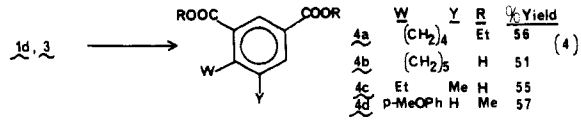
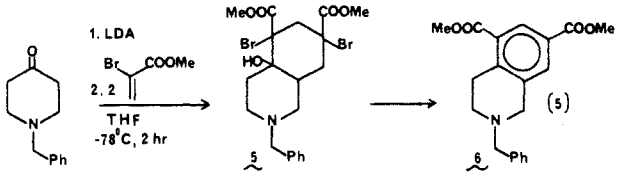
The multifunctionality of the annulated adducts **1c–e** provides much opportunity for many different further chemical manipulations. For example, the two sulfur atoms of bis-α-tolylthio ester **1c** can be oxidized into sulfoxide groups which can be thermally eliminated.[4] In this way, followed by dehydration, we have converted adduct **1c** effectively (55–60% yield) into the corresponding aromatic tetrahydronaphthalene system; dibromocyclohexanol **1d** also was transformed (LiCl/DMF, 100 °C, 12 h) into tetrahydronaphthalene **4a** (eq 4). One-pot dehydration and bisdehydrobromination of dibromocyclohexanols **3a** and **3b** (NaOMe/PhH) and **3c** (pyridinium trifluoroacetate/pyridine, reflux, 12 h) led to the aromatic systems **4** shown in eq 4. This



overall process represents a direct, convenient, two-step procedure for annulating a meta-dicarboxylated benzene ring onto the -$COCH_2$- group of a ketone, thereby regiospecifically forming a trisubstituted or tetrasubstituted aromatic system. Recently, considerable effort has been directed at developing new methods for regiospecific synthesis of polyfunctionalized aromatic compounds.[5]

The lithium enolate of *N*-benzyl-4-piperidone[6] was annulated into dibromocyclohexanol **5** which was isolated on gram scale in 66% overall yield after purification by short-path chromatography (eq 5). One-pot dehydration and bisdehydrobromination ((dimethylamino)pyridine, triethylamine/pyridine, reflux, 12 h) gave tetrahydroisoquinoline **6** in 35% yield. This two-step sequence represents an unusually direct synthesis of the biologically important isoquinoline alkaloid ring system.[7]



The triply convergent,[8] 2 + 2 + 2, *Mi*chael-*Mi*chael-*r*ing *c*losure (MIMIRC)[9] cyclohexannulations[10] shown in eq 1–3 and 5 represent an extremely useful, mild, easy, and convenient (e.g., no motor-driven syringe technique required)[11] means of transforming relatively simple into structurally much more complex cyclic systems.[12] These one-pot, multiple C–C bond-forming annulations will undoubtedly be of substantial value in organic synthesis. We are actively exploring further applications.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a research grant (No. 14645) and for a Summer Research Fellowship to Professor Silversmith. We also thank Professor J. Clardy and Dr. C. He (Cornell) for the X-ray study of adduct **1c** and Professor D. Poland of this department for a helpful discussion. Purchase of a 400-MHz NMR spectrometer was made possible by the NSF (DCM 83-03176) and by the NIH (1 S10 RR0934).

Supplementary Material Available: IR, ^{1}H NMR, mp, and elemental analysis or high resolution mass spectral data for compounds **1–6** (4 pages). Ordering information is given on any current masthead page.

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(10) For some recent cyclohexannulation procedures, see: (a) Danheiser, R.; Fink, D. M.; *Tetrahedron Lett.* **1985**, *26*, 2513. (b) Byers, J. H.; Spencer, T. A. *Ibid.* **1985**, *26*, 713. (c) Meyer, W. L.; Brannon, M. J.; Burgos, C. G.; Goodwin, T. E.; Howard R. W. *J. Org. Chem.* **1985**, *50*, 438. (d) Tang, P.-D.; Wulff, W. D. *J. Am. Chem. Soc.* **1984**, *106*, 1132. (e) Pariza, R. J.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2304. (f) Pietrusiewicz, K. M.; Monkiewicz, J.; Bodalski, R. *Ibid.* **1983**, *48*, 788. (g) Danheiser, R. L.; Martinez-Davila, C.; Sand, H. *Tetrahedron* **1981**, *37*, 3943.

(11) Cf.: Posner, G. H.; Lu, S.-B. *J. Am. Chem. Soc.* **1985**, *107*, 1424.

(12) A typical experimental procedure is as follows: A dry 10-mL flask cooled in an ice bath and fitted with a magnetic stirring bar, an argon inlet, and a serum cap was charged with cyclohexanone enol trimethylsilyl ether (100 mg, 0.59 mmol) in 1 mL of dry THF and treated dropwise via syringe with MeLi in Et_2O (0.59 mL, 1.1 M, 0.65 mmol) over 1 min. After it was warmed to room temperature, the mixture was stirred for 1 h. The reaction flask was then cooled to −78 °C. Ethyl α-bromoacrylate (232 mg, 1.30 mmol) was added without solvent dropwise via syringe over 0.5 min. Stirring was continued for 1 h at −78 °C. Quenching was achieved by the addition of aqueous NH_4Cl (saturated). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3x). The combined organic solution was dried ($MgSO_4$), filtered, concentrated, and subjected to preparative TLC (petroleum ether:ethyl ether = 2:1); 145.6 mg (54.1%) of **1d** was obtained. MIMIRC product **1d** (49 mg, 0.11 mmol) and LiCl (8.6 mg, 0.20 mmol) in 33 μL of dry DMF were stirred at 100 °C overnight under N_2. After cooling the reaction mixture to room temperature, 2 mL of 50% (v/v) of 2.5% sulfuric acid in Et_2O was added. Stirring was continued at room temperature for 4 h. The organic layer was then separated. The aqueous layer was extracted with Et_2O (3x). The combined Et_2O solution was dried over $MgSO_4$, filtered, concentrated, and subjected to preparative TLC. Aromatic **4a** (16.6 mg, 56%) was obtained. Similar results (51% yield) were obtained by dissolving MIMIRC product **1d** in pyridine and refluxing overnight.

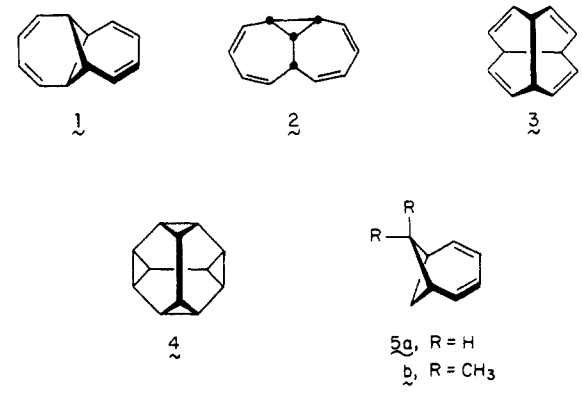
Tricyclo[5.5.0.0^{2,8}]dodecatetraene

Leo A. Paquette,* Jürgen Dressel,[1] and Kent L. Chasey

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Received October 7, 1985

Considerable attention has been focused on the valence isomers of [12]annulene, approximately 40 of which are now known,[2] because their unusual structural features have proven useful in defining the practical limits of orbital symmetry control. Included among the yet unknown $(CH)_{12}$ hydrocarbons, whose acquisition has been thwarted by serious synthetic complications, are **1–4**.[3]



(1) Fulbright Scholar, 1982–1983; Evans Fellow, 1985–1986.

(2) Banciu, M.; Popa, C.; Balaban, A. T. *Chem. Scr.* **1984**, *24*, 28.

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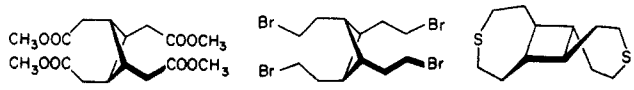
Of this group, the title compound (**1**) commands special interest because of the orthogonal arrangement of its 1,3-diene subunits,[4] the inherent potential for interaction between the perpendicular π systems via the "relay" orbitals of the central cyclobutane ring,[5] and the predicted unlikelihood of its rearrangement into either **2** or **3**.[5] Some time ago, we prepared bicyclo[4.1.1]octa-2,4-diene (**5a**) and demonstrated that interaction between the cyclobutane Walsh orbitals and the olefinic moiety can be described by a resonance integral (β) of −1.9 eV.[6] Subsequently, the same phenomenon was shown to be operative in derivative **5b**.[7] For the above reasons, we have embarked on a synthesis of **1** and herein record the successful realization of our goal.

Although retrosynthetic considerations point to simultaneous twofold cyclization of a *cis*[4]tetrasubstituted cyclobutane as a particularly expedient approach to **1**, Woodward and Brousseau[3f] have previously shown this protocol to be fraught with unresolvable complications. Because all four pendant groups must be projected in the axial direction, energetic demands are substantively heightened and alternative reaction pathways become kinetically favored. Thus, tetraester **6** could not be coerced into intramolecular Dieckmann or acyloin condensation.[3f] Also, tetrabromide **7** reacts with sodium sulfide in HMPA to give **8** and not the disuslfide having structural topography related to **1**.[3f]

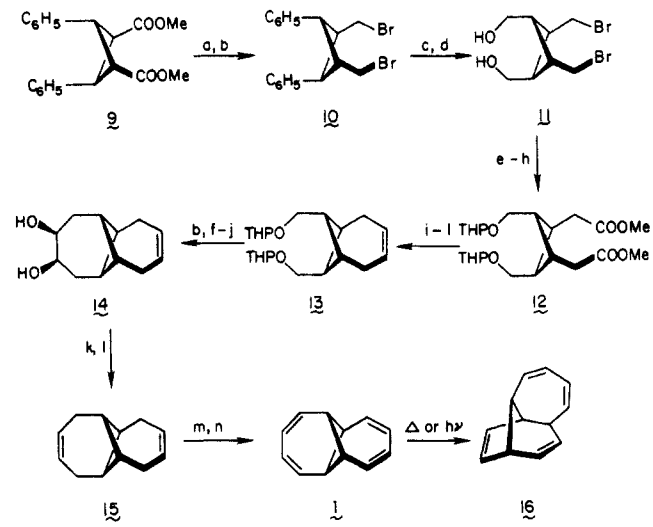


6 **7** **8**

From a different vantage point, construction of the central cyclobutane ring by intramolecular S_N2 alkylation appeared feasible,[8] although ring expansion would likely be required subsequently. On the other hand, photochemically induced transannular closure of an appropriate medium-ring diene was fully expected *not* to result in crossbonding[9] as seen in smaller cyclic networks.[10] The approach described below is striking confirmation that *stepwise* belting of two C_4 chains to alternate carbon atoms of a four-membered ring can lead successfully to the target polyolefin.

In preparation for distinguishing the 1,3- and 2,4-substituent pairs, dimethyl ϵ-truxillate (**9**)[11] was transformed into dibromide **10** (72%).[12] Exposure of **10** to ruthenium tetroxide[13] proceeded with smooth oxidation of both phenyl groups. Treatment of the resultant dicarboxylic acid with the borane–tetrahydrofuran complex afforded **11** as a highly crystalline solid (70%, Scheme I). To ensure noninterference by the hydroxyl groups, conversion to the bis(tetrahydropyranyl) ether preceded homologation to diester **12** (76%).

Scheme I[a]



9 **10** **11** **12** **13** **14** **15** **1** **16**

[a] (a) $LiAlH_4$, THF, reflux. (b) $Ph_3P{\cdot}Br_2$, CH_2Cl_2. (c) $RuO_2{\cdot}XH_2O$, NaOCl; HCl. (d) $BH_3{\cdot}THF$. (e) Dihydropyran, TsOH, CH_2Cl_2. (f) NaCN, Me_2SO, 90–100 °C, 6.5 h. (g) 10 N KOH, CH_3OH, reflux 15 h; HCl to pH 4. (h) CH_2N_2. (i) Na/K, Me_3SiCl, Et_2O, room temperature; KH_2PO_4, KF, H_2O, MeOH, 50 °C. (j) $LiAlH_4$, THF, room temperature. (k) $CSCl_2$, 4-DMAP, CH_2Cl_2, 0 °C. (l) $\overline{CN(Me)P(C_6H_5)N(Me)C}$ 3 h. (m) NBS, (AIBN), CCl_4, 65 °C, sunlamp. (n) Zn/Cu, KI, I_2, DMF, room temperature.

At this juncture, the first of two planned acyloin condensations was implemented. Although the use of sodium and Me_3SiCl in refluxing toluene under high dilution conditions proceeded efficiently, substitution of sodium–potassium alloy (1:1) in ether proved even more serviceable (ambient temperature, 70 g of **12** per 500 mL of solvent). Thus, little difficultly was encountered with compression of the four extraannular groups into close spatial proximity. Direct $LiAlH_4$ reduction gave the cyclic diol, particularly rich in the cis isomer (65–73%). Reaction of its thionocarbonate with 2,5-dimethyl-1-phenyl-2,5-diazaphospholidine[14] resulted in the formation of **13** (86%). Following replacement of the (tetrahydropyranyl)oxy groups in **13** by bromine,[15] the colorless crystalline product exhibited ^1H [(300 MHz, $CDCl_3$) δ 5.57 (br s, 2 H), 3.61 (d, J = 8.6 Hz, 4 H), 2.32 (br d, 4 H), 2.19–2.15 (m, 4 H)] and ^{13}C NMR spectra [($CDCl_3$) ppm 125.3, 42.9, 39.4, 37.8, 34.0] fully consonant with its symmetry.

Completion of the synthesis required homologation of the remaining two chains and the previous procedure was again employed (except for use of 1:4 Na/K alloy). The existing annulated ring was left at the monounsaturated state to avoid labilizing the cyclobutane bond[11a] and to allow for like chemical modification of both bridges at the penultimate stages (see below). The six-step conversion of **13** to **14** proved efficacious (54%). Reductive elimination of the hydroxyl groups in **14** by the Corey–Hopkins procedure[14] provided, in 70% yield, the pivotal diene **15**, a colorless crystalline solid having mp 41.0–43.5 °C. At 300 MHz, its three proton types appear as widely spaced broadened singlets centered at δ 5.58, 2.27, and 2.98 in a 1:2:1 ratio. The three ^{13}C signals (125.1, 39.2, 33.8 ppm) are likewise in agreement with the structural assignment.

The dehydrogenation of **15** has so far proven vexacious. To date, the most reliable method involves conversion to the tetra-

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(12) The structure assigned each compound is in accord with its IR, 300-MHz ^1H NMR, ^{13}C NMR, and mass spectra. In addition, elemental analyses were obtained in a number of cases. The yields reported are the *overall* amounts of product obtained for all of the steps required to proceed from one illustrated compound to the next.

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(14) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, 1979.

(15) Sonnet, P. E. *Synth. Commun.* **1976**, *6*, 21.

bromide with NBS and debromination with zinc–copper couple, potassium iodide, and iodine in DMF (24%).[6,16] Again, C_{2v} symmetry was evident from the NMR spectra.[17] The colorless crystalline substance (mp 27–29 °C) exhibits the following electronic spectrum: λ_{max} cyclohexane 218 (ϵ 8900) and 318 (3000). Photoelectron spectroscopic measurements on **1** will be reported elsewhere. Heating a $CDCl_3$ solution of **1** to 80 °C induces clean rearrangement to **16**[18] ($t_{1/2}$ ~7 h). The same isomerization can be achieved more rapidly by irradiation with a TLC UV lamp (λ 254 nm). Accordingly, **1** finds [1,3] sigmatropic migration to be most accessible from its ground and excited states.

Acknowledgment. This research was supported by a grant from the National Science Foundation (CHE-8317954).

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(17) ^1H NMR (300 MHz, $CDCl_3$) δ 6.03–5.92 (m, 4 H), 5.80–5.70 (m, 4 H), 2.60–2.50 (br d, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.4, 123.1, 32.9.

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Structure of Brevetoxin A (GB-1 Toxin), the Most Potent Toxin in the Florida Red Tide Organism *Gymnodinium breve* (*Ptychodiscus brevis*)

Yuzuru Shimizu,* Hong-Nong Chou, and Hideo Bando

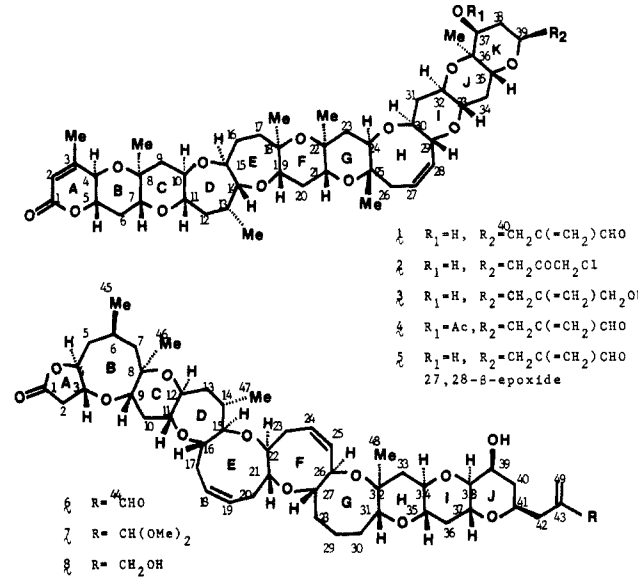
Department of Pharmacognosy and Environmental Health Sciences
College of Pharmacy, University of Rhode Island
Kingston, Rhode Island 02881

Gregory Van Duyne and Jon C. Clardy*

Department of Chemistry, Cornell University
Ithaca, New York 14853-1301

Received September 9, 1985

The dinoflagellate *Gymnodinium breve*[1] is the red tide causing organism responsible for massive fish kills and human intoxications including the so-called neurotoxic shellfish poisoning (NSP) in the Gulf of Mexico.[2] To date the structures of five polyether-type toxins, brevetoxin B (GB-2 toxin) (**1**),[3] brevetoxin C (**2**),[4] GB-3 toxin (**3**),[5] GB-5 toxin (**4**),[6] and GB-6 toxin (**5**),[6] have been established by X-ray crystallography and chemical and spectral correlations. The structure elucidation of the most potent ichthyotoxin, brevetoxin A[7] (LC_{100} 4 ng/mL to guppies), has preoccupied several groups, and a speculative structure was reported by a joint US–Japan group on the basis of NMR and mass spectral data.[8] The toxin is of particular interest not only because



it is the most potent toxin of this family, but also because it uniquely binds to sodium channels on excitable membranes.[9]

Brevetoxin A (**6**) was isolated from the cultured cells of *G. breve* by partition and successive chromatographic separations.[10] It forms fine prisms, mp 197–199 °C/218–220 °C (double melting point) from acetonitrile.[5] High-resolution FAB mass spectrometry gave the molecular formula $C_{49}H_{70}H_{13}$ (MH^+, m/z 867.4894; found, m/z 867.4927; $MH^+ - H_2O$, m/z 849.4789; found, m/z 849.4788). The ^1H and ^{13}C NMR spectra showed the presence of two secondary and two tertiary methyl groups, an α-methylene aldehyde, two disubstituted cis double bonds, and a carbonyl group. The IR absorption at $\nu(CH_2Cl_2)$ 1790 cm^{-1} suggested that the non-aldehydic carbonyl belongs to a γ-lactone. On the basis of extensive spin–spin decoupling, proton–proton coupling correlation (COSY), and proton–carbon correlation spectroscopy (hetero-COSY) experiments, we recently reported the partial structures shown in Figure 1 for **6**.[11] Due to the absence of certain signals in the COSY spectra and the discontinuity of proton couplings at the quarternary carbons, we were unable to connect these fragments with reasonable certainty. Although **6** was crystalline,[5] its X-ray analysis has not yet been successful. In an attempt to circumvent this difficulty, **6** was converted to a dimethyl acetal **7**, prisms, mp 233–235 °C, by treatment with methanol in the

(1) Some authors are using the newly proposed name *Ptychodiscus brevis* (Steidinger, K. A. "Toxic Dinoflagellate Blooms"; Taylor, D. L., Seliger, H. H., Eds.; Elsevier/North Holland: New York, 1979; pp 435–442), but a question has been raised regarding the appropriateness of the taxonomical change (e.g., Dodge, J. D. "Marine Dinoflagellates of the British Isles"; Her Majesty's Stationary Office: London, 1982; p 108). Present authors will use the traditional name until the matter is solved.

(2) Shimizu, Y. "Marine Natural Products"; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. I, pp 1–42. See also a collection of symposium papers on brevetoxins in: *Toxicon* **1985**, *23*, 4.

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(7) There is considerable confusion over the names of the toxins. GB-1 and GB-2 toxins were first reported in crude form by Alam et al. (Alam, M.; Trieff, N. M.; Ray, S. M.; Hudson, J. E. *J. Pharm. Sci.* **1975**, *64*, 865–867) and purified GB-2 with detailed spectroscopic data and structural information by Shimizu et al. (Shimizu, Y.; Alam, M., Fallon, W. F. "Proceedings of Food–Drugs from the Sea 1974"; Webber, H. H., Ruggieri, G. D., Eds.; Marine Technology Society: Washington, DC, 1976; pp 238–251 and ref 2). Later, supposedly identical compounds were reported under different names: T34, T47, and brevetoxin-B for GB-2 toxin and T46 and brevetoxin A for GB-1 toxin. Although we have been using the name GB-1 as the toxin preceding GB-2 toxin since 1974, here we decided to take an initiative to use brevetoxin A in order to avoid further confusion.

(8) Tempesta, M.; Golik, J.; James, J. C.; Nakanishi, K.; Pawlak, J.; Iwashita, T.; Gross, M. L.; Tomer, K. B. "The 1984 International Chemical Congress of Pacific Basin Societies"; Honolulu, HI, dec 16–21, 1984; Abstr. 10E 45. Nakanishi, K. *Toxicon* **1985**, *23*, 473–479. Proposed is a structure with the ring system 5(lactone)/6/6/7/11/8/8/6/6/6 and a trans double bond on the 11-membered ring. One of the major discrepancies is in the B-ring which was postulated as six membered with an angular methyl group.

(9) Catterall, W. A.; Risk, M. *Mol. Pharmacol.* **1981**, *19*, 345–348.

(10) The cells were extracted with methylene chloride, and the extract was partitioned between petroleum ether and 90% methanol. The methanolic extract was chromatographed on SiO_2 first with methylene chloride–benzene–methanol (40:5:1), and then with methylene chloride–ethyl acetate–methanol (5:3:0.1). After removal of brevetoxin B by crystallization, **6** was purified by HPLC [normal-phase SiO_2, isooctane–99% isopropyl alcohol (4:1)] in a yield of 1.2 mg from 10^9 cells. GB-7 (**8**) was separated from GB-3 toxin fraction[3] by HPLC [normal-phase SiO_2, isooctane–99% isopropyl alcohol (4:1)].

(11) Chou, H. N.; Shimizu, Y.; Van Duyne, G. D.; Clardy, J. "The Third International Conference on Toxic Dinoflagellate Blooms"; Anderson, D., Baden, D., Eds.; Elsevier: New York, 1985; in press.

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