below δ 2.65 ppm. The analytical sample was obtained by silica gel chromatography (cyclohexane/EtOAc) followed by bulb-to-bulb distillation. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; H, 7.25. Found: C, 74.53; H, 9.92; N, 7.22.

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Registry No.—**1**, 61714-12-3; **3**, 62930-44-3; **4**, 57147-61-2; **5**, 62930-45-4; **6**, 62930-46-5; Cr, 7440-47-3.

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Generation and Alkylation of the Dianion (Homoenolate) of a 1-Indanone

Barry M. Trost* and Lee H. Latimer

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

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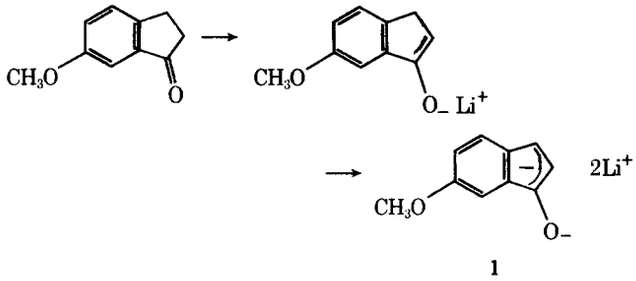
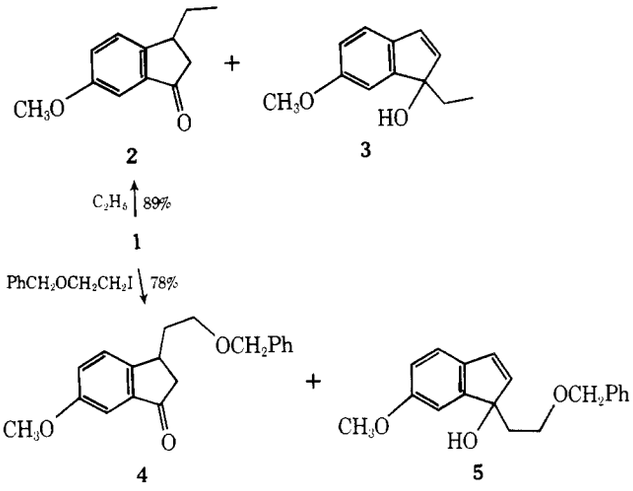
The generation of dianions from monofunctional compounds has been seldom observed and utilized.[1] In conjunction with the chemistry of gibberillins, we required a facile route to 3-substituted 1-indanones. Metalation of the enamines of 1-indanones followed by alkylation does provide access to such compounds.[2] However, a more direct method was envisioned based upon the fact that the enolate of indanone is an oxyindene which should still be reasonably acidic as a result of the generation of the aromatic indenyl anion. We wish to report the facile direct generation of the homoenolate of 1-indanone and its utility in forming both 3-monosubstituted and 2,3-disubstituted 1-indanones.

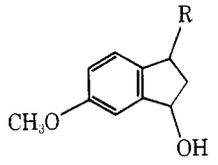


1

Treatment of 6-methoxy-1-indanone[3] with 2 equiv of lithium diisopropylamide at −78 °C in THF produced a white suspension in a yellow solution, which turned deep red upon warming to 0 °C for 4 h. Addition of 1 equiv of ethyl iodide followed by aqueous workup gave a 89% yield of 3-ethyl-1-indanone (**2**) and <3% of 3-ethyl-3-hydroxy-1-indene (**3**).



Similar results were obtained upon alkylation with 2-benzyloxyethyl iodide. The assignment of the 3-substitution for **2** and **4** follows from NMR spectra of the compounds and that of their corresponding alcohols **6** and **7**, respectively.



6, R = C_2H_5
7, R = $PhCH_2OCH_2CH_2$

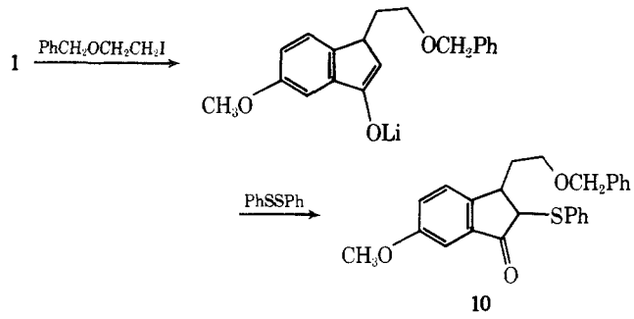
In the starting indanone, the protons at C(2) and C(3) appear at δ 2.66 and 3.05, respectively. In **2** and **4** the absorptions for the benzylic protons appear as a multiplet at δ 3.20 and 3.44, respectively, for one proton each and the methylene groups α to the carbonyl groups appear as a clean doublet of doublets [**2**, δ 2.23 (J = 19, 4 Hz) and 2.74 (J = 19, 7 Hz); **4**, δ 2.32 (J = 19, 3 Hz) and 2.76 (J = 19, 7 Hz)]. In **7** the proton α to the hydroxyl group appears as a doublet of doublets (J = 8, 5 Hz) at δ 5.1 in the presence of D_2O which demands a methylene group at C(2). Further transformations of these compounds reaffirm these conclusions.[4]

While full characterization of the trace by-products was not obtained, spectral data clearly suggest the assigned structures, **3** and **5**. The infrared spectra show the presence of an alcohol group, but the absence of any carbonyl group. The NMR spectra are essentially first order. For example, **5** shows a clean AB pattern for the vinyl protons (δ 6.44 and 6.19, J = 6 Hz) and a single high-field methylene group comprised of diastereotopic protons coupled only to an adjacent methylene group—each proton is a doublet (J = 15 Hz) of triplets (J = 7 Hz) at δ 2.20 and 1.89. Reaction at C(1) of **1** points out the analogy to **8**[5] and **9**,[1h,i] in which the problem of α vs. γ attack

8 9

is well recognized. In contrast to **8**, X = alkyl or silyl, **1** should and does show almost exclusive γ attack due to the electronic repulsion of the charged oxygen, which will be reinforced by the preference to maintain maximum charge stabilization by delocalization in the initial product.

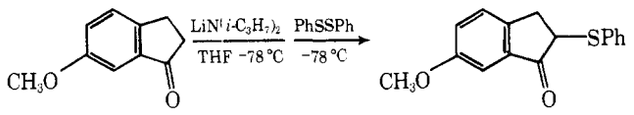
Since the initial product is an enolate, further substitution is quite feasible. Indeed, after alkylation of **1** with benzyloxyethyl iodide, addition of diphenyl disulfide[6] led to the 2,3-disubstituted product **10**. Based upon the fact that the base is the limiting reagent under these conditions, **10** was obtained in 84% yield. The substitution of the phenylthio group at C(2)



10

was confirmed by the NMR spectrum **10** and its corresponding alcohol. No absorptions appeared between δ 2.2 and 3.1 for the methylene group α to the carbonyl group in **10**. The corresponding alcohol showed the methine proton at C(1) as a doublet (J = 6 Hz) at δ 4.9, indicating the presence of a methine group at C(2).

Dianion formation requires warming to 0 °C. Quenching the initial product mixture at −78 °C with diphenyl disulfide led only to 2-phenylthio-1-indanone rather than the 3-substituted isomer. The utility of this method is clearly indicated by its directness and ease of scale-up. The great difference in reactivity between the dianions and monoanion allows facile and flexible substitution at the 3 or 2,3 positions in one step. Further, the direct generation of homoenolates in special cases is clearly feasible and suggests that further exploration in this area would be quite exciting.



Experimental Section

Preparation of 3-Substituted 1-Indanones: 3-(2′-Benzyloxyethyl)-6-methoxyindan-1-one. To a −78 °C solution of 57 g (80 mL, 0.57 mol, 2.37 equiv) of diisopropylamine in 0.4 L of dry THF was added 370 mL (concentrated to 50 mL under vacuum) (0.52 M, 2.18 equiv) of 1.4 N n-butyllithium in hexane. After 1 h, 38.5 g (0.238 M) of 6-methoxyindan-1-one in 500 mL of THF was added dropwise over a 20-min period by cannula. After stirring for 1 h at −78 °C, the yellow slurry was allowed to warm to room temperature for 4 h, during which time the solution became deep wine red. This solution was cooled to approximately −20 °C and a solution of 75 g (0.28 mol, 1.2 equiv) of 2-benzyloxyethyl iodide[4] in 100 mL of THF was added rapidly with vigorous stirring. The red color dissipated almost instantly with substantial evolution of heat and lightening of color to orange red. After 15–30 min the reaction mixture was further quenched by addition of 1 L each of 3 N aqueous hydrochloric acid solution and saturated aqueous sodium chloride solution. Extraction with three 500-mL portions of ether, washing the combined organic layers with water, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium thiosulfate, solution, and brine, followed by drying over magnesium sulfate and concentration in vacuo, yielded 80 g of crude product. This crude product showed only alkyl iodide and desired product spots upon TLC, although multiple elutions showed trace amounts of the 1-alkyl inden-1-ol. Purification by HPLC[7] with ether–hexane (1:3) yielded 54.5 g (0.183 mol, 78%) of alkylated material shown by NMR integration to be >95% of the 3-alkyl indanone. Due to the difficulty of separating the minor component and the ease of removal after subsequent reduction of the indanone, this material was used without further purification. A small sample of the crude mixture, 100 mg, was purified by PLC[8] (two elutions with 3:1 hexane–ether) to yield 67 mg of 3-alkyl indanone (R_f 0.7, 1:1 ether–hexane, two elutions) and 2 mg of the 1-alkyl inden-1-ol (R_f 0.65). Slightly larger amounts of the indenol were seen when the alkylation was performed at room temperature.

3-(2′-Benzyloxyethyl)-6-methoxyindan-1-one: NMR (CCl_4) δ 1.5–1.9 (1 H, m), 2.0–2.3 (1 H, m), 2.33 (1 H, dd, J = 8, 2 Hz), 2.74 (1 H, dd, J = 18, 8 Hz), 3.30–3.65 (3 H, m with td superimposed), 3.80 (3 H, s), 4.48 (2 H, m), 7.05–7.20 (2 H, m), 7.3 (6 H, br s); IR (CCl_4) 3600–3400 (w), 3090, 3060, 3030, 2960, 2940, 2880, 1710, 1610, 1495, 1435, 1320, 1285, 1250, 1115, 1055, 1045, 705 cm^{-1}; MS m/e 296 (5), 206 (11), 205 (100), 194 (25), 188 (24), 187 (10), 175 (40), 165 (10), 162 (5), 161 (30), 147 (15), 92 (6), 91 (65). Anal. Calcd for $C_{19}H_{20}O_3$: 296.141 24. Found: 296.140 97.

1-(2′-Benzyloxyethyl)-6-methoxyinden-1-ol: NMR (CCl_4) δ 1.98 (1 H, dt, J = 18, 7 Hz), 2.20 (1 H, dt, J = 18, 7 Hz), 2.49 (1 H, br s, exchangeable), 3.56 (2 H, t, J = 7 Hz), 3.70 (3 H, s), 4.40 (2 H, s), 6.15 (1 H, d, J = 5.5 Hz), 6.40 (1 H, d, J = 5.5 Hz), 6.60 (1 H, dd, J = 2.5, 8.5 Hz), 6.83 (1 H, d, J = 2.5 Hz), 6.93 (1 H, d, J = 8.5 Hz), 7.22 (5 H, s); IR ($CHCl_3$) 3580, 3450, 3000, 2920, 2870, 1600, 1450, 1280, 1090, 1020 cm^{-1}.

Preparation of 2,3-Disubstituted 1-Indanones: 2-Phenylthio-3-(2′-benzyloxyethyl)-6-methoxyindan-1-one. To a −78 °C solution of 0.40 mL (2.28 mmol, 2.88 equiv) of diisopropylamine in 2.0 mL of THF was added 1.5 mL (2.1 mmol, 2.1 equiv) of 1.4 N n-butyllithium. After 30 min, 165 mg (1.0 mmol) of 6-methoxyindan-1-one in 1.0 mL of THF was added dropwise over 5 min. After 1 h the solution had developed a white precipitate. The bath was removed and the solution allowed to slowly come to room temperature over 4 h, during which time the precipitate dissolved to yield a yellow solution which turned reddish-orange upon further warming. The solution was then cooled to approximately −10 °C and 300 mg (1.15 mmol, 1.15 equiv) of 2-benzyloxyethyl iodide in 0.5 mL of THF was added rapidly by syringe. After 10 min this solution was added to a room temperature solution of 300 mg (1.61 mmol, 1.61 equiv) of diphenyl disulfide in 2 mL of THF and 0.5 mL of HMPA. After 30 min the mixture was diluted with ether and washed twice with aqueous 3 N hydrochloric acid and water, and dried over sodium sulfate and magnesium sulfate. Concentration in vacuo yielded 0.4 g of crude material which was purified by PLC[8] to yield 170 mg (42% or 84% based upon a maximum of 50% conversion) of desired material as a yellow oil, R_f 0.4 in 1:1 ether–hexane: NMR (CCl_4) δ 1.6–2.3 (2 H, m), 3.2–3.5 (1 H, m), 3.50 (2 H, t, J = 7 Hz), 3.64 (1 H, d, J = 3 Hz), 3.78 (3 H, s), 4.38 (2 H, s), 6.95–7.6 (13 H, m with a singlet at 7.20); IR (CCl_4) 3400 (w), 3010, 2940, 1720, 1615, 1490, 1280, 1215, 1100, 1030, 690, 660 cm^{-1}; MS 405 (2), 404 (6), 296 (2), 295 (4), 205 (3), 204 (2), 203 (10), 189 (3), 188 (13), 163 (7), 162 (26), 161 (90), 160 (100), 145 (14), 135 (9), 134 (13), 133 (25), 110 (70), 109 (37), 91 (58), 77 (52). Anal Calcd for $C_{25}H_{24}O_3S$: 404.144 61. Found: 404.145 66.

Preparation of 3-(2′-Benzyloxyethyl)-6-methoxyindan-1-ol. To a 0 °C slurry of 13.6 g (0.36 mol, 2.0 equiv) of lithium aluminum hydride in 300 mL of THF was added dropwise a solution of 54.5 g (0.184 mol) of 3-(2′-benzyloxyethyl)-6-methoxyindan-1-one in 200 mL of THF. The reaction mixture was maintained at 0 °C for 4 h and then quenched by successive addition (carefully) of 13.6 mL of water, 13.6 mL of 15% (w/v) aqueous sodium hydroxide solution, and 40 mL of water. After 5 min of continued vigorous stirring, the off-white to grey precipitate was filtered and the filtrate concentrated under reduced pressure to yield a semisolid mass from which 38.6 g of crystalline alcohol was obtained (mp 64–66 °C dichloromethane–hexane), apparently as one diastereomer. The mother liquor was concentrated and purified by HPLC (1:1 ether–hexane) to yield 5.3 g of crystals from tubes 41–76. The total yield of 43.9 g (0.147 mol) is 80% from the 3-alkyl indanone or 61.7% from 6-methoxyindan-1-one: NMR (CCl_4) (100 MHz) δ 1.5–2.0 (2 H, m), 2.0–2.9 (3 H, m with a br s at 2.4), 2.95–3.2 (1 H, m), 3.5–3.9 (5 H, m with sharp singlet at 3.80), 4.50 (2 H, s), 5.0–5.3 (1 H, m), 6.83 (1 H, dd, J = 8, 2 Hz), 6.95 (1 H, d, J = 2 Hz), 7.10 (1 H, d, J = 8 Hz), 7.38 (5 H, s); IR (CCl_4) 3600, 3450, 3060, 3020, 3000, 2930, 2850, 1610, 1485, 1260, 1090, 1040, 910, 695 cm^{-1}; MS 299 (4), 298 (15), 297 (2), 296 (4), 282 (5), 281 (18), 280 (83), 205 (15), 191 (8), 190 (34), 189 (44), 176 (5), 175 (21), 174 (50), 173 (10), 172 (25), 171 (5), 165 (8), 164 (15), 163 (12), 162 (5), 161 (20), 160 (18), 159 (100), 158 (10), 157 (9), 149 (8), 148 (7), 146 (25), 145 (23), 144 (16), 143 (5), 141 (6), 133 (13), 131 (13), 130 (9), 129 (22), 128 (20), 127 (14), 115 (22), 91 (60). Anal. Calcd for $C_{19}h_{22}O_3$: 298.156 89. Found: 298.157 60. Calcd: C, 76.51; H, 7.38. Found:[9] C, 76.41; H, 7.36.

Acknowledgment: We wish to thank the National Science Foundation for their generous support of our programs.

Registry No.—**2**, 30211-64-4; **3**, 62841-73-0; **4**, 62841-74-1; **5**, 62841-75-2; **7**, 62841-76-3; **10**, 62841-77-4; **10** alcohol, 62841-78-5; 6-methoxyindan-1-one, 13623-25-1; 2-benzyloxyethyl iodide, 54555-84-9.

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(7) A medium-pressure preparative liquid chromatography unit fitted with a 2.5 × 100 cm column packed with 32–63 μm Woelm silica gel. The system utilized a single-stage constant flow pump with a flow of approximately 22 mL/min. The eluent was directed to a Gilson fraction collector.
(8) Plates (10 × 20 or 20 × 40 cm) of Merck (Darmstadt) silica gel PF 254 of 1.5–2.0-mm thickness were employed.
(9) Analysis performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Communications

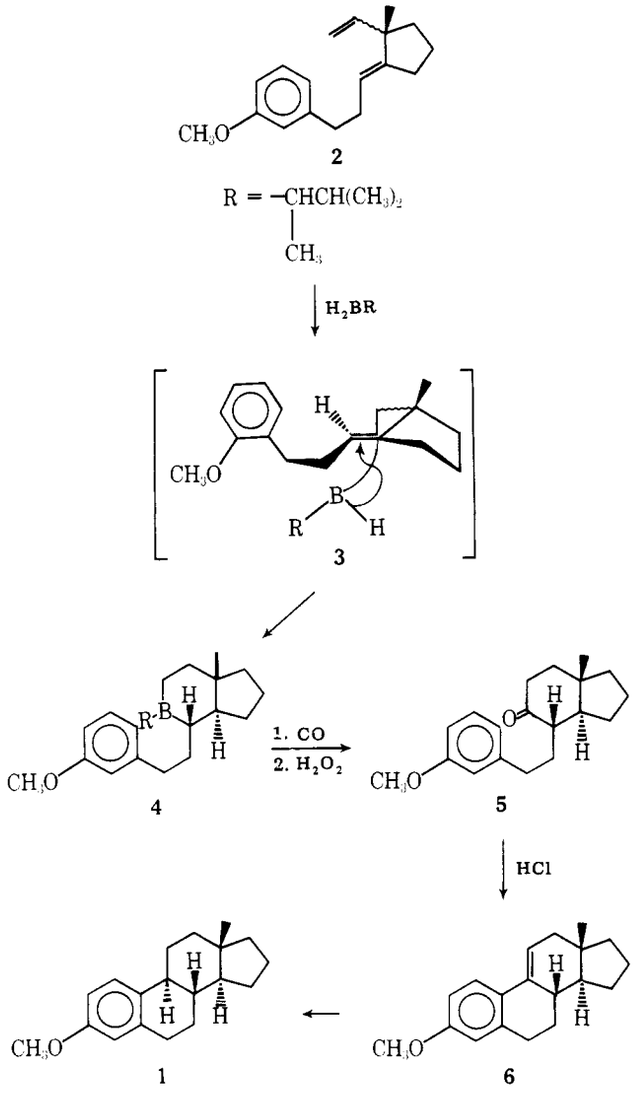
Synthesis of (±)-3-Methoxyestra-1,3,5(10)-triene: Stitching and Riveting as a Tool for Steroid Synthesis

Summary: (±)-3-Methoxyestra-1,3,5(10)-triene has been prepared from 1-chloromethylcyclopentene and 2-(*N*,*N*-dimethylamino)-4-(*m*-methoxyphenyl)butyronitrile.

Sir: We have been exploring the synthetic strategy of stitching and riveting,[1] hydroboration–carbonylation, as a means of preparing steroids and other stereochemically demanding natural products. Described herein are some of the initial results from our investigations directed toward the synthesis of 3-methoxyestra-1,3,5(10)-triene (**1**). This well-characterized steroid[2] was chosen as our first synthetic objective due to the presence of the natural configuration of the ring junctures along with its lack of complicating functional groups, and we envisioned it as evolving from diene **2** through the hydroboration–carbonylation procedures of Brown (Scheme I).[3] The well-documented theory of selectivity in the addition of alkylboranes to olefins led us to the proposition that thexylborane[4] would regioselectively add to the monosubstituted double bond in **2**, boron becoming bonded to the least-substituted end of that double bond, generating carborane **3**. This compound (**3**) would then be predisposed to deliver boron and hydrogen (cis addition) to the trisubstituted olefin (*E* geometry) of compound **3** in an intramolecular process that is stereochemically guided by attachment of these groups to the steroidal "*D* ring" as illustrated in Scheme I. Realization of this stitching process would force formation of all trans tricyclic carborane **4**. Carbonylation and oxidation of **4** would then form hydrindanone **5**, a structure analogous to compounds previously converted to estrone derivatives by Cohen and Smith.[5]

Pursuing these considerations, compound **2** was prepared and added to a solution of thexylborane (BH_3 was generated in situ, $LiAlH_4/BF_3OEt_2$, −78 °C; then 2,3-dimethyl-2-butene was added at 0 °C) forming crude carborane **4** (vinyl proton resonances of **2** absent in ^1H NMR of **4**). This material was immediately treated with carbon monoxide (1200 psi, 50 °C, 5 h) and then oxidized (NaOAc, H_2O_2, aqueous THF) affording **5** (53% from **2**). Studies on **5** have been strongly suggestive of the all trans structure shown in Scheme I.[6,7] Acid-catalyzed cyclization of **5** (10 N HCl/methanol)[5] gave 3-methoxyestra-1,3,5(10),9(11)-tetraene (**6**, mp 82–85 °C),[8] which forms the desired 3-methoxyestra-1,3,5(10)-triene (**1**) via reduction (1 atm H_2, Pd/C; mp 78 °C from methanol).[2] Chromatographic and spectroscopic comparison of this (±)-steroid with optically active 3-methoxyestra-1,3,5(10)-triene (**1**) prepared from natural 3-methoxyestra-1,3,5(10)-trien-17-one via deoxygenation (tosylhydrazone, NaH_3BCN)[9] confirmed the structural identity of these two substances.

Scheme I



Bicyclic diene **2** is accessible (Scheme II) through two sigmatropic rearrangements starting with 1-chloromethylcyclopentene (**7**)[10] and the *N*,*N*-dimethylaminonitrile **8**,[11] the latter of which is derived from *m*-methoxyhydrocinnamaldehyde. These two reagents (**7** and **8**) react to form amorphous salt **9**,[12] which was rearranged to amino nitrile **10** by the action of base (potassium *tert*-butoxide, Me_2SO/THF, −30 °C).[13] Copper sulfate (pentahydrate) assisted hydrolysis[13] (refluxing EtOH, 10 min) and acid-catalyzed bond migration (HCl