NCH_2CH_2), 4.20 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 4.46 (q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 7.42 (d, 1 H, J = 8.6 Hz, Ar-H), 7.43 (s, 1 H, furan H), 8.46 (d, 1 H, J = 8.6 Hz, Ar-H); IR (KBr, cm^{-1}), 1720 (C=O), 1660 (C=O), 1600, 1572, 1485, 1470, 1452, 1430, 1405, 1370, 1340, 1295, 1240, 1185, 1140, 1130, 1120, 1110, 1055, 1020, 990, 815, 765, 645; MS (EI) m/e (relative intensity) 273 (M^+, 65.6), 232 (14.4), 231 (100), 203 (48.9), 202 (20.1), 158 (13.0), 157 (13.3), 130 (23.2), 129 (11.3), 128 (11.7), 102 (11.0), 77 (13.9); HRMS (CI) m/e (M^+) 273.0993 (calcd for $C_{15}H_{15}NO_4$ 273.1001).

6-(Aminocarbonyl)-7,8-dihydro-6*H*-furo[3,2-*e*]indole-2-carboxylic Acid (7). A suspension of **35b** (0.27 g, 1.0 mmol) in methanol (15 mL) was basified with 0.1 N NaOH to pH 10 and was stirred until starting material was consumed as indicated by TLC. The solution was acidified with 0.1 N HCl to pH 1 and chilled, and the solid was filtered and dried over P_2O_5 to yield acid **7** [0.20 g (80%)] as an off-white solid: dec pt >230 °C; ^1H NMR (Me_2SO-d_6) δ 3.30 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 4.01 (t, 2 H, J = 8.6 Hz, NCH_2CH_2), 6.27 (s, 2 H, $CONH_2$), 7.40 (d, 1 H, J = 9.1 Hz, Ar-H), 7.57 (s, 1 H, furan H), 8.13 (d, 1 H, J = 9.0 Hz, Ar-H); IR (KBr, cm^{-1}) 3460 (NH), 3340, 3220, 1690 (C=O), 1565, 1500, 1430, 1355, 1320, 1300, 1240, 1195, 1140, 1050, 950, 920, 810, 790, 775, 685, 640; MS (EI) m/e 246 (M^+, 3.2), 231 (8.0), 204 (12.0), 203 (100.0), 202 (36.5), 158 (11.0), 157 (12.1), 130 (35.0), 129 (12.6), 128 (10.6), 44 (15.3), 43 (22.4); HRMS m/e (M^+) 246.0630 (calcd for $C_{14}H_{12}N_2O_4$ 246.0641).

6-Acetyl-7,8-dihydro-6*H*-furo[3,2-*e*]indole-2-carboxylic Acid (9). A suspension of urea **35b** (0.10 g, 0.4 mmol) in methanol (15 mL) was basified with 0.1 N NaOH to pH 10 and was stirred until starting material was consumed as indicated by TLC. The solution was acidified with 0.1 N HCl to pH 1 and chilled and the solid filtered and dried to yield **9** [78 mg (80%)] as an off-white solid, which crystallized from methanol: dec pt >275 °C; ^1H NMR (Me_2SO-d_6) δ 2.18 (s, 3 H, $COCH_3$), 3.34 (t, 2 H, J = 8.5 Hz, NCH_2CH_2), 4.20 (t, 2 H, J = 8.5 Hz, NCH_2CH_2), 7.48 (d, 1 H, J = 8.9 Hz, Ar-H), 7.63 (s, 1 H, furan H), 8.30 (d, 1 H, J = 8.9 Hz, Ar-H); IR (KBr, cm^{-1}) 2500 (br), 1730 (C=O), 1720 (C=O), 1620, 1580, 1500, 1420, 1365, 1285, 1250, 1190, 1140, 1030, 990, 970, 945, 895, 870, 840, 800, 775, 760, 700, 600; MS (EI) m/e 246 (M + 1, 5.0), 245 (M^+, 36.1), 204 (12.1), 203 (100.0), 202 (36.5), 159 (10.6), 158 (15.5), 130 (17.7), 43 (11.3); HRMS m/e (M^+) 245.0689 (calcd for $C_{13}H_{11}NO_4$ 245.0688).

Acknowledgment. This work was supported by a grant from the National Institutes of Health (No. NIH-CA 41995). We thank Dr. C. Costello and the NIH regional mass spectrometry laboratory at MIT for some HRMS data (National Institutes of Health Research Grant No. RR00317).

Registry No. **1**, 69866-21-3; **4**, 105518-47-6; **5**, 105518-48-7; **6**, 105518-58-9; **7**, 105518-66-9; **8**, 105518-59-0; **9**, 105518-67-0; **11**, 99230-18-9; **12**, 7126-50-3; **14**, 54828-79-4; *cis*-**15**, 105518-37-4; *trans*-**15**, 105518-38-5; **16**, 105518-39-6; *cis*-**17**, 105518-40-9; *cis*-**17** (1*H*,1'*H*-dipyrrole), 105518-41-0; *trans*-**17**, 105537-39-1; *trans*-**17** (1*H*,1'*H*-dipyrrole), 105518-42-1; **18**, 105518-43-2; **19**, 105518-44-3; **20**, 105518-45-4; **21**, 105518-46-5; **22**, 82221-06-5; *cis*-**23**, 105518-49-8; *trans*-**23**, 105518-50-1; *cis*-**24**, 99702-11-1; *trans*-**24**, 99702-10-0; **25**, 105518-51-2; **26**, 99702-03-1; **27**, 95334-62-6; **28a**, 105518-52-3; **28b**, 105518-60-3; **29a**, 105518-53-4; **29b**, 105518-61-4; **32a**, 105518-54-5; **32b**, 105518-62-5; **33a**, 105518-55-6; **33b**, 105518-63-6; **34a**, 105518-56-7; **34b**, 105518-64-7; **35a**, 105518-57-8; **35b**, 105518-65-8; *N*-methylpyrrole, 96-54-8; *N,N*-1-trimethyl-1*H*-pyrrole-2-methanamine, 56139-76-5; *N,N,N*-2-tetramethyl-1*H*-pyrrole-2-methanaminium iodide, 54828-80-7; *N,N*-dimethyl-1*H*-pyrrole-2-methanamine, 14745-84-7; *N,N,N*-trimethyl-1*H*-pyrrole-2-methanaminium iodide, 53267-97-3; pyrrole, 109-97-7; *N*-benzylpyrrole, 2051-97-0; *N,N*-dimethyl-1-(phenylmethyl)-1*H*-pyrrole-2-methanamine, 26235-82-5; *N,N,N*-trimethyl-1-(phenylmethyl)-1*H*-pyrrole-2-methanaminium iodide, 60730-16-7; 2-thiophenecarboxaldehyde, 98-03-3; furfural, 98-01-1.

Enantioselective Ring Construction: Synthesis of (+)-Estrone Methyl Ether

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Received July 18, 1986

A general method for the construction of functionalized cyclopentane derivatives **10** of high optical purity, via diastereoselective intramolecular C–H insertion, is described. A methylation–retro Dieckmann dianion alkylation procedure on **10b** (R = vinyl) gives **12**. Decarbomethoxylation of **12** followed by thermolysis yields (+)-estrone methyl ether **1** having 91% ee.

The estrogenic steroids have been the target of extensive synthetic investigation,[2] both because they are economically significant and because they are among the structurally simplest biologically active representatives of the steroid family. We report herein the details of a general method for the construction of functionalized cyclopentanes of high optical purity[3] and the application of this method to the enantioselective construction of (+)-estrone methyl ether **1**.[4]

In considering a route to estrone that might be modified to allow enantioselection, we were led to the *o*-quinone methide mediated intramolecular Diels–Alder approach pioneered by Oppolzer[5] and Kametani.[6,7] While ketone

(1) Fellow of the Alfred P. Sloan Foundation, 1983–1987.

(2) (a) For a summary of previous routes to the estrogens, see: Taub, D. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed. Wiley: New York, 1973; p 641. (b) For a more recent approach, see: Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1984**, *25*, 2121.

(3) A portion of this work was reported in a preliminary communication: Taber, D. F.; Raman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935.

(4) For a review of enantioselective routes to the steroids, see: (a) Quinkert, G.; Stark, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 637. For more recent approaches, see: (b) Stevens, R. V.; Gaeta, F.C.A.; Lwarence, D. S. *J. Am. Chem. Soc.* **1983**, *105*, 7713. (c) Magriotis, P. A.; Johnson, F. *J. Org. Chem.* **1984**, *49*, 1460. (d) Takahashi, T.; Okumoto, H.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 1975. (e) Hutchinson, J. H.; Money, T. *Tetrahedron Lett.* **1985**, *26*, 1819. (f) Posner, G. H.; Switzer, C. *J. Am. Chem. Soc.* **1986**, *107*, 1239.

(5) Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3833.

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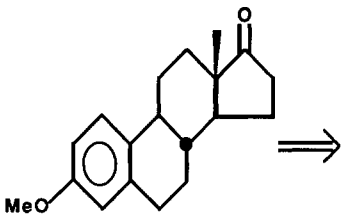
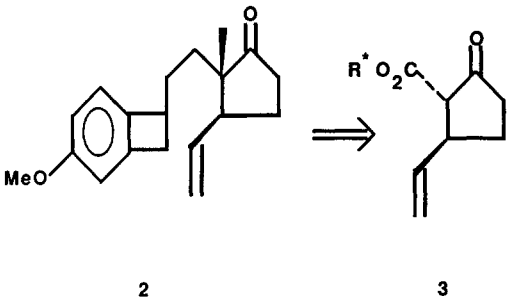


1



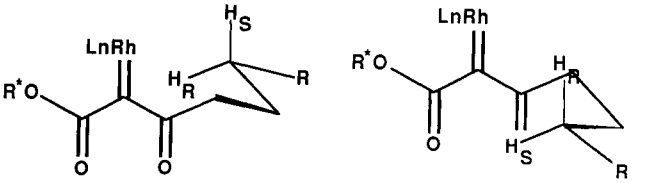
2 3

2, as such, had not previously been prepared, thermolysis to the *o*-quinone methide and subsequent cyclization to give 1 seemed amply precedented.

Intermediate 2 contains two stereogenic[8] centers. The configuration of the center α to the ketone seemed controllable by a geminal alkylation procedure, the second alkylation being expected to occur trans to the β-vinyl group. The absolute stereochemistry of 1, then, would derive directly from the absolute stereochemistry of cyclopentane 3. We had previously prepared racemic 3 (R* = CH_3) by rhodium-mediated intramolecular C–H insertion.[9] We therefore sought a way to make this latter process enantioselective.

Enantioselective C–H Insertion. To achieve enantioselection in the course of intramolecular C–H insertion, it was necessary to first understand the three-dimensional structure of the two enantiomeric transition states. We are handicapped at this point in the synthetic design by our limited understanding of the arrangement of ligands around the central rhodium atom in the intermediate metallocarbene. Making the assumption that the β-dicarbonyl unit is syn-planar,[10] however, and that the ethane units between the ketone and the target methylene will tend to be staggered and knowing the substantial preference for five-membered ring formation,[9] it seemed plausible that the two enantiomeric transition states could be represented as 4 and 5. Implicit in this analysis is the assumption that insertion proceeds with retention of absolute configuration.[22]

To achieve enantioselectivity (diastereoselectivity), it is necessary to selectively destabilize one of these two transition states. We sought to accomplish this by attaching a chiral alcohol R*OH to selectively block one face to the



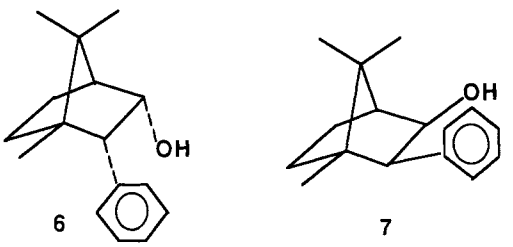
4 5

β-keto ester. The central challenge of this investigation was the judicious design of R*OH.

Our approach was based on the assumption that the ester would adopt the more stable extended conformation.[11] Clearly, if R*OH were a primary alcohol, the system would be too flexible to hope for good diastereoselection. If R*OH were tertiary, the two extended ester conformations would likely be of comparable energy, and thus of equal population, again making the system too flexible. It was clear that R*OH should be a secondary alcohol.

To impart additional rigidity to the system, R*OH should be a *cyclic* secondary alcohol. Ring size was important. If an adjacent group was to cover one face of the β-keto ester, then the substituents on the ring should be eclipsed, rather than staggered. This suggested the use of a cis-substituted cyclopentane.

While optical resolution was possible, it seemed desirable to prepare the desired cyclopentyl R*OH from starting material of high optical purity. A bornane derivative suggested itself, and in fact a brief survey turned up two likely candidates, 6 and 7, both readily available[12] from (+)-camphor.



6 7

While both 6 and 7 might seem plausible candidates, in fact 7 is much better. While esters derived from 6 have two readily available extended conformations, esters derived from 7 have only one, the alternative extended conformation being destabilized by steric interaction with the 7-methyl. In fact, cyclization of the ester derived from 6 led to a 67:33 mixture of diastereomers, while cyclization of the ester derived from 7 gave two diastereomers in a ratio of 81:19.

In a minor modification, the phenyl group in 7 was changed to a 1-naphthyl group, to give 8. An improved procedure for the preparation of the nicely cystalline 8 is given in the Experimental Section.[13]

(6) Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 3378.

(7) For reviews of *o*-quinone methide applications, see: (a) Oppolzer, W. *Synthesis* **1978**, 793. (b) Kametani, T. *Pure Appl. Chem.* **1979**, *51*, 747. (c) Funk, R. L.; Vollhardt, K.P.C. *Chem. Soc. Rev.* **1980**, *9*, 41. (d) Oppolzer, W. *Heterocycles* **1980**, *14*, 1615.

(8) Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.

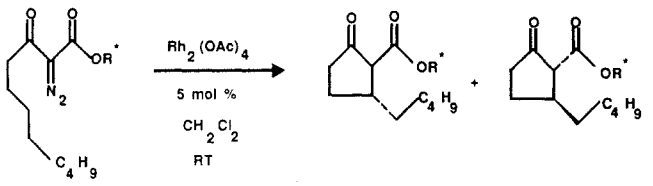
(9) (a) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. (b) The preponderant formation of cyclopentane products can be rationalized by assuming that there is significant bonding between the *carbon* atoms in the transition state, leading to cyclization. We thank Professor Akira Oku for making this suggestion.

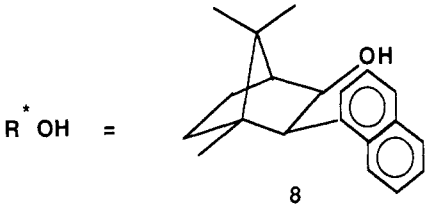
(10) Preliminary calculations indicate a preference for the syn conformer for singlet diacyl carbene: Houk, K. N. personal communication, UCLA.

(11) Grindley, T. B. *Tetrahedron Lett.* **1982**, *23*, 1757 and references cited therein.

(12) Coxon, J. M.; Hartshorn, M. P.; Lewis, A. J. *Aust. J. Chem.* **1971**, *24*, 1017.

(13) Concurrently with our work, others have investigated chiral induction with modified bornyl esters. For leading references, see: (a) Helmchen, G.; Schmierer, R. *Tetrahedron Lett.* **1983**, *24*, 1235. (b) Oppolzer, W.; Chapuis, C. *Tetrahedron Lett.* **1983**, *24*, 4665.





8

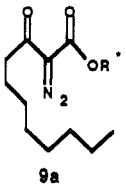
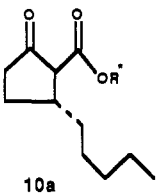
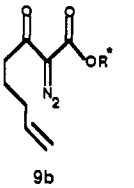
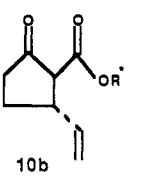
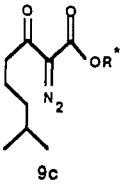
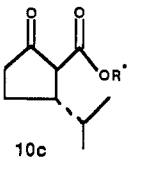
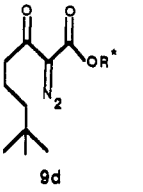
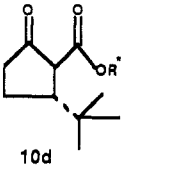
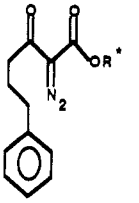
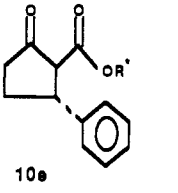
We have briefly surveyed the cyclization of a range of respresentative β-keto esters of **8** (Table I). In three of the five cases (**10a, 10b, 10e**), the absolute stereochemistry of the major diastereomer was confirmed by optical rotation.[14] The other two (**10c, 10d**) are assumed to have the same absolute configuration. While diastereoselectivity is good in all cases, it is better in some cases than in others. We are actively investigating the variables in this reaction, especially the influence of different ligands on rhodium, in an effort to improve diastereoselectivity.[17] In the meantime, it should be noted that the diastereomeric esters are separable chromatographically,[18] opening a practical route to cyclopentane derivatives of high optical purity.

Synthesis of (+)-Estrone Methyl Ether. The key to the elaboration of **2** from **3** (Scheme I) is the development of a new strategy for effecting geminal alkylation of a cyclic β-keto ester. In brief, α methylation of **10b** followed by exposure of the resultant nonenolizable β-keto ester to anhydrous sodium methoxide[19] yields **11**, at the same time liberating R*OH for recycling. In **11**, the target center is once again activated for alkylation, this time via the dianion[20] of the β-keto ester.

The requisite iodide **16** was prepared by a modification of the procedure of Kametani[21] (Scheme II). In the event, dianion formation and alkylation proceeded smoothly to give **12**. Decarbomethoxylation followed by thermolysis then gave (+)-estrone methyl ether.

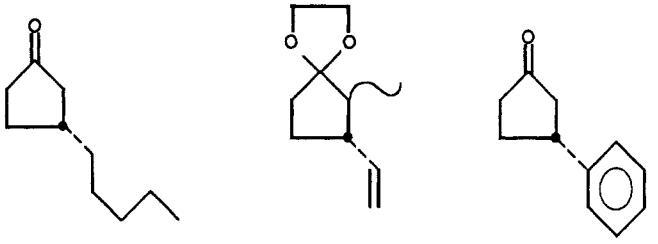
The development of new methods for carbocyclic ring formation is basic to the development of synthetic organic chemistry. As synthetic targets become more sophisticated, the development of strategies for the enantioselec-

Table I

starting diazo ester	product[a]		diastereoselectivity[c]
 9a	 10a	60	87:13
 9b	 10b	62	92:8
 9c	 10c	60	83:17
 9d	 10d	55	83:17
 9e	 10e	62	85:15[d]

[a] The absolute configurations of **10a, 10b,** and **10e** were assigned by correlation with known optical rotations.[14] The major diastereomer is shown. [b] Yield of pure chromatographed material. [c] Diastereoselectivity calculated on the basis of HPLC analysis. [d] Diastereoselectivity calculated by conversion to the α,β-unsaturated ester followed by HPLC analysis.

(14) The absolute configuration of **100** was confirmed by decarbalkoxylation to iv; $[\alpha]_D$ +86.7°. A sample of iv prepared by our published procedure[15] showed $[\alpha]_D$ +107°. Similarly **10b** was converted (ethylene glycol, H+; Dibal; *N,N*-dimethylsulfamoyl chloride; Na, NH_3) to v, $[\alpha]D$ −23.6° (lit.[16] $[\alpha]_D$ −24.1°). Finally, decarbalkoxylation (Me_2SO, H_2O, NaCl, 170 °C) of **10e** proceeded, with substantial racemization, to give vi, $[\alpha]_D$ +45.9°. Professor G. Posner (personal communication) reports $[\alpha]_D$ −87.6° for the enantiomer.

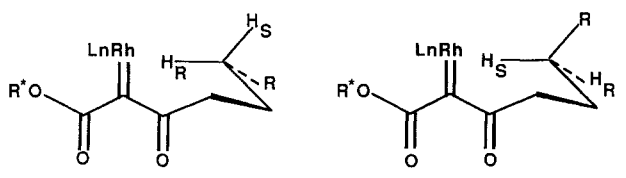


iv v vi

(15) Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699.

(16) Quinkert, G.; Schwartz, U.; Stark, H.; Weber, W.-D.; Baier, H.; Adam, F.; Durner, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1029.

(17) This outcome can be rationalized by postulating a somewhat flattened transition state, as shown. While there would seem to be an inherent preference for the endo transition state, the exo transition state becomes more competitive as R becomes sterically more demanding.



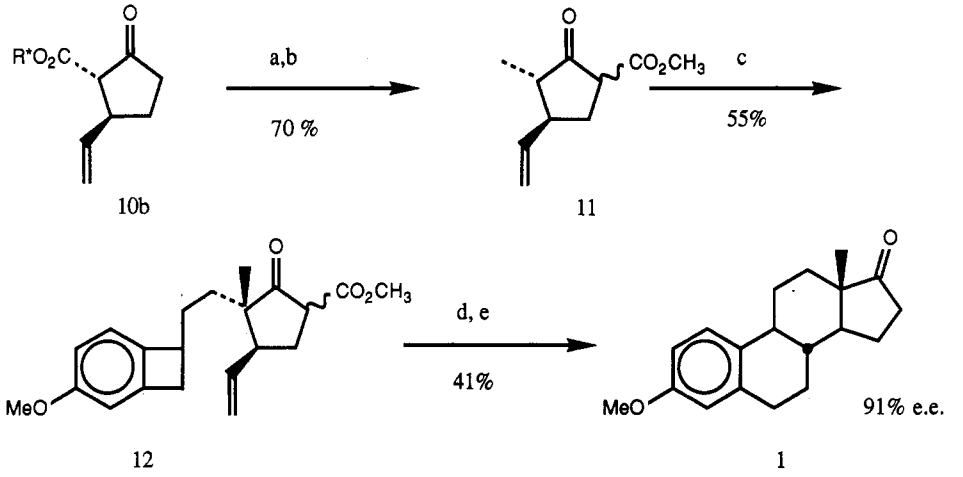
(18) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

(19) Meyer, W. L.; Lobo, A. P.; Marquis, E. T. *J. Org. Chem.* **1965**, *30*, 181.

(20) Schlessinger, R. H.; Wood, J. L.; Poss, A. J.; Nugent, R. A.; Parsons, W. H. *J. Org. Chem.* **1983**, *48*, 1146.

(21) Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Matsumoto, H.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 3461.

Scheme I[a]



[a] Key: (a) CH_3I, *t*-BuOK/THF, Δ; (b) $NaOCH_3$/xylene, Δ; (c) 2.5 LDA, THF, 40 °C, 2.5 h; 16, THF, 0 °C, 1 h; (d) NaCl, H_2O, Me_2SO, Δ; (e) *o*-dichlorobenzene, Δ.

tive construction of carbocycles will be increasingly important.[22] We propose that the approach outlined above, detailed transition-state analysis leading to design of a substrate for which one of two enantiomeric (diastereomeric)[23] transition states is selectively destabilized, should be applicable to a wide variety of ring-forming reactions.[24]

(22) Several strategies for the enantioselective preparation of carbocycles have been reported. Leading references follow. (a) Intermolecular Diels–Alder reaction: Ensley, H. E.; Parnell, C. A.; Corey, E. J. *J. Org. Chem.* **1978**, *43*, 1610. Horton, D.; Machinami, T. *J. Chem. Soc., Chem. Commun.* **1981**, 88. Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Tetrahedron Lett.* **1984**, *25*, 5885. (b) Intramolecular Diels–Alder reaction: Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261. (c) Intermolecular alkylation: Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2718. Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Durelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081. (d) Intramolecular alkylation: Quinkert, G.; Schwartz, U.; Stark, H.; Weber, W.-D.; Baier, H.; Adam, F.; Durner, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1029. Yamamoto K.; Tsuji, J. *Tetrahedron Lett.* **1982**, *23*, 3089. (e) Chiral Michael donor: Takahashi, T.; Okumoto, H.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 1975. Yamamoto, K., Iijima, M.; Ogimura, T.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 2812. Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273. Hua, D. H.; Sinai-Zingde, G.; Venkataraman, S. *J. Am. Chem. Soc.* **1985**, *107*, 4088. (f) Chiral Michael acceptor: Kogen, H.; Tomioka, K.; Hashimoto, S.-I.; Koga, K. *Tetrahedron* **1981**, *37*, 3951. Posner, G. H.; Hulce, M.; Mallamo, J. P.; Drexler, S. A.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 5246. (g) Intramolecular aldol condensation: Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699. (h) Cyclopropanation: Mukaiyama, T.; Fujimoto, K.; Takeda, T. *Chem. Lett.* **1979**, 1207. Monpert, A.; Martelli, J.; Gree, R.; Carrie, R. *Tetrahedron Lett.* **1981**, *22*, 1961. Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1982**, *23*, 685. Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 4290. (i) Biomimetic polyolefin cyclization: Demailly, G.; Solladie, G. *Tetrahedron Lett.* **1980**, *21*, 3355. Sakane, S.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 6154. (j) [2 + 2] cycloaddition: Houge, C.; Frisque-Hesbain, A. M.; Mockel, A.; Declerq, J. P.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *102*, 2920. Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 3035. (k) Intramolecular ene: Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1984**, *49*, 183. (l) Intramolecular C–H insertion: Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196. Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557.

(23) The enantiomeric transition states (e.g., **3** and **4**) become diastereomeric when remote chiral centers (e.g., those of alcohol **7**) are included in the analysis.

(24) The catalytic studies reported here are clearly relevant to stoichiometric studies of Rh-mediated C–H activation reported recently: (a) Periana, R. A.; Bergman, R. G. *Organometallics* **1984**, *3*, 508. (b) Jones, W. D.; Feher, F. J. *J. Am. Chem. Soc.* **1984**, *106*, 1650.

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(27) Preparation of anhydrous sodium methoxide: Dry methanol was prepared by distillation from methyl benzoate, after extended reflux. Clean sodium metal was added to the methanol so prepared. After the reaction had subsided, xylene was added, and excess methanol was removed by distillation.

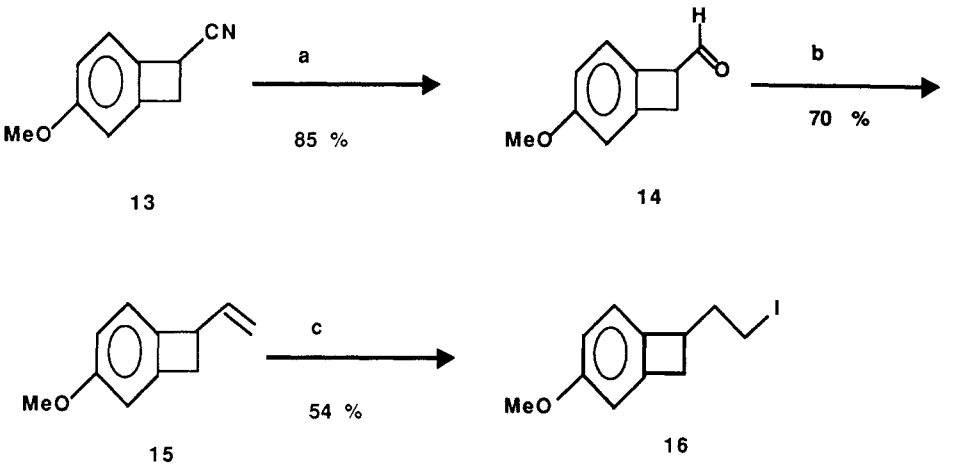
Experimental Section

General Procedures. ^1H NMR spectra were recorded on Perkin-Elmer R12 and Bruker WM-250 spectrometers as solution in $CDCl_3$. ^{13}C NMR spectra were determined on a Bruker WM-250 spectrometer. Chemical shifts are reported in δ units downfield from the internal reference tetramethylsilane. The couplings (*J*) are in hertz (Hz). The infrared (IR) spectra were determined on a Perkin-Elmer 180 spectrometer and are reported in reciprocal centimeters (cm^{-1}). Mass spectra (MS) were taken at 70 eV on a Du Pont 21-492B mass spectrometer and are reported as mass per unit charge (m/z), with intensities as a percentage of the peak of greatest ion current having m/z 100 in parentheses. CH analysis was provided by Galbraith Laboratories. Compounds **10a–10e** are nonvolatile oils that do *not* give acceptable analysis. High-pressure liquid chromatography was done with a Du Pont ZORBAX ODS 4.6 mm × 25 cm column, eluting with 9:1 MeOH/H_2O, at a flow rate of 0.8 mL/min. Rotations were determined on a Rudolph Autopol III automatic polarimeter as solutions in absolute ethanol, unless otherwise noted. Organic chemicals were purchased from Aldrich Chemical Co. Organometallics were obtained from Alfa Inorganics and were titrated before use. Tetrahydrofuran (THF) was purified by distillation from sodium/benzophenone ketyl. The solvent mixtures used for chromatography (e.g., 5% ethyl acetate/hexane) are volume/volume mixtures. R_f values indicated refer to thin-layer chromatography on Analtech 2.5 × 10 cm, 250-μm analytical plates coated with silica gel GF. Column chromatography was carried out using TLC-mesh silica gel, following the procedures we have described.[18]

Preparation of Naphthylborneol (8). A solution of 1-bromonaphthalene (85 mL, 611 mmol, 1.03 equiv) in THF (100 mL) was added dropwise with magnetic stirring to a 3-L, three-necked, round-bottomed flask (equipped with a dropping funnel, condenser, and stopper) constaining magnesium turnings (18.1 g, 745 mmol, 1.26 equiv) in THF (200 mL) under an N_2 atmosphere. After the initial reaction had subsided, the solution was heated to reflux for an additional 10 min. A solution of (+)-camphor (90 g, 591 mmol) in THF (100 mL) was then added, and the reaction mixture was warmed to reflux for 75 h. The mixture was cooled in an ice/water bath and then quenched with saturated aqueous NH_4Cl (150 mL). The organic layer was filtered, and the residual solid was suspended in 10% aqueous HCl (50 mL) and extracted with ether. The ether extracts were combined with the above filtrate, dried (Na_2SO_4), and concentrated in vacuo.

The residual oil was diluted with 250 mL of pyridine, and the mixture was cooled in an ice/water bath. Thionyl chloride (22 mL) was added rapidly dropwise, and the mixture was stirred for 1 h. The reaction mixture was diluted with water (150 mL) and then extracted with petroleum ether (3 × 150 mL). Each petroleum ether extract was washed, sequentially, with 10% aqueous HCl, saturated aqueous $CuSO_4$ solution, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The combined organic

Scheme II[a]



[a] Key: (a) Dibal; H_2SO_4/H_2O; (b) $Ph_3P{=}CH_2$, THF; (c) BH_3·T-HF; chloramine-T, NaI.

layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was distilled bulb-to-bulb at 0.5 mm to remove camphor and naphthalene. The liquid pot residue weighed 65 g.

Borane–methyl sulfide complex (10 M in BH_3, 35 mL, 350 mmol, 1.5 equiv) was added to a solution of the crude olefin in 75 mL of toluene at room temperature. The mixture was warmed to reflux for 5 h then allowed to stir overnight at room temperature. The liberated dimethyl sulfide was allowed to bubble through a breaker of mineral oil as the reaction was heated. The mixture was cooled in an ice/water bath for 0.5 h, and then 50% NaOH (100 mL) was added dropwise followed sequentially by dropwise addition of ethanol (50 mL) and 30% H_2O_2 (75 mL). The mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The layers were separated, and the aqueous phase was extracted with 3 × 100 mL of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Hexane (200 mL) was added, and the solution was cooled to 0 °C and then suction filtered. The dirty white solid collected (12.1 g) contained the desired *exo*-naphthyl alcohol. A second crop of crystals can be obtained by concentrating the mother liquors in vacuo, then adding hexane (100 mL), and cooling: total yield 14.4 g; mp 208–209 °C (sealed capillary); ^{1}H NMR 8.1–7.4 (m, 7 H), 5.1 (dd, J = 6, 4, 1 H), 3.4 (d, J = 6 Hz, 1 H), 1.5–2.2 (m, 5 H), 1.03 (s, 3 H), 0.90 (s, 3 H), 0.52 (s, 3 H); ^{13}C NMR 137.4 (s), 134.1 (s), 133.6 (s), 129.4 (d), 128.8 (d), 126.9 (d), 126.4 (d), 125.4 (d), 125.3 (d), 123.5 (d), 76.3 (d), 57.1 (d), 51.9 (d), 50.9 (s), 48.3 (s), 39.9 (t), 30.9 (t), 21.8 (q), 19.9 (q), 13.8 (q); IR 3650, 3070, 2990, 1570, 1420, 1275, 1230, 1020, 990; exact mass for $C_{20}H_{24}O$, calcd 280.183, obsd 280.183; TLC (10% EtOAc/hexane) R_f 0.14. This material may be recrystallized from ethanol (35 mL)/hot water (7 mL).

A solution of (3-*endo*-hydroxy-2-*exo*-naphthyl)bornane (10.74 g, 38.36 mmol) in 30 mL of CH_2Cl_2 was added to a suspension of freshly ground pyridinium chlorochromate (24.81 g, 115.1 mmol) and anhydrous NaOAc (15.73 g, 191.8 mmol) in 250 mL of CH_2Cl_2. The mixture was stirred for 1 h at room temperature. Florisil (15 g) was added, followed by ether (375 mL). The supernatant was filtered through a bed of Florisil (10 g), eluting first with ether and then acetone (reagent grade). The filtrate was dried over anhydrous Na_2SO_4 and then concentrated in vacuo. The crude residue was chromatographed on 100 g of silica gel using 4.5% EtOAc/petroleum ether. The first 900 mL was discarded. The next 1800 mL was concentrated in vacuo to give 9.82 g (92%) of 2-*exo*-naphthylbornan-3-one: R_f (10% EtOAc/hexane) 0.31; ^{1}H NMR 7.95–7.4 (m, 7 H), 4.12 (s, 1 H), 1.7–2.4 (m, 5 H), 1.1 (s, 3 H), 0.92 (s, 3 H), 0.8 (s, 3 H); ^{13}C NMR 217.7 (s), 134.1 (s, 2), 133.5 (s), 129.0 (d), 127.4 (d, 2), 125.5 (d), 125.4 (d), 125.2 (d), 124.4 (d), 59.5 (d), 58.9 (d), 51.7 (s), 48.3 (s), 38.3 (t), 22.6 (t), 20.5 (q), 20.3 (q), 13.5 (q); IR 3040, 2950, 2860, 1735, 1595, 1500, 1470, 1450, 1385, 1370; MS 278.167.

A solution of 2-*exo*-naphthyl-bornan-3-one (9.815 g, 35.3 mmol) in 20 mL of THF was added dropwise to a suspension of $LiAlH_4$ (1.40 g, 36.89 mmol) in 50 mL of THF. The mixture was stirred 30 min, then cooled in an ice/water bath, and quenched sequentially with 1.4 mL of H_2O, 1.4 mL 10% aqueous NaOH, and 4.5 mL of H_2O. Stirring was continued for 10 min. The mixture was suction filtered through a bed of Celite. The residual solid was washed with ether and then by acetone. The combined filtrates were dried over anhydrous Na_2SO_4 and concentration in vacuo. The residue was chromatographed on 50 g of silica gel with 4% EtOAc/petroleum ether. The first 300 mL was discarded. The next 700 mL was concentrated in vacuo, leaving 6.14 g of the crystalline alcohol 8: mp 152–153.5 °C; R_f (10% EtOAc/hexane) 0.26; ^{1}H NMR 8.25–7.5 (m, 7 H), 4.5 (d, J = 8, 1 H), 4.0 (d, J = 8, 1 H), 1.54–2.00 (m, 5 H), 1.42 (s, 3 H), 1.22 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR 135.0 (s), 133.8 (s), 133.3 (s), 129.3 (d), 128.6 (d), 127.0 (d), 126.5 (d), 125.4 (d), 124.9 (d), 123.2 (d), 79.4 (d), 58.0 (d), 52.0 (d), 49.5 (s), 48.0 (s), 43.0 (t), 23.9 (t), 23.8 (q), 21.5 (q), 15.0 (q); IR 3590, 3050, 2995, 2885, 1590, 1475, 1455, 1385, 1275, 1090, 1035; MS 280.183. This alcohol may be recrystallized from hot ethanol (35 mL)/hot water (5 mL).

Preparation of the Acetoacetate of Alcohol 8. The acylation of (3-*exo*-hydroxy-2-*exo*-naphthyl)bornane was carried out following the procedure of Mauz.[28] Thus, to the alcohol 8 (2.0 g, 7.1 mmol) in 10 mL of acetone was added triethylamine (72 mg, 0.71 mmol) followed by diketene in acetone (50% by weight, 1.6 g, 9.23 mmol, 1.3 equiv). The mixture was warmed to reflux for 4 h, allowed to cool, diluted with aqueous HCl, and extracted with methylene chloride. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on 50 g of silica gel with 4% EtOAc/petroleum ether. The first 600 mL was discarded. Concentration of the next 400 mL in vacuo provided 2.27 g (88%) of acetoacetate: TLC (10% EtOAc/hexane) R_f 0.19; ^{1}H NMR 1.0 (s, 3 H), 1.25 (2, 3 H), 1.26 (s, 3 H), 1.3 (s, 3 H), 1.5–2.0 (m, 5 H), 2.65 (s, 2 H), 4.07 (d, J = 8, 1 H), 5.57 (d, J = 8, 1 H), 7.4–8.05 (m, 7 H); ^{13}C NMR 15 (q), 21.5 (q), 23.8 (q), 23.9 (t), 29 (q), 42.4 (t), 48.3 (s), 49.5 (s), 49.8 (t), 51.2 (d), 55.2 (d), 80.9 (d), 123.5 (d), 124.6 (d), 125.2 (d), 126.1 (d), 126.7 (d), 127.3 (d), 128.9 (d), 133.2 (s), 133.6 (s), 135.2 (s), 166.0 (s), 199.9 (s); IR 3030, 2940, 2850, 1740, 1715, 1640, 1465, 1395, 1230; MS 364 (11), 263 (14), 255 (22), 248 (10), 180 (13), 172 (15), 171 (100), 166 (18), 142 (22); exact mass for $C_{24}H_{28}O_3$, calcd 364.2038, obsd 364.200.

General Procedure for the Alkylation of the Dianion of the Acetoacetate of 8. Alkylation of the dianion of the chiral acetoacetate with 1-bromoheptane was carried out by the procedure of Weiler:[29] yield 59%; R_f (10% EtOAc/hexane) 0.49; ^{1}H NMR 0.89 (t, J = 7, 3 H), 0.99 (s, 3 H), 1.24 (s, 3 H), 1.28 (s, 3 H), 1.48–1.99 (m, 19 H), 2.59 (s, 2 H), 4.05 (d, J = 8, 1 H), 5.54 (d, J = 8, 1 H), 7.38–8.02 (m, 7 H); ^{13}C NMR 14.2 (q), 14.8 (q), 21.6 (q), 22.6 (t), 23.2 (t), 23.8 (q), 23.9 (t), 28.8 (t), 29.1 (t), 29.3 (t), 31.8 (t), 42.1 (t), 42.5 (t), 48.4 (s), 48.8 (t), 49.5 (s), 51.2 (d), 55.3 (d), 80.8 (d), 123.5 (d), 124.5 (d), 125.2 (d), 126.1 (d), 126.7

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(d), 127.3 (d), 128.9 (d), 133.2 (s), 133.5 (s), 135.3 (s), 166.2 (s), 202.3 (s); MS 462 (7), 352 (9), 262 (15), 170 (100), 141 (18); exact mass for $C_{31}H_{42}O_3$, calcd 462.313, obsd 462.314; IR 3030, 2940, 2850, 1740, 1715, 1640, 1465, 1395, 1230.

General Procedure for Diazo Transfer. The diazo ester was prepared by the reported procedure.[30] Thus, to a β-keto ester (1.00 g, 2.16 mmol) in 5 mL of CH_3CN was added triethylamine (436 mg, 4.32 mmol) followed by tosyl azide (470 mg, 2.38 mmol). The mixture was stirred at room temperature for 4 h. The mixture was then diluted with 10% aqueous NaOH and extracted with ether. Combined organic extracts were dried and concentrated in vacuo. The residue was chromatographed on 50 g of silica gel with 4% EtOAc/petroleum ether. The first 250 mL was discarded. The next 250 mL was concentrated in vacuo to give the diazo ester **9a**: 1.0 g (94%); TLC (10% EtOAc/hexane) R_f 0.53.

General Procedure for Rh-Mediated Insertion. Rhodium(II) acetate catalyzed cyclization of the diazo ester was carried out by the reported method.[3] Thus, a solution of diazo ester **9a** (500 mg) in 5 mL of dry methylene chloride (filtered through anhydrous K_2CO_3) was added slowly to a suspension of rhodium(II) acetate (25 mg) in dry methylene chloride in a flame-dried round-bottomed flask. The mixture was stirred at room temperature for 30 min, then concentrated in vacuo, and chromatographed directly on 50 g of silica gel with 3% EtOAc/petroleum ether. The first 1 L was discarded. Concentration of the next 300 mL in vacuo afforded the minor diastereomer. Concentration of the next 700 mL provided the major diastereomer. Total weight of **10a** (both minor and major) was 283 mg (60%): TLC (10% EtOAc/hexane) R_f 0.41 (major diastereomer); ^{1}H NMR 0.89 (t, J = 7, 3 H), 1.03 (s, 3 H), 1.28 (s, 3 H), 1.38 (s, 3 H), 1.22–2.08 (m, 19 H), 4.03 (d, J = 8, 1 H), 5.49 (d, J = 8, 1 H), 7.34–7.99 (m, 7 H); ^{13}C NMR 14.1 (q), 14.8 (q), 21.6 (q), 22.5 (t), 23.9 (q), 24.1 (t), 26.4 (t), 31.7 (t), 33.9 (t), 37.7 (t), 39.9 (t), 42.6 (t), 48.4 (s), 49.4 (s), 51.3 (d), 55.4 (d), 61.4 (d), 65.2 (d), 80.7 (d), 123.5 (d), 124.3 (d), 125.3 (d), 126.3 (d), 126.5 (d), 127.1 (d), 128.7 (d), 133.3 (s), 133.5 (s), 135.7 (s), 168.0 (s), 210.7 (s); MS 460 (8), 263 (8), 262 (9), 171 (13), 170 (100), 165 (9), 142 (11), 141 (13, 12, 21, 33, 18, 31); exact mass for $C_{31}H_{40}O_3$, calcd 460.298, obsd 460.300; IR 3030, 2950, 2900, 1750, 1720, 1650, 1595, 1455, 137; HPLC retention volumes (mL) with peak areas in parentheses for the four diastereomers, 19.42 (1), 22.11 (12), 22.89 (20), 25.58 (67).

Compound 10b: TLC (10% EtOAc/hexane) R_f 0.27 (major diastereomer); ^{1}H NMR 1.0 (s, 3 H), 1.24 (s, 3 H), 1.38 (s, 3 H), 1.58–2.22 (m, 11 H), 4.08 (d, J = 8, 1 H), 4.40 (d, J = 16, 1 H), 4.63 (d, J = 10, 1 H), 5.16 (m, 1 H), 5.56 (d, J = 8, 1 H), 7.54–8.1 (m, 7 H); ^{13}C NMR 14.9 (q), 21.5 (q), 23.9 (t), 24.2 (q), 26.5 (t), 37.4 (t), 42.6 (t), 43.0 (d), 48.4 (s), 49.4 (s), 51.3 (d), 55.4 (d), 60.1 (d), 81.0 (d), 114.5 (t), 123.5 (d), 124.3 (d), 125.3 (d), 126.4 (d), 126.5 (d), 127.1 (d), 128.7 (d), 133.4 (s), 133.5 (s), 135.7 (s), 137.6 (d), 167.4 (s), 209.6 (s); MS 416 (14), 306 (15), 263 (15), 262 (20), 179 (10), 171 (17), 170 (100), 165 (10), 142 (11), 141 (20), 137 (11); exact mass for $C_{28}H_{32}O_3$, calcd 416.235, obsd 416.239; IR 3030, 2950, 2870, 1750, 1720, 1640, 1590, 1475, 1450, 1385, 1225, 1175; HPLC retention volumes (mL) with peak areas in parentheses for four diastereomers, 9.86 (1), 11.3 (7), 11.64 (11), 14.90 (81).

Compound 10c: TLC (10% EtOAc/hexane) R_f 0.31 (major diastereomer); ^{1}H NMR 0.22 (d, J = 7, 3 H), 0.41 (d, J = 7, 3 H), 0.97 (s, 3 H), 1.26 (s, 3 H), 1.41 (s, 3 H), 0.85–2.13 (m, 12 H), 4.03 (d, J = 8, 1 H), 5.48 (d, J = 8, 1 H), 7.33–7.98 (m, 7 H); ^{13}C NMR 14.8 (q), 18.6 (q), 20.0 (q), 21.6 (q), 23.7 (t), 23.9 (t), 24.2 (q), 31.0 (d), 38.2 (t), 42.6 (t), 46.7 (d), 48.4 (s), 49.5 (s), 51.4 (d), 55.3 (d), 59.3 (d), 80.8 (d), 123.5 (d), 124.6 (d), 125.2 (d), 126.3 (d), 126.6 (d), 127.1 (d), 128.8 (d), 133.4 (s), 133.6 (s), 135.5 (s), 168.9 (s), 211.2 (s); MS 432 (9), 263 (13), 262 (16), 171 (16), 170 (100), 165 (9), 153 (14), 141 (16), 109 (10); exact mass for $C_{29}H_{36}O_3$, calcd 432.266, obsd 432.267; IR 3050, 2960, 2870, 1750, 1720, 1595, 1455, 1385, 1230; HPLC retention volumes (mL) with peak area in parentheses for the four diastereomers, 12.5 (7), 13.27 (10), 14.42 (50), 15.19 (33).

Compound 10d: TLC (10% EtOAc/hexane) R_f 0.3 (major diastereomer); ^{1}H NMR 0.30 (s, 9 H), 1.21 (s, 3 H), 1.26 (s, 3 H), 1.43 (s, 3 H), 0.55–2.1 (m, 13 H), 4.09 (d, J = 8, 1 H), 5.41 (d, J = 8, 1 H), 7.24–8.05 (m, 7 H); ^{13}C NMR 14.7 (q), 21.5 (q), 21.6 (q), 23.8 (t), 26.4 (q), 26.6 (q), 29.3 (q), 38.4 (t), 39.5 (t), 42.6 (t), 48.1 (s), 48.4 (s), 49.5 (s), 50.4 (d), 51.2 (d), 55.0 (d), 57.2 (d), 80.9 (d), 123.4 (d), 124.5 (d) 125.3 (d), 126.4 (d), 126.6 (d), 127.2 (d), 128.9 (d), 133.4 (s), 133.7 (s), 135.7 (s), 169.6 (s), 212.0 (s); MS 446 (5), 262 (14), 171 (15), 170 (100), 168 (11), 167 (12), 141 (13), 139 (12); exact mass for $C_{30}H_{38}O_3$, calcd 446.282, obsd 446.282; IR 3060, 2970, 2880, 1750, 1725, 1595, 1470, 1390, 1230; HPLC retention volume (mL) with peak areas in parentheses, 6.35 (16), 7.50 (1), 14.62 (59), 16.92 (24).

Compound 10e: TLC (10% EtOAc/hexane) R_f 0.22 (major diastereomer); ^{1}H NMR 0.93 (s, 3 H), 1.18 (s, 3 H), 1.21 (s, 3 H), 1.39–2.04 (m, 10 H), 2.71 (m, 1 H), 3.96 (d, J = 8, 1 H), 5.39 (d, J = 6, 1 H), 6.64–8.02 (m, 12 H); ^{13}C NMR 14.9 (q), 21.5 (q), 23.9 (q), 24.0 (t), 29.0 (t), 42.5 (t), 44.2 (t), 45.9 (s), 48.2 (d), 49.4 (s), 51.2 (d), 55.3 (d), 60.8 (d), 81.5 (d), 123.5 (d), 124.5 (d), 125.3 (d), 126.0 (d), 126.1 (d), 126.7 (d), 127.2 (d), 128.4 (d), 128.9 (d), 133.2 (s), 133.5 (s), 135.3 (s), 141.5 (s), 167.2 (d), 209.0 (s); MS 466 (8), 263 (11), 262 (13), 187 (10), 171 (13), 170 (100), 141 (17); exact mass for $C_{32}H_{34}O_3$, calcd 466.251, obsd 466.251; IR 3060, 3030, 2960, 2880, 1755, 1720, 1650, 1595, 1450, 1385, 1230.

Preparation of 11. A mixture of β-keto ester **10b** (0.50 g, 1.23 mmol), t-BuOK (1.37 mmol, 1.1 equiv), and methyl iodide (6.0 mmol, 5 equiv), in 5 mL of dry THF, was stirred at room temperature for 2 h. The mixture was then diluted with saturated NH_4Cl solution and extracted with ether. The extract was dried over anhydrous Na_2SO_4 and concentrated to provide 0.50 g (97%) of crude alkylated material, which was used without further purification.

A solution of this crude chiral ester (0.500 g, 1.163 mmol) in 4 mL of dry xylene was added slowly to the stirring suspension of anhydrous sodium methoxide[19,27] (0.634 g, 11.736 mmol) in 6 mL of dry xylene under N_2. The solution turned yellow immediately. The reaction mixture was heated to reflux for 1.5 h and then cooled to give a thick dark yellow-brown solution. The thick mass was diluted with dry xylene and filtered to separate the sodium salt of the product β-keto ester. The solids were repeatedly washed with dry xylene to remove all soluble impurities. The xylene filtrate was concentrated to recover the chiral alcohol. The filtered solids, containing sodium methoxide and the sodium salt of the product, were dissolved in 20 mL of 10% HCl and extracted with 20 × 3 mL of ether. The combined ether extract was concentrated in vacuo. The residue was chromatographed on 10 g of silica gel with 4% EtOAc/petroleum ether. The first 100 mL was discarded. The next 150 mL was concentrated in vacuo to afford 0.148 (70%) of **11** as a colorless oil: R_f (10% EtOAc/hexane) 0.24; ^{1}H NMR 1.13 (d, J = 7, 3 H), 1.83–3.35 (m, 5 H), 3.75 (s, 3 H), 5.08–5.9 (m, 3 H); ^{13}C NMR 11.9 (q), 31.7 (t), 46.8 (d), 49.7 (d), 52.4 (q), 54.2 (d), 116.3 (t), 139.1 (d), 169.7 (s), 211.1 (s); IR 3040, 2910, 2890, 2830, 1735, 1710, 1640, 1595, 1410, 1315, 1220, 1130, 975, 900; MS 182 (29), 167 (17), 164 (43), 151 (100), 150 (73), 122 (48); exact mass for $C_{10}H_{14}O_3$, calcd 182.094, obsd 182.094. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found: C, 66.05; H, 7.71.

Preparation of 2-(4-Methoxybenzocyclobutenyl)ethyl Iodide 16. The iodide was prepared from 1-cyano-4-methoxybenzocyclobutene (**13**).[21] To the nitrile (0.587 g, 3.7 mmol) in 4 mL of THF was added DIBAL (7.4 mL of 1.0 M hexane, 2 equiv) slowly at 0 °C. The solution was stirred for 30 min, and then saturated NH_4Cl solution (2 mL) was added, followed by 10% aqueous H_2SO_4 (2.5 mL). The mixture was stirred for 10 min and then extracted with 3 × 25 mL of ether. The ether extract was dried over Na_2SO_4 and concentrated in vacuo. The crude residue was chromatographed over 50 g of silica gel with 6% EtOAc/petroleum ether. The first 300 mL was discarded. The next 300 mL was concentrated in vacuo to give the aldehyde **14**: 0.51 g (85%); R_f (10% EtOAc/hexane) 0.19; ^{1}H NMR 3.3 (d, J = 4.5, 2 H), 3.75 (s, 3 H), 4.1 (dd, J = 4.5, 1 H), 6.68–7.05 (m, 3 H), 9.65 (d, J = 4, 1 H); ^{13}C NMR 30.5 (t), 52.1 (d), 54.2 (q), 106.5 (d), 112.2 (d), 120.5 (d), 129.1 (s), 142.2 (s), 156.5 (s), 194.4 (d); IR 2970, 2900, 2800, 2760, 2670, 1700, 1590, 1565, 1450, 1310, 1250, 1140, 1050, 1000, 800 cm^{-1}.

To the stirring suspension of methyltriphenylphosphonium bromide (9.45 mmol) and t-BuOK (7.88 mmol) in 5 mL of THF was added the above aldehyde (0.510 g, 3.15 mmol) at 0 °C. Stirring was continued for 10 min. The reaction was quenched with saturated aqueous NaCl and extracted with 3 × 50 mL of

(30) Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 197.

ether. The ether extract was dried over Na_2SO_4 and concentrated in vacuo. Column chromatography of the crude residue on 50 g of silica gel with 2.5% EtOAc/petroleum ether provided 0.350 g (70%) of 1-vinyl-4-methoxybenzocyclobutene (**15**): R_f (10% EtOAc/hexane) 0.5; ^{1}H NMR 2.86 (d, J = 7.5, 2 H), 3.37 (dd, J = 7.7, 1 H), 3.75 (s, 3 H), 4.96–6.12 (m, 3 H), 6.65–7.0 (3H); ^{13}C NMR 36.4 (t), 45.3 (d), 55.2 (q), 108.9 (d), 113.4 (d), 113.8 (t), 123.4 (d), 138.8 (s), 139.6 (d), 144.1 (s), 160.2 (s); IR 3040, 2960, 2910, 2880, 2790, 1610, 1580, 1565, 1450, 1300, 1250, 1140 cm^{-1}.

This olefin was converted to the iodide **9** by the method of Kabalka.[25] The olefin (0.56 g, 3.5 mmol) in 3.5 mL of THF was cooled to 0 °C. To this solution was added BH_3·THF (1.3 equiv), and stirring was continued for 3 h. Methanolic sodium acetate (2 equiv, 1 M), aqueous sodium iodide (2 equiv, 1 M), and methanolic chloramine-T (2 equiv, 0.5 M) were added sequentially to the organoborane solution at 25 °C. The mixture was stirred for 5 min at 25 °C and then quenched by adding aqueous sodium thiosulfate (1 M) and HCl (1 N). The mixture was diluted with water and extracted with 2 × 20 mL of pentane. The pentane extract was dried over Na_2SO_4 and evaporated. The residue was chromatographed on 50 g of silica gel with petroleum ether. The first 200 mL was concentrated in vacuo to recover unreacted olefin (0.15 g). The next 400 mL was concentrated in vacuo to give the iodie **16** [0.395 g (54% based on unrecovered starting olefin)] as a colorless oil: R_f (10% EtOAc/hexane) 0.59; ^{1}H NMR 2.0–2.4 (m, 2 H), 2.44–3.64 (m, 5 H), 3.75 (s, 3 H), 6.7–7.07 (m, 3 H); ^{13}C NMR 3.9 (t), 35.1 (t), 38.7 (t), 43.3 (d), 55.6 (q), 109.4 (d), 113.6 (d), 123.1 (d), 139.7 (s), 144.3 (s), 160.1 (s); IR 3100, 2960, 2890, 1625, 1580, 1450, 1400, 1240, 900 cm^{-1}.

Preparation of 12. The dianion alkylation was carried out by the method of Schlessinger.[20] Thus, 2.5 equiv of LDA were prepared in a flame-dried flask at 0 °C by dropwise addition of n-BuLi (0.9 mmol, 2.3 M) to diisopropylamine (0.9 mmol) in 1 mL of THF. The β-keto ester **11** (0.060 g, 0.35 mmol) in 0.5 mL of THF was added dropwise. The reaction mixture was then warmed to 40 °C for 3 h to complete the formation of the dianion. The solution was cooled to 0 °C, and the iodide **16** (0.53 mmol, 1.5 equiv) and HMPA (0.35 mmol, 1 equiv) were added. The reaction mixture was stirred for 4 h, then diluted with saturated aqueous NH_4Cl, and extracted with 3 × 20 mL of ether. The combined ether extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on 5 g of silica gel with 4% EtOAc/petroleum ether. The first 50 mL was discarded. The next 70 mL was concentrated in vacuo to give **12**: 0.061 g (55%); R_f (EtOAc/hexane) 0.19; ^{1}H NMR 0.92 (s, 3 H), 1.4–3.7 (m, 11 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 5.05–5.87 (m, 3 H), 6.64–7.05 (m, 3 H); ^{13}C NMR 18.3 (q), 28.5 (t), 29.6 (t), 34.2 (t), 35.4 (t), 42.5 (d), 45.0 (d), 46.8 (s), 52.5 (q), 54.9 (d), 55.4 (q), 109.1 (d), 113 (t), 117.5 (d), 122.8 (s), 136.1 (d), 140.9 (s), 144.5 (s), 159.6 (s), 169.7 (s), 214.6 (s); IR 3040, 2920, 2890, 1735, 1710, 1630, 1560, 1545, 1450, 1315, 1250, 1220 cm^{-1}; MS 342 (32), 311 (10), 186 (11), 173 (16), 172 (22), 161 (100), 160 (86), 147 (17), 145 (23); exact mass for $C_{21}H_{26}O_4$, calcd 342.183, obsd 342.182.

Preparation of (+)-Estrone Methyl Ether (1). Decarbomethoxylation was effected by the method of Krapcho.[26] Thus, a mixture of **12** (0.061 g, 0.178 mmol), NaCl (0.89 mmol, 5 equiv), and H_2O (0.06 mL, 5 equiv) in 0.5 mL of Me_2SO was heated at 165 °C for 45 min. The mixture was cooled and extracted with 6 × 5 mL of petroleum ether. The combined petroleum ether extracts were washed with water, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was chromatographed on 2.5 g of silica gel with 3.5% EtOAc/petroleum ether. The first 20 mL was discarded. The next 20 mL was concentrated in vacuo to give the ketone: 0.035 g (69%); R_f (10% EtoAc/hexane) 0.27; ^{1}H NMR 0.88 (s, 3 H), 1.3–3.35 (m, 12 H), 3.78 (s, 3 H), 5.05–5.95 (m, 3 H), 6.60–7.03 (m, 3 H); ^{13}C NMR 14.1 (q), 24.4 (t), 29.3 (t), 29.6 (t), 29.7 (t), 34.1 (t), 35.5 (d), 37.3 (s), 42.7 (d), 55.5 (q), 109.1 (q), 113.1 (t), 116.6 (d), 122.8 (d), 137.3 (d), 138.1 (s), 144.3 (s), 159.1 (s), 212.2 (s); IR 2920, 2890, 1720, 1610, 1540, 1520, 1485, 1240, 1180, 800 cm^{-1}; MS 284 (12), 161 (45), 160 (11), 98 (17); exact mass for $C_{19}H_{24}O_2$, calcd 284.1776, obsd 284.177.

A solution of the ketone (25 mg) in 3 mL of distilled o-dichlorobenzene was stirred under nitrogen for 8 h at 180 °C. The solvent was removed in vacuo, and the residue was chromatographed on 1 g of silica gel with 3% EtOAc/petroleum ether. The first 10 mL was discarded. Concentration of the next 15 mL gave the product **1** [0.015 g (41% from **12**)] as a thick viscous material. This was recrystallized from methanol to give white crystals: mp 163–165 °C (lit. mp 164–165 °C); R_f (10% EtOAc/hexane) 0.19; ^{1}H NMR 0.91 (s, 3 H), 1.4–2.6 (m, 14 H), 2.89 (br t, J = 4.3, 1 H), 3.78 (s, 3 H), 6.65–7.28 (m, 3 H); ^{13}C NMR 13.7 (q), 21.4 (t), 25.7 (t), 26.3 (t), 29.5 (t), 31.5 (t), 35.6 (t), 38.2 (d), 43.5 (d), 47.8 (s), 50.2 (d), 55.1 (q), 111.1 (d), 113.7 (d), 125.8 (d), 131.8 (s), 137.7 (s), 157.4 (s), 213.1 (s); IR 2900, 2820, 2790, 1720, 1630, 1610, 1580, 1520, 1470, 1430, 1250, 1230, 1030, 790 cm^{-1}; MS 284 (24), 199 (6), 186 (4), 160 (6), 32 (13), 28 (43), 19 (1000); exact mass for $C_{19}H_{24}O_2$, calcd 284.186, obsd 284.187. The proton and carbon NMR and IR spectra of the synthetic estrone methyl ether were found to be congruent with those of authentic (+)-estrone methyl ether: $[\alpha]^{27}_D$ = +146° (c 0.002 86, $CHCl_3$); $[\alpha]_D$ +160° ($CHCl_3$) for authentic material.

Acknowledgment. We thank the National Institutes of Health (Grant GM 32027), the National Science Foundation (Grant CHE 8306692), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of Delaware Research Foundation for support of this work. D.F.T. thanks ICI Americas for an unrestricted research grant.

A General Approach to the Synthesis of C_8-Oxygenated Guaianolides†

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Received July 17, 1986

Preparation of an advanced intermediate for the synthesis of several highly oxygenated members of the guaianolide family of sesquiterpene lactones is described. The key hydroxy lactone species is constructed from the readily available hydroazulene **3** via thiophenol-mediated cyclic ether opening followed by a convergent epoxidation–lactonization sequence.

The guaianolides comprise one of the largest and most widely distributed groups of naturally occurring sesquiterpene lactones.[1] In addition to the simple members of this family, a number of species bearing an oxygen substituent at the C_8 position have been identified. Many of these compounds display significant biological activity as well as complex molecular architecture and as such are intriguing candidates for synthetic investigation. To date,

† Taken, in part, from the Ph.D. Thesis of J.Z.W., Wayne State University, 1986.

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