Stereoselective Cycloaddition on Carbohydrates for the Synthesis of New Bicyclic Oxazolidines Bearing a Quaternary Bridgehead

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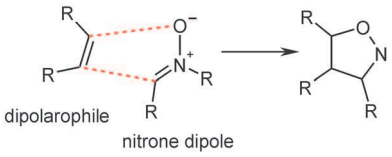
Abstract: A new carbohydrate nitrone intramolecular cycloaddition reaction is described for the enantioselective synthesis of bicyclic oxazolidines. By choice of the precursor, the products possess a chiral quaternary bridgehead aryl substitution. Also described is the diverse synthesis of 6-keto and 6-alkenyl carbohydrates by a general approach. The overall protocol provides versatility through the possibility of introducing diverse reagents at several entry points.

Key words: carbohydrates, cycloaddition, nitrone, oxazolidine, quaternary

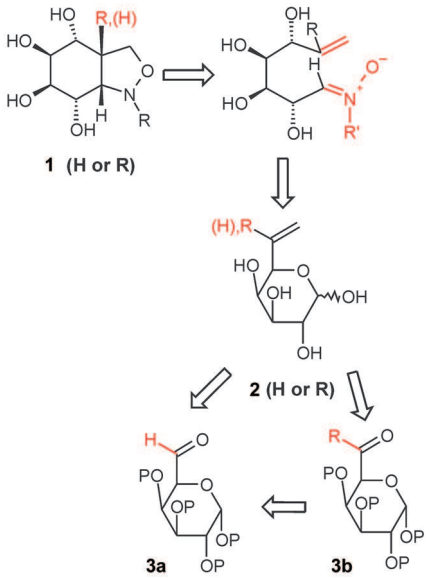
1,2-Oxazolidine compounds have often been used in the synthesis of natural products such as shikimic acid,[1] deoxynojiromycin[2] or other products with potential biological activity.[3] One of the major types of target compounds prepared employing this reaction are β-amino hydroxyl carbocycles, derived from the reductive or alkylating cleavage[1,4] of the N–O bond. The cycloaddition of nitrones is a powerful method for the construction of oxazolidines and has been employed on numerous occasions spanning over several decades (Scheme 1).[5]



Scheme 1 Nitrone cycloaddition

We required a general method for the synthesis of bicyclic heterocyclic compounds **1** containing either a bridgehead substituent or a proton. In addition, the products, whether substituted or not, should be formed in a stereoselective manner. In the present article we describe the use of a carbohydrate intramolecular variant of the nitrone cycloaddition. By this protocol, the nitrone dipole and a non-activated alkene dipolarophile are introduced into carbohydrates **2** in a few steps (Scheme 2).

The nitrone is generated from the masked anomeric aldehyde function. The method was developed in such a manner that the required substitution pattern can be accommodated by the choice of the starting materials employed. It is thus possible to introduce diversity in a combinatorial manner in any of at least three entry points into the reaction sequence. Moreover, the specific chirality of the starting carbohydrate should induce enantioselectivity to the cycloaddition reaction. Naturally, the original chiral centers of the carbohydrate are conserved.



Scheme 2 Protocol for choice of substitution

In order to achieve this goal of a general method, we reasoned that a key intermediate, accessible in a few straightforward steps by known procedures from readily available precursors would be essential. As such, we developed our approach starting from the carbohydrate chiral pool. Indeed the chemistry of functional group modifications on sugars is one of the richest,[6] including selective protections/deprotections, deoxygenations, oxidations, to mention but a few. If required, numerous new derivatives with functional modifications would be accessible by any of these methods.

According to the retrosynthetic sequence described above (Scheme 2), it is possible firstly to oxidize the primary alcohol function of a chosen carbohydrate to a 6-carbaldehyde sugar **3a** and then create the monosubstituted alkene **2** (H), which leads, in turn, to simple bicyclic compounds **1** (H) unsubstituted at the bridgehead. Alternatively, it is possible to introduce any type of aryl or alkyl substituent

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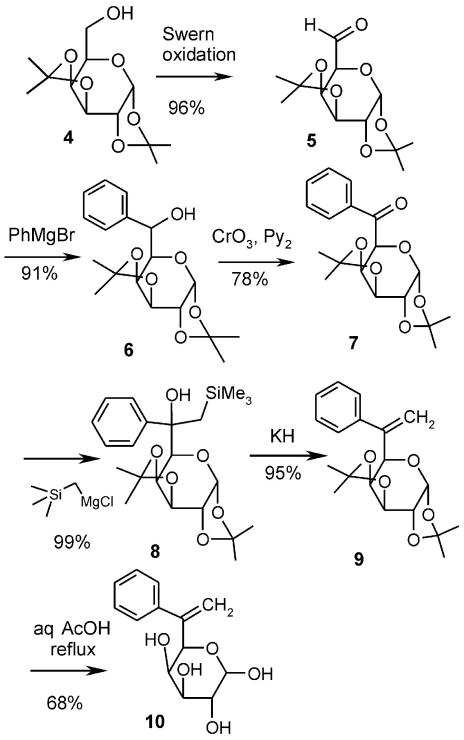
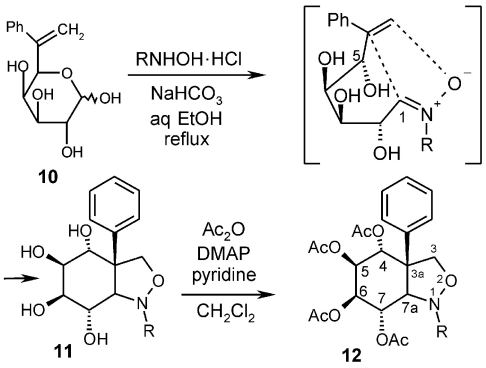
by sequential carbanion addition/oxidation. The resulting ketone **3b** can then be transformed to alkene **2** (R) then to the required bicyclic oxazolidine **1** (R) bearing a chiral quaternary bridgehead substituent. It is worth noting that large diversity can be introduced at this stage of the synthesis by varying the carbanion species.

Thus, suitably protected galactose was employed as a model compound to apply the concept (Scheme 3). Swern oxidation[7] of 1,2:3,4-di-*O*-isopropylidengalactose (**4**) furnished the aldehyde **5** which underwent addition with phenylmagnesium bromide to the secondary alcohol **6**. The following oxidation step of 1,2:3,4-di-*O*-isopropylidene-6-phenyl-α-D-galactopyranose **6** into ketone **7** was attempted using manganese dioxide in dichloromethane, at room temperature during 24 hours,[8] but was unsuccessful. Instead, chromium(VI) trioxide/pyridine[9] in dichloromethane was employed, and the desired ketone **7** was obtained in a satisfactory yield of 78%. Next, the alkene function was introduced by a Wittig reaction[7,10] using methyltriphenylphosphonium bromide and potassium *tert*-butoxide. Since this reaction proceeded in only 35% yield, we decided to perform a Peterson olefination,[11] which successfully afforded the required alkene **9** in an excellent overall yield of 94%. Finally, treatment of 6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-6-phenyl-α-D-galactohept-6-enopyranose (**9**) in refluxing aqueous acetic acid[12] provided deprotected carbohydrate **10** in 68% yield.



Scheme 3 Synthesis of 6,6-disubstituted carbohydrate alkene

The next step, which is also the key of our strategy, is the intramolecular nitrone-alkene cycloaddition reaction (Scheme 4). Being insoluble in the usual cycloaddition solvents such as toluene or xylene,[13] the saccharide precursor (**10**) was treated in refluxing aqueous ethanol with *N*-alkylhydroxylamines of varying substitution[14] (benzyl, methyl and isopropyl). For ease of purification, the crude mixture was submitted to acetylation, and after purification, afforded diasteromerically and enantiomerically pure tetraacetyl bicyclic compounds **12a**, **12b** and **12c** in 64%, 63% and 61% overall yields, respectively, from **10**.[15]



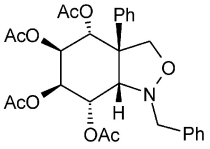
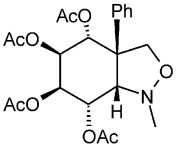
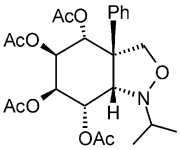
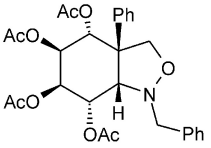
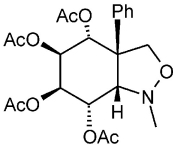
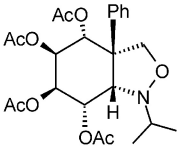
Scheme 4 Intramolecular cycloaddition

The stereochemistry of the cycloadducts (3a*S*,4*R*,5*S*,6*R*,7*S*,7a*S*)-1-alkyl-3a-phenyloctahydrobenzo[*c*]isoxazole-4,5,6,7-tetraol tetraacetates (**12a**–**c**) was assigned by NMR spectroscopic techniques. The observed ^{1}H NMR coupling constants ($J_{7,7a}$) of 2.0 Hz, 0 Hz and 4.2 Hz, for products **12a**, **12b** and **12c**, respectively, are consistent with an equatorial/axial configuration. Since the chirality at C-4, C-5, C-6 and C-7 was unchanged, we concluded that relative configuration between H-7 and H-7a was *cis*. As the cyclic junction C-3a/C-7a is necessarily *cis*, the stereochemistry of the new quaternary center was therefore deduced. Indeed, in every case, intramolecular cycloaddition between the nitrone and the double bond proceeded with high stereoselectivity to provide the (3a*S*)-diastereoisomer (Scheme 4). We suggest that the dipole approaches the alkene function from the face opposite to that of the adjacent 5-hydroxyl group. In consequence, we speculate that the opposite diastereoisomer at the quaternary center would be obtained if a β-C-5 carbohydrate was employed.

As a further development of this method, we reasoned that, since the dipolar reaction intermediates had a marked dipole moment, activation by microwave irradiation should be particularly useful to effect this cycloaddition reaction. In general, microwaves can be advantageously employed for carrying out the synthesis of numerous types of compounds.[16] We thus explored the present intramolecular carbohydrate nitrone-alkene cycloaddition reaction under microwave activation. The experimental conditions employed were straightforward: the reagents were mixed in a minimal amount of solvent to ensure thorough contact in a test tube with a condenser and submitted to microwave irradiation.[17] After the condensation step was concluded, the crude mixture was submitted to classical acetylation conditions, in order to facilitate the purification and structural analysis of the cycloadducts **12a**–**c**

(Table 1). In all cases, the yields were in the 90% range, approximately 30% higher than under classical thermal conditions. Indeed, we also observed a clear advantage in terms of reaction time (80 min vs. 48 h!).

Table 1 Cycloaddition under Thermal and Microwave (MW) Conditions

Entry	Conditions[15]	Product	Yield (%)
1	Thermal: refluxing EtOH, 48 h	 **12a**	64
2	Thermal: refluxing EtOH, 48 h	 **12b**	63
3	Thermal: refluxing EtOH, 48 h	 **12c**	61
4	MW: 100 W, 70 °C, 80 min	 **12a**	87
5	MW: 100 W, 70 °C, 80 min	 **12b**	90
6	MW: 100 W, 70 °C, 80 min	 **12c**	91

In conclusion, we have studied a new carbohydrate nitrone intramolecular cycloaddition, which represents a new approach for the synthesis of chiral bicyclic oxazolidines. The reaction proceeded in a stereoselective manner, providing new oxazolidines as single diastereoisomers. Moreover, the compounds possess a chiral quaternary bridgehead aryl substitution. Also described is the synthesis of 6-keto- and 6-alkenyl carbohydrates by a general synthetic approach. This method is compatible with numerous varieties of precursors (sugars, carbanions, oximes), which can be introduced in the reaction sequence at different entry points. This method is thus amenable to the synthesis of new, diversely substituted compounds.

Acknowledgment

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(14) It should be noted that this is a suitable entry point for introducing diversity, since hydroxylamines of multiple variation are very readily accessible.
(15) **Typical Procedure for the Synthesis of (3a*S*,4*R*,5*S*,6*R*,7*S*,7a*S*)-1-methyl-3a-phenyloctahydrobenzo[*c*]isoxazole-4,5,6,7-tetraol Tetraacetate 12c.**
Thermal conditions: in a two-necked, round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser and a thermometer, $NaHCO_3$ (218 mg, $2.6\cdot10^{-3}$ mol, 2.6 equiv) was added to a solution of carbohydrate **10** (252 mg, $1.0\cdot10^{-3}$ mol) and *N*-isopropylhydroxylamine hydrochloride (290 mg, $2.6\cdot10^{-3}$ mol, 2.6 equiv) in 80% aq EtOH (15 mL). The mixture was stirred under reflux during 48 h. After cooling and removal of the solvent under reduced pressure, Ac_2O (0.6 mL), pyridine (1 mL), DMAP (cat.), and CH_2Cl_2 were added. The mixture was stirred at r.t. during 6 h. The mixture was then washed with 3×6 mL of H_2O. The solvent was removed under reduced pressure and the resulting oil was purified by flash chromatography on silica gel (EtOAc–CH_2Cl_2, 20:80, R_f = 0.36) to provide **12c** in 61% yield as a yellowish oil.
^{1}H NMR ($CDCl_3$): δ = 2.16 (s, 12 H, CH_3-CO-), 2.54 (s, 3 H, H-8), 2.74 (dd, $J_{7,7'}$ = 13.9 Hz, $J_{7\text{-}1}$ = 7.1 Hz, 1 H, H-7), 3.10 (d, $J_{7',7}$ = 13.9 Hz, 1 H, H-7′), 3.58–3.60 (m, 1 H, H-1), 5.00–5.60 (m, 4 H, H-2, H-3, H-4, H-5), 7.23–7.39 (m, 5 H, H-10, H-11, H-12, H-13, H-14) ppm.
^{13}C NMR ($CDCl_3$): δ = 20.3, 20.8, 21.0, 21.1 (*C*H_3-CO-), 33.8 (C-7), 47.0 (C-8), 63.1 (C-1), 71.3 (C-2), 71.4, 71.5,

71.6 (C-3, C-4 et C-5), 86.5 (C-6), 126.5 (C-12), 127.6, 127.7 (C-11, C-13, C-10, C-14), 143.4 (C-9), 168.4, 169.2, 170.1, 170.5 (C=O) ppm.
IR: 3023 s (arom. =CH), 2966 m, 2930 w (CH_n), 1742 s (C=O), 1538 w, 1493 w, 1448 s (arom. C=C), 1372 s (C-N), 1217 s (C-O), 754 s, 703 s (arom. C-H) cm^{-1}.

Compound 12a Major Conformer:
^{1}H NMR ($CDCl_3$): δ = 1.99, 2.02, 2.04, 2.13 (4 s, 12 H, CH_3), 2.27 (dd, $J_{8,8bis}$ = 13.0 Hz, $J_{8,7a}$ = 10.0 Hz, 1 H, H-8), 3.01 (d, $J_{8bis,8}$ = 13.0 Hz, 1 H, H-8bis), 3.60 (dd, $J_{7a,8}$ = 10.0 Hz, $J_{7a,7}$ = 2.0 Hz, 1 H, H-7a), 4.18 (d, $J_{3,3bis}$ = 13.4 Hz, 1 H, H-3), 4.21 (d, $J_{3bis,3}$ = 13.4 Hz, 1 H, H-3bis), 5.11 (dd, $J_{7,6}$ = 8.8 Hz, $J_{7,7a}$ = 2.0 Hz, 1 H, H-7), 5.31 (d, $J_{4,5}$ = 8.6 Hz, 1 H, H-4), 5.40 (dd, $J_{5,4}$ = 8.6 Hz, $J_{5,6}$ = 1.4 Hz, 1 H, H-5), 5.43 (dd, $J_{6,7}$ = 8.8 Hz, $J_{6,5}$ = 1.4 Hz, 1 H, H-6), 7.13–7.31 (m, 10 H, H-arom.) ppm.
^{13}C NMR ($CDCl_3$): δ = 20.1, 20.5, 20.9, 21.0 (CH_3), 34.6 (C-3), 62.9 (C-8), 63.9 (C-7a), 70.2 (C-7), 73.5, 73.6 (C-5, C-6), 74.1 (C-4), 87.0 (C-3a), 126.1, 128.0, 128.2, 128.6, 129.8 (C-10, C-11, C-12, C-13, C-14, C-16, C-17, C-18, C-19, C-20), 134.3 (C-9), 140.0 (C-15), 168.4, 169.3, 169.7, 170.5 (C=O) ppm.
IR: 3020 m (arom. =CH), 2989 s, 2934 m (CH_n), 1741 s (C=O), 1497 m, 1450 m (arom. C=C), 1370 s (C-N), 1218 s (C-O), 755 s, 701 s (arom. C-H) cm^{-1}.

Compound 12a Minor Conformer:
^{1}H NMR ($CDCl_3$): δ = 1.99, 2.02, 2.04, 2.13 (4 s, 12 H, CH_3), 2.81 (dd, $J_{8,8bis}$ = 13.8 Hz, $J_{8,7a}$ = 6.7 Hz, 1 H, H-8), 3.19 (d, $J_{8bis,8}$ = 13.8 Hz, 1 H, H-8bis), 3.57 (d, $J_{3,3bis}$ = 12.9 Hz, 1 H, H-3), 3.86 (dd, $J_{7a,8}$ = 6.7 Hz, $J_{7a,7}$ = 3.9 Hz, 1 H, H-7a), 3.86–3.96 (m, 2 H, H-6, H-4), 3.91 (d, $J_{3bis,3}$ = 12.9 Hz, 1 H, H-3bis), 5.04 (dd, $J_{5,4}$ = 4.1 Hz, $J_{5,6}$ = 1.3 Hz, 1 H, H-5), 5.17 (dd, $J_{7,7a}$ = 3.9 Hz, $J_{7,6}$ = 3.8 Hz, 1 H, H-7), 7.13–7.31 (m, 10 H, H-arom.) ppm.
^{13}C NMR ($CDCl_3$): δ = 20.1, 20.5, 20.9, 21.0 (CH_3), 34.3 (C-3), 62.1 (C-8), 66.2 (C-7a), 71.9 (C-7), 72.4, 72.6 (C-4, C-6), 75.5 (C-5), 88.2 (C-3a), 126.7, 127.7, 127.8, 128.4, 128.9 (C-10, C-11, C-12, C-13, C-14, C-16, C-17, C-18, C-19, C-20), 135.8 (C-9), 142.1 (C-15), 168.4, 169.3, 169.7, 170.5 (C=O) ppm.
IR: 3020 m (arom. =CH), 2989 s, 2934 m (CH_n), 1741 s (C=O), 1497 m, 1450 m (arom. C=C), 1370 s (C-N), 1218 s (C-O), 755 s, 701 s (arom. C-H) cm^{-1}.

Compound 12b:
^{1}H NMR ($CDCl_3$): δ = 2.16 (s, 12 H, CH_3-CO-), 2.54 (s, 3 H, H-8), 2.74 (dd, $J_{3,3bis}$ = 13.9 Hz, $J_{3\text{-}7a}$ = 7.1 Hz, 1 H, H-3), 3.10 (d, $J_{3bis,3}$ = 13.9 Hz, 1 H, H-3bis), 3.58–3.60 (m, 1 H, H-7a), 5.00–5.60 (m, 4 H, H-4, H-5, H-6, H-7), 7.23–7.39 (m, 5 H, H-10, H-11, H-12, H-13, H-14) ppm.
^{13}C NMR ($CDCl_3$): δ = 20.3, 20.8, 21.0, 21.1 (CH_3-CO-), 33.8 (C-3), 47.0 (C-8), 63.1 (C-7a), 71.3 (C-7), 71.4, 71.5, 71.6 (C-4, C-5, C-6), 86.5 (C-3a), 126.5 (C-12), 127.6, 127.7 (C-11, C-13, C-10, C-14), 143.4 (C-9), 168.4, 169.2, 170.1, 170.5 (C=O) ppm.
IR: 3023 s (arom. =CH), 2966 m, 2930 w (CH_n), 1742 F (C=O), 1538 w, 1493 w, 1448 s (arom. C=C), 1372 s (C-N), 1217 s (C-O), 754 s, 703 s (arom. C-H) cm^{-1}.

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(17) **Typical procedure for the synthesis of (3a*S*,4*R*,5*S*,6*R*,7*S*,7a*S*)-1-methyl-3a-phenyloctahydrobenzo[c]isoxazole-4,5,6,7-tetraol tetraacetate 12c.**
Microwave conditions: in a pyrex test tube (2 × 15), $NaHCO_3$ (218 mg, $2.6 \cdot 10^{-3}$ mol, 2.6 equiv), *N*-isopropylhydroxylamine hydrochloride (290 mg, $2.6 \cdot 10^{-3}$ mol, 2.6 equiv), carbohydrate **10** (252 mg, $1.0 \cdot 10^{-3}$ mol) and 80% aq EtOH (1 mL) were submitted to microwave irradiations (CEM *Discover* apparatus. Settings: 70 °C, 100 W) during 80 min. After cooling and the solvent evaporated under reduced pressure, the crude product was acetylated and purified as in Ref. 15.