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SYNTHETIC STUDIES ON ARENE-OLEFIN CYCLOADDITIONS. II. TOTAL SYNTHESIS OF (±)-ISOCOMENE[1]

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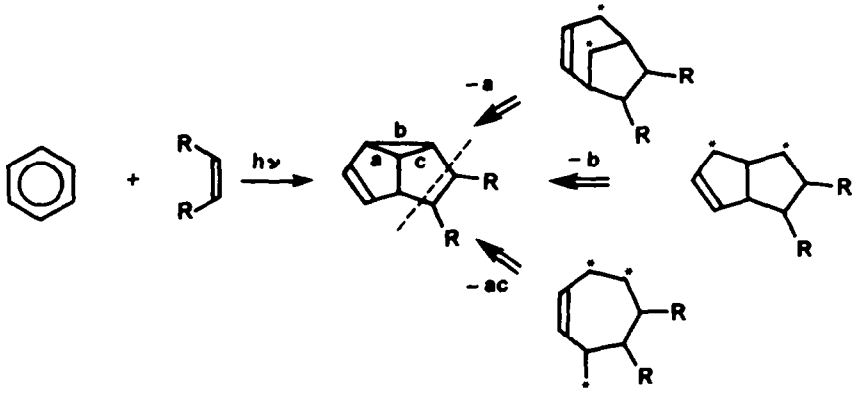
Abstract—The arene-olefin meta-photocycloaddition is shown to provide the basis for an effective and general approach to polyquinane natural products as demonstrated by the synthesis of (±)-isocomene (**5**) in five steps based on Z-2-bromo-2-butene and 2-bromotoluene.

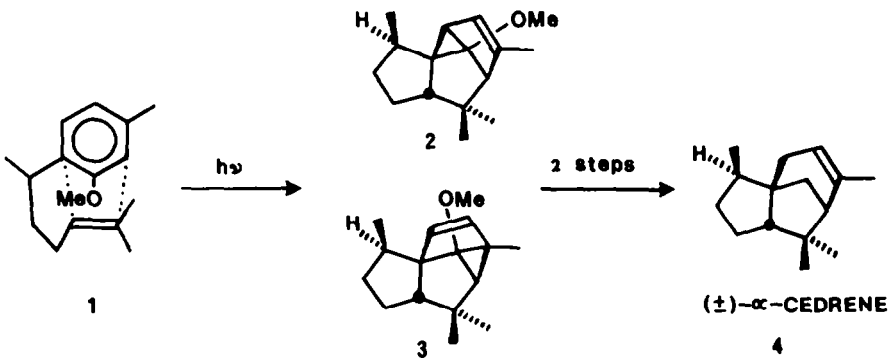
The problems of five-membered ring synthesis have been posed in various ways by numerous natural product families over the past few decades. For much of this period, the development of methodology in this area had been strongly influenced by objectives in steroid and prostaglandin synthesis. More recently, however, the ever-increasing number of natural and non-natural systems completely or partially characterized by the bicyclo[n.3.0]alkane moiety[3] and the potent biological activities of many of these systems have considerably expanded the scope and enhanced the significance of this synthetic problem. The ensuing search for more effective and versatile solutions has produced numerous and widely varied chemical expressions of the basic topologies[4] for five-membered ring construction.[5] We describe herein our continuing studies[1] on a methodology which should find considerable service in 5-membered ring synthesis, the meta-photocycloaddition of olefins to arenes (Scheme 1).[6]

The meta photoaddition of an olefin to an arene was first reported in 1966 by Wilzbach and Kaplan[7] and by Bryce-Smith, Gilbert, and Orger.[8] In 1969, Morrison[9] published an intramolecular version of this reaction discovered in the early stages of his now extensive studies on bichromophoric molecules.[10] More recently, Gilbert and coworkers[11] have described additional examples of the intramolecular process. Our own studies in this area arose from an interest in the above-noted synthetic problems and, particularly, in the design of synthetic approaches to the biologically important members of the hirsutane and tigliane families.[12] It was recognized in this context that these problems as well as a number of other objectives in odd-membered ring synthesis could be served by this cycloaddition process. For example, based on the facility with which cyclopropane bonds undergo cleavage[13] and the orbital overlap control that could be imposed on such cleavages, a meta-cycloadduct would be expected to serve as a precursor (see Scheme I) to 5 and 7-membered rings as well as bicyclo[3.2.1]octanes and bicyclo[3.3.0]octanes common to various natural products. Our preliminary studies in this area have been designed to examine these possibilities and, in particular, the control that could be exercised over the formation and elaboration of the cycloadduct. In this connection, we have shown previously[1] that the cycloaddition of arene olefin **1** proceeds with high control to give cycloadducts **2** and **3** which served effectively as precursors to a now-classical objective in bicyclo[3.2.1]octane synthesis, (±)-α-cedrene (**4**). The isocomene synthesis[14] described herein was designed to further explore the control elements which govern the course of the cycloaddition and its applicability to bicyclo[3.3.0]octane synthesis.

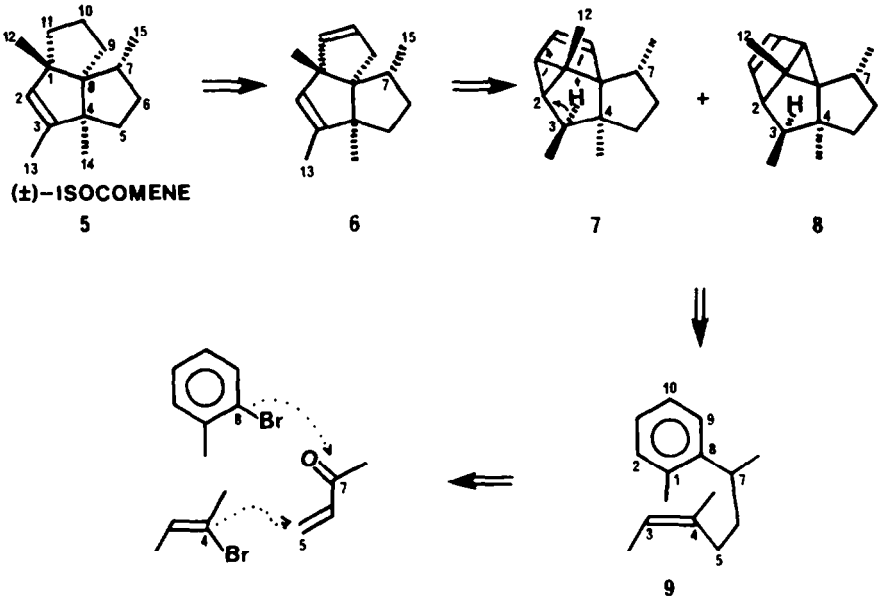
The success of our synthetic plan for isocomene (**5**; see Scheme 3) rested, in part, on the expectation that dehydroisocomene **6**, a reasonable precursor of isocomene, could be formed from the thermolysis of photoadducts **7** and **8**. In the case of **7**, the thermal reorganization would involve a homo-1,5- sigmatropic H-shift, while for **8** an initial pseudo-degenerate vinylcyclopropane isomeriza-



Scheme 1.



Scheme 2.



Scheme 3.

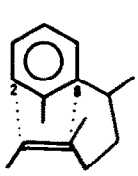
tion to **7** and thence to **6** would be required.[15] In both cases, this strategy required that the stereochemistry at C-3 be set in the indicated configuration in the course of the intramolecular photocycloaddition of aryl-alkene **9**.

Of the three possible modes (ortho, meta, and para)[16] for this cycloaddition, the substitution on the arene and olefin moieties of **9** was expected to favor a meta mode[17] which, due to the geometrical constraints imposed by the intramolecular cycloaddition in question, could only involve additions of the olefin to centers C-2, C-8; C-8, C-10; C-1, C-9 and its regiochemical complement C-9, C-1 (see Scheme 4). When exo/endo, vinylcyclopropane, and C-7 configurational isomers are considered, 24 meta cycloadducts would, therefore, be possible. However, only additions C-2, C-8; C-1, C-9; and C-9, C-1 were expected to benefit from the directing influence of alkyl substitution[18] and, of these, based on an exciplex mechanistic model[19] additions C-1, C-9 and C-9, C-1 were considered to be disfavored by the indicated C-6, C-13 steric interactions. For the remaining meta possibilities, to the extent that proximity between both C-2, C-8 and C-3, C-4 is important in the formation and/or further reaction of the exciplex, an exo orientation (Scheme 4) was expected to be preferred over the more difficult to achieve endo alignment. Furthermore, it was anticipated on the basis of this exo exciplex model, that the methyl group at C-7 would preferentially assume a pro-α orientation due to the unfavorable Me–Me nonbonded interaction that would develop in the pro-β case. Finally, stereospecificity with respect to the alkene geometry would be required.[20]

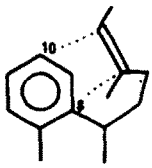
The preparation of the aryl-alkene (**9**) required to test this analysis proved to be straightforward (Scheme 5). Thus, z - 2 - bromo - 2 - butene was converted via its lithio derivative[21] into the corresponding cuprate reagent which reacted with methyl vinyl ketone to provide keto-olefin **10** in 56% yield after distillation. This ketone was then added to a mixture of 2-lithiotoluene and lithium metal resulting from the reaction of 2-bromotoluene with excess lithium.[22] Distillation of ammonia into this mixture effected reductive cleavage of the benzylic alkoxide and formation of aryl-alkene **9**.

The desired cycloaddition was found to be easily effected by irradiation of aryl alkene **9** in cyclohexane (*ca.* 0.075 M) at room temperature for *ca.* 4 hr with Vycor-filtered light from a 450W Hanovia source. Under these conditions, cycloadducts **7** and **8**, representing *ca.* 90% of the reaction mixture obtained from silica chromatography, were formed in the ratio 1:1 and in a yield of 72%, as determined by gas chromatographic

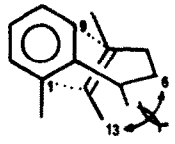
META ADDITION POSSIBILITIES



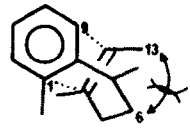
C-2, C-8



C-8, C-10

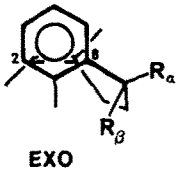


C-1, C-9

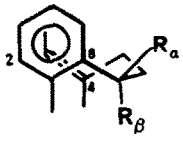


C-9, C-1

EXO/ENDO POSSIBILITIES

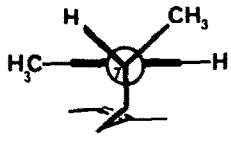


EXO

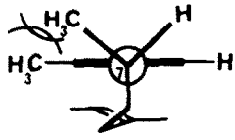


ENDO

C-7 METHYL POSSIBILITIES

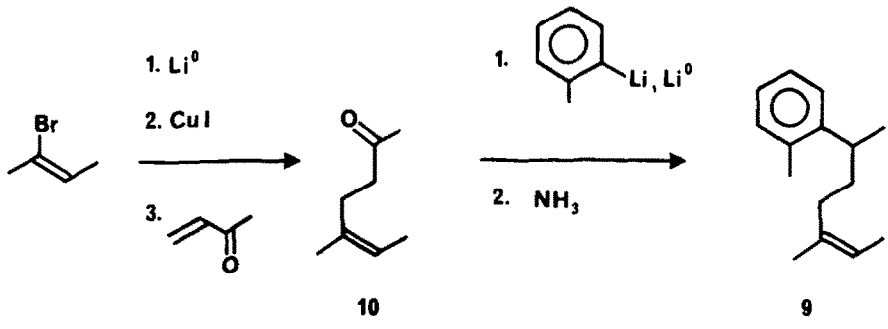


PRO-α



PRO-β

Scheme 4.



Scheme 5.

analysis.[23] Chromatography of this reaction mixture on silica gel impregnated with $AgNO_3$ (5%) provided a mixture of cycloadducts which, upon fractional crystallization from methanol, afforded crystalline samples of **7** and **8**. The ^1H NMR spectrum of each adduct exhibited a pair of methyl singlets, two methyl doublets, and two olefinic hydrogens as would be expected if meta-addition to centers C-2 and C-8 had occurred. Furthermore, the splitting of the olefinic hydrogens, a doublet (δ5.50: J = 5.6Hz) and doublet of doublets (δ5.68: J = 5.6, 2.2Hz) in one case and a pair of doublets of doublets (δ5.69: J = 5.3, 2.3Hz; δ5.41: J = 5.3, 2.3Hz) in the other, is fully consistent with the anticipated adducts **7** and **8**, respectively. Interestingly, however, these data do not exclude adducts arising from addition to C-1 and C-9 (see Scheme 4)[24] an uncertainty which persisted to the very end of the synthesis.

Two aspects of this photocycloaddition proved to be particularly noteworthy. When compound **9** was irradiated (Vycor filter) for a period of only 10 minutes, cyclo-adducts **8** and **7** were formed in the ratio 4.5:1 in contradistinction to the 1:1 ratio obtained after 4 hr of irradiation. Although further studies are needed to establish the basis for this result, this preference might be a reflection of destabilizing steric interaction between C-12 and C-7 in isomer **7** which is attenuated in isomer **8**[25] due to the increased internuclear distance between these centers. The second but related matter is that the cycloadducts, which exhibit a rather substantial vinyl-cyclopropane absorption at ~220 nm, can be easily intercon-

verted photochemically. Thus, irradiation (Vycor filter) of **8** in cyclohexane for 195 min provide a 1.0:1.6 mixture of **8** and **7**. Under essentially identical conditions, irradiation of **7** gave **8** and **7** in the ratio 1.0:2.6. In both cases, other compounds which were also formed in the irradiation of arene olefin **9** and, therefore, qualify as over-irradiation products, were produced in minor amounts. It is noteworthy for synthetic purposes that while the isocomene synthesis was designed to employ both cycloadducts, this demonstration of their interconversion provides the basis for the more efficient use of this methodology in other syntheses where only one cycloadduct can be used.

In accord with the previously noted strategy and the structural assignments for the cycloadducts, thermolysis of **7** in toluene solution for 1 hr at 235–240° gave only dehydroisocomene (**6**) and unreacted starting material in the ratio 5.2:1. Thermolysis of the other cycloadduct (**8**) at 232° for 14 hr proceeded less selectively affording dehydroisocomene (**6**) in only 46% along with unreacted starting material (ca. 12%), and an unidentified third component (*ca.* 20%). Alternatively, because of the difficulty associated with the separation of the hydrocarbon isomers **7** and **8** which was not eased by their chemical and thermal instability, the preparation of dehydroisocomene was effected more conveniently and in *ca.* 50–60% yield by thermolysis of the cycloadduct mixture (**7**:**8** = 1:1) obtained by flash silica chromatography. In accord with the proposed structure, the ^{1}H NMR spectrum of an analytical sample of **6** included signals at 5.05 δ (1H) and 5.46 δ (2H) assignable to the olefinic hydrogens; 3H singlets at 0.97 δ and 1.03 δ for the C-12 and C-14 methyl groups; a 3H doublet (J = 6.8Hz) at 0.96 δ for C-15; and a 3H doublet (J = 1.4Hz) at 1.59 δ for the C-13 methyl. However, since these data could also be assigned to the thermolysis product of cycloadducts obtained from meta addition to C-1, C-9 the proper confirmation of the structure proposed for the pyrolysis product and, consequently, the cycloadducts awaited, once again, completion of the synthesis.

For the fifth and final step of this synthesis, **6**, obtained by silica chromatography, and 5% palladium-on-carbon catalyst in hexane were stirred under 1 atmosphere of hydrogen at room temperature for 75 min. The crude reaction mixture was filtered and the solvent removed *in vacuo* to afford a crystalline solid of 90% purity as determined by VPC. Confirmation of the proposals set forth at the outset of this study was finally realized when a crystalline compound (m.p. 61–63°), obtained by preparative VPC of the solid obtained from this hydrogenation, was found to be spectroscopically identical to a similarly purified sample of (±)-isocomene kindly provided by Prof. Paquette.[26]

In summary, (±)-isocomene (**5**), a molecule characterized by an interesting polyquinane nucleus adorned with four stereocenters including three contiguous quaternary centers, has been synthesized in five steps from Z - 2 - bromo - 2 - butene and 2-bromotoluene. While the preparative potential of this synthesis has not been tested, the strategy, in its present form, allows for synthesis of multigram quantities of (±)-isocomene in a period of less than one week. Of course, in the final analysis, the issue here is not related to the world's supply of isocomene but rather the development of a methodology which would be expected to have considerable utility in total synthesis. The isocomene synthesis was initiated in connection with this recognition and was designed to further develop the scientific foundation needed to realize this goal. Its successful conclusion serves as an indication of the enormous potential of this unique cycloaddition reaction.[27] Research on the further development of this methodology is in progress.

EXPERIMENTAL

M.ps were determined on a Thomas–Hoover apparatus using capillary tubes, and are corrected. Infrared spectra were obtained with a Perkin–Elmer Model 137 spectrometer. Ultraviolet spectra were recorded with a Perkin–Elmer Coleman 124 spectrometer. ^{1}H NMR spectra were obtained in $CDCl_3$ solvent, at 80MHz on a Varian CFT-20 instrument; chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane, using chloroform as a reference. Mass spectra were obtained on an A.E.I. MS-9 instrument operated at 70 ev ionizing voltage and 8 kv accelerating voltage. High resolution mass spectra were measured on a Kratos MS-50L instrument equipped with a DS-55 data system. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

All column chromatography was performed by the method of Still *et al.*,[28] using Woelm silica (32–63 μm). Preparative vapor phase chromatography (VPC) was accomplished on a Varian Model 920 instrument with a 1/4" × 10' stainless steel column packed with 3% SE-30/Anakrom ABS, operated at 130°. Analytical VPC was performed on a Bendix Series 2200 chromatograph equipped with a flame ionization detector and a 1/8" × 20' stainless steel column packed with 3% SE-30/Anakrom ABS, operated at 130°. Relative detector response factors were determined against perhydrofluorene as an internal standard.

Photolyses were performed using a water-cooled quartz immersion well available from Ace Glass Co. The light source was a Hanovia 450W, medium-pressure mercury vapor lamp which was used in conjunction with a Vycor filter. Small-scale photolyses were done in Vycor test tubes placed adjacent to the immersion well. All photolyses were conducted with nitrogen-purged (15–30 min) solutions of the substrate in spectrograde cyclohexane (Eastman). The glassware for photolyses was pretreated with concentrated aqueous ammonia (1–2 hrs) and oven-dried (130°, 12 hr).

Thermolyses were conducted in nitrogen-purged toluene solution, in 1/4" or 1/2" i.d. resealable pyrex tubes (fitted with a steel screw cap and teflon gasket; available from Fischer and Porter Co.). Thermolysis tubes were pre-basified with aqueous ammonia and oven-dried. An oil bath was used for heating.

Ether and toluene were distilled from sodium-benzophenone ketyl. Oxygen- or moisture-sensitive reactions were carried out in oven-dried glassware under nitrogen atmosphere, liquids and solutions being transferred with a dry cannula or syringe.

z - 5 - *Methyl* - 5 - *hepten* - 2 - *one* (**10**). To a suspension of CuI (27.5 g, 0.145 mol)[29] in 30 ml ether cooled to −78°C was added a freshly prepared[21] solution of E - 2 - lithio - 2 - butene (0.29 mol) in 500 ml ether over a 40 min period. After 45 min at −78°, the reaction mixture was warmed to −40° over a 30 min period, then cooled to −65°. Freshly distilled methyl vinyl ketone (9.13 g, 0.116 mol) in ether (25 ml) was added over a 30 min period. The dark green mixture was stirred at −65° for 30 min, then allowed to warm to room temperature. After 1.5 hr the flask was opened and saturated aqueous NH_4Cl (350 ml), buffered to pH 7 with aqueous NH_3, was added. The mixture was stirred for 1 hr, then filtered. The deep blue filtrate was thoroughly extracted with ether, the organic layer was dried (Na_2SO_4), and concentrated at atmospheric pressure. Fractional distillation of the resulting oil through a 6" Vigreux column (95–96°/61 torr) afforded **10** (8.22 g, 65.2 mmol; 56% based on methyl vinyl ketone). IR (film): 3400, 2900, 1720, 1440, 1350, 1160, 820 cm^{-1}. NMR ($CDCl_3$): δ1.63 (6H, m), 2.14 (3H, s), 2.40 (4H, m), 5.23 (1H, qt).

z - 3 - *Methyl* - 6 - (2 - *methylphenyl*) - 2 - *heptene* (**9**). To a suspension of small pieces of lithium (459 mg, 67 mmol; 0.8% Na) in 15 ml ether at 23°C was added a solution of o-bromotoluene (1.353 g, 7.91 mmol) in 10 ml ether. The mixture was stirred for 1 hr, after which enone **10** (554 mg, 4.40 mmol) in ether (12 ml) was added. After further stirring (1 hr), the mixture was cooled to −78°, and about 50 ml liquid ammonia was distilled into the flask.

The resulting deep blue mixture was allowed to warm while several grams of solid NH_4Cl were cautiously added in portions. After a thick white precipitate had developed, the excess NH_3 was allowed to evaporate. The residue was dissolved in 150 ml saturated aqueous NaCl and extracted with ether (3 × 50 ml). The organic layer was dried (Na_2SO_4) and the ether was removed *in vacuo*. Chromatography of the product (1:2 ether: hexanes) gave **9** (697 mg, 3.45 mmol; 78%). IR (film): 3400, 2950, 1670, 1600, 1495, 1460, 1018, 810, 760, 730 cm^{-1}. NMR ($CDCl_3$): δ1.26 (3H, d; J = 6.9 Hz), 1.49 (3H, dm; J = 6.7 Hz), 1.69 (3H,m), 1.7 (2H), 1.94 (2H, m), 2.35 (3H, s), 3.18 (1H, m; J = 6.9 Hz), 5.21 (1H, qm; J = 6.7 Hz), 7.15 (4H, m). UV (Hexane): 263.5 nm (log ϵ = 2.42), 271 nm (log ϵ = 2.36). Mass spectrum: *m/e* 202 (M^+, 17%), 187 (5%), 133 (19%), 132 (100%), 120 (19%), 119 (86%), 117 (22%), 105 (39%), 95 (25%), 91 (25%), 83 (8%), 81 (14%), 79 (14%), 77 (14%), 69 (11%), 67 (11%), 65 (8%), 55 (22%), 41 (28%). Calc. for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.15; H, 11.08%.

Photolysis of Arylalkene **9**. A solution of **9** (1.688 g, 8.356 mmol) in cyclohexane (130 ml) was irradiated through Vycor for 4.5 hr under constant nitrogen purging. Removal of the solvent at reduced pressure and silica chromatography (hexanes) of the remaining light yellow oil yielded a waxy white solid (1.391 g, 82% mass recovery). NMR and VPC analysis showed this to coniist mostly (85–90%) of an equal mixture of **7** and **8**. Polymeric material, removed in the silica chromatography, was also produced. For a mixture of **7**+**8** obtained by silica chromatography: NMR ($CDCl_3$): δ0.76–1.28 (complex), 2.55 (1H, d; J = 2.3Hz), 5.54 (4H, m). Calc. for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.90; H, 11.05%.

Chromatography of the product mixture on silica gel impregnated with 5% $AgNO_3$, with toluene as eluant, separated **7** and **8**, which were then recrystallized from MeOH. For **7**: m.p. 101°–102.5°C (sealed capillary). IR (CCl_4): 2950, 1675, 1600, 1460, 1380, 1360, 1000, 985, 938, 929, 917, 875 cm^{-1}. NMR ($CDCl_3$): δ0.76 (3H, s), 0.96 (3H, d; J = 7.1 Hz), 1.05 (3H, d; J = 8.1Hz), 1.21 (3H, s), 1.3–2.3 (complex), 5.50 (1H, d; J = 5.6 Hz), 5.68 (1H, dd; J_1 = 5.6 Hz, J_2 = 2.2 Hz). UV (hexane): 220 nm (log ϵ = 3.72), 202 nm (log ϵ = 3.75). Mass spectrum: *m/e* 202 (M^+, 12%), 187 (13%), 145 (21%), 132 (100%), 123 (50%), 119 (78%), 105 (37%), 95 (12%), 91 (24%), 69 (7%), 55 (15%). High resolution mass spectrum, Calc. for $C_{15}H_{22}$: 202.17214. Found: 202.17206. Anal. Calc. for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.79; H, 11.07%.

For **8**: m.p. 124.5°–126°C (sealed capillary). IR (CCl_4): 2950, 1680, 1600, 1455, 1375, 1340, 1105, 975, 950, 920, 900, 860 cm^{-1}. NMR ($CDCl_3$): δ 0.89 (3H, d; J = 6.1Hz), 0.98 (3H, d; J = 7.2Hz), 1.17 (3H, s), 1.28 (3H, s), 1.3–2.1 (complex), 2.55 (1H, d; J = 2.3Hz), 5.41 (1H, dd; J_1 = 5.3Hz, J_2 = 2.3Hz), 5.69 (1H, dd; J_1 = 5.3Hz, J_2 = 2.3Hz). UV (hexane): 219 nm (log ϵ = 3.51), 205 nm (log ϵ = 3.47). Mass spectrum: *m/e* 202 (M^+ 15%), 187 (15%), 145 (28%), 132 (100%), 123 (83%), 119 (95%), 105 (51%), 95 (36%), 91 (41%), 69 (23%), 55 (38%). High resolution mass spectrum calc. for $C_{15}H_{22}$: 202.17214. found: 202.17213.

Photolysis of arylalkene **9** *with internal standard*. A solution of **9** (21.2 mg; 0.105 mmol) in cyclohexane (2.5 ml), containing perhydrofluorene as an internal standard, was irradiated for 3.6 hr in a Vycor test tube under nitrogen atmosphere. VPC analysis of the crude product revealed that vinylcyclopropanes **7** and **8** had been formed in a 1:1 ratio in a combined yield of 72%. Minor amounts of other compounds were also detected.

Brief photolysis of **9**. Photolysis of **9** (27 mg, 0.13 mmol) in cyclohexane (2.5 ml) for 10 min gave **7** and **8** in the ratio 1:4.5, as determined by VPC. Several of the additional minor products formed in longer irradiations were also evident here.

Photoequilibration of **7**. Vinylcyclopropane **7** (6.0 mg; 0.30 mmol) in cyclohexane (2.3 ml) was irradiated in a Vycor test tube for 195 min. VPC showed the product to consist of **7**, **8**, and unidentified components in the ratio 2.3:1.0:1.7. Removal of solvent gave 5.7 mg photoisomers, the composition of which was confirmed by NMR. The unknown components corresponded to products observed, in lesser quantity, during photolysis of **9**.

Photequilibration of **8**. Irradiation of vinylcyclopropane **8** (5.8 mg, 0.03 mmol; in 2.3 ml cyclohexane) through Vycor for 195 min gave a product ratio 1.6:1.0:0.4 of **7**, **8**, and the unidentified components observed above. Removal of solvent left 5.2 mg product, with an NMR spectrum qualitatively identical to that found above for equilibration of **7**.

Thermolysis of photoisomer mixture. A solution of the mixture of isomers obtained from photolysis of **9** (505 mg, 2.5 mmol; purified by silica chromatography) in toluene (6 ml) was heated in a nitrogen-purged thermolysis tube at 230–244° for 14.5 hr. The solvent was removed and chromatography (hexanes) of the yellow product gave a colorless liquid (61% mass recovery), which was shown by VPC and NMR to consist of dehydroisocomene **6** (90%), and other products (10%) including some unconverted **8**. The analytical sample of dehydroisocomene **6** was obtained by preparative VPC: IR (film): 3350, 2930, 1660, 1450, 1365, 1340, 1006, 880, 760, 720 cm^{-1}. NMR ($CDCl_3$): δ 0.96 (3H, d; J = 6.8Hz), 0.97 (3H, s), 1.03 (3H, s), 1.26–1.50 (4H, m), 1.59 (3H, d; J = 1.4Hz), 2.0 (1H, m), 2.31 (1H, s), 2.38 (1H, bs), 5.05 (1H, m), 5.46 (2H, bs). Mass spectrum: *m/e* 202 (M^+, 33%), 187 (100%), 145 (48%), 132 (54%), 131 (22%), 119 (19%), 105 (19%), 95 (10%), 91 (19%), 55 (7%). High resolution mass spectrum Calc. for $C_{12}H_{22}$: 202.17214. Found: 202.17215. Calc. for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.00; H, 10.90%.

Under conditions similar to the above, thermolysis of the isomer mixture from photolysis of **9** (36.3 mg, 0.18 mmol; in 2 ml toluene) with added perhydrofluorene as an internal standard, for 14.5 hr at 223–235, gave by VPC analysis a 57% yield of dehydroisocomene **6** and 12% unconverted **8**, along with unidentified minor products.

Thermolysis of **7**. Vinylcyclopropane **7** (5.7 mg, 0.03 mmol) in toluene (0.9 ml) was heated as above, at 235–240° for 1 hr. VPC analysis of the product showed the ratio of **6** to **7** to be 5.2:1. Removal of the solvent gave 4.7 mg colorless oil, consisting of only **6** and **7** by NMR.

Thermolysis of **8**. Vinylcyclopropane **8** (8.3 mg, 0.04 mmol; in 1.5 ml toluene) with added perhydrofluorene (internal standard) was thermolysed as above for 14 hr at 232°. By VPC the yields of dehydroisocomene **6** and recovered **8** were 46% and 12%, respectively. A third compound (*ca.* 20%) was also produced. The product composition was confirmed by NMR.

(±)-*Isocomene* (**5**). To a solution of dehydroisocomene (172 mg, 0.85 mmol; obtained in 90% purity from silica chromatography) in 10 ml hexane was added 5% palladium on carbon (20 mg). The mixture was stirred over H_2 (1 atm.) at room temperature for 75 min. After filtration of the mixture, the solvent was removed *in vacuo*, leaving crystalline (±)-isocomene (170 mg, 0.833 mmol, 98% yield; purity 90% by VPC and NMR). The analytical sample was obtained by preparative VPC: m.p. 61–63°. IR (CCl_4): 3020, 2950, 2870, 1670, 1450, 1375, 1330, 1190, 1005, 850 cm^{-1}. NMR ($CDCl_3$): δ0.86 (3H, d; J = 7.0Hz), 1.04 (6H, s), 1.56 (3H, d; J = 1.5Hz), 4.86 (1H, bs). Mass spectrum: *m/e* 204 (M^+, 15%), 189 (20%), 162 (100%), 148 (15%), 147 (43%), 134 (19%), 133 (19%), 120 (15%), 119 (33%), 107 (19%), 105 (25%), 93 (15%), 91 (25%), 79 (20%), 55 (18%). High resolution mass spectrum calc for $C_{15}H_{24}$: 204.18779. Found: 204.18782.

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[3]Examples include methanoprostacyclins, dodecahedrane, the hirsutanes, capnellanes, illudanes, guaianes, tiglianes, grayanotoxins, daphnanes, ingenanes, along with numerous other classes which are more comprehensively covered in *Specialist Periodical Reports*: *Terpenoids and Steroids*, Vols. 1–9, 1971–79, Burlington House, London.

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gies are: intramolecular closure, 3+2 and 4+1, 3+1+1 and 2+2+1, 2+1+1+1, and 1+1+1+1+1.

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[16]Arene-olefin cycloadditions may proceed with addition of the olefin to adjacent carbons of an aromatic ring (ortho or 1,2 mode), addition to positions 1 and 3 (meta or 1,3 mode) and addition to positions 1 and 4 (para or 1,4 mode).

[17]Mode selectivity has been found to generally correlate with the difference in ionization potential (ΔIP) between the arene and olefin. Generally, meta addition is preferred in the case where ΔIP is small whereas ortho and para cycloaddition is favored in cases where ΔIP is large. For a recent discussion of this point and related references, see: D. Bryce-Smith, B. Foulger, J. Forrester, A. Gilbert, B. H. Orger and H. M. Tyrrell, *J. Chem. Soc. Perkin Trans I* 55 (1980).

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[23]The remaining 10% of the reaction mixture included possible over-irradiation products, compounds arising from rearrangement of the thermally sensitive adducts **7** and **8** in the GC injector port, and possibly trace amounts of other primary photoproducts.

[24]Adducts arising from a C-1, C-9 meta addition would exhibit not only the same type of olefinic activity in the ^{1}H NMR but also the same pattern of methyl singlets and doublets. The assignment of **7** and **8** rested solely on the prediction that C-6-C-13 interactions would disfavor a C-1, C-9 addition.

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[26]We thank Prof. Paquette (Ohio State University) for his prompt response to our request for a comparison sample.

[27]The potential utility of a methodology is subject to many interpretations. However, the utility of the Diels–Alder reaction is fundamentally related to the fact that it delivers, in one operation based on readily available starting materials, a new ring system with up to four stereocenters. By comparison, based on these criteria, the meta addition delivers, in one operation with starting materials which are more readily available than those of the Diels–Alder, three new rings with up to six stereocenters. Importantly, these powerful cycloadditions are complementary in that the Diels–Alder is primarily useful for six-membered ring synthesis while the meta addition can be used for a variety of odd-membered ring syntheses.

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