Tetrahedron Letters 50 (2009) 228–231

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Wittig olefination and thiol mediated 7-*endo*-trig radical cyclization: novel synthesis of oxepin derivatives

K. C. Majumdar *, Abu Taher

Department of Chemistry, University of Kalyani, Kalyani 741 235, WB, India

ARTICLE INFO

Article history:
Received 20 September 2008
Revised 23 October 2008
Accepted 28 October 2008
Available online 31 October 2008

Keywords:
Wittig reaction
Thiophenol
7-*endo* reaction
Oxepin derivatives

ABSTRACT

Thiophenol-mediated 7-*endo* radical cyclization for the synthesis of seven-membered cyclic ethers is described. This method can be successfully applied to synthesize various benzoxepin derivatives, which are present in many natural products as building blocks. Alkenyl radicals are generated from easily available terminal alkynes and thiophenol.

The synthesis of medium- and large-sized cyclic ethers annulated with aromatic ring is a challenging problem to organic chemists due to their presence in many bioactive natural products.[1] The seven-membered benzoxepin moiety is found in many natural products, for example, heliannuol C,[1c] heliannuol D,[2] plumbagic acid lactones,[3] pterulone,[4] heliannuol B, and radulanins A, E, and H.[5] Besides, oxepin is an important structural subunit present in biologically active naphthoxepin derivatives[6] which have been used as antipsychotic drugs. These biological activities encouraged many research groups to synthesize these compounds.

Several methodologies were developed for the construction of medium-sized oxacycle rings including ring-closing metathesis (RCM),[7] Heck reaction,[8] and radical cyclization.[9] Benzo-fused oxa-heterocycles are also obtained by the application of 'direct-*ortho*-metalation-olefin-metathesis' strategy[10] and '[3+3] cyclization-olefin-metathesis' strategy.[11] Roy et al. reported the synthesis of benzoannulated medium-sized cyclic ethers in moderate yields using titanocene(III) chloride (Cp_2TiCl)-mediated radical cyclization of epoxides.[12] Recently, we have also reported[13] the synthesis of eight-membered cyclic ethers. There are several examples for the construction of eight-membered cyclic ethers by radical cyclization.[12a,13,14] To our knowledge, there are only few examples in the literature[12b,15] for the construction of seven-membered cyclic ethers by radical cyclization. Thiophenol is an efficient reagent[16] for carrying out radical cyclization. These reasons have prompted us to undertake a study on the synthesis of oxepin derivatives by

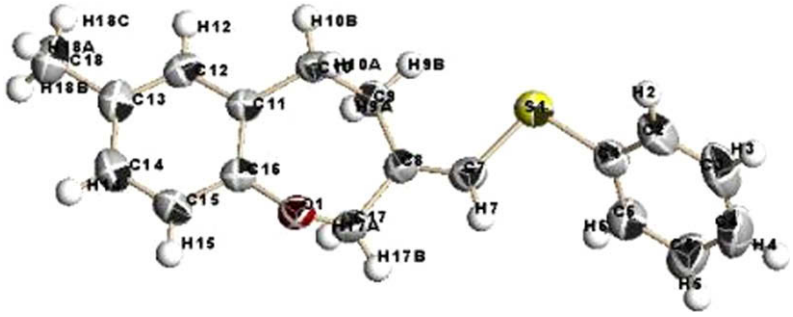
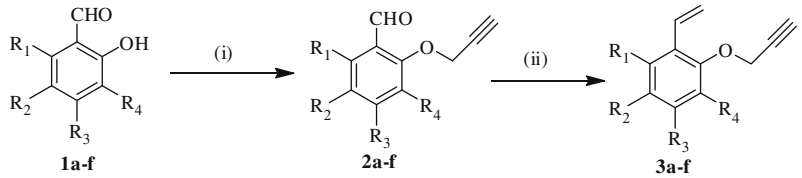


Figure 1. Single X-ray crystal structure of compound **4a**.

* Corresponding author. Tel.: +91 033 25827521; fax: +91 033 2582 8282.
E-mail address: kcm_ku@yahoo.co.in (K. C. Majumdar).

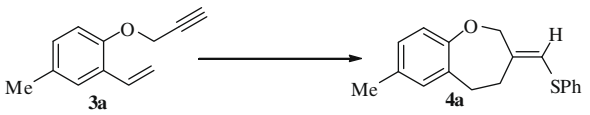
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.10.134



a. R_1, R_3, R_4 = H, R_2 = Me
b. R_1, R_3, R_4 = H, R_2 = Br
c. R_1, R_4 = Me, R_2, R_3 = H
d. R_1 = Me, R_2 = Cl, R_3, R_4 = H
e. R_1, R_3 = Me, R_2, R_4 = H
f. R_1, R_2 = 5,6-C_4H_4 (phenylene)

Scheme 1. Reagents and conditions: (i) propargyl bromide, anhydrous K_2CO_3, acetone, reflux, 3 h; (ii) PPh_3MeI, *n*BuLi, THF, 0 °C–rt, 1 h.

Table 1
Optimization of sulfanyl radical addition cyclization of **3a**



Entry	PhSH[a] (equiv)	AIBN (equiv)	Solvent[b]	Yield (%)
1	1.5	1.5	C_6H_6	88
2	1.5	1.5	*t*-BuOH	16
3	1.5	1.5	MeCN	0
4	1.5	1.5	EtOH	0
5	2.0	1.5	C_6H_6	57
6	1.0	1.5	C_6H_6	32
7	0.5	1.5	C_6H_6	17
8	0.5	1.0	C_6H_6	12
9	1.0	1.0	C_6H_6	15
10	1.5	1.0	C_6H_6	21
11	1.5	0.5	C_6H_6	0
12	1.0	0.5	C_6H_6	0

[a] All reactions were carried out at 80 °C.
[b] All reactions were carried out for 2 h.

thiophenol-mediated radical cyclization. Herein, we report the results (Fig. 1).

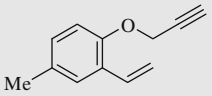
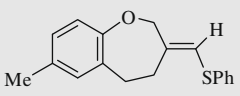
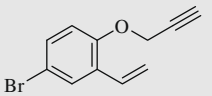
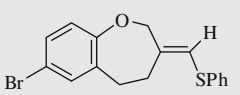
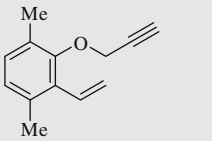
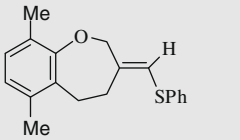
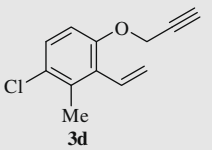
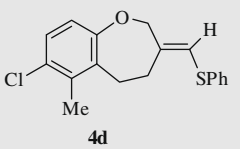
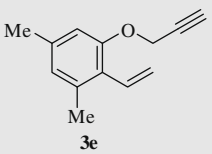
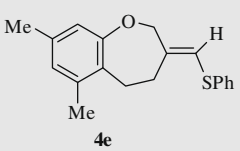
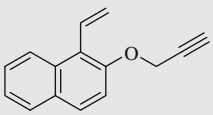
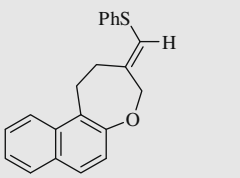
The required radical precursors **3a–f** were prepared in moderate to good yields by the Wittig reaction of substrate **2a–f**. The Wittig reagent was prepared from PPh_3MeI in dry THF in the presence of *n*BuLi at 0 °C for about 1 h. The Wittig precursors **2a–f** were in turn obtained by refluxing hydroxy-aldehyde **1a–f** with propargyl bromide in dry acetone in the presence of anhydrous K_2CO_3 and a catalytic amount of NaI[17] (Scheme 1).

Substrate **3a** when subjected to radical cyclization in the presence of thiophenol (1.5 equiv) and AIBN (1.5 equiv) as radical initiator in refluxing benzene under a nitrogen atmosphere for 2 h gave **4a**[18] in 88% yield. The optimized condition for thiophenol-mediated radical cyclization was established through a series of experiments, in which sequential changes were made in the amount of thiophenol and radical initiator (AIBN) and also by changing the solvent used for the reaction with the substrate **3a** (Table 1).

Among the various solvents used, benzene was proven to be superior than *t*-BuOH, MeCN, and EtOH. When *t*-BuOH was used, only 16% cyclized product was obtained keeping the residual starting material intact. The use of MeCN, EtOH as solvents did not give any cyclized product.

The use of more thiophenol than the requisite amount (1.5 equiv) causes a lower yield of the cyclized product (entry 5). This may be due to the formation of an adduct of thiophenol with the terminal carbon atom of the alkyne. The use of thiophenol in lower concentrations also decreases the yield of cyclized products (entries 6–8).

Table 2
Sulfanyl radical addition cyclization of **3**(**a–f**) to **4**(**a–f**)[a]

Entry	Starting material (**3**)	Product (**4**)	Yield[b] (%)
1	 **3a**	 **4a**	88
2	 **3b**	 **4b**	82
3	 **3c**	 **4c**	72
4	 **3d**	 **4d**	78
5	 **3e**	 **4e**	76
6	 **3f**	 **4f**	86

[a] All reactions were carried out using the optimized reaction conditions.
[b] Isolated yields.

The amount of AIBN played a vital role in this radical cyclization reaction. When 1.5 equiv of AIBN was used, a characteristic yield (12–88%, entries 5–7) of the cyclization product was obtained, and the maximum yield was obtained when 1.5 equiv of thiophenol was used. The use of 1 equiv of AIBN and varying the thiophe-

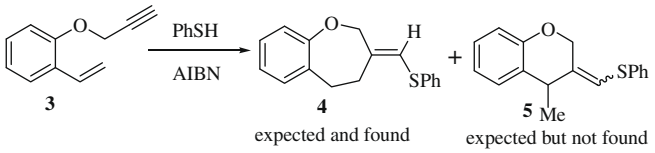
nol concentration reduced the yield of the cyclized product, and the reaction became extremely slow (entries 8 and 9). No reaction occurred when 0.5 equiv of AIBN was used (entries 11 and 12). A stoichiometric amount of AIBN with respect to thiophenol was required to complete the reaction indicating that the chain process is not very efficient under the reaction conditions. This inefficiency can be explained by the dimerization of the thiyl radicals, but when a stoichiometric amount of AIBN was used, free thiyl radical was generated from either thiophenol or disulfides, which brought about the cyclization reaction.

The other substrates **3b–f** were also treated under this optimized condition to afford the oxepin products **4b–f** in 72–86% yields. The results are summarized in Table 2.

The structure of thiophenol-mediated cyclization products **4** has been determined from their spectral data and single crystal XRD data.[19] The compounds **4** were found to be a seven-membered cyclic ether having an exocyclic double bond, and the stereochemistry of the exocyclic double bond of compound **4** was found to be Z, where –SPh and the new C–C bond formed are cis to each other.

Both the 6-*exo*-trig and 7-*endo*-trig modes of cyclizations are favorable, according to Baldwin's rule,[20] to give the products **4** and **5** (Scheme 2). It is remarkable to note that here 7-*endo* cyclization has occurred to afford the oxepin derivative **4**.

The mechanistic rationalization for the formation of product **4** by sulfanyl radical addition cyclization is depicted in Scheme 3. Initially, the phenyl sulfanyl radical generated from thiophenol and AIBN adds to the terminal alkyne moiety to form the corresponding vinyl radical intermediate **6**. This vinyl radical intermediate **6** may undergo a 7-*endo*-trig intramolecular cyclization with the adjacent alkene to form the radical intermediate **9** which, on abstraction of a proton from thiophenol, leads to the formation of product **4**. The predominant formation of product **4** may be explained not only by the stability of the secondary alkyl radical **9** as opposed to that of the primary alkyl radical **7** but also by the stability of the benzylic radical **9** (extended conjugation) which is perhaps the driving force that allowed the reaction to follow pathway a. Alternatively, pathway b, a 6-*exo*-trig cyclization process followed by 1,2-alkenyl migration via a cyclopropyl methyl radical **8** (neophyl rearrangement), would also lead to the same product.



Scheme 2.

We had earlier reported[13] the synthesis of benzoxocine derivatives by thiol-mediated radical cyclization, where *ortho*-C-allylated prop-2-ynyl substrates were utilized for the 8-*endo*-trig cyclization to occur. It is difficult to form a seven-membered ring by the aforesaid protocol. Here, the *ortho*-vinyl prop-2-ynyl ethers have been designed to achieve the exclusive *endo*-trig cyclization with the advantage of forming the stable benzylic radical intermediate. Other available methods[7,21] for the synthesis of benzoxepin involve Pd-catalyzed reactions and ring-closing metathesis, which require costly reagents and complicated reaction conditions.

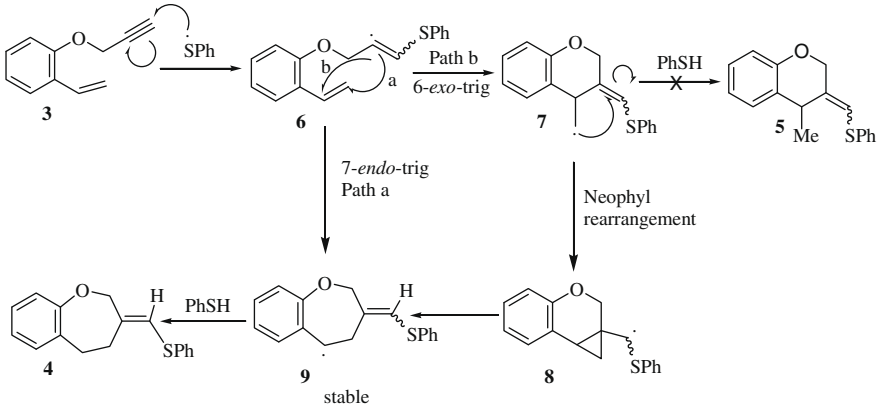
In conclusion, we have developed a useful protocol for the synthesis of benzoxepin derivatives, which are an important core structure of many naturally occurring bioactive compounds via sulfanyl radical addition cyclization. The procedure applied here is mild, less toxic, and less expensive. Finally, the products bear a phenylthio substituent that offers many opportunities for further transformation.[16b,i,22]

Acknowledgments

We thank the CSIR (New Delhi) and DST (New Delhi) for the financial assistance. We thank Professor A. T. Khan, Indian Institute of Technology, Guwahati, for the XRD data of **4a**. One of us (A.T.) is grateful to the CSIR (New Delhi) for the fellowship received.

References and notes

1. (a) Asakawa, Y.; Kusube, E.; Takemoto, T.; Suire, C. *Phytochemistry* **1978**, *17*, 2115; (b) Murata, M.; Yusumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293; (c) Macias, F. A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A.; Fronczek, F. R. *Tetrahedron Lett.* **1993**, *34*, 1999.
2. Macias, F. A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A.; Fronczek, F. R. *J. Org. Chem.* **1994**, *59*, 8261.
3. Dinda, B.; Das, S. K.; Hajra, A. K.; Bhattacharya, A.; De, K.; Chel, G.; Achari, B. *Indian J. Chem., Sect. B* **1999**, *38*, 577.
4. Engler, M.; Anke, T.; Sterner, O. Z. *Naturforsch.* **1998**, *53c*, 318.
5. (a) Asakawa, Y.; Takeda, R.; Toyota, M.; Tsunematsu, T. *Phytochemistry* **1981**, *20*, 858; (b) Asakawa, Y.; Hashimoto, T.; Takikawa, K.; Tori, M.; Ogawa, S. *Phytochemistry* **1991**, *30*, 235; (c) Asakawa, Y.; Toyota, M.; Takemoto, T. *Phytochemistry* **1978**, *17*, 2005; (d) Yamaguchi, S.; Furihata, K.; Miyazawa, M.; Yokoyama, H.; Hirai, Y. *Tetrahedron Lett.* **2000**, *41*, 4787; (e) McCormick, S.; Robson, K.; Bohm, B. *Phytochemistry* **1986**, *25*, 1723; (f) Breuer, M.; Leeder, G.; Proksch, P.; Budzikiewicz, H. *Phytochemistry* **1986**, *17*, 495.
6. Carl, K.; Joseph, L. U.S. Patent 4,073,912, 1972; *Chem. Abstr.* **1978**, *89*, 24156.
7. (a) Sabui, S. K.; Venkateswaran, R. V. *Tetrahedron Lett.* **2004**, *45*, 2047; (b) van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B. *Synlett* **2003**, *12*, 1859; (c) Kahnberg, P.; Lee, C. W.; Grubbs, R. H.; Sterner, O. *Tetrahedron* **2002**, *58*, 5203; (d) Kamei, T.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2003**, *44*, 8505; (e) Kishuku, H.; Shindo, M.; Shishido, K. *Chem. Commun.* **2003**, 350.
8. (a) Majumdar, K. C.; Chattopadhyay, B.; Ray, K. *Tetrahedron Lett.* **2007**, *48*, 7633; (b) Majumdar, K. C.; Chattopadhyay, B.; Sinha, B. *Tetrahedron Lett.* **2008**, *49*, 1319; (c) Majumdar, K. C.; Chattopadhyay, B. *Synlett* **2008**, 979.
9. (a) Ghosh, K.; Ghosh, A. K.; Ghatak, U. R. *J. Chem. Soc., Chem. Commun.* **1994**, 629; (b) Wang, J.; Li, C. *J. Org. Chem.* **2002**, *67*, 1271; (c) Lang, S.; Corr, M.; Muir, N.; Khan, T. A.; Schonebeck, F.; Murphy, J. A.; Payne, A. H.; Williams, A. C.



Scheme 3. Mechanism of sulfanyl radical addition cyclization reaction.

Tetrahedron Lett. **2005**, *46*, 4027; (d) Shanmugam, P.; Rajasingh, P. *Tetrahedron Lett.* **2005**, *46*, 3369.
10. Stefinovic, M.; Snieckus, V. *J. Org. Chem* **1998**, *63*, 2808.
11. (a) Nguyen, V. T. H.; Bellur, E.; Fischer, C.; Langer, P. *Tetrahedron* **2007**, *63*, 8037; (b) Nguyen, V. T. H.; Bellur, E.; Langer, P. *Tetrahedron Lett.* **2006**, *47*, 113.
12. (a) Mandal, S. K.; Roy, S. C. *Tetrahedron* **2007**, *63*, 11341; (b) Mandal, S. K.; Roy, S. C. *Tetrahedron Lett.* **2006**, *47*, 1599.
13. (a) Majumdar, K. C.; Maji, P. K.; Ray, K.; Debnath, P. *Tetrahedron Lett.* **2007**, *48*, 9124; (b) Majumdar, K. C.; Ray, K.; Debnath, P.; Maji, P. K.; Kundu, N. *Tetrahedron Lett.* **2008**, *49*, 5597.
14. (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem.* **2001**, *66*, 1612; (b) Nandi, A.; Mukhopadhyay, R.; Chattopadhyay, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3346; (c) Martinez, A. G.; Vilar, E. T.; Fraile, A. G.; Cerero, S. M.; Morillo, C. D. *Tetrahedron Lett.* **2007**, *48*, 5185; (d) Nandi, A.; Chattopadhyay, P. *Tetrahedron Lett.* **2002**, *43*, 5977; (e) Blake, A. J.; Hollingworth, G. J.; Pattenden, G. *Synlett* **1996**, 643; (f) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Chem. Commun* **1997**, *1*, 637.
15. (a) Wu, S.; Journet, M.; Malacria, M. *Tetrahedron Lett.* **1994**, *35*, 8601; (b) Neogi, A.; Majhi, T. P.; Ghosal, N.; Chattopadhyay, P. *Tetrahedron* **2005**, *61*, 9368; (c) Magono, H.; Hara, S. *Tetrahedron Lett.* **2004**, *45*, 4329.
16. (a) Fernandez, M.; Alonso, R. *Org. Lett.* **2005**, *7*, 11; (b) Lachia, M.; Denes, F.; Beaufils, F.; Renaud, P. *Org. Lett.* **2005**, *7*, 4103; (c) Miyata, O.; Naito, T. C. R. *Acad. Sci. Paris Chim.* **2001**, *4*, 401; (d) Carta, P.; Puljic, N.; Robert, C.; Dhimane, A. L.; Fensterbank, L.; Lacote, E.; Malacria, M. *Org. Lett.* **2007**, *6*, 1061; (e) Harrowven, D. C.; Maj, P. J.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 503; (f) Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S. *Org. Lett.* **2003**, *5*, 1313; (g) Burke, S. D.; Jung, K. W. *Tetrahedron Lett.* **1994**, *35*, 5837; (h) Majumdar, K. C.; Debnath, P. *Tetrahedron* **2008**, *64*, 9799; (i) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 6199.
17. Gazith, M.; Noys, R. M. *J. Am. Chem. Soc.* **1955**, *77*, 6091.
18. *Compound* **4a**: Yield: 88%; colorless solid; mp: 96–98 °C; IR (KBr): ν = 2892, 1473, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 2.27(s, 3H), 2.63–2.65 (m, 2H), 2.84–2.87 (m, 2H), 4.44 (s, 2H), 6.26 (s, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.93–6.95 (m, 2H), 7.20–7.36 (m, 5H) ppm. ^{13}C NMR (125 MHz): 20.5, 30.1, 32.1, 77.2, 120.5, 122.65, 126.5, 128.0, 129.0, 129.3, 131.1, 132.7, 133.1, 135.6, 140.3, 157.2 ppm. HRMS: *m/z* calcd for $C_{18}H_{18}OSH$ $[M+H]^+$: 283.1151; found; 283.1172.
19. CCDC reference no. for the CIF file of compound **4a**: CCDC 702864.
20. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
21. (a) Martins, A.; Marquardt, U.; Kasravi, N.; Alberico, D.; Lautens, M. *J. Org. Chem.* **2006**, *71*, 4937; (b) Campeau, L. C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186; (c) Larock, R. C.; Han, X. *J. Org. Chem.* **1999**, *64*, 1875; (d) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333; (e) Kuwabe, S.-i.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202; (f) Kotha, S.; Mandal, K. *Tetrahedron Lett.* **2004**, *45*, 1391; (g) Pain, C.; Celanire, S.; Guillaumet, G.; Joseph, B. *Synlett* **2003**, 2089.
22. (a) Bachi, D. M.; Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Ploypradith, P.; Xie, S.; Shapiro, T. A.; Posner, G. *J. Med. Chem.* **2003**, *46*, 2516; (b) Miyata, O.; Muroya, K.; Kobayashi, Y.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459; (c) Renaud, P.; Beaufils, F.; Feray, L.; Schenk, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4230; (d) O'Neill, M. P.; Stocks, P. A.; Pugh, M. D.; Araujo, N. C.; Korshin, E. E.; Bickley, J. F.; Ward, S. A.; Bray, P. G.; Pasini, E.; Davies, J.; Verissimo, E.; Bachi, D. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4193.