50% even upon prolonged incubation in the presence of excess geranyl-PP. Since farnesyl pyrophosphate synthetase catalyzes the stereospecific removal of the *pro-R* proton at C(2) of isopentenyl-PP during 1′-4 coupling,[1] it is logical that only (*S*)-2-fluoroisopentenyl-PP is a substrate for 1′-4 condensation,[21] although this point has not been proved.

Experiments with 2-fluoro- and 2,2-difluoroisopentenyl-PP failed to uncover any evidence for X-group involvement. Given the sensitivity with which radioisotopes can be detected and the remarkable stability of the enzyme upon prolonged incubation, the frequency of a chemical event that leads to irreversible inhibition or formation of an X-group bound product not covalently attached to the enzyme relative to the normal reaction under similar conditions must be $<10^{-5}$. It is unlikely that the inability of the fluoro analogues to function as affinity labels can be attributed to poor binding, since both are good inhibitors.[22] It is also unlikely that fluorine has deactivated the double bond to the point where the electrophilically initiated addition of the allylic moiety and X is no longer possible, at least in the 2-fluoro system where the rate of 1′-4 condensation is depressed by only a factor of 4 relative to that for isopentenyl-PP. The simplest explanation for our results is that the 1′-4 condensation does not involve covalent attachment of a nucleophile at C(3) of the isopentenyl moiety,[23] and we suggest that the X-group mechanism[24] be retired until direct support is found.[25]

**Acknowledgments.** Support from the National Institutes of Health, GM 21328 (C.D.P.) and AM 13140 (H.C.R.), is gratefully acknowledged. We also thank the Givaudan Corporation for a generous sample of geranylacetone.

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(7) $^1$H NMR ($\delta$, $CDCl_3$) 1.78 (3, m, methyl at C(3)), 2.80 (1, s, hydroxyl proton), 3.80 (2, d of d, $^3J_{^1H-^{19}F}$ = 24.5, $^3J_{^1H-^1H}$ = 5.0 Hz, H at C(1)), 4.49 (1, d of t, $^2J_{^1H-^{19}F}$ = 49, $^3J_{^1H-^1H}$ = 5.0 Hz, H at C(2)), and 5.10 ppm (2, m, H at C(4)).
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(10) $^1$H NMR ($\delta$, $CCl_4$) 1.82 (3, s, methyl at C(3)), 3.71 (3, m which collapses to a 2 H triplet after exchange with $D_2O$, $^3J_{^1H-^{19}F}$ = 13 Hz, H at C(1) and hydroxyl proton), 5.14 (1, s, H at C(4)), and 5.28 ppm (1, s, H at C(4)).
(11) F. D. Cramer and G. Weimann, *Chem. Ind. (London)*, 46 (1960).
(12) A standard 0.5-mL assay contained 10 mM PIPES buffer, pH 7.0, 10 mM $\beta$-mercaptoethanol, 1 mM magnesium chloride, and 0.1 $\mu$M potassium azide. All kinetic measurements were made at 37 °C using the acid lability technique.[13]
(13) F. M. Laskovics, J. M. Krafcik, and C. D. Poulter, *J. Biol. Chem.*, in press.
(14) W. W. Cleland, *Adv. Enzymol.*, **29**, 1 (1967).
(15) The noncompetitive patterns are expected since the normal substrate, isopentenyl-PP, can inhibit the enzyme by binding to the geranyl-PP region of the active site.[13]
(16) The activity of the enzyme incubated with 2-fluoroisopentenyl-PP decayed slightly faster than the other samples. However, in a second run at higher concentrations of enzyme (9 $\mu$M) and substrates (400 $\mu$M), the rate of loss of activity in the presence of 2-fluoroisopentenyl-PP was identical with that of the control.
(17) The fractions containing active enzyme were determined by the standard assay[13] with [1-$^{14}$C]isopentenyl-PP.
(18) Small amounts of radioactivity in the enzyme-containing fractions of these tubes represented the leading edge of a massive peak for the labeled substrate.
(19) $^1$H NMR ($\delta$, $CDCl_3$) 1.58 (6, s, methyls at C(7) and C(11)), 1.67 (3, s, methyl at C(11)), 1.73 (3, d, $^4J_{^1H-^{19}F}$ = 3.4 Hz, methyl at C(3)), 1.97–2.15 (8, m, H at C(4), C(5), C(8), and C(9)), 4.92 (2, d, $^3J_{^1H-^{19}F}$ = 22 Hz, H at C(1)), 5.08 (2, m, H at C(6) and C(10)), 7.48 (3, m, meta and para H), and 8.08 ppm (2, m, ortho H's); $^{19}$F NMR ($\phi$, $CCl_4$) −119.3 (t of q); mass spectrum (70 eV) 344 (0.8), 222 (5), 207 (7), 105 (72), 77 (40), 69 (100), and 49 (59).
(20) The alcohol was prepared from geranylacetone according to the route previously reported for 2-fluorogeraniol[4] and converted into the benzoate ester by treatment with benzoyl chloride. The stereochemistry of the C(2)–C(3) double bond was established by comparing chemical shifts and $^1$H–$^{19}$F coupling constants for the C(3) methyls of methyl (*E*)- and (*Z*)-2-fluorofarnesate with those of methyl 2-fluorogeranate and methyl 2-fluoronerylate.[4]
(21) By implication, (*R*)-2-fluoroisopentenyl-PP is the potential X-group trap.
(22) Although it is not possible to disect out all of the kinetic constants because of the very complex binding properties of the enzyme, the magnitudes of the slopes and intercepts of the double reciprocal plots indicate that both analogues prefer to bind to the isopentenyl-PP site. Since 2,2-difluoroisopentenyl-PP prefers to bind to the isopentenyl site, it is reasonable that (*R*)-2-fluoroisopentenyl-PP also prefers that site. However, it should be emphasized that our arguments do not require that these analogues bind preferentially to the isopentenyl-PP site, only that some fraction of (*R*)-2-fluoroisopentenyl-PP or 2,2-difluoroisopentenyl-PP forms an enzyme–analogue–geranyl-PP complex whose topology approximates that of the normal enzyme–substrate complex.
(23) The lack of condensation observed for 2,2-difluoroisopentenyl-PP and presumably (*R*)-2-fluoroisopentenyl-PP is not inconsistent with our conclusions. For example, it is possible that elimination of a proton from C(2) of the isopentenyl moiety is concerted with electrophilic addition, thereby bypassing a fully developed tertiary cation at C(3). Failure to remove a proton at C(2) would then abort the condensation step and the allylic pyrophosphate would be regenerated by internal return.
(24) The X-group mechanism enjoys widespread popularity for a variety of enzymatic olefin alkylations, although evidence for the process rests solely on stereochemical arguments for 1′-4 condensation catalyzed by farnesyl-PP synthetase.
(25) There are a wide variety of prenyltransferases and only one, farnesyl-PP synthetase, has been studied in detail. Thus, alternate mechanisms may be uncovered as other enzymes are studied.
(26) (a) Alfred P. Sloan Fellow; (b) National Institutes of Health Research Career Development Awardee, HL 00084, 1975–1980.
(27) University of Utah Graduate Research Fellow, 1978–1980.

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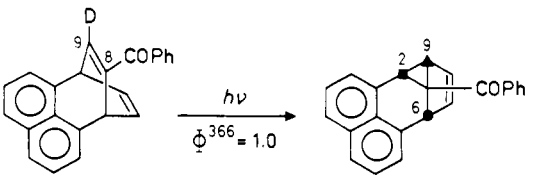
## Thermal Interconversion of Naphthobarrelene- and Naphthosemibullvalene-like Compounds. Ground-State Counterpart of a Di-$\pi$-methane Photorearrangement

*Sir:*

We have recently reported that 8-benzoyl-9-deuteriobicyclo[3.2.2]nona[*de*]naphthalene (**1a**) rearranges quantitatively to the tricyclo[4.3.0.0$^{2,9}$]nona[*de*]naphthalenes **2a–c** in regioselective di-$\pi$-methane-type photoreactions (Scheme I).[1] While **2b** and **2c** could possibly have been formed in concerted [$_\pi$2 + $_\sigma$2 + $_\pi$10(or 2)] processes, **2a** is not accessible by any photochemically allowed concerted path, and evidence was presented that indeed at least one biradical intermediate intervenes in the photorearrangement of **1a**.[1]

Compounds **1** and **2** have now been found to interconvert thermally in the dark (Scheme II). The transformation **1** → **2** is the first example of a ground-state counterpart of a di-$\pi$-methane photorearrangement.[1-3] The interconversion **1** ⇄ **2** combines reaction paths which result in regioselective product formation competing with positional interchanges of the deuterium-labeled carbon atoms. The observed regiose-

**Scheme I.** Photorearrangement of **1a** to **2a–c**




**1a**

**2a** D-6 (●)
**2b** D-2 (■)
**2c** D-9 (▲)

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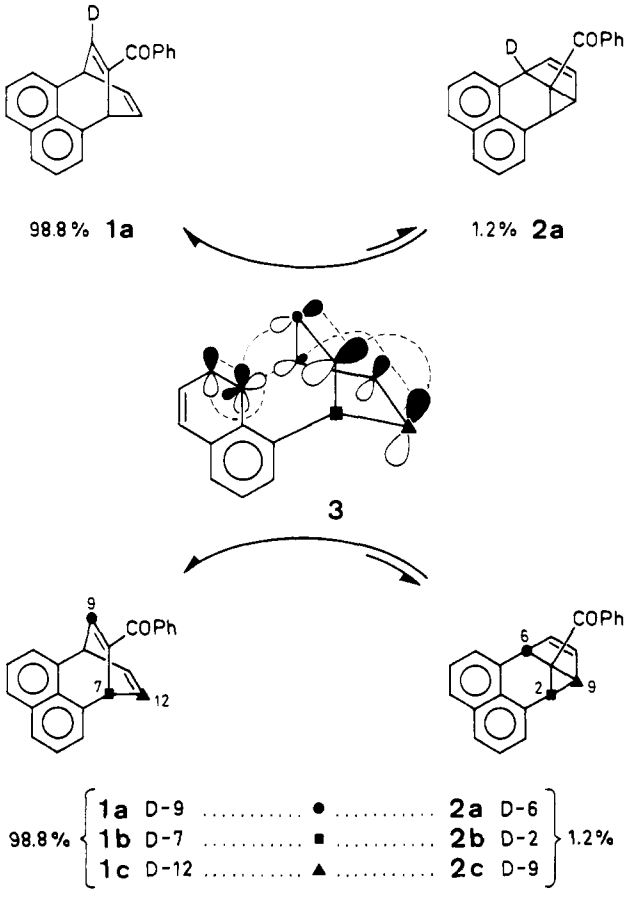
**Table I.** Thermolysis of **1a** and **2a-c**[a]

| run | starting material | reaction time, h | product ratio of **1**:**2** | relative deuterium distribution, %[b] in **1**[c] C(7) (= **1b**) | in **1**[c] C(9) (= **1a**) | in **2**[d] C(2) (= **2b**) | in **2**[d] C(6) (= **2a**) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | 0 | 100:0 | 0 | 100 | | |
| 2 | **1a** | 140[f] | 98.8:1.2 [f] | 6 | 94 | *e* | *e* |
| 3 | **2a-c** | 0 | 0:100 | | | 64 | 36 |
| 4 | **2a-c** | 48 | 19:81 | 63 | 37 | 58 | 42 |
| 5 | **2a-c** | 108 | 61:39 | 58 | 42 | 53 | 47 |
| 6 | **2a-c** | 140 | 89:11 | 53 | 47 | *e* | *e* |
| 7 | **2a-c** | 160 | 98.8:1.2 | 50 | 50 | *e* | *e* |

[a] $2 \times 10^{-3}$ M benzene solutions, 220 °C; for other experimental details see note 5. [b] The deuteration of **1** at C(10) and C(12) (= **1c**), and of **2** at C(7) and C(9) (= **2c**) in runs 2 and 4-7 was qualitatively in evidence by NMR (totally 10% in **1a-c** and in **2a-c**) but too low for quantitative measurement. The deuterium percentages given equal 100% for **1a** + **1b** and for **2a** + **2b**. [c] Combination of $^1H$ and $^2H$ NMR analyses;[6] experimental error ±3%. [d] $^1H$ NMR analysis;[6] experimental error ±3%. [e] Not determined. [f] The 98.8:1.2 ration was attained already after 48 h.

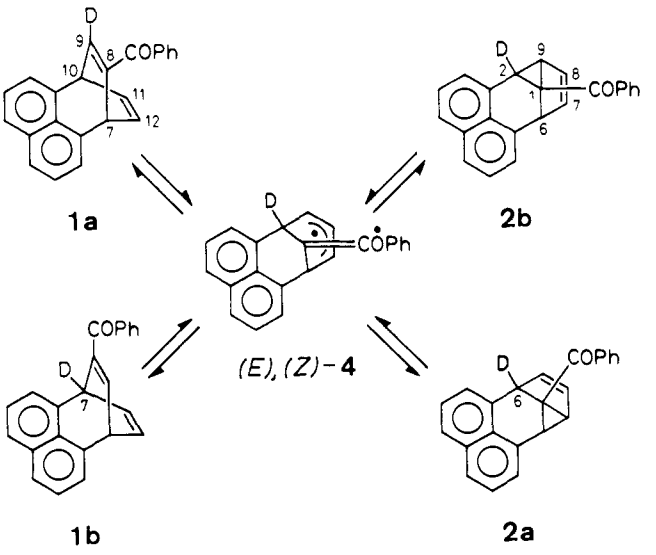
**Scheme II.** Regiospecific Paths for the Thermal Interconversion of **1** and **2**[4c]




lectivity conforms qualitatively to the regiospecificity expected on the basis of a thermally allowed [2 + 2 + 2 + 10] process or 16-electron Möbius cyclic array with one nontrivial sign inversion (**3**).[4]

A thermally equilibrated mixture of 98.8% **1** and 1.2% **2** was obtained when either of the two components was heated in benzene at 220 °C in sealed evacuated Pyrex tubes.[5] Several runs with **1a** and with a mixture[1] of 32% **2a**, 58% **2b**, and 10% **2c** were carried out to various degrees of conversion (Table I: runs 2 and 4-7).[6] The results show that the rearrangement **2** → **1** is initially highly regioselective, i.e., **2a** → **1a** and **2b** → **1b** (and implicitly **2c** → **1c**), and that the deuterium positions are progressively scrambled with increasing conversion until a 1:1 ratio of **1a** and **1b** is attained after maximum conversion of the mixture **2a-c** (run 7). A stepwise rearrangement

**Scheme III.** Paths for Positional Deuterium Scrambling in **1a**/**1b** and **2a**/**2b**




mechanism as delineated in Scheme III is compatible with this regioequilibrating process as well as with the corresponding result with **1a** (→ **1b**, run 2). The experiments do not discriminate between positional scrambling through **1** ⇄ **2** and through **1a** ⇄ **1b** and/or **2a** ⇄ **2b**. In any event, the biradicals (*E*)- and (*Z*)-**4** are likely intermediates common to all these processes.

When the deuterium distributions resulting in product **1** (runs 4-7) are extrapolated to zero conversion, it appears that the rearrangement **2** → **1** is highly regioselective. This can be accommodated by either the concerted mechanism illustrated in Scheme II or the stepwise alternative of Scheme III, and the experiments do not differentiate between the two. The latter mechanism requires that the *E* and *Z* conformers of **4** react regioselectively in either or both directions, and the conformational equilibration be slower. The concerted mechanism, if operative, would represent a novel example of symmetry-controlled pericyclic reactions in terms of a tri-π-methane ⇄ cyclopropyldi-π-methane interconversion.[7]

The rearrangement **2** → **1** occurred also in the presence of strong electrophiles at room temperature; e.g., treatment of **2** in chloroform with trimethylsilyl trifluoroacetate resulted in a clean conversion into **1**. The sequence **1** → **2** (photochemically, $\Phi = 1.0$ at 366 nm[1]) and **2** → **1** (catalytically in the dark) thus represents a model of a cycle for chemical light energy storage which can be conducted without detectable destruction of the reactants.[8]

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(2) For leading references on di-π-methane photoreactions, cf.: Hixson, S. S.; Mariano, P. S.; Zimmerman, H. E. *Chem. Rev.* **1973**, *73*, 531–551. Zimmerman, H. E.; Steinmetz, M. G.; Kreil, C. L. *J. Am. Chem. Soc.* **1978**, *100*, 4146–4162.
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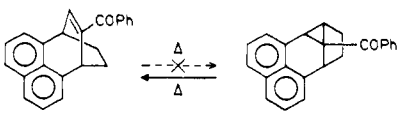
(4) (a) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim, and Academic Press: New York, 1970. Zimmerman, H. E. *J. Am. Chem. Soc.* **1966**, *88*, 1565 and 1566; *Acc. Chem. Res.* **1971**, *4*, 272–280. (b) An analogous—photochemically forbidden—three-bridge mechanism has initially been considered by Zimmerman (Zimmerman, H. E.; Binkley, R. W.; Givens, R. S.; Sherwin, M. A. *J. Am. Chem. Soc.* **1967**, *89*, 3932–3933) for the photorearrangement of barrelene to semibullvalene, but it was ruled out experimentally in favor of the di-π-methane route. (c) The inclusion of a single formal double bond in lieu of the entire naphthalene π system in the orbital array of the transition state **3** (Scheme II) was chosen for simplicity and does not change the orbital symmetry argument. A six-electron process, which does not involve the naphthalene π electrons, is a formally equivalent alternative (however, see Hixson et al.[2] for arguments favoring the participation of the second double bond in di-π-methane photorearrangements).
(5) No rearrangement was observed with **1** and **2** at ≤ 180 °C (70 h). Quantitative analyses of the mixtures were obtained by GLC (glass capillary column, OV 101; experimental error ±5%). The low-percentage product **2** was additionally identified by GC–MS after thermolysis of a nondeuterated sample of **1**.
(6) The deuterium analyses were carried out either by 270-MHz $^1$H NMR or 15.4-MHz FT $^2$H NMR, or by a combination of both, depending on signal shifts and intensities.
(7) It is worthwhile to note in this connection that the dihydro compound **5** did not rearrange to **6** at 250 °C during 48 h. Only the reverse reaction, **6** →




**5** **6**

**5**, was observed under these conditions (2 × $10^{-3}$ M solutions in toluene; no rearrangement of **6** occurred at ≤210 °C).
(8) For a review on energy storage in organic photoisomers, see Jones, G., II; Chiang, S.-H.; Xuan, P. T. *J. Photochem.* **1979**, *10*, 1–18.
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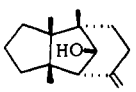
## Stereoselective Synthesis of (±)-Gymnomitrol

*Sir:*

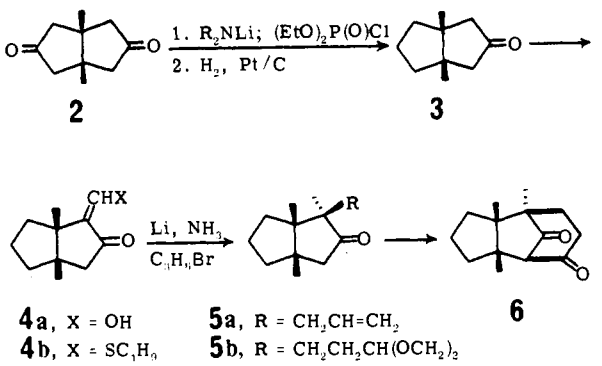
Gymnomitrol, one member of a group related sesquiterpenes isolated from the liverwort *Gymnomitrion obtusum* (Lindb.) Pears, has been assigned the novel tricyclic structure **1** on the




**1**

basis of degradative and spectroscopic evidence.[1] The presumed biogenetic parent, β-gymnomitrene,[2] co-occurs with gymnomitrol and has also been extracted from other species of liverwort.[3-5] Since the rare 4,8-methanoperhydroazulene nucleus[6] of gymnomitrol and cogeners most likely arises from cyclization of a bazzanenyl cation,[1,7] these compounds represent yet another biogenetic branch within the cuparene family of sesquiterpenes. In this communication we report a total synthesis of (±)-gymnomitrol which serves to confirm the structure of this interesting compound.[8]

Scheme I




The plan of the synthesis centered around the regio- and stereoselective geminal dialkylation of 3a,6a-dimethylhexahydro-2(1*H*)-pentalenone (**3**). This known compound[9] was conveniently prepared from the readily available diketone **2**[10] in the following manner (Scheme I). Addition of 1 equiv of the lithium derivative of hexamethyldisilazane to a tetrahydrofuran (THF) solution of **2** (−78 °C, 15 min) evidently produced the monoenolate anion which was phosphorylated with diethyl chlorophosphate (−78 to 25 °C, 2.5 h). Catalytic hydrogenation of the unpurified monoenol phosphate in ethyl acetate (5 atm, 5% Pt/C, 25 °C, 2.5 h)[11] provided monoketone **3** (mp 159–160 °C, sealed capillary) in 77% overall yield. The hydroxymethylene derivative **4** (mp 87–89 °C)[12] was prepared by condensation with ethyl formate (NaH, THF, 25 °C, 14 h, 83%) and converted into the *n*-butylthiomethylene ketone **5** by reaction with butanethiol (TsOH, $C_6H_6$, reflux, 18 h, 84%).[13] Reduction of **5** with lithium in liquid ammonia and 1,2-dimethoxyethane as cosolvent (2 equiv of $H_2O$, −78 to −33 °C, 0.5 h)[14] followed by addition of allyl bromide afforded a stereochemically homogeneous dialkylated ketone (**6**) in yields ranging from 26 to 49%.

Since the stereochemical outcome of the alkylation step in the reduction-alkylation **4a** → **5a** did not seem safely predictable, ketone **5a** was further converted into tricyclic diketone **6** to ascertain the stereochemistry. The allyl side chain was elaborated into an acetal-protected propionaldehyde substituent (**5b**) through a sequence of seven reactions.[15] Hydrolysis of the acetal (10% HCl, acetone, reflux) was accompanied by spontaneous aldol cyclization, and the resulting ketol was oxidized with Jones reagent to diketone **6** (55%; mp 214–216 °C; IR $\nu^{KBr}$ 1740, 1715 cm$^{-1}$). Although the IR and NMR spectral characteristics of **6** are very similar to those of nor diketone **14** previously prepared from natural gymnomitrol,[16] the larger chemical shifts for two of the three quaternary methyl groups in the former ($\delta^{CDCl_3}$ 1.04, 1.07, 1.10) provided convincing proof for the nonidentity of the two compounds.[17] Consequently the three-carbon bridge in diketone **6** is syn to the ring juncture methyl groups, and the alkylation of the methyl-substituted enolate anion from **4b** must have occurred exclusively on the convex surface of the bicyclic structure. It is also evident that the order of introduction of the methyl and three-carbon substituents at C-1 must be reversed in order to establish the correct stereochemistry for the synthesis of gymnomitrol. Cyano ketone **7** proved to be a suitable intermediate for this purpose (Scheme II).

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