(s, 3 H), 2.40 (s, 3 H), 3.85 (s, 3 H), 6.60 (complex d, 2 H).

(b) From 5-Methylcodeinone (8). A solution of 622 mg of 8 in 5 mL of dry tetrahydrofuran was treated at 0 °C under N_2 with 2.4 mL of a 1 M solution of lithium tri-*sec*-butylborohydride in tetrahydrofuran. The mixture was allowed to warm to room temperature over 30 min when a TLC probe indicated complete disappearance of 8 and formation of a single product. Saturated ammonium chloride was added, and the mixture was extracted several times with $CHCl_3$. The extracts were washed with water, filtered through anhydrous Na_2SO_4, and concentrated to give 7: 566 mg (90%); mp 144–145 °C.

5-Methyldihydromorphinone (Metopon). (a) A solution of 132 mg of 7 in 1 mL of 48% HBr was heated to reflux for 30 min. As much as possible of the HBr solution was removed at 100 °C under diminished pressure. The residue (203 mg; theory, 166 mg for the hydrobromide) was triturated with 0.2 mL of concentrated ammonia to give a gray powdery solid which was collected and washed with water (118 mg). Its TLC was indistinguishable from that of an authentic sample of metopon.[10] Crystallization from alcohol gives solvated material of indeterminate melting point, so the sample was sublimed at 129–132 °C (10^{-3} mmHg) to give colorless prismatic needles: 33 mg; mp 242–248 °C dec; mmp (with authentic metopon, mp 238–244 °C dec) 240–246 °C dec. Both its IR and NMR spectra were indistinguishable from those of authentic metopon: IR (Nujol) 3530, 3400 (br), 1730, 1610, 1250, 1030, 850, 800 cm^{-1} inter alia; NMR δ 1.59 (s, 3 H), 2.45 (s, 3 H), 6.59 and 6.70 (AB, 2 H) inter alia.

(b) A suspension of 500 mg of sodium hydride in 5 mL of dry dimethylformamide was treated under N_2 with 313 mg of 5-methyldihydrocodeinone (7) and 620 mg of ethanethiol. After being stirred at room temperature for 15 min, the mixture was heated to 100 °C (bath) for 24 h. TLC indicated complete disappearance of 7 and the production of a single more polar substance. Saturated ammonium chloride was added, and the mixture was extracted several times with chloroform; the extracts were washed with water, filtered through anhydrous Na_2SO_4, and concentrated. The residue was chromatographed on silica gel, eluting with $CHCl_3/CH_3OH$ (9:1) to yield a nearly colorless amorphous powder, 272 mg (96% crude). Recrystallization of a small sample from $CHCl_3$ gave material of melting point 190–192 °C.[11] Its IR spectrum was indistinguishable from that of the sample described above.

5-Methylcodeinone (8). A stirred solution of 5-methylthebaine (1.50 g) in 100 mL of 3 M formic acid was treated under N_2 with 110 mg of mercuric acetate. The mixture was stirred at room temperature for 12 h, 120 mL of a saturated K_2CO_3 solution was added carefully, and the mixture was extracted with $CHCl_3$ four times. The extracts were washed with water and then brine and concentrated to yield 1.42 g of brownish red residue which was passed through a silica gel column in $CHCl_3/CH_3OH$ (50:1). Removal of the solvent and crystallization of the residue from anhydrous ether gave 1.28 g (85%) of 8: mp 178–179.5 °C; IR ($CHCl_3$) 1690 cm^{-1} inter alia; NMR δ 1.61 (s, 3 H), 2.44 (s, 3 H), 3.81 (s, 3 H), 6.01 (dd, 1 H), 6.63 (m, 3 H); $[\alpha]^{23}_D$ −156° (*c* 1.05, alcohol). Anal. Calcd for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.18; H, 6,85; N, 4.40.

Acknowledgment. We are indebted to Dr. Arthur Jacobson and Dr. Everette L. May for a sample of authentic metopon and to Mr. Daniel Mantell for aiding in the preparation of 5-methylthebaine. The generous financial support of the National Institute on Drug Abuse under Grant No. 5 R01 DAO 2469 is also gratefully acknowledged.

Registry No. 3, 115-37-7; 3 anion, 80583-33-1; 4, 80583-34-2; 5, 80583-35-3; 6, 80583-36-4; 7, 63868-37-1; 8, 80630-18-8; 9, 143-52-2.

(10) A sample of metopon was graciously supplied us by Dr. Arthur Jacobson through the intermediacy of Dr. Everette May.

(11) The melting point of metopon appears to depend very much on the history of the sample. When crystallized from alcohol, it melts partially at 155–160 °C, resolidifies, and then melts at 190–192 °C. When crystallized from chloroform it melts at 190–191 °C. Only after sublimation is the higher melting point (242–248 °C dec) observed.

Ring-Forming Reactions: Adjustable Regiocontrol on a Polyfunctional Substrate

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In the course of a study directed at sesquiterpene total synthesis, we had occasion to investigate the intramolecular reactivity of 4-(2,2-dimethyl-4-oxobutyl)-4-acetylcyclopent-2-en-1-one (**1**).[1] The results of this investigation, which uncovered an intriguing regiochemical trichotomy, are reported herein.

Note that in structure **1** (Scheme I) we have designated several potential nucleophilic (check marks) and electrophilic (asterisks) sites. Our ultimate goal, based upon this study, was to effect the conversion of the monocyclic compound **1** to the novel antitumor sesquiterpene quadrone (**3**)[2] via the key tricyclic enedione **2**.[3] The construction of **2** from **1** necessitated a specific double pairing of electrophile–nucleophile conjugates to form the carbon–carbon bonds A and B as shown. This was clearly a demanding requirement in the face of other possibilities (vide infra).

Three conformations of **1**, each highlighting a single electrophile–nucleophile pairing, are represented in Scheme II as **1a–c**. The products which would result from each of these specific pairings are depicted as **4–6**, respectively. Remarkably, by simple adjustment of the reaction conditions we could guide the reaction selectively along each one of these pathways, to the near or complete exclusion of the other two. Details of the entry to this manifold are presented below.

When a solution of the cyclopentenone **1** in tetrahydrofuran (THF) at −35 °C was treated with 1 equiv of $TiCl_4$ followed by 2 equiv of *N*-methylanilinium trifluoroacetate (TAMA)[4] and allowed to warm slowly to ambient temperature, there was obtained a 50% yield of crystalline 7-formyl-6,8,8-trimethylspiro[4.4]nona-1,6-dien-3-one (**4**, mp 108–111 °C) as the sole isolable product.[5,6] It was noted with little satisfaction that in **4** ($C_{13}H_{16}O_2$) we had managed to generate an isomer of the targeted tricyclic **2**.

We felt that the likelihood of triggering the desired Michael addition (closure A in **1**) would be enhanced by acid catalysis. It was hoped that preferential protonation at the cyclopentenone carbonyl with the resultant increase in the electrophilicity of the enone β-carbon would favor closure A over the process which led to the formation of **4**. In the event, treatment of **1** with a catalytic amount

(1) The functionalized cyclopentenone **1** is available in nearly quantitative yield by oxidative cleavate of the trisubstituted olefin linkage in 6,9,9-trimethylspiro[4.5]deca-1,6-dien-3-one (Burke, S. D.; Murtiashaw, C. W.; Dike, M. S.; Strickland, S. M. S.; Saunders, J. O. *J. Org. Chem.* **1981**, *46*, 2400–2402).

(2) (a) Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978**, *31*, 38–42. (b) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499–502. (c) Danishefsky, S.; Vaughan, K.; Gadwood, R. C.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 4262–4263. (d) Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136–4141. (e) Bornack, W. K.; Bhagwhat, S. S.; Ponton, J.; Helquist, P. *J. Am. Chem. Soc.* **1981**, *103*, 4646–4648.

(3) This general strategy for the construction of the key tricyclic unit **2** has been reduced to practice. Details of this and the elaboration to quadrone (**3**) will be presented elsewhere.

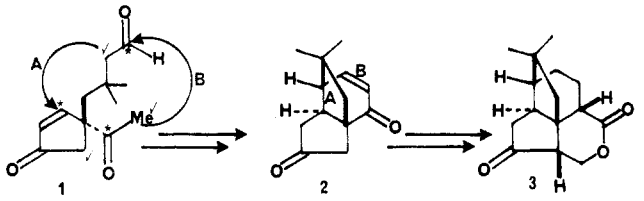
(4) Gras, J.-L. *Tetrahedron Lett.* **1978**, 2111–2114.

(5) All yields reported herein are based on chromatographically homogeneous, crystalline material.

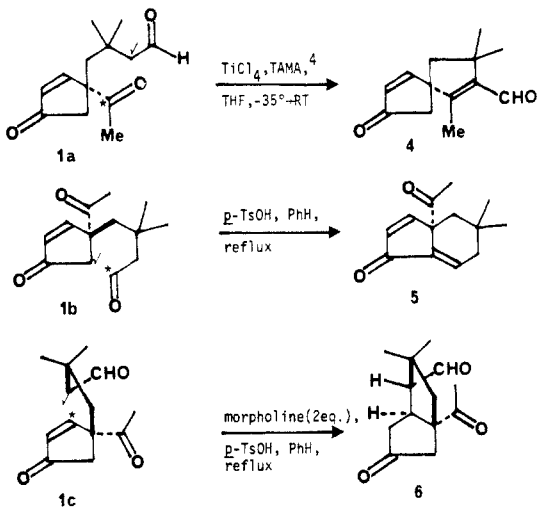
(6) The structures reported herein are fully supported by IR, mass, 400-MHz ^1H NMR, and ^{13}C NMR spectra and by combustion analysis data. See the Experimental Section for details.

0022-3263/82/1947-1349$01.25/0

Scheme I



Scheme II



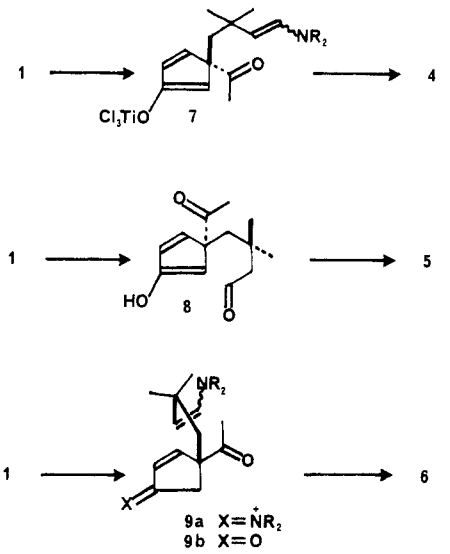
of *p*-toluenesulfonic acid (*p*-TsOH) in benzene at reflux afforded a mixture of a new $C_{13}H_{16}O_2$ isomer (**5**, mp 65–67 °C) and **4** (**5**/**4** ratio of 3:1) in 60% yield.[5,6] This result implicates the expected protonation of the enone carbonyl, followed by enolization and aldol closure to **5** rather than the fugitive Michael addition process.

Finally, a third reaction pathway (which for our ultimate purpose was the desired result) was brought cleanly into effect to provide the crystalline Michael addition product **6** (mp 68–70 °C) in high yield. The functionalized cis-fused bicyclo[3.3.0]octane derivative **6** was produced in 92% yield[5] by refluxing a solution of **1**, 2 equiv of morpholine, and a catalytic amount of *p*-TsOH in benzene under a Dean–Stark trap.[6]

Several control experiments indicated that the three reaction pathways observed are mutually independent. For example, the spiro[4.4]nonadienone **4** was recovered unchanged after subjection to *p*-TsOH in refluxing benzene for 11.5 h. The dienedione **5** was not degraded under the conditions by which **4** was formed ($TiCl_4$, TAMA,[4] THF, −35 °C to room temperature). Also, the product **5** was resubjected to *p*-TsOH in refluxing benzene and was unaffected after 45 min, although it suffered significant degradation to a complex mixture after extended periods. Thus the products **4** and **5** are not interconverted, nor is **5** formed and then selectively degraded under the conditions by which **4** was formed. The Michael addition product **6** was subjected to *p*-TsOH in benzene at reflux. After 45 min there was no reaction; after 6 h there was significant decomposition, but there was no evidence of conversion to **4** or **5**. Finally, a provocative observation was that catalytic amounts (0.04 molar equiv) of either *N*-methylanilinium trifluoroacetate (TAMA)[4] or dibenzylammonium trifluoroacetate (DATA)[7] in THF at reflux effected the conversion of **1** to the Michael addition product **6** in 82% and 81% yields, respectively.[5]

(7) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8031–8034.

Scheme III



These data invite speculation about the mechanistic foundations for the experimental adjustments which led to these three observed pathways. We infer from the observations described above that the regioselective conversions arise from intermediates in which selective electrophile–nucleophile interaction is guided by simultaneous amelioration of one pairing and impedition of another. In Scheme III we advance intermediates **7**–**9** as possibilities consistent with this suggestion.

In summary, compound **1** exhibits remarkably adjustable multiple reactivities. Further investigation of this reaction manifold and subsequent transformations of the derived products will be reported in due course.

Experimental Section

General Procedures. Melting points were recorded on a Büchi capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Beckman IR 4210 spectrometer. Proton magnetic resonance (^1H NMR) spectra were recorded at 400 MHz on a Bruker WH-400 spectrometer. Carbon magnetic resonance (^{13}C NMR) spectra were recorded on a Varian CFT-20 or an IBM NR-80 spectrometer. Chemical shifts for proton and carbon resonances are reported in parts per million (δ) relative to Me_4Si (δ 0.0).

Analytical thin-layer chromatography (TLC) was done on Analtech precoated TLC plates with silica gel GHLF (250-μm layer thickness). Column chromatography was done with E. Merck silica gel 60 (70–230 mesh ASTM) or Baker silica gel (40–140 mesh).

Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl immediately before use. Benzene was distilled from calcium hydride and stored over sodium. All reactions were run under an atmosphere of dry nitrogen.

Elemental analyses were performed by Robertson Laboratory.

7-Formyl-6,8,8-trimethylspiro[4.4]nona-1,6-dien-3-one (4). To a solution of 46 mg (0.21 mmol) of **1** in 4 mL of dry THF at −35 °C was added 23 μL (1 equiv) of $TiCl_4$. After the mixture was stirred at −35 °C for 30 min, 90 mg (2 equiv) of *N*-methylanilinium trifluoroacetate (TAMA)[4] was added, and the reaction was allowed to warm gradually to room temperature. After 8 h at room temperature the reaction was quenched with saturated aqueous sodium bicarbonate and extracted with Et_2O. The combined ether extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography on silica gel. Elution with 2:1 ether–hexanes yielded 21 mg (50%) of the crystalline product **4**: mp 108–111 °C; R_f 0.70 (ether); IR ($CHCl_3$) 1714, 1669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1 H) 7.27 (d, 1 H, J = 5.6 Hz), 6.19 (d, 1 H, J = 5.6 Hz), 2.38 (AB q, 2 H, J_{AB} = 19 Hz, $\Delta\nu_{AB}$ = 23.2 Hz), 1.88 (AB q, 2 H, J_{AB} = 13.4 Hz, $\Delta\nu_{AB}$ = 84.6 Hz), 1.82 (s, 3 H), 1.27 (s, 3 H), 1.20 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.90, 188.96, 168.39, 159.19, 145.20, 134.06, 59.40, 52.33,

47.20, 44.95, 28.04, 27.92, 10.20.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.20; H, 8.08.

3a,4,5,6-Tetrahydro-3a-acetyl-5,5-dimethyl-1*H*-inden-1-one (5). A solution of 103 mg (0.46 mmol) of 1 and 2 mg of *p*-toluenesulfonic acid in 17 mL of dry benzene was heated at reflux for 4.5 h with azeotropic removal of the water produced. The reaction mixture was then cooled to room temperature, and 3 mL of saturated aqueous sodium bicarbonate was added. The mixture was extracted with Et_2O, and the combined ether layers were dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography on silica gel. Elution with 2:1 hexanes–ether gave 14 mg (15%) of 4 and 43 mg (45%) of the crystalline product 5: mp 65–67 °C; R_f 0.81 (ether); IR (CCl_4) 1710, 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, 1 H, J = 5.90 Hz), 6.78 (t, 1 H, J = 4.40 Hz), 6.43 (d, 1 H, J = 5.90 Hz), 2.65 (d, 1 H, J_{gem} = 12.94 Hz), 2.08 (d, 2 H, J = 4.40 Hz), 2.02 (s, 3 H), 1.16 (d, 1 H, J = 12.94 Hz), 0.99 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 205.87, 195.03, 158.67, 140.10, 136.79, 134.58, 62.25, 40.88, 40.22, 33.27, 32.17, 29.84, 25.04.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.14; H, 7.95.

3,3a,4,5,6,6aα-Hexahydro-3aα-acetyl-5,5-dimethyl-6α-formyl-2(1*H*)-pentalenone (6). To a solution of 1.88 g (8.47 mmol) of 1 and 1.47 mL (2 equiv) of morpholine in 200 mL of benzene was added 1 mg of *p*-toluenesulfonic acid. The reaction mixture was heated at reflux under a Dean–Stark trap for 11 h and cooled, and 10 mL of H_2O was added. After the mixture had been stirred 1 h at room temperature, it was poured into saturated aqueous sodium bicarbonate, and the product was extracted with Et_2O. The combined ether extracts were dried ($MgSO_4$) and concentrated. The product was purified by chromatography on silica gel. Elution with 3:1 ether–hexanes provided 1.73 g (92%) of the crystalline product 6: mp 68–70 °C; R_f 0.47 (ether); IR ($CHCl_3$) 1742, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, 1 H, J = 2.2 Hz), 3.64 (td, 1 H, J = 11.20, 10.17, 1.65 Hz), 2.72 (d, 1 H, J_{gem} = 18.67 Hz), 2.60 (ddd, 1 H, J = 19.25, 9.35, 1.10 Hz), 2.40 (d, 1 H, J_{gem} = 13.75 Hz), 2.33 (dd, 1 H, J = 11.20, 2.20 Hz), 2.26 (dd, 1 H, J = 18.67, 1.65 Hz), 2.25 (s, 3 H), 2.14 (d, 1 H, J_{gem} = 19.25 Hz), 1.78 (d, 1 H, J_{gem} = 13.75 Hz), 1.31 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 215.07, 208.45, 201.98 67.77, 60.10, 53.02, 48.93, 43.31, 42.43, 40.64, 29.02, 25.53, 23.70.

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.32; H, 8.08.

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Registry No. 1, 80594-76-9; 4, 80594-77-0; 5, 80594-78-1; 6, 80695-33-6.

TLC Mesh Column Chromatography[1]

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In a usual laboratory day, the greatest share of working time is devoted to sample isolation and purification. Usually, chromatographic separation plays a central role in this effort. We outline here a procedure for column chromatography that is both efficient (mixtures showing ΔR_f = 0.05 by TLC are routinely separated) and easily scaled up.

There are two central concerns in column chromatography: packing of the absorptive bed and sample application. This procedure, a modification of the short-column technique,[2] effectively addresses both of these concerns.

The steps to follow in packing a column are detailed in Figure 1 (Figures 1–3, with accompanying legends describing details of column preparation and operation, are available as supplementary material). Note that the silica gel bed is first allowed to settle by gravity flow and then further compacted by application of air pressure.[3,4] This assures a dense, evenly packed bed. Then, rather than application of the mixture to be chromatographed in liquid form, it is first evaporated onto coarse silica gel.[5] This assures even application of the sample on to the top of the column and avoids concerns about mixtures that are not soluble in the (usually nonpolar) column solvent.

We find it convenient in running such columns to adjust the air pressure so as to collect about one fraction per minute. Fractions are monitored by TLC. For routine separations, the polarity of the eluant is adjusted so that the first component of the mixture appears in about fraction 10. It is usually then sufficient to collect 20 fractions, with fraction collection and TLC monitoring being effected simultaneously. When components of the mixture are widely separated, it is appropriate to switch to a more polar eluant after the less polar components have come off the column. The entire process of column construction, elution, and fraction analysis usually takes a little less than 1 h.

We have used a variety of solvent mixtures following this procedure. Ethyl acetate in petroleum ether appears to be the most generally satisfactory. For less polar mixtures, CH_2Cl_2 in petroleum ether is effective, and for very polar mixtures we use ethyl acetate in CH_2Cl_2. We have found that if it requires more than 40% ethyl acetate in hexane or less than 5% to give a TLC R_f of 0.4 for the mixture to be separated, it is best to switch to the alternative less polar or more polar solvent system. While it is possible to plot "most effective column eluant" as a function of TLC R_f, derivation of the most effective solvent system for a given separation is still best done empirically.[6]

Table I

column diameter, mm	wt of silica gel, g	sample size, g	fraction collected, mL
10.4	1	0.03	1
14	2.5	0.06	2.5
19	5	0.1	5
24	10	0.2	10
41	50	1	50
60	100	3	100
120	300	8	300
170	500	15	500

(1) EM 7747 silica gel (10–15 μm), purchased from Scientific Products, was used.

(2) (a) Hunt, B. J.; Rigby, W. *Chem. Ind. (London)* **1967**, 1868. (b) Still, W. C., unpublished manuscript, Vanderbilt University.

(3) As an alternative to the use of laboratory compressed air, the columns can conveniently be pressurized by pumping air in with a pipet filling bulb. We thank Dr. Matthew Schlecht for this improvement.

(4) Although we have never experienced any difficulty, prudence dictates the use of a safety shield with such pressurized or evacuated glassware.

(5) Coarse silica gel used for sample preadsorption was 60–200 mesh.

(6) We have used this procedure successfully for several years: (a) Taber, D. F.; Korsmeyer, R. W. *J. Org. Chem.* **1978**, *43*, 4925. (b) Taber, D. F.; Gunn, B. P. *Ibid.* **1979**, *44*, 450. (c) Taber, D. F.; Saleh, S. A. *J. Am. Chem. Soc.* **1980**, *102*, 5085. (d) Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699.

0022-3263/82/1947-1351$01.25/0