2.28 (ddd, 1 H, *J* = 10.4, 6.0, 4.5 Hz), 2.21 (s, 3 H), 1.84–1.62 (m, 3 H), 1.45 (ddd, 1 H, *J* = 12.1, 6.0, 2.6 Hz), 0.99–0.98 (m, 1 H), 0.97 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz), 0.90 (d, 3 H, *J* = 6.9 Hz), 0.89 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 74.5, 72.6, 40.0, 33.2, 29.4, 27.4, 24.9, 20.4, 19.5, 18.6, 15.5, −1.8; MS *m/z* (rel int) 198 (100), 124 (18), 82 (39), 74 (6), 73 (74), 59 (10), 45 (11), 43 (8), 42 (12), 41 (9); HRMS (CI, NH_3) calcd for $C_{14}H_{32}NSi$ $(M + H)^+$ 242.2304, found 242.2306. Due to badly overlapping signals, NOE studies were not possible. The stereochemical assignment was based on previous work which detailed the highly stereoselective nature of 2-azaallyl anion cycloadditions with vinyltrimethylsilane.[1b]

1-Methyl-2β,5β-bis(1-methylethyl)-3α-(phenylthio)pyrrolidine (9) and 1-Methyl-2β,5β-bis(1-methylethyl)-3β-(phenylthio)pyrrolidine (10). Formed from **3a** and phenyl vinyl sulfide as a 2.7:1 mixture (300-MHz ^{1}H NMR analysis of crude reaction mixture). Chromatography (0–5% EtOAc/hexane gradient) afforded 100 mg (78%) of the title compounds as a clear, pale yellow oil. Radial chromatography (0–100% EtOAc/hexane gradient) allowed the isolation of pure fractions of each isomer for characterization. Data for **9**: R_f = 0.48 (10% EtOAc/hexane); IR (neat) 3074 (w), 2956 (s), 2869 (s), 2781 (m), 1585 (m), 1480 (s), 1466 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.35–7.15 (m, 5 H), 3.40 (ddd, 1 H, *J* = 6.9, 4.0, 1.3 Hz), 2.62 (ddd, 1 H, *J* = 9.4, 4.1, 1.1 Hz), 2.28–2.25 (m, 4 H), 1.91–1.74 (m, 3 H), 1.62 (ddd, 1 H, *J* = 12.9, 5.5, 1.3 Hz), 0.95 (d, 3 H, *J* = 6.9 Hz), 0.88 (d, 3 H, *J* = 6.9 Hz), 0.84 (d, 3 H, *J* = 6.9 Hz), 0.81 (d, 3 H, *J* = 6.9 Hz); DNOE (C_6D_6), irradiation at 3.43 ppm (H-3β) failed to enhance the signals at 2.70 ppm (H-5α) and 2.38 ppm (H-2α); ^{13}C NMR (75 MHz) δ 137.2, 130.6, 128.9, 126.3, 78.2, 69.8, 45.4, 40.6, 32.9, 31.2, 28.3, 20.2, 19.5, 17.5, 15.3; MS (CI, NH_3) *m/z* (rel int) 278 (75, M + 1), 234 (4), 180 (3), 170 (4), 168 (19), 166 (14), 137 (8), 136 (100), 124 (4), 94 (4); HRMS (CI, NH_3) calcd for $C_{17}H_{28}NS$ $(M + H)^+$ 278.1942, found 278.1929. Data for **10**: R_f = 0.36 (10% EtOAc/hexane); IR (neat) 2959 (s), 1583 (m), 1478 (s), 1382 (m), 737 (s), 689 (m) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.34–7.13 (m, 5 H), 3.70 (ddd, 1 H, *J* = 11.1, 6.8, 3.3 Hz), 2.76 (dd, 1 H, *J* = 8.5, 3.3 Hz), 2.37 (s, 3 H), 2.38–2.26 (m, 1 H), 2.07–1.93 (m, 2 H), 1.85 (d hept, 1 H, *J* = 1.6, 6.9 Hz), 1.71–1.60 (m, 1 H), 1.00 (d, 6 H, *J* = 7.1 Hz), 0.89 (d, 3 H, *J* = 6.9 Hz), 0.88 (d, 3 H, *J* = 6.9 Hz); DNOE, irradiation at 3.7 ppm (H-3α) produced a 2.6% enhancement of the signal at 2.3 ppm (H-5α) and a 6.7% enhancement of the signal at 2.75 ppm (H-2α). Irradiation of the signal at 2.75 ppm (H-2α) produced a 6.2% enhancement of the signal at 2.3 ppm (H-5α) and an 8.1% enhancement of the signal at 3.7 ppm (H-3α); ^{13}C NMR (90 MHz) δ 137.9, 129.1, 128.8, 125.6, 73.2, 71.6, 47.9, 44.0, 34.4, 31.2, 30.0, 21.7, 20.7, 18.5, 16.6; MS (CI, NH_3) *m/z* (rel int) 278 (100, M + 1), 274 (14), 234 (64), 168 (25), 166 (13), 165 (15), 150 (29), 142 (26), 124 (23), 82 (29); HRMS (CI, NH_3) calcd for $C_{17}H_{28}NS$ $(M + H)^+$ 278.1942, found 278.1923.

1-Methyl-2β,5β-bis(1-methylethyl)-3α,4α-diphenylpyrrolidine (11) and 1-Methyl-2β,5β-bis(1-methylethyl)-3β,4α-diphenylpyrrolidine (6). Formed from **3a** and (*Z*)-stilbene as a 1.6:1 mixture (300-MHz ^{1}H NMR analysis of crude reaction mixture). Chromatography (0–5% EtOAc/hexane gradient) afforded 80 mg (54%) of a mixture of the title compounds as a clear, colorless oil. Radial chromatography (0–20% EtOAc/hexane gradient) allowed the isolation of pure fractions for characterization. Data for **11**: R_f = 0.46 (10% EtOAc/hexane); IR (neat) 3028 (s), 2953 (br), 1602 (s), 1454 (s), 1170 (m), 1034 (m), 699 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.02–6.97 (m, 6 H), 6.75–6.72 (m, 4 H), 3.25 (dd, 2 H, *J* = 4.8, 1.7 Hz), 2.97 (dd, 2 H, *J* = 4.8, 4.1 Hz), 2.60 (s, 3 H), 1.85 (d hept, *J* = 4.1, 6.9 Hz), 0.99 (d, 6 H, *J* = 6.9 Hz), 0.74 (d, 6 H, *J* = 6.9 Hz). [Due to the symmetry of this molecule, the relative stereochemistry between the two phenyl groups could not be rigorously assigned. However, only the 2β,3β,4β,5β and 2β,3α,4α,5β isomers (assuming the "W"-form of the 2-azaallyl anion) would show only two methyl doublets in the ^{1}H NMR spectrum and 10 lines in the ^{13}C NMR spectrum. Irradiation at 3.25 ppm (H-3β) produced a 4.6% enhancement of the signal at 1.85 ppm (H-2′) yet failed to enhance the signal at 2.97 ppm (H-2α)]; ^{13}C NMR (75 MHz) δ 142.1, 129.6, 127.5, 125.7, 75.4, 52.3, 41.3, 31.3, 19.3, 18.2; MS *m/z* (rel int) 279 (22, M − C_3H_7), 278 (100), 145 (24), 117 (14), 91 (27), 84 (11), 49 (19), 43 (10), 42 (55), 41 (9); HRMS (CI, NH_3) calcd for $C_{23}H_{32}N$ $(M + H)^+$ 322.2535, found 322.2528. See above for spectral data on **6**.

1-Methyl-5β-(1-methylethyl)-2,2-dimethyl-3β,4α-diphenylpyrrolidine (12) and 1-Methyl-5β-(1-methylethyl)-2,2-dimethyl-3α,4β-diphenylpyrrolidine (13). Formed from **2b** (0.50 mmol) and *trans*-stilbene (0.99 mmol) as a 1.4:1 mixture (360-MHz ^{1}H NMR analysis of crude reaction mixture). Chromatography (5–100% EtOAc/hexane gradient) afforded 100 mg (71%) of a mixture of the title compounds as a pale yellow oil. The mixture was rechromatographed (same solvent system) in order to isolate pure fractions of each isomer for characterization. Data for **12**: R_f = 0.13 (10% EtOAc/hexane); IR (neat) 3061 (w), 3027 (m), 2962 (s), 2779 (m), 1601 (m), 1452 (s) cm^{-1}; ^{1}H NMR (360 MHz) δ 7.23– 7.06 (m, 10 H), 3.31 (dd, 1 H, *J* = 9.6, 9.6 Hz), 2.91 (dd, 1 H, *J* = 9.6, 3.2 Hz), 2.89 (d, 1 H, *J* = 9.6 Hz), 2.31 (s, 3 H), 1.97 (d hept, 1 H, *J* = 3.2, 7.0 Hz), 1.19 (s, 3 H), 1.02 (d, 3 H, *J* = 7.0 Hz), 0.71 (s, 3 H), 0.62 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR (90 MHz) δ 143.9, 142.0, 129.2, 128.2, 127.7, 126.1, 125.8, 73.7, 64.8, 63.0, 51.4, 34.1, 29.7, 26.6, 23.4, 19.9, 16.9; MS *m/z* (rel int) 292 (4, M − CH_3), 265 (22), 264 (100, M-C_3H_7), 132 (9), 131 (29), 117 (8), 112 (7), 91 (18), 56 (13), 42 (10); HRMS (CI, NH_3) calcd for $C_{22}H_{30}N$ $(M + H)^+$ 308.2378, found 308.2368. Stereochemical assignment inferred from the confirmed stereochemistry of **13**, since only two diastereomers are possible (assuming the stereochemical integrity of (*E*)-stilbene). Data for **13**: pale yellow solid, mp 86–88 °C; R_f = 0.23 (10% EtOAc/hexane); IR (neat) 3027 (m), 2962 (s), 1601 (m), 1451 (s), 1363 (m), 1253 (m), 699 (s) cm^{-1}; ^{1}H NMR (300 MHz) δ 7.23–7.05 (m, 10 H), 4.07 (dd, 1 H, *J* = 13.3, 9.8 Hz), 3.46 (d, 1 H, *J* = 13.3 Hz), 2.96 (dd, 1 H, *J* = 9.8, 3.4 Hz), 2.39 (s, 3 H), 1.46 (d hept, 1 H, *J* = 3.4, 6.9 Hz), 1.18 (s, 3 H), 0.76 (d, 3 H, *J* = 6.9 Hz), 0.73 (s, 3 H), 0.72 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR (90 MHz) δ 139.9, 139.3, 129.8, 129.1, 127.8, 127.7, 126.2, 125.7, 71.5, 63.1, 56.8, 48.2, 36.5, 30.5, 27.1, 22.6, 18.1, 16.3; MS *m/z* (rel int) 292 (2, M − CH_3), 265 (21), 264 (100, M − C_3H_7), 132 (11), 131 (32), 117 (10), 115 (5), 91 (18), 56 (8), 42 (10); HRMS (CI, NH_3) calcd for $C_{22}H_{30}N$ $(M + H)^+$ 308.2378, found 308.2364; DNOE, irradiation at 4.07 ppm (H-4α) produced an 8.5% enhancement of the signal at 2.96 ppm (H-5α), yet failed to produce an enhancement of the signal at 3.46 ppm (H-3β).

Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the Americal Chemical Society, for support of this work.

Supplementary Material Available: ^{1}H NMR and ^{13}C NMR spectra of the compounds which had no elemental analysis: **3b**, **3c**, **3d**, **7–13**, and 1-methyl-2,5-bis(1-methylethyl)-3,4-diphenylpyrrole, the oxidation product of **7** (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

A Nonphotochemical Approach for Synthesizing Functionalized Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes Using Samarium(II) Iodide

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Received March 23, 1992

For the last two decades, substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (PCUD)[1] have been explored extensively as intermediates in the synthesis of polycyclic

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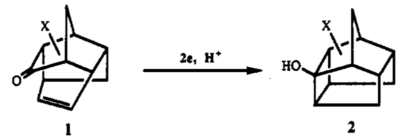
0022-3263/92/1957-6357$03.00/0

cage molecules[2] and of naturally occuring cis–syn–cis fused linear triquinanes.[3] Cookson's photochemical methodology[4] is being used extensively for the synthesis of functionalized PCUDs by employing the Diels–Alder endo-adduct of substituted cyclopentadiene and benzoquinones. We report a nonphotochemical synthesis of functionalized PCUDs by using an efficient one-electron transfer system (SmI_2) via an intramolecular ketone–olefin reductive coupling reaction.

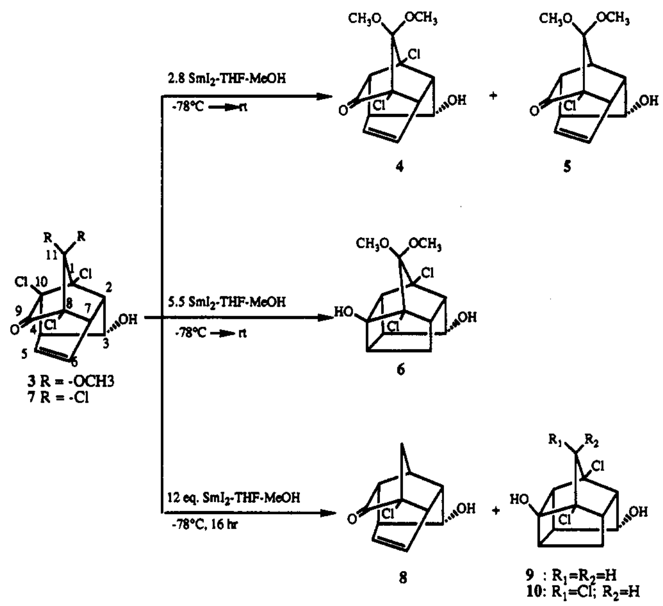
In our approach, a suitably functionalized tetracyclo[6.2.1.$0^{2,7}$.$0^{4,10}$]undec-5-en-9-one (1) is the pivotal precursor of functionalized PCUDs. Since the topology of 1 reflects the close proximity of two π-systems (ketone and olefin), it is envisaged that intramolecular ketyl–olefin reductive coupling should lead to functionalized pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane 2 (eq 1). Many chemical methodologies are reported in the literature to generate a ketyl moiety which is trapped subsequently by an olefin.[5] Samarium(II) iodide[6] is one of the reagents of choice to generate a ketyl moiety, and it has been used extensively for inter-[7] as well as intramolecular[8] synthetic transformations. In addition, samarium(II) iodide provides a mild and convenient method for reductive dehalogenation[9] under proper conditions.



Results and Discussion

Treatment of readily available 1,8,10-trichloro-11,11-dimethoxy-3-*exo*-hydroxytetracyclo[6.2.1.$0^{2,7}$.$0^{4,10}$]undec-5-en-9-one[10] (3) with 2.8 equiv of SmI_2 at −78 °C for 1 h furnished two products 4 (68%) and 5 (1%) (Scheme I). The presence of two olefinic proton signals (δ 6.32 and 5.91) in the ^1H NMR spectrum in conjunction with an upfield carbonyl carbon (δ 197.49), olefinic carbons (δ 137.81 and 127.52), and two low-intensity tertiary chlorinated carbon resonances[11] (δ 83.56 and 78.30) in the ^{13}C NMR spectrum of the major compound 4 suggested that it has the same molecular architecture as that of 3. The presence of two chlorines was confirmed by elemental analysis. Of the three possible dichlorinated structures, the major compound was assigned structure 4 on the basis of nearest-neighbor proton connectivity as revealed by its COSY spectrum.[12] The minor compound 5 was found to be a monochlorinated compound by elemental microanalysis. Its structural similarity with 3 was confirmed by the presence of a carbonyl carbon (δ 202.27), two olefinic carbons (δ 136.75 and 129.67), and a low-intensity chlorinated carbon signal[11] (δ 84.95) in its ^{13}C NMR spectrum. The structure of the minor compound 5 and position of chlorine in 5 was determined unequivocally by single-crystal X-ray diffraction analysis.[13] When 3 was treated

Scheme I



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(1) For an excellent review on PCUD see: Marchand, A. P. In *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI: Greenwich, CT, 1989; Vol. 1, pp 357–399.

(2) Pentaprismane: Eaton, P. E.; Or, Y. S.; Branca, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 2134. Eaton, P. E.; Or, Y. S.; Branca, S. J.; Ravi Shankar, B. K. *Tetrahedron* **1986**, *42*, 1621. Homopentaprismane: Eaton, P. E.; Cassar, L.; Hudson, R. A.; Hwang, D. R. *J. Org. Chem.* **1976**, *41*, 1445. Trishomocubane: Underwood, G. R.; Ramamoorthy, B. *Tetrahedron Lett.* **1970**, 4125. Eaton, P. E.; Hudson, R. A. Giordano, C. *J. Chem. Soc., Chem. Commun.* **1974**, 978. Mehta, G.; Chaudhari, B. *Ind. J. Chem.* **1979**, *17B*, 421 and references cited therein.

(3) Hirsutene: Mehta, G.; Reddy, A. V. *J. Chem. Soc., Chem. Commun.* **1981**, 756. Coriolin: Mehta, G.; Reddy, A. V.; Murthy, A. N.; Reddy, D. S. *J. Chem. Soc., Chem. Commun.* **1982**, 540. $\Delta^{9,12}$-Capnellane: Mehta, G.; Reddy, D. S.; Murthy, A. N. *J. Chem. Soc., Chem. Commun.* **1983**, 824.

(4) Cookson, R. C.; Grundwell, E.; Hudec, J. *Chem. Ind.* (*London*) **1958**, 1003. Cookson, R. C.; Grundwell, E.; Hill, R. R.; Hudec, J. *J. Chem. Soc.* **1964**, 3062.

(5) Pradhan, S. K.; Kadam, S. R.; Kolhe, J. N.; Radhakrishnan, T. V.; Sohani, S. V.; Thaker, V. B. *J. Org. Chem.* **1981**, *46*, 2622. Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821. Ikeda, T.; Yue, S.; Hutchinson, C. R. *J. Org. Chem.* **1985**, *50*, 5193.

(6) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

(7) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669. Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2837. Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236. Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 1195. Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171. Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439. Otsubo, K.; Inanga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763.

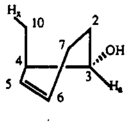
(8) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064. Molander, G. A.; Kenny, C. *J. Org. Chem.* **1988**, *53*, 2132. Shim, S. C.; Hwang, J.-T. *Tetrahedron Lett.* **1990**, *31*, 4765. Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett.* **1990**, 773. Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *30*, 1063. Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463. Enholm, E. J.; Satici, H.; Trivellas, A. *J. Org. Chem.* **1989**, *54*, 5841.

(9) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135. Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485.

(10) Suri, S. C. *Tetrahedron Lett.* **1990**, *31*, 3695.

(11) The tertiary chlorinated carbons were assigned by ^1H–^{13}C correlation experiment (2D HETCOR).

(12) Three nearest-neighbor proton connectivity structures (i–iii) corresponding to three possible dichlorinated products can be derived from their COSY spectra. At first instance proton connectivity structures i and ii appear to be the same but the distinction can be made easily by determining proton connectivity with respect to the proton (H_a) attached to the hydroxycarbon. The COSY spectrum of the major compound reflects proton connectivity H_x–C_{10}–C_4–C_3–H_a and H_x–C_{10}–C_4–C_5–C_6–C_7–C_2–C_3–H_a which corresponds to structure 4.



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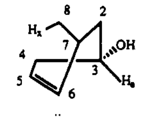
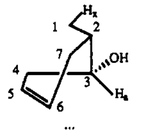


ii



iii

with 5.5 equiv of SmI_2, a single product **6** (70%) was isolated. The assignment of its structure **6** as an olefin–ketone coupling product rested upon the presence of a methylene carbon and transparent olefinic and carbonyl regions in its ^{13}C NMR spectrum. The spectral and analytical data were fully compatible with structure **6**. Further structural confirmation was obtained via single-crystal X-ray diffraction analysis.[13]

To establish the generality of the samarium(II)-promoted nonphotochemical synthesis of PCUD carbon framework, 1,8,10,11,11-pentachloro-3-*exo*-hydroxytetracyclo[6.2.1.0^{2,7}0.^{4,10}]undec-5-en-9-one (**7**) was reacted with 12 equiv of SmI_2 at –78 °C to furnish a mixture of products. After extensive column chromatography, only three compounds (**8–10**) were isolated in pure form. Other minor products were present in the reaction mixture but could not be isolated. The spectral data indicate that the minor compound **8** (3%) has the same structural features as that of **7**. The structure of **8** was further confirmed by the presence of a bridge methylene carbon signal (δ 40.98) and a low-intensity tertiary chlorocarbon signal (δ 73.55) in its ^{13}C NMR spectrum. This compound was found to be monochlorinated on the basis of its analytical data, and it was assigned structure **8** by analogy to compound **5**. The other two compounds were assigned the pentacycloundecane carbon skeleton due to the absence of carbonyl and olefinic signals in their ^{13}C NMR spectra. The carbon NMR spectrum of the minor PCUD **9** (10%) displays two methylene carbons at δ 47.70 and 22.79 other than two low-intensity tertiary chlorocarbons at δ 74.66 and 70.76. The microanalytical and spectral data[11] are fully compatible with **9**. The major functionalized PCUD **10** (30%), apart from having two bridgehead chlorines (δ 77.20 and 75.05), also reflected a secondary chlorocarbon as evident by the presence of a sharp singlet at δ 4.41 in the proton NMR spectrum. The syn-configuration (chlorine syn to tertiary hydroxy group) at the bridge carbon was suggested because of the absence of long-range coupling of the bridge proton[14] of **10**.

The formation of **6**, **9**, and **10** can be described as ring closures of **3** and **7** that occur via the 4-*exo-trig* or the 5-*endo-trig* pathway. Thus, the tetracyclo[6.2.1.0^{2,7}.0^{4,10}]undec-5-en-9-one system (**3** and **7**) contravenes a widely accepted generalization[15,16] of ring closure. Further detailed theoretical investigation is underway to explain the unusual ring closure and shall be reported in due course.

In summary, this paper describes the first examples wherein functionalized pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes have been synthesized via a ketyl–olefin coupling reaction. These reactions introduce substituents in otherwise inaccessible positions on pentacycloundecanes, e.g., the OH group at C(2) and two chlorine atoms at C(3) and C(5) in **6**.

Experimental Section

Melting points were measured in capillary tubes and are uncorrected. ^1H NMR spectra were recorded at 300 MHz, and ^{13}C NMR were recorded at 75.5 MHz. THF was distilled from sodium/benzophenone prior to use.

General Procedure. 1,8-Dichloro-11,11-dimethoxy-3-*exo*-hydroxytetracyclo[6.2.1.0^{2,7}.0^{4,10}]undec-5-en-9-one (4) and 8-Chloro-11,11-dimethoxy-3-*exo*-hydroxytetracyclo[6.2.1.0^{2,7}.0^{4,10}]undec-5-en-9-one (5). SmI_2 was prepared according to Molander's procedure.[9] A solution of **3** (0.34 g, 1 mmol) in a THF–methanol (3 mL, 2:1) mixture was added to a solution of SmI_2 (2.8 equiv, 6 mL) at –78 °C. The reaction mixture was allowed to warm to rt and stirred overnight (16 h). The reaction mixture was worked up by pouring into saturated aqueous K_2CO_3 (25 mL) solution and extracted with ethyl acetate (50 mL). The organic layer was washed with water and brine and dried ($MgSO_4$). The residue obtained after removal of solvent under reduced pressure was applied to a silica gel column. Elution with 10% ethyl acetate–hexane furnished **4** (218 mg, 68%): mp 148–49 °C; IR (KBr) 3526, 2951, 1764, 1215, 1087, 933, 787 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.87 (1 H, ddd, J = 8.8, 4.5, 2.4 Hz), 2.95 (1 H, d, J = 9.3 Hz), 3.30–3.22 (1 H, m), 3.32 (1 H, dd, J = 5.7, 1.4 Hz), 3.37 (1 H, dd, J = 8.1, 2.4 Hz), 3.55 (3 H, s), 3.70 (3 H, s), 3.98 (1 H, dd, J = 9.3, 1.8 Hz), 5.91 (1 H, ddd, J = 8.3, 5.7, 1.1 Hz), 6.32 (1 H, ddd, J = 8.3, 7.1, 1.44 Hz); ^{13}C NMR ($CDCl_3$) δ 197.49, 137.81, 127.52, 99.15, 85.17, 83.56, 78.30, 62.58, 52.09, 49.57, 48.66, 46.75. Anal. Calcd for $C_{13}H_{14}O_4Cl_2$: C, 51.31; H, 4.64; Cl, 23.00. Found: C, 51.24; H, 4.61; Cl, 22.77.

Further elution with 15% ethyl acetate–hexane furnished **5** (28 mg, 1%): mp 153 °C; IR (KBr) 3506, 2976, 1778, 1460, 1294, 1165, 1089, 976 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (1 H, s), 2.36–2.52 (1 H, m), 2.78 (1 H, dt, J = 7.4, 2.1 Hz), 2.94–3.18 (3 H, m), 3.2 (3 H, s), 3.34 (3 H, s), 3.64 (1 H, d, J = 2.1 Hz), 5.83 (1 H, dd, J = 7.7, 6.1 Hz), 6.06 (1 H, dt, J = 7.7, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 202.27, 136.75, 129.67, 103.09, 84.95, 81.41, 51.69, 51.42, 50.12, 48.48, 48.41, 47.78, 42.44. Anal. Calcd for $C_{13}H_{15}O_4Cl$: C, 57.76; H, 5.59; Cl, 12.94. Found: C, 57.65; H, 5.60; Cl, 12.85.

3,5-Dichloro-4,4-dimethoxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-2,8-*exo*-diol (6). The reaction was performed according to the preceding procedure using 1 mmol of **3** and 5.5 equiv of SmI_2. After workup, the product was purified by chromatography on a silica gel column. Elution with 30% ethyl acetate–hexane furnished **6** (215 mg, 70%): mp 151 °C; IR (KBr) 3423, 2964, 1290, 1244, 1091, 974, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.28 (1 H, d, J = 8.4 Hz), 3.67 (3 H, d, J = 2 Hz), 3.65 (3 H, d, J = 2.0 Hz), 3.13 (1 H, dd, J = 6.15, 1.6 Hz), 2.9 (1 H, bt, J = 7.7 Hz), 2.84 (1 H, s), 2.82 (1 H, d, J = 6 Hz), 2.7–2.55 (1 H, m), 2.19 (1 H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 103.67, 83.97, 78.24, 76.57, 74.66, 57.25, 52.48, 51.57 (2 C), 46.72, 41.92, 39.02, 23.31. Anal. Calcd for $C_{13}H_{16}O_4Cl_2$: C, 50.97; H, 5.26; Cl, 22.85. Found: C, 50.84; H, 5.23; Cl, 22.96.

1,8,10,11,11-Pentachloro-3-*exo*-hydroxytetracyclo[6.2.1.0^{2,7}.0^{4,10}]undec-5-en-9-one (7). A solution of 1,8,9,10,11,11-hexachloro-3-*exo*,6-*exo*-dihydroxytricyclo[6.2.1.0^{2,7}]undeca-4,9-diene[17] (5.0 g, 12.98 mmol) in *tert*-butyl alcohol (25 mL) was stirred with *t*-BuOK (26 mL of 1 M solution of *t*-BuOK in *t*-BuOH) at rt overnight (16 h). The reaction mixture was poured on crushed ice and neutralized with 10% aqueous HCl. The solution was extracted with ethyl acetate (100 mL × 2). The organic layer was washed with water and brine and dried ($MgSO_4$). Removal of solvent under reduced pressure

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(13) Crystal data for **5** ($C_{13}H_{14}O_4Cl$): colorless, prismatic crystal (0.18 × 0.43 × 0.50) triclinic, space group $P\bar{1}$ with a = 8.071 (2) Å, b = 11.251 (2) Å, c = 6.911 Å, α = 84.56 (1)°, β = 76.84 (1)°, γ = 79.73°, V = 600.3 (4) Å^3, Z = 2, D_{calc} = 1.49 g cm^{-3}. Crystal data for **7**: ($C_{13}H_{16}O_4Cl_2$): colorless, prismatic crystal (0.25 × 0.35 × 0.50), monoclinic, space group $P2_1/c$, with a = 12.605 (1) Å, b = 9.538 (2) Å, c = 11.394 (1) Å, β = 104.32 (1)°, Z = 4, D_{calc} = 1.54 g cm^{-3}. 4147 unique data for **5** and 4262 unique data for **7** were measured on an Enraf-Nonius CAD4 diffractometer using graphite-monochromated Mo K_α radiation (λ = 0.710 73 Å). The structures were solved by direct methods (SHELXS-86) [Sheldrick, G. M. *SHELXS-86, Program for crystal structure solution*; University of Gottingen, 1986] and refined by full-matrix least-squars (MolEN) to final residuals of R = 0.059, Rw = 0.072, 3384 reflections with $|F_o| > 3\sigma|F_o|$ for **5** and R = 0.047, Rw = 0.059, 3249 reflections with $|F_o| > 3\sigma|F_o|$ for **7**. Hydrogen atoms for each compound were calculated (HYDRO) [Frenz, B. A. The Enraf-Nonius CAD 4 SDP—A Real-time System for Concurrent X-Ray Data Collection and Crystal structure Determination. In *Computing in Crystallography*; Schenk, H., Olthof-Hazelkamp, R., Konigsveld, H., Bassi, G. C., Eds; Delft University Press. Delft, Holland, 1978, pp 64–71] and refined with fixed temperature factors riding on their respective atoms. All other atoms were refined anisotropically. A final difference Fourier for each structure showed no residual electron density greater than 0.7 e Å^{-3}. Additional details of the crystallographic structural results are available as supplementary material.

(14) Williamson, K. L.; Hsu, Y.-F. L.; Lacko, R.; Youn, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 6129. Subramanian, P. M.; Emerson, M. T.; LeBel, N. A. *J. Org. Chem.* **1965**, *30*, 2624.

(15) Beckwith, A. *J. Tetrahedron* **1981**, *37*, 3073.

(16) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(17) Marchand, A. P.; LaRoe, W. D.; Sharma, G. V. M.; Suri, S. C.; Reddy, D. S. *J. Org. Chem.* **1986**, *51*, 1622.

furnished a mixture of products which was applied on silica gel column. Elution with a 30% ethyl acetate–hexane mixture furnished 1,8,10,11,11-pentachloro-3-*exo*-hydroxytetracyclo$[6.2.1.0^{2,7}.0^{4,10}]$undec-5-en-9-one (7) (2.49 g, 55%): mp >270 °C; IR (KBr) 3514, 2926, 1788, 1292, 1246, 1105, 1082, 835 cm^{-1}; ^{1}H NMR (CD_3CN) δ 6.49 (1 H, d, J = 7 Hz), 6.11 (1 H, d, J = 7 Hz), 3.9 (1 H, s), 3.84 (1 H, d, J = 2 Hz), 3.58 (1 H, m), 3.22 (2 H, m); ^{13}C NMR (CD_3CN): δ 193.38, 138.89, 129.06, 93.05, 89.0, 86.77, 82.21, 80.73, 63.95, 50.47, 48.87. Anal. Calcd for $C_{11}H_7O_2Cl_5$: C, 38.16; H, 2.03; Cl, 50.54. Found: C, 38.12; H, 2.04; Cl, 50.5.

8-Chloro-3-*exo*-hydroxytetracyclo$[6.2.1.0^{2,7}.0^{4,10}]$undec-5-en-9-one (8), 3,5-Dichloropentacyclo$[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]$undecane-2,8-*exo*-diol (9), and 3,5,11-Trichloropentacyclo$[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]$undecane-2,8-*exo*-diol (10). The reaction was conducted according to the general procedure using 4 mmol of 7 (1.4 g) and 12 equiv of SmI_2. After workup, the reaction mixture was loaded on a silica gel column. Elution with 20% ethyl acetate–hexane mixture furnished three products; 8 (25 mg, 3%), **9** (0.1 g, 10%), and **10** (0.34 g, 30%).

Data for 8: mp 175 °C; IR (KBr) 3292, 2966, 1738, 1234, 1211, 1186, 1157, 1053, 918 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.79 (1 H, s), 2.16 (1 H, d, J = 19.8 Hz), 2.59–2.41 (1 H, m), 3.04 (1 H, d, J = 7.9 Hz), 3.2–3.5 (4 H, m), 4.05 (1 H, s), 5.73 (1 H, t, J = 7.8 Hz), 6.18 (1 H, t, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 218.13, 133.59, 126.39, 80.41, 73.55, 66.62, 51.19, 50.68, 47.37, 40.98, 33.55. Anal. Calcd for $C_{11}H_{11}O_2Cl$: C, 62.84; H, 5.27; Cl, 16.64. Found: C, 62.23; H, 5.29; Cl, 16.55.

Data for 9: mp 202 °C; IR (KBr) 3422, 2970, 1350, 1302, 1269, 1232, 1074, 1031, 906 cm^{-1}; ^{1}H NMR (CD_3CN) δ 1.42 (1 H, ddd, J = 12.9, 4.0, 2.9 Hz), 1.57 (1 H, d, J = 12.9 Hz), 2.33 (3 H, m), 2.55 (3 H, m), 2.74 (1 H, td J = 6.4, 1.7 Hz) 4.07 (1 H, m), 4.41 (1 H, d, J = 2.85 Hz), 5.95 (1 H, s); ^{13}C NMR (CD_3CN) δ 86.05, 74.66, 72.53, 70.76, 59.89, 54.02, 49.77, 47.7, 41.21, 37.83, 22.79. Anal. Calcd for $C_{11}H_{12}O_2Cl_2$: C, 53.65; H, 4.91; Cl, 28.42. Found: C, 53.83; H, 4.97; Cl, 28.38.

Data for 10: mp 145 °C; IR (KBr) 3354, 2976, 1414, 1306, 1271, 1047, 908 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.69–1.82 (2 H, m), 2.06 (1 H, d, J = 8.0 Hz), 2.66 (3 H, m), 2.8 (2 H, s), 2.9 (1 H, m), 3.29 (1 H, m), 4.34 (1 H, d, J = 8 Hz), 4.41 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 87.48, 77.20, 75.05, 74.82, 71.32, 58.90, 52.24, 47.93, 42.07, 38.02, 23.59. Anal. Calcd for $C_{11}H_{11}O_2Cl_3$: C, 47.14; H, 3.95; Cl, 37.46. Found: C, 46.98; H, 4.06; Cl, 37.38.

Acknowledgment. One of us (S.C.S.) is thankful to Drs. S. L. Rodgers and J. W. Gilman for their unconditional support. The authors are thankful to Mr. Ngo Q. Vu for making starting materials. Financial support of this study by the Air Force Office of Scientific Research, Directorate of Chemistry & Materials Science, is gratefully acknowledged.

Supplementary Material Available: Tables of atomic positional coordinates, anisotropic thermal parameters, bond lengths, and bond angles for compounds **5** and **6** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Anodic Amide Oxidations: The Synthesis of Two Spirocyclic L-Pyroglutamide Building Blocks

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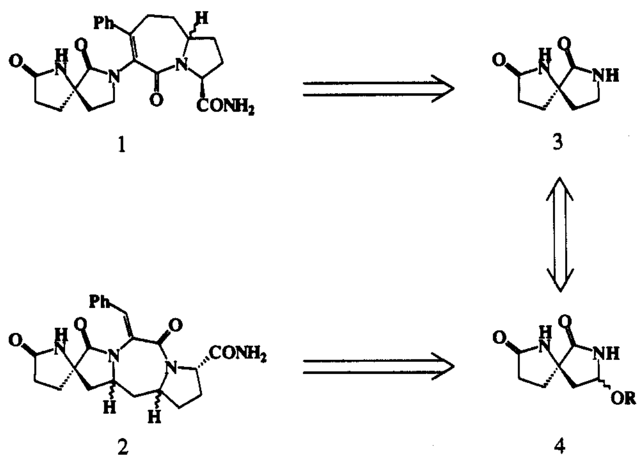
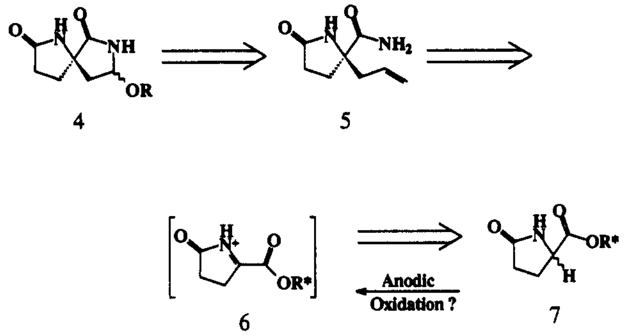
Received July 13, 1992

To date, attempts to use the active-analog approach to computer-assisted drug design in an effort to gain insight into the three-dimensional requirements of thyroliberin (TRH)-receptor binding have utilized active analogs that were both flexible and structurally similar to each other.[1]

Scheme I



Scheme II



These efforts were partially successful in reducing the number of possible TRH conformations that might satisfy the 3-D requirements of the receptor site, but left many questions unanswered. For example, Marshall and Font used the active analog approach to design the conformationally restricted TRH analogs **1** and **2**.[2] However, modeling efforts could not differentiate between the potential effectiveness of these analogs or even attempt to determine the stereochemistry best suited for binding at the centers shown as racemic in **1** and **2**. With this in mind, a program aimed at synthesizing and testing conformationally restricted TRH analogs was undertaken. It was hoped that the biological data obtained from these analogs would serve to clarify the conformation responsible for TRH binding and lead to the design of new, more active analogs. In order to provide a synthetic solution for **1** and **2**, a generally useful method for constructing spirocyclic pyroglutamide analogs was required.[3] We report here the efficient synthesis of spirocyclic building blocks **3** and **4** from pyroglutamic acid (Scheme I).

From the start, it was clear that an asymmetric synthesis of building blocks **3** and **4** was needed in order to control the stereochemistry of the quaternary center relative to the remainder of the TRH analogs. For this reason,

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[1] For reviews concerning the active analog approach see: (a) Marshall, G. R.; Barry, C. D.; Bosshard, H. E.; Dammkoehler, R. A.; Dunn, D. A. In *Computer-Assisted Drug Design*; Olson, E. C., Christoffersen, R. E., Eds.; American Chemical Society: Washington DC, 1979; pg 205. (b) Marshall, G. R. *Ann. Rev. Pharmacol. Toxicol.* **1987**, *27*, 193. (c) Marshall, G. R.; Motoc, I. In *Molecular Graphics and Drug Design*; Burgen, A. S. V., Roberts, G. C. K., Tute, M. S., Eds.; Elsevier: Amsterdam, 1986; p 115.

[2] Font, J. Ph.D. Thesis, Washington University in St. Louis, 1986.

[3] Spirocyclic skeletons have been used to add rigidity to proline analogs: (a) Hinds, M. G.; Richards, N. G. J.; Robinson, J. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1447. (b) Ward, P.; Ewan, G. B.; Jordon, C. C.; Ireland, S. J.; Hagan, R. M.; Brown, J. R. *J. Med. Chem.* **1990**, *30*, 1848.

0022-3263/92/1957-6360$03.00/0