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Synthesis of Chiral 10, 11 and 12-Membered Nitrogen and Oxygen Heterocycles by Intramolecular Nitrile Oxide Cycloaddition of Tethered *N*- and *O*-Allyl Carbohydrate Derivatives

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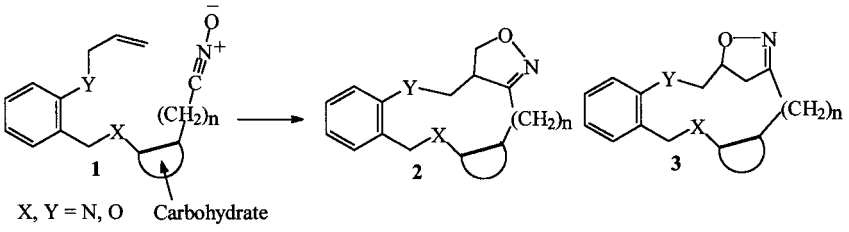
Abstract—Chiral 10 to 12-membered nitrogen and oxygen heterocycles fused to isoxazoline rings have been prepared in a highly regioselective and stereoselective manner by intramolecular nitrile oxide cycloaddition of tethered *N*- and *O*-allyl carbohydrate derivatives. The use of a $-Y-Ar-CH_2$ tether containing a 1,2-disubstituted aromatic ring between the heteroatom attached to the nitrile oxide-bearing carbohydrate scaffold, and the allyl group, facilitates the formation of the medium-sized rings. The cycloaddition afforded bridged isoxazolines in the cases of *O*-tethered allyl carbohydrate derivatives, whereas a fused isoxazoline resulted when a *N*(Ts)-tethered allyl derivative was used.

Introduction

Nitrone and nitrile oxide cycloadditions are two of the most useful and operationally simple cycloaddition reactions.[1,2] The intramolecular variety of these reactions have been extensively used in the preparation of a variety of cyclic skeletons fused to isoxazolidine and isoxazoline rings. Recent applications of these reactions to *N*- and *O*-alkenyl carbohydrate nitrones and nitrile oxides has led to the development of a powerful method for the synthesis of enantiopure cyclic ether derivatives,[3–8] such as tetrahydrofurans, pyrans and oxepanes as well as cyclic amines such as piperidines and azepines.[9,10] Among the alkenyl groups investigated in these cases, allyl or substituted allyl groups are most widely used. We envisaged that if a tether $Y-Ar-CH_2$ (Scheme 1) containing a 1,2-disubstituted aromatic moiety is incorporated between an heteroatom X attached to a carbohydrate scaffold and the allyl moiety, the cycloaddition of a nitrile oxide **1** generated from this tethered carbohydrate system is expected to lead to the formation of chiral isoxazolines **2** or **3**, or both depending on the regioselectivity of the reaction. An important structural feature of **2** and **3** is the presence of a core macroheterocycle, which is fused to an aromatic ring, a carbohydrate ring (such as furanoside), and an isoxazoline ring. The ring size of the core heterocycle is dependent on the value of n, i.e. the number of intervening carbon atoms between the nitrile oxide and the carbohydrate ring, and a bridged isoxazoline **3** has a core ring one carbon atom larger than the fused isoxazoline **2**. It is apparent from the structures of **2** and **3** that the formation of 10 to 12-membered heterocycles is a distinct possibility when $n=0$ and 1. Although 8-membered and other macrocycles have been prepared by intramolecular nitrile oxide cycloadditions,[11–13] to our knowledge, synthesis of the aforementioned ring systems have not to date been reported by this cycloaddition. We describe herein the synthesis of some chiral 10 to 12-membered heterocycles based on the above strategy.



Scheme 1.

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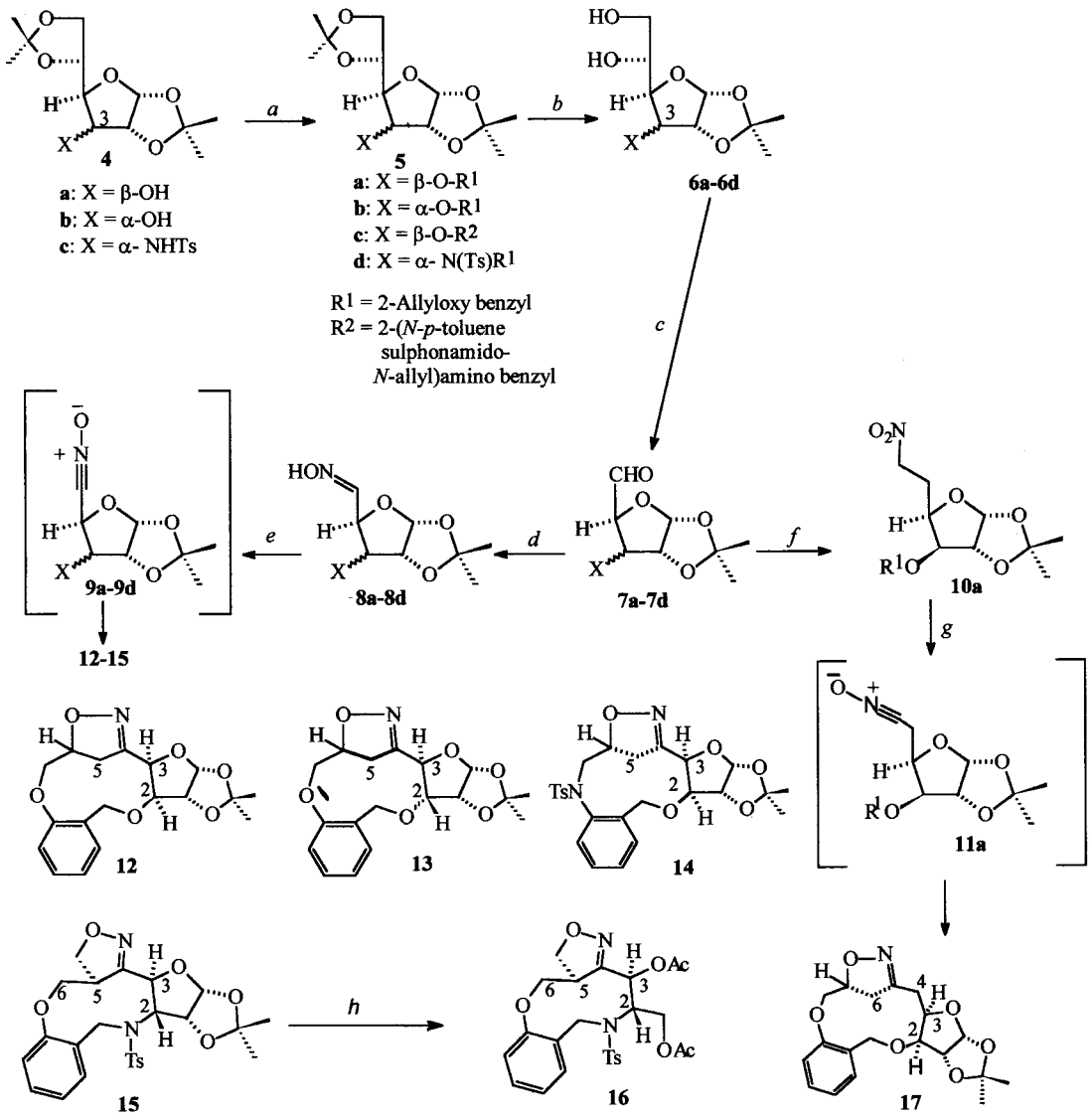

Scheme 2. *Reagents: a*: for **4a→5a** and **4b→5b**, 2-allyloxy benzyl bromide, Bu_4NBr, CH_2Cl_2-50% aq. NaOH (1:1), 25°C, 4 h, 78% (**5a**), 96% (**5b**); for **4c→5d**, 2-allyloxy benzyl bromide, anhydrous K_2CO_3, acetone, 25°C, 16 h, 95%; for **4a→ 5c**, 2-*N*-allyl(Ts)amino benzyl bromide, Bu_4NBr, CH_2Cl_2-50% aq. NaOH (1:1), 25°C, 4 h, 56%; *b*: 75% aq. AcOH; 25°C, 14 h, 83% (**6a**), 78% (**6b**), 72% (**6c**), 72% (**6d**); *c*: $NaIO_4$, MeOH–H_2O (4:1), 0–25°C, 1.5 h; *d*: $NH_2OH{\cdot}HCl$, MeOH-py (4:1), reflux, 8 h; *e*: Chloramine-T hydrate, EtOH, reflux, 8 h, 50% (**12**), 62% (**13**), 35% (**14**), 70% (**15**); *f*: (i) CH_3NO_2, KF, *i*-PrOH, 25°C, 24 h (ii) Ac_2O, DMAP, ether–CH_2Cl_2, 25°C, 12 h (1:1); (iii) $NaBH_4$, EtOH–THF (3;5), 0°C, 4 h, 77%; *g*, PhNCO, Et_3N, C_6H_6, 25°C, 50 h, 50%; *h* (i) 4% H_2SO_4 in CH_3CN–H_2O (10:1), 25°C, 24 h (ii) $NaIO_4$, MeOH–H_2O (2:1), 25°C, 2 h (iii) $NaBH_4$, MeOH, 0°C, 2 h (iv) Ac_2O, py, DMAP, 25°C, 12 h, 52% from **15**.

Results and Discussion

The tethered carbohydrate scaffold was readily prepared by alkylation of the carbohydrate derivatives **4a**–**4c** with 2-allyloxy benzyl bromide and 2-(*N*-*p*-toluenesulphonamido-*N*-allyl)amino benzyl bromide according to Scheme 2. Alkylation of **4a** and **4b** was effected[14] in a biphasic medium consisting of CH_2Cl_2 and 50% aquous NaOH solution in the presence of tetrabutylammonium bromide, while alkylation of **4c** was achieved in acetone in the presence of K_2CO_3. The tethered carbohydrate derivatives **5a**–**5d** were converted to the oximes **8a**–**8d** through a sequence of reactions[4,6] involving selective removal of the 5,6-isopropylidene moiety giving diols **6a**–**6d**, $NaIO_4$ induced oxidative cleavage of the diols to the aldehydes **7a**–**7d**, followed by treatment with NH_2OH in pyridine. It should be mentioned that the intermediates involved in the above sequence of reactions were not rigorously purified although their NMR spectral characteristics were consistent with the expected structures.

Treatment of the oxime **8a** with chloramine-T[15] in ethanol afforded, *via* the cycloaddition of the nitrile oxide **9a**, the bridged isoxazoline **12** exclusively in 50% yield as evident from the ^1H NMR spectrum of the product. The appearance of two sets of double doublets at δ 3.11 (J=17, 3 Hz) and δ 3.26 (J=17, 10 Hz) in the ^1H NMR spectrum and appearance of a $-CH_2-$ peak at δ 39.0 and a quaternary carbon peak (C=N) at δ 160.1 or 157.5 in the ^{13}C NMR spectrum of **12** indicated the presence of the bridged isoxazoline moiety. The structure of **12** was further corroborated by HSQC and DQFCOSY NMR experiments. However, the

stereochemistry of the newly formed chiral centre could not be established even by a NOESY experiment. It was not possible to assign the orientation of the bridge methylene, because of the absence of any cross peak, which could correlate either the bridgehead proton or the bridge methylene protons with other existing carbohydrate chiral centres. The isoxazoline **12** incorporates a 1,5-dioxacycloundecane ring, which is fused to a furanoside ring besides benzo and an isoxazolo rings.

A change in the stereochemistry at 3-C did not alter the regioselectivity of the cycloaddition. This was evident from the cycloaddition of the nitrile oxide **9b**, the 3-C epimer of **9a**, obtained by treatment of the oxime **8b** with chloramine-T. The bridged isoxazoline **13** was formed exclusively in 62% yield. The pattern of the ^{1}H NMR spectrum of **13** was closely similar to that of **12**. The bridged isoxazoline structure of **13** was consistent with the appearance of two sets of double doublets at δ 2.57 (J=16.9, 2.2 Hz) and δ 3.15 (J=17.0, 10.8 Hz) in the ^{1}H NMR spectrum as well as a $-CH_2-$ carbon peak at δ 34.7 and a quaternary carbon peak at δ 158.0 or 158.1 (C=N) in the ^{13}C NMR spectrum. The NOESY spectrum of **13** revealed distinct cross peaks between 2-H and the 5-H_B, i.e. the more shielded of the bridge methylene protons. This correlation established the β-orientation of the bridge methylene; since 2-C in **13** has the same stereochemistry as that of 3-C in **4b**, the 1,5-dioxacycloundecane skeleton present in **13** is diastereomeric with that present in **12**.

The aforementioned observations led to the conclusion that a change in stereochemistry at 3-C of the nitrile oxide had no effect on the regioselectivity of the cycloaddition. In order to investigate whether a change in the heteroatom Y could bring about any change in the regioselectivity, the oxime **8c** was subjected to treatment with chloramine-T. However, the resulting nitrile oxide **9c**, which has *N*(Ts)-allyl group instead of *O*-allyl, again gave rise to a bridged isoxazoline **14** exclusively in 53% yield. The ^{1}H and ^{13}C NMR spectra of **14** exhibited all the characteristics of a bridged isoxazoline observed for **12** and **13**. The appearance of two sets of double doublets at δ 3.21 (J=17.1, 11.4 Hz) and 3.61 (J=17.1, 4.3 Hz) in the ^{1}H NMR spectrum as well as a signal at δ 38.1 (bridge $-CH_2-$) and a quaternary carbon peak at δ 152.7 (C=N) was a clear indication of the bridged isoxazoline nature of **14**. The stereochemistry of **14** could be established on the basis of the NOESY spectrum, the most useful feature of which was the appearance of distinct cross peaks between the less shielded of the 5-CH_2 protons i.e. 5-H_A with 2-H and 3-H and between the more shielded proton i.e. 5-H_B with 3-H. This observation led to an α-orientation of the bridge methylene of the isoxazoline ring, because both 2-H and 3-H are α as 3-H and 4-H in **4a**. The core macrocycle of **14** is a 1-oxa-5-azacycloundecane system.

Thus, it is observed that a change in stereochemistry at 3-C of the nitrile oxide, or substitution of oxygen atom by nitrogen did not affect the regioselectivity of the cycoaddition, and a bridged isoxazoline was the exclusive product in each case. Still another variation was possible through a change in heteroatom X. Thus, oxidation of the oxime **8d** resulted in the formation of the nitrile oxide **9d**, which has a *N*(Ts)-tethered allyl instead of a *O*-tethered allyl in **9b**. Unlike the previous cases, cycloaddition of **9d** led to the formation of a fused isoxazoline **15** in 70% yield. This was evident from the appearance of a one-proton multiplet at δ 3.68 in the ^{1}H NMR spectrum of **15** due to 5-H of the isoxazoline ring, which is coupled to four vicinal protons. In addition, the appearance of a –CH-peak at δ 48.8 due to 5-C in the ^{13}C NMR spectrum was consistent with the presence of the fused isoxazoline moiety in **15**. A conspicuous feature of the ^{1}H NMR spectrum of **15** was the rather unusual chemical shift (δ 2.31) of one of the protons (6-H_B) of 6-CH_2 which is attached to an oxygen atom. This was confirmed by decoupling experiments, which indicated its coupling to 6-H_A at δ 4.12. The attachment of 6-C to an oxygen atom was confirmed by a C,H-COSY experiment, which indicated the attachment of both 6-H_A and 6-H_B with 6-C, the signal for which appeared at δ 69.2. The stereochemistry of the methine proton in **15** could not be established from the NOESY spectrum. In order to explore the possibility of bringing the methine proton in a closer proximity with 2-H or 3-H for a better chance of getting NOESY cross peaks, an attempt was made to transform **15** to a more flexible system. To this end, the isoxazoline **15** was subjected to a known degradation of the furanoside ring.[4,8] A sequence of reactions consisting of acid removal of the isopropylidenedioxy group, vicinal diol cleavage with $NaIO_4$, reduction of the resulting hydroxyaldehyde by $NaBH_4$, and a final acetylation yielded the diacetate **16**. Both the ^{1}H and ^{13}C NMR spectrum of **16** indicated the survival of the isoxazoline-fused azaoxaheterocycle through the degradation procedure. Like its precursor **15**, 6-H_B of $-O$-6-CH_2 in **16** appeared as a high field doublet of doublets at δ 2.04. The assignment was confirmed by decoupling as well as C,H-COSY experiments as was done for **15**. The NOESY spectrum of **16** exhibited a distinct cross peak between 5-H and 3-H. It is well known that the 3-C does not undergo any epimerisation during the degradation procedure leading to **16**.[4,8] Keeping this in mind, the observation in the NOESY experiment indicated clearly that 5-H has an α orientation i.e. the same as that of 3-H. Therefore, the orientation of 5-H in the precursor **15** is also α.

It was apparent, therefore, that cycloaddition of the nitrile oxides **9a**–**9c**, which have a 3-*O*-tethered allyl carbohydrate backbone resulted in the formation of the bridged isoxazolines **12**, **13** and **14**. However, the regioselectivity of the cycloaddition was drastically altered in the cycloaddition of 3-*N*(Ts)-tethered allyl carbohydrate nitrile oxide **9d** resulting in the exclusive formation of the fused isoxazoline **15**. The reason for this change in regioselectivity is not known, although similar change in regioselectivity or chemical reactivity, when oxygen atom is replaced by -*N*(Ts) has been reported earlier.[9,10,16] The fused isoxazoline **15** incorporates a 1-oxa-5-azacyclodecane system. So a change in the regioselectivity of the cycloaddition made available a 10-membered heterocycle, in contrast to the 11-membered one obtained in the previous cases.

In a separate route, the aldehyde **7a** was converted to the nitro compound **10a** following a known protocol,[11] involving condensation with nitromethane, acetylation of the resulting nitroaldol with acetic anhydride, and DMAP and reduction with $NaBH_4$ (Scheme 2). Treatment of **10a** with

phenyl isocyanate led to the exclusive formation of the bridged isoxazoline **17** *via* the nitrile oxide **11a**. The appearance of two double doublets in the ^{1}H NMR spectrum at δ 2.77 and δ 3.23 with large geminal coupling constants (16 Hz), as well as the bridge $-CH_2-$ carbon peak (6-C) at δ 41.6 and a quaternary carbon peak (C=N) in the ^{13}C NMR spectrum, is consistent with the presence of the bridged isoxazoline moiety. The isoxazoline **17** has an extra $-CH_2-$ group over the isoxazoline **12**, and the protons of this methylene group *viz* 4-H_A and 4-H_B appeared as two double doublets at δ 2.75 and 2.56. As expected, many of the ^{1}H NMR spectral features of **17** were similar to those of **12**. Analysis of H,H-COSY, C,H-COSY and NOESY spectra of **17** led to the assignment of α-orientation of the bridge methylene i.e. $-6\text{-}CH_2-$, which was in accordance with the appearance of a cross peak between 6-H_A and 2-H in the NOESY spectrum of **17**. The nitrile oxide **11a** has an extra methylene group between the nitrile oxide moiety and the carbohydrate backbone, and consequently the isoxazoline **17** incorporates a 1,5-dioxacyclododecane ring.

In conclusion, the work described above demonstrates that 10- to 12-membered heterocycles can be prepared through the application of the nitrile oxide strategy depicted in Scheme 1. This strategy can be extended to the synthesis of heterocycles containing one heteroatom and even carbocycles by replacing X or Y in 1 (Scheme 1) by one carbon atom, or both of X and Y by two carbon atoms. The use of a different tether resulting in structural variations adds to the scope of this strategy.

Experimental

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were measured for $CDCl_3$ solutions at 300 and 75 MHz, respectively unless otherwise stated. Mass spectra were recorded on a JEOL AX-500 and JEOL D-300 instrument using electron impact (70 eV) ionisation. Reactions were monitored by thin layer chromatography using Merck 60 F_{254} precoated silica gel plates (No. 5554). Chloramine-T and phenyl isocyanate were purchased from E-Merck (Germany). Silica gel of mesh size 60–120 (SRL, India) was used for column chromatography. Organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed on a rotary evaporator under reduced pressure.

General procedure for the preparation of 5a, 5b and 5c

A mixture of 1,2:5,6-di-*O*-isopropylidene glucose (for **5a** and **5c**) or allose (for **5b**) (5.76 mmol) in CH_2Cl_2 (40 ml), 50% NaOH solution (40 ml), tetrabutylammonium bromide (0.576 mmol) and 2-allyloxy benzyl bromide (for **5a** and **5b**) or 2-*N*-allyl(*p*-toluenesulphonyl)amino benzyl bromide (for **5c**) (5.94 mmol) was vigorously stirred for 4 h at 25°C. Water (50 ml) was added and the mixture extracted with CH_2Cl_2. The combined organic layer was washed with water, dried and the solvent removed under reduced pressure to afford a syrup, which was chromatographed (10% ethyl acetate in hexane) over silica-gel to give **5** as a colourless syrup.

3-*O*-(2-Allyloxy benzyl)-1,2:5,6-diisopropylidene-α-D-glucofuranose (5a). Yield 78%; $[\alpha]_D^{28}=-21.5$ (*c* 0.41, $CHCl_3$); IR (neat) ν_{max} 2988, 1647, 1376 cm^{-1}; ^{1}H NMR δ 7.38 (d, *J*=8.1 Hz, 1H), 7.22 (t, *J*=8.3 Hz, 1H), 6.94 (t, *J*=7.4 Hz, 1H), 6.85 (d, *J*=8.1 Hz, 1H), 6.05 (m, 1H), 5.89 (d, *J*=3.6 Hz, 1H), 5.41 (dd, *J*=17.2, 1.3 Hz, 1H), 5.28 (dd, *J*=10.5, 1.1 Hz, 1H), 4.76 (d, *J*=12.3 Hz, 1H), 4.65 (d, *J*=12.9 Hz, 1H), 4.64 (d, *J*=3.4 Hz, 1H), 4.53 (bd, *J*=5.1 Hz, 2H), 4.38 (dd, *J*=13.1, 6.2 Hz, 1H), 4.18 (dd, *J*=7.2, 3.0 Hz, 1H), 4.05 (m, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C NMR δ 155.8 133.1, 128.9, 128.6, 126.2, 120.4, 117.2, 111.4, 111.2, 108.6, 105.1, 82.3, 81.7, 81.172.5, 68.5, 67.1, 66.9, 26.7, 26.6, 26.1, 25.3; MS (EI) *m/z* 406, 391, 147, 91; Calcd for $C_{22}H_{30}O_7$: C, 64.99; H, 7.44; Found: C, 64.83; H, 7.63%.

3-*O*-(2-Allyloxy benzyl)-1,2:5,6-diisopropylidene-α-D-allofuranose (5b). Yield 96%; $[\alpha]_D^{24}=+69.4$ (*c* 0.49, $CHCl_3$); IR (neat) ν_{max} 1599, 1374 cm^{-1}; ^{1}H NMR δ 7.42 (d, *J*=7.4 Hz, 1H), 7.27 (t, *J*=7.6 Hz, 1H), 6.96 (t, *J*=7.3 Hz, 1H), 6.85 (d, *J*=8.2 Hz, 1H), 6.05 (m, 1H), 5.77 (d, *J*=3.7 Hz, 1H), 5.42 (dd, *J*=17.3, 1.4 Hz, 1H), 5.27 (dd, *J*=10.5, 1.1 Hz, 1H), 4.83 (d, *J*=12.2 Hz, 1H), 4.69 (m, 2H), 4.55 (bd, *J*=5.0 Hz, 2H), 4.37 (dt, *J*=9.6, 7.2, 2.5 Hz, 1H), 4.15 (dd, *J*=8.8, 2.6 Hz, 1H), 3.93 (m, 3H), 1.58 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H); ^{13}C NMR δ 156.4, 133.3, 130.1, 129.1, 126.0, 120.7, 117.3, 112.8, 111.6, 109.5, 103.9, 77.8, 77.7, 77.0, 74.7, 68.8, 66.6, 64.7, 26.8, 26.5, 26.0, 25.3; MS (EI) *m/z* 406, 233, 147, 91; Calcd for $C_{22}H_{30}O_7$: C, 64.99; H, 7.44; Found: C, 64.72; H, 7.23%.

3-*O*-[2-*N*-(*p*-Toluenesulphonyl)-allylamino]benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5c). Yield 56%; $[\alpha]_D^{24}=-25.8$ (*c* 0.38, $CHCl_3$); IR (neat) ν_{max} 1642, 1597, 1378 cm^{-1}; ^{1}H NMR δ 7.62 (d, *J*=7.1 Hz, 1H), 7.53 (d, *J*=8.2 Hz, 2H), 7.30 (m, 3H), 7.11 (t, *J*=8.2 Hz, 1H), 6.48 (d, *J*=7.9 Hz, 1H), 5.91 (d, *J*=6.9 Hz, 1H), 5.76 (m, 1H), 5.09–4.88 (m, 3H), 4.83–4.66 (m, 2H), 4.42 (bd, *J*=4.7 Hz, 2H), 4.18–4.00 (m, 4H), 3.77 (m, 1H), 2.45 (s, 3H), 1.50 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H); ^{13}C NMR δ 143.7, 140.0, 136.7, 135.2, 132.1, 129.5 (2×C), 129.1, 128.7, 128.0 (2×C), 127.6, 127.4, 119.8, 111.7, 109.0, 105.3, 82.4, 81.4, 72.5, 68.3, 67.4, 54.8, 26.8, 26.7, 26.2, 25.4, 21.5; MS (EI) *m/z* 559 (M^+), 544 (M^+-15); Calcd for $C_{29}H_{37}O_8NS$: C, 62.23; H, 6.67; N, 2.50; Found: C, 62.01; H, 6.47; N, 2.41%.

3-Deoxy-3-[-*N*-*p*-toluenesulphonyl)(2-allyloxybenzyl)]amino-1,2:5,6-diisopropylidene-α-D-allofuranose (5d). A mixture of 3-deoxy-3-(*p*-toluenesulphonamido)-1,2:5,6-di-*O*-isopropylidene allofuranose **4c** (3.64 g, 8.81 mmol), anhydrous K_2CO_3 (5 g), 2-allyloxy benzyl bromide (2.0 g, 8.82 mmol) and acetone (50 ml) was stirred vigorously for 16 h at 25°C. The mixture was filtered and residue was washed repeatedly with acetone (100 ml). The syrup obtained after removal of solvent was chromatographed over silica-gel (ethyl acetate–hexane=1:9) to give **5d** as colourless needles (4.71 g, 95%); mp 111–112°C; $[\alpha]_D^{28}=+72.4$ (*c* 0.50, $CHCl_3$); IR (neat) ν_{max} 1375, 1336 cm^{-1}; ^{1}H NMR δ 7.72 (d, *J*=8.2 Hz, 2H), 7.64 (d, *J*=6.8 Hz, 1H), 7.27 (d, *J*=8.1 Hz, 2H), 7.18 (t, *J*=8.5 Hz, 1H), 6.94 (t, *J*=7.4 Hz, 1H), 6.78 (d, *J*=8.2 Hz, 1H), 6.03 (m, 1H), 5.54 (d, *J*=3.6 Hz, 1H), 5.34 (dd, *J*=17.2, 1.4 Hz, 1H), 5.24 (dd, *J*=10.4, 1.1 Hz, 1H), 5.00 (d, *J*=17.2 Hz, 1H),

4.73 (d, J=17.2 Hz, 1H), 4.59 (bd, J=5.3 Hz, 2H), 4.36 (m, 2H), 3.85 (m, 2H), 3.73 (m, 2H), 2.42 (s, 3H), 1.36 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H); ^{13}C NMR δ 155.4, 143.4, 137.4, 133.4, 130.8, 129.4 (2×C), 128.1, 127.5 (2×C), 126.4, 120.5, 117.6, 112.9, 111.2, 109.2, 103.8, 79.8, 75.7, 75.2, 68.9, 64.6, 60.8, 44.8, 26.4, 26.1, 26.0, 25.0, 21.5; MS (EI) m/z 559 (M^+), 544 (M^+-15), 107, 91; Calcd for $C_{29}H_{37}O_8NS$: C, 62.23; H, 6.67; N, 2.50; Found: C, 62.25; H, 6.43; N, 2.49%.

General procedure for the preparation of 6a–6d

A solution of **5** (2.5 mmol) in aqueous acetic acid (75% v/v, 10 ml) was stirred for 14 h at room temperature. The mixture was evaporated under reduced pressure and the residue was repeatedly co-evaporated with dry toluene (3×10 ml) to give a residue, which was chromatographed over silica gel using ethyl acetate as the eluent to afford the diol **6** as a syrup.

6a: Yield 83%; $[\alpha]_D^{28}=-31.9$ (c 0.99, $CHCl_3$); IR (neat) ν_{max} 3500, 2932, 1646, 1377 cm^{-1}; ^{1}H NMR δ 7.30 (m, 2H), 6.95 (m, 2H), 6.04 (m, 1H), 5.94 (d, J=3.7 Hz, 1H), 5.41 (dd, J=17.2, 1.0 Hz, 1H), 5.30 (dd, J=10.5, 1.0 Hz, 1H), 4.70 (m, 2H), 4.59 (m, 3H), 4.13 (m, 2H), 3.97 (m, 1H), 3.78 (dd, J=11.5, 3.3 Hz, 1H), 3.62 (dd, J=11.5, 6.0 Hz, 1H), 1.48 (s, 3H), 1.33 (S, 3H); ^{13}C NMR δ 156.5, 132.9, 130.2, 129.6, 125.4, 120.8, 117.9, 111.9, 111.6, 105.2, 82.2, 81.7, 79.8, 69.5, 69.1, 67.8, 64.2, 26.6, 26.1; MS (EI) m/z 366 (M^+), 351 (M^+-15), 326, 267, 205, 164, 147, 107, 91, 85.

6b: Yield 78%; $[\alpha]_D^{24}=-41.2$ (c 0.66, $CHCl_3$); IR (neat) ν_{max} 3438 (br), 2924, 1452, 1378 cm^{-1}; ^{1}H NMR δ 7.30 (m, 2H), 6.93 (m, 2H), 6.06 (m, 1H), 5.76 (d, J=3.6 Hz, 1H), 5.37 (m, 2H), 4.81 (m, 2H), 4.71 (m, 1H), 4.63 (m, 2H), 4.07 (dd, J=8.9, 3.6 Hz, 1H), 3.91 (m, 1H), 3.62 (m, 3H), 1.58 (s, 3H), 1.36 (s, 3H); ^{13}C NMR δ 156.4, 133.0, 130.1, 129.4, 125.1, 120.9, 118.0, 112.1, 111.6, 105.2, 82.2, 81.5, 79.7, 69.6, 69.0, 67.9, 64.2, 26.3, 25.8; MS (EI) m/z 366 (M^+), 351 (M^+-15).

6c: Yield 72%; $[\alpha]_D^{24}=-32.6$ (c 0.57, $CHCl_3$); IR (neat) ν_{max} 3504 (br), 2930, 1643, 1597, 1451, 1375, 1344 cm^{-1}; ^{1}H NMR δ 7.53 (m, 3H), 7.32 (m, 3H), 7.15 (t, J=8.4 Hz, 1H), 6.48 (t, J=7.6 Hz, 1H), 5.95 (d, J=3.7 Hz, 1H), 5.71 (m, 1H), 5.01 (d, J=9.5 Hz, 1H), 4.84 (m, 4H), 4.44 (m, 1H), 4.15 (m, 3H), 3.84 (dd, J=11.5, 3.3 Hz, 1H), 3.73 (m, 2H), 2.45 (s, 3H), 1.51 (s, 3H), 1.30 (s, 3H); ^{13}C NMR δ 155.6, 142.9, 137.0, 133.3, 130.0, 129.2, 128.3, 127.9 (2×C), 126.0, 120.6, 117.9, 113.0, 111.2, 103.9, 79.2, 77.6, 71.5, 69.0, 62.7, 59.9, 45.9, 26.8, 25.9, 21.4; MS (EI) m/z519 (M^+), 504 (M^+-15).

6d: Yield 75%; $[\alpha]_D^{28}=+64.4$ (c 0.50, $CHCl_3$); IR (neat) ν_{max} 3458, 2932, 1378, 1333 cm^{-1}; ^{1}H NMR δ 7.74 (d, J=8.2 Hz, 2H), 7.62 (d, J=7.2 Hz, 1H), 7.28 (d, J=8.1 Hz, 2H), 7.21 (t, J=8.3 Hz, 1H), 6.95 (t, J=7.6 Hz, 1H), 6.80 (d, J=8.2 Hz, 1H), 6.05 (m, 1H), 5.61 (d, J=3.5 Hz, 1H), 5.36 (dd, J=17.3, 1.3 Hz, 1H), 5.26 (dd, J=10.5, 1.0 Hz, 1H), 5.16 (d, J=16.8 Hz, 1H), 4.75 (d, J=16.8 Hz, 1H), 4.55 (bd, J=5.3 Hz, 2H), 4.26 (m, 2H), 4.05 (dd, J=9.7, 4.3 Hz, 1H), 3.51 (m, 3H), 2.42 (s, 3H), 2.05 (bs, 1H), 1.68 (bs, 1H), 1.45 (s, 3H), 1.14 (s, 3H); ^{13}C NMR δ 155.4, 143.6, 137.1, 133.3, 130.0, 129.4 (2×C), 128.3, 127.5 (2×C), 126.3, 120.6, 117.6, 113.0, 111.4, 103.7, 79.4, 77.8, 71.6, 68.9, 62.3, 59.3, 44.6, 26.5, 25.8, 21.4; MS (EI) m/z 519 (M^+), 504 (M^+-15), 461, 155, 91.

General procedure for cycloaddition of the nitrile oxide 9a–9d

To an ice cold stirred solution of the above mentioned diol (1 mmol) in methanol (20 ml), $NaIO_4$ (1.05 mmol) in water (5 ml) was added. After 30 min of stirring at 0°C, the ice bath was removed and the mixture was stirred for a further 1 h. The residue obtained after removal of methanol was extracted with CH_2Cl_2 (3×20 ml) and the combined organic layer washed with water, dried and evaporated to give the aldehyde as syrup, which was not purified further. IR: **7a**: 1740 cm^{-1}; **7b**: 1737 cm^{-1}; **7c**:1730 cm^{-1}; **7d**: 1728 cm^{-1}. A mixture of this syrup, methanol (20 ml), pyridine (5 ml) and $NH_2OH.HCl$ (1.5 mmol) was heated at reflux for 8 h. After removal of solvent, the residue was extracted with CH_2Cl_2 (2×20 ml). The combined organic extract was washed with water (3×20 ml), dried and evaporated to give the oxime **8** as a syrup, which was used for the next step without further purification. A mixture of **8** (5.7 mmol) and chloramine-T hydrate (10.5 mmol) and ethanol (30 ml) was heated under reflux for 8 h. After completion of the reaction as revealed by TLC, the resulting colourless precipitate was filtered and the filtrate evaporated under reduced pressure. The residue obtained was extracted with with CH_2Cl_2 (3×50 ml) and the combined organic layer was washed with water (3×50 ml), dried, and evaporated to give a thick brown liquid. This crude material was chromatographed over silica-gel using the solvents specified below for individual products.

Isoxazoline 12: $CHCl_3$–MeOH (49:1); Yield 50%; colourless needles, mp196–198°C (chloroform–hexane); $[\alpha]_D^{27}=-89.3$ (c 0.82, $CHCl_3$); IR (KBr) ν_{max} 2988, 2938, 1605, 1449, 1378 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J=8 Hz, 1H), 7.18 (d, J=8 Hz, 1H), 6.90 (t, J=8 Hz, 1H), 6.81 (d, J=8 Hz, 1H), 5.97 (d, J=4 Hz, 1H), 5.25 (d, J=4 Hz, 1H), 4.87 (m, 1H), 4.69 (d, J=8 Hz, 1H), 4.65 (d, J=4 Hz, 1H), 4.52 (d, J=10 Hz, 1H), 4.47 (d, J=10 Hz, 1H), 4.18 (d, J=4 Hz, 1H), 3.83 (d, J=10 Hz, 1H), 3.26 (dd, J=17, 10 Hz, 1H), 3.11 (dd, J=17, 3 Hz, 1H), 1.52 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (25 MHz, acetone-d_6) δ 160.1, 157.5, 131.9, 131.1, 126.7, 121.0, 113.3, 112.5, 106.6, 86.5, 84.9, 78.9, 77.7, 72.7, 72.1, 39.0, 27.3, 26.5; MS (EI) m/z 347, 332, 318, 260, 219, 147, 129, 107, 91, 85; Calcd for $C_{18}H_{21}O_6N$: C, 62.22; H, 6.10; N, 4.03; Found: C, 61.93; H, 5.99; N, 3.93%.

Isoxazoline 13: $CHCl_3$–MeOH (49:1); Yield 62%; colourless needles, mp187–188°C (chloroform–hexane); $[\alpha]_D^{25}=-61.3$ (c 0.6, $CHCl_3$); IR (KBr) ν_{max} 2980, 1598, 1453, 1375 cm^{-1}; ^{1}H NMR δ 7.45 (d, J=7.1 Hz, 1H), 7.30 (t, J=8.2 Hz, 1H), 6.99 (t, J=7.4 Hz, 1H), 6.88 (d, J=8.3 Hz, 1H), 5.68 (d, J=3.4 Hz, 1H), 5.22 (d, J=12.8 Hz, 1H), 5.08 (d, J=8.7 Hz, 1H), 4.86 (bd, 1H), 4.55 (m, 2H), 4.47 (d, J=11.4 Hz, 1H), 4.10 (d, J=11.9 Hz, 1H), 3.69 (dd, J=8.7, 4.4 Hz, 1H), 3.15 (dd, J=17.0, 10.8 Hz, 1H), 2.57 (dd, J=16.9, 2.2 Hz, 1H), 1.64 (s, 3H), 1.36 (s, 3H); ^{13}C

NMR δ 158.1, 158.0, 131.9, 130.0, 125.2, 121.4, 113.6, 111.7, 103.2, 79.8, 78.7, 77.1, 74.1, 71.6, 64.9, 34.7, 26.8, 26.3; MS (EI) *m/z* 348 (M^++1), 347 (M^+), 332 (M^+−15), 318, 190, 149, 107, 91; Calcd for $C_{18}H_{21}O_6N$: C, 62.22; H, 6.10; N, 4.03; Found: C, 62.18; H, 5.83; N, 3.88%.

Isoxazoline 14: $CHCl_3$–MeOH (49:1); Yield 35%; colourless needles, mp 230–231°C (chloroform–ether); $[\alpha]_D^{27}$=+112.7 (*c* 0.30, $CHCl_3$); IR (KBr) ν_{max} 2984, 1596, 1450, 1376, 1348 cm^{-1}; ^1H NMR δ 7.43 (m, 3H), 7.26 (m, 3H), 7.08 (t, *J*=7.7 Hz, 1H), 6.42 (d, *J*=8.0 Hz, 1H), 6.02 (d, *J*=3.5 Hz, 1H), 5.04 (m, 1H), 4.94 (d, *J*=3 Hz, 1H), 4.83 (d, *J*=11.8 Hz, 1H), 4.75 (m, 2H), 4.36 (d, *J*=3.0 Hz, 1H), 3.92 (dd, *J*=14.5, 3.7 Hz, 1H), 3.61 (dd, *J*=17.1, 4.3 Hz, 1H), 3.46 (dd, *J*=14.5, 2.7 Hz, 1H), 3.21 (dd, *J*=17, 11.4 Hz, 1H), 2.45 (s, 3H), 1.52 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ 152.7, 144.4, 138.6, 137.7, 130.4, 129.6, 128.7, 128.2, 128.0, 125.6, 112.0, 105.0, 84.6, 83.5, 78.9, 77.2, 70.5, 53.4, 38.1, 26.9, 26.2, 21.6; MS (EI) *m/z* 500 (M^+), 485 (M^+−15), 155, 91; Calcd for $C_{25}H_{28}O_7N_2S$: C, 59.98; H, 5.64; N, 5.60; Found: C, 60.21; H, 5.65; N, 5.48%.

Isoxazoline 15: $CHCl_3$–MeOH (49:1); Yield 70%; colourless needles, mp 224–225°C (chloroform–hexane); $[\alpha]_D^{28}$=−26.0 (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 2930, 1604, 1459, 1381, 1343, 1248 cm^{-1}; ^1H NMR δ 7.47 (d, *J*=6.4 Hz, 1H), 7.21 (t, *J*=7.6 Hz, 1H), 7.03 (t, *J*=7.4 Hz, 1H), 6.88 (m, 4H), 6.47 (d, *J*=8.0 Hz, 1H), 5.94 (d, *J*=3.3 Hz, 1H), 5.31 (d, *J*=9.2 Hz, 1H), 4.93 (m, 2H), 4.80 (d, *J*=14.7 Hz, 1H), 4.55 (d, *J*=14.7 Hz, 1H), 4.23 (t, *J*=9.2 Hz, 1H), 4.12 (t, *J*=7.2 Hz, 1H), 3.91 (dd, *J*=8.9, 3.3 Hz, 1H), 3.67 (m, 1H), 2.31 (dd, *J*=11.6, 7.6 Hz, 1H), 2.26 (s, 3H), 1.60 (s, 3H), 1.38 (s, 3H); ^{13}C NMR δ 159.6,156.8, 142.1, 139.0, 133.6, 129.3, 128.7, 126.4, 125.3, 122.0, 112.6, 112.5, 103.5, 81.5, 71.5, 70.1, 69.2, 65.5, 48.8, 47.6, 26.6, 26.0, 21.3; MS (EI) *m/z* 500 (M^+), 485 (M^+−15), 470, 441, 413, 254, 229, 202, 155, 91; Anal. Calcd for $C_{25}H_{28}O_7N_2S$: C, 59.98; H, 5.64; N, 5.60; Found: C, 59.69; H, 5.45; N, 5.31%.

Transformation of 15 to 16

A solution of **15** (150 mg, 0.3 mmol) in 10:1 CH_3CN–H_2O (10 ml) containing 4% H_2SO_4 was stirred for 24 h at 25°C. The solution was neutralised by the addition of aq. $NaHCO_3$ and filtered. After removal of solvent the residue obtained was dissolved in methanol (10 ml), to which a solution of sodium metaperiodate (50 mg) in water (5 ml) was added dropwise with stirring over 2 h. The mixture was filtered and the residue was washed with methanol. After concentration of the filtrate, the intermediate hydroxy aldehyde was obtained as a syrup which was dissolved in methanol (5 ml) and cooled to 0°C. To this solution $NaBH_4$ (25 mg) was added and the mixture was stirred for 2 h. The mixture was then acidified with aqueous AcOH (1:1). After extraction with chloroform the syrup obtained was dissolved in pyridine (5 ml). Ac_2O (2 ml) and a catalytic amount of DMAP were added. The reaction was kept overnight at 25°C, and then extracted with $CHCl_3$ (3×10 ml). The combined organic extract was washed with 5% HCl, water (3×20 ml) and dried. The residue obtained after removal of solvent was crystallised from $CHCl_3$–petroleum ether affording **16** as a colourless microcrystalline solid (80 mg, 52% overall yield from **15**), mp 180–181°C; $[\alpha]_D^{27}$=−161.0 (*c* 0.41, $CHCl_3$); IR (KBr) ν_{max} 2960, 1742, 1599, 1440, 1368, 1334 cm^{-1}; ^1H NMR δ 7.47 (d, *J*=7.2 Hz, 1H), 7.23 (dt, *J*=9.2, 7.8, 1.6 Hz, 1H), 7.07 (t, *J*=7.3 Hz, 1H), 6.89 (m, 4H), 6.55 (d, *J*=8.1 Hz, 1H), 5.80 (d, *J*=11.1 Hz, 1H), 5.40 (m, 1H), 4.63 (dd, *J*=12.0, 3.6 Hz, 1H), 4.41 (m, 3H), 4.19 (t, *J*=9 Hz, 1H), 4.04 (t, *J*=6.6 Hz, 1H), 3.91 (m, 1H), 3.77 (dd, *J*=8.6, 3.6 Hz, 1H), 2.26 (s, 3H), 2.18 (s, 3H), 2.04 (dd, *J*=7.3, 3.5 Hz, 1H); ^{13}C NMR δ 170.5, 170.3, 160.8, 157.8, 142.1, 139.3, 133.2, 129.7, 128.6, 127, 125.5, 122.7, 115.5, 71.4, 67.0, 62.2, 59.7, 49.2, 45.8, 21.3, 21.0, 20.7; Calcd for $C_{25}H_{28}O_8N_2S$: C, 58.12; H, 5.47; N, 5.48; Found: C, 57.92; H, 5.41; N, 5.21%.

Isoxazoline 17

A mixture of the aldehyde **7a** (1.25 g, 3.74 mmol), nitromethane (4 ml), anhydrous KF (0.3 g) and isopropanol (20 ml) was stirred at 25°C for 24 h. The residue obtained after removal of solvent under reduced pressure was diluted with ether (70 ml) and the mixture filtered. The syrup obtained after evaporation of the filtrate was dissolved in 1:1 dry ether–CH_2Cl_2 (30 ml) containing a catalytic amount of DMAP. Ac_2O (1.5 ml) was added and the mixture kept overnight at 25°C. Water (25 ml) was added to the mixture, which was then extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with 10% HCl (5 ml), water and dried. The syrup obtained after removal of the solvent was dissolved in THF (25 ml) and this solution was added to a suspension of $NaBH_4$ (0.5 g) in EtOH (15 ml) at 0°C and the resulting mixture was stirred for 4 h. Excess $NaBH_4$ was destroyed by the addition of aqueous AcOH (10%) and the residue obtained after removal of solvent was extracted with EtOAc (3×20 ml). The combined organic layer was washed with water, dried and solvent was removed under reduced pressure. The syrupy residue on chromatography over silica-gel, using $CHCl_3$ as the eluent gave **10a** as a colorless syrup (1.10 g, 77%); $[\alpha]_D^{27}$=−36.9 (*c* 1.15, $CHCl_3$); IR (neat) ν_{max} 2986, 2932, 1648, 1559, 1493, 1455, 1378 cm^{-1}; ^1H NMR δ 7.28 (m, 2H), 6.95 (t, *J*=7.3 Hz, 1H), 6.87 (d, *J*=8.1 Hz, 1H), 6.07 (m, 1H), 5.88 (d, *J*=3.8 Hz, 1H), 5.41 (dd, *J*=17.3, 1.5 Hz, 1H), 5.29 (dd, *J*=10, 1.2 Hz, 1H), 4.74 (d, *J*=11.8 Hz, 1H), 4.69 (d, *J*=3.8 Hz, 1H), 4.53 (m, 5H), 4.25 (m, 1H), 3.9 (d, *J*=3.2 Hz, 1H), 2.41 (m, 1H), 2.30 (m, 1H), 1.47 (s, 3H), 1.32 (s, 3H); ^{13}C NMR δ 156.2, 133.0, 129.6 (2×C), 129.3 (2×C), 125.5, 120.6, 117.5, 111.4, 104.7, 82.1, 76.6, 72.4, 68.7, 67.0, 26.6, 26.1, 26.1; MS (EI) *m/z* 379, 364, 331, 272, 217, 201, 188, 162, 146, 106, 91; Calcd for $C_{19}H_{25}O_7N$: C, 60.13; H, 6.65; N, 3.69; Found: C, 60.30; H, 6.55; N, 3.66.

A mixture of **10a** (0.8 g, 2.1 mmol), PhNCO (3.0 ml), Et_3N (3.5 ml) and benzene (100 ml) was stirred for 50 h at 25°C. Water (50 ml) was added and the mixture stirred for further 24 h. Benzene was removed under reduced pressure and the residue extracted with $CHCl_3$ (2×50 ml). The combined organic layer was washed with water, dried and evaporated to give a residue which was chromatographed over silica-gel using hexane–ethyl acetate (4:1) as the eluent to afford **17** as colourless needles (0.37 g, 50%); mp 193–195°C; $[\alpha]_D^{27}$=−64.6 (*c* 1.2, $CHCl_3$); IR (KBr) ν_{max} 2988, 2934, 1652, 1604, 1455, 1376, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J*=8 Hz, 1H), 7.22 (d, *J*=8 Hz, 1H),

6.90 (t, J=8 Hz, 1H), 6.83 (d, J=8 Hz, 1H), 5.94 (d, J= 4 Hz, 1H), 4.80 (m, 2H), 4.72 (d, J=4 Hz, 1H), 4.50 (m, 2H), 4.26 (d, J=10 Hz, 1H), 4.26 (d, J=10 Hz, 1H), 4.25 (bs, 1H0, 4.03 (d, J=10 Hz, 1H), 3.24 (dd, J=16, 10 Hz, 1H), 2.76 (m, 2H), 2.55 (dd, J=16.0, 10 Hz, 1H), 1.50 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 158.0, 155.7, 131.7, 130.0, 124.7, 120, 113.3, 110.0, 105.0, 82.9, 82.0, 77.4, 76.8, 70.0, 69.1, 41.6, 27.6, 26.9, 26.3; MS (EI) m/z 361 (M^+), 360 (M^+-1), 359 (M^+-2); Calcd for $C_{19}H_{23}O_6N$: C, 63.13; H, 6.42; N, 3.88; Found: C, 62.85; H, 6.58; N, 3.71%.

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References

1. Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425.
2. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909.
3. Bhattacharjya, A.; Chattopadhyay, P.; McPhail, A. T.; McPhail, D. R. *J. Chem. Soc., Chem. Commun.* **1990**; 1508–1509; Corrigendum, *J. Chem. Soc., Chem. Commun.* **1991**, 136.
4. Datta, S.; Chattopadhyay, P.; Mukhopadhyay, R.; Bhattacharjya, A. *Tetrahedron Lett.* **1993**, *34*, 3585–3588.
5. Mukhopadhyay, R.; Kundu, A. P.; Bhattacharjya, A. *Tetrahedron Lett* **1995**, *36*, 7729–7730.
6. Mukhopadhyay, R.; Datta, S.; Chattopadhyay, P.; Bhattacharjya, A.; Patra, A. *Indian J. Chem.* **1996**, *35B*, 1190–1193.
7. Shing, T. K. M.; Fung, W.-C.; Wong, C.-H. *J. Chem. Soc., Chem. Commun.* **1994**, 449–450.
8. Bhattacharjee, A.; Bhattacharjya, A.; Patra, A. *Tetrahedron Lett.* **1995**, *36*, 4677–4680.
9. Majumdar, S.; Bhattacharjya, A.; Patra, A. *Tetrahedron Lett.* **1997**, *38*, 8581–8584.
10. Majumdar, S.; Bhattacharjya, A.; Patra, A. *Tetrahedron* **1999**, *55*, 12157–12174.
11. Kozikowski, A. P.; Murrage, B. M. *J. Chem. Soc., Chem. Commun.* **1988**, 198–199.
12. Rai, K. M. L.; Hassner, A. *Heterocycles* **1990**, *30*, 817–830.
13. Ko, S. S.; Confalone, P. N. *Tetrahedron* **1985**, *41*, 3511–3518.
14. Bhattacharjee, A.; Chattopadhyay, P.; Kundu, A. P.; Mukhopadhyay, R.; Bhattacharjya, A. *Indian J. Chem.* **1996**, *35B*, 69–70.
15. Hassner, A.; Rai, K. M. L. *Synthesis* **1989**, 57–60.
16. Vissor, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291–4298.