Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4681–4686

TETRAHEDRON: *ASYMMETRY*

Synthesis of (*S*)-(−)-β-cuparenone and (*S*)-(−)-cuparene

Bhasker Reddy Aavula, Qi Cui and Eugene A. Mash*

Department of Chemistry, The University of Arizona, Tucson, AZ 85721-0041, USA

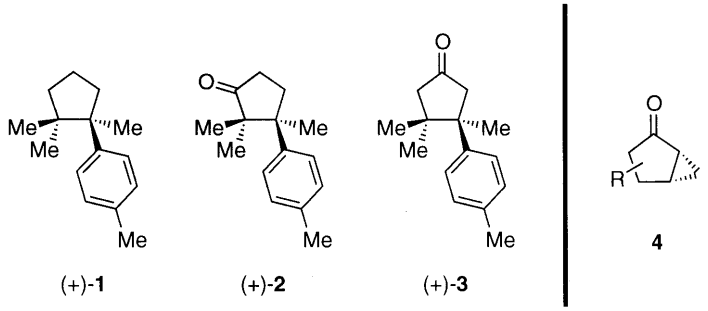
Received 6 October 2000; accepted 6 November 2000

Abstract

A short and efficient synthesis of the title compounds is described. (*S*)-(−)-β-Cuparenone was prepared in 31% yield from *p*-tolualdehyde and mesityl oxide in eight steps. Absolute stereochemistry was established by means of a diastereoselective cyclopropanation using (*R*,*R*)-hydrobenzoin as a recoverable auxiliary.

1. Introduction

In 1958, Erdtman et al. isolated (+)-cuparene, (+)-**1**, and determined its relative structure.[1] In 1964 Chetty and Dev isolated and characterized (+)-α-cuparenone, (+)-**2**, and (+)-β-cuparenone, (+)-**3**.[2] Benesová reported the isolation of (−)-α-cuparenone in 1976,[3a] and Matsuo et al. reported the isolation of (−)-cuparene in 1985.[3b] These sesquiterpenes, which possess adjacent quaternary centers in a cyclopentane ring, have frequently been targets for synthesis.[4–7]



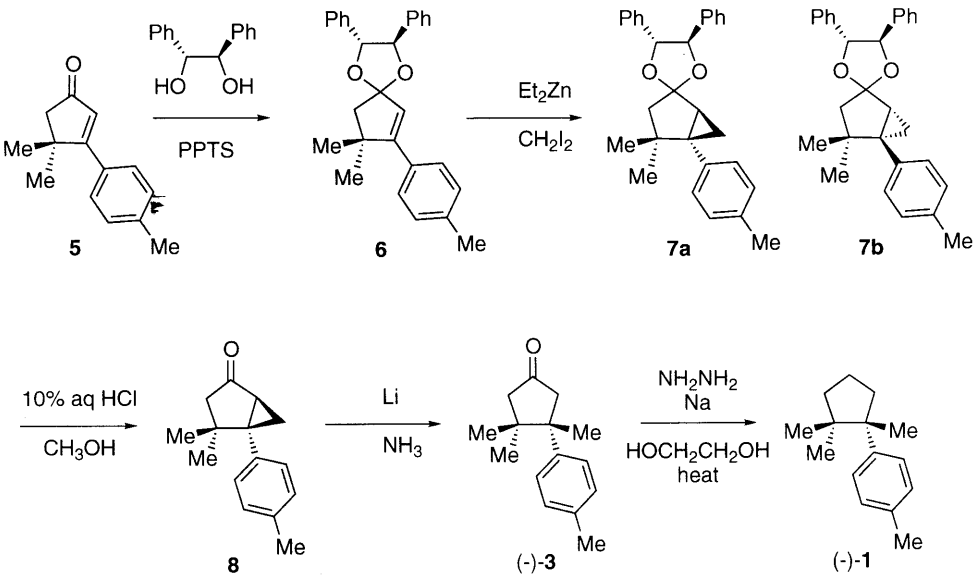
(+)-**1** (+)-**2** (+)-**3** **4**

Substituted bicyclo[*m*.1.0]alkan-2-ones **4** and related compounds are available in either enantiomeric form via diastereoselective cyclopropanation of certain 2-cycloalken-1-one ketals.[8] We have employed such bicycles in natural product synthesis[9] and for establishment of

* Corresponding author. Tel: (520) 621-6321; fax: (520) 621-8407; e-mail: emash@u.arizona.edu

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00457-2

stereogenic quaternary centers.[10] Herein we describe an efficient synthesis of *S*-(−)-β-cuparenone, (−)-**3**,[11] and *S*-(−)-cuparene, (−)-**1** (Scheme 1).



Scheme 1. Synthesis of (*S*)-(−)-β-cuparenone

2. Results and discussion

Ketalization of cyclopentenone 5[6d] using (*R*,*R*)-hydrobenzoin[12] (pyridinium *p*-toluenesulfonate, C_6H_6, reflux, 36 h) gave ketal **6** in 83% yield. Cyclopropanation of **6** using Denmark's protocol[13] (Et_2Zn, CH_2I_2, CH_2Cl_2, 0°C, 2 h) gave an inseparable 14:1 mixture of cyclopropane ketals **7a** and **7b** in 91% yield.[14] Hydrolysis of this mixture (10% aqueous HCl, methanol, room temperature, 1.5 h) gave enantiomerically enriched cyclopropyl ketone **8** in 79% yield.[15] (*R*,*R*)-Hydrobenzoin was also recovered (83%). Assignment of the absolute stereochemistry to the predominant enantiomer of ketone **8** was in keeping with all previous examples.[8,9] Treatment of **8** with lithium in refluxing liquid ammonia[6d,6h] for 15 min afforded *S*-(−)-β-cuparenone, (−)-**3**, in 85% yield, $[\alpha]_D^{25} = -42.1$ (*c* 2.8, $CHCl_3$), lit.[7b] $[\alpha]_D^{29}$ −42 (*c* 0.7, $CHCl_3$).[16] Finally, the Huang–Minlon modified Wolf–Kishner reduction[4e] of (−)-**3** gave *S*-(−)-cuparene, (−)-**1**, $[\alpha]_D^{25} = -58.3$ (*c* 0.3, $CHCl_3$), lit.[3b] $[\alpha]_D = -63$ (*c* 1.6, $CHCl_3$), lit.[5b] $[\alpha]_D^{20} = -59.6$ (*c* 1.9, $CHCl_3$), in 76% yield.[17]

This synthesis of the title compounds is among the most versatile and efficient reported. Both enantiomers of β-cuparenone and cuparene are available from enone **5**[18] and the appropriate hydrobenzoin enantiomer.[12,19] The method can be adapted for the synthesis of the enantiomers of α-cuparenone and for syntheses of other natural products with related structures.

3. Experimental

All reactions were performed in flame-dried glassware under argon. Reaction mixtures were stirred magnetically. Hygroscopic liquids were transferred via syringe. Ketone **5** was prepared by a literature procedure.[6d] Other reagents were purchased from Aldrich Chemical Company. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Dichloromethane was distilled from CaH_2. Analytical thin-layer chromatography was performed on Merck glass-backed pre-coated plates (0.25 mm, silica gel 60, F-254). Visualization of spots was effected by treatment of the plate with a 2.5% solution of anisaldehyde in ethanol containing 6% H_2SO_4 and 2% acetic acid followed by charring on a hot plate. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh). Solutions were concentrated using a rotary evaporator at 30–150 mm Hg. Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ solution. Proton NMR spectra were recorded at 300 MHz using residual $CHCl_3$ (7.24 ppm) as an internal standard. ^{13}C NMR spectra were recorded at 75.0 MHz using the center line of the $CDCl_3$ triplet (77.0 ppm) as an internal standard. All products were judged to be greater than 95% pure on the basis of ^1H and ^{13}C NMR analysis. Diastereomer ratios were determined by GC/MS and confirmed by ^1H and ^{13}C NMR analyses.[14] Mass spectra were obtained from the Mass Spectrometry Lab in the Department of Chemistry at The University of Arizona, Tucson, AZ. Elemental analyses were carried out by Desert Analytics, Tucson, AZ.

*3.1. (2*R*,3*R*)-8,8-Dimethyl-2,3-diphenyl-7-*p*-tolyl-1,4-dioxaspiro[4.4]non-6-ene **6***

To a well stirred solution of 4,4-dimethyl-3-*p*-tolylcyclopent-2-enone **5**[6d] (341 mg, 1.70 mmol) in dry benzene (30 mL) were added (*R*,*R*)-hydrobenzoin[12] (548 mg, 2.56 mmol) and pyridinium *p*-toluenesulfonate (43 mg, 0.17 mmol). The mixture was heated to reflux under argon and water was removed azeotropically by means of a Dean–Stark trap. Progress of the reaction was monitored by TLC. After 36 h the reaction mixture was cooled, diluted with ether (50 mL), washed with sat. aq. $NaHCO_3$ solution (20 mL), sat. aq. NaCl solution (20 mL), dried ($MgSO_4$), and filtered. Volatiles were removed in vacuo and the residue was chromatographed on silica gel eluted with 4% EtOAc/hexanes, affording **6** (563 mg, 1.42 mmol, 83%) as a colorless oil homogeneous by TLC, R_f 0.80 (10% EtOAc/hexanes); $[\alpha]_D^{25} = 11.9$ (*c* 1.5, $CHCl_3$); ^1H NMR δ 7.36–7.26 (m, 12H), 7.18 (d, $J = 7.8$ Hz, 2H), 5.94 (s, 1H), 4.78 (dd, $J = 6.9$, 9.6 Hz, 2H), 2.46 (dd, $J = 11.1$, 24.6 Hz, 2H), 2.38 (s, 3H), 1.4 (s, 3H), 1.34 (s, 3H); ^{13}C NMR δ 158.1, 137.4, 137.0, 136.9, 133.3, 128.7, 128.4, 128.4, 128.2, 127.8, 126.7, 126.7, 126.6, 117.7, 85.6, 85.4, 54.0, 44.9, 28.9, 28.2, 21.2; HRMS (FAB^+) calcd for $C_{28}H_{29}O_2$ ($M+H^+$) 397.2168, found: 397.2167.

*3.2. (1*S*,5*S*,4′*R*,5′*R*)-2,2-Dimethyl-1-*p*-tolyl-4′,5′-diphenylspiro[bicyclo[3.1.0]hexane-4,2′-[1,3]-dioxolane] (**7a**) and (1*R*,5*R*,4′*R*,5′*R*)-2,2-dimethyl-1-*p*-tolyl-4′,5′-diphenylspiro[bicyclo-[3.1.0]hexane-4,2′-[1,3]dioxolane] **7b***

To a well-stirred solution of **6** (500 mg, 1.26 mmol) in CH_2Cl_2 (10 mL) at 0°C was added Et_2Zn (2.5 mL of a 1 M solution in hexanes, 2.5 mmol) via syringe. After 15 min CH_2I_2 (305 μL, 1.01 g, 3.79 mmol) was added and the reaction mixture was stirred at 0°C for 2 h. Saturated aq. $NaHCO_3$ solution (5 mL) was then added slowly and the mixture diluted with CH_2Cl_2 (20 mL). The organic layer was separated, washed with sat. aq. NaCl solution (10 mL), dried ($MgSO_4$), and filtered. Volatiles were removed in vacuo and the residue was chromatographed

on silica gel eluted with 4% EtOAc/hexanes, affording a mixture of **7a** and **7b** (471 mg, 1.15 mmol, 91%) as a colorless oil homogeneous by TLC, R_f 0.81 (10% EtOAc/hexanes); $[\alpha]_D^{25} = -9.96$ (*c* 2.3, $CHCl_3$); ^{1}H NMR δ 7.39–7.30 (m, 10H), 7.26–7.22 (m, 2H), 7.14 (d, $J = 7.8$ Hz, 2H), 4.77 (dd, $J = 8.7$, 14.4 Hz, 2H), 2.36 (s, 3H), 2.08 (dd, $J = 3.0$, 11.7 Hz, 1H), 1.94 (dd, $J = 14.1$, 19.2 Hz, 2H), 1.78 (dd, $J = 3.6$, 5.1 Hz, 1H), 1.16 (s, 3H), 1.01 (s, 3H), 0.89 (dd, $J = 5.4$, 8.4 Hz, 1H); ^{13}C NMR δ 137.6, 137.1, 137.1, 136.2, 130.7, 128.4, 128.4, 128.4, 128.2, 128.2, 126.8, 126.7, 118.1, 85.1, 85.0, 48.2, 41.7, 40.0, 31.4, 27.4, 25.1, 21.1, 14.2; HRMS (FAB$^+$) calcd for $C_{29}H_{31}O_2$ (M+H$^+$) 411.2324, found: 411.2314.

3.3. (1S,5S)-4,4-Dimethyl-5-p-tolylbicyclo[3.1.0]hexan-2-one **8**

To a solution of **7a**/**7b** (400 mg, 0.98 mmol) in methanol (20 mL) at room temperature was added 10% aqueous HCl (2 mL). Progress of the reaction was monitored by TLC. After 90 min the mixture was poured into sat. aq. $NaHCO_3$ solution (20 mL) and extracted with ether (3×50 mL). The combined extracts were dried ($MgSO_4$), and filtered. Volatiles were removed in vacuo and the residue was chromatographed on silica gel eluted with 18% EtOAc/hexanes, affording **8** (165 mg, 0.77 mmol, 79%) as a cream-colored solid, mp 56–57°C, homogeneous by TLC, R_f 0.42 (20% EtOAc/hexanes); $[\alpha]_D^{25} = -16.1$ (*c* 2.6, $CHCl_3$); IR (KBr) 1717 cm^{-1}; ^{1}H NMR δ 7.18 (d, $J = 8.1$ Hz, 2H), 7.11 (d, $J = 8.1$ Hz, 2H), 2.33 (s, 3H), 2.20 (d, $J = 17.4$ Hz, 1H), 2.10 (d, $J = 9.0$ Hz, 1H), 1.88 (d, $J = 18.0$ Hz, 1H), 1.57 (dd, $J = 3.0$, 4.8 Hz, 1H), 1.39–1.34 (m, 1H), 1.21 (s, 3H), 0.91 (s, 3H); ^{13}C NMR 213.0, 137.1, 135.0, 130.3, 128.7, 48.0, 47.0, 38.8, 35.1, 28.3, 24.1, 21.0, 20.6. Anal. calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.13; H, 8.54.

3.4. S-(−)-β-Cuparenone (−)-**3**[6d]

Lithium metal (56 mg, 8.0 mmol) was placed in a flame-dried 50 mL round-bottomed flask under argon. Ammonia (about 20 mL) was condensed into the flask and a solution of cyclopropane **8** (170 mg, 0.79 mmol) and *t*-BuOH (0.5 mL) in dry ether (10 mL) was added via syringe. The mixture was allowed to reflux for 15 min and then solid NH_4Cl (1 g) was added. The ammonia was allowed to evaporate and the remaining solution was diluted with ether (40 mL) and filtered. Volatiles were removed in vacuo and the residue was chromatographed on silica gel eluted with 8% EtOAc/hexanes, affording (−)-**3** (146 mg, 0.68 mmol, 85%) as a colorless oil homogeneous by TLC, R_f 0.43 (20% EtOAc/hexanes); $[\alpha]_D^{25} = -42.1$ (*c* 2.8, $CHCl_3$), lit.[7b] $[\alpha]_D^{29} = -42$ (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 7.20 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.4$ Hz, 2H), 3.13 (d, $J = 18.3$ Hz, 1H), 2.37–2.26 (m, 3H), 2.33 (s, 3H), 1.42 (s, 3H), 1.22 (s, 3H), 0.72 (s, 3H); ^{13}C NMR δ 218.1, 141.2, 135.7, 28.6, 126.4, 52.4, 50.6, 47.7, 41.7, 26.2, 24.4, 24.0, 20.7.

3.5. S-(−)-Cuparene (−)-**1**

To a solution of **8** (100 mg, 0.47 mmol) in diethyleneglycol (2 mL) and ethylene glycol (0.5 mL) was added anhydrous hydrazine (98%, 146 μL). The mixture was heated to 185°C for 2 h, cooled to 70–80°C, and sodium (86 mg, 3.8 mmol) in diethyleneglycol (0.5 mL) was added. After refluxing for 4 h the reaction mixture was poured into ice water (20 mL) and extracted with ether (2×25 mL). The combined extracts were washed with sat. aq. NaCl solution (10 mL), dried ($MgSO_4$), and filtered. Volatiles were removed in vacuo and the residue was chromatographed on silica gel 60 (230–400 mesh) eluted with hexanes, affording pure (−)-**1** (71 mg, 0.36 mmol,

76%) as a colorless oil homogeneous by TLC, R_f 0.72 (hexanes); $[\alpha]_D^{25}$ −58.3 (*c* 0.3, $CHCl_3$), lit.[3b] $[\alpha]_D$ −63 (*c* 1.6, $CHCl_3$), lit.[5b] $[\alpha]_D^{20}$ −59.6 (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.24 (d, $J=7.8$ Hz, 2H), 7.09 (d, $J=7.8$ Hz, 2H), 2.54–2.44 (m, 1H), 2.32 (s, 3H), 1.84–1.63 (m, 4H), 1.59–1.50 (m, 1H), 1.26 (s, 3H), 1.06 (s, 3H), 0.56 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.5, 134.7, 128.2, 126.9, 50.2, 44.2, 39.7, 36.8, 26.4, 24.4, 24.3, 20.8, 19.8.

Acknowledgements

Partial support of this work by the University of Arizona through the Materials Characterization Program is gratefully acknowledged.

References

1. (a) Erdtman, H.; Thomas, B. R. *Acta Chem. Scand.* **1958**, *12*, 267–273; (b) Enzell, C.; Erdtman, H. *Tetrahedron* **1958**, *4*, 361–368.
2. Chetty, G. L.; Dev, S. *Tetrahedron Lett.* **1964**, 73–77.
3. (a) Benesová, V. *Collect. Czech. Chem. Commun.* **1976**, *41*, 3812–3814; (b) Matsuo, A.; Nakayama, N.; Nakayama, M. *Phytochemistry* **1985**, *24*, 777–781.
4. Syntheses of racemic cuparene: (a) Nozoe, T.; Takeshita, H. *Tetrahedron Lett.* **1960**, 14–17. (b) Parker, W.; Ramage, R.; Raphael, R. A. *J. Chem. Soc.* **1962**, 1558–1563. (c) Vig, O. P.; Parti, R. K.; Gupta, K. C.; Bhatia, M. S. *Ind. J. Chem.* **1973**, *11*, 981–982. (d) Bird, C. W.; Yeong, Y. C. *Synthesis* **1974**, 27–28. (e) de Mayo, P.; Suau, R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2559–2561. (f) Kametani, T.; Tsubuki, M.; Nemoto, H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 759–761. (g) Reetz, M. T.; Westermann, J.; Steinbach, R. *J. Chem. Soc., Chem. Commun.* **1981**, 237–239. (h) Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Chem. Commun.* **1985**, 1324–1325. (i) Shiao, M.-J.; Liang, D.; Ku, C.-S.; Yang, C.-H. *Synth. Commun.* **1988**, *18*, 1553–1563. (j) Bovicelli, P.; Mincione, E. *Synth. Commun.* **1988**, *18*, 2037–2050. (k) Ishibashi, H.; So, T. S.; Nakatani, H.; Minami, K.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1988**, 827–828. (l) Bailey, W. F.; Khanolkar, A. D. *Tetrahedron* **1991**, *47*, 7727–7738. (m) Mandelt, K.; Fitjer, L. *Synthesis* **1998**, 1523–1526. (n) Ho, T.-L.; Chang, M.-H *J. Chem. Soc., Perkin Trans. 1* **1999**, 2479–2482.
5. Syntheses of enantiomerically enriched cuparene: (a) Subba Rao, H. N.; Damodaran, N. P.; Dev, S. *Tetrahedron Lett.* **1968**, 2213–2214. (b) Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; García, M. T.; Zaragozá, R. J. *J. Org. Chem.* **1996**, *61*, 5916–5919. (c) Fuganti, C.; Serra, S. *J. Org. Chem.* **1999**, *64*, 8728–8730.
6. Syntheses of racemic β-cuparenone: (a) Lansbury, P. T.; Hilfiker, F. R. *J. Chem. Soc., Chem. Commun.* **1969**, 619–620. (b) Mane, R. B.; Rao, G. S. K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1806–1808. (c) Leriverend, P. *Bull. Soc. Chim. Fr.* **1973**, 3498–3499. (d) Casares, A.; Maldonado, L. A. *Synth. Commun.* **1976**, *6*, 11–16. (e) Jung, M. E.; Radcliffe, C. D. *Tetrahedron Lett.* **1980**, *21*, 4397–4400. (f) Halazy, S.; Zutterman, F.; Krief, A. *Tetrahedron Lett.* **1982**, *23*, 4385–4388. (g) Greene, A. E.; Lansard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *49*, 931–932. (h) Srikrishna, A.; Krishnan, K. *Tetrahedron* **1992**, *48*, 3429–3436. (i) Flemming, S.; Kabbara, J.; Nickisch, K.; Neh, H.; Westermann, J. *Synthesis* **1995**, 317–320.
7. Syntheses of enantiomerically enriched β-cuparenone: (a) Greene, A. E.; Charbonnier, F.; Luche, M.-J.; Moyano, A. *J. Am. Chem. Soc.* **1987**, *109*, 4752–4753. (b) Gharpure, M. M.; Rao, A. S. *Synth. Commun.* **1989**, *19*, 679–688. (c) Asaoka, M.; Hayashibe, S.; Sonoda, S.; Takei, H. *Tetrahedron Lett.* **1990**, *31*, 4761–4764. (d) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.* **1992**, *33*, 329–332. (e) Sato, T.; Hayashi, M.; Hayata, T. *Tetrahedron* **1992**, *48*, 4099–4114. (f) 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.
8. (a) Mash, E. A.; Math, S. K.; Arterburn, J. B. *J. Org. Chem.* **1989**, *54*, 4951–4953; (b) Mash, E. A.; Torok, D. S. *J. Org. Chem.* **1989**, *54*, 250–253; (c) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679–692; (d) Yeh, S.-M.; Huang, L.-H.; Luh, T.-Y. *J. Org. Chem.* **1996**, *61*, 3906–3908.

9. (a) Nelson, K. A.; Mash, E. A. *J. Org. Chem.* **1986**, *51*, 2721–2724; (b) Mash, E. A.; Fryling, J. A. *J. Org. Chem.* **1987**, *52*, 3000–3003; (c) Mash, E. A. *J. Org. Chem.* **1987**, *52*, 4142–4143; (d) Mash, E. A.; Math, S. K.; Flann, C. J. *Tetrahedron* **1989**, *45*, 4945–4950; (e) see also: Kabat, M. M.; Kiegiel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1996**, *61*, 118–124; (f) Cossy, J.; BouzBouz, S. *Tetrahedron Lett.* **1996**, *37*, 5091–5094.
10. (a) Mash, E. A.; Baron, J. A.; Gregg, T. M.; Nimkar, S. K. *Tetrahedron* **1998**, *54*, 2669–2682; (b) Mash, E. A.; Baron, J. A. *J. Org. Chem.* **1999**, *64*, 7412–7418.
11. In some references[7b] (–)-β-cuparenone is incorrectly assigned the *R* configuration.
12. Available from Aldrich Chemical Company. For large scale preparation, see: Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302–8303.
13. Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974–6981.
14. This diastereomer ratio was determined by GC/MS and was confirmed by integration of signals in the ^{13}C NMR. For use of ^{13}C NMR in determining diastereomer ratios, see: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2183–2186.
15. The expected enantiomeric excess (ee) for **8** based on the 14:1 diastereomer ratio obtained for **7a**:**7b** is 87%. Although **8** was obtained as a solid, recrystallization did not increase the ee as determined by measurement of the optical rotation.
16. The maximum specific rotation reported for a β-cuparenone enantiomer is +48.5 (Ref. 5c). The specific rotation of –42.1 obtained in this work thus represents an ee of 87%.
17. The maximum specific rotation reported for a cuparene enantiomer is +66.4 (Ref. 7e). The specific rotation of –58.3 obtained in this work thus represents an ee of 88%.
18. Enone **5** is available from *p*-tolualdehyde and mesityl oxide in >60% yield over four steps; see Ref. 6d.
19. The yield of (–)-**3** from **5** was 51% over four steps.