ORGANIC LETTERS

2012
Vol. 14, No. 21
5476–5479

Stereoselective Synthesis of Oxa- and Aza-Angular Triquinanes Using Tandem Radical Cyclization to Vinylogous Carbonates and Carbamates

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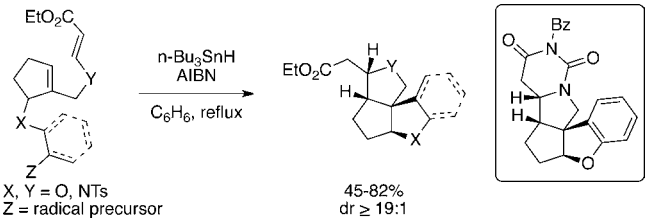
Received September 17, 2012

ABSTRACT



Tandem radical cyclization to vinylogous carbonates and carbamates is developed for a new, highly stereoselective synthesis of heterocyclic angular triquinanes. The strategy is also useful to gain access to oxa- and azatriquinanes, which incorporate the spiroindoline moiety. The method is further extended to the synthesis of lactone-bearing as well as uracil-fused angular triquinanes.

The stereoselective synthesis of triquinanes has attracted considerable attention due to the ubiquity of this important framework in challenging natural products.[1] Triquinanes are typically classified into three types depending on the fusion pattern of the five-membered rings as linear-, angular-, and propellane-type triquinanes (Figure 1). Significant effort has been directed to the synthesis of triquinanes bearing an all-carbon framework as they constitute the core of many sesquiterpene natural products. In contrast, the heteroatom-substituted triquinanes have attracted much less attention from the synthetic community.[2] The majority of the strategies developed to date give access to either aza- or oxa-triquinanes; *however, methods incorporating both oxygen and nitrogen in the same molecule are uncommon*. This is surprising as heteroatom-substituted triquinanes not only serve as important intermediates in the synthesis of carbocyclic triquinanes, but were also suggested to be responsible for bioactivity of many natural products.[3] Thus, a general, rapid, and stereoselective access to heterocyclic angular triquinanes is highly desirable.

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(1) For reviews, see: (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671. (b) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647. (c) Marchand, A. P. *Synlett* **1991**, 73.

(2) Selected examples. Oxa-triquinanes: (a) Yadav, J. S.; Kumar, P. T. K.; Gadgil, V. R. *Tetrahedron Lett.* **1992**, *33*, 3687. (b) Woltering, T. J.; Hoffmann, H. M. R. *Tetrahedron* **1995**, *51*, 7389. (c) Singh, V.; Alam, S. Q. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2517. (d) Ader, T. A.; Champey, C. A.; Kuznetsova, L. V.; Li, T.; Lim, Y.-H.; Rucando, D.; Sieburth, S. McN. *Org. Lett.* **2001**, *3*, 2165. (e) Gurjar, M. K.; Ravindranadh, S. V.; Kumar, P. *Chem. Commun.* **2001**, 917. (f) Singh, V.; Alam, S. Q.; Praveena, G. D. *Tetrahedron* **2002**, *58*, 9729. (g) Kaliappan, K. P.; Nandurdikar, R. S. *Chem. Commun.* **2004**, 2506. (h) Kaliappan, K. P.; Nandurdikar, R. S.; Shaikh, M. M. *Tetrahedron* **2006**, *62*, 5064. (i) Ramakrishna, K.; Kaliappan, K. P. *Synlett* **2011**, 2580. (j) Liao, J.-H.; Maulide, N.; Augustyns, B.; Marko, I. E. *Org. Biomol. Chem.* **2006**, *4*, 1464. (k) Mascal, M.; Hafezi, N.; Meher, N. K.; Fettinger, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 13532. Aza-triquinanes: (l) Clive, D. L. J.; Cole, D. C.; Tao, Y. *J. Org. Chem.* **1994**, *59*, 1396. (m) Hext, N. M.; Hansen, J.; Blake, A. J.; Hibbs, D. E.; Hursthouse, M. B.; Shishkin, O. V.; Mascal, M. *J. Org. Chem.* **1998**, *63*, 6016. (n) Li, Y.; Meng, Y.; Meng, X.; Li, Z. *Tetrahedron* **2011**, *67*, 4002. (o) Zancanella, M. A.; Romo, D. *Org. Lett.* **2008**, *10*, 3685. (p) Kudryavtsev, K. V. *Heterocycles* **2011**, *83*, 323. (q) Bandaru, A.; Kaliappan, K. P. *Synlett* **2012**, 1473.

(3) (a) Huang, J.-M.; Yokoyama, R.; Yang, C.-S.; Fukuyama, Y. *Tetrahedron Lett.* **2000**, *41*, 6111. (b) Huang, J.-M.; Yang, C.-S.; Tanaka, M.; Fukuyama, Y. *Tetrahedron* **2001**, *57*, 4691.

10.1021/ol302557a
Published on Web 10/25/2012

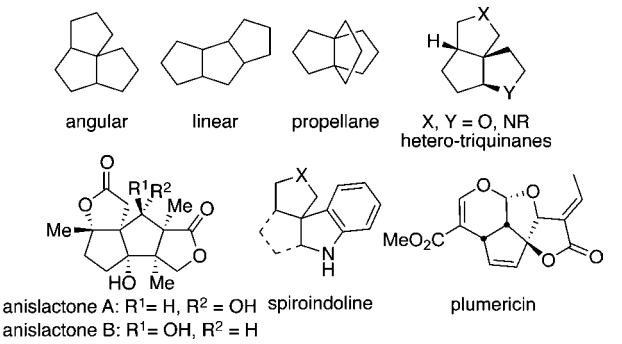


Figure 1. Carbocyclic and heterocyclic triquinanes and spiroindoline.

Vinylogous carbonates and carbamates have come to the forefront as excellent radical acceptors, and they have been used in the stereoselective synthesis of tetrahydrofurans (THFs) and piperidines, respectively.[4,5] However, their utility in the synthesis of heteroatom substituted triquinanes is conspicuous by its absence. In a program directed at using vinylogous functional groups in the synthesis of oxa- and aza-cyclic frameworks,[6] herein we report for the first time a strategy for the stereoselective construction of the heterocyclic angular triquinanes using tandem radical cyclization to vinylogous carbonates and carbamates.[7]

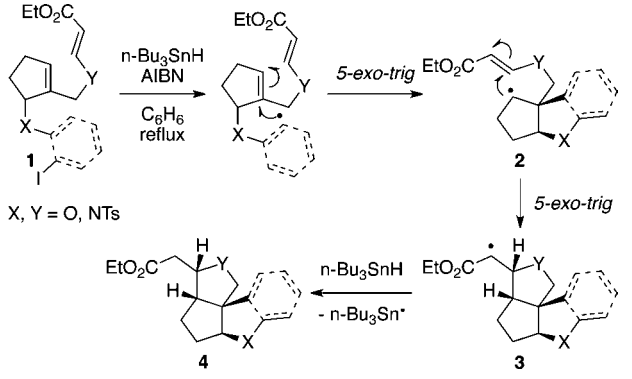
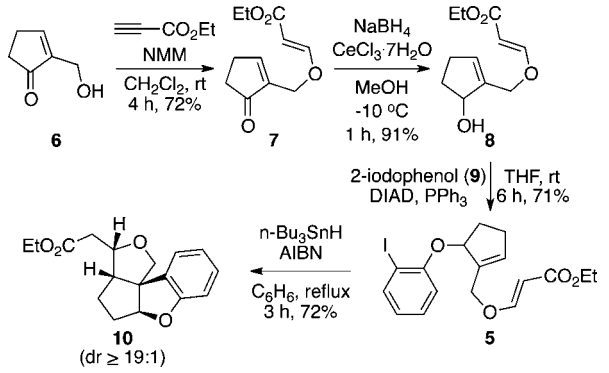


Figure 2. Tandem radical cyclization to vinylogous functional group for heterocyclic angular triquinanes.

Our proposed synthesis of heteroatom-substituted angular triquinane is depicted in Figure 2. It was envisaged that cyclopentene **1** bearing an appropriate radical precursor and tethered vinylogous functional group, upon being subjected to radical conditions, will first undergo a 5-*exo-trig* cyclization to generate the radical **2**. This intermediate **2** will further react with a vinylogous functional group in a 5-*exo-trig* fashion generating radical **3**, which will undergo reduction to generate angularly fused cyclic system **4**. One of the heteroatoms of the triquinane will come from the tether used for attaching radical precursor to cyclopentene moiety, whereas the other heteroatom would be the part of the initial vinylogous carbonate or carbamate.

Scheme 1



In order to test the proposed strategy, synthesis of iodide **5** was undertaken. Thus, known Baylis–Hilmann adduct[8] **6** was reacted with ethyl propiolate in the presence of *N*-methylmorpholine (NMM) to furnish the vinylogous carbonate **7**. Luche reduction[9] of the enone **7** followed by

(4) For some selected examples, see: (a) Lee, E.; Tae, J. S.; Lee, C.; Park, M. C. *Tetrahedron Lett*. **1993**, *34*, 4831. (b) Ko, H. M.; Lee, C. W.; Kwon, H. K.; Chung, H. S.; Choi, S. Y.; Chung, Y. K.; Lee, E. *Angew. Chem., Int. Ed*. **2009**, *48*, 2364. (c) Matsuo, G.; Kadohama, H.; Nakata, T. *Chem. Lett*. **2002**, *31*, 148. (d) Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed*. **1999**, *38*, 3175. (e) Evans, P. A.; Roseman, J. D. *J. Org. Chem*. **1996**, *61*, 2252. (f) Leeuwenburgh, M. A.; Litjens, R. E. J. N.; Codée, J. D. C.; Overkleeft, H. S.; Van der Marel, G. A.; Van Boom, J. H. *Org. Lett*. **2000**, *2*, 1275. (g) Sibi, M. P.; Patil, K.; Rheault, T. R. *Eur. J. Org. Chem*. **2004**, 372. (h) Pandey, G.; Hajra, S.; Ghorai, M. K.; Ravi Kumar, K. *J. Org. Chem*. **1997**, *62*, 5966. (i) Chakraborty, T. K.; Samanta, R.; Ravikumar, K. *Tetrahedron Lett*. **2007**, *48*, 6389 and references therein.

(5) Some selected examples, see: (a) Navarro-Vazquez, A.; Garcia, A.; Dominguez, D. *J. Org. Chem*. **2002**, *67*, 3213. (b) Berlin, S.; Ericsson, C.; Engman, L. *J. Org. Chem*. **2003**, *68*, 8386. (c) Chakraborty, T. K.; Samanta, R.; Roy, S.; Sridhar, B. *Tetrahedron Lett*. **2009**, *50*, 3306. (d) Lee, E.; Kang, T. S.; Joo, B. J.; Tae, J. S.; Li, K. S.; Chung, C. K. *Tetrahedron Lett*. **1995**, *36*, 417. (e) Macdonald, S. J. F.; Mills, K.; Spooner, J. E.; Upton, R. J.; Dowle, M. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3931.

(6) (a) Gharpure, S. J.; Reddy, S. R. B. *Org. Lett*. **2009**, *11*, 2519. (b) Gharpure, S. J.; Shukla, M. K.; Vijayasree, U. *Org. Lett*. **2009**, *11*, 5466. (c) Gharpure, S. J.; Reddy, S. R. B. *Tetrahedron Lett*. **2010**, *51*, 6093. (d) Gharpure, S. J.; Sathiyanarayanan, A. M. *Chem. Commun*. **2011**, *47*, 3625. (e) Gharpure, S. J.; Nanda, L. N.; Shukla, M. K. *Eur. J. Org. Chem*. **2011**, 6632. (f) Gharpure, S. J.; Prasath, V. *J. Chem. Sci*. **2011**, *123*, 943. (g) Gharpure, S. J.; Vijayasree, U.; Reddy, S. R. B. *Org. Biomol. Chem*. **2012**, *10*, 1735. (h) Gharpure, S. J.; Porwal, S. K. *Synlett* **2008**, 242. (i) Gharpure, S. J.; Porwal, S. K. *Tetrahedron Lett*. **2009**, *50*, 7162.

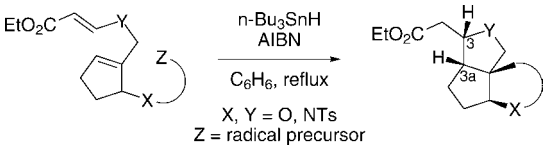
(7) For selected reviews on tandem radical cyclizations, see: (a) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed*. **2001**, *40*, 2224. (b) Malacria, M. *Chem. Rev*. **1996**, *96*, 289. (c) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev*. **1996**, *96*, 177.

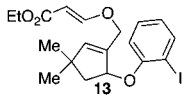
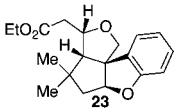
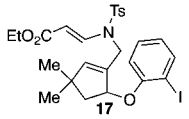
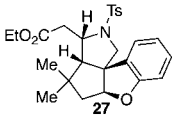
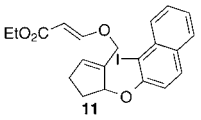
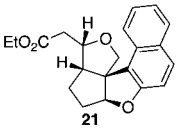
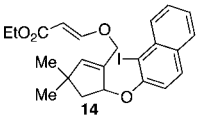
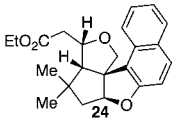
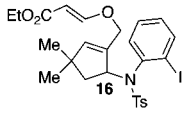
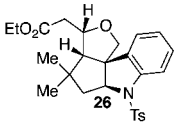
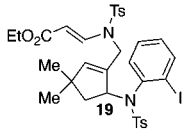
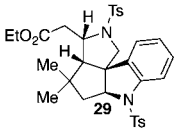
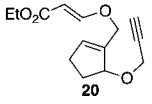
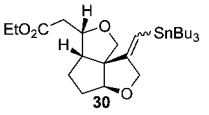
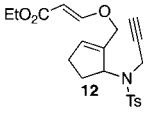
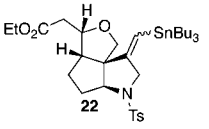
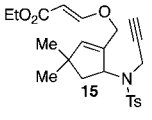
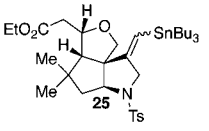
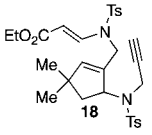
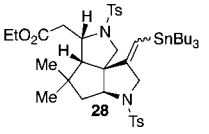
(8) (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev*. **2003**, *103*, 811. (c) Guerra, K. P.; Afonso, C. A. M. *Tetrahedron* **2011**, *67*, 2562.

(9) (a) Luche, J. L. *J. Am. Chem. Soc*. **1978**, *100*, 2226. (b) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc*. **1981**, *103*, 5454.

(10) Recent reviews: (a) Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E.; Pavan Kumar, K. V. P. *Chem. Rev*. **2009**, *109*, 2551. (b) But, T. Y. S.; Toy, P. H. *Chem. Asian J*. **2007**, *2*, 1340.

Table 1. Scope of the Tandem Radical Cyclization to Vinylogous Carbonates and Carbamates for the Synthesis of Oxa- and Aza-triquinaes



entry	substrate	yield (%)[a]	dr[b]	product
1	 **13**	61	≥ 19:1	 **23**
2	 **17**	48	≥ 19:1	 **27**
3	 **11**	74	≥ 19:1	 **21**
4	 **14**	60	≥ 19:1	 **24**
5	 **16**	67	≥ 19:1	 **26**
6	 **19**	49	≥ 19:1	 **29**
7	 **20**	72	≥ 19:1	 **30**
8	 **12**	70	≥ 19:1	 **22**
9	 **15**	81	≥ 19:1	 **25**
10	 **18**	45	≥ 19:1	 **28**

[a] Isolated yield. [b] In all the cases, dr was determined on the crude reaction mixtures by ^{1}H NMR.

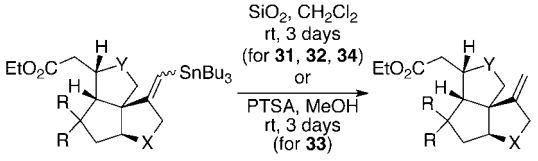
Mitsunobu reaction[10] on the alcohol **8** with 2-iodophenol (**9**) yielded the iodide **5** (Scheme 1). Reaction of the iodide **5** with *n*-Bu_3SnH in the presence of catalytic amount of AIBN in refluxing benzene indeed gave the desired dioxatriquinane **10** in good yield with excellent diastereoselectivity.

After successfully demonstrating the feasibility of the tandem radical cyclization to vinylogous carbonates for the construction of dioxatriquinane, attention was turned toward expanding the scope of this reaction to the synthesis of oxa- and azatriquinanes. To this end, the radical precursors **11**–**20** bearing vinylogous carbonates or carbamates as radical acceptors were synthesized following a strategy similar to that described for the iodide **5** (see the Supporting Information). These vinylogous carbonates and carbamates were subjected to cyclization reaction using the standard radical conditions. The results are summarized in the Table 1.

Various radical precursors could be successfully employed in this reaction. Thus, the iodide derived from iodophenol, iodonaphthol, and protected iodoaniline also participated efficiently in this tandem radical cyclization (Table 1, entries 1–6). Not only aryl iodides but also the alkynes could act as radical precursors and furnished the triquinanes bearing tributylstannyl substitution (Table 1, entries 7–10). The proto-destanylation of angular triquinanes **22**, **25**, **28**, and **30** could be rather easily achieved by simply stirring them with either silica gel or PTSA to furnish the corresponding olefins **31**–**34**, respectively (Scheme 2). Having a *gem*-dimethyl substitution on the cyclopentene ring did not affect the reactivity of the reaction, and oxa- and aza-triquinanes were formed in comparable efficiencies with variety of radical precursors (Table 1, entries 1, 2, 4–6, 9–10). In general, vinylogous carbonates proved to be better acceptors in this tandem radical cyclization process than the vinylogous carbamates, and the yields were better in the former cases.[11] Heterocyclic triquinanes **26** and **29** are particularly noteworthy as they incorporate the spirocyclic indoline moiety, which is part of the structure of many bioactive molecules.[12]

In all the cases, the triquinane formation proceeded with excellent diastereoselectivity. This stereochemical outcome was established on the basis of the ^{1}H NMR data as well as single-crystal X-ray diffraction studies on the hetereocyclic triquinanes **23**, **27**, **29**, **32**, and **33**.[13] As can be noticed, the product oxa- and azatriquianes **21**–**30** had the hydrogens on C3 and C3a *syn* to each other.

Scheme 2



22: X = NTs, Y = O, R = R = H
25: X = NTs, Y = O, R = R = Me
28: X = Y = NTs, R = R = Me
30: X = Y = O, R = R = H

31: X = NTs, Y = O, R = R = H; 72%
32: X = NTs, Y = O, R = R = Me; 62%
33: X = Y = NTs, R = R = Me; 76%
34: X = Y = O, R = R = H; 62%

(11) The lower yields for vinylogous carbamates are partly due to the difficulties associated with purification.

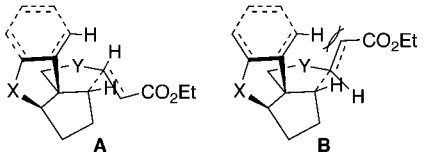


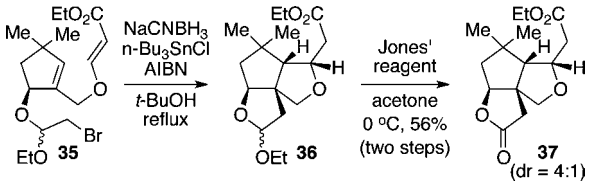
Figure 3. Transition-state structures for the tandem radical cyclization reaction.

The stereochemical outcome of this reaction can be rationalized on the basis of the mechanism of this reaction. The first 5-*exo*-*trig* radical cyclization generated the diquinane with *cis* fusion of the two five-membered rings as expected. In the second step of the tandem radical cyclization, there is a possibility of formation of two diastereomers, the one in which the two hydrogens on C3 and C3a are *syn* (the product formed) or the other where these two hydrogens are *anti* to each other. It is apparent that the transition-state structure **B** leading to the *anti* product suffers from steric interaction between the aryl ring/olefin moiety and the incipient carbethoxymethyl group (Figure 3). No such interaction is present in the transition state structure **A** leading to the *syn* product, and hence, it is formed preferentially.

In order to test this hypothesis, a substrate **35** devoid of any olefin or aryl ring on the radical precursor was conceived. The tandem radical cyclization using sodium cyanoborohydride, tributyltin chloride and catalytic AIBN in refluxing *t*-BuOH followed by Jones' oxidation of the intermediate acetal **36** indeed furnished the dioxatriquinane **37** as a 4:1 mixture of diastereomers (Scheme 3).[14] This clearly suggested that the steric interaction between aryl ring/olefin moiety and the incipient carbethoxymethyl group arising from vinylogous carbonates/carbamates is important for getting good diastereoselectivity. The triquinane **37** is also particularly interesting as it gave an entry into lactone-bearing oxatriquinanes.

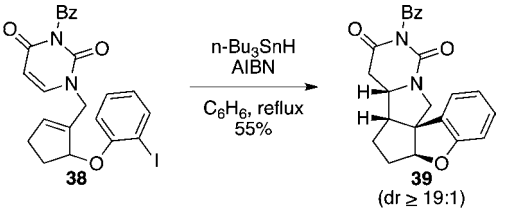
We envisioned that synthesis of uracil-fused oxatriquinane would be challenging and further highlight the utility of this method.[15] Toward this end, we decided to replace the vinylogous carbamate with a uracil moiety bearing

Scheme 3



vinylogous urea as the functional group. When the uracil derivative **38** was indeed subjected to the standard radical cyclization conditions developed in this study, the aza-oxatriquinane **39** fused to the uracil moiety was obtained in good yield and excellent diastereoselectivity (Scheme 4). This is an example which demonstrated that not only vinylogous carbonates and carbamates but also vinylogous ureas can be used as acceptors in tandem radical cyclization for the synthesis of angular triquinanes.

Scheme 4



In conclusion, we have disclosed the first examples of tandem radical cyclizations to vinylogous carbonates and carbamates for the synthesis of heterocyclic angular triquinanes. In general, the reactions were found to be good yielding, and in most cases, the diastereoselectivities obtained were excellent. The method gave access to lactone-bearing oxatriquinanes. Further, conformationally constrained uracil fused angular triquinanes could be synthesized using this protocol.

Acknowledgment. We thank DST, New Delhi, for financial support and Mr. V. Ramkumar of the Department of Chemistry, IIT Madras, for the crystallographic data. We thank CSIR, New Delhi, for the award of research fellowships to P.N. and S.K.P.

Supporting Information Available. Characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(13) See the Supporting Information.

(14) Only a trace amount of triquinane **36** was obtained using *n*-Bu_3SnH and AIBN, with simple reduction without cyclization being the major product.

(15) (a) Evans, P. A.; Lai, K. W.; Zhang, H. R.; Huffman, J. C. *Chem. Commun.* **2006**, 844. (b) Evans, P. A.; Manangan, T.; Rheingold, A. L. *J. Am. Chem. Soc.* **2000**, *122*, 11009 and refrences cited therein.