ORGANIC LETTERS

2007
Vol. 9, No. 4
583−586

Selective Monocyclization of Epoxy Terpenoids Promoted by Zeolite NaY. A Short Biomimetic Synthesis of Elegansidiol and Farnesiferols B–D

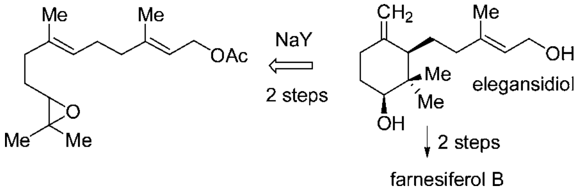
Constantinos Tsangarakis, Elias Arkoudis, Christos Raptis, and Manolis Stratakis*

Department of Chemistry, University of Crete, Voutes 71003 Iraklion, Greece

stratakis@chemistry.uoc.gr

Received November 17, 2006

ABSTRACT



Epoxy terpenes cyclize readily, by confinement within zeolite NaY, to form exomethylenic cyclohexanols as the major products. The selective monocyclization of 10,11-epoxyfarnesyl acetate within NaY provides a short and efficient biomimetic route to (±)-elengasidiol and (±)-farnesiferols B–D.

It is an incontravertable fact that Nature has developed the means to construct complex secondary metabolites with unparalleled efficiency and elegance. These accomplishments might be said to be due to the enzymes she harnesses, which are particularly adept and stereoselective catalysts. As a result, synthetic chemists expend a great deal of effort attempting to mimic the work done by enzymes as they strive for ever greater efficiency in their own syntheses. An underutilized enzyme mimic is the zeolite. Zeolites are mixed aluminosilicates that catalyze reactions[1] by confining the substrates within “active site” cavities, just as enzymes do. However, unlike enzymes, they are stable to a broad range of conditions, can be used with a variety of solvents, and can be easily removed by filtration. We reasoned that zeolites with suitable cavity dimensions to host organic molecules, especially the slightly acidic NaY, would be particularly well suited to promoting the efficient cyclization of various common epoxy terpenoids. The results of our investigation, and the successful application of this new method to the biomimetic syntheses of (±)-elengasidiol and (±)-farnesiferols B−D, are reported herein.

The acid-catalyzed cyclization of epoxy polyenes has attracted much interest during the past 50 years,[2] especially due to the early discovery that an analogous enzyme-catalyzed reaction is involved in the biosynthesis of a vast number of important terpenoids.[3] On many occasions organic chemists have attempted to reproduce this fascinating enzymatic reaction using acid-catalysis with varying degrees of success. Superacids, such as FSO_3H, which are superior catalysts in the cyclization of polyene terpenoids, failed to provide cyclization products from epoxy polyenes, providing instead solvolysis products.[4] On the other hand, Lewis acids such as BF_3,[5] $ZrCl_4$,[6] $FeCl_3$,[7] $Sc(OTf)_3$,[8] $Bi(OTf)_3$,[9] and, especially,

---

[1] Sen, S. E.; Smith, S. M.; Sullivan, K. A. *Tetrahedron* **1999**, *55*, 12657−12698.

[2] (a) Johnson, W. S. *A fifty-year love affair with organic chemistry*; American Chemical Society: Washington, DC, 1998. (b) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730−4756.

[3] (a) van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152−158. (b) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011−3050.

[4] Vlad, P. F. *Pure Appl. Chem.* **1993**, *65*, 1329−1336.

[5] van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. *J. Am. Chem. Soc.* **1963**, *85*, 3295−3296.

[6] Vidari, G.; Beszant, S.; Merabet, J. E.; Bovolenta, M.; Zanoni, G. *Tetrahedron. Lett.* **2002**, *43*, 2687−2690.

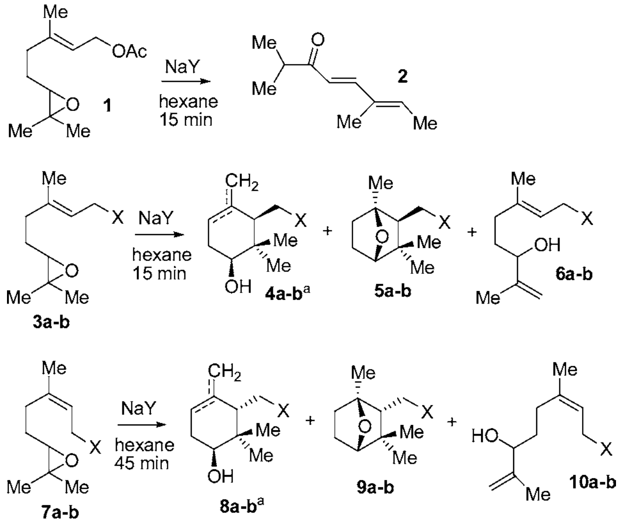
10.1021/ol062798i CCC: $37.00

$MeAlCl_2$[10] have been widely used, often providing efficient polycyclization with good diastereoselectivity. It should be noted here that a free-radical-based methodology for the cascade polycyclization of epoxy terpenes catalyzed by titanocene(III) has also recently been established.[11] Unfortunately, Lewis acids, however adept they may have proved to be in catalyzing polycyclization, cannot be expected to exert the control necessary to effect monocyclization of these substrates, but we felt the right zeolite might be able to accomplish this goal by making use of the confined spaces present in its architecture.

Our belief was based on the fact that, recently, we[12] and others[13] had reported the efficient biomimetic cyclization of small acyclic terpenoids, such as geranyl derivatives, by adsorption within the confined environment of a zeolite. We found that zeolite NaY, a mildly acidic (containing both Lewis and Brønsted acidic sites[14]) catalyst, promoted these cyclizations in surprisingly high yields and with good selectivities. Precedent for the use of acidic zeolites in the cyclization of epoxy terpenoids, however, is limited. Sen and co-workers used the small-pore highly acidic zeolites (HA and HZSM-5) as promoters for the cyclization of certain specific silyl-substituted epoxide-containing polyenes, with moderate to good product selectivity.[15] In this case it was postulated that cyclization was initiated at the opening of the zeolite pores, since the size of those epoxy polyenes does not allow them to diffuse into the interior of the cages.

We felt that the larger pore size and the low acidity of NaY should make it a mild and selective cyclization promoter. We were gratified to find that, with the exception of 6,7-epoxygeranyl acetate (**1**), NaY does indeed promote the fast cyclization of several epoxy terpenoids to form stereoselectively and regioselectively mainly the exomethylenic cyclohexanols (**4a**,**b** or **8a**−**c**, Table 1). The formation of **4** or **8** depends on the configuration of the adjacent nucleophilic double bond. Alkenes with the *E* configuration afford the cis cyclization products (**4**), while those with the *Z* afford trans (**8**). The bicyclic ethers (**5** or **9**) and the allylic alcohols (**6** or **10**) are formed as side products. Once again, the products stereochemistry depends on the configuration of the nucleophilic double bond.

Table 1. NaY-Promoted Cyclization of Epoxy Terpenoids



sub.	X	yield, %	products (relative ratios)
1		78	**2**
3a	−OH	76	**4a/5a/6a** = 70/20/10
3b	$-CH_2COMe$	92	**4b/5b/6b** = 70/25/5
7a	−OAc	78	**8a/9a/10a/2** = 40/20/10/30
7b	$-CH_2COMe$	85	**8b/9b/10b/5b** = 70/6/22/2

[a] Exo/endo = 6−12/1, depending on the substrate and the reaction time.

Generally, at low loading levels (0.1 mmol of substrate per 1 g of dry NaY[16]) the reaction of the geranyl derivatives (**1**, **3a**,**b**) proceeds smoothly at ambient temperature, going to completion within 10−15 min. On the other hand, the neryl derivatives (**7a**,**b**) require approximately 45 min reaction time. At higher loading levels (1 mmol of geranyl derivative per 1 g of NaY), the reactions are completed on heating at 70 °C for 1 h.[17] The combined products yield varies from 75% to 90%. Isomerization of the exo to the endo double bond (in the cases of products **4** or **8**) occurs slowly in the presence of NaY. Prolonged intrazeolite treatment of the polyene epoxides (1−2 h) results in a drop of the exo/endo ratio from a typical 8−12/1 to approximately 4−6/1. The methodology described herein is very simple and provides a powerful and direct route to a series of useful exomethylenic cyclohexanols. For instance, cyclized products **4a**, **5a**,[18] and **4b**[11a] have been used as valuable blocks in the synthesis of terpenoids. In addition, we would like to point out that in our hands treatment of **3b** with a catalytic amount of $SnCl_4$[19] gave the dicyclization product **11** and the bicyclic

---

(7) Sen, S. E.; Roach, S. L.; Smith, S. M.; Zhang, Y. Z. *Tetrahedron Lett.* **1998**, *39*, 3969−3972.

(8) Bogenstatter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206−12207.

(9) Lacey, J. R.; Anzalone, P. W.; Duncan, C. M.; Hackert, M. J.; Mohan, R. S. *Tetrahedron Lett.* **2005**, *46*, 8507−8511.

(10) (a) Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005−7008. (b) Huang, A. X.; Xiong, Z. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999−10003.

(11) (a) Justicia, J.; Rosales, A.; Bunuel, E.; Oller-Lopez, J. L.; Valdivia, N.; Haidour, A.; Oltra, J. E.; Barrero, A. F.; Cardenas, D. J.; Cuerva, J. M. *Chem. Eur. J.* **2004**, *10*, 1778−1788. (b) Barrero, A. F.; del Moral, J. F. Q.; Sanchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem.* **2006**, *10*, 1627−1641.

(12) Tsangarakis, C.; Stratakis, M. *Adv. Synth. Catal.* **2005**, *347*, 1280−1284.

(13) Yu, W.; Bian, F.; Gao, Y.; Yang, L.; Liu, Z.-L. *Adv. Synth. Catal.* **2006**, *348*, 59−62.

(14) Rao, V. J.; Perlstein, D. L.; Robbins, R. J.; Lakshminarasimhan, P. H.; Kao, H.-M.; Grey, C. P.; Ramamurthy, V. *Chem. Commun.* **1998**, 269−270.

(15) (a) Sen, S. E.; Zhang, Y. Z.; Roach, S. L. *J. Org. Chem.* **1996**, *61*, 9534−9537. (b) Sen, S. E.; Zhang, Y. z.; Smith, S. M. *J. Org. Chem.* **1998**, *63*, 4459−4465.

(16) Zeolite NaY was dried and activated as described in ref 12.

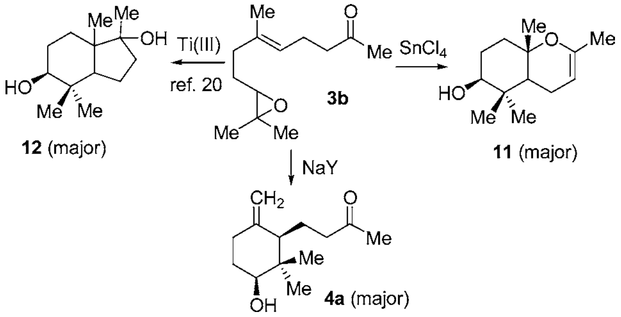
(17) **Typical cyclization procedure:** 9,10-Epoxygeranylacetone (**3b**, 200 mg, 0.95 mmol) was adsorbed onto dry zeolite NaY (1 g) that had been previously suspended in hexane (15 mL). The resultant slurry was heated to 70 °C for 1 h and then filtered. The solid residue was washed with methanol (2 × 10 mL) for 30 min each time. The combined extracts were evaporated under reduced pressure to afford 184 mg of a mixture containing **4b**, **5b**, and **6b** (see Table 1).

(18) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Palomino, P. L. *Tetrahedron* **1994**, *50*, 13239−13250.

(19) van Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *J. Org. Chem.* **1995**, *60*, 7209−7214.

ether **5b** in a relative ratio 3/1 (70% yield), while the Ti(III) radical-based methodology[20] provides mainly bicyclic diol **12** as a mixture of four stereoisomers (Scheme 1). Therefore, the newly developed zeolite NaY methodology compliments the existing cyclization protocols by allowing access to the products of monocyclization.

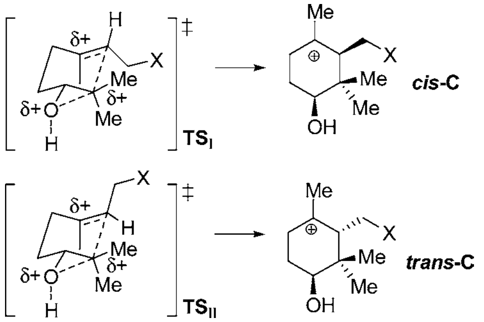
Scheme 1. Cyclization of **3b** Catalyzed by $SnCl_4$, Ti(III), or NaY



It was somewhat surprising that while 6,7-epoxygeraniol (**3a**) cyclizes to form mainly **4a**, the corresponding acetate **1** does not afford any cyclization products. Instead, (4*E*,6*E*)-2,6-dimethylocta-4,6-dien-3-one (**2**) was produced in 78% isolated yield. It is known that dienone **2** along with its (4*E*,6*Z*)-geometrical isomer are formed upon treatment of linallol oxide with 25% H_2SO_4, or through the acid-catalyzed isomerization of myrcene-6,7-epoxide (**13**).[21] In our case, formation of **2** from **1** can be envisoned to have occurred through an epoxide to ketone isomerization in combination with an elimination of the acetate functionality and diene isomerization. At this stage, however, we do not want to speculate as to why we see this switch in mode of reaction upon going from **3a** to its acetoxy analogue **1**, especially in the light of our observation that **13** does not form **2**, but mainly the cyclization products. Further experiments are in progress to examine this interesting transformation.

From a mechanistic point of view, a concerted cyclization mechanism, as postulated by Corey and Staas,[22] could explain the observed diastereoselection in the cyclization of epoxy compounds **3a**,**b** and **7a**−**c** (Scheme 2). The zeolite's acidic sites activate, through epoxide binding, the tertiary *gem*-dimethyl carbon atom for nucleophilic attack by the adjacent double bond thus forming the cyclohexyl ring, via the pseudo-chair transition states **TS$_I$** and **TS$_{II}$**, in which the relative configuration of the nucleophilic double bond dictates the stereochemistry of the cyclized products (***cis*-C** or ***trans*-C**). Regioselective elimination of a proton from the methyl group of ***cis*-C** or ***trans*-C** gives the exomethylenic cyclohexanols **4** or **8** as major products, while intramolecular nucleophilic attack by the hydroxyl group affords the bicyclic ethers **5** or **9** (Table 1).

Scheme 2. Mechanistic Aspects for the NaY-Catalyzed Cyclization of Epoxy Terpenoids



To prove the worth of our new method in a synthetic arena, we chose to apply the protocol to the synthesis of several natural products. To this end, the higher terpene analogue, 10,11-epoxyfarnesyl acetate (**14**),[23] was treated within NaY. The resulting reaction went to completion after 15 min to afford selectively the monocyclization products **15** and **16**, the bicyclic ether **17**, and the corresponding allylic alcohol **18** (analogous to the products **6** or **10**), in a relative ratio **15**/**16**/**17**/**18** = 50/7/30/13, and in 75% combined isolated yield (Scheme 3). The isomeric alcohols **15** and **16** were easily isolated from the crude reaction mixture by column chromatography, and hydrolyzed almost quantitatively using K_2CO_3 in methanol to afford the racemic sesquiterpene elegansidiol (**19**),[24] along with its minor endocyclic isomer **20** (ratio **19**/**20** ~ 8/1). Reaction of the so-formed **19** and **20** with PBr_3 (1.1 equiv) afforded selectively and in high yield the corresponding allylic bromides **21** and **22**. Finally, alkylation of the potassium salt of 7-hydroxycoumarin (umbelliferone) with the allylic bromides **21** and **22** (K_2CO_3 in acetone) yielded a mixture of farnesiferols B[25] (**23**) and D[23c] (**24**) in a ratio of 8/1, and in 78% isolated yield from **19**/**20** (3 steps). In addition, the analogous 3-step transformation of the minor product **19** furnished farnesiferol C (**25**),[24a] in 86% overall yield.

Our synthesis of farnesiferols B and D is the first to be reported. Two independent syntheses of farnesiferol C are already known,[26] albeit with use of different and less efficient strategies. Attempts to perform the more direct biomimetic synthesis of these farnesiferols by using the intrazeolite transformation of epoxide **26**[27] were unsuccessful. Upon adsorp-

---

[20] Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdivia, N. V. *J. Org. Chem.* **2001**, *66*, 4074−4078.

[21] Ho, T.-L.; Liu, S.-H. *Liebigs Ann. Chem.* **1983**, 761−769.

[22] Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526−3527.

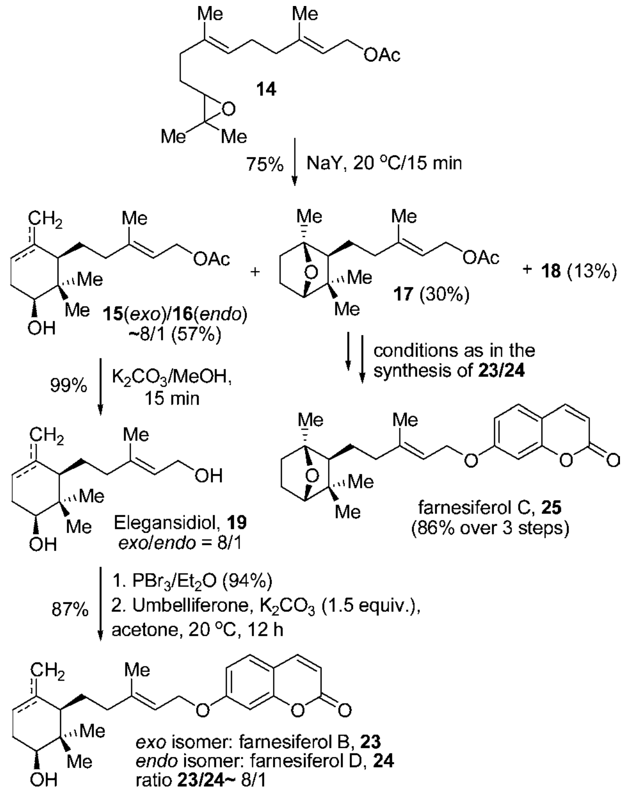
[23] The BF_3-catalyzed cyclization of **14** gives a complex reaction mixture, with a very low yield of bicyclic hydroxy acetates, without any monocyclization products such as **15** or **16** being formed: van Tamelen, E. E.; Storni, A.; Hessler E. J.; Schwartz, M. A. *Bioorg. Chem.* **1982**, *11*, 133−170.

[24] For the isolation and two multistep syntheses of elegansidiol, see: (a) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Herrador, M. M.; Alvarez-Manzaneda, R.; Quilez, J.; Chahboun, R.; Linares, P.; Rivas, A. *Tetrahedron Lett.* **1999**, *40*, 8273−8276. (b) Audran, G.; Galano, J. M.; Monti, H. *Eur. J. Org. Chem.* **2001**, *12*, 2293−2296. (c) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Rivas, A. R.; Palomino, P. L. *Tetrahedron* **2000**, *56*, 6099−6113.

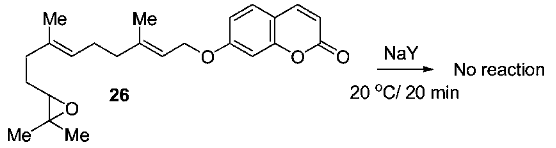
[25] (a) Caglioti, L.; Naef, H.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1959**, *42*, 2557−2570. (b) Nassar, M. I. *Pharmazie* **1994**, *49*, 542−543. (c) Iranshahi, M.; Amin, G.; Shafiee, A. *Pharm. Biol.* **2004**, *42*, 440−442.

[26] (a) Demnitz, F. W. J.; Philippini, C.; Raphael, R. A. *J. Org. Chem.* **1995**, *60*, 5114−5120. (b) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 29−32.

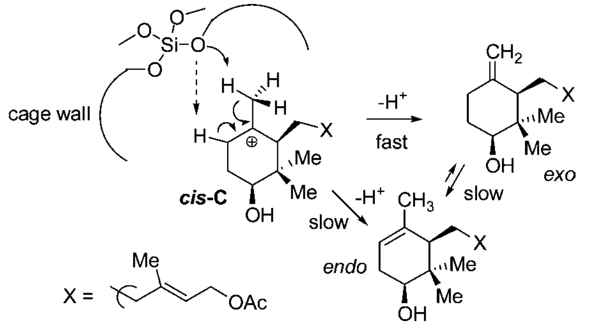
Scheme 3. Selective Monocyclization of **14** Promoted by NaY: Synthesis of Elegansidiol and Farnesiferols B−D



tion of **26** within NaY an intense red color appeared immediately, which faded away upon treatment with methanol (after 20 min), and the epoxide was subsequently recovered intact. On prolonged intrazeolite treatment of **26** at 70 °C (2 h) the reaction turned brown-black and only traces of an unidentified organic material were isolated. The red color may be attributed to the formation of a charge-transfer complex between the coumarin moiety of **26** and an acidic site in the zeolite wall. van Tamelen and Coates[27b] have studied the cyclization of **26** in the presence of BF_3. They observed formation of a complex mixture of products, among which was farnesiferol C (8%); however, no farnesiferol B or D was seen.


26

Scheme 4. Mechanistic Arguments on the Selective and Regioselective Monocyclization of Epoxyfarnesyl Acetate in NaY



The selective formation of the monocyclized exo-isomers in the case of **4**, **8**, or **14** could be envisioned to occur through a kinetically controlled deprotonation of the monocyclized carbocation ***cis*-C**, for instance (Scheme 4) by the oxygen atom of the Si−O−Si or Si−O−Al bonds in the interior walls of the zeolite cage. The methyl group hydrogens adjacent to the carbocation are more accessible for proton abstraction by the "zeolite wall" relative to the hydrogen atoms on the cyclohexyl ring. In addition, the fast deprtotonation of ***cis*-C** prevents nucleophilic attack by the adjacent C2−C3 double bond to form a dicyclization product.

The current synthesis of elegansidiol and farnesiferols by using a controlled cyclization mediated by the zeolite environment may be considered as biomimetic. The incomplete cyclization of epoxy polyene terpenoids in Nature requires the suitable positioning of a basic amino acid residue within the cyclase cavity such that the monocyclized carbocation is deprotonated, thus terminating the polycyclization sequence.[28] In NaY, the oxygen atoms in the interior of the zeolite cage play exactly the same role.

In conclusion, we have presented a simple, mild (as harsh Lewis acids are avoided), and efficient biomimetic methodology for the monocyclization of epoxy terpenes. The developed procedure was applied to the short syntheses of the natural products elengasidiol and farnesiferols B−D. To the best of our knowledge, *NaY is the only known acidic catalyst that can induce a selective monocyclization reaction of epoxy polyene terpenoids*. As is clearly evident in the case of epoxides **3b** and **14**, this methodology provides a valuable tool for the direct synthesis of a wide variety of monocyclized naturally occurring terpenoids. Further synthetic applications and mechanistic studies into this interesting reaction mode are currently under investigation.

Acknowledgment. This project was co-funded by the European Social Fund and National resources (program PYTHAGORAS-II). We thank Dr. Tamsyn Montagnon for assistance during the preparation of this manuscript.

Supporting Information Available: Experimental details for the synthesis of epoxy terpenoids and their intrazeolite reactions. Copies of ^1H, ^{13}C NMR, MS and HRMS spectra of key compounds and reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062798I

---

(27) (a) Cravotto, G.; Balliano, G.; Robaldo, B.; Bosso-Oliaro, S.; Chimichi, S.; Boccalini, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1931−1934. (b) van Tamelen, E. E.; Coates, R. M. *Bioorg. Chem.* **1982**, *11*, 171−196.

(28) For a typical example, see: Matsuda, S. P. T.; Darr, L. B.; Hart, E. A.; Herrera, J. B. R.; McCann, K. E.; Meyer, M. M.; Pang, J. H.; Schepmann, H. G. *Org. Lett.* **2000**, *2*, 2261−2263.