Migratory Selectivity in the Ring Expansion of α,β-Unsaturated Cyclic Ketones via β-Hydroxy Selenides

Leo A. Paquette,* John R. Peterson, and Robert J. Ross[1]

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

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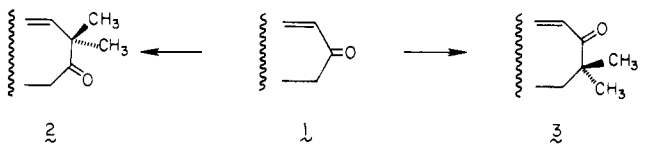
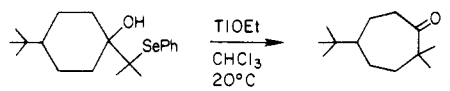
α-Phenylseleno alcohols, available by the direct condensation of α-phenylselenenyl anions with α,β-unsaturated ketones, are efficiently transformed to ring-expanded enones upon reaction with thallium ethoxide in chloroform. Ten examples have been studied for the purpose of evaluating the relative migratory capabilities of the α-vinyl and α′-alkyl groups in a variety of structural contexts. Where the conformationally unconstrained substrate 8 is concerned, exclusive vinyl migration was observed. In more rigid starting materials, the interrelationships of steric and conformational influences associated with proper antiperiplanar alignment of the $PhSeCCl_2H$ leaving group take on considerable importance. The presence of additional double bonds in the reactant does not introduce a serious problem associated with unwanted reaction with the dichlorocarbene intermediate. These various issues are discussed in light of the synthetic potential of the process.

Methods for expanding carbocyclic rings of various sizes have held the fascination of physical organic chemists and have often been employed by synthetic chemists in pursuit of natural and unnatural target molecules. Many of the classical schemes were reviewed by Gutsche and Redmore in 1968.[2] In conjunction with a projected synthesis of ingenol,[3] the need arose for implementation of the enlargement of an α,β-unsaturated cyclic ketone (1) to an β,γ-unsaturated homologue with *concurrent* positioning of a quaternary carbon at the α site as in **2** rather than as in **3**. The ability to achieve this ring expansion effectively



2 **1** **3**



4 **5**

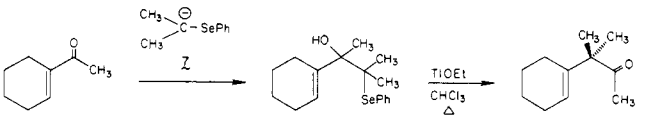
under mild conditions with acceptable control of the migratory ability of the α(sp^2) and α′(sp^3) carbon atoms in **1** was viewed as an important problem in organic synthesis. From our standpoint, the potential for accomplishing the **1** → **2** transposition rested on the interesting recent disclosure by Laboureur and Krief that thallium ethoxide in chloroform was capable of acting on *saturated* β-hydroxy selenides such as **4** to deliver ring-enlarged ketones.[4] The reaction involves the formation of dichlorocarbene, subsequent interaction of $:CCl_2$ at the selenium site to form an Se^+–C^- ylide, and subsequent ejection of $PhSeCHCl_2$ to yield the ketone.

Consideration of the possible extension of this protocol to **1** suggested the need for clarifying several relevant questions: (1) Will the α-carbon atom better able to stabilize positive charge migrate preferentially or is such thinking an oversimplification? (2) To what extent will steric and conformational effects control the relative energies of the transition states for the two possible migrations to carbon and dictate the 2:3 product distribution? (3) Since $:CCl_2$ is a necessary reactive intermediate, will the presence of additional double bonds elsewhere in the starting material be subject to kinetically uncontrollable conversion to a dichlorocyclopropane?

The approach described above appeared particularly attractive for the problem at hand. Simple transition state considerations, particularly the implied need for a stereoelectronic push by an anti-aligned carbon–carbon bond within the ring, suggested that conformational and steric factors would be rather influential in dictating the extent to which the two possible reaction channels would be followed. Nonetheless, the method will be shown to possess distinct advantages, such that it holds considerable promise for future adoption in synthetic strategy.

Results and Discussion

Attention was first directed to 1-acetylcyclohexene (**6**). For all the preparations described here, the α-phenylseleno anions were generated by the best known method, viz., addition of 1 equiv of *sec*-butyllithium to the selenoacetal dissolved in diethyl ether at −78 °C.[5,6] Following formation of **7** in this manner, it was brought into contact with **6** at the same temperature for 1.5 h, and **8** was isolated in 80% yield following purification by medium-pressure liquid chromatography (MPLC). Subsequent heating of **8** for 2 h with 5 equiv of thallium ethoxide in a volume of chloroform adequate to render the solution 1 M in Tl^+ proved interesting. Alkyl migration was totally suppressed, and **9** was isolated in 98% yield. Consequently, the regioselectivity in this example is controlled by the enhanced migratory ability of the trigonal α-carbon. It is seemingly predictable that this reaction pathway will be followed by all conjugated enones in which the migrating origin and terminus are neither geometrically constrained nor excessively bulky.



6 (80%) **8** (98%) **9**

(1) National Science Foundation Graduate Fellow, 1982–1985.
(2) Gutsche, C. D.; Redmore, D. "Carbocyclic Ring Expansion Reactions"; Academic Press, New York, 1968.
(3) Paquette, L. A.; Nitz, T. J.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446.
(4) Laboureur, J. L.; Krief, A. *Tetrahedron Lett.* **1984**, 2713.
(5) Labar, D.; Krief, A. *J. Chem. Soc., Chem. Commun.* **1982**, 564.
(6) For less satisfactory procedures, consult: (a) Van Ende, D.; Krief, A. *Tetrahedron Lett.* **1976**, 457. (b) Van Ende, D.; Dumont, W.; Krief, A. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 700.

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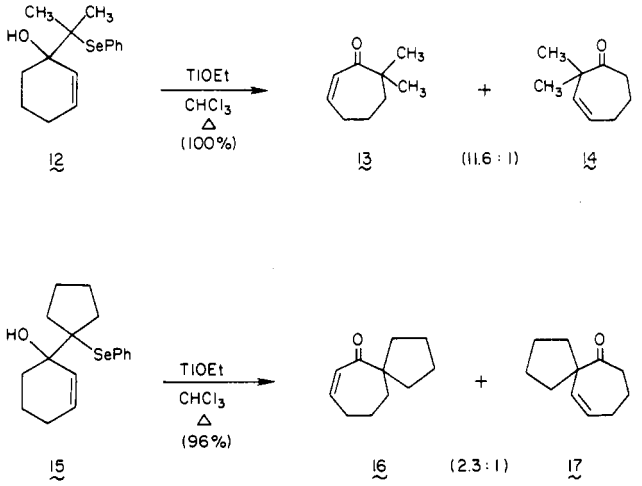
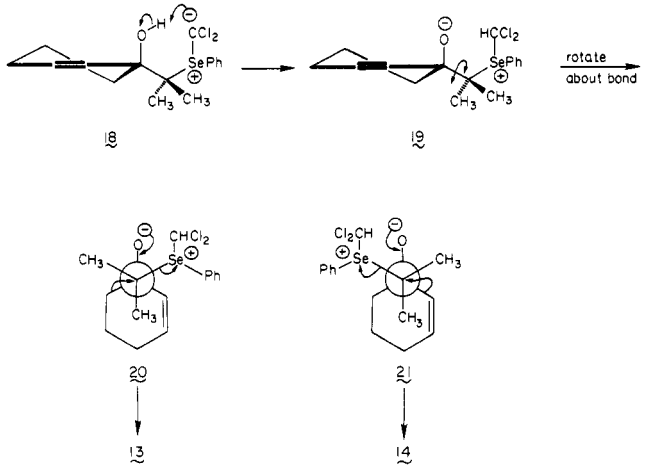
The overall conformational situation changes abruptly in 2-cyclohexenone (**10**). In order to gain insight into the effects of differing steric congestion about the selenium-substituted carbon, **10** was converted initially to **12** (67%) and **15** (60%) by condensation with **7** and the 1-(phenylseleno)cyclopentyl anion (**11**), respectively. Operation



12 **13** **14** **15** **16** **17**

on **12** in the predescribed manner afforded an 11.6:1 mixture of **13** and **14** in quantitative yield. These isomers were readily separated by MPLC and unequivocally identified by 300-MHz ^1H NMR spectroscopy (see Experimental Section). 2,2-Dimethyl-3-cycloheptenone (**14**) has been reported previously.[7] By comparison, the extent of alkyl migration was not as pronounced in the case of **16** and **17** (2.3:1).

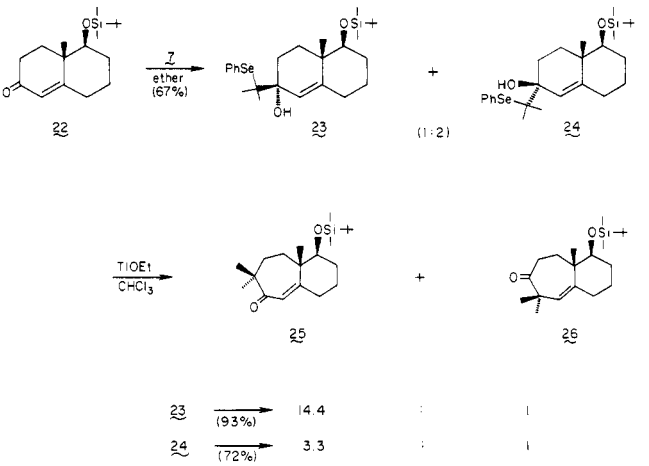
We interpret the striking difference in rearrangement regioselectivity observed for **12** and **15** in the following manner. Subsequent to the initial formation of **18**, an intramolecular proton transfer occurs via a six-membered transition state as indicated. At the instant at which alkoxide **19** is generated, however, synchronous loss of $PhSeCCl_2H$ is not likely because the CR_2–Se^+ bond is not properly aligned stereoelectronically for anti-parallel migration of either flanking C–C bond. Conformational alignment must first occur, and rotation in either a clockwise or counterclockwise direction is in principle necessary. However, **20** and **21** are not isoenergetic and



18 **19** **20** **21** **13** **14**

will not be attained with equal probability. In fact, standard nonbonded steric factors cause **21** to be relatively more congested. This fact can consequently account for the regioselective formation of **13**. When the pair of methyl groups is replaced by a cyclopentane ring, the corresponding intermediates are evidently more comparable in energy, although alkyl migration leading to **16** remains controlling.

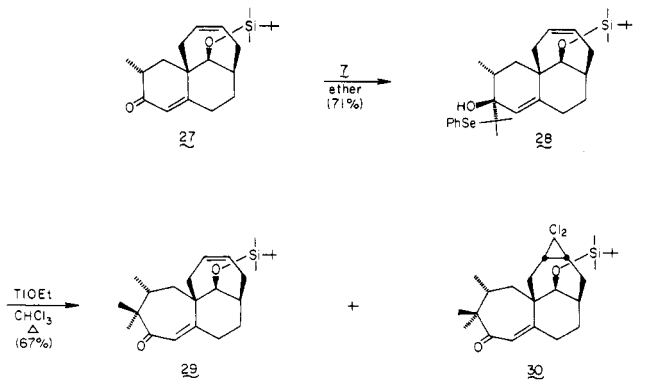
To elucidate the relationship between relative stereochemistry and ring-expanded product distribution, bicyclic ketone **22** was treated with **7**, which yielded the chromatographically separable β-hydroxy selenides **23** and **24** in a 1:2 ratio (67% combined yield). Isomer assignment was



22 **23** **24** **25** **26**

based upon preferential approach of the sterically encumbered anion from the direction of the more open face of the carbonyl functionality, in line with precedent established for other reagents.[8,9] The alkyl/vinyl migration ratios observed when **23** and **24** were separately exposed to the customary conditions revealed a striking dependence on the structure of the starting alcohol. Hence, a subtle balance of steric and conformational effects can be seen to govern the relative rates of competing ring enlargement pathways. In the case of **23**, a marked preference for the formation of **25** relative to **26** (14.4:1) was noted. Conjugated ketone **25** also predominated in the reaction mixture derived from **24**, but to a substantially lesser degree (3.3:1). A key element of these findings is that alkyl migration is favored for both stereoisomers.

It was subsequently observed that **7** adds stereospecifically to **27**[3] in a fashion characteristic of the system,[10] due in large measure to the rigid molecular topography of the enone. Examination of **28**, which contains a distal site of unsaturation, constituted the first test of whether dichlorocarbene chemoselectivity could be reasonably controlled in a useful way. In actuality, reaction of **28** with



27 **28** **29** **30**

thallium ethoxide and chloroform proceeded via exclusive

(7) Paquette, L. A.; Eizember, R. F.; Cox, O. *J. Am. Chem. Soc.* **1968**, *90*, 5153.

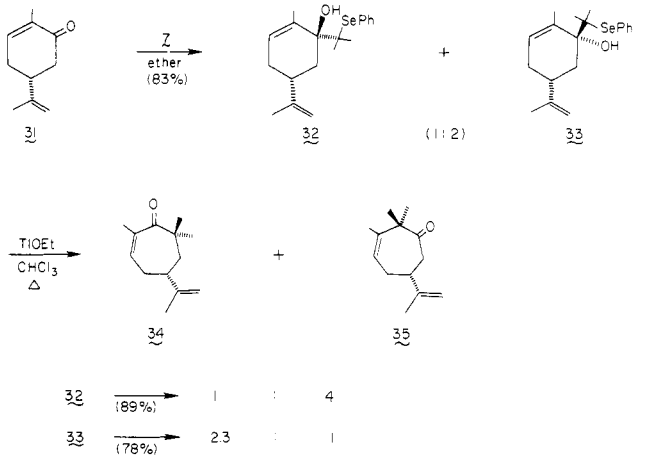
(8) Dauben, W. G.; Dietsche, T. J. *J. Org. Chem.* **1972**, *37*, 1212.

(9) Luche, J. L.; Rodriquez-Hahn, L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601.

(10) Ross, R. J., unpublished findings.

alkyl migration to give **29** (56%) and **30** (11%). In this instance, the added presence of an α'-methyl group forces the selenonium ion to position itself syn to the double bond. This conformational arrangement presumably sets the stage for direct access to the lowest energy transition state, such that the quaternary carbon ultimately finds itself located between the carbonyl and secondary alkyl groups. The predominance of **29** indicates that potential problems arising because of the presence of a second double bond are minimal.

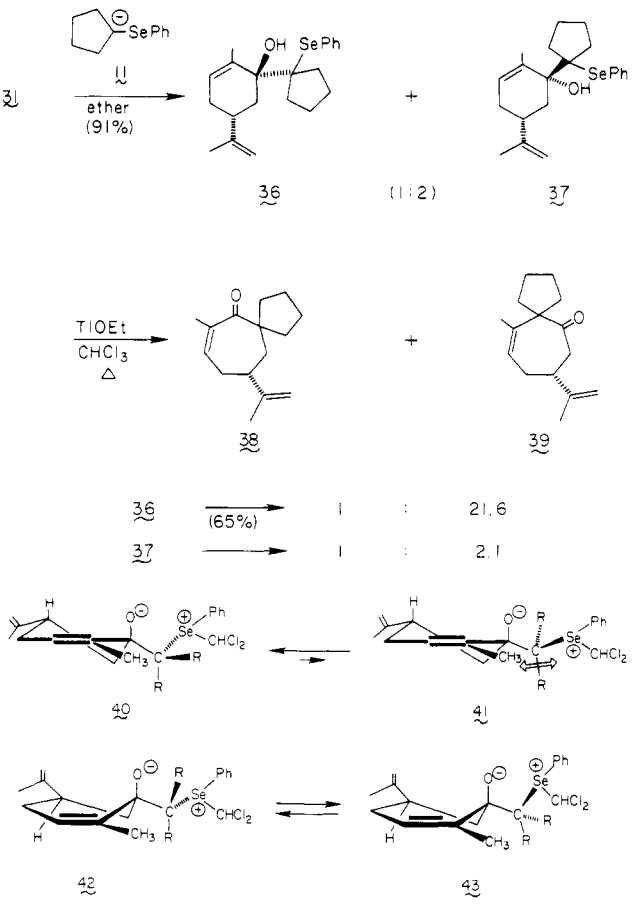
This conclusion was reinforced by the behavior of carvone (**31**). Van Ende and Krief had previously reported a relatively low yield (47%) in the conversion of **31** to **32** and **33** upon treatment with **7** in tetrahydrofuran solution.[6a] In our hands, a strong interdependence between



yield and reaction temperature was noted in this solvent. The use of ether at −78 °C, as in the previous examples studied herein, delivered the mixture of epimers much more efficiently (83%) and with **33** predominating as always. The assignment of stereochemistry was again based on literature precedent.[9,11] Whereas **32** underwent ring expansion to a 1:4 mixture of **34** and **35**, **33** was transformed to a mixture richer in **34** than **35** (2.3:1). The overall efficiencies with which these cycloheptenones were produced (89% and 78%, respectively) attest to the effectiveness with which dichlorocyclopropanation of the isopropenyl double bond can be curtailed.

Because **32** showed a predilection for vinyl migration while **33** engaged in preferential 1,2-alkyl shifting, we investigated whether replacement of the *gem*-dimethyl group by a cyclopentane ring as in **36** and **37** would give rise to a comparable divergence. Not unexpectedly, the percentage composition of **36** and **37** shows the same trend as that observed for **32** and **33**. Hydroxy selenide **36** was completely consumed within 2.5 h to afford in 65% yield a 1:21.6 mixture of **38** and **39**. In contrast, **37** reacted a great deal more slowly. Six hours were required to consume all of the starting material; however, only a 20% yield of **38** and **39** (1:2.1) was realized. Arresting the rearrangement after 2.5 h did not alter the product ratio, though it allowed for a 42% recovery of **37**. Unidentified polymer was produced in substantial quantity in both experiments.

Following the mechanistic logic presented earlier, it was anticipated that the need of the isopropenyl and selenium-substituted moieties to residue as much as possible in equatorial dispositions would dictate that the important reactive conformations be **40**–**43**. Accordingly, the ultimate fate of cis isomers **32** and **36** is dependent upon the attainability and relative reactivity of **40** and **41**. Molecular models reveal that the presence of a methyl group at the α-vinylic center favors the arrangement in **40** where CH_3 bifurcates the angle between the R groups and the selenonium ion is properly disposed for vinyl migration. Furthermore, conformation **40** would seem to be less strained relative to **41** when R = R = cyclopentyl than when R = R = CH_3 because of diminished nonbonded steric interactions. Rotation about the bond to the ring to arrive at **41** having the antiperiplanar arrangement required for alkyl migration brings enhanced steric interactions into play (see formula). Formation of this conformation should therefore be disfavored. Consequently, ring expansion should proceed via **40**, the more so in the case of **36**. On the assumption that **40** is also the more reactive conformation, this analysis correlates well with the experimental observations realized with this pair of stereochemically related isomers.



The situation that develops when the isopropenyl and selenonium groups find themselves in a trans relationship differs in an interesting way. Because of its reluctance to be axially oriented, the isopropenyl group exerts a force that drives the cyclohexene ring into a flatter topology (see **42** and **43**). As a result, rather different dihedral angle demands are placed upon the selenonium substituent for alignment anti to either migrating group. These not insignificant changes cause **42** and **43** to be much more closely aligned energetically than **40** and **41**. Under such circumstances, the electronic advantages associated with vinyl migration should take over, and they do to a certain extent with **37**. The same status quo is evidently not shared by **33** where alkyl migration is favored to some degree.

In summary, the present findings, with respect to the relative migratory ability of neighboring alkyl or vinyl

(11) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

groups, bear some similarity to Baeyer–Villiger oxidations.[12] Several useful features of the new ring expansion process include ready availability of the α-selenenyl anions, rather mild reaction conditions, generally high yields, and formation of potentially useful unsaturated ketone end products. The precise course of the ring enlargement is dictated by an interplay of electronic, steric, and conformational contributions. In geometrically unconstrained systems, vinyl migration can be expected to dominate. When more rigid molecular frameworks are involved, suitable evaluation of Dreiding models can to a first approximation suggest the migratory pathway that will operate preferentially. For these reasons, we expect that this reaction, colloquially referred to in this laboratory as the Krief rearrangement, will find a number of applications in organic symthesis.

Experimental Section

General Procedure for β-Hydroxy Selenide Preparation. A flame-dried, 25-mL, two-necked flask equipped with a 25-mL jacketed addition funnel was charged with a dry diethyl ether solution (6 mL) of the diphenyl diselenoketal[13] (5.40 mmol) under a nitrogen atmosphere. After the reaction mixture was cooled to −78 °C, *sec*-butyllithium in cyclohexane (4.9 mL, 1.1 M) was added dropwise, resulting in a cloudy bright yellow solution. This solution was stirred for 1 h at −78 °C before dropwise addition of a cold (−78 °C) solution of the enone (2.70 mmol) in dry diethyl ether (3 mL) was commenced. After being stirred for 1.5 h at −78 °C, the reaction mixture was quenched with water (10 mL) and allowed to warm to ambient temperature. The phases were separated, and the aqueous layer was extracted with either (2 × 20 mL). The combined ethereal extracts were washed with brine (10 mL), dried, and concentrated in vacuo. The products were purified by chromatography (MPLC, silica gel, elution with 1.5–6% ethyl acetate in petroleum ether).

8: IR (neat, cm^{-1}) 3510, 3080, 2990, 2950, 2880, 2850, 1590, 1485, 1470, 1465, 1445, 1380, 1330, 1310, 1145, 1135, 1100, 1075, 1030, 1010, 925, 900, 850, 700; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66–7.62 (m, 2 H), 7.38–7.25 (m, 3 H), 5.82–5.80 (m, 1 H), 2.55 (s, 1 H), 2.16–2.04 (m, 3 H), 1.63–1.53 (m, 4 H), 1.47 (s, 3 H), 1.38 (s, 3 H), 1.36 (s, 3 H); mass spectrum, m/z (M^+) calcd 324.0992, obsd 324.0970.

12: IR (neat, cm^{-1}) 3420, 3050, 3020, 2950, 2930, 2860, 2830, 1580, 1460, 1430, 1360, 1215, 1150, 1015, 960, 930, 750, 730, 685; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68–7.65 (m, 2 H), 7.39–7.26 (m, 3 H), 5.98–5.92 (m, 2 H), 2.19 (s, 1 H), 2.04 (s, 1 H), 1.95–1.71 (m, 5 H), 1.44 (s, 3 H), 1.32 (s, 3 H); mass spectrum, m/z (M^+) calcd 296.0680, obsd 296.0662.

15: IR (neat, cm^{-1}) 3490, 3080, 3040, 2960, 2880, 2840, 1630, 1590, 1480, 1440, 1405, 1355, 1330, 1170, 1070, 1030, 940, 730, 700; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68–7.64 (m, 2 H), 7.35–7.23 (m, 3 H), 5.94–5.88 (m, 1 H), 5.75–5.71 (br d, J = 10.2 Hz, 1 H), 2.19 (br s, 1 H), 2.10–1.56 (series of m, 14 H); mass spectrum, m/z (M^+) calcd 320.0843, obsd 320.0818.

23: mp 110.5–112 °C dec; IR (Nujol, cm^{-1}) 3550, 3060, 2930, 2860, 1465, 1378, 1365, 1260, 1250, 1040, 1025, 985, 960, 880, 835, 825, 775; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67–7.64 (m, 2 H), 7.40–7.25 (m, 3 H), 5.64 (br s, 1 H), 3.26 (dd, J = 5.46 and 10.22 Hz, 1 H), 2.22–1.20 (m, 11 H), 1.44 (s, 3 H), 1.30 (s, 3 H), 0.98 (s, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); mass spectrum, m/z ($M^+ - C_6H_6SeO$) calcd 320.2536, obsd 320.2575, and m/z ($M^+ - C_9H_{11}Se$) calcd 295.2093, obsd 295.2101.

24: IR (neat, cm^{-1}) 3480, 3080, 3060, 2940, 2860, 1470, 1460, 1440, 1360, 1260, 1250, 1080, 1040, 940, 920, 860, 830, 805, 770, 690; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68–7.65 (m, 2 H), 7.40–7.26 (m, 3 H), 5.71 (br s, 1 H), 3.42 (dd, J = 5.74 and 9.99 Hz, 1 H), 2.24 (dt, J = 4.33 and 7.5 Hz, 1 H), 2.16–0.97 (m, 10 H), 1.46 (s, 3 H), 1.32 (s, 3 H), 1.03 (s, 3 H), 0.90 (s, 9 H), 0.04 (s, 6 H); mass spectrum, m/z ($M^+ - C_6H_6SeO$) calcd 320.2536, obsd 320.2556.

28: IR (neat, cm^{-1}) 3490, 3075, 3020, 2860, 2940, 2900, 2860, 1650, 1585, 1480, 1470, 1440, 1380, 1365, 1260, 1090, 1060, 1030, 885, 840, 775, 695; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67–7.63 (m, 2 H), 7.44–7.20 (m, 3 H), 5.84–5.75 (m, 1 H), 5.72 (d, J = 2 Hz, 1 H), 5.57–5.47 (m, 1 H), 3.61 (d, J = 5.1 Hz, 1 H), 3.10–2.88 (m, 1 H), 2.85–2.72 (m, 1 H), 2.72–2.62 (m, 1 H), 2.35–2.10 (m, 2 H), 2.10–1.93 (m, 3 H), 1.90–1.67 (m, 4 H), 1.50 (s, 3 H), 1.29 (s, 3 H), 1.11 (d, J = 6.4 Hz, 3 H), 0.93 (s, 9 H), 0.79 (d, J = 5.8 Hz, 1 H), 0.08 (s, 3 H), 0.06 (s, 3 H); in this instance, the molecular ion peak was observed, but was too transient for high-resolution measurement.

32: IR (neat, cm^{-1}) 3460, 3080, 2975, 2930, 2860, 1670, 1650, 1585, 1480, 1455, 1440, 1375, 1305, 1160, 1115, 1040, 1025, 1000, 945, 908, 720, 695, 650; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70–7.62 (m, 2 H), 7.40–7.23 (m, 3 H), 5.65–5.60 (m, 1 H), 4.73 (br s, 2 H), 2.79–2.65 (m, 1 H), 2.59–2.48 (m, 1 H), 2.45–2.28 (m, 1 H), 2.08–1.88 (m, 1 H), 1.96 (br s, 3 H), 1.82–1.64 (m, 1 H), 1.74 (s, 3 H), 1.56 (br s, 1 H), 1.44 (s, 3 H), 1.25 (s, 3 H); mass spectrum, m/z ($M^+ - C_9H_{11}Se$) calcd 151.1123, obsd 151.1121.

33: IR (neat, cm^{-1}) 3490, 3080, 2975, 2925, 1650, 1580, 1480, 1440, 1375, 1305, 1160, 1120, 1075, 1055, 1020, 1000, 965, 945, 935, 810, 695; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70–7.62 (m, 2 H), 7.42–7.23 (m, 3 H), 5.75 (br d, J = 6.70 Hz, 1 H), 4.78–4.68 (m, 2 H), 2.80–2.47 (m, 1 H), 2.30 (br t, J = 12.00 Hz, 1 H), 2.18–2.03 (m, 1 H), 1.96 (t, J = 1.16 Hz, 3 H), 2.02–1.71 (m, 2 H), 1.74 (s, 3 H), 1.57 (br s, 1 H), 1.43 (s, 3 H), 1.39 (s, 3 H); mass spectrum, m/z ($M^+ - C_9H_{11}Se$) calcd 151.1123, obsd 151.1121.

36: IR (neat, cm^{-1}) 3500, 3080, 2960, 2880, 1650, 1585, 1480, 1440, 1375, 1305, 1160, 1055, 1025, 950, 890, 695; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72–7.61 (m, 2 H), 7.40–7.20 (m, 3 H), 5.69 (br d, J = 6.30 Hz, 1 H), 4.66 (br s, 1 H), 4.59 (br s, 1 H), 2.60–2.37 (m, 1 H), 2.37–1.52 (m, 13 H), 1.69 (br s, 3 H), 1.61 (br s, 3 H); mass spectrum, m/z ($M^+ - C_6H_7SeO$) calcd 201.1643, obsd 201.1604, ($M^+ - C_6H_8SeO$) calcd 200.1565, obsd 200.1594, and ($M^+ - C_{11}H_{13}Se$) calcd 151.1123, obsd 151.1093.

37: IR (neat, cm^{-1}) 3550, 3080, 3060, 2960, 2870, 1645, 1585, 1480, 1440, 1375, 1305, 1165, 1025, 1005, 945, 890, 810, 690; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66–7.63 (m, 2 H), 7.36–7.19 (m, 3 H), 5.63–5.56 (m, 1 H), 4.77–4.68 (m, 2 H), 2.53–2.34 (m, 3 H), 2.32–1.98 (m, 4 H), 1.98–1.52 (m, 7 H), 1.70 (s, 3 H), 1.68 (d, J = 1.65 Hz, 3 H); mass spectrum, m/z ($M^+ - C_6H_6SeO$) calcd 202.1722, obsd 202.1759, ($M^+ - C_6H_7SeO$) calcd 201.1643, obsd 201.1666, ($M^+ - C_6H_8SeO$) calcd 200.1565, obsd 200.1608, ($M^+ - C_{11}H_{13}Se$) calcd 151.1123, obsd 151.1112, and ($M^+ - C_{11}H_{14}Se$) calcd 150.1043, obsd 150.1050.

General Procedure for the Ring Expansions. A 25-mL, round-bottomed flask equipped with a reflux condenser and a nitrogen inlet was charged with the seleno alcohol (1.14 mmol), thallium ethoxide (0.40 mL, 5.70 mmol), and chloroform (8 mL). The reaction mixture was heated at reflux for 2.5 h, allowed to cool to ambient temperature, and quenched with water (2 mL). The mixture was filtered through Celite (2 g), and the Celite and residue were washed with ether (30 mL). The combined filtrates were diluted with water (10 mL), and the aqueous phase was extracted with ether (15 mL). The combined ethereal extracts were dried, evaporated, and chromatographed (MPLC, silica gel, elution with 1.5–2.5% ethyl acetate in petroleum ether).

9: IR (neat, cm^{-1}) 3015, 2980, 2940, 2840, 1710, 1470, 1460, 1450, 1440, 1380, 1360, 1350, 1230, 1140, 1120, 950, 920, 770; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.67–5.64 (m, 1 H), 2.06–2.03 (m, 2 H), 2.01 (s, 3 H), 1.79–1.75 (m, 2 H), 1.60–1.45 (m, 4 H), 1.17 (s, 6 H); mass spectrum, m/z ($M^+ - CH_3CO$) calcd 123.1173, obsd 123.1141.

13: IR (neat, cm^{-1}) 3020, 2960, 2930, 2870, 1665, 1469, 1450, 1420, 1393, 1380, 1357, 1305, 1265, 1200, 1108, 1071, 899, 811; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.26 (dt, J = 4.29 and 12.62 Hz, 1 H), 5.90 (dt, J = 1.93 and 12.62 Hz, 1 H), 2.38–2.32 (m, 2 H), 1.76–1.66 (m, 4 H), 1.13 (s, 6 H); mass spectrum m/z (M^+) calcd 138.1045, obsd 138.1045.

14: IR (neat, cm^{-1}) 3015, 2965, 2860, 1700, 1465, 1450, 1390, 1370, 1360, 1295, 1260, 1085, 950, 935, 910, 870, 840, 770, 720, 660; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.71–5.63 (m, 1 H), 5.47 (dd, J =

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1.1 and 11.1 Hz, 1 H), 2.65 (t, J = 6.9 Hz, 2 H), 2.09 (q, J = 6.8 Hz, 2 H), 1.88 (quint, J = 6.9 Hz, 2 H), 1.18 (s, 6 H).

16: IR (neat, cm^{-1}) 3010, 2940, 2860, 1650, 1450, 1420, 1380, 1200, 1150, 880, 770, 690, 640; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.30–6.24 (dt, J = 4.48 and 12.5 Hz, 1 H), 5.97–5.92 (dt, J = 2.0 and 12.5 Hz, 1 H), 2.39–2.20 (m, 2 H), 2.15–1.95 (m, 2 H), 1.80–1.70 (m, 2 H), 1.70–1.50 (m, 6 H), 1.48–1.30 (m, 2 H); mass spectrum, m/z (M^+) calcd 164.1201, obsd 164.1185.

17: IR (neat, cm^{-1}) 3020, 2960, 2860, 1705, 1470, 1450, 1440, 1355, 680; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.70–5.60 (m, 1 H), 5.52 (d, J = 11.2 Hz, 1 H), 2.65 (t, J = 6.5 Hz, 2 H), 2.25–2.08 (m, 4 H), 1.90 (quint, J = 6.5 Hz, 2 H), 1.78–1.50 (m, 6 H); mass spectrum, m/z (M^+) calcd 164.1201, obsd 164.1217.

25: IR (neat, cm^{-1}) 2960, 2940, 2870, 1670, 1625, 1475, 1465, 1455, 1385, 1365, 1310, 1260, 1255, 1100, 1075, 890, 850, 835, 775, 670; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.73 (d, J = 0.93 Hz, 1 H), 3.52–3.39 (m, 1 H), 2.34 (ddt, J = 1.32, 4.85, and 13.62 Hz, 1 H), 2.02–1.93 (m, 1 H), 1.85–1.40 (m, 7 H), 1.27 (tq, J = 4.39 and 13.31 Hz, 1 H), 1.10 (s, 3 H), 1.08 (s, 3 H), 1.03 (s, 3 H), 0.86 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H); mass spectrum, m/z ($M^+ - C_4H_9$) calcd 279.1780, obsd 279.1803.

26: IR (neat, cm^{-1}) 2970, 2940, 2860, 1712, 1670, 1475, 1380, 1365, 1260, 1250, 1100, 1085, 1030, 1010, 970, 960, 940, 860, 775, 670, 640; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.10 (d, J = 1.52 Hz, 1 H), 3.35 (dd, J = 4.71 and 10.92 Hz, 1 H), 2.68–2.44 (m, 2 H), 2.34–2.22 (m, 1 H), 1.94–1.48 (m, 7 H), 1.25 (s, 3 H), 1.18 (s, 3 H), 1.00 (s, 3 H), 0.86 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H); mass spectrum, m/z ($M^+ - C_4H_9$) calcd 279.1780, obsd 279.1780.

29: IR (neat, cm^{-1}) 3010, 2960, 2930, 2860, 1660, 1615, 1465, 1455, 1390, 1360, 1250, 1075, 1005, 960, 940, 910, 880, 830, 770; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.79 (s, 1 H), 5.78–5.70 (m, 1 H), 5.60–5.52 (m, 1 H), 3.54 (d, J = 5.8 Hz, 1 H), 3.18 (dt, J = 5.7 and 13.2 Hz, 1 H), 2.85–2.72 (br d, J = 16.0 Hz, 1 H), 2.62–2.51 (dq, J = 4 and 17 Hz, 1 H), 2.40–2.29 (dd, J = 7.7 and 16.7 Hz, 1 H), 2.10–1.85 (m, 5 H), 1.75–1.60 (m, 2 H), 1.30–1.26 (dd, J = 6.7 and 14.6 Hz, 1 H), 1.05 (s, 3 H), 1.01 (s, 3 H), 0.93 (d, J = 7.3 Hz, 3 H), 0.91 (s, 9 H), 0.024 (s, 3 H), 0.018 (s, 3 H); mass spectrum, m/z ($M^+ - C_4H_9$) calcd 331.2093, obsd 331.2080.

30: IR (neat, cm^{-1}) 2960, 2940, 2860, 1660, 1610, 1470, 1450, 1250, 1090, 1005, 950, 905, 850, 835, 770; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.97 (s, 1 H), 3.27 (d, J = 4.26 Hz, 1 H), 3.08–2.94 (dt, J = 6.3 and 13.3 Hz, 1 H), 2.20–1.45 (m, 12 H), 1.20–1.10 (dd, J = 6.25 and 14.6 Hz, 1 H), 1.06 (s, 3 H), 1.03 (s, 3 H), 0.95 (d, J = 7 Hz, 3 H), 0.90 (s, 9 H), –0.02 (s, 6 H); mass spectrum, m/z ($M^+ - C_4H_9$) calcd 413.1470, obsd 413.1466.

34: IR (neat, cm^{-1}) 3080, 2975, 2935, 2900, 2875, 1680, 1650, 1475, 1455, 1400, 1387, 1360, 1223, 1042, 1020, 840; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.94–5.90 (m, 1 H), 4.67–4.63 (m, 2 H), 2.39–2.12 (m, 3 H), 1.85 (q, J = 1.62 Hz, 3 H), 1.68 (t, J = 0.88 Hz, 3 H), 1.77–1.52 (m, 2 H), 1.17 (s, 3 H), 1.05 (s, 3 H); mass spectrum, m/z (M^+) calcd 192.1514, obsd 192.1517.

35: IR (neat, cm^{-1}) 3095, 3030, 2980, 2950, 2875, 1715, 1685, 1650, 1455, 1378, 1365, 1275, 1095, 890; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.45 (dt, J = 1.30 and 7.61 Hz, 1 H), 4.73–4.71 (m, 2 H), 2.82–2.63 (m, 2 H), 2.53–2.42 (m, 1 H), 2.14–1.92 (m, 2 H), 1.73 (s, 3 H), 1.70 (s, 3 H), 1.12 (s, 3 H), 1.11 (s, 3 H); mass spectrum, m/z (M^+) calcd 192.1514, obsd 192.1523.

38: IR (neat, cm^{-1}) 3080, 2960, 2875, 1675, 1650, 1450, 1375, 1220, 1060, 1025, 930, 890; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.05–5.98 (m, 1 H), 4.75–4.65 (m, 2 H), 2.38–2.25 (m, 4 H), 1.97–1.36 (m, 9 H), 1.88 (t, J = 1.60 Hz, 3 H), 1.70 (t, J = 0.97 Hz, 3 H); mass spectrum, m/z (M^+) calcd 218.1671, obsd 218.1660.

39: IR (neat, cm^{-1}) 3098, 3030, 2970, 2950, 2880, 1710, 1650, 1455, 1445, 1380, 1330, 1275, 1220, 1135, 1070, 1030, 890, 840; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.46 (dt, J = 1.29 and 7.48 Hz, 1 H), 4.75–4.72 (m, 2 H), 2.71 (dd, J = 8.46 and 13.15 Hz, 2 H), 2.53 (dd, J = 11.82 and 13.95 Hz, 1 H), 2.24–1.95 (m, 4 H), 1.88–1.55 (m, 6 H), 1.76 (s, 3 H), 1.71 (s, 3 H); mass spectrum, m/z (M^+) calcd 218.1671, obsd 218.1671.

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Investigation of the Formation of Methyl 2-Cyano-2-[(trimethylsilyl)oxy]-4-oxopentanoate from Methyl 2,4-Dioxopentanoate. A Clarification of the Pathway for the Reaction of Trimethylsilyl Cyanide with Enolized β-Diketones

Louise H. Foley

Department of Chemistry, University of New Hampshire, Durham, New Hampshire 03824

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The possible reaction pathways for the reaction of methyl 2,4-dioxopentanoate (1) with trimethylsilyl cyanide, with and without catalysts present, have been investigated by monitoring these reactions by ^1H NMR. While all reactions of 1 with Me_3SiCN, whether catalyzed or uncatalyzed, involve the initial formation of the silyl enol ether **5**, it is not an intermediate in the formation of the cyanohydrin **3** from the reaction of 1 with Me_3SiCN alone or in the presence of ^-CN. Evidence is presented which indicates that the silyl enol ether **5** and HCN are in equilibrium with 1 and Me_3SiCN and that it is the keto tautomer **1a**, containing a very reactive α-keto ester group, which reacts with Me_3SiCN to produce **3** (Scheme III). The existence of the equilibrium **5** + HCN ⇌ 1 + Me_3SiCN is demonstrated by isolation of the cyclic silyl enol ether cyanohydrin **9** when the silyl enol ether **5** is allowed to react with $Me_2Si(CN)_2$. Evidence that trialkylsilyl cyanides react with the keto tautomer of 1, and the exclusion of other possible reaction pathways, is obtained on reaction of 1 with *t*-$BuMe_2SiCN$ to give the *tert*-butyldimethylsilyl enol ether **10** and the unprotected cyanohydrin **11**. The reaction of 2,4-pentanedione (**4**) with Me_3SiCN, with and without the presence of catalysts, was reinvestigated and the mechanism is shown, in contrast with the earlier proposals,[5,6] to be consistent with the mechanistic ideas presented here for the reaction of 1 with Me_3SiCN.

Previously we reported[1] that treatment of 1 at room temperature with 1 equiv of trimethylsilyl cyanide (Me_3SiCN) and a catalytic amount of zinc iodide[2,3] gave a 1:1 mixture of the trimethylsilyl-protected cyanohydrin enol ether **2** and starting material and that by increasing

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