Synthesis, Double Cycloaromatization, and DNA-Cleaving Activities of (*Z*,*Z*)-11-Sulfonylundeca-3,7-diene-1,5,9-triyne System

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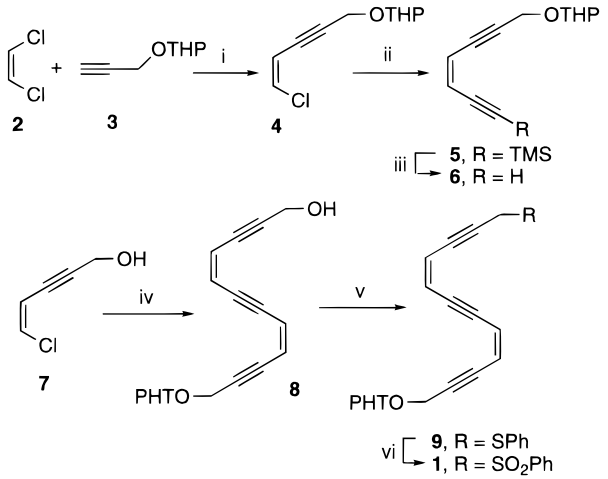
(*Z*)-Allene−ene−yne systems have been shown to undergo mild thermal cyclization to form the biradical α,3-didehydrotoluene[1] and also exhibit DNA-cleaving activity.[2] The barrier to cyclization of (*Z*)-1,2,4-heptatrien-6-yne is considerably lower than that of (*Z*)-hex-3-ene-1,5-diyne.[1c] Introduction of an alkyl substituent at the terminus of the allenic moiety will accelerate the reaction rate of cyclization.[3] Enediyne sulfones are stable at room temperature and are isomerized to eneyne−allene−sulfones under alkaline conditions. These eneyne−allene−sulfones were not isolable, spontaneously cyclized to form biradical intermediates under mild conditions,[3e,4] and exhibited good DNA-cleaving activity.[5,6] In an extension of our research in this area, we have synthesized a new enediyne **1** which contains the (*Z*,*Z*)-11-sulfonylundecan-3,7-diene-1,5,9-triyne system. The double cycloaromatization of **1** through an eneyne−allene−sulfone to form an α,6-didehydro-α-methylnaphthalene and the DNA-cleaving activity of this new enediyne are reported in this note.

The synthesis of the prototype diene−triyne **1** is outlined in Scheme 1. Palladium-catalyzed coupling of *cis*-1,2-dichloroethylene (**2**) with protected propargyl alcohol **3** afforded **4** in 45% yield. Enyne **4** was subsequently coupled with (trimethylsilyl)acetylene using tetrakis(triphenylphosphine)palladium (0) as the catalyst to give **5** in 70% yield. The silyl group of **8** was removed with tetrabutylammonium fluoride in THF to afford **6** in 65% yield. Coupling of (*Z*)-vinyl chloride **7**[1c] with **6** gave **8** in 23% yield. The hydroxyl group of **8** was converted to sulfide by the reported method[4] to afford **9** in 45% yield. Finally, **9** was oxidized with mCPBA to furnish sulfone **1** in 58% yield.

Compound **1** is a stable compound which has been stored in the freezer for more than three months without decomposition. Thermolysis of **1** (0.01 M, 131 °C, 12 h) in chlorobenzene in the presence of 1,4-cyclohexadiene resulted in the slow disappearance of **1** and gave a mixture of unidentified products.[7] However, treatment of **1** with triethylamine (4 equiv) in diluted, degassed benzene solution (0.01 M, 80 °C, 12 h) containing 1,4-cyclohexadiene (1.5 M) afforded **10** in 18% yield. The isolation of naphthalene **10** strongly suggested that the diradical, α,6-didehydro-α-methylnaphthalene, **13**, is formed either by the concerted cyclization of allenyl sulfone **11** or by a stepwise pathway through diradical **12**. (Scheme 2).

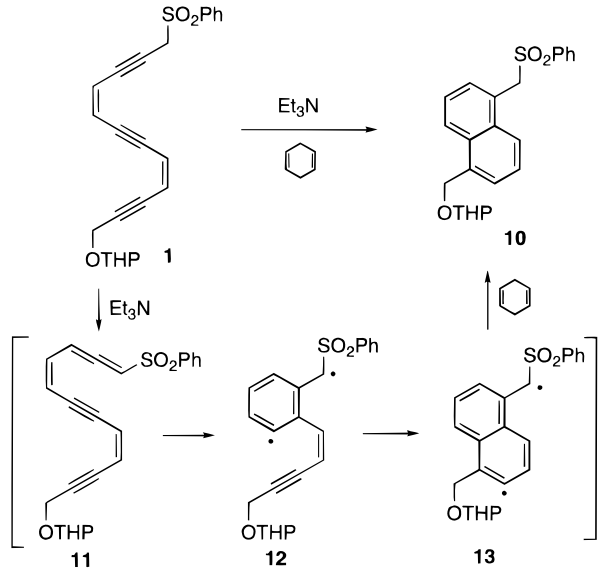
The DNA cleaving activity of **1** was examined by incubation with supercoiled ΦX 174 DNA (form I) at pH 8.3 and 47 °C for 48 h. The agarose gel picture shown in Figure 1 indicates that the proportion of single strand cleavage product (Form II DNA) increased with increas-

Scheme 1



[a]**Reagents and conditions**: (i) $Pd(PPh_3)_2Cl_2$, CuI, $nBuNH_2$, Et_2O, 45%; (ii) $Pd(PPh_3)_4$, CuI, $nBuNH_2$, Et_2O, 70%; (iii) Bu_4NF, THF, 65%; (iv) **6**, $Pd(PPh_3)_4$, CuI, $nBuNH_2$, Et2O, 23%; (v) (a) MsCl, Et_3N, CH_2Cl_2; (b) HSPh, NaOH, THF-H_2O, 45%; (vi) mCPBA, CH_2Cl_2, 58%.

Scheme 2



(1) (a) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130. (b) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057. (c) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 9369.

(2) (a) Toshima, K.; Kazumi, O.; Ohashi, A.; Nakamura, T.; Nakata, M.; Tatsuta, K.; Matsumura, S. *J. Am. Chem. Soc.* **1995**, *117*, 4822. (b) Nicolaou, K. C.; Maligres, P.; Shin, J.; de Leon, E.; Rideout, D. *J. Am. Chem. Soc.* **1990**, *112*, 7825. (c) Saito, I.; Nagata, R.; Yamanaka, H.; Okazaki, E. *Tetrahedron Lett.* **1989**, *30*, 4995. (d) Saito, I.; Nagata, R.; Yamanaka, H.; Murahashi, E. *Tetrahedron Lett.* **1990**, *31*, 2907. (e) Shibuya, M.; Sakai, Y.; Bando, Y.; Shishido, K. *Tetrahedron Lett.* **1992**, *33*, 957. (f) Morokuma, K.; Koga, N. *J. Am. Chem. Soc.* **1991**, *113*, 1907. (g) Fujiwara, K.; Sakai, H.; Hirama, M. *J. Org. Chem.* **1991**, *56*, 1688.

(3) For recent reviews of eneyne−allene chemistry see: (a) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (b) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453.

(4) Wu, M.-J.; Lin, C.-F.; Wu, J.-S.; Chen, H.-T. *Tetrahedron Lett.* **1994**, *35*, 1879.

(5) (a) Wu, M.-J.; Lin, C.-F.; Ong, C.-W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 675. (b) Wu, M.-J.; Lin, C.-F.; Chen, H.-T.; Duh, T.-H.; Wang, S.-S.; Hsu, S.-C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2183.

(6) Dai, W.-M.; Fong, K. C.; Danjo, H.; Nishimoto, S.-i. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 779.

(7) For an example of thermolysis of (*Z*,*Z*)-deca-3,7-diene-1,5,9-triyne, see: Bharucha, K. N.; Marsh, R. M.; Minto, R. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 3120.

S0022-3263(97)00513-6 CCC: $14.00

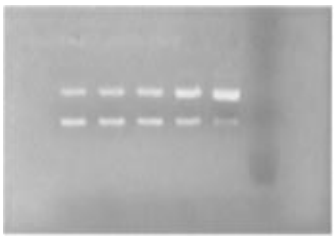


Figure 1. Results of DNA cleavage by **1**. ΦX 174 Form I DNA (50 mM/bp) was incubated for 48 h at 47 °C with **1** in TBE buffer solution (pH 8.3) containing 20% DMSO and analyzed by electrophorisis (1% agarose gel, ethidium bromide stain). Lane 1: DNA control without incubation. Lane 2: DNA control with incubation. Lanes 3−6: DNA with 1, 10, 100, and 500 μM, respectively.

ing amount of **1**. At a concentration of 100 μM (lane 5), more than 90% of the form I DNA was converted into form II DNA.

In summary, diene−triyne **1** was synthesized in eight steps from *cis*-1,2-dichloroethylene. Treatment of **1** with triethylamine in refluxing benzene in the presence of 1,4-cyclohexadiene afforded double cycloaromatization adduct **10**. Compound **1** also exhibits excellent DNA-cleaving activity. Compound **1** and its analogs may have the potential in the development of new anticancer drugs. Currently, biological studies on the cytotoxicity of these molecules against human turmor cell lines are under investigation.

Experimental Section

***(Z)*-1-Chloro-5-[(2-tetrahydropyranyl)oxy]-1-penten-3-yne (4).** A degassed solution of **3** (3.36 mL, 24 mmol) and $nBuNH_2$ (3.3 g, 22 mmol) in dry Et_2O (30 mL) was cannulated into a degassed suspension of **2** (1.6 mL, 20 mmol) in dry Et_2O (40 mL) containing $Pd(PPh_3)_2Cl_2$ (0.3 g, 0.8 mmol) and CuI (0.3 g, 1.55 mmol). The resulting brown suspension was stirred at 25 °C for 6 h. The reaction mixture was poured into a solution of equal parts of saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, 20% EtOAc in hexane as eluent) to give **4** (2.4 g, 45%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.40 (d, 1 H, J = 7.5 Hz), 5.91 (dt, 1 H, J = 7.5, 2.0 Hz), 4.88 (t, 1 H, J = 3.6 Hz). 4.46 (d, 2 H, J = 2.0 Hz), 3.92−3.81 (m, 1 H), 3.61−3.50 (m, 1 H), 1.88−1.50 (m, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 128.7, 111.7, 96.8, 93.6, 79.7, 62.1, 54.6, 30.2, 25.4, 19.1. HRMS (EI) calcd for $C_{10}H_{13}O_2Cl$: 200.0604, found 200.0612.

***(Z)*-1-(Trimethylsilyl)-7-[(2-tetrahydropyranyl)oxy]hept-3-ene-1,5-diyne (5).** To a degassed suspension of **4** (2.4 g, 12 mmol) in dry Et_2O (40 mL) containing $Pd(PPh_3)_4$ (0.7 g, 0.6 mmol) and CuI (0.47 g, 2.5 mmol) was added a degassed solution of (trimethylsilyl)acetylene (2.43 mL, 17.5 mmol) and $nBuNH_2$ (4.8 mL, 49.5 mmol) in dry Et_2O (30 mL). The resulting brown suspension was stirred at 25 °C for 3 h. The reaction mixture was poured into a solution of equal parts of saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, 20% EtOAc in hexane as eluent) to give **5** (2.2 g, 70%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.85 (s, 2 H), 4.88 (t, 1 H, J = 3.5 Hz), 4.47 (d, 2 H, J = 2.4 Hz), 3.91−3.79 (m, 1 H), 3.60−3.52 (m, 1 H), 1.83−1.52 (m, 6 H), 0.22 (s, 9 H). HRMS (EI) calcd for $C_{15}H_{22}O_2Si$: 262.1389, found 262.1375.

***(Z)*-7-[(2-Tetrahydropyranyl)oxy]-hept-3-ene-1,5-diyne (6).** To a stirred solution of **5** (2.7 g, 10.3 mmol) in THF (100 mL) was added a solution of TBAF (1 M in THF, 10.3 mL, 10.3 mmol) at 0 °C. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, 20% EtOAc in hexane as eluent) to give **6** (1.28 g, 65%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.95 (dt, 1 H, J = 11.9, 2.0 Hz), 5.81 (dd, 1 H, J = 11.0, 2.4 Hz), 4.90 (t, 1 H, J = 3.5 Hz), 4.70 (d, 2 H, J = 2.0 Hz), 3.92−3.80 (m, 1 H), 3.59−3.49 (m, 1 H), 3.33 (d, 1 H, J = 2.4 Hz), 1.87−1.50 (m, 6 H). HRMS (EI) calcd for $C_{12}H_{14}O_2$: 190.0994, found 190.1004.

***(Z,Z)*-12-[(2-Tetrahydropyranyl)oxy]dodeca-4,8-diene-2,6,10-triyn-1-ol (8).** To a degassed suspension of **7**[5a] (0.9 g, 7.8 mmol) in dry Et_2O (50 mL) containing $Pd(PPh_3)_4$ (0.7 g, 0.6 mmol) and CuI (0.5 g, 2.6 mmol) was added a solution of **6** (1.28 mL, 6.8 mmol) and $nBuNH_2$ (1.78 mL, 18.3 mmol) in dry Et_2O (50 mL). The resulting brown suspension was stirred at 25 °C for 6 h. The reaction mixture was poured into an aqueous solution comprised of equal parts of saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, 25% EtOAc in hexane as eluent) to give **8** (0.42 g, 23%) as a brown oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.02 (d, 2 H, J = 10.7 Hz), 5.89 (dt, 2 H, J = 10.7, 1.9 Hz), 4.97 (t, 1 H, J = 3.3 Hz), 4.49 (d, 2 H, J = 1.9 Hz), 4.45 (d, 2 H, J = 1.9 Hz), 3.91−3.79 (m, 1 H), 3.60−3.50 (m, 1 H), 2.92 (bs, 1 H), 1.89−1.51 (m, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 119.5, 96.4, 94.0, 93.9, 93.4, 83.4, 82.4, 61.9, 54.6, 51.3, 30.0, 25.3, 18.8.

***(Z,Z)*-12-[(2-Tetrahydropyranyl)oxy]-1-(phenylthio)dodeca-4,8-diene-2,6,10-triyne (9).** To a stirred solution of **8** (0.42 g, 1.6 mmol) in CH_2Cl_2 (20 mL) was added methanesulfonyl chloride (0.16 mL, 2 mmol), followed by Et_3N (0.33 mL, 2.5 mmol). The resulting solution was stirred at 25 °C for 1 h and quenched with 10% aqueous HCl solution and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in THF (5 mL) and added into the solution of PhSH (0.41 mL, 4 mmol) in THF (16 mL) and H_2O (4 mL) containing NaOH (0.1 g, 4 mmol). The reaction mixture was stirred at 25 °C for 3 h, quenched with 10% aqueous NaOH, and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (silica gel, 5% EtOAc in hexane as eluent) to give **9** (0.25 g, 45%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51−7.44 (m, 2 H), 7.35−7.22 (m, 3 H), 6.03−5.80 (m, 4 H), 4.88 (t, 1 H, J = 3.4 Hz), 4.47 (d, 2 H, J = 1.9 Hz), 3.90−3.75 (m, 3 H, including 3.85 (d, 2 H, J = 2.2 Hz)), 3.58−3.49 (m, 1 H), 1.81−1.49 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 130.2, 129.0, 126.8, 119.9, 119.8, 119.6, 119.4, 96.7, 94.2, 94.1, 93.9, 93.8, 83.3, 80.9, 62.0, 54.7, 30.3, 25.4, 23.9, 19.0.

***(Z,Z)*-12-[(2-Tetrahydropyranyl)oxy]-1-(phenylsulfonyl)-dodeca-4,8-diene-2,6,10-triyne (1).** To a stirred solution of **9** (0.25 g, 0.7 mmol) in CH_2Cl_2 (10 mL) was added mCPBA (0.27 g, 1.5 mmol). The resulting solution was stirred at 25 °C for 30 min, quenched with saturated aqueous $NaHCO_3$, and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, 30% EtOAc in hexane as eluent) to give **1** (0.16 g, 58%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03−7.98 (m, 2 H), 7.71−7.52 (m, 3 H), 6.09−5.75 (m, 4 H), 4.87 (t, 1 H, J = 3.5 Hz), 4.45 (d, 2 H, J = 1.9 Hz), 4.21 (d, 2 H, J = 2.3 Hz), 3.90−3.78 (m, 1 H), 3.58−3.50 (m, 1 H), 1.85−1.49 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 134.1, 129.1, 128.9, 121.2, 119.9, 119.5, 118.4, 96.6, 94.7, 94.0, 93.6, 85.0, 84.8, 83.1, 62.0, 54.6, 49.6, 30.2, 25.3, 19.0.

1-[(Phenylsulfonyl)methyl]-5-[[(2-tetrahydropyranyl)-oxy]methyl]naphthalene (10). The degassed solution of **1** (70 mg, 0.18 mmol) in benzene (20 mL) containing 1,4-cyclohexadiene (3 mL, 31.5 mmol) and Et_3N (0.1 mL, 0.76 mmol) was heated at reflux with stirring for 12 h. After cooling to room temperature, the reaction was quenched with 10% aqueous HCl and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by preparative TLC (silica gel, 20% EtOAc in hexane as developing solvent system) to give **10** (13 mg, 18%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60 (dd, 2 H, J = 8.2, 1.2 Hz), 7.54 (t, 2 H, J = 7.8 Hz), 7.40 (t, 2 H, J = 7.5 Hz), 7.08 (t, 1 H, J = 7.7 Hz), 6.89 (d, 1 H, J = 7.7 Hz), 6.73 (d, 1 H, J = 5.3 Hz), 6.69−6.66 (m, 2 H), 4.72−4.66 (m, 2 H), 4.51 (dd, 1 H, J =

13.9, 7.1 Hz), 4.44 (s, 2 H), 3.95−3.85 (m, 1 H), 3.60−3.50 (m, 1 H), 1.85−1.42 (m, 6 H); MS(EI) *m*/*z* 396 (M^+, 1.3%), 171 (53%), 141 (62%), 128 (63%), 77 (100%), HRMS (EI) calcd for $C_{23}H_{24}O_4S$: 396.1396, found 396.1395.

Acknowledgment. We thank the National Science Council of Republic of China for financial support of this work.

Supporting Information Available: ^{1}H NMR spectra of compounds **1**, **8**, and **9** (3 pages). This material is contained in 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.

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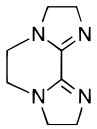
Additions and Corrections

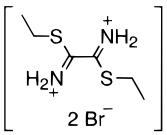
Vol. 61, 1996

Gary R. Weisman* and David P. Reed. A New Synthesis of Cyclen (1,4,7,10-Tetraazacyclododecane).

Pages 5186−5187. Subsequent to publication, we discovered that the reported reaction giving bis-amidine cyclen precursor **2**, while viable, does *not* involve the intermediacy of bis-thioimido ester salt **3**. Isolation and solution NMR studies have shown that dithiooxamide is not detectably alkylated by bromoethane under the reaction conditions employed by us and originally described by Wang and Bauman for the synthesis of 2,2′-bi-2-imidazoline (Wang, J. C.; Bauman, J. E., Jr. *Inorg. Chem.* **1965**, *4*, 1613). In fact, dithiooxamide and triethylenetetraamine cleanly react in the absence of EtBr to give **2**. The sulfur-containing gaseous byproduct of the reaction is therefore H_2S, *not ethanethiol* as reported by us and by Wang and Bauman. The reaction is analogous to the direct reaction of dithiooxamide and ethylenediamine to give 2,2′-biimidazoline, originally reported by Forssell (Forssell, G. *Chem. Ber.* **1891**, *24*, 1846).



2



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As a consequence of these observations, we have developed a modified preparation of **2**, which should be substituted for the preparation originally reported. The revised procedure (below) is experimentally simpler, less expensive, and gives **2** in higher yield (81%). The overall yield of the two-step synthesis is improved to 67%.

2,3,5,6,8,9-Hexahydrodiimidazo[1,2-*a*:2′,1′-*c*]pyrazine (2). [**Caution:** Hydrogen sulfide (toxic) is evolved. This procedure must be carried out in an efficient hood with provisions for H_2S trapping]. A three-neck flask equipped with a fritted gas dispersion tube (initially closed) and reflux condenser was charged with dithiooxamide (3.26 g, 27.1 mmol). The N_2 manifold exit line was routed through two fritted gas washing bottles charged with 20% aqueous NaOH to trap H_2S. (An additional trap consisting of a tube packed with acid gas absorbing carbon granules may be used as a further precaution if desired.) A solution of triethylenetetraamine (3.97 g, 27.1 mmol) in absolute EtOH (33 mL) was added in one portion, the heterogeneous mixture was refluxed under N_2 for 4 h, and the reaction mixture was cooled to rt. Residual H_2S and NH_3 were purged from the solution by entrainment with N_2, which was bubbled through the reaction mixture (fritted gas dispersion tube) for 2 h. Most EtOH was removed by simple distillation (water aspirator) in the hood, $CHCl_3$ (100 mL) was added, and the solution was concentrated by rotary evaporation. Solid residue was taken up in boiling toluene (100 mL) and filtered through a glass wool plug (short-stemmed funnel). Insoluble material was washed with additional boiling toluene (75 mL), and the combined filtrates were concentrated to afford 4.34 g (98%) of crude yellow product (mp 144−146 °C). Sublimation (95 °C, 0.05 Torr) gave 3.59 g (81%) of white solid product; mp 149−150 °C (>98% by NMR; suitable for conversion to **1**). Resublimation gave material having mp 150−151 °C. Characterization as originally reported. (Note: **2** is unstable toward hydrolysis and should be stored in a desiccator.)

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Clifton K.-F. Shen, Kuo-Ming Chien, Chiun-Gung Juo, Guor-Rong Her, and Tien-Yau Luh*. Chiral Bisazafullerenoids.

Page 9242. The correct address is Republic of China, not People's Republic of China.

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