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Quassinoid Support Studies: Fused Carbocycle Synthesis from Benzoic Acid Derivatives via 5-Hexynyl and 6-Heptynyl Radical Cyclizations

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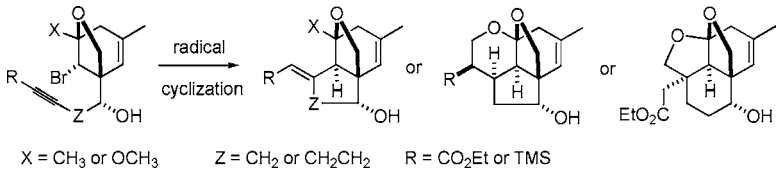
ABSTRACT



Eight bromoalkynes were prepared from substituted benzoic acids and treated with *n*-Bu_3SnH to provide *trans*-fused perhydroindans or *cis*- and *trans*-fused perhydronaphthalenes. Atom-transfer reactions that accompany the free radical reactions resulted in several tandem radical cyclizations with formation of up to three carbon−carbon bonds in a single reaction. The relationship between these reactions and an approach to the quassinoid family of natural products is also described.

We have shown that benzoic acids can be converted to highly functionalized fused carbocycles via a sequence that involves sequential reductive alkylation, halolactonization, and free radical cyclization reactions.[1] An alkene has served as the radical acceptor in most systems studied to date.[2] This paper describes a variation of this sequence in which alkynes are used as the radical acceptor. The motivation for conducting this research was to extend the methodology toward a unified approach to quassinoids containing either perhydroindan or perhydronaphthalene substructures. The quassinoids, exemplified in Figure 1 by chaparrinone (**1**) and (5*R*)-polyandrane (**2**), remain of interest as targets for synthesis due to their complex structures and broad biological activity.[3−5] Extrapolation of this methodology and some surprising observations made along the way are described herein.

Preparation of Cyclization Substrates. Substrates selected for the aforementioned free radical cyclization studies were of types **3** and **4** (Figure 1), which were expected to provide perhydroindans and perhydronaphthalenes, respectively. Substrates where the C_{11} substituent (X) was a methyl

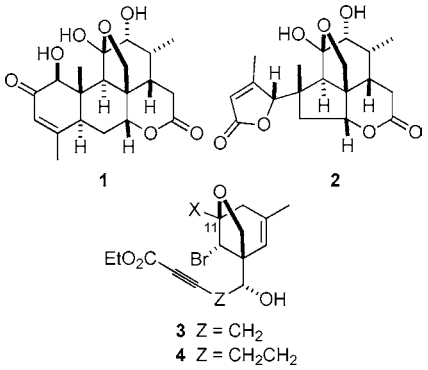


Figure 1. Quassinoids and cyclization substrates.

(1) Chuang, C.-P.; Hart, D. J. *J. Org. Chem.* **1983**, *48*, 1782. Chuang, C.-P.; Gallucci, J. C.; Hart, D. J.; Hoffman, C. *J. Org. Chem.* **1988**, *53*, 3218. Hart, D. J.; Huang, H. C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507.

(2) For oxime ethers, hydrazones, and nitriles, see: Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631. Ellis, D. A.; Hart, D. J.; Zhao, L. *Tetrahedron Lett.* **2000**, *41*, 9357. Chenera, B.; Chuang, C.-P.; Hart, D. J.; Hsu, L.-Y. *J. Org. Chem.* **1985**, *50*, 5409.

(3) For lead reviews, see: Spino, C. *Synlett* **2006**, 23. Kawada, K.; Kim, M.; Watt, D. S. *Org. Prep. Proced. Int.* **1989**, *21*, 521. Polonsky, J. *J. Fortschr. Chem. Org. Naturst.* **1985**, *47*, 221.

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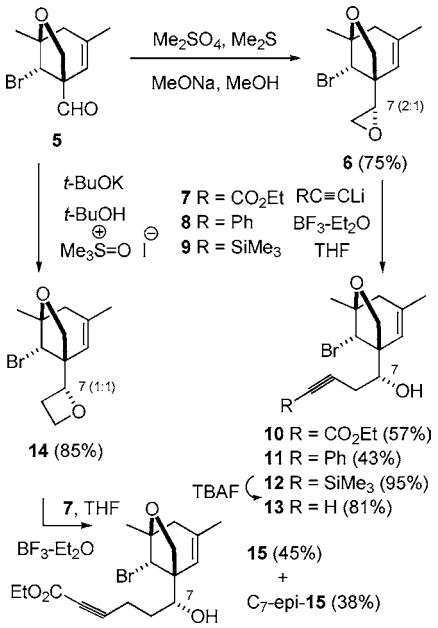
group were studied first because we suspected their synthesis would be simpler than substrates with a C_{11} acetal (X = OCH_3) due to the known sensitivity of the latter type of compound.[6]

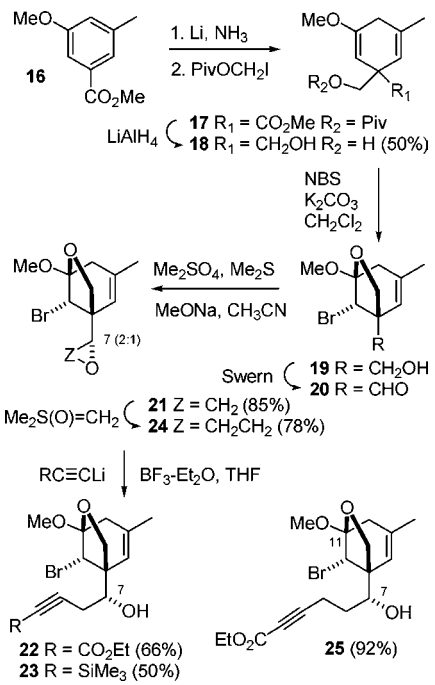
We began with the known aldehyde **5**, prepared in four steps from methyl 3,5-dimethylbenzoate (Scheme 1).[7] Treatment of **5** with dimethylsulfonium methylide gave a separable 2:1 mixture of epoxide **6** and its C_7 diastereomer, respectively, in 75% combined yield.[8] The epoxide was opened with a series of acetylides (**7**−**9**), in the presence of boron trifluoride etherate, to provide homopropargylic alcohols **10**−**12** in variable yields (43−95%).[9] Treatment of **12** with tetra-*n*-butylammonium fluoride also provided cyclization substrate **13** (81%).[10] Treatment of **5** with boron dimethylsulfoxonium methylide under more pressing conditions provided an inseparable 1:1 mixture of oxetane **14** and its C_7 diastereomer in 85% combined yield.[11] Opening of the oxetane with acetylide **7** gave a separable mixture of alkynol **15** (45%) and its C_7 diastereomer (38%).[12]

Scheme 1. Synthesis of Cyclization Substrates



The synthesis of substrates of type **3** and **4** with a C_{11} methoxy group required a different point of departure (Scheme 2). Ester **16** was prepared in 100-g quantities using a known procedure.[13] Birch reduction of **16** was followed by alkylation of the intermediate enolate with iodomethyl pivalate.[14] Reduction of the resulting **17** with lithium aluminum hydride gave crystalline diol **18** in 50% overall yield from **16**. Bromoetherification of **18** using NBS in dichloromethane in the presence of powdered potassium carbonate gave **19**. The base was critical to the success of this reaction. Bromo ether **19** was very sensitive and thus, was oxidized directly to aldehyde **20** using the Swern conditions.[15]

Scheme 2. More Cyclization Substrates



Whereas **20** proved more stable than **19**, it was also sensitive and was treated with dimethylsulfonium methylide to provide a 2:1 mixture of epoxide **21** and its C_7 diastereomer in combined 85% yield. The two epoxides could be separated by column chromatography on a several gram scale. Treatment of pure **21** with acetylides **7** and **9** gave cyclization substrates **22** (66%) and **23** (50%). Conversion of epoxide **21** to oxetane **24** was accomplished using

(4) For some total syntheses of quassinoids, see: Shing, T. K. M.; Yeung, Y. Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 7981 (samaderine Y). Stojanac, N.; Valenta, Z. *Can. J. Chem.* **1991**, *69*, 853 (quassin). Kim, M.; Kawada, K.; Gross, R. S.; Watt, D. S. *J. Org. Chem.* **1990**, *55*, 504 (quassin). Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586 (quassin). Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528 (bruceantin). Grieco, P. S.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078 (chaparrinone). Walker, D. P.; Grieco, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 9891 (polyandranes).

(5) For a lead reference on biological activity, see: Fukamiya, N.; Lee, K.-H.; Ilias, M.; Murakami, C.; Okano, M.; Harvey, I.; Pelletier, M. *Cancer Lett.* **2005**, *220*, 37.

(6) Chenera, B.; Chuang, C.-P.; Hart, D. J.; Lai, C.-S. *J. Org. Chem.* **1992**, *57*, 2018.

(7) Donahue, M. G.; Hart, D. J. *Can. J. Chem.* **2004**, *82*, 314.

(8) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1352. Kutsuma, T.; Nagayama, I.; Okazaki, T.; Sakamoto, T.; Akaboshi, S. *Heterocycles* **1977**, *8*, 397.

(9) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(10) Nakamura, E.; Kuwajima, I. I. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 498. Mohr, P. *Tetrahedron Lett.* **1991**, *32*, 2223.

(11) Okuma, K.; Tanaka, Y.; Kaji, S.; Ohta, H. *J. Org. Chem.* **1983**, *48*, 8, 5133.

(12) Yamaguchi, M.; Nobayashi, Y.; Hirao, I.; *Tetrahedron* **1984**, *40*, 4261. Kurek-Tyrlik, A.; Wicha, J.; Zarecki, A.; Snatzke, G. *J. Org. Chem.* **1990**, *55*, 3484.

(13) Turner, F. A.; Gearien, J. E. *J. Org. Chem.* **1959**, *24*, 1952. Frutos, O.; Atienza, C.; Echavarren, A. M. *Eur. J. Chem.* **2001**, 163.

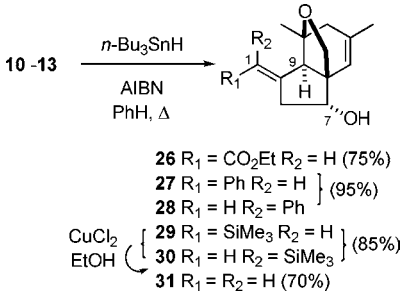
(14) Van Bekkum, H.; Van Den Bosch, C.; Van Minnenpathuis, G.; De Mos, J. C.; van Wijk, A. M. *Recuil* **1971**, *90*, 137. Schultz, A. G.; Taylor, R. E. *J. Am. Chem. Soc.* **1992**, *114*, 3937.

(15) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 3, 2480.

dimethyloxosulfonium methylide in 78% yield. Opening of the oxetane with acetylide **7** gave alkynol **25** in 92% yield.

Free Radical Cyclizations. Cyclization results with compounds of type **3** are summarized in Scheme 3. Treatment of **10** with *n*-Bu_3SnH and AIBN in benzene under reflux provided crystalline *trans*-perhydroindan **26** in 75% yield. The structure of this material was clear on the basis of spectroscopy and was confirmed by X-ray crystallography.[16] The cyclization of substrate **11** also proceeded in high yield (95%) but gave a separable 1:1 mixture of geometrical isomers **27** and **28**.[17] Likewise, the free radical cyclization of TMS-alkyne **12** gave a separable 4:1 mixture of geometrical isomers **29** and **30** in 85% combined yield. Terminal alkyne **13** gave a low yield of the expected cyclization product **31** (24%).[18] We note that **31** was best prepared (70% yield) by protodesilylation of the 4:1 mixture of vinylsilanes **29** and **30** using $CuCl_2$ in ethanol.[19]

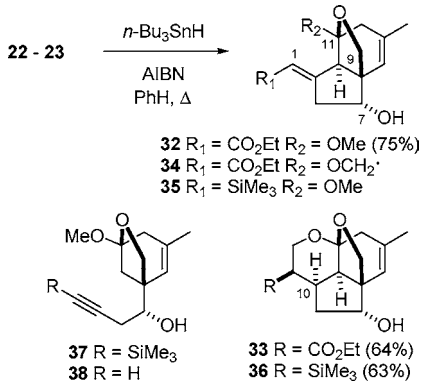
Scheme 3. Cyclization of **10**−**13**



Several aspects of these cyclizations are notable. First, they all produced *trans*-fused perhydroindans. This is in accord with results obtained with the aforementioned alkene substrates and can be rationalized in much the same manner (presence of *cis*-fused 2-oxabicyclo[3.3.0]octane substructure in the product).[1] Second, the clean olefin geometry obtained in the cyclization of **10** was unexpected. Thus, we conducted a labeling experiment in which the cyclization of **10** was initiated using *n*-Bu_3SnD. The resulting **26** was equally labeled with deuterium at the vinylic C_1 position and C_{11} methyl group, indicating that the presumed intermediate vinyl radical is, in part, reduced intramolecularly by a 1,5-hydrogen atom transfer.[20]

The cyclization results with substrates of type **3** (X = OCH_3) are also shown in Scheme 4. Treatment of bromide **22** under the standard cyclization conditions (initial [*n*-Bu_3SnH] = 18 mM, initial [**22**] = 9 mM, 0.06 equiv of AIBN) in benzene gave a mixture of products from which **32** and **33** were isolated in 42% and 31% yields, respectively. Whereas **32** was clearly a cyclization−reduction product, **33** appeared to result from cyclization of the initially formed radical, 1,6-hydrogen atom transfer from the methoxy group to the intermediate vinyl radical, and 6-endo cyclization of the resulting alkoxymethyl radical (**34**) onto the intermediate α,β-unsaturated ester.[21,22] A labeling experiment using *n*-Bu_3SnD indicated that **32** was almost entirely derived from **34**.[23] This suggested that at high concentrations of tri-*n*-butyltin hydride **32** would be the major product and that at low concentrations of tri-*n*-butyltin hydride **33** would become the major product. This was the case. Thus, treatment of **22** (10 mM) with excess *n*-Bu_3SnH (100 mM) gave **32** and **33** in 75% and 10% isolated yields, respectively. On the other hand, slow addition of *n*-Bu_3SnH to a solution of **22** (10 mM in PhH) gave **32** and **33** in 6% and 64% isolated yields, respectively. The behavior of alkynylsilane **23** was qualitatively similar to that of **22**. The standard cyclization conditions provided **35** (11%, *E*/*Z* = 3:1) and **36** (18%), but substantial amounts of reduction product **37** (60%) were also obtained.[24] It was possible to obtain **36** in 63% yield (along with 6% of **35** and 3% of **37**) under high dilution conditions. The cyclization results with substrates of type **4** (X = CH_3 and X = OCH_3) are shown in Scheme 5. Propiolate **15** reacts under standard conditions to afford **39** (23%), **40** (46%), and **41** (12%). Thus, the initially formed radical partitions approximately 2:1 between *trans*-fused (**40** and **41**) and *cis*-fused (**39**) perhydronaphthalenes. The structure of **39** was established by X-ray crystallography.[16] Whereas the origin of **40** is clear, **41** appears to result from a 1,5-hydrogen atom transfer of an intermediate vinyl radical, followed by a rare 5-endo cyclization of the resulting 5-pentenyl radical.

Scheme 4. Preparation of Perhydroindans



(16) We thank Dr. Judith Gallucci (OSU) for performing this X-ray cyrstallographic analysis.

(17) The ratio of products was determined by NMR spectroscopy of the crude product mixture. The isomers were not completely separated by chromatography, but pure samples of each isomer were obtained (see the Supporting Information).

(18) Impure materials that appear to be derived from initial addition of tri-*n*-butylstannyl radical to the terminal acetylene were also detected.

(19) To our knowledge, this is a new method for protodesilylation of vinylsilanes. Protodesilylation using *p*-toluenesulfinic acid (Buchi, G.; Wuest, H. *Tetrahedron Lett*. **1977**, *18*, 4305) proceeded in 43% yield.

(20) The ratio of deuterated products was determined by integration of signals appearing at δ 6.08 (=CD) and δ 1.59 (CH_2D) in the ^2H NMR spectrum deuterated **26**.

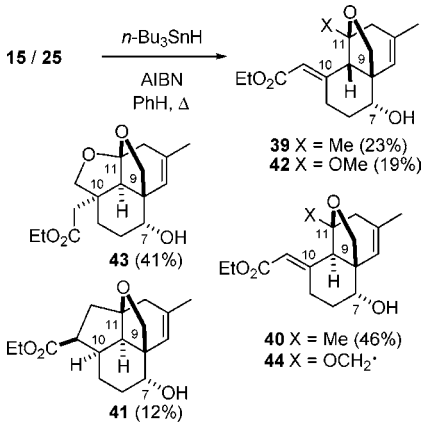
(21) For 5-hexynyl radical cyclizations of ynoates, see: Lowinger, T. B.; Weiler, L. *J. Org. Chem.* **1992**, *57*, 6099.

(22) For 5-hexynyl radical cyclization−radical translocation reactions, see: Martinex-Grau, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 5698. Rochigneux, I.; Fontaneux, M.-L.; Malanda, J.-C.; Doutheau, A. *Tetrahedron Lett.* **1991**, *32*, 2017. Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3159.

(23) The ratio of deuterated products (93% deuteration on the methoxy group and 7% deuteration at C_1) was determined by integration of signals appearing at δ 7.0 (=CD) and δ 3.3 (OCH_2D) in the ^2H NMR spectrum of deuterated **33**.

(24) Alkyne **37** was actually characterized after desilylation to provide **38** (see the Supporting Information).

Scheme 5. Preparation of Perhydronaphthalenes



Substrate **25** provided *cis*-fused perhydronaphthalene **42** (19%) and *trans*-fused perhydronaphthalene **43** (41%). The origin of **43** is most likely alkoxymethyl radical **44**.

The behavior of radicals derived from **3** and **4** are qualitatively similar, with two important differences. Radicals derived from **3** give clean stereochemistry at C_9 while radicals from **4** lead to mixtures of stereoisomers at C_9. This is a consequence of the *absence* of an oxabicyclo[3.3.0]-octane substructure in products derived from **4**, and emphasizes that it is this feature that renders the cyclizations of radicals derived from **3** highly diastereoselective at C_9. In addition, due to ring-size differences the chemistry that follows the 5-hexynyl radical cyclizations (from **3**) is less complex than that following 6-heptynyl radical cyclizations (from **4**). This is due to differences in the proximity of the intermediate C_{11} methyl and alkoxymethyl radicals (from **3** and **4**, respectively) to the intermediate C_{10}-alkylidene groups. In terms of the targets that stimulated this research, perhydroindans **33** and **36** both have features that render them potential intermediates in an approach to C_{19}-quassinoids such as **2**.[25] On the other hand, stereochemical issues at C_9 will have to be addressed before the potential of the 6-heptynyl radical cyclizations for the synthesis of C_{20}-quassinoids such as **1** can be fully realized.[25,26]

Acknowledgment. This paper is dedicated to the memory of Nabi Magomedov, his wife Natalya Scherbinina, and their son Amir Magomedov who died in a tragic accident on February 7, 2006.

Supporting Information Available: Spectroscopic and analytical data for new compounds, crystallographic data, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The conversions of **16** to **33** or **36** each require only seven steps and proceed in 9% and 7% overall yields, respectively.

(26) We note that the C_7 diastereomers of cyclization substrates **12**, **15**, and **25** behave similarly to the substrates described herein.