Carbohydrates

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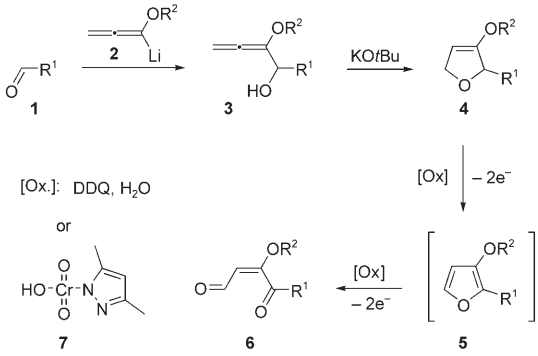
Oxidative Cleavage of 3-Alkoxy-2,5-dihydrofurans and its Application to the De Novo Synthesis of Rare Monosaccharides as Exemplified by L-Cymarose**

*Malte Brasholz and Hans-Ulrich Reissig**

Lithiated alkoxyallenes are very versatile C_3 building blocks and their numerous applications to organic and natural product synthesis have been reported.[1] Treatment of these nucleophiles with various electrophiles such as aldehydes, ketones, nitriles, and imines generated primary adducts of the alkoxyallenes, which serve as convenient precursors for many functionalized heterocycles.[2] As an example, the addition of lithiated alkoxyallenes to aldehydes and subsequent cyclization of the primary adducts lead to 3-alkoxy-2,5-dihydrofurans.[2a,b] Here we report the oxidative cleavage of these allene-based heterocycles to provide β-alkoxy-substituted α,β-unsaturated γ-keto aldehydes. This three-step protocol furnishes 1,4-dicarbonyl compounds, which are formally derived from hardly accessible 3-alkoxyfurans. Several of the products prepared by our method are equivalents of α,β-unsaturated keto sugars, which makes them ideal starting materials in the preparation of rare monosaccharides.

Reactions of lithiated alkoxyallenes **2** with aldehydes **1** yield primary adducts **3** which are cyclized with potassium *tert*-butoxide to afford 3-alkoxy-2,5-dihydrofurans **4** (Scheme 1).[2a] The one-step oxidative cleavage of these substrates can be performed under various conditions: Reaction of compounds **4** with two equivalents of DDQ[3] at room temperature in the presence of a proton source (water or alcohol) or by treatment with an excess of the complex formed between chromium trioxide and 3,5-dimethylpyrazole (**7**)[4] at −20 °C leads to the α,β-unsaturated γ-keto aldehydes **6**. These products can also be accessed by the oxidation of the corresponding 2-substituted 3-alkoxyfurans **5**, but preparation of compounds with this particular substitution pattern is quite difficult.[5] In our method, furans **5** are generated in situ[6] by aromatization of dihydrofurans **4**, thus circumventing their synthesis and isolation.[7,8]



Scheme 1. Preparation of α,β-unsaturated γ-keto aldehydes **6** from aldehydes **1** and lithiated alkoxyallenes **2** via 3-alkoxy-2,5-dihydrofurans **4**. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

To prove scope and limitations we oxidized a series of dihydrofurans **4** to dicarbonyl compounds **6**. Substrates **4**, which were prepared starting from chiral aldehydes **1**, were employed in these reactions as mixtures of diastereomers. Gratifyingly, simple aliphatic as well as highly functionalized substrates **4** were compatible with this process (Table 1). In general, the oxidation selectively yields *E*-configured products ($E/Z > 95:5$). The influence of the C-3 group on the reaction and the stability of products **6** was found by variation of the alkoxy substituent (**4a–c**). In the DDQ-mediated oxidation (Method **A**), substrates bearing a non-oxidizable methoxy substituent generally give the highest yields. Yields slightly decrease to 60% when the C-3 substituent is a benzyloxy or MOMO group. The yield of the oxidation product from substrate **4c** could be significantly improved by buffering the reaction mixture with pH 7 phosphate buffer (Method **B**).[9]) We attribute this finding to the acid-lability of the product **6c**. Furthermore, the proton source can be varied in the oxidation process. If methanol is used instead of water (Method **C**), dimethyl acetals **8** are obtained (**4a**→**8a** and **4h**→**8h**). As demonstrated by examples **4d–f**, our method is compatible with a number of common protective groups such as silyloxy, benzyloxy, and trityloxy groups. Even the acid-sensitive substrate **4g** protected with an *N*-*tert*-butoxycarbonyl (Boc) group could be transformed into **6g** in excellent yield. Methanol only had to be employed as the proton source in the case of dihydrofuran **4h** protected with a cyclohexylidene acetal group, since acetal cleavage and subsequent decomposition occurred in the presence of DDQ and water.[10]

An alternative to DDQ oxidation is the oxidation with the Cr^{IV}-based reagent 7 (Method **D**). As depicted in the conversions **4a**→**6a** and **4b**→**6b**, the yields are generally diminished. The analogous outcomes of the oxidation cascades with both DDQ and complex **7** was not anticipated. Complex **7** selectively oxidizes 2-substituted dihydrofuran **9**

[*] M. Brasholz, Prof. Dr. H.-U. Reissig
Institut für Chemie und Biochemie
Freie Universität Berlin
Takustrasse 3, 14195 Berlin (Germany)
Fax: (+49) 30-8385-5367
E-mail: hans.reissig@chemie.fu-berlin.de

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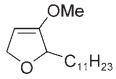
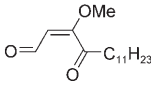
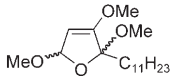
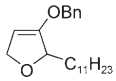
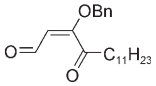
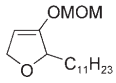
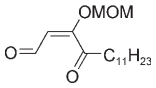
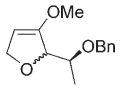
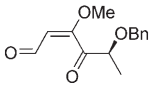
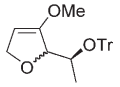
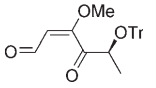
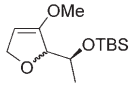
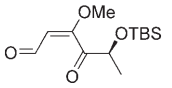
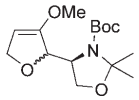
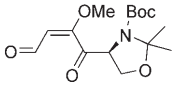
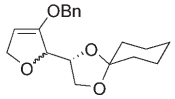
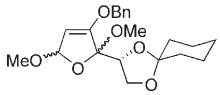
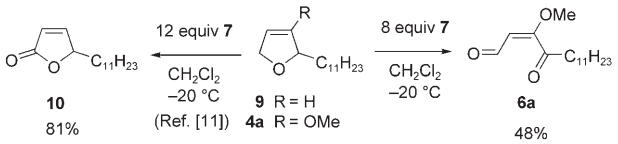
Table 1: Oxidative cleavage of 3-alkoxy-2,5-dihydrofurans **4** to α,β-unsaturated γ-keto aldehydes **6**.

	Substrate	Method[a]	Yield [%]		Product
4a		**A**	79	**6a**	
		D	48		
		C	62	**8a**	
4b		**A**	60	**6b**	
		D	50		
4c		**A**	42	**6c**	
		B	61		
4d		**A**	87	**6d**	
4e		**A**	83	**6e**	
4f[b]		**A**	72	**6f**	
4g		**A**	90	**6g**	
4h		**C**	65	**8h**	

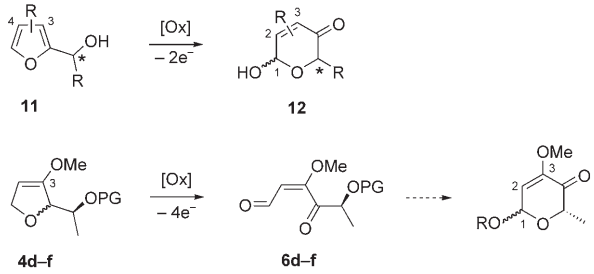
[a] **A**: 2 equiv DDQ, CH_2Cl_2/H_2O 20:1–15:1, RT, 2 h. **B**: 4 equiv DDQ, CH_2Cl_2/pH 7 buffer 10:1, 0 °C→RT, 1.5 h. **C**: 3–4 equiv DDQ, CH_2Cl_2/MeOH 15:1, RT, 4–6 h. **D**: 8 equiv CrO_3, 8 equiv 3,5-dimethylpyrazole, CH_2Cl_2, −20 °C, 2 h. [b] **4f** was prepared by cyclization of the primary adduct with $AgNO_3$ (see Ref. [13]). Bn = benzyl, MOM = methoxymethyl, Tr = triphenylmethyl (trityl), TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl.

to butenolide **10** (Scheme 2).[11] In contrast, the 2,3-disubstituted substrate **4a** does not undergo allylic oxidation but keto aldehyde **6a** is isolated as the sole product. Apparently, only **4a** aromatizes in the presence of **7** to the corresponding furan intermediate, which is then cleaved to the 1,4-dicarbonyl product **6a**, probably along the generally assumed reaction pathway.[12]



Scheme 2. Influence of the substitution pattern of 2,5-dihydrofurans in the oxidation with **7**.

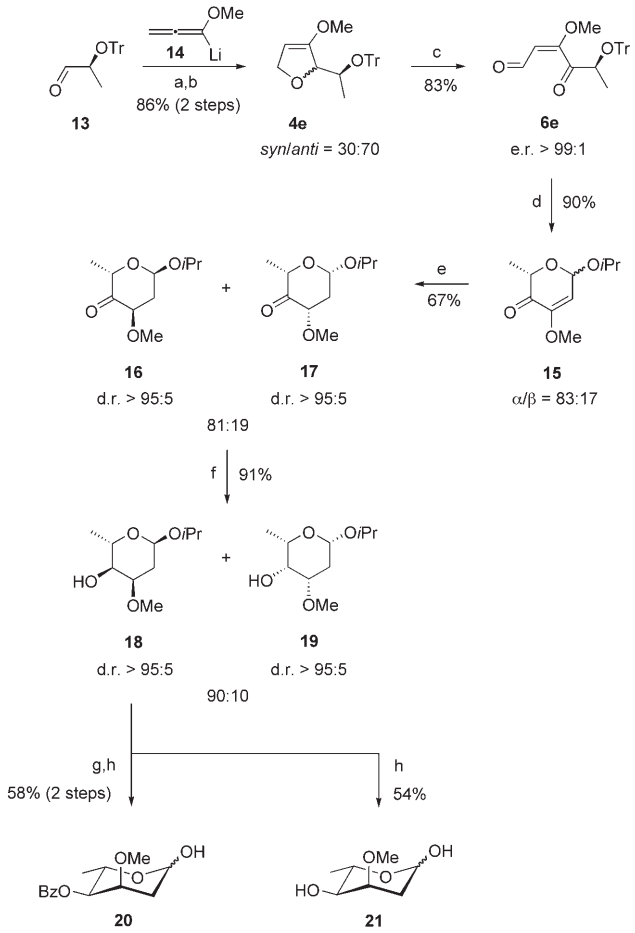
The 1,4-dicarbonyl compounds **6d–f** prepared by our method are structurally related to keto lactols **12**, which can be obtained from the Achmatowicz reaction of furyl alcohols **11**[14] (Scheme 3). This oxidative transformation is a convenient method for the synthesis of carbohydrate precursors. Even though various substituents in the 3- and 4-positions of the furan substrate **11** are tolerated, no examples of Achmatowicz reactions of 3-alkoxyfurans are documented. Generally, oxygenation is carried out at a later stage by functionalization of the double bond present in products **12**. However, the keto aldehydes **6d–f** already bear a methoxy substituent,



Scheme 3. Achmatowicz reaction (**11**→**12**) compared to oxidations **4d–f**→**6d–f**. PG = protecting group.

and are therefore ideal starting materials for the synthesis of 3-*O*-methylpyranoses.

We chose the rare 3-*O*-methyl-2,6-dideoxypyranose L-cymarose (**21**) as our target. Several structurally and biologically interesting antibiotics are glycosides of this deoxy sugar, such as the DNA helicase inhibitor heliquinomycin, whose total synthesis we are currently attempting.[15] We succeeded in the synthesis of L-cymarose (**21**) in only seven steps starting from *O*-trityl-protected lactaldehyde derivative **13**[16] (Scheme 4).



Scheme 4. Synthesis of L-cymarose (**21**). Conditions: a) 3 equiv **14**, Et_2O, −78 °C; b) 0.5 equiv KO*t*Bu, DMSO, 60 °C; c) 2 equiv DDQ, CH_2Cl_2/H_2O 20:1, RT; d) 0.3 equiv I_2, $HC(OiPr)_3$, *i*PrOH/CH_2Cl_2, 60 °C; e) 10 mol% Rh/Al_2O_3, 1 bar H_2, EtOAc, RT; f) $Li(sBu)_3BH$, THF, −78 °C, separation of diastereomers by column chromatography; g) BzCl, DMAP, pyridine, CH_2Cl_2, RT; h) 2 N aq. HCl, THF, RT. Bz = benzoyl, DMSO = dimethylsulfoxide, DMAP = *N*,*N*-dimethylaminopyridine.

Addition of lithiated methoxyallene **14** to aldehyde **13** and cyclization of the primary adduct with potassium *tert*-butoxide[2a] gave dihydrofuran **4e** in high yield (*syn*/*anti* = 30:70, 86% over 2 steps). Oxidation of **4e** with DDQ furnished keto aldehyde **6e** in high optical purity (e.r. > 99:1).[17] The trityl protecting group of **4e** was removed using 30 mol% iodine in 2-propanol[18] and concomitant cyclization cleanly led to isopropyl acetal **15** (α/β = 83:17). Reduction of the double bond of **15** was achieved after careful investigation of suitable reaction conditions. Gratifyingly, hydrogenation of **15** proceeded cleanly with 10 mol% rhodium on aluminum oxide and 1 bar of hydrogen pressure and led to isolation of the diastereomeric glycosides **16** and **17** in 67% combined yield (ratio 81:19). Both anomeric forms of **15** had been hydrogenated with complete diastereoselectivity, presumably under exclusive control by the isopropoxy group. The mixture of ketones **16** and **17** was then reduced with L-selectride, again with perfect stereocontrol, to give alcohols **18** and **19**. At this stage, the diastereomers could be readily separated by column chromatography (isolated in 90:10 ratio). Benzoylation of **18** followed by hydrolysis furnished benzoate **20**, which is a suitable precursor for glycosylations with L-cymarose. Alternatively, direct hydrolysis of **18** yielded the free L-cymarose (**21**; $[\alpha]_D^{22} = -49.8$, $c = 0.27$, H_2O, Ref. [19] −51.5, $c = 0.33$, H_2O). The overall yield for L-cymarose (**21**) was 19% over seven steps.[20,21]

We could demonstrate that the selective DDQ-mediated oxidation of alkoxyallene-based 2,5-dihydrofurans **4** efficiently leads to an interesting new class of 1,4-dicarbonyl compounds. The α,β-unsaturated γ-keto aldehydes **6** thus obtained are highly suitable intermediates in the synthesis of several classes of natural products, as exemplified by the preparation of the rare deoxy sugar L-cymarose (**21**). Further applications of this useful transformation of dihydrofurans may be the chain elongation of carbohydrates by three highly functionalized carbon atoms as well as the synthesis of new heterocyclic compounds. These areas are currently under investigation.

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[1] Reviews dealing with the chemistry of donor-substituted allenes: a) R. Zimmer, *Synthesis* **1993**, 165–178; b) R. Zimmer, H.-U. Reissig, *Modern Allene Chemistry*, *Vol. 1* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**, pp. 425–492; selected examples of the application of alkoxyallenes to natural product synthesis: c) G. Stork, E. Nakamura, *J. Am. Chem. Soc.* **1983**, *105*, 5510–5512; d) S. W. Goldstein, L. E. Overman, M. H. Rabinowitz, *J. Org. Chem.* **1992**, *57*, 1179–1190; e) O. Flögel, M. G. Okala Amombo, H.-U. Reissig, G. Zahn, I. Brüdgam, H. Hartl, *Chem. Eur. J.* **2003**, *9*, 1405–1415; f) S. Kaden, M. Brockmann, H.-U. Reissig, *Helv. Chim. Acta* **2005**, *88*, 1826–1838; g) S. Kaden, H.-U. Reissig, *Org. Lett.* **2006**, *8*, 4763–4766; h) M. A. Chowdhury, H.-U. Reissig, *Synlett* **2006**, 2383–2386.

[2] a) S. Hoff, L. Brandsma, J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609–619; b) S. Hormuth, H.-U. Reissig, *J. Org. Chem.* **1994**, *59*, 67–73; c) M. G. Okala Amombo, A. Hausherr, H.-U. Reissig, *Synlett* **1999**, 1871–1874; d) W. Schade, H.-U. Reissig, *Synlett* **1999**, 632–634; e) O. Flögel, J. Dash, I. Brüdgam, H. Hartl, H.-U. Reissig, *Chem. Eur. J.* **2004**, *10*, 4283–4290; f) M. Gwiazda, H.-U. Reissig, *Synlett* **2006**, 1683–1686.

[3] O. Flögel, H.-U. Reissig, *Eur. J. Org. Chem.* **2004**, 2797–2804.

[4] a) E. J. Corey, G. W. J. Fleet, *Tetrahedron Lett.* **1973**, 4499–4501; b) W. G. Salmond, M. A. Barta, J. L. Havens, *J. Org. Chem.* **1978**, *43*, 2057–2059.

[5] Synthesis of 3-methoxy-2-methylfuran: C. Meister, H.-D. Scharf, *Synthesis* **1981**, 737 – 739.
[6] a) **5** has transient character. When only one equivalent of DDQ is used in the oxidation, keto aldehyde **6** and dihydrofuran **4** are isolated in equal proportions. Attempts to trap species **5** in situ in the presence of various dienophiles were unsuccessful; b) the oxidative cleavage of 3-methoxy-2,5-diphenylfuran with DDQ has been described: S. Sayama, Y. Inamura, *Heterocycles* **1996**, *43*, 1371 – 1374.
[7] Attempts to directly convert dihydrofurans **4** into furans **5** were not successful under various conditions. If DDQ was employed in the absence of a proton source, no aromatization occurred but impure starting material was recovered. Likewise, MnO_2 at reflux failed to aromatize substrates **4**. Oxidation of **4a** with three equivalents of pyridinium chlorochromate (PCC) in pyridine/dichloromethane gave 15% **6a** along with 11% of the highly unstable corresponding furan.
[8] Reviews on Ag^I-and Cu^I-catalyzed cycloisomerizations of alkynes to furans proceeding via allene intermediates: R. C. D. Brown, *Angew. Chem.* **2005**, *117*, 872 – 874; *Angew. Chem. Int. Ed.* **2005**, *44*, 850 – 852.
[9] This method requires four equivalents of DDQ because of partial inactivation of the reagent.
[10] The hydrolysis of acetals with DDQ/H_2O has been described: K. Tanemura, T. Suzuki, T. Horaguchi, *J. Chem. Soc. Chem. Commun.* **1992**, 979 – 980.
[11] J. A. Marco, M. Carda, S. Rodríguez, E. Castillo, M. N. Kneeteman, *Tetrahedron* **2003**, *59*, 4085 – 4101.
[12] The cleavage of furan derivatives with PCC has been described and probably proceeds by a [4+3] cycloaddition of the chromium reagent with the furan followed by cycloreversion: a) G. Piancatelli, A. Scettri, M. D'Auria, *Tetrahedron Lett.* **1977**, 2199 – 2200; b) G. Piancatelli, A. Scettri, M. D'Auria, *Tetrahedron* **1980**, *36*, 661 – 663; c) R. Antonioletti, M. D'Auria, A. De Mico, G. Piancatelli, A. Scettri, *Synthesis* **1984**, 280 – 281.
[13] Cyclizations of allenic alcohols to 2,5-dihydrofurans with Ag^I salts: a) L.-I. Olsson, A. Claesson, *Synthesis* **1979**, 743 – 746; b) J. A. Marshall, X.-J. Wang, *J. Org. Chem.* **1990**, *55*, 2995 – 2996; cyclizations with Au^{III}: c) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537 – 2538.
[14] a) O. Achmatowicz, Jr., P. Bukowski, B. Szechner, Z. Zwierzchowska, A. Zamojski, *Tetrahedron* **1971**, *27*, 1973 – 1996; b) N. L. Holder, *Chem. Rev.* **1982**, *82*, 287 – 332.
[15] Isolation of heliquinomycin: a) M. Chino, K. Nishikawa, M. Umekita, C. Hayashi, T. Yamazaki, T. Tsuchida, T. Sawa, M. Hamada, T. Takeuchi, *J. Antibiot.* **1996**, *49*, 752 – 757; syntheses of several building blocks for heliquinomycin: b) M. Brasholz, H.-U. Reissig, *Synlett* **2004**, 2736 – 2738; c) M. Brasholz, X. Luan, H.-U. Reissig, *Synthesis* **2005**, 3571 – 3580; d) S. Sörgel, C. Azap, H.-U. Reissig, *Eur. J. Org. Chem.* **2006**, 4405 – 4418; e) S. Sörgel, C. Azap, H.-U. Reissig, *Org. Lett.* **2006**, *8*, 4875 – 4878; further examples of cymarose glycosides: the glaucoside family: f) T. Nagawa, K. Hayashi, K. Wada, H. Mitsuhashi, *Tetrahedron* **1983**, *39*, 606 – 612; g) K. Y. Lee, S. H. Sung, Y. C. Kim, *Helv. Chim. Acta* **2003**, *86*, 474 – 483; cynanoside C: h) H. Bai, W. Li, K. Koike, T. Satou, Y. Chen, T. Nikaido, *Tetrahedron* **2005**, *61*, 5797 – 5811.
[16] K. Mori, H. Kikuchi, *Liebigs Ann. Chem.* **1989**, 963 – 967.
[17] The e.r. value was determined by HPLC on a chiral stationary phase (Chiralpak AD, Daicel Chemical Industries Ltd.) by comparison with a racemic reference sample.
[18] J. L. Wahlstrom, R. C. Ronald, *J. Org. Chem.* **1998**, *63*, 6021 – 6022.
[19] K. Toshima, T. Yoshida, S. Mukaiyama, K. Tatsuta, *Carbohydr. Res.* **1991**, *222*, 173 – 188.
[20] This represents the shortest stereoselective synthesis of L-cymarose known to date and the only one starting from non-carbohydrate material; known syntheses: a) J. S. Brimacombe, R. Hanna, M. S. Saeed, L. C. N. Tucker, *J. Chem. Soc. Perkin Trans. 1* **1982**, 2583 – 2587, 5 steps starting from methyl 2,3-*O*-benzylidene-α-L-rhamnopyranoside; b) Ref. [19], 14 steps starting from methyl α-L-glucopyranoside; synthesis of L-oleandrose with L-cymarose as a side product: c) S. V. Ley, A. Armstrong, D. Díez-Martin, M. J. Ford, P. Grice, J. G. Knight, H. C. Kolb, A. Madin, C. A. Marby, S. Mukherjee, A. N. Shaw, A. M. Z. Slawin, S. Vile, A. D. White, D. J. Williams, M. Woods, *J. Chem. Soc. Perkin Trans. 1* **1991**, 667 – 692, 8 steps starting from a lactaldehyde derivative.
[21] Review on the syntheses of deoxy sugars: A. Kirschning, M. Jesberger, K.-U. Schöning, *Synthesis* **2001**, 507 – 540.

