Syntheses of Bicyclo[3.3.0]octanes via Bifurcating Radical Cyclization Pathways

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Summary: The bifurcating cyclization pathways of radicals derived in a one-pot process from acyclic geminal dibromides efficiently afford bicyclo[3.3.0]octane derivatives.

Radical cyclization has become a useful method for carbon–carbon bond formation and is especially appropriate for efficient syntheses of cyclopentanoid compounds.[1] Among the radical cyclizations, simple cyclizations and more complex tandem polycyclizations have been applied to the syntheses of polycyclic products.[2] In this paper we report the first example of intramolecular double-radical-based cyclization based on a bifurcating, rather than tandem, pathway. The method is illustrated using acyclic substrates for efficient syntheses of bicyclo[3.3.0]octane derivatives, the basic carbon skeleton of triquinanes related to hirsutene, coriolin, capnellene, silphiperfolene, silphinene.[3]

As shown in Figure 1, there are two possible strategies to construct the bicyclo[3.3.0]octane ring system via a bifurcating process of double-radical cyclization. Each process would form two carbon–carbon bonds in succession from an acyclic geminal dibromide starting material. The dienes required for these experiments were each chosen to preclude the possibility of tandem radical processes. In a one-pot reaction, two radicals were to be formed sequentially at the same carbon and were expected to take part in independent carbon–carbon bond forming events.

The substrate required to test the double-radical cyclization strategy A (Figure 1) was easily prepared in three steps. Treatment of ethyl formate with the Grignard reagent which was freshly prepared from 4-bromobutene afforded alcohol **4**, which was then oxidized with Jones' reagent to give the ketone **5** in 69% overall yield.[4] Alkylation of **5** with methylene bromide was accomplished by Nozaki's procedure (CH_2Br_2, LDA, THF)[5] in 85% yield and provided **6**, the substrate for cyclization (Scheme I).

The key reaction, double-radical cyclization, was carried out using syringe pump techniques to minimize the concentration of tin hydride.[2d] To a solution of the dibromide **6** (0.025 M) and a catalytic amount of AIBN in benzene at 80 °C was added a solution of $^nBu_3SnH$ (0.2 M) and a catalytic amount of AIBN in benzene over 3 h by syringe pump. After the reaction mixture had been heated at reflux for 3 h, the reaction mixture was worked up to give the bicyclo[3.3.0]octanes **8a** and **8b** in a 84:16 ratio (by capillary GC analysis) in 45% (isolated) yield. These compounds have a low boiling point, and they were difficult to separate at this stage. The reaction was clean, and the yield may be expected to be greater when less volatile products are prepared. Protection of the mixture of alcohols **8a** and **8b** with benzoyl chloride afforded **9a** and **9b**, which were separable by HPLC. We could determine the relative stereochemistry of the products by ^{13}C NMR spectroscopy[6] [**9a**, exo(Me) 20.8 ppm, endo(Me) 14.9 ppm; **9b**, exo(Me) 16.4 ppm].

This process afforded a new route to bicyclo[3.3.0]octanes, but the double-radical cyclization did not proceed in satisfactory yield. Therefore we undertook the key reaction using a suitably protected substrate. The methoxymethyl ether **7** of alcohol **6**, prepared in 74% yield by treatment of **6** with methoxymethyl chloride (MOMCl) in the presence of Hünig's base ($^iPr_2EtN$) and (dimethylamino)pyridine (DMAP), was subjected to radical cyclization under the same conditions described for alcohol **6**. The reaction afforded bicyclo compounds **10a** and **10b** in an 80:20 ratio (by capillary GC analysis) in 64% (isolated) yield [**10a**, exo(Me) 20.8 ppm, endo(Me) 14.9 ppm; **10b**, exo(Me) 16.7 ppm].

Attention turned next to a test of the bifurcating double-radical cyclization reaction represented by strategy B (Figure 1). To prepare the substrate, commercially available 1,5-hexadien-3-ol was subjected to ortho ester Claisen rearrangement conditions (triethyl orthoacetate, propionic acid, 139 °C) and reduction (DIBAL-H, THF) of ester **11** to give the aldehyde **12**.[7] Treatment of this aldehyde with methylene bromide and LDA afforded alcohol **13** in 72% yield. After protection of alcohol **13** in 99% yield, the resulting dibromobenzoate **14** was subjected to the bifurcating double-radical cyclization under the usual conditions to give bicyclo compounds **15a–c** in a 45:20:35 ratio (by capillary GC analysis) in 75% (isolated) yield [**15a**, (CH_3) 15.0 ppm; **15b**, (CH_3) 15.0 ppm; **15c**, (CH_3) 20.6 ppm] (Scheme II).

Assignments of relative configuration at the newly formed stereocenters by ^1H NMR, ^{13}C NMR, 2D-COSY, and 2D-NOESY spectra were supported by the following observations: The benzoate **15a** (Scheme III) was subjected to deprotection (LAH, Et_2O). Oxidation (PCC, Florisil, CH_2Cl_2) of **16** gave ketone **17**, reduction of which with lithium tri-*tert*-butoxyaluminohydride at 0 °C afforded the alcohol **16** and **18** in a 1:6 ratio (by ^1H NMR, 300 MHz spectra). The spectrum of the major alcohol was identical with the spectrum of alcohol **18** prepared by deprotection of the benzoate **15b**, and spectra of the minor alcohol **16** was identical with ^1H NMR spectra of the alcohol **16** derived by deprotection of **15a**. This is good evidence that the C–O bond is exo in **15a** and endo in **15b**. Furthermore, reduction of the ketone **20** (which was prepared by successive deprotection of the benzoate **15c** and

(1) (a) Giese, B. *Radicals in Organic Synthesis; Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Neumann, W. P. *Synthesis* **1987**, 665. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (d) Curran, D. P. *Synthesis* **1988**, 417 and 489.

(2) (a) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720. (b) Beckwith, A. L. J.; Roberts, D. H.; Scheisser, C. H.; Wallner, A. *Tetrahedron Lett.* **1985**, *26*, 3349. (c) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448. (d) Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943. (e) Curran, D. P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991. (f) Wilcox, C. S.; Thomasco, L. H. *J. Org. Chem.* **1985**, *50*, 546. (h) Winkler, J. D.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708. (i) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337.

(3) (a) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41. (b) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. (c) For a recent review, see: Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry: Reactivity and Structure; Concepts in Organic Chemistry*; Springer-Verlag: New York, 1987; Vol. 26.

(4) New compounds were characterized by ^1H NMR, ^{13}C NMR, IR, and low- and high-resolution MS data.

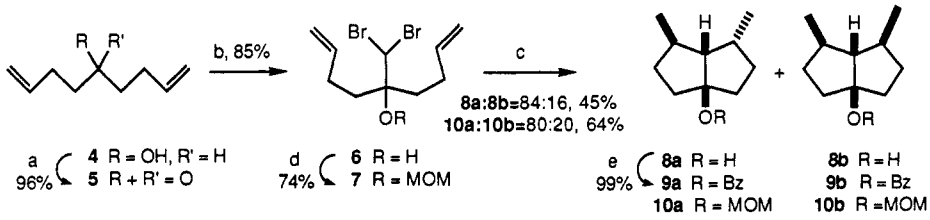
(5) (a) Taguchi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 3010. (b) Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102.

(6) (a) Whitesell, J. K.; Minton, M. A. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: London; New York, 1987. (b) Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878.

(7) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

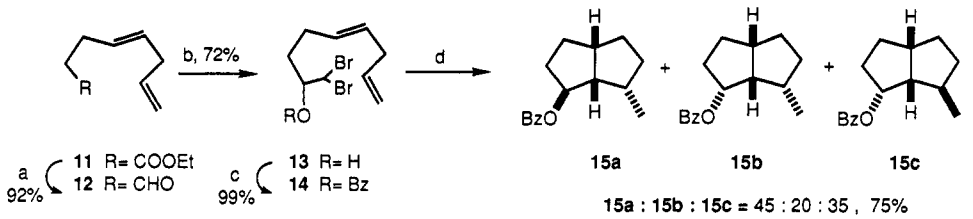
0022-3263/90/1955-3440$02.50/0

Scheme I[a]



[a] (a) Jones' reagent, 0 °C; (b) CH_2Br_2–LDA, THF, −78 °C; (c) $^nBu_3SnH$, AIBN, 80 °C; (d) MOMCl, Et_3N, DMAP, CH_2Cl_2; (e) ^{n}BuLi, C_6H_5COCl, THF, 0 °C.

Scheme II



[a] (a) DIBAL, hexane, −78 °C; (b) CH_2Br_2–LDA, THF, −78 °C; (c) C_6H_5COCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; (d) $^nBu_3SnH$, AIBN, 80 °C.

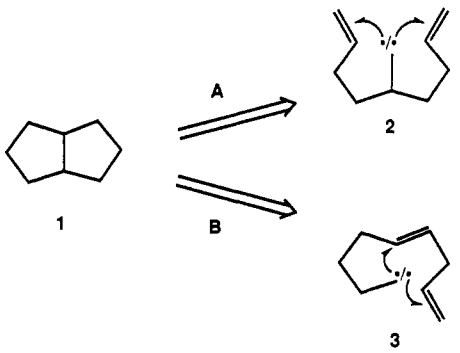
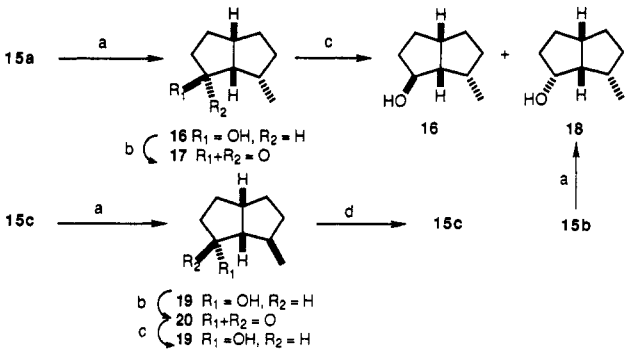


Figure 1. Schematic illustration of bifurcating pathways to the target ring system. The symbol "·/·" represents independent radicals generated at the same nucleus in consecutive events.

Scheme III



[a] (a) LAH, Et_2O, 0 °C; (b) PCC, CH_2Cl_2, 24 °C; (c) LiAl(O-*t*-Bu)$_3$H, THF, 0 °C; (d) C_6H_5COCl, Et_3N, DMAP, CH_2Cl_2, 24 °C.

oxidation of the alcohol **19**) with lithium tri-*tert*-butoxyaluminohydride at 0 °C gave the alcohol **19** selectively. The alcohol **19** was protected by standard conditions (BzCl, Et_3N, DMAP, CH_2Cl_2) and afforded a benzoate, whose spectroscopic properties (IR, ^{1}H NMR, 300 MHz) and TLC behavior were identical with those of bicyclo compound **15c** prepared by radical cyclization. Therefore the benzoate in **15c** must also be of endo orientation. An NOE experiment revealed that irradiation of the methyl group in **15c** caused enhancement of both of the protons at the ring junction. No similar enhancements were observed upon irradiation of the methyl group in **15a** or **15b**. These results are all consistent with the structure assignments shown in Scheme II.

Crude product mixtures were carefully examined, and the absence of expected resonances indicates that if a fourth product isomer was present is was formed at very low levels (<5% of total product). On the basis of the evidence presented above we conclude that it is the exo–exo isomer that is not observed. In the absence of unusual steric interactions, cyclizations similar to the second radical cyclization in these processes are known to favor products bearing an endo methyl group. For example, Wolff and Agosta found in the parent system that formation of the endo product is favored by 8 to 1.[8] If the first cyclization on the pathway to products **15a–c** shows no preference in the orientation of the benzoate group then the 50% of *exo*-benzoate monocyclic intermediate would be expected (on the basis of Wolff and Agosta's observation) to lead to 44% of **15a** and only 6% of the exo–exo product. The 50% of monocyclic *endo*-benzoate would lead to a mixture of **15b** and **15c** but because the *endo*-benzoate would affect the transition states leading to **15b** or **15c**, and steric interactions would disfavor formation of **15b**, the ratio of **15b**/**15c** cannot be expected to follow from Wolff and Agosta's results.[9]

These experiments demonstrate that the bifurcating cyclization pathways of radicals derived from acyclic geminal dibromides efficiently affords bicyclo[3.3.0]octane derivatives.[10] The original analyses illustrated in Figure 1 offer potentially useful approaches to bicyclo[3.3.0]octane derivatives and, by extension of the general concept, to

(8) Wolff, S.; Agosta, W. C. *J. Chem. Res. Synop.* **1981**, 78.

(9) In both cases studied here the bromine atom attached to the radical center during the first cyclization will influence the stereochemical outcome of the reaction. The brief discussion presented here may be further complicated by including estimates of the influence of this bromine atom on the outcome of the first carbon-carbon bond forming reaction. Data bearing on these points will be acquired in our continuing studies.

(10) In a related process, a 1,3-dihalide has been shown to react intramolecularly with a dienoate acceptor to afford a bicyclo[3.3.0]octane: Hanessian, S.; Dhanoa, D. S.; Beaulieu *Can. J. Chem.* **1987**, *65*, 1859–1866.

other multicyclic ring systems. It is expected that in other more complex cases better stereocontrol may be enforced.

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Supplementary Material Available: Complete physical data, including ^{1}H NMR, ^{13}C NMR, IR, and MS, for 15 substances: **4–7**, **9a,b**, **10a,b**, **11–14**, and **15a–c** (5 pages). Ordering information is given on any current masthead page.

Intramolecular Addition of Carbon-Centered Tinthioimidoyl Radicals to Carbon–Carbon Double Bonds. Synthesis of γ- and δ-Thiolactams

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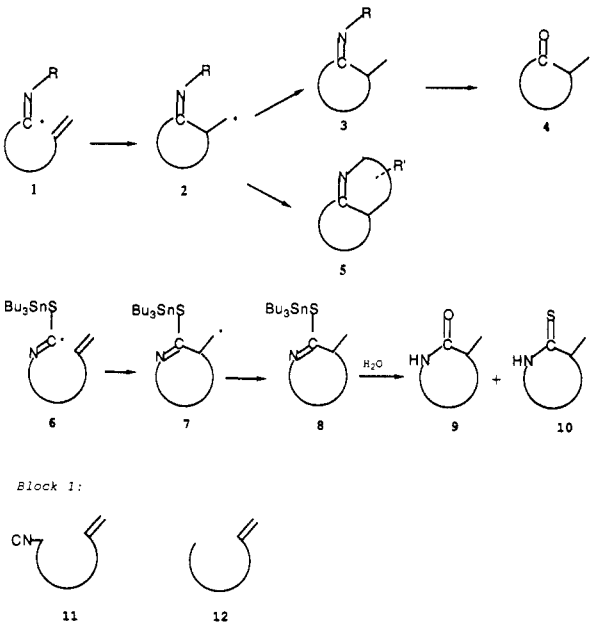
Summary: (Tri-*n*-butyltin)thioimidoyl radicals of type **6**, which were efficiently generated by treatment of alk-3-enyl- and alk-4-enylisothiocyanates with tri-*n*-butyltin hydride and AIBN, underwent exo cyclization to give, after hydrolysis, the corresponding γ- or δ-thiolactams in good to excellent yields.

The formation of cyclic systems through the intramolecular addition of carbon-centered free-radicals to carbon–carbon multiple bonds has been widely exploited in recent years.[1] Educt radicals include a large variety of alkyl, aryl,[2] and ene radicals.[1] To the arsenal of synthetically useful ene radicals, which included vinyl[3] and carbonyl[4] radicals, we recently added imidoyl radicals.[5] We now introduce tinthioimidoyl radicals of type **6**, a novel group of ene radicals, which opens a new avenue for the synthesis of heterocyclic compounds. The difference between the synthetic potential of the previously described[5] imidoyl radicals **1** and that of the tinthioimidoyl radicals **6** is apparent in Scheme I. In imidoyl radicals of type **1** the alkenyl group is linked to the carbon atom of the carbon–nitrogen double bond while in tinthioimidoyl radicals of type **6** the alkenyl group is linked to the nitrogen atom of the carbon–nitrogen double bond. Furthermore, the radical center in **1** is substituted by one heteroatom while in **6** it is substituted by two heteroatoms. Radicals **1** afford cyclic radicals **2**, which carry an exocyclic imine group, and may be transformed into cyclic products of types **4** (via **3**) or **5**.[5] Due to their different structural and functional constitution, tinthioimidoyl radicals **6** may

Scheme I



ring close to cyclic thioimidates **8** (via **7**), which could be subsequently converted into lactams **9** and/or thiolactams **10**. The results described herein provide an interim assessment of the scope and limitation of this reaction for the synthesis of γ- and δ-thiolactams.

Tinthioimidoyl radicals are readily generated through the addition of organotin radicals to isothiocyanates, as in the first step of Barton's method for deamination of primary amines.[6,7] If an analogous degradative process had occurred with tri-*n*-butylthioimidoyl radicals **6** it would produce either isonitriles **11**, by α-elimination, and/or alkene products **12**, by β-elimination. We have previously shown that, provided a multiple bond is judiciously positioned in the molecule, oxycarbonyl radicals undergo 5-exo *or* 6-exo additions rather than degradation to the corresponding desoxy compounds.[4a,f] It was

(1) Reviews: (a) Hart, D. J. *Science* **1984**, *223*, 883. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (d) Neumann, W. P. *Synthesis* **1987**, 665. (e) Curran, D. P. *Synthesis* **1988**, 417, 489.

(2) Sloan, C. P.; Cuevas, J. C.; Snieckus, V. *Tetrahedron Lett.* **1988**, *37*, 4685.

(3) The use of vinyl radicals in synthesis was introduced and developed by Stork, see: (a) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. (b) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829. For other examples see ref 1.

(4) For examples of carbonyl radical cyclizations in synthesis see: (a) Bachi, M. D.; Bosch, E. *Tetrahedron Lett.* **1986**, *27*, 641. (b) Convey, D. J.; Patel, V. F.; Patenden, G. *Tetrahedron Lett.* **1987**, *28*, 5949. (c) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, *53*, 377. (d) Crich, D.; Eustace, K. A.; Richie, T. J. *Heterocycles* **1989**, *28*, 67. (e) Mestre, F.; Tailhan, C.; Zard, S. Z. *Heterocycles* **1989**, *28*, 171. (f) Bachi, M. D.; Bosch, E. *Heterocycles* **1989**, *28*, 579. (g) Bachi, M. D.; Denenmark, D. *Heterocycles* **1989**, *28*, 583.

(5) Bachi, M. D.; Denenmark, D. *J. Am. Chem. Soc.* **1989**, *111*, 1886.

(6) Barton, D. H. R.; Bringmann, G.; Lamotte, G.; Motherwell, W. B.; Motherwell, R. S. H.; Porter, A. E. A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2657.

(7) For another reaction involving tinthioimidoyl radicals, see: John, D. I.; Tyrrell, N. D.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1981**, 901.

0022-3263/90/1955-3442$02.50/0