β-Alkoxy-γ-amino Aldehydes by Internal Redox Ring Cleavages of Carbohydrate-Derived Enantiopure 1,2-Oxazines and Preparation of Heterocycles with Aminopolyol Side Chain

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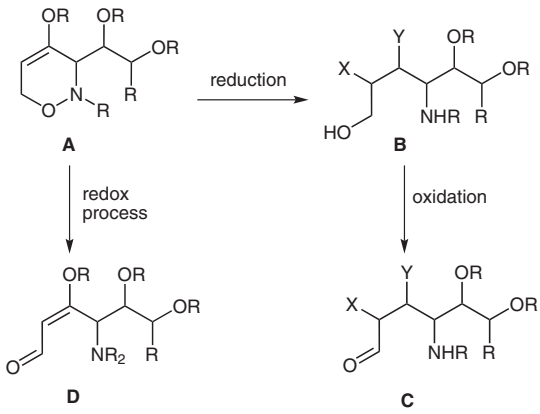
Dedicated to Professor Alberto Brandi on the occasion of his 60th birthday

Abstract: N-Methylation of *syn*- or *anti*-configured 3,6-dihydro-2*H*-1,2-oxazines and subsequent treatment with triethylamine smoothly provided enantiopure α,β-unsaturated β-alkoxy-γ-amino aldehydes bearing different protected diol, triol, or tetrol side chains in good to excellent yields. The N–O bond cleavage occurs under mild conditions and involves an internal redox process. The method is also applicable to tetrahydro-2*H*-1,2-oxazines, which either lead to 4-amino ketose or aldose derivatives (D-sorbose or D-idose configuration). The equivalency of the generated β-alkoxyenal moiety with 1,3-dicarbonyl compounds could be demonstrated by condensation reactions with hydrazine or 2-aminoimidazole derivatives providing a series of new pyrazole or imidazo[1,2-*a*]pyrimidine derivatives with stereodefined and protected aminopolyol side chains.

Key words: carbohydrates, 1,2-oxazines, alkylation, aldehydes, pyrazoles, imidazo[1,2-*a*]pyrimidines

We developed efficient and general protocols for the preparation of 3,6-dihydro-2*H*-1,2-oxazines **A** (Scheme 1) by stereodivergent [3+3] cyclizations of lithiated alkoxyallenes with carbohydrate derived nitrones and subsequently investigated the reactivity and synthetic potential of this easily available heterocycles in various directions.[1] Compounds **A** are remarkably versatile precursors for the synthesis of a wide range of interesting product classes, which are of relevance as biologically active components. Highly functionalized compounds such as polyhydroxylated pyrrolidines or azetidines, aminopolyols and neuramic acid derivatives are accessible.[2,3] Moreover, carbohydrate and peptide mimetics could be prepared via novel skeletal rearrangements of **A** leading to bicyclic compounds as key intermediates.[2h]

Reductive cleavages of the fairly weak N–O bond of **A** have been studied in the past involving hydrogenolysis in the presence of suitable catalysts or employing samarium diiodide as reagent.[2,3] In order to convert the resulting amino polyols **B** into amino carbohydrate derivatives **C**, the terminal primary alcohol has to be oxidized to an aldehyde. Hence, a sequence of reduction and oxidation is required for this overall transformation. In this report, we want to disclose full details[4] on the alternative N–O cleavage process directly furnishing products **D** containing a synthetically useful β-alkoxy-γ-amino aldehyde moiety (Scheme 1). This reaction mode can be classified as an internal redox process. Related transformations have been reported by Murahashi[5] and Fišera[6] for the ring cleavage of isoxazolidine derivatives and by other authors.[7]



Scheme 1 Transformation of 3,6-dihydro-2*H*-1,2-oxazines **A** by subsequent reductive and oxidative processes to aldehydes **C** and alternative redox process directly leading to unsaturated aldehydes **D**

syn-Configured 1,2-oxazine *syn*-**1a** was first methylated at the 1,2-oxazine nitrogen by treatment with methyl triflate in acetonitrile at room temperature. Subsequently, triethylamine was added to the intermediate salt at 0 °C to cleanly furnish compound *syn*-**2a** in 87% yield (Scheme 2). Similarly, *syn*-**1b** was converted into the expected α,β-unsaturated β-trimethylsilylethoxy γ-amino aldehyde *syn*-**2b** in excellent yield. The butanediacetal-derived 1,2-oxazine *syn*-**1c** afforded the desired unsaturated aldehyde *syn*-**2c** again in excellent yield. Under identical reaction conditions, γ-amino aldehyde *syn*-**2d** was obtained in 61% yield from L-threose-derived 1,2-oxazine *syn*-**1d**. Ring opening of the two 1,2-oxazines *syn*-**1e** and *syn*-**1f**, derived from a chain extended enantiopure nitrone, furnished the expected cleavage products *syn*-**2e** and *syn*-**2f**, respectively, in satisfying yield.

The mechanism of this process is simple: the 1,2-oxazinium salt **E**, formed by N-methylation of **A**, is deprotonated at C-6, which induces a synchronous N–O cleavage furnishing the ring-opened product **D** (Scheme 3). Due to the

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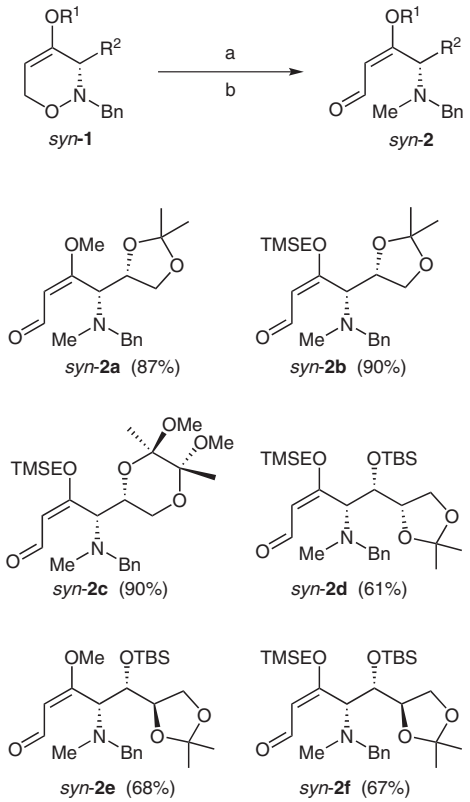
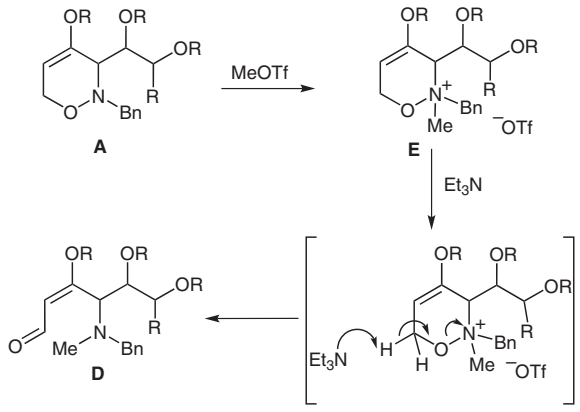


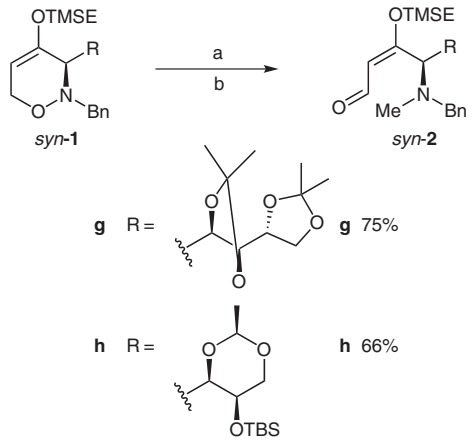
Scheme 2 Redox ring cleavage of 1,2-oxazines *syn*-**1a–f** into α,β-unsaturated β-alkoxy-γ-amino aldehydes *syn*-**2a–f**. *Reagents and conditions*: a) MeOTf (1.1 equiv), MeCN, 6 h, r.t.; b) Et_3N, 0 °C, 1 h. TMSE: trimethylsilylethyl, TBS: *tert*-butyldimethylsilyl.

mild reaction conditions the products entirely retain their diastereomeric and enantiomeric purity. It is worth mentioning that methyl iodide was not sufficiently reactive to effect the N-methylation of 1,2-oxazines **A** despite the moderate yields obtained by Murahashi in his examples with this alkylating reagent.[5]



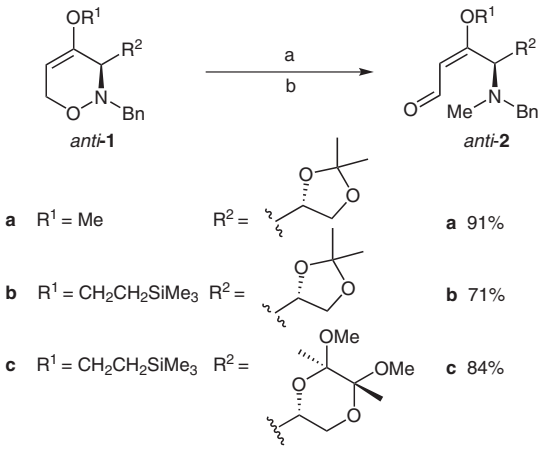
Scheme 3 Mechanism of the internal redox ring cleavage of carbohydrate derived 1,2-oxazines **A** leading to α,β-unsaturated β-alkoxy-γ-amino aldehydes **D**

Arabinose derived 1,2-oxazine *syn*-**1g** with a protected tetrol side chain was smoothly converted into the desired unsaturated aldehyde *syn*-**2g** with good efficacy. Likewise, D-threose derived 1,2-oxazine *syn*-**1h** was treated under standard conditions to deliver the expected aldehyde *syn*-**2h** in 66% yield (Scheme 4).



Scheme 4 Conversion of 1,2-oxazines *syn*-**1g** and *syn*-**1h** into α,β-unsaturated β-alkoxy-γ-amino aldehydes *syn*-**2g** and *syn*-**2h**. *Reagents and conditions*: a) MeOTf (1.1 equiv), MeCN, 6 h, r.t.; b) Et_3N, 0 °C, 1 h. TMSE: trimethylsilylethyl, TBS: *tert*-butyldimethylsilyl.

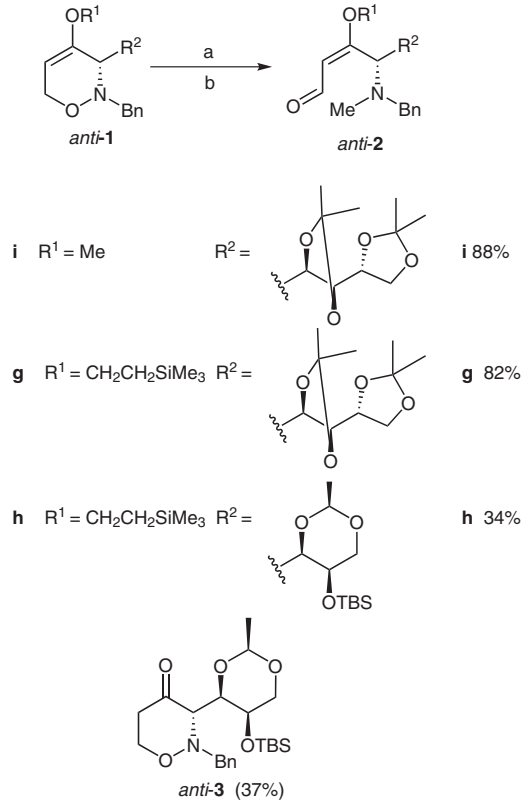
To examine the generality of our ring cleavage method, closely related *anti*-1,2-oxazine derivatives were also exposed to the reaction conditions. 1,2-Oxazines *anti*-**1a** and *anti*-**1b** furnished the corresponding unsaturated aldehydes *anti*-**2a** and *anti*-**2b** in 91% and 71% yield, respectively. The *anti*-derivative of the butanediacetal-protected 1,2-oxazine *anti*-**1c** also afforded the expected aldehyde *anti*-**2c** in excellent yield (Scheme 5).



Scheme 5 Conversion of *anti*-configured 1,2-oxazines *anti*-**1a-c** into α,β-unsaturated β-alkoxy-γ-amino aldehydes *anti*-**2a-c**. *Reagents and conditions*: a) MeOTf (1.1 equiv), MeCN, 6 h, r.t.; b) Et_3N, 0 °C, 1 h.

In the *anti*-series, the arabinose derived 1,2-oxazines *anti*-**1i** and *anti*-**1g** also provided the desired unsaturated aldehydes *anti*-**2i** and *anti*-**2g**, respectively, in excellent yields. When the D-threose derivative 1,2-oxazine *anti*-**1h** was used as the precursor, a mixture of two products was obtained. After chromatography of the product mixture,

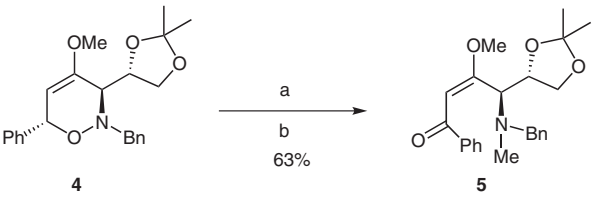
the expected aldehyde *anti*-**2h** was isolated in 34% yield. The second product was identified to be 1,2-oxazin-4-one derivative *anti*-**3**, which was isolated in 37% yield (Scheme 6). The formation of this ketone is possibly due to the cleavage of the trimethylsilylethoxy group of **1h** during the alkylation step.



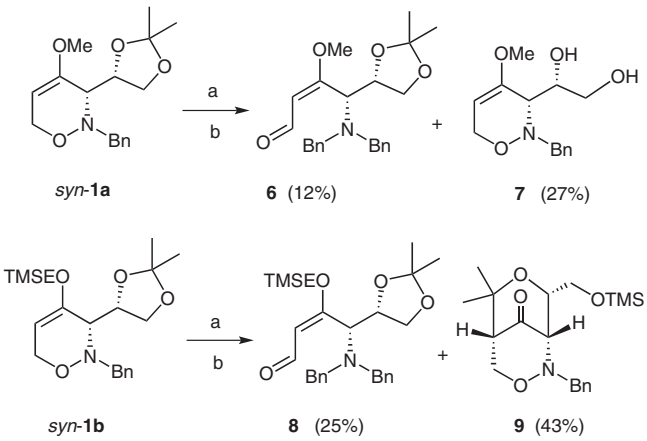
Scheme 6 Conversion of 1,2-oxazines *anti*-**1i**,**g**,**h** into α,β-unsaturated β-alkoxy-γ-amino aldehydes *anti*-**2i**,**g**,**h**. *Reagents and conditions*: a) MeOTf (1.1 equiv), MeCN, 6 h, r.t.; b) Et_3N, 0 °C, 1 h. TMSE: trimethylsilylethyl, TBS: *tert*-butyldimethylsilyl.

We envisioned that 1,2-oxazines such as **4**,[8] which are substituted at C-6, may serve as good candidates for the generation of α,β-unsaturated β-alkoxy-γ-amino ketones like **5**. Actually, addition of methyl triflate to compound **4** and stirring for 6 hours followed by addition of triethylamine smoothly afforded the expected ketone derivative **5** in good yield (Scheme 7). This typical example clearly demonstrates that substituents at C-6 are tolerated and encourage for the investigation of other substituents at this position, for example, alkyl or alkoxy substituents. The later are expected to deliver the corresponding esters and may subsequently lead to interestingly functionalized γ-lactams.[5,9]

We then examined benzyl triflate as alkylating agent in order to prepare the unsaturated aldehydes with a dibenzylamino group. This could be particularly valuable since it is well known that these N-substituents can be removed under reductive conditions. Benzyl triflate was prepared in situ by the addition of silver triflate to benzyl bromide and then added to *syn*-1,2-oxazine derivative *syn*-**1a**. Unfortunately, only 12% of the desired aldehyde **6** and 10% of starting material *syn*-**1a** were isolated together with 27% of compound **7**, which is the result of a cleavage of the acetonide unit (Scheme 8). Addition of benzyl triflate to trimethysilylethoxy substituted *syn*-**1b** afforded the desired aldehyde in slightly improved, but still unsatisfying yield. Interestingly, the major product isolated in this experiment was bicyclic 1,2-oxazine **9** (Scheme 8). The formation of compound **9** can be explained by a Lewis acid mediated rearrangement of 1,2-oxazine *syn*-**1b**. The promoter Lewis acid is very likely silver triflate in this case, which is apparently still present due to incomplete generation of benzyl triflate. The formation of bicyclic 1,2-oxazines such as **9** and their subsequent transformations into enantiopure aminopyrans has been systematically studied in our group. They are versatile building blocks for the synthesis of amino carbohydrates and oligosaccharide mimetics as well as of sugar amino acids.[2] It is obvious that syntheses of useful carbohydrate derivatives with dibenzylamino groups such as **6** and **8** need further optimization.



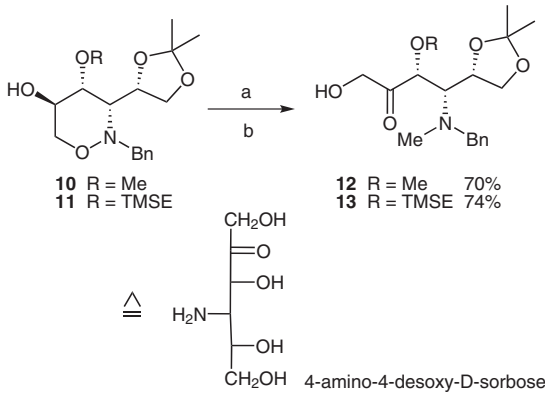
Scheme 7 Conversion of 6-substituted 1,2-oxazine **4** into α,β-unsaturated β-methoxy-γ-amino ketone **5**. *Reagents and conditions*: a) MeOTf (1.1 equiv), MeCN, 6 h, r.t.; b) Et_3N, 0 °C, 1 h.



Scheme 8 Reactions of 1,2-oxazines *syn*-**1a-b** with in situ generated benzyl triflate. *Reagents and conditions*: a) AgOTf (1.5 equiv), BnBr (1.5 equiv), Et_2O then MeCN, 6 h, r.t.; b) Et_3N, 0 C, 1 h. TMSE: trimethylsilylethyl.

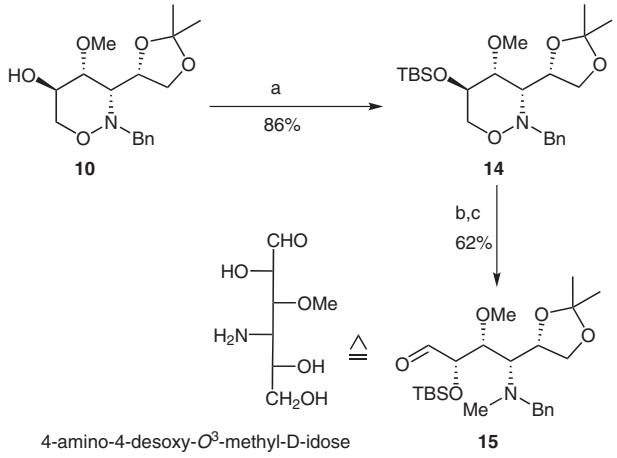
The redox cleavage method was further extended to tetrahydro-2*H*-1,2-oxazines **10** and **11**.[3b] Applying the reaction conditions directly to these precursors furnished 1-hydroxy-2-oxohexane derivatives **12** and **13**, respectively, in good yields (Scheme 9). The unexpected formation of ketoses **12** and **13**, equivalents of 4-amino-4-desoxy-D-

sorbose, can be rationalized by a tautomerization of the resulting primary products via an enediol intermediate delivering the more stable ketones **12** and **13** under the basic reaction conditions of the second step.



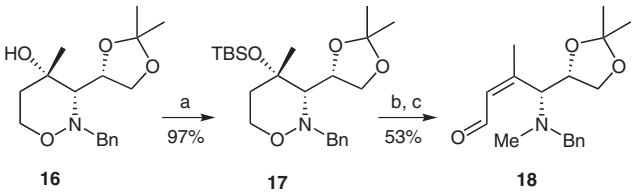
Scheme 9 Conversion of 1,2-oxazines **10** and **11** into protected D-sorbose derivatives **12** and **13**. *Reagents and conditions*: a) MeOTf (1.1 equiv), MeCN, 6 h, r.t.; b) Et_3N, 0 °C, 1 h.

In order to obtain the desired aldose derivative, the 5-hydroxy group of **10** was protected with a *tert*-butyldimethylsilyl group. Now the resulting compound **14** could be smoothly converted into the expected γ-dialkylamino aldose **15** in 62% yield which is an equivalent of 4-amino-4-desoxy-O^3-methyl-D-idose (Scheme 10). Although there is still room for improvements, this experiment clearly demonstrates that the redox cleavage process is also applicable to fully reduced 1,2-oxazine derivatives leading directly to 4-amino aldoses. This route to unusual carbohydrate derivatives can certainly be further explored in the future.



Scheme 10 Conversion of protected 1,2-oxazine **14** into D-idose derivative **15**. *Reagents and conditions*: a) TBSOTf, Et_3N, CH_2Cl_2, 1 h; b) MeOTf (1.1 equiv), MeCN, 6 h, r.t.; c) Et_3N, 0 °C, 1 h.

As an additional example, the internal redox process with 1,2-oxazine **16**[10] bearing a tertiary alcohol moiety at C-4 was examined. With the free hydroxy group only unidentified products were obtained and therefore a *tert*-butyldimethylsilyl protection of this substituent was carried out. Treatment of the resulting **17** with methyl triflate and subsequently with triethylamine under reflux furnished the α,β-unsaturated aldehyde **18**, which now contains a β-methyl group instead of an alkoxy substituent (Scheme 11). The formation of enal **18**, which is obtained as a single isomer, can be attributed to an elimination of the siloxy group under the relatively harsh conditions during the second step.

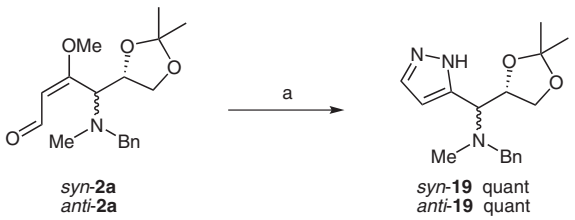


Scheme 11 Conversion of 1,2-oxazine **17** into α,β-unsaturated aldehyde **18**. *Reagents and conditions*: a) TBSOTf, Et_3N, CH_2Cl_2, 1 h; b) MeOTf (1.1 equiv), MeCN, 6 h, r.t.; c) Et_3N, 0 °C, 1 h, then reflux, 1 h.

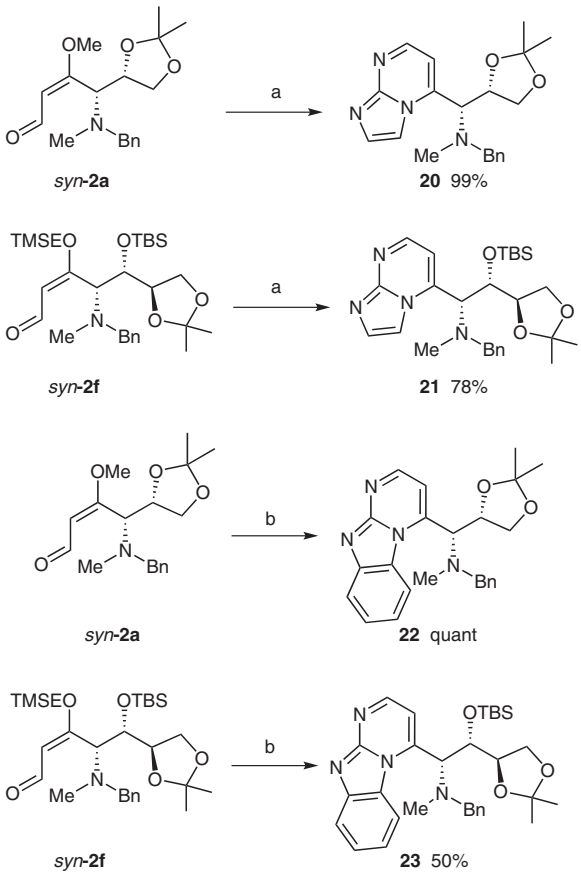
The redox transformations of 1,2-oxazines presented in Schemes 2, 4, 5, and 6 demonstrate that a broad range of α,β-unsaturated β-alkoxy-γ-amino aldehydes with protected diol, triol, or tetrol side chains (with different relative and absolute configurations) is easily available. These enantiopure intermediates should be versatile intermediates for subsequent synthetic adventures, since their β-alkoxyenal moiety is equivalent to a 1,3-dicarbonyl unit. It is therefore conceivable that they can serve as components for cyclocondensations leading to heterocycles containing carbohydrate related side chains. The resulting products should not only be of interest by themselves, but are also possible precursors of new peptidomimetics or even of drug candidates. More specifically, pyrazole derivatives are particularly interesting due to the presence of this class of heterocycles as essential substructure in a number of biologically active compounds.[11] Continuous efforts have been reported towards the development of synthetic methods leading to functionalized pyrazole derivatives.[12] The most general preparation of the pyrazole core consists in the reaction of 1,3-dicarbonyl compounds or their synthetic equivalents with hydrazine derivatives.[13] On the other hand, 2-aminoimidazole derivatives and 1,3-dicarbonyl compounds or their equivalents are known to lead to imidazo[1,2-*a*]pyrimidines.[14]

Treatment of β-alkoxy-γ-amino aldehydes *syn*-**2a** and *anti*-**2a** with hydrazine hydrate in the presence of trifluoroacetic acid[15] quantitatively led to the desired pyrazole derivatives *syn*-**19** and *anti*-**19** (Scheme 12). When the reaction of α,β-unsaturated β-methoxy aldehyde *syn*-**2a** with hydrazine hydrate was carried out in the absence of trifluoroacetic acid, the reaction did not proceed to afford the pyrazole derivative. When 2-aminoimidazole and 2-aminobenzimidazole were combined with *syn*-**2a** or *syn*-**2f** the expected fused heterocycles **20**–**23** could be obtained in good to excellent yield (Scheme 13).[16] These examples impressively demonstrate the assumed

equivalency of our precursors with 1,3-dicarbonyl compounds and their potential in synthesis of new functionalized heterocycles.

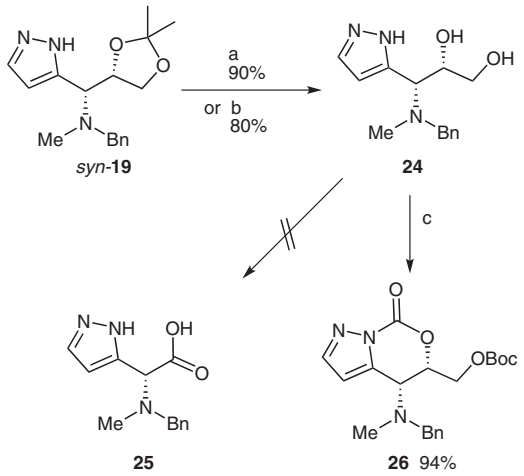


Scheme 12 Synthesis of pyrazole derivatives **19**. *Reagents and conditions*: a) hydrazine hydrate, TFA, EtOH, reflux, 2 h.



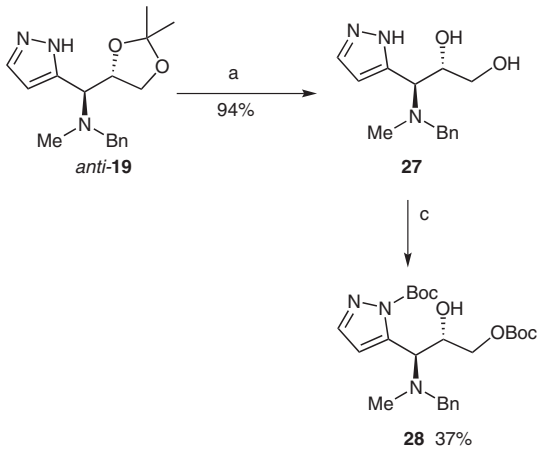
Scheme 13 Synthesis of heterocycles **20**, **21**, **22** and **23**. *Reagents and conditions*: a) 2-aminoimidazole sulfate, NaOAc, EtOH, reflux, overnight; b) 2-aminobenzimidazole, EtOH, reflux, overnight.

The possibilities to modify the chiral side chain of compounds such as **19** were examined briefly. The hydrolysis of the dioxolane ring in *syn*-**19** proceeded smoothly either by treatment with acetic acid or with *p*-toluenesulfonic acid in refluxing methanol to furnish the corresponding diol **24** in 90% or 80% yield. An oxidative cleavage of diol **24** might provide the corresponding aldehyde and finally the unusual amino acid derivative **25**, however, the expected product could not be obtained. An attempt to protect the NH at the pyrazole moiety of **24** by a Boc group resulted in the formation of pyrazolo-1,3-oxazine derivative **26** (Scheme 14).



Scheme 14 Hydrolysis of pyrazole derivative *syn*-**19** and attempted subsequent reactions. *Reagents and conditions*: a) AcOH, reflux, 2 h; b) *p*-toluenesulfonic acid, MeOH, reflux, 3 h; c) $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, r.t., 12 h.

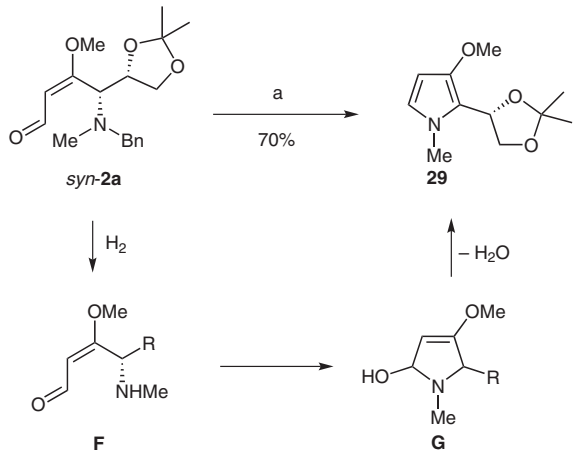
Similarly, treatment of *anti*-**19** with *p*-toluenesulfonic acid in refluxing methanol delivered the corresponding 1,2-diol **27** in 94% yield (Scheme 15). Treatment of this product with an excess of Boc-anhydride in the absence of DMAP furnished the bis-Boc protected product **28** in low yield. Although our orientating experiments for the oxidative cleavage of the pyrazole side chain as described in Scheme 14 were not successful so far we are confident that by appropriate protection and cleavage conditions analogues of phenyl glycine with a pyrazole group such as **25** should be accessible in enantiopure fashion following our route.



Scheme 15 Hydrolysis of pyrazole derivative *anti*-**19**. *Reagents and conditions*: a) *p*-toluenesulfonic acid, MeOH, reflux, 3 h; b) $(Boc)_2O$, Et_3N, CH_2Cl_2, r.t., 12 h.

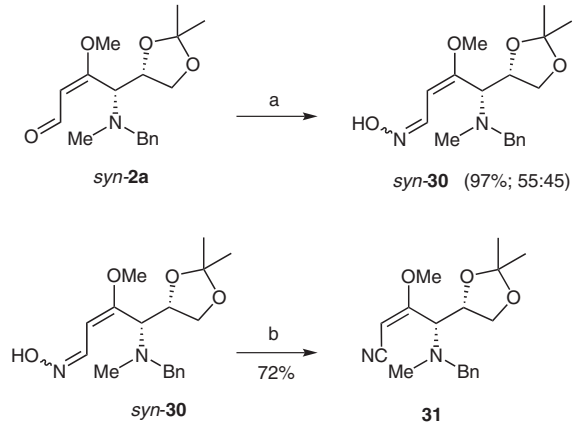
In additional orientating experiments we further investigated the reactivity of our β-alkoxy-γ-amino aldehydes **2**. The hydrogenolysis of *syn*-**2a** in the presence of Raney nickel provided the unstable 3-methoxypyrrole derivative **29** in 70% yield (Scheme 16). We assume that after reductive removal of the *N*-benzyl group the secondary amine

F is formed. Intramolecular addition of the nitrogen atom to the carbonyl group leads to intermediate **G**, which can undergo elimination of water finally affording pyrrole derivative **29**.



Scheme 16 Formation of pyrrole **29** from *syn*-**2a**. *Reagents and conditions*: a) H_2, Raney-Ni, MeOH, r.t., 1 h.

Aldehyde *syn*-**2a** was also treated with hydroxylamine hydrochloride in refluxing methanol in the presence of sodium methoxide. This protocol did not afford the desired isoxazole derivative, but in all attempts oxime *syn*-**30** was isolated in excellent yield (Scheme 17). This product should be a suitable precursor for the synthesis of the corresponding nitrile.[17] Hence, by addition of tosyl chloride and triethylamine oxime *syn*-**30** was efficiently converted into the corresponding nitrile **31**. This known transformation can also be regarded as an internal redox reaction.



Scheme 17 Conversion of aldehyde *syn*-**2a** into oxime *syn*-**30** and subsequent transformation into nitrile **31**. *Reagents and conditions*: a) $NH_2OH{\cdot}HCl$, NaOMe, MeOH, reflux, 24 h; b) TsCl, Et_3N, CH_2Cl_2, r.t., 6 h.

In conclusion, starting from readily available carbohydrate derived enantiopure 1,2-oxazines **1** we have developed a new cleavage protocol to provide α,β-unsaturated β-alkoxy-γ-amino aldehydes **2** involving an internal redox ring cleavage. The examples presented herein demonstrate the potential of intermediates **2** for the synthesis of heterocycles with different amino polyol side chain. These compounds should allow an entry to many interesting product classes, for example, nonproteinogenic amino acids in both enantiomeric forms or to unusual carbohydrate derivatives.

Reactions were generally performed under argon in flame-dried flasks, and the components were added by syringe. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck). Unless otherwise stated, yields refer to analytically pure samples. ^{1}H NMR [$CHCl_3$ (δ = 7.26), TMS (δ = 0.00) as internal standard] and ^{13}C NMR spectra [$CDCl_3$ (δ = 77.0) as internal standard] were recorded with Bruker AC 250, ECP 400, AVIII 700, or Joel Eclipse 500 instruments in $CDCl_3$ solutions. Integrals are in accordance with assignments; coupling constants are given in Hz. IR spectra were recorded on Nicolet 5 SXC FTIR or a Nicolet Smart DuraSamplIR ATR spectrometer. MS and HRMS analyses were performed with Finnigan MAT 95 (EI, 70 eV), MAT CH7A (EI, 80 eV, 3 kV) or Agilent ESI-TOF 6210 (4 mL/min, 1 bar, 4000 V) instruments. The elemental analyses were recorded with Elemental-Analyzers (Perkin–Elmer or Carlo Erba). Melting points were measured with a Reichert apparatus and are uncorrected. Optical rotations ($[\alpha]_D$) were determined with PerkinElmer 141 or PerkinElmer 241 polarimeter at the temperatures given. All other chemicals are commercially available and were used without further purification.

Internal Redox Ring Cleavage of 1,2-Oxazine Derivatives; General Procedure 1 (GP1)

1,2-Oxazine **1** (1.0 equiv) was dissolved in MeCN (6 mL/mmol of **1**). The solution was treated with MeOTf (1.1 equiv) at 0 °C. The mixture was stirred at r.t. for the given time in the individual experiments until the starting material was consumed. The reaction mixture was then cooled to 0 °C and treated with Et_3N (3 equiv) and stirred for the given time. H_2O (5 mL/mmol of **1**) was added to the residue followed by extraction with CH_2Cl_2 (3 × 10 mL), drying (Na_2SO_4), and concentration.

(4*S*,4′*S*)-4-(Benzylmethylamino)-4-(2′,2′-dimethyl-1,3-dioxolan-4′-yl)-3-methoxybut-2-enal (*syn*-2a)

1,2-Oxazine *syn*-**1a** (350 mg, 1.15 mmol) was treated with MeOTf (1.26 mL, 1.26 mmol) as described in GP1. The mixture was stirred at r.t. for 6 h. Then it was cooled to 0 °C, treated with Et_3N (0.47 mL, 3.45 mmol), and stirred for 1 h. After workup, the crude product (383 mg) was purified by column chromatography (silica gel, hexane–EtOAc, 2:1) to yield 322 mg (87%) of aldehyde *syn*-**2a** as colorless crystals; mp 42–44 °C; $[\alpha]_D^{22}$ +118.2 (*c* 0.77, $CHCl_3$).

IR (KBr): 3085–3030 (=C–H), 2985–2795 (C–H), 1660 (C=O), 1605 cm^{-1} (C=C).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.38, 1.41 (2 s, 3 H each, CH_3), 2.39 (s, 3 H, NCH_3), 3.51 (m_c, 1 H, 5′-H_B), 3.52 (d, *J* = 13.5 Hz, 1 H, N*C*H_2Ph), 3.66 (s, 3 H, OCH_3), 3.90 (d, *J* = 13.5 Hz, 1 H, N*C*H_2Ph), 3.97 (dd, *J* = 6.5, 8.6 Hz, 1 H, 5′-H_A), 4.06 (d, *J* = 8.6 Hz, 1 H, 4-H), 4.65 (dt, *J* = 6.5, 8.6 Hz, 1 H, 4′-H), 5.50 (d, *J* = 7.5 Hz, 1 H, 2-H), 7.20–7.34 (m, 5 H, C_6H_5), 9.47 (d, *J* = 7.5 Hz, 1 H, CHO).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 25.3, 26.6 (2 q, CH_3), 38.9 (q, NCH_3), 55.4 (q, OCH_3), 58.9 (t, N*C*H_2Ph), 63.8 (d, C-4), 66.9 (t, C-5′), 73.6 (d, C-4′), 107.4 (d, C-2), 109.7 (s, C-2′), 127.0, 128.2, 128.6, 138.5 (3 d, s, C_6H_5), 174.4 (s, C-3), 189.6 (d, CHO).

MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 319 (M^+, 4), 218 ($M^+ - C_5H_9O_2$, 14), 91 (CH_2Ph^+, 100).

HRMS: *m*/*z* [M^+] calcd for $C_{18}H_{25}NO_4$: 319.17834; found: 319.17744.

Anal. Calcd for $C_{18}H_{25}NO_4$ (319.4): C, 67.69; H, 7.89; N, 4.39. Found: C, 67.38; H, 7.65; N, 4.36.

(4*R*,4′*S*)-4-(Benzylmethylamino)-4-(2′,2′-dimethyl-1,3-dioxolan-4′-yl)-3-[2-(trimethylsilyl)ethoxy]but-2-enal (*anti*-2b)

1,2-Oxazine *anti*-**1b** (200 mg, 0.510 mmol) was treated with MeOTf (0.61 mL, 0.610 mmol) as described in GP1. The mixture was stirred at r.t. for 6 h. Then it was cooled to 0 °C, treated with Et_3N (0.21 mL, 1.54 mmol) and stirred at this temperature for 1 h. After workup, the crude product (275 mg) was purified by column chromatography (silica gel, hexane–EtOAc, 3:1) to yield 147 mg (71%) of aldehyde *anti*-**2b** as a colorless oil; $[\alpha]_D^{22}$ –25.7 (*c* 0.4, $CHCl_3$).

IR (film): 3085–3030 (=C–H), 2985–2895 (C–H), 1760 (C=O), 1655 cm^{-1} (C=C).

^1H NMR ($CDCl_3$, 500 MHz): δ = 0.07 [s, 9 H, $Si(CH_3)_3$], 1.05 (m_c, 2 H, CH_2Si), 1.32, 1.33 (2 s, 3 H each, CH_3), 2.24 (s, 3 H, NCH_3), 3.42 (d, *J* = 13.8 Hz, 1 H, NC*H*$_2$Ph), 3.65 (d, *J* = 13.8 Hz, 1 H, NC*H*$_2$Ph), 3.53, 3.97 (2 m_c, 1 H each, 5′-H), 4.08 (d, *J* = 8.6 Hz, 1 H, 4-H), 4.15 (dd, *J* = 5.1, 8.6 Hz, 1 H, OCH_2), 4.18 (dd, *J* = 6.0, 8.6 Hz, 1 H, OCH_2), 4.58 (dt, *J* = 6.6, 8.6 Hz, 1 H, 4′-H), 5.65 (d, *J* = 7.8 Hz, 1 H, 2-H), 7.22–7.31 (m, 5 H, C_6H_5), 9.64 (d, *J* = 7.8 Hz, 1 H, CHO).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = –1.5 [q, $Si(CH_3)_3$], 17.5 (t, CH_2Si), 25.3, 26.9 (2 q, CH_3), 39.2 (t, NCH_3), 58.7 (t, N*C*H$_2$Ph), 63.9 (d, C-4), 65.8 (t, C-5′), 66.7 (t, OCH_2), 73.5 (d, C-4′), 109.0 (d, C-2), 109.6 (s, C-2′), 128.2, 128.3, 128.4, 138.7 (3 d, s, C_6H_5), 173.6 (s, C-3), 189.7 (d, CHO).

MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 405 (M^+, 3), 101 ($C_5H_9O_2^+$, 12), 91 (CH_2Ph^+, 100).

HRMS: *m*/*z* [M^+] calcd for $C_{22}H_{35}NO_4Si$: 405.23355; found: 405.23467.

(4*R*,4′*S*)-4-(Benzylmethylamino)-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-3-methoxy-1-phenylbut-2-en-1-one (5)

1,2-Oxazine **4** (100 mg, 0.263 mmol) was treated with MeOTf (0.29 mL, 0.290 mmol) as described in GP1. The mixture was stirred at r.t. for 6 h. Then it was cooled to 0 °C, treated with Et_3N (0.11 mL, 0.800 mmol), and stirred for 1 h. After workup, the crude product (113 mg) was purified by column chromatography (silica gel, hexane–EtOAc, 2:1) to yield 65 mg (63%) of ketone **5** as a colorless oil; $[\alpha]_D^{22}$ –240.9 (*c* 1.1, $CHCl_3$).

IR (film): 3085–3025 (=C–H), 2985–2800 (C–H), 1650 (C=O), 1585 cm^{-1} (C=C).

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.35, 1.40 (2 s, 3 H each, CH_3), 2.15 (s, 3 H, NCH_3), 3.60 (d, *J* = 13.9 Hz, 1 H, NC*H*$_2$Ph), 3.69 (d, *J* = 13.9 Hz, 1 H, NC*H*$_2$Ph), 3.88 (s, 3 H, OCH_3), 4.19 (dd, *J* = 6.0, 8.6 Hz, 1 H, 5′-H_B), 4.27 (dd, *J* = 4.7, 8.6 Hz, 1 H, 5′-H_A), 4.60 (ddd, *J* = 4.7, 6.0, 10.1 Hz, 1 H, 4′-H), 5.22 (d, *J* = 10.1 Hz, 1 H, 4-H), 6.41 (s, 1 H, 2-H), 7.20–7.85 (m, 10 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 25.9, 26.7 (2 q, CH_3), 38.6 (q, NCH_3), 55.0 (q, OCH_3), 58.7 (t, N*C*H$_2$Ph), 63.5 (d, C-4), 68.2 (t, C-5′), 73.9 (d, C-4′), 100.1 (d, C-2), 109.5 (s, C-2′), 126.7, 127.7, 128.1, 128.3, 128.4, 131.9, 139.6, 140.4 (6 d, 2 s, C_6H_5), 172.0 (s, C-3), 189.7 (s, C=O).

MS (EI, 80 eV, 120 °C): *m*/*z* (%) = 395 (M^+, 22), 294 ($M^+ - C_5H_9O_2$, 71), 105 ($C_7H_5O^+$, 36), 91 (CH_2Ph^+, 100).

HRMS: *m*/*z* [M^+] calcd for $C_{24}H_{29}NO_4$: 395.20966; found: 395.20897.

Anal. Calcd for $C_{24}H_{29}NO_4$ (395.5): C, 72.89; H, 7.39; N, 3.54. Found: C, 72.55; H, 7.39; N, 3.28.

(4*S*,4′*S*)-4-(Dibenzylamino)-4-(2′,2′-dimethyl-1,3-dioxolan-4′-yl)-3-[2-(trimethylsilyl)ethoxy]but-2-enal (8) and (1*S*,5*R*,8*S*)-2-Benzyl-6,6-dimethyl-8-(trimethylsiloxy)methyl-3,7-dioxa-2-azabicyclo[3.3.1]nonan-9-one (9)

Benzyl triflate was prepared by the addition of AgOTf (201 mg, 0.772 mmol) to benzyl bromide (0.090 mL, 0.772 mmol) in anhyd Et_2O (2 mL). The yellow precipitate of AgBr was filtered off and the formed clear solution was added to 1,2-oxazine *syn*-**1b** (200 mg, 0.511 mmol) in MeCN (4 mL) at 0 °C. The mixture was stirred at r.t. for 6 h until the starting material was consumed, then cooled to 0 °C, treated with Et_3N (0.21 mL, 1.54 mmol) and stirred for 1 h at r.t. The solvent and Et_3N were removed on a rotary evaporator. H_2O (10 mL) was added to the residue, which was extracted three times with Et_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated to yield 293 mg. The product was purified by column chromatography (silica gel, hexane–EtOAc, 3:1) to yield aldehyde **8** (61 mg, 25%) as a pale yellow oil and 80 mg (43%) of bicyclic ketone **9** as colorless crystals.

Aldehyde 8

$[\alpha]_D^{22}$ +23.3 (*c* 0.35, $CHCl_3$).

IR (film): 3085–3030 (=C–H), 2985–2895 (C–H), 1760 (C=O), 1655 cm^{-1} (C=C).

^1H NMR ($CDCl_3$, 500 MHz): δ = 0.06 [s, 9 H, $Si(CH_3)_3$], 1.09 (m_c, 2 H, CH_2Si), 1.42, 1.44 (2 s, 3 H each, CH_3), 3.54 (dd, *J* = 6.6, 8.6 Hz, 1 H, 5′-H_B), 3.56 (d, *J* = 13.9 Hz, 2 H, NC*H*$_2$Ph), 3.90 (m_c, 1 H, OCH_2), 3.95 (m_c, 1 H, 5′-H_A), 4.00 (m_c, 1 H, OCH_2), 4.05 (d, *J* = 13.9 Hz, 2 H, NC*H*$_2$Ph), 4.06 (d, *J* = 8.6 Hz, 1 H, 4-H), 4.68 (dt, *J* = 6.6, 8.6 Hz, 1 H, 4′-H), 5.48 (d, *J* = 7.7 Hz, 1 H, 2-H), 7.22–7.35 (m, 10 H, C_6H_5), 9.44 (d, *J* = 7.7 Hz, 1 H, CHO).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = –1.6 [q, $Si(CH_3)_3$], 17.6 (t, CH_2Si), 25.5, 26.7 (2 q, CH_3), 57.7 (t, N*C*H$_2$Ph), 63.7 (d, C-4), 66.0 (t, OCH_2), 67.3 (t, C-5′), 73.7 (d, C-4′), 107.9 (d, C-2), 109.9 (s, C-2′), 127.2, 127.3, 128.3, 128.4, 128.7, 128.8, 138.3, 136.4 (6 d, 2 s, C_6H_5), 172.9 (s, C-3), 189.9 (d, CHO).

MS (EI, 80 eV, 120 °C): *m*/*z* (%) = 481 (M^+, <1), 91 (CH_2Ph^+, 100).

Ketone 9[18]

Mp 61–63 °C; $[\alpha]_D^{22}$ +62.5 (*c* 0.35, $CHCl_3$).

IR (KBr): 3110–3030 (=C–H), 2975–2875 (C–H), 1730 (C=O), 1250 cm^{-1} (C–O).

^1H NMR ($CDCl_3$, 500 MHz): δ = 0.06 [s, 9 H, $Si(CH_3)_3$], 1.19, 1.38 (2 s, 3 H each, CH_3), 2.32 (dd, *J* = 2.8, 5.2 Hz, 1 H, 5-H), 3.32 (m_c, 1 H, 1-H), 3.75 (dd, *J* = 5.2, 9.0 Hz, 1 H, 8-CH_2), 3.92 (ddd, *J* = 2.0, 5.2, 8.2 Hz, 1 H, 8-H), 3.96 (d, *J* = 13.9 Hz, 1 H, NC*H*$_2$Ph), 4.01 (dd, *J* = 8.2, 9.0 Hz, 1 H, 8-CH_2), 4.14 (d, *J* = 13.9 Hz, 1 H, NC*H*$_2$Ph), 4.44 (dd, *J* = 5.2, 12.1 Hz, 1 H, 4-H_B), 4.51 (dd, *J* = 2.8, 12.1 Hz, 1 H, 4-H_A), 7.25–7.35 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = –0.6 [q, $Si(CH_3)_3$], 23.7, 26.7 (2 q, CH_3), 58.0 (d, C-5), 60.1 (t, N*C*H$_2$Ph), 61.2 (t, 8-CH_2), 68.9 (t, C-4), 70.0 (d, C-1), 76.0 (d, C-8), 78.3 (s, C-6), 127.4, 128.3, 128.7, 136.5 (3 d, s, C_6H_5), 207.8 (s, C=O).

MS (EI, 80 eV, 90 °C): *m*/*z* (%) = 363 (M^+, 13), 91 (CH_2Ph^+, 100).

HRMS: *m*/*z* [M^+] calcd for $C_{19}H_{29}NO_4Si$: 363.18658; found: 363.18477.

(3*S*,4*R*,4′*S*)-4-(Benzylmethylamino)-4-(2′,2′-dimethyl-1,3-dioxolan-4′-yl)-1-hydroxy-3-methoxybutan-2-one (12)

1,2-Oxazine **10** (100 mg, 0.314 mmol) was treated with MeOTf (0.31 mL, 0.314 mmol) as described in GP1. The mixture was stirred at r.t. for 6 h. Then it was cooled to 0 °C, treated with Et_3N (0.13 mL, 0.96 mmol), and stirred at this temperature for 1 h. After workup, the crude product (121 mg) was purified by column chro-

matography (silica gel, hexane–EtOAc, 3:1) to yield 74 mg (70%) of ketone **12** as a colorless oil; $[\alpha]_D^{22}$ +5.2 (*c* 1.0, $CHCl_3$).

IR (film): 3445 (O–H), 3090–3030 (=C–H), 2985–2875 (C–H), 1725 (C=O), 1250 cm^{-1} (C–O).

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.40, 1.45 (2 s, 3 H each, CH_3), 2.39 (s, 3 H, NCH_3), 3.13 (dd, *J* = 4.4, 8.5 Hz, 1 H, 4-H), 3.33 (s, 3 H, OCH_3), 3.70 (t, *J* = 7.7 Hz, 1 H, 5′-H_B), 3.74–3.83 (m, 3 H, 1-H, 3-H), 4.02 (dd, *J* = 6.0, 7.7 Hz, 1 H, 5′-H_A), 4.32 (d, *J* = 19.3 Hz, 1 H, NCH_2Ph), 4.45 (d, *J* = 19.3 Hz, 1 H, NCH_2Ph), 4.63 (ddd, *J* = 6.0, 7.7, 8.5 Hz, 1 H, 4′-H), 7.15–7.33 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 25.7, 26.8 (2 q, CH_3), 38.3 (q, NCH_3), 60.1 (q, OCH_3), 62.1 (t, C-1), 66.9 (d, C-4), 67.4 (t, C-5′), 67.5 (t, NCH_2Ph), 73.6 (d, C-4′), 88.3 (d, C-3), 109.3 (s, C-2′), 126.8, 128.1, 128.8, 139.6 (3 d, s, C_6H_5), 210.9 (s, C=O).

MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 337 (M^+, <1), 236 (M^+ – $C_5H_9O_2$, 28), 101 ($C_5H_9O_2^+$, 16), 91 (CH_2Ph^+, 100).

HRMS: *m*/*z* [M^+ – CH_3] calcd for $C_{18}H_{27}NO_5$: 322.16516; found: 322.16654.

(2*S*,3*S*,4*R*,4′*S*)-4-(Benzylmethylamino)-2-(*tert*-butyldimethylsiloxy)-4-(2′,2′-dimethyl-1,3-dioxolan-4′-yl)-3-methoxybutyraldehyde (15)

1,2-Oxazine **14** (100 mg, 0.230 mmol) was treated with MeOTf (0.23 mL, 0.230 mmol) as described in GP1. The mixture was stirred at r.t. for 6 h. Then it was cooled to 0 °C, treated with Et_3N (93 μL, 0.690 mmol), and stirred at this temperature for 1 h. After workup, the crude product (108 mg) was purified by column chromatography (silica gel, hexane–EtOAc, 2:1) to yield 64 mg (62%) of aldehyde **15** as a colorless oil; $[\alpha]_D^{22}$ +24.6 (*c* 0.8, $CHCl_3$).

IR (film): 3090–3030 (=C–H), 2985–2855 (C–H), 1730 (C=O), 1255 cm^{-1} (C–O).

^1H NMR ($CDCl_3$, 500 MHz): δ = 0.06, 0.14 [2 s, 3 H each, $Si(CH_3)_2$], 0.90 [s, 9 H, $C(CH_3)_3$], 1.39, 1.43 (2 s, 3 H each, CH_3), 2.20 (s, 3 H, NCH_3), 2.99 (dd, *J* = 2.7, 8.9 Hz, 1 H, 4-H), 3.35 (dd, *J* = 2.7, 5.1 Hz, 1 H, 3-H), 3.43 (s, 3 H, OCH_3), 3.59 (t, *J* = 7.9 Hz, 1 H, 5′-H_B), 3.73 (d, *J* = 12.8 Hz, 1 H, NCH_2Ph), 3.99 (d, *J* = 12.8 Hz, 1 H, NCH_2Ph), 4.04 (dd, *J* = 5.9, 7.9 Hz, 1 H, 5′-H_A), 4.12 (dd, *J* = 5.1, 7.5 Hz, 1 H, 2-H), 4.61 (ddd, *J* = 5.9, 7.9, 8.9 Hz, 1 H, 4′-H), 7.19–7.30 (m, 5 H, C_6H_5), 9.55 (d, *J* = 7.5 Hz, 1 H, CHO).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = –5.3, –4.5 [2 q, $Si(CH_3)_2$], 18.2, 25.8 [s, q, $C(CH_3)_3$], 25.7, 26.8 (2 q, CH_3), 38.2 (q, NCH_3), 58.9 (q, OCH_3), 59.0 (t, NCH_2Ph), 63.0 (d, C-4), 68.0 (t, C-5′), 73.2 (d, C-2), 73.9 (d, C-4′), 89.5 (d, C-3), 108.9 (s, C-2′), 126.8, 127.9, 128.6, 138.7 (3 d, s, C_6H_5), 196.6 (d, CHO).

MS (EI, 80 eV, 70 °C): *m*/*z* (%) = 451 (M^+, <1), 350 (M^+ – $C_5H_9O_2$, 38), 91 (CH_2Ph^+, 100).

HRMS: *m*/*z* [M^+ – $C_5H_9O_2$] calcd for $C_{24}H_{41}NO_5Si$: 350.21515; found: 350.21475.

(2*R*,4′*S*)-Benzyl-[(2′,2′-dimethyl-1,3-dioxolan-4′-yl)(2*H*-pyrazol-3-yl)methyl]methylamine (*syn*-19)

Aldehyde *syn*-**2a** (250 mg, 0.780 mmol) and hydrazine hydrate (0.40 mL, 9.50 mmol) were mixed in anhyd EtOH (6 mL). TFA (58 μL, 0.780 mmol) was added and the mixture was stirred under reflux for 2 h. EtOH was removed in vacuo and H_2O (5 mL) was added to the residue, which was extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated to yield 243 mg (quant) of pyrazole derivative *syn*-**19** as colorless crystals; mp 68–70 °C; $[\alpha]_D^{22}$ –30.7 (*c* 1.7, $CHCl_3$).

IR (KBr): 3260 (N–H), 3085–3030 (=C–H), 2985–2800 (C–H), 1675 cm^{-1} (C=C).

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.40, 1.42 (2 s, 3 H each, CH_3), 2.23 (s, 3 H, NCH_3), 3.47 (d, *J* = 13.3 Hz, 1 H, NCH_2Ph), 3.58 (t, *J* = 7.7 Hz, 1 H, 5′-H_B), 3.83 (d, *J* = 13.3 Hz, 1 H, NCH_2Ph), 3.97 (m_c, 1 H, 5′-H_A), 3.90 (d, *J* = 6.5 Hz, 1 H, 2-H), 4.69 (td, *J* = 6.5, 7.7 Hz, 1 H, 4′-H), 6.17 (d, *J* = 2.2 Hz, 1 H, 4-H), 7.21–7.38 (m, 5 H, C_6H_5), 7.50 (d, *J* = 2.2 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 25.4, 26.6 (2 q, CH_3), 38.5 (q, NCH_3), 59.2 (t, NCH_2Ph), 61.9 (d, C-2), 67.6 (t, C-5′), 75.5 (d, C-4′), 105.1 (d, C-4), 109.7 (s, C-2′), 127.0, 128.2, 129.2, 138.9 (3 d, s, C_6H_5), 135.6 (d, C-5), 174.4 (s, C-3).

MS (EI, 80 eV, 110 °C): *m*/*z* (%) = 301 (M^+, <1), 200 (M^+ – $C_5H_9O_2$, 91), 91 (CH_2Ph^+, 100).

HRMS: *m*/*z* [M^+] calcd for $C_{17}H_{23}N_3O_2$: 301.17902; found: 301.17854.

Anal. Calcd for $C_{17}H_{23}N_3O_2$ (301.4): C, 67.75, H, 7.69; N, 13.94. Found: C, 67.08; H, 7.22; N, 13.01.

(2*S*,3*R*)-3-(Benzylmethylamino)-3-(2*H*-pyrazol-3-yl)propane-1,2-diol (24)

Pyrazole derivative *syn*-**19** (440 mg, 1.46 mmol) was dissolved in AcOH (90%, 10 mL) and stirred under reflux for 2 h. AcOH was removed under reduced pressure and the residue was recrystallized from hexane–EtOAc to give the pure product **24** (342 mg, 90%) as colorless crystals; mp 153–155 °C; $[\alpha]_D^{22}$ –6.0 (*c* 0.4, $CHCl_3$).

IR (KBr): 3325 (O–H), 3085–3030 (=C–H), 2985–2865 cm^{-1} (C–H).

^1H NMR (CD_3OD, 500 MHz): δ = 2.10 (s, 3 H, CH_3), 3.28 (dd, *J* = 4.7, 11.7 Hz, 1 H, 1-H_B), 3.35 (d, *J* = 12.5 Hz, 1 H, NCH_2Ph), 3.56 (dd, *J* = 5.9, 11.7 Hz, 1 H, 1-H_A), 3.65 (d, *J* = 12.5 Hz, 1 H, NCH_2Ph), 3.95 (d, *J* = 8.9 Hz, 1 H, 3-H), 4.06 (m_c, 1 H, 2-H), 6.30 (s, 1 H, 5-H), 7.22–7.35 (m, 5 H, C_6H_5), 7.65 (s, 1 H, 6-H).

^{13}C NMR (CD_3OD, 125 MHz): δ = 37.8 (q, NCH_3), 59.7 (t, NCH_2Ph), 62.4 (d, C-3), 64.4 (t, C-1), 71.2 (d, C-2), 105.1 (d, C-5), 128.0, 129.2, 130.2, 139.6 (3 d, s, C_6H_5), 135.6 (s, C-4); the signal for C-6 could not be detected.

MS (FAB): *m*/*z* (%) = 289 (M^+ + Na, 23), 262 (M^+ + H, 46), 200 (M^+ – $C_2H_5O_2$, 35), 91 (CH_2Ph^+, 100).

HRMS: *m*/*z* [M^+ – $C_2H_5O_2$] calcd for 200.11765; found: 200.11877.

Anal. Calcd for $C_{14}H_{19}N_3O_2$ (261.3): C, 64.35; H, 7.33; N, 16.08. Found: C, 63.78; H, 7.05; N, 15.72.

2-[(4′*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-methoxy-1-methyl-1*H*-pyrrole (29)

A suspension of Raney-Ni in H_2O (ca. 67 mg) was washed with MeOH (3 × 5 mL). Then, anhyd MeOH (3 mL) was added and the solution was saturated with H_2 for 1 h. Then a solution of aldehyde *syn*-**2a** (30 mg, 0.095 mmol) in anhyd MeOH (2 mL) was added and the mixture was stirred for 1 h under H_2 atmosphere at normal pressure at r.t. Filtration through a pad of Celite and removal of the solvent in vacuo afforded 23 mg of pyrrole **29**. The product was purified by column chromatography (silica gel, hexane–EtOAc, 6:1) to yield 14 mg (70%) as a colorless oil; $[\alpha]_D^{22}$ –8.0 (*c* 0.45, $CHCl_3$).

IR (film): 2985–2850 (C–H), 1620 cm^{-1} (C=C).

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.42, 1.50 (2 s, 3 H each, CH_3), 3.63 (s, 3 H, NCH_3), 3.72 (s, 3 H, OCH_3), 4.11 (dd, *J* = 6.9, 8.2 Hz, 1 H, 5′-H_B), 4.21 (t, *J* = 8.2 Hz, 1 H, 5′-H_A), 5.27 (dd, *J* = 6.9, 8.2 Hz, 1 H, 4′-H), 5.81 (d, *J* = 3.0 Hz, 1 H, 4-H), 6.40 (d, *J* = 3.0 Hz, 1 H, 5-H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 25.3, 26.5 (2 q, CH_3), 35.3 (q, NCH_3), 58.6 (q, OCH_3), 66.6 (t, C-5′), 69.1 (d, C-4′), 94.6 (d, C-4), 108.6 (s, C-2′), 110.8 (s, C-2), 120.7 (d, C-5), 147.4 (s, C-3).

MS (EI, 80 eV, 30 °C): *m*/*z* (%) = 211 (M^+, 74), 140 (100).

HRMS: *m/z* [M$^+$] calcd for $C_{11}H_{17}NO_3$: 211.12085; found 211.12066.

(4*S*,4′*S*)-4-(Benzylmethylamino)-4-(2′,2′-dimethyl-1,3-dioxolan-4′-yl)-3-methoxybut-2-enal Oxime (*syn*-30)

Aldehyde *syn*-**2a** (50 mg, 0.157 mmol), hydroxylamine hydrochloride (44 mg, 0.631 mmol), and NaOMe (51 mg, 0.940 mmol) were stirred in anhyd MeOH (1 mL) under reflux for 24 h. MeOH was removed in vacuo and H_2O was added to the residue, and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated to yield 51 mg (97%) of the crude product. The pure product *syn*-**30** was obtained as colorless crystals of a mixture of two diastereomers (55:45); mp 112–114 °C; $[\alpha]_D^{22}$ +33.4 (*c* 1.5, $CHCl_3$).

IR (KBr): 3365 (O–H), 3085–3025 (=C–H), 2985–2935 (C–H), 1635 cm^{-1} (C=C).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.40, 1.44 (2 s, 3 H each, CH_3), 2.37 (s, 3 H, NCH_3), 3.47 (dd, *J* = 5.8, 7.1 Hz, 1 H, 5′-H_B), 3.49 (d, *J* = 13.9 Hz, 1 H, NC*H*$_2$Ph), 3.60, 3.66 (2 s, 3 H, OCH_3), 3.69 (d, *J* = 8.9 Hz, 1 H, 4-H), 3.91 (d, *J* = 13.9 Hz, 1 H, NC*H*$_2$Ph)*, 3.92 (d, *J* = 13.9 Hz, 1 H, NC*H*$_2$Ph), 3.96 (m_c, 1 H, 5′-H_A), 4.63 (m_c, 1 H, 4′-H), 5.56 (d, *J* = 10.2 Hz, 1 H, 2-H), 6.62 (d, *J* = 9.6 Hz, 1 H, 2-H)*, 7.04 (d, *J* = 9.6 Hz, 1 H, 1-H), 7.22–7.37 (m, 5 H, C_6H_5), 7.72 (d, *J* = 10.2 Hz, 1 H, 1-H)*; signals of the minor isomer are marked with *.

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 25.4, 26.7 (2 q, CH_3), 39.0 (q, NCH_3), 54.6, 54.8 (2 q, OCH_3), 59.9 (t, N*C*H$_2$Ph), 63.8, 64.1 (2 d, C-4), 67.2 (t, C-5′), 73.9 (d, C-4′), 92.8, 97.9 (d, C-2), 109.7 (s, C-2′), 126.7, 128.2, 128.9, 138.9 (3 d, s, C_6H_5), 144.4, 148.0 (2 d, C-1), 161.3, 163.3 (2 s, C-3).

MS (EI, 80 eV, 60 °C): *m/z* (%) = 334 (M$^+$, 4), 233 (M$^+$ – $C_5H_9O_2$, 100), 91 (CH_2Ph^+, 99).

HRMS: *m/z* [M$^+$] calcd for $C_{18}H_{26}N_2O_4$: 334.18927; found: 334.18847.

Anal. Calcd for $C_{18}H_{26}N_2O_4$ (334.4): C, 64.65; H, 7.84; N, 8.38. Found: C, 64.21; H, 7.63; N, 8.33.

(3*S*,4′*S*)-3-[Benzylmethylamino]-4-[2′,2-dimethyl-1′,3′-dioxolan-4′-yl]-1-cyano-2-methoxyprop-1-ene (31)

TsCl (40 mg, 0.210 mmol) was added in small portions to a stirred solution of oxime *syn*-**30** (70 mg, 0.210 mmol) in CH_2Cl_2 (1 mL) followed by the addition of Et_3N (67 μL, 0.490 mmol). The resulting solution was stirred at r.t. for 6 h, washed with H_2O (4 × 1 mL), then extracted with CH_2Cl_2 (3 × 5 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated to yield 63 mg of the crude product. This was purified by column chromatography (silica gel, hexane–EtOAc, 2:1) to yield 48 mg (72%) of nitrile **31** as colorless crystals; mp 69–71 °C; $[\alpha]_D^{22}$ +159.7 (*c* 1.0, $CHCl_3$).

IR (KBr): 3080–3025 (=C–H), 2985–2875 (C–H), 2215 (C≡N), 1610 cm^{-1} (C=C).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.39, 1.45 (2 s, 3 H each, CH_3), 2.31 (s, 3 H, NCH_3), 3.59 (d, *J* = 13.6 Hz, 1 H, NC*H*$_2$Ph), 3.63 (dd, *J* = 7.0, 8.2 Hz, 1 H, 5′-H_B), 3.67 (s, 3 H, OCH_3), 3.87 (d, *J* = 13.6 Hz, 1 H, NC*H*$_2$Ph), 3.91 (d, *J* = 8.8 Hz, 1 H, 3-H), 3.97 (dd, *J* = 6.3, 8.2 Hz, 1 H, 5′-H_A), 4.56 (ddd, *J* = 6.3, 7.0, 8.8 Hz, 1 H, 4′-H), 4.57 (s, 1 H, 1-H), 7.21–7.37 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 25.6, 26.7 (2 q, CH_3), 38.8 (q, NCH_3), 56.1 (q, OCH_3), 58.9 (t, N*C*H$_2$Ph), 66.9 (t, C-5′), 68.0 (d, C-3), 73.7 (d, C-4′), 73.8 (d, C-1), 109.9 (s, C-2′), 117.1 (s, CN), 127.0, 128.2, 128.8, 139.2 (3 d, s, C_6H_5), 174.6 (s, C-2).

MS (EI, 80 eV, 90 °C): *m/z* (%) = 316 (M$^+$, 13), 215 (M$^+$ – $C_5H_9O_2$, 76), 91 (CH_2Ph^+, 100).

HRMS: *m/z* [M$^+$] calcd for $C_{18}H_{24}N_2O_3$: 316.17868; found: 316.17733.

Anal. Calcd for $C_{18}H_{24}N_2O_3$ (316.4): C, 68.33; H, 7.65; N, 8.85. Found: C, 68.16; H, 7.55; N, 8.94.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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References

(1) (a) Schade, W.; Reissig, H.-U. *Synlett* **1999**, 632. (b) Pulz, R.; Cicchi, S.; Brandi, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2003**, 1153. (c) Helms, M.; Schade, W.; Pulz, R.; Watanabe, T.; Al-Harrasi, A.; Fišera, L.; Hlobilová, I.; Zahn, G.; Reissig, H.-U. *Eur. J. Org. Chem.* **2005**, 1003. For alternative approaches to synthetically very versatile 1,2-oxazines, see: (d) Reissig, H.-U.; Homann, K.; Hiller, F.; Zimmer, R. *Synthesis* **2007**, 2681. (e) Zimmer, R.; Collas, M.; Czerwonka, R.; Hain, U.; Reissig, H.-U. *Synthesis* **2008**, 237. (f) Zimmer, R.; Schmidt, E.; Andrä, M.; Duhs, M.-A.; Linder, I.; Reissig, H.-U. *Beilstein J. Org. Chem.* **2009**, *5*, No. 44; and references cited therein.

(2) Recent reviews: (a) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45. (b) Pfrengle, F.; Reissig, H.-U. *Chem. Soc. Rev.* **2010**, *39*, 549. (c) Lechel, T.; Reissig, H.-U. *Pure Appl. Chem.* **2010**, *85*, 1835. For selected recent applications developed by our group, see: (d) Yekta, S.; Prisyazhnyuk, V.; Reissig, H.-U. *Synlett* **2007**, 2069. (e) Pfrengle, F.; Al-Harrasi, A.; Brüdgam, I.; Reissig, H.-U. *Eur. J. Org. Chem.* **2009**, 282. (f) Bressel, B.; Reissig, H.-U. *Org. Lett.* **2009**, *11*, 527. (g) Pfrengle, F.; Lentz, D.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **2009**, *48*, 3165; *Angew. Chem.* **2009**, *121*, 3211. (h) Al-Harrasi, A.; Pfrengle, F.; Prisyazhnyuk, V.; Yekta, S.; Koóš, P.; Reissig, H.-U. *Chem. Eur. J.* **2009**, *15*, 11632. (i) Dekaris, V.; Reissig, H.-U. *Synlett* **2010**, 42. (j) Dekaris, V.; Bressel, B.; Reissig, H.-U. *Synlett* **2010**, 47. (k) Al-Harrasi, A.; Fischer, S.; Zimmer, R.; Reissig, H.-U. *Synthesis* **2010**, 304.

(3) (a) Bressel, B.; Egart, B.; Al-Harrasi, A.; Pulz, R.; Reissig, H.-U.; Brüdgam, I. *Eur. J. Org. Chem.* **2008**, 467. (b) Pulz, R.; Al-Harrasi, A.; Reissig, H.-U. *Org. Lett.* **2002**, *4*, 2353. (c) Pulz, R.; Watanabe, T.; Schade, W.; Reissig, H.-U. *Synlett* **2000**, 983.

(4) Preliminary report: Al-Harrasi, A.; Reissig, H.-U. *Synlett* **2005**, 1152.

(5) (a) Murahashi, S.-I.; Kodera, Y.; Hosomi, T. *Tetrahedron Lett.* **1988**, *29*, 5949. (b) For fragmentations of 5,6-dihydro-4*H*-1,2-oxazines by N-alkylation followed by base treatment, see also: Lidor, R.; Shatzmiller, S. *J. Am. Chem. Soc.* **1981**, *103*, 5916.

(6) Dugovič, B.; Wiesenganger, T.; Fišera, L.; Hametner, C.; Prónayová, N. *Heterocycles* **2005**, *65*, 591.

(7) (a) Meske, M. J. *J. Prakt. Chem.* **1997**, *339*, 426. (b) Bayón, P.; de March, P.; Figueredo, M.; Font, J. *Tetrahedron* **1998**, *54*, 15691. (c) Machetti, F.; Cordero, F. M.; De Sarlo, F.; Brandi, A. *Tetrahedron* **2001**, *57*, 4995. (d) Chevrier, C.; Defoin, A. *Synthesis* **2003**, 1221. (e) Dugovič, B.; Fišera, L.; Reissig, H.-U. *Eur. J. Org. Chem.* **2008**, 277.

(8) The 6-phenyl-substituted 1,2-oxazine derivative **4** was prepared from 1-methoxy-3-phenylprop-2-yne in a deprotonation–protonation–deprotonation–addition sequence with D-glyceraldehyde nitrone, analogously to the procedure described in: Chowdhury, M. A.; Reissig, H.-U. *Synlett* **2006**, 2383.

(9) (a) Tchissambou, L.; Benechie, M.; Khuong-Huu, F. *Tetrahedron* **1982**, *38*, 2687. (b) Nilsson, B. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1990**, *33*, 580. (c) Bergman, R.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 492. (d) Braña, M. F.; Garranzo, M.; de Pascual-Teresa, B.; Pérez-Castells, J.; Torres, M. R. *Tetrahedron* **2002**, *58*, 4825.

(10) Compound **16** was prepared by Grignard reaction of the corresponding 4-oxo-1,2-oxazine of **16** with MeMgBr: Hyrosová, E.; Reissig, H.-U., unpublished results.

(11) Review: Schweizer, F. *Angew. Chem. Int. Ed.* **2002**, *41*, 230; *Angew. Chem.* **2002**, *114*, 240.

(12) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*, Vol. 3; Katritzky, A. R.; Rees, C. W.; Scriven, E. V. C., Eds.; Pergamon: Oxford, **1996**, 1–75.

(13) Lee, K.; Kim, J.; Kim, J. *Tetrahedron Lett.* **2003**, *44*, 6737; and references cited therein.

(14) Reviews: (a) Tully, W. R.; Gardner, C. R.; Westwood, R. *Drug Dev. Res.* **1991**, *22*, 299. (b) Hajos, G.; Riedl, Z. In *Science of Synthesis*, Vol. 12; Neier, R., Ed.; Thieme: Stuttgart, **2002**, 613. Some selected publications: (c) Künstlinger, M.; Breitmaier, E. *Synthesis* **1983**, 161. (d) Drescher, M.; Öhler, E.; Zbiral, E. *Synthesis* **1991**, 362. (e) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Javadi, G. J.; Cai, D.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835. (f) Aggarwal, R.; Sumran, G. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2006**, *45*, 2690; and references cited therein.

(15) For related reaction conditions, see: Sosnicki, J. *Monatsh. Chem.* **2000**, *131*, 475.

(16) For related reactions of 2-aminobenzimidazole with carbohydrate derivatives, see: (a) Bari, A.; Feist, H.; Michalik, D.; Michalik, M.; Peseke, K. *Synthesis* **2004**, 2863. (b) Bari, A.; Feist, H.; Michalik, M.; Peseke, K. *Molecules* **2005**, *10*, 837. (c) Bari, A.; Milicevic, S.; Feist, H.; Michalik, D.; Michalik, M.; Peseke, K. *Synthesis* **2005**, 2758.

(17) Skattebøl, L. *J. Org. Chem.* **1966**, *31*, 1554.

(18) Al-Harrasi, A.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **2005**, *44*, 6227; *Angew. Chem.* **2005**, *117*, 6383.