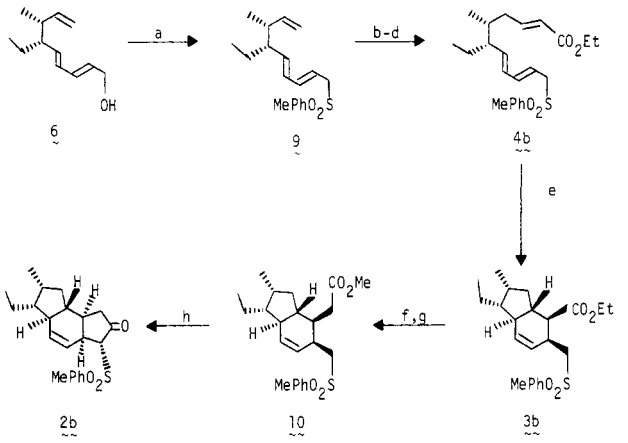
Scheme III[a]



[a] All reactions were carried out under nitrogen. (a) (*i*) MeLi (1.05 equiv), 3:1 Et_2O/HMPA, 0 °C, 30 min; (*ii*) TsCl (1.2 equiv), HMPA, 0 °C, 2.5 h; (*iii*) $MePhSO_2Na \cdot 2H_2O$ (1.2 equiv), DMF, 25 °C, 16 h (88% overall). (b) (*i*) 9-BBN (1.2 equiv), THF, 25 °C, 2.5 h; (*ii*) NaOH, H_2O, H_2O_2, 25 °C, 2.5 h (81%). (c) PCC (8.0 equiv), CH_2Cl_2, 25 °C, 2.5 h (89%). (d) $(EtO)_2P(O)CH_2CO_2Et$, (1.05 equiv), KOH (3.8 equiv), THF, 25 °C, 15 min (71%). (e) **4b** in *m*-xylene (0.05 M), degassed, 139 °C, 32 h (70%). (f) 1:8 6 N aqueous KOH/EtOH, reflux, 2 h (95%). (g) (*i*) $SOCl_2$ (2.0 equiv), pyridine (0.02 equiv), CH_2Cl_2, 25 °C, 4 h; (*ii*) CH_2N_2 (2.5 equiv), 2:1 Et_2O/THF, 0 °C for 30 min and 25 °C for 30 min; (*iii*) Ag_2O (1.6 equiv), MeOH, 64 °C, 2 h (75% overall). (h) NaH (4.0 equiv), THF, 25 °C, 1 h (90%).

With lactone **7** in hand, annulation via a carbonyl insertion procedure was broached. While tetrahydrofuran formation was problematic in the bistosylation of the diol obtained by lithium aluminum hydride reduction of **7**, bismesylation to **8**[11] was well disposed (76% from **7**). Treatment of **8** with disodium tetracarbonylferrate (Collman's reagent)[14] in 1-methyl-2-pyrrolidinone containing triphenylphosphine gave **2a**[11] in disappointingly low yield (5%).[15]

In light of this outcome, a congener was sought which would facilitate ring C formation. An arylsulfone modified Diels–Alder substrate appeared ideal inasmuch as the arylsulfone moiety might (a) accommodate a variety of synthetic manipulations, (b) access condensative ring C formation, and (c) regiospecifically functionalize the incipient octahydro-*as*-indacenone, thus extricating elaboration to ikarugamycin. Scheme III delineates our realization of these objectives.

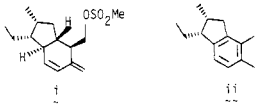
A convenient one-pot tosylation/sulfinate displacement sequence[16] converted **6** to sulfone **9**[6] in 88% yield. The series of reactions described for **6** → **4a** were now repeated on sulfone **9**. Thus, regioselective hydroboration with 9-BBN, PCC oxidation, and finally Horner–Emmons condensation led to **4b**[6] in 52% overall yield from **9**. Diastereoface selective Diels–Alder cycloaddition of **4b** afforded crystalline **3b**[11] in 70% isolated yield. Two minor isomers were obtained in 14% yield.[17] Elaboration of **3b** to **2b** required one carbon ester homologation and was accomplished via a standard Arndt–Eistert procedure.[18] Accordingly, **3b** was saponified and the crude acid converted to the acid chloride. Diazomethane treatment followed by silver oxide promoted Wolff rearrangement in refluxing methanol furnished ester **10**[11] in 72% overall yield from **3b**. Sulfone/ester cyclization was effected with sodium hydride in THF, providing octahydro-*as*-indacenone **2b** as the only isolable product in 90% yield. The stereochemical integrity of **2b**[19] was verified by its desulfurization[20] to **2a**[19] (76%).

The enantioselective preparation of **2** is currently in progress.[21] Further developments stemming from these investigations will be forthcoming.

Acknowledgment is made to the Committee on Research of the University of California, Davis and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research. We gratefully acknowledge IBM Instruments for donation of an LC/9533 ternary high-pressure liquid chromatography system.

(14) Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342.

(15) The only other compound isolated was elimination product i[11] (23% from **8**) which readily aromatized to indan ii.



(16) Altman, L. J.; Ash, L.; Marson, S. *Synthesis* **1974**, 129.

(17) While MPLC afforded pure **3b**, the two minor isomers, which are presumed to be the methyl epimer of **3b** and the exo addition isomer, were cross-contaminated.

(18) Boeckman, R. K., Jr.; Sum, F.-W. *J. Am. Chem. Soc.* **1982**, *104*, 4604.

(19) (a) Data for **2a**: ^1H NMR (360 MHz, $CDCl_3$) δ 5.91 (d, *J* = 9.9 Hz, 1 H, H-5), 5.76 (dt, *J* = 9.9, 3.3 Hz, 1 H, H-4), 2.95 (m, 1 H, H-3a), 2.46 (dd, *J* = 18.7, 9.0 Hz, 1 H, H-3), 2.42 (ddd, *J* = 18.5, 8.5, 1.3 Hz, 1 H, H-1), 2.34–2.23 (m, 3 H, H′-1, H-7, H-8b), 2.11 (dt, *J* = 12.6, 7.2, 1 H, H-8α), 1.98 (ddd, *J* = 18.7, 11.5, 1.3 Hz, 1 H, H′-3), 1.65 (br t, *J* = 9.0 Hz, 1 H, H-5a), 1.55–1.31 (m, 4 H, CH_2-10, H-8a, H-6), 0.94 (t, *J* = 7.2 Hz, 3 H, CH_3-11), 0.90 (d, *J* = 7.2 Hz, 3 H, CH_3-9), 0.73 (ddd, *J* = 11.9, 11.9, 6.8 Hz, 1 H, H-8β); IR ($CHCl_3$) 3020, 1735, 1595 cm^{-1}; mass spectrum, *m/e* 218 (molecular ion); exact mass spectrum calcd for $C_{15}H_{22}O$ 218.1671, found 218.1643. (b) Data for **2b**: mp from hexane/ethyl acetate 126–127.5 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.8 Hz, 2 H, H-Ar), 7.36 (d, *J* = 8.8 Hz, 2 H, H-Ar), 5.98 (d, *J* = 9.8 Hz, 1 H, H-5), 5.69 (dt, *J* = 9.8, 3.3 Hz, 1 H, H-4), 3.60 (m, 1 H, H-3a), 3.44 (dd, *J* = 9.3, 1.4 Hz, 1 H, H-3), 2.64 (dd, *J* = 17.6, 8.4 Hz, 1 H, H-1β), 2.46 (s, 3 H, CH_3-Ph), 2.33 (br d, *J* = 17.6 Hz, 1 H, H-1α), 2.36–2.18 (m, 2 H, H-7, H-8b), 2.05 (dt, *J* = 12.0, 7.4 Hz, 1 H, H-8α), 1.65 (br t, *J* = 10.9 Hz, 1 H, H-5a), 1.55–1.30 (m, 3 H, H-6, CH_2-10), ca. 0.95 (m, 1 H, H-8a), 0.92 (t, *J* = 7.0 Hz, 3 H, CH_3-11), 0.87 (d, *J* = 7.2 Hz, 3 H, CH_3-9), 0.71 (ddd, *J* = 12.0, 12.0, 6.7 Hz, 1 H, H-8β); IR (CCl_4) 3024, 1748, 1592 cm^{-1}; mass spectrum, *m/e* 372 (molecular ion). Anal. Calcd for $C_{22}H_{28}O_3S$: C, 70.93; H, 7.58. Found: C, 70.78; H, 7.59.

(20) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345. Anal. Calcd for $C_{22}H_{28}O_3S$: C, 70.93; H, 7.58. Found: C, 70.78; H, 7.59.

(21) For economic and esthetic reasons, our approach focuses on the enantioselective preparation of pentenoic acid **5** via an aza-Claisen rearrangement. For preliminary results, see: Kurth, M. J.; Decker, O. H. W. *Tetrahedron Lett.* **1983**, *24*, 4535.

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On the Stability of Trimethylenemethane Dications

Summary: Substituted trimethylenemethane dications do not show the expected "Y-aromatic" stabilization in solution. The triphenyl-substituted system cyclizes to an indenyl monocation (**2**). The 2-(2-propenyl)-1,1,3-trimethylallyl cation **5** is not protonated a second time in magic acid. The highly stabilized tri(1-ethanolidene)-methane dication **9** has, however, been generated and is found to persist to at least 0 °C.

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Sir: MNDO calculations[1] indicate that doubly charged Y-conjugated systems may be more stable than their cyclic Hückel aromatic counterparts. Dianion chemistry supports this conclusion. Thus, the six-electron trimethylenemethane dianion[2] and its derivatives[3] are easily synthesized whereas comparably substituted cyclobutadiene dianions were only obtained recently with some difficulty.[4] In contrast, doubly positively charged systems appear to behave differently. While Olah's group and other workers have studied a large number of carbodications,[5] including derivatives of the 2π Hückel aromatic cyclobutadiene dication,[6] "Y-aromatic"[7] 2π trimethylenemethane dications have not been reported. We have therefore attempted to synthesize several trimethylenemethane dicaton derivatives. In contrast to the dianionic systems, Y-conjugation does not appear to lead to stable dications in most instances.

Diol **1** did not give the Y-conjugated tribenzylidenemethane dication on treatment with magic acid at −115 °C, but rather the ring-closed singly charged species **2**. Similar ring closures are well-known; for example, phenylallyl cations can only be observed at low temperatures if the 2-position is unsubstituted.[8]

Diol **3**, on the other hand, gave only monocation **5** at −85 °C in magic acid. The ^{13}C NMR spectrum shows at least 90% of one isomer, **5** (^{13}C chemical shifts relative to external Me_4Si are shown). The fact that **5** and not **7** is observed suggests that dication **6** is not formed but rather that water eliminates directly from **4** to give **5** rather than the more stable isomer **7**. The ^{13}C NMR spectrum gives no indication that **5** is protonated to give **6**. This result indicates that the trimethylenemethane dication system is not favorable energetically. Whereas cyclobutadiene dications with only four methyl substituents are observable,[6] **6**, with five stabilizing methyl groups, is not found under similar conditions. A sixth methyl group is not expected to improve the situation. Steric crowding would prevent the hexamethyl-substituted Y-dication from becoming planar. This difficulty may be overcome in appropriate polycyclic systems, and we are pursuing such possibilities.

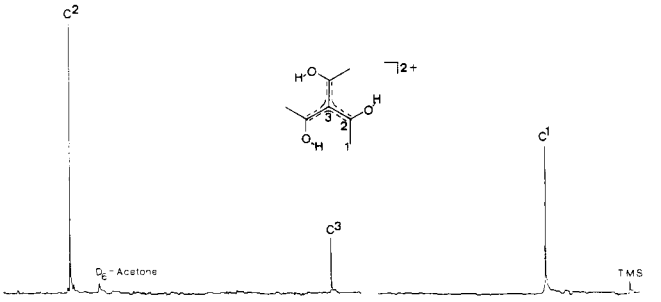
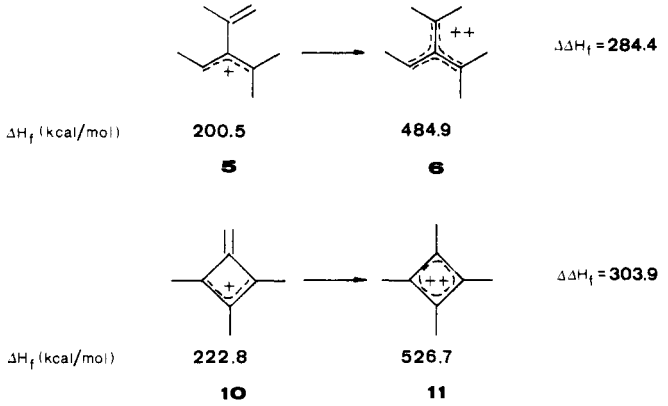


Figure 1. ^{13}C NMR spectrum of **9** in SO_2ClF/MA at 0 °C.

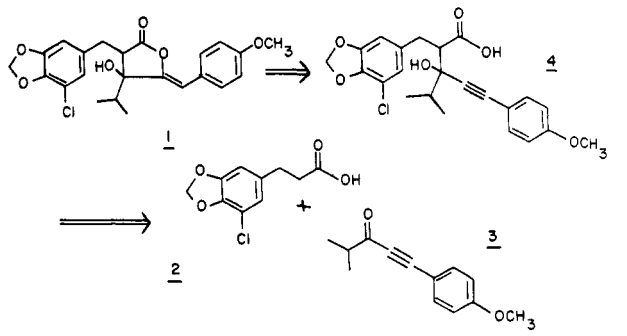
The enol/triketone system **8** does, however, lead to a symmetrical trimethylenemethane dication derivative **9** on double protonation in magic acid at −80 °C. Only three ^{13}C NMR signals and two ^1H resonances (at δ 3.6 (CH_3) and 13.2 (OH)) are observed. Although **9** is stable at least up to 0 °C, the ^{13}C chemical shifts indicate that the charge is situated predominantly on the three oxygen atoms. The difference in total ^{13}C chemical shifts between the predominate enol form of **8** and **9** (shown in the Figure 1) is 76.6 ppm, which corresponds[9] to an increase of π charge on only +0.48 on the carbons. In other carbodications, total ^{13}C chemical shift differences of up to 830 ppm have been reported.[5,10] The behavior of the tribenzylidenemethane dianion,[3] which delocalizes less charge to the phenyl substituents than its Hückel cyclobutadiene dianion equivalent,[4] is quite different. The ^{13}C spectrum of **9** does not change from −90 to 0 °C, suggesting either that only one conformer with C_3 symmetry is present or that the barrier to rotation in the central C–C bonds is less than 9 kcal/mol.

The reason for the observed instability of trimethylenemethane dications may be thermodynamic or kinetic. However, in agreement with our general conclusions,[1] the protonation of **5** to give **6** is calculated to be more favorable by MNDO[11] than the corresponding reaction to give the known[6] tetramethylcyclobutadiene dication. As in other cases,[1] the greater stability of dication **6** can be attributed to lower electrostatic repulsion than is possible in **11**. These arguments apply more particularly to the gas phase. Solvation in superacid solution should decrease the effective atomic charges and may therefore

(1) Clark, T.; Wilhelm, D.; Schleyer, P. v. R. *Tetrahedron Lett.* **1982**, *23*, 3547.
(2) Klein, J.; Medlik, A. *J. Chem. Soc., Chem. Commun.* **1973**, 275.
(3) Wilhelm, D.; Clark, T.; Schleyer, P. v. R.; Buckl, K.; Boche, G. *Chem. Ber.* **1983**, *116*, 1669. Mills, N. S.; Schapiro, J.; Hollingsworth, M. J. *J. Am. Chem. Soc.* **1981**, *103*, 1236. But see also: Mills, N. S. *Ibid.* **1982**, *104*, 5689.
(4) Boche, G.; Etzrodt, H.; Marsch, M.; Thiel, W. *Angew. Chem.* **1982**, *94*, 141, *Angew. Chem. Suppl.* **1982**, 345, 355; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 132, 133.
(5) Review: Prakash, G. K.; Rawdah, T. N.; Olah, G. A. *Angew. Chem.* **1983**, *95*, 356; *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 390.
(6) Olah, G. A.; Staral, J. S. *J. Am. Chem. Soc.* **1967**, *98*, 6290.
(7) Gund, P. *J. Chem. Ed.* **1972**, *49*, 100. Phelan, N. F.; Orchin, M. *Ibid.* **1968**, *45*, 633. Inagaki, S.; Hirabayashi, Y. *Chem. Lett.* **1982**, 709.
(8) Dytnerski, D. M.; Ranganayakulu, K.; Singh, P. B.; Sorensen, T. S. *Can. J. Chem.* **1982**, *60*, 2993. Olah, G. A.; Asensio, G.; Mayr, H. *J. Org. Chem.* **1978**, *43*, 1518.
(9) Spiesecke, H.; Schneider, W. G. *J. Chem. Phys.* **1961**, *35*, 731. Also see: ref 5.
(10) Schleyer, P. v. R.; Lenoir, D.; Mison, P.; Liang, G.; Surya Prakash, G. K.; Olah, G. A. *J. Am. Chem. Soc.* **1980**, *102*, 683.
(11) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899, 4907.



Scheme I



negate the electrostatic advantage of Y-conjugation, so that the Hückel resonance energy, which favors **11**, dominates.

Alternatively, our failure to observe **6** may be due to kinetic inhibition of protonation of **5**, which must be produced by a concerted elimination. In this context Olah[12] has noted that the 2,4-dimethylpenta-2,4-diyl dication has, at best, a transient existence. Our results suggest that **6** is not an intermediate in the elimination.

These observations indicate no special stabilization of trimethylenemethane dications in solution to be present. We are continuing to investigate such systems, which clearly behave differently from their dianionic counterparts.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

(12) Olah, G. A.; Grant, J. L.; Spear, R. J.; Bollinger, J. M.; Serianz, A.; Sipos, G. *J. Am. Chem. Soc.* **1976**, *98*, 2501.

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Total Synthesis and X-ray Structure Determination of Cyanobacterin[1]

Summary: Racemic cyanobacterin has been synthesized and subjected to X-ray diffraction analysis in order to establish unambiguously the structure.

Sir: Antibiotic activity was reported recently from the ether extract of a freshwater cyanobacterium, *Syctonema hofmanni*.[2] The active antibiotic, designated cyanobacterin, also inhibits the growth of numerous blue-green algae. This algicidal activity suggests that cyanobacterin may be an allelopathic substance that allows the *Scytonema* to compete favorably with more prolific algae. The structure of cyanobacterin, lacking stereochemistry, was reported as **1**.[2] This is the first chlorinated, fresh-water derived antibiotic and represents a new natural product skeleton. We report herein the first total synthesis and X-ray crystal structure determination of racemic cyanobacterin.

An expeditious route to cyanobacterin is given retrosynthetically in Scheme I. The key steps of our synthesis are depicted as addition of **2** to **3** and subsequent enol lactonization of **4**. The two starting materials in Scheme I, i.e., **2** and **3**, have not been prepared previously. Our preparation of both of these compounds is given in Scheme II.[3] This sequence of reactions allows for the preparation of both **2** and **3** on a multigram scale.

In Scheme III, the results of addition of lithium ester enolates **13a**, **13b**, or **13c** to ketone **3** are presented. These additions are carried out by adding **3** to a preformed enolate at −78 °C in THF, followed by warming to 0 °C.[8] Only the products of direct 1,2-addition of **13a**, **13b**, or **13c**, to **3** are observed.[9] The overall yields and isomer ratios for diastereomeric priority antireflective (PARF)[10] **14** and priority reflective (PREF)[10] products **15** are also given. The transition state pictured correctly predicts diastereoselection in favor of the PREF isomers, **15a** and **15c**, for the monoanion additions.

The diastereomeric esters **14a** and **15a**, from the reaction of **13a** with **3**, are readily separable by column chromatography. The less polar, minor isomer **14a** crystallized as long white needles, allowing for its unambiguous structure determination by X-ray crystallography.[11] It was not possible to hydrolyze the ethyl esters **14a** or **15a** without causing a retroaldol reaction or a dehydration. Consequently, it became advantageous to utilize the monoanion of trimethylsilyl ester **13c** because the trimethylsilyl ester hydrolyzes spontaneously upon workup. Both the yield and the diastereoselection of the reaction of **13c** with **3** are most favorable. Thus, the diastereomeric carboxylic acids **14b** and **15b** are obtained from reaction

(1) A preliminary account of this work, in which the first total synthesis of cyanobacterin was disclosed, was presented at the 186th National Meeting of the American Chemical Society, Washington, DC, Aug 1983, ORGN 293.

(2) Mason, C. P.; Edwards, K. R.; Carlson, R. E.; Pignatello, J.; Gleason, F. K.; Wood, J. M. *Science (Washington, D.C.)* **1982**, *215*, 400.

(3) All new compounds reported herein were characterized by ^{1}H and ^{13}C NMR, IR, UV, and mass spectroscopy. Yields reported refer to distilled or chromatographically pure, isolated material.

(4) Weissenfels, M.; Schurig, H.; Huehsam, G.; *Z. Chem.* **1966**, *6*, 471.

(5) Bodendorf, K.; Mayer, R. *Chem. Ber.* **1965**, *98*, 3554.

(6) Hann, R. M.; Spencer, G. C. *J. Am. Chem. Soc.* **1927**, *49*, 535.

(7) Clark, J. H.; Holland, H. L.; Miller, J. M. *Tetrahedron Lett.* **1976**, 3361.

(8) Enolate **13a** is prepared by addition of a THF solution of **12** to a slight excess of LDA in THF at −78 °C. Enediolate **13b** is formed from the carboxylic acid **2** and a slight excess of 2 equiv of LDA analogously. Trimethyl silyl ester enolate **13c** is prepared by treatment of the corresponding trimethyl silyl ester, formed in situ from **3**, Me_3SiCl and LDA, with excess LDA. No significant dehydrohalogenation of **13a–c** is observed at −78 °C.

(9) We do not observe equilibration between 1,2-addition and 1,4-addition of the enolates **13a–c** to **3** at 0 °C as has been observed in the reaction of α-substituted ester enolates with cyclohexenone; cf. Schultz, A. G.; Lee, Y. K. *J. Org. Chem.* **1976**, *41*, 4044.

(10) Carey, F. A.; Kuehne, M. E. *J. Org. Chem.* **1982**, *47*, 3811.

(11) Crystallographic parameters appear in the microfilm edition. Publication of complete crystallographic details is planned: P. G. Williard and T.-T. Jong, manuscript in preparation.

0022-3263/84/1949-0735$01.50/0