 13.0 Hz, 1H), 3.58 (d, J = 8.9 Hz, 1H), 3.70 (d, J = 8.9 Hz, 1H), 4.27 (d, J = 12.5 Hz, 1H), 4.35 (d, J = 12.5 Hz, 1H), 5.38 (dd, J = 2.5, 9.9 Hz, 1H), 5.66 (dt, J = 2.5, 7.6 Hz, 1H), 7.06 (m, 1H), 7.09-7.18 (m, 4H), 7.20-7.36 (m, 3H), 7.47 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ -2.4, -2.0, 18.4, 25.8, 26.7, 29.4, 31.8, 36.5, 46.1, 73.2, 74.6, 75.4, 124.0, 125.0, 125.1, 125.8, 126.9, 127.07, 127.1, 128.1, 128.5, 135.3, 139.0, 141.1; IR (film) 3064, 3028, 1256, 1116, 1100, 834, 772, 757, 746 cm⁻¹; MS(Cl) m/z 435.2711 (435.2719 calcd for C₂₈H₃₉O₂Si, MH), 419, 377, 303, 285, 197, 195, 181, 157; Anal. Calcd for C₂₈H₃₈O₂Si: C, 77.37; H, 8.81; Found: C, 77.12; H, 8.88.

10a β -tert-butylidimethylsilyloxy-4a β -hydroxymethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (26). A 1:1.2 mixture of **22** and **23** (58 mg, 0.133 mmol) was treated in MeOH (1.3 mL) with H₂ (balloon) and 10% Pd-C (7 mg). After stirring overnight at 23 °C, a single peak was observed by GC analysis. Removal of the catalyst by filtration and concentration gave 41 mg (89%) of **26** as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 0.20 (s, 3H), 0.22 (s, 3H), 0.97 (s, 9H), 1.21 (m, 1H), 1.37 (m, 1H), 1.54 (m, 3H), 1.72-1.87 (m, 2H), 2.06 (bd, J = 14.3 Hz, 1H), 2.08 (dt, J = 2.9, 13.6 Hz, 1H), 2.31 (bs, 1H), 2.48 (dd, J = 11.4, 19.4 Hz, 1H), 2.91 (ddd, J = 7.3, 11.4, 18.0 Hz, 1H), 2.99 (ddd, J = 1.5, 7.7, 18.0 Hz, 1H), 3.58 (bd, J = 10.6 Hz, 1H), 3.78 (d, J = 11.4 Hz, 1H), 7.10 (d, J = 7.3 Hz, 1H), 7.14 (dt, J = 1.5, 7.3 Hz, 1H), 7.18 (bt, J = 7.0 Hz, 1H), 7.31 (d, J = 7.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ -1.8, -1.3, 18.7, 21.35, 21.4, 26.3, 27.7, 32.7, 33.9, 47.6, 70.8, 78.4, 125.99, 126.02, 126.7, 129.2, 135.8, 139.0; IR (film) 3450, 3060, 3016, 1256, 1057,

1042, 835, 777, 735 cm^{-1} ; MS(CI) m/z 347.2337 (347.2406 calcd. for $\text{C}_{21}\text{H}_{35}\text{O}_2\text{Si}$ MH), 331, 315, 289, 197, 185, 184, 183, 166, 159.

Acetal (27). A solution of silylether **26** (37 mg, 0.107 mmol), THF (0.3 mL) and $(n\text{-Bu})_4\text{NF}$ (1M in THF, 0.16 mL, 1.5 eq) was maintained for 25 min at 23 °C, and after diluting with EtOAc, the organic layer was washed (saturated aqueous NH_4Cl , brine), dried (MgSO_4) and concentrated. This crude product then was dissolved in CH_2Cl_2 (0.4 mL) and pyridine *p*-toluenesulfonate (2.7 mg, 0.011 mmol) and an excess of dimethoxypropane (0.5 mL, 4.9 mmol) were added at 0 °C. After stirring at 23 °C for 4 h, EtOAc was added, the solution was washed (aqueous saturated NaHCO_3 , H_2O , brine) and the organic phase was dried ($\text{MgSO}_4/\text{K}_2\text{CO}_3$) and concentrated. Purification of the residue by flash chromatography (30:1 hexane-EtOAc, plus 0.2% NEt_3) gave 23 mg (79%) of **27** as a clear oil. Further filtration through a plug of silica gave a clear oil (22 mg, 76%), which crystallized after several days (mp 74-75 °C): ^1H NMR (500 MHz, C_6D_6) δ 1.04 (m, 1H), 1.30 (m, 1H), 1.35 (s, 3H), 1.42 (m, 1H), 1.48-1.55 (m, 2H), 1.59 (s, 3H), 1.63 (m, 1H), 1.76-1.87 (m, 2H), 2.32 (m, 1H), 2.45 (m, 1H), 2.71 (m, 2H), 3.45 (d, $J = 11.8$ Hz, 1H), 3.82 (d, $J = 11.8$ Hz, 1H), 6.96 (m, 1H), 7.03 (m, 2H), 7.10 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 22.3, 22.5, 26.8, 28.4, 31.2, 31.8, 34.6, 40.2, 67.9, 74.5, 98.0, 126.2, 126.5, 126.8, 128.3, 129.6, 136.3; IR (film) 1378, 1367, 1254, 1245, 1205, 1191, 1081, 1066, 1012, 755, 741 cm^{-1} ; MS (CI) m/z 273.1857 (273.1854 calcd for $\text{C}_{18}\text{H}_{25}\text{O}_2$; MH), 257, 215, 214, 197, 185, 184, 131.

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