Polymer-Supported Bisacetoxybromate(I) Anion – An Efficient Co-Oxidant in the TEMPO-Mediated Oxidation of Primary and Secondary Alcohols

Marco Brünjes,[a] Georgia Sourkouni-Argirusi,[b] Andreas Kirschning[a,*]

[a] Institut für Organische Chemie, Universität Hannover, Schneiderberg 1B, 30167 Hannover, Germany
Fax: +49 511 762–3011, e-mail: andreas.kirschning@oci.uni-hannover.de
[b] Institut für Organische Chemie, TU Clausthal, Leibnizstr. 6, 38678 Clausthal-Zellerfeld, Germany

Received: December 28, 2002; Accepted: February 8, 2003

Dedicated Prof. Dr. Peter Welzel (Leipzig) on the occasion of his 65th birthday.

Abstract: A polymer-bound reagent for the efficient oxidation of primary alcohols to aldehydes and secondary alcohols to ketones in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyl-oxyl (TEMPO) is described. The oxidation process is particular mild and allows one to prepare aldehydes with α-chirality without racemization. This also includes the synthesis of α-aminoaldehydes. In most cases, work-up of this heavy metal-free oxidation is achieved by simple filtration followed by removal of the solvent. Insight into the role of the bromate(I) anion in the oxidation process was gained from the TEMPO-mediated oxidation of benzaldehyde in the presence of the hypochlorite anion loaded on an anion exchange resin.

Keywords: aldehyde; aminoaldehyde; oxidation; polymer-bound reagent; radical reaction

Introduction

In view of the dramatic developments in the need for compound libraries in pharmaceutical and agrochemical research, polymer-supported reagents have seen renewed interest lately and have become a widely recognized synthetic technique.[1] The intrinsic advantage of this hybrid solid/solution phase technique lies in the simple purification and the possibility to use these reagents in excess to drive reactions in solution to completion. Furthermore, they may be adapted to continuous flow processes and hence are useful for automated synthesis.[2,3]

Oxidation of alcohols is a process which has been achieved with various polymer-bound reagents.[1] Commonly, functionalized polymers were developed that are functionalized with heavy metals such as CrO_3,[4] $Cr_2O_7^{2-}$,[5] $ClCrO_3^-$,[6] $HCrO_4^-$,[6a,7] MnO_4^-,[8] and RuO_4^-[9] ions.[10] In most cases, these oxidants are attached *via* different *N*-heterocycles or simple quaternary ammonium cations to the polymeric backbone. Recently, Kita and coworkers reported on polymer-bound (diacetoxy)iodobenzene which, in the presence of a catalytic amount of bromide, is an efficient oxidant for the transformation of secondary alcohols into ketones. Furthermore, it was shown that this reagent system oxidizes primary alcohols to the corresponding carboxylic acids.[11]

The use of *N*-oxoammonium ions like 2,2,6,6-tetramethylpiperidine-1-oxonium **2** and the stable free nitroxyl radical precursor **1** (TEMPO) are an alternative to metal-based oxidants (Figure 1).[12] *N*-Oxoammonium ions **2** can be applied stoichiometrically or more conveniently catalytically in combination with a co-oxidant. The oxoammonium ion itself is transformed into the secondary hydroxylamine **3** during that process, but it is reoxidized by the co-oxidant in the following steps. Numerous such co-oxidants are known. They include halogen-based oxidants,[13] peroxide-derived oxidants[14] and electrochemical methods.[15] Rychnovsky and coworkers postulated that when the TEMPO-catalyzed oxidation of alcohols is carried out in the presence of *m*-CPBA and halide ions, hypobromite was the effective oxidant which oxidizes the nitroxyl radical **1** to the *N*-oxoammonium ion **2**.[14d] In addition, it was shown that TEMPO-catalyzed oxidations can be performed on a large industrial scale.[16] The excellent activity and selectivity of *N*-oxoammonium ions in oxidation reactions led to the development of polymer-assisted strategies. One option is the immobilization of *N*-oxoammonium ions to a solid phase and stoichiometric employment in the presence of the alcohol or catalytically and use of an stoichiometric co-oxidant in solution. Polymer-supported nitroxyl radicals have widely been applied as catalysts in oxidation reactions.[17,18] However, Bolm and coworkers[19] were the first to utilize the power of these immobilized oxidants

 DOI: 10.1002/adsc.200202208

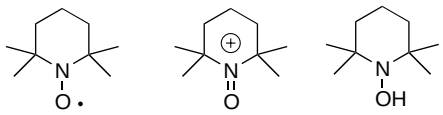


Figure 1. Species relevant in TEMPO-mediated oxidations.

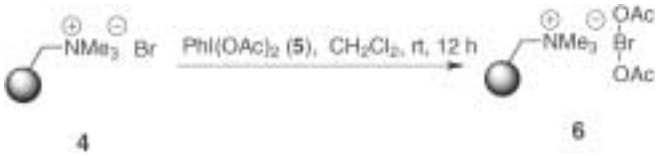
in the oxidation of complex and delicate alcohols.[20] They attached TEMPO to a silica support and employed the material under Anelli's and Montanari's conditions.[13a, b]

In a reversed mode of application a catalytic amount of soluble TEMPO is reoxidized by a stoichiometrically immobilized co-oxidant. This technique has one major advantage as it avoids minimum contamination of the reaction mixture. Here, the stoichiometrically used reagent is loaded onto the polymer so that no phase separation and extraction is necessary for work-up. This strategy is particularly appealing if the co-oxidant can easily be regenerated. Recently, we communicated on the use of the polymer-supported bisacetoxybromate(I) anion **6**.[21,22] Among the different modes of attachment of active species to a polymer, ion exchange is probably best suited for regeneration. In this report, we give a detailed account on this reagent system which includes its scopes and limitations.

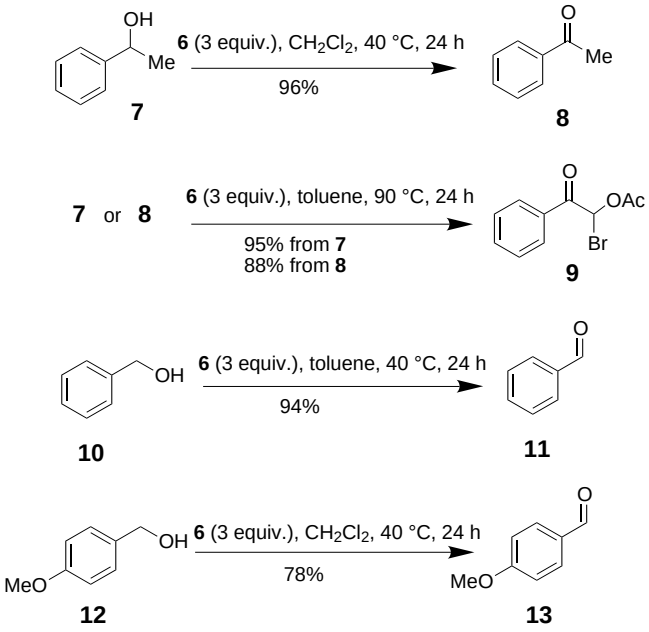
Results and Discussions

In accordance with our related work on haloate(I) complexes,[23] anion **6** can be prepared by oxidative ligand transfer from bisacetoxyiodobenzene **5** onto anion exchange resin (IRA-900: bromide form) **4** (Scheme 1).

Electrophilic bromate(I)-complex **6** alone is not an efficient oxidant for most alcohols. It works solely with activated alcohols such as 1-phenyl-ethanol **7** affording high yields of acetophenone **8** at 40 °C (Scheme 2). The oxidative properties of functionalized polymer **6** are highly dependent on the reaction conditions. Thus, when the solvent was changed to toluene and the temperature was raised to 90 °C α-acetoxy-α-bromo ketone **9** became the major product. Presumably, ketone **9** was generated from alcohol **7** by double electrophilic bromination followed by nucleophilic displacement of one bromine atom by the acetate ion. This hypothesis was proven



Scheme 1. Preparation of polymer-bound bromate(I) complex **6**.

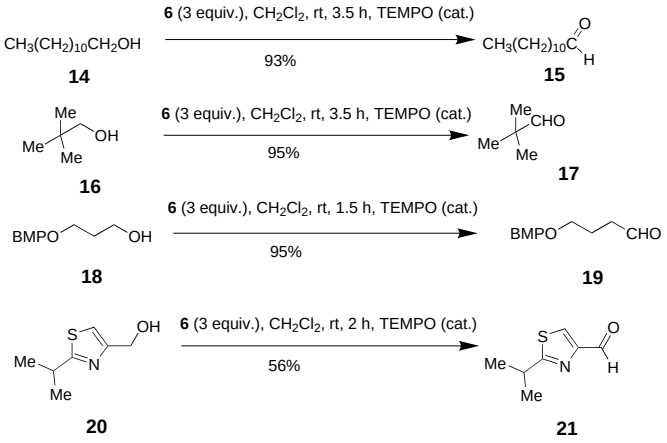


Scheme 2. TEMPO-free oxidations with bromate(I) complex **6**.

when acetophenone **8** was subjected to the same reaction conditions thus furnishing ketone **9** with similar yield. Under these uncatalyzed conditions also benzyl alcohols **10** and **12** were converted into the corresponding aldehydes **11** and **13**. Apart from these selected examples, bromate(I) complex **6** is not broadly applicable for the oxidation of alcohols. Cyclohexanol was unreactive under the reaction conditions depicted in Scheme 2. Indeed, earlier we showed that reagent **6** and its soluble analogue is well suited for 1,2-haloacetoxylation of alkenes under very mild conditions.[23a, c,24]

However, addition of a catalytic amount of the nitroxyl radical **1** (0.5 – 1 mol %) to the reaction mixture led to a dramatic acceleration of the oxidation process (Schemes 3 – 6). For example, benzyl alcohol **10** is converted at room temperature into benzaldehyde **11** (94%) within 1 h using the reagent system TEMPO **1** and functionalized polymer **6**. Similarly, primary alcohols **14**, **16** and **18** afforded aldehydes **15**, **17** and **19** in excellent yields. Quantitative transformation of alcohols are achieved both in dichloromethane as well as in toluene. Considering that a polymer-bound reagent is employed, the reactions proceed rather rapidly. Importantly, overoxidation is not observed. The reaction is terminated by filtration and removal of the solvent. In solution acetic acid may be present as a by-product which either can be scavenged by addition of the weakly basic resin Amberlite A-21 or by removal of the solvent in high vacuum.[25]

In an attempt to prepare (–)-cystothiazol E,[26] it became necessary to synthesize 2-isopropylthiazole-4-carbaldehyde **21** by oxidation of the corresponding alcohol **20**. Under the usual reaction conditions we did



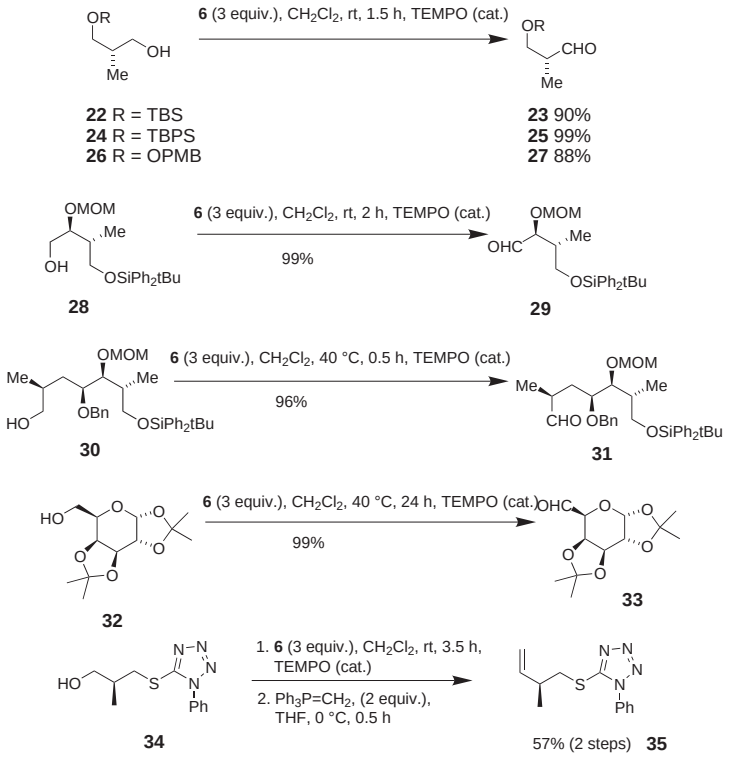
Scheme 3. TEMPO-mediated oxidations of primary alcohols.

not observe any oxidation of the sulfur atom. In direct comparison with existing methods[27] the isolated yield of aldehyde **21** was satisfying after chromatographic purification.

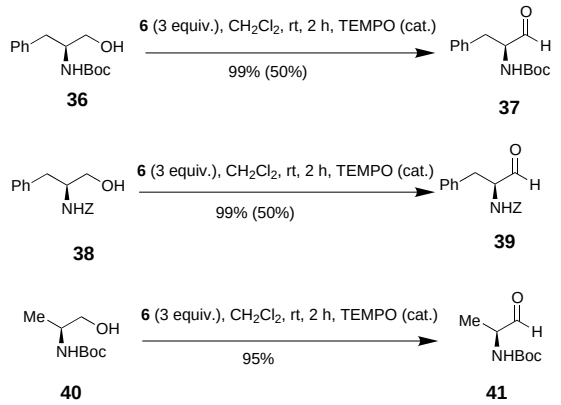
Aldehydes with a stereogenic center in the α-position are also smoothly generated without racemization of the chiral center (Scheme 4). In contrast to this observation, we found that silyl-protected aldehyde **25** undergoes partial racemization when prepared from alcohol **24** by the Swern oxidation. In addition, the examples depicted in Scheme 4 demonstrate that this oxidation method is compatible with diverse other functional groups. Common protecting groups for alcohols such as acetals, benzyl and silyl ethers are stable under the conditions employed. The compatibility with other functional groups is also demonstrated in the oxidative transformation of alcohol **34** which contains a thioether substituent of the tetrazole heterocycle. This moiety is a suitable precursor of the Kocieński variant of the Julia olefination.[28] After Wittig homologation of the crude aldehyde alkene **35** was obtained in good yield.[29]

Protected aminoaldehydes are particularly versatile for preparing β-amino acids and alkaloids. For their preparation solid phase assisted oxidation of the corresponding aminoalcohol is particularly helpful, as work-up of these labile aldehydes which are prone to racemization can be carried out very rapidly. In our case, Boc- and Z-protected aminoalcohols **36**, **38** and **40** were consumed within two hours to yield the α-amino-aldehydes **37**, **39** and **41**. For most of these transformations there is no need for a final purification due to the negligible contamination with TEMPO. Further chromatographic purification (Scheme 5, reduced yields in parenthesis after chromatographic isolation due to lability of aldehyde) inevitably lead to a dramatically reduced yield. Unfortunately *N*,*N*-dialkylated amino-alcohols seem to be inapplicable for this method due to complete decomposition of the starting material within 15 minutes.[30]

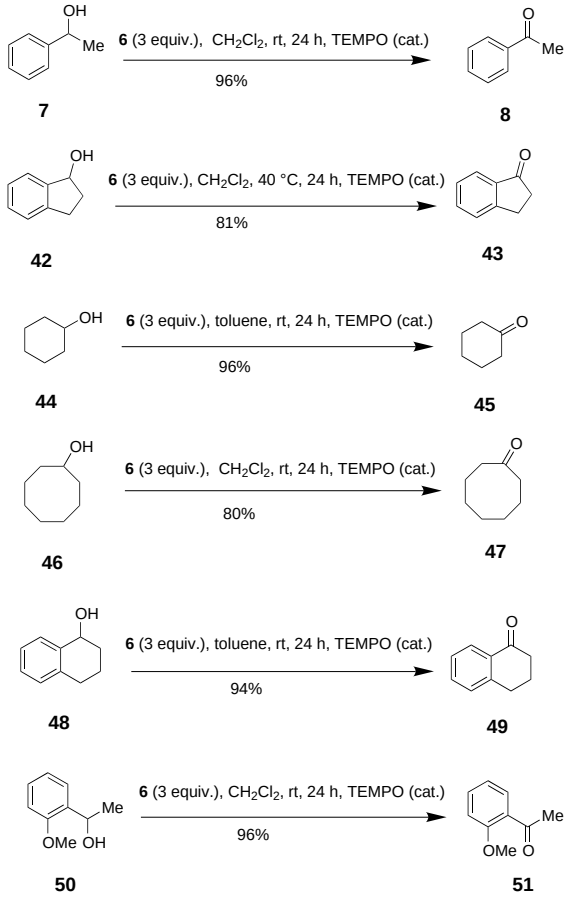
Finally, this reagent system allows one to oxidize secondary aryl-substituted as well as aliphatic alcohols



Scheme 4. TEMPO-mediated oxidation of primary alcohols with a stereogenic center in the α-position.

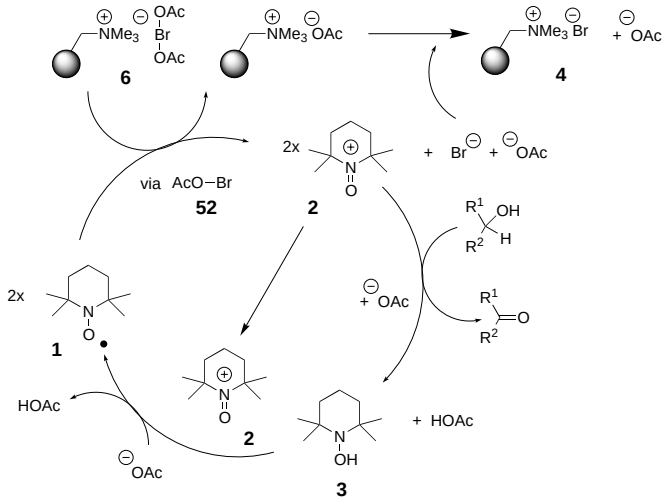


Scheme 5. TEMPO-mediated oxidation of α-aminoalcohols.



Scheme 6. TEMPO-mediated oxidation of secondary alcohols.

7, **42**, **44**, **46**, **48** and **50** with similar efficiency compared to primary alcohols. Due to the reduced activity, oxidation of secondary alcohols took longer compared to primary alcohols. At this point it is not clear why the conditions for oxidizing acetophenone **7** in the absence (refer to Scheme 2) or in the presence of TEMPO (Scheme 6) are comparable. However, these transformations are noteworthy because not many versatile

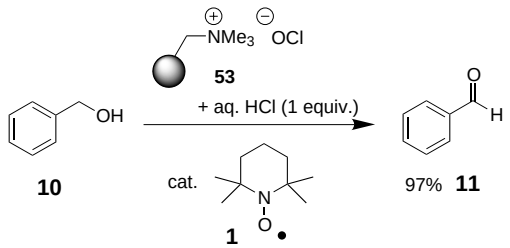


Scheme 7. Proposed mechanism of TEMPO-mediated oxidation of alcohols using polymer-bound bromate(I) complex **6** as co-oxidant.

oxidants for secondary alcohols which are attached to a solid phase have been reported. For example, we found that although chromium(VI)-based polymer-bound-reagents[6a,7,21] are strong oxidants with comparable reactivity to our reagent system, the polystyrene-based versions tend to decompose which results in substantial contamination of the solution and difficulties during the filtration. On the other hand, immobilization of the permanganate(VII) anion to exchange resins[8,21] leads to an oxidant which allows one to transform allylic and benzylic alcohols to the corresponding aldehydes but fails to effectively oxidize secondary alcohols.

A possible mechanism of this process is depicted in Scheme 7. The bisacetoxybromate(I) anion **6** or hypobromite **52** which may be formed upon fragmentation of **6** initiates the process by oxidation of two equivalents of TEMPO **1** to the active catalyst the *N*-oxoammonium ion **2**.[31] One equivalent of the latter species is responsible for the oxidation of the hydroxy group. Thereby, hydroxylamine **3** is formed as by-product. Finally, rapid *syn* proportionation between the oxoammonium salt **2** and hydroxylamine **3** occurs to give two nitroxyl radicals **1**.

At this point we searched for primary evidence that the polymer-bound bromate anion **6** is not the active co-oxidant for TEMPO but rather the acylated hypobromite **52**. We reckoned that it is slowly released from the ion exchange resin into solution prior to oxidation of reagent **1**. For obtaining indirect evidence, we immobilized hypochlorite anion by ion exchange to yield functionalized resin **53**.[32] Hypochlorite is a well established co-oxidant for the catalytic use of TEMPO in alcohol oxidations.[12] However, in this context functionalized resin **53** was inactive. Likewise, the corresponding ion exchange resin which was loaded with the hypobromite anion did not induce TEMPO-catalyzed oxidation



Scheme 8. TEMPO-mediated oxidation of alcohols using polymer-bound hypochlorite **53** as co-oxidant in the presence of a proton source.

either. Only when one equivalent of acid (6 M aqueous HCl or 60 mM HCl in wet CH_2Cl_2) was added did we observe rapid oxidation of benzyl alcohol **10** to benzaldehyde **11** in the presence of TEMPO. Addition of a proton source results in release of hypochloric acid into solution where it initiates oxidation of TEMPO to the oxonium ion **2**. Similar to the TEMPO-catalyzed oxidation of alcohols mediated by hypochlorite as co-oxidant it was necessary to add a minimum amount of water (wet CH_2Cl_2) to the reaction medium when employing polymer-attached hypochlorite. Based on these observations, it is reasonable to assume that these immobilized anions are not able to oxidize TEMPO **1**. Instead, neutral co-oxidants in solution are required to initiate the catalytic cycle.

Conclusion

In summary, we have developed a new polymer-bound non-heavy metal-based oxidant. In the presence of a catalytic amount of TEMPO it is a powerful reagent for the oxidation of primary and secondary alcohols. In view of the easy recycability of the co-oxidant and the purity of the products this procedure may find application in large-scale processes of industrial relevance. In this context however, more atom-efficient and cheaper co-oxidants such as resin **53** need to be investigated in greater detail.

Experimental Section

General Remarks and Starting Materials

^1H and ^{13}C NMR spectra were measured on DPX 200 (Bruker) with 200 MHz (50 MHz) and AM-400, ARX 400 (Bruker) 400 MHz (100 MHz), respectively, using tetramethylsilane as the internal standard. $CDCl_3$ is the solvent for all NMR experiments. Mass spectra were recorded on a type LCT-spectrometer (Micromass). Optical rotations [α] were collected on a Polarimeter 341 (Perkin Elmer) at a wavelength of 589 nm. All solvents used were of reagent grade and were further dried. Reactions were monitored by TLC on silica gel 60_{P254} and detected either by UV-absorption or by staining with H_2SO_4/4-methoxybenzaldehyde in ethanol. Where necessary, flash column chromatography was performed on silica gel 60 (230–400 mesh). Except for alcohols **18**, **20**, **22**, **24**, **26**, **28**, **30**, **34**, **36**, and **38** all starting compounds are commercially available. Alcohols **22**, **24**, and **26** were prepared from commercial (2*R*)-3-hydroxy-2-methylpropionic methyl ester by standard protection of the alcohol group and dibal-promoted reduction of the ester functionality under standard conditions. In a similar manner, aminoalcohols **36**, **38** and **40** were prepared from the corresponding amino acid esters. Alternatively, alcohols **36** (Acros) and **38** (Fluka) are commercially available. Polymer-bound bromide **4** was purchased from Fluka (3.5 mmol/g bromide). Recycling of used polymer was achieved by treatment with aqueous HBr for 1 h at room temperature. Aldehydes and ketones **8**, **11**, **13**, **15**, **17**, **43**, **45**, **47**, **49** and **51** are known and are commercially available. The spectroscopic and physical data of aldehydes and ketones **19**,[33] **21**,[36] **23**,[34] **37**,[37] **39**[38] and **41**[39] are listed in the literature.

Preparation of Bisacetoxybromate(I) Resin 6

A suspension of polymer-bound halide **4** (available from Fluka; 3.5 g/mmol bromide) and $PhI(OAc)_2$ 5 (1.8 equivs.) in dry CH_2Cl_2 (2.5 mL/mmol halide anion) under nitrogen was shaken at 300 rpm for 12 h at room temperature. The yellowish suspension was protected from light. Filtration and washing of the resin with CH_2Cl_2 (3 $\times$) and drying under vacuum afforded the light yellow reagent. The functionalized resin can be stored under nitrogen at $-20\,^\circ C$ for 6 months without loss of activity.

General Procedure for the Oxidation of Alcohols

A mixture of the alcohol (1 equiv.) resin **6** (typically 3 theoretical equivalents based on the loading given by the commercial provider) in dry CH_2Cl_2 (2.5 mL/mmol bromide) with optional (refer to Schemes) 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) under nitrogen was shaken at 300 rpm. The reaction temperature (room temperature, $40\,^\circ C$ or $90\,^\circ C$) varied according to the choice of alcohol. Completion of the reaction was monitored by TLC. Filtration terminated the reaction. The resin was washed with CH_2Cl_2 (3 $\times$) and the combined organic washings and filtrate were concentrated under reduced pressure. Typically, further purification steps were unnecessary ($>95\%$ purity) and the carbonyl compounds could directly be employed for the next step. Still, for generating analytically pure samples and in order to remove oligomeric impurities from the resin purification by flash column chromatography was carried out in some cases. We found that these oligomeric impurities commonly arose when charges of the commercial resins were employed for the first time. After regeneration and reuse we typically did not note this phenomenon.

Acetic Acid 1-Bromo-2-oxo-2-phenylethyl Ester (9)

By treatment of 1-phenylethanol **7** (61.1 mg, 0.5 mmol) with reagent **6** in toluene at $90\,^\circ C$ for 24 h the title compound **9** (123 mg, 0.48 mmol, 95%) was prepared. Under these conditions, conversion of **7** was quantitative. Final purification was

achieved by flash column chromatography (petroleum ether/ethyl acetate 7:1). Colorless crystals; mp 50 °C; IR (KBr): ν = 694, 773, 899, 957, 1017, 1053, 1103, 1201, 1229, 1381, 1452, 1597, 1710, 1748, 1765, 2953 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.25 – 7.25 (m, 5H), 7.6 (s, 1H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 188.7 (s), 168.6 (s), 134.2 (d), 133.1 (s), 128.8 (d), 128.7 (d), 86.2 (d), 20.6 (q); anal. calcd. for $C_{10}H_9BrO_3$: C 46.72, H 3.53, Br 31.08; found: C 46.55, H 3.57, Br 30.78.

Likewise, acetophenone **8** (60 mg, 0.5 mmol) was used to prepare the title compound **9** (114 mg, 0.44 mmol, 88%) according the procedure described above.

(2*R*)-3-(*tert*-Butyldiphenylsiloxy)-2-methyl-1-propanal (25)

By treatment of (2*S*)-3-(*tert*-butyldiphenylsiloxy)-2-methyl-1-propanol **24** (65.6 mg, 0.2 mmol) with reagent **6** and TEMPO in CH_2Cl_2 at room temperature for 1.5 h the title compound **25** was prepared; yield: 65 mg (0.2 mmol, 99%); oil; $[\alpha]_D^{23}$: − 24° ($CHCl_3$, *c* 1); IR (film): ν = 428, 613, 702, 740, 823, 937, 1035, 1112, 1391, 1427, 1472, 1736, 2858, 2932, 3071, 3384 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.76 (d, 1H, *J* = 1.6 Hz), 7.7 – 7.35 (m, 10H), 3.90 (dd, 2H, *J* = 5.2 Hz, 10.4 Hz), 3.85 (dd, 1H, *J* = 6.2 Hz, 10.4 Hz), 2.57 (dddq, 1H, *J* = 1.6 Hz, 5.2 Hz, 6.2 Hz, 7.0 Hz), 1.10 (d, 3H, *J* = 7.0 Hz), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$): δ = 204.5 (d), 135.5 (d), 133.1 (s), 129.7 (d), 127.7 (d) 64.0 (t), 48.7 (d), 26.7 (q), 19.1 (s), 10.2 (q); anal. calcd. for $C_{20}H_{26}O_2Si$: C 73.57, H 8.03; found: C 73.76, H 8.07.

(2*R*)-3-(4-Methoxybenzyloxy)-2-methyl-1-propanal (27)

By treatment of (2*S*)-3-(4-methoxybenzyloxy)-2-methyl-1-propanol **26** (39 mg, 0.185 mmol) with reagent **6** and TEMPO in CH_2Cl_2 for 1.5 h the title compound **27** was prepared; yield: 34 mg (0.163 mmol, 88%); oil; $[\alpha]_D^{20}$: − 33° ($CHCl_3$, *c* 1); ^1H NMR ($CDCl_3$): δ = 9.64 (d, 1H, *J* = 1.5 Hz, 1-H), 7.16, 6.80 (2× m, 2× 2H, H-aromat.), 4.38 (s, 2H, C*H*$_2$PhOMe), 3.73 (s, 3H, OMe), 3.58 (dd, 1H, *J* = 9.3, 6.7 Hz, 3-H), 3.53 (dd, 1H, *J* = 9.3, 5.3 Hz, 3-H'), 2.58 (m, 1H, 2-H), 1.05 (d, 3H, *J* = 7.2 Hz, 2-Me); ^{13}C NMR ($CDCl_3$): δ = 203.9 (d), 159.2 (s), 129.9 (s), 2× 129.2 and 2× 113.8 (4× d), 72.9 (t), 69.8 (t), 55.2 (q), 46.7 (d), 10.7 (q). For additional spectroscopic and physical data refer to ref.[35]

(2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2-(methoxymethoxyl)-3-methyl-1-butanal (29)

By treatment of (2*S,3R*)-4-(*tert*-butyldiphenylsiloxy)-2-(methoxymethoxyl)-3-methyl-1-butanol **28** (40.2 mg, 0.1 mmol) with reagent **6** and TEMPO in CH_2Cl_2 at room temperature for 2 h the title compound 29 was prepared; yield: 40 mg (0.1 mmol, 99%); oil; $[\alpha]_D^{23}$: − 6° ($CHCl_3$, *c* 1); IR (film): ν = 449, 613, 703, 741, 823, 919, 1036, 1111, 1154, 1215, 1390, 1428, 1472, 1732, 2932 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.74 (d, 1H, *J* = 1.6 Hz), 7.70 – 7.33 (m, 10H), 4.72 and 4.70 (2d, 2H), 4.22 (dd, 1H, *J* = 1.2 Hz, 3.8 Hz), 3.64 (ddd, 1H, *J* = 5.6 Hz, 10.0 Hz), 3.60 (dd, 1H, *J* = 7.8 Hz, 10.0 Hz), 3.40 (s, 3H), 2.22 (m, 1H), 1.05 (s, 9H), 0.86 (d, 1H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 203.7 (d), 135.5 (d), 133.3 (s), 129.7 (d), 127.6 (d), 97.1 (t), 82.6 (d), 64.4 (t), 55.9 (q), 37.9 (d), 26.7 (q), 19.1 (s), 10.9 (q); anal. calcd. for $C_{23}H_{32}O_4Si$: C 68.96, H 8.05; found: C 68.77, H 8.11.

(2*R*,3*S*,4*S*,6*S*)-4-Benzyloxy-7-(*tert*-butyldiphenylsiloxy)-2,6-dimethyl-5-methoxymethoxyheptanal (31)

By treatment of heptanol **30** (0.56 g, 1.0 mmol) with reagent **6** and TEMPO in CH_2Cl_2 at 40 °C for 0.5 h the title compound **31** was prepared; yield: 0.540 g (0.96 mmol, 96%); oil; ^1H NMR ($CDCl_3$): δ = 9.5 (d, 1H, *J* = 2.2 Hz), 7.69 – 7.61 (m, 4H), 7.45 – 7.23 (m, 11H), 4.71 and 4.66 (2d, 2H, *J*=6.6 Hz), 4.68 and 4.42 (2d, 2H, *J*=11.7 Hz), 3.85 (dd, 1H, *J* = 3.2 Hz, 6.5 Hz), 3.67 (dd, 1H, *J* = 7.5 Hz, 10.0 Hz), 3.56 (ddd, 1H, *J* = 2.7 Hz, 6.5 Hz, 10.1 Hz), 3.48 (dd, 1H, *J*=6.5 Hz, 10.0 Hz), 2.43 (dddq, 1H, *J*=2.2 Hz, 6.4 Hz, 7.0 Hz, 7.4 Hz), 1.94 (dddq, 1H, *J*=3.2 Hz, 6.5 Hz, 6.7 Hz, 7.5 Hz), 1.87 (ddd, 1H, *J*=6.4 Hz, 10.1 Hz, 14.8 Hz), 1.47 (ddd, 1H, *J*=2.7 Hz, 7.4 Hz, 14.2 Hz), 1.05 (s, 9H), 0.99 (d, 3H, *J*=0.7 Hz), 0.92 (d, 3H, *J*=6.7 Hz); ^{13}C NMR ($CDCl_3$): δ = 204.6 (d), 138.0 (s), 2× 129.6 (d), 128.3, 2× 128.1, 5× 127.6 (d), 98.2 (t), 78.8, 78.3 (d), 72.7 (t), 66.4 (t), 55.9 (d), 44.0 (d), 36.7 (d), 32.7 (d), 26.9 (d), 19.2 (s), 13.6 (d), 11.6(d); anal. calcd. for $C_{34}H_{46}O_5Si$: C 72.56, H 8.24; found: C 72.45, H 8.31.

1,2:3,4-Di-*O*-isopropylidene-6-oxo-α-D-galactopyranose (33)

By treatment of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **32** (130 mg, 0.5 mmol) with reagent **6** and TEMPO in CH_2Cl_2 at 40 °C for 24 h the title compound **33** was prepared; yield: 129 mg (0.49 mmol, 99%); ^1H NMR ($CDCl_3$): δ = 9.63 (s, 1H) 5.67 (d, 1H, *J* = 5.0 Hz), 4.65 (2dd, 2H, *J* = 2.2 Hz, 8.0 Hz), 4.39 (dd, 1H *J* = 2.2 Hz, 4.8 Hz), 4.2 (d, 1H, *J* = 2.2 Hz), 1.52, 1.44, 1.36, 1.32 (3 s, 12H); ^{13}C NMR ($CDCl_3$): δ = 200.3 (d), 110.0 (s), 109,0 (s) 96.2 (d), 73.2 (d), 71.7 (d), 70.4 (d), 70.3 (d), 25.9 (q), 25.8 (q), 24.8 (q), 24.2 (q). For additional spectroscopic and physical data refer to ref.[40]

(2*S*)-5-(2-Methyl-3-butenylsulfanyl)-1-phenyl-1*H*-tetrazole (35)

By treatment of alcohol **34** (134 mg, 0.535 mmol) with reagent **6** (6 equivs.) and a catalytic amount of TEMPO in CH_2Cl_2 at room temperature for 3.5 h the corresponding aldehyde was prepared; yield: 130 mg (0.524 mmol, 98%).

The crude product was dissolved in dry THF (20 mL), cooled to 0 °C and added to a solution of Ph_3PCH_3Br (2 equiv.) and LDA (2 equiv.; 2 M in THF/ν-heptane) in dry THF (100 mL). After work up with aqueous NH_4Cl and extraction of the aqueous phase, the crude product was purified by column chromatography (silica gel; petroleum ether/ethyl acetate, 10:1) to afford the title product **35**; yield: 74 mg (0.3 mmol; 57% after two steps); oil; $[\alpha]_D^{20}$: − 15.9° ($CHCl_3$, *c* 1); ^1H NMR ($CDCl_3$): δ = 7.49 – 7.63 (m, 5H), 5.75 (ddd, 1H, *J* = 17.3 Hz, 10.2 Hz, 2 Hz), 5.02 – 5.12 (m, 2H), 3.42 (d, 1H, *J* = 2.5 Hz), 3.41 (d, 1H, *J* = 3.1 Hz), 2.68 (pseudo-sept, 1H, *J* = 7.0 Hz), 1.17 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ = 154.5

(s), 140.8 (d), 133.7 (s), 130.0 (d), 129.7 (d), 123.8 (d), 115.3 (t), 39.5 (t), 37.3 (d), 19.3 (q); HRMS (EI): calcd. for $C_{12}H_{14}N_4S$: 246.0939; found: 246.0934.

Acknowledgements

This work was supported by the Fonds der Chemischen Industrie. We thank Solvay Pharmaceuticals (Hannover) for the donation of chemicals. We are grateful to Dr. H. Monenschein and C. Jasper for expert preparative assistance. Finally, we thank Prof. Dr. M. Kalesse (FU Berlin) for providing us with selected alcohols.

References and Notes

[1] Reviews: a) A. Kirschning, H. Monenschein, R. Wittenberg, *Angew. Chem. Int. Ed.* **2001**, *40*, 650 – 679; b) S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, S. J. Taylor, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3815 – 4195; c) D. H. Drewry, D. M. Coe, S. Poon, *Med. Res. Rev.* **1999**, *19*, 97 – 148.

[2] S. V. Ley, I. R. Baxendale, *Nat. Rev. Drug Disc.* **2002**, *1*, 573 – 586.

[3] a) A. Kirschning, C. Altwicker, G. Dräger, J. Harders, N. Hoffmann, U. Hoffmann, H. Schönfeld, W. Solodenko, U. Kunz, *Angew. Chem. Int. Ed.* **2001**, *40*, 3995 – 3998; b) W. Solodenko, U. Kunz, G. Jas, A. Kirschning, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1833 – 1835.

[4] T. Brunelet, G. Gelbard, *Nouv. J. Chim.* **1983**, *7*, 483 – 490.

[5] H. Yang, B. Li, *Synth. Commun.* **1991**, *21*, 1521 – 1526.

[6] a) S. Abraham, P. K. Rajan, K. Sreekumar, *Polym. Int.* **1998**, *45*, 271 – 277; b) J. M. J. Fréchet, J. Warnock, M. J. Farrall, *J. Org. Chem.* **1978**, *43*, 2618 – 2621; c) J. M. J. Fréchet, P. Darling, M. J. Farrall, *J. Org. Chem.* **1981**, *46*, 1728 – 1730.

[7] G. Cainelli, G. Cardillo, M. Orena, S. Sandri, *J. Am. Chem. Soc.* **1976**, #98#6737 – 6738.

[8] a) M. Caldarelli, J. Habermann, S. V. Ley, *J. Chem. Soc. Perkin Trans. 1*, **1999**, 107 – 110; b) T. Takemoto, K. Yasuda, S. V. Ley, *Synlett* **2001**, 1555 – 1556.

[9] a) B. Hinzen, S. V. Ley, *J. Chem. Soc. Perkin Trans. 1*, **1997**, 1907 – 1908; b) B. Hinzen, R. Lenz, S. V. Ley, *Synthesis* **1998**, 977 – 979.

[10] Also the polymer-supported versions of the Swern oxidation: a) J. M. Harris, Y. Liu, S. Chai, M. D. Andrews, J. C. Vederas, *J. Org. Chem.* **1998**, *63*, 2407 – 2409; b) Y. Liu, J. C. Vederas, *J. Org. Chem.* **1996**, *61*, 7856 – 7859 as well as the Corey oxidation: c) G. A. Crosby, N. M. Weinshenker, H.-S. Uh, *J. Am. Chem. Soc.* **1975**, *97*, 2232 – 2235.

[11] a) H. Tohma, S. Takizawa, T. Maegawa, Y. Kita, *Angew. Chem. Int. Ed.. Engl.* **2000**, *39*, 1306 – 138; b) H. Tohma, T. Maegawa, S. Takizawa, Y. Kita, *Adv. Synth. Catal.* **2002**, *344*, 328 – 337.

[12] Review on TEMPO: A. E. J. de Nooy, A. C. Besemer, H. van Bekkum, *Synthesis* **1996**, 1153 – 1175.

[13] a) P. L. Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559 – 2562; b) P. L. Anelli, S. Banfi, F. Montanari, S. Quici, *J. Org. Chem.* **1989**, *54*, 2970 – 2972; c) M. Zhao, J. Li, E. Mano, Z. Song, D. M. Tschaen, E. J. J. Grabowski, P. J. Reider, *J. Org. Chem.* **1999**, *64*, 2564 – 2566; d) T. Inokuchi, S. Matsumoto, T. Nishiyama, S. Torii, *J. Org. Chem.* **1990**, *55*, 462 – 466; e) F. Melvin, A. McNeill, P. J. F. Henderson, R. B. Herbert, *Tetrahedron Lett.* **1999**, *40*, 1201 – 1202; f) J. Einhorn, C. Einhorn, F. Ratajczak, J.-L. Pierre, *J. Org. Chem.* **1996**, *61*, 7452 – 7454; g) A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974 – 6977; h) J. B. Epp, T. S. Widlanski, *J. Org. Chem.* **1999**, *64*, 293 – 295.

[14] a) C. Bolm, A. S. Magnus, J. P. Hildebrand, *Org. Lett.* **2000**, *2*, 1173 – 1175; b) J. A. Cella, J. A. Kelley, E. F. Kenehan, *J. Org. Chem.* **1975**, *40*, 1860 – 1862; c) J. A. Cella, J. P. McGrath, J. A. Kelley, O. ElSoukkary, L. Hilpert, *J. Org. Chem.* **1977**, *42*, 2077 – 2080; d) S. D. Rychnovsky, R. Vaidyanathan, *J. Org. Chem.* **1999**, *64*, 310 – 312; e) W. A. Herrmann, J. P. Zoller, R. W. Fischer, *J. Organomet. Chem.* **1999**, *579*, 404 – 407; f) H. Kochkar, L. Lassalle, M. Morawietz, W. F. Hölderich, *J. Catal.* **2000**, *194*, 343 – 351; g) B. Betzemeier, M. Cavazzini, S. Quici, P. Knochel, *Tetrahedron Lett.* **2000**, *41*, 4343 – 4346.

[15] a) M. F. Semmelhack, C. S. Chou, D. A. Cortés, *J. Am. Chem. Soc.* **1983**, *105*, 4492 – 4494; b) T. Inokuchi, S. Matsumoto, S. Torii, *J. Org. Chem.* **1991**, *56*, 2416 – 2421; c) Y. Kashiwagi, Y. Yangisawa, F. Kurashima, J.-I. Anzai, T. Osa, J. M. Bobbitt, *Chem. Commun.* **1996**, 2745 – 2746; d) Y. Yangisawa, Y. Kashiwagi, F. Kurashima, J.-I. Anzai, T. Osa, J. M. Bobbitt, *Chem. Commun.* **1996**, 1043 – 1044.

[16] a) K. Drauz, M. Kottenhahn, K. Stingl, *US Patent* 5,631,385, **1997**; b) T. Kükenhöhner, N. Goetz, *German Patent* 4,007,923, **1990**.

[17] a) T. Miayazawa, T. Endo, *J. Polym. Sci., Polym. Chem. Ed.* **1985**, *23*, 2487 – 2497; b) T. Miayazawa, T. Endo, *J. Mol. Catal.* **1988**, *49*, L31-L34; c) A. Deronzier, D. Lìmosin, J.-C. Moutet, *Electrochim. Acta* **1987**, *32*, 1643 – 1647; d) T. Osa, U. Akiba, I. Segawa, J. M. Bobbitt, *Chem. Lett.* **1988**, 1423 – 1426; e) F. MacCorquodale, J. A. Crayston, J. C. Walton, D. J. Worsfold, *Tetrahedron Lett.* **1990**, *31*, 771 – 774; f) C. Amiel, B. Sebille, H. Hommel, A. P. Legrand, *J. Colloid Interface Sci.* **1994**, *165*, 236 – 243; g) A. W. Bosman, A. J. Janssen, E. W. Meijer, *Macromolecules* **1997**, *30*, 3606 – 3611; h) L. D. Hall, J. C. Waterton, *J. Am. Chem. Soc.* **1979**, *101*, 3697 – 3698; i) N. Tsubokawa, T. Kimoto, T. Endo, *J. Mol. Catal. A Chem.* **1995**, *101*, 45 – 50.

[18] S. Weik, G. Nicholson, G. Jung, J. Rademann, *Angew. Chem.* **2001**, *113*, 1489 – 1492; *Angew. Chem. Int. Ed.* **2001**, *40*, 1436 – 1439.

[19] a) C. Bolm, T. Frey, *Chem. Commun.* **1999**, 1795 – 1996; b) T. Frey, H. Fischer, S. Bachmann, K. Albert, C. Bolm, *J. Org. Chem.* **2001**, *66*, 8154.

[20] a) D. Brunel, P. Lentz, P. Sutra, B. Deroide, F. Fajula, J. B. Nagy, *Stud. Surf. Sci. Catal*. **1999**, *125*, 237 – 244; b) M. J. Verhoef, J. A. Peters, H. van Bekkum, *Stud. Surf. Sci. Catal*. **1999**, *125*, 465 – 472; c) R. Ciriminna, J. Blum, D. Avnir, M. Pagliaro, *Chem. Commun*. **2000**, 1441 – 1442; d) A. Dijksman, I. W. C. E. Arends, R. A. Sheldon, *Chem. Commun*. **2000**, 271 – 272.
[21] G. Sourkouni-Argirusi, A. Kirschning, *Org. Lett*. **2000**, *2*, 3781 – 3784.
[22] J. Rudolph, F. Hannig, H. Theis, R. Wischnat, *Org. Lett.* **2001**, *3*, 3153 – 3155.
[23] a) H. Monenschein, G. Sourkouni-Argirusi, K. M. Schubothe, T. O'Hare, A. Kirschning, *Org. Lett*. **1999**, *1*, 2101 – 2104; b) A. Kirschning, H. Monenschein, C. Schmeck, *Angew. Chem*. **1999**, *111*, 2720 – 2722; *Angew. Chem. Int. Ed. Engl,* **1999**, *38*, 2594 – 2596; c) A. Kirschning, M. Jesberger, H. Monenschein, *Tetrahedron Lett*. **1999**, *40*, 8999 – 9002.
[24] A. Hashem, A. Jung, M. Ries, A. Kirschning, *Synlett* **1998**, 195 – 197.
[25] By adding acetonitrile to the crude product acetic acid can be removed by evaporation.
[26] T. Bach, S. Heuser, *Angew. Chem. Int. Ed.* **2001**, *40*, 3184 – 3185; *Angew. Chem.* **2001**, *113*, 3283 – 3284.
[27] Aldehyde **21** was obtained in 21% yield using MnO_2 and 67% when Dess–Martin periodinane was used as oxidant.
[28] P. R. Blakemore, W. J. Cole, P. J. Kocieński, A. Morley, *Synlett* **1998**, 26 – 28.
[29] The oxidation proceeded in 98% yield. The Wittig olefination has to be made responsible for the reduced yield.
[30] Complete decomposition of (2*S*)-2-diallylamino-3-phenyl-1-propanol and (2*S*)-2-dibenzylamino-3-phenyl-1-propanol was observed within 15 minutes under standard conditions.
[31] a) A. E. J. de Nooy, A. C. Besemer, H. van Bekkum, *Tetrahedron* **1995**, *51*, 8023 – 8032; b) R. Ben-Daniel, P. Alsters, R. Neumann, *J. Org. Chem*. **2001**, *66*, 8650 – 8653.
[32] M. Schneider, J.-V. Weber, P. Faller, *J. Org. Chem*. **1982**, *47*, 364 – 365.
[33] a) R. D. Walkup, M. D. Mosher, *Tetrahedron* **1993**, *49*, 41, 9285 – 9294; b) T. Ishikawa, S. Ikeda, M. Ibe, S. Saito, *Tetrahedron* **1998**, *54*, 22, 5869 – 5882.
[34] Y. Guindon, L. Murtagh, V. Caron, S. R. Landry, G. Jung, M. Bencheqroun, A.-M. Faucher, B. Guérin, *J. Org. Chem*. **2001**, *66*, 5427 – 5437.
[35] Analytical data of *S*-**27**: R. D. Walkup, J. D. Kahl, R. R. Kane, *J. Org. Chem.* **1998**, *63*, 9113 – 9116.
[36] S. E. Hagen, J. Domagala, C. Gajda, M. Lovdahl, B. D. Tait, E. Wise, T. Holler, D. Hupe, C. Nouhan, A. Urumov, G. Zeikus, et. al., *J. Med. Chem.* **2001**, *44*, 14, 2319 – 2332.
[37] J. McNulty, I. W. J. Still, *J. Chem. Soc. Perkin Trans. 1* **1994**, *10*, 1329 – 1338.
[38] a) L. De Luca, G. Giacomelli, A. Porcheddu, *J. Org. Chem.* **2001**, *66*, 23, 7907 – 7909; b) C. Kashima, K. Harada, Y. Fujioka, T. Maruyama, Y. Omote, *J. Chem. Soc. Perkin Trans. 1* **1988**, 535 – 540.
[39] A. Alexakis, N. Lensen, J.-P. Tranchier, P. Mangeney, J. Feneau-Dupont, J. P. Declercq, *Synthesis* **1995**, *8*, 1038 – 1050.
[40] H. H. Lee, P. G. Hodgson, R. J. Bernacki, W. Korytnyk, M. Sharma, *Carbohydr. Res.* **1988**, *176*, 59 – 72.

