Enantioselective Construction of Angular Triquinanes through an Asymmetric Intramolecular Pauson−Khand Reaction. Synthesis of (+)-15-Nor-pentalenene

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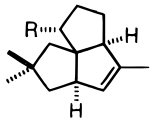
Introduction

(+)-Pentalenene (**1a**), an angularly fused triquinane isolated in 1980[1] from *Streptomyces griseochromogenes*, has been the touchstone for different methodologies aimed at the regio- and stereocontrolled construction of cyclopentanoid systems.[2]



1a R = CH_3

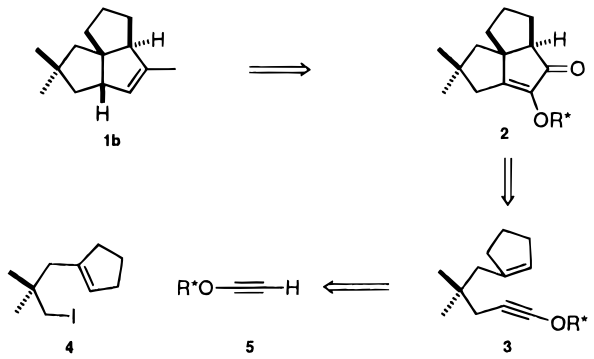
1b R = H

Among these methods, the Pauson−Khand reaction has gained a central role in recent years, due to its broad applicability and excellent overall performance.[3] Both the inter-[4] and the intramolecular[5] Pauson−Khand reactions have been employed for the stereocontrolled synthesis of angularly fused triquinanes in racemic form and, in fact, Schore and co-workers have constructed the triquinane system of racemic **1a** employing a diastereoselective intramolecular Pauson−Khand reaction,[2a] while the only enantioselective synthesis of **1a** so far reported, due to Hua, relied on the kinetic resolution of 7,7-dimethylbicyclo[3.3.0]oct-1-en-3-one prepared, in turn, by an intramolecular Pauson−Khand reaction.[6]

In recent years, we have been involved in the development of reliable enantioselective versions of this powerful reaction,[7] and we have applied them to the synthesis of natural products such as (+)-hirsutene,[7a] (+)-brefeldin A,[8] and (+)-β-cuparenone.[9] We have also quite recently shown that the intramolecular Pauson−Khand reaction of 1-(5-alkoxypent-4-ynyl)cyclopentenes derived from chiral alcohols takes place with high levels of diastereoselectivity, affording in a single step the angular triquinane skeleton with optimal control of the stereochemistry of the newly created stereogenic centers.[10]

As a continuation of our studies in this field, we wish to report now on the application of this strategy to the enantioselective synthesis of angular triquinanes, as illustrated by the preparation of (+)-15-nor-pentalenene (**1b**), an advanced model of the natural product (**1a**), in enantiomerically pure form.

Scheme 1



Results and Discussion

Our retrosynthetic analysis, shown in Scheme 1, presents as the key feature the stereocontrolled construction of the angular triquinane system from a monocyclic precursor (**3**) which, in turn, offers good possibilities for ready assembly from the primary iodide **4** and a chiral alkoxyacetylene **5**. In contrast to previous diastereoselective approaches to the angularly fused triquinane skeleton, the present one is based on a (except for the chiral auxiliary) prochiral substrate. In this way, neither kinetic resolutions[6] nor mismatching of stereogenic centers can occur along the synthetic sequence, with the derived advantage of a quantitative maximum theoretical yield.

For the preparation of iodide **4**, 1-(bromomethyl)cyclopentene[11] was first treated with the lithium enolate of ethyl isobutyrate in THF solution. The resulting ester, obtained in 88% yield, was reduced to the corresponding primary alcohol with lithium aluminum hydride in THF solution (82% yield), and this alcohol was converted into the target iodide by treatment with methyltriphenoxyphosphonium iodide in DMF solution at 80 °C (88% yield). By this sequence, the preparation of multigram amounts of iodide **4** can be easily achieved from readily available precursors in 63% overall yield (Scheme 2).

The alkoxyacetylenes **5** required for the coupling with **4** were prepared through a one-pot process from the corresponding enantiomerically pure alcohols following a well established protocol,[12] and conditions for the assembly of the cyclization precursor **3** were evaluated

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1997.

(1) Seto, H.; Yonehara, H. *J. Antibiot.* **1980**, *33*, 92−93.

(2) For recent work see: (a) Rowley, E. G.; Schore, N. E., *J. Org. Chem.* **1992**, *57*, 6853−6861, (b) Hatanaka, M.; Ueno, F.; Ueda, I. *Tetrahedron Lett.* **1996**, *37*, 89−90, and references therein.

(3) For recent reviews on the Pauson−Khand reaction, see (a) Schore, N. E. *Org. React.* **1991**, *40*, 1−90. (b) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; vol. 5, pp 1037−1064.

(4) Montaña, A.; Moyano, A.; Pericàs, M. A.; Serratosa, F. *Tetrahedron* **1985**, *41*, 5995−6003.

(5) Knudsen, M. J.; Schore, N. E. *J. Org. Chem.* **1984**, *49*, 5025−5026.

(6) Hua, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 3835−3837.

(7) (a) Castro, J.; Sörensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388−9389. (b) Poch, M.; Valentí, E.; Moyano, A.; Pericàs, M. A.; Riera, A.; Castro, J.; DeNicola, A.; Greene, A. E. *Tetrahedron Lett.* **1990**, *31*, 7505−7508. (c) Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Greene, A. E.; Alvarez-Larena, A.; Piniella, J. F. *J. Organomet. Chem.* **1992**, *433*, 305−310. (d) Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Bernardes, V.; Greene, A. E.; Alvarez-Larena, A.; Piniella, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 2153−2154. (e) Bernardes, V.; Verdaguer, X.; Kardos, N.; Riera, A.; Moyano, A.; Pericàs, M. A.; Greene, A. E., *Tetrahedron Lett.* **1994**, *35*, 575−578.

(8) Bernardes, V.; Kann, N.; Riera, A.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 6670−6671.

(9) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A.; Greene, A. E.; Alvarez-Larena, A., Piniella, J. F. *J. Org. Chem.* **1996**, *61*, 9016−9020.

(10) Tormo, J.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1996**, *52*, 14021−14040.

(11) Pal, P. R,; Skinner, C. G.; Dennis, R. L.; Shive, W. *J. Am. Chem. Soc.* **1956**, *78*, 5116−5118.

(12) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919−2922.

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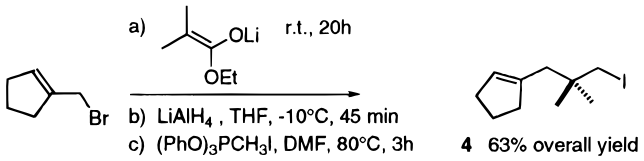
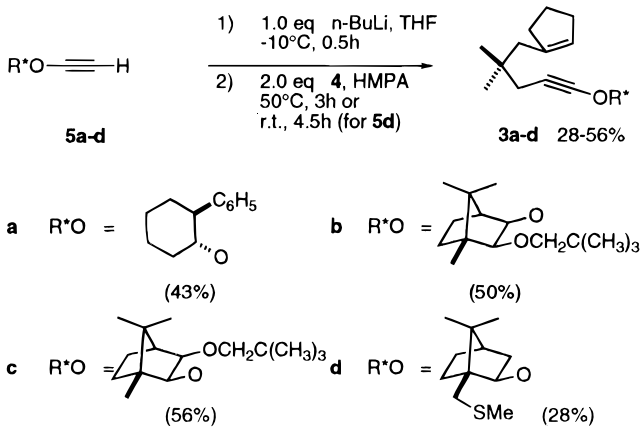
Scheme 2



Scheme 3



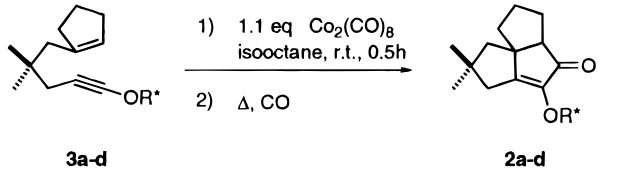
using readily available (±)-*trans*-2-phenylcyclohexanol[13] as the chiral auxiliary.

According to precedents in related systems,[7a,14] the copper-mediated coupling of the zincate reagent[15] derived from **4** with (±)-1-iodo-2-(*trans*-2-phenylcyclohexyloxy)-ethyne[16] was first attempted. Although several strategies for the generation of the zincate reagent were examined,[15,17] in all cases the iodide **4** was recovered unaffected.

In view of these negative results we turned our attention to simple alkylation methodology which, albeit made difficult by the neopentylic nature of **4**, allows ample variation of reaction conditions in order to improve reaction yields. After some experimentation, we found that the lithium acetylide derived from (±)-(*trans*-2-phenylcyclohexyloxy)ethyne (**5a**), generated in THF solution, when treated with 2.0 equiv of iodide **4** dissolved in HMPA for 3 h at 50 °C, afforded enyne **3a** in 43% yield (Scheme 3). It is worth noting that these reaction conditions represent a critical compromise, since operation at either higher or lower temperatures had a deletereous effect on the yield of the reaction.

The optimized reaction conditions were subsequently applied to a family of enantiomerically pure alkoxyacetylenes containing camphor-derived chiral auxiliaries[18,19] (**5b**−**d**), which have provided high diastereoselectivities in the intramolecular Pauson−Khand reactions of acetylenic ethers.[7c,10] The synthesis of enynes **3b** and **3c** could be achieved in this way in 50% and 56% yield, respectively. On the other hand, the assembly of enyne **3d** proved to be more difficult and only could be performed, albeit in rather low yield, at room temperature.

Scheme 4



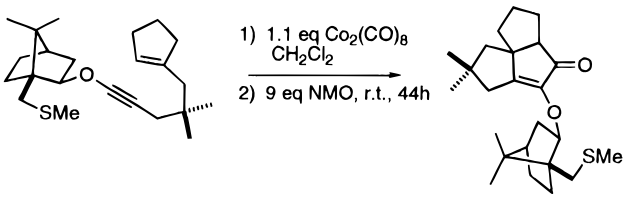
3a-d **2a-d**

Table 1. Pauson−Khand Cyclization[a] of Enynes 3a−d

enyne	conditions	yield (%)	diast ratio	adduct
3a	80 °C, 10 h	70	1.1:1	**2a**
3b	60 °C, 16 h	61	1.7:1	**2b**
3c	60 °C, 24 h	82	5.4:1	**2c**[b]
3d	60 °C, 12 h	74	9.0:1	**2d**

[a] All reactions were performed in isooctane solution under a CO atmosphere. [b] Diastereomers were readily separable by column chromatography.

Scheme 5



3d (63% yield, 8:1 d.r.) **2d**

The intramolecular Pauson−Khand reaction of **3a**−**d** was first studied under thermal conditions in isooctane solution (Scheme 4). The results of this study are summarized in Table 1.

Whereas the cyclizations of **3a** and **3b** took place with low diastereoselectivity, both 3-(neopentyloxy)isoborneol (in **3c**) and 10-methylthioisoborneol (in **3d**) showed to be adequate controllers for this reaction, the corresponding cyclization products being formed in high yield with satisfactory selectivity. In an attempt to even improve the characteristics of this process, the *N*-oxide-promoted Pauson−Khand reactions[20] of enynes **3c** and **3d** were also studied. Quite dissapointingly, exposure of **3c** to 6 equiv of NMO for 24 h in dichloromethane solution led to a complex reaction crude from which no **2c** could be isolated. In the case of **3d** (Scheme 5) the reaction took place in the desired sense, but with lower yield and diastereoselectivity than under thermal conditions.

It is worth noting that all yields in Table 1 are consistently higher than those recorded in analogous systems containing the same auxiliaries, but lacking the *gem*-dimethyl group.[10] This behavior can probably be attributed to *gem*-dialkyl effects.[21]

The selection of the optimal controller for the projected synthesis of 15-nor-pentalenene is not as straightforward as it could be deduced from the simple inspection of the diastereoselectivities in Table 1. When the yields for the

(13) Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1−9.

(14) Sörensen, H.; Greene, A. E. *Tetrahedron Lett.* **1990**, *31*, 7597−7598.

(15) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799−4802.

(16) This compound was prepared in 76% yield from the corresponding alkoxyacetylene (±)-**5a**, by generation of the lithium acetylide with 1.0 equiv of *n*-butyllithium in THF solution at 0 °C and subsequent treatment with 1.0 equiv of iodine at −78 °C for 15 min.

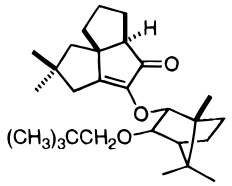
(17) (a) Bronk, B. S.; Lippard, R. L.; Danheiser, R. L. *Organometallics* **1993**, *12*, 3340−3349. (b) Tucker, C. E.; Knochel, P. *Synthesis* **1993**, 530−536. (c) Rozema, M. J.; Sidduri, A. R.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956−1958.

(18) Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta* **1985**, *68*, 2100−2114.

(19) Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222−4224.

(20) (a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289−5292. (b) Jeong, N.; Chung, Y. K.; Lee, B.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204−206.

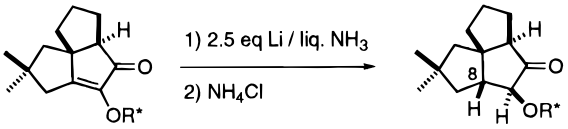
(21) For recent discussions of the *gem*-dialkyl effect or Thorpe−Ingold effect, see: (a) Jung, M. E. *Synlett* **1990**, 186−190. (b) Eliel, E. L.; Wilen, S.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley Interscience: New York, 1994; pp 682−684.



2c (major diastereomer)

Figure 1. Absolute configuration of the major diastereomer of **2c** arising from the Pauson−Khand cyclization of **3c**.

Scheme 6



2c (major) **6i** 13%

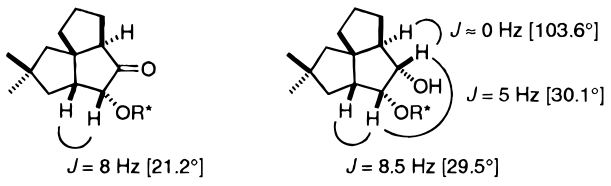
construction of the enyne **3** and its subsequent cyclization to **2** are considered together, along with the diastereoselectivity of the cyclization step, it becomes obvious that 3-(neopentyloxy)isoborneol (in **3c**) is the chiral auxiliary of choice. Moreover, the diastereomers of **2c** can be readily separated by simple column chromatography, so that the major one (that depicted in Figure 1, possessing a 1*R*,5*R* absolute configuration in the triquinane skeleton)[22] can be isolated in diastereomerically pure form in 69% yield after the Pauson−Khand reaction.

For the conversion of **2c** into 15-nor-pentalenene, only two operations remained: (i) reductive elaboration, involving stereoselective hydrogenation of the enol ether moiety and cleavage of the C_α-alkoxy bond with recovery of the chiral auxiliary, and (ii) nucleophilic alkylation with dehydration at the carbonyl site.

For the reduction of the carbon−carbon double bond, a Birch protocol was first attempted (Scheme 6). Although the process was satisfactory in terms of stereoselectivity, leading exclusively to the α-alkoxy ketone **6i**, the balance of matter was poor, and the isolated yield of **6i** was only 13%. Once the presence of *trans*-fused rings in the tricyclic skeleton is discarded,[2a] the stereochemical assignment of **6i** is easily performed on the basis of ^{1}H NMR considerations. Thus, the proton α to the alkoxy group appears as an unresolved doublet (J < 1 Hz), in good agreement with the AM1[23] predicted dihedral angle with the single vicinal proton at C-8 (117°).[24]

More satisfactory results were obtained through hydrogenation of **2c** over Pearlman's catalyst in EtOH solution (Scheme 7). Under these conditions, however, a 9:1 mixture of epimers at the carbon atom bearing the alkoxy group (**6ii**/**6i**) was formed in 50% yield, and some overreduction leading to the α-alkoxy alcohol **7** (35% yield) took place. The stereochemical assignment of **6ii** and **7** could be done from the analysis of coupling constants in the ^{1}H NMR spectra, taking into account the geometrical predictions of AM1 calculations (Figure 2).

Since alcohol **7** could be efficiently reoxidized to **6ii** with PCC in CH_2Cl_2 (83%) the joint yield of alkoxy ketones **6** was 79%.



6ii **7**

Figure 2. Selected vicinal coupling constants in the ^{1}H NMR spectra of **6ii** and **7**. Values in brackets refer to the AM1 calculated values for the dihedral angles defined by the same pairs of vicinal hydrogen atoms.

For convenience, the subsequent reductive removal of the alkoxy group was studied on the major stereoisomer, **6ii**. With SmI_2 in THF−MeOH,[25] a method that generally affords excellent results in the reductive cleavage of α-alkoxy ketones,[7a,b,d,e] a large excess of the reagent and unusually harsh reaction conditions had to be employed, and the main products of the reaction were the epimeric alcohols **8** (Scheme 7).[26] The difficulties met in the reduction of **6ii** can be traced to geometrical reasons; i.e., to the low value of the dihedral angle defined by the carbonyl and the α-alkoxy bond in this molecule (ca. 47°, as predicted by AM1 calculations), far away from the optimal orthogonal arrangement. Probably due to this fact also, substantial amounts of the α-alkoxy alcohol **7** and its C-6 epimer, arising from the direct reduction of the carbonyl group, were formed in the reaction. After one recycle of **7** and its epimer, by oxidation with PCC in CH_2Cl_2 and subsequent reduction with SmI_2, the epimeric mixture of alcohols **8** was obtained in 60% yield, and the chiral auxiliary was recovered in 63% yield.

For the completion of the synthesis, alcohols **8** were first oxidized to the ketone **9** with PCC in CH_2Cl_2 (81% yield). This ketone, which exhibited a negative Cotton effect in its CD spectrum, plays a central role in the synthetic sequence, since it allows the establishment of the absolute configuration of the tricyclic skeleton: Since both ring fusions in **9** have to be *cis*, application of the octant rule leads to the absolute configuration depicted in Figure 3. Once the configuration of **9** is established, those of **2c**, **6**, **7**, and **8** are also unambiguously determined. This result can be rationalized, within the framework of the accepted mechanism for the Pauson−Khand reaction,[28] by assuming a preferential cobaltacycle formation from a dicobalt pentacarbonyl complex in which the more accessible *pro-S* cobalt atom coordinates to the $C_{2'}$-*re* face of the cyclopentenyl moiety, leading to the observed (1*R*,5*R*) configuration via a *cis*-cobaltatricyclic intermediate.

The final conversion of **9** into **1b** was readily performed by Wittig olefination and acid-promoted isomerization of the exocyclic double bond, a method already applied with success by Schore in his synthesis of (±)-pentalenene.[2a] Our synthetic product has been found to be dextrorotatory, as natural pentalenene also is.

(22) The absolute configuration of this compound is derived from that of the more advanced intermediate **9** (see text).

(23) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.

(24) Calculations were performed on a Apple PowerBook 5300cs computer, with the MacSpartan 1.0 software (Wavefunction, Inc.).

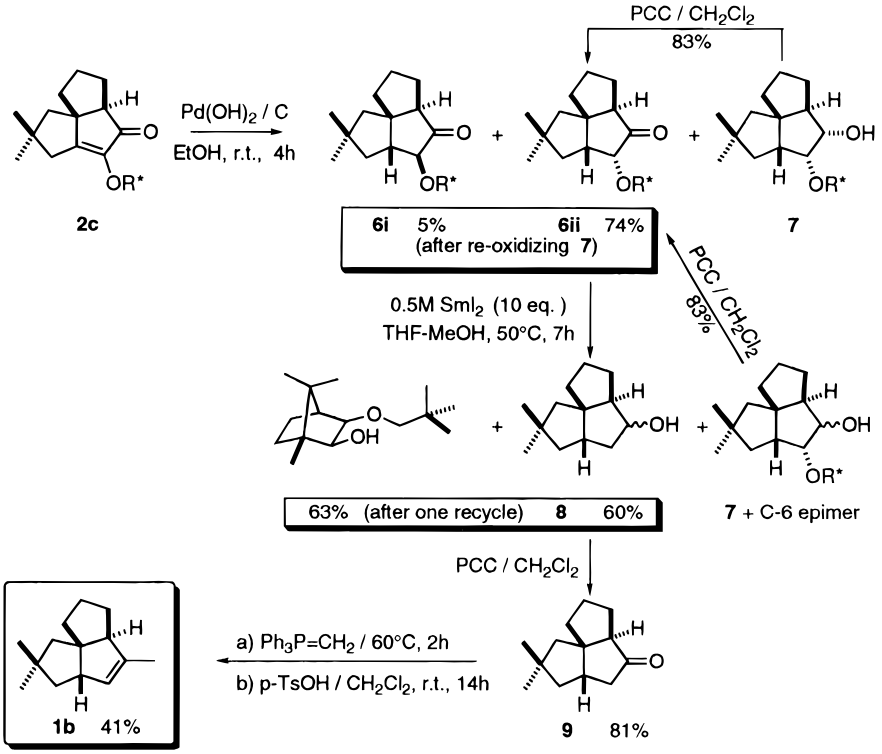
(25) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135−1138.

(26) Alternatively, the use of Zn−Cu in the presence of NH_4Cl[8,27] was also attempted for the removal of the chiral auxiliary from **6ii**, but the main product of the reaction was alcohol **7**, arising from the reduction of the carbonyl group (53% yield). A small amount (12%) of ketone **9** was also obtained, along with 3-(neopentyloxy)isoborneol (15%).

(27) Johnston, B. D.; Slessor, K. N.; Oehlschlager, A. C. *J. Org. Chem.* **1985**, *50*, 114−117.

(28) (a) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861−5869. (b) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851−4854. (c) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1995**, *51*, 6541−6556.

Scheme 7



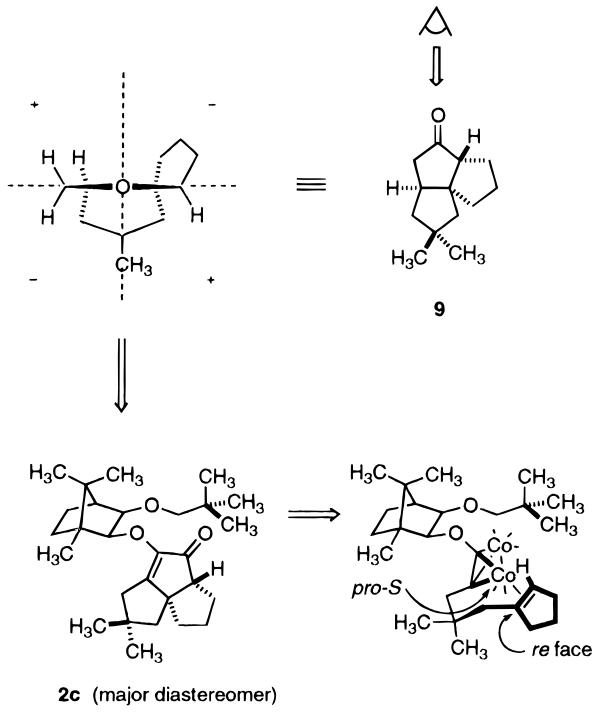


Figure 3. Absolute configuration of **9**, as deduced from the application of the octant rule, and mechanistic rationalization of the stereoselectivity in the Pauson−Khand reaction leading to **2c**.

In summary, we have demonstrated for the first time that a structurally complex angular triquinane, (+)-15-nor-pentalenene, can be obtained in a short, convergent, and enantioselective manner by a process involving an intramolecular Pauson−Khand reaction in which the stereochemical control is exclusively effected by a peripheral, eliminable chiral alkoxy group. Interestingly, the absolute configuration of (+)-15-nor-pentalenene is the same found in natural (+)-pentalenene; this should facilitate the election of the chiral auxiliary for the extension of the present work to the enantioselective synthesis of the natural product.

Experimental Section

General. The ^{1}H NMR spectra were recorded at 200 or 300 MHz in $CDCl_3$ unless specified otherwise. *J* values are given in hertz. The ^{13}C NMR spectra were recorded at 50.3 or 75.4 MHz in $CDCl_3$ unless specified otherwise. Signal multiplicities were established by DEPT experiments. In all cases, chemical shifts are in ppm downfield of TMS. Mass spectra were recorded at 70 eV ionizing voltage; unless specified otherwise, methane was used for chemical ionization (CI) and glycerol for fast atom bombardment (FAB). THF and diethyl ether were distilled from sodium benzophenone ketyl, and CH_2Cl_2 from CaH_2. All reactions were performed in oven-dried glassware under a N_2 or CO atmosphere, as specified. Reaction progress was followed by TLC. Chromatographic separations were carried out using Et_3N pretreated (2.5% v/v) SiO_2 (70−230 mesh), eluting with hexane/diethyl ether mixtures of increasing polarity.

1-(3-Iodo-2,2-dimethylpropyl)cyclopentene (4). (a) To a solution of LDA in THF (20 mL), prepared at −20 °C from diisopropylamine (2.03 mL, 0.014 mol) and *n*-butyllithium in hexanes (9.6 mL, 1.5 M), was added a solution of ethyl isobutyrate (1.66 g, 0.014 mol) in THF (10 mL) at −20 °C, and the mixture was stirred at −20 °C for 1 h. To the resulting solution, 1-(bromomethyl)cyclopentene (2.29 g, 0.014 mol) in THF (10 mL) was added at −78 °C, and the reaction mixture was stirred for 1 h at −78 °C, allowed to warm up to room temperature, and stirred for a 20 h additional period. The reaction mixture was then poured into saturated aqueous NaCl, the aqueous layer was extracted with hexanes (2 × 50 mL), and the combined organic extracts were washed with saturated aqueous NH_4Cl. Drying ($MgSO_4$), filtration, and solvent evaporation gave 3.01 g of crude ester which was purified by column chromatography, to afford 2.46 g (88%) of ethyl 3-(1-cyclopentenyl)-2,2-dimethylpropanoate as a colorless oil: IR (film) ν_{max} 1740, 1655 cm^{-1}; ^{1}H NMR (200 MHz) δ 5.36 (t, J = 2 Hz, 1H); 4.04 (q, J = 7 Hz, 2H); 2.36 (d, J = 1 Hz, 2H); 2.34−2.05 (m, 4H); 1.79 (quintet, J = 8 Hz, 2H); 1.24 (t, J = 7 Hz, 3H); 1.15 (s, 6H); ^{13}C NMR (50 MHz) δ 178.0 (C), 141.1 (C), 127.6 (CH), 60.2 (CH_2), 42.1 (CH_2), 35.6 (CH_2), 32.2 (CH_2), 30.3 (C), 25.6 (CH_3), 23.8 (CH_2), 14.1 (CH_3); MS (CI) *m*/*e* 197 (M + 1$^+$, 100%). (b) To a stirred suspension of $LiAlH_4$

(0.455 g, 0.012 mol) in THF (30 mL) was added a solution of the ester prepared in part a (2.35 g, 0.012 mol) in THF (20 mL) at −10 °C. The mixture was stirred for 0.75 h at −10 °C and sequentially treated with H_2O (0.5 mL), 10% aqueous NaOH (0.5 mL), and H_2O (1.5 mL). The liquid phase was decanted and dried ($MgSO_4$), and the solvent was removed under vacuum to afford 1.71 g of crude product. Purification by column chromatography afforded 3-(1-cyclopentenyl)-2,2-dimethyl-1-propanol (1.515 g, 82%) as a colorless oil: IR (film) ν_{max} 3350, 1650 cm^{-1}; ^1H NMR (200 MHz) δ 5.38 (s, 1H); 3.30 (s, 2H); 2.28 (t, J = 8 Hz, 4H); 2.05 (s, 2H); 1.98−1.71 (m, 3H); 0.88 (s, 6H); ^{13}C NMR (50 MHz) δ 142.1 (C), 127.8 (CH), 72.0 (CH_2), 40.1 (CH_2), 37.5 (CH_2), 36.1 (C), 32.4 (CH_2), 24.6 (CH_3), 24.1 (CH_2); MS (CI) m/e 155 ($M + 1^+$, 63%), 137 ($M - OH^+$, 100%). (c) To a stirred solution of methyltriphenoxyphosphonium iodide (5.21 g, 0.011 mol) in DMF (30 mL) at room temperature was added a solution of the alcohol prepared in part b (0.89 g, 5.78 mmol) in DMF (10 mL). The reaction mixture was stirred at 80 °C for 3 h and was then poured into saturated aqueous Na_2SO_3. The resulting aqueous phase was extracted with hexane (3 × 25 mL), and the combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and evaporated to afford 2.92 g of crude product. Purification by column chromatography on silica gel, eluting with hexane, afforded 1.34 g (88%) of iodide **4** as a colorless oil, exhibiting a single spot by TLC (R_f 0.83 5:1 hexane:AcOEt): ^1H NMR (200 MHz) δ 5.48 (s, 1H), 3.19 (s, 2H), 2.30 (t, J = 7.8 Hz, 4H), 2.17 (s, 2H), 1.83 (quintet, J = 7.8 Hz, 2H), 1.04 (s, 6H); ^{13}C NMR (50 MHz) δ 141.1 (C), 128.5 (CH), 40.7 (CH_2), 37.5 (CH_2), 34.4 (C), 32.5 (CH_2), 27.5 (CH_3), 25.1 (CH_2), 24.1 (CH_2); MS (CI) m/e 265 ($M + 1^+$, 41%), 137 ($M - I^+$, 100%).

1-{2,2-Dimethyl-5-[(1*R*,2*S*,3*R*,4*S*)-3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yloxy]pent-4-enyl}-cyclopentene (3c). To a stirred solution of alkoxyacetylene **5c** (2.59 g, 9.8 mmol) in THF (10 mL) was added *n*-butyllihium (6.1 mL, 1.6 M in hexanes) at −10 °C. The mixture was stirred at −10 °C for 0.5 h, a solution of iodide **4** (5.19 g, 19.1 mmol) in HMPA (19 mL) was added and the resulting mixture was heated at 50 °C during 3.5 h. The reaction mixture was poured into saturated aqueous NH_4Cl, and the aqueous phase was extracted with hexane (4 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated, and the residue was purified by column chromatography on silica gel, eluting with hexanes to afford **3c** (2.19 g, 56%) as a colorless oil, exhibiting a single spot by TLC (R_f 0.53 hexane): IR (film) ν_{max} 3040, 2270, 1650 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.46 (s, 1H), 3.90 (part A of AX system, J = 6.5 Hz, 1H), 3.30 (part X of AX system, J = 6.5 Hz, 1H), 3.37 (part A of AX system, J = 8 Hz, 1H), 3.03 (part X of AX system, J = 8 Hz, 1H), 2.49 (t, J = 7.5 Hz, 4H), 2.19 (s, 2H), 2.15 (s, 2H), 1.78 (quintet, J = 7.5 Hz, 2H), 1.67 (d, J = 5 Hz, 1H), 1.42−0.82 (m, 4H), 1.28 (s, 3H), 1.07 (s, 9H), 1.05 (s, 3H), 1.04 (s, 6H), 0.65 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 142.3 (C), 127.9 (CH), 97.6 (CH), 94.3 (C), 84.7 (CH), 82.0 (CH_2), 49.7 (CH), 48.6 (C), 47.0 (C), 42.6 (CH_2), 37.9 (CH_2), 34.7 (C), 33.6 (C), 33.1 (CH_2), 32.8 (CH_2), 32.3 (C), 31.5 (CH_2), 27.5 (CH_3), 27.0 (CH_3), 24.5 (CH_2), 24.1 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 11.4 (CH_3); MS (FAB) m/e 401 ($M + 1^+$, 2%), 153 ($M - C_{17}H_{28}O + 1^+$, 100%); $[\alpha]^{25}_D = -43$ (CH_2Cl_2, c = 0.9).

(1*R*,5*R*)-7-[(1*R*,2*S*,3*R*,4*S*)-3-(2,2-Dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yloxy]-10,10-dimethyltricyclo-[6.3.0.0^{1,5}]undec-7-en-6-one (2c). To a stirred solution of **3c** (1.83 g, 4.58 mmol) in anhydrous isooctane (170 mL), was added dicobalt octacarbonyl (1.72 g, 5.03 mmol) in one portion, and the resulting dark-colored solution was stirred at room temperature for *ca.* 1 h, until the formation of the hexacarbonyl dicobalt complex was complete (TLC). The reaction mixture was heated to 60 °C under a CO atmosphere for 24 h until complete disappearence of the complex, filtered through Celite, evaporated, and directly submitted to a short column chromatography to afford **2c** (1.597 g, 82%) as a 5.4:1 diastereomeric mixture. Separation of diastereomers is achieved by column chromatography on silica gel eluting with hexanes. The fast eluting diastereomer, isolated in 69% yield, possesses the (1*R*,5*R*) configuration. Colorless oil exhibiting a single spot by TLC (R_f 0.25 95:5 hexane:AcOEt): IR (film) ν_{max} 1705, 1655 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.09 (part A of AX system, J = 7 Hz, 1H), 3.65 (part X of AX system, J = 7 Hz, 1H), 3.13 (part A of AB system, J = 8.5 Hz, 1H), 3.07 (part B of AB system, J = 8.5 Hz, 1H), 2.56 (part A of AB system, J = 15 Hz, 1H), 2.17 (part B of AB system, J = 15 Hz, 1H), 2.34−2.27 (m, 1H), 2.18−2.12 (m, 1H), 1.81 (d, J = 5.5 Hz, 1H), 1.67−0.81 (m, 11H), 1.47 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.95 (s, 9H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 204.8 (C), 159.3 (C), 148.4 (C), 86.2 (CH), 85.2 (CH), 81.0 (CH_2), 58.1 (CH), 55.1 (C), 53.1 (CH_2), 49.4 (C), 48.6 (CH), 47.4 (C), 41.0 (C), 40.2 (CH_2), 38.6 (CH_2), 33.6 (CH_2), 32.2 (CH_3), 31.7 (CH_3), 29.0 (CH_2), 27.3 (CH_3), 25.4 (CH_2), 24.3 (CH_2), 21.6 (CH_3), 21.3 (CH_3), 11.8 (CH_3); MS (FAB): 429 ($[M + 1]^+$, 8%); $[\alpha]^{25}_D = +9$ (CH_2Cl_2, c = 1.5).

Catalytic Hydrogenation of 2c: (1*S*,5*R*,7*R*,8*R*)-7-[(1*R*,2*S*,-3*R*,4*S*)-3-(2,2-Dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yloxy]-10,10-dimethyltricyclo[6.3.0.0^{1,5}]undecan-6-one (6ii). To a stirred solution of the major diastereomer of **2c** (0.067 g, 0.16 mmol) in ethanol (2 mL) at room temperature was added in one portion 0.017 g of $Pd(OH)_2/C$ (20%). The resulting suspension was stirred at room temperature and under a hydrogen atmosphere for 4 h. The resulting suspension was filtered through Celite, and the solvent was evaporated *in vacuo* to afford 0.065 g of crude product. This residue was purified by column chromatography on silica gel, eluting with hexanes, to afford 0.030 g (46% yield) of α-alkoxy ketone **6ii**, 0.003 g (5% yield) of α-alkoxy ketone **6i**, and 0.023 g (35% yield) of α-alkoxy alcohol **7**. Since this alcohol can be oxidized to **6ii** in 83% yield (see following procedure), the joint yield of **6ii** from **2c** is 74%. Alkoxy ketone **6ii**, colorless oil exhibiting a single spot by TLC (R_f 0.75 5:1 hexane:AcOEt): IR (film) ν_{max} 1745 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 4.33 (d, J = 8 Hz, 1H), 3.55 (part A of AB system, J = 6.8 Hz, 1H), 3.39 (part B of AB system, J = 6.8 Hz, 1H), 3.14 (part A of AB system, J = 7.5 Hz, 1H), 3.09 (part B of AB system, J = 7.5 Hz, 1H), 2.61−2.51 (m, 1H), 2.20 (dd, J = 10 Hz, J = 5 Hz, 1H), 1.81−1.26 (m, 15H), 1.52 (s, 3H), 1.03 (s, 3H), 1.01 (s, 9H), 0.98 (s, 3H), 0.97 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 215.3 (C), 86.9 (CH), 85.9 (CH), 83.9 (CH), 81.1 (CH_2), 58.3 (CH), 57.3 (CH_2), 54.7 (C), 49.5 (C), 49.1 (CH), 48.2 (CH), 47.0 (C), 44.1 (CH_2), 43.9 (CH_2), 39.6 (C), 34.1 (CH_2), 32.2 (C), 31.5 (CH_2), 29.9 (CH_3), 29.3 (CH_3), 27.6 (CH_2), 27.2 (CH_3), 24.4 (CH_2), 21.4 (CH_3), 21.3 (CH_3), 12.1 (CH_3); MS (EI): 430 (M^+, 2%), 222 ($M - C_{13}H_{20}O_2^+$, 100%); $[\alpha]^{25}_D = -149$ (CH_2Cl_2, c = 0.9). Alkoxy alcohol **7**, colorless oil exhibiting a single spot by TLC (R_f 0.70 5:1 hexane:AcOEt): IR (film): 3410 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 4.15 (d, J = 5 Hz, 1H), 4.07 (s, 1H), 3.87 (dd, J = 8.5 Hz, J = 5 Hz, 1H), 3.27 (part A of AB system, J = 6.5 Hz, 1H), 3.25 (part B of AB system, J = 6.5 Hz, 1H), 3.05 (part A of AB system, J = 8 Hz, 1H), 3.01 (part B of AB system, J = 8 Hz, 1H), 2.57−2.23 (m, 4H), 1.82−1.35 (m, 13H), 1.33 (s, 3H), 1.21 (s, 3H), 1.06 (s, 3H), 0.99 (s, 9H), 0.98 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 88.2 (CH), 86.2 (CH), 86.0 (CH), 81.0 (CH_2), 80.3 (CH), 60.0 (C), 57.3 (CH_2), 56.8 (CH), 55.3 (CH), 49.7 (C), 47.1 (CH), 47.0 (C), 45.8 (CH_2), 44.8 (CH_2), 41.9 (C), 33.6 (CH_2), 32.0 (C), 31.0 (CH_2), 29.9 (CH_3), 28.1 (CH_3), 27.4 (CH_2), 27.2 (CH_3), 24.6 (CH_2), 21.4 (CH_3), 21.1 (CH_3), 11.6 (CH_3); MS (EI): 432 (M^+, 2%), 414 ($[M - H_2O]^+$, 6%), 344 ($[M - C_5H_{12}O]^+$, 32%), 222 ($[M - C_{13}H_{22}O_2]^+$, 18%); $[\alpha]^{25}_D = -74$ (CH_2Cl_2, c = 1.0).

Oxidation of 7 with PCC: 6ii. To a stirred solution of **7** (0.033 g, 0.076 mmol) in CH_2Cl_2 (3 mL) at room temperature was added pyridinium chlorochromate (PCC) (0.196 g, 0.9 mmol) in one portion. The resulting mixture was stirred at room temperature for 72 h and filtered through Celite, and the solvent was evaporated to afford 0.028 g of crude product. This residue was purified by column chromatography on silica gel, eluting with hexane, to afford 0.027 g (83%) of α-alkoxy ketone **6ii** as a colorless oil.

(1*S*,5*R*,6*RS*,8*S*)-10,10-Dimethyltricyclo[6.3.0.0^{1,5}]undecan-6-ol (8). Into a Schlenck reactor under Ar were placed powdered samarium 0.283 g (1.88 mmol), 1,2-diiodoethane 0.505 g (1.79 mmol), and anhydrous THF (3 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h and to the so-formed dark blue solution, cooled at 0 °C, was added a solution of alkoxyketone **6ii** (0.077 g, 0.179 mmol) in 0.6 mL of THF/MeOH (2:1). The mixture was heated at 50 °C for 7 h; THF (5 mL) was then added and oxygen was passed through the solution until decoloration. The resulting mixture was washed with saturated aqueous K_2CO_3, and the aqueous layer was extracted with pentane (2 × 25 mL). The combined organic extracts were washed with H_2O, dried ($MgSO_4$), filtered, and evaporated to give 0.059 g of crude material. The crude was

purified by column chromatography on silica gel, eluting with pentane, to afford 0.017 g (49% yield) of **8**, as an epimeric mixture at C-6, 0.022 g (51% recovery) of 3-(neopentyloxy)-isoborneol, and 0.015 g (20% yield) of the alkoxy alcohol **7** and its C-6 epimer. After one recycle of alcohols **7** (oxidation with PCC and reduction with SmI_2), the recovery of 3-(neopentyloxy)-isoborneol is 63%, and the combined yield of **8** is 60%. Epimeric mixture of alcohols **8**. Colorless oil exhibiting a single spot by TLC (R_f 0.12 95:5 hexane:AcOEt): IR (film) ν_{max} 3450 cm^{-1}; ^1H NMR (300 MHz), *major diastereomer* δ 4.46−4.38 (m, 1H), 2.23−1.18 (m, 15H), 0.99 (s, 3H), 0.94 (s, 3H), *minor diastereomer* δ 4.04−3.92 (m, 1H), 1.03 (s, 3H), 0.98 (s, 3H), ^{13}C NMR (75 MHz), *major diastereomer* δ 73.9 (CH), 59.8 (C), 56.8 (CH), 56.6 (CH_2), 49.7 (CH_2), 48.5 (CH), 45.3 (CH_2), 41.7 (C), 38.5 (CH_2), 29.3 (CH_3), 27.7 (CH_2), 27.2 (CH_3), 25.1 (CH_2), *minor diastereomer* δ 82.2 (CH), 61.9 (CH), 57.1 (CH_2), 51.3 (CH), 49.9 (CH_2), 44.7 (CH_2), 41.4 (CH_2), 41.2 (C), 30.6 (CH_2), 30.0 (CH_3), 28.2 (CH_3), 26.7 (CH_2); MS (CI, NH_3): 229 ($M + 35^+$, 50%), 212 ($M + 18^+$, 100%), 195 ($M + 1^+$, 5%), 176 ($M - H_2O^+$, 33%).

(1*S*,5*R*,8*S*)-10,10-Dimethyltricyclo[6.3.0.0^{1,5}]undecan-6-one (9). To a stirred solution of alcohols **8** (0.015 g, 0.077 mmol) in CH_2Cl_2 (2 mL) at room temperature was added PCC (0.050 g, 0.23 mmol) in one portion. The resulting mixture was stirred at room temperature for 1 h and filtered through Celite, and the solvent was evaporated to afford 0.018 g of crude product. This residue was purified by column chromatography on silica gel, eluting with pentane, to afford 0.012 g (81% yield) of ketone **9** as a colorless oil exhibiting a single spot by TLC (R_f 0.34 95:5 hexane:AcOEt): IR (film) ν_{max} 1735 cm^{-1}; ^1H NMR (300 MHz) δ 2.58−2.41 (m, 1H), 2.51 (part A of AB system, J = 16 Hz, 1H), 2.16 (part B of AB system, J = 16 Hz, 1H), 2.32 (dd, J = 10.5 Hz, J = 4 Hz, 1H), 2.03−1.42 (m, 7H), 1.37−1.15 (m, 3H), 1.05 (s, 3H), 1.04 (s, 3H), ^{13}C NMR (75 MHz) δ 224.0 (C), 61.6 (CH), 58.8 (C), 56.3 (CH_2), 50.3 (CH_2), 45.1 (CH), 44.8 (CH_2), 43.7 (CH_2), 40.1 (C), 30.8 (CH_2), 29.9 (CH_3), 28.9 (CH_3), 27.2 (CH_2); MS (CI, NH_3) *m*/*e* 227 ($M + 35^+$, 67%), 210 ($M + 18^+$, 100%), 193 ($M + 1^+$, 5%); $[\alpha]^{25}_D = -91$ (CH_2Cl_2, c = 0.6) $[\Psi]^{25} = -2496$ (λ_{max}= 301.5 nm, CH_2Cl_2, $c = 2.4 \times 10^{-3}$).

(+)-15-Nor-pentalenene (1b). KH (0.083 g, 0.73 mmol, 35% in oil) was rinsed with hexane and allowed to react with 1 mL of DMSO for 10 min. To this suspension was added methyltriphenylphosphonium iodide (0.316 g, 0.78 mmol), and the mixture heated at 60 °C for 15 min. To the resulting mixture was added a solution of ketone **9** (0.010 g, 0.052 mmol) in DMSO (0.3 mL), and the heating was continued for 2 h. The resulting mixture was poured into 25 mL of water and extracted with 3 × 20 mL of diethyl ether. The combined organic layers were washed with H_2O and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and evaporated to afford 0.028 g of a yellow solid. This crude product was dissolved in 1 mL of CH_2Cl_2 and stirred at room temperature for 14 h with 0.010 g (0.053 mmol) of *p*-toluensulfonic acid. The resulting mixture was poured into 25 mL of saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with 2 × 20 mL of CH_2Cl_2. The combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and evaporated to give 0.022 g of crude product. This residue was purified by column chromatography on silica gel, eluting with pentane, to afford 0.0040 g (41%) of pure (+)-15-nor-pentalenene **1b**. Colorless oil exhibiting a single spot by TLC (R_f 0.92 hexane). IR (film NaCl): 3030, 2920, 2840, 1655, 1470, 1435, 1380, 1365, 1330, 1265, 1205, 1165, 1125, 1085, 1065, 1015, 950, 890, 790 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, TMS int): 5.17 (d, J = 1.5 Hz, 1H), 2.71−2.63 (m, 1H), 2.50 (d, J = 9 Hz, 1H), 1.68−1.23 (m, 8H), 1.14−1.09 (m, 2H), 1.59 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS int): 139.9 (C), 129.6 (CH), 62.7 (CH), 60.9 (C), 59.3 (CH), 56.4 (CH_2), 47.7 (CH_2), 44.3 (CH_2), 40.6 (C), 30.6 (CH_2), 29.3 (CH_3), 29.0 (CH_3), 26.0 (CH_2), 15.5 (CH_3); mass calcd for $C_{14}H_{22}$: 190.1722; found: 190.1729; $[\alpha]^{25}_D = +32$ (CH_2Cl_2, c = 0.2).

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Supporting Information Available: ^{13}C NMR spectra of compounds **4**, **3a**, **3b**, **3c**, **3d**, **2a**, **2b**, **2c** (major diastereomer), **2d**, **6i**, **6ii**, **7**, **8**, **9**, and **1b**. Experimental procedures and characterization data for compounds **3a**, **3b**, **3d**, **2a**, **2b**, **2d**, and **6i** (21 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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