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Radical and Palladium-Catalyzed Cyclizations to Cyclobutenes: An Entry to the BCD Ring System of Penitrem D

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A novel approach toward the synthesis of the BCD ring system of penitrem D is described. The strategy capitalizes on the fast cyclization rates of aryl radicals into cyclobutenes and allows access to a variety of fused tricyclic structures. Radical/polar crossover reactions of precursors **24**−**29** promoted by samarium diiodide in the presence of HMPA and acetone allow access to the fully functionalized BCD ring system of penitrem D. The stereochemical implications of these processes are evaluated, and a Pd-mediated cyclization approach toward the penitrems is also introduced.

Introduction

The penitrems represent a class of novel indole alkaloids that have attracted attention as a result of their potent neurotoxic activity and complex architectures.[1] The structures of this family of compounds feature nine interlocking rings, including both a cyclobutane and an eight-membered cyclic ether, as well as eleven stereogenic centers (Figure 1). The juxtaposition of rings B−F on the periphery of ring A represents a significant synthetic challenge to existing methodology that has recently been met by Smith and co-workers.[2]

We have been interested in the development of novel radical cyclization approaches toward the construction of the unusual A−F ring core present in the penitrems.[3] Central to our investigations has been the development of a radical/polar crossover reaction of a precursor **1**[4,5] that could provide access to the fully functionalized BCD ring system of penitrem D **2** with different substituents R^1, R^2 in the ring C (Figure 2). In the planned synthetic strategy, we generate an aryl radical **3** from a precursor **1** that is expected to undergo a 6-*exo*-*trig* cyclization into the cyclobutene to give an intermediate cyclobutyl radical

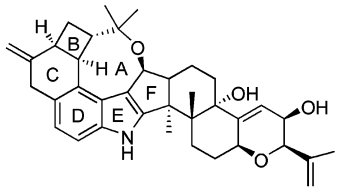

FIGURE 1. Structure of penitrem D.

4. This intermediate is further reduced under the reaction conditions (SmI_2·HMPA, acetone) to the corresponding cyclobutyl samarium species **5** (or its equivalent), which then adds to acetone to provide the corresponding samarium alkoxide **6**. Aqueous workup of the reaction mixture provides the target alcohol **2** (Figure 2).[6,7] A key feature of this synthetic approach is the ability of a cyclobutene to intercept an aryl radical in an intramolecular fashion. Although cyclobutenes are expected to be good radical acceptors[8] and have been used in bimolecular reactions,[9] we could not locate any examples

(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) For the first total synthesis of penitrem D, see: (a) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254−11255. (b) Kanoh, N.; Smith, A. B., III; Ishiyama, H.; Minakawa, N.; Rainier, J. D.; Hartz, R. A.; Cho, Y. S.; Cui, H.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 8228−8237.

(3) For a recent communication of our synthetic work in this area, see: Rivkin, A.; Nagashima, T.; Curran, D. P. *Org. Lett.* **2003**, *5*, 419−422.

(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. *Advances In Free Radical Chemistry*; Zard, S. Z., Ed.; Jai Press: Stamford, CT, 1999; Vol. 2, pp 123−150.

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

(6) (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, 1991; Vol. 4, pp 779−831. (e) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943−961.

(7) The reaction was carried out under "Barbier conditions": addition of halide and ketone together in THF to a solution of SmI_2·4HMPA. See: Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050−6058.

(8) 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.

(9) Examples of radical additions to cyclobutenes: (a) Ferjančić, Z.; Čeković, Z.; Saičić, R. N. *Tetrahedron Lett.* **2000**, *41*, 2979−2982. (b) Campbell, E. F.; Park, A. K.; Kinney, W. A.; Fengl, R. W.; Liebeskind, 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.

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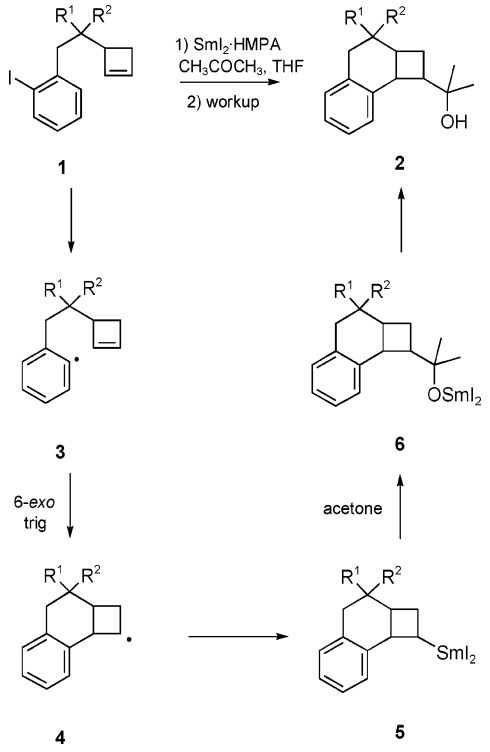


FIGURE 2. Tandem radical/polar reaction.

of intramolecular additions of radicals to cyclobutenes. Herein, we provide the full account of our investigations in this area, including rate constant determination and experimental evidence for the stereochemical outcome of these processes.[3]

Results and Discussion

Synthesis of Precursors. The study started with the synthesis of substrates **24**−**29** with different R^1, R^2, and R^3 groups to prove the generality of the approach, keeping in mind that the R^1, R^2 groups should be converted into the *exo*-methylene group present in the penitrems. Starting from the readily available ketones **7** or **8**,[10] ketals **24**−**26**, silyl ether **27**, and *exo*-methylene substrate **28** were synthesized by a common strategy that involved a selenoxide elimination in the final step. The synthesis of the precursors **24**−**26** started with the ketalization of **7** or **8** with the appropriate diols. Subsequent phenylselenide formation of intermediates **9**−**11** led to compounds **14**−**16** that underwent selenoxide elimination to give the desired ketal precursors **24**−**26**.

The synthesis of the silyl ether **27** involved reduction of the ketone **7**, followed by phenyl selenide formation to give secondary alcohol **12**. Protection of the alcohol as the silyl ether **17** and finally selenoxide elimination allowed access to both diastereoisomers of the silyl ether substrate **27**.[11] In the case of the *exo*-methylene substrate **28**, the synthesis involved conversion of the ketone **7** to the *exo*-methylene **13**, followed by formation of the phenyl selenide **18** and final selenoxide elimination.

The nitrile precursor **29** was synthesized starting from the chlorocyclobutane **19**. This was transformed into **20** by reaction with sodium phenylselenide in refluxing DME. Tosylation of the primary alcohol in **20** gave **21**, which was reacted with potassium cyanide to produce the desired cyclobutane **22**. An alkylation reaction between the nitrile **22** and 2-iodo-1-iodomethyl-3-methyl-benzene, followed by selenoxide elimination in **23** provided the desired nitrile precursor **29** as a 1:1 mixture of diastereoisomers (Scheme 1).

Radical Cyclizations and Radical/Polar Crossover Reactions. To test the feasibility of the radical cyclizations, reactions of the substrates **24**−**29** were first conducted using the tributyltin hydride method.[12] In a typical experiment, the cyclization of precursor **1** was performed in refluxing benzene (80 °C) in the presence of AIBN (0.2 equiv). Purification by flash column chromatography allowed the separation of both the cyclized and reduced compounds when the reaction was performed with precursors **24**−**26** and *syn*-**27** (entries 1−4, Table 1). With *anti*-**27**, **28**, and **29** the cyclized and reduced products could not be separated preparatively, so the ratios were determined by ^{1}H NMR spectroscopic analysis of the mixtures.

The effect of different substituents on the rates of cyclization was determined by standard competition kinetics. In a typical sequence of experiments, the cyclization of precursor **1** was performed under the conditions described above at 3−5 different concentrations of tributyltin hydride (Figure 3).[12e] The ratios of the cyclized (**31**) to reduced products (**30**) (k_C/k_H) were determined either by GC or ^{1}H NMR spectroscopic analysis of the crude reaction products. Finally, the corresponding rate constant (k_c) of the different cyclization reactions were calculated by using the recommended rate constant for reduction of an aryl radical by Bu_3SnH at 80 °C in benzene ($k_H = 1.0 \times 10^9$ $M^{-1}s^{-1}$).[12g]

The results of these experiments are summarized in Table 1. The intramolecular radical cyclization of an aryl radical into a cyclobutene is a facile process with isolated yields of cyclized products ranging from 49% to 90%. Estimated cyclization rate constants, k_c, fall in a narrow range of $2.8-6.5 \times 10^8$ s^{-1}. Cyclizations of the dioxane ketal precursor and the lower dioxolane homologue occurred in similar yields (entries 1 and 2; 84% and 82%), whereas the *o*-methyl-substituted analogue gave a slightly lower yield (entry 3, 59%).[13] This suggests that the size of the ketal and presences of ortho substituents have little influence on the cyclization process. In the cases of the diastereomeric alcohols (entries 4 and 5), the

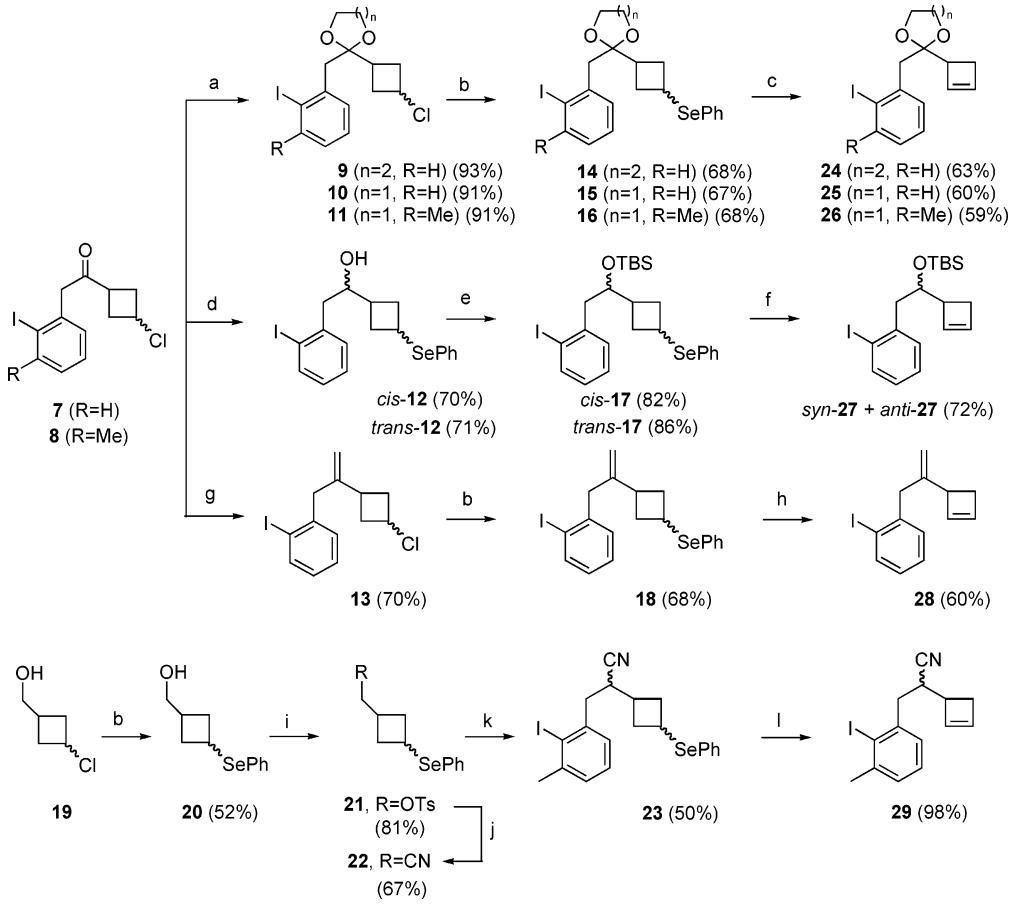
(10) A detailed description of the syntheses can be found in Supporting Information. See also Supporting Information of ref 3.

(11) The relative stereochemistry of the *syn*-**27** and *anti*-**27** precursors was assigned on the basis of the relative stereochemistry of the corresponding cyclized products **38** and **40** (these were assigned by analysis of the coupling constant between the secondary benzylic hydrogens and the neighboring tertiary silyl ether hydrogen).

(12) (a) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925−3941. (c) Beckwith, A. L. J.; Zimmermann, J. *J. Org. Chem.* **1991**, *56*, 5791−5796. (d) Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickrema, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594−4596. (e) Abeywickrema, A. N.; Beckwith, A. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 464−465. (f) Beckwith, A. L. J.; Gara, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 795−802. (g) Garden, S. J.; Avila, D. V.; Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1996**, *61*, 805−809. (h) Beckwith, A. L. J.; Gerba, S. *Aust. J. Chem.* **1992**, *45*, 289−308.

(13) For a discussion of the influence of ortho substituents in radical mediated cyclizations, see: Curran, D. P.; Fairweather, N. *J. Org. Chem.* **2003**, *68*, 2972−2974.

SCHEME 1[a]



[a] Reagents and conditions: (a) Dean−Stark, $HOCH_2CH_2OH$, PTSA, PhH; (b) PhSeNa, DME, reflux; (c) (1) *m*-CPBA, CH_2Cl_2, −78 to 25 °C, (2) Et_2NH, CH_2Cl_2, reflux; (d) (1) $NaBH_4$, MeOH, rt, (2) PhSeNa, DME, reflux; (e) TBSCl, DMF, imidazole; (f) (1) *m*-CPBA, CH_2Cl_2, (2) Et_2NH, 1,2-dichloroethane, 14 h, reflux; (g) Tebbe reagent, toluene; (h) (1) *m*-CPBA, CH_2Cl_2, −78 °C, (2) $CHCl_3$, Et_2NH, reflux; (i) TsCl, Et_3N, DMAP, CH_2Cl_2; (j) KCN, DMSO, 80 °C; (k) NaHMDS, −78 °C, **22**, 90 min, then 2-iodo-1-iodomethyl-3-methyl-benzene, HMPA, −78 to 25 °C; (l) (1) *m*-CPBA, CH_2Cl_2, −78 to 25 °C, (2) Et_2NH, 1,2-dichloroethane, 5 h, reflux.

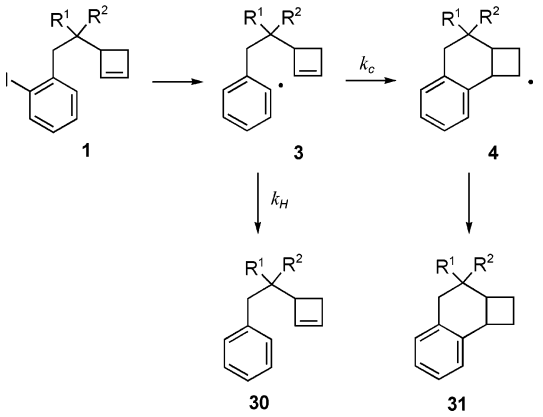


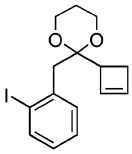
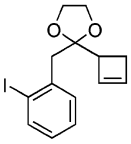
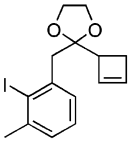
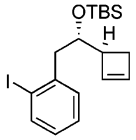
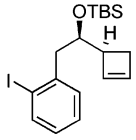
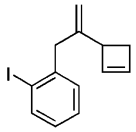
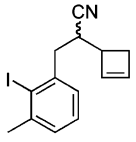
FIGURE 3. Competition kinetics for aryl radical cyclization.

exo-methylene radical (entry 6), and the nitriles (entry 7), we observe somewhat lower cyclization rate constants and the combined yields of the corresponding cyclized and reduced products range between 76% and 90%. These studies establish the generality of the cyclization reaction with different substituents R^1, R^2, and R^3 and suggest that ketal (and perhaps other quaternary) substituents are better suited than the protected hydroxy, methylene, or nitrile groups for the reaction.

Having established the viability of the radical cyclizations of the substrates **24**−**29**, we investigated radical reactions of these substrates with *tert*-butyl alcohol promoted by samarium diiodide and HMPA. The results of these studies are also shown in Table 1. In a typical reaction, the cyclization precursor **24** (entry 1, Table 1) was added to a solution of SmI_2 (3 equiv), HMPA (12 equiv), and *tert*-butyl alcohol in THF at 25 °C, and the resulting reaction mixture was stirred for 30 min. Aqueous workup followed by flash column chromatography provided the cyclized product **32** in 73% yield along with the reduced product **33** in 16% yield. The directly reduced product most likely results from hydrogen abstraction by the intermediate aryl radical from the medium, although this has not been demonstrated experimentally.[6c] The trends of yields employing this cyclization method were similar to those obtained with tributyltin hydride, which suggests that the cyclization is independent of the method employed to generate the aryl radical.

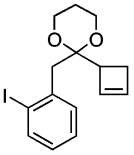
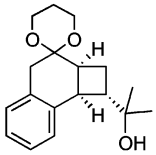
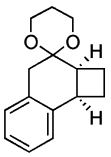
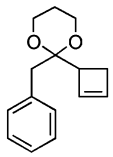
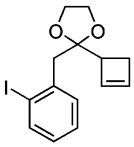
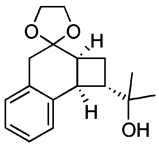
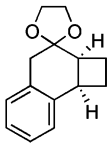
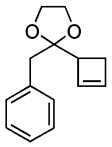
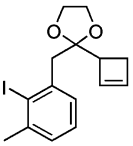
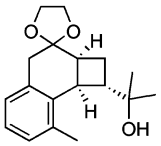
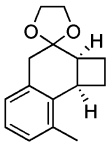
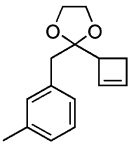
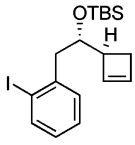
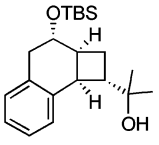
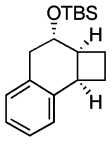
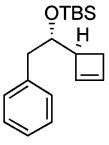
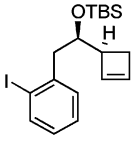
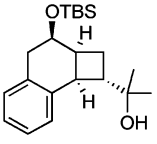
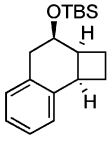
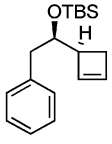
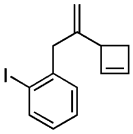
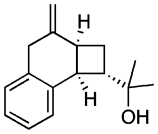
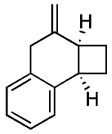
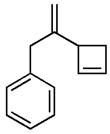
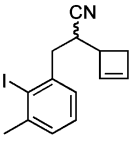
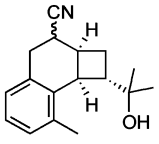
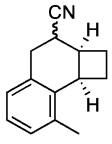
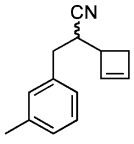
With the success of the SmI_2-mediated reactions with *tert*-butyl alcohol established, we then tested the viability of the tandem radical/polar crossover reactions with acetone. In a typical experiment, a solution of substrate **24** (entry 1, Table 2) and acetone in THF was added to a solution of SmI_2 (4 equiv) and HMPA (16 equiv) in THF

TABLE 1. Bu_3SnH- and SmI_2/*t*-BuOH-Mediated Cyclization Reactions

Entry	Substrate	Conditions	Product (Yield)		Rate Constant
1	 **24**	Bu_3SnH:	**32** (84%)[a]	**33** (11%)	$6.5 \times 10^8\ s^{-1}$
		SmI_2/*t*BuOH:	(73%)	(16%)	
2	 **25**	Bu_3SnH:	**34** (82%)[a]	**35** (13%)	$4.5 \times 10^8\ s^{-1}$
		SmI_2/*t*BuOH:	(75%)	(15%)	
3	 **26**	Bu_3SnH:	**36** (59%)[b]	**37** (29%)	$4.06 \times 10^8\ s^{-1}$
		SmI_2/*t*BuOH:	(63%)	(29%)	
4	 *syn*-**27**	Bu_3SnH:	*syn*-**38** (49%)[b]	*syn*-**39** (38%)	$2.5 \times 10^8\ s^{-1}$
		SmI_2/*t*BuOH:	(54%)	(39%)	
5	 *anti*-**27**	Bu_3SnH:	*anti*-**40** (90%,62:38)[b,c,e]	*anti*-**41**	$3.2 \times 10^8\ s^{-1}$
		SmI_2/*t*BuOH:	(90%, 67:32)[e]		
6	 **28**	Bu_3SnH:	**42** (76%, 61:39)[b,c,e]	**43**	$3.1 \times 10^8\ s^{-1}$
		SmI_2/*t*BuOH:	(81%, 67:37)[e]		
7	 **29**	Bu_3SnH:	**44** (76%, 74:26)[a,c,d,e]	**45**	$2.8 \times 10^8\ s^{-1}$
		SmI_2/*t*BuOH:	(78%, 65:35)[c,d,e]		

[a] Reaction carried out at 0.1 M. [b] Reaction carried out at 0.2 M. [c] Ratio determined by ^1H NMR. [d] Mixture (1:1) of diastereoisomers. [e] Products inseparable, ratio determined on mixture.

TABLE 2. SmI_2-Mediated Cyclization Reactions with Acetone

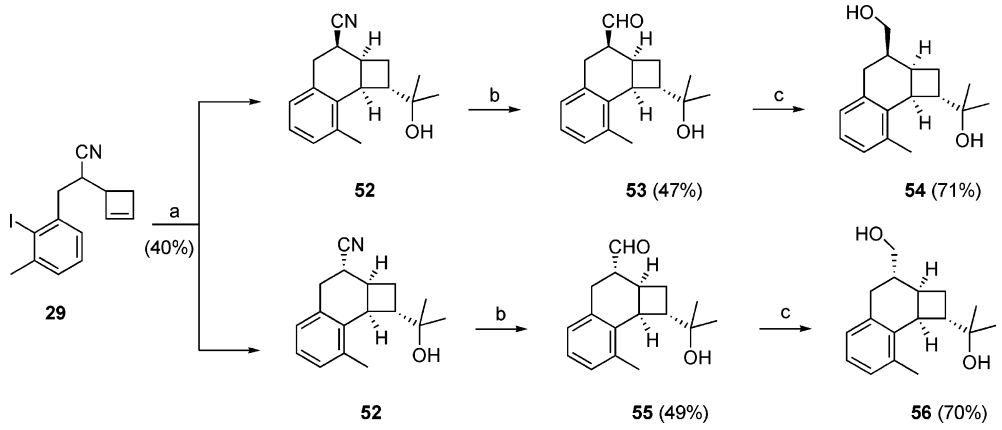
Entry	Substrate	Product (Yield)		
1	 **24**	 **46** (60%)	 **32** (2%)	 **33** (19%)
2	 **25**	 **47** (59%)	 **34** (2%)	 **35** (13%)
3	 **26**	 **48** (59%)	 **36** (3%)	 **37** (23%)
4	 *syn*-**27**	 **49** (40%)	 **38** (3%)	 **39** (38%)
5	 *anti*-**27**	 **50** (45%)	 **40** (40%, 10:90)[a]	 **41**
6	 **28**	 **51** (41%)	 **42** (45%, 9:91)[a]	 **43**
7	 **29**[b]	 **52** (40%)[b]	 **44** (40%, 10:90)[a,b]	 **45**

[a] Inseparable, ratio determined by ^{1}H NMR. [b] Mixture (1:1) of diastereoisomers.

at 25 °C and the resulting reaction mixture was stirred for 30 min. Aqueous workup followed by flash column chromatography provided the desired products in yields shown in Table 2.

The radical/polar crossover reactions with acetone trapping proceed in acceptable yields with different R^1 and R^2 substituents. In particular, we observed that the yields of the corresponding products of the ketal-bearing substrates **24**−**26** (entries 1−3, 59−60%) were similar, which reinforced the idea of that there was very little effect of the ring size of the ketal or the *o*-methyl group on the cyclization reaction. The diastereomeric alcohols *syn*-**27** and *anti*-**27** (entries 4 and 5) cyclized to give the corresponding products **49** and **50** in 40% and 45%

SCHEME 2[a]



[a] Reagents and conditions: (a) (i) SmI_2, HMPA, acetone, (ii) flash chromatography; (b) DibalH, DCM, −78 to 25 °C, 5 h; (c) $NaBH_4$, MeOH, 2 h.

isolated yields, respectively.[14] Reductive cyclization of the *exo*-methylene substrate **28** (entry 6, Table 2) provided the hydroxyalkylated tricycle **51** in 41% isolated yield, and the nitrile precursor **29** (entry 7, Table 2) yielded a 1:1 mixture of two diastereoisomers **52** that were separated by column chromatography. In all cases, two side products were formed, which were reduced products (13−38%) and small amounts (2−5%) of the products from successful radical cyclization but failed polar addition. Yields of the directly reduced products were in line with expectations from the Bu_3SnH and SmI_2/*tert*-butyl alcohol experiments.

The cyclizations are expected to give the corresponding *cis* ring fusion products based on previous observations in the formation of bicycles of different ring sizes by radical cyclizations.[15] The *exo* addition of acetone was 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.[16] Further evidence was obtained when the two separated diastereoisomers of the nitrile **52** were independently reduced to the corresponding diols **54** and **56**. These transformations were performed by a two-step procedure employing DibalH in dichloromethane to give aldehydes **53** and **55** (Scheme 2), followed by treatment with $NaBH_4$ in methanol that gave the corresponding diols **54** and **56**.

The relative configuration of **54** was confirmed by X-ray crystallography, and that of the alcohol **56** was established by comparison of its spectroscopic properties with a closely related intermediate (**57**) reported by Smith and co-workers (Figure 4).[2] Notably, **56** exhibited ^1H NMR (both multiplicity and chemical shift) and ^{13}C NMR data in the upfield region almost identical to those of the diol **57**. These spectra only differed in the signals corresponding to the substitution pattern of the aromatic ring.

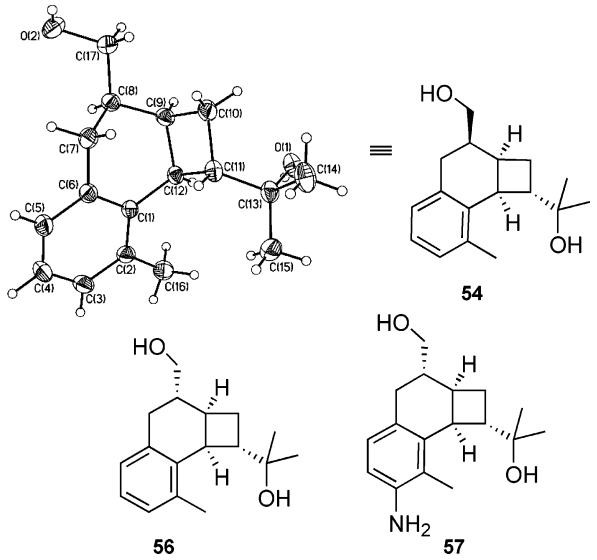


FIGURE 4. Establishment of configurations by crystallography of **54** and comparison of **56** to known **57**.

Palladium-Catalyzed Cyclizations. Palladium-catalyzed cyclizations have been frequently applied toward the synthesis of complex polycyclic ring systems.[17] Since we were unable to locate any examples of palladium(0)-mediated cyclizations of cyclobutene, we decided to test this idea using substrates **24**−**29**. The results of these studies are shown in Table 3. In a typical experiment, the substrate **24** (entry 1, Table 3) was added to a solution of $Pd(PPh_3)_4$ (20% mol) and triethylamine in acetonitrile, and the resulting mixture was refluxed for 12 h. Aqueous workup followed by flash column chromatography provided the tricycle **58** in 84% yield.

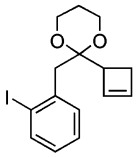
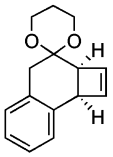
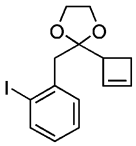
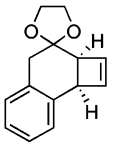
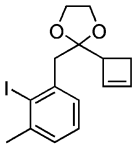
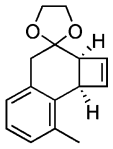
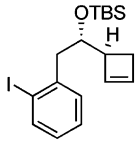
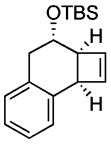
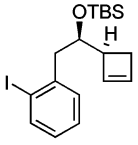
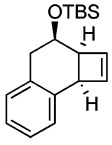
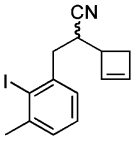
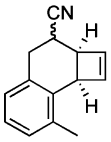
(14) Configurations were tentatively assigned on the basis of the observation of a *trans*-diaxial coupling constant (11 Hz) between the proton adjacent to the OTBS group and one of the benzylic methylene protons in *anti*-**27**. Both modeling and the crystal structure of **54** indicated a dihedral angle of close to 180° in this isomer.

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

(16) Experiment performed in the cyclized products **48** and **50**.

(17) Examples of Heck cyclizations: (a) Zhang, Y.; O'Conner, B.; Negishi, E. *J. Org. Chem*. **1988**, *53*, 5590−5592. (b) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett*. **1988**, *24*, 2919−2922. (c) Jin, Z.; Fuchs, P. L. *Tetrahedron Lett*. **1993**, *33*, 5205−5208. (d) Negishi, E.; Zhang, Y.; O'Conner, B. *Tetrahedron Lett*. **1988**, *24*, 2915−2918. (e) Grigg, R.; Santhakumar, V.; Sridharan, V. *Tetrahedron Lett*. **1993**, *34*, 3163−3164. (f) Torii, S.; Okumoto, H.; Ozaki, H.; Nakayasu, S.; Tadokoro, T.; Kotani, T. *Tetrahedron Lett*. **1992**, *24*, 3499−3502.

TABLE 3. Palladium(0)-Mediated Cyclization Reactions

Entry	Substrate	Product (Yield)	
1	 **24**	 **58**	84%
2	 **25**	 **59**	81%
3	 **26**	 **60**	79%
4	 *syn*-**27**	 *syn*-**61**	77%
5	 *anti*-**27**	 *anti*-**61**	78%
6	 **29**[a]	 **62**[b]	78%

[a] Mixture (1:1) of diastereoisomers. [b] Mixture (1:1) of diastereoisomers, compounds separated by column chromatography.

Cyclization of the other substrates occurred in comparable yields. In contrast to radical cyclization trends, the similarity of the yields of the Heck products suggests that variation of the substitution had very little effect on the reaction. This result can be attributed to the lack of side reaction pathways present in the palladium(0)-mediated cyclizations of the substrates.

Conclusions

In summary, we have shown that cyclization reactions of derivatives of 1-(2-cyclobutenyl)-2-(2-iodoaryl)ethanones are efficiently promoted by tributyltin hydride, samarium diiodide, and palladium(0) to provide the target cyclized products in moderate to high yields. Rate constant studies with tributyltin hydride established the success and the broad scope of radical cyclizations to cyclobutenes. This reaction tolerates several substituents at the key carbon atom that bears a *exo*-methylene group in the penitrems. Radical/polar crossover reactions of derivatives of 1-(2-cyclobutenyl)-2-(2-iodoaryl)ethanones with acetone or *tert*-butyl alcohol promoted by samarium diiodide have been used to construct the BCD ring system of the penitrems. Furthermore, we have described the first examples of palladium(0)-mediated cyclizations to cyclobutenes. This reaction may prove to be useful for syntheses of fused cyclobutene rings in complex ring systems. Radical and Pd-catalyzed cyclizations to cyclobutenes provide a powerful strategy for the synthesis of fused cyclobutane and cylobutene rings, and this encourages further development of such strategies toward the penitrem class of natural products.

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Supporting Information Available: Detailed experimental procedures and characterization for syntheses of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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