(Me)C_6H_4, 104-93-8; 1,3-MeO(Me)C_6H_4, 100-84-5; 1,2,4,5-$Me_4C_6H_2$, 95-93-2; 1,2,3,4-$Me_4C_6H_2$, 488-23-3; Fe(5-NO_2phen)$_3^{3+}$, 22327-24-8; Fe(5-Clphen)$_3^{3+}$, 22327-23-7; Fe(phen)$_3^{3+}$, 13479-49-7; Fe(4,7-Ph_2phen)$_3^{3+}$, 53204-05-0; Fe(2,2′-bpy)$_3^{3+}$, 18661-69-3; H_2C=CH_2·Br_2, 16489-63-7; H_2C=CHMe·Br_2, 15506-62-4; H_2C=CHEt·Br_2, 16489-65-9; n-PrCH=CH_2·Br_2, 16489-66-0; H_2C=CMe_2·Br_2, 6742-50-3; H_2C=CMe(Et)·Br_2, 83561-88-0; (Z)-MeCH=CHMe·Br_2, 16489-68-2; (E)-MeCH=CHEt·Br_2, 83561-87-9; (E)-MeCH=CH(t-Bu)·Br_2, 77836-23-8; t-BuCH=CH_2·Br_2, 77836-22-7; Me_2C=CMe(Et)·Br_2, 52766-91-3; Me_2C=CMe_2·Br_2, 16489-45-5; Me_2C=CMe(n-Pr)·Br_2, 52766-93-5; Me_2C=CMe(n-Bu)·Br_2, 52766-95-7; C_6H_6·Br_2, 6142-76-3; MeC_6H_5·Br_2, 16734-75-1; EtC_6H_5·Br_2, 78716-30-0; i-PrC_6H_5·Br_2, 78716-47-9; $MeOC_6H_5$·Br_2, 78716-58-2; o-$Me_2C_6H_4$·Br_2, 16840-57-6; m-$Me_2C_6H_4$·Br_2, 78716-66-2; p-$Me_2C_6H_4$·Br_2, 78716-71-9; 1,3,5-$Me_3C_6H_3$·Br_2, 78717-12-1; Me_6C_6·Br_2, 78717-25-6; cyclohexene·Br_2, 16489-73-9; 2,3-dimethyl-2-heptene, 3074-64-4; 2,3-dimethyl-2-hexene, 7145-20-2; 2,3-dimethyl-2-pentene, 10574-37-5; 2,3-dimethyl-2-butene, 563-79-1; 3-ethyl-3-hexene, 16789-51-8; 2-methyl-2-butene, 513-35-9; cycloheptene, 628-92-2; cyclohexene, 110-83-8; 4,4-dimethyl-2-pentene, 26232-98-4; 1-octene, 111-66-0.

Syntheses of Polycyclic Ring Systems Based on the New Generation of *o*-Quinodimethanes

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Abstract: A mild and efficient generation of *o*-quinodimethane intermediates, in which fluoride anion is simply added to [*o*-[α-(trimethylsilyl)alkyl]benzyl]trimethylammonium halides at room temperature, and their inter- and intramolecular Diels–Alder reactions leading to polycycles are described in detail. The starting [*o*-[α-(trimethylsilyl)alkyl]benzyl]trimethylammonium halides are readily prepared via alkylation of the silicon-stabilized benzyl carbanion of [*o*-((trimethylsilyl)methyl)benzyl]-dimethylamine. Of interest is that the 1,4 elimination of a diastereoisomeric mixture of [α-[*o*-[α-(trimethylsilyl)alkyl]-phenyl]alkyl]trimethylammonium halides generates (*E*,*E*)-α,α′-dialkyl-*o*-quinodimethanes selectively. But the 1,4 elimination of [4-(trimethylsilyl)-1,2,3,4-tetrahydronaphth-1-yl]trimethylammonium halide proceeds as well, producing (*Z*,*Z*)-α,α′-di-substituted-*o*-quinodimethane, i.e., 2,3-dihydronaphthalene. Moreover, [2-(trimethylsilyl)-3-picol-3-yl]trimethylammonium bromide is treated with fluoride anion to generate a pyridine analogue of *o*-quinodimethane, of which inter- and intramolecular cycloadditions produce N-containing polycycles. Finally, on the basis of the new generation of *o*-quinodimethane intermediates, stereoselective synthesis of steroidal structures such as estrone methyl ether, 4-methoxyestra-1,3,5(10)-trien-17-one, and 6β-methylestra-1,3,5(10)-trien-17-one is achieved.

The intramolecular Diels–Alder reaction has been widely used as a key step in the stereocontrolled construction of complex frameworks. *o*-Quinodimethane as an enophile in the Diels–Alder reaction is very reactive, because of the restoration of aromaticity on the cycloaddition, and has been utilized for the synthesis of polycyclic ring systems that are otherwise difficult to prepare. Especially the successful applications of the *o*-quinodimethane intermediate for the syntheses of steroid and alkaloid structures having an aromatic A ring have profoundly aroused the interest of synthetic organic chemists.

Since the existence of this elusive *o*-quinodimethane species was first recognized by Cava[1a] in 1957, a variety of methodologies for the generation of *o*-quinodimethanes have been developed.[1-3] Those methodologies may be differentiated by their applicabilities to the syntheses of steroidal structures, e.g., estrone, that require an efficient generation of appropriately α-substituted-*o*-quinodimethanes, of which precursors are prepared via a regiocontrolled carbon–carbon bond formation. The intramolecular Diels–Alder reaction with *o*-quinodimethanes generated by thermal electrocyclic ring-opening of benzocyclobutene precursors has so far found wide applications in construction of various complex molecules including steroids[4] and alkaloids.[5] Elegant preparations of appropriately substituted benzocyclobutenes by cobalt-catalyzed cotrimerization of acetylene derivatives[6] have made the benzocyclobutene methodology more attractive. But the generation of *o*-quinodimethanes by the ring-opening of benzocyclobutenes as well as cheletropic desulfurization from 1,3-dihydrobenzo[*c*]-thiophene-2,2-dioxides[7] needs relatively higher temperature, around 200 °C, although it is not a serious drawback.

In the previous communications,[8] we described a mild and efficient generation of *o*-quinodimethane intermediates, in which fluoride anion is simply mixed with [*o*-(α-(trimethylsilyl)alkyl)-benzyl]trimethylammonium halides at ambient temperature and its application to the estrone synthesis. Herein, we give full details of polycycle synthesis on the basis of our methodology of *o*-quinodimethane generation.

Results and Discussions

Preparations of Precursors for Generation of *o*-Quinodimethane Intermediates. The new method for the generation of *o*-quino-

(1) Metal-induced debromination of *o*-xylylene dibromides. (a) Cava, M. P.; Napier, D. R. *J. Am. Chem. Soc.* **1957**, *79*, 1701. (b) Cava, M. P.; Diena, A. A.; Muth, K. *Ibid.* **1959**, *81*, 6458. (c) Alder, K.; Fremery, M. *Tetrahedron* **1961**, *14*, 190. (d) Sisido, K.; Kusano, N.; Noyori, R.; Nozaki, Y.; Simosaka, M.; Nozaki, H. *J. Polymer Sci., Part A* **1963**, *1*, 2101. (e) Nozaki, H.; Noyori, R. *Tetrahedron* **1966**, *22*, 2163. (f) Ito, Y.; Yonezawa, K.; Saegusa, T. *J. Org. Chem.* **1974**, *39*, 2769.

(2) Iodide anion induced debromination of *o*-xylylene dibromides. (a) Kerdesky, F. A. J.; Ardecky, R. J.; Lakshmikantham, M. V.; Cava, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 1992. (b) McOmie, F. W.; Perry, D. H. *Synthesis* **1973**, 416.

(3) Hofmann degradation of (*o*-methylbenzyl)trimethylammonium hydroxide. Errede, L. A. *J. Am. Chem. Soc.* **1961**, *83*, 949.

(4) (a) Oppolzer, W.; Bättig, K.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 1945. (b) Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Matsumoto, H.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 3461. (c) Grieco, P. A.; Takigawa, T.; Schllinger, W. J. *J. Org. Chem.* **1980**, *45*, 2247. (d) Oppolzer, W. *Synthesis* **1978**, 793. (e) Kametani, T.; Fukumoto, K. *Heterocycles* **1977**, *8*, 519.

(5) (a) Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3833. (b) Oppolzer, W.; Keller, K. *Ibid.* **1971**, *93*, 3836. (c) Kametani, T.; Takemura, M.; Ogasawara, M.; Fukumoto, K. *J. Heterocycl. Chem.* **1974**, *11*, 179. (d) Kametani, T.; Kajiwara, M.; Takahashi, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 737.

(6) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5245 and 5253.

(7) (a) Sisido, K.; Noyori, R.; Nozaki, H. *J. Am. Chem. Soc.* **1962**, *84*, 3562. (b) Oppolzer, W.; Roberts, D. A.; Bird, T. G. C. *Helv. Chim. Acta* **1979**, *62*, 2017. (c) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463.

(8) (a) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 863. (b) Ito, Y.; Nakatsuka, M.; Saegusa, T. *Ibid.* **1981**, *103*, 476.

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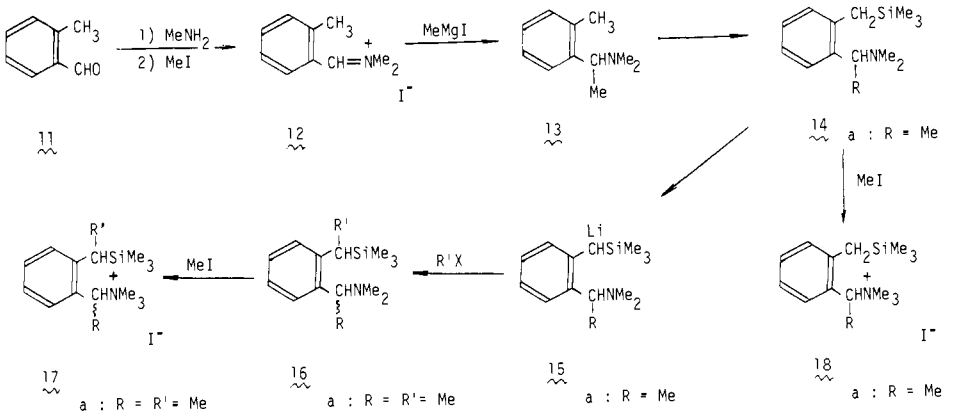
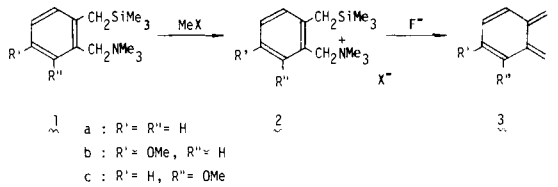
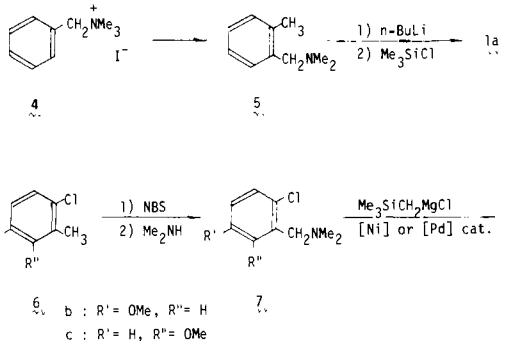
Scheme I



dimethane in the present study is based on 1,4-conjugative elimination from [*o*-((trimethylsilyl)methyl)benzyl]trimethylammonium halide (**2**), which was triggered by fluoride anion such

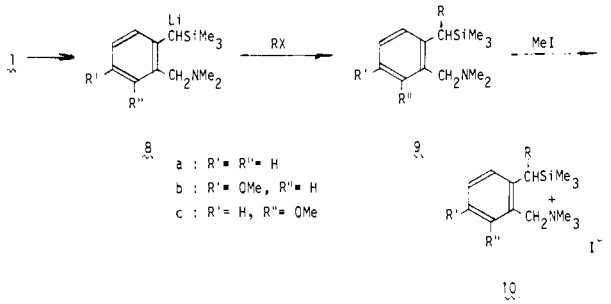


as tetrabutylammonium fluoride and cesium fluoride by virtue of the large bond energy between silicon and fluorine.[9] A striking feature of the present generation of *o*-quinodimethane intermediates is the ready availability of the precursors as well as the remarkably mild reaction conditions. The preparation of [*o*-((trimethylsilyl)methyl)benzyl]dimethylamine (**1a**) was most conveniently achieved by the Sommelet rearrangement[10] of benzyltrimethylammonium iodide (**4**) and the subsequent selective



lithiation[11] at the *o*-methyl group of the resulting (*o*-methylbenzyl)dimethylamine (**5**) followed by treatment with trimethylchlorosilane. [*o*-((Trimethylsilyl)methyl)benzyl]dimethylamine (**1a**) could be also prepared by Ni- and Pd-catalyzed coupling[12] of (*o*-chlorobenzyl)dimethylamine with [(trimethylsilyl)methyl]magnesium chloride. The latter preparative route was especially useful for preparations of [2-((trimethylsilyl)methyl)-5-methoxybenzyl]dimethylamine (**1b**) and [2-((trimethylsilyl)methyl)-6-methoxybenzyl]dimethylamine (**1c**), which were difficult to prepare by the former route because (2-methyl-5-methoxybenzyl)- and (2-methyl-6-methoxybenzyl)dimethylamines were preferentially lithiated at the aromatic carbons ortho to the methoxy substituent.

As a leaving group in the 1,4 elimination of **2**, the trimethylamine is not essential. *o*-((Trimethylsilyl)methyl)benzyl halide also underwent the fluoride anion induced 1,4 elimination to generate *o*-quinodimethane. However, the trimethylamine leaving group is the best choice in the present *o*-quinodimethane generation because of the ready synthetic availability of [*o*-((trimethylsilyl)methyl)benzyl]dimethylamine (**1**) and its feasible elaboration through the silicon-stabilized benzylic carbanion **8** leading to the



requisite precursor for the generation of α-substituted *o*-quinodimethane. In the above lithiation, it is conceivable that the benzylic carbanion (**8**) may also be stabilized by the neighboring participation of the ortho dimethylaminomethyl substituent. On treatment of [*o*-((trimethylsilyl)methyl)benzyl]dimethylamine (**1a**) with 1 equiv of *n*-BuLi in THF at 0 °C, the silicon-stabilized benzylic carbanion (**8a**) was selectively generated, which was alkylated to produce [*o*-[α-(trimethylsilyl)alkyl]benzyl]dimethylamines (**9a**) in fairly good yields. However, a similar treatment of [5-methoxy-2-((trimethylsilyl)methyl)benzyl]dimethylamine (**1b**) with *n*-BuLi or *sec*-BuLi in THF at 0 °C caused preferential lithiation at the aromatic carbons ortho to the methoxy substituent. And it was found that the aryllithium compound thus generated at 0 °C was converted on warming at 55 °C for 2 h to the silicon-stabilized benzylic carbanion **8b**, which on alkylation afforded [2-[α-(trimethylsilyl)alkyl]-5-methoxybenzyl]dimethylamine (**9b**) but in an unsatisfactory yield. Finally, this problem was overcome by treatment of **1b** with *n*-BuLi in THF at −10 to −20 °C in the presence of HMPA, resulting in the selective formation of the thermodynamically stable **8b**.

A selective lithiation of [2-((trimethylsilyl)methyl)-6-methoxybenzyl]dimethylamine (**1c**) at the benzylic carbon α to the silicon was also achieved by treatment with *n*-BuLi in THF in the presence of HMPA.

Alkylations via the lithiation at benzylic carbon α to silicon of [α-[*o*-((trimethylsilyl)methyl)phenyl]alkyl]dimethylamine (**14**) may provide [α-[*o*-[α-(trimethylsilyl)alkyl]phenyl]alkyl]dimethylamines (**16**), whose quaternization gives precursors for generation of symmetrically and unsymmetrically α,α'-disubstituted-*o*-quinodimethanes. For instance, [α-[*o*-[α-(trimethylsilyl)ethyl]phenyl]ethyl]trimethylammonium iodide (**17a**) was prepared as a 3:2 diastereomeric mixture according to Scheme I. [α-[*o*-((Trimethylsilyl)methyl)phenyl]ethyl]dimethylamine

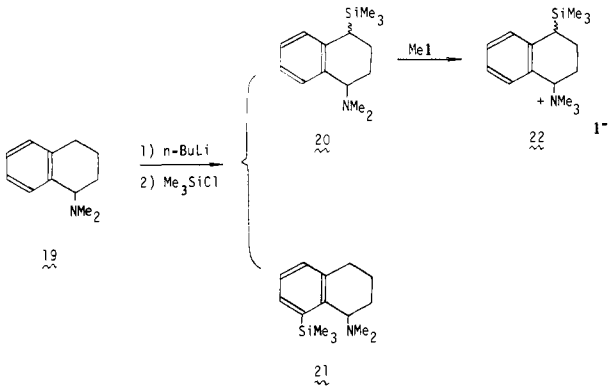
(9) It is known that fluoride anion promotes β elimination of halosilane, leading to strained alkene and benzyne. (a) Cunico, R. F.; Dexheimer, E. M. *J. Organomet. Chem.* **1973**, *59*, 153. (b) Chan, T. H.; Massuda, D. *J. Am. Chem. Soc.* **1977**, *99*, 936.

(10) Brasen, W. R.; Hauser, C. R. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 585.

(11) (a) Jones, F. N.; Zinn, M. F.; Hauser, C. R. *J. Org. Chem.* **1963**, *28*, 663. (b) Viswanathan, C. T.; Wilkie, C. A. *J. Organomet. Chem.* **1973**, *54*, 1.

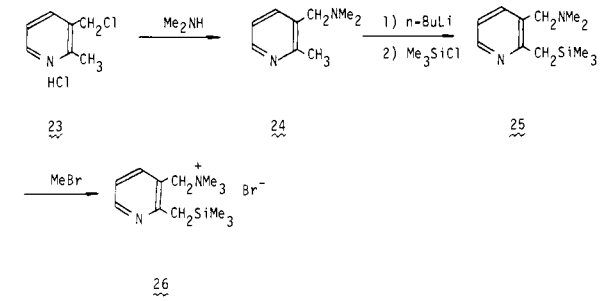
(12) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.

(**14a**) was prepared by lithiation at the *o*-methyl group of [α-(*o*-methylphenyl)ethyl]dimethylamine (**13**) followed by treatment of trimethylchlorosilane. In this case, the use of *sec*-BuLi in ether at room temperature or *n*-BuLi in refluxing ether enabled the desired lithiation at the *o*-methyl group (selectivity = 97%), suppressing lithiation at aromatic nucleus ortho to α-(dimethylamino)ethyl, which led to silylation on the aromatic ring. The [α-[*o*-((trimethylsilyl)methyl)phenyl]ethyl]dimethylamine (**14a**) thus obtained was readily lithiated with *n*-BuLi in ether to furnish the silicon-stabilized carbanion (**15a**) selectively, which was reacted with methyl iodide in the presence of HMPA to give [α-[*o*-[α-(trimethylsilyl)ethyl]phenyl]ethyl]dimethylamine (**16a**). Another example of precursor for the generation of α,α′-disubstituted-*o*-quinodimethane is given by the preparation of 1-(trimethylsilyl)-4-(dimethylamino)-1,2,3,4-tetrahydronaphthalene (**20**) starting with 1-(dimethylamino)-1,2,3,4-tetrahydro-



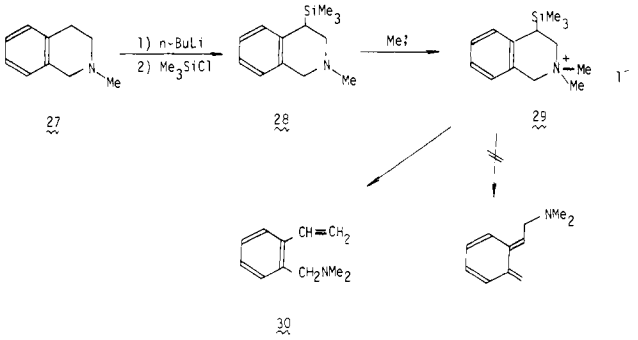
naphthalene (**19**). Attempts to lithiate **19** with *n*-BuLi followed by treatment with trimethylchlorosilane afforded the desired 1-(trimethylsilyl)-4-(dimethylamino)-1,2,3,4-tetrahydronaphthalene (**20**) (ca. 60%) along with a substantial amount of 1-(dimethylamino)-8-(trimethylsilyl)-1,2,3,4-tetrahydronaphthalene (**21**) (30%). On acid treatment of the reaction mixture, the desired **20** was easily isolated as 7:3 diastereomeric mixture by fractional distillation, since **21** was susceptible to desilylation[13] with acid to give the starting amine (**19**).

Moreover, a precursor for the generation of the pyridine analogue of *o*-quinodimethane was prepared. As shown in the following scheme, 2-((trimethylsilyl)methyl)-3-((dimethylamino)-methyl)pyridine (**25**) was prepared from β-picolyl chloride (**23**)[14]

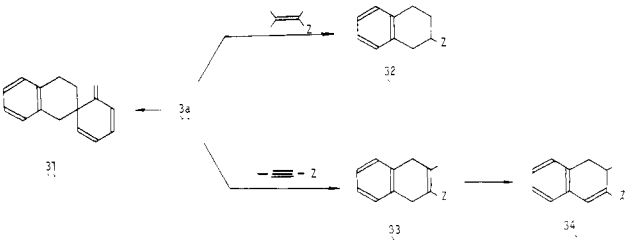


via dimethylamination, lithiation at the 2-methyl group with *n*-BuLi, and silylation. The dimethylamino group of **25** was quaternized with methyl bromide at 0 °C in acetonitrile, leaving the pyridine nitrogen intact.

Finally, 2-methyl-4-(trimethylsilyl)-1,2,3,4-tetrahydroisoquinoline (**28**) was prepared from 2-methyl-1,2,3,4-tetrahydroisoquinoline (**27**). It was expected that its quaternary ammonium salt (**29**) might undergo 1,4 elimination to an *o*-quinodimethane intermediate, but actually fluoride anion promoted only Emde-type 1,2 elimination of **29** to afford (2-vinylbenzyl)dimethylamine (**30**) quantitatively.



Generation of *o*-Quinodimethanes and Their Trapping with Dienophiles. On treatment of [*o*-((trimethylsilyl)methyl)-benzyl]trimethylammonium halide (**2a**) in acetonitrile or in methylene chloride with tetrabutylammonium fluoride (TBAF) at room temperature, 1,4 elimination took place instantaneously to generate *o*-quinodimethane **3a** almost quantitatively with the concomitant formations of trimethylfluorosilane and trimethylamine.[15] A suspension of cesium fluoride in acetonitrile can also be used instead of an acetonitrile solution of TBAF in the generation of *o*-quinodimethane. *o*-Quinodimethane **3a** thus generated in situ was dimerized in the absence of dienophile to produce a spiro dimer (**31**) in a fairly good yield, whose structure was



confirmed by the comparison of spectral data with those reported by Errede[3] as well as by the mass spectrum. The generation of *o*-quinodimethane in the presence of various dienophiles provided cycloadducts in high yields. As already reported,[8a] electron-deficient olefins and acetylene such as acrylate, acrylonitrile, and acetylenedicarboxylate afforded Diels–Alder cycloadducts **32** and **34** with *o*-quinodimethane **3a** under ambient temperature in high yields. Unexpectedly, maleate and fumarate were not so reactive toward **3a**, giving cycloadducts in moderate yields with concomitant spiro dimer formation (**31**), and maleic anhydride did not react at all. Nonactivated olefins such as cyclohexene and cyclopentadiene could not trap **3a**, resulting in the exclusive formation of **31**.

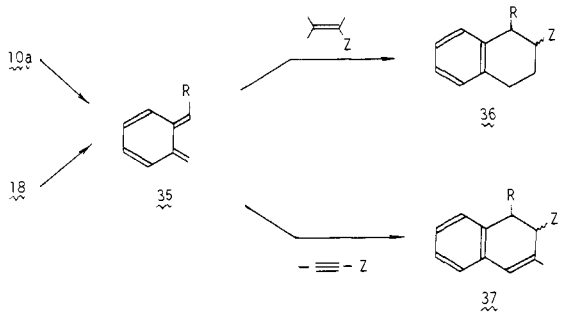
o-Quinodimethanes **3b** and **3c** with a methoxy substituent on the nucleus were similarly generated by the fluoride anion induced 1,4 elimination of [2-((trimethylsilyl)methyl)-5-methoxybenzyl]- and [2-((trimethylsilyl)methyl)-6-methoxybenzyl]trimethylammonium iodides (**2b** and **2c**) and produced cycloadducts with methyl acrylate as regioisomeric mixtures (Table I, run 3 and 4).

Similarly, [*o*-[α-(trimethylsilyl)alkyl]benzyl]trimethylammonium halides (**10a**), which were prepared via alkylations and the subsequent quaternizations of **1a**, were treated with TBAF to generate α-alkyl-*o*-quinodimethanes (**35**) quantitatively. [α-[*o*-((Trimethylsilyl)methyl)phenyl]alkyl]trimethylammonium halides (**18**) also generated the same α-alkyl-*o*-quinodimethanes (**35**) on treatment with fluoride anion. Cycloaddition reactions of **35** thus generated with dienophiles produced a mixture of regio- and stereoisomeric cycloadducts **36** and **37** (Table II). In the cycloadditions of **35** with electron-deficient olefins such as acrylate or acrylonitrile, the corresponding 1,2-disubstituted tetrahydronaphthalenes were produced as the major product. A whole

(13) Eaborn, C.; Walton, D. R. M.; Young, D. J. *J. Chem. Soc. B* **1969**, 15.

(14) (a) Tsuda, K.; Satch, Y.; Ikekawa, N.; Mishima, H. *J. Org. Chem.* **1956**, *21*, 800. (b) Sato, Y. *Chem. Pharm. Bull.* **1959**, *7*, 241.

(15) The progress of the reaction of **2a** with TBAF was monitored by NMR, which revealed that a doublet with a coupling constant of $J = 6.9$ Hz assignable to trimethylfluorosilane and a singlet of trimethylamine appeared as a singlet attributed to the trimethylsilyl group of the starting ammonium salt **2a** disappeared.

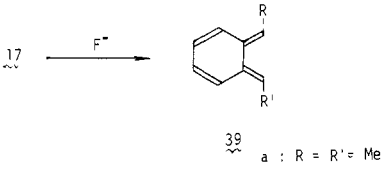


product mixture obtained from the reaction of α-methyl-*o*-quinodimethane (**35a**) and acrylonitrile was subjected to dehydrogenation on Pd/C to give 1-methyl-2-cyanonaphthalene as the sole isolable product, which was identified by ^{13}C NMR and its melting point reported. Moreover, a product mixture obtained from the reaction of α-butyl-*o*-quinodimethane (**35b**) and methyl acrylate consisted of three regio- and stereoisomeric cycloadducts in a ratio of 8:1:1, each of which showed very similar IR spectra. In the NMR spectrum (100 MHz, CCl_4) of the major product, irradiation at δ 1.55 simplified a broad multiplet (1 H) centered at δ 3.15 (quaternary benzylic proton of **36b**) into a sharp doublet with a coupling constant J = 4.5 Hz. On the basis of this finding, the major product was identified as *cis*-1-butyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene, whose formation may be predicted from selective formation of (*E*)-α-butyl-*o*-quinodimethane (**35b**) and its cycloaddition according to the Diels–Alder endo rule, taking into consideration the electronic effect of the α-butyl substituent in **35b**.

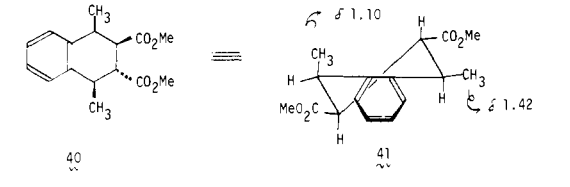
The cycloaddition of α-(carbethoxymethyl)-*o*-quinodimethane (**35d**) with activated olefins afforded the corresponding disubstituted tetrahydronaphthalene (**36d**) together with a small amount of ethyl *trans*-*o*-methylcinnamate (**38**), which may have been derived by the 1,5-hydrogen shift in the α-(carbethoxymethyl)-*o*-quinodimethane intermediate (**35d**).

In the cycloaddition reaction of α-alkyl-*o*-quinodimethanes (**35**) with acetylenedicarboxylate, conjugated 1,2-dihydronaphthalenes (**37**) were produced as the major isomer, which arose from isomerization of the nonconjugated cycloadducts initially formed. Isomeric 3,4-dihydronaphthalene was produced as a minor product.

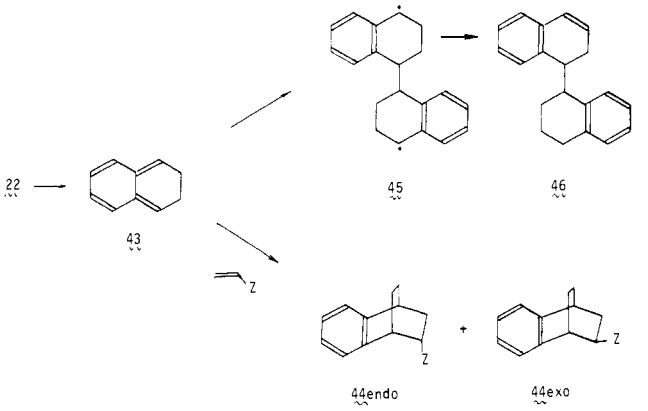
α,α′-Disubstituted-*o*-quinodimethanes (**39**) were also quantitatively generated by the fluoride anion induced 1,4 elimination of the corresponding [α-[*o*-[α-(trimethylsilyl)alkyl]phenyl]alkyl]trimethylammonium halides (**17**). Noteworthy is that



(*E*,*E*)-α,α′-disubstituted-*o*-quinodimethanes (**39**) were selectively generated regardless of the threo or erythro stereochemistry of the starting materials **17**, as demonstrated in the cycloaddition between α,α′-dimethyl-*o*-quinodimethane (**39a**) and dimethyl fumarate. On treatment of a 3:2 diastereoisomeric mixture of [α-[*o*-[α-(trimethylsilyl)ethyl]phenyl]ethyl]trimethylammonium iodide (**17a**) with cesium fluoride in the presence of dimethyl fumarate, a single stereoisomeric cycloadduct (**40**) was produced in a quantitative yield, which can be derived only from (*E*,*E*)-α,α′-dimethyl-*o*-quinodimethane (**39a**). The identity of the cycloadduct **40**, existing in the depicted conformer **41**, was established by ^{13}C and ^{1}H NMR associated with a decoupling technique. ^{1}H NMR exhibited doublets at δ 1.10 and 1.42, which are assignable to the aliphatic methyl groups. Irradiation at δ 1.10 simplified the multiplet centered at δ 3.29 to a doublet with a coupling constant of J = 4.8 Hz without any significant change in other absorptions. On the other hand, irradiation at δ 1.42 simplified the multiplet centered at δ 2.95 to a doublet with a coupling constant of J = 10.0 Hz. The cycloaddition of the α,α′-dimethyl-*o*-quinodimethane (**39a**) with dimethyl maleate furnished in a quantitative yield the expected cycloadduct **42**, which showed one spot on the TLC plate (silica gel). The ^{1}H NMR spectrum of **42** exhibited only one doublet (6 H) at δ 1.37, which is assigned to aliphatic methyl. However, an addition of a shift reagent $Eu(fod)_3$ to the NMR sample induced splitting of the doublet into two doublets, whose relative peak area was 5:2. These observations may be taken to suggest that the cycloadduct of (*E*,*E*)-α,α′-dimethyl-*o*-quinodimethane (**39a**) with dimethyl maleate consists of endo cycloadduct (**42**endo) and exo cycloadduct (**42**exo), each of which is flipping rapidly enough in the NMR time scale.



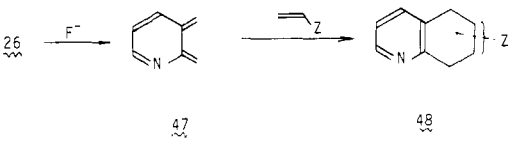
Unlike [α-[*o*-[α-(trimethylsilyl)alkyl]phenyl]alkyl]trimethylammonium halide **17**, [4-(trimethylsilyl)-1,2,3,4-tetrahydronaphth-1-yl]trimethylammonium iodide (**22**) is only permitted



to generate (*Z*,*Z*)-α,α′-disubstituted-*o*-quinodimethane, 2,3-dihydronaphthalene (**43**).[16] Reaction of a 7:3 diastereomeric mixture of **22** with fluoride anion proceeded in the presence of dienophile as well, producing a large amount of dimeric product (**46**) and a mixture of the expected bicyclic endo and exo cycloadducts (**44**endo and **44**exo) in low to moderate yields with endo cycloadduct (**44**endo) predominating. The formation of a different type of dimer **46** may be reasonably explained by a coupling of **43** through a radical mechanism.

As expectedly, the presence of a large excess of dienophile in the generation of **43** favored the production of cycloadducts **44**. The endo and exo stereochemistry was established by ^{1}H NMR spectra, taking the anisotropic effect of the benzene ring[17] into consideration. Cycloadditions of α,α′-disubstituted-*o*-quinodimethanes **39** and **43** are listed in Table III.

A pyridine analogue of *o*-quinodimethane **47**[18] was similarly



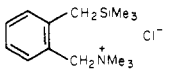
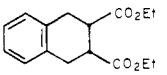
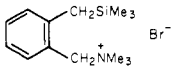
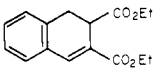
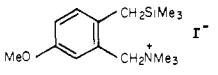
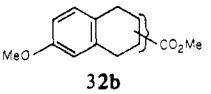
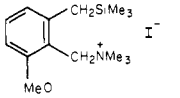
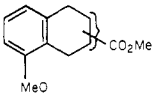
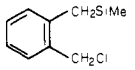
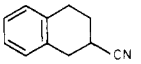
generated by treating [2-((trimethylsilyl)methyl)picol-3-yl]trimethylammonium bromide (**26**) with cesium fluoride. The cycloaddition reactions of **47** with acrylate and acrylonitrile gave rise to two isomeric cycloadducts (**48**) with no regioselectivity.

(16) (a) Dinulescu, I. G.; Avram, M.; Nenitzescu, C. D. *Chem. Ber.* **1960**, *93*, 1795. (b) Avram, M.; Dinulescu, I. G.; Dinu, D.; Nenitzescu, C. D. *Chem. Ind.* (*London*) **1962**, 555.

(17) Tori, K.; Takano, Y.; Kitahonoki, K. *Chem. Ber.* **1964**, *97*, 2799.

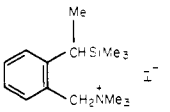
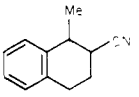
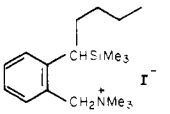
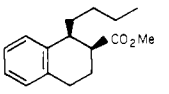
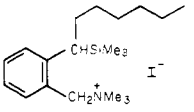
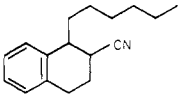
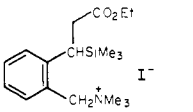
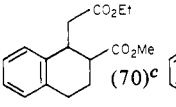
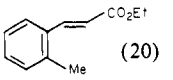
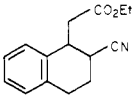
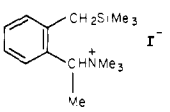
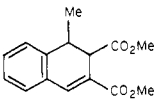
(18) (a) Naiman, A.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 411. (b) Thummel, R. P. *Acc. Chem. Res.* **1980**, *13*, 70.

Table I. Cycloadditions of *o*-Quinodimethanes (3) with Dienophiles[a]

run	ammonium salts	dienophiles (molar equiv)	cycloadducts (% yield)[b]
1	 **2a-Cl**	$EtO_2CCH{=}^{c}CHCO_2Et$[c] (3)	 **32a** (46) + spiro dimer (38) **31**
2	 **2a-Br**	$EtO_2CC{\equiv}CCO_2Et$ (1.3)	 **34a** (76)[c]
3	 **2b**	$CH_2{=}CHCO_2Me$ (3)	 **32b** (97)[d]
4	 **2c**	$CH_2{=}CHCO_2Me$ (3)	 **32c** (~100)[e]
5		none	spiro dimer (64) **31**
6		$CH_2{=}CHCN$ (3)	 **32d** (89)[c]

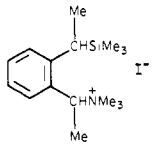
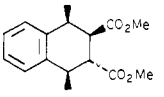
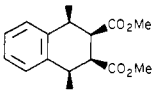
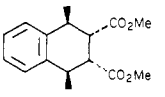
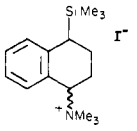
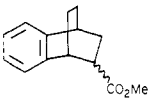
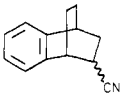
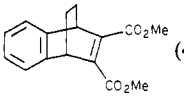
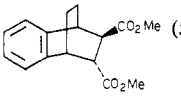
[a] Reaction was carried out at room temperature. CH_2Cl_2 solvent was used for **2a** and CH_3CN for other precursors. Tetrabutylammonium fluoride was used for the reaction except for that with **2c** (CsF). [b] Yields are based on the precursors used and not optimized. [c] Reference 1f. [d] Ca. 3:2 regioisomeric mixture. [e] Ca. 2:1 regioisomeric mixture.

Table II. Cycloadditions of α-Alkyl-*o*-quinodimethanes (35) with Dienophiles[a]

run	ammonium salts	dienophiles (molar equiv)	cycloadducts (% yield)[b]
1	 **10a-i**	$CH_2{=}CHCN$	 **36a** (90)[c]
2	 **10a-ii**	$CH_2{=}CHCO_2Me$	 **36b** (88)[c]
3	 **10a-iii**	$CH_2{=}CHCN$	 **36c** (89)[c]
4	 **10a-iv**	$CH_2{=}CHCO_2Me$	 **36d** (70)[c]  **38** (20)
5		$CH_2{=}CHCN$	 **36e** (61)[c] **38** (10)
6	 **18a**	$MeO_2CC{\equiv}CCO_2Me$	 **37a** (88)[d]
7		$CH_2{=}CHCN$	**36a** (~100)[c]

[a] Reaction was carried out in acetonitrile at room temperature. Tetra-*n*-butylammonium fluoride was used for all reactions except that of **18a** with acrylonitrile (CsF). [b] Yields are based on ammonium salts used. [c] Contaminated with about 20% stereo- and regioisomers as judged by ^1H NMR. [d] Contaminated with about 10% of the olefinic isomer as judged by ^1H NMR.

Table III. Cycloadditions of α,α'-Disubstituted-*o*-quinodimethanes (39a) and (43) with Dienophiles[a]

run	ammonium salts	dienophiles (molar equiv)	cycloadducts (% yield)[b]
1	 17a	$MeO_2CCH^{t}=CHCO_2Me$[b] (1.3)	 40 (~100)
2		$MeO_2CCH^{c}=CHCO_2Me$[b] (1.5)	 42endo  42exo (~100)
3		$MeO_2CCH^{c}=CHCO_2Me$[c] (1.2)	42endo + 42exo (51)
4	 22	$CH_2=CHCO_2Me$[d] (3)	 44a (25) (endo/exo = 11/1) dimer (51) 46
5		$CH_2=CHCO_2Me$[d] (10)	44a (64) (endo/exo = 15/1) dimer (36) 46
6		$CH_2=CHCN$[d] (10)	 44b (70) (endo/exo = 8/1) dimer (30) 46
7		$MeO_2CC\equiv CCO_2Me$[e] (1.1)	 44c (41) dimer (44) 46
8		$MeO_2CCH^{f}=CHCO_2Me$[f] (1.1)	 44d (57)

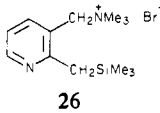
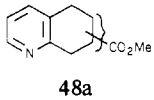
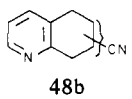
[a] All reactions were carried out in acetonitrile solvent. [b] Tetrabutylammonium fluoride was used. Reaction temperature: 50 °C. [c] Tetrabutylammonium fluoride was used. Reaction temperature: 0 °C. [d] Cesium fluoride was used. Reaction temperature: room temperature. [e] Tetrabutylammonium fluoride was used. Reaction temperature: room temperature. [f] Tetrabutylammonium fluoride was used. Reaction temperature: 45 °C.

In comparison to that with the parent *o*-quinodimethane **3a**, the cycloaddition reactions with the pyridine analogue of *o*-quinodimethane **47** seemed to require a slightly higher reaction temperature in order to get satisfactory yields (Table IV).

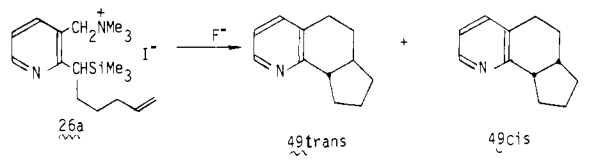
Intramolecular Cyclization of *o*-Quinodimethane Intermediates. As mentioned in the preliminary papers,[8] α-alkenyl-*o*-quinodimethanes generated from the corresponding ammonium halides underwent the intramolecular Diels–Alder reaction to give polycycles. When [*o*-(1-(trimethylsilyl)-6-heptenyl)benzyl]trimethylammonium iodide (**10e**) was added in an acetonitrile solution of TBAF at room temperature, the intramolecular cyclization of the α-(hex-5-enyl)-*o*-quinodimethane **35e** generated took place to give 22% yield of octahydrophenanthrene along with olefinic hydrocarbon, which was not stable on standing and tentatively assigned to be a spirotype of dimer by its NMR and IR spectra.[8a] But the generation and cyclization of **35e** in refluxing acetonitrile produced a 14:1 mixture of *trans*- and *cis*-octahydrophenanthrene in 77% yield with the dimeric byproduct (8%). The same degree of trans stereoselectivity has also been observed in the intramolecular cyclizations via the corresponding benzocyclobutene[4] and 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide precursors[7] and explained by assuming an exo transition state for the cyclization, which violates the so-called endo transition state for a Diels–Alder reaction.

Another synthesis of tricyclic ring systems is given by the intramolecular cyclization with a pyridine analogue of *o*-quinodimethane. On treatment of [2-(1-(trimethylsilyl)-5-hexenyl)-picol-3-yl]trimethylammonium bromide (**26a**) with cesium fluoride in acetonitrile at reflux, trans and cis nitrogen-containing tricycles **49**trans and **49**cis were produced in a 47:53 ratio in 88% yield.

Table IV. Cycloadditions of Pyridine Analogue of *o*-quinodimethane (47) with Dienophiles[a]

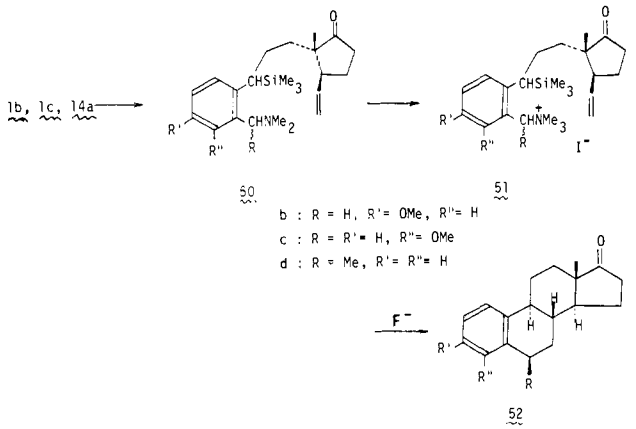
run	ammonium salt	dienophiles (molar equiv)	cycloadducts (% yield)[b]
1	 26	$CH_2=CHCO_2Me$ (5)	 48a (75)[c]
2		$CH_2=CHCO_2Me$ (3)	48a (65)[d]
3		$CH_2=CHCN$ (5)	 48b (76)[c]

[a] Reactions were carried out in acetonitrile solvent. [b] Yields are based on **26** used and not optimized. [c] Ca. 1:1 regioisomers mixture. Reaction temperature: 55 °C. [d] Ratio of the regioisomers was not determined. Reaction temperature: room temperature.



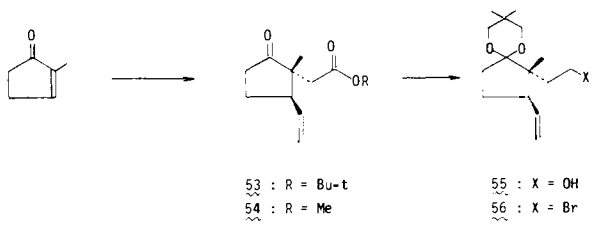
The stereochemistry of the tricycles (**49**) was determined by ^1H NMR spectroscopy. In the ^1H NMR spectrum of the trans-tricycle (**49**trans), the methine proton α to the pyridine ring resonated at δ 3.06 (broad quartet, 1 H, J = 8.0 Hz), which was significantly shifted to lower field on addition of Eu(fod)$_3$ (e.g., δ 4.25 at 9 mol % Eu(fod)$_3$). On the other hand, the ^1H NMR spectrum of the cis-tricycle (**49**cis) did not show any separated signal that may be assigned to methine proton α to pyridine ring. Moreover, the presence of Eu(fod)$_3$ did not induce any significant shift of signals. These observations seem to be consistent with serious steric hindrance in the complexation of europium at the pyridine nitrogen of cis-tricycle **49**cis, as revealed by inspection with molecular model. The formation of trans- and cis-tricycles **49** with no stereoselectivity may be taken to imply that there is no significant energy difference between the respective exo and endo transition states in the intramolecular Diels–Alder reaction. No stereoselectivities have been reported in some intramolecular cyclizations via *o*-quinodimethanes accompanied with concurrent formation of a fused five-membered ring.[4,7]

On the basis of our methodology, which has been described above, steroidal frameworks with 8,9 trans, 8,14 anti, and 13,14 trans stereochemistry were constructed.[19] Stereoselective syntheses of (±)-estrone methyl ether (**52b**) and 6β-methyl-



estra-1,3,5(10)-trien-17-one (**52d**)[20] have been already reported in a previous communication.[8] Herein, the details of the steroid synthesis are given by stereoselective synthesis of 4-methoxy-estra-1,3,5(10)-trien-17-one (**52c**) as shown. The key in the construction of **52c** is a selective generation of the silicon-stabilized carbanion **8c** from [2-((trimethylsilyl)methyl)-6-methoxybenzyl]dimethylamine (**1c**) and its alkylation with cyclopentanone moiety **56**. Like the formation of **8b** from **1b**, the selective formation of the silicon-stabilized carbanion **8c** was achieved under the reaction conditions of the thermodynamic deprotonation (*n*-BuLi in THF and HMPA, −10 to −20 °C).

In a parallel line of experiments, *trans*-2-(β-bromoethyl)-2-methyl-3-vinylcyclopentanone 2,2-dimethyl-1,3-propanediol ketal (**56**) was prepared with higher stereoselectivity by a modification



of the method already known.[4a,7c] Copper-catalyzed conjugate addition of vinylmagnesium bromide to 2-methylcyclopentenone and the subsequent treatment of the resulting cyclopentanone enolate with *tert*-butyl bromoacetate afforded keto ester **53** with >96% stereoselectivity[24] in 78% yield, which was subjected without stereochemical purification to the following sequence of reactions. After transesterification with methanol, the ketone carbonyl of **54** was protected with 2,2-dimethyl-1,3-propanediol, and then the carbomethoxy group was reduced, yielding alcohol **55**, which was converted via the corresponding tosylate to *trans*-2-(β-bromoethyl)-2-methyl-3-vinylcyclopentanone 2,2-dimethyl-1,3-propanediol ketal (**56**) in a stereoisomerically pure form in 47% overall yield. A protection of the ketone carbonyl of **54** with ethylene glycol was not suitable. The final conversion of *trans*-2-(β-hydroxyethyl)-2-methyl-3-vinylcyclopentanone ethylene glycol ketal or its tosylate to the corresponding bromide resulted in a poor yield of the bromide with several byproducts in spite of many attempts with conventional methods.

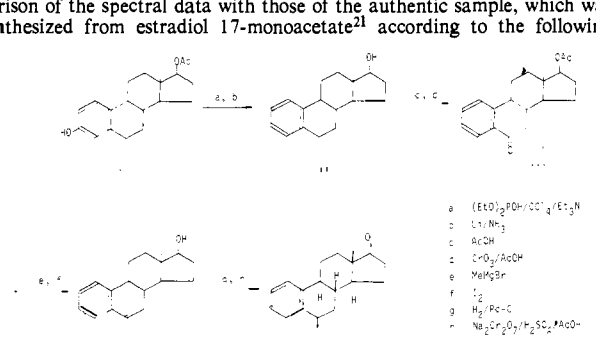
With cyclopentanone moiety **56** thus prepared in hand, preparation of the requisite ammonium iodide precursor **51c** and its cyclization via the *o*-quinodimethane intermediate were performed as follows. The silicon-stabilized benzylic carbanion **8c**, which was generated in situ at −10 to −20 °C, was cooled down to −75 °C and then treated with the bromide **56** to furnish **50c** as a diastereoisomeric mixture in 94% yield after deketalization. The ammonium iodide **51c** obtained by quaternization of **50c** with methyl iodide was reacted with cesium fluoride in refluxing acetonitrile to give 8,9-trans, 8,14-anti, 13,14-trans 4-methoxy-estra-1,3,5(10)-trien-17-one (**52c**) containing 7–8% of the C(9) epimer in 86% overall yield. In this synthesis of **52c**, the intermediates were not isolated for several steps starting from alkylation of **1c** with cyclopentanone moiety **56**. Isomerically pure **52c** was isolated as a pale yellow solid by recrystallization from ethyl acetate and identified by ^1H NMR and ^{13}C NMR.

Experimental Section

General Data. Melting points and boiling points are uncorrected. ^1H NMR spectra were recorded on a Hitachi R-20B (60 MHz) or a JEOL JNM MH-100 (100 MHz) instrument, and the chemical shifts are referenced with respect to internal Me_4Si unless otherwise noted. ^{13}C NMR spectra were recorded by using a Hitachi R-900 ^{13}C spectrometer. In-

(19) This methodology has also been utilized for the synthesis of 11α-hydroxyestrone: Djuric, S.; Sarkar, T.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 6885.

(20) 6β-Methylestra-1,3,5(10)-trien-17-one (**52d**) was identified by comparison of the spectral data with those of the authentic sample, which was synthesized from estradiol 17-monoacetate[21] according to the following



scheme. Estradiol 17-monoacetate (i) was first converted to diethyl phosphate ester, which was reduced by Li/NH$_3$[22] to produce ii. After the 17-hydroxy group of ii was protected as acetate, it was oxidized by chromic anhydride to give ketone (iii). Methylmagnesium bromide was added to the ketone (iii) to afford tertiary benzylic alcohol, which was dehydrated[23] to produce 6-methyl-17-hydroxyestra-1,3,5(10),6-tetraene (iv). Finally, compound iv was hydrogenated on Pd/C, and then the resultant 17-alcohol was oxidized to give **52d**.

(21) We are grateful to Teikoku Horm. Manufacturing Co. for providing estradiol 17-monoacetate.

(22) Japanese Patent Publication 4071, **1963**; Teikoku Horm. Manufacturing Co.

(23) Hibbert, H. *J. Am. Chem. Soc.* **1915**, *37*, 1749.

(24) Use of methyl bromoacetate resulted in 88% stereoselectivity. Oppolzer and Nicolaou reported that the cyclopentanone enolate, which was generated by their own methods, was trapped with bromoacetates to give the keto esters corresponding to **54** in 86%[4a] and 78%[7c] stereoselectivity.

frared spectra were obtained on a Hitachi 260-50 infrared spectrometer. Low-resolution mass spectra were recorded on a JEOL JMS-D300 (24 eV) or a Hitachi RMS-4 (70 eV) mass spectrometer. High-resolution mass spectra were obtained by the courtesy of Kao Soap Co. Elemental analyses were performed at the Institute of Elemental Analysis, Kyoto University.

All solvents were dried over appropriate desiccants and distilled under nitrogen. Tetra-*n*-butylammonium fluoride, which is very hygroscopic powder, was prepared by neutralization of commercial tetra-*n*-butylammonium hydroxide with 5% hydrofluoric acid. Cesium fluoride was purchased from Aldrich Chemical Co. and dried by heating in vacuo before use. *n*-BuLi (hexane solution) was purchased from Aldrich Chemical Co. and titrated before use.

[*o*-((Trimethylsilyl)methyl)benzyl]dimethylamine (1a).[11] To a solution of (*o*-methylbenzyl)dimethylamine (16.2 g, 109 mmol), which was prepared according to the reported procedure[10] in about 90% yield starting from benzyldimethylamine, in 250 mL of anhydrous ether was added *n*-BuLi (218 mmol) at 0 °C over 30 min, and the solution was stirred at room temperature for 22 h. To the resultant reddish homogeneous solution was added a mixture of trimethylchlorosilane (35 mL, 2.5 molar equiv) and triethylamine (4 mL) at 0 °C at once, and the solution was stirred at room temperature for 4 h. The mixture was quenched with a cold aqueous solution of sodium bicarbonate and extracted with ether. The ethereal solution was washed with brine, dried over $MgSO_4$, and evaporated. The residue was distilled [bp 69–70 °C (0.1 mmHg)] to give **1a** as a colorless liquid (23.0 g, 96%).

[*o*-((Trimethylsilyl)methyl)benzyl]trimethylammonium Chloride (2a-Cl). To a solution of *o*-methylbenzyl alcohol (7.8 g, 64 mmol) in 250 mL of anhydrous diglyme was added *n*-BuLi (192 mmol) under nitrogen at −78 °C over 30 min, resulting a cream-yellow slurry, which on warming to −20 °C became an almost homogeneous dark-red solution. After stirring for 30 min at −10 to −20 °C, a mixture of trimethylchlorosilane (25 g, 230 mmol) and triethylamine (7 mL) was added at once to this solution, and the solution was stirred at room temperature for 3 h. The reaction mixture was quenched with ice water, extracted repeatedly with ether, and the extract washed twice with ice water and brine. The ethereal solution was evaporated and then subjected to fractional distillation [bp 74–78 °C (0.3 mmHg)] to give *o*-((trimethylsilyl)methyl)benzyl trimethylsilyl ether [^{1}H NMR (CCl_4) δ 0.06 (s, 9 H), 0.18 (s, 9 H), 2.10 (s, 2 H), 4.55 (s, 2 H), 6.7–7.3 (m, 4 H); mass spectrum, *m/e* 266]. In practice, the crude *o*-((trimethylsilyl)-methyl)benzyl trimethylsilyl ether was dissolved in 200 mL of 90% aqueous methanol and refluxed until silyl ether was hydrolyzed, which was monitored by GLC (PEG column). After the reaction was complete, methanol was evaporated and the organic residue extracted with ether. Concentration of the ether extract and subsequent distillation [bp 90–94 °C (0.2 mmHg)] afforded *o*-((trimethylsilyl)methyl)benzyl alcohol (7.8 g, 63% based on *o*-methylbenzyl alcohol) [^{1}H NMR (CCl_4) δ −0.03 (s, 9 H), 2.00 (s, 2 H), 2.44–2.83 (br, 1 H), 4.16–4.38 (br, 2 H), 6.61–7.22 (m, 4 H); mass spectrum, *m/e* 194]. Next, to a solution of *o*-((trimethylsilyl)methyl)benzyl alcohol (7.8 g, 40 mmol) in 110 mL of THF was added slowly 1 molar equiv of *n*-BuLi at −78 °C under nitrogen, and the solution was stirred for 20 min. To the mixture methanesulfonyl chloride (5.1 g, 44 mmol) was added, and the solution was stirred for 30 min at −78 °C and then for 2 days at room temperature. A large excess of *n*-hexane was added to the reaction mixture, and the lithium methanesulfonate that precipitated was filtered off and the filtrate distilled to afford *o*-((trimethylsilyl)methyl)benzyl chloride: bp 54 °C (0.2 mmHg); (8.1 g, 95%); IR (neat) 1263, 1249, 840–855 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.04 (s, 9 H), 2.23 (s, 2 H), 4.49 (s, 2 H), 6.9–7.3 (m, 4 H); mass spectrum, *m/e* (relative intensity) 212 (2.7), 214 (1). Anal. Calcd for $C_{11}H_{17}ClSi$: C, 62.09; H, 8.05; Cl, 16.66. Found: C, 62.35; H, 8.23; Cl, 16.77.

Finally, a mixture of *o*-((trimethylsilyl)methyl)benzyl chloride (1.88 g, 8.8 mmol), trimethylamine (3.5 mL), and acetonitrile (9 mL) was placed in a glass tube and sealed. The mixture was heated at 70 °C for 3 h. A large excess of ether was added to the reaction mixture, precipitating a fine white solid, which was the analytically pure ammonium chloride **2a**-Cl (2.05 g, 85%): mp 239–241 °C dec; IR (KBr disk) 1492, 1247, 1152, 1104, 850 cm^{-1}; ^{1}H NMR (CD_3CN, Me_4Si as an external reference) δ −0.19 (s, 9 H), 2.17 (s, 2 H), 3.01 (s, 9 H), 4.49 (s, 2 H), 6.7–7.5 (m, 4 H). Anal. Calcd for $C_{14}H_{26}NSiCl$: C, 61.84; H, 9.64; N, 5.15. Found: C, 61.85; H, 9.66; N, 5.08.

[*o*-((Trimethylsilyl)methyl)benzyl]trimethylammonium Bromide (2a-Br). A mixture of [*o*-((trimethylsilyl)methyl)benzyl]dimethylamine (**1a**) (1.32 g), methyl bromide (1.4 mL), and acetonitrile (4 mL) was placed in a glass tube and sealed and heated at 80 °C for 6 h. Excess ether was added to the reaction mixture, resulting in precipitation of **2a**-Br as a white solid, which was filtered and dried (1.57 g, 83%): 218–220 °C dec (recrystallized from methylene chloride); IR (KBr disk) 1246, 855 cm^{-1}; ^{1}H NMR (CD_3CN, Me_4Si as an external reference) δ −0.32 (s, 9 H), 2.05 (s, 2 H), 2.78 (s, 9 H), 4.22 (s, 2 H), 6.6–7.3 (m, 4 H). Anal. Calcd for $C_{14}H_{26}NSiBr$: C, 53.15; H, 8.28; N, 4.43. Found: C, 53.00; H, 8.35; N, 4.22.

[*o*-((Trimethylsilyl)methyl)benzyl]trimethylammonium Iodide (2a-I). A solution of [*o*-((trimethylsilyl)methyl)benzyl]dimethylamine (**1a**) and 2–3 molar equiv of methyl iodide in acetonitrile was refluxed for 1 h, and a large amount of ether was added to the reaction mixture to precipitate ammonium salt **2a**-I as a white solid (>90%): mp 189.5–190.5 °C (needles from acetone–ethyl acetate); IR (KBr disk) 1483, 1243, 1156, 859, 791 cm^{-1}; ^{1}H NMR (CD_3CN, Me_4Si as an external reference) δ −0.32 (s, 9 H), 2.07 (s, 2 H), 2.85 (s, 9 H), 4.36 (s, 2 H), 6.6–7.3 (m, 4 H). Anal. Calcd for $C_{14}H_{26}NSiI$: C, 46.28; H, 7.21; N, 3.85. Found: C, 45.99; H, 7.28; N, 3.86.

[2-((Trimethylsilyl)methyl)-5-methoxybenzyl]dimethylamine (1b). To a solution of (2-chloro-5-methoxybenzyl)dimethylamine (**7b**)[25] (5.25 g, 26.3 mmol) in 60 mL of benzene containing 0.38 g (2.2 mol %) of dichlorobis(triphenylphosphine)nickel(II) was added an ethereal solution of ((trimethylsilyl)methyl)magnesium chloride (20 mL, 1.15 molar equiv). After being stirred for 2 h at room temperature, the reaction mixture was refluxed until **7b** was consumed completely, which was monitored by GLC. In this case, 15 h was required. Aqueous ammonium chloride was added to the reaction mixture, and it was extracted with ether. The extract was washed with aqueous ammonium chloride and brine, dried over $MgSO_4$, and evaporated. The residue was distilled to give **1b** in >90% yield: bp 92 °C (0.5 mmHg); IR (neat) 1606, 1247, 844 cm^{-1}; ^{1}H NMR (CCl_4, Me_4Si as an external reference) δ 0.00 (s, 9 H), 2.04 (s, 2 H), 2.10 (s, 6 H), 3.16 (s, 2 H), 3.66 (s, 3 H), 6.3–6.9 (m, 3 H); mass spectrum, *m/e* (relative intensity) 251 (9), 206 (23), 192 (19), 191 (100), 73 (30). Anal. Calcd for $C_{14}H_{25}NOSi$: C, 66.88; H, 10.02; N, 5.57. Found: C, 66.60; H, 10.02; N, 5.84.

[2-((Trimethylsilyl)methyl)-5-methoxybenzyl]trimethylammonium Iodide (2b). Quaternization of **1b** with methyl iodide afforded **2b** in 83% yield as a white solid: mp 165 °C (recrystallized from acetone–ethyl acetate); IR (KBr disk) 1611, 1252, 850 cm^{-1}; ^{1}H NMR (CD_3CN, Me_4Si as an external reference) δ −0.36 (s, 9 H), 1.91 (s, 2 H), 2.78 (s, 9 H), 3.40 (s, 3 H), 4.16 (s, 2 H), 6.4–6.8 (m, 3 H). Anal. Calcd for $C_{15}H_{28}NOSiI$: C, 45.80; H, 7.17; N, 3.56. Found: C, 45.62; H, 7.32; N, 3.38.

[2-((Trimethylsilyl)methyl)-6-methoxybenzyl]dimethylamine (1c). A mixture of 2-chloro-6-methoxytoluene[26] (28.7 g, 183 mmol), *N*-bromosuccinimide (35.9 g, 201 mmol), carbon tetrachloride (80 mL), and 0.1 g of benzoyl peroxide (BPO) was stirred at reflux, and additional 0.1-g quantities of BPO were added after 2, 6, and 9 h. After refluxing for 12 h, succinimide was filtered off, and the filtrate was washed with water, dried over $MgSO_4$, and concentrated at reduced pressure. The residual oil was distilled to afford 2-chloro-6-methoxybenzyl bromide [bp 103 °C (0.6 mmHg)] in 80% yield [IR (neat) 1459, 1261, 1037, 894, 773 cm^{-1}; ^{1}H NMR (CCl_4) δ 3.83 (s, 3 H), 4.60 (s, 2 H), 6.59–7.31 (m, 3 H)]. To a mixture of ethanol (70 mL) and 50% aqueous solution of dimethylamine (70 mL) was added 2-chloro-6-methoxybenzyl bromide (34.3 g, 146 mmol) over 1 h at 0 °C. After being stirred at room temperature for 15 h, the reaction mixture was extracted with ether, and the ethereal solution was extracted with dilute hydrochloric acid. The aqueous layer was made alkaline with sodium hydroxide, and the liberated free amine was extracted with ether. Distillation of the ether solution afforded (2-chloro-6-methoxybenzyl)dimethylamine (**7c**) [bp 80–84 °C (0.6 mmHg)] in 85% yield: IR (neat) 1458, 1253, 1040, 766, 711 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.20 (s, 6 H), 3.46 (s, 2 H), 3.70 (s, 3 H), 6.40–7.10 (m, 3 H).

To a solution of **7c** (5.6 g, 28 mmol) in 20 mL of benzene containing nickel(II) acetylacetonate (320 mg, 4.4 mol %) was added an ethereal solution of ((trimethylsilyl)methyl)magnesium chloride (45 mL, 1.4 molar equiv) at 0 °C. After being stirred at room temperature for 36 h, the reaction mixture was quenched with aqueous ammonium chloride. An extractive workup of the mixture followed by distillation afforded **1c** [bp 84–85 °C (0.2 mmHg)] in 80% yield (5.68 g): IR (neat) 1465, 1249, 1085, 842 cm^{-1}; ^{1}H NMR (CCl_4, Me_4Si as an external reference) δ 0.00 (s, 9 H), 2.18 (s, 6 H), 2.30 (s, 2 H), 3.31 (s, 2 H), 3.70 (s, 3 H), 6.25–6.52 (m, 2 H), 6.88 (t, 1 H, J = 8 Hz); mass spectrum, *m/e* (relative intensity) 251 (88), 236 (28), 207 (24), 206 (90), 193 (27), 192 (38), 191 (100), 73 (40). Anal. Calcd for $C_{14}H_{25}NOSi$: C, 66.88; H, 10.02; N, 5.57. Found: C, 66.82; H, 10.06; N, 5.58.

[2-((Trimethylsilyl)methyl)-6-methoxybenzyl]trimethylammonium

(25) (a) Klein, K. P.; Hauser, C. R. *J. Org. Chem.* **1967**, *32*, 1479. (b) Bhati, A. *J. Chem. Soc.* **1963**, 730. (c) Wilkinson, R. G.; Fields, T. L.; Boothe, J. H. *J. Org. Chem.* **1961**, *26*, 637.

(26) Finnegan, R. A.; Patel, J. K. *J. Chem. Soc., Perkin Trans. 1* **1972**, *15*, 1896.

Iodide (2c). Quaternization of **1c** with methyl iodide afforded **2c** in 97% yield as a white solid: mp 183–184 °C; IR (KBr disk) 1472, 1268, 1092, 849 cm^{-1}; ^1H NMR (CD_3CN, Me_4Si as an external reference) δ –0.23 (s, 9 H), 2.07 (s, 2 H), 2.79 (s, 9 H), 3.48 (s, 3 H), 4.19 (s, 2 H), 6.34–6.62 (m, 2 H), 7.05 (t, 1 H, J = 8.2 Hz). Anal. Calcd for $C_{15}H_{28}NOSiI$: C, 45.80; H, 7.17; N, 3.56. Found: C, 45.77; H, 7.14; N, 3.63.

Alkylations of [*o*-((Trimethylsilyl)methyl)benzyl]dimethylamine (1a). Preparations of [*o*-[α-(Trimethylsilyl)alkyl]benzyl]trimethylammonium Halides (10). A typical procedure is given by the preparation of [*o*-[1-(trimethylsilyl)-6-heptenyl]benzyl]trimethylammonium iodide (**10a**-v).

To a solution of **1a** (2.85 g, 12.9 mmol) in THF (30 mL) was added 1.05 equiv of *n*-BuLi dropwise at 0 °C, and the mixture was stirred for 2 h at 0 °C. To the mixture was added 5-hexenyl iodide (2.75 g, 13.1 mmol) at once, and the solution was stirred for 1 h at 0 °C and then for 2 h at room temperature. The reaction mixture was diluted with ether, washed with brine, and dried over $MgSO_4$. Evaporation of the ethereal solution followed by Kugelrohr distillation afforded [*o*-[1-(trimethylsilyl)-6-heptenyl]benzyl]dimethylamine [bp 105 °C (0.1 mmHg)] in 82% yield (3.2 g), which had a >96% purity as determined by GLC: IR (neat) 1638, 1247, 854, 837, 747 cm^{-1}; ^1H NMR (CCl_4, Me_4Si as an external reference) δ 0.01 (s, 1 H), 1.1–2.4 (m, 8 H), 2.20 (s, 6 H), 2.64 (br t, 1 H, J = 7 Hz), 3.30 (s, 2 H), 4.7–5.1 (m, 2 H), 5.4–6.0 (m, 1 H), 6.9–7.2 (m, 4 H); mass spectrum, *m/e* (relative intensity) 303 (6), 288 (5), 258 (6), 230 (32), 190 (10), 184 (7), 73 (100).

To a solution of [*o*-[1-(trimethylsilyl)-6-heptenyl]benzyl]dimethylamine (3.18 g, 10.5 mmol) in acetonitrile (6 mL) was added methyl iodide (1.3 mL, 21 mmol) at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was gently refluxed for 1 h. Ether was added to the mixture, and the precipitating solid of **10a**-v was collected by filtration (4.23 g, 91%): mp 159.5 °C (recrystallized from ethyl acetate–acetone); IR (KBr disk) 1641, 1246, 842 cm^{-1}; ^1H NMR (CD_3CN, Me_4Si as an external reference) δ –0.36 (s, 9 H), 1.2–2.1 (m, 8 H), 2.30 (br t, 1 H, J = 7 Hz), 2.76 (s, 9 H), 4.18 (dd, AA′ type, 2 H), 4.3–4.7 (m, 2 H), 5.0–5.8 (m, 1 H), 6.6–7.3 (m, 4 H). Anal. Calcd for $C_{20}H_{36}NSiI$: C, 53.92; H, 8.14; N, 3.14. Found: C, 53.89; H, 8.00; N, 3.13.

According to the above procedure, some [*o*-[α-(trimethylsilyl)alkyl]-benzyl]dimethylamines (**9**) and their quaternary ammonium salts (**10**) were prepared.

[*o*-[1-(Trimethylsilyl)ethyl]benzyl]dimethylamine (9a-i): 70% yield; bp 73 °C (0.1 mmHg); IR (neat) 1248, 851, 837 cm^{-1}; ^1H NMR (CCl_4, Me_4Si as an external reference) δ 0.01 (s, 9 H), 1.34 (d, 3 H, J = 7.2 Hz), 2.17 (s, 6 H), 2.75 (q, 1 H, J = 7.2 Hz), 3.26 (dd, AA′ type, 2 H), 6.8–7.1 (m, 4 H); mass spectrum, *m/e* (relative intensity) 235 (12), 190 (24), 175 (41), 162 (28), 117 (27), 73 (100).

[*o*-[1-(Trimethylsilyl)ethyl]benzyl]trimethylammonium Bromide (10a-i): 65% yield; mp 195 °C dec (recrystallized from ethyl acetate–acetone); IR (KBr disk) 1239, 833 cm^{-1}; ^1H NMR (CD_3CN, Me_4Si as an external reference) δ –0.29 (s, 9 H), 1.07 (d, 3 H, J = 6.9 Hz), 2.1–2.5 (m, 1 H), 2.78 (s, 9 H), 4.31 (dd, AA′ type, 2 H), 6.6–7.3 (m, 4 H). Anal. Calcd for $C_{15}H_{28}SiNBr$: C, 54.53; H, 8.54; N, 8.50. Found: C, 54.30; H, 8.66; N, 8.37.

[*o*-[1-(Trimethylsilyl)pentyl]benzyl]dimethylamine (9a-ii): 92% yield; bp 97 °C (0.1 mmHg); IR (neat) 1247, 855, 838, 747 cm^{-1}; ^1H NMR (CCl_4, Me_4Si as an external reference) δ 0.03 (s, 9 H), 0.7–2.0 (m, 9 H), 2.26 (s, 6 H), 2.66 (t, 1 H, J = 6 Hz), 3.32 (s, 2 H), 6.9–7.3 (m, 4 H); mass spectrum, *m/e* (relative intensity) 277 (5), 262 (5), 232 (14), 204 (26), 117 (24), 73 (100).

[*o*-[1-(Trimethylsilyl)pentyl]benzyl]trimethylammonium Iodide (10a-ii): 81% yield; mp 202 °C dec (recrystallized from ethyl acetate–acetone); IR (KBr disk) 1248, 843 cm^{-1}; ^1H NMR (CD_3CN, Me_4Si as an external reference) δ –0.29 (s, 9 H), 0.4–1.9 (m, 9 H), 2.33 (br t, 1 H, J = 6 Hz), 2.81 (s, 9 H), 4.24 (dd, AA′ type, 2 H), 6.7–7.3 (m, 4 H). Anal. Calcd for $C_{18}H_{34}NSiI$: C, 51.54; H, 8.17; N, 3.34. Found: C, 51.54; H, 8.27; N, 3.43.

[*o*-[1-(Trimethylsilyl)heptyl]benzyl]dimethylamine (9a-iii): 81% yield; bp 125 °C (0.2 mmHg); IR (neat) 1247, 856, 837, 746 cm^{-1}; ^1H NMR (CCl_4, Me_4Si as an external reference) δ 0.02 (s, 9 H), 0.7–1.8 (m, 13 H), 2.16 (s, 6 H), 2.57 (t, 1 H, J = 7.4 Hz), 3.24 (s, 2 H), 6.8–7.2 (m, 4 H); mass spectrum, *m/e* (relative intensity) 305 (4), 290 (4), 260 (11), 232 (21), 186 (7), 131 (17), 117 (30), 105 (16), 73 (100).

[*o*-[1-(Trimethylsilyl)heptyl]benzyl]trimethylammonium Iodide (10a-iii): 89% yield; mp 174 °C (recrystallized from ethyl acetate–acetone); IR (KBr disk) 1247, 842 cm^{-1}; ^1H NMR (CD_3CN, Me_4Si as an external reference) δ –0.37 (s, 9 H), 0.4–0.7 (m, 3 H), 0.7–1.8 (m, 10 H), 2.46 (t, 1 H, J = 7 Hz), 2.90 (s, 9 H), 4.26 (dd, AA′ type, 2 H), 6.7–7.5 (m, 4 H). Anal. Calcd for $C_{20}H_{38}NSiI$: C, 53.68; H, 8.56; N, 3.13. Found: C, 53.38; H, 8.71; N, 2.87.

[*o*-[1-(Trimethylsilyl)-2-(carbethoxy)ethyl]benzyl]dimethylamine (9a-iv): 47% yield; bp 92 °C (0.05 mmHg); IR (neat) 1735, 1249, 1174, 838 cm^{-1}; ^1H NMR (CCl_4, 100 MHz, Me_4Si as an external reference) δ 0.00 (s, 9 H), 1.06 (t, 3 H, J = 7 Hz), 2.22 (s, 6 H), 2.62 (br d, 2 H, J = 7 Hz), 3.06 (d, 1 H, J = 12 Hz), 3.07 (t, 1 H, J = 7 Hz), 3.73 (d, 1 H, J = 12 Hz), 3.90 (q, 2 H, J = 7 Hz), 6.8–7.2 (m, 4 H); mass spectrum, *m/e* (relative intensity) 307 (47), 293 (44), 262 (48), 234 (40), 217 (41), 134 (40), 73 (100). Exact mass calcd for $C_{17}H_{29}NO_2Si$: 307.1968. Found: 307.1982.

[*o*-[1-(Trimethylsilyl)-2-(carbethoxy)ethyl]benzyl]trimethylammonium Iodide (10a-iv): 76% yield (very hygroscopic yellow solid); ^1H NMR (CD_3CN, Me_4Si as an external reference) δ –0.32 (s, 9 H), 0.85 (t, 3 H, J = 7 Hz), 2.4–2.8 (m, 3 H), 2.92 (s, 9 H), 3.66 (q, 2 H, J = 7 Hz), 4.37 (br s, 2 H), 6.7–7.4 (m, 4 H).

[α-[*o*-((Trimethylsilyl)methyl)phenyl]ethyl]dimethylamine (14a). A 30% aqueous solution of dimethylamine (16 mL) was added to *o*-tolualdehyde (10.4 g, 87 mmol) over 5 min at 10–15 °C, and stirring was continued for 15 h. The reaction mixture was extracted with ether, and the ether extract was washed with brine, dried over $MgSO_4$, and evaporated. The residue was distilled to give *o*-tolualdehyde *N*-methylimine in 90% yield. To an acetonitrile (20 mL) solution of *o*-tolualdehyde *N*-methylimine (10.35 g, 77.8 mmol) was added methyl iodide (7.3 mL, 117 mmol). The reaction mixture was stirred for 1 h and then refluxed for 1 h. Addition of ether to the reaction mixture precipitated immonium iodide (**12**) as a lemon yellow crystalline compound in 94% yield. To a suspension of **12** (19.6 g, 71 mmol) in 100 mL of THF was added methylmagnesium bromide, which was prepared from 2.6 g of magnesium and methyl bromide in 100 mL of ether, over 2 h in an ice bath. Then the reaction mixture was gently refluxed for 1.5 h, quenched with aqueous ammonium chloride, and extracted with ether. The ether extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was distilled to afford [α-(*o*-methylphenyl)ethyl]dimethylamine (**13**) [bp 80 °C (7 mmHg)] in 73% yield. To a solution of **13** (6.58 g, 40 mmol) in 130 mL of ether was added *sec*-BuLi (1.31 M cyclohexane solution, 80 mmol), and the solution was stirred for 40 h at room temperature. To the resulting red solution containing brown solid was added a mixture of trimethylsilyl chloride (12.8 mL, 100 mmol) and triethylamine (2 mL) at 0 °C during 2 min. After being stirred for 2 h at room temperature, the reaction mixture was quenched with ice cold aqueous sodium carbonate and extracted with ether repeatedly. The combined ether solution was washed with brine and dried over anhydrous $MgSO_4$. Concentration of the ether solution followed by distillation afforded [α-[*o*-((trimethylsilyl)methyl)phenyl]ethyl]dimethylamine (**14a**) [bp 85–88 °C (0.4 mmHg)] in 95% yield, which contained 3–4% of [α-[2-(trimethylsilyl)-6-methylphenyl]ethyl]dimethylamine.

14a: IR (neat) 1246, 847 cm^{-1}; ^1H NMR (CCl_4, Me_4Si as an external reference) δ 0.09 (s, 9 H), 1.26 (d, 3 H, J = 6.2 Hz), 2.13 (s, 6 H + 2 H), 3.33 (q, 1 H, J = 6.2 Hz), 6.6–7.4 (m, 4 H); mass spectrum, *m/e* (relative intensity) 235 (8), 220 (47), 149 (54), 73 (100). Anal. Calcd for $C_{14}H_{25}NSi$: C, 71.42; H, 10.70; N, 5.95. Found: C, 71.21; H, 10.96; N, 6.03.

[α-[*o*-((Trimethylsilyl)methyl)phenyl]ethyl]trimethylammonium Iodide (18a). Compound **14a** was quaternized by methyl iodide in acetonitrile according to the aforementioned procedure.

18a: mp 168–170 °C dec (recrystallized from ethyl acetate–acetone); IR (KBr disk) 1258, 1248, 1243, 857, 840 cm^{-1}; ^1H NMR (CD_3CN, Me_4Si as an external reference) δ –0.21 (s, 9 H), 1.52 and 1.41 (dt, 3 H, J = 3.8 Hz), 2.12 (dd, AA′ type, 2 H), 2.74 (s, 9 H), 4.64 (q, 1 H, J = 6.7 Hz), 6.7–7.3 (m, 4 H). Anal. Calcd for $C_{15}H_{28}NSiI$: C, 47.74; H, 7.48; N, 3.71. Found: C, 47.66; H, 7.42; N, 3.72.

[α-[*o*-[α-(Trimethylsilyl)ethyl]phenyl]ethyl]trimethylammonium Iodide (17a). To a solution of **14a** (0.98 g, 4.17 mmol) in 8 mL of THF was added *n*-BuLi (8.34 mmol) at 0 °C. After being stirred for 5 h at 0 °C, the reaction mixture was cooled in an ice–salt bath, to which methyl iodide (0.52 mL, 8.35 mmol) was added all at once. Stirring was continued for 0.5 h at 0 °C and 1 h at room temperature. The usual workup followed by distillation afforded [α-[*o*-[α-(trimethylsilyl)ethyl]phenyl]-ethyl]dimethylamine (**16a**) [bp 70 °C (0.1 mmHg)] in 78% yield: IR (neat) 1242, 833, 746 cm^{-1}; ^1H NMR (CCl_4 Me_4Si as an external reference) (3:2 diastereoisomeric mixture) δ 0.03 and 0.05 (s, 9 H), 1.1–1.5 (m, 6 H), 2.12 and 2.20 (s, 6 H), 2.2–2.9 (m, 1 H), 3.2–3.7 (two q, 1 H, J = 6.6 Hz), 6.9–7.6 (m, 4 H).

Quaternization of **16a** with methyl iodide afforded **17a** as a hygroscopic white powder (68% yield): mp 174–182 °C dec (recrystallized from ethyl acetate–acetone); IR (KBr disk) 1240, 834 cm^{-1}; ^1H NMR (CD_3CN, Me_4Si as an external reference) (3:2 diastereoisomeric mixture) δ –0.27 and –0.09 (s, 9 H), 0.90 and 1.10 (d, 3 H, J = 7.2 Hz), 1.3–1.6 (m, 3 H), 2.0–2.6 (m, 1 H), 2.67 (br s, 9 H), 4.4–5.1 (m, 1 H), 6.6–7.3 (m, 4 H). Anal. Calcd for $C_{16}H_{30}NSiI$: C, 49.10; H, 7.73; N, 3.58. Found: C, 48.84; H, 7.76; N, 3.63.

(1-(Trimethylsilyl)-1,2,3,4-tetrahydronaphth-4-yl)trimethylammonium Iodide (22). A solution of 1-(dimethylamino)-1,2,3,4-tetrahydronaphthalene (**19**) (5.95 g, 34 mmol) in 90 mL of ether was treated with 2 equiv of *n*-BuLi at room temperature for 22 h. To the resulting orange red solution containing solid was added a mixture of trimethylchlorosilane (9.5 mL, 75 mmol) and triethylamine (1 mL) all at once at 0 °C. After being stirred at room temperature for 2 h, the mixture was quenched with cold aqueous sodium carbonate and extracted with ether. The ether extract was washed with brine and evaporated to afford a mixture of the starting **19**, 1-(trimethylsilyl)-4-(dimethylamino)-1,2,3,4-tetrahydronaphthalene (**20**), and 1-(dimethylamino)-8-(trimethylsilyl)-1,2,3,4-tetrahydronaphthalene (**21**) in a ratio of 1:5.5:3. This mixture was dissolved in 10 M sulfuric acid (50 mL) and acetic acid (70 mL) and heated at 50 °C. Periodically a small aliquot was taken out and analyzed by ^{1}H NMR, which exhibited that the trimethylsilyl group of **21** resonated at 0.36 ppm lower magnetic field relative to the trimethylsilyl group of **20**. After the desilylation of **21** was complete (ca. 10 h was required), the reaction mixture was made alkaline by addition of solid sodium carbonate and extracted with ether. The ether extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvent followed by fractional distillation afforded almost pure **20** as a 7:3 diastereoisomeric mixture [bp 82 °C (0.3 mmHg)] in 41% yield on the basis of the amount of **19** employed: IR (neat) 1243, 850, 834 cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si as an external reference) δ 0.11 and 0.16 (s, 9 H), 1.61–2.61 (m, 5 H), 2.39 (s, 6 H), 3.70 (br t, 1 H, J = 5.5 Hz), 7.04–7.39 (m, 3 H), 7.58–7.90 (m, 1 H); mass spectrum, *m/e* (relative intensity) 247 (21), 232 (22), 218 (16), 203 (26), 202 (84), 174 (14), 130 (39), 129 (65), 128 (93), 74 (21), 73 (100). Anal. Calcd for $C_{15}H_{25}NSi$: C, 72.81; H, 10.18; N, 5.66. Found: C, 73.05; H, 10.36; N, 5.64.

Quaternization of **20** with methyl iodide gave ammonium iodide **22** in 97% yield as a 7:3 diastereoisomeric mixture: mp 137 °C dec; IR (KBr disk) 1483, 1248, 851, 834 cm^{-1}; ^{1}H NMR (CD_3CN, Me_4Si as an external reference) δ 0.18 and 0.34 (s, 9 H), 1.80–3.12 (m, 5 H), 3.36 and 3.46 (two s, 9 H), 5.16–5.52 (m, 1 H), 7.03–7.73 (m, 4 H). Anal. Calcd for $C_{16}H_{28}NSiI$: C, 49.35; H, 7.25; N, 3.60. Found: C, 49.06; H, 7.33; N, 3.58.

2-((Trimethylsilyl)methyl)-3-((dimethylamino)methyl)pyridine (25). To a solution of 2-methyl-3-(chloromethyl)pyridine hydrochloride in 30 mL of acetonitrile, which was prepared from known 2-methyl-3-(hydroxymethyl)pyridine[14] (5.9 g, 48 mmol) and thionyl chloride, was added dimethylamine (25.4 mL, 380 mmol) at once at −10 to −20 °C. After the mixture was kept below 0 °C for 2 h, it was stirred overnight at room temperature. Ether was added to the mixture, and it was extracted repeatedly with dilute hydrochloric acid. The acid extracts were made alkaline with sodium hydroxide and extracted several times with ether. The combined ethereal solution was dried over $MgSO_4$ and evaporated. The residue was distilled to afford 2-methyl-3-((dimethylamino)-methyl)pyridine (**24**) [bp 96 °C (7 mmHg)] in 73% yield based on 2-methyl-3-(hydroxymethyl)pyridine [IR (neat) 1573, 1438, 1012 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 6 H), 2.44 (s, 3 H), 6.89 (dd, 1 H, J = 4.8 and 8.1 Hz), 7.39 (dd, 1 H, J = 8.1 and 1.8 Hz), 8.23 (dd, 1 H)]. To a solution of **24** (5.02 g, 33.4 mmol) in 70 mL of THF was added *n*-BuLi (43.4 mmol) over 1 h at −78 °C, and the solution was stirred for 1 h. To the mixture was added a mixture of trimethylchlorosilane (6.4 mL, 50 mmol) and triethylamine (0.5 mL) at once at −78 °C, and stirring was continued for 3 h at room temperature. The reaction mixture was quenched with ice-cold aqueous sodium carbonate and extracted with ether. The ether extract was washed with brine and dried over $MgSO_4$. Evaporation of the ether solution followed by distillation afforded **25** [bp 58 °C (0.2 mmHg)] in 58% yield: IR (neat) 1246, 842 cm^{-1}; ^{1}H NMR ($CDCl_3$, Me_4Si as an external reference) δ 0.12 (s, 9 H), 2.20 (s, 6 H), 2.44 (s, 2 H), 3.23 (s, 2 H), 6.84 (dd, 1 H, J = 7.7, 4.7 Hz), 7.43 (dd, 1 H, J = 7.7, 1.7 Hz), 8.28 (dd, 1 H); mass spectrum, *m/e* (relative intensity) 222 (29), 207 (76), 179 (78), 176 (49), 164 (84), 162 (88), 150 (36), 149 (100), 106 (41), 73 (97). Anal. Calcd for $C_{12}H_{22}N_2Si$: C, 64.81; H, 9.97; N, 12.60. Found: C, 64.85; H, 10.16; N, 12.58.

[3-(2-(Trimethylsilyl)methyl)picolyl]trimethylammonium Bromide (26). To a solution of **25** (1.11 g, 5 mmol) in 4 mL of acetonitrile was added methyl bromide (1.1 mL, 20 mmol) at 0 °C and the solution was stirred for 2 h at 0 °C. The solvent was removed from the reaction mixture at reduced pressure at 0 °C, and the resulting solid was triturated with ether and filtered. The ammonium bromide **26**, which was obtained in an almost quantitative yield, turned pink even during filtration and produced acetonitrile-insoluble material on standing. However, this compound could be practically used as a precursor of the pyridine analogue of *o*-quinodimethane **47** without any problem.

26: IR (KBr disk) 1439, 1257, 1241, 1132, 846 cm^{-1}; ^{1}H NMR (CD_3CN, Me_4Si as an external reference) δ −0.23 (s, 9 H), 2.29 (s, 2 H), 2.83 (s, 9 H), 4.41 (s, 2 H), 6.67 (dd, 1 H, J = 7.9, 4.8 Hz), 7.58 (dd, 1 H, J = 7.9, 1.8 Hz), 8.15 (dd, 1 H).

2,2-Dimethyl-4-(trimethylsilyl)-1,2,3,4-tetrahydroisoquinolinium Iodide (29). To a solution of 2-methyl-1,2,3,4-tetrahydroisoquinoline (9.85 g, 67 mmol) in 100 mL of THF was added *n*-BuLi (87 mmol) at −75 °C over 1 h; stirring was continued for 1 h at −40 to −50 °C and a mixture of trimethylchlorosilane (12.8 mL, 100 mmol) and triethylamine (1.5 mL) was added at once. The mixture was stirred for 0.5 h at −40 to −50 °C and then at room temperature for 2 h and quenched with ice. The usual workup furnished 2-methyl-4-(trimethylsilyl)-1,2,3,4-tetrahydroisoquinoline (**28**) [bp 68 °C (0.4 mmHg)] in 79% yield: IR (neat) 1246, 843 cm^{-1}; ^{1}H NMR (CCl_4, Me_4Si as an external reference) δ 0.01 (s, 9 H), 2.72 (s, 3 H), 2.05–2.58 (m, 2 H), 2.82 (ddd, 1 H, J = 10.9, 2.8, 1.3 Hz), 3.17 (d, 1 H, J = 15.1 Hz), 3.73 (d, 1 H, J = 15.1 Hz), 6.84 (br s, 4 H).

Quaternization of **28** with methyl iodide afforded the ammonium iodide **29** as a white crystalline solid with a very low solubility in organic solvents: mp 283 °C dec (recrystallized from acetonitrile); IR (KBr disk) 1250, 844 cm^{-1}. Anal. Calcd for $C_{14}H_{24}NSiI$: C, 46.54; H, 6.69; N, 3.88. Found: C, 46.40; H, 6.78; N, 3.75.

Reaction of Ammonium Salt 29 with Fluoride Anion. To a suspension of **29** (219 mg, 0.61 mmol) in 2 mL of acetonitrile and 3 molar equiv of methyl acrylate was added a solution of tetra-*n*-butylammonium fluoride (TBAF) (206 mg, 0.79 mmol) in 3 mL of acetonitrile at room temperature over 10 min. Soon after completion of the addition, the reaction mixture became homogeneous. After being stirred for 2 h, the mixture was concentrated and the residue was triturated with ether. Tetra-*n*-butylammonium iodide was filtered off, and the filtrate was concentrated to give a colorless oil, of which GLC analysis showed a single product, (2-vinylbenzyl)dimethylamine (**30**): IR (neat) 1622, 1020, 908 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.05 (s, 6 H), 3.21 (s, 2 H), 5.06 (dd, 1 H, J = 11.0, 1.8 Hz), 5.40 (dd, 1 H, J = 17.6, 1.8 Hz), 6.78–7.48 (m, 5 H).

Generation and Dimerization of *o*-Quinodimethane 3a. To a solution of **2a**-Br (225 mg, 0.71 mmol) in 1.5 mL of acetonitrile was added a solution of TBAF (205 mg, 0.78 mmol) in 5 mL of acetonitrile over 1 h under nitrogen at room temperature. After the reaction mixture was stirred for 1 h, the mixture was concentrated and the residue was triturated with a 1:1 mixed solvent of ether and hexane. The precipitated insoluble materials were filtered off, and the filtrate was concentrated. The residue was subjected to preparative TLC on silica gel with hexane solvent (R_f 0.24) to afford 47 mg (64%) of spirodimer **31**, which was identified by comparison of its ^{1}H NMR and IR spectra with those reported:[3] mass spectrum, *m/e* (relative intensity) 208 (31), 195 (16), 194 (100), 193 (74), 179 (45), 178 (28), 117 (14), 116 (24), 115 (12), 104 (15).

Cycloaddition of *o*-Quinodimethane 3a with Dienophiles. Cycloaddition of *o*-quinodimethane **3a** with dienophiles is exemplified by synthesis of *cis*-2,3-dicarbethoxy-1,2,3,4-tetrahydronaphthalene (**32a**). In the sample procedure, methylene chloride was used as a solvent. But in general, acetonitrile may be more preferable, because most ammonium salts can be dissolved easily in it.

***cis*-2,3-Dicarbethoxy-1,2,3,4-tetrahydronaphthalene (32a).** To a solution of **2a**-Cl (68 mg, 0.25 mmol) and diethyl maleate (129 mg, 0.77 mmol) in 1.5 mL of methylene chloride was added a solution of TBAF (85 mg, 0.33 mmol) in 3.5 mL of methylene chloride over 40 min at room temperature. After being stirred for 1 h, the reaction mixture was diluted with ether and insoluble materials were filtered off. The filtrate was concentrated, and the residue was subjected to preparative TLC on silica gel to afford 32 mg of **32a** (46%) [TLC R_f 0.22 (2:1 $CHCl_3$–C_6H_6)] and 10 mg of spirodimer **31** (38%) (R_f 0.83). Even when the above reaction was carried out in the presence of 10 molar equiv of maleate, the yield of **32a** was not improved (47%): IR (neat) 1728, 1182 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 Hz) δ 1.28 (t, 6 H, J = 7 Hz), 3.01 (m, 2 H), 3.17 (br d, 4 H, J = 3.5 Hz), 4.21 (q, 4 H, J = 7 Hz), 7.05 (s, 4 H); mass spectrum, *m/e* (relative intensity) 276 (20), 231 (33), 202 (99), 130 (25), 129 (100), 128 (43). Exact mass calcd for $C_{16}H_{20}O_4$: 276.1362. Found: 276.1347.

According to the procedure mentioned above, the following cycloadducts (**32b–d** and **34a**) were prepared.

2- and 3-Carbomethoxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (32b): TLC R_f 0.36 (silica gel, 1:2 C_6H_6–$CHCl_3$); IR (neat) 1744, 1611, 1267, 1218, 1138, 832, 804 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.5–2.2 (m, 5 H), 2.3–3.1 (m, 5 H), 3.67 (s, 3 H), 3.72 (s, 3 H), 6.46–7.55 (m, 3 H); mass spectrum, *m/e* (relative intensity) 220 (36), 161 (51), 160 (100), 159 (36), 145 (28), 91 (30). Exact mass calcd for $C_{13}H_{16}O_3$: 220.1099. Found: 220.1106.

Compound **32b**, which consists of two regioisomers, showed one spot on TLC and one set of signals in ^{1}H NMR (60 MHz) spectrum. But the ^{1}H NMR spectrum of **32b** in the presence of $Eu(fod)_3$ exhibited splitting of singlets at δ 3.67 and 3.72 into two singlets with a 3:2 peak area, respectively.

2- and 3-Carbomethoxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (32c): TLC R_f 0.39 (silica gel, 1:2 C_6H_6–$CHCl_3$); IR (neat) 1732, 1582, 1463, 1163, 1092, 758 cm^{-1}; ^1H NMR (CCl_4) δ 1.38–3.00 (m, 7 H), 3.46 (s, 3 H), 3.54 (s, 3 H), 6.22–6.51 (m, 2 H), 6.78 (t, 1 H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, values in parentheses may be assigned to the minor regioisomeric cycloadduct) δ (22.60), (24.94), 25.48, 25.66, 28.76, (31.82), 39.77, 51.68, 55.19, 107.11, 121.09, 121.27, (123.92), (124.68), 126.26, (136.28), 137.09, 157.41, (176.02), 176.15; mass spectrum, m/e (relative intensity) 220 (35), 161 (39), 160 (100), 159 (29), 145 (21), 129 (20), 128 (10). Exact mass calcd for $C_{13}H_{16}O_3$: 220.1099. Found: 220.1081.

Compound **32c**, which consists of two regioisomers, showed one spot on TLC and one set of signals in the ^1H NMR (60 MHz) spectrum. A 2:1 ratio of regioisomers was estimated by the relative intensity of carbonyl carbon at δ 176.02 and 176.15 in the ^{13}C NMR spectrum.

2-Cyano-1,2,3,4-tetrahydronaphthalene (32d):[1f] TLC R_f 0.48 (silica gel, 1:1 C_6H_6–$CHCl_3$); IR (neat) 2234, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.9–2.3 (m, 2 H), 2.7–3.2 (m, 5 H), 7.11 (s, 4 H); mass spectrum, m/e (relative intensity) 155 (47), 130 (45), 116 (56), 104 (100), 78 (21).

2,3-Dicarbethoxy-1,2-dihydronaphthalene (34a):[1f] TLC R_f 0.42 (silica gel, $CHCl_3$); IR (neat) 1733, 1710, 1631, 1277, 1185 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.14 (t, 3 H, J = 7 Hz), 1.34 (t, 3 H, J = 3 Hz), 3.10 (dd, 1 H, J = 16.8, 7.8 Hz), 3.35 (dd, 1 H, J = 16.8, 4.2 Hz), 3.86 (dd, 1 H, J = 7.8, 4.2 Hz), 4.06 (q, 2 H, J = 7 Hz), 4.30 (q, 2 H, J = 7 Hz), 7.24 (br s, 4 H), 7.64 (s, 1 H); mass spectrum, m/e (relative intensity) 274 (4), 201 (46), 200 (30), 173 (24), 155 (48), 129 (100), 128 (46), 127 (36). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.13; H, 6.70.

Cycloadditions of α-Substituted-*o*-quinodimethanes (35) with Dienophiles. A general procedure for the cycloadditions of α-substituted-*o*-quinodimethanes with dienophiles is given by the preparation of 1-*n*-butyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene (**36b**).

To a solution of [*o*-[1-(trimethylsilyl)pentyl]benzyl]trimethylammonium iodide (**10a**-ii) (915 mg, 2.1 mmol) and methyl acrylate (550 mg, 6.3 mmol) in 8 mL of acetonitrile was added a solution of TBAF (688 mg, 2.6 mmol) in 16 mL of acetonitrile at room temperature over 1 h. After being stirred for 1 h, the acetonitrile solution was evaporated, and ether was added to the residue. Insoluble materials were filtered off, and the filtrate was concentrated. The residue was subjected to preparative TLC on silica gel with benzene solvent (R_f 0.64) to afford the cycloadduct, which consisted of three isomers. A major isomer was *cis*-1-*n*-butyl-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene (**36b**): IR (neat) 1733, 1175, 758 cm^{-1}; ^1H NMR (CCl_4, 100 MHz) δ 0.8–1.2 (m, 3 H), 1.2–1.8 (m, 6 H), 2.12 (quasi q, 2 H, J = 8 Hz), 2.6–3.3 (m, 4 H), 3.77 (s, 3 H), 7.10 (s, 4 H); mass spectrum, m/e (relative intensity) 246 (8), 190 (10), 187 (12), 130 (23), 129 (100), 128 (16). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.80; H, 9.19.

According to the procedure mentioned above, some cycloadducts of α-substituted-*o*-quinodimethanes **35** were prepared.

1-Methyl-2-cyano-1,2,3,4-tetrahydronaphthalene (36a): TLC R_f 0.60 (silica gel, 1:3 $CHCl_3$–C_6H_6); IR (neat) 2221, 1492, 1444, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (br d, 3 H, J = 6.5 Hz), 1.8–2.3 (m, 2 H), 2.6–3.3 (m, 4 H), 7.05 (br s, 4 H); mass spectrum, m/e (relative intensity) 171 (57), 156 (49), 129 (57), 118 (100), 117 (60). Exact mass calcd for $C_{12}H_{13}N$: 171.1048. Found: 171.1031.

1-*n*-Hexyl-2-cyano-1,2,3,4-tetrahydronaphthalene (36c): TLC R_f 0.54 (silica gel, 1:1 C_6H_{13}–C_6H_6); IR (neat) 2226, 1492, 1468, 1453, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.6–1.0 (m, 3 H), 1.0–2.3 (m, 12 H), 2.6–3.2 (m, 4 H), 7.00 (s, 4 H); mass spectrum, m/e (relative intensity) 241 (11), 156 (100), 131 (27), 130 (62), 129 (72), 115 (32). Exact mass calcd for $C_{17}H_{23}N$: 241.1830. Found: 241.1830.

1-(Carbethoxymethyl)-2-carbomethoxy-1,2,3,4-tetrahydronaphthalene (36d): TLC R_f 0.25 (silica gel, C_6H_6); IR (neat) 1731, 1172, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.21 (t, 3 H, J = 7 Hz), 1.9–2.2 (m, 2 H), 2.3–2.7 (m, 2 H), 2.7–3.1 (m, 3 H), 3.68 (s, 3 H), 3.6–3.9 (m, 1 H), 4.09 (q, 2 H, J = 7 Hz), 7.07 (br s, 4 H). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29. Found: C, 69.66; H, 7.58.

GLC–MS analysis revealed that compound **36d** consisted of three isomers in a ratio of 5:80:15, all of which showed the same parent mass peak (M^+ 276) and similar mass fragmentation patterns. The mass fragmentation of the major isomer is as follows: m/e (relative intensity) 276 (14), 216 (51), 202 (35), 188 (23), 143 (61), 129 (100), 128 (60).

Ethyl *o*-Methylcinnamate (38): IR (neat) 1711, 1634, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.32 (t, 3 H, J = 6.9 Hz), 2.42 (s, 3 H), 4.26 (q, 2 H, J = 6.9 Hz), 6.32 (d, 1 H, J = 15.9 Hz), 6.9–7.4 (m, 3 H), 7.4–7.6 (m, 1 H), 7.95 (d, 1 H, 15.9 Hz); mass spectrum, m/e (relative intensity) 190 (33), 145 (100), 144 (27), 117 (44), 116 (51), 115 (38).

1-(Carbethoxymethyl)-2-cyano-1,2,3,4-tetrahydronaphthalene (36e): TLC R_f 0.27 (silica gel, 1:1 $CHCl_3$–C_6H_6); IR (neat) 2224, 1732, 1176 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz), 1.7–2.3 (m, 2 H), 2.3–3.8 (m, 6 H), 4.11 (q, 2 H, J = 7 Hz), 7.07 (br s, 4 H); mass spectrum, m/e (relative intensity) 243 (17), 216 (100), 169 (37), 156 (36), 142 (58), 129 (43), 128 (100), 88 (56). Exact mass calcd for $C_{15}H_{17}NO_2$: 243.1259. Found: 243.1250.

1-Methyl-2,3-dicarbomethoxy-1,2-dihydronaphthalene (37a): TLC R_f 0.25 (silica gel, $CHCl_3$); IR (neat) 1715, 1637, 1574, 1195, 782 cm^{-1}; ^1H NMR (CCl_4) δ 1.13 and 1.38 (two d, 3 H, J = 7.2 Hz), 2.9–3.9 (m, 2 H), 3.46 (s, 3 H), 3.67 and 3.70 (two s, 3 H), 7.07 (br s, 4 H), 7.40 and 7.45 (two s, 1 H); mass spectrum, m/e (relative intensity) 260 (97), 202 (33), 201 (100), 200 (53), 169 (78), 157 (96), 142 (97). Exact mass calcd for $C_{15}H_{16}O_4$: 260.1048. Found: 260.1033 and 260.1058.

Oxidation of 1-Methyl-2-cyano-1,2,3,4-tetrahydronaphthalene (36a) into 1-Methyl-2-cyanonaphthalene. A mixture of **36a** (187 mg) and 5% palladium charcoal (600 mg) in tetralin (6 mL) was refluxed for 26 h. Palladium charcoal was filtered off, and the tetralin solution was passed through a short silica gel column first with hexane as an eluting solvent to separate tetralin and then with chloroform. The chloroform solution was evaporated, and the residue was subjected to preparative TLC on silica gel with *n*-hexane–benzene (1:3) (R_f 0.34) to afford 48 mg of 1-methyl-2-cyanonaphthalene as a yellow solid: mp 65.5–66.0 °C (recrystallized from EtOH) (lit.[27] 64–66 °C); IR (neat) 2212, 822, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.77 (s, 3 H), 7.2–8.1 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 17.44, 109.68, 118.94, 124.76, 126.31, 127.18, 127.33, 128.41, 128.62, 131.56, 134.52, 141.24. Anal. Calcd for $C_{12}H_{13}N$: C, 86.26; H, 5.43; N, 8.38. Found: C, 86.46; H, 5.51; N, 8.43.

Generation and Cycloaddition of α,α'-Dimethyl-*o*-quinodimethane 39a. Preparation of ($1\beta,2\beta,3\alpha,4\beta$)-2,3-dicarbomethoxy-1,4-dimethyl-1,2,3,4-tetrahydronaphthalene (40). To a solution of **17a** (166 mg, 0.42 mmol) and dimethyl fumarate (93 mg, 0.64 mmol) in 5 mL of acetonitrile was added a solution of TBAF (150 mg, 0.57 mmol) in 5 mL of acetonitrile at 50 °C over 30 min. After being stirred for 30 min at 50 °C, the acetonitrile solution was evaporated and ether was added. Insoluble materials were filtered off, and the filtrate was evaporated. The residue was subjected to preparative TLC (silica gel) with an 8:1 hexane and acetone mixed solvent to afford **40** almost quantitatively as a white crystalline solid: mp 77–79 °C (recrystallized from hexane); IR (neat) 1736, 1263, 1195, 1168, 759 cm^{-1}; ^1H NMR (CCl_4, 100 MHz) δ 1.10 (d, 3 H, $J_{H\text{-}H_{eq}}$ = 6.9 Hz), 1.42 (d, 3 H, $J_{H\text{-}H_{ax}}$ = 6.5 Hz), 2.72 (dd, 1 H, $J_{H_{ax}\text{-}H_{ax}}$ = 10.0 Hz, $J_{H_{ax}\text{-}H_{ax}}$ = 11.7 Hz), 2.95 (qd, 1 H, $J_{H\text{-}H_{ax}}$ = 6.5 Hz, $J_{H_{ax}\text{-}H_{ax}}$ = 10.0 Hz), 3.12 (dd, 1 H, $J_{H_{ax}\text{-}H_{ax}}$ = 11.7 Hz, $J_{H_{ax}\text{-}H_{eq}}$ = 4.8 Hz), 3.29 (qd, 1 H, $J_{H\text{-}H_{eq}}$ = 6.9 Hz, $J_{H_{eq}\text{-}H_{ax}}$ = 4.8 Hz), 3.67 (s, 3 H), 3.69 (s, 3 H), 7.9–8.3 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.91, 21.03, 35.32, 36.31, 44.99, 46.65, 51.86 (2C), 126.26, 126.80, 127.33, 128.59, 138.30, 140.01, 173.95, 176.19; mass spectrum, m/e (relative intensity) 276 (4), 216 (62), 157 (100), 143 (40), 142 (54), 141 (33), 128 (37), 115 (26). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.85; H, 7.21.

Cycloaddition of α,α'-Dimethyl-*o*-quinodimethane 39a with Dimethyl Maleate. Reaction of **17a** with dimethyl maleate was similarly carried out in the presence of TBAF at 50 °C to afford **42** in a quantitative yield, which showed one spot on silica gel TLC (R_f 0.47, $CHCl_3$) but consisted of two stereoisomers in a ratio of 5:2 as discussed in the text: IR (neat) 1738, 1594, 1196, 759 cm^{-1}; ^1H NMR (CCl_4) δ 1.37 (d, 6 H, J = 6 Hz), 2.8–3.7 (m, 4 H), 3.50 and 3.55 (2 s, 6 H), 6.93 and 6.99 (two br s, 4 H); mass spectrum, m/e (relative intensity) 276 (4), 216 (31), 157 (100), 156 (35), 143 (46), 142 (64), 141 (43), 128 (44), 105 (34). Exact mass calcd for $C_{16}H_{20}O_4$: 276.1362. Found (2 peaks): 276.1336 and 276.1367.

Generation of 2,3-Dihydronaphthalene (43) and Its Cycloaddition with Dienophiles. A general procedure is given by the preparation of 2-carbomethoxy-5,6-benzobicyclo[2.2.2]octane (**44a**).

To a solution of **22** (250 mg, 0.64 mmol) and methyl acrylate (0.58 mL, 6.4 mmol) in 3 mL of acetonitrile was added a suspension of cesium fluoride (200 mg, 1.3 mmol) in 4 mL of acetonitrile all at once at room temperature. After being stirred overnight, the reaction mixture was concentrated in vacuo and ether was added. The ether solution was filtered to remove insoluble materials, and the filtrate was evaporated. The residue was subjected to preparative TLC on silica gel with benzene to afford 83 mg (60%) of **44a**-endo (R_f 0.37), 6 mg (4%) of **44a**-exo (R_f 0.50), and 30 mg (36%) of **46** (R_f 0.91).

44a-endo: IR (neat) 1732, 1198, 1171, 746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09–1.77 (m, 6 H), 2.59 (ddd, 1 H, C*H*CO_2Me, $J_{cis} \simeq J_{trans}$ = 7.4 Hz, $J_{bridgehead}$ = 2.3 Hz), 2.83 (br s, 1 H), 3.17 (br s, 1 H), 3.24 (s, 3 H), 6.89 (s, 4 H); mass spectrum, m/e (relative intensity) 216 (25), 149 (86), 130 (100), 129 (94), 128 (82), 127 (30), 115 (40), 104 (31), 94 (30), 76 (27). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.48; H, 7.27.

44a-exo: IR (neat) 1735, 1197, 1180, 758 cm^{-1}; ^1H NMR (CCl_4) δ 3.52 (s, 3 H, CO_2Me, 3.30 for **44**-endo); mass spectrum, m/e (relative

(27) (a) Bergman, E. D.; Blum, J. *J. Org. Chem.* **1961**, *26*, 3214. (b) Raaen, V. F.; Eastham, J. F. *J. Am. Chem. Soc.* **1960**, *82*, 1349.

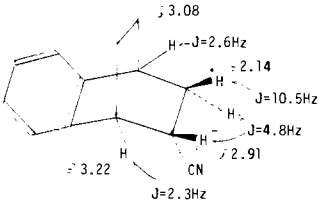
intensity) 216 (17), 149 (18), 130 (100), 129 (80), 128 (43), 115 (21), 87 (22), 74 (29).

46: IR (neat) 1487, 1448, 788, 748 cm^{-1}; ^1H NMR (CCl_4) δ 1.32–2.04 (m, 4 H), 2.10–2.40 (m, 2 H), 2.52–2.88 (m, 2 H), 2.88–3.52 (m, 2 H), 5.76 (dt, 1 H, J = 4.1 and 9.5 Hz), 6.33 (dt, 1 H, J = 1.8, 9.5 Hz), 6.56–7.12 (m, 8 H); mass spectrum, m/e (relative intensity) 260 (3), 132 (35), 129 (74), 128 (100). Exact mass calcd for $C_{20}H_{20}$: 260.1565. Found: 260.1565.

According to the procedure mentioned above, some cycloadducts of **43** with dienophiles were prepared.

2-Cyano-5,6-benzobicyclo[2.2.2]octane (44b). **44b**-endo and **44b**-exo were separated and isolated by preparative TLC on silica gel with benzene solvent.

44b-endo: TLC R_f 0.30 (C_6H_6); IR (KBr disk) 2240, 1482, 1461, 1142, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.16–1.92 (m, 5 H), 2.14 (ddd, 1 H), 2.91 (ddd, 1 H), 3.08 (m, 1 H), 3.22 (m, 1 H), 7.06–7.38 (m, 4 H) (the NMR assignment shown is based on coupling constants obtained by decoupling techniques); mass spectrum, m/e (relative intensity) 183 (32), 130 (100), 129 (97), 128 (60), 127 (36), 115 (67). Anal. Calcd for $C_{13}H_{13}N$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.39; H, 7.02; N, 7.50.



44b-exo: TLC R_f 0.43 (C_6H_6); IR (KBr disk) 2238, 1482, 1140, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.22–2.17 (m, 5 H), 2.31 (ddd, 1 H, J = 10.3, 8.1, 2.3 Hz), 2.57 (m, 1 H), 3.09 (m, 1 H), 3.26 (m, 1 H), 7.08–7.32 (m, 4 H); mass spectrum, m/e (relative intensity) 183 (45), 130 (100), 129 (99), 128 (76), 127 (52), 115 (74).

2,3-Dicarbomethoxy-5,6-benzobicyclo[2.2.2]oct-2-ene (44c): TLC R_f 0.64 (alumina, C_6H_6); IR (neat) 1720, 1635, 1262–1292, 1069, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29–1.84 (m, 4 H), 3.61 (s, 6 H), 4.22 (br s, 2 H), 6.85–7.24 (m, 4 H); mass spectrum, m/e 272, 245, 214, 213. Exact mass calcd for $C_{16}H_{16}O_4$: 272.1049. Found: 272.1059.

***trans*-2,3-Dicarbomethoxy-5,6-benzobicyclo[2.2.2]octane (44d)**:[17] TLC R_f 0.34 (silica gel, 6:1 hexane–acetone); mp 73.5 °C (recrystallized from hexane); IR (KBr disk) 1724, 1202 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87–2.00 (m, 4 H), 2.81–3.06 (m, 1 H), 3.25–3.48 (m, 3 H), 3.40 (s, 3 H), 3.62 (s, 3 H), 7.06 (s, 4 H); mass spectrum, m/e (relative intensity) 274 (10), 145 (42), 130 (54), 114 (100). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.32; H, 6.73.

Generation of Pyridine Analogue of *o*-Quinodimethane 47 and Its Cycloadditions with Methyl Acrylate. To a suspension of cesium fluoride (400 mg, 2.6 mmol) in 6 mL of acetonitrile containing 0.58 mL (6.4 mmol) of methyl acrylate was added a solution of **26** (405 mg, 1.28 mmol) at 55 °C over 30 min. The mixture was dark violet at the beginning and then turned to pale brown within 1 h. After heating at 55 °C for additional 2 h, the mixture was evaporated and ether was added. The ether solution was filtered to remove inorganic materials, and the filtrate was evaporated. The residue was subjected to preparative TLC on silica gel with ethyl acetate–acetone (1:1) to give 86 mg of **48a**-i (R_f 0.49) and 97 mg of **48a**-ii (R_f 0.61). Two regioisomers **48a**-i and **48a**-ii were very difficult to completely be separated from one another but were characterized spectroscopically. An addition of $Eu(fod)_3$ to an NMR sample of each regioisomer induced significant low-field shift of the methylene proton at C-8, which was superimposed on the multiplet at δ 1.5–3.0; i.e., cycloadduct **48a**-i showed a very broad multiplet while **48a**-ii showed two broad doublets (J = 5.3 and 9.8 Hz). On the basis of this finding, two regioisomers **48a**-i and **48a**-ii were assigned to 6-carbomethoxy-5,6,7,8-tetrahydroquinoline and 7-carbomethoxy-5,6,7,8-tetrahydroquinoline, respectively. A mass spectrum and an exact mass value were measured for the regioisomeric mixture. IR spectra of these regioisomers are almost identical: IR (neat) 1736, 1572, 1164, 785 cm^{-1}; mass spectrum, m/e (relative intensity) 191 (25), 132 (100), 131 (62), 130 (91), 117 (38). Exact mass calcd for $C_{11}H_{13}NO_2$: 191.0946. Found: 191.0942.

48a-i: ^1H NMR δ 1.6–3.0 (m, 7 H), 3.60 (s, 3 H), 6.90 (dd, 1 H, J = 8.1, 4.8 Hz), 7.28 (br d, 1 H, J = 8.1 Hz), 8.26 (dd, 1 H, J = 4.8, 1.8 Hz).

48a-ii: ^1H NMR δ 1.5–3.1 (m, 7 H), 3.60 (m, 3 H), 6.92 (dd, 1 H, J = 8.0, 4.8 Hz), 7.28 (br d, 1 H, J = 8.0 Hz), 8.30 (dd, 1 H, J = 4.8, 1.9 Hz).

Similarly, the cycloaddition of **26** with acrylonitrile was performed, producing 6-cyano-5,6,7,8-tetrahydroquinoline (**48b**-i) and 7-cyano-5,6,7,8-tetrahydroquinoline (**48b**-ii), which were assigned by NMR spectra in the presence of $Eu(fod)_3$.

48b-i: TLC R_f 0.52 (silica gel, acetone); IR (neat) 2235, 1566, 1455, 1430, 1110, 795 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0–2.4 (m, 2 H), 2.8–3.3 (m, 5 H), 7.10 (dd, 1 H, J = 8.0, 5.0 Hz), 7.44 (dd, 1 H, J = 8.0, 1.8 Hz), 8.45 (br d, 1 H, J = 5.0 Hz).

48-ii: TLC R_f 0.70 (silica gel, acetone); IR (neat) 2240, 1574, 1447, 1435, 1116, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8–2.3 (br t, 2 H, J = 6 Hz), 2.7–3.3 (m, 5 H), 7.10 (dd, 1 H, J = 8.0, 4.9 Hz), 7.45 (dd, 1 H, J = 8.0, 1.4 Hz), 8.43 (br d, 1 H, J = 4.9 Hz).

A mass spectrum and an exact mass value were obtained for the regioisomeric mixture (**48b**): mass spectrum, m/e (relative intensity) 158 (44), 157 (24), 149 (100), 130 (27), 118 (31), 105 (47), 104 (61), 94 (24), 76 (31). Exact mass calcd for $C_{10}H_{10}N_2$: 158.0844. Found: 158.0821.

Preparation of [2-(1-(Trimethylsilyl)-5-hexenyl)picol-3-yl]trimethylammonium Bromide (26a). The ammonium bromide (**26a**) was prepared from **25** via alkylation and subsequent quaternization as follows. To a solution of **25** (640 mg, 2.88 mmol) in 6 mL of THF was added *n*-BuLi (3.17 mmol) at −78 °C over 10 min. After the solution was stirred for 30 min at −78 °C, 4-pentenyl iodide (645 mg, 3.29 mmol) was added to the reaction mixture at once. The reaction mixture was stirred at −78 °C for 30 min and at room temperature overnight. The usual workup of the reaction mixture afforded 702 mg (84%) of 2-(1-(trimethylsilyl)-5-hexenyl)-3-((dimethylamino)methyl)pyridine: bp 112 °C (0.2 mmHg); IR (neat) 1640, 1586, 1568, 1431, 1246, 1023, 838 cm^{-1}; ^1H NMR (CCl_4, Me_4Si as an external reference) δ −0.04 (s, 9 H), 0.9–2.2 (m, 6 H), 2.10 (s, 6 H), 2.45 (dt, 1 H, J = 9.9, 2.4 Hz), 3.13 (s, 2 H), 4.50–4.93 (m, 2 H), 5.21–5.91 (m, 1 H), 6.69 (dd, 1 H, J = 7.7, 4.8 Hz), 7.25 (dd, 1 H, J = 7.7, 1.8 Hz), 8.23 (dd, 1 H, J = 4.8, 1.8 Hz); mass spectrum, m/e (relative intensity) 290 (3), 191 (44), 190 (100), 172 (26), 132 (26), 130 (28), 118 (41), 73 (69). Anal. Calcd for $C_{17}H_{30}N_2Si$: C, 70.28; H, 10.41; N, 9.64. Found: C, 70.00; H, 10.45; N, 9.51.

The amine thus obtained was quaternized with methyl bromide according to the procedure described for the preparation of **26** to furnish **26a** in 98% yield. The ammonium bromide **26a** was slightly unstable and on standing turned to a light pink solid, which was difficultly dissolved in acetonitrile. However, **26a** was spectroscopically characterized and practically used for further reactions without any problems: IR (KBr disk) 1639, 1584, 1562, 1434, 1245, 837 cm^{-1}; ^1H NMR (CD_3CN, Me_4Si as an external reference) δ −0.02 (s, 9 H), 0.8–2.2 (m, 6 H), 2.6–2.9 (m, 1 H), 2.96 (s, 9 H), 4.44–4.81 (m, 2 H + 2 H), 5.14–5.83 (m, 1 H), 6.85 (dd, 1 H, J = 8.1, 4.9 Hz), 7.72 (dd, 1 H, J = 8.1, 1.9 Hz), 8.31 (dd, 1 H, J = 4.9, 1.9 Hz).

Intramolecular Cyclization of 26a via Pyridine Analogue of *o*-Quinodimethane. A solution of **26a** (250 mg, 0.65 mmol) in 5 mL of acetonitrile was added to a suspension of cesium fluoride (224 mg, 1.48 mmol) in 5 mL of acetonitrile at reflux over 30 min, and refluxing was continued for 3 h. The reaction mixture was evaporated, and ether was added. The ether solution was filtered off, and the filtrate was concentrated. The residue was subjected to preparative TLC on silica gel with ethyl acetate to give 47 mg (42%) of *trans*-tricycle (**49**trans) (R_f 0.48) and 52 mg (46%) of *cis*-tricycle (**49**cis) (R_f 0.62).

49trans: IR (neat) 1591, 1566, 1442, 1428, 1111, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–2.7 (m, 11 H), 3.06 (br q, 1 H, J = 8.0 Hz), 6.80 (dd, 1 H, J = 8.0, 4.9 Hz), 7.18 (br d, 1 H, J = 8.0 Hz), 8.25 (dd, 1 H, J = 4.9, 1.7 Hz); mass spectrum, m/e (relative intensity) 173 (46), 172 (51), 145 (86), 144 (84), 132 (100), 130 (91), 117 (42), 77 (54). Exact mass calcd for $C_{12}H_{15}N$: 173.1204. Found: 173.1215.

49cis: IR (neat) 1590, 1562, 1442, 1426, 1109, 779 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–4.0 (m, 12 H), 6.88 (dd, 1 H, J = 8.4, 4.9 Hz), 7.26 (br d, 1 H, J = 8.4 Hz), 8.26 (br d, 1 H, J = 4.9 Hz); mass spectrum, m/e (relative intensity) 173 (39), 172 (38), 145 (100), 144 (55), 130 (50), 117 (23). Exact mass calcd for $C_{12}H_{15}N$: 173.1204. Found: 173.1210.

Preparation of *trans*-2-(β-Bromoethyl)-2-methyl-3-vinylcyclopentanone 2,2-Dimethyl-1,3-propanediol Ketal (56). To a slightly brownish slurry of vinylmagnesium bromide (1.5 M THF solution, 119 mmol) in dimethyl sulfide (16 mL) and THF (100 mL) was added cuprous iodide (650 mg, 3.2 mol % to 2-methyl-2-cyclopentenone) at −78 °C and then 2-methyl-2-cyclopentenone (10.4 g, 108 mmol) in 20 mL of THF over 40 min at −50 to −60 °C to give a dark brown thick solution. After being stirred at the same temperature for 50 min, the reaction mixture was cooled down to −78 °C, 47 mL (270 mmol) of HMPA was added slowly, and then 44 mL (270 mmol) of *tert*-butyl bromoacetate was added. The reaction mixture was warmed very slowly to 0 °C over 6 h, and stirring was continued for 18 h at room temperature, resulting a brown solution with a white precipitate. The reaction mixture was quenched with an aqueous solution of ammonium chloride and extracted with ether three times, and the combined extract was washed with water twice and brine, dried over $MgSO_4$, and evaporated. Fractional distillation of the residue

afforded 22.2 g (114 mmol) of *tert*-butyl bromoacetate and 20.3 g (78%) of **53** with 96% stereoselectivity [**53**: bp 80–82 °C (0.4 mmHg); IR (neat) 3060, 1730, 1639, 1151, 919 cm^{-1}; ^1H NMR (CCl_4) δ 0.77 (s, 3 H), 1.40 (s, 9 H), 1.6–2.5 (m, 6 H), 2.7–3.2 (m, 1 H), 4.9–5.2 (m, 2 H), 5.5–6.1 (m, 1 H)]. The stereoselectivity was calculated by the relative peak area of a singlet at δ 0.77 with that of a small singlet at δ 1.07, which was tentatively assigned to the 2-methyl protons of the cis isomer.

Methanol (80 mL), which was saturated with dry HCl, was added to 18 g of **53** at 0 °C, and stirring was continued at 0 °C for 2 h. The reaction mixture was quenched with ice and extracted with ether several times. The combined extract was washed with aqueous sodium bicarbonate and brine, dried over $MgSO_4$, and evaporated. The residue was distilled to afford 14.8 g (92%) of **54** with 96% stereoisomeric purity [bp 72–74 °C (0.4 mmHg)]; [IR (neat) 3060, 1740, 1638, 1200, 1138, 918 cm^{-1}; ^1H NMR (CCl_4) δ 0.83 (s, 3 H), 1.4–3.1 (m, 7 H), 3.52 (s, 3 H), 4.8–5.2 (m, 2 H), 5.4–6.0 (m, 1 H) (a small singlet at δ 1.10 was tentatively assigned to the 2-methyl protons of the cis isomer); mass spectrum, *m/e* (relative intensity) 196 (12), 181 (16), 165 (14), 124 (16), 123 (100), 122 (19)].

A mixture of **54** (16.6 g, 85 mmol), 2,2-dimethyl-1,3-propanediol (13.3 g, 1.5 molar equiv), trimethyl orthoformate (13.9 mL, 1.5 molar equiv), and 160 mg of *p*-toluenesulfonic acid monohydrate was stirred at room temperature. After being stirred for 12 h, the reaction mixture was quenched with aqueous sodium bicarbonate and extracted with hexane. Distillation of the hexane extract afforded 22.1 g (89%) of *trans*-2-(carbomethoxymethyl)-2-methyl-3-vinylcyclopentanone 2,2-dimethyl-1,3-propanediol ketal: bp 112 °C (0.4 mmHg); IR (neat) 3070, 1732, 1636, 913 cm^{-1}; ^1H NMR (CCl_4) δ 0.70 (s, 3 H), 0.88 (s, 3 H), 1.16 (s, 3 H), 1.4–2.6 (m, 4 H), 2.32 (d, 2 H, J = 3.3 Hz), 2.87 (br q, 1 H, J = 7.5 Hz), 3.1–3.7 (m, 4 H), 3.47 (s, 3 H), 4.7–5.1 (m, 2 H), 5.3–5.9 (m, 1 H).

To a suspension of $LiAlH_4$ (1.53 g, 2 molar equiv) in 125 mL of ether was added a solution of the ketal ester (11.32 g, 40 mmol) prepared above in 25 mL of ether over 1 h at 0 °C. The reaction mixture was stirred for 3 h at 0 °C, and 1.53 mL of H_2O, 1.53 mL of 15% aqueous sodium hydroxide, and 5 mL of H_2O were successively added to hydrolyze the aluminum complex. The granular white solid was filtered off, and the filtrate was washed with aqueous ammonium chloride and brine, dried over $MgSO_4$, and evaporated to afford **55**: IR (KBr disk) 3498, 3100, 1644, 918 cm^{-1}; ^1H NMR (CD_3CN, Me_4Si as an external reference) δ 0.47 (s, 3 H), 0.58 (s, 3 H), 0.94 (s, 3 H), 1.0–2.6 (m, 8 H), 2.9–3.6 (m, 6 H), 4.4–4.8 (m, 2 H), 5.1–5.8 (m, 1 H).

The ketal alcohol **55** was dissolved in 30 mL of pyridine; 8.4 g (1.1 molar equiv) of *p*-tosyl chloride was added portionwise at 0 °C. After being stirred for 5 h at 0 °C, the reaction mixture was diluted with pyridine and added to 1 L of ice water with vigorous stirring to give 15.1 g (92% based on *trans*-2-(carbomethoxymethyl)-2-methyl-3-vinylcyclopentanone 2,2-dimethyl-1,3-propanediol ketal) of *trans*-2-(β-(*p*-tosyloxy)ethyl)-2-methyl-3-vinylcyclopentanone 2,2-dimethyl-1,3-propanediol ketal as a white solid: IR (KBr disk) 3090, 1643, 1602 cm^{-1}; ^1H NMR (acetone-d_6, Me_4Si as an external reference) δ 0.22 (s, 3 H), 0.28 (s, 3 H), 0.50 (s, 3 H), 0.8–2.2 (m, 7 H), 2.00 (s, 3 H), 2.6–3.3 (m, 4 H), 3.5–4.0 (m, 2 H), 4.1–5.5 (m, 3 H), 6.7–7.4 (m, 4 H).

Lithium bromide monohydrate (7.9 g, 75 mmol) was dried in vacuo at 150 °C and dissolved in 40 mL of DMF, which became slurry on cooling. To this slurry at 0 °C was added 14.4 g (35 mmol) of the tosylate prepared above, and the mixture was stirred for 2 days at room temperature. The reaction mixture was diluted with water and extracted with hexane several times. The combined hexane extract was washed with water, dried over $MgSO_4$, and evaporated to give a light brown solid, which was recrystallized twice from 25 mL of hexane at −50 to −60 °C. *trasn*-2-(β-Bromoethyl)-2-methyl-3-vinylcyclopentanone 2,2-dimethyl-1,3-propanediol ketal (**56**) was obtained in 82% yield in stereoisomerically pure form: mp 53–54 °C; IR (KBr disk) 3078, 1642, 1105, 921 cm^{-1}; ^1H NMR (CCl_4) δ 0.73 (s, 3 H), 0.82 (s, 3 H), 1.19 (s, 3 H), 1.4–2.7 (m, 7 H), 3.0–3.9 (m, 6 H), 4.7–5.9 (m, 3 H); mass spectrum, *m/e* (relative intensity) 236 (M^+ − HBr, 18), 135 (100), 124 (56), 123 (43), 107 (41), 95 (61), 79 (67), 67 (56). Anal. Calcd for $C_{15}H_{25}O_2Br$: C, 56.79; H, 7.94; O, 10.09. Found: C, 56.68; H, 8.17; O, 10.38.

Alkylation of [2-((Trimethylsilyl)methyl)-5-methoxybenzyl]dimethylamine (1b) with Bromide (56). Preparation of 50b. To a solution of **1b** (276 mg, 1.1 mmol) in 1.5 mL of THF and 1 mL of HMPA was added 1.5 equiv of *n*-BuLi dropwise below −20 °C. The resultant dark red solution was stirred at −10 to −20 °C for 2 h, and a solution of **56** (383 mg, 1.2 mmol) in 1.5 mL of THF was added at −20 °C. The reaction mixture was warmed very slowly, stirred at room temperature overnight, and treated with a mixture of 70% perchloric acid (2 mL), water (5 mL), and THF (10 mL). After being stirred for 2 h at room temperature, the reaction mixture was made alkaline with solid sodium carbonate and extracted with ether. The ether extract was washed with brine, dried over $MgSO_4$, and evaporated. The residue was subjected to preparative TLC on silica gel with a 3:2 ethyl acetate–benzene mixture to afford 413 mg (94%) of **50b** as a 2:1 diastereoisomeric mixture (R_f 0.60): IR (neat) 1738, 1639, 1246, 862, 838 cm^{-1}; ^1H NMR (CD_3CN, Me_4Si as an external reference) δ −0.25 (s, 9 H), 0.52 and 0.55 (two s, 3 H), 1.1–2.6 (m, 10 H), 2.02 (s, 6 H), 3.08 (s, 2 H), 3.50 (s, 3 H), 4.5–5.0 (m, 2 H), 5.1–5.9 (m, 1 H), 6.3–6.8 (m, 3 H).

Preparation of Estrone Methyl Ether (52b). A solution of **50b** (465 mg, 1.1 mmol) in 2 mL of acetonitrile was treated with 0.23 mL (3 molar equiv) of methyl iodide at 0 °C for 3 h. Evaporation of the reaction mixture afforded **51b**, which was used for further reaction without purification: ^1H NMR (CD_3CN, Me_4Si as an external reference) δ −0.26 (s, 9 H), 0.57 (s, 3 H), 1.0–2.8 (m, 10 H), 3.09 (br s, 9 H), 3.85 (s, 3 H), 4.53 (s, 2 H), 4.75–5.2 (m, 2 H), 5.4–6.1 (m, 1 H), 6.9–7.2 (m, 3 H).

To a refluxing solution of **51b** in 20 mL of acetonitrile was added at once a suspension of cesium fluoride (350 mg, 2.3 mmol) in 10 mL of acetonitrile, and refluxing was continued for 1.5 h. After evaporation of the reaction mixture, methylene chloride was added to the residue and insoluble materials were filtered off. The filtrate was concentrated and subjected to preparative TLC on silica gel with chloroform to give 282 mg (86%) of estrone methyl ether (**52b**) (R_f 0.45). Thus prepared estrone methyl ether **52b** contained ca. 7–8% of the C(9) epimer, but recrystallization from ethyl acetate afforded pure estrone methyl ether: mp 183.5–185 °C (lit.[28] 183.2–184 °C); ^{13}C NMR ($CDCl_3$) δ 13.65, 20.37, 25.74, 26.36, 29.16, 31.44, 35.62, 38.18, 43.76, 47.71, 50.18, 54.91, 111.41, 113.75, 126.15, 131.86, 137.52, 157.48, 220.37.

Preparation of 4-Methoxyestra-1,3,5(10)-trien-17-one (52c). To a solution of **1c** (311 mg, 1.24 mmol) in 2 mL of THF and 1.3 mL of HMPA was added dropwise 1.5 molar equiv of *n*-BuLi at −30 °C, and the resulting solution was stirred for 2 h at −10 to −20 °C. The reaction mixture was cooled down to −75 °C, and a solution of **56** (432 mg, 1.1 equiv) in 2 mL of THF was added dropwise. After warming up gradually to 0 °C, the mixture was stirred at room temperature overnight and then treated with a mixture of 70% perchloric acid (2 mL), water (5 mL), and THF (10 mL) for 2 h. Solid sodium carbonate was added to the mixture to liberate **50c**, which was extracted with ether. The ether extract was dried over $MgSO_4$ and evaporated. To the viscous residue were added 3 mL of acetonitrile and 0.23 mL (3 molar equiv) of methyl iodide. The mixture was stirred at room temperature overnight and evaporated in vacuo to give **51c** as a yellow solid. This crude ammonium salt **51c** in 10 mL of acetonitrile was added dropwise over 1.5 h to a refluxing suspension of cesium fluoride (500 mg, 2.7 molar equiv) in 8 mL of acetonitrile, and refluxing was continued for an additional hour. Evaporation of the reaction mixture followed by extraction with methylene chloride afforded crude **52c**, which was subjected to preparative TLC on silica gel with chloroform to give 293 mg (83% overall yield) of **52c** as a pale yellow solid: R_f 0.40; mp 144 °C (recrystallized from ethyl acetate); IR (KBr disk) 1732, 1578, 1467, 1256, 1097, 783, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3 H), 1.05–3.25 (m, 15 H), 3.82 (s, 3 H), 6.61–7.35 (m, 3 H) (a small singlet at δ 0.93 may be assigned to 18-methyl protons of the C(9) epimer); ^{13}C NMR ($CDCl_3$) δ 13.38, 21.15, 22.99, 25.60, 25.73, 31.35, 35.35, 37.20, 44.12, 47.31, 50.10, 54.73, 106.87, 117.21, 124.26, 125.79, 140.58, 156.85, 219.78, and trace signals (7–8%) from the C(9) epimer at δ 18.99, 21.37, 23.76, 24.12, 27.26, 32.97, 34.72, 37.78, 41.69, 106.46, 118.11, 125.43, 125.97, 130.42, 138.33, 219.60. Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.98; H, 8.58.

Alkylation of [α-[*o*-((Trimethylsilyl)methyl)phenyl]ethyl]dimethylamine (14a) with Bromide (56). Preparation of 50d. To a solution of **14a** (293 mg, 1.24 mmol) in 1.5 mL of THF was added 1.5 molar equiv of *n*-BuLi at 0 °C. After being stirred for 2 h at 0 °C, the reaction mixture was cooled down to −75 °C, 1 mL of HMPA and a solution of **56** (434 mg, 1.37 mmol) in 1.5 mL of THF were successively added. The reaction mixture was warmed up slowly and stirred at room temperature overnight. To the resulting solution was added a mixture of 70% perchloric acid (2 mL), water (5 mL), and THF (10 mL), and the mixture was stirred for 2 h at room temperature. Solid sodium carbonate was added to the mixture to liberate **50d**, which was extracted with ether. The ether extract was evaporated and subjected to preparative TLC on silica gel with a 3:2 ethyl acetate–benzene solvent to give two diastereoisomers of **50d** in 95% total yield: R_f 0.59, 145 mg and R_f 0.38, 311 mg; IR (neat) (two diastereoisomers showed almost same spectra) 1734, 1634, 1242, 856, 831 cm^{-1}; ^1H NMR (CD_3CN, Me_4Si as external reference) (less polar isomer) δ −0.26 (s, 9 H), 0.50 (s, 3 H), 0.96 (d, 3 H, J = 6.4 Hz), 1.2–2.6 (m, 10 H), 1.85 (s, 6 H), 3.20 (q, 1 H, J = 6.4 Hz), 4.5–4.9 (m, 2 H), 5.0–5.8 (m, 1 H), 6.6–7.2 (m, 4 H), (polar isomer) δ −0.24 (s, 9

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H), 0.56 (s, 3 H), 1.07 (d, 3 H, J = 6.3 Hz), 0.9-2.7 (m, 10 H), 1.99 (s, 6 H), 3.44 (q, 1 H, J = 6.3 Hz), 4.4-5.0 (m, 2 H), 5.1-5.8 (m, 1 H), 6.6-7.3 (m, 4 H).

Preparation of 6β-Methylestra-1,3,5(10)-trien-17-one (52d). Compound **50d** (663 mg, 1.72 mmol) (diastereoisomeric mixture) was quaternized with methyl iodide to produce ammonium iodide **51d**: ^{1}H NMR ($CDCl_3$, Me_4Si as an external reference) δ 0.15 and 0.28 (two s, 9 H), 0.82 and 0.90 (two s, 3 H), 1.2-3.2 (m, 13 H), 3.42 (br s, 9 H), 4.8-6.3 (m, 4 H), 6.9-7.6 (m, 4 H).

Thus obtained ammonium salt **51d** was treated with cesium fluoride (540 mg, 3.55 mmol) as in the preparation of 4-methoxyestra-1,3,5-(10)-trien-17-one (**52c**). The crude reaction product was subjected to preparative TLC on silica gel with a 1:1 chloroform-benzene solvent to give 440 mg (95%) of **52d** (R_f 0.46) as a pale yellow solid, which contained 7-8% of the C(9) epimer: mp 89.5-91.5 °C (recrystallized from ethyl acetate); IR (KBr disk) 1739, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3 H), 1.25 (d, 3 H, J = 6.6 Hz), 1.1-3.2 (m, 14 H), 6.9-7.3 (m, 4 H) (a small singlet at δ 0.89 may be assigned to 18-methyl protons of the C(9) epimer); ^{13}C NMR ($CDCl_3$) δ 13.60, 21.32, 24.29, 25.15, 31.35, 31.71, 33.06, 35.48, 44.29, 47.75, 50.13, 124.62, 125.65 (2C), 128.44, 139.27, 141.52, 220.05, and trace signals (7-8%) from the C(9) epimer at δ 13.38, 18.36, 21.59, 27.84, 30.04, 34.36, 34.81, 47.26, 49.96, 123.18, 138.91, 141.74, 143.68, 220.32. Anal. Calcd for $C_{19}H_{24}O$: C, 85.03; H, 9.01. Found: C, 84.77; H, 9.20.

Synthetic Studies in the Indole Series. Preparation of the Unique Antibiotic Alkaloid Chuangxinmycin by a Nitro Group Displacement Reaction

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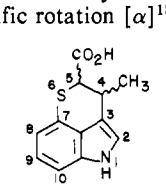
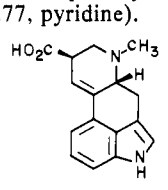
Abstract: The total synthesis of the unique sulfur-containing antibiotic indole alkaloid chuangxinmycin is described. This compound, first isolated by Chinese chemists at the Institute of Materia Medica, was assembled from 2,6-dinitrotoluene by a scheme that combines the nitro group displacement reaction with the Leimgruber indole synthesis to produce a 4-sulfur-substituted indole. Further transformations involving acetylation of the indole 3-position, an intramolecular Knoevenagel condensation to dehydrochuangxinmycin methyl ester, and a stereospecific hydrogenation reaction furnish chuangxinmycin methyl ester. The synthesis scheme does establish the cis relationship between the carboxylic acid and methyl group in the natural product.

A new species of microorganism *Actinoplanes tsinanensis* n. sp. was obtained by the Mainland Chinese from a soil sample collected in Tsinan, Shantung Province. In culture filtrates of this organism, an antibiotic was secreted that could be isolated through a process that began with adjustment of the pH to 3 and extraction with butyl acetate. The organic layer was then extracted with sodium hydroxide, the pH again brought to 3, and the butyl acetate extraction repeated. A secondary sodium hydroxide extraction and pH adjustment then led to deposition of the crystalline product. This material, named chuangxinmycin (a new kind of mycin), was found to be active in vitro against a number of Gram-positive and Gram-negative bacteria. In vivo, the product was found to be active in mice against *Escherichia coli* and *Shigella dysenteria* infections. Preliminary clinical results (140 cases) have shown that chuangxinmycin is effective in the treatment of septicaemia, urinary, and biliary infections caused by *E. coli*.[1]

The structure of the antibiotic was assigned through examination of its UV, IR, NMR, and mass spectral characteristics. The gross structure **1** reveals a unique heterocyclic skeleton bearing two centers of asymmetry. The product is optically active with a specific rotation $[\alpha]^{18}_D$ -249° (c 0.77, pyridine).



Chuangxinmycin (1)



Lysergic acid (2)

Chuangxinmycin is related in a structural sense to alkaloids of the ergot family (e.g., lysergic acid (**2**)). These pharmacologically important substances are also comprised of an indole unit that is specifically substituted at its 3- and 4-positions.[2] In the ergot alkaloids, however, the C-4 appendage is linked through a carbon atom rather than a sulfur atom. As a consequence of the gross structural similarity, tactics and/or methods that might thus be developed in the construction of chuangxinmycin in the laboratory could well be carried over to the development of synthetic routes to the ergot alkaloids.[3]

In selecting a synthetic route to chuangxinmycin, we took cognizance of the fact that the early work of the Chinese had failed to discern whether the carboxyl group and methyl group of the product were related in a cis or trans manner.[1] It thus seemed prudent to select a reaction scheme wherein one of these compounds, either the cis or the trans material, could be produced stereoselectively, thus allowing an unambiguous assignment of structure to be made.

While a variety of possible strategies for the assembly of this material could be envisioned on the basis of a single-stage retrosynthetic analysis, we felt that pathway B appeared to be the most promising from a stereochemical standpoint. If we consider X = O in **4**, then C ring closure by an internal Knoevenagel condensation should afford dehydrochuangxinmycin.[4] This intermediate might then be converted by a stereospecific cis hydrogenation reaction to that chuangxinmycin isomer with the methyl and carboxyl groups cis related.[5] If this cis material failed

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