7-(β-D-Ribofuranosyl)imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-Dioxide (9c). A mixture of 1.06 g (6.2 mmol) of imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide (**8a**), 58 g of hexamethyldisilazane, and $(CH_3)_3SiCl$ (1.2 mL) was heated under reflux for 20 h with the exclusion of moisture and then evaporated to dryness under vacuum. To the residue was added 160 mL of dry CH_3CN, 3.42 g (6.8 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, and $SnCl_4$ (1.0 mL). The mixture was stirred at room temperature for 3 h, neutralized to ca. pH 8 with $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried (Na_2SO_4), evaporated to dryness, and chromatographed on silica gel (1:1 petroleum ether/ethyl acetate) to yield the tribenzoyl derivative of **9c**, 3.21 g (84%), as colorless crystals: mp 124–126 °C; NMR δ 11.32 (s, 1, exch NH), 8.11–7.89 (m, 8, C(3)H, C(6)H, and C_6H_5), 7.60–7.32 (m, 9, C_6H_5's), 6.34 (d, 1, J = 4.3 Hz, C(1)'H), 6.09–5.99 (m, 2, C(2)'H and C(3)'H), 4.98–4.86 (m, 3, C(4)'H, C(5)'H_2).

Anal. Calcd for $C_{30}H_{24}N_4O_9S$: C, 58.44; H, 3.92; N, 9.09; S, 5.20. Found: C, 58.46; H, 3.98; N, 8.85; S, 5.21.

A solution of 1.36 g (2.2 mmol) of 7-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxide in 150 mL of methanolic ammonia was allowed to react at 20 °C for 2 days, was evaporated to about 15 mL, and was added to 150 mL of CH_2Cl_2 to precipitate the ammonium salt of **9c**; 0.50 g (75%). The salt was converted to **9c** by percolating a CH_3OH solution of the product over a column containing Bio-Rad AG-50 (H^+) and eluting with MeOH. Removal of the solvent under vacuum afforded **9c**, 0.45 g (69%), as colorless crystals: mp 166–169 °C; $[\alpha]^{20}_D$ −48° (*c* 4, H_2O); NMR (Me_2SO-d_6) δ 13.16 (br d, 1, exch NH), 8.39 (s, 1, C(6)H), 7.94 (d, 1, C(3)H), 5.69 (d, 1, J = 4.9 Hz, C(1)'H), 5.57 (d, 1, exch OH), 5.11 (b, 1, exch OH), 4.93 (b, 1, exch OH), 4.39 (b, 1, C(2)'H), 4.08–3.95 (m, 2, C(3)'H and C(4)'H), 3.63 (s, 2, C(5)'H). Addition of D_2O gave 8.37 (s, 1, C(6)H), 7.92 (s, 1, C(3)H), 5.70 (d, 1, J = 4.9 Hz, C(1)'H), 4.42 (t, 1, J = 4.9 Hz, C(2)'H), 4.09 (t, 1, J = 4.9 Hz, C(3)'H), 3.98 (m, 1, C(4)'H), and 3.67 (m, 2, C(5)'H). Irradiation at 5.70 ppm gave a 20% increase in the integration at 8.37 ppm. Irradiation at 4.42 ppm caused the doublet at 5.70 ppm to collapse to a singlet. The analytical sample was dried under vacuum (P_2O_5, 20 °C) overnight.

Anal. Calcd for $C_9H_{12}N_4O_6S$: C, 35.53; H, 3.98; N, 18.41; S, 10.54. Found: C, 35.48; H, 4.03; N, 18.22; S, 10.51.

The isopropylidine derivative of **9c** was prepared by reacting a solution of **9c** (0.25 g, 0.8 mmol) in 30 mL of dry acetone with 2 drops of concentrated H_2SO_4 overnight and then neutralizing with NaOEt. The solution was filtered, and the filtrate was evaporated to dryness to afford an oil. This was purified by preparative TLC (silica gel developed in 7.5% CH_3OH in EtOAc), eluted with CH_3OH, and recrystallized from CH_3OH/EtOAc to afford 195 mg (65%) of the isopropylidine derivative of **9c** as the sodium salt: mp 272 °C dec; NMR δ 7.94 (s, 1, CH), 7.14 (s, 1, CH), 5.85 (d, 1, J = 3.3 Hz, C(1)'H), 5.27–5.06 (m, 1, C(2)'H), 4.86–4.77 (m, 2, C(3)'H and 5'-OH), 4.04 (m, 1, C(4)'H), 3.54 (m, 2, C(5)'H), 1.51 (s, 3, CH_3), 1.29 (s, 3, CH_3).

Anal. Calcd for $C_{12}H_{15}N_4O_6SNa$: C, 39.36; H, 4.10; N, 15.30; S, 8.76. Found: C, 39.18; H, 4.03; N, 15.24; S, 8.78.

Acknowledgment. We express our appreciation to Dr. George Bosworth Brown for his encouragement and support and thank Mary Jane Lauzon and Michael T. Ricciardi for skilled technical assistance and Marvin J. Olsen, who was supported in part by Grant No. CA 17085, for determining the NMR spectra. Mass spectra were performed at the Mass Spectrometric Biotechnology Resource at the Rockefeller University, New York, NY, which is supported in part by Grant No. RR-862-01 from the Division of Research Facilities and Resources, NIH.

Registry No. 1a, 71518-15-5; **1b**, 71518-16-6; **2**, 6963-63-9; **3a**, 6339-55-5; **3b**, 71518-17-7; **4a**, 71518-18-8; **4b**, 71537-27-4; **5**, 61006-94-8; **6a**, 71518-19-9; **6b**, 71518-20-2; **7a**, 71518-21-3; **7b**, 71518-22-4; **8a**, 71518-23-5; **8b**, 71518-24-6; **9a**, 71518-25-7; **9b**, 71518-26-8; **9c**, 71518-27-9; **9c** tribenzoyl derivative, 71518-28-0; **9c** ammonium salt, 71518-29-1; **9c** isopropylidine derivative sodium salt, 71518-30-4; **10**, 71518-31-5; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, 6974-32-9.

Structures and Mechanisms of Formation of the Major Side Products from the Preparation of 4,4-Dimethylcyclohex-2-enone by the Potassium Hydroxide Promoted Annelation of Methyl Vinyl Ketone and Isobutyraldehyde†

Herman O. Krabbenhoft

Chemical Synthesis and Engineering Branch, General Electric Corporate Research and Development Center, Schenectady, New York 12301

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Reaction of equimolar quantities of methyl vinyl ketone and isobutyraldehyde in aqueous methanol in the presence of potassium hydroxide produced 4,4-dimethylcyclohex-2-enone (**1**, 38%), 3-methoxy-4,4-dimethylcyclohexanone (**2**, 2%), (*E*)-4,4-dimethyl-6-(2-methylpropylidene)cyclohex-2-enone (**3**, 25%), 4,4-dimethyl-2-(1-hydroxy-2-methylpropyl)cyclohex-2-enone (**4**, 14%), and 6,6-dimethyl-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone (**5**, 3%). The structures of compounds **2–5** were elucidated from spectral data. Increasing the molar ratio of methyl vinyl ketone to isobutyraldehyde from 2:2 to 2:1.5 to 2:1 resulted in modest improvements in the yield of **1** (42 and 47%, respectively). The mechanisms for formation of the major side products **2–5** are discussed. It was found that 3,4,4-trimethylcyclohex-2-enone and 4,4,5-trimethylcyclohex-2-enone do not interconvert when treated with potassium carbonate in aqueous methanol; similarly, no crossover was observed between 2,4,4-trimethylcyclohex-2-enone and 4,4,6-trimethylcyclohex-2-enone. These results suggested that hydroxy ketone **4** was not formed via a pathway involving a [1,5] sigmatropic shift of hydrogen but rather by an aldol reaction between 3-hydroxy-4,4-dimethylcyclohex-2-enone (or **2**) and isobutyraldehyde followed by the loss of water (or methanol).

In connection with another study, 4,4-dimethylcyclohex-2-enone (**1**) was required. The method usually chosen for the preparation of **1** has been the base-promoted annelation reaction involving methyl vinyl ketone and isobutyraldehyde (eq 1),[1-8] although the enamine approach[9]

† Dedicated to Professor William G. Dauben on the occasion of his 60th birthday.

(1) Franke, W.; Bueren, J. German Patent 833645, 1952.
(2) Eliel, E. L.; Lukach, C. A. *J. Am. Chem. Soc.* **1957**, *79*, 5986.
(3) Bergmann, E. D.; Corret, R. *J. Org. Chem.* **1958**, *23*, 1507.

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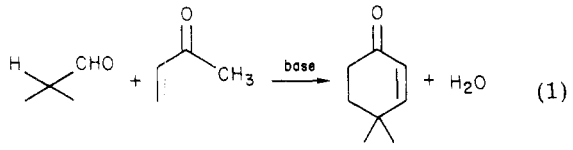
(eq 2) has also been demonstrated to be useful.[10] The



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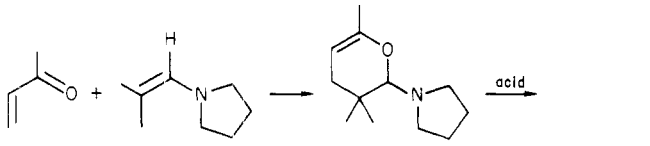

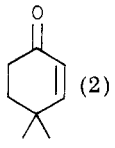

(2)

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yields of 1 (purity not specified) prepared according to eq 1 are in the range of about 25–45%.[1-8] In none of these reports (where explicit experimental details were given) was any mention made of side products and material balance.[11] In this paper, these important points are addressed.

Results and Discussion

Basically, we followed the procedure of Eliel and Lukach for the preparation of 1;[2,6,7] our results are summarized in Table I. The overall material balance was close to 90%, which is pretty good considering that no attempt was made to recover any of the volatile, unreacted starting materials. Fractions 1–3 were virtually pure 4,4-dimethylcyclohex-2-enone (1), which corresponds to a yield of 35%. The identity of 1 was confirmed by spectral data and further by its conversion in 93% yield to 4,4-dimethylcyclohexanone by catalytic hydrogenation.[7] Preparative gas chromatography was utilized to obtain pure samples of the major side products **2–5** in order to elucidate their structures.

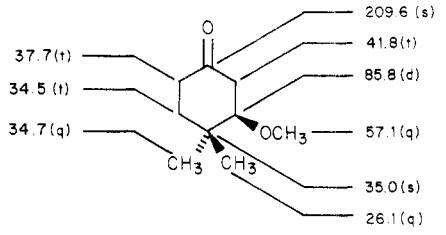
Structure of 2. The mass spectrum of **2** displayed a molecular ion at *m/e* 156. Combining this information with its elemental analysis gave a molecular formula of $C_9C_{16}O_2$. The infrared spectrum of **2** showed a carbonyl band at 1720 cm^{-1} (consistent with a saturated cyclohexanone) and a C–O–C absorption signal at 1100 cm^{-1};

Table I. Preparation of 4,4-Dimethylcyclohex-2-enone from Methyl Vinyl Ketone and Isobutyraldehyde in a 2:2 Molar Ratio[a]

fraction	amt, g	bp,[b] °C (mmHg)	composition[c] 1	2	3	4	5
1[d]	6.7	85 (27)	>95				
2[d]	66.9	85-90 (27-28)	>95				
3[d]	14.1	90-95 (25)	>95				
4[e]	22.9	95 (25)	35	19	46		
5[e]	13.0	95-135 (26)		8	74	18	
6[f]	40.1	135-110 (26)			53	38	9
7[f,g]	18.8	110 (26)			16	49	35
residue[h]	38.7		not analyzed				

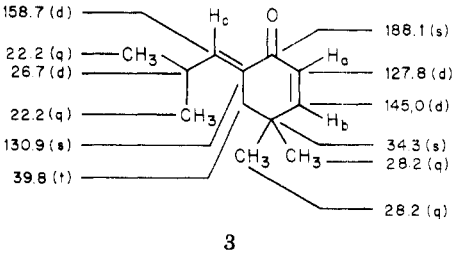
[a] See Experimental Section for details. [b] Not corrected. [c] Weight percent according to gas chromatography and/or carbon-13 NMR integrations of the geminal methyl groups. [d] Water white. [e] Slightly yellow. [f] Yellow. [g] A few other relatively minor, unidentified materials were also present. [h] Dark brown, glassy solid.

there were no signals for hydroxyl or olefinic groups. The key features of the proton magnetic resonance spectrum of **2** were three methyl singlets at 3.37 ppm [OCH_3] and 1.15 and 1.08 ppm [$C(CH_3)_2$] and a one-proton signal at approximately 3.1 ppm attributable to a hydrogen attached to a carbon also bearing oxygen. These data are consistent with 4,4-dimethyl-3-methoxycyclohexanone as the structure of **2**. The carbon-13 nuclear magnetic resonance spectral data (given in ppm with the structural formula) are also in accord with the assignment.



2

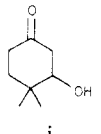
Structure of 3. The mass spectrum of side product **3** exhibited a molecular ion at *m/e* 178, which in conjunction with its elemental analysis gave a molecular formula of $C_{12}H_{18}O$. The infrared spectrum of **3** showed key absorptions at 3025 cm^{-1} (olefinic carbon–hydrogen stretch) and 1675 and 1630 cm^{-1} (cross-conjugated dienone carbonyl stretch). Diagnostic features in the proton magnetic resonance spectrum were one-proton doublets at δ 6.02 (J = 10 Hz) and δ 6.55 (J = 10 Hz) (due to H_a and H_b, respectively), a slightly broadened one-proton doublet at δ 6.51 (J = 9 Hz) (assigned to H_c), a broad three-proton signal at about δ 3.0–2.4 (attributable to the three allylic protons), a six-proton doublet at δ 1.07 (J = 8 Hz) (for the isopropyl methyl hydrogens), and a six-proton singlet at δ 1.18 (due to the geminal dimethyl protons). On the basis of these data, compound **3** has the structure shown. Additional



3

support for the proposed structure of **3** obtains from its carbon-13 magnetic resonance spectral parameters (given in ppm with the structural formula).[12]

(4) Conia, J.-M.; LeCraz, A. *Bull. Soc. Chim. Fr.* **1960**, 1934.
(5) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 1347.
(6) Dauben, W. G.; Shaffer, G. W.; Vietmeyer, N. D. *J. Org. Chem.* **1968**, *33*, 4060.
(7) Cook, K. L.; Waring, A. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 529.
(8) Paris, C.; Geribaldi, S.; Torri, G.; Azzard, M. *Bull. Soc. Chim. Fr.* **1973**, 997.
(9) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.
(10) (a) Chan, Y.; Epstein, W. W. *Org. Synth.* **1973**, *53*, 48. (b) Smith, H. A.; Huff, B. J. L.; Powers, W. J., III; Caine, D. *J. Org. Chem.* **1967**, *32*, 2851. (c) Harris, R. L. N.; Komitsky, F., Jr.; Djerassi, C. *J. Am. Chem. Soc.* **1967**, *89*, 4765. (d) Rettig, T. A. "The Photochemistry of Some 2-Cyclohexenones", University Microfilms International: Ann Arbor, Michigan, 1966; p 176.
(11) Franke and Bueren claimed that they also isolated the ketol i in



i

20% yield, although no data whatsoever in support of such a structure assignment were supplied.[1]

Scheme I

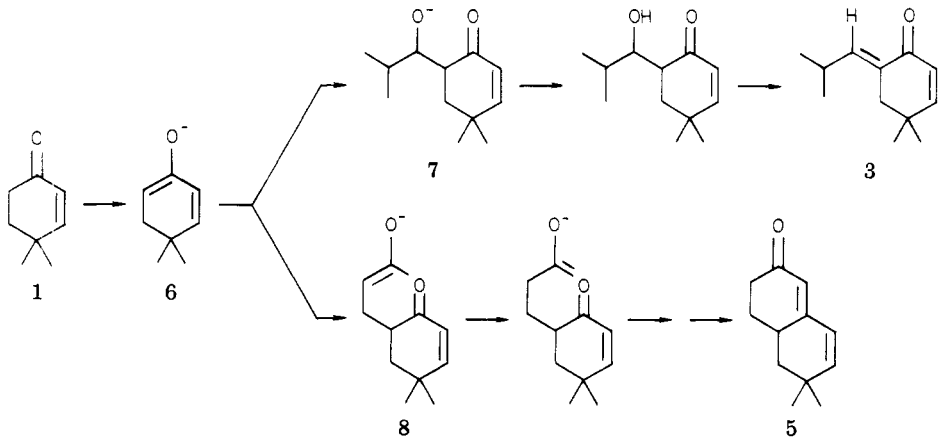


Table II. Preparation of 4,4-Dimethylcyclohex-2-enone from Methyl Vinyl Ketone and Isobutyraldehyde in a 2:1.5 Molar Ratio[a]

fraction	amt, g	bp,[b] °C (mmHg)	composition[c] 1	2	3	4	5
1[d]	1.7	81-82 (25)	>95				
2[d]	62.5	82-93 (26)	>95				
3[d]	11.9	93 (26)	>95				
4[e]	16.9	93-135 (26)	22	13	65		
5[f]	18.8	135-147 (26)			62	22	16
6[f]	5.3	147-132 (26)			6	43	51
residue[h]	63.6		not analyzed				

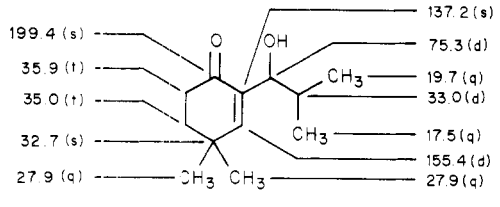
[a] See Table I for footnote explanations.

Table III. Preparation of 4,4-Dimethylcyclohex-2-enone from Methyl Vinyl Ketone and Isobutyraldehyde in a 2:1 Molar Ratio[a]

fraction	amt, g	bp,[b] °C (mmHg)	composition[c] 1	2	3	4	5
1[d]	4.6	75-82 (23)	>95				
2[d]	43.1	82-86 (23)	>95				
3[d]	8.1	86-91 (23)	>95				
4[e]	4.2	91-120 (22)	64	18	18		
5[e]	11.0	122-143 (21)	10	10	62	10	8
6[f]	4.9	143-145 (21)			64	18	18
7[f]	20.6	88-115 (0.5)			17	29	54
residue[h]	73.0		not analyzed				

[a] See Table I for footnote explanations.

Structure of 4. The mass spectrum of **4** showed a weak molecular ion at *m/e* 196 and the base ion at *m/e* 153. The elemental analysis established that the molecular formula of **4** was $C_{12}H_{20}O_2$. The infrared spectrum of **4** showed diagnostic absorptions at 3460 cm^{-1} (hydroxyl) and 1665 cm^{-1} (α,β-unsaturated ketone carbonyl). The proton magnetic resonance spectrum showed *only* a one-proton singlet (at δ 6.60) in the olefinic region, a one-proton doublet at δ 3.98 (J = 7 Hz), a one-proton slightly broadened singlet (which disappeared on treatment with D_2O) at δ 3.17, a slightly distorted two-proton triplet at δ 2.50, a complex multiplet at about 2.2–1.6 ppm integrating for three protons, a six-proton singlet at δ 1.20, and two three-proton doublets at δ 0.92 (J = 6 Hz) and δ 0.82 (J = 6 Hz). Combining the above data with the carbon-13 magnetic resonance data (given in ppm with the structural formula), one can confidently assign the identity of **4** to 4,4-dimethyl-2-(1-hydroxy-2-methylpropyl)cyclohex-2-enone.



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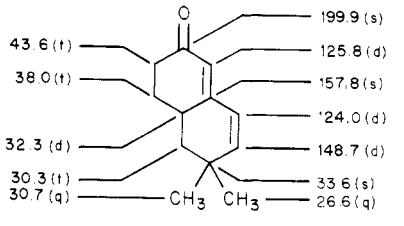
Structure of 5. The mass spectrum showed a molecular ion at *m/e* 176, and the elemental analysis gave the molecular formula of $C_{12}H_{16}O$. The infrared spectrum of **5** showed diagnostic absorptions at 3020, 1660, 1620, and 1590 cm^{-1}, consistent with a conjugated dienone unit. The proton magnetic resonance spectrum showed three olefinic protons as a multiplet at δ 6.0–5.8, complex absorption signals from about 2.7 to 1.3 ppm (integrating for seven protons), and a slightly broadened six-proton singlet at δ 1.2. On the basis of the above data, the carbon-13 magnetic resonance spectral parameters (given in ppm with the structural formula), and the excellent agreement of the



5

empirically determined wavelength of maximum absorption [λ_{max} (95% ethanol) 281 nm (log ϵ 4.34)] with the value of 280 nm predicted by the Woodward rules,[13] the side product **5** is 6,6-dimethyl-4,4a,5,6-tetrahydro-2(3*H*)-naphthalenone.

Having elucidated the structures of major side products **2–5**, we turned our attention toward trying to avoid the side reactions. It is obvious that a significant part of the problem is due to the presence of isobutyraldehyde which becomes an excess reagent as the methyl vinyl ketone is consumed in competing polymerization reactions. In order to circumvent the problem of depletion of methyl vinyl ketone, excess methyl vinyl ketone was used. The results are collected in Tables II and III. The overall material

(12) The dienone **3** can exist in two diastereomeric forms: the *E* isomer (shown) and the *Z* isomer. Apparently, only one of the two isomers is formed to any significant extent (as a result of thermodynamic control), although which isomer is not yet known with certainty. On the basis of proton magnetic resonance data for the *E* and *Z* isomers of 2-ethenylcyclohexanone [Paquette, L. A.; Eizember, R. F. *J. Am. Chem. Soc.* **1967**, *89*, 6205. Crandall, J. K.; Arrington, J. P.; Hen, J. *Ibid.* **1967**, *89*, 6208] the *E* isomer of **3** is the one produced (in major amount).

(13) Williams, D. H.; Fleming, I. "Spectroscopic Methods in Organic Chemistry", McGraw-Hill: London, 1966; p 23.

Scheme II

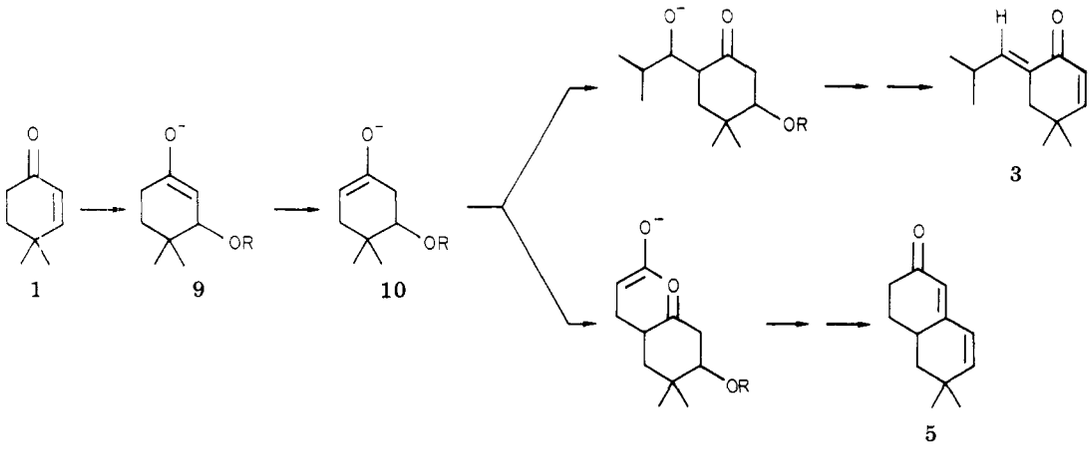


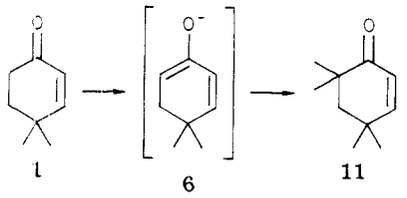
Table IV. Overall Yield Data (%) for the Production of Compounds 1-5[a]

MVK/IBA[b]	1	2	3	4	5	IBA[c]
2/2	38	2	25	14	3	83
2/1.5	42	1	17	5	2	67
2/1	47	1	16	9	7	80

[a] Yields were calculated from data in Tables I–III and are based upon the amount of isobutyraldehyde (IBA) started with (MVK = methyl vinyl ketone). [b] Molar ratio of methyl vinyl ketone to isobutyraldehyde. [c] Percent of isobutyraldehyde that ended up in products 1-5.

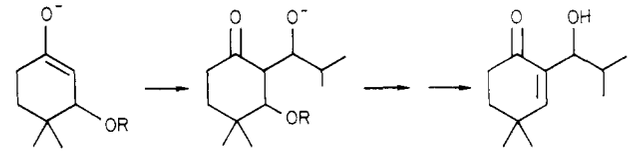
balances for the reactions summarized in Tables II and III were approximately 80 and 87%, respectively, while the yields of purified enone 1 (i.e., fractions 1–3 in each case) were 41 and 45%, respectively. The overall yields for the production of compounds 1–5 are presented in Table IV. Thus, only modest improvements in the yield of 1 ensued by increasing the relative amount of methyl vinyl ketone.

The mechanisms by which side products 2–5 are formed merit discussion. The methoxy derivative 2 is probably produced by the conjugate addition of methoxide anion to enone 1 in a straightforward fashion. However, for compounds 3–5 at least two reasonable mechanistic interpretations can be advanced for the generation of each substrate. Schemes I and II portray the two possible routes envisioned for the formation of dienones 3 and 5. In Scheme I, the enolate 6 is generated from enone 1 and subsequently alkylated by either isobutyraldehyde or methyl vinyl ketone to produce species 7 and 8, respectively. Protonation of 7 followed by loss of water would provide 3. Enolate isomerization within 8 followed by cyclization and dehydration would afford 5. Alternatively, as illustrated in Scheme II, enone 1 could first undergo a conjugate addition of a nucleophile to give enolate 9 (R = H or CH_3) which could isomerize to 10, which could then react with isobutyraldehyde or methyl vinyl ketone in standard fashion and go on ultimately to the observed products 3 and 5. There is evidence which is corroborative of each pathway. Thus, in support of Scheme I it has been reported that enone 1 was converted into 4,4,6,6-tetramethylcyclohexenone (11) by treatment with a strong, nonnucleophilic base [sodium amide or sodium bis(trimethylsilyl)amide] followed by methyl iodide (eq 3).[14]

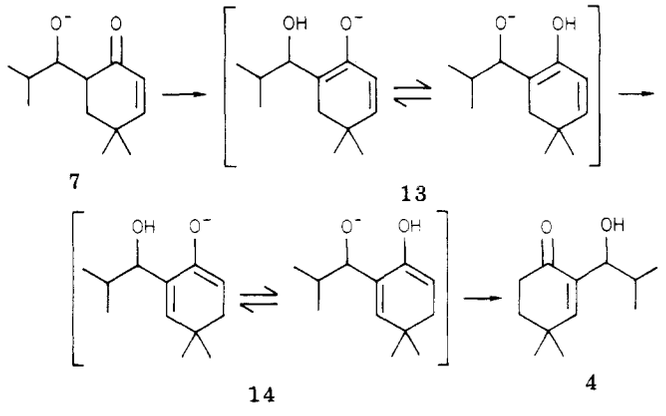


(3)

Scheme III



Scheme IV



And the isolation of the methoxy compound 2 supports the mechanism outlined in Scheme II. It may well be that both pathways (Schemes I and II) are operative.

For the formation of the hydroxy enone 4, the two possible mechanistic interpretations advanced are shown in Schemes III and IV. In the former proposal (Scheme III), enolate 9 reacts with isobutyraldehyde to give the keto alkoxide 12, which goes on to 4 by way of protonation and elimination of ROH. In the latter proposal (Scheme IV), keto alkoxide 7 isomerizes to hydroxy enolate 13, which then undergoes a [1,5] sigmatropic shift of hydrogen to produce the hydroxy enolate 14, which upon protonation affords 4. With regard to the mechanism outlined in Scheme IV, it must be pointed out that in previous examples of [1,5] sigmatropic shifts of hydrogen in cyclohexadienes rather elevated temperatures (approximately 300 °C) were required;[15] in the present work the reaction temperatures were in the range of 70–80 °C. Therefore, the proposal of Scheme IV might not seem to be a likely possibility. However, it has recently been demonstrated for the oxy-Cope rearrangement (a [3,3] sigmatropic shift

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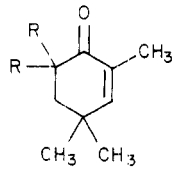
Table V. Carbon-13 NMR Shieldings (ppm) of Enones 1 and 15-18[a]

compd	C-1	C-2	C-3	C-4	C-5	C-6	C-7a	C-7e	other
1	198.25	126.82	159.18	32.72	34.32	36.13	27.64	27.64	
15	199.26	132.60	154.80	32.95	34.51	36.51	28.03	28.03	15.93
16	201.35	126.56	158.41	33.66	45.23	37.67	25.47	30.57	15.00
17	199.11	126.27	169.01	35.38	34.45	37.64	26.26	26.26	20.05
18	199.56	126.55	160.60	35.98	38.34	38.34	20.07	27.62	15.84

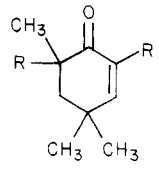
[a] In ppm from internal Me_4Si.

of carbon) that conversion of diene alcohols to diene alkoxides results in observed rate accelerations of 10^{10}–10^{17}; the reactions were fastest with potassium alkoxides.[16] Similar results have been reported for [1,3] and [1,5] sigmatropic rearrangements.[17] Since the key intermediate (**13**) in Scheme IV is also an enolate with a potassium counterion, the aforementioned difficulty associated with Scheme IV might in fact not be severe.

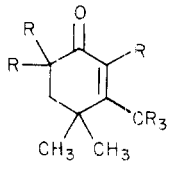
In order to gain some insight to the feasibility of the hypothesis of Scheme IV, the following experiments were conducted. Treatment of 2,4,4-trimethylcyclohex-2-enone (**15**) with potassium carbonate in D_2O/CD_3OD at 85 °C for 6 h [conditions similar to those used in the preparation of **1** (and **2**–**5**)] gave only the 6,6-dideuterio analogue **15a**. Similarly, 4,4,6-trimethylcyclohex-2-enone (**16**) gave only its 2,6-dideuterio counterpart **16a**. There was no detect-



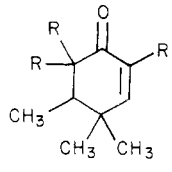
15, R = H
15a, R = D



16, R = H
16a, R = D



17, R = H
17a, R = D



18, R = H
18a, R = D

able crossover between **15**/**15a** and **16**/**16a**. Parallel results were also found with the 3,4,4- and 4,4,5-trimethylcyclohex-2-enones **17** and **18**. Therefore, it would appear that the [1,5] sigmatropic shift mechanism (Scheme IV) is untenable and that **4** arises via the pathway shown in Scheme III. To test this conclusion, enone **1** was treated with 1 equiv of isobutyraldehyde and potassium hydroxide in aqueous methanol. The only products formed were ketones **2**, **3**, and **4** in the approximate ratios 1.5:1.0:3.2, respectively; this result is consistent with the mechanism of Scheme III (as well as Schemes I and/or II for the formation of dienones **3** and **5**).

Experimental Section

Materials. The methyl vinyl ketone and isobutyraldehyde were distilled before use. Enones **15**–**18** were prepared according to published procedures and exhibited spectral characteristics in agreement with those reported previously;[18] samples of **15**–**18** were purified by preparative-scale gas chromatography. The carbon-13 NMR shieldings of enone **1** and **15**–**18** are presented in Table V.[19]

General Comments. Boiling points are uncorrected. Mass spectra were measured with a Du Pont CEC 21104 mass spectrometer at 70 eV. Infrared spectra were recorded (neat films) with a Perkin-Elmer 457 spectrophotometer. ^1H NMR spectra were obtained with a Varian Associates T-60 instrument employing deuteriochloroform solutions with internal tetramethylsilane (Me_4Si) as the reference. ^{13}C NMR spectra were obtained with Varian CFT-20, Varian XL-100, and Varian CFT 80 instruments employing deuteriochloroform solutions with internal Me_4Si as the reference. Ultraviolet spectra were recorded on a Cary 14 spectrophotometer. Gas chromatographic analyses and preparations were carried out with a Varian Aerograph 1520 instrument equipped with a 5 ft × 0.25 in. aluminum column packed with 20% SE-30 on Chromosorb W. Elemental analyses were carried out by the Materials Characterization Branch at the GE Corporate Research and Development Center, Schenectady, NY.

General Procedure for Preparation of 1–5.[2,6,7] In a three-necked round-bottomed 1-L flask equipped with a mechanical stirrer, a Claisen adaptor fitted with a thermometer and a condenser, and an additional funnel charged with a solution of 140.2 g (2.00 mol) of methyl vinyl ketone, 144.2 g (2.00 mol) of isobutyraldehyde, 200 mL of H_2O, and sufficient CH_3OH (approximately 150 mL) to render the mixture homogeneous were placed 7.4 g of potassium hydroxide and 40 mL of CH_3OH. While the mixture was stirred and maintained at a temperature of 75–80 °C with a heating mantle, the contents of the addition funnel were discharged dropwise. After addition was complete, stirring was continued for 1 h, and then the reaction mixture cooled to room temperature and processed by diluting with 300 mL of H_2O and extracting with ether (4 × 200 mL and 3 × 100 mL). The combined extracts were washed with H_2O and saturated aqueous NaCl solutions, dried over $MgSO_4$, filtered, and concentrated with a rotary evaporator to give 223.6 g of a golden brown liquid which was distilled (see Table I).

In the preparations of **1**–**5** employing methyl vinyl ketone/isobutyraldehyde ratios of 2:1.5 and 2:1 (Tables II and III) the only changes in the above procedure were the amounts of isobutyraldehyde used.

General Procedure for Deuteration of 15–18. In a 5-mm NMR tube was placed approximately 50 mg (0.36 mmol) of enone (purified by preparative gas chromatography), 0.25 mL of CD_3OD, and 0.25 mL of D_2O. A ^1H NMR spectrum was recorded, and then approximately 20 mg of K_2CO_3 was added; the tube was shaken to bring about dissolution and then placed in an oil bath maintained at approximately 85 °C. The tube was removed periodically to record the NMR spectrum. In each case deuterium exchange to give **15a**–**18a** was complete after 1 h, and no further changes resulted after 24 h.

Treatment of 4,4-Dimethylcyclohex-2-enone with Isobutyraldehyde. In a three-necked round-bottomed 50-mL flask equipped with a magnetic stir bar, a condenser, and a dropping

(16) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765. See also: Evans, D. A.; Baillargeon, D. J. *Tetrahedron Lett.* **1978**, 3319 and references therein.

(17) Krow, G. R.; Reilly, J. *J. Am. Chem. Soc.* **1975**, *97*, 3837. Thies, R. W.; Seitz, E. P. *J. Chem. Soc., Chem. Commun.* **1976**, 846. Franzus, B.; Scheinbaum, J. L.; Waters, D. L.; Bowlin, H. B. *J. Am. Chem. Soc.* **1976**, *98*, 1241. Thies, R. W.; Seitz, E. P. *J. Org. Chem.* **1978**, *43*, 1050. Wilson, S. R.; Mao, D. T.; Jernberg, K. M.; Ezmirly, S. T. *Tetrahedron Lett.* **1977**, 2559. Miyashi, T.; Hazato, A.; Mukai, T. *J. Am. Chem. Soc.* **1978**, *100*, 1008.

(18) **15**: Yanagita, M.; Inayama, S. *J. Org. Chem.* **1954**, *19*, 1725; ref 10d, pp 161–2. **16**: ref 10b. **17**: ApSimon, J. W.; Hooper, J. W.; Laishes, B. A. *Can. J. Chem.* **1970**, 48, 3064. **18**: ref 7.

(19) The carbon-13 NMR chemical shifts have been reported for compounds **1**, **15**, and **16** [Torri, J.; Azzaro, M. *Bull. Soc. Chim. Fr.* **1974**, 1633]. The values cited in Table V agree quite well with those reported except for the C-1 assignments which differ by as much as 13 ppm. The shieldings in Table V are correct. See also: Stothers, J. B. "Carbon-13 NMR Spectroscopy", Academic Press: New York, 1972; p 290.

funnel charged with 1.42 g (0.02 mole) of isobutyraldehyde, 1.0 mL of H_2O, and enough CH_3OH to bring the total volume to 5 mL were placed 0.16 g of potassium hydroxide, 1.0 mL of CH_3OH, and 2.42 g (0.02 mol) of 4,4-dimethylcyclohex-2-enone (1). The contents of the dropping funnel were discharged dropwise over a period of about 20 min. The reaction mixture was stirred at room temperature for 2 h and then processed by diluting with 50 mL of H_2O and extracting with ether (4 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated under vacuum to give 3.4 g of pale yellow liquid which was shown (by comparison of spectra obtained with samples isolated by preparative gas chromatography) to consist of ketones **2**, **3**, and **4** in the approximate ratios of 1.5:1.0:3.2, respectively, in addition to starting materials.

Acknowledgment. The author thanks Mrs. A. M. Colley for excellent technical assistance, Mr. P. E. Donahue for the carbon-13 NMR measurements, Mr. G. P. Schacher and Mr. Hans Grade for mass spectral measurements, and Professors J. R. Wiseman and S. Danishefsky for helpful comments.

Registry No. 1, 1073-13-8; 2, 65080-55-9; 3, 71549-37-6; 4, 71549-38-7; 5, 71516-29-5; 15, 13395-71-6; 15a, 71516-30-8; 16, 13395-73-8; 16a, 71516-31-9; 17, 17299-41-1; 17a, 71516-32-0; 18, 17429-29-7; 18a, 17429-30-0; methyl vinyl ketone, 78-94-4; isobutyraldehyde, 78-84-2.

Stereochemical Studies with 1,2,5-Trimethyl-1-silacyclopentanes

Fritz Franke and Peter R. Wells*

Chemistry Department, University of Queensland, Brisbane 4067, Australia

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Chlorination of 1,2,5-trimethyl-1-silacyclopentane by benzoyl peroxide/carbon tetrachloride proceeds with 100% retention of configuration at silicon, but reaction with triphenylmethyl chloride in benzene gives two-thirds retention and one-third inversion. 1-Chloro-1,2,5-trimethyl-1-silacyclopentane isomerizes slowly in nonpolar solvents, but salts strongly enhance the rate of isomerization. Displacement of chloride by fluoride and by methoxide is nonstereospecific but, in the case of the latter, is stereoselective. Displacement of chloride by acetate proceeds with predominant inversion of configuration at silicon. The kinetics of the isomerization of 1-acetoxy-1,2,5-trimethyl-1-silacyclopentane by methoxide have been studied.

The 1,2,5-trimethyl-1-silacyclopentane system is an excellent substrate to study the stereochemical course of reactions in which silicon is involved. Assignment of configuration of its *Z,Z* and *E,E* isomers can be made with confidence by determination of the chemical shifts of silicon methyls in the proton and ^{13}C NMR spectra and comparison of these values with those of the *E,Z/Z,E* isomer, which can be identified unambiguously.[1]

1-Chloro-1,2,5-trimethyl-1-silacyclopentane. Conversion of 1,2,5-trimethyl-1-silacyclopentane into the chloride by hydrogen–halogen exchange with triphenylmethyl chloride in benzene proceeded smoothly but nonstereospecifically. Thus a mixture of (*E,E*)- and (*E,Z/Z,E*)-1,2,5-trimethyl-1-silacyclopentanes was converted into a mixture consisting of all three 1-chloro-1,2,5-trimethyl-1-silacyclopentanes with the *E,Z/Z,E* content unchanged but now having *Z,Z*:*E,E* ≈ 2:1. This is not the equilibrium distribution for the *Z,Z* and *E,E* isomers as determined by isomerization studies described below. It is clear that the simple S_Ni-Si mechanism postulated for this exchange reaction in benzene on the basis of retention stereochemistry[2] must be revised in the light of this finding of two-thirds retention and one-third inversion. S_Ni-Si and S_N2-Si mechanisms may be operative competitively. Alternatively, the silicon–hydrogen bond may be broken before the silicon–chloride bond is formed, thus allowing attack from either side of the silicenium ion pair. Similar results were reported for acyclic asymmetric silicon compounds.[3]

The reaction between 1,2,5-trimethyl-1-silacyclopentane and carbon tetrachloride, initiated by thermal decomposition of benzoyl peroxide, proceeded stereospecifically. Thus, a mixture of isomers with *E,E*:*E,Z/Z,E*:*Z,Z* = 2:2:96 was converted into a mixture of chlorides with a ratio of 2:2:96 and a mixture with *E,E*:*E,Z/Z,E*:*Z,Z* = 57:43:0 into a chloride mixture with a 57:43:0 ratio, within experimental error (±1).

The assignment of configuration of the chlorides was based on their proton and carbon NMR properties, which are given, together with those of the *E,Z/Z,E* isomer, in Tables I and II. The same arguments concerning mutual shielding and deshielding were used as for the corresponding hydrides.[1] Thus the *Z,Z* chloride, corresponding to the *E,E* hydride, has the least shielded silicon methyl in the proton and ^{13}C spectra while these are most shielded in the *E,E* isomer. The C-2 methyls are similarly affected although to smaller extent.

The CCl_4 reaction proceeds with retention of configuration at silicon, in agreement with analogous reports for 1,2-dimethyl-1-silacyclobutane[4] and 1,2-dimethyl-1-silacyclopentane,[5] where retention stereochemistry was ascribed to the pyramidal structure of the silyl radical intermediate postulated for this reaction and the fact that there were no known examples of stereospecific inversion reactions at a radical center.

The *E,E* and *Z,Z* chlorides are configurationally stable in pure form but isomerize slowly in chloroform solutions in the course of a few days. In some cases however, due

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(5) F. K. Cartledge, J. M. Wolcott, J. Dubac, P. Mazerolles, and P. Fagoage, *Tetrahedron Lett.*, **42**, 3593 (1975).

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