Tricyclo[3.2.2.0^{2,4}]non-2(4)-ene: Synthesis and Trapping of a Strained Cyclopropene[1]

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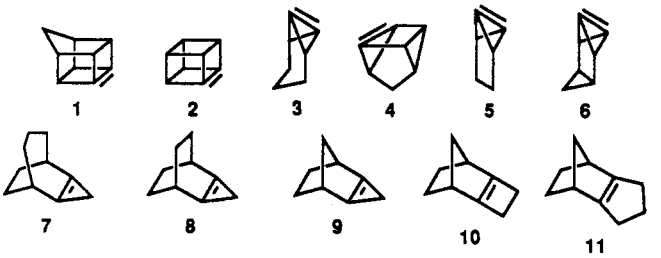
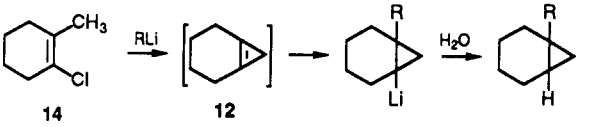
The title compound **8** has been synthesized in situ from dibromide **18** via debromination with *tert*-butyllithium in THF at −78 °C. In the presence of diphenylisobenzofuran (**27**), the Diels–Alder adduct **29** is formed. Cyclopropene **8** was also trapped with diene **28** to give a second adduct **30**. The synthetic methodology for precursor dibromide **18** appears to have general application for other similar highly strained tricyclic cyclopropenes.

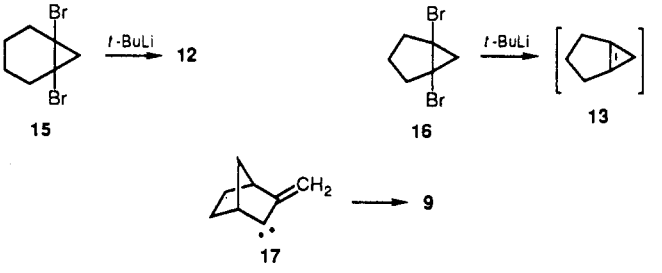
Although cyclopropenes have been known for some time,[2] they continue to fascinate organic chemists because of their unique structure, high degree of ring strain, and difficulty of synthesis. The recent rebirth of interest in strained olefin chemistry[3] has been highlighted by the synthesis and trapping of polycyclic cyclobutene-containing compounds such as homocubene (**1**)[4] and cubene (**2**).[5] The pioneering work of highly strained cyclopropenes in various polycyclic frameworks done by Szeimies has led to some important studies of **3**,[6] the dehydroquadricyclane **4**,[7,8] and other strained compounds such as **5**[9] and **6**.[9] We proposed for study fusing a cyclopropene ring to a bicyclic skeleton. In order to determine the significance of increasing ring strain on the difficulty of synthesis as well as on the chemical paths taken by these compounds during subsequent reactions of the double bonds, we initiated synthetic studies of tricyclic cyclopropenes **7**, **8**, and **9**, where a cyclopropene is fused to a two-carbon bridge of a bicyclic [3.2.2], [2.2.2], or [2.2.1] ring respectively. Although larger cyclic olefins have been fused to a norbornyl structure as in Aue's[10] work with cyclobutene **10** and Takaishi's[11] and Bartlett's[12] syntheses of **11**, different chemistry had to be employed for the synthesis of the corresponding cyclopropenes.



We looked to the literature of some bicyclic cyclopropene-containing compounds such as **12** and **13** and found some interesting approaches. Gassman and coworkers[13] treated the methyl chloride **14** with alkyllithiums and proved that **12** was formed as an intermediate before



addition of excess alkyllithium and hydrolysis. Wiberg and Bonneville[14] employed dehalogenation of dibromides **15** and **16** with *tert*-butyllithium and trapped **12** and **13** with a number of Diels–Alder dienes before the olefins dimerized or were alkylated by excess reagent. Szeimies' work was done with alkyllithium-induced dehydrohalogenations of cyclopropyl halides. Carbene insertion as in structure **17** is another possible route for the synthesis of tricyclic



(1) (a) A preliminary communication of part of this work has been published: Chenier, P. J.; Southard, D. A., Jr. *J. Org. Chem.* **1989**, *54*, 3519. Portions of this work have also been presented: (b) Southard, D. A., Jr.; Chenier, P. J. *Abstracts of Papers*, 32nd Minnesota Undergraduate Research Symposium in Chemistry, River Falls, WI, May 1989. (c) Chenier, P. J.; Southard, D. A., Jr. *Abstracts of Papers*, 22nd Great Lakes Regional Meeting of the American Chemical Society, Duluth, MN, June 1989, paper 91. (d) Chenier, P. J.; Southard, D. A., Jr. *Abstracts of Papers*, 198th National Meeting of the American Chemical Society, Miami Beach, FL; American Chemical Society: Washington, DC, 1989; ORGN 25.

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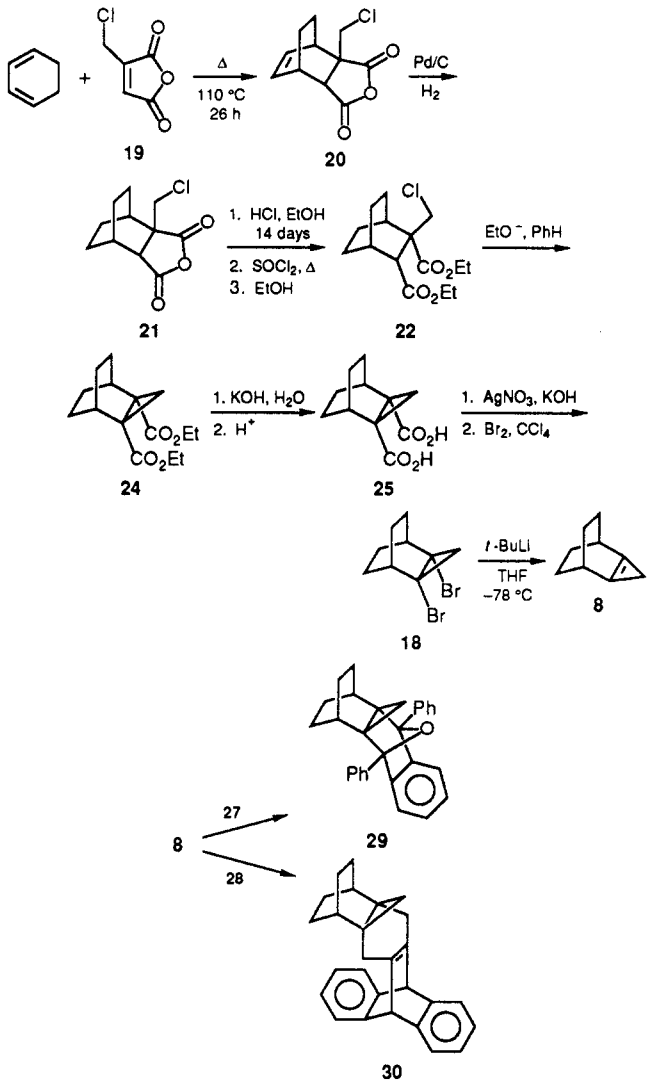
Scheme I



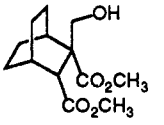
cyclopropenes 7–9. We report here details of the complete synthesis of olefin 8 via dehalogenation and trapping experiments to establish proof of its existence.

Results and Discussion

Synthesis of the Precursor. Dibromide 18, the immediate precursor via dehalogenation to our title olefin tricyclo[3.2.2.0^{2,4}]non-2(4)-ene (8), was synthesized by a route similar to Wiberg's preparation[14] of dibromide 15, though substantial changes in experimental procedure were necessary. Scheme I outlines the synthesis of dibromide 18 and olefin 8. (Chloromethyl)maleic anhydride (19) can be made in two steps from itaconic anhydride.[15] Cyclohexadiene reacts with anhydride 19 in a 26-h toluene reflux to give an 87% yield of adduct 20.[16] The exclusive product probably has the anhydride group endo or syn in analogy to many other cycloadditions that favor groups containing π electrons forming endo products, since in the transition state for this isomer maximum overlap of π systems is maintained. The bridgehead-exo hydrogen coupling is 3.3 Hz.

Hydrogenation of the unsaturated chloroanhydride adduct 20 with palladium on carbon in ethyl acetate gave the saturated chloro anhydride 21. However, the hydrogenation proceeds very slowly, and the catalyst is easily poisoned by the mixture. The endo anhydride group blocking one side of the double bond and the extra ethano bridge blocking the opposite side must combine to slow the hydrogenation. With patience and successive additions of catalyst a 99% yield of product is realized. Only one isomer was again detected with a coupling of 3.9 Hz between the bridgehead and the hydrogen α to the anhydride.

Perhaps the step in the synthesis of tricyclic cyclopropene 8 that varies most from the analogous step in the synthesis of bicyclic cyclopropene 12 is the opening of chloro anhydride 21 to the chloro diester 22. Wiberg's nonbridged chloro anhydride was opened to an ester–acid by refluxing methanol in only 3 h. After a number of basic or neutral conditions failed to give this result on chloro anhydride 21, we found that alcohol (methanol or ethanol) saturated with hydrogen chloride and refluxed for 14 days gave ring opening. Subsequent treatment of the ester–acid with thionyl chloride and additional alcohol gave the chloro diester 22. Even then the starting anhydride can sometimes contaminate the product. We believe that deesterification can sometimes occur in a subsequent ring closure somewhere in the sequence of steps to cause at least a part of this anhydride impurity. One interesting product discovered in an attempted base-catalyzed esterification is hydroxy diester 23, presumably formed in an aqueous



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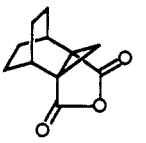
quench of a sodium methoxide/methanol reflux of chloro anhydride 21 followed by the usual subsequent treatment with thionyl chloride and methanol. Refluxing chloro diester 22 in benzene with sodium ethoxide results in a γ-elimination of HCl to form cyclopropyl diester 24, which was saponified with potassium hydroxide in ethanol–water to cyclopropyl diacid 25.

The final step of the synthesis of dibromide 18 could not be performed in the manner in which Wiberg synthesized dibromide 15, i.e., via the Cristol–Firth modification[17] of the Hunsdiecker reaction. Apparently the mercuric salt of diacid 25 is quite unreactive. The cyclic anhydride 26



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may be formed from the diacid in a competing reaction. The reaction was not investigated further. Instead, the original Hunsdiecker reaction[18] conditions with silver nitrate and potassium hydroxide to give the silver salt were utilized. An extra step, stirring the crude dibromide 18 for 48 h at room temperature with 5% aqueous sodium hydroxide, was necessary to remove an impurity, presumably the anhydride 26. The ^{13}C NMR spectrum shows the expected simplicity of the five peaks that by refocused

(15) Schreiber, J.; Leimgruber, W.; Pesaro, M.; Schudel, P.; Threlfall, T.; Eschenmoser, A. *Helv. Chim. Acta* **1961**, *44*, 540.

(16) Preliminary experiments with cyclopentadiene and chloromethylmaleic anhydride show that the adduct is formed at 25 °C in ether in a slightly exothermic reaction. This is the first step in the synthesis of olefin 9 by a route analogous to Scheme I.

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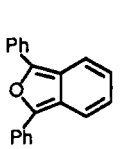
INEPT showed three methylenes, a methine, and a quaternary carbon. The latter is only at δ 24.7 because of the heavy atom effect of bromine.

Generation and Trapping of the Cyclopropene. A common method of proving the existence of a strained olefin such as cubene (2) or bicyclo[4.1.0]hept-1(6)-ene (12) is by generating the compound from an appropriate precursor in the presence of a good Diels–Alder diene to trap the olefin before it can react in other ways. Diphenylisobenzofuran (27, DPIBF) is very reactive with most olefins because of the extra resonance energy gained by formation of an aromatic ring during a [4 + 2] cycloaddition. It was used by Wiberg to trap bicyclic cyclopropenes 12 and 13 when other dienes failed. It was used by Hrovat and Borden to trap homocubene (1). Diene 28, recently synthesized by Hart[19] in two steps from anthracene, has been used by Eaton[5a] to trap cubene. When 18 was mixed with *tert*-butyllithium at −78 °C in dry tetrahydrofuran (THF) with DPIBF, the adduct 29 was formed. There are two possible stereoisomers of 29, depending on whether the methylene of the cyclopropane ring is syn or anti to the oxygen. Only one isomer was evident by spectroscopic methods. ^{13}C NMR spectroscopy showed 13 different carbons (7 aromatic, 5 aliphatic, and the indicative Ph–C–O absorption at δ 93.0 similar to other analogous adducts[14b]), mass spectrometry showed the correct exact mass for the molecular ion which was also the base peak, and a correct elemental analysis left no doubt of the compound's structure. When Wiberg and Bonneville trapped bicyclic cyclopropene 12 with DPIBF only one isomer was found. They assigned the syn stereochemistry of methylene and oxygen from the finding that the chemical shift of one of the cyclopropyl protons was much farther downfield than normal (δ 2.21 vs 1.00). High-field ^{1}H NMR spectroscopy[20] does indeed show a large difference in chemical shift for the two cyclopropyl protons (δ 1.27 vs 0.09) for adduct 29 as well. Thus the stereochemistry of 29, with the methylene and oxygen syn, is analogous. Many attempts at preparing large enough crystals for single-crystal X-ray structural analysis were unfruitful.



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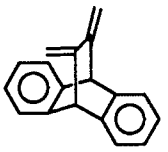
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Stereochemical differentiation is not a problem when diene 28 is used as the trap because of its symmetry and its adduct's (30) lack of stereochemistry. We believe that we do indeed form adduct 30 when this diene is used in place of DPIBF, but unfortunately we could not completely purify 30 even with chromatography and recrystallization. However, the correct exact mass was observed for the molecular ion and base peak.

These experiments leave no doubt that tricyclo[3.2.2.0^{2,4}]non-2(4)-ene (8) has been synthesized and trapped in a cycloaddition. We are developing syntheses for 7 and 9 similar to this one.

Experimental Section

Melting points are uncorrected and were taken on a Thomas–Hoover apparatus. The following instruments were used: an IBM NR80AF FT-NMR spectrometer, Nicolet 5DXC FT-IR and Perkin-Elmer 1420 IR spectrophotometers, and Hewlett-Packard 5890 FID and Varian Aerograph 700 Autoprep TCD gas chromatographs with helium as carrier gas. NMR data are given in parts per million relative to Me_4Si. ^{1}H and ^{13}C NMR spectra were obtained at 80 and 20 MHz, respectively, unless noted otherwise. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN. Mass spectra were taken by the Department of Chemistry, University of Minnesota, Minneapolis, MN.

(Chloromethyl)maleic Anhydride (19). Prepared by the method of Schreiber et al.[15] from itaconic anhydride[21] via chlorination followed by dehydrochlorination.

Unsaturated Choro Anhydride 20. (Chloromethyl)maleic anhydride (19, 77.25 g, 0.527 mol) was dissolved in toluene (500 mL), and cyclohexadiene[21] (42.25 g, 0.527 mmol) was added, whereupon a bright green color was formed. The solution was refluxed for 26 h. Rotary evaporation and final drying in vacuo gave 20 as an off-white solid (98.53 g, 0.457 mol, 87%). Two recrystallizations from acetone–petroleum ether (60–110 °C) gave pure material: mp 119.4–120.6 °C; ^{1}H NMR ($CDCl_3$) δ 6.3–6.6 (m, 2 H, vinyl CH), 3.6–4.2 (AB, 2 H, CH_2Cl, J = 11 Hz), 3.1–3.3 (m, 1 H, bridgehead), 3.10 (d, 1 H, CHCO, J = 3.3 Hz), 2.8–3.1 (m, 1 H, bridgehead), 1.1–2.1 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 173.7, 171.3, 134.7, 132.9, 55.6, 48.8, 46.3, 35.3, 32.4, 21.9, 19.4; MS (EI, 30 eV, 150 °C) m/e (%) 226 (M^+, 3.4), 154 ($M^+ - C_2O_3$, 52), 126 (C_7H_7Cl, 100), 119 (C_9H_{11}, 34), 91 (C_7H_7, 100), 80 (C_6H_8, 100), 79 (C_6H_7, 91), 77 (C_6H_5, 41); HRMS calcd for $C_{11}H_{11}ClO_3$ 226.0396, found 226.0390. Anal. Calcd for $C_{11}H_{11}ClO_3$: C, 58.31; H, 4.86. Found: C, 57.76; H, 4.95.

Saturated Chloro Anhydride 21. Unsaturated chloro anhydride 20 (48.77 g, 0.227 mol) was dissolved in ethyl acetate (200 mL) and hydrogenated in a Parr apparatus with 10% palladium on carbon (1.3 g) at 20 psi until the uptake of hydrogen ceased. An additional 1.4 g of catalyst and further hydrogenation for 2 h, followed by filtration of the catalyst, rotary evaporation of the solvent, and vacuum drying, gave 21 as a brown solid (49.0 g, 0.226 mol, 99%). Four recrystallizations from acetone–petroleum ether (60–110 °C) gave a white solid: mp 107.9–108.8 °C; IR (KBr) 2953, 2882, 1856, 1779, 1215, 984, 941, 893, 736; ^{1}H NMR ($CDCl_3$) δ 3.6–4.1 (AB, 2 H, CH_2Cl, J = 11 Hz), 3.11 (d, 1 H, CHCO, J = 3.9 Hz), 2.2–2.5 (m, 1 H, bridgehead), 1.9–2.1 (m, 1 H, bridgehead), 1.3–1.9 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 174.6, 172.1, 54.0, 47.3, 30.0, 26.8, 23.4, 20.4, 20.3; MS (EI, 30 eV, 100 °C) m/e (%) 156 ($M^+ - C_2O_3$, 57), 128 (C_7H_9Cl, 100), 93 (C_7H_9, 33), 91 (C_7H_7, 26), 79 (85), 77 (C_6H_5, 15); HRMS calcd for $C_9H_{13}Cl$ ($M^+ - C_2O_3$) 156.0705, found 156.0711. Anal. Calcd for $C_{11}H_{13}ClO_3$: C, 57.78; H, 5.73. Found: C, 57.88; H, 5.77.

Attempted Ring Opening of Chloro Anhydride 21 under Neutral Conditions. When chloro anhydride 21 is refluxed in absolute methanol up to 8 days under nitrogen, very little reaction occurs and starting material is recovered.

Attempted Ring Opening of Chloro Anhydride 21 under Basic Conditions. Chloro anhydride 21 (55.52 g, 0.243 mmol) was dissolved in absolute methanol (500 mL) containing sodium methoxide (0.30 mmol, made from 6.9 g of sodium) with stirring. After the solution was stirred for 20 h, it was diluted with water (500 mL) and acidified with 1:1 HCl–H_2O. The mixture was extracted with ether (4 × 600 mL). The ether layers were combined and washed with water (2 × 600 mL) and brine. The solution was dried with anhydrous magnesium sulfate and filtered, and the filtrate was rotary evaporated and dried in vacuo to a yellow liquid. The usual treatment and procedure[14b] with thionyl chloride followed by methanol gave 39.94 g of a viscous oil. Triple distillation gave bp 172–3 °C (3.5 mm) and crystallization on standing. The product was recrystallized three times from petroleum ether (60–110 °C) and identified as hydroxy diester 23: mp 60.5–62.0 °C; IR (neat) 3515, 3415, 2945, 2865, 1780, 1735, 1455, 1432, 1281, 1205, 1167, 1098, 1070, 1017, 977, 937, 902; ^{1}H NMR[22] ($CDCl_3$, 500 MHz) δ 4.05 (d, 1 H, CHOH, J = 9.2 Hz), 3.81 (s, 1 H, OH), 3.80 (d, 1 H, CHOH, J = 9.2 Hz), 3.73 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 2.35 (m, 1 H, CHCO), 2.12 (m, 1 H, bridgehead), 1.95 (m, 2 H), 1.72 (m, 1 H), 1.4–1.6 (m, 6 H); ^{13}C

(19) Hart, H.; Bashir-Hasheni, A.; Luo, J.; Meador, M. A. *Tetrahedron* **1986**, *42*, 1641.
(20) We thank Professor Joseph B. Lambert, Northwestern University, for these spectra.
(21) Aldrich Chemical Co., Milwaukee, WI.
(22) We thank Dr. Bruce R. Adams, University of Wisconsin–Madison, for these spectra and spectral analyses.

NMR[22] ($CDCl_3$) δ 175.0 (s), 174.8 (s), 69.8 (t), 53.8 (s), 51.84 (q), 51.80 (q), 49.7 (d), 30.1 (d), 25.9 (t), 25.8 (d), 23.3 (t), 21.7 (t), 20.7 (t); MS (EI, 30 eV, 30 °C) *m/e* (%) 256 (M^+, 2.4), 194 ($C_{11}H_{14}O_3$, 100), 166 ($C_{10}H_{14}O_2$, 74), 143 ($C_6H_7O_4$, 60), 138 ($C_8H_{10}O_2$, 85), 79 (C_6H_7, 86); HRMS calcd for $C_{13}H_{20}O_5$ 256.1310, found 256.1324. Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.79; H, 7.34.

Ring Opening of Chloro Anhydride 21 under Acidic Conditions: Preparation of Chloro Diester 22. Chloro anhydride **21** (98.00 g, 0.430 mol) was dissolved in absolute ethanol (500 mL), and hydrogen chloride was bubbled through the solution for 1 h. The solution was refluxed for 14 days. Hydrogen chloride was bubbled into the solution for 30 min every third day. Rotary evaporation gave a brown oil. Thionyl chloride (102.3 g, 0.860 mol) was cautiously added dropwise with stirring to the oil. The solution was heated under nitrogen at 55–60 °C for 3 h. Rotary evaporation gave a brown solid. Absolute ethanol (500 mL) was added at 0 °C with stirring. The solution was then allowed to come to room temperature. The solution was rotary evaporated to a brown solid. This was vacuum distilled, bp 150–170 °C (1.5 mm). Three recrystallizations from acetone–petroleum ether (60–110 °C) failed to give pure chloro diester **22**, mp 78–92 °C, but the product was pure enough to be identified and used in the next step despite anhydride **21** being present: IR (KBr) 2951, 2924, 2878, 1856, 1782, 1742, 1231, 1204, 1165, 985, 939, 905; ^1H NMR ($CDCl_3$) δ 3.5–4.4 (m, 6 H), 1.4–2.6 (m, 11 H), 1.26 (t, 6 H); ^{13}C NMR ($CDCl_3$) δ 174.5, 172.1, 60.4, 60.3, 51.1, 50.6, 28.4, 26.3, 25.6, 23.4, 22.0, 20.7, 13.9; MS (EI, 70 eV, 100 °C) *m/e* (%) 302 (M^+, 1.1), 156 ($M^+ - 2CO_2CH_2CH_3$, 33), 128 (C_7H_9Cl, 65), 93 (C_7H_9, 45), 91 (C_7H_7, 74), 79 (C_6H_7, 100), 77 (C_6H_5, 37), 41 (C_3H_5, 38), 39 (C_3H_3, 32); HRMS calcd for $C_{15}H_{23}ClO_4$ 302.1282, found 302.1291.

Cyclopropyl Diester 24. Chloro diester **22** (83.50 g, 0.276 mol) was dissolved in dry benzene (100 mL, distilled from sodium) and added over 0.5 h to a stirred mixture of sodium ethoxide (37.56 g, 0.550 mol) in dry benzene (1200 mL). The mixture was refluxed and stirred overnight. The organic layer was washed with water (3 × 400 mL), and the aqueous layers were extracted with ether (400 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and the filtrate was rotary evaporated and vacuum-dried to a pale yellow liquid which crystallized to a solid. The solid was used without further purification to make the cyclopropyl diacid **25** but was identified by its spectral characteristics as cyclopropyl diester **24**. The approximate crude yield is 53%: IR (KBr) 2978, 2945, 2878, 1725, 1373, 1287, 1186, 1081; ^1H NMR ($CDCl_3$) δ 4.10 (q, 4 H, CH_2O), 1.8–2.3 (m, 4 H), 1.2–1.8 (m, 8 H), 1.23 (t, 6 H, CH_3CH_2O); ^{13}C NMR ($CDCl_3$) δ 171.4, 60.2, 34.3, 26.4, 24.2, 23.0, 16.3, 13.6.

Cyclopropyl Diacid 25. Cyclopropyl diester **24** (39.11 g, 0.147 mol) was dissolved in ethanol–water (80:20, v/v, 300 mL) and potassium hydroxide (47.34 g of 87% = 0.735 mol) was added with stirring. The solution was refluxed overnight. The solution was rotary evaporated, and the residue was dissolved in a minimum amount of water. The solution was extracted with ether (200 mL), which was discarded. Then the aqueous layer was acidified with concentrated hydrochloric acid. The acidified solution was extracted with ether (4 × 400 mL), and the extracts were combined, rotary evaporated, and vacuum-dried to give crude cyclopropyl diacid **25** as a white solid which could be used in the preparation of dibromide **18**. The approximate crude yield of diacid **25** is 62%. Three recrystallizations from acetone–water followed by a sublimation at 190 °C (1.2 mm) gave the pure diacid: mp 259.5–260.5 °C; IR (KBr) 2500–3600, 1707, 1489, 1468, 1433, 1412, 1331, 1293, 1271, 1237, 1194, 1130, 949, 814; ^1H NMR (acetone-d_6) δ 4.0–5.0 (very broad, 2 H), 1.3–2.4 (m, 12 H); ^{13}C NMR (acetone-d_6) δ 184.3, 37.6, 29.4, 26.7, 25.5, 18.5; MS (EI, 30 eV, 220 °C) *m/e* (%) 210 (M^+, 6.7), 192 ($M^+ - H_2O$, 90), 164 ($C_{10}H_{12}O_2$, 87), 119 (100), 91 (C_7H_7, 100), 79 (C_6H_7, 85), 41 (76); HRMS calcd for $C_{11}H_{14}O_4$ 210.0891, found 210.0894. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.81; H, 6.64.

Cyclopropyl Dibromide 18. Potassium hydroxide (1.32 g of 85% = 20.0 mmol) was dissolved in distilled water (50 mL) followed by diacid **25** (2.10 g, 10.0 mmol). A silver nitrate solution (3.40 g, 20.0 mmol in 40 mL of distilled water) was added over 15 min with stirring. The precipitate was suction filtered, washed with methanol (10 mL), and vacuum-dried. This silver salt was manually broken into finer pieces, placed in the flask to be used for the next reaction, and dried in vacuo at 105 °C for 36 h.

Carbon tetrachloride (25 mL, dried via distillation from P_2O_5) was added to the flask. Bromine (3.20 g, 20.0 mmol, dried via shaking with concentrated H_2SO_4) was added dropwise with stirring and intermittent cooling with an ice bath. After the addition was complete the mixture was heated on a steam bath for 15 min. The solution was suction filtered, and the residue was washed with methylene chloride. The filtrate was washed with sodium metabisulfite solution, water, 10% sodium bicarbonate, and water (40 mL each). The solution was dried over anhydrous magnesium sulfate and filtered, and the filtrate was rotary evaporated and dried in a vacuum to give an amber semisolid, dibromide **18** (1.21 g, 4.32 mmol, 22%).

The dibromide was stirred at ambient temperature for 48 h with 5% sodium hydroxide solution and then extracted with methylene chloride (2 × 25 mL). Rotary evaporation and vacuum-drying of the organic solutions gave 0.64 g of purer dibromide. One recrystallization from acetone gave dibromide of 100% purity by GC (SE-54, 175 °C, 200 mL/min). An analytical sample was prepared by an additional recrystallization from acetone and vacuum sublimation: mp 158–60 °C; IR (KBr) 2951, 2878, 1456, 1384, 1178, 1084, 1046; ^1H NMR ($CDCl_3$) δ 1.3–2.8 (m); ^{13}C NMR ($CDCl_3$) δ 42.6 (t), 35.6 (d), 24.7 (s), 24.4 (t), 22.4 (t); MS (EI, 30 eV, 120 °C) *m/e* (%) 199 ($M^+ - Br$, 30), 155 (27), 131 (39), 119 (100), 91 (93); HRMS calcd for $C_9H_{12}Br$ ($M^+ - Br$) 199.0121, found 199.0113. Anal. Calcd for $C_9H_{12}Br_2$: Br, 57.07. Found: Br, 57.36.

Generation and Trapping of Tricyclo[3.2.2.0^{2,4}]non-2(4)-ene (8) with Diphenylisobenzofuran (27). To a solution of dibromide **18** (280 mg, 1.00 mmol) and DPIBF (**27** 270 mg, 1.00 mmol) in THF (15 mL, dried by distillation from sodium) at −78 °C was added *tert*-butyllithium (1.70 mmol) in pentane (1.7 M, 1.0 mL) during 15 min under nitrogen. A dark brown color occurred with each drop and remained at the end of the addition. The mixture was stirred for 0.5 h, quenched with methanol (2.3 mL) at −78 °C, and allowed to warm to ambient temperature for 1 h. Water (15 mL) was added, and the mixture was extracted with ether (2 × 20 mL). The ether layers were dried with anhydrous magnesium sulfate and filtered, and the filtrate was rotary evaporated and vacuum-dried to a yellow solid (380 mg). TLC showed that no starting materials were present. High-field proton NMR and a COSY spectrum[20] showed one isomer of adduct **29** and only trace impurities. Column chromatography on silica gel and elution with 80:20 hexane–ethyl acetate, along with three recrystallizations from hexane or hexane–ether, gave pure **29** as a white solid which showed one spot on TLC: mp 207–9 °C; IR (KBr) 3057, 3030, 2917, 2874, 1603, 1496, 1454, 1335, 1307, 970, 920, 745, 702, 667; ^1H NMR[20] (400 MHz, $CDCl_3$) δ 7.3–7.7 (m, 10 H, 2 Ph), 6.8–7.1 (AA'BB', 4 H, Ar), 2.09 (m, 2 H, bridgeheads), 1.75 (d, 2H, J = 8.2 Hz, decouples with δ 0.99), 1.2–1.3 (m, 5 H, 2 CH_2's and 1 cyclopropyl), 0.99 (d, 2 H, J = 8.2 Hz, decouples with δ 1.75), 0.09 (d, 1 H, J = 7.3 Hz, cyclopropyl); ^{13}C NMR ($CDCl_3$) δ 147.7, 137.7, 128.2, 127.0, 126.6, 126.4, 118.3, 93.0, 32.5, 26.6, 25.6, 24.8, 23.2; MS (EI, 30 eV, 200 °C) *m/e* (%) 390 (M^+, 100), 217 (19), 105 (32), 91 (30); HRMS calcd for $C_{29}H_{26}O$ 390.1982, found 390.1982. Anal. Calcd for $C_{29}H_{28}O$: C, 89.19; H, 6.71. Found: C, 88.70; H, 6.86.

Generation and Trapping of Cyclopropene 8 with Diene 28. To a solution of dibromide **18** (560 mg, 2.00 mmol) and diene **28** (460 mg, 2.00 mmol) in benzene (25 mL, dried by distillation from sodium) at 25 °C was added *tert*-butyllithium (3.40 mmol) in pentane (1.7 M, 2.0 mL) over 15 min. The mixture was stirred for 1 h, quenched with methanol (4.5 mL) over 10 min, and stirred for 1.5 h. Water was added, and the mixture was extracted with ether (3 × 25 mL). The ether layers were dried from anhydrous magnesium sulfate and filtered, and the filtrate was rotary evaporated and vacuum-dried to a yellow foam (790 mg). TLC showed no more than a trace of starting materials present.

The product was column chromatographed on silica gel and eluted with hexane–ethyl acetate mixtures. One fraction of 170 mg, though not pure, contained aromatic and aliphatic protons in the ^1H NMR spectrum and had seven main carbons in the δ 120–150 aromatic–olefinic region of the ^{13}C NMR spectrum along with some aliphatic carbons. Recrystallization of this material twice from hexane gave a solid, mp 200–220 °C, which is believed to be adduct **30** though TLC still showed a faint second spot and

the ^{13}C NMR spectrum had extra aliphatic peaks still present. The HRMS showed a molecular ion peak, which was also the base peak, with the correct exact mass: ^1H NMR ($CDCl_3$) δ 7.0–7.3 (m, 4 H), 6.7–7.0 (m, 4 H), 4.5–5.0 (m, 2 H), 2.0–2.5 (m, 4 H), 0.7–1.7 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 146.3, 145.4, 142.0, 139.6, 124.2, 122.7, 122.3, 57.5, 55.7, 55.4, 44.6, 33.0, 31.6, 30.3, 29.3, 25.3, 22.4, 14.1, 9.2; MS (EI, 70 eV, 170 °C) *m/e* (%) 350 (M^+, 100), 216 ($C_{17}H_{12}$, 100), 215 ($C_{17}H_{11}$, 31), 192 ($C_{15}H_{12}$, 30), 179 ($C_{14}H_{11}$, 36), 178 ($C_{14}H_{10}$, 99); HRMS calcd for $C_{27}H_{28}$ 350.2032, found 350.2033.

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A New Synthetic Route to the Previously Unattainable 2-Arylpyrido[2,3-*b*][1,5]thiazepin-4(5*H*)-ones

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A variety of 2-arylpyrido[2,3-*b*][1,5]thiazepin-4(5*H*)-ones has been efficiently synthesized by treatment of the anion of 2-chloro-3-(*N*-methylacetamido)- and -3-acetamidopyridine with the appropriate *O*-ethyl thiocarboxylates.

In recent years members of the benzothiazepinone class of compounds have generated considerable interest owing to their remarkable diversity of biological activity. In particular, the 2-aryl-1,5-benzothiazepin-4(5*H*)-one skeleton constitutes the framework of several biologically active compounds, e.g., antidepressants like Thiazesim,[1] coronary vasodilators like Diltiazem,[2,3] and antiulcer and antisecretory agents such as BTM-1086.[4] Paradoxically, despite the considerable development of procedures for efficiently constructing nitrogen-containing rings, the pyridothiazepinone skeleton still remains difficultly accessible. To our knowledge the only reported method for the elaboration of this polyheterocyclic system consists of treating 2-mercapto-3-aminopyridine with 3-bromopropanoic acid.[5] However, the method is not general in scope and is rather restrictive, especially with regard to the eventual introduction of various substituents in the seven-membered heterocyclic moiety.

In this paper we report a novel, general and effective synthetic approach to the previously unattainable N-substituted or unsubstituted 2-arylpyrido[2,3-*b*][1,5]thiazepin-4(5*H*)-ones **6a–g** and **7a–c**. Our strategy consists of reacting aromatic thiocarboxylates **4a–g** with the anion of 2-chloro-3-(*N*-methylacetamido)- or -3-acetamidopyridine, (**1** and **2**), respectively (Scheme I).

The *O*-ethyl thiocarboxylates **4a–g** are efficiently prepared by treatment of aromatic and heteroaromatic carboximidic acid esters, readily accessible from the appropriate nitriles via the Pinner reaction, with hydrogen sulfide at low temperature.[6] The anion of 2-chloro-3-(*N*-methylacetamido)pyridine (**1**) is generated by treatment with 1.1 molar equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF). This metalation reaction must be carried out at −78 °C to prevent thermal decomposition of the intermediate carbanion.[7] The addition of the ap-

Scheme I

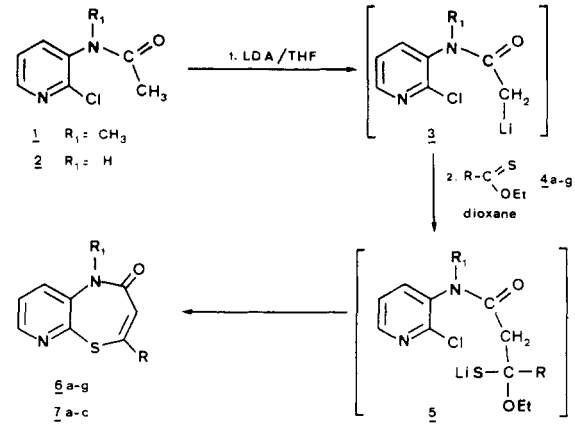
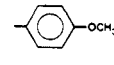
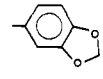
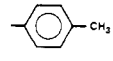
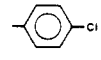


Table I. 2-Substituted Pyrido[2,3-*b*][1,5]thiazepin-4(5*H*)-ones from Condensation of Lithiated Acetamidopyridines with Thioesters

amide		thioester 4, R =	product	yield (%)
1 (R_1 = CH_3)	a		6a	59
1	b		6b	57
1	c		6c	66
1	d		6d	61
1	e		6e	60
1	f		6f	59
1	g		6g	61
2 (R_1 = H)	a	4a	7a	56
2	b	4b	7b	55
2	c	4c	7c	61

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