and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent afforded crude **2**. Chromatography as described previously afforded 13.6 mg (28%) of **2**.

(±)-Nootkatone (2) via Boron Trifluoride Etherate Catalysis. To a solution of 50 mg (0.17 mmol) of **1** in 1 mL of anhydrous ether at 0 °C was added 0.022 mL (0.17 mmol) of boron trifluoride etherate. The reaction was stirred for 1 h after which it was quenched with 5 mL of wet ether and allowed to warm to room temperature. The solution was washed with brine and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent afforded crude **2**. Chromatography as described previously afforded 9.8 mg (23%) of **2**.

(±)-Valencene. To a stirred solution of 340 mg (1.56 mmol) of **2** in 5 mL of ether at room temperature was added 5 mg of ZnI_2 (catalytic amounts), followed by the dropwise addition of 408 mg (1.71 mmol) of (ethylenedithio)bis(trimethylsilane). The resulting mixture was stirred at room temperature for 14 h. The reaction was quenched with 1 drop of water and directly purified via column chromatography (elution with 3:1 hexanes/ether; **2**, R_f 0.52; **11**, R_f 0.89) to afford 427 mg (93%) of thioketal **11**, which was homogeneous by TLC: ^{1}H NMR (CCl_4) δ 5.3 (s, 1 H), 4.52 (s, 2 H), 3.0–3.4 (m, 4 H), 1.4–2.3 (m, 13 H), 1.75 (s, 3 H), 0.95 (s, 3 H), 8.7 (d, 3 H, J = 6 Hz); IR (neat) 3060, 2960, 2910, 1640, 1430, 1290, 1285, 1235, 1145, 885 cm^{-1}; mass spectrum, m/z 294 (M^+).

To a solution of 100.0 mg (0.31 mmol) of **11**, in 0.6 mL of ether and 14.3 mL of liquid ammonia, was added 14.3 mg (0.62 mmol) of metallic sodium. Upon addition of the sodium, the reaction mixture turned a dark blue. The color was discharged upon slow dropwise additon of 9.5 mL of absolute ethanol. The ammonia was then allowed to evaporate and the residue was extracted with two 15-mL portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent afforded crude **3**. The crude product was purified by column chromatography (elution with 1:1 hexane/ether; **11**, R_f 0.89; **3**, R_f 0.9), and 20 mg (22%) was isolated: ^{1}H NMR ($CDCl_3$) δ 5.3 (s, 1 H), 4.69 (s, 2 H), 1.7 (s, 3 H), 0.95 (s, 3 H), 0.9 (d, 3 H, J = 6 Hz); IR (neat) 3075, 2935, 1660, 1435, 1380, 1350, 1290, 1270, 1210, 940, 880, 840, 820, 640 cm^{-1}; mass spectrum, m/z 214 (M^+).

4,4a,5,8,9,10-Hexahydro-4,4a,7-trimethyl-2(3*H*)-benzocyclooctenone (10). A reaction vessel containing 50 mg of 4-Å molecular sieves was flame-dried under vacuum (5 min) and placed under nitrogen. A solution of 3 mL of DMF containing 2.5 mg of TBAF was added and then 73 mg (0.48 mmol) of HMPA added. The resulting mixture was stirred at room temperature for 10 min. A solution of **1** in 2 mL of DMF was added dropwise over 2 h (via syringe pump). The resulting mixture was stirred at room temperature for 1.5 h and then diluted with 15 mL of water. This mixture was then extracted with three 15-mL portions of ether. The combined ethereal extracts were washed with brine and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent afforded crude **10**. Chromatography (elution with 1:1 hexane/ether) afforded 14 mg (42%) of **10**: ^{1}H NMR (CCl_4) δ 5.4 (s, 1 H), 5.05 (m, 1 H), 2.3–1.6 (m, 11 H), 1.55 (s, 3 H), 0.91 (d, 3 H, J = 6 Hz), 0.88 (s, 3 H); IR (neat) 3010, 2950, 2850, 1680, 1620, 1465, 1445, 1425, 1380, 1360, 1340, 1295, 1265, 1225, 1190, 960, 940, 920, 860, 800, 780, 760, 700, 620 cm^{-1}.

Acknowledgment. Special thanks are extended to Professor A. R. Pinder for generous samples of natural and synthetic nootkatone and valencene. Thanks are also due to Richard Desmond for technical assistance. This research was supported by a grant from the Research Corporation. Acknowledgement is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

Registry No. (±)-**1**, 97551-21-8; (±)-**2**, 28834-25-5; (±)-**3**, 24741-64-8; (±)-**4**, 61484-10-4; (±)-**5**, 97551-22-9; (±)-**5** (*trans*-dimethyl isomer), 97551-28-5; (±)-**6**, 97551-23-0; (±)-(*E*)-**7**, 97551-24-1; (±)-(*Z*)-**7**, 97590-58-4; (±)-**10**, 97551-25-2; (±)-**11**, 97551-26-3; CH_2=CHLi, 917-57-7; $Ph_3PEt^+Br^-$, 1530-32-1; *cis*-5,6-dimethyl-3-ethoxy-2-cyclohexenone, 97551-27-4; prenyl bromide, 870-63-3.

Preparation of β-Keto Esters by 4-DMAP-Catalyzed Ester Exchange

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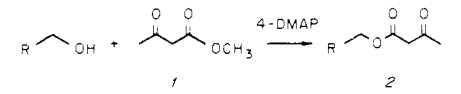
We recently needed to prepare a series of differentially substituted acetoacetate derivatives. Two methods have been described for acetoacetate formation, reaction of an alcohol with diketene[3] and transesterification with methyl acetoacetate.[4] Camphorsulfonic acid has been employed



1 *2*

to catalyze the latter reaction.[5] As these methods proved ineffective for the case we had in hand, we explored alternative catalysts for the transesterification reaction.

We have found that reacting acetoacetate **1** with a primary or secondary alcohol in the presence of a catalytic amount of 4-(dimethylamino)pyridine[6] (4-DMAP) in toluene solution at reflux will yield acetoacetate **2**. The reaction of a variety of β-keto esters with representative alcohols is summarized in Table I.

It can be seen that only enolizable β-keto esters react and that tertiary alcohols do not participate in the reaction. Entry 4 suggests that there is a competing pathway leading to decomposition of the acetoacetate. This has led us to a procedure for selective decarbalkoxylation of enolizable β-keto esters which will be reported separately.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker WM-250 spectrometer as solutions in $CDCl_3$. 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 Unicam SP1100 spectrometer as solutions in CCl_4 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 $m/z \geq 100$) in parentheses. CH analysis was provided by Galbraith Laboratories, Inc. Organic chemicals were purchased from Aldrich Chemical Co. Toluene was distilled from CaH_2 and stored over sodium metal. The extracting solvent used was a mixture of recovered organic solvents, including methylene chloride, ethyl acetate, and petroleum ether. The solvent mixtures used for chromatography 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 with TLC-mesh silica gel, following the procedure we have described.[7]

Preparation of *l*-Menthyl Acetoacetate 3. A flame-dried two-necked 50-mL round-bottomed flask equipped with a reflux condenser and a nitrogen purge was flushed with N_2 and charged with 300 mg (1.92 mmol) of *l*-menthol, 70 mg (0.577 mmol) of

(1) Fellow of the Alfred P. Sloan Foundation, 1982–1987.
(2) Undergraduate research participant.
(3) Mauz, O. *Justus Liebigs Ann. Chem.* **1974**, 345.
(4) Bader, A.; Cummings, Lowell O.; Vogel, Henry A. *J. Am. Chem. Soc.* **1951**, *73*, 4195.
(5) Stork, G. Columbia University, personal communication.
(6) (a) Steglich, W.; Hofle, G. *Angew Chem., Int. Ed. Engl.* **1969**, *8*, 981. (b) For the use of 4-DMAP to catalyze acetoacetylation with diketene, see: Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722.
(7) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

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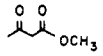
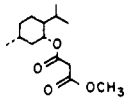
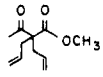
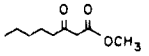
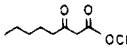
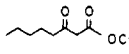
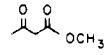
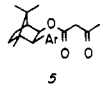
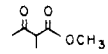
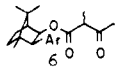
Table I

reaction no.	acetoacetate	alcohol	products	yield, %
1			 3	83
2				*a*
3	 EXCESS ESTER		 4	74
4		 EXCESS ALCOHOL	 4	41
5				*a*
6			 5	71
7			 6	55

[a] No reaction.

4-(dimethylamino)pyridine (4-DMAP), and 6 mL of toluene. The mixture was magnetically stirred until the *l*-menthol and 4-DMAP were in solution, and then 0.62 mL (5.77 mmol, 3.0 equiv) of methyl acetoacetate was added. The mixture was warmed to reflux for 42 h.[8] The reaction mixture was cooled in an ice/water bath and quenched with 20 mL of saturated ammonium chloride solution. Extracting solvent (20 mL) was added, and the two layers were separated. The aqueous layer was extracted three times with extracting solvent (25-mL portions). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was bulb-to-bulb distilled to remove excess methyl acetoacetate (bp_{50} 70 °C). The pot residue was chromatographed on 10 g of silica gel with 3.0% EtOAc/petroleum ether. The first 30 mL was discarded. The next 60 mL was concentrated in vacuo to give 385 mg (1.6 mmol, 83%) of *l*-menthyl acetoacetate **3** as a clear oil: R_f (20% EtOAc/hexane) 0.53; ^{1}H NMR 2.3 (s, 3 H), 3.4 (s, 2 H), 4.7 (dt, J = 4.4, 10.9 Hz, 1 H), 0.7–1.2 (m, 10 H) [which includes 0.91 (d, J = 6.5 Hz, 3 H), 0.89 (d, J = 7.0 Hz, 3 H), 0.77 (d, J = 6.9 Hz, 3 H); ^{13}C NMR 16.2 (q), 20.7 (q), 22.0 (q), 23.3 (t), 26.1 (q), 30.1 (d), 31.4 (d), 34.2 (t), 40.7 (t), 46.9 (d), 50.6 (t), 75.5 (d), 166.7 (s), 198.8 (s); IR 2975, 1728, 1655, 1245, 1155; MS; 240 (200), 138 (100), 123 (550), 95 (170). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.95; H, 10.07. Found: C, 70.06; H, 10.20.

Preparation of 4: R_f (20% EtOAc/hexane) 0.47; ^{1}H NMR 0.8–1.1 (m, 6 H), 1.2–1.8 (m, 10 H), 2.54 (t, J = 2.3 Hz, 2 h), 3.44 (3, 2 H), 4.13 (t, J = 6.6 Hz, 2 H); ^{13}C NMR 13.6 (q), 13.8 (q), 19.1 (t), 22.4 (t), 23.3 (t), 30.7 (t), 31.3 (t), 43.0 (t), 49.4 (t), 65.2 (t), 167.0 (s), 202.5 (s); IR 2975, 1755, 1730, 1660, 1475, 1240, 1205, 1155; MS, 214 (36), 158 (330), 103 (490), 99 (71), 43 (100).

Preparation of 5: R_f (20% EtOAc/hexane) 0.42; ^{1}H NMR 1.0 (s, 3 H), 1.25 (s, 3 H), 1.29 (s, 3 H), 1.4–2.1 (m, 8 H), 2.6 (s, 3 H), 4.1 (d, J = 8.9 Hz, 1 H), 5.6 (d, J = 8.716 Hz, 1 H), 7.3–7.5 (m, 3 H), 7.6 (d, J = 7.2 Hz, 1 H), 7.7 (d, J = 8.1 Hz, 1 H); 7.8 (d, J = 7.9 Hz, 1 H), 8.04 (d, J = 8.3 Hz, 1 H); IR 2970, 1750, 1725, 1555, 1400, 1245, 1035; MS, 364 (50), 262 (40), 254 (63), 170 (100), 141 (36).

Preparation of 6: R_f (20% EtOAc/hexane) 0.31; ^{1}H NMR 0.45 (d, J = 7.1 Hz, 1.5 H), 0.58 (d, J = 7.1 Hz, 1.5 H), 1.0 (s, 3 H), 1.26–1.4 (m, 12 H), 2.65 (q, J = 7.2 Hz, 0.5 H), 2.74 (q, J = 7.1 Hz, 0.5 H), 4.08 (d, J = 8.8 Hz, 1 H), 5.55 (d, J = 8.9 Hz, 1 H), 7.61 (d, J = 7.5 Hz, 1 H), 7.69 (d, J = 7.9 Hz, 1 H), 7.80 (d, J = 7.9 Hz, 1 H); 8.03 (d, J = 8.2 Hz, 1 H). ^{13}C NMR 14.7, 21.5, 23.8, 27.1, 27.5, 42.5, 48.3, 49.4, 51.3, 53.1, 53.6, 55.4, 80.5, 123.4, 124.5, 125.1, 126.1, 126.7, 127.2, 128.9, 133.2, 133.6, 135.2, 169.4, 202.41; IR 2970, 1745, 1725, 1655, 1400, 1240, 1205, 1035; MS, 378 (17), 279 (45), 262 (43), 254 (54), 170 (100), 167 (62), 149 (87).

(8) Reaction times are reduced if larger quantities of 4-DMAP are used.

Acknowledgment. We thank the National Science Foundation (CHE 8306692) and the National Institutes of Health (GM 32027) for support of this work. D.F.T. thanks ICI Americas for an unrestricted research grant.

Registry No. 1, 105-45-3; 3, 97403-74-2; 4, 97403-75-3; *l*-menthol, 2216-51-5; 4-(dimethylamino)pyridine, 1122-58-3; 4-(methoxycarbonyl)-4-acetyl-1,6-heptadiene, 3666-84-0; methyl 3-oxooctanoate, 22348-95-4; methyl 2-methyl-3-oxobutyrate, 17094-21-2.

A Short Enantiospecific Synthesis of 2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN)

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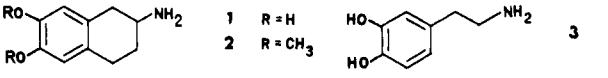
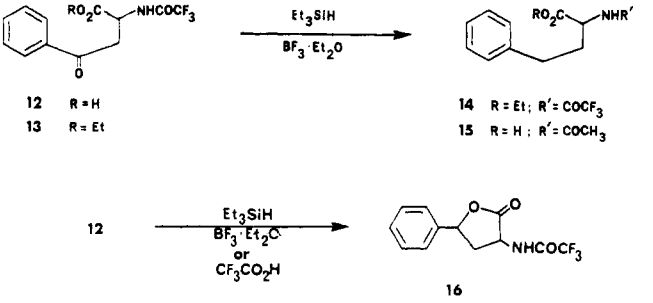
2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN) (**1**) has received intense neuropharmacological study in recent years as a powerful agonist of dopamine (**3**).[1] Several approaches have been developed for the



synthesis of racemic **1** and related 2-aminotetralins.[2] McDermed and co-workers have obtained the enantiomers of **1** by classical resolution of the bis(methyl ether) **2** followed by demethylation.[3] We report here the first enantiospecific synthesis of ADTN bis(methyl ether), making readily available in high purity either enantiomer of ADTN.

Our route to (*R*)-(+)-ADTN bis(methyl ether) (**10**) was based on (*R*)-*N*-(trifluoroacetyl)aspartic anhydride[4] (**5**) as a chiral synthon[5] (Scheme I). The C,N complement of the product was assembled by Friedel–Crafts acylation of veratrole (**4**) with 1.05 equiv of **5** in the presence of 2.0 equiv of anhydrous $AlCl_3$ in CH_2Cl_2 at room temperature with efficient stirring under N_2.[6,7] A single isomeric ketone **6**, was obtained in 55% yield after conventional workup and recrystallization from EtOAc/hexane.

The regiochemistry of the reaction of **4** and **5** was established from the analogous product **12**, from C_6H_6 + (racemic) **5**. Reduction of the ethyl ester **13** with Et_3SiH in $BF_3{\cdot}Et_2O$[8] gave the norketo compound **14**, which was



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