(s), 130.9 (s), 170.8 (s), 172.3 (s). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.19; N, 10.76. Found: C, 64.38; H, 6.17; N, 10.67.

Photocycloadduct 17: mp 141-142 °C; IR (KBr) 3200, 3130, 1775, 1670, 1650, 1595, 1495, 1380, 1200, 1130, 760 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.63 (s, 3 H), 2.70 (dd, 1 H, J = 7.8, 11.7 Hz), 3.23 (dd, 1 H, J = 8.8, 11.7 Hz), 4.45 (dd, 1 H, J = 7.8, 8.8 Hz), 4.70 (dd, 1 H, J = 2.0, 6.4 Hz), 5.00 (dd, 1 H, J = 2.0, 14.3 Hz), 6.80-7.19 (m, 4 H), 7.37 (dd, 1 H, J = 6.4, 14.3 Hz), 9.99 (br s, 1 H); ^{13}C NMR δ ($CDCl_3$) 26.6 (q), 35.3 (t), 62.1 (d), 62.8 (s), 98.8 (t), 115.8 (d), 123.0 (d), 124.2 (d), 124.9 (d), 130.6 (s), 131.7 (s), 140.9 (d), 169.0 (s), 171.2 (s). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.64; N, 10.84. Found: C, 64.92; H, 5.48; N, 10.67.

Photocycloadduct 18: mp 191-192 °C; IR (KBr) 3185, 2150, 1675, 1600, 1495, 1370, 770, 745, 700 cm^{-1}; ^1H NMR δ ($CDCl_3$-Me_2SO-d_6) 1.55 (s, 3 H), 3.20 (d, 1 H, J = 5.4 Hz), 3.30 (d, 1 H, J = 5.4 Hz), 6.82-7.06 (m, 4 H), 7.28-7.52 (m, 5 H), 10.63 (br s, 1 H); ^{13}C NMR δ ($CDCl_3$-Me_2SO-d_6) 20.0 (q), 42.4 (t), 54.9 (s), 63.5 (s), 114.3 (d), 119.8 (s), 120.2 (d), 121.6 (d), 122.9 (2 × d), 123.4 (d), 126.0 (d), 126.6 (2 × d), 131.0 (2 × s), 139.6 (s), 165.2 (s). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.22; N, 14.52. Found: C, 74.84; H, 5.23; N, 14.32.

Photocycloadduct 18′: mp 250 °C (sublimation); IR (KBr) 3270, 2225, 1680, 1650, 1600, 1505, 1490, 1355, 765, 695 cm^{-1}; ^1H NMR δ ($CDCl_3$-Me_2SO-d_6) 1.79 (s, 3 H), 2.27 (d, 1 H, J = 11.7 Hz), 3.52 (d, 1 H, J = 11.7 Hz), 6.88-7.13 (m, 4 H), 7.25-7.49 (m, 5 H), 10.69 (br s, 1 H); ^{13}C NMR δ ($CDCl_3$-Me_2SO-d_6) 26.0 (q), 42.7 (t), 58.1 (s), 63.5 (s), 114.6 (d), 117.9 (s), 121.2 (d), 121.6 (d), 123.2 (2 × d), 124.3 (d), 126.1 (d), 126.6 (2 × d), 131.6 (s), 131.7 (s), 139.6 (s), 165.0 (s). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.22; N, 14.52. Found: C, 74.93; H, 5.21; N, 14.47.

Registry No. **1a**, 6479-18-1; **1b**, 1196-57-2; **1c**, 3149-25-5; **1d**, 73148-14-8; **1e**, 21943-45-3; **1f**, 14003-34-0; **1g**, 2048-37-5; **1h**, 88392-55-6; **1i**, 1504-78-5; **2a**, 107-13-1; **2b**, 126-98-7; **2c**, 96-33-3; **2d**, 80-62-6; **2e**, 2177-18-6; **3**, 88392-56-7; **3′**, 88392-57-8; **4**, 88392-58-9; **5**, 88392-59-0; **6**, 88392-60-3; **7**, 88392-61-4; **8**, 88392-62-5; **9**, 88392-63-6; **9′**, 88392-64-7; **10**, 88392-65-8; **11**, 88392-66-9; **12**, 88392-67-0; **12′**, 88392-68-1; **13**, 88392-69-2; **14**, 88392-70-5; **14′**, 88392-71-6; **15**, 88392-72-7; **16**, 88392-73-8; **16′**, 88392-74-9; **17**, 88392-75-0; **18**, 88392-76-1; **18′**, 88392-77-2; O_2, 7782-44-7; *m*-methoxyacetophenone, 586-37-8; *trans*-stilbene, 103-30-0.

Intramolecular [2 + 2] Photochemical Cycloadditions. 3. Perhydrohistrionicotoxin Synthetic Studies: Synthesis of Spiro[4.5]decanones via Intramolecular [2 + 2] Photocycloaddition[1]

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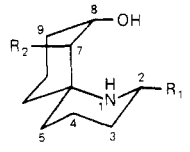
Received August 25, 1983

We describe here a full account of our efforts directed toward the synthesis of **4**, a known intermediate in the synthesis of perhydrohistrionicotoxin (**2**). Irradiation of **7** followed by oxidative cleavage of the derived cyclobutene **6** produced **5** or **11**, depending on the method of cyclobutene cleavage. While **5** could not be decarbonylated with $(Ph_3P)_3RhCl$, thermal decarboxylation of **11** furnished **12a** and **12b** with the undesired stereochemistry at C(6) predominating, vis a vis perhydrohistrionicotoxin. Thus, while this strategy does not appear to be viable for perhydrohistrionicotoxin, the photocycloaddition cyclobutene cleavage sequence constitutes a valuable method for the rapid construction of the spiro[4.5]decanone ring system with a high degree of stereocontrol.

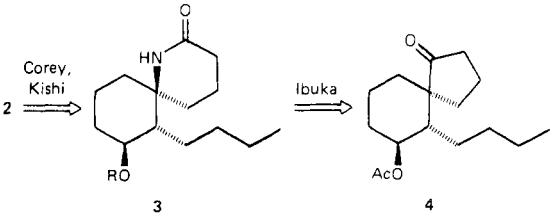
Introduction

Since the initial report in 1971 on the isolation and characterization of histrionicotoxin A (**1**)[3] from the Columbian frog *Dendrobates histrionicus*, it and its perhydro derivative **2**[4] have been the subject of considerable synthetic effort.[5,6] In the perhydro series the majority of approaches converge at spiro lactam **3**, which was first prepared by Corey[7] and Kishi[8] in 1975.



1: R_1 = $CH_2CH{=}CHC{\equiv}CH$ (*cis*); R_2 = $CH{=}CHC{\equiv}CH$ (*cis*)
2: R_1 = *n*-C_5H_{11}; R_2 = *n*-C_4H_9

Our interest in **2** as a synthetic target derived from Ibuka's report[6a,b] on the stereospecific preparation of **4** and its conversion to **3** via the Beckmann rearrangement sequence developed by Corey,[7] in conjunction with our recent



3 4

exploitation of the intramolecular [2 + 2] photocycloaddition of enones to acetylenic moieties.[9] From the

(1) For the previous paper in this series, see: Koft, E. R.; Smith, A. B., III. *J. Am. Chem. Soc.* **1982**, *104*, 5568.

(2) Camille and Henry Dreyfus Teacher Scholar, 1978-1983; national Institutes of Health (National Cancer Institute) Career Development Award, 1980-1985.

(3) Witkop, B. *Experimentia* **1971**, *27*, 1121. Daly, J. W.; Karle, I.; Meyers, W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870.

(4) For a review of the biological activity of the histrionicotoxins, see: ref 5. Also: Takahashi, K.; Jacobson, A. E.; Mak, C.-P.; Witkop, B.; Brossi, A.; Albuquerque, E. X.; Warnick, J. E.; Maleque, M. A.; Baroso, A., Silverton, J. V. *J. Med. Chem.* **1982**, *25*, 919. Takahashi, K.; Witkop, B.; Brossi, A.; Maleque, M. A.; Albuquerque, E. X. *Helv. Chim. Acta* **1982**, *65*, 252.

(5) Daly, J. W. In "Fortschifte der Chemie Organischer Naturstoffe"; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1982; Vol. 41, pp 247-276.

(6) (a) Ibuka, T.; Mitsui, Y.; Hayashi, K.; Minakata, H.; Inubushi, Y. *Tetrahedron Lett.* **1981**, *22*, 4425. (b) Ibuka, T.; Minakata, H.; Mitsui, Y.; Tabushi, E.; Taga, T.; Inobushi, Y. *Chem. Lett.* **1981**, 1409. (c) Godleski, S. A.; Heacock, D. J. *J. Org. Chem.* **1982**, *47*, 4820. (d) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695. (e) Glanzmann, M.; Karalai, C.; Ostersehlt, B.; Schon, U.; Frese, C.; Winterfeldt, E.; *Tetrahedron* **1982**, *38*, 2805. (f) Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3590.

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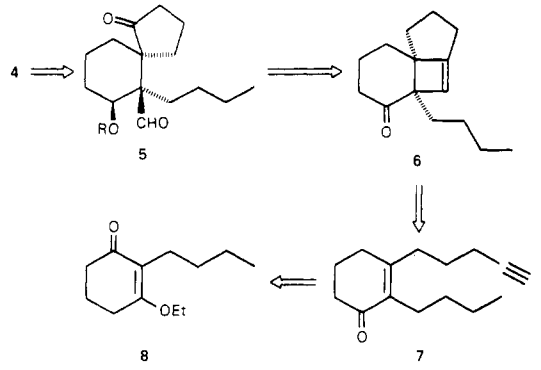
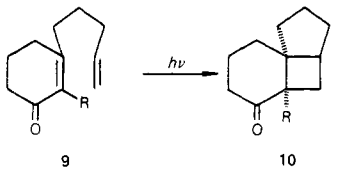
Scheme I



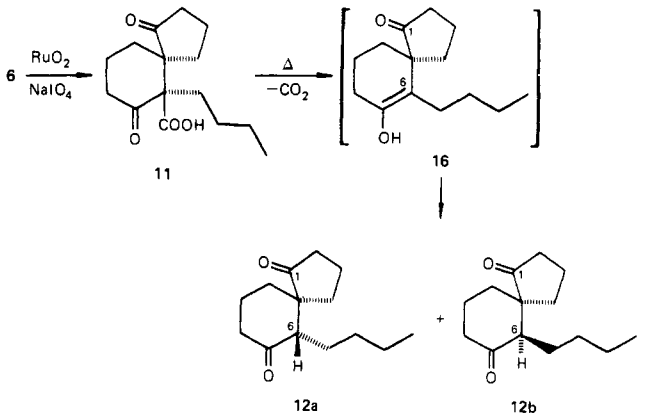
retrosynthetic perspective (see Scheme I) we envisioned that hydride reduction of **6** followed by ozonolysis would produce **5**; rhodium-mediated decarbonylation[10,11] would then furnish intermediate **4**. Cyclobutene **6** was seen to arise from the photocycloaddition[12,13] of **7**, which in turn could be anticipated to be readily available via nucleophilic addition of a 4-pentynyl unit to **8**,[8] followed by acidic hydrolysis.

Execution of such a strategy, however, was not without anticipated difficulties. First, although the feasibility of internal cycloadditions of the type **9** → **10** have been amply



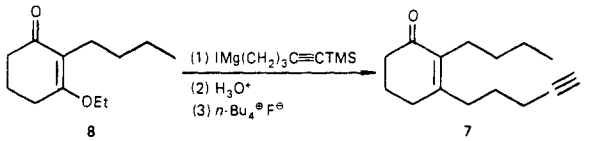
demonstrated in the case of olefinic enones,[14] molecular models indicate that considerable additional strain is present in the corresponding cyclobutene (i.e., **6**). Second, decarbonylation of **5** was by no means assured. Despite the observation that the decarbonylation of aldehydes with Wilkinson's catalyst takes place with retention of configuration,[15] the reaction is known to be quite sensitive to steric constraints.[10,11] Consequently, the congested nature of neopentyl aldehyde **5** did not bode well for the success of this process.

An alternative opportunity to remove the C(6) carbon would be oxidation of the cyclobutene ring to give keto acid **11**. Decarboxylation could then be carried out by thermolysis; such a process, however, would almost certainly scramble the stereochemistry at C(6), built in via the [2 + 2] cycloaddition, unless advantage of the cyclopentanone carbonyl could be taken in the decarboxylation process. A subsequent problem in this strategy would entail the differentiation of the C(1) and C(7) carbonyl groups in **12a**.

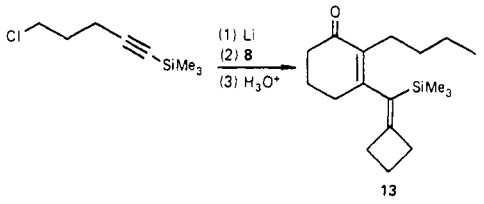


Results and Discussion

As introduced above, the obvious route to photochemical substrate **7** appeared to be addition of the Grignard reagent derived from 1-iodo-5-(trimethylsilyl)-4-pentyne[16] to enone **8**[8] followed by hydrolysis and removal of the



trimethylsilyl group. Unfortunately, this sequence at best provided **7** in only 42% yield based on **8**, the problem being enolization of **8** via the Grignard reagent.[17] Since enolization is less of a problem with organolithiums,[18] we explored this possibility. Reaction of 1-chloro-5-(trimethylsilyl)-4-pentyne with lithium powder in ether at 0 °C produced a solution of the derived organolithium reagent which was then added to **8**. Quite surprisingly the only product isolated from the reaction mixture after hydrolysis was **13**. Structure **13** was deduced from its

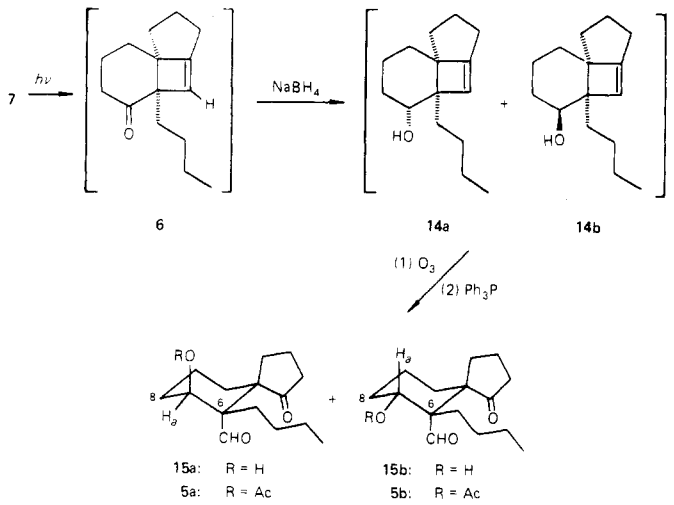


spectroscopic properties. Particularly characteristic was the appropriate parent ion in the high-resolution mass spectrum, the appearance of three distinct two-proton multiplets in the NMR, corresponding to the six hydrogens on the four-membered ring, and a strong carbonyl band at 1660 cm^{-1} in the infrared spectrum. Although intramolecular cyclizations are known to occur during the preparation of unsaturated organometallics,[19] we are unaware of any literature examples involving trimethylsilyl acetylenes.

Given that considerable experimentation would be necessary to improve on our original synthesis of **7**, we turned attention to the [2 + 2] photocycloaddition process. Irradiation of **7** through uranium glass in methanol buffered with sodium acetate resulted in the disappearance of starting material within 48–72 h. The uranium glass filter

(7) Corey, E. J.; Arnett, J. F.; Widiger, G. N. *J. Am. Chem. Soc.* **1975**, *97*, 430.
(8) Fukuyama, T.; Dunkerton, L. V.; Aratani, M.; Kishi, Y. *J. Org. Chem.* **1975**, *40*, 2011.
(9) For a successful application of this methodology to the total synthesis of the furanosesquiterpene hibiscone C (gmelofuran), see ref 1.
(10) Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* **1968**, *90*, 99.
(11) Tsuji, J.; Ohno, K. *Synthesis* **1969**, 157.
(12) For a review of the synthetic aspects of [2 + 2] photocycloadditions of α,β-unsaturated carbonyl compounds, see: Baldwin, S. W. In "Organic Photochemistry", Padwa, A., Ed.; Marcel Dekker: New York, 1981; Vol. 5, p 123.
(13) For a recent review of the synthetic utility of intramolecular [2 + 2] photocycloadditions, see: Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135.
(14) For example, see: Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130; **1983**, *103*, 82.
(15) Walborsky, H. M.; Allen, L. E. *J. Am. Chem. Soc.* **1971**, *93*, 5465.
(16) Cochrane, J. S.; Hanson, J. R. *J. Chem. Soc., Perkin Trans. 1*, **1972**, 361.
(17) A similar difficulty in adding an unsaturated Grignard reagent to 3-ethoxycyclohexenone has been reported by Hoye; see: Hoye, T. R.; Martin, S. J.; Peck, D. R. *J. Org. Chem.* **1982**, *47*, 331.
(18) Whitmore, F. C.; George, R. S. *J. Am. Chem. Soc.* **1942**, *64*, 1239.
(19) Hill, E. A.; Richey, H. G.; Rees, T. C. *J. Org. Chem.* **1963**, *28*, 2161.

Scheme II

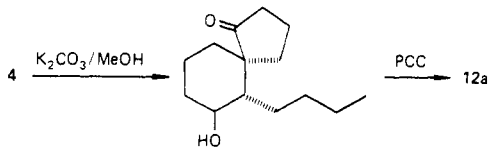


was employed to avoid secondary photolysis of derived β,γ-unsaturated ketones. That at least some polymerization had occurred was evidenced by a white intractable deposit that accumulated in the photolysis vessel. Nevertheless, examination of the photolysate by NMR revealed a singlet at δ 5.6, which we attributed to the vinylic hydrogen in **6**. Unfortunately, all attempts to purify **6** by chromatography proved fruitless, presumably due to the considerable strain inherent in the tricyclic skeleton. Reduction of the crude photolysate with sodium borohydride in methanol, on the other hand, gave two products assumed to be alcohols **14a** and **14b**. (Scheme II). Again without purification, ozonolysis followed by reductive workup with triphenylphosphine gave a 2:1 mixture of aldehydes **15a** and **15b** in an overall yield of 25% based on **7**. To facilitate both purification and separation of this mixture, the corresponding acetates (i.e., **5a** and **5b**) were prepared and then completely characterized. Stereochemical assignments for **5a** and **5b** were based on analysis of their high-field (250 MHz) ^{1}H NMR spectra. Assuming that their conformation is controlled by the C(6)-butyl appendage, one could predict that the signal for H_a in **5b** would be split by a large (~15 Hz) coupling constant due to the trans diaxial hydrogen at C(8). Proton H_a in **5a**, on the other hand, would experience a much smaller coupling (ca. 8 Hz) owing to the smaller dihedral angle between it and either hydrogen at C(8). In the event, the observed width at half height for the signal attributed to H_a in **5a** was 10 Hz, while this value in **5b** was 20 Hz.

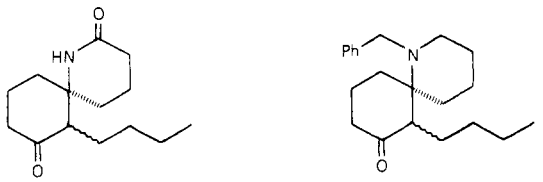
With aldehyde **5b** in hand, all that remained to complete a formal total synthesis of perhydrohistrionicotoxin was to effect the stereospecific decarboxylation of the C(6)-aldehyde functionality. Unfortunately, when this material or its isomer **5a** was treated with Wilkinson's reagent under a wide variety of conditions, including stoichiometric treatment in hot benzonitrile, only starting material or complete decomposition resulted.

As a final chapter in this study, we decided to explore the decarboxylation strategy in the off chance that the stereochemistry at C(6) of **12** could be controlled. Toward this end RuO_4 oxidation[20] of **6**, obtained directly from the irradiation of **7**, afforded a crystalline carboxylic acid (i.e., **11**) in 23% overall yield. As alluded to above, it was thought (hoped) that decarboxylation of this material might furnish **12a** as the major product due to intramolecular proton transfer in enol **16** mediated by the carbonyl oxygen at C(1). In practice, decarboxylation of **11** occurred smoothly in refluxing toluene to afford a mixture of spiro diones. Encouragingly, the ratio was 10:1. Equilibration via acid treatment reduced this ratio to 2.3:1. Unfortunately, the minor isomer **12a** proved to have the requisite stereochemistry for perhydrohistironicotoxin.

Stereochemical assignments for **12a** and **12b** were secured via chemical correlation. Toward this end, an authentic sample of **4**, kindly provided by Professor Ibuka,[21] was saponified with potassium carbonate in methanol and



then oxidized with pyridinium chlorochromate under conditions shown not to epimerize the C(6) substituent (see Experimental Section). The diketone thus obtained was shown to be identical in all respects with **12a** obtained from **11**. It should be noted that the observed thermodynamic preferrence for **12b** over **12a** is in sharp contrast with that observed in both spiro lactam system **17**[8] and spiropiperidine system **18**.[6c]



Finally, although it appears that our strategy is not viable for the synthesis of **4** (and hence perhydrohistrionicotoxin), we have demonstrated that the intramolecular [2 + 2] photocycloaddition of acetylenic enones such as **7** is a viable method for the stereoselective construction of highly functionalized spiro[4.5]decanones. Studies to further explore the utility of such intramolecular [2 + 2] photocycloadditions for natural product synthesis continue in our laboratory.

Experimental Section

Materials and Methods. All solvents used were reagent grade. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone prior to use. Organolithium reagents were titrated with diphenylacetic acid.[22] Irradiations were carried out in the solvent indicated, employing a standard Hanovia 450-W medium-pressure Hg arc fitted with a uranium glass filter to prevent secondary photochemical decomposition of the derived β,γ-unsaturated ketones. Analytical TLC was performed with precoated 0.25-mm E. Merck silica gel plates with fluorescent indicator. Visualization of TLC plates was accomplished with either ultraviolet light or by staining with 1% H_2SO_4 in ether.

Flash chromatography[23] and MPLC were performed on E. Merck silical gel (particle size 0.04–0.063 mm). Melting points were obtained on a Thomas-Hoover apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Proton NMR spectra were recorded on either a Varian Model T-60 (60 MHz) or a Bruker WM-250 (250 MHz) spectrometer. Carbon NMR spectra were recorded on an IBM WP-200 (50.23 MHz) instrument. Chemical shifts are reported in parts per million (δ values) relative to tetramethylsilane or chloroform. High-resolution mass

(20) Calrson, Per H. J.; Katsuki, T.; Martin, U. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(21) See ref 5a and 5b. We thank Professor Ibuka for a generous gift of this material.

(22) Kofron, W. C.; Baclawski, L. M. *J. Org. Chem.* **1979**, *41*, 1879.

(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

spectra were obtained at the University of Pennsylvania Mass Spectrometry Service on either a Hitachi-Perkin-Elmer RMH-2 or VG 70/70 micromass spectrometer interfaced to a Kratos DS-50-S data system.

Preparation of 1-Iodo-5-(trimethylsilyl)-4-pentyne.[16] 1-Chloro-4-pentyne (Farchan Labs; 10.2 g, 0.1 mol) was dissolved in 100 mL of dry ether and cooled to −78 °C under argon. *n*-Butyllithium (Alfa-Ventron; 62.5 mL, 1.6 M) was added dropwise, and the reaction mixture was stirred at −78 °C for 2 h. Chlorotrimethylsilane (16.5 mL, 0.13 mol) was then added, and the reaction mixture was allowed to warm to 25 °C and stir for 1 h. The precipitated salt was filtered and the solvent was removed by distillation at atmospheric pressure. Continued distillation at 0.6 mmHg afforded 12.7 g of 1-chloro-5-(trimethylsilyl)-4-pentyne: bp 40 °C; NMR (CCl_4 60 MHz) δ 0.1 (s, 9 H), 1.6–2.4 (m, 4 H), 3.6 (t, J = 7 Hz, 2 H).

This material (10.4 g, 0.06 mol) was then dissolved in 100 mL of acetone along with 13.5 g (0.09 mol) of NaI. The mixture was heated at reflux for 24 h and cooled and the solvent was removed in vacuo. The residue was then partitioned between pentane and H_2O and the organic phase dried ($MgSO_4$) and evaporated in vacuo. Distillation of the residue at 0.6 mmHg afforded 15 g of 1-iodo-5-(trimethylsilyl)-4-pentyne: bp 60–65 °C; NMR (CCl_4, 60 MHz) δ 0.1 (s, 9 H), 1.6–2.4 (m, 4 H), 3.4 (t, J = 7 Hz, 2 H).

Preparation of 2-Butyl-3-(4-pentynyl)-2-cyclohexenone (7). Magnesium turnings (1.7 g, 0.07 mol) were placed in a 50-mL flask equipped with a stirring bar and reflux condensor. The apparatus was flame dried and purged with argon. Dry THF (10 mL) was added and the magnesium cleaned by the addition of 0.2 mL of dibromoethane. The mixture was then heated to reflux whereupon a solution of 1-iodo-5-(trimethylsilyl)-4-pentyne (12.2 g, 0.047 mol) in 10 mL of THF was added dropwise over 30 min. After an additional 15 min, the reaction mixture was cooled to 0 °C and a solution of 3-ethoxy-2-butyl-2-cyclohexenone[8] (6 g, 0.031 mol) in 10 mL of THF was added. The mixture was then allowed to warm to 25 °C and held at that temperature of 30 min. The reaction mixture was carefully acidified with 10% HCl and then extracted with ether and the extract dried ($MgSO_4$) and evaporated in vacuo. The residue was passed through a short column of SiO_2 and eluted with 20:1 ethyl acetate/hexane. The forerun containing nonpolar material was discarded. The remainder of the eluant was concentrated in vacuo and dissolved in 10 mL of THF. A 1 M solution of tetrabutylammonium fluoride (20 mL) was added, and the dark mixture was stirred for 10 min at 25 °C. The mixture was partitioned between ether and water; the organic phase was dried ($MgSO_4$) and evaporated. Chromatography (SiO_2, ethyl acetate/hexane, 1:20) gave 2.88 g (43%) of **7**: IR (CCl_4) 3320, 2950 (s), 2870, 1680 (s), 1370, 1180 cm^{-1}: NMR ($CDCl_3$ 250 MHz) δ 0.9 (t, J = 7 Hz, 3 H), 1.2–1.4 (m, 4 H), 1.6–1.8 (m, 2 H), 1.8–2.0 (m, 2 H), 2.04–2.4 (m, 11 H); exact mass calcd for $C_{15}H_{22}O$ 218.1683, found 218.1667.

Preparation of Enone 13. Lithium powder containing 1% Na (Alfa; 0.42 g, 0.06 mol) was placed under argon in a 50-mL, flame-dried, argon-blanketed flask equipped with a stirring bar. Dry ether (10 mL) was added, and the mixture was cooled to 0 °C. With stirring, a solution of 1-chloro-5-(trimethylsilyl)-4-pentyne (3.5 g, 0.02 mol) in 10 mL of ether was added dropwise over a 2-h period; the internal temperature of the reaction was kept at 2–4 °C. The reaction mixture was allowed to stand for 30 min and then filtered. Titration of the resultant solution indicated that is was 0.34 M in organometallic compound. Enone 8 (0.88 g, 4.5 mmol) was added to this solution at 0 °C. After 30 min, the reaction mixture was acidified with 10% HCl and extracted into ether. The organic phase was dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography (SiO_2, ethyl acetate/hexane, 1:20) gave 0.45 g (35%) of **13**: IR (CCl_4) 2960, 2870, 1660 (s), 1350 (s), 1240, 840 (s) cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 0.06 (s, 9 H), 0.8 (t, J = 7, 3 H), 1.1–1.3 (m, 4 H), 1.8–2.1 (m, 8 H), 2.2 (m, 2 H), 2.38 (t, J = 7.2 Hz, 2 H), 2.7 (m, 2 H); exact mass calcd for $C_{19}H_{30}O$ 290.2071, found 290.2066.

Preparation of 6-*n*-Butyl-6-formyl-7-acetoxyspiro[4.5]decan-1-ones (5a and 5b). Acetylenic enone **7** (1.2 g, 5.5 mmol) was dissolved in 200 mL of methanol along with 0.8 g NaOAc. The solution was irradiated for 48 h, at which time examination by TLC revealed that the starting enone had been consumed. The reaction mixture was concentrated to 50 mL and $NaBH_4$ (1.0 g, 25 mmol) was added. After 30 min at 25 °C, 20 mL of 1.5 N aqueous sodium hydroxide was added, and most of the methanol was removed in vacuo. The residue was extracted in methylene chloride; the extracts were dried ($MgSO_4$) and filtered. This solution was cooled to −78 °C and ozone was passed through until a blue color persisted. The excess ozone was removed via a stream of argon, and 2 g (7 mmol) of triphenylphosphine was added. The reaction mixture was then allowed to warm to 25 °C. After removal of the solvent, the excess triphenylphosphine and triphenylphosphine oxide were removed by chromatography (SiO_2, ethyl acetate/hexane, 1:10). The remainder of the eluant containing **15a** and **15b** was evaporated and combined with 2 mL of pyridine, 0.5 mL of acetic anhydride and 50 mg of (dimethylamino)pyridine in 3 mL of dichloromethane. After 4 h at 25 °C, the reaction mixture was partitioned between methylene chloride and 10% aqueous HCl, washed with water, and dried ($MgSO_4$) and the solvent removed in vacuo. Flash chromatography (SiO_2, ethyl acetate/hexane, 1:10) gave 0.14 g (9%) of **5b** and 0.28 g (17%) of **5a**.

Spectral data for **5b**: IR (CCl_4) 2950, 2860, 1715 (br, s), 1230 (s), 1020, 740 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 0.9 (t, J = 7 Hz, 3 H), 0.7–0.9 (m, 1 H), 1.1–1.3 (m, 4 H), 1.6–2.2 (m, 11 H), 2.1 (s, 3 H), 2.3–2.42 (m, 2 H), 4.8 (m, 1 H), 10.42 (s, 1 H); exact mass calcd for $C_{17}H_{26}O_4$ 294.1909, found 294.1910.

Spectral data for **5a**: IR (CCl_4) 2950, 2860, 1715 (br, s), 1230, 1020 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 0.9 (t, J = 7 Hz, 3 H), 1.05–1.24 (m, 4 H), 1.3–2.2 (m, 11 H), 2.16 (s, 3 H), 2.24–2.44 (m, 3 H), 5.58 (m, 1 H), 9.9 (s, 1 H); exact mass calcd for $C_{17}H_{26}O_4$ 294.1909, found 294.1915.

Attempted Decarbonylation of 5b. Aldehyde **5b** (40 mg, 1.4×10^{-4} mol) was dissolved in 0.5 mL of benzonitrile. Wilkinson's catalyst (0.5 equiv, 63 mg) was added, and the mixture was heated to 190 °C under argon. After 4 h, the solvent was removed by distillation at aspirator pressure and the residue purified by flash chromatography (SiO_2, ethyl acetate/hexane, 1:10) to yield 17.3 mg (43%) of **5b**.

Preparation of 6-Butyl-6-carboxyspiro[4.5]decane-1,7-dione (11). Enone **7** (0.95 g, 4.36 mmol) was dissolved in 200 mL of acetonitrile that was deoxygenated with a stream of argon. Irradiation for 72 h at 25 °C resulted in disappearance of **7** as judged by TLC. The reaction mixture was concentrated to a volume of 10 mL and added to a rapidly stirred mixture of 4.7 g (220 mmol, 5 equiv) of $NaIO_4$, 87 mg of RuO_2 (3 mol %), 15 mL of H_2O, and 10 mL of CCl_4. After 30 min at room temperature, the reaction mixture was diluted with CH_2Cl_2, and the organic phase was separated, dried ($MgSO_4$), filtered through Celite, and then evaporated. Flash chromatography (ethyl acetate/hexane/acetic acid, 10:50:1) afforded **11** as a crystalline solid after recrystallization from ether (mp 85–90 °C, with decomposition). The yield of **11** was 0.26 g (22.5% overall from **7**): IR (CCl_4) 3600–3200 (br, m), 3020, 2960, 1770, 1740, 1710 (s), 1420, 1200 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 0.88 (t, J = 7 Hz, 3 H), 0.8–0.9 (m, 1 H), 1.15–1.36 (m, 2 H), 1.4–2.1 (m, 10 H), 2.18–2.5 (m, 5 H) (carboxylic acid proton not observed); exact mass calcd for $C_{15}H_{22}O_4$ 266.1519, found 266.1515.

Preparation of 6-*n*-Butylspiro[4.5]decane-1,7-diones (12a and 12b). Acid **11** (90 mg, 0.38 mmol) was added to 5 mL of toluene and heated at reflux for 5 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, ethyl acetate/hexane, 1:10) to yield 75 mg (87%) of a mixture of **12b** and **12a** (10:1).

Spectral data for **12b**: IR (CCl_4) 2960, 2875, 1735 (s), 1715 (s), 1450, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.8 (t, J = 7 Hz, 3 H), 0.9–1.2 (m, 5 H), 1.3 (m, 1 H), 1.4–2.1 (m, 12 H), 2.2 (td, J = 6.2, 9, 14 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.32 MHz)[24] 13.88 (q), 18.53 (t), 22.27 (t), 22.65 (t), 25.66(t), 30.61 (t), 30.86 (t), 35.37 (t), 37.70 (t), 39.25 (t), 54.87 (d), 62.49 (s), 210.50 (s), 218.90 (s); exact mass calcd for $C_{14}H_{22}O_2$ 222.1619, found 222.1604.

Spectral data for **12a**: IR (CCl_4) 2960, 2860, 1745, 1720 (s), 1450, 1180, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.7 (m, 1 H), 0.8 (t, J = 7 Hz, 3 H), 1.1 (m, 1 H), 1.2–1.4 (m, 3 H), 1.6–2.2 (m, 10 H), 2.3–2.5 (m, 3 H), 2.7 (d, J = 10 Hz, 1 H); ^{13}C NMR ($CDCl_3$,

(24) Multiplicities were determined by the spin-echo (GASPE) technique, see: LeCocq, C.; Lalemand, J., *J. Chem. Soc., Chem. Commun.* **1981**, 150.

50.32 MHz)[24] 13.68 (q), 18.78 (t), 22.61 (t), 23.91 (t), 25.37 (t), 28.33 (t), 30.66 (t), 32.02 (t), 37.74 (t), 41.53 (t), 54.53 (d), 57.93 (s), 211.23 (s), 219.72 (s); exact mass calcd for $C_{14}H_{22}O_2$ 222.1624, found 222.1604.

Equilibration of 12a and 12b. A mixture of spiro diones **12b** and **12a** (10:1, 131 mg) was dissolved in 5 mL of THF and 10 drops of 10% HCl was added. After 48 h at 25 °C, the mixture was diluted with ether and extracted with saturated $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated; purification via elution through a short column of silica gel with 5% ethyl acetate in hexane afforded 110 mg (77%) of **12b** and **12a** (2.3:1 as determined by NMR integration).

Preparation of 12a from 6-*n*-Butyl-7-acetoxyspiro[4.5]-decan-1-one (4). Keto acetate **4**[21] (5.3 mg) was dissolved in 1 mL of methanol containing 10 mg of potassium carbonate. After stirring for 5 h at 25 °C, the saponification was judged to be complete by TLC. The solvent was removed under reduced pressure and the residue purified by passage through a short column of silica gel eluting with 10% ethyl acetate in hexane to yield the corresponding keto alcohol: IR (CCl_4) 3650-3200, 2940 (s), 2860, 1725 (s), 1450, 1155, 900 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 0.8 (t, J = 7 Hz, 3 H), 1.2-1.5 (m, 11 H), 1.54-2.2 (m, 8 H), 2.3 (m, 1 H), 3.3 (m, 1 H).

The above keto alcohol was treated with 7.5 mg of pyridinium chlorochromate and 7.5 mg of anhydrous sodium acetate in 1 mL of dry methylene chloride. After 1 h the reaction mixture was diluted with ether, filtered, and washed with 10% HCl. The organic layer was dried ($MgSO_4$) and evaporated; filtration through a plug of silica gel afforded **12a** identical in all respects (IR, NMR, and TLC) with that prepared from **11**.

Reduction/Oxidation of 12a. Dione **12a** (44 mg, 0.2 mmol) was added to a suspension of 20 mg (0.5 mmol) of $LiAlH_4$ in 2 mL of ether. After 1 h at 25 °C, the excess hydride was destroyed by the addition of $Na_2SO_4 \cdot 10H_2O$. The resulting mixture of diols (four compounds by TLC) was filtered, evaporated, and combined with 60 mg of pyridinium chlorochromate and 60 mg of anhydrous sodium acetate in 2 mL of dry methylene chloride. After 1 h at 25 °C, workup and purification as in the previous experiment gave 16 mg (36%) of a single product whose 250-MHz NMR was identical with authentic **12a**.

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Registry No. **2**, 40709-29-3; **4**, 80090-50-2; **4** (keto alcohol), 88643-14-5; **5a**, 88564-18-5; **5b**, 88643-12-3; **7**, 88564-19-6; **8**, 56459-18-8; **11**, 88564-20-9; **12a**, 88564-21-0; **12b**, 88564-22-1; **13**, 88564-23-2; **15a**, 88564-24-3; **15b**, 88643-13-4; $Cl(CH_2)_3C{\equiv}CH$, 14267-92-6; $Cl(CH_2)_3C{\equiv}CSiMe_3$, 77113-48-5; $I(CH_2)_3C{\equiv}CSiMe_3$, 35761-91-2.

Acid-Stable, Solvolytically Deblocked Amino-Protecting-Groups Applications of the 1,3-Dibromo-2-methyl-2-propyloxycarbonyl (DB-*t*-Boc) Group

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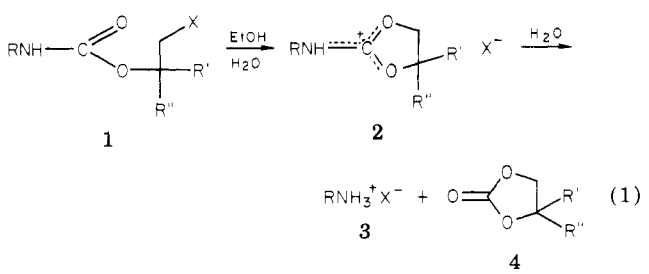
The effects of structure on the ease of solvolytic deblocking of an array of α-halo-*tert*-alkyl carbamates **1** have been studied. The corresponding thiolcarbamates were shown to undergo isomerization and other reactions due to participation of the sulfur atom. 1,1,1,3,3,3-Hexachloro-2-(bromomethyl)-2-propyl carbamates were relatively unreactive toward solvolytic deblocking. On the other hand the 1,3-dibromo-2-methyl-2-propyloxycarbonyl group (DB-*t*-Boc) was easily deblocked by warming in ethanol or methanol and therefore recommended as an acid-stable, solvolytically deblocked amino-protecting group. The key chloroformate **22** was readily synthesized from methallyl chloride by conversion to methallyl bromide followed by reaction with hypobromous acid to give the bromohydrin and treatment of the latter with phosgene. Practical use of the DB-*t*-Boc group was demonstrated by synthesis of the dipeptide phenylalanylleucine.

Only a limited number of amino-protecting groups are known that are deblocked simply by dissolving or warming in an appropriate neutral solvent.[1,2] The first such group reported was the α-bromo-*tert*-butyloxycarbonyl (α-Br-*t*-Boc) group, as in urethane **1** (R = C_6H_5, R′ = R″ = Me, X = Br) which undergoes self cleavage upon warming in methanol or ethanol (eq 1). Application of this protective group in peptide synthesis has been reported by Ohnishi, Sugano, and Miyoshi.[3] For such solvent-sensitive protective groups to be maximally useful, the solvent sensitivity should be narrowly limited so that protection and coupling reactions can be readily carried out in appropriate solvents without fear of premature deblocking. In the case of the α-Br-*t*-Boc system self cleavage does not occur in nonpolar solvents such as chloroform, methylene dichloride, or benzene. In dry dimethyl sulfoxide (Me_2SO) reaction is relatively slow, although self cleavage takes place readily in wet Me_2SO or wet acetonitrile. A deficiency of the α-Br-*t*-Boc group is its moderate sensitivity toward acidic reagents. If a group of this type were far more stable toward acidic conditions, it would lend itself to selective utility[4] in the presence of *t*-Boc and/or other



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