β-Scission of 9-Decalinoxyl and Related Free Radicals

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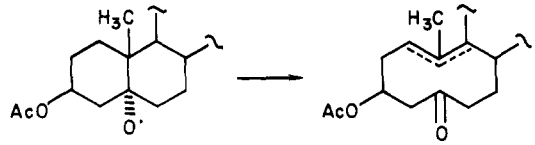
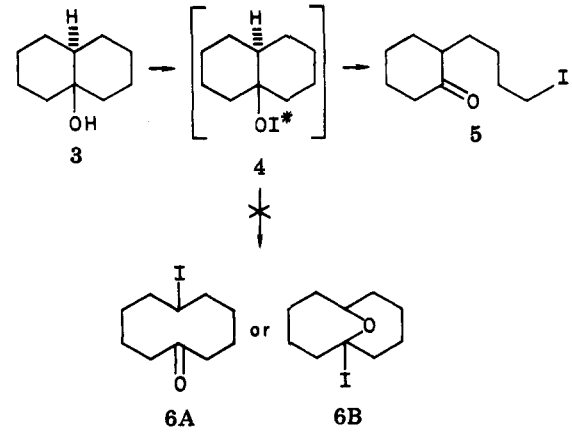
The synthesis of medium and large carbocyclic natural products often proceeds by the transformation of an existing carbocycle into a larger one.[1] A widely employed stategy for such ring expansion involves the vicinal annulation of a new carbocyclic ring onto an existing framework followed by regiospecific cleavage of the ring-fusion (or annelation) bond. Most approaches to cleavage of the ring fusion bond such as the methods of Grob,[2a] Wharton,[2b-d] and Marshall[1e,2e] require a bifunctional intermediate and possess strict stereoelectronic constraints for the fragmentation reaction. In principle, the β scission of alkoxyl free radicals[3] situated at ring-fusion sites, first introduced as an entry into medium-ring seco-AB steroids (**1** → **2**) by Akhtar[4] in 1966, could circumvent these limitations. The present study has examined the potential of such methodology for cyclodecan(en)one synthesis via β scission of alkoxyl free radicals derived from several structurally related 9-decalinol and 9-octalinol systems.



1 **2**

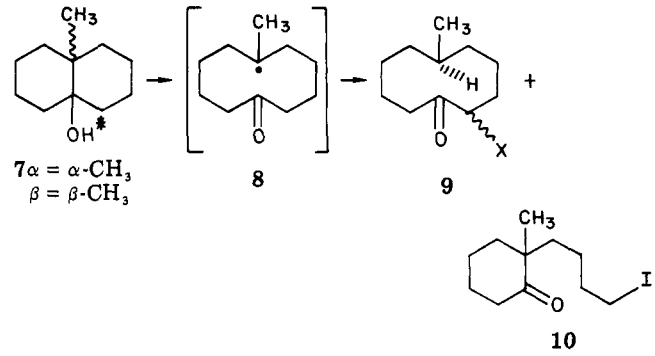
The mode of β scission in unsymmetrical alkoxyl free radicals has been rationalized by considerations of the relative stabilities of the resultant carbon-centered free radicals[5a] and carbonyl[5a] or cyclic ketone[3a] components and of stereoelectronic factors[3e] and more recently by frontier molecular orbital theory[5b]. None of these factors appears to predominate in a priori analysis of the direction of fragmentation in the examples studied here. For example, thermally induced (77 °C) β scission of the alkoxyl free radical derived from hypoiodite **4** generated in situ from decalinol **3**,[7a] and in the presence of excess iodine, produced exclusively 2-(4-iodobutyl)cyclohexanone **5** (68% isolated).



3 **4** **5** **6A** **6B**

This direction of cleavage is consonant with the predictions of Holmquist et al.[6] for the thermal cleavage of the hydroperoxide **4** (I* = OH) and contrasts with the exclusive cleavage of the ring-junction bond [e.g., to **6B** (I* = OCOPh)] observed in the Criegee–Hock rearrangement of the corresponding perbenzoate **4** (I* = OCOPh).[8] The Criegee–Hock rearrangement is postulated to proceed via the incipient decalinol oxenium species.[8] This dichotomy in mode of thermally induced rearrangement of the analogous species **4** (I* = I, OH, OCOPh) is presumably a consequence of the difference in electronic character of the alkoxy oxygen in the transition state for rearrangement.

Alkyl substitution at the ring junction has a dramatic impact on the direction of β scission in decalinol substrates. Either methyldecalinol epimer **7**[7b] gave predominant cleavage of the ring-fusion bond, affording 2-iodo-6-methylcyclodecanone epimers **9** (X = I). Both 7α and 7β



7α = α-CH_3
β = β-CH_3 **8** **9** **10**

isomers gave identical product ratios [**9** (X = I) (94):**10** (6) based on ^1H NMR analysis of the crude reaction mixture], reflecting either a lack of stereoelectronic control in the fragmentation process or a preequilibrium decalinol radical epimerization[9] prior to iodine trapping of the carbon-centered free radical [e.g., 7α (OH* = O·) ⇄ **8** ⇄ 7β (OH* = O·)]. Formation of iodocyclodecanone **9** (X = I) presumably occurs by initial ring-junction cleavage to **8** fol-

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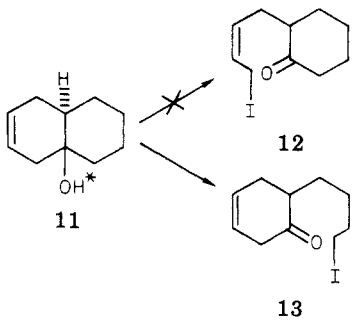
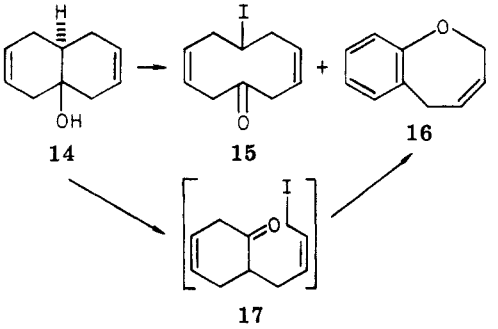
lowed by transannular hydrogen abstraction adjacent to the carbonyl function via a six-membered transition state and subsequent iodine quenching. Related 1,5 transfers of hydrogen in the cyclodecane skeleton are well precedented.[10] The exclusive formation of the internal hydrogen transfer product **9**, however, appears unique and may be a reflection of thermodynamic considerations of radical stability [e.g., ·CHC(O) more stable in the cyclodecane ring than ·C(CH$_3$)]. A single 2-iodocyclodecanone epimer **9a** is initially formed, which is tentatively assigned the pseudo-axial iodo configuration [**9**, X = α-I] and which subsequently equilibrates upon workup to a mixture of epimers [**9a** (4):**9b**[11a] (1)]. The labile, isomeric α-iodo ketones **9** could not be cleanly isolated and were only detected spectrally prior to reaction workup. Mild reduction (aqueous $NaSO_3H$) of the methyldecalinol **7** reaction mixture afforded the isolated product 6-methylcyclododecane **9** (X = H)[2c,11b] (63%). A second compound, tentatively identified as the isomeric 2-methyl-2-(4-iodobutyl)cyclohexanone (**10**)[12] was isolated in low yield (~2%).

The introduction of unsaturation into the bicyclo[4.4.0]decanol framework has a substantial influence on the course of ring cleavage. *trans*-Octalinol **11**[7c,d] was anticipated upon alkoxyl radical mediated ring opening to proceed predominantly to cyclohexanone **12** based upon

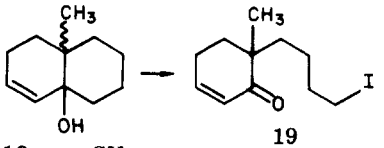


the stabilization afforded the intermediate allyl free radical. In fact, β-scission of the in situ generated alkoxyl radical **11** (OH* = O·) gave solely cyclohexenone **13** (77% isolated). The transition state for cleavage of the allylic carbon–carbon bond in **11** must not benefit from allylic stabilization of the incipient carbon-centered radical, possibly due to the orthogonality of the π framework and the allylic carbon–carbon bond in the *trans*-octalinol system. However, the alkoxyl radical fragmentation process proceeded by way of the less stable (primary) radical of the two alternate options for carbon radical formation. This observation concerning fragmentation pathway in unsaturated substrates was reinforced by examination of *trans*-dienol **14**,[7c,d] which afforded a 2:1 mixture of cyclodecadienone **15** (52% isolated) and dihydrobenzoxepin **16** (25% isolated). Dihydrooxepin **16** is postulated to be



formed by initial allylic iodide **17** generation, followed by internal O-alkylation of the derived enol and subsequent iodine-mediated oxidation of the dihydroaromatic system. Analysis of the fragmentation products observed from these unsaturated *trans*-decalinol substrates **11** and **14** suggests that the alkoxyl radical induced cleavage of allylic carbon–carbon bonds is deterred relative to alternative cleavage pathways.

trans- and *cis*-octalinols **18**[7e] were examined in an attempt to ascertain the impact of olefin regiochemistry on the direction of fragmentation. Both 18α and 18β generated exclusively cyclohexenone **19** (95% isolated from 18α; 91% from 18β). Olefin positioning and incorporation in



18α = α-CH$_3$
β = β-CH$_3$

the substrate clearly has a dominant influence on the course of the cleavage reaction (cf. **7** → **9**). In addition, this result is notable in view of the considerable energy difference (~9 kcal/mol) between the tertiary radical which would have been generated via cleavage of the ring fusion bond and the primary radical generated via the observed cleavage process.

The course of alkoxyl radical β-scission in these decalinyl substrates is acutely sensitive to changes in the molecular geometry of the system. It is clear that either substituent effects on radical stability or cyclic ketone ring strain does not independently dictate the direction of ring opening; the mode of β scission must be a consequence of the interplay of several factors. Possible intrusions of *tert*-alkoxyl radical isomerization (e.g., 7α ⇄ 7β or 18α ⇄ 18β) or a stereoelectronic preference for axial or pseudo-axial carbon–carbon bond breakage (or formation) in these six-membered ring further complicates mechanistic analysis or rationale of the examples presented here. We are currently examining the β-scission of fused-ring tertiary hydroxyl systems with altered stereochemical and stereoelectronic features in an attempt to determine the dominant factors in these β-scission processes. In addition, we are examining the employment of these reactions in the synthesis of medium-sized-ring natural products and in controlling stereochemical elements of acyclic chains bound to cyclohexane ring systems.

Experimental Section

General Procedures. Proton magnetic resonance spectra were recorded at 100 MHz with a JEOL JNM-MH-100 spectrometer, employing tetramethylsilane as an internal standard. ^{13}C magnetic resonance spectra were recorded at 22.50 MHz, employing a JEOL FX-90Q Fourier transform spectrometer with deutriochloroform (77 ppm) as internal standard. Relative product percentages were

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(11) (a) The minor iodocyclodecanone isomer, **9b**, assigned the X = β-I configuration, could not be cleanly isolated and had the following spectral characteristics as a mixture with **9a** (X = α-I): ^{1}H NMR ($CDCl_3$) δ 4.50 (dd, J = 7.0, 2.5 Hz, 1 H), 0.80 (d, J = 3.0 Hz, 3 H); IR 1720 cm^{-1}. (b) ^{13}C NMR spectrum of 6-methylcyclodecanone (**9**, X = H): ($CDCl_3$) 214.2, 41.9, 33.0, 29.5, 23.7, 23.5, 21.6 ppm.

(12) The basis for the structure assignment of this compound stems from the following data: ^{1}H NMR ($CDCl_3$) δ 3.19 (t, J = 3.0 Hz), 1.07 (s); mass spectrum, m/e (relative abundance, %) 294 (2), 112 (100).

Table I. Spectral Data for Characterized Products

compd	^{1}H NMR ($CDCl_3$, Me_4Si), δ	^{13}C NMR ($CDCl_3$), ppm	IR (neat), cm^{-1}	mass spectrum, m/e (relative abundance, %)
5	3.16 (t, J = 3.0 Hz, 2 H), 2.00-2.49 (br m, 3 H), 1.60-2.00 (br m, 8 H), 1.08-1.60 (m, 4 H)	212.6, 50.5, 41.9, 33.9, 33.6, 28.3, 28.1, 27.9, 24.9, 6.7	2900 (s), 2875 (m), 17.0 (s), 1450 (m), 730 (w)	280 (1.6), 279 (4.9), 153 (5.4), 98 (100)
9a	5.12 (dd, J = 7.0, 2.5 Hz, 1 H), 3.10 (m, 1 H), 2.50 (br m, 3 H), 1.00-2.67 (br m, 11 H)	215.0, 41.8, 32.8, 37.7, 30.7, 29.2, 23.5 (dbled), 23.3 (dbled), 21.5	2950 (s), 2875 (m), 1705 (s), 1450 (m), 780 (m)	199 (24), 167 (28), 127 (20), 112 (100)
13	5.70 (m, 2 H), 3.16 (t, J = 3.0 Hz, 2 H), 2.87 (m, 2 H), 2.52 (m, 1 H), 1.60-2.00 (br m, 4 H), 1.10-1.00 (br m, 4 H)	210.9, 126.3, 124.4, 47.7, 40.4, 33.9, 32.5, 28.0 (dbled), 6.6	3150 (w), 2950 (s), 2875 (m), 1715 (s)	278 (35), 196 (37), 151 (100), 9 (90)
15[a]	5.40-5.80 (m, 4 H), 4.42 (quintet, J = 3.0 Hz, 1 H), 3.20 (br s, 4 H), 2.68 (t, J = 3.0 Hz, 4 H)	206.5, 131.3, 124.9, 42.3, 36.3, 28.6	3025 (m), 2910 (s), 2850 (m), 1710 (s), 1645 (w), 660 (m)	149 (18), 127 (32), 79 (55), 67 (100)
16	6.74-7.70 (br m, 4 H), 5.72-6.14 (m, 1 H), 5.64 (s, 1 H), 5.00-5.50 (m, 2 Hz), 3.08 (t, d, J = 4.0, 8.0 Hz, 2 H)	162.5, 137.5, 128.1, 125.9, 124.8, 120.5, 116.6, 109.5, 83.4, 29.7	3025 (m), 2910 (m), 2850 (m), 1540 (m), 1440 (s)	146 (4.1), 145 (3.3), 105 (100), 77 (33)
19	6.72 (d, t, J = 5.0, 2.0 Hz, 1 H), 5.84 (d, J = 5.0 Hz, 1 H), 3.12 (t, J = 4.0 Hz, 2 H), 2.20-2.45 (m, 2 H), 1.00-2.00 (m, 2 H), 1.10-1.50 (m, 6 H), 1.07 (s, 3 H)	203.6, 148.4, 128.3, 44.1, 35.0, 33.7, 33.1, 24.7, 22.9, 21.6, 6.4	2950 (s), 2875 (m), 1705 (m), 167 (s), 1450 (m), 1380 (w), 1.110 (w)	292 (2.5), 165 (75), 110 (100), 69 (100)

[a] Mp 98-99 °C. Anal. Calcd for $C_{10}H_{13}OI$: C, 43.50; H, 4.74. Found: C, 44.10; H, 4.93.

determined by NMR integration of the crude reaction products prior to workup (due to the lability of these compounds to VPC) and are reproducible to within ±5%. Low-resolution mass spectra were obtained by direct insertion with an LKB 9000 spectrometer at 70 eV. The parent ion and the most intense peaks (2-4) are reported. Infrared spectra were obtained on a Perkin-Elmer 727 infrared spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. For column chromatography, E. Merck (type 60) silica gel or Florisil (100 mesh) and short-column techniques were utilized, and for TLC analysis E. Merck silica gel 60, F-254 precoated (0.25 mm) plates were employed. Calcium chloride was used as drying agent thoughout and all experimental procedures were performed under an atmosphere of dry nitrogen.

General Procedure for β-Scission Reactions as Illustrated for 9-Decalinol (3). A representative experimental procedure which was employed for all the β-scission reactions reported here follows. A solution of iodine (0.330 g, 1.30 mmol) in carbon tetrachloride (30 mL) was added slowly (1 h) to a refluxing solution of 9-decalinol (**3**)[7b] (0.100 g, 0.65 mmol) in carbon tetrachloride (15 mL) containing yellow mercuric oxide (0.280 g, 1.30 mmol). The solution was refluxed (1 h), cooled, filtered, and then extracted twice with a saturated aqueous solution of sodium metabisulfite (50 mL) and finally with brine. The organic layer was dried and filtered, the solvent was removed in vacuo, and the residue was chromatographed (Florisil, 5% ethyl acetate–95% petroleum ether) to yield 2-(4-iodobutyl)cyclohexanone (**5**, 0.124 g, 68%). In an identical fashion were treated decalinols 7α and 7β (0.100 g, 0.60 mmol), octalinol **11** (0.091 g), hexalinol **14** (0.090 g), and methyloctalinols 18α and 18β (0.099 g), affording the isolated yields of ring-opened products noted in the text. Spectral data of characterized new compounds are presented in Table I.

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Registry No. **3**, 1654-87-1; **5**, 76402-75-0; 7α, 5173-73-9; 7β, 5173-74-0; 9α, 76402-76-1; 9β, 76465-79-1; **11**, 33066-07-8; **13**, 76402-77-2; **14**, 76402-78-3; **15**, 76402-79-4; **16**, 76402-80-7; 18α, 67497-82-9; 18β, 68211-44-9; **19**, 76402-81-8.