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Six- versus Five-Membered Ring Formation in Radical Cyclizations of 7-Bromo-Substituted Hexahydroindolinones

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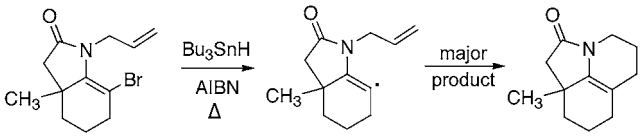
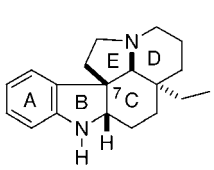
ABSTRACT

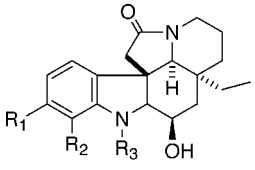


Radical cyclization of *N*-allyl-7-bromo-3a-methyl-hexahydroindol-2-one affords a six-membered ring product that prevails over the isomeric five-membered compound. The former product is generated through two reaction pathways: (a) 6-*endo-trig* ring closure and (b) rearrangement of an intermediate methylenecyclopentyl radical obtained by 5-*exo-trig* cyclization.

The aspidosperma indole alkaloid family constitutes an important class of naturally occurring compounds that has attracted the attention of synthetic chemists due to the interesting biological properties of some of its members.[1] These alkaloids share as part of their structure the [6.5.6.5]-ABCE ring system found in aspidospermidine (**1**) and spegazzinidine (**2**). The presence of the sterically congested



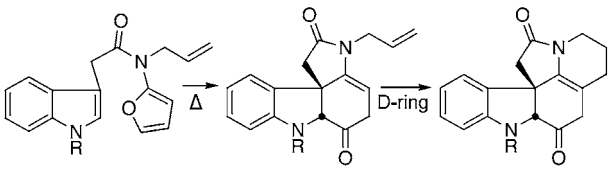
Aspidosperminidine (**1**)



Spegazzinidine (**2**)
$R_1 = R_2 = OH$; $R_3 = COCH_3$

C(7) quaternary carbon center represents a particular challenge toward the synthesis of this family of natural products.[2] A number of creative strategies have emerged over the years to address this problem.[3] Our interest in this area led us to consider an approach to the ABCE tetracyclic core **4**, wherein an amido-substituted furan undergoes an intramolecular Diels−Alder reaction across a tethered indole π-bond. In an earlier report we demonstrated that the [4 + 2]-cycloaddition/rearrangement sequence was remarkably efficient given that two aromatic rings were compromised in the reaction (Scheme 1).[4] To apply this strategy to the synthesis of the indole alkaloid spegazzinidine (**2**), we needed to address the problem of assembling the final D-ring of the pentacyclic skeleton. In this communication we report an efficient general strategy for construction of the remaining six-membered D-ring that is based on a cyclohexenyl radical cyclization of a hexahydroindolinone intermediate.

Scheme 1



3 **4** **5**

(1) (a) Saxton, J. E. *Nat. Prod. Rep.* **194**, *11*, 493. (b) *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: San Diego, 1990; Vol. 37, pp 145−204.

(2) Overman, L. E.; Sworin, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1985; Vol. 3, pp 275−307.

10.1021/ol036347z CCC: $27.50
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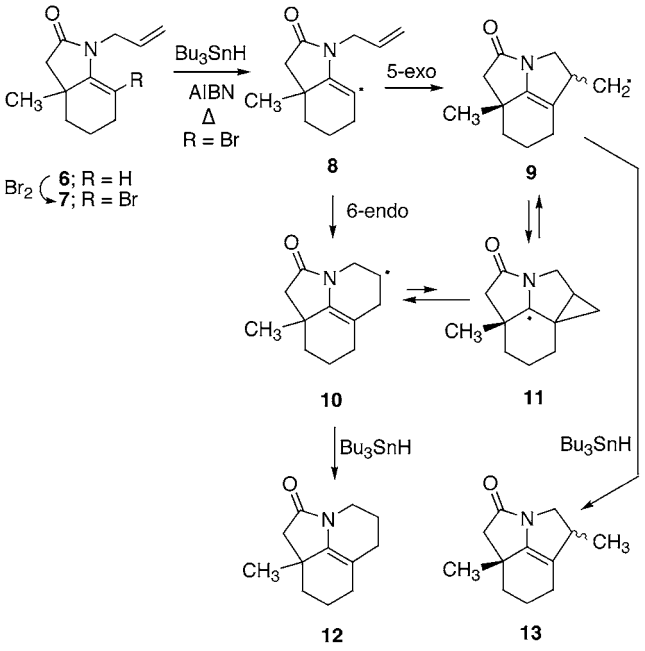
Scheme 2



Scheme 2 depicts the basic features of our strategy directed toward aspidospermidine construction. The first step, selective bromination of the enamido π-bond, should be extremely rapid and efficient since analogous examples are known.[5] We hoped that generation of a cyclohexenyl radical (i.e., **8**) from **7** would initiate a 6-*endo*-*trig* cyclization ultimately leading to **12** after abstraction of hydrogen from tributyltin hydride. A model study designed to test the feasibility of this concept began by the condensation of allylamine with 1-methyl-(2-oxocyclohexyl) acetic acid to give the desired bicyclic lactam **6** in 96% yield.[6] Hexahydroindolinone **6** was subsequently treated with bromine in CH_2Cl_2 followed by reaction with NEt_3 to deliver the cyclization precursor **7** in 95% yield. Exposure of **7** to several radical cyclization conditions led to various mixtures of the 6-*endo*- and 5-*exo*-*trig* cyclization products **12** and **13**, with the best yield and product ratio obtained using *n*-Bu_3SnH/AIBN in refluxing benzene under slow addition conditions.

Since their introduction in 1982,[7] vinyl radical cyclizations have been widely used in organic synthesis,[8] although preparative sequences incorporating vinyl radicals as part of a heterocyclic array are much less common. Seminal studies by Bechwith[9] and Stork's groups[10] have shown that, under tin hydride mediated reaction conditions, vinyl radical cyclization gives a mixture of both 5-*exo* and 6-*endo* products. The kinetic work by Beckwith revealed that formation of the six-membered ring is not solely due to a 6-*endo*-*trig* cyclization but is the result of a rapid rearrangement of the methylene cyclopentyl radical, via a reversible 3-*exo*-*trig* cyclization.[11] It was envisioned that by keeping the hydride concentration low, rearrangement of the kinetically formed radical **9** derived from bromide **7** to the thermodynamically more stable radical **10** would occur, leading to product **12**. Comparison of the strain energies of **9** and **10**, as well as radical stability, supports this idea. Indeed, when **7** (0.01 M) was treated with tributyltin hydride and a catalytic amount of AlBN, six-membered ring product **12** was the major product formed in 89% yield. In contrast, when bromide **7** was treated with Bu_3SnH at a concentration of 0.1 M, a significant quantity (20%) of the 5-*exo* cyclization product **13** (3:1 mixture of diastereomers) was obtained along with the 6-*endo* cyclization product **12** in a ratio of 1:3, together with the simple reduction product **6** (19%). These results clearly indicate that the vinyl radical rearrangement pathway is responsible, to a considerable extent, for the regiochemical outcome of the reaction.

The cyclization method was next extended to the *N*-benzyl-substituted hexahydroindolinones **14** and **15**. Exposure of bromo-enamide **14** to Bu_3SnH under standard radical forming conditions furnished pyrrolo[3.2.1-*de*]phenanthridinone **16** in 68% yield together with 27% of the reduced hexahydroindolinone **17**. In this case, selective 6-*endo* cyclization took place on the aromatic ring. Interestingly, the closely related *o*-bromobenzyl-substituted hexahydroindolinone **15** failed to cyclize but instead gave largely the reduction product **17** in 75% yield. The different behavior observed with these two systems is presumably reflective of the slower rate of addition to the enamido π-bond.[12] The successful cyclization of **14** encouraged us to also apply the reaction to the simpler 8-bromo-hexahydro-1*H*-quinolinone system **18**. Gratifyingly, subjecting a sample of **18** to the standard radical conditions furnished the cyclized pyrido[3.2.1-*jk*]carbazolonone **19** in 81% yield, thereby demonstrating the facility of the 5-*exo*-*trig* cyclization pathway.[13] At this juncture, we decided to extend our studies toward the homologous *N*-butenyl hexahydroindolinone **20**. A review of the literature revealed, somewhat surprisingly, that simple 1,6-heptadienyl radicals

(3) (a) Woodward, R. B.; Cava, M.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954,** *76*, 4749. (b) Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98. (c) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. (d) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872. (e) Marino, J. P.; Rubio, M. B.; Cao, G.; Dios, de, A. G. *J. Am. Chem. Soc.* **2002**, *124*, 13398. (f) Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913. (g) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 1891.

(4) Lynch, S. M.; Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4643.

(5) (a) Wei, L. L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459. (b) Goffin, E.; Legrand, Y.; Viehe, H. G. *J. Chem. Res., Synop.* **1977**, 105.

(6) (a) Ragan, J. A.; Claffey, M. C. *Heterocycles* **1995**, *41*, 57. (b) Ennis, M. D.; Hoffman, R. L.; Ghazal, N. B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813.

(7) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.

(8) (a) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301. (b) Motherwell, W. B.; Crich, D. *Free Radical Reactions in Organic Synthesis*; Academic Press: London, 1992. (c) Curran, D. P. *Synthesis* **1988**, 4117. (d) Curran, D. P. *Synthesis* **1988**, 489. (e) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1**,** 1237.

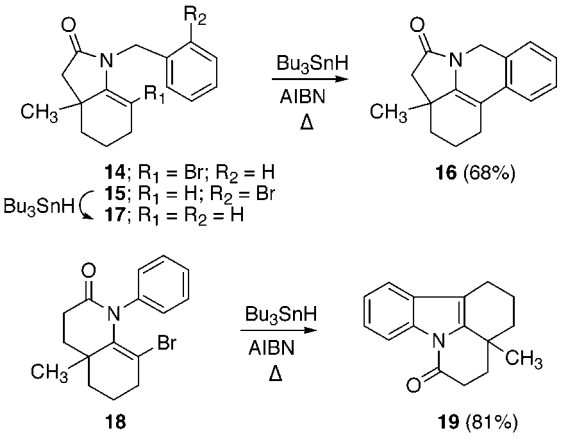
(9) Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525.

(10) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529.

(11) More recently, Crich's group reported preferential formation of the 5-*exo* product when the reaction was conducted in a rapid radical quenching environment (i.e., PhSeSePh/Bu_3SnH), reconfirming that the five-membered ring closure is the kinetically favored process; see Crich, D.; Hwang, J.-T.; Liu, H. *Tetrahedron Lett.* **1996**, *37*, 3105.

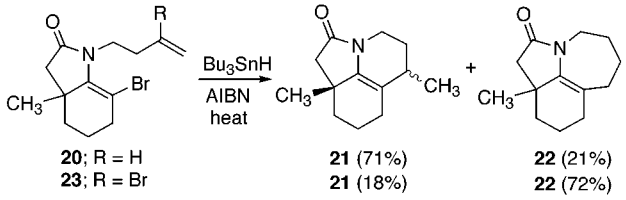
(12) Vazquez, A. N.; Garcia, A.; Dominguez, D. *J. Org. Chem.* **2002**, *67*, 3213.

Scheme 3



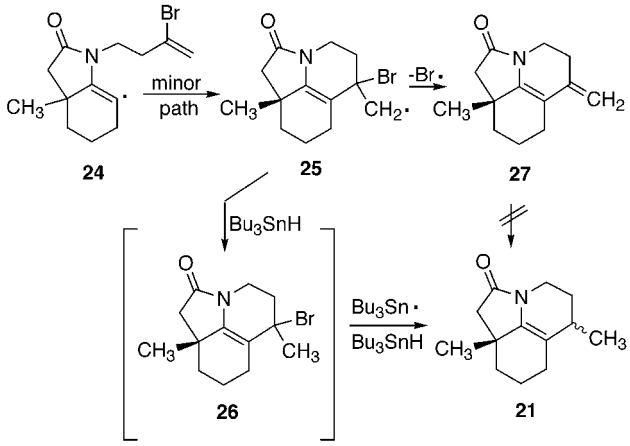
have not been thoroughly investigated.[7] This state of affairs is most likely attributable to the poorer prospects for synthetic utility of this higher homologue of the 1,5-hexadienyl radical. On the basis of studies using the parent 6-heptenyl radical as a model,[14] the rate of 6-*exo-trig* cyclization is expected to be an order of magnitude slower than the 1,5-hexadienyl cyclization, its ring closure should be considerably less regioselective, and it is also possible that a [1,5]-hydrogen atom transfer could occur to produce a 1-butenylallyl radical. A solution of **20** in benzene was treated with Bu_3SnH/AIBN

Scheme 4



at 80 °C for 12 h. Workup and chromatography led to a 7:2 mixture of the 6-*exo* and 7-*endo* cyclization products.[15] The regiochemical preference in cyclization of vinyl radicals is known to parallel that of the alkyl analogues.[16] Although 6-*exo-trig* and 7-*endo-trig* modes of cyclization are possible with hexahydroindolinone **20**, six-membered ring formation predominates. Interestingly, when *N*-(3-bromo-but-3-enyl) hexahydroindolinone **23** was reacted with Bu_3SnH/AIBN under similar conditions, the same two products were formed but in a strikingly different ratio. With this system, the preferred route now corresponds to 7-*endo-trig* cyclization leading to **22** in 72% yield together with minor quantities of the 6-*exo* cyclized product **21** (18%). The presence of a 3-bromo substituent on the *N*-but-3-enyl π-bond sufficiently retards the 6-*exo-trig* cyclization, so that 7-*endo* closure now becomes the predominant path. Formation of azepine[3.2.1-*hi*]indolone **22** from the initially generated 7-*endo* cyclized radical would involve hydrogen atom abstraction from Bu_3SnH followed by further reaction of the resulting secondary bromide with tributyltin radical in the traditional manner. The isolation of **21** as the minor product from this reaction is also consistent with the suggestion that the 6-*exo* cyclized radical (i.e., **25**) is rapidly quenched by hydrogen abstraction to give tertiary bromide **26**, which is then reduced under the reaction conditions. Another possible explanation is that

Scheme 5



radical **25** ejects the adjacent bromine atom to give diene **27**, which in turn is reduced to **21**.[17] Although this pathway seemed less likely, we decided to prepare a sample of **27** in order to probe the likelihood of this possibility. We found (vide infra) that when diene **27** was subjected to the standard Bu_3SnH/AIBN conditions, it could be recovered unchanged, thereby eliminating this mechanistic possibility.

Our approach toward the synthesis of diene **27** was based on an intramolecular Stille cross-coupling reaction[18] of hexahydroindolinone **28**. The intramolecular Stille reaction was performed with $PdCl_2(PPh_3)_2$ (5% mol) as catalyst using a microwave reactor at 100 °C. To our surprise, the palladium-catalyzed reaction of **28** gave the seven-membered cyclized diene **29** as the major product in 48% yield together with lesser quantities of the six-ring diene **27** (16%). The formation of **29** presumably results from a preferential 7-*endo-trig* cyclization, and the regiochemical outcome is similar to that encountered with the radical cyclization of

(13) The cyclization of **18** to **19** is somewhat related to systems studied by Ishibashi and co-workers. For leading references, see: Ishibashi, H.; Ishita, A.; Tamura, O. *Tetrahedron Lett.* **2002**, *43*, 473.

(14) (a) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472. (b) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739. (c) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

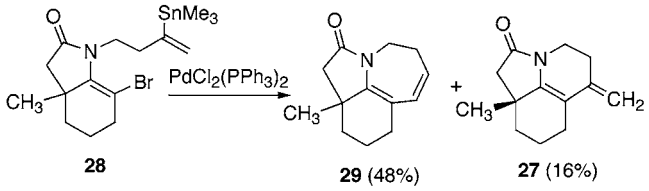
(15) Pyrrolo[3.2.1-*ij*]quinolin-2-one **21** was obtained as a 2.3:1 mixture of diastereomers.

(16) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980.

(17) Still another possibility is the occurrence of a 1,2-bromo group migration followed by quenching of the tertiary radical and eventual reduction of the resulting primary bromide.

(18) (a) Marsault, E.; Deslongchamps, P. *Org. Lett.* **2000,** *2*, 3317. (b) Brückner, S.; Abraham, E.; Klotz, P.; Suffert, J. *Org. Lett.* **2002**, *4*, *3391*. (c) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

Scheme 6



dibromide **23**. In conclusion, our studies have shown that the D-ring of the aspidospermidine skeleton can be efficiently achieved by a free radical cyclization of a *N*-alkenyl-7-bromo hexahydroindolinone derivative. The present methodology should be useful for the construction of other heterocyclic ring systems. Further work on these cyclizations and the synthesis of spegazzinidine and its analogues is currently underway and will be reported in due course.

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Supporting Information Available: Complete description of the synthesis and characterization of all compounds prepared in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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