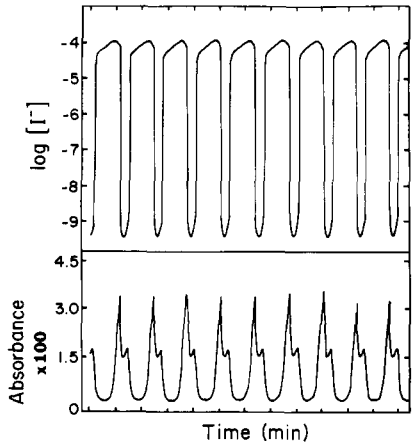

Figure 1. Oscillations of the iodide concentration and absorption per cm path length at 460 nm for $[KIO_3]_0 = 24 \times 10^{-3}$ M, $[As_2O_3]_0 = 2 \times 10^{-3}$ M, $[NaClO_2]_0 = 2 \times 10^{-3}$ M with $[Na_2SO_4]_0 = 0.1$ M, $[H_2SO_4]_0 = 0.01$ M, residence time = 400 s and $T = 25$ °C. Concentrations are given in the reactor after mixing but before any reaction takes place.

In some regions of the phase diagram, one or more stable steady states may coexist with the oscillatory state. Because of this complication, it is most convenient to initiate the oscillations by a single addition of 10^{-3} M iodide to the reactor.

In future papers we shall present further experimental data as well as a discussion of the mechanism of the oscillating arsenite–iodate–chlorite system. Detailed treatments of the mechanism of the arsenite–iodate bistability and of the chlorite–iodide system in a CSTR will also appear elsewhere.

This work was supported by a grant (CHE 79-05911) from the National Science Foundation.

Pentaprismane[1]

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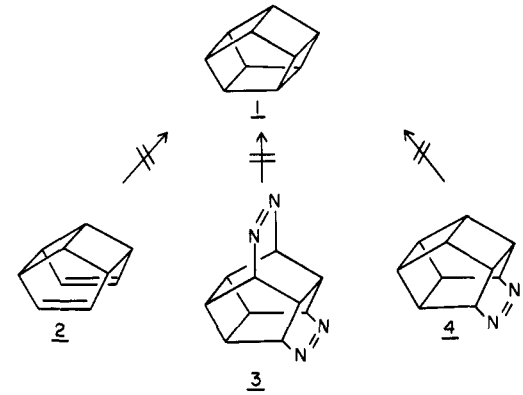
Received January 29, 1981

Pentaprismane (**1**) is composed of ten identical methine units arranged at the corners of a regular pentagonal prism (D_{5h} symmetry) and bound into two parallel 5-membered rings conjoined by five 4-membered rings. Empirical force-field calculations put the total strain energy at 135–145 kcal/mol.[2] Many efforts to construct this ring system have failed. Hypostrophene (**2**), an attractive and seemingly appropriate precursor, has been prepared in this laboratory and independently in those of Paquette and Pettit, but no one has been able to effect the called-for photoclosure to pentaprismane.[3] Synthesis by photo/thermal extrusion of molecular nitrogen from diaza compounds **3** and **4** has been attempted by Shen and by Allred, respectively, but again without success.[4] Various rationalizations for these failures have been put forth;[4,5] suffice it to say here, pentaprismane has been recognized for its "extraordinary synthetic inaccessibility".[4b] We



report now the first synthesis of pentaprismane; the route starts with a new synthesis of homopentaprismanone and proceeds by bridgehead functionalization of this cage compound and ultimate ring contraction.

Homopentaprismanone (**12**) was first prepared by Pettit and co-workers in 1971 starting with photoaddition of cyclobutadiene iron tricarbonyl to tropone ketal.[6] Although conceptually fascinating, the approach is useless synthetically; the starting materials are difficult to obtain, and the ultimate yield of homopentaprismanone is very low. Taking cues from our own and the various other published preparations of homohypostrophene and homopentaprismane,[7] we have developed a new approach to this ketone (Scheme I). The overall yield is now reasonable (34%), and as the starting material is easily made by Diels–Alder reaction of readily available addends,[8] substantial amounts of homopentaprismanone can be accumulated without difficulty.

Favorskii contractions (semibenzilic rearrangements) have been uniquely successful for the synthesis of strained polycyclic compounds related to cubane.[9] The reaction as usually done requires an α-haloketone. An early idea in our planning for pentaprismane was to take compound **6** through Scheme I without the dechlorination step. This might have given tetrachlorohomopentaprismanone, seemingly ready for contraction to the prismane.[9b-e] However, on reflection, it seemed likely that the chlorine substituents would not be passive through the sequence. Further, it is known that Haller–Bauer cleavage of nonenolizable ketones, the competing reaction in Favorskii contractions,[9b,d] is favored by such electronegative, anion-stabilizing groups. Thus, the decision was made to remove the chlorines at the beginning of the scheme and, consequently, to develop methodology to introduce the necessary leaving group directly onto homopentaprismanone.

Functionalization of homopentaprismanone α to the carbonyl groups involves invasion at the bridgehead, a serious problem in such rigid systems. We speculate that the best way will in time turn out to be via the bridgehead anion, taking advantage of inductive stabilization by the carbonyl group. The technology for doing this has yet to be found. Perforce, we developed the quite different approach shown in Scheme II. This cleavage-recoupling procedure should be applicable to α functionalization of other 7-norbornanones as well. For the case at hand, the yield averages 40–45% overall. There is little problem preparing several

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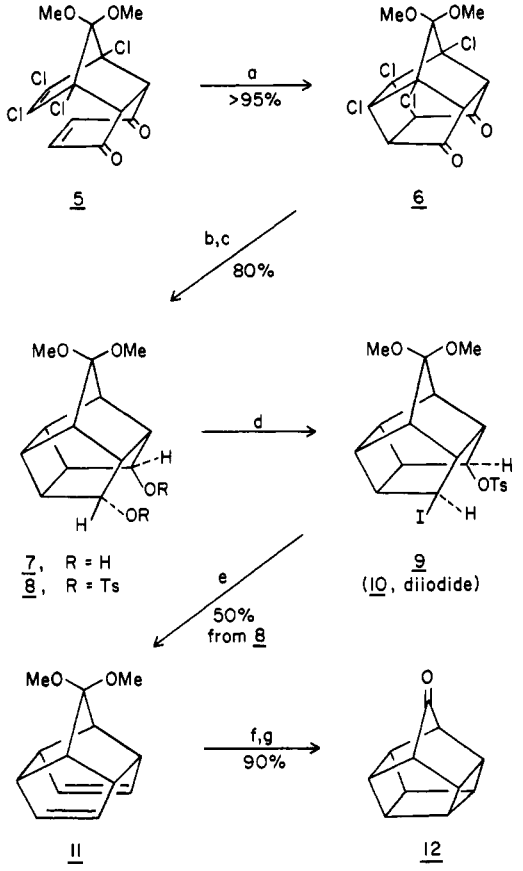
Scheme I[a]



[a] (a) $h\nu$/acetone; **6**, mp 151–152 °C (lit.[8c] 151.5–152.5 °C). (b) Li/liquid NH_3/THF/*t*-BuOH(H_2O)/–33 °C; **7**, mp 182–183 °C. (c) TsCl/py/0 °C; **8**, mp 153.7–154.5 °C. (d) NaI/HMPA/110 °C/48 h; **9**, mp 143–145 °C; **10**, mp 132.5–133 °C. (e) *t*-BuLi–pentane/ether/25–30 °C on **9**/**10** mixture; **11**, purified via $AgNO_3$ complex, mp 70.5–73 °C. (f) $h\nu$/acetone; **12**–dimethyl ketal, mp 64–66 °C. (g) ether/30 wt% H_2SO_4/20 °C; **12**, mp 154.8–155.2 °C (lit.[6] 154 °C).

Table I. Some Properties of the Known Parent Prismanes[14,15]

	triprismane	tetraprismane	pentaprismane
point group	D_{3h}	O_h	D_{5h}
mp, °C	liquid	130–131	127.5–128.5
IR ν, cm^{-1} [a]	3066, 1765, 1640, 1233, 950, 881, 798, 733, 670	2992, 1235, 852	2973, 1273, 1231, 1069, 875, 768
δ ^{1}H	2.28	4.04	3.48
δ ^{13}C	30.6	47.3	48.6
J^{13}C–H (Hz)	180	155	148
~% *s* (C–H)[b]	36	31	30

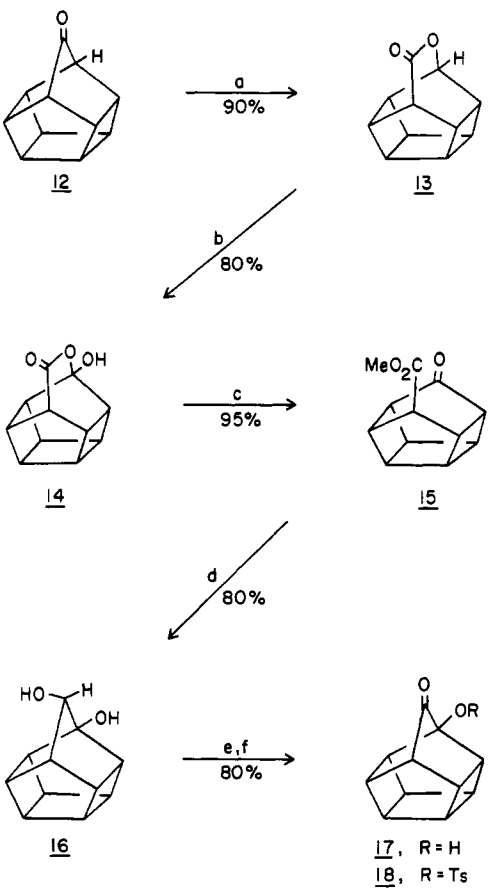
[a] In the region 3800–625 cm^{-1}. [b] Calculated as J (^{13}C–H)/5.

grams of hydroxyhomopentaprismanone (**17**) in one run.

As illustrated in the final reaction sequence (Scheme III), heating the tosylate of **17** with strong aqueous base effects successful contraction to pentaprismanecarboxylic acid [**19**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 12.6 (1 H), 3.88 (1 H, t, $J \sim 4$ Hz), 3.74 (2 H, m, $w_{h/2} \sim 10$ Hz), 3.59, 3.56, 3.52 (6 H total, overlapping m, each $w_{h/2} \sim 10$ Hz); ^{13}C NMR ($CDCl_3$, 22.63 MHz, H decoupled) δ 180.6, 60.5, 52.6, 50.9 (2 C), 49.1 (2 C), 48.2 (2 C), 46.4 (2 C)]. The contraction yield is reproducibly 60–65%;[13]

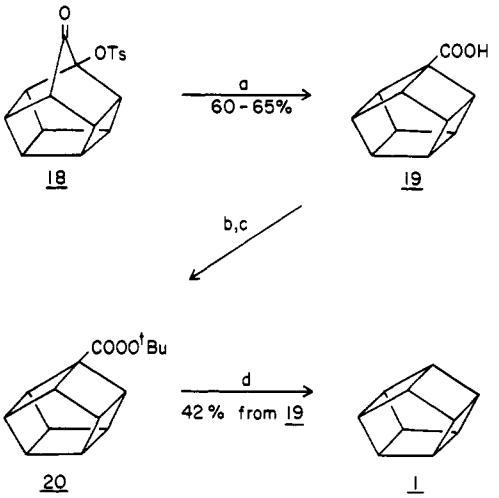
(13) Interestingly, use of the mesylate of **17** is much less successful (~30% yield of **19**).

Scheme II[a]



[a] (a) *m*-chloroperbenzoic acid/CH_2Cl_2/room temperature; **13**, mp 150 °C dec. (b) RuO_2 (catalytic)/$NaIO_4$/1 M aqueous KOH/room temperature/overnight;[10] **14**, mp 214 °C dec. (c) CH_2Cl_2/CH_2N_2–ether/0 °C; **15**, mp 93–95 °C. (d) Na/liquid NH_3/reflux; **16**, mp 200 °C dec. (e) $Me_2S{\cdot}Cl_2$/CH_2Cl_2/–25 °C then $(C_2H_5)_3N$;[11] **17**, mp 75.5–76.5 °C. (f) TsCl/py/95 °C/30 min.; **18**, mp 118.5–119.5 °C.

Scheme III[a]



[a] (a) 20% aqueous KOH/110 °C/5 h, then acidification *cold* with 50% H_2SO_4; **19**, mp 158.5–159.5 °C. (b) $(COCl)_2$/reflux. (c) *t*-BuOOH (dry!)/py/room temperature/overnight; **20**, mp 105–110 °C, crude. (d) 2,4,6-triisopropylnitrobenzene[12]/120–150 °C; **1**, see text.

thus, substantial quantities of the pentaprismane ring system can be prepared. Decarboxylation of pentaprismanecarboxylic acid via thermolysis of its *tert*-butyl perester (**20**) gives pentaprismane itself in 42% yield.[9a,c]

Some physical properties of pentaprismane are listed in Table I, along with those of triprismane (Ladenburg's benzene)[14] and tetraprismane (cubane),[15] the only other known parent prismanes. We shall report on the chemistry of pentaprismane as soon as possible.

Acknowledgment. The research effects of the principal investigator were supported by the National Science Foundation (CHE-78-07430) and the National Cancer Institute of the National Institutes of Health (CA-12961). The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by NCI via the University of Chicago Cancer Research Center (CA-14599).

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Trichodiene Biosynthesis and the Enzymatic Cyclization of Farnesyl Pyrophosphate

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Received December 29, 1980

The original formulation of the Isoprene Rule, and its evolution into the Biogenetic Isoprene Rule, remains one of the major theoretical achievements of modern organic chemistry.[1] On the basis of the unifying concept that a single acyclic activated substrate, farnesyl pyrophosphate (**1**), serves as the precursor of all sesquiterpenes, extensive biogenetic schemes have been proposed by several authors to account for the formation of the nearly 200 different carbon skeletons in this family of natural products.[2] In spite of these theoretical achievements, however, the precise stereochemistry of the farnesyl pyrophosphate isomer which undergoes cyclization has been a subject of considerable debate.[3] The difficulty stems from the realization that the formation of six-membered rings from trans-allylic pyrophosphates requires isomerization of the trans-2,3 double bond in order to avoid formation of *trans*-cyclohexene (Scheme IA). Most available evidence is consistent with initial formation of *trans,trans*-farnesyl pyrophosphate, and attempts to explain the subsequent isomerization and cyclization have generated two conflicting theories: (1) Trans–cis isomerization–cyclization via the intermediate tertiary allylic pyrophosphate, nerolidyl pyrophosphate (**2**), has been suggested by several groups of investigators[3,4] (Scheme IA). (2) Various redox schemes for the trans–cis isomerization have been proposed.[3] Although differing in detail, these latter theories all require removal of one of the C-1 hydrogen atoms. For example, several authors have proposed that isomerization might occur at the level of the derived unsaturated aldehyde, farnesal (**3**) (Scheme IB). Much of the evidence bearing on both theories has recently been reviewed in detail[3] and need not be considered here. One of the strongest arguments favoring the redox theories, however, has been the claim by Hanson[5] that conversion of farnesyl pyrophosphate to trichodiene (**5**), the parent hydrocarbon of the trichothecane family of sesquiterpene antibiotics,[6,7] involves loss of a C-1 hydrogen atom. Thus incubation of [1,5,9-$^3H_6$,4,8,12-$^{14}C_3$]-*trans,trans*-farnesyl pyrophosphate [$^3H/^{14}C$ atom ratio 6:3] with a cell-free system from *Trichothecium roseum* was reported to yield trichodiene [$^3H/^{14}C$ atom ratio 5.2:3]. This original report did not verify the reported isotope ratios of either substrate or product by recrystallization of suitable derivatives to constant activity or substantiate the apparent isotope distribution by the requisite chemical degradations.[8] Several recent studies have cast doubt on the generality of the Sussex group's findings. In a series of careful investigations using enzymes from sage and fennel, Croteau has demonstrated that several cyclic monoterpenes are biosynthesized without loss of isotope from C-1 of geranyl pyrophosphate and with no requirement for nicotinamide coenzymes.[11] Independently Arigoni and Gotfredsen have found that the whole cell biosynthesis of the sesquiterpene coccinol (**6**), a metabolite of *Fusidium coccineum*, takes place with complete retention of tritium from [5-$^3H_2$,2-^{14}C]mevalonate.[12] The latter result is particularly relevant since coccinol is apparently derived from a bisabolyl cation (**4**) similar to that which ultimately gives rise to trichodiene. We have therefore reexamined the cell-free biosynthesis of trichodiene and our results, reported below, establish unambiguously that conversion of *trans,trans-farnesyl pyrophosphate to trichodiene takes place without loss of hydrogen from C-1 of the precursor.*

trans,trans-[1-^3H,12,13-^{14}C]Farnesol was synthesized as previously described[13] and a portion was converted to farnesyl diphenyl

Table I. Conversion of [1-$^3H_2$,12,13-^{14}C]Farnesyl Pyrophosphate to Trichodiene and Distribution of the Label

compd	^{14}C specific activity, dpm/mmol	$^3H/^{14}C$
1[a]	1×10^8	9.04 ± 0.12[b]
5[c]	5.06×10^4[d]	8.70
8	5.32×10^4	9.29
11	6.14×10^4	8.23 ± 0.12
13	6.23×10^4	0.0
15	5.84×10^4	4.49 ± 0.09

[a] Amount incubated, 1×10^6 dpm ^{14}C (10 μmol). [b] Based on recrystallization of farnesyl diphenylurethane. [c] Total recovered activity, 1.8×10^4 dpm ^{14}C. [d] Diluted to 110 mg.

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