ORGANIC LETTERS

2001
Vol. 3, No. 8
1181−1183

Construction of Bridged Polycyclic Systems via Radical Cyclizations. Uncovering of a Novel Carbocyclization–Ring Expansion Sequence

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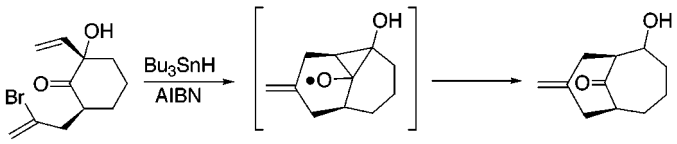
Received February 1, 2001

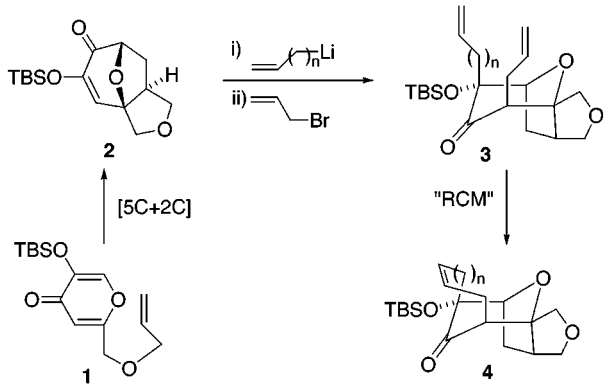
ABSTRACT



While exploring the application of radical cyclizations to the construction of bridged polycyclic systems, we have discovered a novel tandem process consisting of an *endo*-cyclization of a vinyl radical onto a terminal alkene followed by a one-carbon ring expansion promoted by the resulting secondary radical.

The development of synthetic methods capable of generating complex polycyclic systems from simple starting materials in a rapid and efficient way continues to be a major challenge in contemporary organic synthesis.[1] Recently we reported a concise, atom-economical entry to relatively complex oxabicyclic[3.2.1]octane systems from readily available pyrones based on a thermal [5C + 2C] pyrone−alkene cycloaddition.[2] These oxabicyclic adducts, such as **2**, by virtue of their rich functionalization, can be readily elaborated into relatively complex bridged systems (**4**) by means of a dialkylation−RCM sequence (Scheme 1).[3] The simplicity and versatility of the dialkylation step prompted us to explore the feasibiliy of carrying out other types of cyclizations that could generate more versatile functionalities than the alkene

Scheme 1



(1) (a) Hudlicky, T.; Natchus, M. G. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; Jai Press: 1993; Vol 2, p 1. (b) Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; Jai Press: 1993; Vol 2, p 27. (c) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.* **1997**, 766. (d) Sheldon, R. A. *ChemTech* **1994**, March, p 38. (e) Hall, N. *Science* **1994**, *266*, 32. (e) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Vögtle, F., Stoddart, J. F., Shibasaki, M., Eds; Wiley-VCH: 2000; p 39.

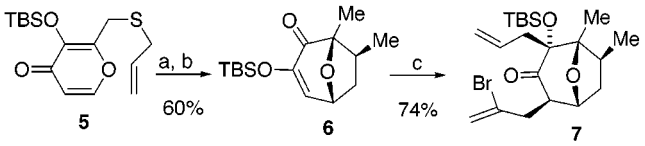
(2) (a) Rumbo, A.; Castedo, L.; Mouriño, A.; Mascareñas, J. L. *J. Org. Chem.* **1993**, *58*, 5585. (b) Mascareñas, J. L.; Pérez, I.; Rumbo, A.; Castedo, L. *Synlett* **1997**, 81. (c) Rodríguez, J. R.; Rumbo, A.; Castedo, L.; Mascareñas, J. L *J. Org. Chem.* **1999**, *64*, 966. (d) Rodríguez, J. R.; Rumbo, A.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1999**, *64*, 4560 (e) Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L *J. Org. Chem.* **2000**, *65*, 2528. For a recent review, see: (f) Mascareñas, J. L. In *Advances in Cycloaddition*; Harmata, M., Ed.; Jai Press: Stamford, 1999; Vol. 6, p 1.

10.1021/ol015643d CCC: $20.00
Published on Web 03/17/2001

obtained in the RCM. We were particularly interested in obtaining exocyclic dienes that might be able to participate in a Diels−Alder reaction and hence allow the fusion of a six-membered compound to the polycyclic system.[4]

We envisaged that an alkenyl bromide such as **7** might produce the required dienic system by means of an intramolecular Heck type of cyclization. This oxabicyclic precursor was readily and efficiently prepared in three steps from the pyrone **5**,[2a] as shown in Scheme 2.

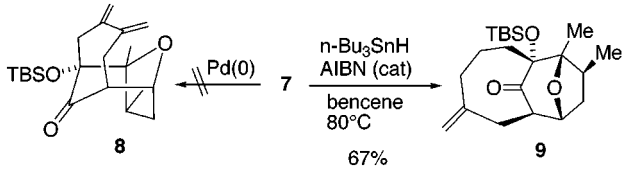
Scheme 2[a]



[a] (a) Toluene, 150 °C; (b) Raney Ni, THF, 60 °C; (c) (i) CH_2=$CHCH_2Li$, THF, −78 °C; (ii) CH_2=$CHBrCH_2Br$, −78 °C.

Rather surprisingly, submmiting **7** to standard Heck reaction conditions [$Pd(PPh_3)_4$, Et_3N, CH_3CN, 80 °C] provided no traces of the expected diene **8**, the starting bromide being largely recovered (Scheme 3). Neither use

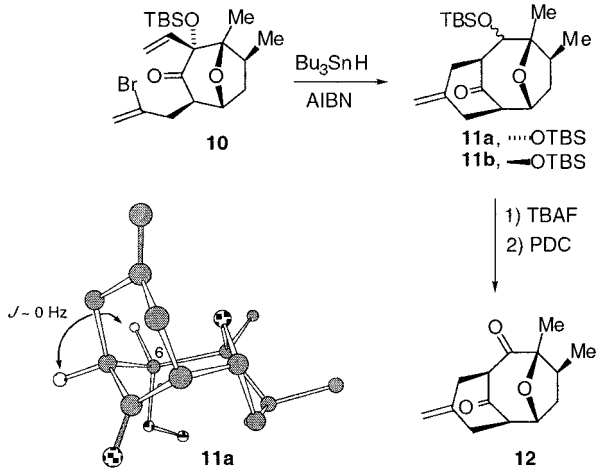
Scheme 3



of additives such as Ag_2CO_3 nor an increase in the reaction temperature provided better results. These failures led us to turn our attention to the reactivity of compound **7** under free radical cyclization conditions. Although it is well-known that the assembly of medium-sized rings via radical cyclization methods is a difficult process,[5] it was interesting to learn whether the particularly favorable preorientation of the alkenyl chains in **7** might facilitate their reaction. Certainly, slow addition of *n*-tributyltin hydride (TBTH, 1.5 equiv) to a solution of **7** and AIBN (0.2 equiv) in boiling benzene smoothly led to the *8-endo-trig* radical cyclization product **9** in 67% yield. This result is noteworthy owing to the scarce precedents on *8-endo* cyclization of 7-octenyl radicals.[6]

The ready availability of vinyl bromide **10**,[7] which features an alkenyl chain one carbon short with respect to **7**, prompted us to examine its behavior under the above radical cyclization conditions. Interestingly, treatment of **10** with TBTH did not afford the expected cyclization product but rather two chromatographically inseparable compounds which were identified as the oxa-bridged bicyclo[5.3.1]undecanes **11a** and **11b** (approximate 3:1 ratio, 81% combined yield, Scheme 4).[8] Further characterization of these products was

Scheme 4



achieved by desilylation and oxidation to ketone **12**. The stereochemistry of the major isomer **11a** was easily deduced by ^{1}H NMR on the basis of the almost negligible coupling constant observed for H-6.

A plausible mechanistic scenario for the above remarkable transformation (**10** to **11**) might entail an initial *7-endo* cyclization of the vinyl radical onto the terminal alkene[9] followed by an internal 1,2-acyl transfer induced by the resulting secondary radical. In light of the well-known "Beckwith−Dowd" ring expansion of α-halomethyl and related cyclic ketones,[10] it seems reasonable to postulate that

(3) Mascareñas, J. L.; Rumbo, A.; Castedo, L. *J. Org. Chem.* **1997**, *62*, 8620.

(4) Subsequent carbon−carbon bond cleavage at the α-silyloxyketone functionality would afford compounds featuring the basic polycyclic skeleton of the sarcodictyins and related compounds, see, for instance: Nicolaou, K. C.; Kim, S.; Pfefferkorn, J. X.; Ohshima, T.; Hosokawa, S.; Vourloumis, D.; Li, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1419.

(5) For a comprehensive review on radical-mediated cyclizations, see: Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996** *48* 301. See also: Malacria, M. *Chem. Rev.* **1996**, *96*, 289. For a review in radical cyclizations to medium-sized rings, see: Yet, L. *Tetrahedron* **1999**, *55*, 9349.

(6) (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (b) Ghosh, K.; Ghosh, A. K.; Ghatak, U. R. *J. Chem. Soc., Chem. Commun.* **1994**, 629. (c) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186. (d) Chattopadhhyay, P.; Mukherjee, M.; Ghosh, S. *Chem. Commun.* **1997**, 2139. (e) Monovich, L. G.; Huérou, Y. L.; Rönn, M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 52. (f) Marco-Contelles, J.; Opazo, E. *Tetrahedron Lett.* **2000**, *41*, 5341.

(7) Prepared as **7** but using vinyllithium instead of allyllithium in the addition reaction (79% yield).

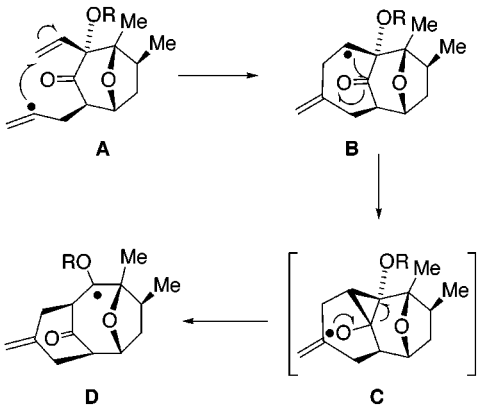
(8) In the ^{1}H NMR spectrum the signals for H-6 appear at δ 3.59 ppm (s) for **11a** and 3.48 ppm (d, J = 7 Hz) for **11b**.

(9) For precedents on 7-*endo trig* radical cyclizations, see: (a) Knight, J.; Parsons, P. J.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1986**, *78*. (b) Ghosh, A. K.; Ghosh, K.; Pal, S.; Ghatak, U. R. *J. Chem. Soc. Chem. Commun.* **1993**, 809.

(10) (a) Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc., Chem. Commun.* **1987**, 666. (b) Dowd, P.; Choi, S. C. *J. Am. Chem. Soc.* **1987**, *109*, 3493. (c) For a review, see: Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

the above rearrangement reaction occurs by addition of the carbon-centered secondary radical **B** to the carbonyl group to form a strained, short-lived oxycyclopropyl radical intermediate (**C**),[11] which then fragments to the ring-expanded product (Scheme 5). The silyloxy substituent most

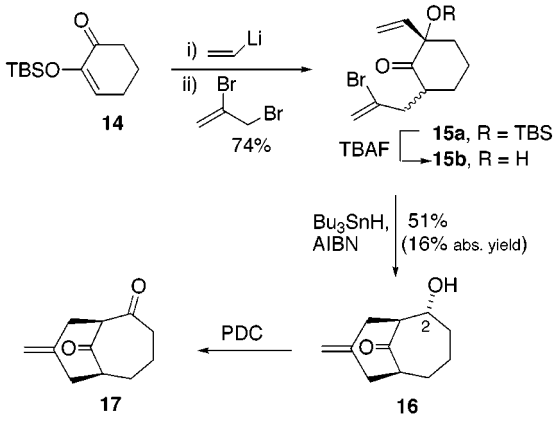
Scheme 5



likely plays an important role in driving the reaction owing to its ability as a radical stabilizing group. It should be noted that we have not detected any of the potential intermediates arising from H-atom transfer to **B** or **C**, even when running the reaction under a high concentration of TBTH (1 M). Using these conditions we also obtained a good yield of the ring-expanded product (75%) and a slight proportion of the reduced starting material (approximately 10%).

To learn whether the above radical-mediated tandem cyclization−ring expansion process can be extended to cyclic systems other than the rigid oxabridged cycloheptanes, the reactivity of the simple cyclohexyl derivative **15a** was next studied. This compound was readily obtained from enone **14** in a single pot using an addition−alkylation step, albeit the product consisted of a chromatographically inseparable 3:7 mixture of *cis*/*trans* isomers (Scheme 6).[12] Although treatment of this mixture with TBTH provided only uncyclized reduced starting material, the desilylated derivative **15b** did afford the expected ring-expanded bicycle as a single steroisomer (**16**)[13] in 51% yield, based on the proportion of *cis* isomer present in the starting material (16% absolute

Scheme 6



yield).[14] Most probably, the presence of the free hydroxyl group results in a higher proportion of the cyclization reactive conformation, which is that with the alkenyl chains in a pseudoaxial position.[12] This result confirms that the above-described radical cyclization−rearrangement sequence is not restricted to the oxabicyclic systems but is of more general applicability. It should finally be noted that the resulting bicyclo[5.3.1] and [4.3.1] skeletons form part of the basic carbocyclic core of a number of interesting natural products.[15]

While there are several reports on tandem one-step ring expansion−radical cyclizations processes,[16] to our knowledge we have described herein the first example of the reverse sequence: a radical carbocyclization followed by a ring expansion reaction. The feasibility of using this type methodology to construct other types of complex polycyclic structures from simple substrates is currently under research and will be reported on due course.

Acknowledgment. Support of this research by the Spanish Ministry of Education and Culture under Grant PB97-0524 is gratefully acknowledged. J.R.R. thanks the Spanish Ministry of Education and Culture for a predoctoral research grant.

Supporting Information Available: Relevant experimental procedures and main characterization data for **7**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Several reports point to the cyclopropoxy radical as a transition state rather than an intermediate: (a) Beckwith, A. L. J.; O′Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565. (b) Ryu, I.; Fukushima, H.; Okuda, T.; Matsu, K.; Kambe, N.; Sonoda, N.; Komatsu, M. *Synlett* **1997**, 1265.

(12) The isomers could be identified on the basis of the ^{1}H NMR shift of the hydrogen in α to the ketone and by comparison with related cyclic ketones that we have previously characterized, see: Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2000**, *2*, 3209.

(13) The stereochemistry of this isomer was tentatively assigned on the basis of the coupling pattern (br t, J = 5.2 Hz) observed for H-2 in the ^{1}H NMR spectrum, see the Supporting Information.

(14) Most of *trans*-**15b** was recovered as reduced product arising from bromide to hydrogen exchange.

(15) See, for instance: (a) Arbuck, S. G.; Blaylock, B. A. *Taxol, Science and Applications*; Duffness, M., Ed.; CRC Press: Boca Raton, FL, 1995. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7. (c) White, J. D.; Somers, T. C.; Yager, K. M. *Tetrahedron Lett.* **1990**, *31*, 59. (d) Kwon, O.; Su, D. S.; Meng, D.; Deng, W.; D′Amico, D. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1877.

(16) (a) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1990**, *55*, 5442. See also, ref 10c. (b) Booker-Milburn, K. I. *Synlett* **1992**, 809.