Thermal, Photochemical, and Transition-metal Mediated Routes to Steroids by Intramolecular Diels–Alder Reactions of *o*-Xylylenes (*o*-Quinodimethanes)

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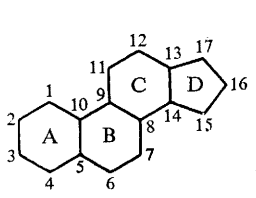
1 Introduction

The pronounced physiological activity of the steroid nucleus has made it the target of numerous, often ingenious, synthetic strategies. Although total syntheses are currently economically inferior to partial syntheses beginning from naturally occurring analogues, the synthetic challenge, the desire to find economically and ecologically more advantageous sources of steroid drugs, and the ongoing search for unknown modified structures with improved medicinal potential, has spurred recent activity in the design and execution of steroidal total synthesis.

Inspection of two excellent monographs on the subject[1] indicates that the basic framework of the steroids [*e.g.* (1)], with its four annulated rings designated A, B, C, D, may be constructed starting with either one or several of the rings containing appropriate functionality as suitable precursors for the addition of the remaining cycles by cycloadditions, condensations, and other bond-forming reactions. The various successful synthetic routes may be conceptualized in an abbreviated fashion as AB→ABCD, BD→ABCD *etc.* depending on the sequence in which the individual cycles are added or formed. Of the many possibilities, the AD→ABCD approach has been applied relatively infrequently. A rare example is the Smith–Hughes synthesis[1a] highlighted by the key condensation (2) → (3),



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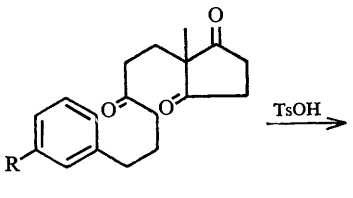

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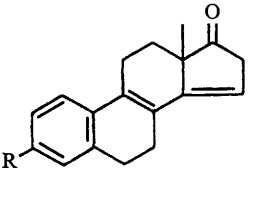
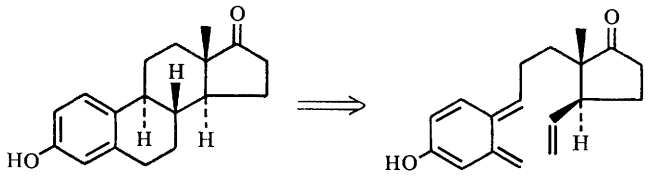


(3)

[1] (a) A. A. Akhrem and Y. A. Titov, 'Total Steroid Synthesis', Plenum Press, New York, 1970; R. T. Blickenstaff, A. C. Ghosh, and G. C. Wolf in 'Organic Chemistry. A Series of Monographs', ed. A. T. Blomquist and H. Wasserman, Vol. 30, 'Total Synthesis of Steroids', Academic Press, New York, 1974; (b) P. A. Bartlett and W. S. Johnson, *J. Amer. Chem. Soc.*, 1973, **95**, 7501.

leading to A-ring aromatic steroids. The method is amenable to a multistep synthesis of estrone (4). A more recent application of this approach uses a cationic olefin cyclization in the crucial step.[1b]

In a retro-synthetic analysis of estrone one notices that an alternative to the Smith–Hughes AD→ABCD approach, which might allow the stereospecific construction of the BC-rings in one step, is an intramolecular Diels–Alder reaction of an appropriate intermediate of the type (5). The latter contains an *o*-xylylene moiety which might be generated from a variety of precursors.



(4) (5)

Routes to steroids which rely on this concept have recently been developed by several groups. The present review will attempt to highlight the events that led to the successful application of intramolecular cycloadditions[2] of *o*-xylylenes to steroid synthesis. Other selected uses of *o*-xylylenes in synthetic schemes will be described as they appear important in a historical context and relevant to the main theme of this article.

2 Generation of *ortho*-Xylylenes

The first *o*-xylylene to be generated appears to be (6b). In 1909, Finkelstein[3] treated $\alpha\alpha\alpha'\alpha'$-tetrabromo-*o*-xylene with sodium iodide and obtained 1,2-dibromobenzocyclobutene (7b) presumably through the intermediacy of (6b). However, five decades elapsed before it was shown by Cava, Deana, and Muth that the latter was indeed an intermediate in this reaction by trapping it with *N*-phenylmaleimide to give (after dehydrobromination) the Diels–Alder adduct (8).[4a] Jensen, Berlin, and Coleman obtained a cycloadduct similar to (8) by heating (7b) with maleic anhydride to give naphthalene-2,3-dicarboxylic anhydride (after dehydrobromination), thus demonstrating that *o*-xylylene (6b) could be regenerated by thermolysis of (7b).[4b]

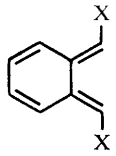
After this initial work it was soon realized that *ortho*-xylylenes could have great potential in organic synthesis when employed as Diels–Alder dienes. New ways of generating them were quickly developed. Several of these new methods utilized retro-cycloadditions. For example, thermal extrusion of sulphur dioxide

[2] For comprehensive reviews on intramolecular Diels–Alder reactions see: W. Oppolzer, *Angew. Chem. Internat. Edn.*, 1977, **16**, 10; *Synthesis*, 1978, 793.

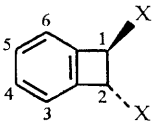
[3] H. Finkelstein, *Chem. Ber.*, 1910, **43**, 1528.

[4] (a) M. P. Cava, A. A. Deana, and K. Muth, *J. Amer. Chem. Soc.*, 1959, **81**, 6458; (b) F. R. Jensen, W. E. Coleman, and A. J. Berlin, *Tetrahedron Letters*, 1962, 15.

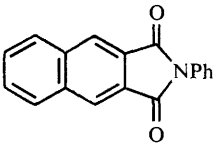
from sulphone (9) generated *ortho*-xylylene (6a),[5] and photochemical expulsion of carbon monoxide from 2-indanone (10) produced *o*-quinodimethane (6c).[6] A more recent development has been the pyrolysis of 3-isochromanones such as (11) which proceeds smoothly to generate *ortho*-xylylenes.[7] Finally, Michl and co-workers were able to prepare and observe the parent *o*-xylylene (6a) by irradiating 1,4-dihydrophthalazine (11) at −196 °C in a glass matrix.[8] The absorption spectra confirmed the expectation that the ground state is a singlet.



(6a) X = H
(6b) X = Br
(6c) X = Ph



(7a) X = H
(7b) X = Br



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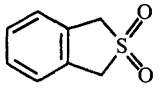

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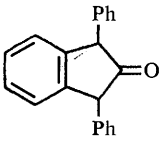

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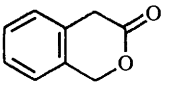

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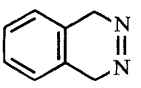
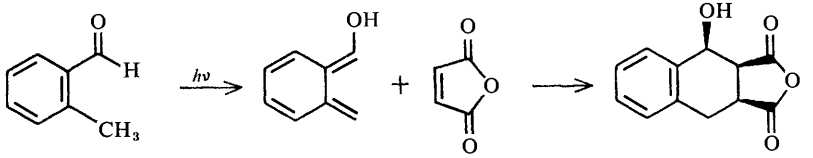


(12)

A unique approach to a specific type of *o*-xylylene is the photoenolization of *ortho*-alkyl-benzaldehydes.[9] For example irradiation of 2-methylbenzaldehyde in the presence of maleic anhydride gave one adduct, shown to be the unstable, all-*cis* hydroxy-anhydride (14).[10] The adduct (14) could arise by *endo*-addition of



(13) (14)

maleic anhydride to the (*E*)-dienol (13) or *exo*-addition to the (*Z*)-dienol. The authors preferred the former pathway due to the known preference for *endo*-addition in the Diels–Alder reaction. Although this approach can also be applied

[5] M. P. Cava and A. A. Deana, *J. Amer. Chem. Soc.*, 1959, **81**, 4266.
[6] G. Quinkert, K. Opitz, W. W. Wiersdorff, and J. Weinlich, *Tetrahedron Letters*, 1963, 1863.
[7] R. J. Spangler, B. G. Beckmann, and J. H. Kim, *J. Org. Chem.*, 1977, **18**, 2989.
[8] C. R. Flynn and J. Michl, *J. Amer. Chem. Soc.*, 1974, **96**, 3280.
[9] P. G. Sammes, *Tetrahedron*, 1976, **32**, 405.
[10] S. M. Mellows and P. G. Sammes, *J.C.S. Chem. Comm.*, 1971, 21.

to *o*-alkyl-styrenes,[11] relatively few synthetic applications of this mode of *o*-xylylene generation have been reported. Despite the accessibility of the necessary precursors, the method might be limited by the possibility of photochemical side-reactions.

The most frequent way of producing *o*-xylylenes has been by thermolysis of benzocyclobutenes. This transformation takes place *via* a thermally allowed conrotatory electrocyclic ring opening. Benzocyclobutenes having a substituent on the cyclobutene ring presumably open outward in a conrotatory manner to produce the sterically least hindered (*E*)-diene in preference to the (*Z*)-form, and open at lower temperatures than does benzocyclobutene (alkoxy-substituent, 110 °C; alkyl substituent, 140—170 °C; benzocyclobutene, 200 °C).[12] It appears that a more electronegative substituent on the cyclobutene ring lowers the temperature required for ring opening. Furthermore, 1,1-dialkylated benzocyclobutenes such as (15) open readily to *o*-xylylenes, in this case (16) and (17). However, the use of these dienes in Diels–Alder reactions is limited due to ready [1,5]-sigmatropic hydrogen migrations to produce mixtures of styrenes (18) and (19).[13]

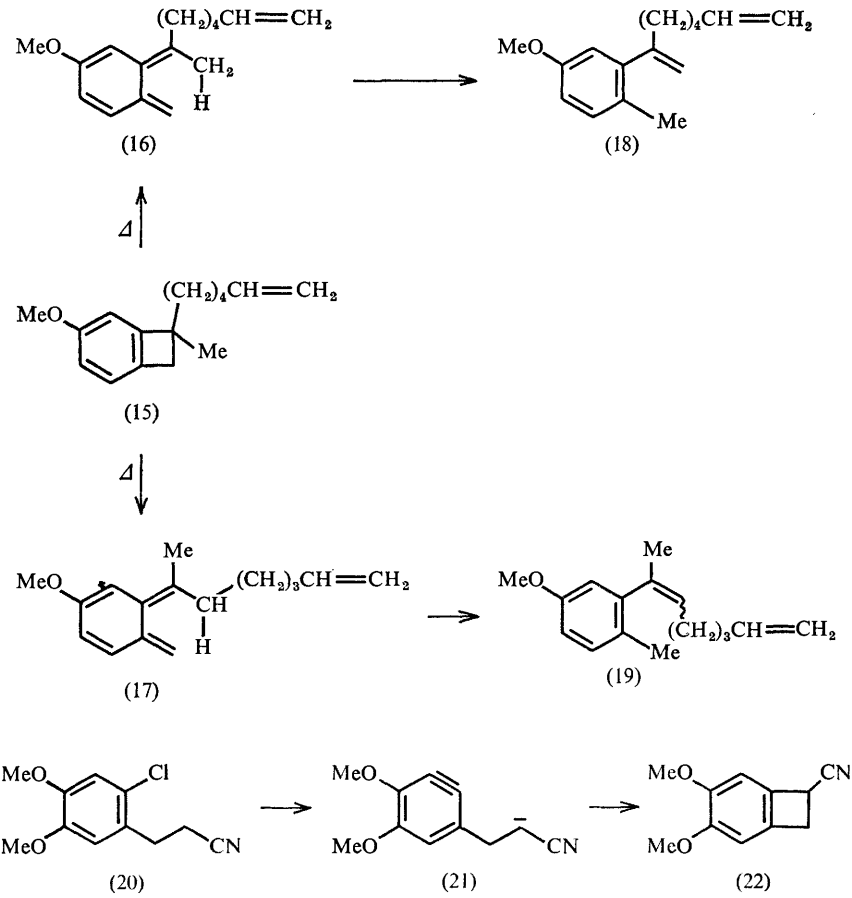
The chemistry and synthesis of benzocyclobutenes have been reviewed.[2,14] In addition to *o*-xylylene generation followed by ring closure, few methods for preparing benzocyclobutenes exist. The most frequently used and one of the more versatile approaches to the preparation of benzocyclobutenes substituted on the aromatic ring was developed by Bunnett and co-workers.[15] Reaction of the hydrocinnamonitrile (20) with potassium amide in ammonia produces the intermediate benzyne (21) which undergoes ring closure to produce 1-cyanobenzocyclobutene (22) in 46% yield. Unfortunately, this method suffers from inaccessibility of starting materials, and frequently transformation of the nitrile group into more useful functionality involves multi-step synthetic manipulations.

Approaches to substituted benzocyclobutenes *via* aromatic electrophilic substitution suffers from two major complications: first, the fused four-membered ring deactivates the 3- and 6-positions. Thus, benzocyclobutene does not react with acetyl chloride and $AlCl_3$ in CS_2 solvent; in nitromethane mixtures of products are formed from which 4-acetylbenzocyclobutene can be obtained in 27% yield.[14] Second, the four-membered ring is readily cleaved under Friedel–Crafts conditions.[16]

3 *ortho*-Xylylenes in Synthesis

A. Intermolecular Cycloadditions.—Although it was discovered in the early

[11] A. C. Pratt, *J.C.S. Chem. Comm.*, 1974, 183; J. M. Hornback, *Tetrahedron Letters*, 1976, 3389.
[12] T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, *Tetrahedron*, 1975, **31**, 949.
[13] T. Kametani, M. Tsubuki, Y. Shiratori, Y. Kato, H. Nemoto, M. Ihara, K. Fukumoto, F. Satoh, and H. Inoue, *J. Org. Chem.*, 1977, **42**, 2672.
[14] I. L. Klundt, *Chem. Rev.*, 1970, **70**, 471.
[15] J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, 1962, **27**, 3836.
[16] L. H. Schwartz, J. Landis, S. B. Lazarus, and S. H. Stoldt, *J. Org. Chem.*, 1972, **37**, 1979.

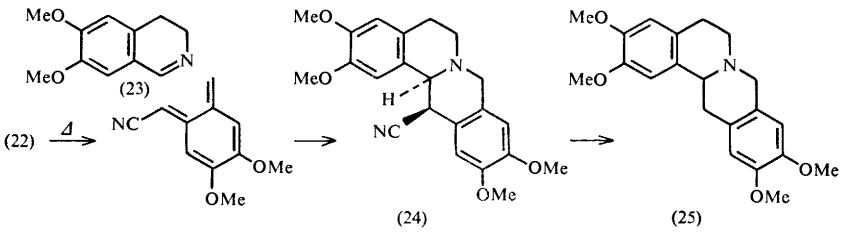


1950's that *o*-xylylenes could function as Diels–Alder dienes in the construction of functionalized tetralin derivatives, they were not used in natural product synthesis until much later.

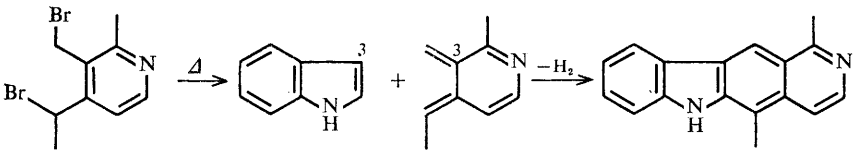
Intermolecular cycloadditions have resulted in several interesting syntheses, the majority of which are due to the Kumetani group.[17] Some examples are outlined below. 1-Cyano-3,4-dimethoxybenzocyclobutene (22) reacted regio- and stereo-selectively with 3,4-dihydroisoquinoline (23) at 150—180 °C *via* the *endo* approach to give cyanotetrahydroprotoberberine (24) in 81 % yield.[18] Reductive decyanation of the Diels–Alder adduct with lithium in liquid ammonia in the

[17] For reviews see: T. Kametani, *Pure Appl. Chem.*, 1979, **51**, 747; T. Kametani and K. Fukumoto, *Heterocycles*, 1977, **8**, 519; *Synthesis*, 1976, 319.
[18] T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, *J.C.S. Perkin I*, 1975, 737.

presence of isopropyl alcohol afforded norcoralydine (25), erroneously referred to as xylopinine.



The profound reactivity of *o*-xylylenes is evident in Kametani's synthesis of olivacine.[19] Heating indole with the dibromopyridine (26) in *NN*-dimethylformamide at 150 °C gave, regioselectively, olivacine (28) in 30% yield. The regioselectivity is due to the nucleophilicity of the C-3 position in the indole ring and the electrophilic influence exerted by the nitrogen on the 3-methylene position in (27).

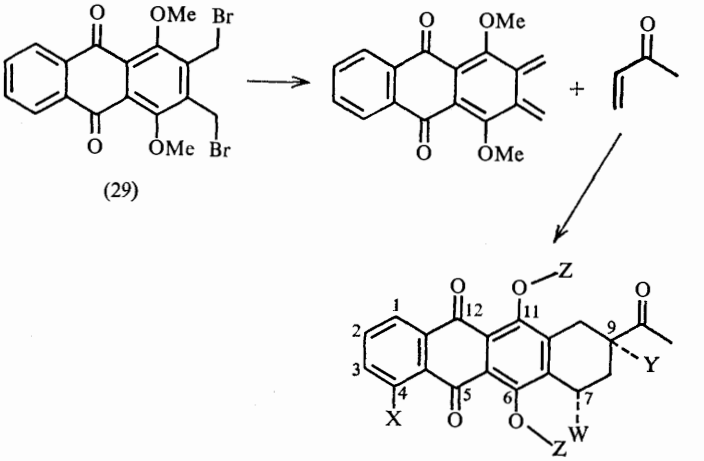


(26) (27) (28)

Ortho-xylylenes have also been involved in the construction of the ring skeleton of daunomycinone (30a),[20] one of the aglycones of the promising tumour-inhibiting anthracyclines. Reaction of the dibromide (29) with zinc dust in *NN*-dimethylformamide in the presence of an excess of methyl vinyl ketone gave the cycloadduct (30b) in 52% yield.[20a] Oxidation with Bu^tOK/O_2 followed by cleavage of the methyl ethers completed the synthesis of 7-dehydroxy-4-demethoxy-daunomycinone (30c). In another approach to this compound an *o*-xylylene was used to form the C-ring rather than the A-ring.[20c] Treatment of *αaα'α'*-tetrabromo-*o*-xylene with NaI in *NN*-dimethylformamide gave rise to *o*-xylylene (6b) which was trapped by the quinone (31) to give, after dehydrobromination, the cycloadduct (32). Reduction, oxidation, and hydrolysis produced

[19] T. Kametani, Y. Ichikawa, T. Suzuki, and K. Fukumoto, *J.C.S. Perkin I*, 1975, 2102.

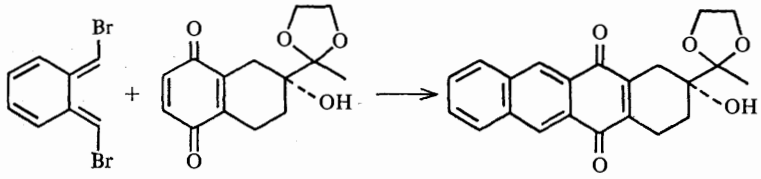
[20] (a) F. A. J. Kerdesky and M. P. Cava, *J. Amer. Chem. Soc.*, 1978, **100**, 3635; (b) T. Kametani, Y. Hirai, F. Satoh, and K. Fukumoto, *Chem. and Pharm. Bull., (Japan)*, 1974, **22**, 2159; (c) J. R. Wiseman, N. I. French, R. K. Hallmark, and K. G. Chiong, *Tetrahedron Letters*, 1978, 3765; (d) T. Kametani, M. Chihiro, M. Takeshita, K. Takahashi, K. Fukumoto, and S. Takano, *Chem. and Pharm. Bull. (Japan)*, 1978, **26**, 3820.



(29)

(30a) X = OMe; W,Y = OH; Z = H
(30b) W,X,Y = H; Z = Me
(30c) W,X,Z = H; Y = OH

(30c). Approaches to the ring system *via* reactions of benzocyclobuten-1-ol derivatives with synthons of the type (31) have also been reported.[20d]

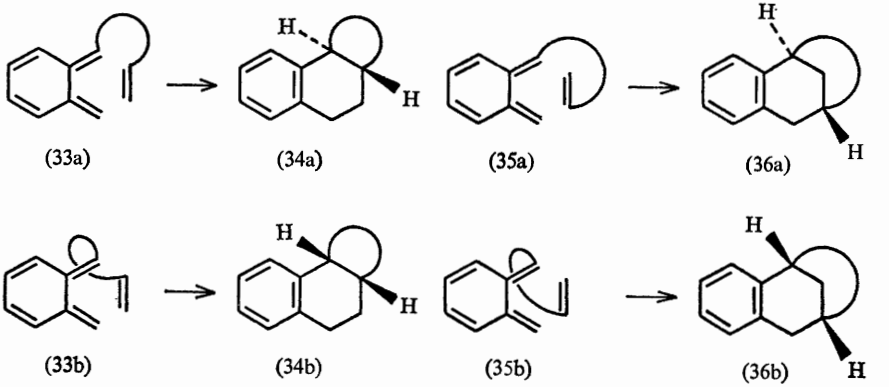


(6b) (31) (32)

B. Intramolecular Cycloadditions.—The intramolecular variant of the Diels–Alder reaction of *o*-xylylenes constitutes a powerful method for the construction of complex poly-carbo- and -hetero-cyclic systems. In principle, starting with an achiral substrate, two *exo*- (33a and 35a) and two *endo*-transition states (33b and 35b) may be distinguished on account of the possibility of regioisomeric modes of addition. Pioneering work by Oppolzer[2] revealed interesting selectivity in this reaction.[21] First, the reaction proceeds regiospecifically through either *exo*-transition state (33a) or *endo*-transition state (33b) to provide annelated

[21] (a) W. Oppolzer, *J. Amer. Chem. Soc.*, 1971, **93**, 3833; (b) *ibid.*, p. 3834; (c) W. Oppolzer and K. Keller, *ibid.*, 1971, **93**, 3836; (d) W. Oppolzer, *Tetrahedron Letters*, 1974, 1001; (e) W. Oppolzer, *Angew. Chem. Internat. Edn.*, 1972, **11**, 1031; (f) W. Oppolzer and K. Keller, *ibid.*, p. 728; (g) *ibid.*, 1977, **16**, 10.

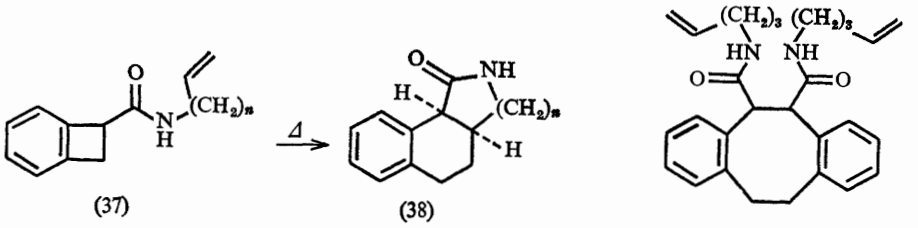
adducts (34a, b) to the exclusion of the bridged adducts (36a,b) which would result from *exo*-transition state (35a) or *endo*-(35b). Second, complications were



(33a) (34a) (35a) (36a)

(33b) (34b) (35b) (36b)

noticed when the length of the dienophilic chain was increased.[21a] For example, while the pyrolysis of (37a) and (37b) furnished respectively the five- and the six-membered lactams (38a) and (38b) (80% yield), similar heating of (37c) formed the seven-membered lactam (38c) in drastically reduced yield (20%) along with the dimerization product (39) (6% yield). Third, the addition succeeds even with unreactive dienophiles, *e.g.*, aldehydes, nitriles, acetylenes, and oxime

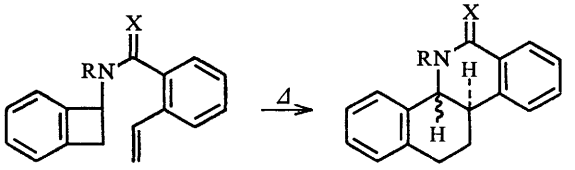


(37) (38) (39)

(a) $n = 1$, (b) $n = 2$, (c) $n = 3$.

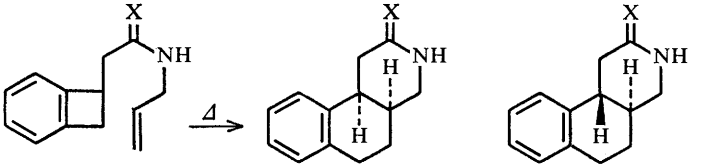
ethers.[21e] Fourth, the cycloadditions generally give high stereoselectivity. Fifth, the *endo–exo* product ratio can be affected dramatically by simply changing the conformation of the bridge.[21d] For example, pyrolysis of the urethane (40a) leads exclusively to the *cis*-fused cycloadduct (41a), whereas the amide (40b) gives only the *trans*-product (41b). In a similar example, pyrolysis of the amide (42b) afforded mostly the *cis*-isomer (43a), whereas for the amine (42a) the *trans*-isomer (44a) predominates. Clearly, the stereochemical outcome of intramolecular *o*-xylylene cycloadditions is not easily predicted, but it appears

that by appropriate structural manipulation control of stereochemistry is attainable.



(40a) X = H_2, R = CO_2Me
(40b) X = O, R = H

(41a) *cis*
(41b) *trans*



(42a) X = H_2
(42b) X = O

(43) 12%
83%

(44) 87%
16%

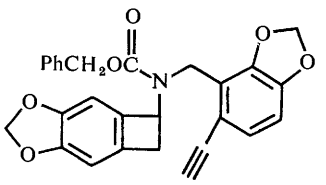
Oppolzer was also the first to exploit the synthetic potential of the method in a total synthesis of (±)-chelidonine (47).[21c] The benzocyclobutene (45), available in six steps from 1-cyano-4,5-methylenedioxybenzocyclobutene, cyclized smoothly in *o*-xylene at 120 °C within one hour to give the chelidonine skeleton (46) in 73% yield.

Further transformation (hydroboration and peroxide oxidation, chromium trioxide oxidation, $NaBH_4$ reduction, hydrogenolysis, and *N*-methylation) furnished (±)-chelidonine (47).

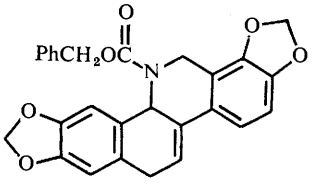
Kametani has shown that intramolecular cycloaddition of *o*-quinodimethanes provides a convenient and stereoselective route to the basic framework of unsymmetrical pentacyclic triterpenes.[22a] Heating the benzocyclobutene (48) in a sealed tube at 210 °C for 3 hours gave in 60% yield the pentacyclic compound (50). It is important to note that this reaction proceeds with complete stereoselectivity through one (49) of four transition states (2 *exo*, 2 *endo*) (*vide infra*). The nitrile groups in cycloadduct (50) were converted into methyl groups (treatment with di-isobutylaluminium hydride, followed by Wolff–Kishner reduction) to provide a key intermediate which has been converted into the triterpene friedelin by Ireland and Walba.[22b]

In a synthetic sequence originally aimed at steroid construction it was discovered that benzocyclobutenes of the type (51) are converted pyrolytically into bicyclo[3.2.1]octane derivatives (52). One of these (5-MeO) was converted into

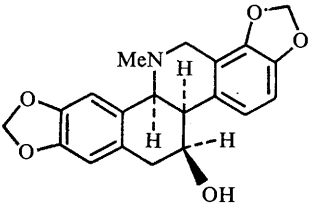
[22] (a) T. Kametani, Y. Hinai, Y. Shiratori, K. Fukumoto, and F. Satoh, *J. Amer. Chem. Soc.*, 1978, **100**, 554; (b) R. E. Ireland and D. M. Walba, *Tetrahedron Letters*, 1976, 1071; (c) T. Kametani, K. Suzuki, H. Nemoto, and K. Fukumoto, *J. Org. Chem.*, 1979, **44**, 1036.



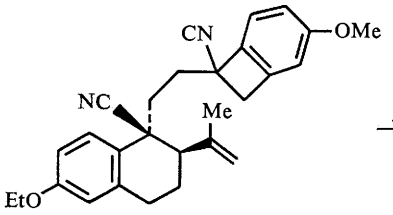
(45)



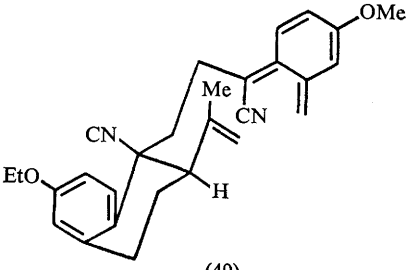
(46)



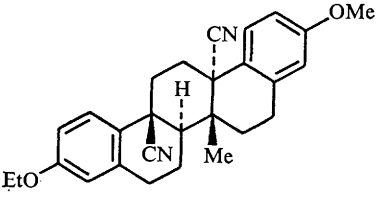
(47)



(48)

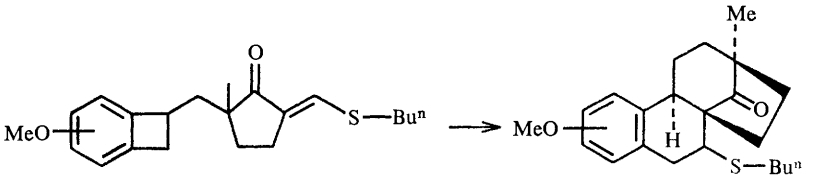


(49)

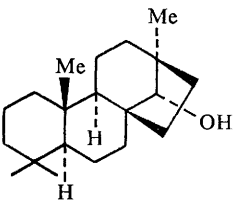


(50)

the triterpene hibaol (53)[22c] in 13 steps. Since the requisite benzocyclobutene (51) in turn necessitated 17 steps from the original starting material (*p*-methoxybenzaldehyde) the total effort (30 steps, 0.013% overall) is admirable.



(51) (52)

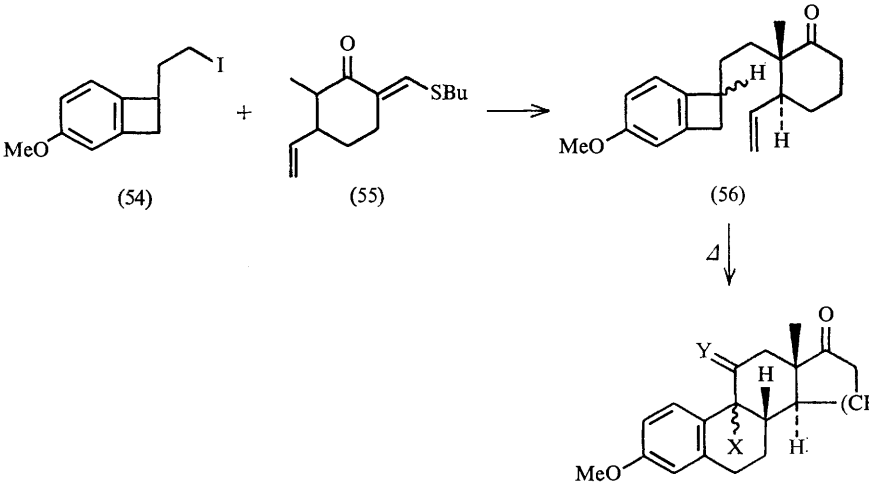


(53)

4 The Synthesis of Steroids

A. Thermal Generation of *o*-Xylylenes.—Several groups independently and virtually simultaneously realized that intramolecular *o*-xylylene cycloadditions could provide a convenient approach to the aromatic steroid skeleton. Kametani and co-workers applied this scheme to the synthesis of D-homo-estrone.[23] The synthesis started with the 5-step conversion (31% overall yield) of 3-methoxybenzaldehyde into 1-cyano-3-methoxybenzocyclobutene followed by further transformation (5 steps, 29% overall yield) into the benzocyclobutenylethyl iodide (54). Alkylation of the enolate of cyclohexanone (55) with (54) (t-butoxide, t-butyl alcohol) from the less hindered side proceeded stereospecifically (at the cyclohexanone ring) in low (16%) yield to give, after basic hydrolysis of the n-butylthiomethylene group (44%), the benzocyclobutene (56) as a mixture of diastereomers. An attempt to synthesize the cyclopentanone analogue of (56) failed. Thermolysis of the diasteromeric benzocyclobutenes (56) proceeded smoothly to afford racemic *O*-methyl-D-homo-estrone (57a) (overall 0.67%, 12 steps). The reaction is remarkably stereospecific choosing one out of four possible (two *exo*, two *endo*) transition states to give the thermodynamically preferred *trans–anti–trans* steroidal framework.

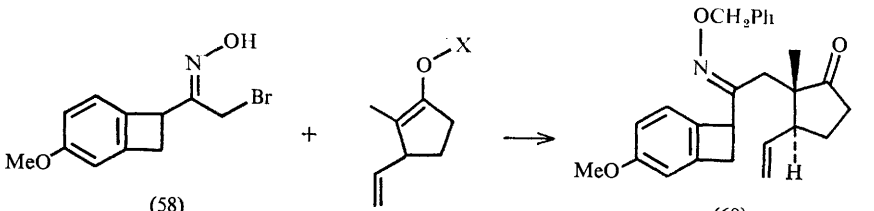
[23] T. Kametani, H. Nemoto, H. Ishikawa, K. Shirogama, H. Matsumoto, and K. Fukumoto, *J. Amer. Chem. Soc.*, 1977, **99**, 3461.



(54) (55) (56)

(57a), X = α−H, Y = H_2, n = 2
(57b), X = β−H, Y = N−OCH_2Ph, n = 1
(57c), X = β−H, Y = O
(57d), X = α−OH, Y = H_2, n = 1

In a second application of this scheme, Oppolzer improved the coupling of the benzocyclobutene unit with the dienophile-carrying future D-ring part of the steroid by employing a reactive alkylating agent.[24] One equivalent of the α-bromo-oxime (58) (available in 10 steps, 32% from *m*-hydroxybenzaldehyde) was added slowly to two equivalents of the enolate (59b) (generated from silyl enol ether (59a) with methyl-lithium) to give a 77% yield [based on oxime (58)] of the desired benzocyclobutene which was benzylated in 70% yield to provide benzocyclobutene (60). When heated, (60) furnished cycloadduct (57b) (50%) with the 'unnatural' *cis–anti–trans* stereochemistry, a result of exclusive *endo*-cycloaddition. Hydrogenolysis, followed by acid treatment resulted in the 11-oxo-steroid (57c). The overall yield of the sequence is 2.3% (15 steps).



(58)

(59a), X = $SiEt_3$
(59b), X = Li

(60)

[24] W. Oppolzer, M. Petrzilka, and K. Bättig, *Helv. Chim. Acta.*, 1977, **60**, 2965.

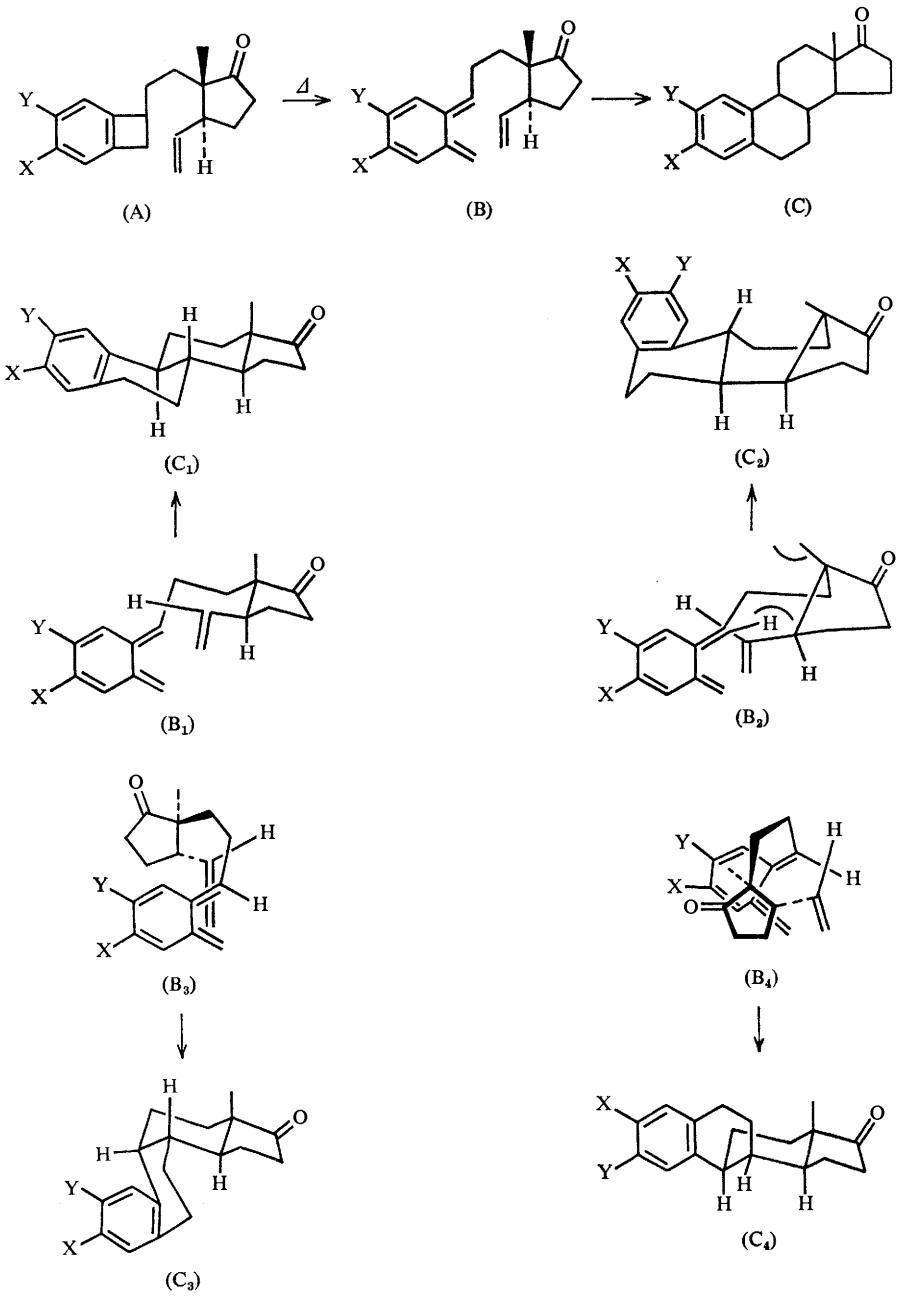
What is the origin of the astonishing stereoselectivity in the above reactions? Scheme 1 delineates the reaction paths available to a benzocyclobutene (A) *en route* to steroid (C) after conrotatory (sterically dictated) outward opening furnishes *o*-xylylene (B). It should be noted that this ring-opening leads to the same diene regardless of the stereochemistry at C-1 of the benzocyclobutene. Intermediate (B) has a choice of two *exo*-($B_{1,2}$) and two *endo* transition states ($B_{3,4}$) potentially yielding four isomeric steroids (C_{1-4}). If one examines molecular models depicting the first two alternatives, one concludes that (B_1) (addition of the vinyl group from the β-face) should be preferred over (B_2) (addition of the vinyl group from the α-face). The reason for this preference may be found in steric considerations. *exo*-Addition as in (B_1) proceeds *via* a chair-like transition state to lead to the natural *trans–anti–trans* arrangement of isomer (C_1) [as found in the (56)→(57a) interconversion], whereas *exo* transition state (B_2) adopts a boat-like conformation *en route* to the unnatural *trans–syn–trans* isomer (C_2) containing a fused boat in a carbocyclic framework. Transition state (B_2) suffers from the typical steric interferences found in the boat conformation of cyclohexanes, *i.e.*, a methyl *o*-xylylene–proton bowsprit–flagpole-type interaction and eclipsing of the hydrogens on the bridging methylene groups (C-11 and C-12; steroid numbering).

Inspection of molecular models representing the two *endo*-transition states ($B_{3,4}$) allows one to recognize a clear preference for (B_3) with a pseudochair framework and absence of serious steric interactions leading to *cis–anti–trans*-isomer (C_3). The alternative *endo*-addition (B_4), a boat-like transition state, is considerably less favoured because of a serious methyl group–*o*-xylylene ring steric interaction. As a result of this analysis one would predict that steroids (C_1) and (C_3) should be the predominant products arising from intramolecular *o*-xylylene cycloadditions, a prediction that is gratifyingly verified by the above experiments [*cf.* formation of (57a) and (57c)].

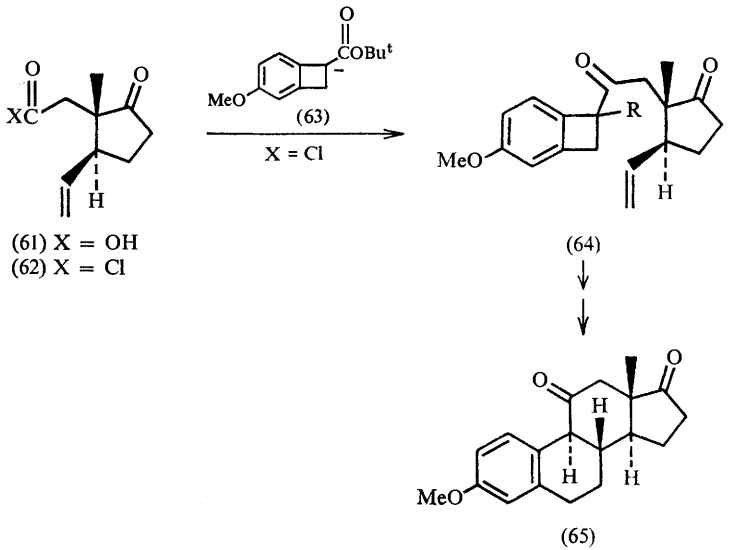
The factors that control preferential formation of *exo*-derived products in one case, and *endo*-products in the other are more difficult to understand and seemingly rather subtle. For example, a minor variation of the synthetic scheme *en route* to (57c) allows the synthesis of (optically pure) material in the desired *trans–anti–trans* configuration.[25] Here acid (61) (prepared in two steps from 2-methylcyclopentenone) is first resolved [(+)-ephedrine], then converted into the acid chloride (62) [$(COCl)_2$] and subsequently coupled with anion (63) to give (64). After removal of the ester group (R = CO_2Bu^t; a. CF_3CO_2H, b. $HCONMe_2$–pyridine) thermolysis furnishes (65) in addition to a small amount of the *cis–anti–trans*-epimer (10:1 ratio). Evidently the two transition states of the type ($B_{1,3}$) are competing in this case, with the former predominating. The overall efficiency of the sequence may be computed starting from *m*-hydroxybenzaldehyde [precursor to (63)] (9.4%, 11 steps), or from 2-methylcyclopentenone (10.5%, 8 steps).

Kametani, using the ready availability of the optically active CD-synthon

[25] W. Oppolzer, K. Bättig, and M. Petrzilka, *Helv. Chim. Acta.*, 1978, **61**, 1945.



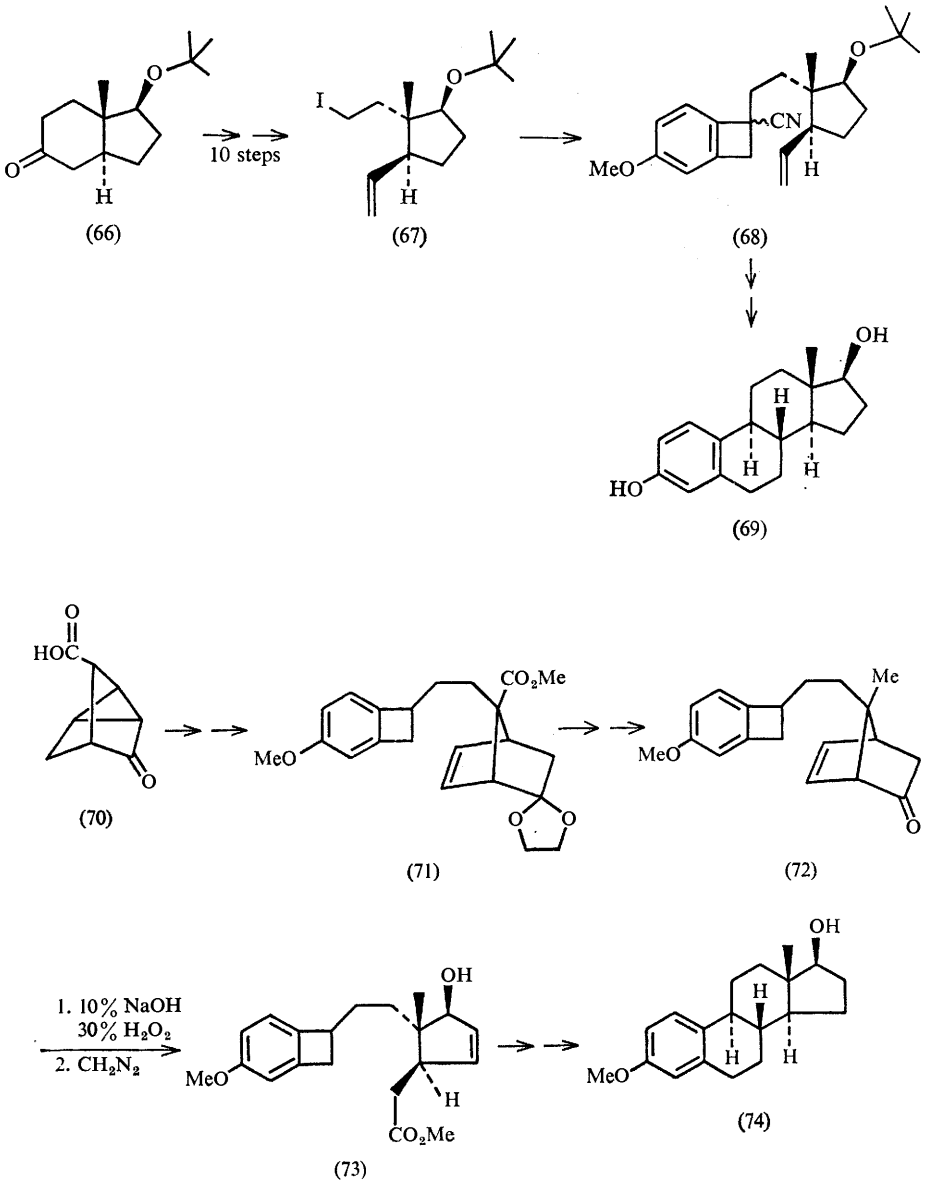
Scheme 1



(66)[26] achieved an overall asymmetric synthesis of estradiol (61) in high optical purity.[27] The key features were the coupling of iodide (67) with 1-cyano-4-methoxybenzocyclobutenyl anion to give (68) which cyclized (*via exo*-analogue B_1) to give the desired BCD-stereochemistry of (+)-estradiol. The sequence required nine steps (6.9%) from *m*-methoxybenzaldehyde, and 15 steps (5.2%) from (66). The latter is made ultimately from 2-methylcyclopentane-1,3-dione in 8 steps (*ca.* 50—60% yield). In yet another modification, racemic 14*α*-hydroxyestrone methyl ether was synthesized *via* an appropriately modified precursor of the type (68).[28]

An unusual synthesis has been developed by Grieco and co-workers[29] in which the CD-portion of estrone is constructed starting from norbornadiene. The acid (70) is elaborated in two steps and resolved, and this building block is connected to the benzocyclobutene part in an alkylation step employing 1-(2-iodoethyl)-4-methoxybenzocyclobutene to give (71). In a series of transformations the bicyclo[2.2.1]-portion is transformed into (72) which is then exposed to alkaline H_2O_2 followed by CH_2N_2 to furnish (73). Subsequently, the double bond is hydrogenated, the acetic ester moiety converted into a vinyl group, and the *o*-xylylene generated thermally to be trapped by the vinylic functionality to give the estratrienol derivative (74). Two more steps furnish optically-active estrone.

[26] R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, C. A. Portland, W. Sciamanna, M. A. Scott, and P. A. Wehrli, *J. Org. Chem.*, 1975, **40**, 675.
[27] T. Kametani, H. Matsumoto, H. Nemoto, and K. Fukumoto, *Tetrahedron Letters*, 1978, 2425.
[28] T. Kametani, H. Nemoto, M. Tsubuki, and M. Nishiuchi, *Tetrahedron Letters.*, 1979, 27.
[29] P. A. Grieco, personal communication; P. A. Grieco, T. Takigawa, and D. R. Moore, *J. Amer. Chem. Soc.*, 1979, **101**, 4380.

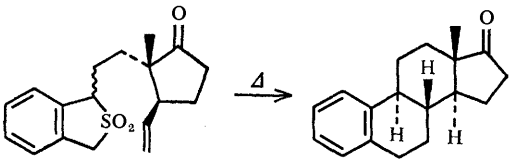


The complete sequence from norbornadiene to estrone takes 20 steps (maximum 4.5%); from *m*-methoxybenzaldehyde, estrone is obtained in 23 steps (*ca.* 2%).

Another variation on the theme[30] uses the diastereomeric *o*-xylylene precursors

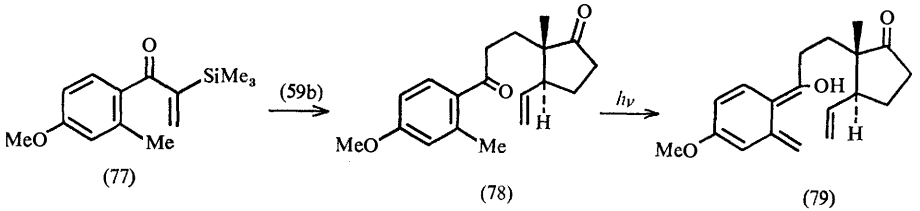
[30] K. C. Nicolaou and W. E. Barnette, submitted for publication.

(75) (which could be separated) to provide racemic estratrienone (76) in 5 steps (49%) from 2-methylcyclopentenone.



(75) (76)

B. A Photochemical Approach.—Expanding on Oppolzer's initial photochemical model studies,[21f] Quinkert completed a photochemical approach to the steroid skeleton using the intramolecular *o*-xylylene cycloaddition scheme.[31] Alkylation of the cyclopentanone enolate (59b) with enone (77) gave, after protodesilyation, the Michael adduct (78) in 43% yield. Photoenolization afforded, stereospecifically, the 9α-hydroxyestrone (57d) *via* intramolecular *exo*-cycloaddition of *o*-xylylene (79) in low (30%) yield. Catalytic hydrogenation furnished racemic *O*-methylestrone. From the preliminary results in the literature[31] no overall yield can be computed but they are moderate, at best.

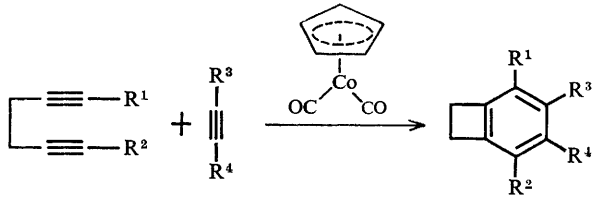


(77) (78) (79)

C. Cobalt-mediated Co-oligomerizations of Hexa-1,5-diynes.—The most serious drawback of the synthetic approaches mentioned so far lies in the relative difficulty of synthesizing appropriately substituted benzocyclobutenes (or other precursors) amenable to further cyclization. Frequently, multistep syntheses are employed, resulting in low overall yields. A potential solution to this problem is provided by the discovery that hexa-1,5-diynes (as well as other αω-diynes) may be co-cyclized with substituted acetylenes in the presence of a cobalt(I) catalyst (η^5-cyclopentadienyldicarbonylcobalt) to furnish substituted benzocyclobutenes (Scheme 2). Yields are best when sterically hindered monoalkynes such as bis(trimethylsilyl)acetylene (BTMSA) are employed in large excess.

In this manner 4,5-bis(trimethylsilyl)benzocyclobutene may be obtained in 68% yield from commercially available starting materials.[32]

[31] G. Quinkert, *Chimia* (*Switz.*), 1977, **31**, 225.
[32] K. P. C. Vollhardt, *Accounts Chem. Res.*, 1977, **10**, 1; R. L. Hillard and K. P. C. Vollhardt, *J. Amer. Chem. Soc.*, 1977, **99**, 4058.



Scheme 2

Based on the work of several investigators, the trimerization of alkynes to benzenes catalysed by low-valent transition metals proceeds through the intermediacy of discrete transition-metal complexes.[33] Cobalt(I) species, as in cpCo $(CO)_2$, seem to react *via* the intermediate formation of dialkyne complexes, followed by oxidative coupling of the two alkyne units to a metallocycle capable of reacting with another molecule of alkyne to result eventually in the final benzenic product.[32,34] A plausible mechanism for the cobalt-catalysed cocyclization of hexa-1,5-diyne with BTMSA is indicated in Scheme 3. The rate-determining step in the catalytic cycle appears to be initial dissociation of carbon monoxide from the starting catalyst (as indicated by the inhibition observed in the presence of added carbon monoxide). Sequential displacement of the two CO ligands with BTMSA and one end of the diyne, respectively, produces intermediate (A). Oxidative coupling proceeds selectively to metallocycle (B), presumably for steric reasons (carbon–carbon bond formation to a proton bearing *sp*-carbon is easier than to an alkylated centre) and electronic reasons [the uncomplexed end of the diyne might be involved in the transition state leading to (B)]. The latter then undergoes ring-expansion to (C). Reductive elimination of the cobalt-containing unit furnishes the final product.

The synthetic utility of *o*-bis-silylated arenes is demonstrated in Scheme 4. Quantitative selective and stepwise introduction of electrophiles occurs under mild conditions,[32] allowing access to a wide variety of substituted derivatives. Employment of a substituted hexa-1,5-diyne (80) incorporating a potential dienophile proceeds *via* (sometimes isolable) benzocyclobutene (81) to the tricyclic systems (83) (minor), and (82) (major) where X,Y, and Z may be CH_2, O, NOR, in good yield.[35] For example (80) (X = Y = Z = CH_2) furnishes (82) in 80% yield, contaminated with *ca.* 4% of *cis*-isomer (83).

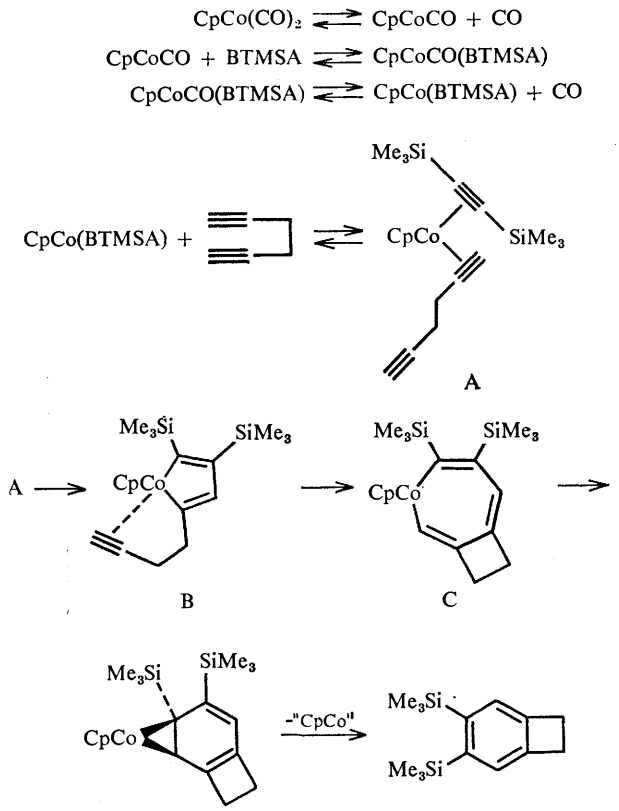
Since (82) constitutes what one might envisage to be the ABC-ring portion of the steroid nucleus, the synthetic Scheme 5 was designated[36] to provide access to this class of compound *via* the above methodology. A convergent approach

[33] J. P. Collman, J. W. Kang, W. F. Little, and M. F. Sullivan, *Inorg. Chem.*, 1968, **7**, 1298; J. P. Collman, *Accounts Chem. Res.*, 1968, **1**, 136; P. M. Maitlis, *ibid.*, 1976, **9**, 93; G. M. Whitesides and W. J. Ehmann, *J. Amer. Chem. Soc.*, 1969, **94**, 3800.

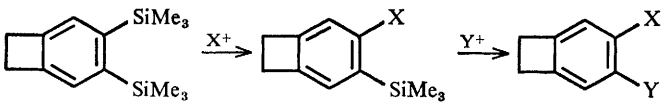
[34] D. R. McAlister, J. E. Bercaw, and R. G. Bergman, *J. Amer. Chem. Soc.*, 1977, **99**, 1666; H. Yamazaki and Y. Wakatsuki, *J. Organometallic Chem.*, 1977, **139**, 157; L. P. McDonnell Bushnell, E. R. Evitt, and R. G. Bergman, *ibid.*, 1978, **157**, 445.

[35] R. L. Funk and K. P. C. Vollhardt, *J. Amer. Chem. Soc.*, 1976, **98**, 6755.

[36] R. L. Funk and K. P. C. Vollhardt, *J. Amer. Chem. Soc.*, 1977, **99**, 5483.

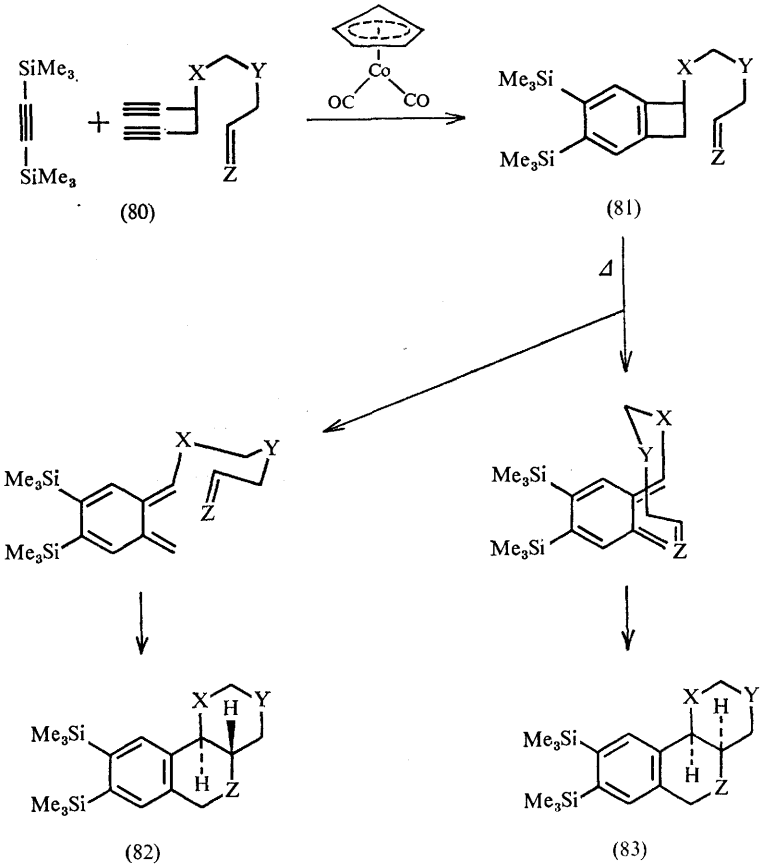


Scheme 3



Scheme 4

leads to the crucial precursor (84) (mixture of diastereoisomers). This material, when cyclized in the presence of BTMSA (solvent) and cobalt catalyst (5 mol%), yields in a chemo-, regio-, and stereo-specific process the steroid (85) in 71% yield. This constitutes the first successful completion of a D → ABCD route to the steroid nucleus and the first in which *three* rings are constructed simultaneously. The bis-silylated estratrienone (85) may be selectively monodesilylated at the 2-position (CF_3CO_2H–CCl_4, −30 °C) and the remaining phenyl–silicon bond



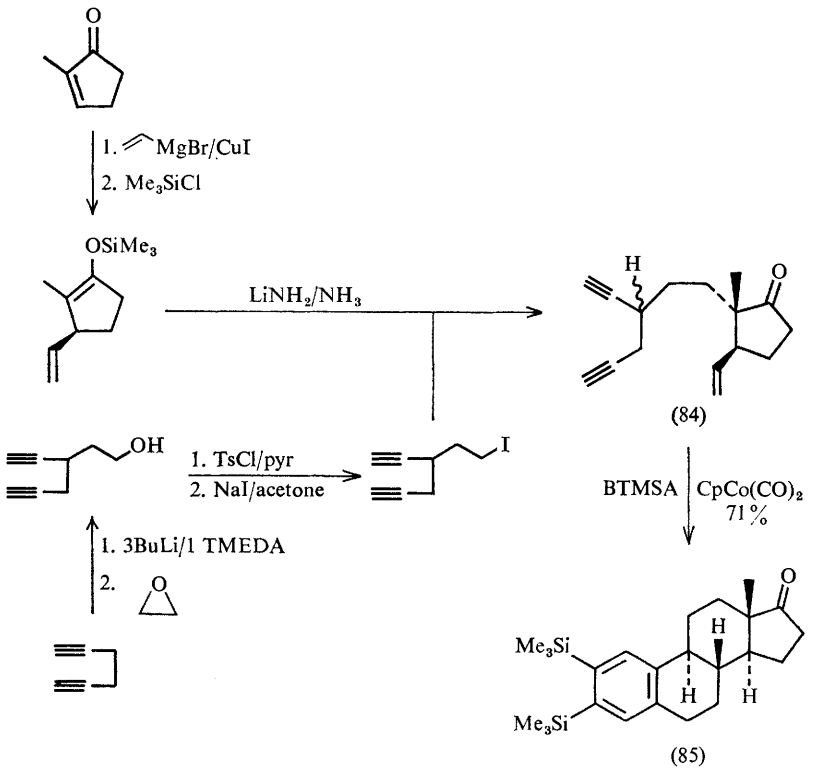
cleaved oxidatively (lead tetrakistrifluoroacetate) to yield (±)-estrone.[37] Total efficiency: five steps from 2-methylcyclopentenone (24%), and seven steps from acyclic hexa-1,5-diyne (17%). Optimization of the preparation of (84), which suffers from a relatively poor last step (*ca.* 40%), could improve overall yields significantly.

A more direct route to estrone involves co-cyclization of (84) with 2-methoxy-1-trimethylsilylacetylene. Protodesilylation of the steroid products furnishes (±)-estrone methyl ether, albeit in low yield (*ca.* 20%) because of side reactions of the catalyst with the monoacetylene, and poor regioselectivity in the cobalt-catalysed step.

5 Conclusion

It is clear that synthetic approaches to natural products and/or medicinally

[37] R. L. Funk and K. P. C. Vollhardt, *J. Amer. Chem. Soc.*, 1979, **101**, 215.



Scheme 5

active compounds utilizing intramolecular cycloadditions of suitable dienophiles to intermediately generated *o*-xylylenes provide the desired polycyclic framework with remarkable stereoselectivity and good yields in the crucial steps. Improvements of the methodology will come from the development of modified, simplified, and shortened routes to starting materials in optically pure form. Overcoming these obstacles should make this synthetic route industrially competitive with currently employed partially synthetic processes relying on natural product sources.

Part of the reported work was carried out by one of the authors (R.L.F.) as part of a doctoral thesis. R. L. F. was a Regents' Intern Fellow (1975—1978), K. P. C. V. is a Fellow of the Alfred P. Sloan Foundation (1976—1980) and a Camille and Henry Dreyfus Teacher Scholar (1978—1983). R. L. F. is now Assistant Professor of Chemistry at the University of Nebraska. Financial support from NIH and NSF is gratefully acknowledged. We thank Professors P. A. Grieco and K. C. Nicolaou for making research results available to the authors prior to publication.