Asymmetric Approach to (+)-β-Cuparenone by Intramolecular Pauson−Khand Reaction

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Introduction

The Pauson−Khand reaction[1] has become the most widely used among the transition-metal-promoted methods for the construction of five-membered carbocycles, as evidenced by an ever increasing number of synthetic applications.[2] Well aware of the possibilities offered by this reaction, which produces in a single step a 2-cyclopentenone with up to two stereogenic carbon atoms, we have devoted our efforts to the objective of rendering the Pauson−Khand cyclization asymmetric. Our initial strategy, based on the use of chiral alkoxy groups directly linked either to the olefinic or the acetylenic components, has resulted in the development of reliable, practical asymmetric approaches for both the intramolecular[3] and the intermolecular[4] versions of the Pauson−Khand reaction. Contrasting to other methodologies aiming at a similar goal,[5] our approximation has already been applied to the enantioselective synthesis of complex natural products such as (+)-hirsutene[3b] and (+)-brefeldin A.[6] We describe in the present paper how the Pauson−Khand bicyclization of 1-alkoxy-4-thia-1-hepten-6-ynes can be applied to the formation of enantioenriched cyclopentanones with asymmetric quaternary carbon centers,[7] as exemplified by an enantioselective synthesis of (+)-β-cuparenone.

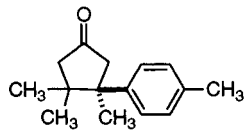

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Figure 1.

Results and Discussion

Together with the regioisomeric α-cuparenones, (+)-β-cuparenone (**1**), a 3,3,4,4-tetrasubstituted cyclopentanone isolated from the essential oil of the "Mayur pankhi" tree,[8] has been the subject of much synthetic effort, aimed generally to its preparation in racemic form.[9] Following the first enantioselective synthesis,[10] other approaches to the enantiomerically pure compound have relied upon the resolution of 2-methyl-2-(*p*-tolyl)-succinic acid[11] or the enzymatic hydrolysis of 2-methyl-2-(*p*-tolyl) malonic esters[12a,b] and of 1-acetoxydicyclopentadiene[12c] or on the ring contraction of optically active 5-(trimethylsilyl)-2-cyclohexenones.[13]

The key concept in the present chiral auxiliary-based asymmetric intramolecular Pauson−Khand route to natu-

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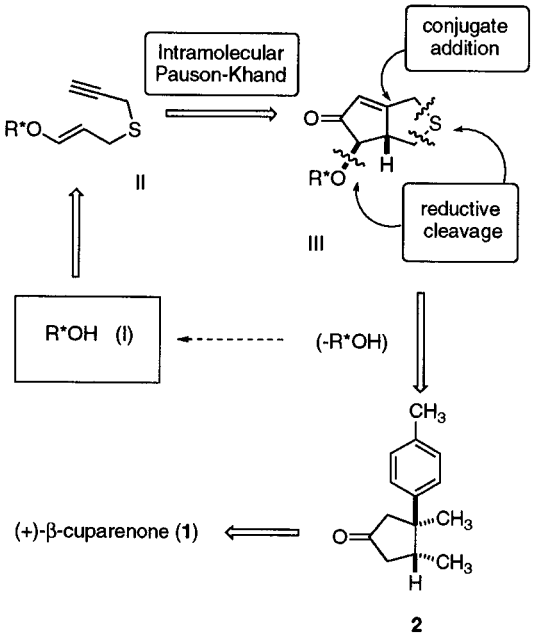
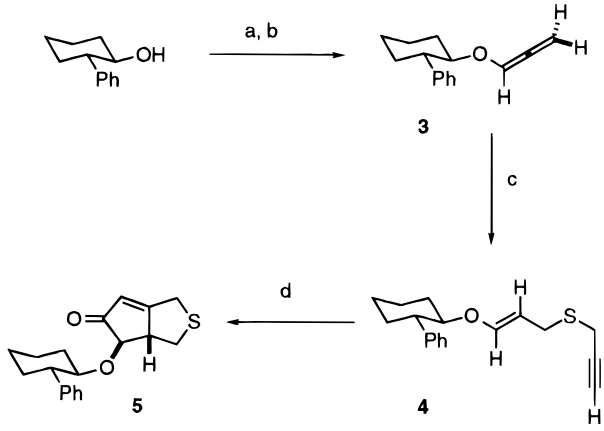
Scheme 1



Scheme 2[a]



[a] Reaction conditions and yields: (a) NaH (1.1 equiv), THF, reflux, 5 h; $NBu_4^+I^-$ (cat.), $HC{\equiv}CCH_2Br$ (1.1 equiv), rt, 12 h (89% based on recovered starting material); (b) K^{t}BuO (1.5 equiv), ^{t}BuOH, reflux, 2 h (80%); (c) $HC{\equiv}CCH_2SH$ (1.3 equiv), $HBF_4{\cdot}Et_2O$ (cat.), CH_2Cl_2, −78 °C to rt, 12 h (77%); (d) $Co_2(CO)_8$ (1.1 equiv), isooctane, rt, 30 min; reflux, 2.5 h (38%, 12:1 dr), or $Co_2(CO)_8$ (1.2 equiv), CH_2Cl_2, rt, 2 h; NMO (6 equiv), rt, 12 h (56%, 8:1 dr).

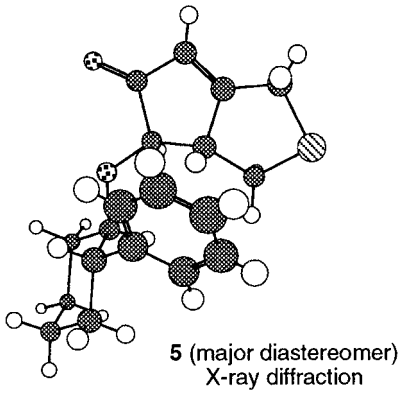


Figure 2.

ral (+)-*β*-cuparenone, summarized in Scheme 1, lies on the identification of the alkoxythiabicyclooctenone III, arising from the cobalt-promoted bicyclization of an alkoxythiaheptenyne such as II, as a suitable precursor of the key cyclopentanone **2**, whose conversion into **1** requires only the introduction of a methyl group at C-4.

Enantiopure (−)-(1*R*,2*S*)-2-phenylcyclohexanol was selected as the chiral alcohol (I) of choice for this application, on the basis both of its ready availability[14] and of the predictable sense and consistently high degree of asymmetric induction that it imparts to the Pauson−Khand bicyclization of other 1-alkoxy-1-hepten-6-ynes.[3b,e]

The required enyne II could be efficiently assembled from the homochiral alkoxyallene **3** (prepared by base-promoted isomerization[15] of the corresponding propargyl ether) and 2-propynethiol[16] through a regio- and stereoselective acid catalyzed[17] addition. In this way, (*E*)-1-alkoxy-4-thiahepten-6-yne **4** was obtained in 77% yield (Scheme 2) as a 9:1 mixture with the corresponding (*Z*) isomer. Exposure of **4** to $Co_2(CO)_8$ in isooctane followed by heating of the resulting dicobalt hexacarbonyl complex (90 °C, 2.5 h) produced a *ca.* 12:1 mixture of diastereomeric bicyclo[3.3.0]octenones **5** from which the major one could be isolated in moderate yield (33%) by column chromatography; this yield could be considerably improved by promoting the reaction with *N*-methylmorpholine *N*-oxide,[18] at the cost of a slight decrease in diastereoselectivity (56% yield, 8:1 diastereomeric ratio). In no case were we able to detect products arising from the cobalt-induced bicyclization of the (*Z*)-isomer of **4**, in accordance with the low Pauson−Khand reactivity exhibited by other *cis*-alkoxyenynes.[3b] The (4*R*,5*S*) absolute configuration of the major diastereomer, established through X-ray diffraction[23] (Figure 2), turned out to be fully coincident with that predicted by our working model for the stereochemical outcome of the intramolecular Pauson−Khand reaction of *trans*-2-phenylcyclohexanol-derived enynes.[3b,e] On the other hand, ^{1}H NMR spectra show that, as expected, the minor diastereomer of **5** has a (4*S*,5*R*) stereochemistry.

Since the chromatographic separation of synthetically useful amounts of the diastereomeric bicyclooctenones **5** involved extended periods of time and was usually accompanied by substantial losses due to partial product decomposition, the synthesis was continued with the readily available 8:1 diastereomeric mixture. In this way, the cuprate reagent generated from *p*-tolyllithium with cuprous iodide effected the desired conjugate addition on **5** to give in 41% yield after column chromatography the 7-thiabicyclo[3.3.0]octanone **6** as a 8:1 diastereomer mixture (Scheme 3). Subsequent Raney-Ni-promoted transformation of the five-membered sulfur-containing ring into a *vic*-dimethyl moiety (**7**, 95% yield of a 8:1 diastereomer mixture), followed by reductive removal (with 95% recovery) of the chiral auxiliary accomplished with SmI_2−MeOH,[19] furnished (90% yield) the key cyclopentanone **2**, whose absolute configuration,

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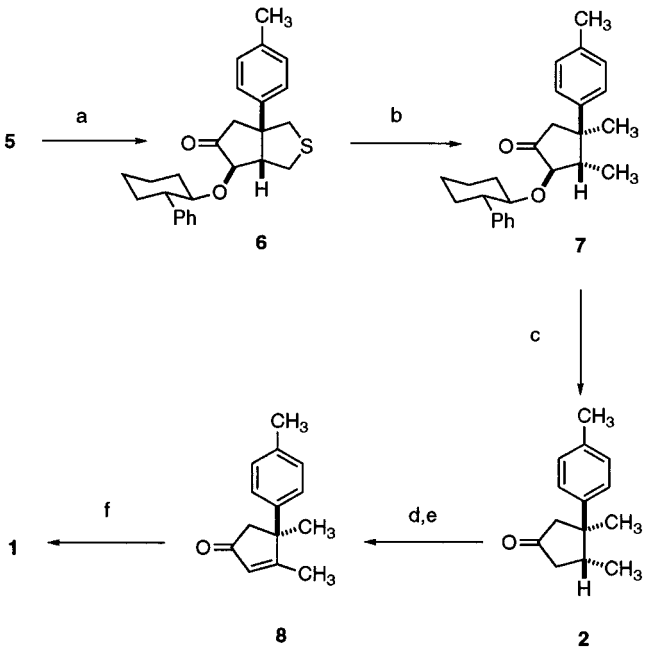
Scheme 3[a]



[a] Reaction conditions and yields: (a) *p*-Tolyllithium (5 equiv), CuI (2.5 equiv), Et_2O, −10 to 0 °C, 10 min; **6**, rt, 12 h (41%); (b) Ni-Raney, EtOH, reflux, 1 h (95%); (c) SmI_2 (3.3 equiv), THF−MeOH, −70 °C, 5 min (90%, 95% recovery of the chiral alcohol); (d) LDA (1.1 equiv), THF, −78 °C, 20 min; PhSeBr (1.2 equiv), −78 °C, 30 min; 0 °C, 1 h (85%); (e) H_2O_2 (6 equiv), AcOH−H_2O, rt, 1 h (90%); (f) $(CH_3)_2Zn$ (5 equiv), $Ni(acac)_2$ (cat.), Et_2O, rt, 15 h (86%, ref 10).

established by CD,[20] showed that the conjugate addition had taken place *cis* to the bridgehead hydrogen atom of **5**, as expected. Accurate determination (both by ^{13}C NMR and HPLC analysis of the diastereomeric acetals formed with both (−)- and (+)-2,3-butanediol)[21] of the enantiomeric composition of **2** indicated a 77% enantiomeric excess, in agreement with the diastereomeric composition of **5**−**7**. Finally, when an enolate mixture generated from **2** (LDA, THF, 0 °C) was treated with phenylselenenyl bromide at −78 °C, the product arising from deprotonation of the less hindered methylene group was obtained in very high yield. This intermediate selenide was then oxidized without further purification to give (89% yield) the dextrorotatory cyclopentenone **8**, which has been previously converted to natural (+)-*β*-cuparenone (**1**) by simple methyl conjugate addition.[10,13]

In summary, the intramolecular Pauson−Khand bicyclization of a 1-alkoxy-4-thia-1-hepten-6-yne derived from a chiral alcohol provides a novel asymmetric approach to *β*-cuparenone. Further synthetic applications and methodological investigations of the asymmetric Pauson−Khand reaction are underway in our laboratories and will be reported in due course.

Experimental Section

General. Melting points were determined in an open capillary tube and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. The ^1H NMR spectra were recorded at 200 or 300 MHz in $CDCl_3$ unless specified otherwise. *J* values are given in Hz. 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; ammonia was used for chemical ionization (CI). Elemental analyses were performed by the "Servei d'Anàlisis Elementals del CSIC de Barcelona". THF and diethyl ether were distilled from sodium benzophenone ketyl, and CH_2Cl_2 was distilled from CaH_2. All reactions were performed in flame or oven-dried glassware under a N_2 atmosphere. Reaction progress was followed by TLC (Merck DC-Alufolien KIESELGEL 60 F254).

1-[(1*R*,2*S*)-(2-Phenylcyclohexyl)oxy]-1,2-propadiene (3). (a) (1*R*,2*S*)-2-Phenylcyclohexyl Propargyl Ether. To a cold (0 °C), stirred suspension of sodium hydride (18.7 mmol, from 0.562 g of a 80% oil suspension) in dry THF (5 mL) was added dropwise a solution of (−)-(1*R*,2*S*)-2-phenylcyclohexanol[14] (3.00 g, 17.0 mmol) in THF (20 mL). The resulting mixture was heated to reflux for 5 h, cooled to 0 °C, and treated with solid tetrabutylammonium iodide (0.135 g). After 10 min at 0 °C, a 80% toluene solution of propargyl bromide (2.1 mL, 18.6 mmol) was added dropwise; the reaction mixture was stirred overnight at room temperature and poured into hexane/water. The aqueous phase was separated and extracted with diethyl ether (3 × 15 mL), and the combined organic phases were washed with brine and dried over Na_2SO_4. Distillation of the solvents at reduced pressure gave 4 g of a crude product which was purified by column chromatography on silica gel (12 g), eluting with hexane/diethyl ether mixtures of increasing polarity that allowed the recovery of 1.79 g of the starting alcohol and the isolation of 2.08 g (89% yield based on the consumed chiral alcohol) of the desired propargyl ether as a colorless oil: $[\alpha]^{23}_D = -29.3$ (*c* 5.93, CCl_4); IR (NaCl film) ν_{max} = 3300, 2100, 1600 cm^{-1}; ^1H NMR (200 MHz) δ 1.2−2.0 (m, 7H), 2.25 (t, J = 2.5 Hz, 1H), 2.52 (td, J = 11.5 Hz, J' = 7.5 Hz, 1H), 3.56 (td, J = 12 Hz, J' = 7.5 Hz, 1H), 3.75−3.90 (m, 2H), 7.10−7.40 (m, 5H); ^{13}C NMR (50.3 MHz) δ 25.0 (CH_2), 25.9 (CH_2), 32.2 (CH_2), 34.1 (CH_2), 51.0 (CH), 56.2 (CH_2,), 73.4 (CH), 80.4 (C_q), 80.9 (CH), 126.1 (CH), 127.7 (2CH), 128.2 (2CH), 144.2 (C_q).

(b) Base-Promoted Isomerization. A stirred suspension of (1*R*,2*S*)-2-phenylcyclohexyl propargyl ether (2.0 g, 9.34 mmol) and potassium *tert*-butoxide (1.57 g, 14.01 mmol) in *tert*-butyl alcohol (25 mL) was heated to reflux for 2 h. At this point, the reaction progress was monitored by TLC (hexane/ethyl acetate 5:1) and, if some propargyl ether still remained, 0.5 equiv of base was added and heating was continued for 1 h, until complete disappearance of the starting material. The reaction mixture was cooled down to room temperature and poured into diethyl ether/water (100 mL + 100 mL). After phase separation, the aqueous one was extracted with diethyl ether (3 × 25 mL), and the combined organic extracts were dried over Na_2SO_4. Elimination of solvents at reduced pressure gave a crude product which was purified by column chromatography on Et_3N pretreated (2.5% v/v) SiO_2 (8 g) eluting with hexane, to afford 1.6 g (80%) of alkoxyallene **3** as a white solid: Mp 50.0−51.4 °C; $[\alpha]^{23}_D$ = +130.2 (*c* 2.6, CCl_4); IR (NaCl film) ν_{max} = 1960, 1610, 1500 cm^{-1}; ^1H NMR (200 MHz) δ 1.2−2.0 (m, 7H), 2.15−2.35 (m, 1H), 2.66 (td, 1H, J = 10 Hz, J' = 4.5 Hz), 3.8 (td, J = 11 Hz, J' = 4.5 Hz, 1H), 5.25−5.40 (m, 2H), 6.40 (t, 1H, J = 5.9 Hz), 7.10−7.40 (m, 5H); ^{13}C NMR (50.3 MHz) δ 24.5 (CH_2), 25.8 (CH_2), 31.6 (CH_2), 34.2 (CH_2), 50.2 (CH), 80.0 (CH,), 88.8 (CH_2), 120.7 (CH), 126.2 (CH), 127.6 (2CH), 128.3 (2CH), 144.0 (C_q), 201.4 (C_q); MS (CI-NH_3) *m*/*e* = 215 (M^+ + 1, 16%), 232 (M^+ + 18, 21%). Anal. Calcd for $C_{15}H_{18}O$: C 84.00%, H 8.46%. Found: C 84.32%, H 8.54%.

(*E*)-1-[(1*R*,2*S*)-(2-Phenylcyclohexyl)oxy]-4-thia-1-hepten-6-yne (4). An anhydrous 0.34 M dichloromethane solution of 2-propynethiol[16] (1 mL, 0.34 mmol) was added *via* cannula to a cold (−78 °C) reaction flask containing solid alkoxyallene **3** (0.056 g, 0.26 mmol) and activated molecular sieves (dust; 3 Å); 4.4 μL (0.03 mmol) of $HBF_4 \cdot Et_2O$ was then added, and the resulting mixture was stirred overnight at room temperature and poured into dichloromethane/saturated aqueous $NaHCO_3$. After separation of the layers, the organic one was washed with water, dried over Na_2SO_4, and stripped of solvents at reduced pressure. The crude product was purified by column chroma-

(20) Negative Cotton effect, $[\theta]_{296} = -4848$ ($c = 2.47 \times 10^{-3}$ M, CH_2Cl_2, 20 °C).

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(23) 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.

tography on Et_3N-pretreated (2.5% v/v) SiO_2, eluting with hexane/diethyl ether mixtures of increasing polarity, to afford 0.057 g (77% yield) of a *ca.* 9:1 mixture of the (*E*)-enyne **4** and its (*Z*) diastereomer, as a colorless oil. $[\alpha]^{23}_D = -30.4$ (*c* 0.028, CH_2Cl_2); IR (NaCl film) $\nu_{max} = 3300, 1660, 1640\ cm^{-1}$; ^1H NMR (200 MHz) δ 1.0−2.0 (m, 8H), 2.15 (t, $J = 2.5$ Hz, 1H, acetylene), 2.62 (td, $J = 10.5$ Hz, $J' = 4.5$ Hz, 1H), 2.91 (dd, $J = 5.1$ Hz, $J' = 2.6$ Hz, 2H), 3.03 (dd, $J = 7.6$ Hz, $J' = 1.0$ Hz, 2H), 3.79 (td, $J = 10.5$Hz, $J' = 4.5$ Hz, 1H), 4.60 (dt, $J = 12.3$ Hz, $J' = 7.8$ Hz, 1H), 6.00 (d, $J = 12.3$ Hz, 1H), 7.10−7.40 (m, 5H); [only the signals corresponding to **4** are quoted, the (*Z*) diastereomer being easily identified on the basis of a characteristic olefinic proton signal: δ 5.90 (d, $J = 6$ Hz, 1H)]; ^{13}C NMR (50.3 MHz) δ 17.2 (CH_2), 24.8 (CH_2), 25.7 (CH_2), 29.5 (CH_2), 32.4 (CH_2), 34.0 (CH_2), 50.4 (CH), 70.6 (CH), 80.0 (C_q), 83.0 (CH), 99.4 (CH), 126.3 (CH), 127.5 (2CH), 128.2 (2CH), 143.4 (C_q), 148.0 (CH); MS (CI-NH_3) *m/e* = 287 ($M^+ + 1$, 100%), 304 ($M^+ + 18$, 5%).

When the reaction was effected on a larger scale (4.67 mmol of allene), **4** was obtained with essentially the same yield (76%).

(4*R*,5*S*)-4-[(1*R*,2*S*)-(2-Phenylcyclohexyl)oxy]-7-thiabicyclo-[3.3.0]oct-1-en-3-one (5). Thermal Reaction. To a stirred solution of $Co_2(CO)_8$ (0.050 g, 0.146 mmol) in isooctane (3 mL), under argon, was added dropwise a solution of the enyne **4** (0.035 g, corresponding to 0.110 mmol of the (*E*) isomer) in isooctane (3 mL), and the resulting solution was stirred at room temperature until complete disappearance of the starting material (TLC) and subsequently heated for 2.5 h at 90 °C. The reaction mixture was cooled to room temperature and filtered through Celite/SiO_2, which was thoroughly washed with dichloromethane. The solvents were distilled at reduced pressure, and the crude product was purified by column chromatography on Et_3N-pretreated (2.5% v/v) SiO_2 (6 g), eluting with hexane diethyl ether mixtures of increasing polarity) to give: (a) 0.011 g (33%) of pure, solid (4*R*,5*S*)-4-[(1*R*,2*S*)-(2-phenylcyclohexyl)oxy]-7-thiabicyclo[3.3.0]oct-1-en-3-one, and (b) 0.002 g of a 1:1 mixture of the same product with its (4*S*,5*R*) diastereomer. The overall yield of the reaction was 38%.

***N*-Oxide-Promoted Reaction.** To a stirred solution of $Co_2(CO)_8$ (0.093 g, 0.272 mmol) in dry dichloromethane (20 mL) under Ar at room temperature was added dropwise a solution of the enyne **5** (0.065 g, 0.204 mmol of the (*E*) isomer) in dichloromethane (15 mL). After 2 h of stirring at room temperature, solid *N*-methylmorpholine *N*-oxide (0.159 g, 1.36 mmol) was added in one portion. Although the reaction was complete after 1 h, as shown by TLC, the reaction mixture was left overnight so that the violet Co precipitate settles out. Working up and filtration through a short pad of Et_3N-pretreated (2.5% v/v) SiO_2 afforded 0.035 g (56% yield) of a 8:1 diastereomer mixture, which was subsequently used without further purification.

Major diastereomer: $[\alpha]^{23}_D = +24.6$ (*c* 0.6, CH_2Cl_2); IR (KBr) $\nu_{max} = 1720, 1630, 1600\ cm^{-1}$; ^1H NMR (200 MHz) δ 1.2−2.0 (m, 7H), 2.30−2.70 (m, 4H), 3.32 (d, $J = 3$ Hz, 1H), 3.57 (s, 2H), 3.50−3.80 (m, 1H), 5.85 (d, $J = 1.4$ Hz, 1H), 7.10−7.40 (m, 5H); ^{13}C NMR (50.3 MHz) δ 25.2 (CH_2), 25.7 (CH_2), 30.2 (CH_2), 33.1 (CH_2), 33.3 (CH_2), 33.6 (CH_2), 51.7 (CH), 53.7 (CH), 85.1 (CH), 86.5 (CH), 124.0 (CH), 126.4 (CH), 128.0 (2CH), 128.3 (2CH), 144.5 (C_q), 177.9 (C_q), 207.8 (CO); MS (CI-NH_3) *m/e* = 315 ($M^+ + 1$, 8%), 332 ($M^+ + 18$, 100%).

When the same reaction was run starting from 3.14 mmol of the enyne, the yield was only 33%, mainly due to decomposition during the chromatographic purification.

(1*R*,4*R*,5*S*)-1-*p*-Tolyl-4-[(1*R*,2*S*)-(2-phenylcyclohexyl)oxy]-7-thiabicyclo[3.3.0]octan-3-one (6). To a cold (−10 °C) suspension of CuI (0.304 g, 1.6 mmol) in anhydrous diethyl ether (0.5 mL) was added dropwise a 1.2 M diethyl ether solution of *p*-tolyllithium (2.65 mL, 3.18 mmol, from *p*-bromotoluene and lithium). After stirring for 10 min at 0 °C, the light green suspension was cooled at −50 °C and treated with a solution of **5** (0.200 g, 0.637 mmol, 8:1 mixture of diastereomers from the *N*-oxide-promoted reaction) in diethyl ether (0.5 mL). The reaction mixture was slowly allowed to warm up to room temperature, stirred overnight, and poured into a mixture of diethyl ether (40 mL), aqueous saturated NH_4Cl (40 mL), and ice. The phases were separated and the organic one was washed with aqueous saturated NH_4Cl until no more blue color appeared in the aqueous layer. The aqueous phases were extracted with diethyl ether (2 × 20 mL), and the combined organic extracts were washed with brine. Drying over Na_2SO_4 and elimination of the solvents at reduced pressure gave a crude product which was purified by column chromatography on SiO_2, eluting with hexane/methylene chloride (5/1) to afford 0.108 g (41% yield) of the bicyclic ketone **6**, as a 8:1 mixture with its (1*S*,4*S*,5*R*) diastereomer, as a colorless oil. $[\alpha]^{23}_D = -53$ (*c* 1.69, CH_2Cl_2); IR (NaCl film) $\nu_{max} = 1750, 1600, 1520\ cm^{-1}$; ^1H NMR (200 MHz, *major diastereomer*) δ 1.0−2.0 (m, 8H), 2.29 (s, 3H), 2.1−2.8 (m, 6H), 3.20 (d, $J = 11.5$ Hz, 1H), 3.56 (d, $J = 10$ Hz, 1H), 3.60−3.70 (m, 1H), 6.90−7.20 (m, 9H); ^{13}C NMR (50.3 MHz, *major diastereomer*) δ 20.8 (CH_3), 25.2 (CH_2), 25.8 (CH_2), 29.7 (CH_2), 33.3 (CH_2), 33.7 (CH_2), 34.4 (CH_2), 44.0 (C_q), 48.8 (CH_2), 51.8 (CH), 56.7 (CH), 85.7 (CH), 85.8 (CH), 125.2 (2CH), 126.5 (CH), 127.9 (2CH), 128.4 (2CH), 129.5 (2CH), 136.5 (C_q), 141.6 (C_q), 144.5 (C_q), 214.2 (CO); MS (CI-NH_3) *m/e* = 407 ($M^+ + 1$, 2%), 424 ($M^+ + 18$, 100%).

(2*R*,3*S*,4*R*)-3,4-Dimethyl-2-[(1*R*,2*S*)-(2-phenylcyclohexyl)oxy]-4-(*p*-tolyl)cyclopentanone (7). A mixture of Raney nickel (0.365 g from a 50% aqueous suspension, rinsed with acetone and ethanol) and the ketone **6** (0.020 g, 0.05 mmol) in ethanol (0.5 mL) was heated to reflux until TLC analysis showed the complete disappearance of starting material (1 h). The Raney nickel was then filtered off and thoroughly rinsed with dichloromethane. Solvent evaporation at reduced pressure gave an oil which was purified by column chromatography on SiO_2, eluting with hexane/methylene chloride (5/1) to afford 0.018 g (95% yield) of **7**, as a 8:1 mixture with its (2*S*,3*R*,4*S*) diastereomer, as an oil. $[\alpha]^{23}_D = -78$ (*c* 0.97, CH_2Cl_2); IR (NaCl film) $\nu_{max} = 1748, 1603, 1514\ cm^{-1}$; ^1H NMR (200 MHz, *major diastereomer*) δ 0.30 (d, $J = 7$ Hz, 3H), 0.40−2.20 (m, 10 H),1.06 (s, 3H), 2.28 (s, 3H), 3.25 (d, $J = 10$ Hz, 1H), 3.75 (td, $J = 10$ Hz, $J' = 4$Hz, 1H), 6.90−7.20 (m, 9H); ^{13}C NMR (50.3 MHz, *major diastereomer*) δ 10.8 (CH_3), 20.7 (CH_3), 21.0 (CH_3), 25.2 (CH_2), 25.8 (CH_2), 34.1 (CH_2), 34.4 (CH_2), 40.1 (C_q), 46.9 (CH), 51.9 (CH), 53.0 (CH_2), 84.3 (CH), 86.2 (CH), 125.5 (2CH), 126.2 (CH), 128.1 (4CH), 128.9 (2CH), 135.6 (C_q), 143.3 ($1C_q$), 144.6 ($1C_q$), 216.4 ($1C_q$, CO); MS (CI-NH_3) *m/e* = 377 ($M^+ + 1$, 1%), 394 ($M^+ + 18$, 100%).

(3*R*,4*R*)-3,4-Dimethyl-3-(*p*-tolyl)cyclopentanone (2). To a cold (−70 °C) 0.1 M THF solution of SmI_2 (Aldrich, 3.06 mL, 0.3 mmol) was added dropwise a solution of the alkoxy ketone **7** (0.045 g, 0.12 mmol) in anhydrous, degassed THF (0.50 mL) and methanol (0.25 mL). After a short time, the progress of the reaction was monitored by TLC and, if some **7** was still present, more 0.1 M SmI_2 solution (1.0 mL) was added and the disappearance of **7** tested again. When the reaction was complete, the remaining Sm(II) was destroyed by addition of moist THF; the reaction mixture was diluted with pentane and treated with aqueous saturated K_2CO_3 solution. The phases were separated, the aqueous one was extracted three times with hexane, and the combined organic extracts were dried over $MgSO_4$. Solvents were removed under vacuum, and the residue was purified by column chromatography on SiO_2, eluting with 1% ethyl acetate/hexane, to afford 0.022 g (91% yield) of **2**, of 77% enantiomeric excess, as a colorless oil, and 0.020 g (95% recovery) of (1*R*,2*S*)-2-phenylcyclohexanol. $[\alpha]^{23}_D = -58$ (*c* 0.5, CH_2Cl_2, 77% ee); IR (NaCl film) $\nu_{max} = 1742, 1603, 1516\ cm^{-1}$; ^1H NMR (200 MHz) δ 1.01 (d, $J = 6.6$ Hz, 3H), 1.05−1.15 (m, 1H), 1.29 (s, 3H), 2.0−2.8 (m, 4H), 2.34 (s, 3H), 7.0−7.2 (m, 4H); ^{13}C NMR (50.3 MHz) δ 14.3 (CH_3), 20.0 (CH_3), 20.8 (CH_3), 29.7 (C_q), 40.8 (CH), 44.5 (CH_2), 55.3 (CH_2), 125.6 (2CH), 129.1 (2CH), 135.8 ($1C_q$), 143.4 (C_q), 217.9 (CO); MS (CI-NH_3) *m/e* = 220 ($M^+ + 18$, 1%), 291 ($M^+ + 35$, 1%), 310 ($M^+ + 90 + 18$, 60%).

(4*R*)-3,4-Dimethyl-4-(*p*-tolyl)-2-cyclopentenone (8). A solution of ketone **2** (0.029 g, 0.143 mmol) in anhydrous THF (0.5 mL) was added *via* cannula to a cold (−78 °C), stirred 0.67 M solution of LDA in THF (0.235 mL, 0.158 mmol). The resulting mixture was stirred for 20 min at the same temperature and treated with a solution of phenylselenenyl bromide (0.040 g, 0.170 mmol) in THF (0.5 mL). After 30 min at −78 °C and 1 h at 0 °C, the reaction mixture was poured into an hexane/saturated aqueous NH_4Cl mixture (10 mL each). The phases were separated, the aqueous one was extracted twice with hexane, and the combined organic extracts were washed with brine and dried over Na_2SO_4. Elimination of the solvents at reduced pressure and subsequent purification by column chromatography on SiO_2 (2 g), eluting with hexane, gave 0.037 g of

(2*R*,3*S*,4*R*)-(3,4-dimethyl)-2-(phenylselenyl)-4-(*p*-tolyl)cyclopentanone (of 77% ee) and 0.008 g of starting material.

α-Phenylseleno Ketone: ^{1}H NMR (200 MHz) δ 1.05 (d, J = 6.6 Hz, 3H), 1.05−1.25 (m, 1H), 1.29 (s, 3H), 2.0−2.8 (m, 2H), 2.31 (s, 3H), 3.30 (d, J = 10 Hz, 1H), 6.9−7.5 (m, 7H), 7.6−7.8 (m, 2H).

A solution of this 2-phenylseleno ketone (0.014 g, 0.039 mmol) in THF (0.5 mL) was treated with water (30 μL), 33% hydrogen peroxide (25 μL), and acetic acid (8 μL), stirred for 1 h at room temperature, poured into a hexane/diethyl ether mixture (5 mL each), and washed with water (3 × 10 mL) and aqueous saturated $NaHCO_3$ solution. The aqueous phase was extracted twice with hexane, and the combined organic phases were first washed with brine and then dried over Na_2SO_4. The solvents were removed at reduced pressure, and the crude product was purified by column chromatography on SiO_2, eluting with pentane/diethyl ether mixtures of increasing polarity, to afford 0.003 g of the starting 2-phenylseleno ketone and 0.0055 g (91% overall yield, based on reacted starting material) of (4*R*)-3,4-dimethyl-4-(*p*-tolyl)-2-cyclopentenone (**8**), whose spectral data were fully coincident with those reported in the literature,[22] as a colorless oil: $[\alpha]^{23}_D$ = +211 (*c* 0.38, $CHCl_3$, 77% ee) {lit.: $[\alpha]^{23}_D$ = +253 (*c* 1.7, $CHCl_3$);[10] $[\alpha]^{29}_D$ = +233 (*c* 1.32, $CHCl_3$)[12c]}; IR (NaCl film) ν_{max} = 1710, 1625, 1515 cm^{-1}; ^{1}H-NMR (300 MHz) δ 1.63 (s, 3H), 1.82 (d, J = 1.2 Hz, 3H), 2.32 (s, 3H), 2.59 (AB system, 2H), 6.02 (q, J = 1.2 Hz, 1H), 7.00−7.20 (m, 4H); ^{13}C NMR (75.4 MHz) δ 14.9 (CH_3), 20.9 (CH_3), 23.7 (CH_3), 49.8 (C_q), 54.4 (CH_2), 125.6 (2CH), 129.4 (2CH), 130.2 (CH), 136.3 (C_q), 141.2 (C_q), 184.70 (C_q), 208.6 (CO).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **2**−**8** (14 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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