Naphtho[*b,e*]dicyclobutene

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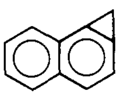
Abstract: The Diels–Alder addition of 1,2-dimethylenecyclobutane to dimethyl cyclobutene-1,2-dicarboxylate provides the tricyclic diester **10.** Pyrolysis promotes cyclobutene ring opening to diene **11** which can then add a second equivalent of dienophile to give the tetracyclic tetraester **12.** Hydrolysis to tetraacid followed by oxidative decarboxylation and aromatization gives naphtho[*b,e*]dicyclobutene. The physical properties of this molecule (melting point, ^{1}H and ^{13}C NMR, UV) are compared to those of analogous ring-fused naphthalenes.

Recently Vogel and co-workers have reported the preparation of naphtho[*a*]cyclopropene (**1**) via a retro-Diels–Alder reaction.[1] This synthesis afforded the last remaining isomer of ring fused naphthalenes. Naphtho[*b*]cyclopropene (**2**) was first reported by Billups and Chow in 1973[2] while naphtho[*a*]cyclobutene (**3**) and naptho[*b*]cyclobutene (**4**) were both prepared by Cava and co-workers more than 15 years ago.[3]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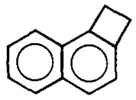
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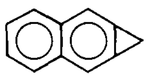
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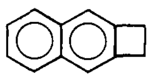
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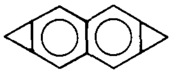
When two small rings are fused to the naphthalene nucleus, a variety of isomeric combinations are possible. Perhaps the most intriguing for symmetry reasons are the linearly fused naphtho[*b,e*]dicycloalkenes. The smallest possible member of this series, **5,** was prepared by Vogel and Ippen utilizing a double-barreled version of the Billups benzocyclopropene synthesis.[4] More recently Garratt and Davalian have prepared the next higher homologue, **6.**[5] In their synthesis they employ an approach which combines well-established routes to benzocyclopropene[6] and benzocyclobutene.[7] In this paper we would like to present the synthesis of the next homologue, naphtho[*b,e*]dicyclobutene (**7**). Having now completed a series of three closely related compounds, we will also discuss and compare some of the structural features and physical properties of these molecules.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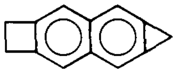
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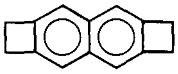
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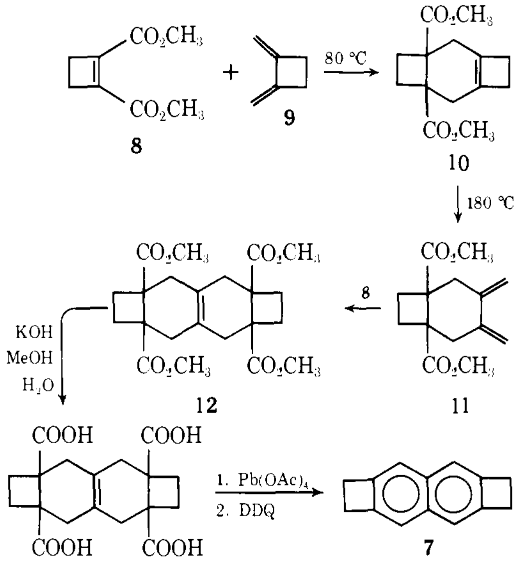
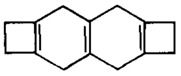
Synthesis of Naphtho[*b,e*]dicyclobutene

In an earlier paper[8] we have reported the preparation of the tricyclic diester **10** by the Diels–Alder addition of 1,2-dimethylenecyclobutane (**9**) to dimethyl 1,2-cyclobutenedicarboxylate (**8**). It was found that two additional synthetic steps could convert this material into benzo[1,2:4,5]dicyclobutene in 56% overall yield. Attempted collection of **10** by preparative gas chromatography with an injection port temperature of 260 °C resulted in the isolation of a single pure component. This material showed olefinic NMR resonances at δ 5.5 and 4.9 ppm indicating that opening of the cyclobutene ring had occurred to provide the diene **11.** If an equimolar mixture of **10** and **8** were heated to 180 °C in a sealed tube, the diene **11** could be trapped by a second [2 + 4] addition to provide the tetraester **12.** Careful NMR analysis of **12** showed two methyl ester singlets at 3.7 (65%) and 3.8 ppm (35%) accounting for the two possible Diels–Alder adducts: all-cis and cis,trans. Recrystallization provided the major isomer pure, mp 151–153 °C. However, separation of these isomers was not essential since both could ultimately provide the desired product. Hydrolysis of the tetraester to the corresponding tetracarboxylic acid was accomplished by refluxing overnight with excess potassium hydroxide in aqueous methanol followed by acidification.



13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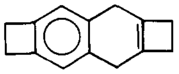
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Tetracarboxylic acid **13** was then treated with 2 equiv of lead tetraacetate in dimethyl sulfoxide with pyridine added to scavenge the acetic acid formed. An exothermic reaction was observed, accompanied by the evolution of approximately 4 equiv of carbon dioxide gas. The material isolated after silica gel chromatography gave an NMR spectrum which showed singlets at 7.28, 6.68, 3.30, 3.10, and 2.5 ppm (several peaks). The peaks at 7.28 and 3.30 ppm were assigned to the desired product **7.** By comparison with the NMR spectrum of benzocyclobutene,[9] the peaks at 6.68 and 3.10 ppm were assigned to the aromatized half of structure **15** while the peaks for the other half of this molecule appear at about 2.5 ppm by analogy with 1,4-dihydronaphtho[*b*]cyclobutene.[10] The two signals expected for structure **14** also appear at about 2.5 ppm as has been observed for the closely analogous bicyclo[4.2.0]octa-1(6),3-diene.[9] By integration of the NMR spectrum, the ratio of **14**:**15**:**7** was determined to be 1:2:1. When 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is added to the NMR tube and the solution allowed to stand overnight, the NMR

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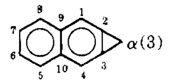
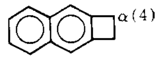
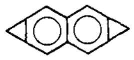
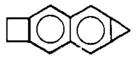
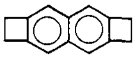
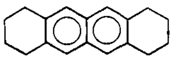
Table I. NMR Chemical Shift Data for fused Naphthalenes

	ref	H1	H8	Hα(3)	Hα(4)	C1	C2	C7	C8	C9	Cα(3)	Cα(4)
	14	7.40		3.40		112.3	123.4	125.4	128.4	136.7	18.56	
	10	7.42			3.33	120.3	144.6	124.5	128.0	133.9		29.4
	4	7.59		3.52		113.5	122.8			140.1	19.9	
	5	7.52	7.47	3.45	3.28	112.7	122.1	144.3	121.5	136.2	19.3	29.3
		7.28			3.30	120.5	144.1			*a*		29.22
		7.36				125.1	134.6			130.5		

[a] Too weak to measure.

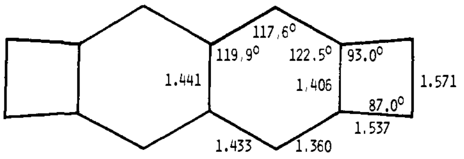
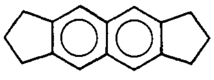


Figure 1. Bond lengths (Å) and internal bond angles of the carbon framework of naphtho[*b,e*]dicyclobutene.

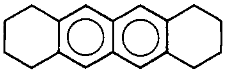
spectrum simplifies to two singlets at 7.28 (4 H) and 3.30 ppm (8 H) indicating conversion of intermediates **14** and **15** to the fully aromatized **7**.

High-quality crystals of **7** were grown by slow evaporation of an ether solution and found to have mp 220–222 °C. As a final proof of structure, a single-crystal X-ray structure has been determined. The preliminary crystallographic measurements are set forth in Figure 1 and reveal the symmetrical carbon framework associated with structure **7**. A more highly refined structural analysis will be reported in a separate publication.[11]

It is interesting to note that the melting point of **7** is substantially greater than that of the higher homologues **16**[12] and

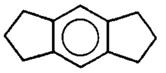


(mp 183 °C)
16

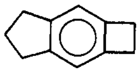


(mp 174 °C)
17

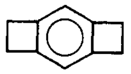
17. Although these three molecules possess the same symmetry, the cyclobutene-fused system is more planar and thus capable of tighter packing in the crystal lattice. A calculated density of 1.27 g/cm^3 obtained from the crystallographic measurements bears out this point. The importance of symmetry is indicated by the lower melting point of **6** (mp 144–146 °C[5]), which should also be quite planar. Unfortunately the actual melting point of **5** is undetermined since this molecule decomposes explosively at 132–133 °C.[4] The same unusual melting point behavior is evidenced for benzo[1,2:4,5]dicyclobutene (**20**) when compared to the homologous compounds **18, 19,** and **21.**[8,13]



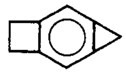
(mp 53–55 °C)
18



(mp 32–33 °C)
19



(mp 100–101 °C)
20



(liquid)
21

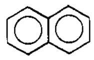
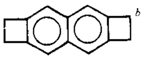
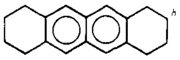
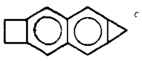
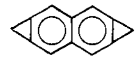
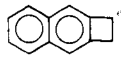
Spectral Properties

Table I presents a compilation of ^{1}H and ^{13}C spectral data for the fused naphthalenes **2, 4–7,** and **17.** An interesting dichotomy may be observed for the aromatic proton chemical shifts. In going from naphtho[*b*]cyclopropene (**2**) to naphtho[*b,e*]dicyclopropene (**5**) the proton ortho to the three-membered ring shifts downfield by 0.19 ppm. However, in going from naphtho[*b*]cyclobutene (**4**) to naphtho[*b,e*]dicyclobutene (**7**), the proton ortho to the four-membered ring shifts upfield by 0.14 ppm. This latter upfield shift is consistent with what is found upon comparison of benzocyclobutene ($\delta_{\text{ortho ArH}}$ 6.90)[14] with benzo[1,2:4,5]dicyclobutene (**20**) (δ_{ArH} 6.64)[8] where an upfield shift of 0.26 ppm is observed. This shift may be attributed to a number of causes not the least of which would be increased shielding caused by an alkyl inductive effect. Cyclopropene fused systems do not comply with this trend. For these systems the electron-withdrawing inductive effect of the small ring predominates, causing an increased polarization of the C–H bond ortho to the cyclopropene ring. This polarization is manifested in benzocyclopropene by a large aromatic C–H coupling constant (167.5 Hz)[15] and by deshielding and thus a downfield shift of the aromatic proton resonance. For example, the ortho aromatic proton of **21** appears at δ 6.85.[13] Such observations permit us to designate the previously unassigned aromatic resonances for compound **6**, the lower field proton (7.52 ppm) being adjacent to the three-membered ring. Note that the proton ortho to the four-membered ring in this compound has shifted downfield from naphtho[*b*]cyclobutene presumably owing to the inductive deshielding effect of the additional fused cyclopropene ring.

The ^{13}C chemical shifts of the fused naphthalenes are very consistent for carbons in similar environments allowing for very facile peak assignments. It is worthwhile to note that the arguments set forth above are further supported by the ^{13}C data. An aromatic carbon (C1) adjacent to a ring fused between carbons 2 and 3 resonates further upfield as the size of this fused ring is decreased. Similarly, the carbon atom (C9) common to both aromatic rings moves downfield with increasing strain. It is the bridgehead carbon (C2) of the fused ring which does not show a consistent trend in that for the cyclopropene-fused systems the chemical shift of C2 occurs at unusually high field. This observation can be explained by shielding due to the electronegativity of the three-membered ring. Such an inductive effect also induces a polarization of the C1–H bond, increasing electron density on this carbon atom. The large coupling constant of 167 Hz[14] observed for the C–H bond on the central ring of naphtho[*b*]cyclopropene further testifies to the polar nature of this bond.

The ultraviolet absorption spectra of naphtho[*b,e*]dicyclobutene and naphthalene in isooctane solution are illustrated in Figure 2. Table II summarizes the available data on similar substituted naphthalenes. For naphtho[*b,e*]dicyclobutene the three principal absorption bands ($^1B_{3u}$, $^1B_{2u}$, $^1B_{3u}$) are clearly

Table II. Ultraviolet Absorption Maxima (nm) and Extinction Coefficients (ϵ) for Naphthalene and 2,3;6,7-Substituted Naphthalenes[a]

 [b]	 [b]	 [b]	 [c]	 [d]	 [e]
219 (150 000)	221 (145 000)	229 (64 100)	227 (83 500)	226 (74 200)	223 (75 860)
	238 (s, 3070)	236 (93 600)			
247 (2060)	248 (1260)	258 (14 450)	256 (3120)		250 (s, 1860)
256 (3500)	258 (2610)				259 (s, 3310)
264 (5180)	268 (4590)	274 (3050)	267 (4830)	273 (7050)	267 (4790)
274 (5830)	279 (6060)	283 (3500)	288 (5630)		278 (6030)
282 (3750)	289 (s, 4880)				286 (s, 3980)
285 (3910)	291 (5120)	294 (2900)			290 (4270)
296 (275)	302 (1810)		297 (1910)		
300 (250)	308 (3250)	308 (s, 1500)	304 (2210)		304 (1150)
303 (200)	315 (3240)	316 (900)	310 (3620)		311 (1150)
310 (230)	322 (5920)	323 (s, 430)	324 (5430)	326 (6000)	318 (1620)
		331 (1400)			

[a] The horizontal arrangement of absorption values is not meant to imply any direct correlation of vibrational structure. s denotes a shoulder peak. [b] Isooctane. [c] Reference 5. [d] Reference 4. (cyclohexane). [e] Reference 3b (ethanol).

evident with their longest wavelength, or 0-0 bands, appearing at 322, 291, and 221 nm, respectively. All three bands exhibit a bathochromic shift relative to naphthalene which is characteristic for alkyl-substituted aromatic systems.[16] This bathochromic shift is more pronounced for the lower energy band and this band also shows a great deal more intensification than the central band. This shift and intensification are in agreement with the longitudinal polarization expected for the $(\cdots b_{1u}{}^2 a_u{}^2)^1A_{1g} \rightarrow (\cdots b_{1u}{}^2 a_u{}^1 b_{2g}{}^1)^1B_{3u}$ transition associated with the lower energy band.[17]

CNDO/2 calculations based upon experimental geometries[18] indicate that the naphthalene π MOs are delocalized into the p_z AOs of the methylene carbons and the 1s AOs of their appended out-of-plane hydrogen atoms. Thus the originally pure π MOs of the naphthalene moiety are now subject to a significant σ–π mixing from the methylene hydrogens, i.e., hyperconjugation. The bathochromic shift and significant intensification of the low-energy transition are therefore due to this electron delocalization and orbital mixing. As expected, other similarly substituted naphthalenes show this same behavior.

Also noteworthy is the high degree of resolution which is observed particularly in the longer wavelength band. By comparison, other naphthalenes, regardless of substitution, show considerably less fine structure.[19] This effect can best be attributed to a combination of the high symmetry, rigidity, and longitudinal polarization of the system.

Experimental Section

Dimethyl sulfoxide was distilled under vacuum from calcium hydride. Pyridine was distilled from barium oxide. Just prior to use, lead tetraacetate was recrystallized from acetic acid and dried under vacuum, protected from oxygen and light. Proton magnetic resonance spectra were obtained on a Varian Associates T-60 or XL-100 spectrometer and chemical shifts are reported in parts per million downfield from Me_4Si. Infrared spectra were obtained on a Beckman IR-4250 spectrometer. Mass spectra were obtained by direct sample introduction into a Hewlett-Packard 5933 A GC-mass spectrometer system. All melting points are uncorrected.

Dimethyl Tricyclo[6.2.0.0^{3,6}]dec-3(6)-ene-1,8-dicarboxylate (10). In a heavy-wall glass tube were placed 3.16 g (0.04 mol) of 1,2-dimethylenecyclobutane,[20] 6.48 g (0.04 mol) of dimethyl cyclobutene-1,2-dicarboxylate,[21] and 0.05 g of hydroquinone. The tube was sealed and heated in an oil bath at 80 °C for 20 h. After the tube was cooled and opened, the ether-soluble portion was chromatographed on 60/200 mesh silica gel, eluting with 5:95 ether-petroleum ether to provide 1.58 g (16%) of solid diester adduct: mp 137-142 °C; NMR (CCl_4) δ 3.66 (s, 6 H, CO_2CH_3), 2.6-2.0 (m, 10 H), and 1.7 ppm (m, 2 H); IR (thin film) 2878, 2864, 1742, 1436, 1288, 1125, and 1094 cm^{-1}.

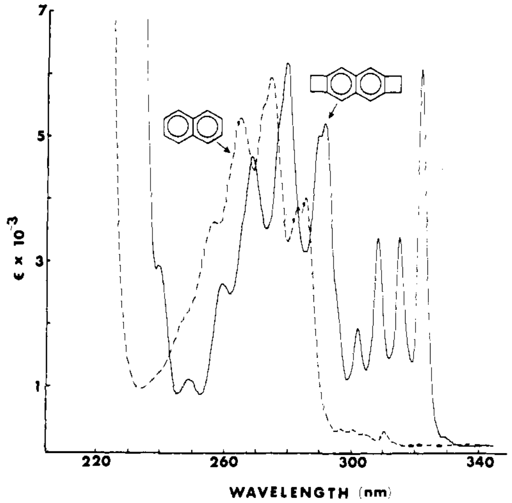


Figure 2. Ultraviolet absorption spectra (isooctane) of naphthalene and naphtho[*b,e*]dicyclobutene.

Diels-Alder Preparation of Tetraester 12. In a heavy-wall glass tube were placed 2.6 g (0.015 mol) of **8**, 3.76 g (0.015 mol) of **10**, and 0.05 g of hydroquinone. The tube was sealed and heated in an oil bath to 180 °C for 14 h. The tube was then cooled and opened, and the contents were washed out with dichloromethane. Evaporation of the dichloromethane gave a crude product which was chromatographed on 130 g of 60-200 mesh silica gel, eluting with 1:1 chloroform-petroleum ether, to provide 1.48 g (23%) of **12** as a thick oil which showed two methyl ester singlets in the NMR at δ 3.7 (65%) and 3.8 ppm (35%). Recrystallization from hexane provided the major isomer pure: mp 151-153 °C; NMR ($CDCl_3$) δ 3.72 (s, 12 H, CO_2CH_3) and 2.6-1.4 ppm (16 H, m); IR (KBr) 2960, 1785, 1440, 1290, 1245, 1130, and 910 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 420 (15, parent), 388 (80), 360 (33), 328 (38), 300 (46), 269 (20), 241 (100), 209 (64), and 181 (76).

Tetracyclo[10.2.0.0^{5,8}.0^{1,12}]tetradec-3(10)-ene-1,5,8,12-tetracarboxylic Acid (13). To a solution of 0.2 g (0.5 mmol) of **12** in 5 mL of methanol was added a solution of 0.43 g of potassium hydroxide in 0.5 mL of water and the resulting mixture was refluxed overnight. The flask was cooled and the contents poured into 25 mL of saturated NaCl solution. Concentrated HCl was added to acidify the aqueous phase which was then extracted four times with ether. The combined ether extracts were dried over sodium sulfate and filtered, and the solvent was evaporated to give 0.18 g (99%) of **13**: mp 125-130 °C; NMR (Me_2SO-d_6) δ 2.6-1.5 ppm (m, 16 H); IR (KBr) 3200-2900 (b), 1710, 1435, 1400, 1290, 1265, and 1225 cm^{-1}. The low melting point and lack of COOH peak in the NMR are attributed to the rapid and reversible formation of anhydride from the *cis*-1,2-cyclobutanedicarboxylic acid moieties. This behavior has been observed in previous work.[8]

Naphtho[*b,e*]dicyclobutene (7). To a solution of 0.18 g (0.5 mmol) of **13** in 5 ml of dry dimethyl sulfoxide and 0.197 g (2.5 mmol) of dry pyridine was added 0.48 g (1.08 mmol) of lead tetraacetate in small portions. An exothermic reaction was observed with copious gas evolution. Monitoring of this gas evolution with a water manometer showed that approximately 4 equiv of gas was given off. An ice bath was used to maintain reaction temperature at 35 °C. After stirring for 1 h, the reaction mixture was poured into 50 mL of saturated sodium chloride solution and extracted five times with ether. The combined ether extracts were dried over magnesium sulfate. Filtration and evaporation of ether gave a solid material which was taken up in hexane and washed with water to remove lead(II) acetate. The hexane solution was dried over sodium sulfate and evaporated to give 36 mg of a white solid. This material was purified by passing through a short silica gel column eluted with petroleum ether, providing 10.4 mg of material which appeared by NMR to be a 1:2:1 mixture of **14:15:7** (see discussion). To the NMR sample (0.5 mL of CCl_4) was added 0.10 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and the tube allowed to stand overnight at room temperature, thereby accomplishing complete oxidation to **7**: NMR (CCl_4) δ 7.28 (s, 4 H, ArH) and 3.30 ppm (s, 8 H, $ArCH_2$). Filtration through silica gel to remove hydroquinone and unreacted DDQ gave a crystalline solid, mp 220–222 °C, from which several high-quality crystals could be grown by slow evaporation of an ether solution: mass spectrum (70 eV) *m/e* (rel intensity) 180 (100, parent), 179 (22), 178 (23), 165 (16), 152 (17), and 28 (33). Anal. Calcd for $C_{14}H_{12}$: *m/e* 180.0939. Found: 180.0946.

1,2,3,4,7,8,9,10-Octahydronaphthacene (17) was prepared according to the method of Skvarchenko et al.,[22] mp 173–175 °C (lit.[22] mp 174 °C).

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Studies in Terpene Biosynthesis. Synthesis and Resolution of Presqualene and Prephytoene Alcohols

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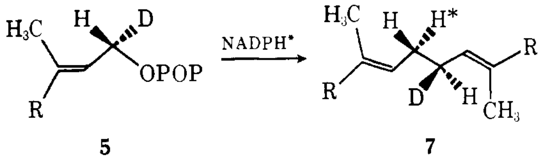
Abstract: Presqualene alcohol and prephytoene alcohols have been synthesized and resolved through their etienate esters. Only (1*R*,2*R*,3*R*)-presqualene alcohol (as its tritiated pyrophosphate) is efficiently converted to squalene by a yeast microsomal fraction. Similarly, only (1*R*,2*R*,3*R*)-prephytoene alcohol (as its tritiated pyrophosphate) is efficiently converted to carotenoids. Thus, the stereochemical course of carotene biosynthesis parallels that of sterol biosynthesis.

In the late 1960's one remaining unresolved transformation in the biosynthesis of sterols from acetate was the elucidation of the biochemical transformations involved in the head-to-head dimerization of two farnesyl pyrophosphate molecules to yield squalene. The elegant work of Cornforth and Popjak[2] had established the overall stereochemistry of the transformation (Scheme I). Numerous proposals[3-5] were set forth to accommodate the observed stereochemistry of this transformation. In 1966,[6] Rilling isolated a free intermediate, now called presqualene pyrophosphate, from a TPNH-starved microsomal yeast fraction to which he assigned structure **3**. Corey and Ortiz de Montellano[7] showed that the original structure assignment was incorrect by synthesizing a mixture of all possible stereoisomers of **3** and demonstrating that none of the components of the mixture had the properties of the isolated intermediate. On the basis of further work and more material Rilling and Epstein,[8] in 1969, revised the proposed

Scheme I. Stereochemistry of Squalene Formation



$R = C_{11}H_{19}$