ORGANIC
LETTERS

2001
Vol. 3, No. 16
2447−2449

One-Step Transformation of Tricyclopentabenzene (Trindane, $C_{15}H_{18}$) to Bicyclo(10.3.0)pentadec-1(12)ene-2,6,7,11-tetrone ($C_{15}H_{18}O_4$) and Its Aldol Product, 12-Hydroxy-16-oxatetracyclo-$(10.3.1.0.^{1,5}0^{7,11})$hexadec-7(11)ene-2,6-dione ($C_{15}H_{18}O_4$)[⊥]

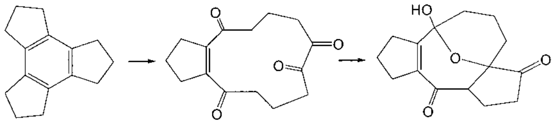
Subramania Ranganathan,[*,†,‡] K. M. Muraleedharan,[†] CH. Chandrashekhar Rao,[†] M. Vairamani,[§] and Isabella L. Karle[*,||]

Discovery Laboratory, Indian Institute of Chemical Technology,
Hyderabad 500 007, India, Jawaharlal Nehru Center for Advanced Scientific Research,
Bangalore 560 067, India, Mass Spectrometry Laboratory, Indian Institute of Chemical
Technology, Hyderabad 500 007, India, and Laboratory for the Structure of Matter,
Naval Research Laboratory, Washington, D.C. 20375-5341

williams@harker.nrl.navy.mil

Received April 26, 2001

ABSTRACT



1 2 3

Ozonolysis of 1 largely results in 2 and 3, having features similar to several classes of natural products. The retention of the C_{15} pericycle suggests preference for the cleavage of π-bonds *endo* to the cyclopentane ring. This unique property of trindane offers opportunities for synthesis of complex natural products from this hydrocarbon that can be made in quantity by acid-catalyzed trimerizatiion of cyclopentanone.

Spectroscopic properties of the tethered systems tricyclopentabenzene (trindane, **1**) and tricyclohexabenzene show no evidence of any serious perturbation of aromaticity.[1] Recent studies have shown that the fixation of the π-bonds in the ring can only be achieved by highly restraining the pericycle.[2]

In connection with studies on the transformation of **1** to modules suitable for self-assembly, we noted a marked difference in the reactivity profiles of **1** and tricyclohexabenzene toward ruthenium tetroxide oxidation. Trindane yielded only highly condensed, heavily oxygenated compounds having a resemblance to the naturally occurring ginkgolides, retaining the C_{15} periphery and arising from the

---

[⊥] Fondly dedicated to Darshan Ranganathan on the occasion of her 60th birthday.

[†] Indian Institute of Chemical Technology.

[‡] Jawaharlal Nehru Center for Advanced Scientific Research.

[§] Mass spectrometry laboratory, Indian Institute of Chemical Technology.

[||] Naval Research Laboratory.

(1) Heilbronner, E.; Kovac, B.; Nutakul, W.; Taggart, A. D.; Thummel, R. P. *J. Org. Chem.* **1981**, *46*, 5279−5284.

(2) (a) Boyku, E. R.; Vaughan, P. A. *Acta Crystallogr*. **1964**, *17*, 152−158. (b) Meier, V. H.; Muller, Eu.; Sur, H. *Tetrahedron* **1967**, *23*, 3713−3721. (c) Meier, V. H.; Heiss, J.; Sur, H.; Muller, Eu. *Tetrahedron* **1968**, *24*, 2307−2325. (d) Siegal, J. S. *Angew.Chem., Int. Ed. Engl*. **1994**, *33*, 1721−1723. (e) Burgi, H. B.; Baldridge, K. K.; Hardcastle, K.; Frank, N. L.; Gatzel, P.; Siegal, J. S.; Ziller, J. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1454−1456. (f) Frank, N. L.; Siegal, J. S. *Adv. Theor. Interesting Mol.* **1995**, *3*, 209−260. (g) Durr, R.; Lucchi, O. D.; Cossu, S.; Lucchini, V. *Chem. Commun*. **1996**, 2447−2448. (h) Stanger, A.; Ashkenazi, N.; Boese, R.; Blaser, D.; Stelolberg, P. *Chem. Eur. J.* **1997**, *3*, 208−211.

10.1021/ol010086g CCC: $20.00

exclusive oxidation of *endo* π-bonds.[3] In sharp contrast, tricyclohexabenzene gave products exclusively from benzylic oxidation.

The present work tends to further support the concept of a preference for *endo* π oxidation in **1** that retains the pericycle and should provide a general route to medium ring oxygenated compounds that can undergo further intramolecular changes to complex condensed systems having features similar to those of naturally occurring compounds.

A methylene chloride solution of trindane was ozonized for 3 h. Reductive workup using dimethyl sulfide, followed by chromatography of the neutral fraction on silica gel, yielded compounds **2**, **3**, and **4** (Figure 1).[4] The ^{1}H and ^{13}C NMR spectra showed the presence or absence of the benzene core. Thus, it was easily seen that while compound **4** retained the trindane core, in **2** and **3** the aromatic framework was absent. Whereas the structure for **4** could be derived from spectral data, those for **2** and **3** depended on the crystal structure of **3** and the ready transformation of compound **2** to its isomer **3**.

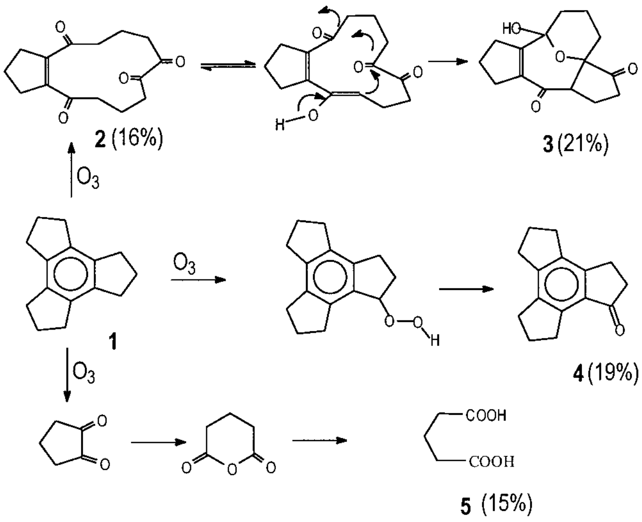


Figure 1. Products from ozonolysis of trindane (**1**).

Analytical and mass spectral data suggested the formulas of **2** and **3** to be $C_{15}H_{18}O_4$,[4] arising from the introduction of four oxygen atoms to the unsaturated hydrocarbon. Compound **2** was quite sensitive, and traces of acid transformed it mostly to **3**, which could be easily followed by IR and TLC. While the ^{1}H and ^{13}C NMR spectra of **2** and **3** exhibited a similar profile, their IR and TLC profiles were quite divergent. In the IR, the former showed no hydroxyl, which was present in **3**. In terms of polarity, the R_f values of **2** and **3** were respectively 0.75 and 0.25 (TLC, eluent = 40:60 benzene:ethyl acetate).

Compound **3** was found to possess the highly condensed structure shown in Figure 2B, by X-ray crystallography[5] of fine needles of this compound produced by crystallization from benzene−ethyl acetate. The structure of **2** (Figure 2A) followed directly from **3**, largely based on the facile transformation noted earlier. Diazomethane esterification and subsequent chromatography afforded dimethyl glutarate. The course of ozonolysis of trindane (**1**) is rationalized in Figure 1, where the yields of the various products secured are also given. A noteworthy feature here is the simple manner in which the bicyclic species **2** folds to generate the complex tetracyclic system **3**, initiated by enolate addition from the top side, as shown in Figure 1.

The action of either ruthenium tetroxide or ozone gave, largely or exclusively, products arising from attack on the π-bond *endo* to the cyclopentane present in **1**. While the "milder" ruthenium reagent led to oxidation products of all three π-bonds, ozonolysis resulted in the oxidative cleavage of two of the three endocyclic olefins. What seems to be general is that trindane and its derivatives can give oxidation products retaining the pericycle in complex condensed compounds. Surprisingly, although the pathways are grossly dissimilar, with both oxidizing agents the substances formed were closely related to the complex naturally occurring products.

The remarkable similarity of the product from ruthenium tetroxide oxidation of **1** to ginkgolides has been mentioned

---

[3] Ranganathan, S.; Muraleedharan, K. M.; Bharadwaj, P.; Madhusudanan, V. P. *Chem. Commun.* **1998**, 2239−40.

[4] Spectral data and experimental procedures for compounds **2**−**4**: Ozone was bubbled through a solution of trindane (0.495 g, 2.5 mmol) in dry CH_2Cl_2 (30 mL) at ~ −70 to −80 °C for 3.0 h, admixed with dimethyl sulfide (0.8 mL), and left stirring for 2 h, during which time it was allowed to reach room temperature, treated with saturated $NaHCO_3$ (10 mL), and stirred for an additional 1 h. The organic layer was separated, the aqueous layer was washed with additional CH_2Cl_2 (3 × 10 mL), the layers were combined, washed with distilled water (1 × 10 mL), dried ($MgSO_4$), and evaporated in vacuo, and the residue was chromatographed on a silica gel column, prepared initially in hexane. Elution with benzene:ethyl acetate (6:4) afforded, in sequence, **4** (0.100 g, 19%), **2** (0.105 g, 16%), and **3** (0.138 g, 21%), which crystallized from benzene:ethyl acetate as fine needles, mp 138−140 °C. **2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.80−2.32 (m, 6H, CH_2), 2.40−2.60 (m, 8H, $COCH_2$), 2.72−3.14 (m, 4H, allyl CH_2); ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.14, 19.62, 21.58. 29.63, 33.92, 34.30, 34.95, 35.34 (CH_2), 140.88 (C=C), 154.50 (C=C), 198.41 (C=O), 212.51 (α,β-unsaturated C=O); IR (neat) 3064, 1737, 1698, 1596, 1450, 1301, 1201, 1178, 1016, 690 cm^{-1}; GC-MS (*m/z*) (%) 262 (M) (11), 244 (M − 18) (13), 234 (M −1 × 28) (9), 206 (M -2 × 28) (14), 178 (M − 3 × 28) (16), 150 (M − 4 × 28) (78). **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41−2.21 (m, 10H, CH_2), 2.31−2.71 (m, 3H, $COCH_2$, t-CH), 2.75−3.29 (m, 4H, allyl CH_2); ^{13}C NMR (300 MHz, $CDCl_3$) δ 18.32, 20.01, 21.38, 30.15, 33.77, 34.32, 35.47, 35.81 (CH_2), 141.12 (C=C), 154.55 (C=C), 198.89 (C=O), 213.43 (α,β-unsaturated C=O); IR (neat) 3400, 2944, 1752, 1680, 1440, 1344, 1040 cm^{-1}; EI-MS (*m/z*) (%) 262 (M) (17), 246 (M − 16) (9), 234 (M − 1 × 28) (39), 206 (M − 2 × 28) (17). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.70; H, 6.87. Found: C, 68.57; H, 6.61. **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10−2.25 (m, 4H, CH_2), 2.65−3.05 (m, 10H, benzylic), 3.12−3.23 (m, 2H, $COCH_2$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 24.46, 24.98, 25.66. 28.89, 30.02, 31.34, 32.26, 36.66 (CH_2), 131.20−149.87 (aromatic), 207.80 (C=O); IR (neat) 2944, 1712, 1600, 1400, 1272, 1120 cm^{-1}; FAB-MS (*m/z*) (%) 213 (M + H) (74). The bicarbonate layer was adjusted to pH 2 with citric acid, extracted with ethyl acetate (3 × 15 mL), washed with water (1 × 10 mL), dried ($MgSO_4$), evaporated, and esterified with ethereal diazomethane to afford 0.06 g (15%) of dimethyl glutarate, identical to an authentic sample.

[5] Crystal structure data for **3**: $C_{15}H_{18}O_4$ (four independent molecules), space group $P(-1)$, $Z = 8$, $a = 11.471(1)$ Å, $b = 14.158(1)$ Å, $c = 17.121(1)$ Å, $\alpha = 73.02(0)°$, $\beta = 89.26(0)°$, $\gamma = 89.44(0)°$, $V = 2659.1$ Å^3, $d_{calc} = 1.310$ g/cm^3, $R_1 = 6.07\%$ for 4855 data observed with $F_o > 4\sigma$, Cu Kα radiation. X-ray data collected on Bruker P4 diffractometer, $\theta{-}2\theta$ scan mode, scan speed 13°/min, scan width 1.9°. Structure was determined by direct phase determination. Coordinates, bond lengths, bond angles, anisotropic thermal parameters, and hydrogen coordinates are deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

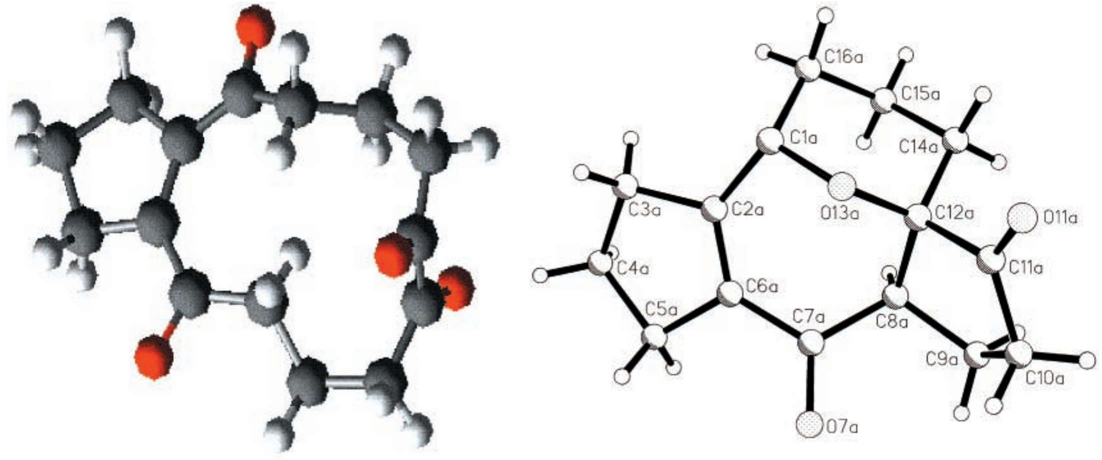


Figure 2. (A) Energy-minimized structure of **2**. (B) X-ray structure of **3**.

earlier.[3] The 12-membered ring present in **2** is common to several classes of natural products such as bertyadiomol, cubegene, curculothyrane, esulone, jatrophone, and euphoscopin.[6a−f]

Compound **3** presents a composite feature of several classes of natural products. The oxygen-bridged hemiketal arising from transannular addition is present in rugosic acid[7] and curcumenol.[8] The nine-membered bicyclic system present in **3** is a feature seen in taxane diterpenes, xeniphyllane, acanthamolide, acetyl coriacenone, acahetolide, dilopholide, physaline, and sanadaol.[9a−h] Finally, the overall profile of **3** can be compared with that of taxols, dolastanes, isodancanediol, germacren, oxycurcumenol, and guainaolide.[10a−f]

The structural similarities of **3** and the above-mentioned natural products are shown in Figure 3.

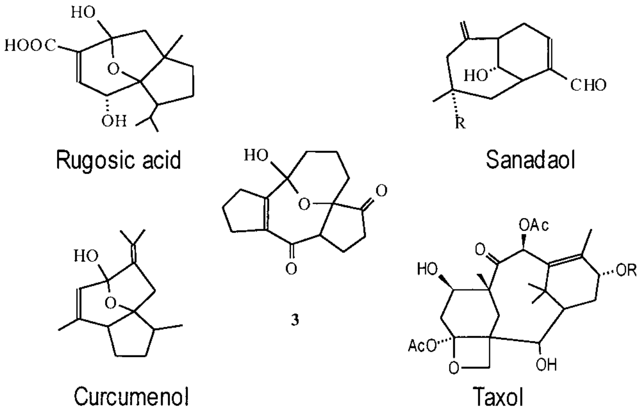


Figure 3. Structural similarities of **3** with classes of natural products having common features.

Our studies on trindane tend to suggest that suitably tethered benzene rings can be expected to show a preference for *endo* π-activity, thus providing a target in synthetic design for diverse open and condensed systems.

Acknowledgment. Financial support was provided by a National Institutes of Health Grant (GM-30902), the Office of Naval Research, and the Department of Science and Technology, New Delhi.

Supporting Information Available: X-ray crystallographic data for **3.** This material is available free of charge via the Internet at http://pubs.acs.org.

OL010086G

---

(6) (a) Ghisalderti, E. L.; Jefferies, P. R.; Pyne, T. G.; Worth, G. K. *Tetrahedron* **1973**, *29*, 403−412. (b) Tempesta, M. S.; Pawlak, J. K.; Iwashita, T.; Naya, Y.; Nakanishi, K. S.; Preastwich, G. D. *J. Org. Chem.* **1984**, *49*, 2077−2079. (c) Naengechomnong, W.; Phebtaranonth, Y.; Wiriyachitu, P.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1986**, *27*, 5675−5678. (d) Manners, G. D.; Wong, R. Y. *J.Chem. Soc., Perkin Trans.* 1 **1985**, 2075−2081. (e) Kupchan, S. M.; Sigel, C. W.;. Matz, M. J.; Renauld, S. J. A.; Haltiwanger, R. C.;. Bryan, R. F.; *J. Am.Chem. Soc.* **1970**, *92*, 4476−4477. (f) Yamamura, S.; Shizuri, Y.; Kosemura, S.; Ohtsuka, J.; Tayama, T.; Ohba, S.; Ito, M.; Saito, Y.; Terada, Y. *Phytochemistry* **1989**, *28*, 3421−3436.

(7) Hashidoko, Y.; Tahara, S.; Mizutani, J. *Phytochemistry* **1989**, *28*, 425−430.

(8) Hikino, H.; Sakurai, Y.; Numabe, S.; Takenoto, T. *Chem. Pharm. Bull. (Tokyo)* **1968**, *16*, 39−42.

(9) (a) Swindell, C. S. *Studies in Natural Products Chemistry*; Atta-ur-Rahmann, Ed; Elsevier: 1993; Vol. 12, p 170. (b) Groweiss. A.; Kashman. Y.; *Tetrahedron* **1983**, *39*, 3385−3396. (c) Saleh, A. A.; Cordell, G. A.; Farnsworth, N. R.; *J. Chem. Soc., Perkin Trans. 1* **1980**, 1090−1097. (d) Ishitsuka, M.;.Kusumi, T.; Katisawa, H. *J. Org. Chem.* **1983**, *48*, 1937−1938. (e) Bodo, B.; Molho, L.; Davoust, D.; Molho, D. *Phytochemistry* **1983**, *22*, 447−451. (f) Bouaicha, N.; Pesando, D.; Puel, J. *J. Nat. Prod.* **1993**, *56*, 1747−1752. (g) Row: R. L.; Reddy, S. K.; Sharma, S. N.; Matsuura, T.; Nakashima, R. *Phytochemistry* **1980**, *19*, 1175−1181.(h) Ishitsuka, M.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1982**, *23*, 3179−3180.

(10) (a) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881−930. (b) Ochi, M.; Miura, I.; Tokorayana, T. *Chem. Commun.* **1981**, 100. (c) Sung, T. V.; Kutschabsky, L.; Porzel, A.; Steglich, W.; Adam, G. *Phytochemistry* **1992**, *31*, 1659−1661. (d) Bohlmann, F.; Singh, P.; Jakupovic, J. *Phytochemistry* **1982**, *21*, 157−160. (e) Firman, K.; Kinoshita, T.; Itai, A.; Sankawa, W. *Phytochemistry* **1988**, *27*, 3887−3891. (f) Fukai, T.; Takahashi, C.; Nomura, T.; Uno, J.; Arai, T. *Heterocycles* **1988**, *27*, 2333−2340.