Simple Stereoselective Synthesis of (±)-Oplopanone

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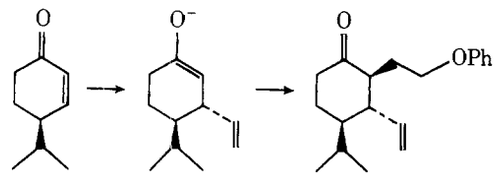
A practical two-step preparation of polysubstituted cyclohexanones from 2-alkoxybenzoic acid derivatives, exemplified by the conversion of **7** to **9**, is detailed. Ketone **9** is converted in eight steps to (±)-oplopanone (**1**).

Oplopanone (**1**), a sesquiterpene originally isolated from *Oplopanax japonicus*[1] and since detected in many diverse organisms,[2] offers an interesting synthetic challenge. The bicyclic structure incorporates five asymmetric centers, including a 6/5-trans ring fusion. An elegant synthesis of **1** based on an efficient photochemical rearrangement has been published.[3] We detail here our retrosynthetic analysis of **1** and the resultant synthesis.

A methyl carbinol such as that at C-8 (Retrosynthetic Scheme; Scheme I) could be derived either from the addition of a methyl anion to a ketone or by addition of oxygen to an exocyclic methylene. As attack at such an sp^2 center tends to give the equatorial adduct,[4,5] the latter approach was appropriate.

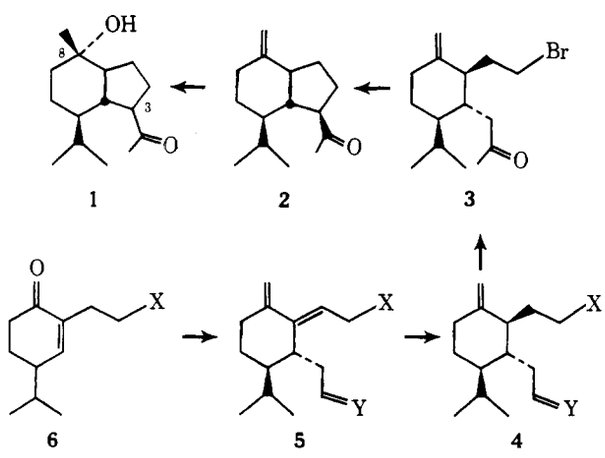
The next challenge was the construction of the trans 6/5 system. We chose to approach this by intramolecular alkylation.[6] The facility of such an intramolecular displacement was expected to easily overcome the strain being incorporated in



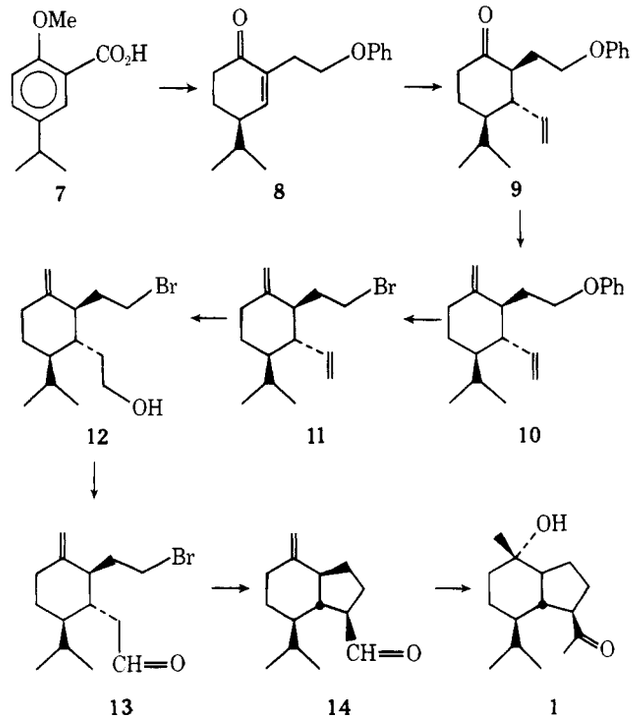
the molecule. Inspection of models led to the conclusion that the C-3 configuration assigned[1] should be the more stable, so cyclization with a small excess of base in a protic solvent was expected to give the appropriate relative configuration at this center.

After converting the reactive halo and keto functional groups to masked forms, dissection of the exocyclic methylene led to the simple 2,3,4-trisubstituted cyclohexanone **5**. We chose to construct **5** by conjugate addition to **6**. We expected that such addition would take place predominantly trans to the isopropyl group.[7] Epimerization of the α side chain should then give the all-equatorial diastereomer desired.

Scheme I. Retrosynthetic Scheme



Scheme II. Synthetic Scheme



Results

The starting material for the synthesis was the known[8] *o*-methoxybenzoic acid derivative **7** (Synthetic Scheme; Scheme II). Reductive alkylation[9] with β-bromophenetole provided enone **8**, which reacted smoothly with vinylmagnesium bromide/cuprous iodide[10-12] to give the desired trans,trans-trisubstituted cyclohexanone **9**. Wittig olefination[14] of **9** gave **10**.

As we had hoped, BBr_3 cleavage[15] of **10** proceeded smoothly to give the unstable bromide **11**, which was hydroborated[16] directly to give **12**.[17] Oxidation[19] of **12** to the aldehyde **13** followed by brief base treatment gave the fragrant bicyclic aldehyde **14**. Addition of methyllithium to **14** followed by oxymercuration[5] and oxidation[19] then led to crystalline (±)-oplopanone (**1**).

Discussion

The key to this simple synthesis of a relatively complex sesquiterpene is the facile synthesis of the trisubstituted cyclohexanone **9**. This approach offers several advantages over the obvious alternative, conjugate addition/enolate trapping performed on a γ-substituted cyclohexenone.

First, essentially any alkylating agent can be used to attach the α side chain. The dihydrobenzoic acid dianion is both flat and reactive, so that even isopropyl iodide[20] reacts cleanly. This should be compared to the necessity of using very reactive alkylating agents (alkyl bromides and primary iodides) to successfully trap specific enolates.

Further, the α side chain stabilizes the α,β isomer of the

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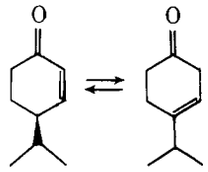
enone. This is particularly important in the case of γ-substitution; the enone in question (cryptone) is 40% deconjugated at equilibrium.[21]



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Finally, having the α side chain in place allows the addition of nucleophiles (e.g., malonates and amines) that do not in the course of addition lead to a trapable enolate. These considerations, coupled with the ready availability of 2-alkoxybenzoic acid derivatives, lead us to suggest that this method for the construction of polysubstituted cyclohexanones could find widespread application in the field of carbocyclic natural product synthesis.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. ^1H NMR spectra were determined on a JEOLCO MH-100 spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in δ units downfield from the internal reference tetramethylsilane. Couplings (J) are in hertz (Hz). The infrared spectra (IR) were recorded on a Perkin-Elmer 257 spectrometer as solutions in CCl_4 and are reported in reciprocal centimeters (cm^{-1}). Mass spectra (MS) were determined at 70 eV on an LKB 9000 gas chromatograph-mass spectrometer interfaced with a PDP-12 computer system and are reported as mass per unit charge (m/e), with intensities as a percentage of the peak of greatest ion current having $m/e \geq 100$. Organic chemicals were purchased from Aldrich Chemical Co. Organometallics were purchased from Alfa Inorganics and were titrated prior to use. Solvent mixtures (e.g., 5% ethyl acetate/hexane) are volume/volume. R_f values indicated refer to thin-layer chromatography on microscope slides coated with EM silica gel 60 PF-254. Column chromatography was carried out using the short column technique,[22] modified by running the columns under air pressure (5–20 psig). Samples for microanalysis were prepared by short column chromatography followed by bulb-to-bulb distillation (Aldrich Kugelrohr). The bromine-containing intermediates in the synthesis were not stable to distillation, so they were not submitted for analysis. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

2-Methoxy-5-isopropylbenzoic Acid (7). The carboxylation of 4-isopropylanisole[23] was effected by the method of Shirley.[24] Thus, 4-isopropylanisole (0.86 mol, 129 g), TMEDA (0.88 mol, 100 g), and 1 L of anhydrous ether were combined in a 3000-mL three-neck round-bottom flask. The solution was stirred magnetically under nitrogen at room temperature, and n-butyllithium (1.0 mol, 385 mL of a 2.6 M hexane solution) was added dropwise over 15 min. The mixture was refluxed overnight. A slurry consisting of 500 g of crushed dry ice and 1600 mL of anhydrous ether was prepared in a large plastic bucket, and the reaction mixture was diluted with an additional 1300 mL of dry ether and added with stirring (*Caution: vigorous reaction!*). The mixture was allowed to warm to room temperature, water (1000 mL) was added, and the mixture was made alkaline with 50% aqueous NaOH. The ether layer was removed, and the aqueous layer was washed twice with ether and then made acidic with concentrated aqueous HCl. The acidic mixture was then extracted three times with ether. The ethereal solution was dried over Na_2SO_4 and concentrated in vacuo. Crystallization of the residue from hexane afforded 104 g (62%) of white crystals: mp 64.0–64.5 °C (lit.[8] mp 60–61 °C; IR 3300, 2950, 1730, 1680, 1605, 1170 cm^{-1}; NMR δ 8.08 (d, J = 2 Hz, 1 H), 7.48 (dd, J = 2 and 9 Hz, 1 H), 7.00 (d, J = 9 Hz, 1 H), 4.05 (s, 3 H), 2.92 (m, 1 H), 1.20 (d, J = 7 Hz, 6 H).

2-(Phenoxyethyl)cyclohexenone 8. The reductive alkylation was carried out by a modification of our published[9] method. Thus, acid 7 (100 mmol, 19.5 g) was placed in a 1-L three-neck flask equipped with a mechanical stirrer, a gas inlet, and a cold finger condenser (dry ice/acetone) fitted with a KOH drying tube. THF (100 mL) was added, and the mixture was stirred in a −78 °C bath as NH_3 was distilled in until the flask was approximately half full. The NH_3 stream was replaced by N_2, and pieces of lithium, washed sequentially in hexane, methanol, and ether, were added to the well-stirred mixture until a deep blue color was obtained. β-Bromophenetole (110 mmol, 22.1 g in 50 mL of THF with a 1 mL of dibromoethane) was immediately added in one portion. After stirring briefly, the cooling bath was removed and the NH_3 was allowed to evaporate under a stream of N_2. 1,2-Dichloroethane (100 mL), hydroquinone (200 mg), concentrated HCl (100 mL), and water (100 mL) were then added, and the two-phase mixture was refluxed for 2 h. The organic layer was separated and the aqueous layer extracted twice with methylene chloride. The combined organic phase was dried over K_2CO_3, concentrated in vacuo, and distilled through a 14/20 short-path apparatus to give 14.2 g of colorless oil (55%): $bp_{0.4}$ 155–170 °C; IR 1665, 1230, 1590, 1030, 690 cm^{-1}; NMR δ 6.7–7.2 (m, 6 H), 4.04 (t, J = 6 Hz, 2 H), 1.4–2.8 (m, 8 H), 0.94 (d, J = 7 Hz, 6 H); MS m/e 258 (M^+, 1.58), 177 (13), 166 (14), 165 (100). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.02; H, 8.60. Found: C, 78.83; H, 8.56.

Vinyl Ketone 9. $(CH_3)_2S{\cdot}CuBr$[10b] (18 mmol, 3.7 g) was placed in a 50-mL round bottom flask with 20 mL of THF. Methyl sulfide (~6 mL) was added until all of the solid was dissolved. The flask was then flushed with N_2 and cooled to −30 °C (aqueous $CaCl_2$/dry ice). Vinylmagnesium bromide (30 mmol, 25 mL of a 1.2 M THF solution) was added dropwise over 5 min. The mixture was stirred for 20 min, and the enone 8 (3.05 g, 11.8 mmol) in 15 mL of THF was added dropwise over 5 min. The mixture was stirred for an additional 10 min at −20 to −30 °C. The cooling bath was removed and stirring continued for 45 min. The reaction mixture was quenched by pouring it into 10% aqueous NH_3 and extracted into petroleum ether (separation of phases required a centrifugation[25]). Solvent was removed in vacuo, and the crude product was chromatographed on 50 g of TLC silica gel with 4% ethyl acetate in petroleum ether to give, after evaporation, 1.74 g (52%) of colorless oil: R_f (20% ethyl acetate/hexane) 0.5; IR 1700, 1590, 1230, 1030, 910, 690 cm^{-1}; NMR δ 6.7–7.2 (m, 5 H), 4.9–5.7 (m, terminal vinyl, 3 H), 3.96 (m, 2 H), 1.2–2.9 (m, 10 H), 0.96 (d, J = 7 Hz, 3 H), 0.70 (d, J = 7 Hz, 3 H); MS m/e 286 (M^+, 0.74), 194 (16), 193 (100), 175 (5), 109 (11), 107 (9). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.66; H, 9.17. Found: C, 79.52; H, 9.07.

Diene 10. Methyltriphenylphosphonium bromide (9.7 mmol, 3.46 g) and DME (20 mL) were placed in a dry flask under N_2. Potassium *tert*-butoxide (8.1 mmol, 0.905 g) was added to give a bright yellow suspension. Ketone 9 (6.47 mmol, 1.85 g) in 10 mL of DME was added. The mixture was stirred overnight at room temperature. The mixture was then poured into saturated aqueous NaCl, made acidic with HCl, and extracted with petroleum ether. The extract was dried over K_2CO_3 and concentrated in vacuo. The residue was then filtered through 60–200 mesh silica gel with 5% ethyl acetate in petroleum ether. Solvent removal left 1.68 g (87%) of residual yellow oil: R_f (5% ethyl acetate/hexane) 0.5; IR 3030, 1630, 1590, 1490, 1460, 1230, 1030, 910, 890, 690 cm^{-1}; NMR δ 6.7–7.4 (m, 5 H), 4.9–5.7 (m, terminal vinyl, 3 H), 4.80 (s, 1 H), 4.66 (s, 1 H), 3.95 (m, 2 H), 1.0–2.5 (m, 10 H), 0.88 (d, J = 7 Hz, 3 H), 0.68 (d, J = 7 Hz, 3 H); MS m/e 284 (M^+, 54), 149 (90), 147 (100), 134 (75), 121 (78), 107 (88). Anal. Calcd for $C_{20}H_{28}O$: C, 84.43; H, 9.94. Found: C, 84.50; H, 9.95.

Bromo Alcohol 12. The diene 10 (0.88 mmol, 250 mg) was taken up in 10 mL of methylene chloride and stirred at −78 °C under N_2. BBr_3 (1.3 mmol, 125 μL) was added, and the mixture was stirred for 15 min. Anhydrous sodium acetate (~0.5 g) was added followed by methanol (1 mL). Stirring at −78 °C was continued for 5 min, and then the mixture was allowed to warm to room temperature. The mixture was diluted with 10 mL of methylene chloride, washed twice with 20 mL of 10% aqueous NaOH, dried over K_2CO_3, and evaporated to give a yellow oil: NMR δ 4.9–5.8 (m, 3 H, terminal vinyl), 4.80 (s, 1 H), 4.58 (s, 1 H), 3.40 (m, 2 H), 1.1–2.6 (m, 10 H), 0.88 (d, J = 7 Hz, 3 H), 0.68 (d, J = 7 Hz, 3 H).

Hydroboration was carried out with disiamylborane following the procedure of Brown.[16] Thus, 2-methyl-2-butene (3.2 mmol, 280 μL) was placed in a dry flask under N_2 at 0 °C. BH_3 (1.06 mmol, 1.06 mL of a 1 M THF solution) was added dropwise over 1 min, and the mixture was stirred for 20 min. The crude bromodiene was dissolved in 2 mL of THF and added. The mixture was stirred for 20 min at 0 °C, the cooling bath was removed, and stirring was continued for 45 min. The mixture was again cooled to 0 °C, and *cold* NaOH (1 mL of a 50% aqueous solution) was added followed by *cold* H_2O_2 (1 mL of a 30% aqueous solution). Stirring was continued for 10 min, and the mixture was extracted with three 15-mL portions of methylene chloride. The extract was washed with aqueous $Na_2S_2O_3$ and dried over K_2CO_3. The crude product was chromatographed on 10 g of TLC silica gel with 8% acetone in petroleum ether to give 115 mg (45%) of colorless oil: R_f (20% ethyl acetate/hexane) 0.5; IR 3610, 3300, 3030, 2860, 1635, 1430, 1020, 885 cm^{-1}; NMR δ 4.84 (s, 1 H), 4.65 (s, 1 H), 3.68 (t, J = 7 Hz, 2 H), 3.45 (br t, J = 7 Hz, 2 H), 1.1–2.5 (m, 13 H), 0.97 (d, J = 7 Hz, 3 H), 0.82 (d, J = 7 Hz, 3 H).

Bromoaldehyde 13. The bromo alcohol 12 (2.4 mmol, 686 mg) was taken up in 30 mL of methylene chloride and stirred with ~500 mg

of Celite. PCC[19] (3.6 mmol, 786 mg) was added and the mixture stirred at room temperature for 1 h. The mixture was then diluted with 150 mL of ether and stirred for 10 min. The crude mixture was filtered through Florisil with ether and evaporated to give 602 mg (88%) of colorless oil: R_f (20% ethyl acetate/hexane) 0.6; IR 3030, 2900, 2700, 1715, 1635, 1430, 1230, 890 cm^{-1}; NMR δ 9.83 (t, J = 1 Hz, 1 H), 4.83 (s, 1 H), 4.66 (s, 1 H), 3.40 (m, 2 H), 2.54 (d, J = 4 Hz, 2 H), 1.0–2.0 (m, 10 H), 0.96 (d, J = 7 Hz, 3 H) 0.78 (d, J = 7 Hz, 3 H).

Bicyclic Aldehyde 14. Bromoaldehyde **13** (1.8 mmol, 519 mg) and *tert*-butyl alcohol (purged with N_2, 50 mL) were stirred at room temperature under N_2, and potassium *tert*-butoxide (2.4 mmol, 264 mg) was added. The pale yellow mixture was stirred for 1.5 h. The mixture was poured into 50 mL of 5% aqueous HCl and extracted with three 30-mL portions of ether. The ethereal solution was washed with $NaHCO_3$, dried over K_2CO_3, and evaporated to give 518 mg of crude product, which was distilled bulb-to-bulb to give 331 mg (89%) of colorless oil: $bp_{0.5}$ 110 °C; R_f (5% acetone/hexane) 0.3; IR 2920, 2870, 2850, 1690, 1450, 1360, 910, 890 cm^{-1}; NMR δ 9.59 (d, J = 5 Hz, 1 H), 4.68 (s, 1 H), 4.56 (s, 1 H), 0.8–2.6 (m, 13 H), 0.95 (d, J = 7 Hz, 3 H), 0.69 (d, J = Hz, 3 H); MS *m/e* 206 (M^+ 75), 163 (90), 145 (100), 135 (79), 107 (85), 105 (52). Anal. Calcd for $C_{14}H_{22}O$: C, 81.48; H, 10.77. Found: C, 81.43; H, 10.61.

(±)-Oplopanone (1). To a solution of bicyclic aldehyde **14** (1.1 mmol, 231 mg) in 20 mL of ether under N_2 was added methyllithium (1.4 mmol, 1.3 mL of a 1.08 M ether solution). The mixture was stirred for 10 min at room temperature and poured into 20 mL of 3% aqueous HCl. The ether layer was separated, and the aqueous layer was extracted with two 20-mL portions of ether. The combined ether extracts were dried over K_2CO_3 and evaporated. The residue was washed into a small centrifuge tube with 5 mL of THF. Mercuric acetate (1.4 mmol, 450 mg) and 4 mL of water were added, and the tube was shaken vigorously for twice the time (~5 min) required to discharge the initial bright yellow color (the solution remained pale yellow due to the presence of excess reagent). A 1-mL amount of 3 N NaOH and 1 mL of 0.5 M $NaBH_4$ in 3 N NaOH were added. The mixture was saturated with sodium chloride, and the tube was shaken and spun to remove the precipitated mercury. The THF layer was removed via pipet, and the aqueous layer was extracted with two 10-mL portions of ether. The combined organic layers were evaporated in vacuo and the residue was dissolved in 20 mL of methylene chloride and further dried with sodium sulfate. The dried solution was decanted, and Celite (~0.5 g) and PCC[19] (2.2 mmol, 470 mg) were added to it. The mixture was stirred for 2 h at room temperature, diluted with 100 mL of ether, and filtered through Florisil with ether. The crude product was chromatographed on 10 g of TLC silica gel with 40% ethyl acetate in petroleum ether to give 86 mg (33%) of colorless oil, R_f (50% ethyl acetate/hexane) 0.34, which crystallized upon standing. A portion recrystallized from ether/hexane had a melting point of 97–98 °C (lit.[3] mp 100–101 °C). This material was identical with natural material by NMR, TLC, and GC/MS.

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Registry No.—**1**, 35049-27-5; **7**, 68014-67-5; **8**, 68014-68-6; **9**, 68014-69-7; **10**, 68014-70-0; **11**, 68014-71-1; **12**, 68014-72-2; **13**, 68014-73-3; **14**, 68014-74-4; β-bromophenetole, 589-10-6.

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(11) Neither malonate nor acetoacetate could be induced to add to **8**, even under forcing conditions.
(12) Allyltrimethylsilane[13] reacted with **8** to give a mixture of at least three epimeric cyclohexanones which were isomeric (IR, NMR, MS) with the desired structure. While we were able to purify one component of this mixture by careful chromatography on silica gel, we were not able to ascertain its structure.
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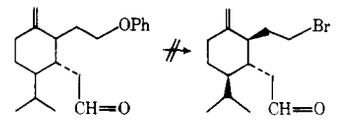
(17) We thought it conceptually more elegant to effect the ether cleavage on phenoxyaldehyde i. However, all attempts[15,18] to do so led to only trace amounts of ii. NMR analysis of the crude reaction mixtures showed loss of both aldehyde and exocyclic methylene functionality.



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(18) Besides BBr_3, reagents tried were (a) trimethylsilyl iodide [M. E. Jung and Mark A. Lyster, *J. Org. Chem.*, **42**, 3761 (1977).] and (b) ferric chloride-acetic anhydride [B. Ganem and V. R. Small, Jr., *J. Org. Chem.*, **39**, 3728 (1974).].
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(25) In subsequent work we have found that slow addition of the crude reaction mixture to a cold 0.2 M solution of $K_2Cr_2O_7$ in 0.2 M H_2SO_4 gives a readily extractable mixture free from intractable sludge.