14-endo, and 17-endo were conducted by Dr. P. Fanwick of the Purdue University X-ray crystallography facility.

Supplementary Material Available: Full experimental details for the preparation of 3-4, representative experimental procedures for the Diels-Alder reactions, full physical and spectroscopic characterization of 3-17, ^{1}H NMR spectra of 3-17, a summary of NOE difference experiments, a summary of the interconversion/epimerization studies (Scheme II), and details of the X-ray structure determinations of 9-endo, 14-endo, and 17-endo (91 pages). Ordering information is given on any current masthead page.

Tandem Free-Radical Ring Expansion and 5-*exo-dig* 5-Hexynyl Radical Cyclization: A Useful Approach to Fused Bicyclic Carbocycles

Dale L. Boger* and Robert J. Mathvink

Department of Chemistry, Purdue University West Lafayette, Indiana 47907

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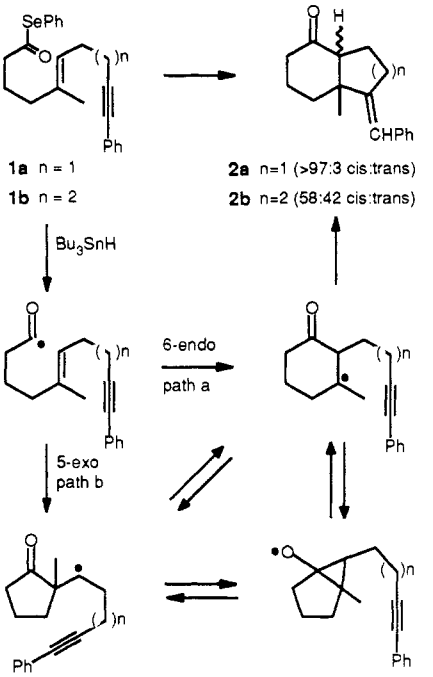
Summary: The effective preparation of hydrindan-1,4-diones, hydroazulene-1,4-diones, and hydrocyclopentacyclooctene-1,4-diones through implementation of an efficient tandem free-radical ring expansion, 5-*exo-dig* 5-hexynyl radical cyclization is detailed.

In recent studies, we have shown that acyl radicals[1] generated from phenyl selenoesters participate in effective intramolecular,[2] intermolecular,[3] macrocyclization,[4] and tandem[5] alkene addition reactions at rates greater than that of tri-*n*-butyltin hydride hydrogen abstraction (reduction)[6] and decarbonylation[7] reactions. In the course of these studies, we observed clean polycyclization of the acyl radicals generated from phenyl selenoesters **1a-b** to provide **2a-b** initiated with clean 6-*endo-trig* versus 5-*exo-trig* 5-hexenoyl radical cyclization (Scheme I). Based on past efforts, this preference for 6-*endo-trig* versus 5-*exo-trig* free-radical cyclization may be attributed to kinetic deceleration of 5-*exo-trig* cyclization due to the C-5 olefin substituent,[8] acceleration of 6-*endo-trig* cyclization[8,9]

Scheme I



(radical stability), and/or thermodynamic equilibration of initial cyclization products (5-*exo-trig* → 6-*endo-trig*).[10]

The intramolecular addition of alkyl or aryl radicals to a carbonyl group has been demonstrated to be an effective process for acyl group transfer[11] and in cases where the

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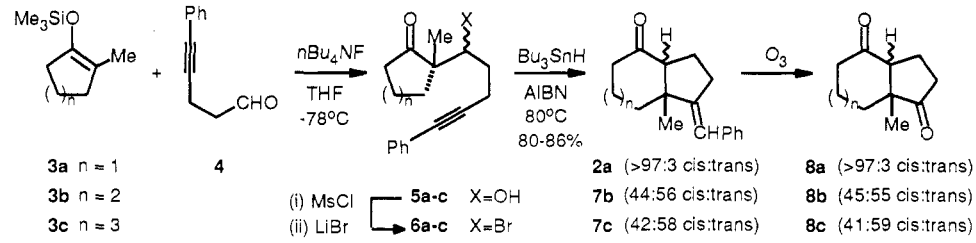
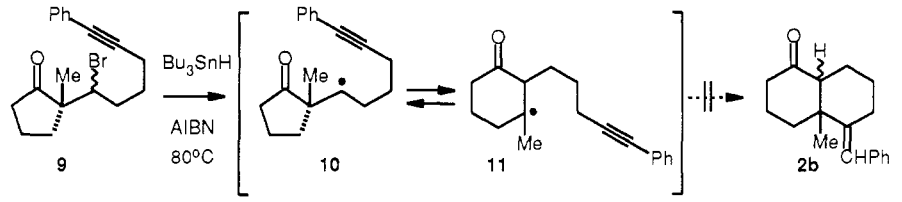
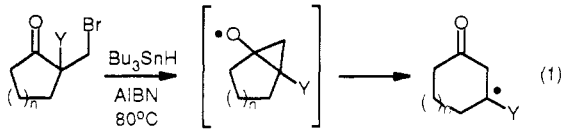
Scheme II



Scheme III



carbonyl acceptor resides within a cyclic framework, the acyl transfer constitutes useful methodology for effecting net ring expansion.[11a-c] Since such ring expansions proceed readily when the rearrangement results in the generation of a more stable radical, the majority of prior examples studied have focused on systems bearing a radical stabilizing substituent adjacent to the carbonyl acceptor (equation 1, Y = CO_2R, CN).[11a-c] Thus, in the course of efforts to determine the origin of the observed preference for 6-*endo-trig* cyclization of 5-hexenoyl radicals, we have examined the viability of the related free radical rearrangement (ring expansion) potentially operative in a thermodynamic equilibration of initial cyclization products of **1a** and **1b** (5-*exo-trig* → 6-*endo-trig*, Scheme I).



(1)

Herein, we report the clean generation and rearrangement of the secondary alkyl radicals derived from β-bromo ketones **6a–c** resulting in the generation of intermediate tertiary alkyl radicals and their subsequent 5-*exo-dig* cyclization onto a suitably positioned alkyne providing high yields of the bicyclic products **7a–c** (Scheme II). Crossed aldol condensation[12] of the silyl enol ethers **3a–c**[13] with aldehyde **4** followed by bromide ion displacement of the corresponding mesylates afforded the bromo ketones **6a–c**. Slow addition (1 h) of 1.2 equiv of tri-*n*-butyltin hydride to a solution of **6a** and a catalytic amount of AIBN in refluxing benzene cleanly provided the cis-fused hydrindenone **2a** (>97% cis) in excellent yield (86%, Scheme II). Similarly, subjecting **6b** and **6c** to the identical reaction conditions furnished the hydroazulenone **7b** (80% yield) and hydrocyclopentacyclooctenone **7c** (85% yield), respectively.[14] Ozonolysis (O_3, CH_2Cl_2, −78 °C; Me_2S) of **2a**, **7b–c** provided the corresponding bicyclic 1,4-diones **8a–c**, thus establishing the tandem free-radical ring expansion, 5-*exo-dig* 5-hexynyl radical cyclization sequence as an effective method for the construction of useful 6,5-, 7,5-, and 8,5-bicyclic ring systems. In contrast to the empirical observations detailed in the study of acyl radical polycyclization reactions,[5] the 5-*exo-dig* cyclizations of the intermediate tertiary alkyl radicals derived from **6b–c** provided cis:trans ring fusion ratios that differed significantly from the equilibrium ratios experimentally established by base-catalyzed equilibration[15] of the individual bicyclic products. Although the thermodynamically more stable trans-fused products **7b–c** were found to predominate in the cyclizations of **6b–c**, the extent of the observed diastereoselectivity in each case was lower than that anticipated based on the relative stabilities of the cis and trans ring-fused products. Thus, **2a** can be isolated in pure cis form from the rearrangement–cyclization reaction of **6a**, and the relative proportions of trans-fused **7b** and **7c** can be enhanced by simple base-catalyzed equilibration of the cis:trans reaction mixture.[15]

The rearrangement–cyclization reaction utilizing **6a** was originally designed to distinguish between the 6-*endo* cyclization and 5-*exo* cyclization–rearrangement (Scheme I) reaction pathways potentially operative in the effective preparation of **2a** from **1a**[5] and the successful formation of **2a** from **6a** provides direct experimental evidence establishing the viability of the 5-*exo-trig* mechanism (path b, Scheme I). In order to fully define the mechanistic course of the acyl radical polycyclization reactions of **1a–b**, **9** was subjected to the same reaction conditions (Scheme III). Notably, while the acyl radical derived from **1b** undergoes clean polycyclization to furnish **2b**, bromo ketone **9** failed to provide even a trace of the same bicyclic ketone.[16] Consequently, the latter result provides convincing evidence to support the direct 6-*endo-trig* tandem cyclization pathway for the conversion of **1b** to **2b** and eliminates the potential competitive 5-*exo-trig* cyclization–rearrangement pathway (**1b** → **10** → **2b**).

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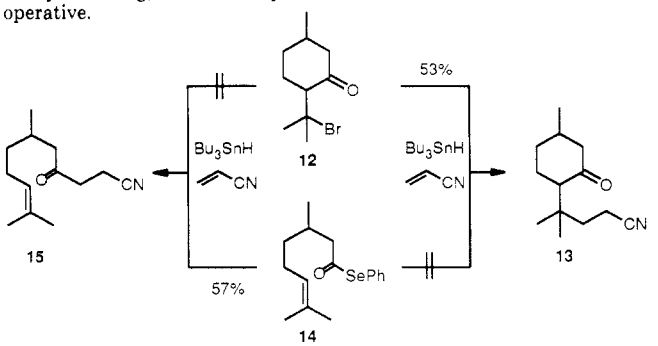
(14) The relative stereochemistry of the bicyclic ketone isomers was unambiguously established by a combination of one-dimensional ^1H NMR NOE difference experiments and equilibration experiments. Full details are provided in supplementary material.

(15) Base-catalyzed equilibration (catalytic NaOMe, MeOH, reflux) of **7b** and **7c** provided equilibrium ratios of 72:28 (**7b**) and 90:10 (**7c**) for the trans:cis ring fusion for **7b–c**.

(16) The crude isolated product from the reaction of **9** with tri-*n*-butyltin hydride was found to consist of a complex mixture at least five components (by GLC and ^1H NMR analysis), none of which corresponded (GLC retention times and ^1H NMR olefinic proton absorptions) to the previously described (ref 5) hydrindenone **2b** stereoisomers which would be anticipated to arise from intermediate radical **11**. Presumably, the products derived from **9** result from 5-*exo-dig* cyclization of the initial secondary radical onto the proximal alkyne. The corresponding iodide and phenyl thionocarbonate ester (Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059) produced comparable results.

Thus, although the ring expansion rearrangement has proven operationally viable for the observed **1a** → **2a** cyclization, it cannot be operative in the observed conversion of **1b** → **2b**. These observations coupled with the lack of observation of reversible acyl radical-alkene addition reactions[17] suggest that **2a-b** are derived from a direct, kinetically and thermodynamically preferred 6-*endo-trig* acyl radical-alkene cyclization. However, as detailed herein, the free-radical ring expansion (rearrangement) has proven effective and when combined with a subsequent 5-*exo-dig* 5-hexynyl free radical cyclization provides a useful entry into the preparation of fused 5,6-, 5,7- and 5,8-bicyclic 1,4-diones.

(17) The potential of a reversible acyl radical-alkene addition reaction was experimentally addressed by subjecting **12** to standard free radical cyclization conditions (Bu_3SnH, catalytic AIBN, benzene, 80 °C) in the presence of 4 equiv of acrylonitrile. The lack of evidence for formation of **15** (the major product obtained by generation of the acyl radical derived from phenyl selenoester **14** under identical conditions) suggests that an equilibrating, reversible acyl radical-alkene addition reaction is not operative.



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Supplementary Material Available: Full details of the preparation and free-radical rearrangement-cyclization reactions of **6a-c** and **9** (8 pages). Ordering information is given on any current masthead page.

Linkage Position Determination in Oligosaccharides: MS/MS Study of Lithium-Cationized Carbohydrates

Zhongrui Zhou, Sherri Ogden, and Julie A. Leary*

College of Chemistry, University of California, Berkeley, Berkeley, California 94720

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Summary: Tandem mass spectrometry of the $[M + 2Li - H]^+$ ion of isomeric disaccharides is used to distinguish differences in the linkage position of the glycosidic bond. This technique can be applied to larger oligosaccharides with mixed linkages and still allow for correct determination of position and type of linkage.

Fast atom bombardment (FAB) combined with tandem mass spectrometry (MS/MS) has been shown to be useful for determining the sequence, and to a lesser extent, the pattern of branching of oligosaccharides.[1,2] The sequence-related fragment ions are produced from protonated molecular ions mainly by cleavage of the glycosidic bond with positive charge retained on either side of the molecule. Since the process of alkali metal ion attachment can strongly influence fragmentation of various organic molecules,[3,4] the fragmentation behavior of carbohydrates coordinated to lithium has been investigated in this study.

It is known that the alkali metal cationized species, compared to protonated molecular ions, undergo a larger number of structurally informative fragmentations of the sugar ring.[5] Our experiments with various oligosaccharides using collision-induced dissociation (CID) of lithiated molecular ions indicate that these structurally informative fragmentations can be greatly enhanced by using the dilithiated species, $[M + 2Li - H]^+$, as the precursor ion.[6] The CID spectra of dilithiated carbohydrates show predominantly fragmentations which are produced by ring cleavages of the sugar unit and provide important information for characterizing the glycosidic linkage position in oligosaccharides.

Figure 1 shows the CID spectra of the $[M + 2Li - H]^+$ of three isomeric disaccharides.[7] The differences among these isomers are quite obvious. The disaccharide with the 1→6 linkage shows characteristic ions at m/z 235, 265, and 295. However, the disaccharide with the 1→4 linkage shows the absence of m/z 265. All three of these ions are absent in the disaccharide possessing the 1→1 linkage. Although not shown here, the spectrum of the 1→3 isomer does not exhibit m/z 295 and the 1→2 isomer shows no m/z 265 (like the 1→4 isomer).[8] The latter isomer also produces an ion which is 18 units lower than the precursor ion and is absent in the spectra of all the other isomeric disaccharides.

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(5) Cerny, R. L.; Tomer, K. B.; Gross, M. L. *Org. Mass Spec.* **1986**, *21*, 655.

(6) CID spectra of the monolithiated disaccharides show large ion abundances from the nonreducing end with little differentiation between the various isomers of different linkages. The dilithiated spectra, however, show higher abundances of ions which characterize the linkage position and work from the reducing end back toward the nonreducing end. This applies as well to furanose moities at the reducing end (see the supplementary material).
(7) CID spectra were collected on a VG ZAB 2-EQ mass spectrometer of BEqQ geometry using argon as a collision gas at a cell pressure of 1×10^{-6} mbar and 40-110 eV collision energy (lab-frame of reference). The matrix used was 50:50 dithiothreitol:dithioerythritol with Li_2CO_3 as the source of lithium. All carbohydrates were purchased commercially, and no further purification steps were undertaken. Microgram quantities of the various sugars were diluted in 5 μL of Li_2CO_3/water and mixed with 5 μL of matrix.
(8) Both the 1→3 and the 1→2 compounds are also isomeric with the other three disaccharides shown in Figure 1.

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