Generation of Libraries of Pharmacophoric Structures with Increased Complexity and Diversity by Employing Polymorphic Scaffolds

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During the last decade we have witnessed the emergence of combinatorial chemistry as a tool for the discovery of new lead compounds.[1] Outstanding examples of sophisticated directed libraries have been reported, including pharmacophoric scaffolds,[2] bioactive metabolites,[2] designed "unnatural", diversity-oriented, pharmacophore-like, rigid, and versatile structures,[3] and even natural products with highly complex architectures.[4] The state-of-the-art in this field combines three main features: 1) suitably functionalized druglike "privileged structures"[5] having specific spatial architecture and rigidity, 2) short synthetic pathways comprising reliable, clean, and high-yielding reactions, and 3) an overall "diversification strategy" resulting ideally in "libraries of libraries"[6] of scaffolds resembling evolution-selected molecules like natural products or drugs.

Libraries are mainly based on a core molecule that is subjected to functional group manipulation which leads to a number of derivatives with the same central structure. Several versatile molecules that were key intermediates used by traditional medicinal chemists, for example, Corey's lactone, the Wieland–Miescher ketone, and the Prelog–Djerassi lactone, could lead to a variety of apparently unrelated pharmacophoric frameworks. These starting materials are small molecules equipped with many reactive sites and functionalities, which can undergo both skeletal rearrangements and functional group interconversions. The use of such a polymorphic compound as the cornerstone of a library would be of great advantage since: 1) Many known synthetic key intermediates lead to medicinally important or "privileged" scaffolds; 2) they possess high potential for both structural and functional diversification; 3) their chemical transformations and modifications in solution are well documented; and 4) the pharmacological activity of their descending structures is well precedented.

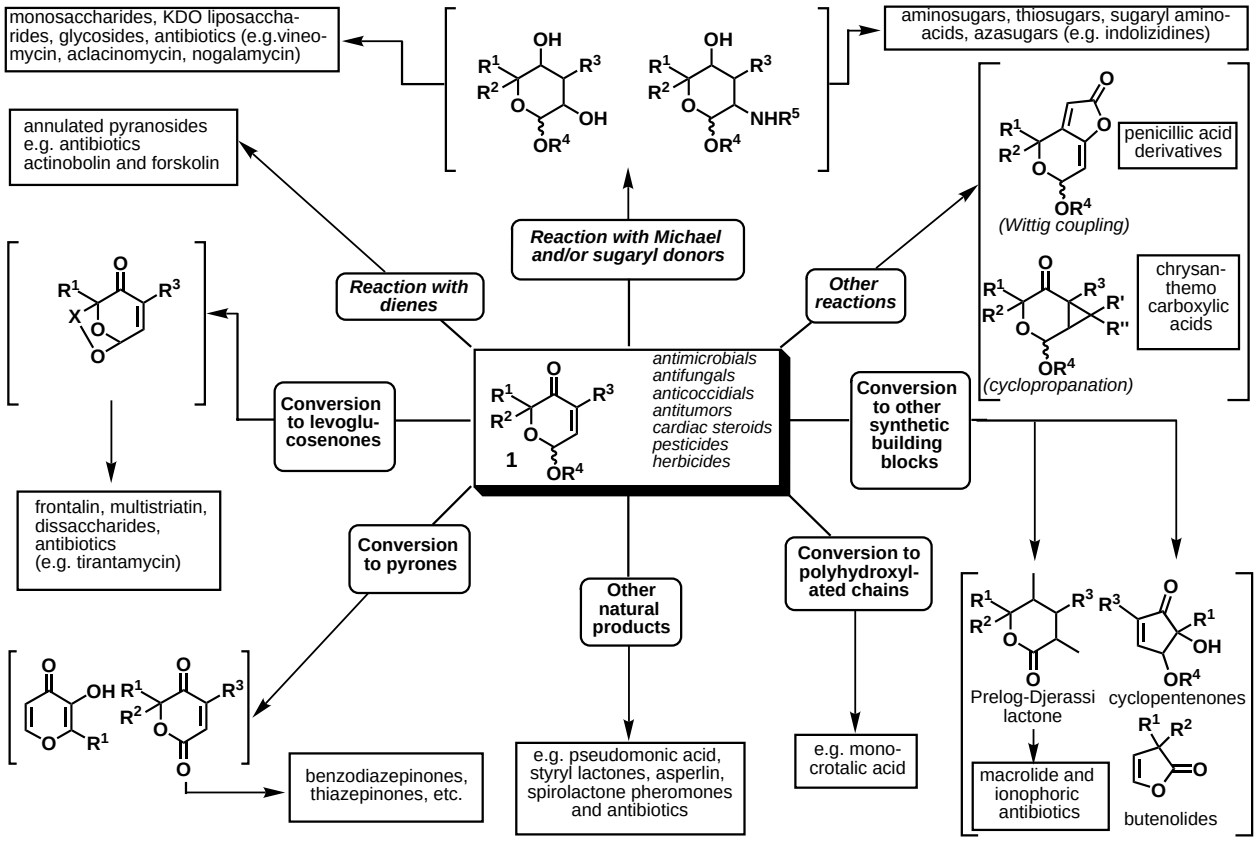

Figure 1. Representative reported derivatizations and applications of pyranone **1**.

To demonstrate the above concept, 2*H*-pyran-3(6*H*)-one (**1**)[7,8] was selected from among several synthetic key intermediates listed in the literature. As shown in Figure 1, derivatives of pyranone **1** exhibit significant biological activities, including antibacterial, antifungal, anticoccidial, antiinflamatory, and anticancer properties. Besides serving as intermediates in several natural product syntheses, such

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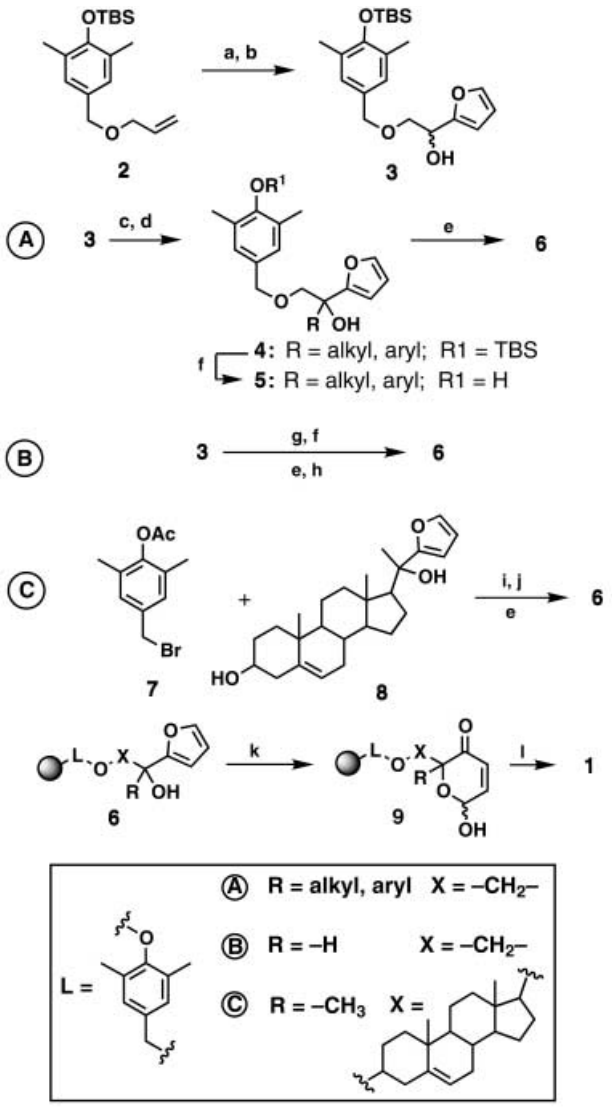
compounds have also acted as templates for the synthesis of monosaccharides and glycosides. In addition, they undergo skeletal rearrangements to yield a wide range of structures ranging from polyhydroxylated chains and benzodiazepines to butenolides and anthraquinones.

The primary concern and prerequisite for the effective use of this molecule in combinatorial chemistry is the identification of a suitable linker to attach the pyranone core on the resin (**9**, Scheme 1). This linker should be able to withstand a variety of chemical transformations, be cleavable under specific, relatively mild conditions, and be compatible with many functionalities. We tested several possibilities before we



Scheme 1. Loading of pyranone precursors on resin. Reagents and conditions: a) $OsO_4/NaIO_4$, THF/H_2O 1:1; b) furyllithium, Et_2O, 0 °C; c) SO_3·py, $DMSO/Et_3N/CH_2Cl_2$, 0 °C; d) RMgX, Et_2O, 0 °C; e) Merrifield resin, Cs_2CO_3, Bu_4NI, CH_2Cl_2, 5 d; f) TBAF, THF, 0 °C; g) Ac_2O, Et_3N, DMAP, CH_2Cl_2; h) MeONa, THF/MeOH 4:1, 25 °C, 8 h; i) Cs_2CO_3, Bu_4NI, 60 °C, DMF; j) $LiOH_{(aq)}$/THF/MeOH 1:1:1; k) NBS, THF/H_2O 4:1, 0→25 °C, 1 h; l) DDQ, CH_2Cl_2/H_2O 18:2, 25 °C, 2–3 h, then aqueous ascorbic acid or CH_2Cl_2/TFA 6:1, 25 °C, 8–10 h. TBS = *tert*-butyldimethylsilyl, py = pyridine, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBAF = tetrabutylammonium fluoride, DMAP = 4-dimethylaminopyridine, NBS = *N*-bromosuccinimide, TFA = trifluoroacetic acid.

selected an oxidatively cleavable aromatic ether (linker L, Scheme 1). This linker was designed[9] to tolerate basic and mildly acidic or oxidative conditions and be cleaved rapidly upon treatment with DDQ or TFA. In the optimum loading procedure the respective furyl alcohol (pyranone precursor) was coupled with the linker and then loaded on Merrifield resin by using Cs_2CO_3 (Scheme 1). Thus, furyl alcohol **3** was prepared by conversion of allyl ether **2** into the corresponding aldehyde, followed by addition of furyllithium. This alcohol, after oxidation and subsequent derivatization with Grignard reagents, was transformed into tertiary alcohols **4** (route A). The latter, after desilylation, were loaded on the resin to afford supported furyl alcohols **6**, which were oxidized to 2*H*-pyran-3(6*H*)-ones **9** in high yields following a slightly modified reported protocol.[7c] Secondary alcohol **3** could also be loaded on the resin in the same fashion after protection of the hydroxy group (route B). Complicated substrates could also be loaded by using an additional "handle" on the side chain (e.g., route C). Most of the compounds were cleaved efficiently and isolated in satisfactory yields and purity; cleavage conditions, yields, and purity are presented in Table 1.

For the practical demonstration of the use of 2*H*-pyran-3(6*H*)-ones **9** as key intermediates with great potential for diversification we carried out a significant number of derivatizations and transformations (Scheme 2). Upon treatment with isocyanates they were converted into carbamates **10**, scaffolds known to show anticoccidial and antimicrobial activities.[8a,b] These carbamates were treated with further alcohols to give bioactive ethers **11** by using catalytic $HClO_4$ or, under alkaline conditions, quantitatively converted into pharmacophoric oxazolediones **12**.[10] A patented procedure was applied to convert substrates **12** into angiogenesis inhibitor **13**,[8k] albeit in low yield.

Further oxidation of substrate **9** with the Dess–Martin reagent afforded pyrones **14**, which were transformed, after reduction with $NaBH_4$, into lactones **15**. The latter may serve as the core structures for the generation of new libraries since they have many reactive sites for derivatization with either nucleophilic or electrophilic reagents, as well as with dienes. Moreover, pyrone **14**, after treatment with several binucleophiles,[11] was transformed into medicinally important heterocycles such as thiazinones **16**, benzothiazinones **17**, and diazepinones **18**. Pyranone **9** was also directly esterified (to give **19**) or etherified (to give **21**). These classes of compounds are known for their antimicrobial (against both Gram-positive and Gram-negative bacteria), antifungal, pesticidal, and anticoccidial activities.[8] Acetate **19** ($R^3 = CH_3$) served as a model glycosyl acceptor and was efficiently glycosylated with 6-*O*-methyl-2,3,4-triacetylglycopyranoside.[12] Methyl ether **21** ($R^5 = CH_3$) was used as a Michael acceptor to yield deoxysugar derivatives **22** and **23**. The same substrate (**21**) was reduced with $NaBH_4$ and subsequently epoxidized to afford epoxide **24**, which was further derivatized to give sugar derivatives **25**.[7b,8l]

Application of additional known transformations already listed in Figure 1 should lead efficiently to further structurally diversified substrates. Furthermore, new reactions and novel transformations might be applied on these highly reactive

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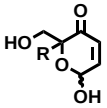
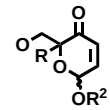
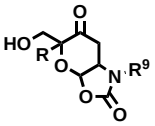
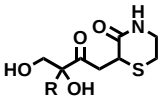
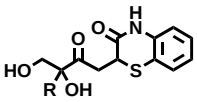
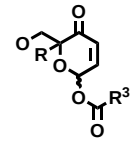
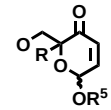
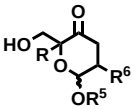
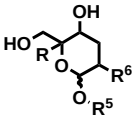
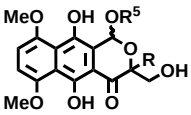
Table 1. Structures, cleavage conditions, yields, and purity of selected members of the library.

Substrate	Cleavage[a]	Structure	Substituents	Yield [%] (Purity [%])[b]
9	A		R = Ph	95 (95)
9	A		R = $(CH_2)_9CH_3$	85 (80)
11	A		R = Ph, $R^2 = CH_3$	90 (85)
11	A		R = Ph, R^2 = Bn	75 (80)
11	A		R = Ph, $R^2 = (CH_2)_7CH_3$	85 (85)
11	A		R = $(CH_2)_9CH_3$, $R^2 = CH_3$	85 (85)
12	A		R = Ph, R^9 = Bn	90 (90)
12	A		R = Ph, $R^9 = CH_3$	90 (90)
12	A		R = $(CH_2)_9CH_3$, $R^9 = CH_3$	90 (90)
16	B		R = Ph	75 (pur.)
16	B		R = $(CH_2)_9CH_3$	65 (pur.)
17	B		R = Ph	70 (pur.)
17	B		R = $(CH_2)_9CH_3$	67 (pur.)
19	A		R = Ph, $R^3 = C_6H_5$	95 (95)
19	A		R = Ph, $R^3 = pNO_2C_6H_4$	95 (95)
19	A		R = Ph, $R^3 = CH_3$	95 (95)
19	A		R = $(CH_2)_9CH_3$, $R^3 = pNO_2C_6H_4$	80 (85)
19	A		R = $(CH_2)_9CH_3$, $R^3 = C_6H_5$	80 (85)
21	A		R = Ph, $R^5 = CH_3$	95 (95)
21	A		R = Ph, $R^5 = CH_2CH_3$	90 (95)
21	A		R = $(CH_2)_9CH_3$, $R^5 = CH_3$	85 (95)
22	A		R = Ph, $R^5 = CH_3$, $R^6 = S(CH_2)_3CH_3$	90 (95)
22	A		R = $(CH_2)_9CH_3$, $R^5 = CH_3$, $R^6 = S(CH_2)_3CH_3$	90 (95)
23	A		R = Ph, $R^5 = CH_3$, $R^6 = N_3$	70 (80)
26	B		R = Ph, $R^5 = CH_3$	80 (pur.)

[a] For details on the cleavage conditions and compound characterization see the Supporting Information. Method A: DDQ, CH_2Cl_2/H_2O 18:2, 25 °C, 2–3 h; then ascorbic acid. Method B: CH_2Cl_2/TFA 6:1, 25 °C, 8–10 h. [b] Yields and purities (HPLC) pertain to the mixture after cleavage before any purification unless (purity) is stated.

molecules, thus expanding the range of targeted chemical classes. For example, 2*H*-pyran-3(6*H*)-ones (**21**) were efficiently transformed into pharmacophoric naphthoquinones **26** upon treatment with a dipole equivalent (Scheme 2).[13]

In conclusion, we have demonstrated that a polymorphic synthetic key intermediate can be used as the core structure of a directed library leading through structural modifications to well-defined classes of compounds, each of which may subsequently serve as the intermediate for the construction of new directed libraries of medicinally important molecules.

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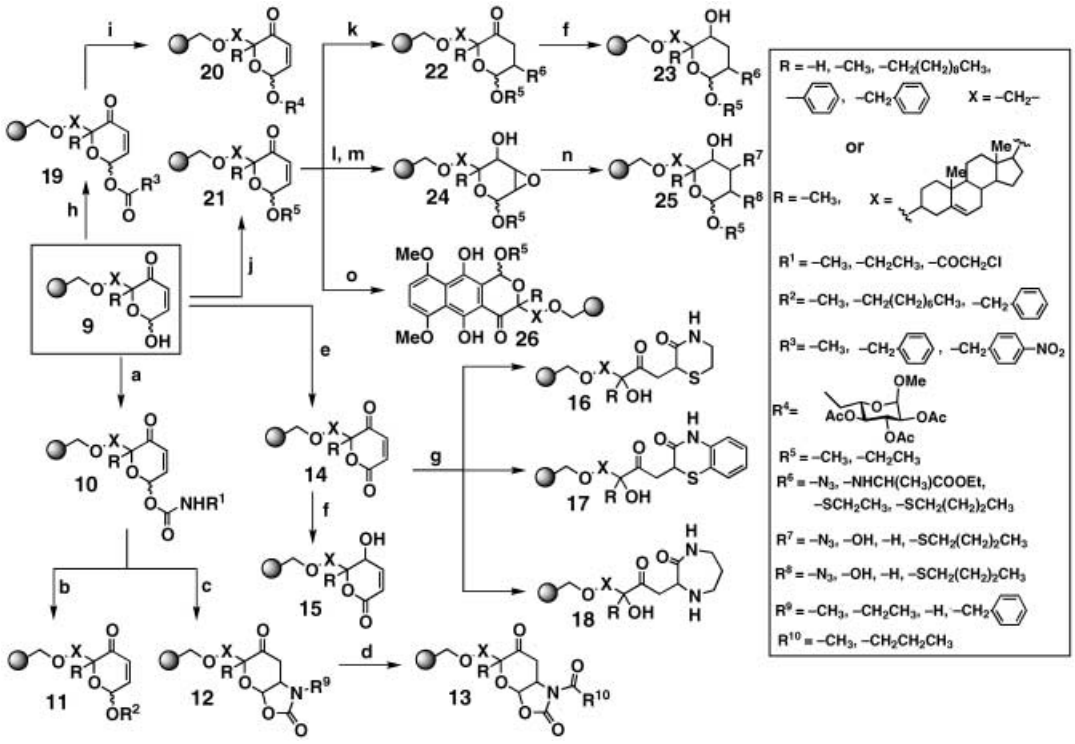
[1] a) L. A. Thomson, J. A. Ellman, *Chem. Rev.* **1996**, *96*, 555–600; b) J. S. Früchtel, G. Jung, *Angew. Chem.* **1996**, *108*, 19–46; *Angew. Chem. Int. Ed.* **1996**, *35*, 17–42; c) S. L. Schreiber, *Science* **2000**, *287*, 1964–1969; d) K. C. Nicolaou, R. Hanko, W. Hartwig, *Handbook of Combinatorial Chemistry*, Wiley-VCH, Weinheim, **2002**.

[2] a) R. E. Dolle, K. H. Nelson, Jr., *J. Comb. Chem.* **1999**, *1*, 235–282; b) R. E. Dolle, *J. Comb. Chem.* **2000**, *2*, 383–432.

[3] D. S. Tan, M. A. Foley, B. R. Stockwell, M. D. Shair, S. L. Schreiber, *J. Am. Chem. Soc.* **1999**, *121*, 9073–9087.

[4] a) K. C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature* **1997**, *387*, 268–272; b) K. C. Nicolaou, N. Winssinger, R. Hughes, C. Smethurst, Y. S. Cho, *Angew. Chem.* **2000**, *112*, 1126–1130; *Angew. Chem. Int. Ed.* **2000**, *39*, 1084–1088; c) K. C. Nicolaou, J. Pastor, N.

  0044-8249/02/11419-3831 $ 20.00+.50/0



Scheme 2. Construction of a library from **9**. Reagents and conditions: a) R^1NCO, Et_3N, 0→25 °C, 2 h; b) R^2OH, THF, cat. $HClO_4$ 70 %, 25 °C, 1 h; c) DBU, CH_2Cl_2, 25 °C, 12 h; d) for $R^9 = H$: $R^{10}COCl$, Et_3N, CH_2Cl_2, 25 °C, 6 h; e) Dess–Martin reagent, CH_2Cl_2, 25 °C, 12 h; f) $NaBH_4$, THF/H_2O 1:4, 25 °C, 0.5 h; g) binucleophile, CH_2Cl_2, 25 °C, 10 h; h) R^3COCl, Et_3N, 25 °C, 12 h; i) glycosyl donor, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 5 °C, 6 h; j) $CH(OR^5)_3$, $BF_3{\cdot}Et_2O$, THF, 0 °C, 1 h; k) R^6SH, Et_3N, CH_2Cl_2, 25 °C, 2 h or $NaN_{3(aq)}$, CH_3COOH, pH 5, 25 °C, 1 h; l) $NaBH_4$, THF/H_2O 1:4, 25 °C, 2 h; m) *m*CPBA, CH_2Cl_2, 25 °C, 6 h; n) nucleophile, CH_2Cl_2, 25 °C, 8 h; o) 4,7-dimethoxy-3-oxodihydroisobenzofuran-1-carbonitrile, LDA, THF, −78→0 °C, 4 h. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, *m*CPBA = *m*-chloroperoxybenzoic acid, LDA = lithium diisopropylamide.

Winssinger, F. Murphy, *J. Am. Chem. Soc.* **1998**, *120*, 5132 – 5133; d) D. Brohm, S. Metzger, A. Bhargava, O. Müller, F. Lieb, H. Waldmann, *Angew. Chem.* **2002**, *114*, 319 – 323; *Angew. Chem. Int. Ed.* **2002**, *41*, 307 – 311.

[5] a) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. Hirshfield, *J. Med. Chem.* **1988**, *31*, 2235 – 2246; b) J. S. Mason, I. Morize, P. R. Menard, D. L. Cheney, C. Hulme, R. F. Labaudiniere, *J. Med. Chem.* **1999**, *42*, 3251 – 3264, and references therein.

[6] J. M. Ostrech, G. M. Husar, S. E. Blondelle, B. Dörner, P. A. Weber, R. A. Houghten, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 11138 – 11142.

[7] For preparation of 2*H*-pyran-3(6*H*)-ones from furyl alcohols see: a) Y. Lefebvre, *Tetrahedron Lett.* **1972**, 133 – 136; b) O. Achmatowicz, Jr., P. Bukowski, B. Szechner, Z. Swiezchowska, A. Zamojski, *Tetrahedron* **1971**, 1973 – 1996; c) M. P. Georgiadis, E. A. Couladouros, *J. Org. Chem.* **1986**, *51*, 2725 – 2727.

[8] For some leading references see: a) R. Laliberte, G. Medawar, Y. Lefebvre, *J. Med. Chem.* **1973**, *16*, 1084; b) M. P. Georgiadis, E. A. Couladouros, A. K. Delitheos, *J. Pharm. Sci.* **1992**, *81*, 1126 – 1131; c) R. Tsang, B. Fraser-Reid, *J. Org. Chem.* **1992**, *57*, 1065 – 1067; d) M. A. Bates, P. G. Sammes, G. A. Thomson, *J. Chem. Soc. Perkin Trans. 1* **1988**, 3037; e) J. M. Harris, M. D. Keranen, G. A. O'Doherty, *J. Org. Chem.* **1999**, *64*, 2982 – 2983; f) N. Prevost, F. Rouessac, *Tetrahedron Lett.* **1997**, *38*, 4215 – 4218; g) S. F. Martin, D. E. Guinn, *J. Org. Chem.* **1987**, *52*, 5588 – 5593; h) M. Tsubuki, K. Kanai, H. Nagase, T. Honda, *Tetrahedron* **1999**, *55*, 2493 – 2514; i) M.-R. Brescia, Y. Class Shimshock, P. DeShong, *J. Org. Chem.* **1997**, *62*, 1257 – 1263; j) C. Neukom, D. P. Richardson, J. H. Myerson, P. A. Bartlett, *J. Am. Chem. Soc.* **1986**, *108*, 5559 – 5568; k) D. C. Billington, F. S. Perron, G. Atassi, A. Pierre, M. Burbridge, N. Guilbaud, Fr. Pat. 2733499 **1995**; for a general review see: l) N. L. Holder, *Chem. Rev.* **1982**, *82*, 287 – 332.

[9] a) T. L. Deegan, O. W. Gooding, S. Baudart, J. A. Porco, Jr., *Tetrahedron Lett.* **1997**, *38*, 4973 – 4976; b) K. Fukase, Y. Nakai, K. Egusa, J. A. Porco, Jr., S. Kusumoto, *Synthesis* **1999**, 1074 – 1078.

[10] M. P. Georgiadis, E. A. Couladouros, *J. Heterocycl. Chem.* **1990**, *27*, 1757 – 1760.

[11] C. D. Apostolopoulos, M. P. Georgiadis, E. A. Couladouros, *J. Heterocycl. Chem.* **1996**, *33*, 703 – 708.

[12] P. Shanmugam, V. Nair, *Synth. Commun.* **1996**, *26*, 3007 – 3008.

[13] This transformation has not been well investigated so far, see: a) B. Hoffmann, A. Schonebaum, H. Lacker, *Liebigs Ann. Chem.* **1993**, 333; b) K. Tatsuta, K. Akimoto, M. Annaka, Y. Ohno, M. Kinoshita, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1699.

  0044-8249/02/11419-3832 $ 20.00+.50/0