ORGANIC LETTERS

2011
Vol. 13, No. 20
5552–5555

Marrying Iterative Synthesis to Cascading Radical Cyclization: 6-*endo*/5-*exo* Radical Cascade across Bis-Vinyl Ethers

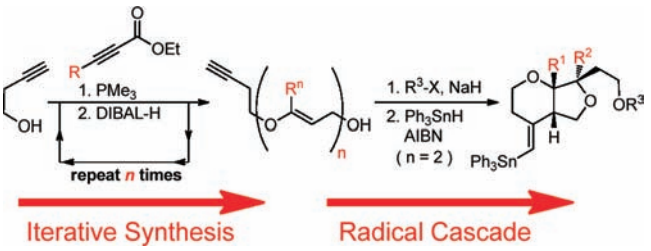
Katherine A. Davies and Jeremy E. Wulff*

Department of Chemistry, University of Victoria, Victoria, British Columbia, Canada, V8W 3V6

wulff@uvic.ca

Received August 23, 2011

ABSTRACT



Application of iterative protocols to the synthesis of functionally and stereochemically complex small molecules is an emerging area of research with the potential to create new efficiencies in complex molecule synthesis. Similarly, the discovery of tandem or cascade reactions can aid in the rapid generation of new structures for biological screening programs. This report describes a cascading 6-*endo-trig*/5-*exo-trig* radical cyclization across bis-vinyl ether substrates, which are themselves iteratively synthesized from simple building blocks.

The introduction of solid phase synthesis techniques in the 1960s[1] stimulated an explosion in the development of efficient iterative protocols for the synthesis of polynucleic acids (i.e., DNA and RNA)[2] and polyamino acids (i.e., peptides or proteins).[3] Ready access to these synthetic materials revolutionized biochemistry and molecular biology and inspired the subsequent development of related approaches to oligosaccharides.[4]

Historically, the application of iterative techniques to the synthesis of secondary metabolite natural products, or other functionally and stereochemically complex small molecules, has been less actively pursued—notwithstanding some excellent contributions to the syntheses of polyketides,[5] "ladder"-type polyethers,[6] and other select classes of oligomeric natural products.[7] More recently, the invention of protective groups for aryl or vinyl boranes has led to the development of powerful iterative Suzuki coupling strategies for small molecule synthesis.[8]

As is the case for iterative synthesis, the use of tandem or cascade reactions in the assembly of complex molecules can significantly enhance the efficiency of the overall

(1) Merrifield, R. B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 799–810.
(2) Caruthers, M. H. *Science* **1985**, *230*, 281–285.
(3) Atherton, E.; Sheppard, R. C. *Solid-Phase Peptide Synthesis: A Practical Approach*; Oxford Univ. Press: Oxford, U.K., 1989.
(4) For leading reviews, see: (a) Weishaupt, M.; Eller, S.; Seeberger, P. H. *Methods Enzymol.* **2010**, *478*, 463–484. (b) Sears, P.; Wong, C.-H. *Science* **2001**, *291*, 2344–2350. (c) Wong, C.-H. *J. Org. Chem.* **2005**, *70*, 4219–4225.
(5) (a) Paterson, I.; Scott, J. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1003–1014. (b) Kesavan, S.; Su, Q.; Shao, J.; Porco, J. A., Jr.; Panek, J. S. *Org. Lett.* **2005**, *7*, 4435–4438. (c) Paterson, I.; Gottschling, D.; Menche, D. *Chem. Commun.* **2005**, 3568–3570.
(6) (a) Evans, P. A.; Roseman, J. D.; Garber, L. T. *J. Org. Chem.* **1996**, *61*, 4880–4881. (b) Marmsäter, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144–5145. (c) Kadota, I.; Takamura, H.; Sato, K.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 3494–3498. (d) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630–6666. (e) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056–1057.
(7) For a recent review, see: Snyder, S. A.; ElSohly, A. M.; Kontes, F. *Nat. Prod. Rep.* **2011**, *28*, 897–924.
(8) (a) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717. (b) Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 758–759. (c) Lee, S. J.; Anderson, T. M.; Burke, M. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8860–8863. (d) Gillis, E. P.; Burke, M. D. *Aldrichimica Acta* **2009**, *42*, 17–27. (e) Manabe, K.; Ohba, M.; Matsushima, Y. *Org. Lett.* **2011**, *13*, 2436–2439.
(9) For recent reviews, see: (a) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993–3009. (b) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. (c) Bur, S. K.; Padwa, A. *Adv. Heterocycl. Chem.* **2007**, *94*, 1–105.

10.1021/ol202286q
Published on Web 09/15/2011

approach by reducing the number of steps requiring independent optimization.[9]

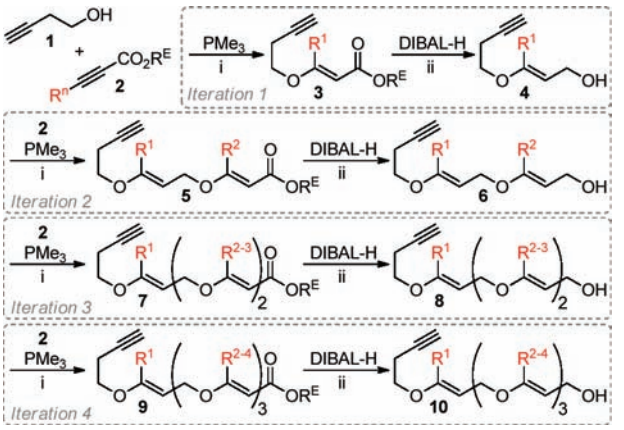
In principle, ***combining*** the inherently complementary strategies of iterative synthesis and cascade methodology could reduce the development time associated with the synthesis of certain types of architecturally complex structures. Specifically, we propose the use of short iterative protocols to prepare reactive oligomers, followed by the application of a cascade cyclization to access a (poly)cyclic target with good regiochemical and stereochemical control. In this way, the synthesis of structural analogues should only require input of an array of simple monomeric building blocks, while the core structures of the (poly)cycles themselves might be altered through the use of chemically orthogonal cascades.

In this Letter, we describe an iterative conjugate addition/reduction sequence leading to a family of oligo-vinyl ethers (e.g., **4**–**10**, Table 1). These highly functionalized structures (or related congeners) should be amenable to cascade cyclization through a variety of orthogonal transformations; as a proof of concept, we demonstrate here the conversion of bis-vinyl ethers **6** to functionalized hexahydro-2*H*-furo[3,4-*b*]pyrans **15** through an unusual 6-*endo*-*trig*/5-*exo*-*trig* radical cascade. To the best of our knowledge, this is the first radical cascade reported for a bis-vinyl ether substrate.

In the first iterative step, reaction of 1 equiv of alcohol (**1**, **4**, **6**, or **8**, Table 1) with 1 equiv of alkyne **2** proceeded smoothly under the influence of 10 mol % of PMe_3[10] to afford addition products (**3**, **5**, **7**, or **9**) with generally high yield and good selectivity for the *E* isomer.[11] With more hindered electrophiles (particularly those bearing a trifluoromethyl group), the *E*:*Z* selectivity was substantially eroded; in these cases (**3f** and **5i**) the two isomers were separated chromatographically before proceeding. Depending on the substitution at the R^1 and R^2 positions, bis-vinyl ethers **5** were occasionally prone to unwanted Claisen rearrangements. These were particularly problematic when the R^2 substituent was an electron-withdrawing group (unless R^1 was also an electron-withdrawing group, as in the case of **5i**), or an aromatic group. We therefore focused our methodology on substrates incorporating alkyl groups or protons at the R^2 position. After reduction with diisobutylaluminum hydride (DIBAL), rearrangement was no longer observed.

Products **3**–**10** were purified over triethylamine-treated silica. However, both the addition and reduction steps yielded relatively pure material for most substrates (ca. 90% purity by NMR) even in the absence of column chromatography; simple filtration through basic alumina was sufficient to remove impurities in the addition reaction, while aqueous workup removed most of the aluminum-based byproducts following DIBAL reduction. This lack of required chromatographic purification steps suggests that the iterative conjugate addition/reduction sequence

Table 1. Iterative Synthesis of Vinyl Ethers[a]



	R^1	R^2	R^3	R^4	R^E	addition yield (*E*:*Z*)[b]	reduction yield (*E*:*Z*)[b]
1	Me	–	–	–	Et	**3a** 100% (>20:1)	**4a** 99% (>20:1)
2	H	–	–	–	Me	**3b** 99% (7:1)	**4b** 95% (>20:1)
3	Et	–	–	–	Et	**3c** 96% (7:1)	**4c** 89% (>20:1)
4	Ph	–	–	–	Et	**3d** 69% (5:1)	**4d** 95% (8:1)
5	CH_2OTHP	–	–	–	Me	**3e** 73% (3:1)	**4e** 92% (3:1)
6	CF_3	–	–	–	Et	**3f** 38%[c]	**4f** 91% (>20:1)
7	Me	Me	–	–	Et	**5a** 99% (20:1)	**6a** 74% (>20:1)
8	Me	H	–	–	Me	**5b** 93% (20:1)	**6b** 78% (>20:1)
9	Et	H	–	–	Me	**5c** 99% (20:1)	**6c** 75% (>20:1)
10	Et	Et	–	–	Et	**5d** 68% (20:1)	**6d** 86% (>20:1)
11	Ph	H	–	–	Me	**5e** 98% (14:1)	**6e** 90% (>20:1)
12	Ph	Me	–	–	Et	**5f** 99% (>20:1)	**6f** 97% (>20:1)
13	CH_2OTHP	H	–	–	Me	**5g** 92% (4:1)	**6g** 82% (3:1)
14	CF_3	H	–	–	Me	**5h** 64%[d] (14:1)	**6h** 77% (>20:1)
15	CF_3	CF_3	–	–	Et	**5i** 41%[e]	**6i** 84% (9:1)
16	CF_3	Me	–	–	Et	**5j** 99% (13:1)	**6j** 97% (9:1)
17	Me	H	H	–	Me	**7a** 95% (>20:1)	**8a** 84% (4:1)
18	Me	H	H	H	Me	**9a** 89% (3:1)	**10a** 92% (3:1)

[a] Conditions: (i) CH_2Cl_2, 0 to 23 °C, 24 h. (ii) Et_2O, −78 to −40 °C, 4 h. [b] For compounds with more than one vinyl ether, the *E*:*Z* ratio refers the ratio of the all-*E* product to all other adducts. [c] Pure *E* isomer, separated from 59% of the corresponding *Z* isomer. [d] Isolated along with 22% of a transesterification product. [e] Pure *E* isomer, separated from 58% of the corresponding *Z* isomer.

(10) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241–244.

(11) A similar sequence of reactions was recently used by our group to prepare a family of juvenile hormone mimics; see: Davies, K. A.; Kou, K. G. M.; Wulff, J. E. *Tetrahedron Lett.* **2011**, *52*, 2302–2305.

(12) (a) Lubineau, A.; Augé, J.; Bellanger, N.; Caillebourdin, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1631–1636. (b) Krompiec, S.; Kuźnik, N.; Urbala, M.; Rzepa, J. *J. Mol. Catal. A: Chem.* **2006**, *248*, 198–209. Also see ref 11.

described here could form the basis for an automated or semiautomated assembly of oligo-vinyl ethers.

Barring a few reports of Claisen rearrangements,[12] the chemistry of bis-vinyl ethers like **6** is unknown. We opted to first explore their reactivity in radical cascade reactions, since this would provide an opportunity to directly compare the behavior of bis-vinyl ethers with that of the analogous polyene systems, for which numerous radical cascades have been described previously.[13] To better understand the reactivity of these substrates, we also briefly investigated the radical cyclization of monovinyl ethers **4a** and **4b**. Following methylation[14] of the alcohol in **4a** (to provide **11**, Scheme 1), treatment with triphenyltin hydride and azobisisobutyronitrile (AIBN) in refluxing benzene afforded a good yield of **12**, consistent with results for related systems.[15] No 5-*exo* product was observed. The methyl ether of **4b** also provided mostly the corresponding 6-*endo* product, but with less selectivity. Subsequent reactions were exclusively carried out with alkyl or aryl substituents at the R^1 position.

Moving on to the cascading cyclization of bis-vinyl ethers (**6**, and alkylated derivatives thereof), we found that many such substrates engaged in a highly selective 6-*endo*-*trig*/5-*exo*-*trig* reaction to provide **15**.[16] Not surprisingly, the reaction leading to **15** was most efficient for substrates in which R^2 was a proton (Table 2, entries 1−5), presumably owing to the reduced steric hindrance for the final bond-forming step.

Substrates bearing alkyl groups at the R^2 position were more resistant to bicycle formation (Table 2, entries 6−9). Nonetheless, the use of high dilution (Table 2, entry 7) provided an acceptable yield of **15f** (R^1 = Me, R^2 = Me), containing two adjacent quaternary centers. Further increasing the size of the substituents (Table 2, entries 8 and 9) blocked the formation of **15**, such that only monocyclic products **16g** and **16h** were isolated cleanly. The presence of a free hydroxyl group (Table 2, entry 10) or a benzyl function in place of the terminal methyl ether (entry 11) did not adversely affect the yield, but in both cases the diastereoselectivity was eroded.

Assignment of the relative stereochemistry for **15** was complicated by the presence of minor isomers visible in the NMR spectra. To simplify the assignment, representative structures **15a** and **15f** were subjected to protodestannylation with aqueous HCl (Scheme 2). The structures of the products were fully assigned by 2D NMR methods (see Supporting Information); assignments of the major products in Table 2 were made by analogy. Destannylation of **15a** (as a 4:1 ratio of major isomers, each of which could be further resolved by NMR into a mixture of secondary isomers) afforded both possible diastereomers of product (**17a** and **18a**, again in a 4:1 ratio), while destannylation of **15f** (as a 5:1 mixture of isomers) provided a single diastereomer (**17f**) in excellent yield. These results indicate that the bicyclic structure of **15f** is formed as a single diastereomer and that the minor isomer visible spectroscopically corresponds to a second geometric isomer at the double bond. By contrast, the less-substitued analogues (**15a** − **15e**,

Scheme 1. Radical Cyclization onto a Mono-Vinyl Ether

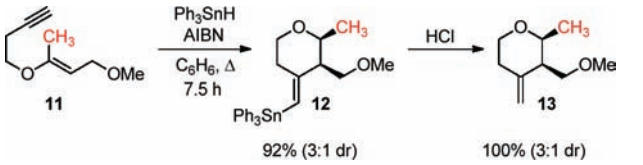
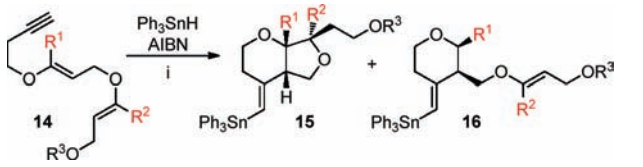


Table 2. Radical Cyclization across Bis-Vinyl Ethers[a]



	R^1	R^2	R^3	concentration	yield (dr)[b] 15	16
1	Me	H	Me	8 mM	**15a** 77% (4:1)	–[c]
2	Et	H	Me	8 mM	**15b** 76% (8:1)	–[c]
3	Ph	H	Me	8 mM	**15c** 80% (4:1)	–[c]
4	CF_3	H	Me	8 mM	**15d** 64% (7:1)	–[c]
5	CH_2OTHP	H	Me	8 mM	**15e** 67% (2:1)	–[c]
6	Me	Me	Me	8 mM	**15f** 33% (5:1)	**16f** 54% (4:1)
7	Me	Me	Me	1.6 mM	**15f** 55% (5:1)	**16f** 27% (3:1)
8	Et	Et	Me	8 mM	–[c]	**16g** 67% (2:1)
9	Ph	Me	Me	8 mM	–[c]	**16h** 72% (12:1)
10	Me	H	H	8 mM	**15i** 81% (1.4:1)	–[c]
11	Me	H	Bn	8 mM	**15j** 74% (2.7:1)	–[c]

[a] Conditions: (i) Ph_3SnH (1.5 equiv), AIBN (0.1 equiv) added over 6 h to a refluxing solution of **14** in benzene. Heating was continued for 1.5 h prior to workup. Major diastereomers are shown for products **15** and **16**. [b] Reported values refer to the ratio between the major observed product and the next most abundant species; refer to the Supporting Information for more details. [c] Product was not observed in ≥10% yield.

(13) (a) Handa, S.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 843–845. (b) Handa, S.; Nair, P. S.; Pattenden, G. *Helv. Chim. Acta* **2000**, *83*, 2629–2643.

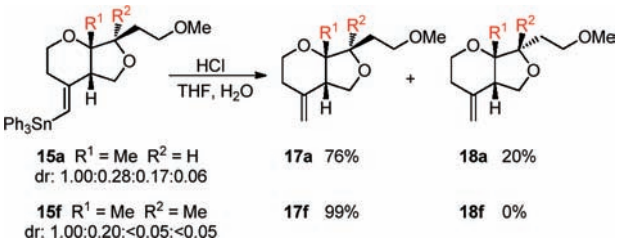
(14) See Supporting Information for alkylation conditions.

(15) (a) Munt, S. P.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1989**, 480–482. (b) Maguire, R. J.; Munt, S. P.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2853–2864.

(16) The methyl ether of **6i** (R^1 = R^2 = CF_3) reacted through a different process that we have tentatively assigned as a 5-*exo*-*trig*/*β*-scission, suggesting the possibility that all of the substrates in Table 2 arise through initial 5-*exo* cyclization, followed by rearrangement to the more stable radical intermediate, as has been previously suggested for other 6-*endo*-*trig* reactions. Further mechanistic investigations are underway.

as well as **15i** and **15j**) are formed as mixtures of epimers at the carbon bearing R^2, as well as geometric isomers at the double bond. No evidence of trans-fused products was observed.

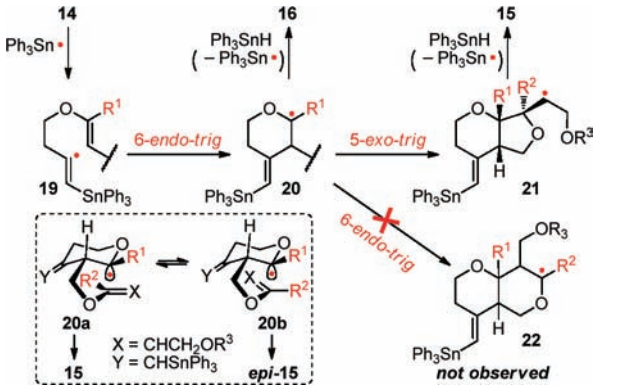
Scheme 2. Protodestannylations



As described in a series of papers by Pattenden, polyenes that are structurally related to **6a** (but which lack polarized double bonds) react in radical cascades through a series of 6-*endo-trig* cyclizations, a fact that has been attributed to steric control.[13,17] Thus, the first ring-closing event in the synthesis of **15** (i.e., **19** → **20**, Scheme 3) is in keeping with the reactivity observed for the corresponding olefinic system (and is, likewise, probably due largely to steric factors),[16] while the second ring closure takes the opposing 5-*exo* pathway. We attribute this regiochemical switch to the electronic properties of intermediate **20** (Scheme 3); due to electronic donation from the adjacent oxygen atom to the radical-bearing carbon, the energy of the SOMO is increased, thereby enhancing the nucleophilicity of the radical.[18] Although a second 6-*endo-trig* cyclization (to afford **22**) would be favored on steric grounds (at least for derivatives of **6a**) this pathway is disfavored electronically, since it would require the nucleophilic radical to add to the nucleophilic end of the vinyl ether function. Addition to the more hindered, but less nucleophilic, end of the vinyl ether group in a 5-*exo-trig* cyclization[19] (to provide **21**) is therefore favored on electronic grounds.

Regarding the relatively high levels of diastereoselectivity observed in the cascade reaction (particularly in the formation of **15f**), we hypothesize that the allylic ether side chain is preferentially oriented away from the tetrahydro-

Scheme 3. Proposed Mechanism for the Radical Cascade



2*H*-pyran core during the final cyclization event (as represented by **20a**, Scheme 3).[20] This picture is consistent with both the increase in selectivity for **15f** over **15a** (a methyl group in the R^2 position is more easily accommodated *anti* to the R^1 substituent) and the decrease in selectivity for **15e** (in which the bulky protecting group in the R^1 position may present an obstacle to the allylic ether).

Hexahydrofuropyrans of the type described here (and oxidized forms thereof) comprise the core structures of several natural products[21] and have also been utilized in medicinal chemistry programs.[22] Their selective formation through a high-yielding radical cascade reaction across iteratively synthesized vinyl ether precursors provides a compelling validation of the potential efficiency that may be achieved by uniting iterative synthesis and cascade cyclization methodologies.

Acknowledgment. We are grateful to NSERC (Canada), Merck Frosst, and the University of Victoria for financial support.

Supporting Information Available. Experimental procedures including spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) Less substituted 1,5-dienes (where both alkenes were disubstituted) were reported to engage in tandem 6-*endo-trig*/5-*exo-trig* cyclization, but the presence of additional substituents favored the 6-*endo* pathway; see: Batsanov, A.; Chen, L.; Gill, G. B.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 45–55.

(18) Fleming, I. *Molecular Orbitals and Organic Chemical Reactions*; John Wiley & Sons: West Sussex, U.K., 2010; pp 369−400.

(19) 5- and 6-*exo* radical cyclizations onto vinyl ethers bearing electron-withdrawing directing groups are well-known; see for example: (a) Lee, E. *Pure Appl. Chem.* **2005**, *77*, 2073–2081. (b) 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*, 1275–1277.

(20) Anomeric radicals generally react through axial approach of the radical acceptor; see for example: Abe, H.; Shuto, S.; Matsuda, A. *J. Am. Chem. Soc.* 2001, *123*, 11870−11882 and references therein.

(21) (a) Shibano, M.; Okuno, A.; Taniguchi, M.; Baba, K.; Wang, N.-H. *J. Nat. Prod.* **2005**, *68*, 1445–1449. (b) Li, C.-Y.; Wu, T.-S. *J. Nat. Prod.* **2002**, *65*, 1452–1456. (c) Seaforth, C. E.; Mohammed, S.; Maxwell, A.; Tinto, W. F.; Reynolds, W. F. *Tetrahedron Lett.* **1992**, *33*, 4111–4114. (d) Oulad-Ali, A.; Guillaume, D.; Jiang, Y.; Weniger, B.; Anton, R. *Nat. Prod. Lett.* **1993**, *2*, 203–207. (e) Krohn, K.; Biele, C.; Drogies, K.-H.; Steingröver, K.; Aust, H.-J.; Draeger, S.; Schulz, B. *Eur. J. Org. Chem.* **2002**, 2331–2336. (f) Qin, S.; Krohn, K.; Flörke, U.; Schulz, B.; Draeger, S.; Pescitelli, G.; Salvadori, P.; Antus, S.; Kurtán, T. *Eur. J. Org. Chem.* **2009**, 3279–3284. (g) Gao, X.; Nakadai, M.; Snider, B. B. *Org. Lett.* 2003, *5*, 451−454 and references therein.

(22) See for example: (a) Stewart, A. M.; Meier, K.; Schulz, B.; Steinert, M.; Snider, B. B. *J. Org. Chem.* **2010**, *75*, 6057–6060. (b) Ghosh, A. K.; Chapsal, B. D.; Baldridge, A.; Steffey, M. P.; Walters, D. E.; Koh, Y.; Amano, M.; Mitsuya, H. *J. Med. Chem.* **2011**, *54*, 622–634. (c) Fathi, A. R.; Krautheim, A.; Kaap, S.; Eger, K.; Steinfelder, H. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1605–1608.