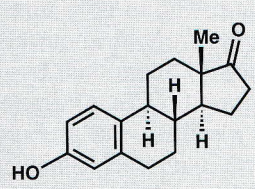


1: estrone

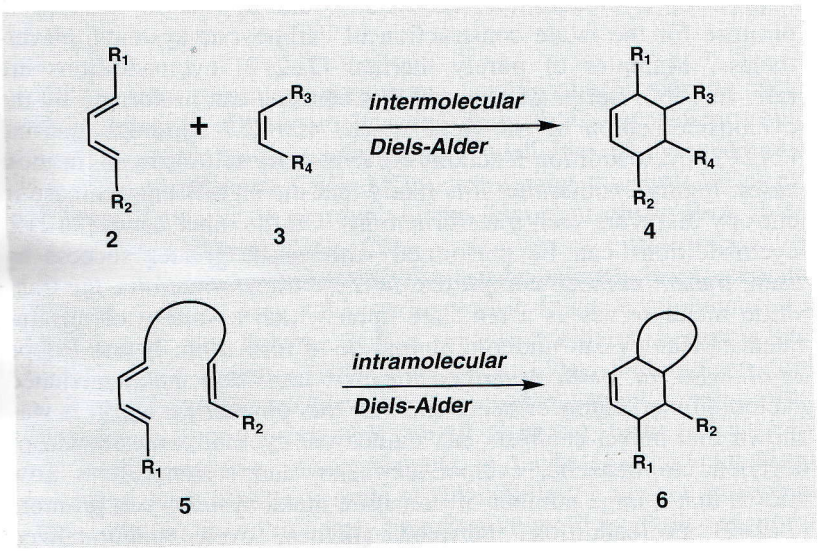
10

K. P. C. Vollhardt (1977)

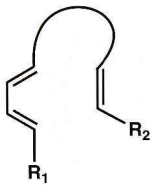
Estrone

10.1 Introduction

Reaction processes that can bring about significant increases in molecular complexity from simple building blocks occupy a special place in organic chemistry. In this regard, the venerable Diels–Alder reaction is noteworthy because it accomplishes the union of a 4π electron system with a 2π electron system, creating two new carbon–carbon bonds, a six-membered ring, and up to four contiguous stereocenters in one efficient step (see **2**+**3**→**4**, Scheme 1). The



Scheme 1. Inter- and intramolecular Diels–Alder reactions.



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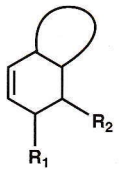

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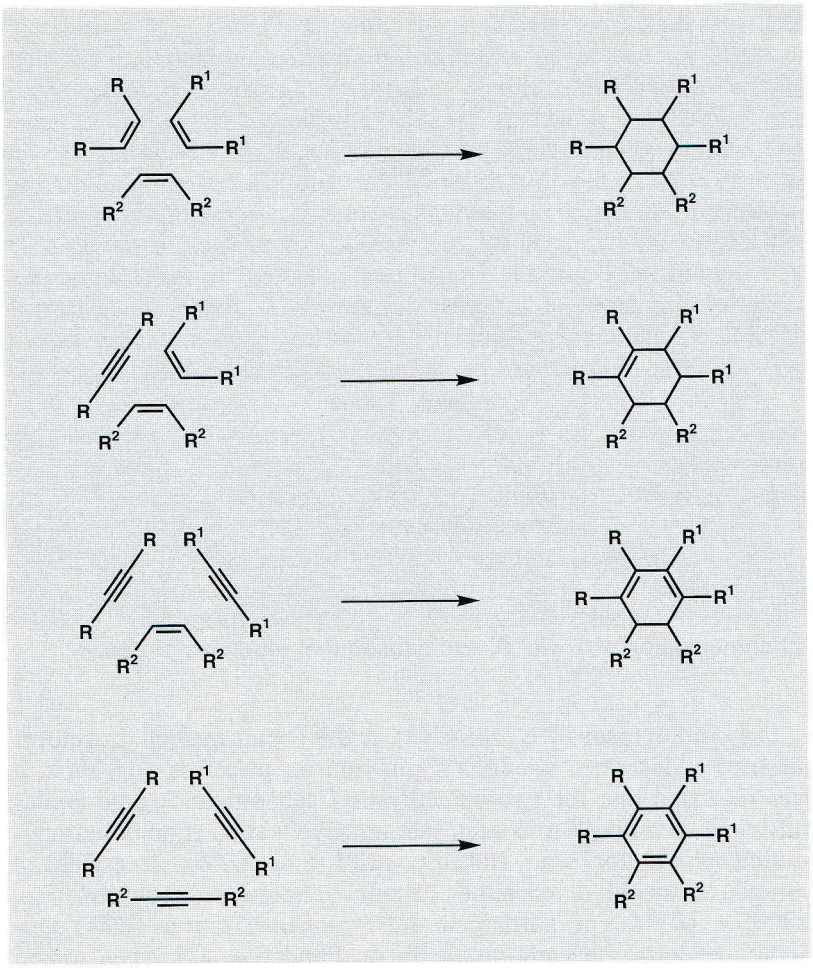
impressive scope and utility of this intermolecular [4+2] cycloaddition process for the construction of stereochemically complex six-membered rings is well recognized.[1] It is interesting to note that an even more substantial structural change can be brought about simply by connecting the two unsaturated reaction partners (see **5**, Scheme 1). In **5**, the diene (4π e) and dienophilic (2π e) components are part of the same molecule. In such a setting, the probability that the two unsaturated moieties will react with each other can be enhanced, and the structural change that attends the intramolecular [4+2] cycloaddition event is impressive.[2] In a single operation, a rather complex bicyclic framework can be fashioned from a comparatively simple polyunsaturated acyclic molecule. The Diels–Alder cycloaddition is indeed a most productive process because it involves a simple summation of the reaction partners; all of the atoms that constitute the diene and dienophilic components are expressed in the [4+2] cycloadduct, none are wasted.[3]

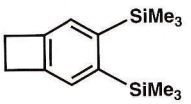
The Diels–Alder reaction accomplishes the formation of two carbon–carbon σ bonds at the expense of two carbon–carbon π bonds, and is among the most atom-economical[3] and reliable carbon–carbon bond forming methods known in organic chemistry. Nonetheless, a potentially more powerful bond-forming strategy would be based on the [2+2+2] cycloaddition of three unsaturated entities (see Scheme 2).[4] In these striking cyclotrimerizations, three new carbon–carbon bonds and a new carbocyclic ring with varying degrees of unsaturation would be produced in a single step. The efficiency of these general transformations is obvious. For example, the cyclotrimerization of three simple achiral alkenes could, in principle, furnish a saturated six-membered ring with six contiguous stereocenters! As in the case of the Diels–Alder reaction, these [2+2+2] cycloadditions would furnish products that are simply the sum of the starting materials.[3]

[2+2+2] Cycloaddition reactions would appear to hold great promise for the facile construction of carbocyclic systems. Nevertheless, examples of purely thermal [2+2+2] cycloadditions are rare. In 1866, Berthelot reported that benzene can be formed by the cyclotrimerization of acetylene at *ca.* 400 °C.[5] Although thermal [2+2+2] cycloaddition reactions are symmetry-allowed and, in most cases, highly exothermic, it is likely that the significant decrease in entropy disfavors such transformations. On the other hand, [2+2+2] cycloadditions can be performed with much greater success by using transition metal complexes. In these transformations, the transition metal serves as a template upon which a variety of unsaturated molecules can undergo mutual bond formation. It was Reppe *et al.* who, in 1948, described the first transition metal mediated cyclooligomerization of acetylene.[6] In this pioneering work, it was shown that nickel catalysts can induce the cyclooligomerization of acetylene to benzene, cyclooctatetraene, and styrene. It is now known that a large number of transition metal systems can promote [2+2+2] cycloadditions between alkynes, even functionalized alkynes, to give a variety of benzene derivatives.[4b,7]



Scheme 2. Prototypical [2+2+2] cycloadditions.

Of the transition metal complexes capable of effecting the cyclotrimerization of alkynes to benzene derivatives, low-valent cobalt complexes such as the commercially available (η^5-cyclopentadienyl)cobalt dicarbonyl, $CpCo(CO)_2$, are among the most efficient.[8] In 1975, Vollhardt *et al.* reported the important observation that a catalytic amount of $CpCo(CO)_2$ can effect a cyclotrimerization reaction between 1,5-hexadiyne (**7**) and bis(trimethylsilyl)acetylene (BTMSA) (**8**) to give 4,5-bis(trimethylsilyl)benzocyclobutene **9** in >60 % yield (see Scheme 3).[9] In organic synthesis, benzocyclobutenes are very attractive substances because they undergo reversible opening of the four-membered ring on heating to give *ortho*-quinodimethanes (*ortho*-xylylenes) (see **10**, Scheme 3); the latter species are highly reactive and participate in facile [4+2] cycloaddition reactions with a wide variety of dienophiles.[10] In fact, compound **11** can be produced in nearly quantitative yield from the reaction of **9** with maleic anhydride at 200 °C.



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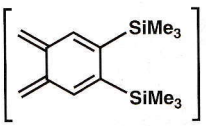

***o*-quinodimethane**

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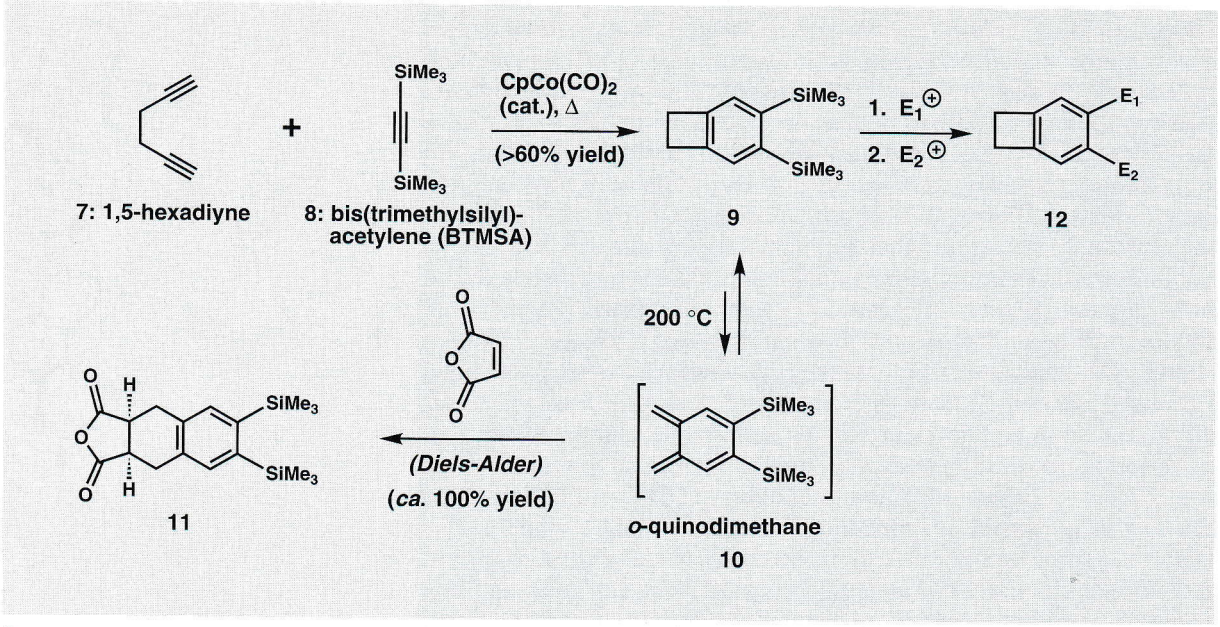
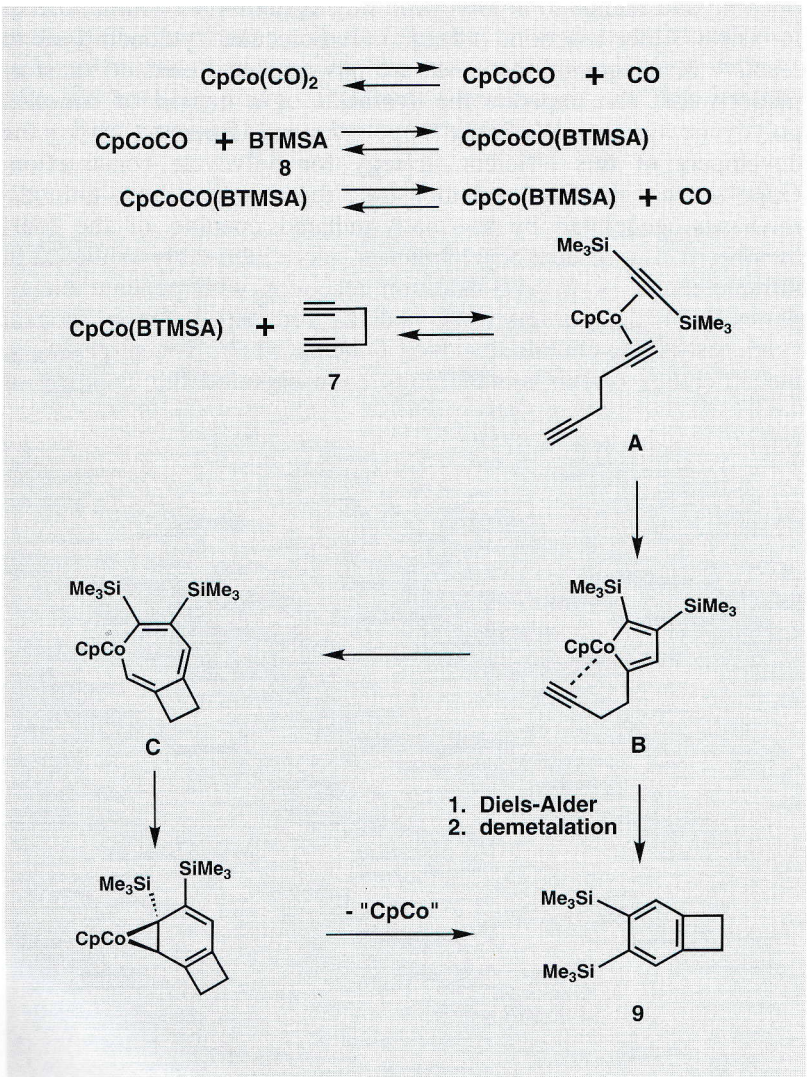


Scheme 3. $CpCo(CO)_2$-catalyzed cyclotrimerization of **7** with **8**, and subsequent reactions of benzocyclobutene **9**.

The employment of BTMSA (**8**) in the cobalt-mediated cyclotrimerization described above is significant for three reasons. First, it was reasoned that the two trimethylsilyl substituents would confer sufficient steric bulk to **8** such that autocyclization (homooligomerization) would not occur. But in contrast to di-*tert*-butylacetylene, a compound too hindered either to autocyclize or to cyclotrimerize, BTMSA (**8**) might participate in cyclotrimerizations with α,ω-diynes because the carbon(sp)–silicon bond (*ca.* 1.9 Å) is longer than the carbon(sp)–carbon(sp^3) bond (1.46 Å). As shown in Scheme 3, BTMSA (**8**) indeed undergoes cyclotrimerization with an α,ω-diyne in the presence of a catalytic amount of $CpCo(CO)_2$. At least on the time scale of the cyclization experiment, BTMSA (**8**) does not react with itself. Second, because compound **8** is symmetrical, regiochemical problems would not arise in cyclotrimerizations with unsymmetrical α,ω-diynes. And third, the silylbenzene products that emerge from cyclotrimerizations of silylated alkynes are amenable to a variety of electrophilic aromatic substitution reactions.[11] For example, the two trimethylsilyl groups in benzocyclobutene **9** can be replaced by electrophiles, selectively and stepwise (see **9**→**12**, Scheme 3).[9] Interestingly, the rate associated with the replacement of the first trimethylsilyl group is *ca.* 40 times greater than that for the second. Differentially substituted benzene derivatives are thus readily available.

With respect to reaction mechanism, it is likely that $CpCo(CO)_2$-mediated alkyne cyclotrimerizations proceed through discrete organometallic intermediates and are therefore not concerted.[12] A plausible mechanistic pathway for the $CpCo(CO)_2$-catalyzed cyclotri-

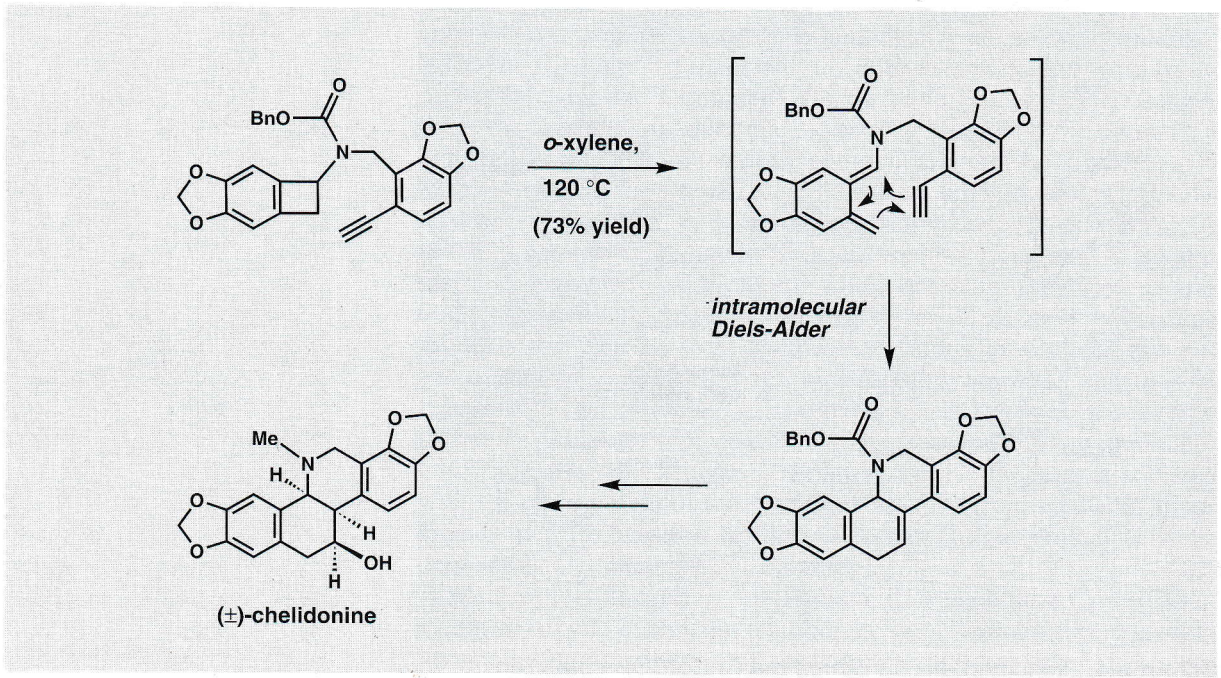
merization of BTMSA (**8**) with 1,5-hexadiyne (**7**) is presented in Scheme 4. After rate-determining dissociation of one molecule of carbon monoxide from $CpCo(CO)_2$, the resulting coordinatively unsaturated cobalt complex [CpCoCO] associates with an alkyne, probably BTMSA (**8**); it is likely that BTMSA functions as the first new ligand because BTMSA is used as the solvent in most of these reactions. At this point, the coordination site created upon dissociation of the remaining CO ligand can be occupied by one of the alkyne moieties of 1,5-hexadiyne to give the bisalkyne complex A. It is currently believed that the formation of complex A is followed by an oxidative coupling to give metallacyclopentadiene B. The conversion of A to B is described as an oxidation because the for-



Scheme 4. Presumed mechanism of the $CpCo(CO)_2$-catalyzed cocyclization of **7** with **8**.

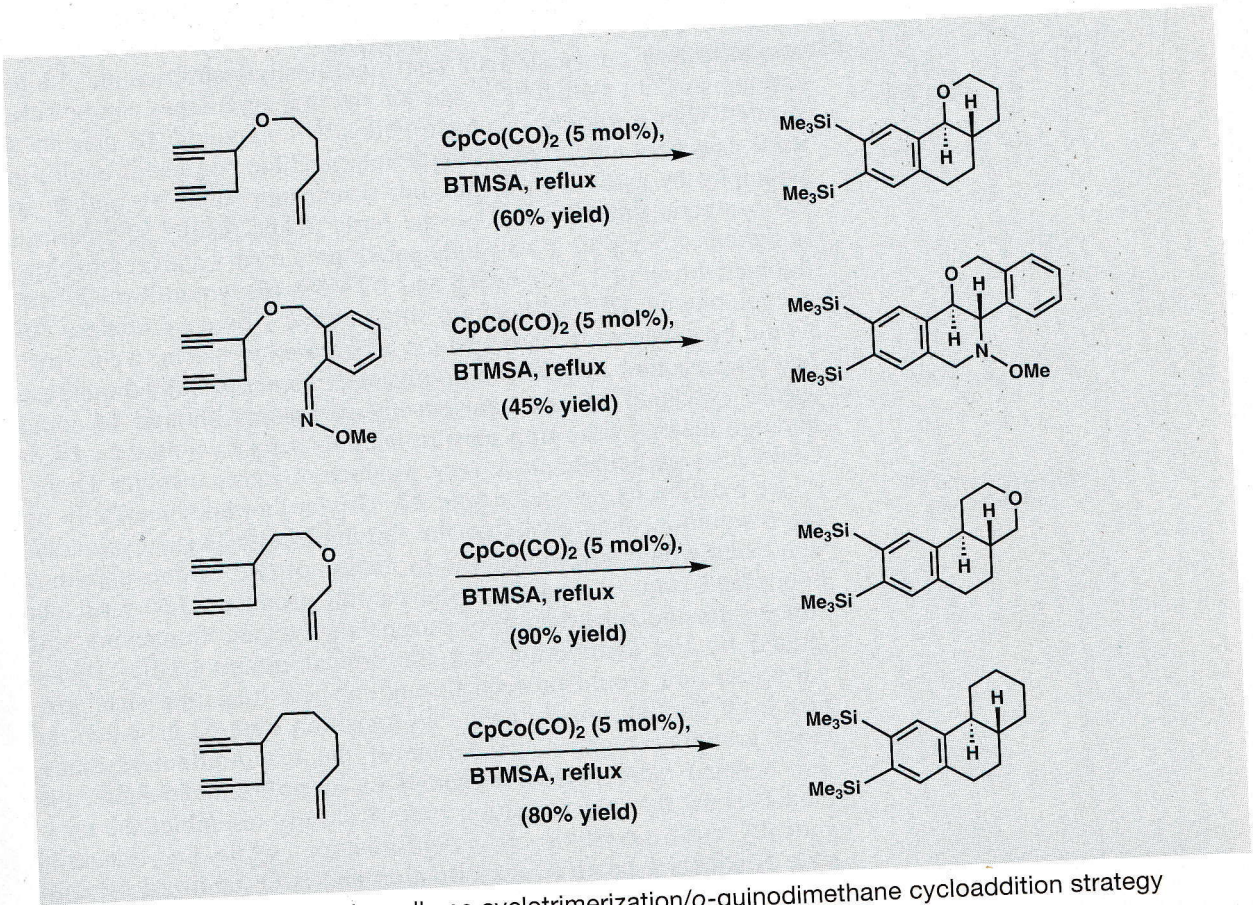
mal oxidation state of cobalt in B is two units higher than it is in A. Insertion of the remaining alkyne into the vinyl–cobalt bond would then give the metallacycloheptatriene C, after which ring contraction (reductive elimination) and extrusion of CpCo would furnish the final product. Alternatively, complex B could undergo conversion to the benzocyclobutene product through an intramolecular Diels–Alder reaction, followed by demetalation.

With a new method for the construction of benzocyclobutenes in hand, it was of interest to determine if a 1,5-hexadiyne substituted with a potential dienophile would take part in cobalt(I)-induced cyclotrimerization reactions. If so, then the initially formed benzocyclobutene product could, in principle, be converted *in situ* to a highly reactive *ortho*-quinodimethane through conrotatory ring opening and thence to a polycyclic ring system via an intramolecular Diels–Alder reaction. Indeed, intramolecular cycloadditions to reactive *ortho*-quinodimethanes are powerful and elegant transformations that can expedite the synthesis of a myriad of complex polycyclic systems. Wolfgang Oppolzer stands foremost among the developers of this efficient strategy for polycycle construction. Oppolzer was the first to demonstrate that reactive *ortho*-quinodimethanes, generated by thermally-induced opening of the four-membered ring of benzocyclobutenes, serve admirably as dienes in intramolecular [4+2] cycloaddition reactions with pendant dienophiles.[13] This important work laid the foundation for an elegant synthesis of (±)-chelidonine (see Scheme 5).[13c] Not surprisingly, the efficiency of this methodology soon captured the attention of



Scheme 5. Oppolzer's synthesis of (±)-chelidonine.

numerous groups; impressive achievements in the arena of natural products total synthesis soon followed, and these successes have been documented in several excellent reviews.[10] But in spite of these achievements, the paucity of simple and effective methods for the synthesis of functionalized benzocyclobutenes has diminished the scope of this otherwise very attractive strategy for polycycle construction. The efficient cobalt-mediated alkyne cyclotrimerization methodology developed by Vollhardt *et al.* and the results summarized in Scheme 6 are thus particularly noteworthy. To bring about these productive transformations, a readily accessible 1,5-hexadiyne is simply added slowly to a refluxing solution of $CpCo(CO)_2$ (5 mol %) in neat BTMSA.[14] The resulting benzocyclobutene cyclotrimerization products are then converted *in situ* to the indicated polycyclic compounds via the intermediacy of *ortho*-quinodimethanes. These elegant tandem transformations[15] accomplish the formation of five new carbon–carbon or carbon–nitrogen bonds and two contiguous stereocenters, and require only a catalytic amount of the cobalt(I) catalyst.

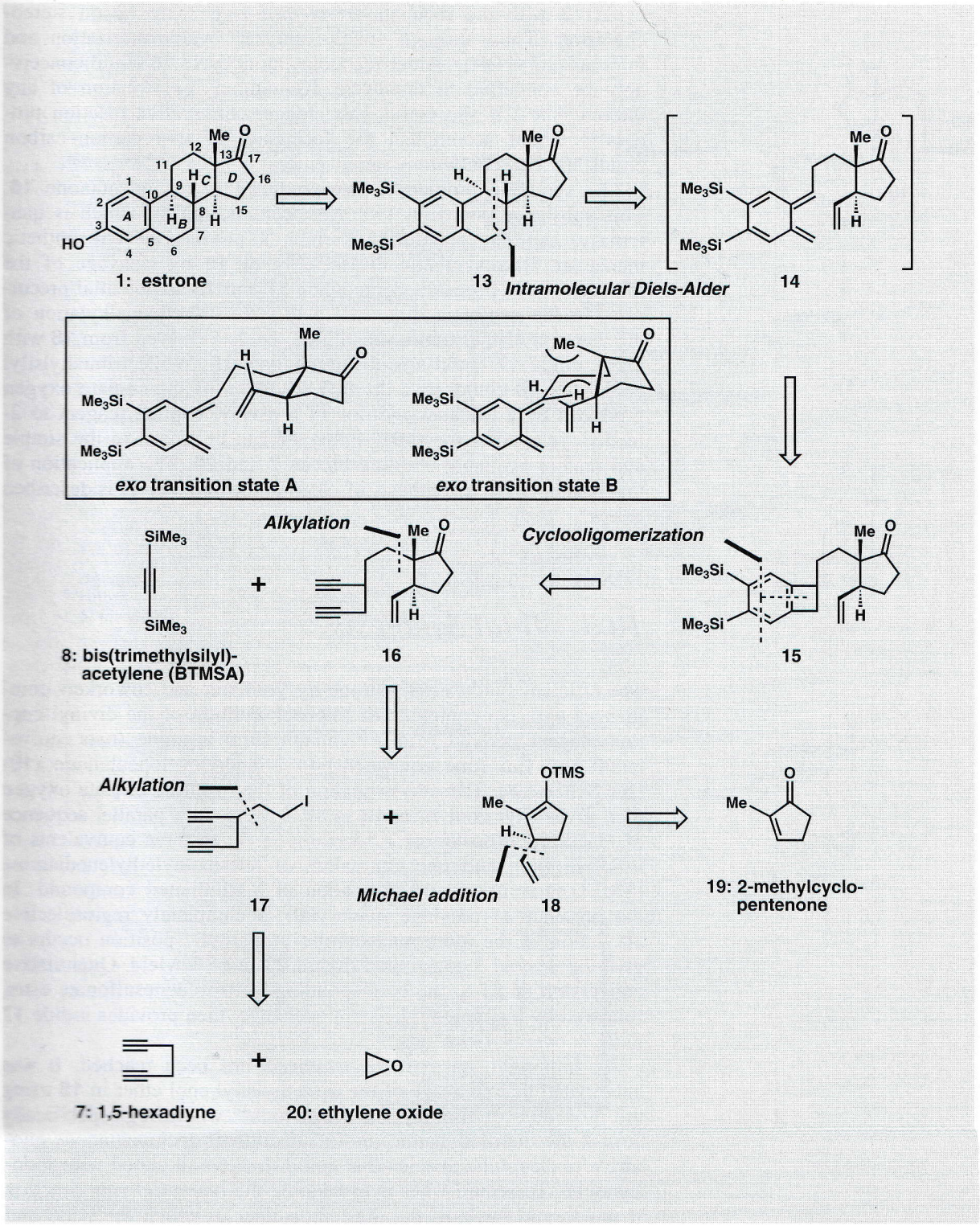


Scheme 6. Vollhardt's tandem alkyne cyclotrimerization/*o*-quinodimethane cycloaddition strategy for polycycle synthesis.

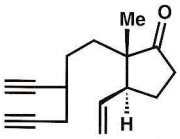
The homology of the tricyclic products in Scheme 6 to the ABC-ring portion of the steroid nucleus is obvious. In fact, the facility with which these tricyclic materials can be constructed from simple building blocks provided the impetus for the development of an exceedingly efficient synthesis of the female sex hormone, estrone (**1**). This important biomolecule has stimulated the development of numerous synthetic strategies and these have been amply reviewed.[16] The remainder of this chapter is devoted to the brilliant synthesis of racemic estrone by K. P. C. Vollhardt *et al.*[12,17]

10.2 Retrosynthetic Analysis and Strategy

The tetracyclic steroidal framework of the estrone molecule comprises four contiguous stereocenters and is distinguished by *trans–anti–trans* ring fusion stereochemistry. Compound **13** could serve as a retrosynthetic precursor for the natural product provided, of course, that the former compound can be manipulated in a regioselective manner (Scheme 7). Although direct precedent for the regioselective conversion of bis(trimethylsilyl)estratrienone **13** to estrone was not available, it was known that arylsilanes can be substituted with a variety of electrophiles.[11] Compound **13** presented itself as a very attractive synthetic intermediate because it could, in principle, be assembled in one pot from compounds **16** and **8**. In the synthetic direction and on the basis of the results summarized in Schemes 3 and 6, it was anticipated that cobalt-catalyzed cyclooligomerization of 1,5-diyne **16** and BTMSA (**8**) would furnish benzocyclobutene **15**. On heating, the strained benzocyclobutene **15** would be expected to participate in a conrotatory electrocyclic ring-opening reaction to give the highly reactive *ortho*-quinodimethane (*ortho*-xylylene) **14** as a transient intermediate. Although **14** could undergo electrocyclic ring closure back to benzocyclobutene **15**, it could also participate in a very productive intramolecular Diels–Alder reaction to give tetracycle **13**. Driven thermodynamically by the restoration of aromaticity, the intramolecular [4+2] cycloaddition event would accomplish the formation of two carbon–carbon σ bonds and rings B and C of the natural product. This particular strategy for the construction of estrone's polycyclic framework was guided by the assumption that the crucial intramolecular Diels–Alder reaction would proceed through an *exo* transition state geometry. Of the two possibilities, *exo* transition state A, in which the vinyl grouping engages the β face of the *ortho*-quinodimethane, was deemed more favorable than B on steric grounds; molecular models show that *exo* transition state A closely resembles the energetically more favorable chair conformation, while *exo* transition state B adopts a boatlike conformation and is destabilized by nonbonding interactions. You will note that intramolecular [4+2] cycloaddition through *exo* transition state A would furnish tetra-



Scheme 7. Retrosynthetic analysis of estrone (**1**).



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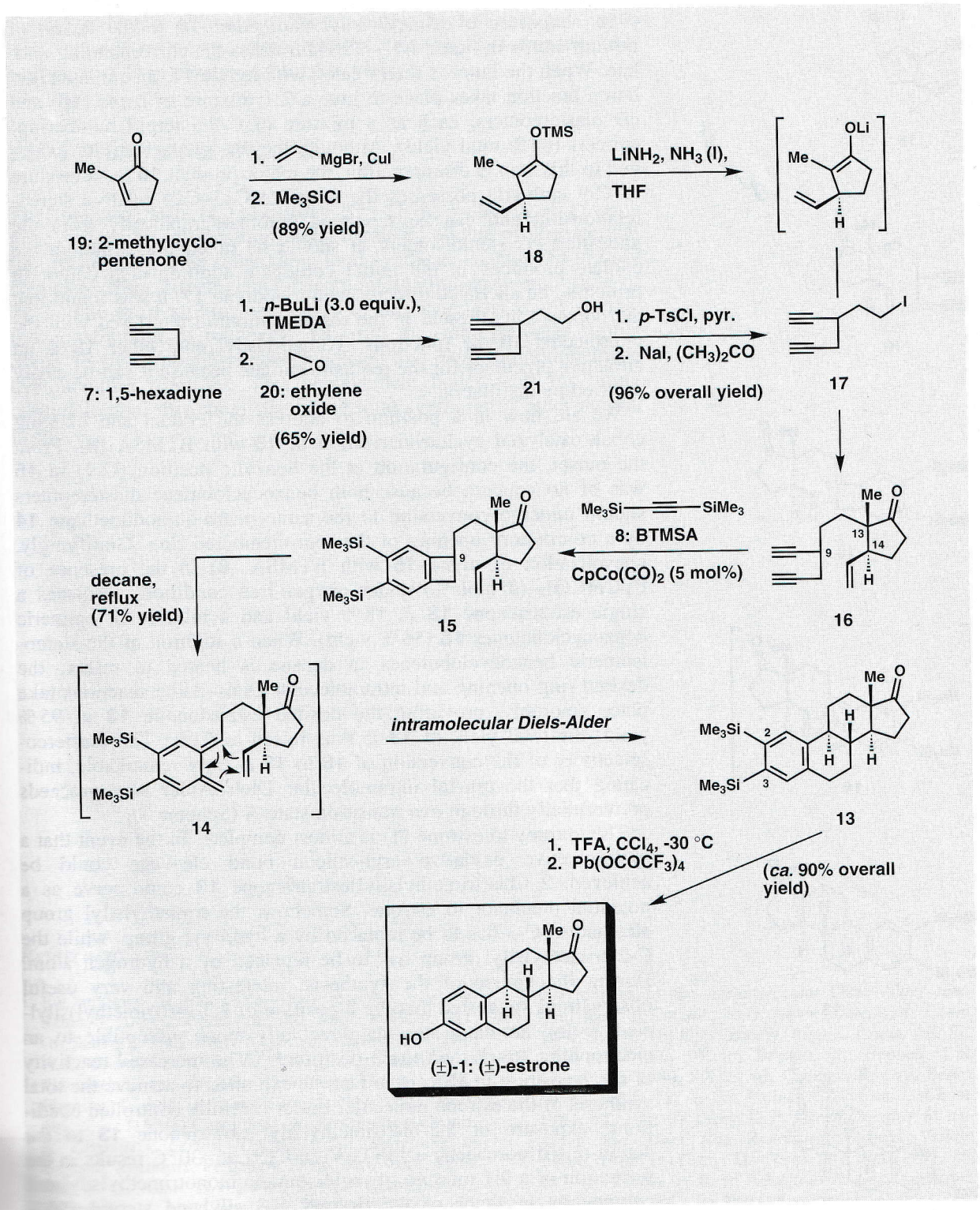
cycle **13** with the requisite *trans–anti–trans* ring fusion stereochemistry. Thus, through cobalt-catalyzed cyclotrimerization and intramolecular Diels–Alder reactions, monocycle **16** could conceivably be converted to tetracycle **13** without the isolation of any intermediates; if successful, this elegant consecutive reaction process[15a] would accomplish the formation of five carbon–carbon bonds and two contiguous stereocenters!

The synthetic problem is now reduced to cyclopentanone **16**. This substance possesses two stereocenters, one of which is quaternary, and its constitution permits a productive retrosynthetic maneuver. Retrosynthetic disassembly of **16** by cleavage of the indicated bond furnishes compounds **17** and **18** as potential precursors. In the synthetic direction, a diastereoselective alkylation of the thermodynamic (more substituted) enolate derived from **18** with alkyl iodide **17** could afford intermediate **16**. While trimethylsilyl enol ether **18** could arise through silylation of the enolate oxygen produced by a Michael addition of a divinyl cuprate reagent to 2-methylcyclopentenone (**19**), iodide **17** can be traced to the simple and readily available building blocks **7** and **20**. The application of this basic plan to a synthesis of racemic estrone [(±)-**1**] is described below.

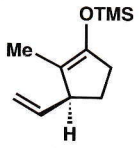
10.3 Total Synthesis

The efficient synthesis of estrone by Vollhardt and coworkers commences with the conjugate or Michael addition of the divinyl cuprate reagent derived from vinylmagnesium bromide (two equivalents) and CuI (one equivalent) to 2-methylcyclopentenone (**19**) (see Scheme 8). Trimethylsilylation of the resulting enolate oxygen then gives silyl enol ether **18** in 89 % yield. In a parallel sequence of reactions, exposure of 1,5-hexadiyne (**7**) to three equivalents of *n*-butyllithium and one equivalent of tetramethylethylenediamine (TMEDA) results in the formation of a trilithiated compound. In the presence of ethylene oxide (**20**), a completely regioselective alkylation of the more nucleophilic propargylic position occurs to give the desired 3-substituted diynol **21** in 65 % yield. Quantitative conversion of **21** to the corresponding *para*-toluenesulfonate ester, followed by a simple Finkelstein exchange, then provides iodide **17** in 96 % overall yield.

An important stage in the synthesis has been reached. It was anticipated that cleavage of the trimethylsilyl enol ether in **18** using the procedure of Binkley and Heathcock[18] would regiospecifically furnish the thermodynamic (more substituted) cyclopentanone enolate, a nucleophilic species that could then be alkylated with iododiyne **17**. To secure what is to become the *trans* CD ring junction of the steroid nucleus, the diastereoisomer in which the vinyl and methyl substituents have a *cis* relationship must be formed. In the



Scheme 8. Synthesis of (±)-estrone [(±)-**1**].



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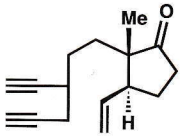

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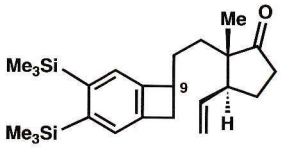

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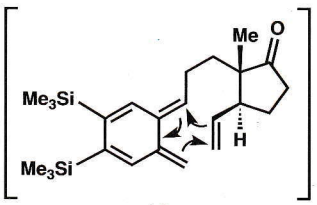

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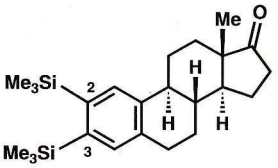

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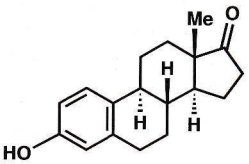

(±)-1: (±)-estrone

event, exposure of trimethylsilyl enol ether **18** to the action of lithium amide in liquid NH_3–THF furnishes the corresponding enolate. When the latter is then treated with iodide **17**, an enolate alkylation reaction takes place to give a 2:1 mixture of *trans* (**16**) and *cis* diastereomers, each as a mixture of C-9 (steroid numbering) epimers (64 % total yield). Although the diastereoselectivity exhibited in this step is disappointing, the major product **16** (as a mixture of C-9 epimers) possesses the requisite C13–C14 relative stereorelationship and can be separated chromatographically from the undesired *cis* stereoisomers. It should be noted that although the enolate produced in the initial conjugate addition step could, in principle, be alkylated directly with iododiyne **17**, it was found that the copper salts present in the reaction mixture interfered with the unprotected alkyne functions. Trimethylsilyl enol ether **18** is an attractive precursor for the requisite enolate because it can be easily purified by distillation.

We are now in a position to address the crucial and exciting cobalt-catalyzed cyclotrimerization of **16** with BTMSA (**8**). From the outset, the configuration at the benzylic position (C-9) in **15** was of no concern because both benzocyclobutene diastereomers should undergo conversion to the same *ortho*-quinodimethane **14** by a conrotatory opening of the four-membered ring. Gratifyingly, cocyclization of diyne **16** with BTMSA (**8**) in the presence of $CpCo(CO)_2$ (5 mol %) under oxygen-free conditions furnishes a single estratrienone **13** in 18 % yield and a mixture of epimeric benzocyclobutenes **15** (56 % yield). When a solution of the stereoisomeric benzocyclobutenes in decane is heated to reflux, the desired ring opening and intramolecular Diels–Alder reactions take place smoothly, providing the desired estratrienone **13** in 95 % yield; the total yield of **13** is thus raised to 71 %. The diastereoselectivity of the conversion of **16** to **13** is truly remarkable, indicating that the crucial intramolecular Diels–Alder step proceeds preferentially through *exo* transition state A (Scheme 7).

The journey to estrone (**1**) is almost complete. In the event that a regioselective oxidative aryl–silicon bond cleavage could be achieved, 2,3-bis(trimethylsilyl)estratrienone **13** could serve as a potential precursor to estrone. Somehow, the trimethylsilyl group attached to C-3 has to be replaced by a hydroxyl group, while the C-2 trimethylsilyl group has to be replaced by a hydrogen atom. During the course of the synthesis, interesting and very useful observations suggested that the 2-position of 2,3-bis(trimethyl)silylated A-ring aromatic steroids is actually more susceptible to an electrophilic attack than the 3-position.[17c] The increased reactivity of the 2-position in **13** can, in fact, be exploited to achieve the total synthesis of the estrone molecule. Under carefully controlled conditions, exposure of 2,3-bis(trimethylsilyl)estratrienone **13** to the action of trifluoroacetic acid (TFA) in CCl_4 at –30 °C results in the formation of a 9:1 mixture of regioisomeric monotrimethylsilylated compounds in favor of the desired C-3 silylated steroid (90 % yield). A regioselective protodesilylation of **13** was thus achieved.

Finally, oxidative cleavage of the remaining aryl–silicon bond with lead tetrakis(trifluoroacetate), $[Pb(OCOCF_3)_4]$[19], furnishes (±)-estrone [(±)-**1**] in nearly quantitative yield.

10.4 Conclusion

The total synthesis of (±)-estrone [(±)-**1**] by Vollhardt *et al.* is a novel extension of transition metal mediated alkyne cyclotrimerization technology. This remarkable total synthesis is achieved in only five steps from 2-methylcyclopentenone (**19**) in an overall yield of 22%. The most striking maneuver in this synthesis is, of course, the construction of tetracycle **13** from the comparatively simple diyne **16** by combining cobalt-mediated and *ortho*-quinodimethane cycloaddition reactions. This achievement bodes well for future applications of this chemistry to the total synthesis of other natural products.

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