dynamically stable with respect to fragmentation by 28 kcal/mol).[5]

The PE spectra of **1** and **2** are very similar to the previously published spectrum of 3,4-dimethylenecyclobutene (**8**).[8] Substituting one or two hydrogen atoms by methyl groups at the endo double bond of **8** yields the expected shift toward lower energies which can be explained by the hyperconjugative and inductive effect of a methyl group. The assignment given is based on the analogy of the spectra of **1**, **2**, and **8**.

Experimental Section

The He(I) PE spectra were measured at room temperature on a PS-18 instrument (Perkin-Elmer Ltd., England) and calibrated with reference to the Ar line at 15.76 eV. A resolution of about 25 meV of the $^2P_{3/2}$ Ar line was obtained. 1-Methyl- (**2**) and 1,2-dimethyl-3,4-dimethylenecyclobutene (**1**) were prepared by pyrolysis (410 °C, flow system) of 1,5-heptadiyne and 2,6-octadiyne, respectively, according to published procedures.[9,10] Analytically pure samples were obtained by preparative gas chromatography with a 3-m 20% Carbowax column at 80 °C. The spectral data of **1** and **2** agree with those reported in the literature.[9,10]

Acknowledgment. We are grateful to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the BASF Aktiengesellschaft in Ludwigshafen for financial support.

Registry No. 1, 25467-12-3; 2, 14309-11-6.

(8) Heilbronner, E.; Gleiter, R.; Hopf, H.; Hornung, V.; de Meijere, A. *Helv. Chim. Acta* **1971**, *54*, 783.
(9) Huntsman, W. D.; Wristers, H. J. *J. Am. Chem. Soc.* **1967**, *89*, 342.
(10) Criegee, R.; Dekker, J.; Engel, W.; Ludwig, P.; Noll, K. *Chem. Ber.* **1963**, *96*, 2362.

Regiospecific Alkylative Ring Expansion of 2,2-Disubstituted Cyclobutanones via α-Lithio Selenoxides

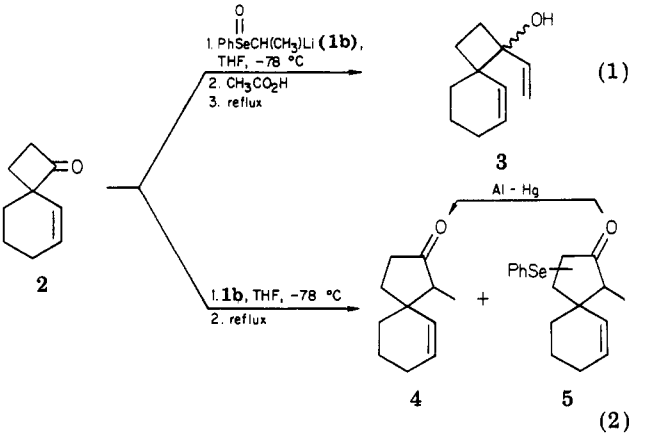
Robert C. Gadwood

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received November 17, 1982

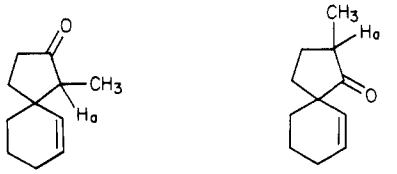
In connection with a synthetic program aimed at the total synthesis of cyclooctanoid natural products,[1] an efficient means for the preparation of 1,2-dialkenylcyclobutanols was needed. More specifically, a method was sought that avoided the formation of a labile 1,2-dialkenylcyclobutoxide intermediate. Such a method appeared to be the allylic alcohol synthesis of Reich and Shah,[2] involving the addition of an α-lithio selenoxide to a carbonyl compound, followed by neutralization and thermolysis to induce selenoxide elimination.

In practice, addition of 1-lithioethyl phenyl selenoxide (**1b**) to spiro[3.5]non-5-en-1-one (**2**) followed by neutralization with acetic acid and thermolysis in refluxing THF cleanly afforded the allylic alcohol **3** (eq 1) in 72% yield (8:1 mixture of diastereomers).[1] However, it was discovered somewhat serendipitously that if the reaction mixture was refluxed in THF without prior protonation, a regiospecific ring expansion occurred within minutes. Upon workup, the cyclopentanone **4** and its α-selenenylated

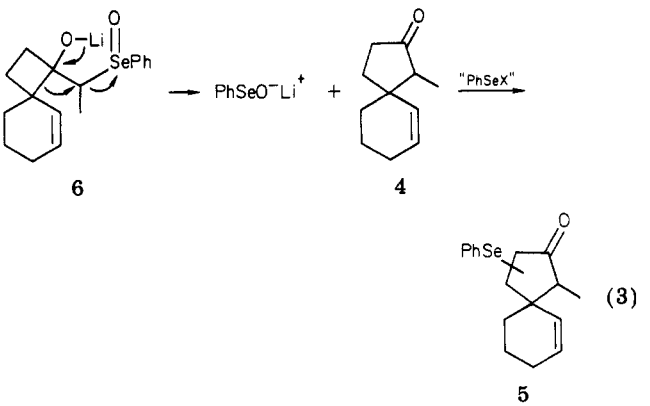


derivatives **5** were isolated (eq 2). No trace of allylic alcohol **3** could be seen in the crude NMR spectrum. Conversion of the α-selenenylated ketones **5** into the cyclopentanone **4** could be accomplished most conveniently by treatment of the crude reaction mixture with aluminum amalgam. Simple Kugelrohr distillation of the crude product afforded pure **4** (1:1 mixture of diastereomers) in 71% yield from the cyclobutanone **2**.

That the more highly substitued carbon atom had migrated exclusively was obvious by 270-MHz NMR analysis. Each diastereomer of **4** showed a one-proton downfield quartet (1.97 and 2.09 ppm, respectively) that collapsed to a singlet upon selective irradiation of the methyl group and thus was assigned to the methine proton (H_a). In contrast, the corresponding methine in the other possible regioisomer (**4a**) would have shown residual vicinal splittings after decoupling of the methyl group.



The mechanism of this ring expansion is apparently a direct pinacol-like rearrangement of the initial adduct **6** (eq 3) in which the more highly substituted carbon migrates preferentially. No spirocyclic epoxide was ever isolated even in cases using lithiomethyl phenyl selenoxide as the nucleophile.[6e] The α-selenenylated ketones **5** presumably arise from reaction of the cyclopentanone **4** with electrophilic selenium species produced in the course of the reaction.[3]



(1) Gadwood, R. C.; Lett, R. M. *J. Org. Chem.* **1982**, *47*, 2268.
(2) Reich, H. J.; Shah, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 3250. Reich, H. S.; Shah, S. K.; Chow, F. *Ibid.* **1979**, *101*, 6648.
(3) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. Reich, H. J.; Wollowitz, S.; Trend, S. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697.

0022-3263/83/1948-2098$01.50/0

Literature examples of selenoxide displacement in preference to elimination are relatively few. Shimizu and Kuwajima[4] have reported the intramolecular displacement of phenylselenenate anion by ketone enolate, resulting in formation of a cyclopropane. Trost and Scudder[5] have investigated the pinacol-type ring expansion of phenylseleninylcarbinylcyclopropanols to cyclobutanones. However, this reaction occurred under protic conditions and was presumed to involve initial loss of phenylselenenate anion to produce an ion-paired carbonium ion. The present case appears to be the first example of an anionic pinacol-like rearrangement involving phenylselenenate anion as a leaving group.

The generality of this method for regiospecific, alkylative ring expansion of 2,2-disubstituted cyclobutanones is illustrated by the examples shown in Table I. In each case, exclusive migration of the more substituted carbon occurred, based upon 270-MHz NMR analysis of the cyclopentanone products. All yields refer to isolated products obtained by treatment of the crude material with aluminum amalgam and purification by Kugelrohr distillation or column chromatography.

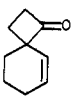
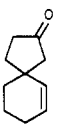
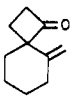
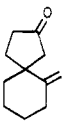
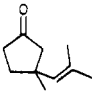
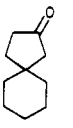
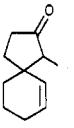
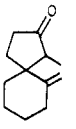
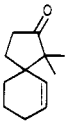
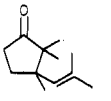
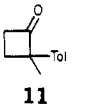
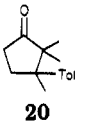
The α-lithioalkyl phenyl selenoxides[2] used in this study (**1a–c**) were prepared by deprotonation of the corresponding selenoxides with lithium diisopropylamide (LDA) in THF at −78 °C. The required selenoxides were in turn obtained from the readily available alkyl phenyl selenides via oxidation with *m*-chloroperbenzoic acid in THF at −20 °C.

As illustrated by Table I, it is possible to insert an unsubstituted, a monosubstituted, or a disubstituted carbon into the cyclobutanone ring.[17] This procedure therefore offers an advantage over those methods of cyclobutanone ring expansion that are limited to the insertion of methylene or monoalkyl-substituted carbons.[6a-c] Furthermore, the alkyl phenyl selenoxides required for this ring-expansion process are more readily available than the reagents required by other methodologies.[6,7]

As shown by the examples of Table I, ring expansion proceeds smoothly with 2-alkenyl-2-alkylcyclobutanones (entries 1–3, 6–9) and with 2-alkyl-2-arylcyclobutanones (entries 4 and 10). The simple 2,2-dialkylcyclobutanone **10** (entry 5) also undergoes ring expansion, but more slowly than those cyclobutanones having α π systems. Thus, whereas all other cyclobutanones in Table I showed complete reaction after 5 min in refluxing THF, **10** required 45 min of thermolysis.

To further demonstrate the utility of this ring expansion, a short synthesis of (±)-α-cuparenone[8,9] (**20**) was carried out (entry 10). Reaction of 2-methyl-2-tolylcyclobutanone[6e] (**11**) with the anion of isopropyl phenyl selenoxide (**1c**),

Table I. Ring Expansion of Cyclobutanones to Cyclopentanones

entry	α-lithio selenoxide	cyclobutanone	cyclopentanone	yield, %
1	PhSe(O)CH_2Li **1a**	 **2**	 **12**	73
2	**1a**	 **7**	 **13**	88
3	**1a**	 **8**	 **14**	82
4	**1a**	 **9**	 **15**	92
5	**1a**	 **10**	 **16**	82
6	PhSe(O)$CH(CH_3)$Li **1b**	**2**	 **4**[a]	71
7	**1b**	**7**	 **17**[a]	93
8	PhSe(O)$C(CH_3)_2$Li **1c**	**2**	 **18**	63
9	**1c**	**8**	 **19**	52 (61)[b]
10	**1c**	 **11**	 **20**	39 (57)[b]

[a] This compound was isolated as a 1:1 mixture of diastereomers. [b] Yield in parentheses refers to yield based on recovered cyclobutanone.

(4) Shimizu, M.; Kuwajima, I. *J. Org. Chem.* **1980**, *45*, 2921, 4063.
(5) Trost, B. M.; Scudder, P. H. *J. Am. Chem. Soc.* **1977**, *99*, 7601.
(6) The following reagents have been used to accomplish ring expansion of cyclobutanones. (a) $(PhS)_3CLi/HgCl_2$: Knapp, S.; Trope, A. F.; Ornaf, R. M. *Tetrahedron Lett.* **1980**, *21*, 4031. $(PhS)_2CHLi/CuOSO_2CF_3$: Cohen, T.; Kuhn, D.; Falck, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 4749. (c) $(CH_3)_2S{=}CH_2$/LiI: Leriverend, M.-L.; Leriverend, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1975**, *280*, 791. Leriverend, P. *Bull. Soc. Chim. Fr.* **1973**, 3498. (d) $R^1R^2C(OR)_2/BF_3$: Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 961. Kuwajima, I.; Azegami, I. *Tetrahedron Lett.* **1979**, 2369. (e) $(CH_3Se)(CH_3)_2CLi/CH_3OSO_2F$: Halazy, S.; Zutterman, F.; Krief, A. *Ibid.* **1982**, *23*, 4385. (f) $N_2CHCO_2Et/Et_3O^+BF_4^-$: Farcasiu, D.; Schleyer, P. v. R.; Ledlie, D. B. *J. Org. Chem.* **1973**, *38*, 3455. Liu, H. J.; Ogino, T. *Tetrahedron Lett.* **1973**, 4937. (g) CH_2N_2: Greene, A. E.; Depreś, J.-P.; Nagano, H.; Crabbé, P. *Ibid.* **1977**, 2365. Greene, A. E.; Depres, J.-P. *J. Am. Chem. Soc.* **1979**, *101*, 4003. Au-Yeung, B.-W.; Fleming, I. *J. Chem. Soc., Chem. Commun.* **1977**, 81.
(7) For other ring-expansion methods, see the following: Smith, P. A. S.; Baer, D. R. *Org. React.* **1960**, *11*, 157. Gutsche, C. D.; Redmore, D. "Carbocyclic Ring Expansion Reactions", Academic Press: New York, 1968.
(8) α-Cuparenone isolation and structure determination: Chetty, G. L.; Dev, S. *Tetrahedron Lett.* **1964**, 73. Dire, T.; Suzuki, T.; Ito, S.; Kurosawo, E. *Ibid.* **1967**, 3187.
(9) Previous syntheses of (±)-cuparenone: Parker, W.; Ramage, R.; Raphael, R. A. *J. Chem. Soc.* **1952**, 1558. Leriverend, P. *Bull. Chim. Soc. Fr.* **1973**, 3498. Wenkert, E.; Buckwalter, B. L.; Craveiro, A. A.; Sanchez, E. L.; Sathe, S. S. *J. Am. Chem Soc.* **1978**, *100*, 1267. Hayakawa, Y.; Shimizu, F.; Noyori, R. *Tetrahedron Lett.* **1978**, 993. Sakurai, H.; Shirakata, A.; Hosomi, A. *Angew, Chem., Int. Ed. Engl.* **1979**, *18*, 163. See also ref 6e.

followed by thermolysis and treatment with aluminum amalgam, afforded (±)-α-cuparenone in 39% yield (57% based on recovered cyclobutanone).

It is anticipated that the regiospecific cyclobutanone ring-expansion procedure presented here will find application in the synthesis of other cyclopentanoid natural products. Further efforts in this area are currently underway.

Experimental Section

Cyclobutanones. Cyclobutanones **2**, **7**, and **8** were prepared as described in ref 1. Cyclobutanones **9**, **10**, and **11** were prepared as described by Trost[10] (see also ref 6e).

Alkyl Phenyl Selenides. The alkyl phenyl selenides needed as precursors to the α-lithio selenoxides **1a–c** were prepared by reaction of PhSeNa (from PhSeSePh and $NaBH_4$) with the appropriate alkyl iodide in refluxing ethanol.[11] In this way were prepared methyl phenyl selenide [85%, bp 90 °C (20 mm) [lit.[12] bp 70–72 °C (7 mm)]]; ethyl phenyl selenide [88%, bp 58 °C (0.95 mm) [lit.[12] bp 63 °C (3 mm)]], and isopropyl phenyl selenide [86%, bp 47 °C (0.5 mm) [lit.[13] bp 63 °C (3 mm)]].

General Procedure for Ring Expansion of Cyclobutanones. The appropriate alkyl phenyl selenide (1.05 mmol) was dissolved in 8 mL of dry THF (distilled from sodium benzophenone ketyl) in a flame-dried 25-mL round-bottom flask under nitrogen. This solution was cooled to −20 °C (H_2O/EtOH/dry ice bath), and a solution of MCPBA (Aldrich, 85%, 1.05 mmol of peracid) in 5 mL of dry THF was added. After 15 min at −20 °C, the solution was chilled to −78 °C, and a solution of LDA (0.7 M in THF, 3.57 mL, 2.50 mmol) was added by syringe, After 10 min at −78 °C, the appropriate cyclobutanone was added (1.00 mmol) in 3 mL of cold (−78 °C), dry THF. After an additional 10 min at −78 °C, the reaction was transferred to a 0 °C ice bath for 5 min and then to an 80 °C oil bath. After the reaction had refluxed for 5 min (45 min for **10**), it was cooled to room temperature and quenched with 5 mL of saturated aqueous NH_4Cl. The aqueous layer was removed and extracted with ether. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The resulting residue was freed of inorganic salts by the addition of 10 mL of a 5% ethyl acetate in hexane solution and filtration through Celite. After removal of the solvent, the crude product was dissolved in 10 mL of a 10% water in THF solution, and aluminum amalgam[14] (from 50 mg of aluminum foil[15]) was added. After being stirred for 45 min at room temperature, the reaction was filtered through Celite and then aerated with air or O_2 for 10 min (to oxidize traces of PhSeH to PhSeSePh; omission of this step causes the workup and purification to be quite unpleasant). The yellow solution was extractd with ether, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The major impurity in the product is PhSeSePh, which can easily be removed by distillation or chromatography. Spectral data for the cyclopentanones thus prepared are presented below.

1-Methylspiro[4.5]dec-6-en-2-one (4): bp 60 °C (0.15 mm); 270-MHz NMR ($CDCl_3$) (more polar diastereomer) δ 5.82 (1 H, dt, J = 10, 4 Hz), 5.41 (1 H, d, J = 10 Hz), 2.25 (2 H, m), 2.09 (1 H, q, J = 7 Hz), 1.98 (3 H, m), 1.67 (3 H, m), 1.40 (1 H, m), 1.26 (1 H, m), 0.94 (3 H, d, J = 7 Hz); (less polar diastereomer) δ 5.78 (1 H, dt, J = 10, 4 Hz), 5.31 (1 H, d, J = 10 Hz), 2.30 (2 H, m), 2.05 (3 H, m), 1.97 (1 H, q, J = 7 Hz), 1.72 (5 H, m), 0.96 (3 H, d, J = 7 Hz); IR (CCl_4) 3010, 2930, 2870, 2830, 1740, 1440, 1185 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.41; H, 9.85.

Spiro[4.5]dec-6-en-2-one (12): bp 70 °C (0.25 mm); 270-MHz NMR ($CDCl_3$) δ 5.73 (1 H, dt, J = 10, 4 Hz), 5.51 (1 H, d, J = 10 Hz), 2.30 (2 H, t, J = 8 Hz), 2.17 (1 H, H_A of AB, J_{AB} = 18 Hz), 2.13 (1 H, H_B of AB, J_{AB} = 18 Hz), 2.00 (2 H, m), 1.89 (2 H, t, J = 8 Hz), 1.60 (4 H, m); IR (CCl_4) 3020, 2930, 2880, 2870, 2840, 1745, 1405, 1190, 1155, 910 cm^{-1}; MS (70 eV), m/e 150 (M^+), 108, 94, 79 (base), 77, 39.

6-Methylenespiro[4.5]decan-2-one (13): bp 65 °C (0.15 mm); 270-MHz NMr ($CDCl_3$) δ 4.74 (1 H, s), 4.58 (1 H, s), 2.45 (1 H, d, J = 18 Hz), 2.23 (5 H, m), 2.11 (1 H, d, J = 18 Hz), 1.85 (1 H, m), 1.60 (6 H, m); IR (CCl_4) 3080, 2925, 2850, 1740, 1635, 1440, 1405, 1195, 1160, 900 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.59; H, 10.02.

3-Methyl-3-(2-methylpropen-1-yl)cyclopentanone (14): bp 55 °C (0.45 mm); 270-MHz NMR ($CDCl_2$) δ 5.28 (1 H, s); 2.37 (1 H, H_A of AB, J_{AB} = 18 Hz), 2.26 (2 H, t, J = 8 Hz), 2.21 (1 H, H_B of AB, J_{AB} = 18 Hz), 1.99 (2 H, m), 1.69 (6 H, s), 1.23 (3 H, s); IR (CCl_4) 2970, 2930, 2870, 1740, 1445, 1405, 1370, 1165 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.91; H, 10.58.

3-Methyl-3-phenylcyclopentanone (15):[16] bp 90 °C (0.25 mm); 270-MHz NMR ($CDCl_3$) δ 7.29 (5 H, m), 2.64 (1 H, H_A of AB, J_{AB} = 17.5 Hz), 2.47 (1 H, H_B of AB, J_{AB} = 17.5 Hz), 2.32 (4 H, m), 1.38 (3 H, s); IR (CCl_4) 3095, 3065, 3040, 2965, 2940, 1740, 1445, 1405, 1200 cm^{-1}; MS (70 e V), m/e 174 (M^+), 159, 145, 131, 118 (base), 103, 91, 77, 56.

Spiro[4.5]decan-2-one (16):[18] bp 65 °C (0.45 mm); 270-MHz ($CDCl_3$) δ 2.24 (2 H, t, J = 8 Hz), 2.08 (2 H, s), 1.78 (2 H, t, J = 8), 1.40 (10 H, m); IR (CCl_4) 2930, 2850, 1740, 1445, 1400, 1160, 905 cm^{-1}; MS (70 eV), m/e 152 (M^+ and base), 123, 109, 94, 81, 67, 55.

1-Methyl-6-methylenespiro[4.5]decan-2-one (17): bp 70 °C (0.15 mm); 80-MHz NMR ($CDCl_3$) (mixture of diastereomers) δ 4.77 (0.5 H, br s), 4.69 (0.5 H, br s), 4.52 (1 H, s), 2.23 (5 H, m), 1.57 (8 H, m), 1.00 (1.5 H, d, J = 7 Hz), 0.92 (1.5 H, d, J = 7 Hz); IR (CCl_4) 3085, 2980, 2945, 2865, 1745, 1640, 1445, 900, 890 cm^{-1}; MS (70 eV), m/e 178 (M^+ and base), 163, 1498 136, 121, 107, 93, 79, 67.

1,1-Dimethylspiro[4.5]dec-6-en-2-one (18): bp 70 °C (0.20 mm); 270-MHz NMR ($CDCl_3$) δ 5.72 (1 H, dt, J = 10, 4 Hz), 5.37 (1 H, d, J = 10 Hz), 2.31 (2 H, m), 2.1–1.5 (8 H, m), 1.93 (6 H, s); IR (CCl_4) 3020, 2970, 2940, 2880, 2840, 1740, 1460, 1380, 1195, 1085, 905 cm^{-1}; MS (70 eV), m/e 178 (M^+), 163, 122, 120, 107, 91, 79 (base), 77, 71, 67, 41.

3-(2-Methylpropen-2-yl)-2,2,3-trimethylcyclopentanone (19). Isolated by flash chromatography with 2.5% ethyl acetate/hexane: 80-MHz NMR ($CDCl_3$) δ 5.20 (1 H, septet, J = 1.3 Hz), 2.20 (4 H, m), 1.75 (3 H, d, J = 1.3 Hz), 1.73 (3 H, d, J = 1.3 Hz), 1.02 (3 H, s), 0.94 (3 H, s), 0.92 (3 H, s); IR (CCl_4) 2970, 2930, 2870, 1740, 1455, 1383, 1370, 1095, 1050, 905 cm^{-1}; MS (70 eV), m/e 180 (M^+), 165, 137, 125, 109 (base), 95, 81, 67.

(±)-α-Cuparenone (20). Isolated by flash chromatography with 2.5% ethyl acetate/hexane. The following spectral values agree with those in the literature:[8,9] 60-MHz NMR ($CDCl_3$) δ 7.18 (4 H, m), 2.50 (3 H, m), 2.31 (3 H, s), 1.85 (1 H, m), 1.23 (3 H, s), 1.15 (3 H, s), 0.60 (3 H, s); IR (CCl_4) 3100, 3070, 3040, 2980, 2925, 2880, 1740, 1445, 1385, 1370, 1090, 1050 cm^{-1}.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. **1a**, 85662-39-1; **1b**, 85662-40-4; **1c**, 85662-41-5; (±)-**2**, 85662-42-6; (±)-**4** (isomer 1), 85662-43-7; (±)-**4** (isomer 2), 85662-44-8; **5**, 85680-81-5; (±)-**7**, 85662-45-9; (±)-**8**, 85662-46-0; (±)-**9**, 85662-47-1; **10**, 29800-45-1; (±)-**11**, 85090-90-0; (±)-**12**, 85662-48-2; (±)-**13**, 85662-49-3; (±)-**14**, 85662-50-6; (±)-**15**,

(10) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Rigby, J. H.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 3080. Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bogdanowicz, M. J. *Ibid.* **1977**, *99*, 3088.

(11) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

(12) Okamoto, Y.; Chellappa, K. K.; Homsany, R. *J. Org. Chem.* **1973**, *38*, 3172.

(13) Okamoto, Y.; Yano, T. *J. Organomet. Chem.* **1971**, *29*, 99.

(14) Aluminum amalgam was prepared according to: Smith, M. In "Reduction"; Augustine, R. L., Ed.; Marcel Dekker: New York, 1968; p 136.

(15) The aluminum foil used was "Alcoa Wrap", Aluminum Company of America, Pittsburgh, PA 15219.

(16) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.

(17) The yield is decreased somewhat in the reactions with the anion of isopropyl phenyl selenoxide, due in part to competitive enolization of the cyclobutanone.

(18) Larock, R. C.; Oertle, K.; Potter, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 190.

85662-51-7; **16**, 3643-16-1; (±)-**17** (isomer 1), 85662-52-8; (±)-**17** (isomer 2), 85662-53-9; (±)-**18**, 85662-54-0; (±)-**19**, 85662-55-1; (±)-**20**, 51704-29-1; methyl phenyl selenide, 4346-64-9; ethyl phenyl selenide, 17774-38-8; isopropyl phenyl selenide, 22233-89-2.

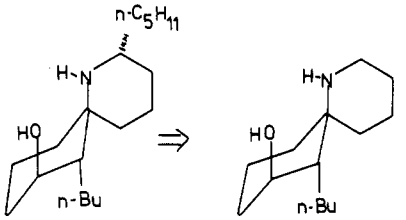
Formal Total Synthesis of Perhydrohistrionicotoxin. An Organopalladium Route

Stephen A. Godleski,* Deborah J. Heacock, James D. Meinhart, and Shawn Van Wallendael

Department of Chemistry, University of Rochester, Rochester, New York 14627

Received October 21, 1982

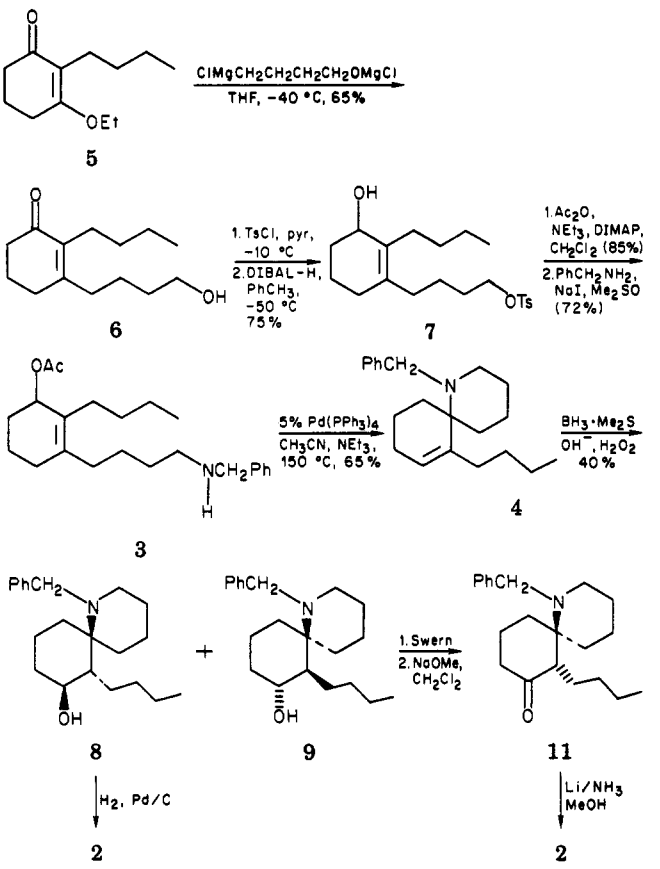
Members of the histrionicotoxin family of alkaloids have attracted considerable interest among synthetic chemists because of their unique structural features and their important properties as cholinolytics and modifiers of specific ion channels in nerves.[1,2] Syntheses of perhydrohistrionicotoxin (**1**,[3-6] PHTx), a nonnaturally occurring congener of histrionicotoxin with comparable activity, and accounts describing approaches to **1**[7-9] have appeared in the literature. A resurgence of interest in these alkaloids has recently occurred on the basis of reports that a variety of structurally simpler analogues of **1** also possess significant neurological activity.[10,11]



1 **2**

Having recently developed a general methodology for the preparation of spirocycles based on (π-allyl)palladium chemistry,[12-14] we sought to further demonstrate its utility by applying it in a synthesis of **1**. We selected deamylperhydrohistrionicotoxin (**2**) as our primary synthetic target because it had been efficiently carried on by Corey[3a] to PHTx (**1**) and had recently been found to possess equal bioactivity to **1**.[10] Model studies[12] had indicated that the key spirocyclization could be readily achieved by a palladium-catalyzed reaction of the amino allylic acetate **3**. Transformation of the product of this cyclization (**4**) to **2** via a hydroboration–oxidation seemed likely.

Scheme I



The (π-allyl)palladium precursor **3** was assembled as indicated in Scheme I. The sequence was initiated by treatment of the known vinylogous ester **5**[15] with the Normant Grignard[16] reagent derived from 4-chlorobutanol which provided on acidic workup the enone alcohol **6** in 65% yield. Tosylation of **6** (TsCl, pyr, -10 °C, 8 h) and reduction[17] (DIBAL-H, $PhCH_3$, -50 °C, 5 h) yielded the allylic alcohol–tosylate **7** (75% yield for two steps). Conversion of **7** to **3** was accomplished by acetylation of the alcohol (Ac_2O, 1 equiv of NEt_3, catalytic amount of DIMAP, CH_2Cl_2, 0 °C, 2 h; 85%) and amination of the tosylate ($PhCH_2NH_2$, catalytic amount of NaI, Me_2SO, room temperature, 18 h;[17] 72%).

Reaction of the amino allylic acetate **3** with 5–7% Pd(PPh_3)$_4$ (1 equiv of NEt_3, CH_3CN, 150 °C, sealed tube) gave the spirocyclic olefin **4** in 65% isolated yield. Conversion of **4** to *N*-benzyldeamylperhydrohistrionicotoxin proved, however, to be other than routine. The optimal conditions that were developed for this transformation included the use of 1.1 equiv[18] of BH_3·Me_2S in THF at room temperature for 18 h, followed by oxidation with a large excess of basic hydrogen peroxide in diglyme at 85 °C (10 h),[19] which provided the isomeric alcohols **8** and **9**

(1) Witkop, B. *Experimentia* **1971**, *27*, 1121.
(2) Albuquerque, E. Y.; Barnard, E. P.; Chui, T. H.; Lapa, A. J.; Dolly, J. O.; Jansson, S.; Daly, J.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 949.
(3) (a) Corey, E. J.; Arnett, J. F.; Widiger, G. N. *J. Am. Chem. Soc.* **1975**, *97*, 430. (b) Corey, E. J.; Petrzikla, M.; Veda, Y. *Helv. Chim. Acta* **1977**, *60*, 2294. (c) Corey, E. J.; Balanson, R. D. *Heterocycles* **1976**, *5*, 445.
(4) (a) Kishi, Y.; Arantani, M.; Dunkerton, L. V.; Fukuyama, T.; Kakoi, H.; Sugiura, S.; Inoue, S. *J. Org. Chem.* **1975**, *40*, 2009. (b) Kishi, Y.; Fukuyama, T.; Dunkerton, L. V.; Arantani, M. *Ibid.* **1975**, *40*, 2011.
(5) Evans, D. A.; Thomas, E. W., *Tetrahedron Lett.* **1979**, 411.
(6) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, 4811; *Tetrahedron* **1980**, *36*, 951.
(7) Venit, J. J.; Magnus, P. *Tetrahedron Lett.* **1980**, *21*, 4815.
(8) Tuffariello, J. J.; Trybulski, E. J. *J. Org. Chem.* **1974**, *39*, 3378.
(9) Gossinger, E.; Inhof, R.; Wehrli, H. *Helv. Chim. Acta* **1975**, *58*, 96.
(10) Takahashi, K.; Witkop, B.; Brossi, A.; Malequie, M.; Albuquerque, E. Y. *Helv. Chim. Acta* **1982**, *65*, 252.
(11) Albuquerque, E.; Maleque, M.; Brossi, A.; Witkop, B.; Godleski, S. A. *J. Pharmacol. Exp. Ther.*, submitted for publication.
(12) 1-Azaspirocycles: Godleski, S. A.; Meinhart, J. D.; Miller, D. J.; Van Wallendael, S. *Tetrahedron Lett.* **1981**, *22*, 2247.
(13) Carbospirocycles: Godleski, S. A.; Valpey, R. S. *J. Org. Chem.* **1982**, *47*, 381.
(14) 1-Oxaspirocycles: Godleski, S. A.; Stanton, S.; Felman, S.; Schutte-Parkhurst, C. *J. Am. Chem. Soc.* **1983**, *105*, 1964.
(15) Rosenmund, K.; Bach, H.; *Chem. Ber.* **1961**, *94*, 2394 and ref 4.
(16) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, 3013.
(17) Wilson, K. E.; Seidner, R. T.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1970**, 213.
(18) It has been reported that allyl amines require 2 equiv of hydroborating agent, the first equivalent complexing to the amine and being rendered inert. This did not prove to be the case for **4**. Lyle, R. E.; Spicer, C. K. *Tetrahedron Lett.* **1970**, *14*, 1133. Lyle, R. E.; Carle, K. R.; Ellefson, C. R.; Spicer, C. K. *J. Org. Chem.* **1970**, *35*, 801.

0022-3263/83/1948-2101$01.50/0