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ENANTIOMER RECOGNITION DURING ANIONIC COUPLING OF A RACEMIC 2-NORBORNENONE

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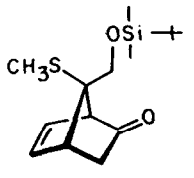
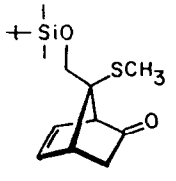
Summary: Following deprotonation, 1 enters into highly selective bonding to a second enone molecule of the same absolute configuration. The resulting hypothetical homoenolate anion (4) progresses to 3 by antiplanar ejection of CH_3S^-.

In the course of studies aimed at the total synthesis of ikarugamycin,[3] the stereocontrolled preparation of C(7)-isomeric 2-norbornenones 1 and 2 was carried out.[4] As expected, the significant steric shielding about the ketone carbonyl group in these substrates retards the endo-



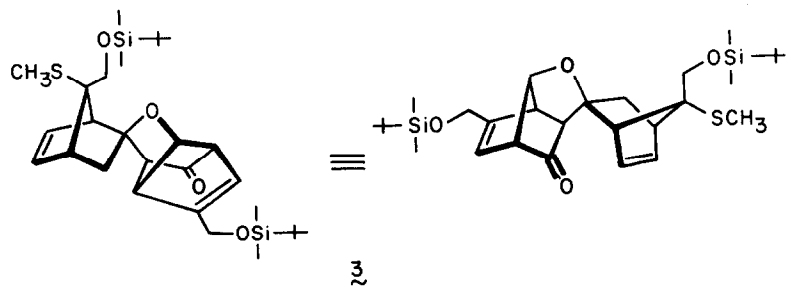
1



2

directed 1,2-addition of organometallic reagents and is conducive to promoting competitive enolization. Our inability to recover unalkylated 1 efficiently from such reactions and the detection of a higher molecular weight by-product in this case prompted direct examination of the chemical behavior of 1^-. The unique reactivity of this enolate anion constitutes the subject of this report.

When tetrahydrofuran solutions of 1 were allowed to stir at room temperature for 18 h in the presence of 0.6 equiv of lithium diisopropylamide, conversion to a crystalline solid of formula $C_{29}H_{48}O_4SSi_2$ (combustion analysis) occurred with reasonable efficiency (63%). Separation from unreacted 1 was expediently achieved by MPLC on silica gel (elution with 13% ethyl acetate in petroleum ether). Several other complex substances, the combined yield of which has never exceed 8%, remain incompletely characterized.[5] Although the spectral data of the major product corroborated the loss of a CH_3S group and revealed the annihilation of one carbonyl group,[6] the complete

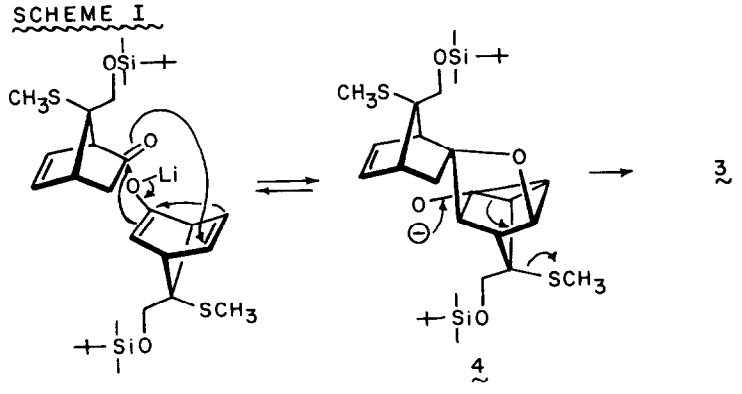


structural connectivity was rigorously established to be as in **3** by X-ray analysis (Figure 1).

The framework of **3** suggests that enolization of **1** is followed by endo addition to the neutral ketone and unprecedented intramolecular capture of the alkoxide ion as shown in Scheme I. Apparently, the regiochemistry of addition to the double bond is controlled by formation of homoenolate anion **4**.[7] Plausibly, **4** would seemingly have the option of returning to its individual fragments (thus the equilibrium arrow) or advancing irreversibly to **3** by ejection of methylmercaptide ion, which finds itself suitably positioned for antiperiplanar elimination. This last process appears to be fully stereocontrolled as the enolate anion of **2** does not enter into analogous reaction under comparable conditions.

Noteworthily, product **3** must necessarily arise from the coupling of two identical enantiomers of **1** (the (1R) + (1R) option is shown in Scheme I). Should bonding have taken place between unlike optical antipodes, a diastereomer of **3**, viz., **6**, would have resulted instead (Scheme II).[5] Discrimination by the enolate anion between the two diastereomeric transition states materializes because of appreciably different steric requirements. Thus, while the pathway leading

SCHEME I



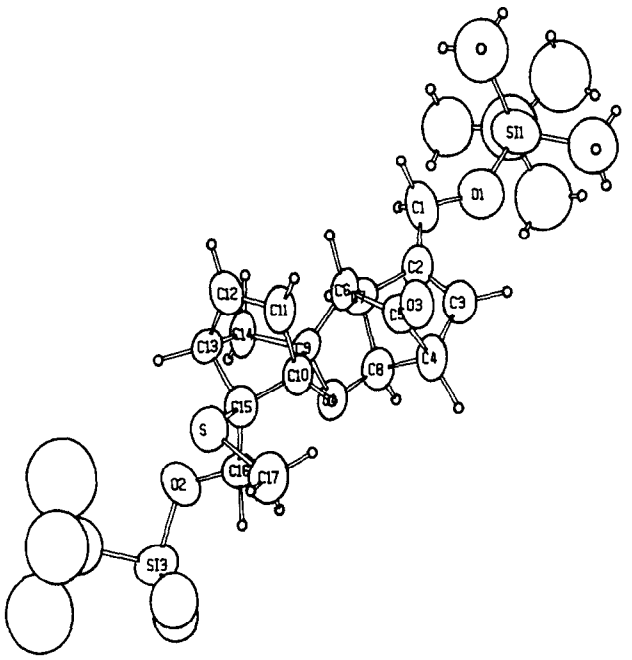
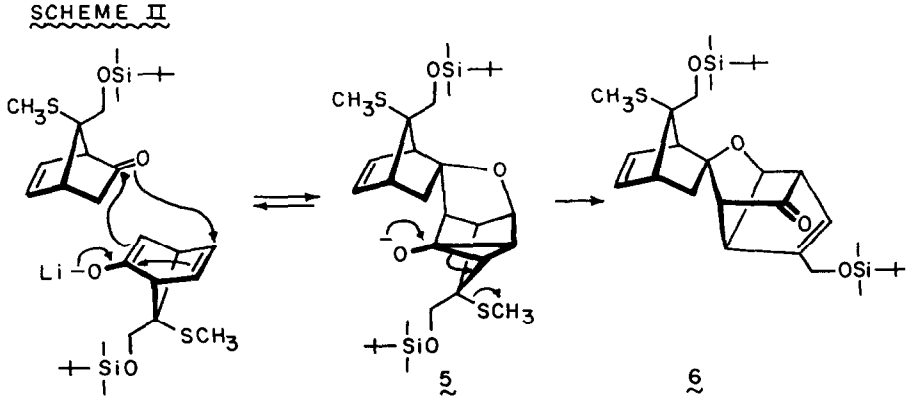


Figure 1. A computer-generated perspective view of the final X-ray model of **3**. Particular note should be taken of the relative stereodisposition of C(14) and C(5).

to **3** involves merely a staggered corner-to-corner approach of the reacting partners, that leading to **6** necessitates that the endo C(2)-C(3) surfaces of both norbornenones be simultaneously compressed.

Highly selective bonding between molecules of the same absolute configuration has been observed on a singular prior occasion during electrolytic reduction of a tricyclic enone.[8]

SCHEME II



However, homoenolate anion generation in the manner adopted by 1^- has not been recognized previously.[7] This highly diastereoselective process promises new opportunities for the utilization of 2-norbornenones in synthetic design.

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References and Notes

(1) Postdoctoral Fellow of the Deutscher Akademischer Austauschdienst (NATO), 1983-1984.

(2) Author to whom inquires concerning the X-ray crystal structure analysis should be directed.

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(4) Ketone **1** was obtained by stereospecific thiomethylation of the anion of 7-carbomethoxy-2,2-ethylenedioxybicyclo[2.2.1]hept-5-ene, followed by $(i\text{-Bu})_2AlH$ reduction and silylation: ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (dd, J = 5.7 and 2.8 Hz, 1 H), 6.02 (m, 1 H), 3.88 (d, J = 11.6 Hz, 1 H), 3.81 (d, J = 11.6 Hz, 1 H), 3.13 (br s, 1 H), 2.90 (br s, 1 H), 2.27 (dd, J = 16.7 and 3.3 Hz, 1 H), 2.01 (s, 3 H), 1.97 (d, J = 16.7 Hz, 1 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR ($CDCl_3$) ppm 210.9 (s), 144.6 (d), 128.5 (d), 76.2 (s), 65.7 (t), 61.4 (d), 46.8 (d), 35.2 (t), 25.8 (q), 18.2 (s), 13.8 (q), 5.7 (q), 5.5 (q). Comparable thiomethylation of exo-2-bromo-5,5-ethylenedioxybicyclo[2.2.1]heptane-syn-7-carboxylic acid methyl ester [Grieco, P. A., J. Am. Chem. Soc. **1977**, 99, 4111] proceeded with 4:1 stereoselection in the same direction. The minor alcohol, which could be separated chromatographically, was transformed into **2**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.57 (dd, J = 5.7 and 3.0 Hz, 1 H), 6.0 (m, 1 H), 4.00 (d, J = 10.3 Hz, 1 H), 3.95 (d, J = 10.3 Hz, 1 H), 3.0 (br s, 1 H), 2.95 (br s, 1 H), 2.64 (dd, J = 16.3 and 3.3 Hz, 1 H), 2.11 (s, 3 H), 1.86 (d, J = 16.3 Hz, 1 H), 0.86 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR ($CDCl_3$) ppm 210.6 (s), 143.2 (d), 128.5 (d), 73.3 (s), 64.9 (t), 61.6 (d), 44.9 (d), 35.3 (t), 25.8 (q), 18.2 (s), 12.7 (q), 5.5 (q).

(5) None of these products is **6**. The composite 300 MHz ^1H NMR spectrum (in $CDCl_3$) [δ 6.55-6.53 (m, 1 H), 6.18-6.08 (m, 3H), 4.23 (m, 1 H), 3.99-3.80 (m, 2 H), 3.09-2.55 (m, 4 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 2.04-1.97 (m, 1 H), 1.64-1.22 (m, 2 H), 0.91-0.87 (several s, total 18 H), 0.13-0.03 (several s, total 12 H)] and mass spectrum (m/z 594.3347) rule out this possibility.

(6) Mp 92-93°C; calcd for $C_{29}H_{48}O_4SSi_2$: C, 63.45; H, 8.81. Found: 63.46; H, 8.79; IR (KBr, cm^{-1}) 2955, 2930, 2857, 1747, 1255, 1245, 1120, 1100, 1062, 845, 830, 770; ^1H NMR (300 MHz, $CDCl_3$) δ 6.36 (dd, J = 5.6 and 3.3 Hz, 1 H), 6.15 (dd, J = 5.6 and 2.9 Hz, 1 H), 5.53 (m, 1 H), 4.86 (m, 1 H), 4.25 (d, J = 11.1 Hz, 2 H), 4.24 (dd, J_{AB} = 15.0 and J_{AX} = 1.7 Hz, 1 H), 4.14 (dd, J_{AB} = 15.0 and J_{AX} = 1.7 Hz, 1 H), 3.80 (d, J = 11.1 Hz, 1 H), 3.14 (m, 1 H), 3.03 (m, 1 H), 2.91 (br s, 1 H), 2.61 (br s, 1 H), 2.21 (br s, 1 H), 2.07 (dd, J = 12.9 and 3.4 Hz, 1 H), 2.02 (s, 3 H), 1.46 (d, J = 12.9 Hz, 1 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.049 (s, 3 H), 0.046 (s, 3 H), 0.029 (s, 6 H); ^{13}C NMR ($CDCl_3$) ppm 209.05, 147.30, 137.42, 134.83, 117.23, 97.17, 96.84, 76.07, 65.23, 61.98, 61.58, 57.59, 54.31, 50.08, 47.83, 40.01, 25.94, 25.82, 18.36, 18.32, 14.84, -5.29, -5.38.

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