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# A Short Synthesis of Tricyclo[4.2.0.0$^{1,4}$]octanes

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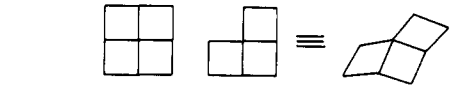
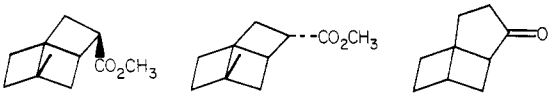
Photolysis of **11** furnishes 67% of **13**, which undergoes efficient ring contraction to esters **3** and **4**, derivatives of tricyclo[4.2.0.0$^{1,4}$]octane (**2**). Similarly, photolysis of **32** gives **5**, which has previously been converted to **2**.

The considerable theoretical and experimental interest[1,2] in tetracyclo[5.1.1.0$^{3,8}$.0$^{5,8}$]nonane or fenestrane (**1**) has resulted recently in preparation and close study of the related hydrocarbon tricyclo[4.2.0.0$^{1,4}$]octane (**2**) by Wiberg and his co-workers.[3] In addition, we have briefly described synthesis of two derivatives of this ring system, the epimeric esters **3** and **4**.[4] We now provide details of the preparation of these esters and also report application of our synthetic approach to afford a particularly simple route to the tricyclic ketone **5**, an intermediate in the original preparation of the parent hydrocarbon **2**.[3]

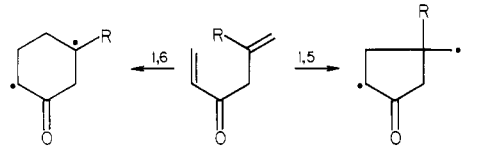


**1** **2**

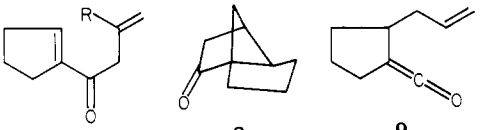



**3** **4** **5**

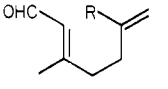
Our methodology is based on two observations made in the course of an extensive study of factors that influence the regiochemistry of intramolecular [2 + 2] photochemical cycloaddition in derivatives of 1,5-hexadiene.[5] We found that in 1,5-hexadien-3-ones (**6**) alkyl substitution at C(5) (R in **6**) enhances 1,6 (straight) cyclization at the expense of the 1,5 (crossed) process on photolysis. Thus, irradiation of **6a** furnishes both straight and crossed products in the ratio of ~2:3,[6] while the parent dienone **6b** undergoes only 1,5 closure.[7] Further, we noted that incorporation of the conjugated double bond of **6** into a five- or six-membered ring significantly increases the proportion of 1,6 closure. For example, the acylcyclopentene **7b** yields both **8** (1,5) and **9** (1,6, and isolated as the derived methyl ester).[5] When these two features were combined in a single structure, **7a**, only 1,6 cyclization occurred.[5] We were




**6**




**7** **8** **9**




**10**

a, R = $CH_3$; b, R = H

encouraged in the expectation that these effects also might be operative in 1-acylhexadienes by the observation that the regiospecific 1,5 closure seen in **10b** changes to a 1,6 to 1,5 ratio of ~85:15 in **10a**.[5] These findings suggested that 3-(3-methyl-3-butenyl)-2-cyclopentenone (**11**), a 1-acylhexadiene with both the structural features favoring 1,6 closure, could be a useful starting material for preparation of tricyclic compounds related to **2**.

(1) Wiberg, K. B.; Burgmaier, G. J. *J. Am. Chem. Soc.* **1972**, *94*, 7396. Wiberg, K. B.; Ellison, G. B.; Wendoloski, J. J. *Ibid.* **1976**, 98, 1212. Georgian, V.; Saltzman, M. *Tetrahedron Lett.* **1972**, 4315. Keese, R.; Pfenninger, A.; Roesle, A. *Helv. Chim. Acta.* **1979**, *62*, 326. Ten Hoeve, W.; Wynberg, H. *J. Org. Chem.* **1980**, *45*, 2925, 2930. Bastan, W. C.; Saltzman, M. D. "Abstracts of Plenary Lectures and Contributed Papers", 8th IUPAC Symposium on Photochemistry, Seefeld, Austria, July 1980, p 308. Minkin, V. I.; Minyaer, R. M.; Natanzon, V. I. *Zh. Org. Khim.* **1980**, *16*, 673. Würthwein, E.-U.; Chandrasekhar, J.; Jemmis, E. D.; Schleyer, P. v. R. *Tetrahedron Lett.* **1981**, *22*, 843.

(2) For a review, see Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311.

(3) Wiberg, K. B.; Olli, L. K.; Golembeski, N.; Adams, R. D. *J. Am. Chem. Soc.* **1980**, *102*, 7467.

(4) Wolff, S.; Agosta, W. C. *J. Chem. Soc., Chem. Commun.* **1981**, 118.

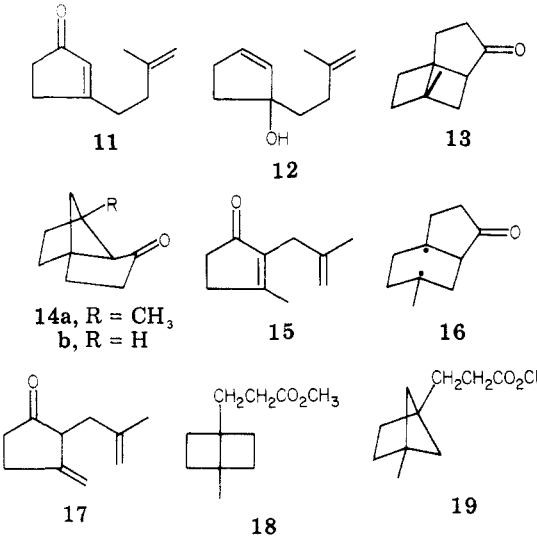
(5) Agosta, W. C.; Wolff, S. *J. Org. Chem.* **1980**, *45*, 3139; and unpublished work.

(6) Smith, A. B., III; Agosta, W. C. *J. Am. Chem. Soc.* **1973**, *95*, 1961.

(7) Bond, F. T.; Jones, H. C.; Scerbo, L. *Tetrahedron Lett.* **1965**, 4685.

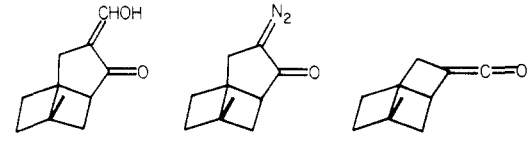
0022-3263/81/1946-4821$01.25/0 

Starting ketone **11** was available through addition of isopentenylmagnesium bromide to cyclopentenone followed by oxidative rearrangement of the intermediate allylic alcohol **12** with chromium trioxide in aqueous sulfuric acid.[8] Photolysis of **11** in benzene solution ($\lambda > 330$ nm) led to regiospecific 1,6 closure with formation of tricyclic ketone **13** in a yield of 67%. The structural assignment for this product, and particularly the conclusion that it is not the isomeric crossed adduct **14a** resulting from 1,5 cyclization is based on several considerations. Thermolysis of **13** in benzene at 160 °C for 10 h gave virtually quantitatively a mixture of **11** (98%) and **15** (2%). Cyclopentenone **15** was identified by spectral comparisons with the authentic compound.[9] This pyrolysis is expected[10] to lead to biradical **16**, which can then open to **11** or **17**. Subsequent conjugation of the double bond in **17** would give **15**. A control experiment showed that **11** is stable to the thermolysis conditions, ruling out the possibility that secondary Cope rearrangement of **11** is the source of **17** and subsequently **15**. It is significant that the pathway from **13** to **15** does not involve **11**, since the alternative cycloadduct **14a** could open thermally to **11** but not directly to **15** or **17**. Further, irradiation of **13** ($\lambda > 280$ nm) in benzene–methanol furnished an $\alpha$-cleavage product that from its nuclear magnetic resonance (NMR) spectrum was the bicyclo[2.2.0]hexane **18** rather than the isomeric **19**. Also, the NMR spectrum of **13** was quite different from that of **14b**, an adduct available to us and discussed below. In reaching these assignments we made use of the well-documented differences between the NMR spectra of bicyclo[2.2.0]hexanes[11] and the isomeric bicyclo[2.1.1]hexanes,[12] and also of the fact that simple bicyclo[2.2.0]hexanes undergo pyrolytic fragmentation at lower temperatures (~130–175 °C)[13] than do their [2.1.1] isomers (~330–375 °C).[14] Finally, we note that the transformations discussed below are plausible on the basis of structure **13** but not **14a** for this adduct.




The only other photoproduct isolated from the irradiation of **11** was cyclopentenone **15** (22%), which results from initial 1,6 cyclization followed by fragmentation and migration of the double bond. Thus, in this 1-acylhexadiene, as in the 1,5-hexadien-3-ones previously examined, the presence in a single molecule of both structural features discussed above leads to complete suppression of the crossed cycloaddition usually seen in 1,5-hexadienes.

Ring contraction of **13** to **3** and **4** proceeded in the following fashion. Reaction[15] of **13** with methyl formate and base furnished a crystalline $\alpha$-hydroxymethylene ketone **20**, and treatment[16] with *p*-toluenesulfonyl azide then gave **21**. On irradiation in methanol **21** underwent photochemical Wolff rearrangement[17] to a mixture of the two methyl esters **3** (~68%) and **4** (~12%), which were separated by vapor phase chromatography (VPC).

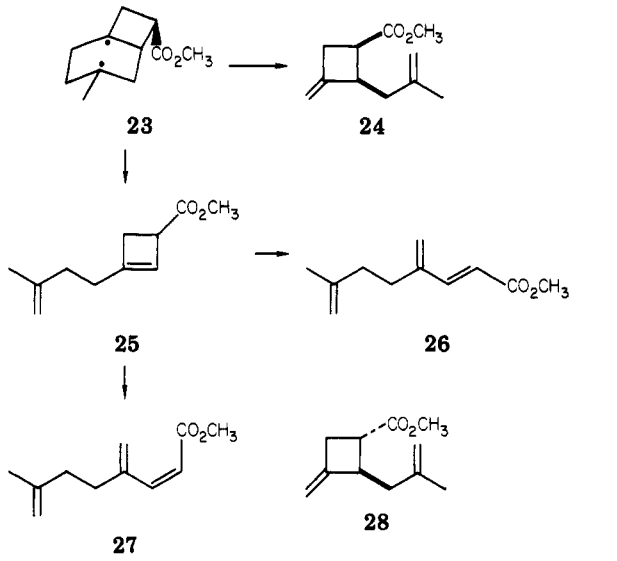



**20** **21** **22**

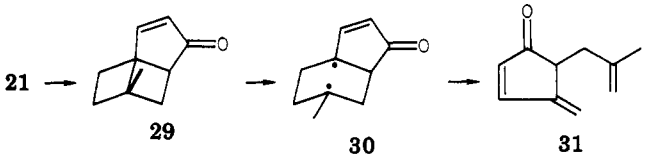
These esters result from addition of methanol to the ketene **22**, and preferential formation of the sterically more hindered isomer **3** through attack from the less congested side is expected.[18] In keeping with this prediction, treatment of **3** with methanolic sodium methoxide led to >90% inversion to the more stable isomer **4**.[19] The structures of **3** and **4** rest not only on the NMR data presented below but also on pyrolysis of each ester at 190 °C in benzene to furnish three products in overall essentially quantitative yield. From **3** these products are **24** (78%), **26** (17%), and **27** (5%), which can be accounted for as follows. Thermolysis[10] of **3** leads exclusively to the bis-tertiary biradical **23**, which fragments in both possible senses, forming **24** and **25**. Thermal conrotatory opening of **25** then gives mainly the *E*-substituted ester **26** plus a small amount of its *Z* isomer **27**, as expected.[20] A similar scheme can be written for fragmentation of ester **4**; here the products are **28** (74%), **26** (23%), and **27** (3%). The structures of these pyrolysis products are strongly supported by their NMR spectra, which are largely interpretable on inspection and are given in the Experimental Section. Analogous hydrocarbon products are formed on thermolysis of **2** and have been accounted for by the same sort of mechanism.[3]

We have also found that pyrolysis of **21** at 210 °C, most conveniently on VPC, yields a single product that is formulated as **31** on the basis of its spectroscopic properties. This ketone presumably arises by way of cyclopentenone **29**, formed on loss of nitrogen and 1,2 shift of hydrogen[21]

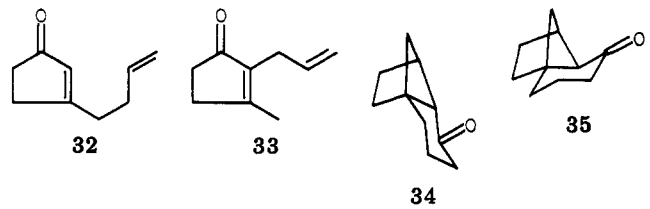
(8) Büchi, G.; Egger, B. *J. Org. Chem.* **1971**, *36*, 2021. McCurry, P. M., Jr.; Singh, R. K. *Ibid.* **1974**, *39*, 2317.
(9) Crombie, L.; Edgar, A. J. B.; Harper, S. H.; Lowe, M. W.; Thompson, D. *J. Chem. Soc.* **1950**, 3552. Kueh, J. S. H.; Mellor, M.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1978**, 5. We thank Dr. Gerald Pattenden, Nottingham University, for providing data for authentic **15**.
(10) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 5119 and references cited therein.
(11) Srinivasan, R. *J. Am. Chem. Soc.* **1961**, *83*, 4923. Lüttke, W.; Schabacker, V. *Justus Liebigs Ann. Chem.* **1966**, *698*, 86. Srinivasan, R.; Sonntag, F. I. *Tetrahedron Lett.* **1967**, 603. Dauben, W. G.; Chitwood, J. L.; Scherer, K. V., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 1014.
(12) Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1980**, *45*, 1332 and references cited therein.
(13) Steel, C.; Zand, R.; Hurwitz, P., Cohen, S. G. *J. Am. Chem. Soc.* **1964**, *86*, 679.
(14) Srinivasan, R.; Levi, A. A. *J. Am. Chem. Soc.* **1963**, *85*, 3363.
(15) Ainsworth, C. "Organic Syntheses", Collect. Vol. 4; Wiley: New York, 1963; p 536.
(16) Regitz, M.; Rüter, J.; Liedhegener, A. *Org. Synth.* **1971**, *51*, 86.
(17) Wiberg, K. B.; Furtek, B. L.; Olli, L. K. *J. Am. Chem. Soc.* **1979**, *101*, 7675.
(18) Meinwald, J.; Gassman, P. G. *J. Am. Chem. Soc.* **1960**, *82*, 2857 and references cited therein.
(19) This epimerization and a parallel reaction in the parent series lacking the methyl substituent (ref 3) stand in contrast to the unexplained resistance of methyl *endo*-bicyclo[2.2.0]hexane-2-carboxylate to base-catalyzed inversion: McDonald, R. N.; Davis, G. E. *J. Org. Chem.* **1969**, *34*, 1916.
(20) Frey, H. M.; Marshall, D. C.; Skinner, R. F. *Trans. Faraday Soc.* **1965**, *61*, 861. Extensive references are given by Marvell, E. N. "Thermal Electrocyclic Reactions"; Academic Press: New York, 1980; Chapter 5.




in **21**. A path parallel to that given above for pyrolysis of **13** then leads to biradical **30** and dienone **31**. Attempts to decompose **21** in hot methanol were unsuccessful, and it was recovered largely unchanged.



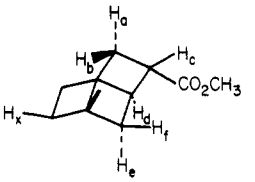

With these results in hand it was of interest to investigate the photochemistry of 3-(3-butenyl)-2-cyclopentenone (**32**), a lower homologue of **11** that lacks the




methyl substituent favoring 1,6 cyclization. This ketone was prepared as **11**, but using 3-butenylmagnesium bromide. Irradiation in benzene yielded a mixture of three products, **5** (35%), **33** (20%), and **14b** (15%). These structural assignments are based on spectroscopic properties, as well as the observations that pyrolysis of **5** at 160 °C causes reversion to **32**, while **14b** is recovered unchanged under these conditions. In addition, spectroscopic comparison showed **5** to be identical with the compound prepared following a totally different route and assigned this structure by Wiberg.[3,22] The stereochemistry assigned to the crossed cycloadduct **14b** follows from spectral comparisons with its epimeric homologues **34** and **35**.[5,23] In view of the previous conversion of **5** into hydrocarbon **2**,[3] this simple preparation of **5** constitutes formally a short alternative synthesis of **2**.

The NMR spectra of esters **3** and **4** are presented in Table I. The spectrum (220 MHz) of **3** could be interpreted largely by inspection, but signals in **4** are less well separated. Assignments here were facilitated by measurements in solvent pyridine-$d_5$ as indicated, and also by use of the $\alpha$-deuterated ester, formed when the Wolff rearrangement of **21** is performed in methanol-*O*-*d*. The coupling constants resulting from this analysis are in reasonable agreement with those obtained by computer simulation of a five-spin portion of the spectrum of **2**.[3]

**Table I. NMR Spectral Data of Tricyclo[4.2.0.0$^{1,4}$]octanes 3 and 4**




| proton | 3 | 4 |
|---|---|---|
| $H_a$ | 2.00 dd, $J_{ab} + J_{ac} = 24.6$ Hz | 2.24 d, $J_{ab} = 12.5$,[a] $J_{ac} = 7.8$ Hz |
| $H_b$ | 2.46 dd, $J_{ab} = 13.3$, $J_{bc} = 5.7$ Hz | 2.24 d, $J_{ab} = 12.5$,[a] $J_{bc} = 7.8$[a] Hz |
| $H_c$ | 3.38 ddd, $J_{ac} = 11.3$, $J_{bc} = 5.7$, $J_{cd} = 9.6$ Hz | 2.75-2.86 m (with $H_d$) |
| $H_d$ | 3.00 ddd, $J_{cd} = 9.6$, $J_{de} = 7.0$, $J_{df} = 3.0$ Hz | 2.82 dd,[b] $J_{de} = 6.3$,[b] $J_{df} = 2.0$[b] Hz |
| $H_e$ | 2.18 dd, $J_{ef} = 13.0$, $J_{de} = 7.0$ Hz | 2.43 dd, $J_{ef} = 12.3$, $J_{de} = 6.3$ Hz |
| $H_f$ | 1.74 ddd, $J_{ef} = 13.0$, $J_{df} = 3.0$, $J_{fx} = 1.4$ Hz | |
| $OCH_3$ | 3.63 s | 3.60 s |
| $CH_3$ | 1.12 s | 1.19 s |
| remaining protons | 1.80-2.16 m (4 H) | 1.83-2.14 m (5 H) |

[a] Observed in pyridine-$d_5$. [b] Observed in $\alpha$-deuterio-4 ($H_c$ = D), where $H_a$, $H_b$ give 2.24 s (2 H).

## Experimental Section

**Materials and Equipment.** These have been previously described.[24] All VPC was carried out with a Varian Aerograph Model 920 gas chromatograph with one of the following columns: A, 25% XF-1150, 3 ft; B, 25% QF-1, 2 ft; C, 25% QF-1, 10 ft; D, 25% XF-1150, 2.5 ft; E, 25% QF-1, 25 ft; F, 25% FFAP, 16 ft; G, 25% XF-1150, 10 ft; H, 25% CDA, 30 ft; I, 25% Carbowax 20 M with 15% $AgNO_3$, 5 ft. All columns were packed in 0.25-in. aluminum tubing, using 45/60 Chromosorb W. NMR spectra were recorded on Varian Model T-60 (60 MHz) and HR-220 (220 MHz, Fourier transform mode) spectrometers, and the 600-MHz instrument at Carnegie-Mellon University.

**3-(3-Methyl-3-butenyl)cyclopent-2-enone (11).** To a solution of (3-methyl-3-butenyl)magnesium bromide, prepared from the addition of 1-bromo-3-methyl-3-butene (11.2 g, 75 mmol) in anhydrous ether (40 ml) to magnesium (2.19 g, 90 mmol) in ether (20 mL) was added cyclopent-2-enone (5.0 g, 60.9 mmol) in ether (35 mL) at a rate that caused gentle refluxing.

The reaction mixture was refluxed for an additional 0.5 h. It was then cooled to 25 °C, poured into saturated $NH_4Cl$ solution, and extracted with $Et_2O$ twice. The combined ethereal extracts were washed with saturated $NH_4Cl$ and brine and were dried. Solvent was removed in vacuo to afford **12** (9.3 g).

The crude alcohol (9.3 g) was taken up in ether (125 mL) and was treated with $CrO_3$ (6.5 g) in 5% $H_2SO_4$ (60 mL) at 0 °C according to the method of Büchi.[8] After removal of pentane, the residue was distilled to give **11** (3.66 g, 40%): bp 78–82 °C (0.5 mm); NMR (60 MHz) $\delta$ 5.80 (m, 1 H), 4.68 (br s, 2 H), 2.72–2.02 (m, 8 H), 1.73 (d, $J$ = 0.5 Hz, 3 H), IR 3095 (w), 2930 (m), 1710 (s), 1618 (s), 1435 (m), 1177 (m), 885 cm$^{-1}$ (m). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.15; H, 9.49.

**Photolysis of 11.** A solution of **11** (244 mg) in $C_6H_6$ (150 mL) was irradiated at 25 °C, using an uranium glass filter until VPC analysis on column A (165 °C) indicated the absence of starting

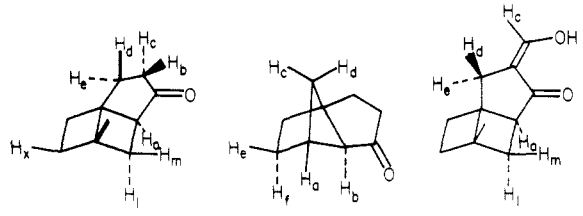
(21) Franzen, V. *Justus Liebigs Ann. Chem.* **1957**, *602*, 199. Matlin, S. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1972**, 11.

(22) We are grateful to Professor Kenneth B. Wiberg, Yale University, for providing a comparison sample of his ketone **5**.

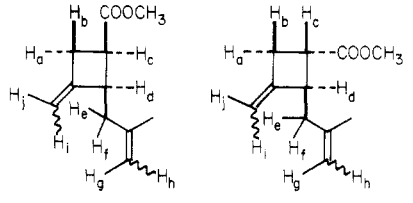
(23) Ketones **34** and **35** are formed on photolysis of 3-(3-butenyl)-2-cyclohexenone and will be discussed in detail elsewhere: Agosta, W. C.; Wolff, S., unpublished results.

(24) Wolff, S.; Barany, F.; Agosta, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2378.

material and the formation of two products (4 days). Benzene was removed by distillation through a Vigreux column and the residue was bulb-to-bulb distilled (130 °C, 20 mm) to give the product mixture (218 mg, 89%). Separation was achieved by preparative VPC. The first eluted product was 7-methyltricyclo[5.2.0.0$^{1,5}$]nonan-4-one (**13**, 67%): NMR (600 MHz) $\delta$ 2.60 (ddd, $H_a$, $J_{al}$ = 8.9, $J_{am}$ = 4.6, $J_{ac}$ = 1.7 Hz), 2.48 (dd, $H_l$, $J_{lm}$ = 12.6, $J_{al}$ = 9.1 Hz), 2.43 (ddd, $H_b$, $J_{bc}$ = 18.1, $J_{be}$ = 12.0, $J_{bd}$ = 9.4 Hz), 2.21 (dddd, $H_c$, $J_{bc}$ = 18.1, $J_{ce}$ = 9.4, $J_{cd}$ = 1.8, $J_{ac}$ = 1.7 Hz), 2.19–2.08 (m, 4 H), 2.05 (ddd, $H_d$, $J_{de}$ = 13.9, $J_{db}$ = 9.4, $J_{cd}$ = 1.6 Hz), 1.82 (ddd, $H_m$, $J_{lm}$ = 12.6, $J_{am}$ = 4.7, $J_{mx}$ = 1.7 Hz), 1.58 (ddd, $H_e$, $J_{de}$ = 13.9, $J_{be}$ = 12.0, $J_{ce}$ = 9.4 Hz), 1.12 (s, 3 H); IR 2945 (s), 2850 (w), 1733 (s), 1439 (w), 1368 (w), 1269 (w), 1153 (w), 1067 cm$^{-1}$ (w); mass spectrum, $m/z$ 150.1042 (M$^+$, calcd for $C_{10}H_{14}O$ 150.1045).



13 14b 20



24 28

The second component was identified as **15** (22%) by comparison of its NMR and IR spectra with those reported for an authentic sample.[9]

For preparative purposes, photolyses were carried out on $C_6H_6$ solutions of **11** heated to reflux. Thus a distillate (1.743 g) consisting of **13** (85%) and **15** (15%) was obtained from **11** (1.929) in 4–5 days. This mixture could be used without further purification in subsequent synthetic steps.

Three deuterium atoms were incorporated when **13** was heated with $K_2CO_3$ in MeOD–$D_2O$. Confirmation of the assignments made above was provided by the NMR spectrum of **13**-$d_3$ (220 MHz): $\delta$ 2.46 (br d, $J$ = 12.6 Hz, 1 H), 2.19–1.90 (br m, 5 H), 1.81 (br d, $J$ = 12.6 Hz, 1 H), 1.56 (br d, $J$ = 13.9 Hz, 1 H), 1.12 (s, 3 H).

**Thermolysis of 7-Methyltricyclo[5.2.0.0$^{1,5}$]nonan-4-one (13).** A sealed, evacuated tube of **13** (~50 mg) in $C_6H_6$ (2.5 mL) was heated at 160 °C for 10 h. VPC analysis on column A (165 °C) indicated virtually no remaining **13** and the formation of two products. These were collected and identified as **15** (2%) and **11** (98%) on the basis of their VPC retention times and IR spectra. No **15** was formed when a solution of **11** was heated at 175 °C for 5 h.

**Photolysis of 13.** A solution of **13** (181 mg) in $C_6H_6$ (60 mL)–$CH_3OH$ (2 mL) was irradiated through Pyrex in the usual manner. After 51.5 h, ~33% of **13** remained. Solvent was removed by distillation and the major product was obtained by preparative VPC on column E (165 °C). This material was further purified on column F (165 °C) and was identified as **18**: NMR (220 MHz) $\delta$ 3.58 (s, 3 H), 2.13–1.86 (m, 10 H), 1.73–1.65 (m, 2 H), 1.04 (s, 3 H); IR 2942 (s), 2839 (m), 1747 (s), 1436 (m), 1166 (s), 1107 (w) cm$^{-1}$; mass spectrum, $m/z$ 182.1297 (M$^+$, calcd for $C_{11}H_{18}O_2$ 182.1306).

**3-(Hydroxymethylene)-7-methyltricyclo[5.2.0.0$^{1,5}$]nonan-4-one (20).** Ketone **13** (978 mg, 6.51 mmol) in ethyl formate (2.6 mL) and ether (5 mL) was added to a suspension of NaH (314 mg of a 60% oil dispersion, 7.85 mmol) in ether (15 mL) containing four drops of EtOH at 0 °C according to the published procedure.[15] The reaction mixture was stirred at 25 °C overnight. Work up yielded crystalline yellow material (817 mg, 70%). Analytically pure **20** was obtained by preparative VPC on column B (140 °C): mp 107.5–108 °C; NMR (220 MHz) $\delta$ 12.1 (br s, 1 H), 7.54 (m, $H_c$), 3.03 (dd, $H_a$, $J_{am}$ = 4.8, $J_{al}$ = 8.8 Hz), 2.62 (d, $H_d$ or $H_e$, $J_{de}$ = 15.5 Hz), 2.55 (dd, $H_l$, $J_{al}$ = 8.7, $J_{lm}$ = 12.4), 2.30–1.92 (m, 6 H), 1.06 (s, 3 H); IR 2945 (s), 2860 (m), 1667 (s), 1587 (m), 1435 (m), 1177 (m), 1154 (m), 1045 (m), 937 (w) cm$^{-1}$. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.19; H, 7.85.

***endo*- and *exo*-6-Methyltricyclo[4.2.0.0$^{1,4}$]octane-3-carboxylic Acid, Methyl Ester (3 and 4).** The hydroxymethylene ketone **20** (571 mg, 3.03 mmol) in $CH_2Cl_2$ (10 mL) and triethylamine (675 mg, 6.68 mmol) was treated with *p*-toluenesulfonyl azide (598 mg, 3.03 mmol) in $CH_2Cl_2$ (8 mL) according to the literature procedure.[16] Workup afforded **21** (621 mg): IR 2955 (m), 2860 (m), 2085 (s), 1670 (s), 1440 (m), 1315 cm$^{-1}$ (s).

A methanol solution (3 mL) of the crude diazo ketone (371 mg) was degassed and irradiated through Pyrex for 6 h. The photolysate was partioned between water and pentane. After drying and removal of pentane, the residue was chromatographed on neutral alumina (10 g, activity III). The material eluted with pentane contained three components upon analysis by VPC on column C (140 °C). The first (trace) was not collected. The second component (~68%) was identified as **3**: IR 2965 (s), 2940 (s), 2860 (m), 1735 (s), 1430 (m), 1340 (m), 1188 (s), 1164 (s), 1038 (m) cm$^{-1}$; mass spectrum, $m/z$ 180.1148 (M$^+$, calcd for $C_{11}H_{16}O_2$ 180.1150). The third component (~12%) was **4**: IR 2960 (s), 2865 (m), 1737 (s), 1431 (m), 1194 (m), 1159 cm$^{-1}$ (s); mass spectrum, $m/z$ 180.1170 (M$^+$, calcd for $C_{11}H_{16}O_2$ 180.1150).

**Epimerization of 3.** A solution of $NaOCH_3$ was prepared from rigorously dried $CH_3OH$ (2 mL) and sodium. VPC purified **3** was added and the mixture was allowed to stand at 25 °C for 24 h under a $N_2$ atmosphere. VPC analysis on column C (140 °C) indicated ~85% **3** and ~15% **4**. After 24 h at 57 °C the mixture consisted of ~7% **3** and ~93% **4**. A 220-MHz NMR spectrum of the latter component was identical with that of the photochemically derived material.

**Thermolysis of 3.** A sealed, evacuated tube of **3** (~65 mg) in $C_6H_6$ (2.5 mL) was heated for 3 h at 190 °C. VPC analysis of this reaction on column I indicated the absence of **3** and the formation of three products. These were collected by preparative VPC and identified as follows (in order of elution). **24** (78%): NMR (220 MHz) $\delta$ 4.76 (d, $H_j$, $J_{aj}$ = 2.6, $J_{bj}$ = 5.2 Hz), 4.74 (dd, $H_i$, $J_{ai}$ = 4.9, $J_{bi}$ = 2.3 Hz), 4.69 (br s, $H_g$), 4.62 (br s, $H_h$), 3.58 (s, 3 H), 3.39 (m, $H_c$), 3.17 (ddd, $H_d$, $J_{cd}$ = 6.3, $J_{de}$ = 7.6, $J_{df}$ = 8.2 Hz), 3.00 (dddd, $H_b$, $J_{ab}$ = 15.6, $J_{bc}$ = 5.7, $J_{bj}$ = 5.2, $J_{bi}$ = 2.3 Hz), 2.70 (dddd, $H_a$, $J_{ab}$ = 15.7, $J_{ac}$ = 8.6, $J_{aj}$ = 2.6, $J_{ai}$ = 4.9 Hz), 2.24 (dd, $H_e$, $J_{ef}$ = 14.9, $J_{de}$ = 7.6 Hz), 2.11 (dd, $H_f$, $J_{ef}$ = 14.9, $J_{df}$ = 8.2 Hz), 1.70 (s, 3 H); IR 3100 (m), 2992 (m), 2962 (m), 1735 (s), 1675 (w), 1648 (w), 1430 (s), 1348 (s), 1188 (s), 1163 (s), 876 cm$^{-1}$ (s); mass spectrum, $m/z$ 180.1158 (M$^+$, calcd for $C_{11}H_{16}O_2$ 180.1150). **27** (5%): NMR (220 MHz) $\delta$ 6.36 (d, $J$ = 12.5 Hz), 1 H), 5.68 (d, $J$ = 12.5 Hz, 1 H), 5.12 (s, 2 H), 4.65 (s, 2 H), 3.65 (s, 3 H), 2.44–2.07 (m, 4 H), 1.72 (s, 3 H); IR 3100 (w), 2965 (m), 1727 (s), 1595 (w), 1436 (m), 1162 (s), 869 cm$^{-1}$ (m); mass spectrum, $m/z$ 180.1151 (M$^+$, calcd for $C_{11}H_{16}O_2$ 180.1150). **26** (17%): NMR (220 MHz) $\delta$ 7.23 (d, $J$ = 16 Hz, 1 H), 5.84 (d, $J$ = 16 Hz, 1 H), 5.37 (s, 1 H), 5.30 (s, 1 H), 4.70 (s, 1 H), 4.68 (s, 1 H), 3.70 (s, 3 H), 2.39–2.15 (m, 4 H), 1.75 (s, 3 H); IR 3100 (w), 2960 (m), 1720 (s), 1630 (m), 1600 (m), 1430 (m), 1305 (m), 1270 (s), 1185 (m), 1165 (s), 977 (m), 885 cm$^{-1}$ (m); mass spectrum, $m/z$ 180.1152 (M$^+$, calcd for $C_{11}H_{16}O_2$ 180.1150).

**Thermolysis of 4.** Heating a benzene solution (1.5 mL) of **4** (35 mg) as described above for **3** afforded (in order of elution): **28** (74%), NMR (220 MHz) $\delta$ 4.81 (dd, $H_j$, $J_{aj}$ = 2.3, $J_{dj}$ = 4.9 Hz), 4.72 (dd, $H_i$, $J_{ai}$ = 2.4, $J_{di}$ = 5.0 Hz), 4.69 (d, $H_g$, $J$ = 0.9 Hz), 4.68 (d, $H_h$, $J$ = 0.9 Hz), 3.63 (s, 3 H), 3.35 (m, $H_c$), 2.91–2.65 (m, $H_a$, $H_d$), 2.62 (dd, $H_b$, $J_{ab}$ = 15.6, $J_{bc}$ = 8.3 Hz), 2.33 (dd, $H_e$, $J_{ef}$ = 14.5, $J_{de}$ = 6.6 Hz), 2.14 (dd, $H_f$, $J_{ef}$ = 14.5, $J_{df}$ = 8.5 Hz), 1.72 (s, 3 H); IR (3090 (w), 2975 (m), 1736 (s), 1677 (w), 1648 (w), 1428 (m), 1210 (s), 1188 (s), 1168 (s), 1150 (s), 1023 (m), 883 cm$^{-1}$ (s); mass spectrum, $m/z$ 180.1145 (M$^+$, calcd for $C_{11}H_{16}O_2$ 180.1150); **27** (3%); and **26** (23%).

**4-Methylene-5-(2-Methyl-2-propenyl)cyclopent-2-enone (31).** Preparative VPC of a benzene solution of crude diazo ketone **21** on column D (injector temperature 210 °C, column temperature 130 °C) afforded one peak, which was collected and identified as **31**: NMR (220 MHz) 7.59 (d, $J$ = 5.6 Hz, 1 H), 6.18 (dd, $J$ = 5.5, ~0.5 Hz, 1 H), 5.27 (s, 1 H), 5.24 (s, 1 H), 4.76 (s, 1 H), 4.69 (s, 1 H), 2.81 (ddd, $J$ = 9.3, 4.0, ~0.5 Hz, 1 H), 2.55 (dd, $J$ = 14.3,

4.0 Hz, 1 H), 2.14 (dd, $J$ = 14.3, 9.3 Hz, 1 H), 1.77 (s, 3 H); IR 3100 (w), 2950 (w), 1710 (s), 1650 (w), 1640 (w), 1545 (m), 895 (m), 882 cm$^{-1}$ (m); UV 268 nm ($\epsilon$ 9.6 × 10$^3$); mass spectrum, $m/z$ = 148.0887 (M$^+$, calcd for $C_{10}H_{12}O$ 148.0889).

**3-(3-Butenyl)cyclopent-2-enone (32).** Following the procedure described above for the preparation of **11**, the alcohol obtained from 3-butenylmagnesium bromide and cyclopent-2-enone (5.0 g, 61 mmol), after treatment with acidic $CrO_3$, gave **32** (1.403 g, 17% overall), bp 110–115 °C (10 mm); further purification was achieved by preparative VPC on column D (175 °C): NMR (60 MHz) $\delta$ 6.13–5.47 (m, 1 H), 5.83 (dd, $J$ = 1, 1 Hz, 1 H), 5.22–4.8 (m, 2 H), 2.72–2.10 (m, 8 H); IR 3070 (w), 2955 (m), 1715 (s), 1672 (w), 1643 (m), 1617 (s), 1435 (m), 981 (m), 910 cm$^{-1}$ (m); mass spectrum, $m/z$ 136.0887 (M$^+$, calcd for $C_9H_{12}O$ 136.0887).

**Photolysis of 32.** A solution of **32** (176 mg) in $C_6H_6$ (67 mL) was irradiated at 25 °C through an uranium glass filter for 10 days. VPC analysis on column G (178 °C) indicated two components and a considerable amount (~40%) of **32** remaining. After preparative VPC, a NMR spectrum of the first component indicated it was a mixture. Further separation was achieved on column H (150 °C); the first eluted component was identified as **14b**: NMR (220 MHz) $\delta$ 2.71 (m, $H_a$, $J_{ad} \sim J_{ae} \sim J_{af} \sim 1.3$, $J_{ac} = J_{ab} = 0$ Hz), 2.61 (dd, $H_d$, $J_{cd}$ = 7.9, $J_{ad}$ = 1.4 Hz), 2.57 (d, $H_b$, $J_{bc}$ = 9.2 Hz), 2.03–1.89 (m, 4 H), 1.78–1.58 (m, 4 H), 1.11 (dd, $H_c$, $J_{bc}$ = 9.2, $J_{cd}$ = 7.7 Hz); IR 2960 (s), 2875 (s), 1736 (s), 1448 (w), 1402 (w), 1319 (w), 1277 (m), 1189 (m), 1127 (m), 1024 cm$^{-1}$ (w); mass spectrum, $m/z$ 136.0864 (M$^+$, calcd for $C_9H_{12}O$ 136.0888).

The second component from column H was identified as **5** by comparison of its NMR and IR spectra with those of an authentic sample.[3,22] The second component from column G was identified as **33**: NMR (60 MHz) $\delta$ 6.02–5.37 (m, 1 H), 5.08–4.85 (m, 2 H), 2.88 (d, $J$ = 5 Hz, 2 H), 2.63–2.10 (m, 4 H), 2.03 (s, 3 H); IR 3070 (w), 2950 (m), 1705 (s), 1648 (s), 1620 (w), 1376 (m), 1172 (m), 905 cm$^{-1}$ (m); mass spectrum, $m/z$ 136.0887 (M$^+$, calcd for $C_9H_{12}O$ 136.0889).

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# 1,4-Dipole-Metalated Quinone Strategy to (±)-4-Demethoxydaunomycinone and (±)-Daunomycinone. Annelation of Benzocyclobutenedione Monoketals with Lithioquinone Bisketals

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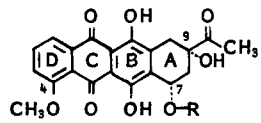
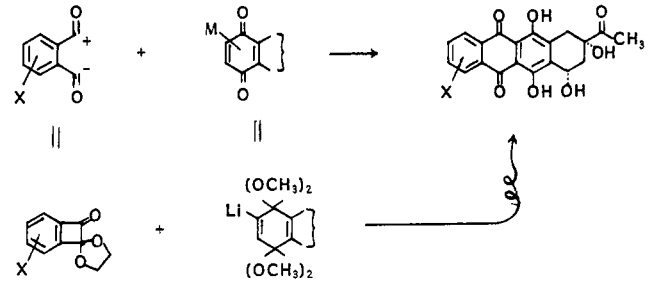
A strategy for total synthesis of anthracyclinones is outlined in which a benzocyclobutenedione monoketal, serving as a 1,4-dipole equivalent, is reacted with a lithiated quinone bisketal, serving as a metalated quinone equivalent, to afford in one step a fully functionalized tetracyclic ring system. A convenient synthesis of the AB-ring system with the eventual $C_7$ and $C_9$ oxygen functions of the anthracyclinone present has been developed. In addition, a trimethylsilyl-mediated benzylic bromination serves as one of the key steps in a novel methylene-to-carbonyl transformation, resulting in a regiospecific route to benzocyclobutenedione monoketals. The potential general synthetic utility arising from trimethylsilyl-stabilized radical intermediates is noted. The chemistry described above resulted in a convergent, regiospecific route to (±)-4-demethoxydaunomycinone and (±)-daunomycinone.

Anthracycline antibiotics have been of much interest in recent years due to their demonstrated therapeutic value in cancer chemotherapy.[1] The intact antibiotic consists of a glycon and an aglycon portion, and since the coupling of these two segments has been achieved,[2] synthetic efforts have concentrated on the synthesis of the rhodomycinone aglycons (i.e., daunomycinone, R = H). Most of the early




studies focused on synthesis of the 7-deoxy- or 9-deoxydaunomycinone without regiochemical control or the 7-deoxy-4-demethoxy analogue.[3] This was followed by benzylic bromination and solvolysis of the labile 7-bromo

Scheme I. Quinone Bisketal 1,4-Dipole Strategy

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