New Stereoselective Synthesis of Steroids

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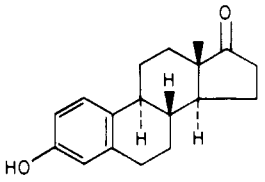
Synthesis of steroidal systems has been of special interest among synthetic chemists. Some methodologies have been developed for synthesis of steroid frameworks on the basis of intramolecular cyclization of *o*-quinodimethanes, generated by thermolysis of benzocyclobutene precursors[1a-e] and thermal cheletropic elimination of SO_2 from 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxides.[1f,g] In the previous paper[2] we described a simple and versatile method for an efficient generation of *o*-quinodimethanes in which [*o*-[(trimethylsilyl)methyl]benzyl]trimethylammonium iodide was treated with fluoride anion at room temperature. We now wish to report a stereoselective synthesis of estrone (**1**) and 6β-methylestra-1,3,5(10)-trien-17-one (**2**) on the basis of the new methodology.



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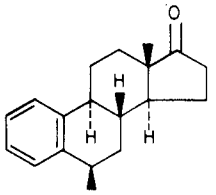
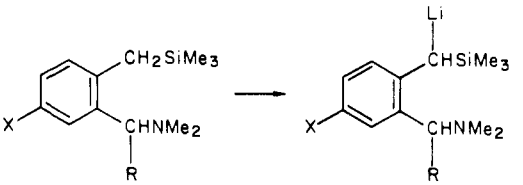


2

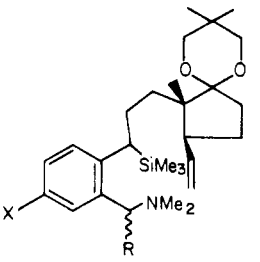
The key in the construction of the steroidal structures is a selective generation of the silicon-stabilized carbanions from [2-[(trimethylsilyl)methyl]-5-methoxybenzyl]dimethylamine (**3**)[3] and α-[*o*-[(trimethylsilyl)methyl]phenyl]ethyldimethylamine (**4**)[5] and their alkylations to prepare the requisite precursors **7** and **8** to lead to the polycyclic frameworks.

The generation of the silicon-stabilized benzylic carbanion **6** from **4** was performed by the addition of 1.5 equiv of *n*-butyllithium in THF at 0 °C according to the reported procedure.[2] On the other hand, an attempt to generate the silicon-stabilized benzylic carbanion **5** from **3** was hampered by kinetically favored lithiation at the carbons ortho to the methoxy substituent on the aromatic ring. Finally, the selective generation of **5** was achieved by treating **3** in THF with *n*-butyllithium in the presence of HMPA [**3** (1 mmol), *n*-BuLi (1.5 mmol), HMPA (1 mL), THF (1.5 mL); between -10 and ~-20 °C; 2 h].

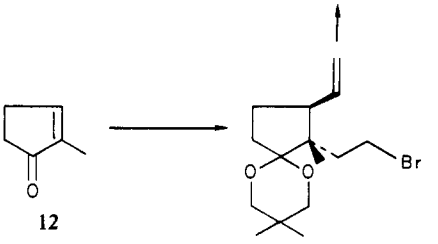


3, X = OMe; R = H
4, X = H; R = CH_3

5, X = OMe; R = H
6, X = H; R = CH_3



7, X = OMe; R = H
8, X = H; R = CH_3

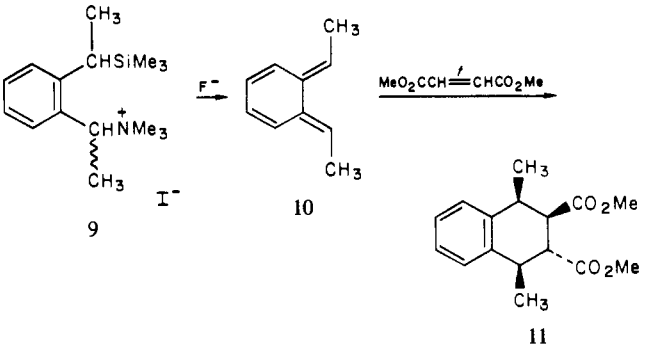


12

13

It is to be noted that a 3:2 mixture of diastereoisomers (**9**),[6] which was prepared by methylation of **6** and subsequent quaternization with methyl iodide, was treated with tetrabutylammonium fluoride in acetonitrile at 50 °C in the presence of dimethyl fumarate to give a single product, which was unambiguously assigned to **11** by NMR spectra,[7] in a quantitative yield.

This finding indicates that the fluoride anion induced 1,4-elimination of a mixture of diastereoisomers **9** afforded stereoselectively (*E*,*E*)-α,α'-dimethyl-*o*-quinodimethane (**10**).



9

10

11

This also implies that a variety of symmetrical and unsymmetrical (*E*,*E*)-α,α'-disubstituted *o*-quinodimethanes may be

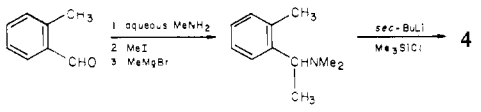
(1) (a) Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Matsumoto, H.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 3461. (b) Funk, R. L.; Vollhardt, K. P. C. *Ibid.* **1977**, *99*, 5483. (c) *Ibid.* **1980**, *102*, 5253. (d) Oppolzer, W.; Battig, K.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 1945. (e) For a recent review, see: Oppolzer, W. *Synthesis* **1978**, 793. (f) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463. (g) Oppolzer, W.; Roberts, D. A.; Bird, T. G. C. *Helv. Chim. Acta* **1979**, *62*, 2017.

(2) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 863.

(3) Compound **3** was synthesized in >90% yield by a nickel-catalyzed coupling reaction[4] of [(trimethylsilyl)methyl]magnesium chloride with (2-chloro-5-methoxybenzyl)dimethylamine which is readily prepared from commercially available 3-methyl-4-chlorophenol. **3**: ^{1}H NMR (CCl_4 with 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).

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

(5) Compound **4** was synthesized in 95% yield by lithiation (*sec*-BuLi/



Et_2O) at the *o*-methyl group of [α-(*o*-methylphenyl)ethyl]dimethylamine, which is prepared from *o*-tolualdehyde, and subsequent treatment with trimethylsilyl chloride. **4**: ^{1}H NMR (CCl_4 with Me_4Si as an external reference) δ 0.09 (s, 9 H), 1.26 (d, 3 H), 2.13 (s, 6 H + 2 H), 3.33 (q, 1 H), 6.6-7.4 (m, 4 H).

(6) **9**: ^{1}H NMR (CD_3CN, Me_4Si as an external reference) δ -0.27 and -0.09 (s, 9 H), 0.90 and 1.10 (d, 3 H), 1.3-1.6 (br dt, 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).

(7) **11**: IR (neat) 1734, 1263, 1196, 1167, 758 cm^{-1}; ^{1}H NMR (100 MHz, CCl_4) δ 1.10 (d, 3 H, $J_{H-H_{eq}}$ = 6.9 Hz), 1.42 (d, 3 H, $J_{H-H_{ax}}$ = 6.5 Hz), 2.72 (dd, 1 H, $J_{H_{ax}-H_{ax}}$ = 10.0 Hz, $J_{H_{ax}-H_{eq}}$ = 11.7 Hz), 2.95 (qd, 1 H, $J_{H-H_{ax}}$ = 6.5 Hz, $J_{H_{ax}-H_{ax}}$ = 10.0 Hz), 3.12 (dd, 1 H, $J_{H_{ax}-H_{ax}}$ = 11.7 Hz, $J_{H_{ax}-H_{eq}}$ = 4.8 Hz), 3.29 (qd, 1 H, $J_{H-H_{eq}}$ = 6.9 Hz, $J_{H_{eq}-H_{ax}}$ = 4.8 Hz), 3.67 (s, 3 H), 3.69 (s, 3 H), 7.9-8.3 (m, 4 H); ^{13}C NMR ($CDCl_3$ with Me_4Si) δ 19.91, 21.03, 35.32, 36.31, 44.99, 46.65, 51.86 (2 C), 126.26, 126.80, 127.33, 128.59, 138.30, 140.01, 173.95, 176.19; TLC on silica gel (8:1 hexane-acetone), R_f 0.26.

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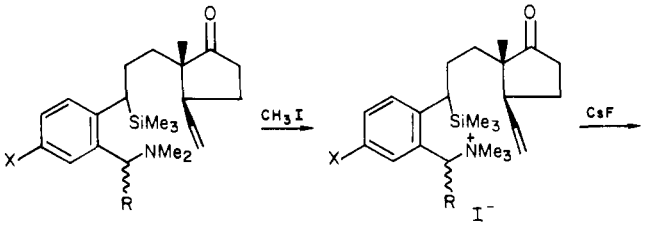
generated by the present method, since their precursors are readily accessible from *o*-tolualdehyde.[5]

In a parallel line of experiments, cyclopentanone moiety **13** was prepared in an almost stereoisomerically pure form, starting from 2-methyl-2-cyclopentenone (**12**) by modification[8] of the reported method.[1c,d,f]

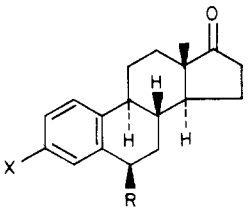
The assembly of the bromide **13** with **3** was carried out by adding **13** to the benzylic carbanion **5** at −75 °C to room temperature, which had been generated in situ from **3**, according to the procedure described above. In the assembly of the bromide **13** with **4**, HMPA was added to the carbanion **6**, generated in situ prior to the alkylation. Deketalization of the coupling products **7** and **8** afforded the crucial precursors **14** and **15**[10] as stereoisomeric mixtures [**14**, 2:1;[11] **15**, 1:2 (the former is less polar)] in 94% and 95% yields, respectively, after preparative TLC [**14**: TLC on silica gel, R_f 0.60 (6:4 AcOEt-C_6H_6); **15**: TLC on silica gel, R_f 0.59 and 0.38 (6:4 AcOEt-C_6H_6)].

The final intramolecular cyclization of **14** and **15** via the corresponding *o*-quinodimethanes was exemplified with the estrone synthesis. To an acetonitrile solution (20 mL) of a diastereo-



14, X = OMe; R = H
15, X = H; R = CH_3

16, X = OMe; R = H
17, X = H; R = CH_3



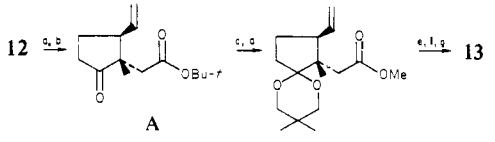
18, X = OMe; R = H
2, X = H; R = CH_3

isomeric mixture of **16**, which had been prepared by quaternization of **14** (1.1 mmol) with CH_3I at 0 °C, was added a suspension of CsF (2.2 mmol) in 10 mL of acetonitrile at once at reflux; the mixture was heated for 1.5 h. The reaction mixture was evaporated in vacuo, triturated with CH_2Cl_2, and filtered to remove the insoluble materials. The filtrate was evaporated and chromatographed on silica gel with chloroform solvent (TLC, R_f 0.45) to afford estrone methyl ether (**18**)[12] in 86% yield based on **14**, which was identified by comparison of its spectral data with those of the authentic sample. The similar treatment of **15** gave rise to 6β-methylestra-1,3,5(10)-trien-17-one (**2**)[14] in 95% yield. It was identified by comparison of the spectral data with those of the authentic sample, which was independently prepared via hydrogenation on Pd/C of 6-methylestra-1,3,5(10),6-tetraen-17-ol, starting with estradiol 17-monoacetate.[15,16]

The simplicity and versatility of the present methodology for the generation of *o*-quinodimethane intermediate have been demonstrated by the stereoselective syntheses of estrone and 6β-methylestra-1,3,5(10)-trien-17-one. Furthermore, the generation of *o*-quinodimethanes with appropriate substituents on the aromatic nucleus and the α and α′ carbons is expected in our methodology, which makes derivatization of steroidal skeleton possible.[17] Further extensions of the methodology are now in progress in our laboratory.

Acknowledgment. We are grateful to Shin-etsu Chemical Industry Co., Ltd., for the generous gift of trimethylchlorosilane. We also thank Teikoku Horm. Manufacturing Company for providing estradiol 17-monoacetate, which was used to prepare the authentic sample of 6β-methylestra-1,3,5(10)-trien-17-one.

(8) The bromide **13**[9] was prepared stereoselectively in 47% overall yield from 2-methyl-2-cyclopentenone **12** via the keto ester A (>96% stereochemical purity) as shown. **13**: [bp 115–117 °C (0.3 mmHg); mp 53–54 °C, recrystallization from hexane]; IR (KBr disk) 1642, 1105, 921 cm^{-1}; ^1H NMR (CCl_4 with Me_4Si) 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).



(a) CH_2=CHMgBr/CuI (3 mol %)/THF. (b) $BrCH_2CO_2Bu$-*t*/HMPA. (c) MeOH/dry HCl. (d) $HOCH_2C(CH_3)_2CH_2OH$/$CH(OCH_3)_3$/*p*-TsOH. (e) $LiAlH_4$. (f) TsCl/Py. (g) LiBr/DMF.

(9) All attempts to prepare the ethylene glycol ketal corresponding to the bromide **13** from its precursor tosylate and alcohol by conventional methods provided the desired bromide in low yields with several products.

(10) **14**: IR (neat) 1738, 1639, 1246, 862, 838 cm^{-1}; ^1H NMR (CD_3CN with Me_4Si as an external reference) δ −0.25 (s, 9 H), 0.52 and 0.55 (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). **15**: IR (neat) (two stereoisomers show almost same spectrum) 1734, 1634, 1242, 856, 831 cm^{-1}; ^1H NMR (CD_3CN with Me_4Si as an external reference) (less polar isomer) δ −0.26 (s, 9 H), 0.50 (s, 3 H), 0.96 (d, 3 H), 1.2–2.6 (m, 10 H), 1.85 (s, 6 H), 3.20 (q, 1 H), 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 H), 0.56 (s, 3 H), 1.07 (d, 3 H), 0.9–2.7 (m, 10 H), 1.99 (s, 6 H), 3.44 (q, 1 H), 4.4–5.0 (m, 2 H), 5.1–5.8 (m, 1 H), 6.6–7.3 (m, 4 H).

(11) The ratio of the stereoisomers was determined by NMR spectrum.

(12) Estrone methyl ether thus obtained contained ca. 7–8% of C(9) epimer, but recrystallization from AcOEt afforded pure estrone methyl ether, mp 183.5–185 °C (lit.[13] 183.2–184 °C).

(13) Johnson, W. S.; Banerjee, D. K.; Schneider, W. P.; Gutsche, C. D.; Shelberg, W. E.; Chinn, L. J. *J. Am. Chem. Soc.* **1952**, *74*, 2832.

(14) **2**: mp 89.5–91.5 °C, recrystallization from AcOEt; IR (neat) 1738, 758 cm^{-1}; ^1H NMR ($CDCl_3$ with Me_4Si) δ 0.84 (s, 3 H), 1.25 (d, 3 H), 1.1–3.2 (m, 17 H), 6.9–7.3 (m, 4 H). ^{13}C NMR ($CDCl_3$ with Me_4Si) δ 13.60, 21.32, 24.29, 25.15, 31.35, 31.71, 33.06, 33.55, 35.48, 44.29, 47.75, 50.13, 124.62, 125.65 (2 C), 128.44, 139.27, 141.52, 220.05.

(15) Japanese Patent Publication 4071, 1963; Teikoku Horm. Manufacturing Company.

(16) (a) Douglas, G. H.; Buzby, G. C., Jr.; Walk, C. R.; Smith, H. *Tetrahedron* **1966**, *22*, 1019. (b) Velarde, E.; Iriarte, J.; Ringold, H. J.; Djerassi, C. *J. Org. Chem.* **1959**, *24*, 311.

(17) We have been informed through a private communication from Professor P. Magnus of The Ohio State University that he has developed a synthetic route to 11α-hydroxyestrone [*J. Am. Chem. Soc.* **1980**, *102*, 6885] on the basis of our methodology for generation of *o*-quinodimethane intermediates.

Directional Preferences of Nonbonded Atomic Contacts with Divalent Sulfur in Terms of Its Orbital Orientations. 2. S···S Interactions and Nonspherical Shape of Sulfur in Crystals

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Our earlier studies[1] of nonbonded atomic contacts with divalent sulfur in crystals revealed that electrophiles tend to approach sulfur roughly 20° from the perpendicular to the plane through atoms Y-S-Z, whereas nucleophiles tend to approach approximately along the extension of one of the covalent bonds to S, indicating

(1) Rosenfield, R. E., Jr.; Parthasarathy, R. "Program and Abstracts, American Crystallographic Association"; American Crystallographic Association: 1975; Series 2, Vol. 3, p 28. Rosenfield, R. E., Jr.; Parthasarathy, R.; Dunitz, J. D. *J. Am. Chem. Soc.* **1978** *99*, 4860–4862.

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