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Regio- and Stereoselective Ruthenium Catalyzed Hydrovinylation of 1,3-Dienes: Application to the Generation of a 20S-Steroidal Sidechain

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Regio- and Stereoselective Ruthenium-Catalyzed Hydrovinylation of 1,3-Dienes: Application to the Generation of a 20(S) Steroidal Side Chain

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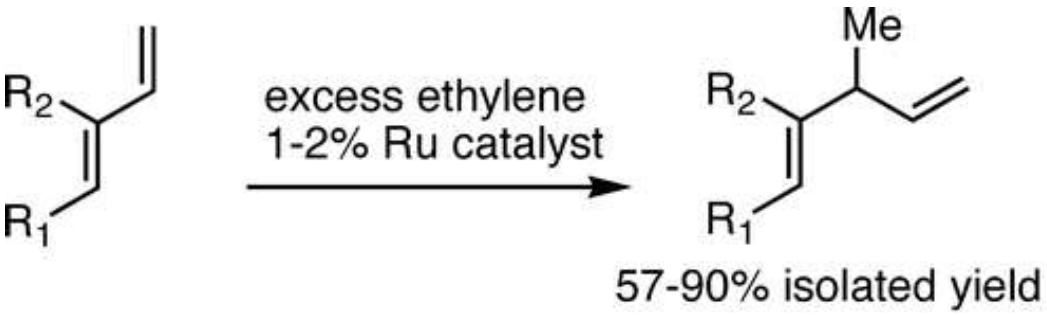
Abstract



The addition of ethylene to 1,3-dienes and 1-vinylcycloalkenes, catalyzed by two ruthenium complexes, proceeds in a regioselective fashion to afford 3-methyl-1,4-dienes as products. For a steroidal-based 1-vinylcycloalkene, the addition is stereospecific, giving a product with a 20(*S*) configuration.

Transition metal-catalyzed hydrovinylation[1] holds tremendous potential as a generally useful C−C bond-forming reaction, since it uses a cheap feedstock (ethylene) and proceeds in an "atom economical" fashion.[2] This reaction has largely focused on 1-arylethylenes as substrates since the products, 3-aryl-1-butenes, may be transformed into useful analgesics (e.g., ibuprofen, naproxen). While a number of recent reports describe highly enantioselective hydrovinylation of styrenes,[3] further development of this reaction as a general synthetic tool will require broadening the scope of applicable substrates. Only limited examples of the hydrovinylation of cyclic dienes have been reported.[4] In the course of examining the ruthenium-catalyzed coupling of ethylene with alkynes, one of our labs recently reported the use of two ruthenium catalytic systems **1** and **2** for the coupling of ethylene with alkynes and alkenes.[5] We herein report the ruthenium-catalyzed hydrovinylation of unsymmetrically substituted 1,3-dienes. Reaction of 1,3-dienes **3a**−**h** with excess ethylene, in the presence of either catalyst **1** or **2** gave predominantly the corresponding 3-methyl-1,4-dienes **4a**−**h**, the products resulting from 1,2-hydrovinylation (Table 1).[6] The structural assignment for **4** was based on its ^{1}H NMR spectral data. In particular, signals at ca. δ 5.9 (ddd, 1H), 5.05 (m, 2H), and 1.2 ppm (d, 3H) are characteristic of the vinyl and methyl groups of a 3-substituted-1-butenyl functionality. In certain cases, the reaction was terminated prior to complete consumption of starting material **3**, as prolonged contact with the

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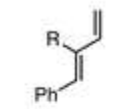
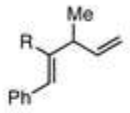
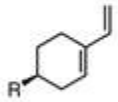
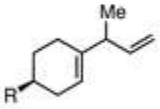
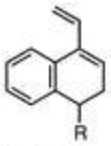
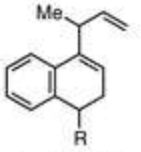
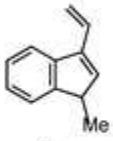
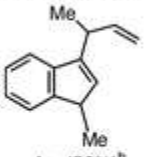
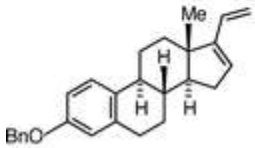
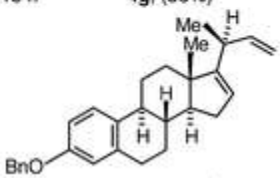
catalyst led to isomerization of the initially formed **4** to the more stable conjugated 3-methyl-1,3-diene.[7] Any unreacted starting material or the isomerized 1,3-diene product could be chemically separated from the desired 1,4-diene **4** by treatment of the reaction mixture with phenyl triazodione (PTAD); the PTAD undergoes cycloaddition with the conjugated dienes, and the desired product **4** can be cleanly separated from these cycloaddition products.

Figure 1 Ruthenium catalyst structures.

Table 1. Ru-Catalyzed Hydrovinylation of 1,3-Dienes

1-vinylcycloalkene	catalyst/rxn time	product (isolated yield)
 **3a**, R = Ph **3b**, R = Me	1% **2**, 6 h 1% **1**, 16 h	 **4a**, R = Ph (90%)[a] **4b**, R = Me (75%)
 **3c**, R = H **3d**, R = C(Me)=CH$_2$	1% **1**, 22 h 1% **2**, 20 h	 **4c**, R = H (62%) **4d**, R = C(Me)=CH$_2$ (57%)[b]
 **3e**, R = H **3f**, R = Me	1% **2**, 20 h 1.5% **1**, 15 h	 **4e**, R = H (67%) **4f**, R = Me (75%)[b]
 **3g**	1.5% **1**, 15 h	 **4g**, (56%)[b]
 **3h**	2% **2**, 7 h	 **4h**, (88%)[c]

[a] From ref 5b.[b] Mixture of diastereomers (1:1).[c] Single diastereomer.

Hydrovinylation of dienes bearing aryl substituents (**3a**,**b**) as well as 1-vinylcycloalkenes (**3c**−**h**) proceeded with excellent 1,2-addition regioselectivity. For certain substrates bearing a resident stereocenter (e.g., **3d**,**f**,**g**), hydrovinylation was not stereoselective, giving a 1:1 mixture of diastereomeric products. In contrast, hydrovinylation of the steroidal diene **3h** proceeded with excellent regio- and stereoselectivity, giving a single diastereomer **4h** in good isolated yield. Since assignment of the C20 configuration of the product **4h** was not possible on the basis of NMR spectral data, a crystalline derivative was sought. To this end, hydroboration/oxidation of **4h** proceeded only at the vinyl group to afford the primary alcohol **5** (Scheme 1). Oxidation of **5** with Jones reagent, followed by treatment

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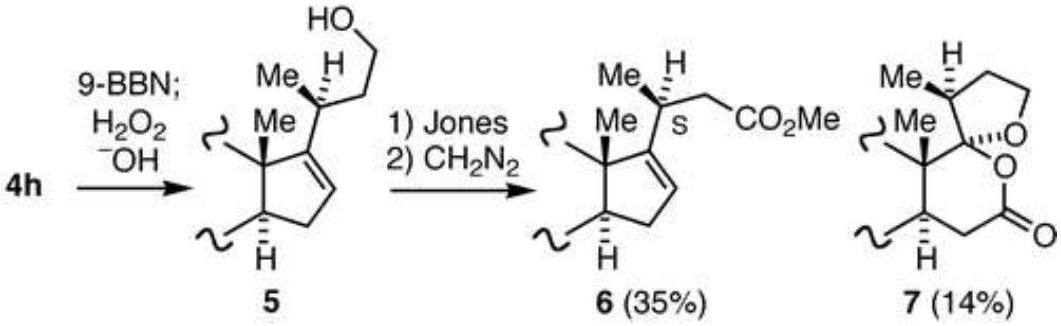
of the crude product with diazomethane, gave a separable mixture of ester **6**[8] and spirocyclic lactone **7**.[9] Crystals of **7** suitable for X-ray diffraction analysis revealed the relative configurations within the molecule;[10] since the precursor **3h** was prepared from optically pure estrone,[11] the absolute configurations at the C17 and C20 stereocenters of **7** were assigned as (*R*) and (*S*), respectively. Thus, the hydrovinylation product **4h** has the 20(*S*) configuration, which is opposite to the configuration of most naturally occurring steroids [i.e., 20(*R*)]. Recently, a nonnatural 20(*S*) vitamin D_3 analogue has been reported that selectively induces bone formation.[12] While there are many strategies for the preparation of the 20(*R*) side chain,[13] there is a general lack of *stereoselective* routes to side chains with the 20(*S*) configuration.[14]



Scheme 1

To demonstrate the synthetic potential of this diastereoselective hydrovinylation reaction, alcohol **5** was transformed into unsaturated alcohol **9a** via a three-step protocol (Scheme 2). Structure **9a** is a hybrid between estrone and the Roche vitamin D_3 analogue, Ro 26-9228 (**9b**), which is reported to increase bone mineral density in rats.[12a] Additionally, functionalized estrone analogues structurally similar to **9a** are described as agents for the modulation of cell growth and differentiation.[12d]

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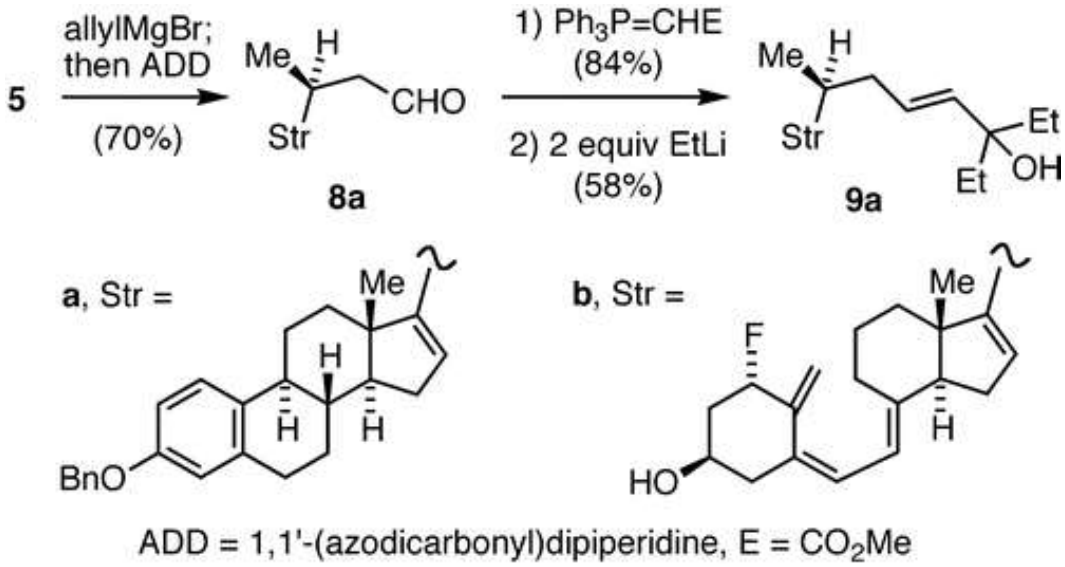

Scheme 2

The hydrovinylation of 1,3-dienes with either **1** or **2** is proposed to involve a ruthenium hydride species **10** in which the less substituted olefin of the diene is coordinated to Ru (Scheme 3).[15] Insertion of the conjugated diene into the Ru−H bond generates the 1-methyl-π-allyl intermediate **11** in a reversible fashion. Ethylene insertion into the σ-allyl species **12**, with retention of configuration, followed by β-hydride and subsequent ligand exchange with a 1,3-diene, regenerates species **10**, and affords the product 1,4-diene. The stereoselective formation of **4h** may be rationalized on the preferential formation of π-allyl intermediate **13** (Scheme 3) in which Ru is trans to the sterically bulky angular methyl group and the allylic methyl group occupies the anti position in order to avoid steric interaction with the C12 methylene (steroid numbering).

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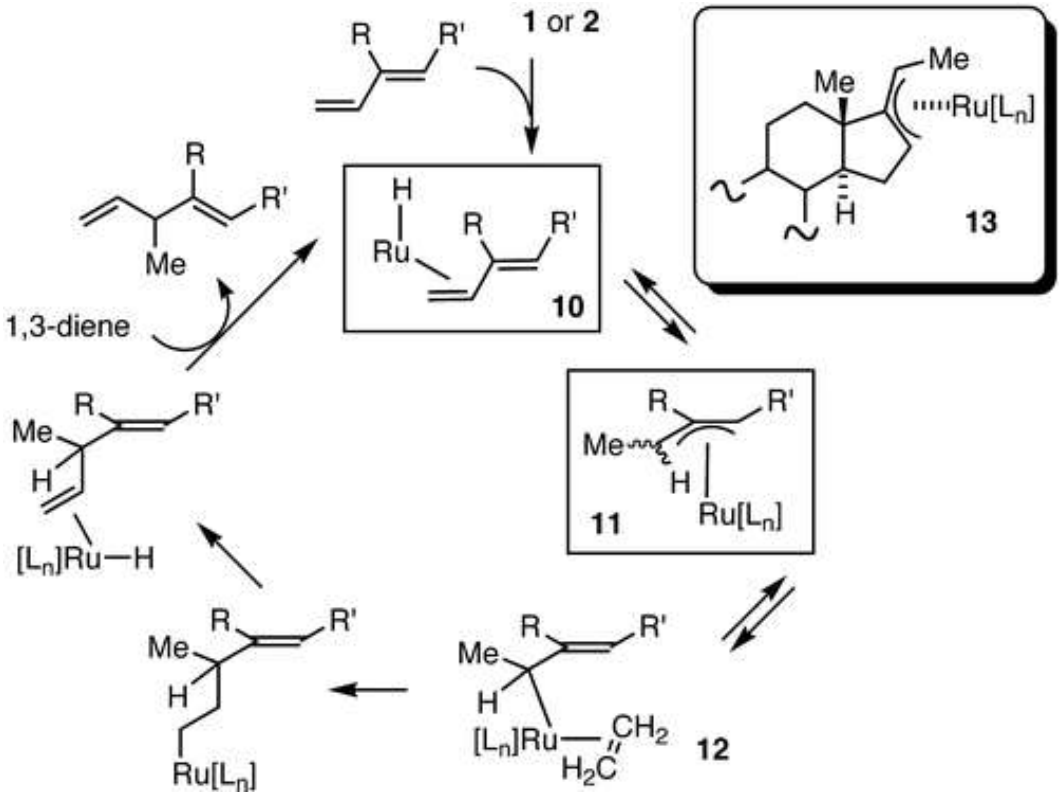

Scheme 3

In summary, regio- and stereoselective hydrovinylation of 1,3-dienes **3** has been achieved by using Ru catalysts **1** or **2**. Further developments in the scope of this reaction as well as synthetic applications will be reported in due course.

Acknowledgment

Financial support for this work was provided by the National Institutes of Health (GM-42641 to W.A.D. and GM-55987 to C.S.Y.). High-resolution mass-spectral determinations were made at the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant P41RR0954). W.A.D. acknowledges stimulating discussions with Prof. T. V. RajanBabu.

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[6]Neither 1,4-diphenyl-1,3-butadiene or 2,5-dimethyl-2,4-hexadiene reacted with ethylene in the presence of either **1** or **2**.

[7]Isomerization (over longer reaction periods) is observed with both catalysts **1** and **2**. Thus, at least for catalyst **1**, this isomerization cannot be attributed to the presence of acid.

[8]Both the 20(*S*)- and 20(*R*)-isomers of the methyl ether corresponding to benzyl ether **6** have been previously prepared. The close similarity of their literature NMR spectral data does not allow for an unambiguous assignment. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435−3443.

[9]Formation of γ-lactones from 4-penten-1-ols or δ-lactones from 5-hexen-1-ols via oxidation with chromium reagents has been previously reported. (a) Chakraborty, T. K.; Chandrasekaran, S. *Tetrahedron Lett.* **1984**, *25*, 2895−2896. (b) Schlecht, M. F.; Kim, H. *Tetrahedron*

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[13]For a review, see: Gui-Dong, Z.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877−1952. For a more recent synthesis, see: Yan, J.; Herndon, J. W. *J. Org. Chem.* **1998**, *63*, 2325−2331 and references therein.

[14]20(*S*) vitamin D_3 precursors have been prepared by ozonolytic degradation of ergocalciferol, followed by a base-catalyzed epimerization and separation of the 20(*R*)- and 20(*S*)-diastereomers: Hijikuro, D. T.; Takahashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 3716−3722. For a route to the 20(*S*) side chain that uses stoichiometric palladium, see ref 8.

[15]Notably, the Ru−H species **10** has been proposed as an intermediate in the coupling of alkynes with ethylene using catalyst **1** (see ref 5a).

Supporting Information Available

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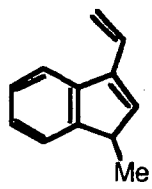
Supporting Information

Experimental Section

General Data: All ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively. For those products that are mixtures of stereoisomers, diastereomeric ^{13}C NMR resonances are noted in square brackets. Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. Elemental analyses were obtained from Midwest Microlabs, Ltd., Indianapolis, IN and high resolution mass spectra were obtained from the Washington University Resource for Mass Spectroscopy.

Solvents were distilled from Na, Na-benzophenone, or CaH_2, and degassed prior to use. All reactions were carried out in a nitrogen-filled glove-box or using standard Schlenk techniques unless otherwise noted. Catalysts **1** and **2** were prepared according to the literature procedures.[1] The conjugated 1,3-diene substrates were prepared by Wittig olefination of the corresponding enal (**3b-d**), or prepared by palladium catalyzed Stille coupling of the enoltriflate with tributylvinyltin[2] (**3e-h**). Dienes **3b**,[3] **3c**,[4] **3d**,[5] **3e**,[6] **3f**,[7] and **3h**[8] were identified by comparison of their spectral data with the literature values.



1-Methyl-3-vinyl-1H-indene (3g): ^1H NMR ($CDCl_3$) δ 7.59 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 6.9 Hz, 1H), 7.34-7.22 (m, 2H), 6.77 (ddd, J = 0.9, 10.5, 18.0 Hz, 1H), 6.49 (t, J = 2.4 Hz, 1H), 5.85 (d, J = 18.0 Hz, 1H), 5.36 (d, J = 10.5 Hz, 1H), 3.53 (q, J = 7.5 Hz, 1H), 1.36 (d, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 149.4, 141.9, 139.3, 137.9, 130.1, 125.8, 124.6, 122.4, 119.7, 115.5, 43.9, 16.7.

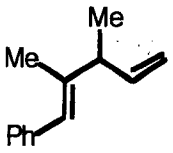
General Procedure for Ru-catalyzed hydrovinylation with Catalyst 1.

A 25 mL medium walled vacuum Schlenk tube (Kontes catalog # 218710-0025) equipped with stirring bar and Teflon stopcock was charged with degassed diene (1.0-2.0 mmol), catalyst **1** (1.0-2.0 mol%), and methylene chloride (3.0 mL) in a nitrogen-filled glove box. The tube was removed from the glove box, cooled in a liquid N_2 bath, and excess ethylene (ca. 6.4 mmol) was condensed into the tube. The tube was stoppered, removed from the liquid N_2 bath, warmed to rt, and immersed in a 75 °C oil bath for a specified period of time (Table 1). (CAUTION: These conditions result in an increase in pressure in the medium wall reaction vessel. Heating of the

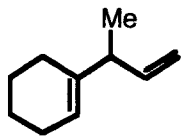
reaction flask should be conducted in a fume hood behind a closed safety sash). After this time, the reaction mixture was cooled to rt, and the tube opened to the air. The reaction mixture was concentrated and the residue was dissolved in hexanes/methylene chloride (5 mL) and passed through a short column of silica gel in a disposable pipet (ca. 5 cm). Evaporation of the solvent gave the crude product. The crude product was dissolved in methylene chloride (10 mL) and to the stirred solution was added small amounts of N-phenyltriazodione (PTAD), until the red color of PTAD persisted. The mixture was concentrated and the residue purified by column chromatography (hexanes).

General Procedure for Ru-catalyzed hydrovinylation with Catalyst 2.

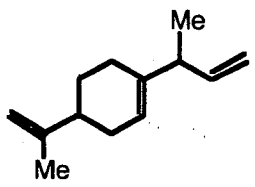
In a 25 mL medium walled vacuum Schlenk tube (Kontes catalog # 218710-0025) equipped with magnetic stirring bar and Teflon stopcock, the diene (1.0-2.0 mmol) was added and the tube was degassed. The tube was placed into a glovebox, where catalyst **2** (8.0 mg., 0.01 mmol) was added, followed by the addition of benzene (3.0 mL). The sealed tube was removed from the glove box and under a stream of dry N_2, HBF_4:OEt_2 in ether (4.0 μl., ca. 2.0 μmol) was injected by the means of a syringe. The mixture was stirred at rt for 15 min. The reaction tube was cooled in a liquid N_2 bath, and excess ethylene (ca. 6.4 mmol) was condensed into the tube. The tube was stoppered, removed from the liquid N_2bath, warmed to rt, and immersed in a 75 °C oil bath for a specified period of time (Table 1). (CAUTION: These conditions result in an increase in pressure in the medium wall reaction vessel. Heating of the reaction flask should be conducted in a fume hood behind a closed safety sash). After this time, the reaction mixture was cooled to rt, and the tube opened to the air. The reaction mixture was concentrated and the residue was dissolved in hexanes/methylene chloride (5 mL) and passed through a short column of silica gel in a disposable pipet (ca. 5 cm). In all cases, *except for* ***4h***, the crude product was dissolved in methylene chloride (10 mL) and to the stirred solution was added small amounts of N-phenyltriazodione (PTAD), until the red color of PTAD persisted. The mixture was concentrated and the residue purified by column chromatography (hexanes).



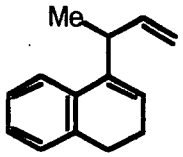
2,3-Dimethyl-1-phenyl-1,4-pentadiene (4b): ^{1}H NMR ($CDCl_3$) δ 7.37-7.21 (m, 5H), 6.36 (s, 1H), 5.89 (ddd, J = 17.1, 10.2, 6.9 Hz, 1H), 5.15-5.05 (m, 2H), 3.03-2.90 (m, 1H), 1.84 (d, J = 1.2 Hz, 3H), 1.28 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 142.2, 142.0, 138.4, 128.9, 128.0, 125.9, 124.5, 113.6, 46.8, 18.1, 15.7. Anal. calcd. for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 90.41; H, 9.47.



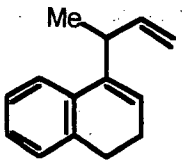
1-(1-Methyl-2-propenyl)-cyclohexene (4c): ^{1}H NMR ($CDCl_3$) δ 5.79 (ddd, J = 17.1, 10.2, 7.2 Hz, 1H), 5.47 (br s, 1H), 5.01 (d, J = 17.1 Hz, 1H), 4.96 (d, J = 10.2 Hz, 1H), 2.78-2.65 (m, 1H), 2.10-1.88 (m, 4H), 1.65-1.50 (m, 4H), 1.11 (d, J = 7.2 Hz, 3H). This compound was identified by comparison of its spectral data with the literature values.[9]



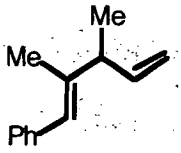
1-(1-Methyl-2-propenyl)-4-(1-methylethylene)cyclohexene (4d): ^{1}H NMR ($CDCl_3$) δ 5.77 (ddd, J = 17.4, 10.2, 7.2 Hz, 1H), 5.48 (br s, 1H), 5.03-4.94 (m, 2H), 4.71 (br s, 2H), 2.80-2.70 (m, 1H), 2.20-1.78 (m, 6H), 1.75 (s, 3H), 1.54-1.40 (m, 1H), 1.13 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 149.58 [149.55], 142.3 [142.2], 139.9 [139.7], 119.6 [119.4], 112.6 [112.5], 108.1, 44.8 [44.7], 41.7 [41.6], 31.26 [31.23], 28.4, 27.3 [27.2], 21.3, 18.9 [18.4]; Anal. calcd. for $C_{13}H_{20}$: C, 88.57; H, 11.43. Found: C, 88.37; H, 11.38.



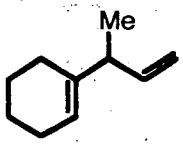
1,2-Dihydro-4-(1-methyl-2-propenyl)naphthalene (4e): ^{1}H NMR ($CDCl_3$) δ 7.34 (d, J = 7.8 Hz, 1H), 7.26-7.10 (m, 3H), 5.99 (ddd, J = 16.8, 9.9, 6.0 Hz, 1H), 5.93 (t, J = 4.8 Hz, 1H), 5.15-5.05 (m, 2H), 3.53 (dq, J = 6.9, 6.9 Hz, 1H), 2.76 (t, J = 7.8 Hz, 1H), 2.35-2.26 (m, 2H), 1.32 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 142.3, 139.2, 136.4, 134.2, 127.1, 126.0, 125.7, 123.6, 122.4, 113.1, 38.3, 28.9, 23.6, 19.8. This compound was identified by comparison of its spectral data with the literature values.[10]



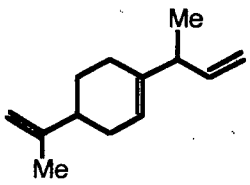
1,2-Dihydro-1-methyl-4-(1-methyl-2-propenyl)naphthalene (4f): ^{1}H NMR ($CDCl_3$) δ 7.40-7.34 (m, 1H), 7.26-7.18 (m, 3H), 6.07-5.93 (m, 1H), 5.85 and 5.84 (2 x t, J = 4.0 Hz, 1H total), 5.18-5.03 (m, 2H), 3.55 (dq, J =



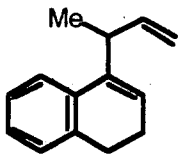
2,3-Dimethyl-1-phenyl-1,4-pentadiene (4b): ^{1}H NMR ($CDCl_3$) δ 7.37-7.21 (m, 5H), 6.36 (s, 1H), 5.89 (ddd, J = 17.1, 10.2, 6.9 Hz, 1H), 5.15-5.05 (m, 2H), 3.03-2.90 (m, 1H), 1.84 (d, J = 1.2 Hz, 3H), 1.28 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 142.2, 142.0, 138.4, 128.9, 128.0, 125.9, 124.5, 113.6, 46.8, 18.1, 15.7. Anal. calcd. for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 90.41; H, 9.47.



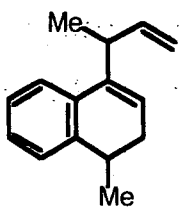
1-(1-Methyl-2-propenyl)-cyclohexene (4c): ^{1}H NMR ($CDCl_3$) δ 5.79 (ddd, J = 17.1, 10.2, 7.2 Hz, 1H), 5.47 (br s, 1H), 5.01 (d, J = 17.1 Hz, 1H), 4.96 (d, J = 10.2 Hz, 1H), 2.78-2.65 (m, 1H), 2.10-1.88 (m, 4H), 1.65-1.50 (m, 4H), 1.11 (d, J = 7.2 Hz, 3H). This compound was identified by comparison of its spectral data with the literature values.[9]



1-(1-Methyl-2-propenyl)-4-(1-methylethylene)cyclohexene (4d): ^{1}H NMR ($CDCl_3$) δ 5.77 (ddd, J = 17.4, 10.2, 7.2 Hz, 1H), 5.48 (br s, 1H), 5.03-4.94 (m, 2H), 4.71 (br s, 2H), 2.80-2.70 (m, 1H), 2.20-1.78 (m, 6H), 1.75 (s, 3H), 1.54-1.40 (m, 1H), 1.13 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 149.58 [149.55], 142.3 [142.2], 139.9 [139.7], 119.6 [119.4], 112.6 [112.5], 108.1, 44.8 [44.7], 41.7 [41.6], 31.26 [31.23], 28.4, 27.3 [27.2], 21.3, 18.9 [18.4]; Anal. calcd. for $C_{13}H_{20}$: C, 88.57; H, 11.43. Found: C, 88.37; H, 11.38.



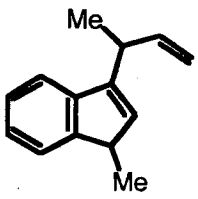
1,2-Dihydro-4-(1-methyl-2-propenyl)naphthalene (4e): ^{1}H NMR ($CDCl_3$) δ 7.34 (d, J = 7.8 Hz, 1H), 7.26-7.10 (m, 3H), 5.99 (ddd, J = 16.8, 9.9, 6.0 Hz, 1H), 5.93 (t, J = 4.8 Hz, 1H), 5.15-5.05 (m, 2H), 3.53 (dq, J = 6.9, 6.9 Hz, 1H), 2.76 (t, J = 7.8 Hz, 1H), 2.35-2.26 (m, 2H), 1.32 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 142.3, 139.2, 136.4, 134.2, 127.1, 126.0, 125.7, 123.6, 122.4, 113.1, 38.3, 28.9, 23.6, 19.8. This compound was identified by comparison of its spectral data with the literature values.[10]



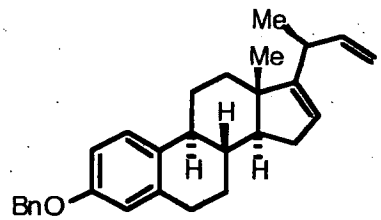
1,2-Dihydro-1-methyl-4-(1-methyl-2-propenyl)naphthalene (4f): ^{1}H NMR ($CDCl_3$) δ 7.40-7.34 (m, 1H), 7.26-7.18 (m, 3H), 6.07-5.93 (m, 1H), 5.85 and 5.84 (2 x t, J = 4.0 Hz, 1H total), 5.18-5.03 (m, 2H), 3.55 (dq, J =

6.6, 6.6 Hz, 1H), 2.89 (ddq, J = 7.2, 7.2, 7.2 Hz, 1H), 2.53-2.42 (br d, J = 16.8 Hz, 1H), 2.19-2.07 (m, 1H), 1.33 and 1.32 (2 x d, J = 6.9 Hz, 3H total), 1.28 and 1.25 (2 x d, J = 6.9 Hz, 3H total); ^{13}C NMR ($CDCl_3$) δ 142.3, 141.23 [141.16], 138.6 [138.4], 133.3, 126.3, 125.73 [125.71], 125.56 [125.52], 122.6 [122.5], 122.04 [121.97], 113.1; 38.25 [38.20], 32.61 [32.58], 31.42 [31.36], 20.3, 19.7. Anal. calcd. for $C_{15}H_{18}$:1/4H_2O: C, 88.83; H, 9.62. Found: C, 88.87; H, 9.65.

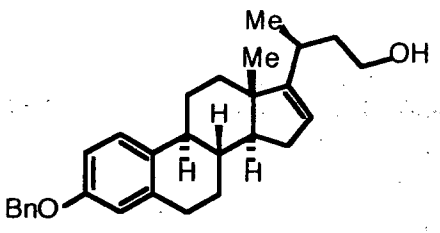
1-Methyl-3-(1-methyl-2-propenyl)-1H-indene (4g): ^{1}H NMR ($CDCl_3$) δ 7.42-7.16 (m, 4H), 6.18 (s, 1H), 6.01 (ddt, J = 17.1, 10.5, 7.2 Hz, 1H), 5.12 (br d, J = 17.1 Hz, 1H), 5.06 (br d, J = 10.5 Hz, 1H), 3.55-3.40 (m, 2H), 1.41 and 1.40 (2 x d, J = 6.9 Hz, 3H total), 1.32 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 149.4, 145.1, 143.2, 141.3, 134.0, 125.5, 124.2, 122.2, 119.4, 113.3, 43.8, 36.7 [36.6], 19.6, 16.94 [16.86]. EI-HRMS m/z 184.1249 (calcd for $C_{14}H_{16}$ (M^+) m/z 184.1252).



17-(1-Methyl-2-propenyl)-3-(phenylmethoxy)-estra-1,3,5(10),16-tetraene (4h): $[\alpha]_D$ +80.6 (c 1.6, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.33 (d, J = 7.5 Hz, 1H), 7.24-7.08 (m, 5H), 6.87 (dd, J = 7.5, 2.0 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 5.86 (ddd, J = 17.1, 9.9, 7.2 Hz, 1H), 5.41 (br s, 1H), 5.06 (d, J = 17.1 Hz, 1H), 4.98 (d, J = 9.9 Hz, 1H), 4.82 (s, 2H), 2.90-2.64 (m, 3H), 2.28-1.40 (m, 11H), 1.21 (d, J = 7.2Hz, 3H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.4, 156.5, 143.6, 137.9, 137.2, 133.2, 128.4, 127.7, 127.3, 125.9, 121.9, 114.7, 112.4, 112.0, 69.9, 56.4, 47.6, 44.4, 37.4, 36.7, 35.2, 30.9, 29.8, 27.8, 26.5, 20.8, 16.5. Anal. calcd. for $C_{29}H_{34}O$: C, 87.39; H 8.60. Found: C, 87.22; H, 8.60.



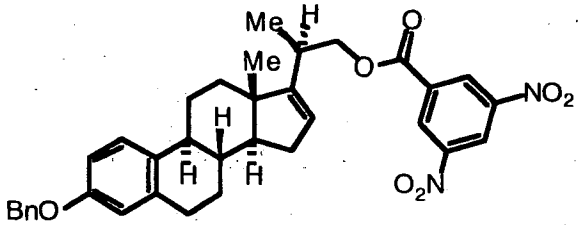
17-(3-Hydroxy-1-methylpropyl)-3-(phenylmethoxy)-estra-1,3,5(10),16-tetraene (5): To a solution of **4h** (0.33 g, 0.83 mmol) in THF (10 mL), under N_2 at 0 °C, was added dropwise a solution of 9-BBN (2.0 mL, 0.5 M in THF, 1.0 mmol). After 1 h, the reaction mixture was warmed to rt, stirred overnight, and



treated with a mixture of 30% H_2O_2 (1 mL) and 1.0 M aqueous KOH (2 mL). The reaction mixture was stirred for 30 min and poured into a separatory funnel containing brine (20 mL) and ether (70 mL). The layers were separated and the ether layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes-EtOAc = 5:1) to afford **5** as a white solid (0.30 g, 87%).

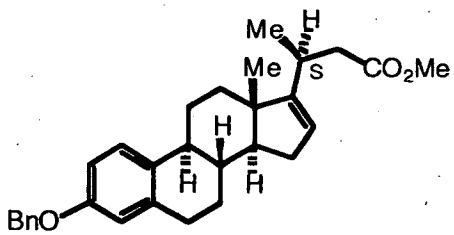
5: mp 90-92 °C; $[\alpha]_D$ +61.8 (c 3.7, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.46-7.30 (m, 5H), 7.20 (d, J = 8.4 Hz, 1H), 6.79 (dd, J = 8.4, 2.7 Hz, 1H), 6.74 (d, J = 2.9 Hz, 1H), 5.45 (br s, 1H), 5.05 (s, 2H), 3.77-3.63 (m, 2H), 2.95-2.87 (m, 2H), 2.42-1.40 (m, 15H), 1.16 (d, J = 6.9 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.2, 155.9, 137.5, 136.7, 132.8, 128.0, 127.3, 127.0, 125.5, 121.3, 114.4, 111.8, 70.0, 61.6, 56.4, 47.9, 44.6, 40.2, 37.7, 35.4, 31.3, 30.2, 29.0, 28.2, 26.9, 21.1, 17.1. Anal. calcd. for $C_{29}H_{36}O_2$: C, 83.61; H, 8.71. Found: C, 83.47; H, 8.65.

3,5-Dinitrobenzoate ester of 5. A sample of **4h** (0.18 g, 0.45 mmol) was treated with 9-BBN as above, followed by oxidation with alkaline H_2O_2. The crude alcohol was dissolved in THF (10 mL) and 3,5-dinitrobenzoyl chloride (0.11 g, 0.48 mmol), NEt_3 (0.07 g, 0.72 mmol) and DMAP (one crystal) were added. The reaction mixture was stirred overnight, and then diluted with ether (50 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 15 mL), followed by water. The ethereal layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes- CH_2Cl_2 = 2:1) to give a pale yellow solid (0.090 g, 33%). ^1H NMR ($CDCl_3$) δ 9.24-9.15 (m, 3H), 7.46-7.28 (m, 5H), 7.19 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.73 (br s, 1H), 5.50 (br s, 1H), 5.04 (s, 2H), 4.55-4.40 (m, 2H), 2.95-2.82 (m, 2H), 2.50-1.30 (m, 15H), 1.22 (d, J = 6.6 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.3, 159.3, 156.5, 148.5, 137.9, 137.2, 134.0, 133.0, 129.3, 128.4, 127.7, 127.3, 125.9, 122.4, 122.2, 114.8, 112.1, 69.9, 65.7, 56.3, 47.7, 44.3, 37.4, 35.7, 35.2, 31.0, 29.8, 28.6, 27.8,

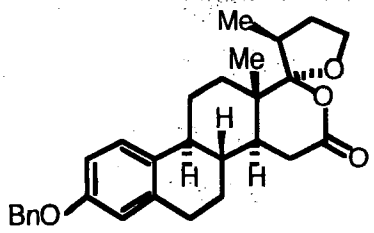


26.5, 21.8, 16.8. Anal. calcd. for $C_{36}H_{38}N_2O_7$: C, 70.81; H, 6.27; N, 4.59. Found: C, 71.05; H, 6.35; N, 4.52.

Preparation of 6 and 7. A sample of **4h** (0.389 g, 0.98 mmol) was treated with 9-BBN as above, followed by oxidation with alkaline H_2O_2. The crude alcohol was dissolved in acetone (10 mL) and Jones reagent (0.30 g CrO_3/mL concentrated H_2SO_4) was added portionwise until the orange color persisted. The reaction mixture was stirred for 50 min. The mixture was concentrated on a rotary evaporator, and then 2N HCl (10 mL) was added and the mixture was extracted with ether (70 mL). The ethereal extracts were dried (Na_2SO_4) and concentrated. The residue (0.310 g) was dissolved in ether (10 mL) in a plastic beaker and the mixture was cooled in a ice-water bath. To the mixture was cautiously added an ethereal solution of diazomethane (prepared from MNNG and KOH) until the yellow color persisted. The reaction mixture was flushed with N_2 until colorless, and then dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (hexanes-EtOAc -CH_2Cl_2 = 5:1:1) to give **6** as a colorless oil (0.156 g, 36% based on **4h**) followed by **7** as a white solid (0.059 g, 14%). Slow recrystallization of **7** from methanol-CH_2Cl_2 gave colorless flakes which were suitable for X-ray diffraction analysis.

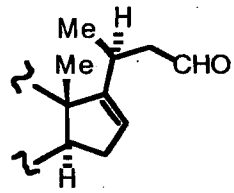


(20*S*)-3-Benzyloxy-19,24-dinorchola-1,3,5(10),16-tetraen-23-oic acid, methyl ester (6): ^1H NMR ($CDCl_3$) δ 7.50-7.30 (m, 5H), 7.20 (d, J = 8.7 Hz, 1H), 6.78 (dd, J = 8.7, 2.4 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 5.43 (br s, 1H), 5.04 (s, 2H), 3.68 (s, 3H), 3.00-2.64 (m, 3H), 2.56 (dd, J = 14.7, 5.1 Hz, 1H), 2.40-1.30 (m, 12H), 1.14 (d, J = 6.6 Hz, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.0, 159.2, 156.5, 137.9, 137.2, 133.1, 128.4, 127.7, 127.3, 125.9, 122.0, 114.7, 112.0, 69.9, 56.4, 51.4, 47.4, 44.3, 41.8, 37.4, 34.9, 30.9, 29.8, 27.8, 26.5, 21.1, 16.7. Anal. calcd. for $C_{30}H_{36}O_3$: C, 81.04; H, 8.16. Found: C, 80.83; H, 8.29.

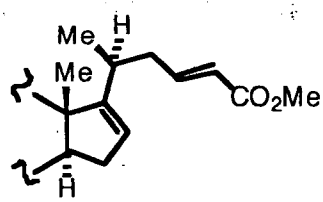


7: mp 221-223 °C, ^{1}H NMR ($CDCl_3$) δ 7.45-7.30 (m, 5H), 7.19 (d, J = 8.7 Hz, 1H), 6.80 (dd, J = 8.7, 2.4 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 5.03 (s, 2H), 4.08 (dt, J = 8.7, 3.9 Hz, 1H), 3.79 (q, J = 8.1 Hz, 1H), 2.90-2.78 (m, 3H), 2.50-1.26 (m, 13H), 1.21 (d, J = 6.6 Hz, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.3, 156.7, 137.5, 137.0, 132.0, 128.4, 127.8, 127.3, 126.1, 115.5, 114.4, 112.5, 69.9, 67.0, 42.3, 39.0, 38.6, 37.2, 33.5, 32.6, 32.0, 29.9, 25.8, 25.7, 15.4, 14.8. Anal. calcd. for $C_{29}H_{34}O_4$: C, 78.00; H, 7.67. Found: C, 77.21; H, 7.63.

(20*S*)-3-Benzyloxy-19,24-dinorchola-1,3,5(10),16-tetraen-23-al (8a). To a



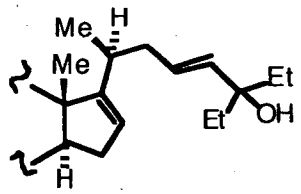
solution of alcohol **5** (0.15 g, 0.36 mmol) in THF was added a solution of allyl magnesium bromide (0.4 mL, 1.0M in ether, 0.4 mmol). The solution was stirred at room temperature for 15 min, at which time solid (azodicarbonyl)dipiperidine (0.10 g, 0.40 mmol) was added in one portion. The reaction mixture was stirred for 1 h, and then brine was added. The reaction mixture was extracted with ether, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (hexanes-EtOAc = 10:1) to give **8a** as a colorless solid (0.10 g, 70% based on consumed **5**) followed by recovered **5** (0.03 g, 20%). **8a:** mp 100-102 °C, $[\alpha]_D$ +56.7 (c 0.36, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 9.71 (t, *J* = 2.1 Hz, 1H), 7.45-7.25 (m, 5H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.73 (d, *J* = 2.1 Hz, 1H), 5.45 (br s, 1H), 5.04 (s, 2H), 2.95-2.78 (m, 3H), 2.62 (ddd, *J* = 16.5, 6.3, 2.1 Hz, 1H), 2.41 (ddd, *J* = 16.5, 7.6, 2.1 Hz, 1H), 2.36-1.30 (m, 11H), 1.20 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 201.7, 158.2, 155.9, 137.5, 136.7, 132.6, 128.0, 127.4, 127.0, 125.5, 122.7, 114.5, 111.8, 70.0, 56.6, 50.8, 47.7, 44.6, 37.7, 35.3, 31.3, 30.1, 28.1, 27.5, 26.9, 21.9, 17.2. Anal. calcd. for $C_{29}H_{34}O_2$: C, 84.02; H, 8.27. Found: C, 83.73; H, 8.18.



(20*S*)-3-Benzyloxy-19,26(27)-dinorchola-1,3,5(10),16,23*E*-pentaen-25-oic acid, methyl ester (i). To a solution of aldehyde **8a** (0.20 g, 0.48 mmol) in CH_2Cl_2 (15 mL),

cooled to 0 °C, was added solid (carbomethoxymethylene)triphenylphosphorane (0.187 g, 0.53 mmol). The reaction mixture was stirred at 0 °C for 4 h, and then at rt for 20 h. The reaction mixture was concentrated, and the residue was taken up in ether (20 mL). The by-product insoluable Ph_3PO was removed by filtration and the solid washed with ether. The combined ethereal extracts were washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (hexanes-EtOAc = 10:1) to give **i** as a colorless oil (0.19 g, 84%). **i:** $[\alpha]_D$ +30.6 (c 2.30, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.46-7.30 (m, 5H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.94 (dt, *J* = 15.0, 7.2 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 5.83 (d, *J* = 15.9 Hz, 1H), 5.42 (br s, 1H), 5.05 (s, 2H), 3.75 (s, 3H), 2.94-2.86 (m, 2H), 2.50-2.15 (m, 6H), 2.00-1.88 (m, 3H), 1.64-1.40 (m, 5H), 1.12 (d, *J* = 6.9 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.2, 158.5, 155.9, 147.7, 137.5, 136.7, 132.7, 128.0, 127.3, 127.0, 125.5, 121.9, 121.6, 114.4, 111.8, 70.0, 56.4, 51.7, 47.8, 44.6, 40.0, 37.7, 35.3, 31.6, 31.3, 30.2, 28.2, 26.9, 21.3, 17.1. Anal. calcd. for $C_{32}H_{38}O_3$: C, 81.66; H, 8.14. Found: C, 81.26; H, 8.05.

19-Nor-26,27-homo-cholesta-1,3,5(10),16,23E-pentaene-3,25-diol (9a). To a solution of the enoate **i** (0.275 g, 0.585 mmol) in ether (10 mL), under N_2, cooled to –78 °C, as added dropwise a solution of ethyl lithium (4.68 mL, 0.5 M in benzene/hexane, 2.34 mmol). The reaction mixture was stirred at –78 °C for 1 h, and then warmed to 0 °C and stirred for 2 h. At this time, water (5 mL) was cautiously added. The ethereal layer was separated and the aqueous layer was extracted with ether (20 mL). The combined ethereal extracts were washed with water (2 x 10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (hexanes-EtOAc = 10:1) to give **9a** as a colorless viscous oil (0.168 g, 58%). **9a:** $[\alpha]_D$ +26.6 (c 0.44, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.46-7.30 (m, 5H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.78 (br d, *J* = 8.4 Hz, 1H), 6.73 (br s, 1H), 5.57 (dt, *J* = 15.6, 6.6 Hz, 1H), 5.39 (d, *J* = 15.6 Hz, 1H), 5.36 (br s, 1H), 5.04 (s, 2H), 2.95-2.84 (m, 2H), 2.40-1.86 (m, 8H), 1.66-1.26 (m, 11H), 1.09 (d, *J* = 6.3 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 6H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.5, 155.9,



137.5, 136.8, 136.1, 132.8, 128.0, 127.3, 127.0, 126.8, 125.5, 121.0, 114.5, 111.8, 75.4, 70.0, 56.4, 47.8, 44.7, 40.3, 37.8, 35.4, 33.6, 32.4, 31.3, 30.2, 28.2, 27.0, 21.0, 17.1, 8.5. Anal. calcd. for $C_{35}H_{46}O_2$:1/3H_2O: C, 83.28; H, 9.32. Found: C, 83.30; H, 9.21.

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