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Samarium(II) Iodide Mediated Radical/Polar Crossover Reactions of Cyclobutenes. An Efficient Approach to the BCD Ring System of the Penitrems

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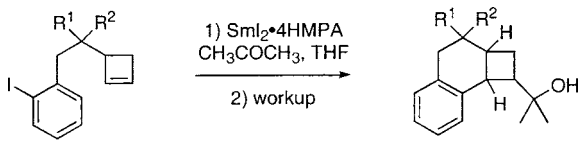
ABSTRACT



Radical/polar crossover reactions of derivatives of 1-(2-cyclobutenyl)-2-(2-iodoaryl)ethanones with acetone promoted by samarium diiodide and HMPA provide 1-(1-hydroxy-1-methylethyl)-2,2a,4,8b-tetrahydro-1*H*-cyclobuta[*a*]naphthalen-3-one derivatives in about 50% isolated yield. This reaction shows promise for construction of the BCD ring fragment of the penitrems.

The penitrems are a small but important family of structurally complex and biologically active indole alkaloids. Typified by penitrem D (Figure 1), family members contain at least nine interlocking rings in sizes ranging from four to seven members.[1] The unusual juxtaposition of rings B−F on the periphery of ring A provides a challenge to existing methodology that has already been met by Smith and co-workers.[2] We are interested in developing novel approaches to the A−F ring core of the penitrems by using radical/polar crossover reactions[3,4] mediated by samarium(II) iodide,[5] and we deploy here a new strategy to make the BCD unit of the penitrems that features a cyclization of an aryl radical to a cyclobutene followed by reduction and trapping with acetone. Although cyclobutenes are expected to be good radical acceptors[6] and have been used occasionally in bimolecular reactions,[7] we could not locate any examples of intramolecular additions (cyclizations) of radicals to cyclobutenes.

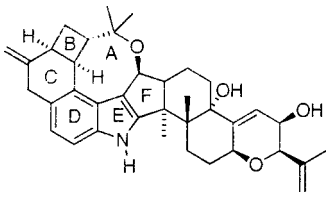


Figure 1. Penitrem D.

(1) (a) Wilson, B. J.; Wilson, C. H.; Hayes, A. W. *Nature* **1968**, *220*, 77. (b) de Jesus, A. E.; Steyn, P. S.; van Heerrden, F. R.; Vleggar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1857−1861.

(2) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254−11255.

(3) (a) Nagashima, T., Ph.D. Thesis, University of Pittsburgh, 1999. (b) Rivkin, A., Ph.D. Thesis, University of Pittsburgh, 2001.

(4) We use here the "radical/polar crossover" terminology of Murphy, but such reactions are also called by other names such as "cascade radical/ionic" reactions. Bashir, N.; Patro, B.; Murphy, J. A. In *Advances in Free Radical Chemistry*; Zard, S. Z., Ed.; Jai Press: Stamford, CT, 1999; Vol. 2, pp 123−150.

(5) (a) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 745−778. (b) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. (c) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321−3354. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4, pp 779−831. (e) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943−961.

(6) For example, the ketone group of cyclobutanones has often been used in radical cyclization reactions: Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091−2115. Cyclizations to methylene cyclobutanes are also known: Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1995**, *36*, 8539−8542.

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The general plan for the model study is outlined in Figure 2. Cyclization of **1** with samarium iodide and acetone by

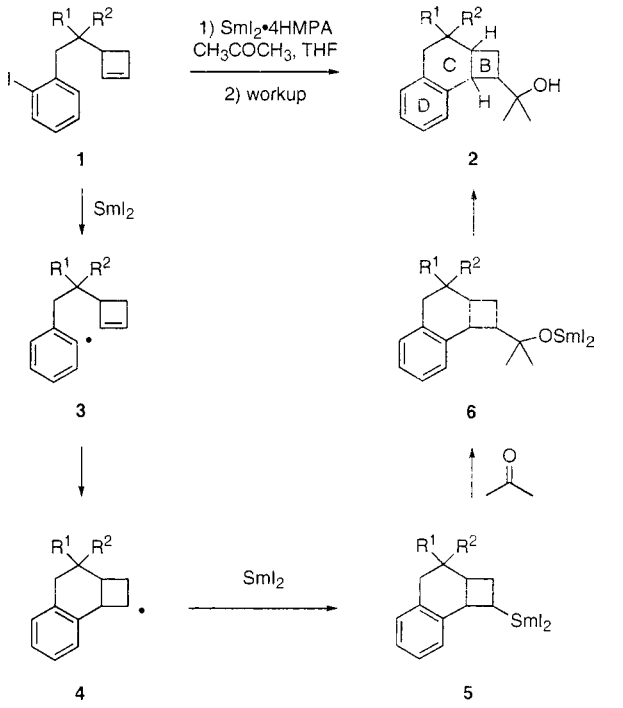
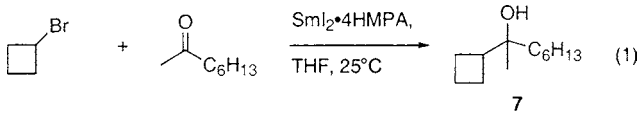


Figure 2. SmI_2 radical/polar crossover reaction.

either Grignard or Barbier procedures[8] is expected to yield **2** through the sequence of one-electron reduction to give aryl radical **3**, cyclization to give cyclobutyl radical **4**, further reduction to cyclobutyl samarium species **5** (or its equivalent), and addition to acetone to give samarium alkoxide **6**. In addition to determining the viability of the proposed sequence and its stereochemical outcome, we selected substrates with different R^1 and R^2 groups to probe generality, keeping in mind that these should be precursors of the exo methylene group present in the penitrems.

The viability of the polar stage of the proposed sequence was readily demonstrated by the experiments shown in eq 1. Addition of cyclobutyl bromide to 2-octanone was effected

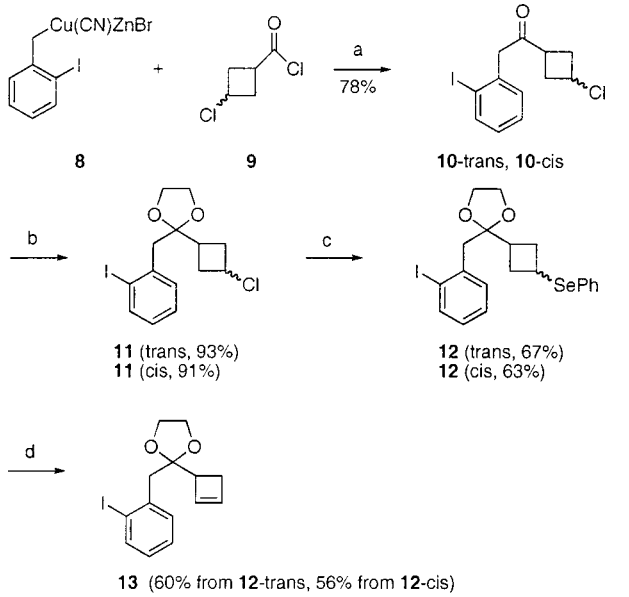


Grignard method, 33%
Barbier method, 69%

by treatment with SmI_2 (2 equiv) and HMPA (8 equiv) under Grignard and Barbier conditions.[5d,8] Both reactions succeeded but the Barbier procedure gave the superior yield (69% for Barbier compared to 33% for Grignard). Accordingly, the Barbier procedure was used for the subsequent cascade reactions.

The synthesis of a representative substrate **13** for the radical/polar cascade introduces a new approach to make acyl cyclobutenes that is shown in Scheme 1. Generation of

Scheme 1



(a) THF, −20°C; (b) Dean-Stark, ethylene glycol, pTSA, PhH; (c) PhSeNa, DME, reflux; (d) 1. mCPBA, CH_2Cl_2, 25°C; 2. $ClCH_2CH_2Cl$, Et_2NH, Mol. Sieves, reflux

benzyl cuprate **8**[9] from the corresponding benzyl bromide followed by quenching with the 3-chlorocyclobutane carboxylic acid chloride **9**[10] provided a 1/1 mixture of the cis and trans diastereomers of ketone **10** in a combined yield of 78%. These were easily separated by flash chromatography, and pure cis and trans diastereomers of ketone **10** were independently carried through the synthesis to cyclization precursor **13** to simplify characterization of the intermediates.

Protection of ketones **10**-trans and **10**-cis as the 1,3-dioxolane ketals via Dean−Stark azeotropic distillation with ethylene glycol and pTSA in benzene provided **11**-trans and **11**-cis in 93% and 91% yield, respectively. Exposure of chlorides **11** to the benzeneselenolate anion in DME at reflux for 12 h provided **12**-trans (67%, from **11**-cis) and **12**-cis (63%, from **11**-trans). Separate oxidation of **12**-trans and **12**-

(7) Examples of radical additions to cyclobutenes: (a) Ferjancic, Z.; Cekovic, Z.; Saicic, R. N. *Tetrahedron Lett.* **2000**, *41*, 2979−2982. (b) Campbell, E. F.; Park, A. K.; Kinney, W. A.; Fengel, R. W.; Liebskind, L. S. *J. Org. Chem.* **1995**, *60*, 1470−1472. (c) Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000**, *41*, 9815−9818. (d) Chen, X.-P.; Sufi, B. A.; Padias, A. B.; Hall, H. K., Jr. *Macromolecules* **2002**, *35*, 4277−4281.

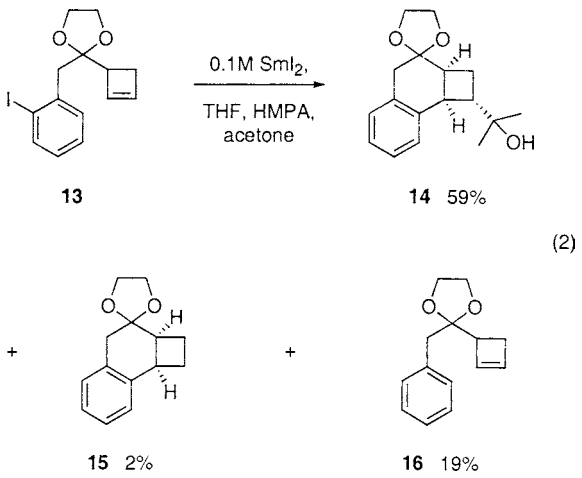
(8) Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050−6058. Grignard conditions: addition of halide to SmI_2•4HMPA followed by addition of ketone. Barbier conditions: addition of halide and ketone together in THF to SmI_2•4HMPA.

(9) (a) Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789−5791. (b) Knochel, P.; Singer R. D. *Chem. Rev.* **1993**, *93*, 2117−2188.

(10) Hall, H. K.; Smith, C. D.; Blanchard, E. P.; Cherofsky, S. C.; Sieja, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 121−130.

cis with *m*-CPBA in dichloromethane followed by selenoxide elimination in 1,2-dichloroethane at reflux for 12 h provided the same cyclobutene **13** in 60% and 56% yields after silica gel chromatography. The other substrates shown in Table 1 were made from ketone **10**-cis/trans by similar sequences.[3] Conveniently, these cyclobutenes were not prone to thermal electrocyclic ring opening either under the conditions of elimination or on storage at or below room temperature.

The results of the samarium(II) iodide mediated tandem cyclization of **13** are shown in eq 2. A solution of the iodide



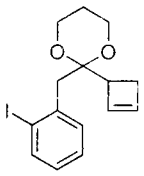
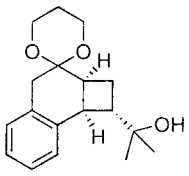
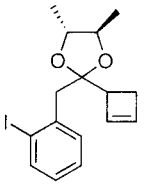
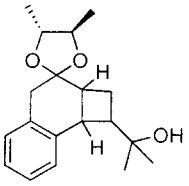
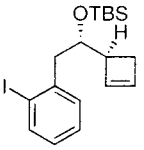
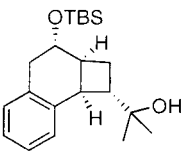
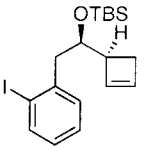
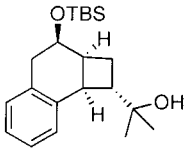
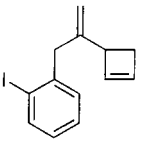
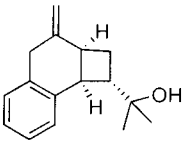
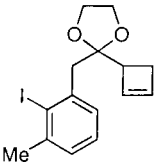
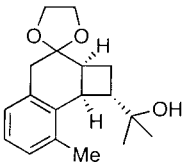
13 **14** 59% (2)

+ **15** 2% + **16** 19%

and acetone (4 equiv) in THF was added to a THF solution of SmI_2 (4 equiv) and HMPA (16 equiv). Standard aqueous workup and flash chromatography gave the target radical/polar crossover product **14** in 59% yield as a single stereoisomer alongside the directly reduced product **16** (19%) and a small amount of the product **15** (2%) derived from successful radical cyclization but failed polar addition. The cis ring fusion can readily be anticipated from much precedent in formation of bicycles of other sizes by radical cyclization,[11] and the exo addition of acetone is supported by the observation of a strong cross-peak between one of the methyl groups and the adjacent ring fusion hydrogen in a 2D noe NMR experiment. The directly reduced product most likely results from hydrogen abstraction by the intermediate aryl radical from the medium,[5e] although this has not been demonstrated experimentally.

The generality of the process is shown by the examples in Table 1. Reductive cyclization of the dioxane acetal gave results comparable to its lower homologue (compare entry 1 to the results in eq 2). Cyclization of a chiral acetal (entry 2) gave an inseparable mixture of diastereomers in a 1/1 ratio in 55% isolated yields. The diastereomeric alcohols in entries 3 and 4 cyclized to give the corresponding products in 40% and 45% isolated yield, respectively. Reductive cyclization of *exo*-methylene substrate in entry 5 provided the hydroxyalkylated tricycle in 41% isolated yield. Finally, the *o*-methyl-substituted analogue of **13** in entry 6 provided the tricycle

Table 1. Examples of Radical/Polar Crossover Reactions

entry	substrate	product	yield
1.			60%
2.			55%[a]
3.			40%
4.			45%
5.			41%
6.			53%

[a] The product is a 1/1 mixture of diastereomers with the ring fusion hydrogens and the hydroxypropyl group on the cyclobutyl ring either all α or all β.

in 53% isolated yield.[12] This success is important since the substituent pattern of the precursor better models that needed for the penitrems.

These successful model studies introduce radical cyclizations to cyclobutenes, expand the capabilities of the already powerful radical/polar crossover reactions of SmI_2, and encourage further development of the planned strategy toward the penitrem class of natural products. The reaction

(11) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, Germany, 1996.

(12) For more detailed studies on the effects of ortho substituents on aryl radical reactions, see: Fairweather, N., M.S. Thesis, University of Pittsburgh, 2002.

tolerates several substituents at the key carbon atom that bears a methylene group in the penitrems, but trends in yields suggest that acetal (and perhaps other quaternary) substituents give better yields than protected hydroxy groups or methylene groups. In a subsequent full paper, we will report on rate constant studies that confirm and quantify this trend and we will also describe other reductive and organometallic methods to cyclize these types of substrates.

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Supporting Information Available: Detailed experimental procedures and compound characterization for synthesis and cyclization of **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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