to less than 1% of the crude material and then a large red-orange band of the major product. From the infrared spectra, the product was either a perchlorate salt (**8a**) or a tetrafluoroborate salt (**8b**) (bands at 1097 and 1084 cm^{-1}, respectively, depending upon whether the electrolyte had been TEAP or $TEABF_4$. The yield of 8 was found to be significantly better from the BF_4 medium: **8a**, 60%; **8b**, 80%. These products were recrystallized from ethanol/benzene (1:1), giving crystals that melted to red liquids over a rather wide temperature range: **8a**, red crystals, 180–189 °C; **8b**, orange crystals, 177–184 °C.

Although **8a** and **8b** show different colors in the solid state, their UV–Vis spectra (in acetonitrile) are identical: λ_{max} (log ϵ, ϵ in L/mol cm) 415 (3.16); 297 (4.34); 255 (4.53) nm; MS for **8b** (direct probe, 250 °C), *m/z* (% base peak) 567 (17, M + 2), 566 (42, M + 1), 565 (54, M^+), 564 (100), 563 (29), 562 (55), 552 (16), 551 (49), 550 (100), 490 (11), 489 (48), 488 (100), 486 (10), 485 (20), 284 (6), 283 (24). The MS for **8a** is similar; however, peaks due to loss of phenyl and product cleavage (283) are much less prominent (less than 5%). An additional peak at 580 (35) may indicate decomposition of the perchlorate salt. **8a**: ^{13}C NMR ($CDCl_3$) δ 31.3 (NCH_3), 114.8 (C-3), 110.3 (C-7), 37.7 ($N'CH_3$), 186.9 (C-2′), 74.1 (C-3′), 141.6, 142.5 (C-8′, C-9′), 117.4 (C-7′), other peaks uncertain. Primed numbers refer to positions on the indolenine ring. Anal. (**8a**) Calcd for $C_{42}H_{33}N_2 \cdot ClO_4$: C, 75.84; H, 5.00; N, 4.21. Found: C, 75.77; H, 5.35; N, 4.11. (**8b**) Calcd for $C_{42}H_{33}N_2 \cdot BF_4$: C, 77.31; H, 5.10; N, 4.29. Found: C, 77.40; H, 5.35; N, 4.14.

Acknowledgment. This work was sponsored, in part, by Grant CA 33195 from the National Cancer Institute of the National Institutes of Health to the University of Connecticut. We thank Dr. Thomas Leipert and Marvin Thompson of the Department of Chemistry at Connecticut for help with the NMR and MS, respectively, and S. Longchamp[18] of the Faculte des Sciences et des Techniques de Rouen, France, for a sample of **4** with the higher melting point. Grateful acknowledgment is also made to William Comstock of the National Heart, Lung, and Blood Institute, Bethesda, MD, for obtaining the mass spectra of the *N*-methyl-2,3-diphenylindole oxidation products.

Registry No. **2**, 110417-94-2; **3**, 66785-53-3; **5**, 110417-95-3; **7**, 6121-45-5; **8a**, 110417-97-5; **8b**, 110417-98-6; 3-chloroaniline, 108-42-9; benzoin, 119-53-9; 4-chloro-2,3-diphenyl-1*H*-indole, 81303-08-4; *N*-methylaniline, 100-61-8.

(18) Longchamp, S.; Caullet, C. *Electrochim. Acta* **1984**, *29*, 1074.

A Convenient Preparation of 4- and 5-Substituted Cyclopentenones: A Short Synthesis of Methylenomycin B

Carmelo J. Rizzo, Norma K. Dunlap,[1a] and Amos B. Smith, III*[1b]

Department of Chemistry, The Laboratory for Research on the Structure of Matter, and The Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received April 2, 1987

Methods for the preparation of substituted cyclopentenones have been the subject of much attention, given the ubiquitous nature of this structural unit in both natural and unnatural products. Classical approaches have rested largely on 1,4-dicarbonyl condensations,[2] molecular rearrangements,[3] Friedel–Crafts reactions,[4] and the Nazarov cyclization.[5] All of these methods have been useful in preparing 2- and/or 3-substituted cyclopentenones. However, 4- and 5-substituted cyclopentenones have proven more difficult to prepare. Stork resolved the problem by protecting the enone double bond as its cyclopentadiene adduct.[6] More recently, the heteroatom-directed Nazarov cyclization developed by Denmark,[7a–d]

Scheme I

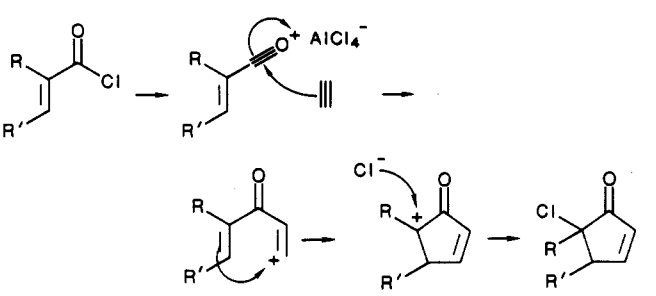
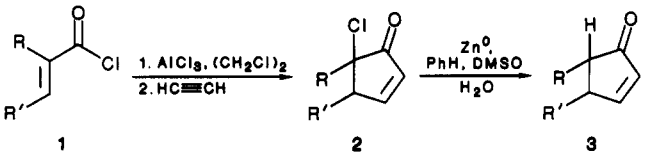


Table I[a]



			yield, %		
entry	R	R′	chlorocyclopentenone	cyclopentenone	overall yield, %
a	H	H	45[9c]	71[16]	32
b	H	Me	69[9c]	74[17]	51
c	Me	H	67[9c]	65[19]	44
d	Me	Me	66[9c]	75[18]	50
e	H	Ph	30	91[4d,7b,6h]	27
f	Me	Ph	50	84	42
g	$-(CH_2)_3-$		72	68[7b,7h,8h]	49
h	$-(CH_2)_4-$		68	92[7b,7d,8h]	63
i	$-(CH_2)_5-$		68	90[7b,7d]	61

[a] References are for previous preparations.

(1) (a) NIH NRSA Postdoctoral Fellow, 1985–1986. (b) NIH Career Development Awardee, 1980–1985, and J. S. Guggenheim Foundation Fellow, 1985–1986.

(2) Ellison, R. A. *Synthesis* **1973**, *397*.

(3) (a) Jackson, D. A.; Rey, M.; Drieding, A. S. *Helv. Chim. Acta* **1985**, *68*, 439. (b) Ravienstrauch, V. *J. Org. Chem.* **1984**, *49*, 950. (c) Baudouy, R.; Delbecq, F.; Gore, J. *Tetrahedron* **1980**, *36*, 189. (d) Bloch, R. *Tetrahedron Lett.* **1979**, *3945*. (e) Salomon, R. G.; Coughlin, D. J.; Easler, E. M. *J. Am. Chem. Soc.* **1979**, *101*, 3961. (f) Roumestant, M. L.; Malacria, M.; Grimaldi, J.; Bertrand, M. *Synthesis* **1976**, 755.

(4) (a) Magnus, P.; Quagliato, D. *J. Org. Chem.* **1985**, *50*, 1621. (b) Cooke, F.; Moerck, R.; Schwindeman, J.; Magnus, P. *J. Org. Chem.* **1980**, *45*, 1046. (c) Cooke, F.; Moerck, R.; Schwindeman, J.; Magnus, P. *Tetrahedron Lett.* **1979**, 1995. (d) Kjeldsen, G.; Knudsen, J. S., Ravn-Petersen, L. S.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2237. (e) Schegolev, A. A.; Smit, W. A.; Roitburd, G. V.; Kucherov, V. F. *Tetrahedron Lett.* **1974**, 3373. (f) Conia, J. M.; Leriverend, M. L. *Tetrahedron Lett.* **1968**, 2101. (g) Rand, L.; Dolinski, R. J. *J. Org. Chem.* **1966**, *31*, 3063. (h) Dev, S. *J. Indian Chem. Soc.* **1957**, *34*, 169. (i) Also see ref 8a–f.

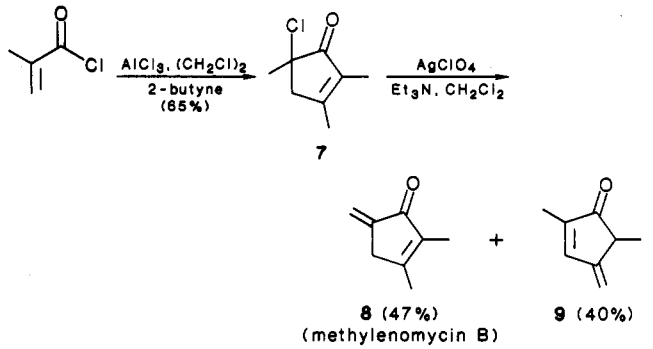
(5) (a) Tius, M. A.; Astrab, D. P.; Fauq, A. H.; Ousset, J. B.; Trehan, S. *J. Am. Chem. Soc.* **1986**, *108*, 3438. (b) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429. (c) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1981**, *46*, 3696. (d) Schostrez, H.; Paquette, L. A. *Tetrahedron* **1981**, *37*, 4431. (e) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017. (f) Hirano, S.; Takagi, S.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 169. (g) Fristad, W. E.; Dime, D. S.; Bailey, T. R.; Paquette, L. A. *Tetrahedron Lett.* **1979**, 1999. (h) Jacoabson, R. M.; Lahm, G. P. *J. Org. Chem.* **1979**, *44*, 462. (i) Also see ref 4a–c.

(6) Stork, G.; Nelson, G. L.; Rouessac, F.; Gringore, O. *J. Am. Chem. Soc.* **1971**, *93*, 3091.

(7) (a) Denmark, S. E.; Habermas, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821. (b) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2377. (c) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2397. (d) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642. (e) For recent examples of a tin-directed Nazarov cyclization, see: Peel, M. R.; Johnson, C. R. *Tetrahedron Lett.* **1986**, *27*, 5947.

0022-3263/87/1952-5280$01.50/0

Scheme II

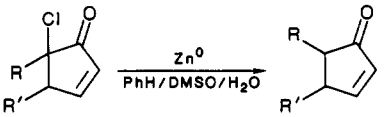


Magnus,[4a] and Johnson[7e] and the high-temperature techniques of Dreiding[8] have also provided elegant solutions to this problem.

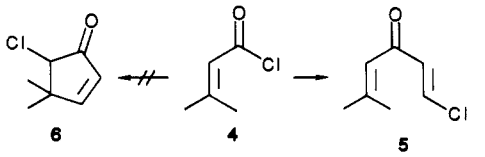
In 1969, Martin and co-workers published the first of a series of papers on the synthesis of 5-chloro-2-cyclopentenones via reaction of α,β-unsaturated acid chlorides and acetylene in the presence of aluminum chloride.[9]

Presumably the reaction involves attack of the oxonium ion by the π-system of the acetylene to generate a vinyl carbonium ion. Cyclization then generates an α-acyl carbonium ion, which is subsequently trapped by chloride ion (Scheme I).

Surprisingly, this apparently versatile reaction has found little recent application.[10] Given that the reaction provides convenient access to 4- and/or 5-substituted 5-chloro-2-cyclopentenones with complete control over the position of the double bond, we conjectured that reductive removal of the chloride, under nonequilibrating conditions, would permit preparation of the parent 4- and 5-substituted cyclopentenones.



To explore this scenario, we prepared a variety of simple 5-chloro-2-cyclopentenones by the method of Martin and subjected them to activated zinc reduction.[11] Our results are illustrated in Table I. The overall yields for the two-step sequence were, in general, good (40–65%). Of considerable importance, the reaction sequence can be conveniently carried out on the 100-mmol scale. The only exception encountered was 3,3-dimethylacryloyl chloride (**4**), which afforded divinyl ketone **5** instead of 4,4-dimethyl-5-chlorocyclopentenone (**6**).[12]



To demonstrate further the synthetic utility of the 5-chloro-2-cyclopentenone intermediates, a short, expedient synthesis of the cyclopentenoid antibiotic methylenomycin B was carried out (Scheme II). Toward this end, reaction of methacryloyl chloride with 2-butyne in the presence of aluminum chloride at 0 °C provided 5-chloro-2,3,5-trimethyl-2-cyclopentenone in 65% yield. Dehydrohalogenation with silver perchlorate and triethylamine led to a mixture of two compounds, **8** and **9**, which were readily separable by flash column chromatography. The major product of this reaction, methylenomycin B,[13] was thus available in two steps (31% overall yield) from commercially available starting materials.

In summary, we have demonstrated that the Martin preparation of 4- and/or 5-substituted 5-chlorocyclopentenones in conjunction with reductive removal of the chloride provides a convenient, preparatively useful approach to these synthetically important compounds. That the intermediate 5-chloro derivatives are also useful was demonstrated by an expedient synthesis of methylenomycin B.

Experimental Section[14]

Preparation of Substituted 5-Chlorocyclopentenones. A typical experimental procedure is described for the preparation of 5-chloro-5-methylcyclopentenone (**2c**).

In a flame-dried three-neck 250-mL round-bottom flask equipped with a magnetic stirrer, reflux condenser, and gas inlet is placed 26.13 g of freshly distilled methacryloyl chloride (250 mmol) in 100 mL of dry 1,2-dichloroethane. The solution is cooled to 0 °C and 35 g of anhydrous $AlCl_3$ (262 mmol) is added in portions. The reaction mixture is stirred at 0 °C for 15 min and then warmed to 35 °C for 90 min, after which time acetylene gas (dried by passing through concentrated sulfuric acid and then Drierite) is passed through the solution for 8 h, during which time

(8) (a) Koller, M.; Karpf, M.; Drieding, A. S. *Tetrahedron Lett.* **1986**, *27*, 19. (b) Ackroyd, J.; Karpf, M.; Drieding, A. S. *Helv. Chim. Acta* **1985**, *68*, 338. (c) Ackroyd, J.; Karpf, M.; Drieding, A. S. *Helv. Chim. Acta* **1984**, *67*, 1963. (d) Huguet, J.; Karpf, M.; Dreiding, A. S. *Tetrahedron Lett.* **1983**, *24*, 4177. (e) Karpf, M.; Huguet, J.; Drieding, A. S. *Helv. Chim. Acta* **1982**, *65*, 13. (f) Karpf, M.; Drieding, A. S. *Helv. Chim. Acta* **1981**, *64*, 1123. (g) Karpf, M.; Drieding, A. S. *Tetrahedron Lett.* **1980**, *21*, 4569. (h) Karpf, M.; Drieding, A. S. *Helv. Chim. Acta* **1979**, *62*, 852.

(9) (a) Martin, G. J.; Durand, H.; Daviaud, G.; Martin, M. *C. R. Seances Acad. Sci., Ser C.* **1968**, *266*, 478. (b) Martin, G. J.; Rabiller, Cl.; Mabon, G. *Tetrahedron Lett.* **1970**, 3131. (c) Martin, G. J.; Rabiller, Cl.; Daviaud, G. *Bull. Soc. Chim. Fr.* **1970**, 3098. (d) Martin, G. J.; Rabiller, Cl.; Guidoin, R. *Bull. Soc. Chim. Fr.* **1971**, 4554. (e) Martin, G. J.; Rabiller, C.; Mabon, G. *Tetrahedron* **1972**, *28*, 4027. (f) Rabiller, Cl.; Guidoin, R.; Martin, G. J. *Bull. Soc. Chim. Fr.* **1974**, *3055*.

(10) (a) Pradere, J. P.; Quiniou, H.; Rabiller, C.; Martin, G. J. *Bull. Chim. Soc. Fr.* **1976**, 991. (b) Ronald, R. C. *Tetrahedron Lett.* **1976**, 4413. (c) Ronald, R. C.; Gewali, M. B.; Ronald, B. P. *J. Org. Chem.* **1980**, *45*, 2224. (d) Gewali, M. B.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2792. (e) Schuster, D. I.; Brisimitzakis, A. C. *J. Org. Chem.* **1987**, *52*, 3644.

(11) Spencer, T. A.; Britton, R. W.; Watt, D. S. *J. Am. Chem. Soc.* **1967**, *89*, 5727.

(12) (a) Divinyl ketones were observed in the original work by Martin.[8c] In our hand, divinyl ketones are side products in many of the reactions. In the case of cinnamoyl chloride, it was the major product (54%). (b) For a previous preparation of 4,4-dimethylcyclopentenone, see: Magnus, P. D.; Nobbs, M. S. *Synth. Commun.* **1980**, *10*, 273.

(13) Haneishi, T.; Kitahara, N.; Takiguchi, Y.; Arai, M. *J. Antibiot.* **1974**, *27*, 386. For a synthesis and the structure reassignment, see: Jernow, J.; Fautz, W.; Rosen, P.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 4212. For other syntheses, see: Tonari, K.; Machiya, K.; Ueda, H. *Agric. Biol. Chem.*, **1981**, *45*, 295. Newton, R. F.; Reynolds, D. P.; Eyre, T. *Synth. Commun* **1981**, *11*, 527. Siwapinyoyos, T.; Thebtaranonth, Y. *J. Org. Chem.* **1982**, *47*, 598. Mikolajczyk, M.; Grzejszczak, S.; Lyzwa, P. *Tetrahedron Lett.* **1982**, *23*, 2237. Takahashi, Y.; Kosugi, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1982**, 496. Billington, D. C.; Pauson, P. L. *Organometallics* **1982**, *1*, 1560. Strunz, G. M.; Lal, G. L. S. *Can J. Chem.* **1982**, *60*, 2528. Doutheau, A.; Sartoretti, J.; Gore, J. *Tetrahedron* **1983**, *39*, 3059. Negishi, E. I.; Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6761. Ho, T. L. *Synth. Commun.* **1983**, *13*, 435. Cameron, A. G.; Hewson, A. T.; Osammor, M. I. *Tetrahedron Lett.* **1984**, *25*, 2267. Mikolajczyk, M.; Midura, W.; Grzejszczak, S. *Tetrahedron Lett.* **1984**, *25*, 2489. Mikolajczyk, M.; Balczewski, P. *Synthesis* **1984**, 691. Pohmakotr, M.; Chancharuee, S. *Tetrahedron Lett.* **1984**, *25*, 4141. Stetter, H.; Haese, W. *Chem. Ber.* **1984**, *117*, 682. Tius, M. A.; Patterson, G. M. L.; Astrab, D. P. *J. Antibiot.* **1985**, *38*, 1061. Camps, F.; Coll, J.; Moreto, J. M.; Torras, J. *Tetrahedron Lett.* **1985** *26*, 6397. Welch, S. C.; Assercq, J. M.; Loh, J. P.; Glase, S. A. *J. Org. Chem.* **1987**, *52*, 1440. Mikolajczy, K. M.; Balczewski, P. *Synthesis* **1987**, 659. Also see ref 5a and 8a.

the solution turns dark and thickens considerably. The reaction is quenched by pouring the solution over a large excess of ice. The aqueous layer is then extracted three times with ethyl acetate, and the combined organic phases are washed with saturated sodium sulfate solution, dried over magnesium sulfate, filtered, and evaporated to give a thick dark oil. The product is obtained by fractional distillation at reduced pressure (76 °C, 12 Torr) or by flash chromatography (10% ethyl acetate in hexane) to give 22.20 g (68%) of 5-chloro-5-methylcyclopentenone (**1c**): ^{1}H NMR δ 7.60 (1 H, m), 6.30 (1 H, m), 3.20 (1 H, m), 3.00 (1 H, m), 1.70 (3 H, s); IR 1722, 1590, 1422, 1343, 802 cm^{-1}.

It should be noted that the intermediate chlorides partially decompose at room temperature within a few days; however, they are nicely stable in the freezer for several weeks.

5-Chlorocyclopentenone (2a):[9c] bp 91 °C (18 Torr); IR 1725, 1585, 1350, 1170 cm^{-1}; ^{1}H NMR δ 7.70 (1 H, m), 6.30 (1 H, m), 4.24 (1 H, dd, J = 6.7, 2.6 Hz), 3.39–3.27 (1 H, m), 2.92–2.05 (1 H, m).

4-Methyl-5-chlorocyclopentenone (2b):[9c] bp 88 °C (12 Torr); IR 1710, 1670, 1587, 1493, 1182, 945, 700 cm^{-1}; ^{1}H NMR δ 7.53 (1 H, dd, J = 6.05, 2.28 Hz), 6.25 (1 H, dd, J = 6.02, 2.0 Hz), 3.81 (1 H, d, J = 2.97 Hz), 3.18–3.02 (1 H, m), 1.36 (3 H, d, J = 7.35 Hz).

4,5-Dimethyl-5-chlorocyclopentenone (2d):[9c] bp 97 °C (25 Torr). The reaction afforded a 1.2:1 mixture of *cis*-dimethyl **2d** and *trans*-dimethyl **2d**, which could be purified by HPLC in 11% EtOAc/Hexane.

Cis isomer: t_R 8.07 min; IR 1720, 1588, 1460, 1440, 1385, 1340, 830 cm^{-1}; ^{1}H NMR δ 7.51 (1 H, m), 6.22 (1 H, dd, J = 6.0, 2.46 Hz), 3.43–3.28 (1 H, m), 1.53 (3 H, s), 1.21 (3 H, d, J = 7.6 Hz).

Trans isomer: t_R 9.05 min; IR 1718, 1586, 1450, 1375, 1340, 1065 cm^{-1}; ^{1}H NMR δ 7.45 (1 H, dd, J = 5.83, 2.27 Hz), 6.21 (1 H, dd, J = 6.02, 2.32 Hz), 3.02–2.90 (1 H, m), 1.66 (3 H, s), 1.32 (3 H, d, J = 7.3 Hz).

4-Phenyl-5-chlorocyclopentenone (2e): purified by flash chromatography (10% ethyl acetate in hexane); IR 1710, 1668, 1587, 1492, 1180, 945, 695 cm^{-1}; ^{1}H NMR δ 7.68 (1 H, dd, J = 6.00, 2.25 Hz), 7.40 (3 H, m), 7.23 (2 H, m), 6.46 (1 H, dd, J = 6.00, 2.20 Hz), 4.20 (1 H, m), 4.07 (1 H, d, J = 3.25 Hz); high-resolution mass spectrum calcd for $C_{11}H_{13}ClNO$ ($M^+ + NH_4$) 210.0686, found 210.0675.

4-Phenyl-5-chloro-5-methylcyclopentenone (2f): purified by flash chromatography (10% ethyl acetate in hexane); IR 1725, 1590, 1490, 1375, 695 cm^{-1}; ^{1}H NMR δ 7.71 (1 H, dd, J = 6.03, 2.50 Hz), 7.35 (3 H, m), 7.13 (2 H, m), 6.49 (1 H, dd, J = 6.05, 2.20 Hz), 4.57 (1 H, dd, J = 2.45, 2.25 Hz), 1.13 (3 H, s); high-resolution mass spectrum calcd for $C_{12}H_{11}ClO$ ($M^+ + H$) 157.0420, found 157.0417.

***cis*-6a-Chloro-4,5,6,6a-tetrahydro-1(3a*H*)-pentalenone (2g)**: purified by flash chromatography (20% ethyl acetate in hexane); IR 1720, 1585, 1345, 1295, 905, 800 cm^{-1}; ^{1}H NMR δ 7.52 (1 H, dd, J = 5.88, 2.79 Hz), 6.24 (1 H, dd, J = 5.80, 1.74 Hz), 3.46 (1 H, m), 2.37–2.29 (1 H, m), 2.15–1.95 (2 H, m), 1.86–1.63 (2 H, m), 1.38–1.23 (1 H, m); high-resolution mass spectrum calcd for $C_8H_{10}ClO$ ($M^+ + H$) 157.0420, found 157.0417.

***cis*-7a-Chloro-3a,4,5,6,7,7a-hexahydro-1*H*-inden-1-one (2h)**: purified by flash chromatography (15% ethyl acetate in hexane); IR 2950, 1727, 1587, 1550 cm^{-1}; ^{1}H NMR δ 7.55 (1 H, dd, J = 6.04, 2.50 Hz), 6.25 (1 H, dd, J = 6.04, 2.30 Hz), 3.22 (1 H, m), 1.98 (2 H, dd, J = 5.80, 5.5 Hz), 1.80–1.55 (1 H, m), 1.55–1.35 (3 H, m); high-resolution mass spectrum calcd for $C_9H_{11}ClO$ (M^+) 170.0798, found 170.0486.

8a-Chloro-4,6,6,7,8,8a-hexahydro-1(3a*H*)-azulenone (2i): purified by flash chromatography (5% ethyl acetate in hexane); IR 2940, 2865, 1720, 1595, 1455, 1190 cm^{-1}; ^{1}H NMR δ 7.51 (1 H, dd, J = 6.00, 2.64 Hz), 6.23 (1 H, dd, J = 6.00, 2.10 Hz), 3.43–3.35 (1 H, m), 2.30–2.17 (1 H, m), 1.95 (1 H, m), 1.94–1.32 (8 H, m); high-resolution mass spectrum calcd for $C_{10}H_{13}ClO$ (M^+) 184.0655, found 184.0649.

Activated Zinc Reduction of Substituted 5-Chlorocyclopentenones. A typical experimental procedure is described for the reduction of 5-chloro-5-methylcyclopentenone (**2c**) to give 5-methylcyclopentenone (**3c**).[18]

A solution of 7.0 g (54 mmol) of 5-chloro-5-methylcyclopentenone (**2c**), 28 mL of dimethyl sulfoxide, 280 mL of benzene, and 11 mL of water was stirred at 25 °C with 17.5 g (269 mmol) of activated zinc for 6 h. The zinc was then removed by filtration, and the filtrate was diluted with ether and washed twice with brine. The aqueous layer was extracted three times with ether, and the combined organic layers were dried over anhydrous magnesium sulfate. The ether was removed via distillation through a 3-ft Vigreux column employing an 80 °C water bath. The benzene was then removed by distillation through a 6-in. Vigreux column at ambient pressure. Distillation of the remaining crude product at ~50 mm afforded 3.35 g (65%) of 5-methylcyclopentenone: bp 68–70 °C (~50 mmHg); IR 1705, 1590, 1430, 1340, 950 cm^{-1}; ^{1}H NMR δ 7.67 (1 H, m), 6.18 (1 H, m), 3.02–2.88 (1 H, m), 2.45–2.20 (2 H, m), 1.19 (3 H, d, UV λ_{max} 273 (CH_3CN, $\epsilon = 1.07 \times 10^4$);[20]

Cyclopentenone (3a):[16] bp 70 °C (450 mmHg); IR 1708, 1688, 1437, 1345, 1183 cm^{-1}; ^{1}H NMR δ 7.77–7.72 (1 H, m), 6.24–6.20 (1 H, m), 2.74–2.67 (2 H, m).

4-Methylcyclopentenone (3b):[17] purified by flash chromatography (10% ether in pentane); IR 1712, 1590, 1410, 1345, 1190, 890, 840 cm^{-1}; ^{1}H NMR δ 7.60 (1 H, dd, J = 5.27, 2.48 Hz), 6.13 (1 H, dd, J = 5.60, 1.95 Hz), 3.10–2.96 (1 H, m), 2.60 (1 H, dd, J = 18.8, 6.4 Hz), 1.95 (1 H, dd, J = 18.8, 2.2 Hz), 1.21 (3 H, d, J = 7.25 Hz).

***trans*-4,5-Dimethylcyclopentenone (3d)**:[19] purified by flash chromatography (10% ethyl acetate in hexane); IR 1705, 1585, 1465, 1380, 1230, 825 cm^{-1}; ^{1}H NMR δ 7.52 (1 H, dd, J = 5.68, 2.30 Hz); 6.11 (1 H, dd, J = 5.65, 2.00 Hz), 2.62–2.48 (1 H, m), 1.95–1.82 (1 H, m), 1.23 (3 H, d, J = 7.28 Hz), 1.19, (3 H, d, J = 7.42 Hz).

4-Phenylcyclopentenone (3e):[4d,7b,7e] purified by flash chromatography (10% ethyl acetate in hexanes); IR 1712, 1587, 1490, 1280, 845, 700 cm^{-1}; ^{1}H NMR δ 7.68 (1 H, dd, J = 5.54, 2.55 Hz), 7.30 (3 H, m), 7.15 (2 H, m), 6.33 (1 H, dd, J = 5.55, 2.20 Hz), 4.18 (1 H, m), 2.90 (1 H, dd, J = 19.0, 2.45 Hz).

(14) Materials and Equipment: ^{1}H NMR spectra (250 MHz) were obtained on a Bruker WM-250 FT spectrometer in deuteriochloroform solution. Chemical shifts are reported as δ values relative to tetramethylsilane (δ = 0). All infrared spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer for chloroform solutions. High-resolution mass spectra, reported for all new compounds, were obtained from the University of Pennsylvania Mass Spectrometry Service. Precoated silica gel plates (250 μm) with fluorescent indicator (Merck) were used for analytical thin-layer chromatography, and visualization was achieved via ultraviolet light or with anisaldehyde stain. 1,2-Dichloroethane (Aldrich) was dried by heating at reflux over CaH_2 for 90 min and then by fractional distillation through a Vigreux column. Zinc dust (Mallinckrodt) was activated within 24 h of use, exploiting the following procedure: zinc dust was washed three times with 5% hydrochloric acid, twice with water, once with methanol, and once with ether. The ether was decanted, and the zinc was dried in vacuo for several hours. Acid chlorides **1a–c** are commercially available (Aldrich) and were freshly distilled immediately prior to use. Acid chlorides **1d–i** were prepared from the corresponding carboxylic acid by treatment with $SOCl_2$, PCl_3, or oxalyl chloride followed by distillation. Carboxylic acids corresponding to acid chlorides **1d–f** were commercially available (Aldrich), while **1g–i** were prepared by literature methods.[15]

(15) (a) Carboxylic acids were prepared by the hydrolyzes of the corresponding ethyl ester according to the procedure of Dev., S. *J. Indian Chem. Soc.* **1956**, *33*, 769. (b) Buchi, G.; Hochstrasser, U.; Pawlak, W. *J. Org. Chem.* **1973**, *38*, 4348. (c) Ciabatti, R.; Padova, G. *Chem. Abstr.* **1982**, *96*, 143322z. (d) Ethyl cyclohept-1-enecarboxylate was prepared in 90% yield by the $RhCl_3 \cdot 3H_2O$ isomerization (in deoxygenated 95% ethanol at reflux for 24 h) of ethyl cyclohept-4-enecarboxylate.

(16) (a) DePuy, C. H.; Eilers, K. L. *Org. Synth.* **1962**, *42*, 38. Zakharychev, A. V.; Torgov, I. V. *Chem. Abstr.* **1963**, *58*, 3323h. Furdik, M.; Sidoova, E. *Chem. Abstr.* **1963**, *59*, 1497f. DePuy, C. H.; Eilers, K. L. *J. Org. Chem.* **1959**, *24*, 1380. Alders, K.; Flock, F. H. *Chem. Ber.* **1956**, *89*, 1732.

(17) Strike, D. P.; Smith, H. *Tetrahedron Lett.* **1970**, 4393. Cavill, G. W. K.; Goodrich, B. S.; Laing, D. G. *Aust. J. Chem.* **1970**, *23*, 83. Also see ref 3b, 5, 6b and 6d.

(18) Liotta, D.; Saindane, M.; Brothers, D. *J. Org. Chem.* **1982**, *47*, 1598. Also see ref 3b, 5, 6b, 6d.

(19) 5-Methylcyclopentenone has previously been prepared from 5-chloro-5-methylcyclopentenone via Raney nickel reduction. However, the reaction is complicated by overreduction to 2-methylcyclopentanone, incomplete reaction, and poor yield (ref 8a). Also see: Pohmakotr, M.; Phinyocheep, P. *Tetrahedron Lett.* **1984**, *25*, 2249. Paquette, L. A.; Taylor, R. T. *J. Am. Chem. Soc.* **1977**, *99*, 5708. Vandewalle, M.; Compernolle, F. *Bull. Soc. Chim. Belg.* **1967**, *76*, 43.

***trans*-4-Phenyl-5-methylcyclopentenone (3f)**: purified by flash chromatography (10% ethyl acetate in hexanes); IR 1715, 1595, 1495, 1455, 1180, 850, 700 cm^{-1}; ^1H NMR δ 7.70 (1 H, dd, J = 5.73, 2.66 Hz), 7.32 (3 H, m), 7.03 (2 H, m), 6.41 (1 H, dd, J = 5.71, 1.97 Hz), 4.31 (1 H, m), 2.73 (1 H, dt, J = 7.0, 7.50 Hz), 0.70 (3 H, d, J = 7.50 Hz), (3 H, s); high-resolution mass spectrum calcd for $C_{12}H_{12}O$ (M^+) 172.0888, found 172.0888.

***cis*-4,5,6,6a-Tetrahydro-1(3a*H*)-pentalenone (3g)**:[7b,7d,8h] purified by flash chromatography (15% ethyl acetate in hexanes); IR 1710, 1585, 1450, 1345, 840 cm^{-1}; ^1H NMR δ 7.54 (1 H, dd, J = 5.50, 2.68 Hz), 6.15 (1 H, dd, J = 5.75, 1.77 Hz), 3.36 (1 H, m), 2.73–2.67 (1 H, m), 1.95–1.55 (5 H, m), 1.32–1.13 (1 H, m).

***cis*-3a,4,5,6,7,7a-Hexahydro-1*H*-inden-1-one (3h)**:[7b,7d,8h] purified by flash chromatography (15% ethyl acetate in hexanes); IR 2950, 1703, 1580, 1550 cm^{-1}; ^1H NMR δ 7.66 (1 H, dd, J = 5.73, 2.85 Hz), 6.16 (1 H, dd, J = 5.30, 1.55 Hz), 2.96 (1 H, m), 2.41 (1 H, q, J = 6.17 Hz), 1.82–2.05 (2 H, m), 1.63–1.80 (1 H, m), 1.45–1.60 (2 H, m), 1.05–1.45 (3 H, m).

***cis*/*trans*-4,5,6,7,8,8a-Hexahydro-1(3a*H*)-azulenone (3i)**:[7b,7d] purified by flash chromatography (10% ethyl acetate in hexanes); IR 2940, 2370, 1700, 1595, 1455, 1185 cm^{-1}; ^1H NMR δ 7.55 (1 H, dd, J = 5.67, 2.50 Hz), 6.15 (1 H, dd, J = 5.70, 2.20 Hz), 3.06–2.15 (1 H, m), 2.55–2.44 (1 H, m), 2.10–1.85 (4 H, m), 1.85–1.65 (4 H, m), 1.55–1.35 (4 H, m).

5-Chloro-2,3,5-trimethyl-2-cyclopentenone (7). A solution of 1.05 g of freshly distilled methacryloyl chloride (10 mmol) in 2 mL of 1,2-dichloroethane was cooled to 0 °C, and 1.5 g of anhydrous aluminum chloride (12 mmol) was added. The reaction mixture was stirred at 0 °C for 15 min, warmed to room temperature for 30 min, cooled to 0 °C, and then 3.62 g of 2-butyne (67 mmol; Farchan) was added dropwise via syringe. The reaction, which was immediately exothermic, was complete within 10 min. The mixture was then carefully added to ice and diluted with ether. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic fractions were then washed with saturated brine, dried over magnesium sulfate, and filtered, and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, 10% ether in pentane) afforded 1.07 g (65%) of 5-chloro-2,3,5-trimethyl-2-cyclopentenone: IR 3020, 2915, 1715, 1650, 1435, 1390, 1335 cm^{-1}; ^1H NMR δ 3.05 (d, 1 H, J = 18.8 Hz), 2.81 (d, 1 H, J = 18.8 Hz), 2.05 (s, 3 H), 1.77 (s, 3 H), 1.64 (s, 3 H); high resolution mass spectrum calcd for $C_8H_{12}OCl$ (M + H) 159.0577, found 159.0600.

2,3-Dimethyl-5-methylene-2-cyclopentenone (Methylenomycin B). A solution of 383 mg of 5-chloro-2,3,5-trimethyl-2-cyclopentenone (2.41 mmol), 1.26 g of triethylamine (12.5 mmol) in 5 mL of methylene chloride was cooled to 0 °C, whereupon 678 mg of silver perchlorate monohydrate (3.0 mmol; Alfa) was added. The solution was then stirred at 0 °C for 20 min and warmed to ambient temperature for an additional 2 h, during which time a dark precipitate formed. The reaction mixture was then filtered through a short plug of Celite, the solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, eluted with 10% ether in pentane) to yield 140 mg (47%) of methylenomycin B (**8**) and 119 mg (40%) of 2,5-dimethyl-3-methylene-2-cyclopentenone (**9**). **8**:[13] IR 3010, 1690, 1665, 1630, 1405, 1390, 1340, 1035, 940 cm^{-1}; ^1H NMR δ 6.05 (br s, 1 H), 5.34 (br s, 1 H), 3.09 (br s, 2 H), 2.09 (s, 3 H), 1.79 (s, 3 H); ^{13}C NMR (62.5 MHz) 164.1, 141.5, 138.1, 114.9, 36.8, 16.6, 8.2 (carbonyl carbon not reported); high-resolution mass spectrum calcd for $C_8H_{11}O$ (M + H) 123.0810, found 123.0798. **9**: IR 3005, 2985, 1705, 1640, 1605, 1325, 910 cm^{-1}; ^1H NMR δ 7.41 (br s, 1 H), 5.24 (br s, 1 H), 5.12 (br s, 1 H), 2.79 (qdd, 1 H, J = 7.60, 1.25, 1.36 Hz), 1.88 (s, 3 H), 1.24 (d, 3 H, J = 7.60 Hz); UV λ_{max} 273 (CH_3CN, $\epsilon = 1.07 \times 10^4$);[20] high-resolution mass spectrum calcd for $C_8H_{11}O$ (M + H) 123.0810, found 123.0817.[20]

Acknowledgment. Support for this investigation was provided by the National Institutes of Health (Grant GM-19033) and by Merck Sharp and Dohme Research Laboratories.

(20) For the spectral data on the closely related 4-methylene-5-(2-methyl-2-propenyl)cyclopenten--one, see: Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1981**, *46*, 4821. We thank Professor Agosta (Rockefeller University) for bringing this compound to our attention.

Registry No. **1a**, 814-68-6; **1b**, 625-35-4; **1c**, 920-46-7; **1d**, 35660-94-7; **1e**, 17082-09-6; **1f**, 38449-13-7; **1g**, 59253-90-6; **1h**, 36278-22-5; **1i**, 72233-47-7; **2a**, 19931-06-7; **2b**, 35493-80-2; **2c**, 19931-04-5; *cis*-**2d**, 19946-58-8; *trans*-**2d**, 19946-60-2; **2e**, 110456-76-3; **2f**, 110456-77-4; *cis*-**2g**, 110456-78-5; *cis*-**2h**, 110456-79-6; *cis*-**2i**, 110456-80-9; *trans*-**2i**, 110456-82-1; **3a**, 930-30-3; **3b**, 23033-96-7; **3c**, 14963-40-7; *trans*-**3d**, 32556-65-3; **3e**, 81255-96-1; *trans*-**3f**, 110456-81-0; *cis*-**3g**, 23668-30-6; *cis*-**3h**, 81255-91-6; *cis*-**3i**, 81255-92-7; *trans*-**3i**, 81255-92-7; **4**, 3350-78-5; **5**, 110456-84-3; **6**, 63577-40-2; **7**, 38380-52-8; **8**, 52775-77-6; **9**, 110456-83-2; HC≡CH, 74-86-2; 2-butyne, 503-17-3.

Selectively Protected L-Dopa Derivatives: Application of the Benzylic Hydroperoxide Rearrangement

Dale L. Boger*[1] and Daniel Yohannes

Department of Chemistry and Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907

Received April 1, 1987

Bouvardin (**1**, NSC 259968) and deoxybouvardin (**2**), bicyclic hexapeptides isolated initially from *Bouvardia ternifolia* (Rubiaceae) and unambiguously identified by single-crystal X-ray structure analysis (bouvardin) and chemical correlation (deoxybouvardin),[2] are the initial members of a growing class of selective, exceptionally potent antitumor antibiotics,[2-4] now including the additional, provisionally named, bicyclic hexapeptides RA-I–RA-VII.[3,4] The unusual 14-membered para- and metacyclophane unit of the naturally occurring materials has been postulated to arise from the oxidative coupling of two adjacent L-tyrosine residues in cyclic hexapeptide precursors[2,3] and has been suggested to be responsible for attainment and/or maintenance of the active, normally inaccessible, conformation of the parent, cyclic hexapeptides necessary for inhibition of protein synthesis.[5,6] The parent 14-membered para- and metacyclophane has been recently disclosed in the characterization and structure determination of piperazinomycin (**9**),[7] an an-

(1) National Institutes of Health research career development award recipient, 1983–88 (CA 01134). Alfred P. Sloan research fellow, 1985–89.

(2) Jolad, S. D.; Hoffmann, J. J.; Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Gargiulo, R. L. Kriek, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 8040.

(3) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Mihashi, S.; Hamanaku, T. *Chem. Pharm. Bull.* **1986**, *34*, 3762. Itokawa, H.; Takeya, K.; Mihara, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Iitaka, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1424. Itokawa, H.; Takeya, K.; Mori, N.; Kidohoro, S.; Yamamoto, H. *Planta Med.* **1984**, *51*, 313.

(4) Natural and synthetic derivatives of RA bicyclic hexapeptides: Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Serisawa, N.; Hamanaka, T.; Mihashi, S. *Chem. Pharm. Bull.* **1984**, *32*, 3216. Itokawa, H.; Takeya, K.; Mori, N.; Takanashi, M.; Yamamoto, H.; Sonobe, T.; Kidokoro, S. *Gann.* **1984**, *75*, 929. Itokawa, H.; Takeya, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Mihara, K. *Chem. Pharm. Bull.* **1984**, *32*, 284. Microbial conversion of bouvardin to *O*-demethylbouvardin and bouvardin catechol: Petroski, R. J.; Bates, R. B.; Linz, G. S.; Rosazza, J. P. *J. Pharm. Sci.* **1983**, *72*, 1291.

(5) Zalacain, M.; Zaera, E.; Vazquez, D.; Jimenez, A. *FEBS Lett.* **1982**, *148*, 95, and references cited therein.

(6) Conformational studies. Separable, conformational isomers of bouvardin, *O*-methylbouvardin: Hoffmann, J. J.; Torrance, S. J.; Cole, J. R. *J. Chromatog. Sci.* **1979**, *17*, 287. Solution forms of bouvardin: Bates, R. B.; Cole, J. R.; Hoffmann, J. J.; Kriek, G. R.; Linz, G. S.; Torrance, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 1343.

0022-3263/87/1952-5283$01.50/0