An Efficient Stereoselective Synthesis of a Racemic CD-Intermediate of Vitamin D

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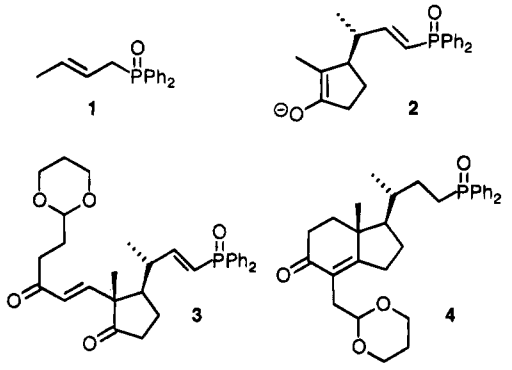
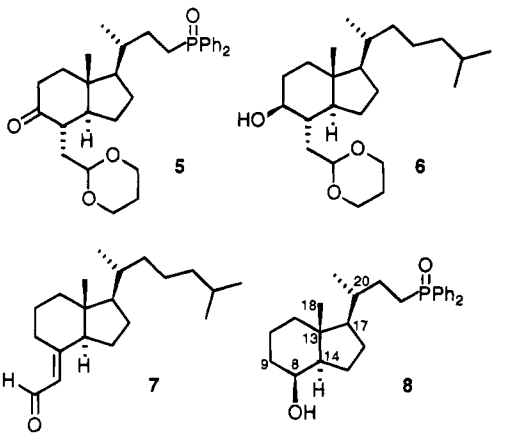
A highly efficient four-step approach to the racemic CD-intermediate **8** from the racemic hydrindenone **10** has been developed. In the key step, the hydrindenone **10** is converted stereoselectively into the (±)-bromohydrindenone **17**. Oxygen transposition from C-9 to C-8 is effected by means of conversion of **17** to the epoxide **20** and regioselective reductive ring opening of **20** with DIBALH. The resulting (±)-hydrindanol **8** was converted by the Horner–Wittig reaction with α-methacrolein into the diene **24**, hydrogenation of which provided the racemic hydrindanol **25**. This is a direct precursor of racemic Grundmann's ketone **9** and bears the alkyl side chain and the correct relative configuration at C13, C14, C17, and C20 of Vitamin D.

Introduction

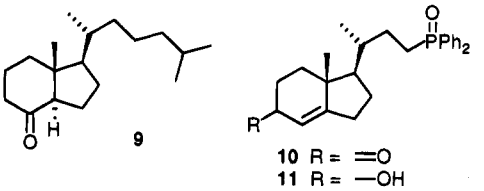
The enolate **2** generated by conjugate addition of the lithiated anion of (*E*)-but-2-enyldiphenylphosphine oxide **1** to 2-methylcyclopent-2-enone in THF reacts efficiently with β-sulfonyl or β-chlorovinyl ketones to provide adducts, such as **3**, which have been converted into racemic hydrindanone precursors, such as **4**, of Vitamin D.[1–4] Stereoselective hydrogenation of the hydrindenone **4** to



the *trans*-hydrindanone **5**, followed by reduction and side chain extension gives the racemic CD-intermediate precursor **6**. However, the projected transformation of the precursor **6** into the racemic Inhoffen aldehyde **7** was unsuccessful as hydrolysis of the acetal could not be achieved.[5] The use of electrophiles in the initial enolate trapping step bearing other more labile acetal protecting groups could not be prepared, and thus we had to turn to the hitherto unknown racemic hydrindanol **8**. This would serve as a convenient precursor of racemic Grundmann's ketone **9**, which has been used for the synthesis of vitamin D compounds.[6] The racemic hydrindenone **10** is a logical precursor to **8**.



The change of target, however, brings with it the difficult task of introducing the trans stereochemistry at the ring junction. Hydrogenation, metal–amine reduction, or dissolving metal reductions of various methyl hydrindenones unfunctionalized at C8 give predominantly the cis-isomers.[7] In addition, groups at C17 (steroid numbering), regardless of their size, have little influence on the stereochemistry of reduction in the absence of specialized reagents.[8]



Discussion

Stereoselective functionalization of deoxygenated alkene intermediates or the allylically transposed counterparts derived from the (±)-hydrindenone **10**[2,4] and (±)-

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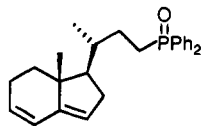
hydrindenol **11**[2,4] was initially addressed. However attempted reduction and deoxygenation with electrophilic reductants such as $LiAlH_4$ with $AlCl_3$,[9] or attempted radical deoxygenation[10,11] of the (±)-hydrindenol **11**, were unsuccessful. Although, the (±)-diene **12** arising from dehydration of the (±)-hydrindenol **11** was able to be obtained in high yields during attempted reduction, it was not suitable for further work.

Thus reduction of the double bond in the (±)-hydrindenone **10** and subsequent functionalization at C8 had now to be considered. Conjugate reduction involving the use of hydride delivered from a bulky metal complex is required to impart stereocontrol in the absence of a large group at C8. However, conjugate reduction of the (±)-hydrindenone **10** with diphenylsilane, catalytic tetrakis(triphenylphosphine)palladium(0) and a Lewis acid[12] gave a 58:42 mixture of the racemic *trans*- and *cis*-hydrindanones **13** and **14** (58%) together with unchanged **10** (25%). By way of comparison, hydrogenation of the (±)-hydrindenone **10** over palladium on charcoal under medium pressure gave a 39:61 mixture of the racemic *trans*- and *cis*-hydrindanones **13** and **14** (48%). Stereochemical identity of the individual epimers were assigned on the basis of NOE experiments on the racemic *cis*-hydrindanone **14**. Confirmation of this assignment was carried out later by HPLC and ^1H NMR correlation with the product from another reaction involving the α-epimer **13** (see below).



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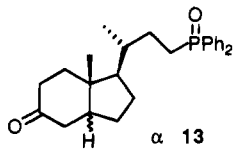


α **13**
β **14**

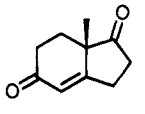
The stereoselective conjugate reduction of α,β-unsaturated ketones with DIBALH and alkylcopper reagents in the presence of HMPA[13,14] is believed to proceed via a hydride transfer from a complex formed between the alkyl copper reagent and DIBALH to the enone and simultaneous generation of a diisobutylaluminum enol. The stereoselectivity is dependent both upon the bulkiness of the alkyllithium reagent and also on the amount of the alkylcopper reagent prepared *in situ*. In applying the reaction to (±)-hydrindenone **10**, the sequence of reagent addition to generate the complex was found to be of critical importance. Thus, the conditions were modified in the following way. Methylmagnesium iodide was added to copper(I) cyanide and HMPA in THF. The resulting mixture was treated with DIBALH and then the (±)-hydrindenone **10**. The saturated ketone was

Table 1. Conjugate Reduction and Bromination of the Hydrindenone 10

reaction reagents					**17** (C14 epimers)
MeMgI	Cu(I)I	DIBALH	HMPA	Br_2	79:21
n-BuLi	Cu(I)I	DIBALH	HMPA	Br_2	94:6
n-BuLi	Cu(I)CN	DIBALH	HMPA	Br_2	98:2
n-BuLi	Cu(I)CN	DIBALH		Br_2	98:2

obtained in good yield (70%) as a 98:2 mixture of the racemic *trans*- and *cis*-hydrindanones **13** and **14**. The reagents were varied according to Table 1. The use of copper(I) cyanide in place of copper(I) iodide to generate the alkylcopper complex was of decisive advantage. The cyanide ligand remains bonded to the copper in the formation of the complex and thus contributes to the steric bulk of the reagent. In addition, the resulting copper complex is soluble in THF whereas that from the copper iodide is insoluble. HMPA is not required; the yield of product and stereoselectivity were unchanged in its absence.[15] Thus, a highly stereoselective method for the conjugate reduction of the (±)-hydrindenone **10** was now at hand.

In the case of the hydrindendione **15** a diisobutylaluminum enol **16** has been proposed as the immediate product of reduction. Nevertheless, this is reported to be unreactive toward most electrophiles,[14] except bromine and NBS. As a functional group has to be introduced



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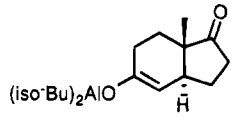

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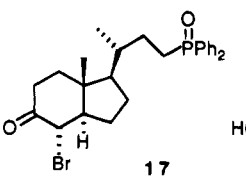
which will facilitate transposition of the C9 oxygen, we treated the (±)-hydrindenone **10** with the *n*-butyllithium–copper(I) cyanide–DIBALH system and then with bromine to give a 63% yield of the racemic *trans*-bromohydrindanone **17** as a 98:2 mixture with the corresponding cis-isomer. In general, the racemic *trans*-hydrindanone **13** resulting from protonation of the enol was also isolated in about 10% yield. The stereochemistry of **17** was confirmed by NOE measurements in C_6D_6 at 200 MHz. Irradiation of the signal due to 18-CH_3 resulted in enhancements at H15β (2.1%), H16β and H12β (1.4%), H11β (1.7%), and H8β (5.2%) only. Irradiation of the signal due to H8β resulted in enhancements at 18-CH_3 (8.0%), H15β (1.4%), and H11β (1.7%). These results indicate that H14 and the 18-CH_3 are in a trans relationship.



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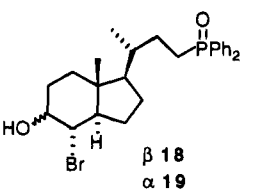

β **18**
α **19**

Reduction of the racemic *trans*-bromohydrindanone **17** to the (±)-bromohydrindanol **18** followed by epoxide formation and reductive ring opening would provide a CD precursor. This method for oxygen transposition has been developed by Daniewski and provides a most

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(15) It is to be noted that our substrate incorporates a potentially chelating phosphine oxide group.

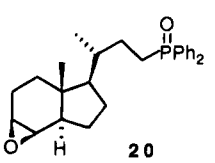
Table 2. Reduction in the Bromohydrindanone 17

reaction conditions			reaction time, h	18:19	18/19, %	17, %
DIBALH	CH_2Cl_2	−50 °C	6	60:40	85	
$LiAl(O\text{-}t\text{-}Bu)_3H$	THF	25 °C	3	75:25	73	
$LiAlH_4$	THF	25 °C	1	83:17	81	
$LiAlH_4$	THF	−20 °C	3	87:13	60	20
$NaBH_4$	EtOH	25 °C	1	complex mixture		

concise means of effecting this otherwise difficult transformation.[14,16]

The conditions used for the reduction of (±)-bromohydrindenone **17** are summarized in Table 2. The bromine substituent at C8 and the axial proton at C14 partly shield the α-face, and the β-face is also shielded by the axial protons at C8 and C11. The sterically least demanding reducing agent listed in Table 2, $LiAlH_4$, gave an epimer ratio of 83:17 of the (±)-bromohydrindanols **18** and **19**. A minor increase in the ratio of the β- to α-epimers to 87:13 was observed, at −20 °C, but now starting material **17** was also recovered. Although other reducing reagents have not been examined, higher stereoselectivity in the reduction may not be obtainable because those substituents required to exert the necessary stereochemical bias are absent. $LiAlH_4$ in THF at room temperature was adopted as the most favorable system, as the reaction goes to completion in a short time and the stereochemical outcome is acceptable. Confirmation of the stereochemistry of **18** and **19** was provided by 400 MHz ^1H NMR spectroscopic analysis. In the β-epimer, **18** H8β displayed axial couplings of 9.0 Hz and 11.5 Hz to H14 and H9α, respectively. H9α displayed axial couplings of 10.5 Hz and 9.5 Hz to H8β and H11β, respectively, and an equatorial coupling of 5.0 Hz to H11α. However, in the α-epimer **19**, H8β displayed an axial coupling of 12.5 Hz to H14 and an equatorial coupling of 2.5 Hz to H9β. Conclusive proof of the correct relative configuration at C8, C9, C13, C14, and C17 in the major (±)-bromohydrindanol **18** was obtained from the X-ray crystal structure analysis[21] as indicated in the supplementary material.

Whereas treatment of the β-epimer **18** with an excess of sodium hydride in DMF at room temperature gave the (±)-epoxide **20** in 94% yield, treatment of the α-epimer **19** gave unchanged starting material **19** and a small amount of a complex mixture of products after 6 h. The α-epimer **19** does not possess the stereochemistry required for formation of the epoxide. For larger scale reactions, the two racemic bromohydrindanol epimers **18** and **19**, which can only be separated by preparative HPLC, were submitted as a mixture to the epoxide forming reaction, and the unreacted α-epimer **19** was separated by flash chromatography after subsequent ring opening as described below.



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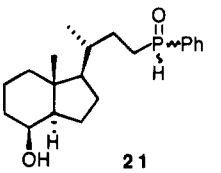
Reductive ring opening of the (±)-epoxide **20** with $LiAlH_4$ in refluxing THF was unexpectedly complicated by hydride attack at the phosphine oxide group causing loss of a phenyl group. The eventual product isolated was the (±)-phenylphosphine oxide **21**, formed as a mixture of diastereomers in 79% yield. The 400 MHz ^1H NMR spectrum contained a multiplet due to one proton at 7.47 ppm with $^2J_{HP}$ of 465 Hz. However, treatment of the (±)-epoxide **20** with 2 equiv of DIBALH in dichloromethane cleanly gave the desired (±)-hydrindanol **8** in 80% yield, without any traces of side products. The overall process embodying the above sequence represents a highly efficient approach to the racemic CD intermediate which has been obtained in seven steps from butenyldiphenylphosphine oxide **1**, in an overall yield of 18%.



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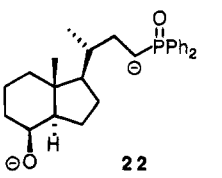
Side chain extension of the (±)-hydrindanol **8** for the synthesis of a CD intermediate was now examined with the use of Horner–Wittig methodology essentially as previously described.[2] Treatment of the dianion **22** with α-methacrolein in THF at low temperature gave the racemic β-hydroxyphosphine oxide **23** as a mixture of diastereomers. This was treated with sodium hydride in DMF at 70 °C to give a 76:24 mixture of the racemic *E*- and *Z*-diene isomers **24** in an overall yield of 51% from the (±)-hydrindanol **8** (68% based on recovery of the (±)-hydrindanol **8**) and the (±)-hydrindanol **8** (25%). The formation of the (±)-hydrindanol **8** has been discussed for a related case.[2] The mixture of (±)-dienes **24** was hydrogenated in quantitative yield to give the saturated (±)-hydrindanol **25**.[17] The conversion of the (±)-hydrindanol **25** to racemic Grundmann's ketone **9** has been previously reported.[18]



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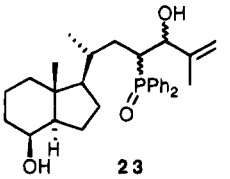

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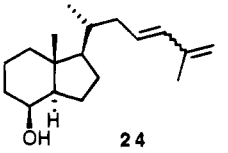

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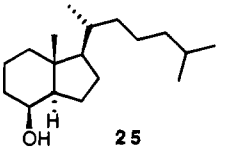

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Conclusion

The synthesis of the (±)-hydrindanol **25** in 10 steps from butenyldiphenylphosphine oxide **1** in an unoptimized overall yield of 12% represents, as far as we are aware, the most expeditious route to racemic Grundmann's ketone **9** by total synthesis to date. It also represents the realization of the prime aims of this work, namely the development of a diastereoselective synthesis of a CD intermediate precursor.

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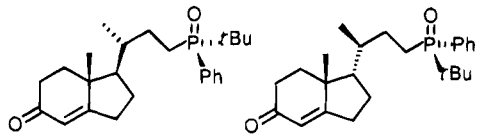

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The ultimate aim of this work is to apply the reactions described herein to the preparation of enantiomerically pure target compounds. Our group has already carried out the enantioselective synthesis of the hydrindenones **26** and **27**.[3,19] Through the use of the conjugate reduction methodology and chain extension described herein, conversion of these compounds into optically pure CD intermediates should be straightforward. However the steric and electronic differences between phenyl and other groups attached to phosphorus as used to impart enantioface selection in the intial conjugate addition–enolate trapping sequence will have important consequences for the Horner–Wittig side chain extension as well. The presence of groups, such as *tert*-butyl, will render the derived phosphine oxide anion more nucleophilic. Thus the Horner–Wittig adducts corresponding to the dilithiated alkoxides of **22** will be less prone to dissociation (*cf.* formation of **21** from dilithiated **22**), and thus yields of chain extension products will be enhanced. Results of this work will be reported shortly.

Experimental Section

The general experimental conditions,[1-4] the preparation of (*E*)-but-2-enyldiphenylphosphine oxide **1**[20] and characterization of **10** and **11** have been described elsewhere.[2,4]

Attempted Chlorination of the Hydrindanol 11. Dimethyl sulfide (54 μL, 1.5 equiv) was added to a stirred solution of NCS (98 mg, 1.5 equiv) in dichloromethane (2 mL) at 0 °C under nitrogen. The resultant yellow suspension was stirred for 30 min. The mixture was cooled to −20 °C and hydrindenol **11** (200 mg, 0.49 mmol) was added as a solid. The solution was warmed to −10 °C and stirred for 1.25 h during which time the suspended solid dissolved and the solution became clear. The reaction mixture was poured into an ice–brine solution (10 mL), and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure at about 5 °C left the crude product as a cream foam. Purification by alumina chromatography (neutral, grade IV) with dichloromethane and then 19:1 dichloromethane:methanol afforded **(1*RS*,1′*RS*,7a*RS*)-7a-methyl-1-[1′-methyl-3′-(diphenylphosphinoyl)propyl]-2,6,7,7a-tetrahydro-1*H*-indene (12)** as a white foam (172 mg, 90%). HRMS: calcd for $C_{26}H_{31}OP$ 390.2112, found 390.2113. ^{1}H NMR (400 MHz): δ 0.844 (3 H, s), 0.982 (3 H, d, J = 6.5 Hz), 1.35–1.46 (2 H, m), 1.54 (1 H, ddd, J = 12.0, 10.0, 7.5 Hz), 1.70–1.86 (4 H, m), 1.96 (1 H, ddd, J = 12.0, 4.5, 2.3 Hz), 2.05–2.29 (3 H, m), 2.29–2.37 (1 H, dddd, J = 14.0, 12.0, 12.0, 4.0 Hz), 5.296 (1H, br s, $W_{h/2}$ = 6.45 Hz), 5.684 (1 H, ddd, J = 9.0, 4.5, 2.25 Hz), 6.118 (1 H, dd, J = 9.0, 2.25 Hz), 7.43–7.53 (6 H, m), 7.69–7.78 (4 H, m). ^{13}C NMR (100 MHz): δ 15.48, 18.4, 23.6, 26.1, $^1J_{CP}$ = 72 Hz, 27.2, 34.5, $^3J_{CP}$ = 13 Hz, 35.1, 36.2, $^2J_{CP}$ = 7 Hz, 45.2, 56.3, 121.0, 123.1, 128.2, 128.3 and 128.5, $^2J_{CP}$ = 11 Hz, 130.6, 130.7, $^3J_{CP}$ = 4 Hz, 131.5, 147.8.

Hydrogenation of the hydrindenone 10. A solution of hydrindenone **10** (440 mg, 1.08 mmol) in ethyl acetate (20 mL) was shaken with 10% palladium on charcoal (45 mg) under a hydrogen atmosphere at 1000 psi for 1 week. The palladium residue was removed by filtration. Removal of the solvent under reduced pressure left a pale yellow gum. Purification by radial chromatography with 99:1 ethyl acetate:methanol afforded unreacted hydrindenone **10** (220 mg, 50%) and a 39:61 mixture of the *trans*- and *cis*-hydrindanones **13** and **14** (211 mg, 48%). The mixture was submitted to preparative HPLC with ethyl acetate (Whatman Partisil 10 M20 column, 13.5 mL/min, 900 psi) which gave firstly **(1*RS*,1′*RS*,3a*SR*,7a*SR*)-7a-methyl-1-[1′-methyl-3′-(diphenylphosphinoyl)propyl]-octahydro-5*H*-indan-5-one (13)** as a colorless viscous gum (t_R 99 min) which crystallized after *ca.* 4 months on standing as a grainy white solid, mp 109–110.5 °C. Anal. Calcd for $C_{26}H_{33}O_2P$: C, 76.44; H, 8.14. Found: C, 76.17; H, 8.11%. ^{1}H NMR (400 MHz): δ 0.873 (3 H, s), 0.964 (3 H, d, J = 6.50 Hz), 1.13–1.44 (4 H, m), 1.47–1.61 (3 H, m), 1.72–1.90 (3 H, m), 2.03–2.22 (3 H, m), 2.22–2.44 (4 H, m), 7.44–7.56 (6 H, m), 7.70–7.78 (4 H, m). ^{13}C NMR (100 MHz): δ 10.5, 16.1, 26.7, $^1J_{CP}$ = 54 Hz, 25.7, 26.2, 27.0, 28.7, 36.2, $^3J_{CP}$ = 12 Hz, 37.5, $^2J_{CP}$ = 15 Hz, 41.6, 42.7, 49.9, 54.0, 126.5 and 126.6, $^2J_{CP}$ = 11 Hz, 130.7 and 130.8, $^3J_{CP}$ = 7 Hz, 131.6, $^4J_{CP}$ <1.0 Hz, 211.7.

The next fraction consisted of **(1*RS*,1′*RS*,3a*RS*,7a*SR*)-7a-methyl-1-[1′-methyl- 3′-(diphenylphosphinoyl)propyl]-octahydro-5*H*-indan-5-one (14)**, a colorless viscous gum (t_R 114 min). Anal. Calcd for $C_{26}H_{33}O_2P$: C, 76.44; H, 8.14. Found: C, 76.40; H, 8.21%. ^{1}H NMR (400 MHz): δ 0.925 (3 H, s), 0.983 (3 H, d, J = 6.50 Hz), 1.036 (1 H, dddd, J = 10.5, 10.5, 7.0, 5.0 Hz), 1.12–1.29 (1 H, m), 1.35–1.53 (2 H, m), 1.618 (1 H, dddq, J = 11.5, 6.5, 6.5, 2.5 Hz), 1.71–1.90 (6 H, m), 2.09–2.40 (6 H, m), 7.44–7.56 (6 H, m), 7.72–7.79 (4 H, m). Preirradiation of the signal at δ 0.925 (7a-CH_3) resulted in enhancements at δ 1.12–1.29 (H2β) of 1.0%, at δ 1.35–1.53 (H1, H2′) of 0.6%, at δ 1.618 (H1′) of 3.0%, at δ 1.71–1.90 (H3a, H7β) of 4.5%, and at δ 2.09–2.40 (H4β, H6β) of 0.7%. ^{13}C NMR (100 MHz): δ 16.7, 23.1, 26.4, $^1J_{CP}$ = 68 Hz, 27.2, $^2J_{CP}$ = 4 Hz, 28.6, 30.2, 34.5, $^3J_{CP}$ = 11 Hz, 34.8, 35.8, 41.8, 44.0, 48.7, 52.3, 126.5 and 126.6, $^2J_{CP}$ = 11.4 Hz, 130.6 and 130.7, $^3J_{CP}$ = 8.5 Hz, 131.59 and 131.61, $^4J_{CP}$ = 2 Hz, 213.6, C5.

Conjugate Reduction of the Hydrindenone 10. (a) With Diphenylsilane. Diphenylsilane (0.32 mL, 3.5 equiv), zinc chloride (268 mg, 4.0 equiv), and tetrakis(triphenylphosphine)palladium(0) (51 mg, 0.09 equiv) were added to a stirred solution of the hydrindenone **10** (200 mg, 0.49 mmol) in chloroform (6 mL) at room temperature. The dark brown mixture was monitored by TLC until no further reaction was observed (ca. 9.5 h). The mixture was then diluted with chloroform (20 mL), and water (50 mL) was added. The water layer was extracted with chloroform (2 × 20 mL), and the combined chloroform layers were washed with brine (100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a brown oily residue. Purification by column chromatography with 24:1 ethyl acetate:methanol gave the mixture of products as a gum. Subsequent analysis by analytical HPLC with ethyl acetate (Whatman Partisil 5 column, 1.5 mL/min, 1300 psi) indicated the presence of the following products in order of elution a 58:42 mixture of the hydrindanones **13** and **14** (116 mg, 58%) and the starting hydrindenone (50 mg, 25%) **10**.

(b) With MeMgI–Cu^{I}CN–DIBALH. Methyl iodide (0.68 mL, 10.9 mmol) was added to magnesium turnings (0.33 g, 13.7 mg-atom, 1.5 equiv) in dry ether (20 mL) under nitrogen. The Grignard reagent was added dropwise over 5 min to a stirred suspension of copper(I) cyanide (900 mg, 1.2 equiv) in dry ether (10 mL) at −20 °C under nitrogen. The yellow suspension was stirred for 20 min and then an aliquot (1.35 mL, 0.5 mmol) was transferred to THF (10 mL) at −20 °C under nitrogen and cooled to −50 °C. DIBALH (0.66 mL, 1 M, 1.0 mmol) and HMPA (0.5 mL) were added dropwise so as to maintain the temperature at −50 °C. The green-light brown solution was stirred at −50 °C for 30 min, and then the hydrindenone **10** (100 mg 0.246 mmol) in THF (2 mL) was added dropwise over 10 min. After stirring for 1.5 h the reaction mixture was quenched with hydrochloric acid (1 M, 10 mL). Ethyl acetate (100 mL) was added, and the resultant mixture was filtered. The aqueous layer was separated and

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(21) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2, 1EZ, UK.

further extracted with ethyl acetate (100 mL, 2 × 50 mL). The combined organic layers were washed with water (2 × 100 mL) and brine (100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a toffee-like gum. Purification by alumina chromatography (neutral, Grade IV) with ethyl acetate afforded the hydrindanone **13** (70 mg, 70%) as a white foam.

(c) With BuLi–Cu^ICN–DIBALH. Butyllithium (4.28 mL, 2.3 M, 2.0 equiv) was added dropwise over 5 min to a stirred suspension of copper(I) cyanide (900 mg, 2.04 equiv) in THF (50 mL) at −20 °C under nitrogen. The suspended solid dissolved to give a yellow mixture which became brown in color. The solution was stirred for 30 min at −20 °C and then cooled to −50 °C. DIBALH (19.6 mL, 1 M, 4.0 equiv) was added dropwise so as to maintain the temperature at −50 °C. The dark brown solution was stirred at −50 °C for 1 h, and then the hydrindenone **10** (2.0 g, 4.9 mmol) in THF (5 mL) was added dropwise over 10 min. After stirring for 2.5 h the solution was warmed to −20 °C and bromine (5 mL) was added. The dark green solution was stirred at −20 °C for 30 min, and then the reaction was quenched with water (50 mL). Ethyl acetate (100 mL) was added, and the resultant mixture was filtered. The aqueous layer was separated and further extracted with ethyl acetate (100 mL, 2 × 50 mL). The combined organic layers were washed with aqueous sodium metabisulfite (saturated, 100 mL), water (2 × 100 mL), and brine (100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a toffee-like gum. Purification by alumina chromatography (neutral, Grade IV) with ethyl acetate afforded the bromohydrindanone **17** (1.51 g, 63%) and the *trans*-hydrindanone **13** (0.21 g, 9%) as a white foam. An analytical sample of **(1*RS*,1′*RS*,3a*RS*,4*SR*,7a*RS*)-4-bromo-7a-methyl-1-[1′-methyl-3′-(diphenylphosphinoyl)propyl]-octahydro-5*H*-indan-5-one (17)** was obtained by using preparative HPLC with ethyl acetate (Whatman Partisil 10 M20 column, 13.5 mL/min, 900 psi) as an inseparable 98:2 mixture of trans- and cis-isomers and as a white foam (t_R 73 min). Anal. Calcd for $C_{26}H_{32}BrO_2P$: C, 64.07; H, 6.62. Found: C, 63.78; H, 6.93%. ^1H NMR (200 MHz) (C_6D_6): δ 0.363 (3 H, s), 0.610 (3 H, d, J = 6.5 Hz), 0.54–0.79 (1 H, m), 0.85–1.08 (3 H, m), 1.09–1.36 (2 H, m), 1.42–1.78 (5 H, m), 1.80–2.09 (3 H, m), 2.240 (1 H, ddd, J = 15.0, 5.2, 2.5 Hz,), 4.075 (1 H, d, J = 13.0 Hz), 7.00–7.25 (6 H, m), 7.60–7.83 (4 H, m). Preirradiation of the signal at δ 0.363 (7a-CH_3) resulted in enhancements at δ 0.85–1.08 (H2β, H7β) of 1.4%, at δ 1.09–1.36 (H3β, H1′) of 2.1%, at δ 1.80–2.09 (H6β) of 1.7%, and at δ 4.075 (H4β) of 5.2%. Preirradiation of the signal at δ 4.075 (H4β) resulted in enhancements at δ 0.363 (7a-CH_3) of 8.0%, at δ 1.09–1.36 (H3β) of 1.4%, and at δ 1.80–2.09 (H6β) of 1.7%. ^{13}C NMR (50 MHz): δ 10.8, 17.7, 25.7, $^1J_{CP}$ = 72 Hz, 26.4, 26.7, 27.4, 33.4, 35.5, $^3J_{CP}$ = 14 Hz, 36.85, $^2J_{CP}$ = 5 Hz, 44.9, 54.8, 58.5, 58.6, 129.0, $^2J_{CP}$ = 11.9 Hz, 130.9 and 131.1, $^3J_{CP}$ = 4.3 Hz, 132.1, $^4J_{CP}$ < 1.0 Hz, 202.5, C5.

Reduction of Bromohydrindanone 17. Powdered $LiAlH_4$ (140 mg, 1.5 equiv) was added in several portions over 15 min to a stirred solution of the bromohydrindanone **17** (1.176 g, 2.41 mmol) in THF (30 mL) at room temperature under nitrogen. A white precipitate formed, and after 30 min a gum formed in the solution. The heterogeneous mixture was stirred for a further 1 h and then quenched cautiously with aqueous ammonium chloride (saturated, 50 mL). The suspension was extracted with ethyl acetate (4 × 50 mL), and the aqueous layer was filtered and further extracted with ethyl acetate (50 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a brittle gum. Purification by alumina chromatography (neutral, Grade IV) with ethyl acetate afforded an 83:17 mixture of the *trans*- and *cis*-bromohydrindanols **18** and **19** (0.955 g, 81%) as a brittle white foam. Analytical samples of each isomer were obtained by preparative HPLC with ethyl acetate (Whatman Partisil 10 M20 column, 13.5 mL/min, 900 psi) which gave firstly **(1*RS*,1′*RS*,3a*RS*,4*SR*,5*RS*,7a*RS*)-4-bromo-7a-methyl-1-[1′-methyl-3′-(diphenylphosphinoyl)propyl]octahydro-1*H*-indan-5-ol (19)** (t_R 69 min) which crystallized from ethyl acetate:ether as fine needles mp 81–83 °C. Anal. Calcd for $C_{26}H_{34}BrO_2P$: C, 63.81; H, 7.00. Found: C, 63.86; H, 7.19%. ^1H NMR (400 MHz): δ 0.689 (3 H, s), 0.929 (3 H, d, J = 6.5 Hz), 1.09–1.43 (4 H, m), 1.515 (1 H, dddd, J = 10.5, 8.0, 6.5, 2.5 Hz), 1.52–1.83 (6 H, m), 1.83–2.01 (2 H, m), 2.07–2.19 (2 H, m), 2.288 (1 H, dddd, J = 15.0, 12.5, 12.0, 4.0 Hz), 4.020 (1 H, ddd, J = 4.5, 2.5, <1.0 Hz), 4.278 (1 H, dd, J = 12.5, 2.5 Hz), 7.44–7.56 (6 H, m), 7.69–7.78 (4 H, m). ^{13}C NMR (50 MHz): δ 10.8, 18.0, 25.9, $^1J_{CP}$ = 72 Hz, 26.9, $^2J_{CP}$ = 3 Hz, 26.2, 26.8, 28.7, 33.2, 36.0, $^3J_{CP}$ = 13 Hz, 46.2, 49.3, 55.6, 63.2, 69.8, 128.6, $^2J_{CP}$ = 11.2 Hz, 130.7 and 130.8, $^3J_{CP}$ = 3.2 Hz, 131.6 and 131.6, $^4J_{CP}$ = 4 Hz.

The next fraction consisted of **(1*RS*,1′*RS*,3a*RS*,4*SR*,5*SR*,7a*RS*)-4-bromo-7a-methyl-1-[1′-methyl-3′-(diphenylphosphinoyl)propyl]octahydro-1*H*-indan-5-ol (18)** (t_R 75 min) which crystallized from ethyl acetate:ether as small white rosettes of needles, mp 103.5–105 °C. Anal. Calcd for $C_{26}H_{34}BrO_2P$: C, 63.81; H, 7.00. Found: C, 63.84; H, 7.12%. ^1H NMR (400 MHz): δ 0.725 (3 H, s), 0.923 (3 H, d, J = 6.3 Hz), 1.19–1.42 (5 H, m), 1.45–1.55 (1 H, m), 1.61–1.84 (5 H, m), 1.86–1.99 (2 H, m), 2.115 (1 H, dddd, J = 15.0, 14.0, 13.0, 4.0 Hz), 2.290 (1 H, dddd, J = 15.0, 14.0, 13.0, 4.0), 2.75 (1 H, br s, $W_{h/2}$ = 74 Hz), 3.625 (1 H, ddd, J = 10.5, 9.0, 5.0 Hz), 3.960 (1 H, dd, J = 11.5, 9.0 Hz), 7.43–7.56 (6 H, m), 7.68–7.78 (4 H, m). ^{13}C NMR (50 MHz): δ 11.5, 16.0, 26.1, $^1J_{CP}$ = 72 Hz, 26.8, $^2J_{CP}$ = 4 Hz, 26.1, 27.4, 30.2, 38.5, 36.1, $^3J_{CP}$ = 13 Hz, 45.7, 55.4, 55.7, 64.1, 76.6, 128.6, $^2J_{CP}$ = 13 Hz, 130.6 and 130.8, $^3J_{CP}$ = 3.5 Hz, 131.6, $^4J_{CP}$ < 1.0 Hz.

Conversion of Bromohydrindan-5-ol 18 to the Epoxide 20. Sodium hydride (190 mg, 3.9 equiv, 80% dispersion in oil prewashed in hexanes) suspended in DMF (1 mL) was added in portions to a stirred solution of the bromohydrindanol **18** (800 mg, 1.64 mmol) in DMF (30 mL) under nitrogen at room temperature. The reaction mixture was stirred for 2.5 h during which time it became dark brown in color. The mixture was cautiously quenched with water (50 mL) and the aqueous layer extracted with ethyl acetate (100 mL, 2 × 50 mL). The combined organic layers were washed with aqueous sodium metabisulfite (saturated, 100 mL), water (100 mL), and brine (100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a cream foam (688 mg). Subsequent analysis by analytical HPLC with ethyl acetate (Whatman Partisil 5 column, 1.5 mL/min, 1000 psi) indicated that the epoxide **20** had formed in 94% yield. Conditions for chromatographic purification which did not incur substantial loss of material were unable to be found and therefore the crude mixture was used without purification in the next step. An analytical sample was obtained by purification of the crude product by alumina chromatography (neutral, Grade IV) with 7:3 ethyl acetate:light petroleum, and then preparative HPLC with ethyl acetate (Whatman Partisil 10 M20 column, 13.5 mL/min, 900 psi) which gave **(1*RS*,1′*RS*,3a*RS*,4*RS*,5*SR*,7a*RS*)-7a-methyl-1-[1′-methyl-3′-(diphenylphosphinoyl)propyl]-4,5-epoxyoctahydro-1*H*-indane (20)** as a white foam (t_R 71 min). Anal. Calcd for $C_{26}H_{33}O_2P$: C, 76.44; H, 8.14. Found: C, 76.34; H, 8.29%. ^1H NMR (400 MHz): δ 0.809 (3 H, s), 0.888 (3 H, d, J = 7.0 Hz), 0.86–1.78 (3 H, m), 1.27–1.39 (1 H, m), 1.39–1.48 (1 H, m), 1.52–1.62 (2 H, m), 1.62–1.80 (3 H, m), 1.848 (1 H, ddd, J = 13.0, 6.5, 1.0 Hz), 1.908 (1 H, dddd, J = 15.0, 7.0, 4.5, <1.0 Hz), 2.023 (1 H, ddd, J = 12.5, 7.0, <1.0 Hz), 2.103 (1 H, dddd, J = 15.0, 12.0, 12.0, 4.5 Hz), 2.303 (1 H, dddd, J = 14.5, 12.5, 12.0, 4.5 Hz), 3.065 (1 H, ddd, J = 5.0, 4.5 <1.0 Hz), 3.168 (1H, dd, J = 4.5, <1.0 Hz), 7.44–7.55 (6 H, m), 7.70–7.77 (4 H, m). ^{13}C NMR (50 MHz): δ 12.4, 18.0, 21.6, 23.4, 27.1, 35.7, 26.2, $^1J_{CP}$ = 73 Hz, 26.9, $^2J_{CP}$ = 4 Hz, 36.0, $^3J_{CP}$ = 13.8 Hz, 42.0, 48.6, 50.2, 54.97, 55.07, 128.6, $^2J_{CP}$ = 12 Hz, 130.7 and 130.75, 131.6 and 131.7, $^4J_{CP}$ = 2 Hz, 132.8 and 132.9, $^1J_{CP}$ = 96 Hz.

Ring Opening of the Epoxide 20. (i) With $LiAlH_4$. Powdered $LiAlH_4$ (20 mg, 2.15 equiv) was added to a solution of the epoxide **20** (100 mg, 0.24 mmol) in THF (10 mL) under nitrogen at room temperature. The suspension was refluxed for 1 h and then quenched with aqueous ammonium chloride (saturated, 10 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and then filtered. The aqueous layer was further extracted with ethyl acetate (20 mL), and the combined organic layers were washed with water (50 mL) and brine (50 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a yellow gum which possessed a

strong odor. Purification by column chromatography with ethyl acetate afforded a 1:1 mixture of isomers, diastereomeric at phosphorus, of the phenylphosphine oxide **21** (66 mg, 79%) as a gum. An analytical sample of the 1:1 mixture of diastereomers of **(1*RS*,1′*RS*,3a*RS*,4*SR*,7a*RS*)-7a-methyl-1-[1′-methyl-3′-(phenylphosphinoyl)propyl]octahydro-1*H*-indan-4-ol (21)** was obtained by preparative HPLC with ethyl acetate (Whatman Partisil 10 M20 column, 13.5 mL/min, 900 psi) as a colorless gum (t_R 147 min). Anal. Calcd for $C_{20}H_{31}O_2P$: C, 71.83; H, 9.34. Found: C, 71.56; H, 9.69%. ^{1}H NMR (400 MHz): δ 0.88−0.91 (6 H, m), 0.98−1.62, (10 H, m), 1.63−2.11 (8 H, m), 4.03−4.07 (1 H, dm, $J_{4,OH}$ = 2.5 Hz), 7.48−7.60 (3 H, m), 7.65−7.73 (2 H, m), 6.85−8.10 (1 H, dm, J = 464 Hz). ^{13}C NMR (50 MHz): δ 13.5, 17.4, 17.93 and 17.98, 22.4, 26.7, and 26.8, $^1J_{CP}$ = 68 Hz, 26.9, 27.0, $^2J_{CP}$ = 3 Hz, 33.5, 35.7, $^3J_{CP}$ = 14.6 Hz, 40.3, 41.8, 52.5, 55.8, 69.2, 128.8, $^2J_{CP}$ = 12.2 Hz, 129.8, $^3J_{CP}$ = 11 Hz, 132.4, $^4J_{CP}$ = 3 Hz.

(ii) With DIBALH. DIBALH (2.01 mL, 1 M, 2.5 equiv) was added dropwise over 10 min to a stirred solution of the epoxide **20** (337 mg, 0.83 mmol) in refluxing dichloromethane (30 mL) under nitrogen. The solution was refluxed for a further 1.25 h, and then water (50 mL) was added. The mixture was filtered and the aqueous layer extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a viscous yellow gum. Purification by column chromatography with ethyl acetate afforded the alcohol **8** (270 mg, 80%) as a brittle gum. An analytical sample of **(1*RS*,1′*RS*,3a*RS*,4*SR*,7a*RS*)-7a-methyl-1-[1′-methyl-3′-(diphenylphosphinoyl)propyl]-octahydro-1*H*-indan-4-ol (8)** was obtained by preparative HPLC with ethyl acetate (Whatman Partisil 10 M20 column, 13.5 mL/min, 900 psi) as a brittle white foam (t_R 105 min). Anal. Calcd for $C_{26}H_{35}O_2P$: C, 76.07; H, 8.59. Found: C, 76.17; H, 8.63%. ^{1}H NMR (400 MHz): δ 0.893 (3 H, s), 0.924 (3 H, d, J = 6.5 Hz), 1.00−1.22 (3 H, m), 1.24−1.57 (7 H, m), 1.67−1.84 (4 H, m), 1.950 (1 H, dddd, J = 13.0, 4.0, 2.0, <1.0 Hz), 2.1 (br s, $W_{h/2}$ = ca. 80 Hz), 2.115 (1 H, dddd, J = 14.0, 12.5, 12.0, 4.5 Hz), 2.358 (1 H, dddd, J = 14.0, 13.0, 12.0, 4.5 Hz), 4.04−4.07 (1 H, m), 7.44−7.55 (6 H, m), 7.70−7.78 (4 H, m). ^{13}C NMR (50 MHz): δ 13.5, 17.4, 18.0, 22.4, 26.8, 26.1, $^1J_{CP}$ = 72 Hz, 26.9, $^2J_{CP}$ = 4 Hz, 33.5, 35.7, $^3J_{CP}$ = 13.6 Hz, 40.3, 41.8, 52.5, 55.7, 69.2, 128.6, $^2J_{CP}$ = 11.5 Hz, 130.7 and 130.8, $^3J_{CP}$ = 8 Hz, 131.6, $^4J_{CP}$ = 2.8 Hz, 133.0, $^1J_{CP}$ = 97 Hz.

Note on Larger Scale Preparations. When the hydrindanol **8** was prepared from the bromohydrindenone **10** on larger scales (ca. 2−3 g), some modifications in the purification procedures were used. Separation of the β-bromohydrindanol **18** from the α-bromohydrindanol **19** was not carried out. That is, the bromohydrindanone **17** was reduced with lithium aluminum hydride and the resulting mixture of bromohydrindanols **18** and **19** was separated from the side-product by column chromatography (ethyl acetate). The bromohydrindanol mixture **18** and **19** was treated with sodium hydride but only the β-bromohydrindanol **18** formed the epoxide **20** which cochromatographs on HPLC with the unreacted α-bromohydrindanol **19**. This mixture was treated with DIBALH to obtain the hydrindanol **8** which was readily separated by column chromatography from the α-bromohydrindanol **19**.

Side Chain Extension of the Hydrindanol 8 with Methacrolein. Butyllithium (2.2 M) was added dropwise to a stirred solution of the alcohol **8** (100 mg, 0.24 mmol) in THF (5 mL) at −15 °C under nitrogen, until the first permanent orange color of the dianion persisted. During the addition of the first equivalent of base, the dianion quickly equilibrated to the colorless alkoxide anion and a fine white precipitate formed. More butyllithium (0.22 mL, 2.2 M, 2.0 equiv) was added to effect complete deprotonation, and the solution was stirred at −15 °C for 20 min and then cooled to −90 °C. Methacrolein (66 mL, 3.3 equiv) was added dropwise and the solution became pale yellow in color. The reaction mixture was allowed to warm to 0 °C over 2 h during which time it became colorless. Aqueous ammonium chloride (saturated, 20 mL) was added and the mixture was diluted with ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were washed with water (2 × 50 mL) and brine (50 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure left the α-hydroxy phosphine oxide **23** as a mixture of diastereomers at C3′ and C4′ and as a viscous yellow oil (115 mg). Minor nonpolar impurities were removed by column chromatography with 99:1 ethyl acetate:methanol to afford (1*RS*,1′*RS*,3a*RS*,3′*RS* and 3′*SR*,4*SR*,4′*RS* and 4′*SR*,7a*RS*)-7a-methyl-1-[(4′-hydroxy-5′,1′-dimethyl-3′-diphenylphosphinoyl)hex-5′-enyl]octahydro-1*H*-indan-4-ol (**23**) as a pale yellow gum (92 mg, 80%). The α-hydroxy phosphine oxide mixture was used without further purification.

Sodium hydride (16 mg, 3.5 equiv, 80% dispersion in oil prewashed with hexanes) suspended in DMF (1 mL) was slowly added to the α-hydroxy phosphine oxide mixture **23** (92 mg, 0.19 mmol) dissolved in DMF (3 mL) at room temperature under nitrogen. The solution was refluxed for 1 h during which time it became orange brown in color. Water (20 mL) was added cautiously and the mixture was diluted with ethyl acetate (20 mL) and filtered. The aqueous layer was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were washed with water (2 × 50 mL) and brine (50 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a yellow oil. Purification by column chromatography with ethyl acetate afforded the diene **24** as a colorless viscous oil (32 mg, 51% from the α-hydroxy phosphine oxide **23** or 68% based on recovered hydrindanol **8**) and the phosphine oxide hydrindanol **8** as a brittle gum (25 mg, 25% overall recovery). Further purification by radial chromatography with 70:30 light petroleum:ethyl acetate gave **(1*RS*,1′*RS*,3*E* and 3*Z*,3a*RS*,4*SR*,7a*RS*)-7a-methyl-1-(5′,1′-dimethylhexa-3′,5′-dienyl)octahydro-1*H*-indan-4-ol (24)** as a 71:29 mixture of (*E*)- and (*Z*)-isomers as a very unstable colorless viscous oil. ^{1}H NMR (400 MHz) (* denotes the *Z* isomer): δ 0.863*, 0.908 (3 H, d, J = 6.5 Hz), 0.916*, 0.945 (3 H, s), 0.87−0.94 (1 H, m), 1.04−1.19 (2 H, m), 1.21−1.64 (10 H, m), 1.75−2.13 (2 H, m), 1.835 (3 H, br s, $W_{h/2}$ = *ca.* 3.0 Hz), 1.878* (3 H, br s, $W_{h/2}$ *ca.* 3.6 Hz), 2.20−2.27, 2.27−2.35* (1 H, dm, J = 13.0 Hz), 4.078 (1 H, br m, $W_{h/2}$ = 8.0 Hz), 4.825* (1 H, br s, $W_{h/2}$ = 5.0 Hz), 4.858 (2 H, br s, $W_{h/2}$ = 3.0 Hz), 4.930* (1 H, br s, $W_{h/2}$ = 5.0 Hz), 5.405* (1H, ddd, J = 11.2, 9.0, 6.5 Hz), 5.625 (1 H, ddd, J = 15.5, 9.0, 6.5 Hz), 5.883* (1 H, br d, J = 11.2 Hz), 6.123 (1 H, br d, J = 15.5 Hz). ^{13}C NMR (50 MHz): δ 13.2, 13.7*, 17.1, 18.3, 18.4*, 22.9, 23.2*, 22.2, 25.8, 26.6*, 26.9, 33.3, 35.6, 35.9*, 40.0, 41.4, 41.7*, 52.4, 56.2, 56.4*, 69.4, 114.3, 115.4*, 126.6*, 129.6, 131.0*, 133.5, 142.5.

Hydrogenation of the diene 24. The diene **24** (20 mg, 76 mmol) in ethyl acetate (5 mL) containing 10% palladium on charcoal was stirred vigorously under a hydrogen atmosphere (1 atm) for 1 h. The catalyst was removed by filtration through Celite, and concentration of the filtrate under reduced pressure left the saturated product **25** as a viscous oil. Purification by column chromatography with 70:30 light petroleum:ethyl acetate afforded (1*RS*,1′*RS*,3a*RS*,4*SR*,7a*RS*)-7a-methyl-1-(5′,1′-dimethylhexanyl)octahydro-1*H*-indan-4-ol (**25**)[17] (20 mg, 99%) as a colorless viscous oil. ^{1}H NMR (400 MHz): δ 0.860 (3 H, d, J = 6.5 Hz), 0.864 (3 H, d, J = 6.5 Hz), 0.890 (3 H, d, J = 6.5 Hz), 0.929 (3 H, s), 0.81−1.19 (5 H, m), 1.22−1.62 (12 H, m), 1.76−1.90 (3 H, m), 1.96−2.03 (1 H, dddd, J = 13.0, 3.0, 3.0, <1.0 Hz), 4.05−4.09 (1 H, dm, J = 2.0 Hz). ^{13}C NMR (50 MHz): δ 13.5, 17.4, 18.6, 22.52, 22.55, 22.6, 23.8, 27.2, 28.0, 33.6, 35.3, 36.0, 39.5, 40.4, 41.6, 52.6, 56.7, 69.5.

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Supplementary Material Available: Infrared, ^{1}H NMR, ^{13}C NMR, and mass spectral data for compounds **8**, **12**−**14**, **17**−**21**, and **25**, and crystallographic data for compound **18**, (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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