Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 2999–3012

# Intramolecular 1,3-dipolar nitrone and nitrile oxide cycloaddition of 2- and 4-*O*-allyl and propargyl glucose derivatives: a versatile approach to chiral cyclic ether fused isoxazolidines, isoxazolines and isoxazoles

Subir Ghorai, Ranjan Mukhopadhyay, Asish P. Kundu and Anup Bhattacharjya*

*Indian Institute of Chemical Biology, 4, Raja S. C. Mullick Road, Kolkata 700032, India*

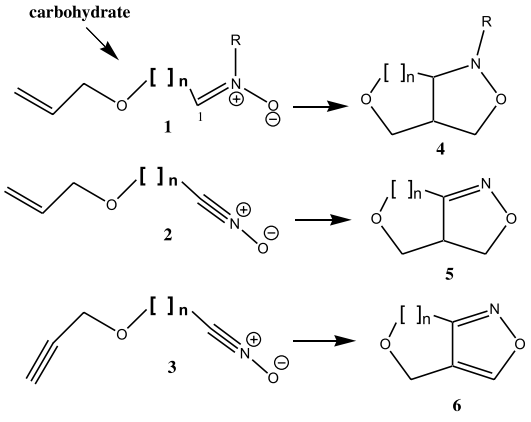
Received 28 October 2004; revised 13 January 2005; accepted 28 January 2005

**Abstract**—2-*O*- and 4-*O*-Allyl and -propargyl glucose and the corresponding oxime derivatives were prepared from readily available glucose dithioacetals. Intramolecular 1,3-dipolar cycloaddition of the *N*-benzyl and *N*-methyl nitrones of the above acyclic 2-*O*-allyl glucose derivatives led to the diastereoselective formation of chiral isoxazolidines incorporating the tetrahydrofuran ring. The EI mass spectra revealed a characteristic cleavage of the C-alkyl group adjacent to the furan oxygen atom. An enantiopure trisubstituted tetrahydrofuran was obtained by the reductive cleavage of the isoxazolidine ring of one of the cycloadducts. In contrast, the nitrile oxide cycloaddition of the 2-*O*-allyl derivatives afforded diastereomeric mixtures of the corresponding dihydroisoxazolines, the stereochemistry of which was tentatively assigned on the basis of the principle of optical superposition. The exclusive formation of a tetrahydrofuran ring from pentaallyl nitrone or nitrile oxide demonstrated the preferred formation of a five-membered ring to that of six or seven-membered rings. The nitrile oxide generated from a 3,4,5,6,7-pentaallyloxy-1-nitroheptane derivative obtained from pentaallylglucose underwent diastereoselective cycloaddition to give an isoxazoline fused to a pyran ring. Enantiopure isoxazoles containing tetrahydrofuran and oxepane rings were also prepared in good yields by the nitrile oxide cycloaddition of the 2-*O*- and 4-*O*-propargyl derivatives.


## 1. Introduction

One of the frequently used strategies employed for the synthesis of heterocyclic compounds is the 1,3-dipolar cycloaddition reactions involving a nitrone or nitrile oxide and an alkene or alkyne.[1–4] Recently, these two cycloaddition reactions have been successfully applied to *O*- and *N*-alkenylcarbohydrate derivatives leading to the synthesis of enantiomerically pure cyclic ethers and amines fused to isoxazolidine and dihydroisoxazoline rings.[5–7] Most of these cycloadditions have been applied to 3-*O*-allyl carbohydrate derivatives giving rise to pyran and oxepane rings.[8] Examples of the synthesis of tetrahydrofuran rings from carbohydrate derivatives by employing these cycloadditions have remained scarce.[9–11] Earlier, we reported the formation of tetrahydrofuran rings via the nitrone cycloaddition of acyclic 2-*O*-allyl glucose derivatives.[9] Herein, we describe in detail the earlier work[9] and hitherto unreported nitrile oxide cycloaddition of acyclic 2-*O*- and 4-*O*-allyl and propargyl glucose derivatives leading to enantiopure isoxazolidine, dihydroisoxazoline and isoxazole ring fused tetrahydrofuran, pyran and oxepane derivatives.

The general strategy for the above cycloaddition reactions is depicted in Scheme 1. A nitrone or nitrile oxide




**Scheme 1.** *O*-Allyl and -propargylcarbohydrate nitrone and nitrile oxide cycloaddition strategy.

*Keywords*: Nitrone; Nitrile oxide; Cycloaddition; Glucose; Isoxazolidine; Isoxazoline; Isoxazole.
* Corresponding author. Tel.: +91 33 2472 8697; fax: +91 33 2472 3967; e-mail: anupbh@hotmail.com

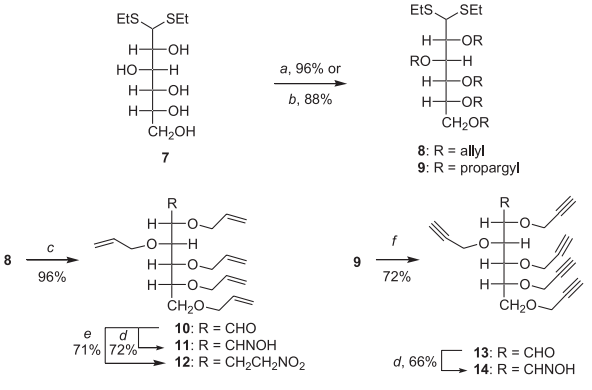
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.01.119

functionality is generated at the 1-C of an acyclic glucose derivative having a 2-*O*- or 4-*O*-allyl or propargyl moiety corresponding to the values of $n=1$ and 3. The nitrone **1** or the nitrile oxides **2** and **3** formed in this manner undergo cycloaddition to afford an isoxazolidine **4**, a dihydroisoxazoline **5** and an isoxazole **6**, respectively. A noteworthy feature of this strategy is the availability of different sizes of cyclic ethers fused to diverse types of heterocyclic rings.

## 2. Results and discussion

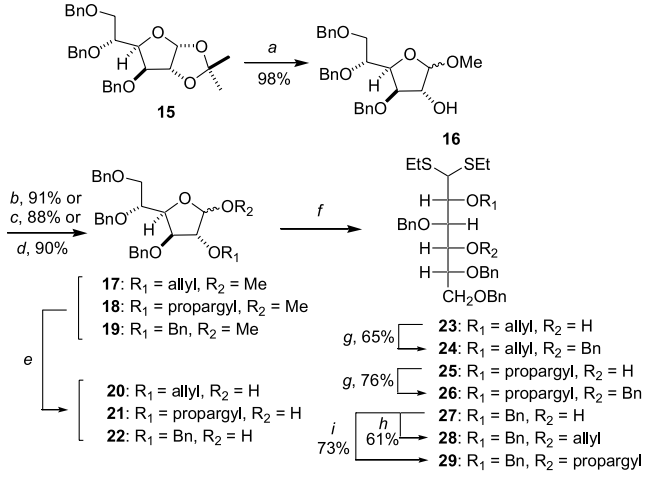
### 2.1. Preparation of the nitrone and nitrile oxide precursors

The nitrones used in this work were prepared from the reaction of the corresponding aldehydes and *N*-benzylhydroxylamine or *N*-methylhydroxylamine, whereas nitrile oxides were generated from the corresponding aldoximes using chloramine-T,[12] and in one case from a primary nitro compound using 4-chlorophenyl isocyanate.[13] The starting acyclic aldehydes were prepared by the cleavage of the corresponding dithioacetals, which were obtained from readily available glucose derivatives according to Scheme 2. The glucose dithioacetal **7**[14] was converted to the pentaallyl and pentapropargyl derivatives **8** and **9** by alkylation with allyl bromide and propargyl bromide using sodium hydride in DMF. The dithioacetal **8** was converted to the aldehyde **10** by treatment with $HgCl_2$ and $CaCO_3$ in aqueous acetonitrile.[15] The aldehyde **10** and other aldehyde intermediates in this study were used directly for the next steps, because they were found to be sensitive to chromatographic purification. The penta-*O*-propargyl glucose dithioacetal **9** was converted to the aldehyde **13** by a two-step procedure involving oxidation with $NaIO_4$ followed by treatment of the crude sulfoxide intermediate with $H_2SO_4$ and THF,[16,17] because the direct $HgCl_2$ mediated cleavage of **9** failed to afford **13**. The aldehydes **10** and **13** were converted to the respective oximes **11** and **14** by treatment with $NH_2OH.HCl$ in pyridine–methanol. The primary nitro derivative **12** was prepared from **10** by following a known protocol[18] involving treatment with nitromethane and acetylation followed by reduction with $NaBH_4$ without isolation of the intermediates (Scheme 2).

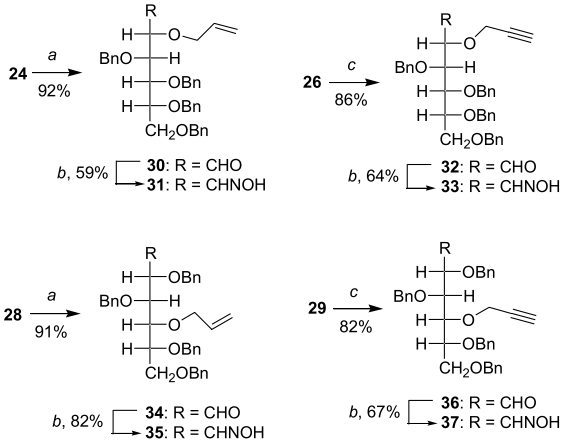



**Scheme 2.** Synthesis of penta-*O*-allyl and penta-*O*-propargyl glucose, their respective oximes and the nitro derivative **12**. Reagents and conditions: (a) NaH, allylbromide, DMF, 25 °C, 12 h; (b) NaH, propargylbromide, DMF, 25 °C, 12 h; (c) $HgCl_2$, $CaCO_3$, $CH_3CN$–$H_2O$ (4:1), 25 °C, 6 h; (d) $NH_2OH.HCl$, pyridine, MeOH, reflux, 8 h; (e) (i) $CH_3NO_2$, KF, 2-propanol, 25 °C, 15 h, (ii) $Ac_2O$, DMAP, $CH_2Cl_2$, 25 °C, 12 h, (iii) $NaBH_4$, EtOH, 0–25 °C, 6 h; (f) (i) $NaIO_4$, EtOH, 25 °C, 10 h, (ii) THF, conc $H_2SO_4$, 25 °C, 12 h.

Another set of acyclic intermediates were prepared from the 1,2-isopropylidene glucose derivative **15**,[19] which was converted to the methyl glycoside **16** as an anomeric mixture, alkylation of which with allyl bromide, propargyl bromide and benzyl bromide separately afforded the anomeric mixtures of the 2-*O*-allyl, 2-*O*-propargyl and 2-*O*-benzyl derivatives **17**, **18** and **19**, respectively (Scheme 3). Although, the respective α and β anomers in the mixtures could be separated by column chromatography, in this study the mixtures were used without separation for the next steps viz. deglycosylation to **20**, **21** and **22** and dithioacetylation to **23**, **25** and **27** followed by alkylation of the 4-OH with either benzyl or allyl or propargyl bromide giving rise to the dithioacetal derivatives **24**, **26**, **28** and **29**.




**Scheme 3.** Synthesis of 2-*O*- and 4-*O*-allyl and -propargyl glucose dithioacetals. Reagents and conditions: (a) *p*-TsOH, MeOH, reflux, 6 h; (b) allylbromide, $Bu_4NBr$, $CH_2Cl_2$, 50% aq NaOH, 25 °C, 12 h; (c) propargylbromide, $Bu_4NBr$, $CH_2Cl_2$, 50% aq NaOH, 25 °C, 12 h; (d) benzylbromide, $Bu_4NBr$, $CH_2Cl_2$, 50% aq NaOH, 25 °C, 12 h; (e) 50% aq TFA, 25 °C, 24 h, **20** (96%), **21** (94%), **22** (89%); (f) EtSH, conc $H_2SO_4$, 0 °C, 20 h, **23** (81%), **25** (76%), **27** (73%); (g) NaH, benzylbromide, THF, 25 °C, 12 h; (h) NaH, allylbromide, THF, 25 °C, 12 h; (i) NaH, propargylbromide, THF, 25 °C, 12 h.



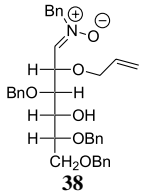
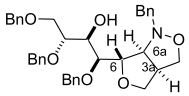
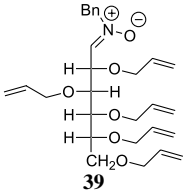
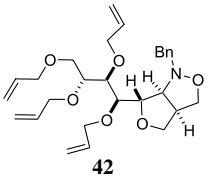
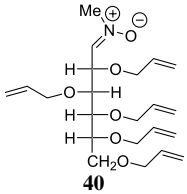
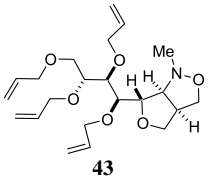

**Scheme 4.** Synthesis of 2-*O*- and 4-*O*-allyl and -propargyl glucose oximes from their dithioacetals. Reagents and conditions: (a) $HgCl_2$, $CaCO_3$, $CH_3CN$:$H_2O$ (4:1), 25 °C, 6 h; (b) $NH_2OH.HCl$, pyridine, MeOH, reflux, 8 h; (c) (i) $NaIO_4$, EtOH, 25 °C, 10 h, (ii) THF, conc $H_2SO_4$, 25 °C, 12 h.

The *O*-allylcarbohydrate aldehydes **30** and **34** were obtained from the corresponding dithioacetal derivatives **24** and **28** by treatment with $HgCl_2$ and $CaCO_3$ in aqueous acetonitrile (Scheme 4). The *O*-propargyl aldehydes **32** and **36** were obtained in good yields from the *O*-propargyl dithioacetals **26** and **29** via the earlier mentioned oxidative method using $NaIO_4$ followed by treatment with an acid. The aldehydes **30**, **32**, **34** and **36** were converted to the corresponding oximes **31**, **33**, **35** and **37**, respectively, as described before (Scheme 4).

### 2.2. 2-*O*-Allyl carbohydrate nitrone cycloaddition

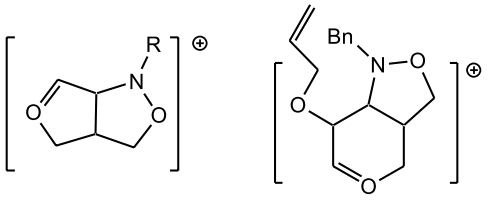
As reported earlier the *N*-benzyl nitrones **38** and **39** prepared from 3,5,6-tri-*O*-benzylglucofuranose **20** and **10** by treatment with *N*-benzylhydroxylamine in refluxing ethanol afforded via in situ cycloaddition the fused isoxazolidines **41** (70%) and **42** (75%), respectively, as exclusive products (Table 1).[9] The presence of a one-proton multiplet at $\delta$ 3.36 (3a-H) in the $^1$H NMR spectrum and a peak at $\delta$ 47.5 (3a-C) in the $^{13}$C NMR spectrum clearly indicated **41** to be a fused isoxazolidine.[20] The mass spectrum of **41** exhibited besides the molecular ion at *m/z* 595 a strong peak at *m/z* 204 due to the fragment **44**, which is indicative of the presence of the furoisoxazolidine skeleton. The presence of multiple allyl groups in **42** caused extensive overlapping of signals in its $^1$H NMR spectrum. However, the occurrence of cycloaddition was evident from the appearance of peaks in the spectrum due to the phenyl group as well as the ratio (5:4) of the relative integrations of the aromatic protons and the vinylic methine protons. The $^{13}$C NMR spectrum, however, appeared to be more helpful, and clearly indicated the ring juncture 3a-C and 6a-C at $\delta$ 48.4 (CH) and 71.9 (CH), respectively.

**Table 1**. 2-*O*-Allyl carbohydrate nitrone cycloaddition[a]

| Nitrone precursor | Nitrone | Product | Yield[b] |
|---|---|---|---|
| **20** |  **38** |  **41** | 70% |
| **10** |  **39** |  **42** | 75% |
| **10** |  **40** |  **43** | 75% |

[a] Conditions: for *N*-benzyl nitrones–*N*-benzyl hydroxylamine, benzene, reflux; for *N*-methyl nitrone **40**–*N*-methyl hydroxylamine hydrochloride, $NaHCO_3$, 80% aq EtOH, reflux.
[b] Yields refer to chromatographically isolated products.

However, it was more difficult to ascertain whether **42** was a tetrahydrofuran derivative arising out of the cycloaddition to the 2-*O*-allyl group or a tetrahydropyran derivative due to the cycloaddition to the 3-*O*-allyl group of **39**. The problem was resolved by the analysis of the EI mass spectrum

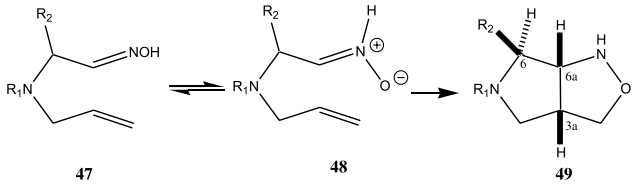


**44**: R = Bn *m/z* 204
**45**: R = Me *m/z* 128

**46**: *m/z* 274

of **42**, in which the fragment **44** at *m/z* 204 appeared besides the molecular ion at *m/z* 485 indicating the presence of the tetrahydrofuran skeleton. The absence of any peak corresponding to the mass spectral fragment **46** (*m/z* 274) in the mass spectrum ruled out the alternative pyran structure. The occurrence of the furoisoxazolidine fragment appeared to be a characteristic of the EI mass spectra of furoisoxazolidines, because the mass spectrum of **43**, formed in 75% yield by the cycloaddition of the *N*-methyl nitrone **40**, also exhibited a strong peak at *m/z* 128 corresponding to the furoisoxazolidine fragment **45**.

The assignment of the ring-junction stereochemistry in **41**, **42** and **43** proved difficult by NMR spectral analysis due to the presence of a number of allyl and benzyl moieties. Hassner et al. reported a number of tetrahydropyrroloisoxazolidine derivatives of the type **49** by the oxime-olefin cycloaddition of **47** (Scheme 5).[21,22] It is generally believed that oxime-olefin cycloaddition proceeds via the formation of the NH nitrone such as **48**. The *cis–trans* stereochemistry of the sequence 3a–6a–6 in **49** was established on the basis of NMR spectral analysis.[22] This stereochemical assignment was also corroborated by MM2 calculations, which revealed a 3.8 kcal difference in energy between the *cis–cis* and the *cis–trans* isomers in favor of the latter.[22] Due to close structural resemblance, the transition state geometries of the nitrones **38**–**40** are not expected to be much different from that of **48**, and the sequence 3a–6a–6 in **41**–**43** was accordingly assigned the *cis–trans* stereochemistry.



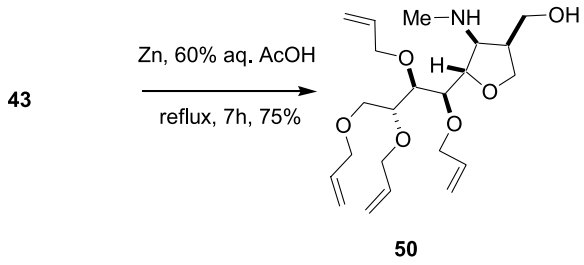
**47** **48** **49**

**Scheme 5.** Reported examples of isoxazolidines prepared by oxime-olefin cycloaddition.

An interesting feature of the cycloaddition of the pentaallyl nitrones **39** and **40** is that although they contain three potentially reactive alkenes viz. 2-, 3- and 4-*O*-allyl residues available for cycloaddition to the dipole, the tetrahydrofuran ring was formed exclusively. The result reflected the great

propensity of the formation of five-membered rings compared to six- and seven-membered rings.

The cleavage of the isoxazolidine ring is frequently a necessary step in any synthetic exercise involving the application of the cycloaddition strategy. Although attempted reaction of **43** with $LiAlH_4$ led to intractable products, Zn and aqueous acetic acid successfully cleaved **43** to the trisubstituted tetrahydrofuran derivative **50** in 75% yield (Scheme 6).

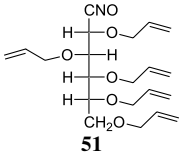
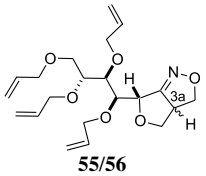
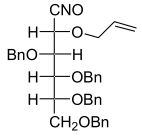
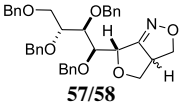
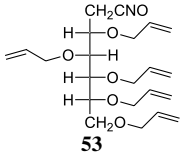
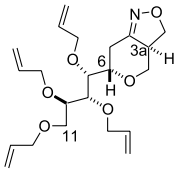
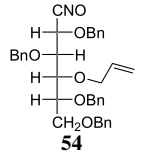
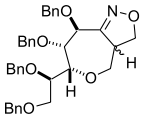



**Scheme 6.** Cleavage of the isoxazolidine ring of **43**.

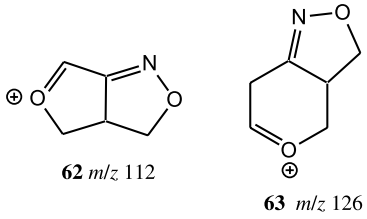
### 2.3. *O*-Allyl and -propargyl nitrile oxide cycloaddition

The results of the hitherto unreported application of the intramolecular nitrile oxide cycloaddition to acyclic 2-*O*-allyl and 4-*O*-allyl carbohydrate derivatives are presented in Table 2. In contrast to the diastereoselective nitrone cycloaddition of the 2-*O*-allyl carbohydrate derivatives, the corresponding nitrile oxide cycloaddition appeared to furnish mixtures of diastereomers. The nitrile oxide **51**, generated from the pentaallyl carbohydrate oxime **11** by treatment with chloramine-T in ethanol under reflux, underwent in situ cycloaddition giving rise to a separable mixture of the diastereomeric dihydrofuro[3,4-*c*]isoxazoles **55** and **56**. The presence of the isoxazoline rings in these compounds was evident from the appearance of 3a-C signals at $\delta$ 44.7 and $\delta$ 50.4 as well as quaternary carbon signals due to C=N at $\delta$ 156.1 and $\delta$ 157.7 in their $^{13}$C NMR spectra. The furoisoxazole nature of the rings in **55** and **56** was evident from the appearance of strong peaks at *m*/*z* 112 corresponding to the ion **62** in their mass spectra.

**Table 2**. *O*-Allyl carbohydrate nitrile oxide cycloaddition[a]

| Nitrile oxide precursor | Nitrile oxide | Product[b] | Yield (%)[c] |
|---|---|---|---|
| **11** |  **51** |  **55/56** | 61 |
| **31** |  **52** |  **57/58** | 54 |
| **12** |  **53** |  **59** | 68 |
| **35** |  **54** |  **60/61** | 64 |

[a] Conditions: nitrile oxides from (a) oximes–chloramine-T, ethanol, reflux; (b) the nitro derivative **12**–4-chlorophenyl isocyanate, triethylamine, benzene, 25 °C.
[b] Except for **59**, all the cycloadducts were isolated as mixtures of diastereomers.
[c] Yields refer to chromatographically isolated mixtures.

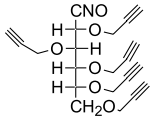
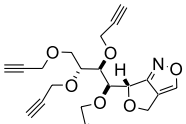
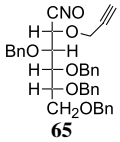
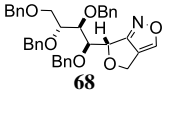
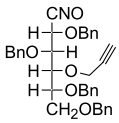
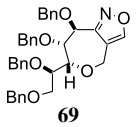



The formation of epimeric pairs of racemic dihydroisoxazolines fused to tetrahydrofuran rings has also been observed in the cycloaddition of nitrile oxides generated from 2-allyloxynitroethanes.[23] The configurations at the newly formed chiral center 3a-C could not be established by NMR spectral analysis, for example, NOESY due to extensive overlapping of relevant signals in the $^1$H NMR spectrum. However, a tentative assignment was made on the basis of an empirical correlation of optical rotation with configuration, which will be described later in this study. The cycloaddition of the tetra-*O*-benzyl-2-*O*-allyl nitrile oxide **52** prepared from the oxime **31** afforded an inseparable mixture of the diastereomers **57** and **58**. The $^1$H and $^{13}$C NMR spectra of the enriched chromatographic fractions of the mixture had closely similar features, which indicated that they were indeed 3a-epimers. In contrast, the pentaallyl nitrile oxide **53**, the homolog of the nitrile oxide **51** and generated from the nitro derivative **12** by treatment with 4-chlorophenyl isocyanate, underwent cycloaddition to give exclusively the pyran-fused isoxazoline **59** in 68% yield. The pyranoisoxazoline ring in **59** was characterized by the facile cleavage of the substituent at 6-C in the EI mass spectrum, which exhibited a strong peak at *m*/*z* 126 corresponding to the ion **63**. The 500 MHz $^1$H NMR spectrum exhibited the 3a-H as a multiplet centered around $\delta$ 3.42. The gross structure of **59** was established by DQFCOSY and HMQC spectra. The NOESY spectrum of **59** revealed cross peaks between 3a-H and 11-$CH_2$, and hence the stereochemistry of 3a-C was assigned as shown. The cycloaddition of the 4-*O*-allyl carbohydrate nitrile oxide **54** prepared from the oxime **35** by treatment with chloramine-T led to the formation of a diastereomeric mixture of the oxepanoisoxazolines **60** and **61**, which were separated by column chromatography and characterized. The appearance of 3a-C signals at $\delta$ 52.7 and 50.2 as well as quaternary C=N carbon signals at $\delta$ 159.7 and 157.7 in the $^{13}$C NMR spectra indicated the presence of the isoxazoline ring in the above compounds.

The general yields of the abovementioned nitrile oxide cycloadditions were found to be rather poor compared to the results observed for the corresponding nitrone cycloaddition. Although nitrile oxides are known to be susceptible to dimerization, no dimeric products were detected in the reactions. Intractable polymeric products were observed, and the reasons for the inefficiency of the reaction in these cases are not known to us.

The approach described above for the synthesis of chiral isoxazolines from 2-*O*- and 4-*O*-allyl nitrile oxides was also suitable for preparing chiral isoxazole derivatives by the nitrile oxide cycloaddition of the corresponding *O*-propargyl derivatives. Although the synthesis of chiral isoxazolopyrans and isoxazolooxepanes from 3-*O*-propargyl carbohydrate derivatives has been reported,[24] to our knowledge synthesis of similar systems from the acyclic counterparts is not yet known. In Table 3 are presented the results of the cycloaddition of the nitrile oxides **64**, **65** and **66**. The 2-*O*-propargyl nitrile oxides generated from the corresponding oximes **14** and **33** by treatment with chloramine-T smoothly underwent cycloaddition giving rise to the isoxazoles **67** and **68** in yields of 72 and 77%, respectively. The cycloaddition of 4-*O*-propargyl nitrile oxide **66** obtained from the oxime **37** led to the formation of the oxepinoisoxazole derivative **69** in 80% yield. The presence of the isoxazole ring in **67**–**69** was clearly evident from the appearance of singlets at $\delta$ 8.05, 7.96 and 8.18 in their $^{1}$H NMR spectra due to the isoxazole protons. The $^{13}$C NMR spectra also exhibited peaks due to C=N and quaternary C=C at $\delta$ 170.5/123.6, 171.1/124.0 and 160.3/118.5, respectively. The yields encountered in the alkyne-nitrile oxide cycloadditions in the present study were found to be considerably higher than those of the corresponding alkene-nitrile oxide reactions, and reflected the high efficiency of the reaction leading to the formation of a stabilized heterocyclic ring.

**Table 3**. *O*-Propargyl carbohydrate nitrile oxide cycloaddtion[a]

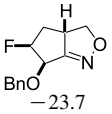
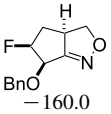
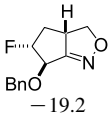
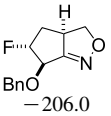
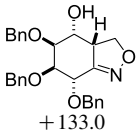
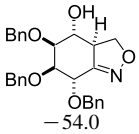
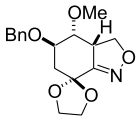
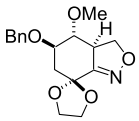
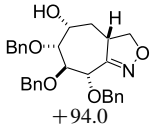
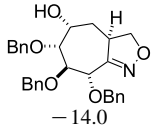
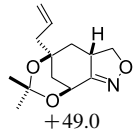
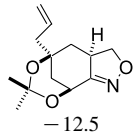
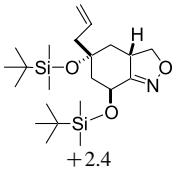
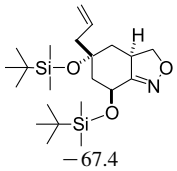
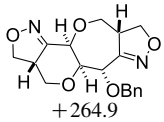
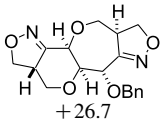
| Nitrile oxide precursor | Nitrile oxide | Product | Yield (%)[b] |
|---|---|---|---|
| **14** |  **64** |  **67** | 72 |
| **33** |  **65** |  **68** | 77 |
| **37** |  **66** |  **69** | 80 |

[a] Conditions: chloramine-T, ethanol, reflux.
[b] Yields refer to chromatographically isolated products.

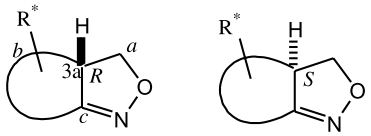
## 2.4. Empirical assignment of stereochemistry of the 3a-epimeric pairs of isoxazolines 55/56 and 60/61

As mentioned earlier that although individual components of the epimeric pairs of the isoxazolines **55/56** and **60/61** were available, the stereochemistry of the newly formed chiral centres in these compounds could not be established by NOE due to overlapping of signals. The application of X-ray diffraction analysis was precluded by their liquid nature. In the past several attempts were made to empirically assign stereochemistry on the basis of the comparison of optical rotation values.[25,26] With recourse to such an assignment a survey of literature revealed that a number of epimeric pairs of enantiomerically pure isoxazolines with known optical rotation values exist, and are listed in Table 4.[27–32] It is apparent if the isoxazolines are represented by **70** and **71**, the former with the *R*

**Table 4**. Examples of epimeric dihydroisoxazolines and their $[\alpha]_D$ values reported in the literature

| Entry | 3a *R*-isoxazoline $[\alpha]_D$ | 3a *S*-isoxazoline $[\alpha]_D$ | Reference |
|---|---|---|---|
| 1 |  −23.7 |  −160.0 | 27 |
| 2 |  −19.2 |  −206.0 | 27 |
| 3 |  +133.0 |  −54.0 | 28 |
| 4 |  +34.7 |  −20.4 | 29 |
| 5 |  +94.0 |  −14.0 | 30 |
| 6 |  +49.0 |  −12.5 | 31 |
| 7 |  +2.4 |  −67.4 | 31 |
| 8 |  +264.9 |  +26.7 | 32 |

configuration of the newly formed center 3a-C (with the arbitrarily assigned sequence priority as shown) has the higher positive rotation. An interesting feature of the optical rotation values is that the difference in the specific rotation values of epimers is appreciable and ranges from +55.1 to +238.2, although the magnitude of the differences does not conform to any correlation with the structural




**70** **71**

pattern. Following this trend, the isoxazolines **55**, **56**, **60** and **61** were empirically assigned the stereochemistry shown in Figure 1.

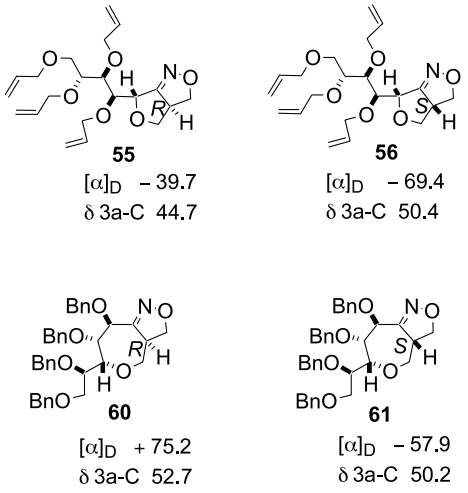



**Figure 1.** Empirically assigned stereochemistry of isoxazolines.

In conclusion, the work described here demonstrated that intramolecular nitrone and nitrile oxide cycloaddition of readily available acyclic 2- and 4-*O*-allyl and -propargyl carbohydrate derivatives can furnish diverse types of chiral cyclic ether fused isoxazolidine, isoxazoline and isoxazole rings.

## 3. Experimental

### 3.1. General

Melting points are uncorrected. Unless otherwise mentioned $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. Assignment of $CH_3$, $CH_2$, CH and quaternary (q) carbon atoms in $^{13}$C NMR spectra was based on DEPT analysis. Elemental analyses were performed at the Indian Association for the Cultivation of Science, Kolkata. Reactions were monitored by thin layer chromatography using Merck 60 $F_{254}$ precoated silica gel plate (No. 1.05554). Organic extracts were dried over anhydrous sodium sulfate. Unless otherwise mentioned 60–120 mesh silica gel was used for column chromatography. Solvents were distilled and dried immediately prior to use. Petroleum ether refers to a fraction boiling between 60 and 80 °C. Room temperature refers to 25 °C.

**3.1.1. Penta-*O*-allylglucose diethyl dithioacetal 8.** The glucose dithioacetal **7**[14] (4.00 g, 14.00 mmol) was added in portions to a stirred suspension of NaH (2.00 g, 83.00 mmol) in DMF (60 mL) at 0 °C. After the addition was over, the mixture was stirred at 25 °C for 1 h. A solution of allyl bromide (7.5 mL, 87.00 mmol) in DMF (20 mL) was added dropwise to the mixture at 0 °C and the stirring was continued for 30 min. The mixture was then stirred for another 12 h at 25 °C. The whole reaction mixture was poured into water (500 mL) and extracted with $CH_2Cl_2$. The combined organic layers were washed with water, dried and concentrated in vacuo affording a yellowish liquid, which on chromatography (EtOAc–petroleum ether, 1:24) gave **8** (6.50 g, 96%) as a light yellow liquid, $[\alpha]_D^{25}$ +13.2 (*c* 0.97, $CHCl_3$); IR (Neat): 3080, 3013, 1645, 1455 cm$^{-1}$; MS (FAB): *m/z* 487 (M+H); $^1$H NMR: $\delta$ 6.03–5.85 (m, 5H), 5.37–5.09 (m, 10H), 4.34–3.97 (m, 12H), 3.88–3.80 (m, 2H), 3.73–3.56 (m, 3H), 2.82–2.61 (m, 4H), 1.25 (t, 6H, *J*=7.6 Hz); $^{13}$C NMR: $\delta$ 135.1 (CH), 134.9 (CH), 134.7 (2×CH), 134.5 (CH), 116.5 ($CH_2$), 116.4 ($CH_2$), 116.0 (2×$CH_2$), 115.8 ($CH_2$), 82.7 (CH), 80.4 (CH), 78.8 (CH), 78.1 (CH), 74.2 ($CH_2$), 73.7 ($CH_2$), 72.5 ($CH_2$), 71.9 ($CH_2$), 70.6 ($CH_2$), 69.2 ($CH_2$), 52.9 (CH), 24.7 ($CH_2$), 24.6 ($CH_2$), 14.2 (2×$CH_3$). Anal. Calcd for $C_{25}H_{42}O_5S_2$: C, 61.69; H, 8.70. Found: C, 61.61; H, 8.39.

**3.1.2. Penta-*O*-propargylglucose diethyl dithioacetal 9.** The above procedure using **7** (1.50 g, 5.24 mmol) and propargyl bromide (4.84 mL, 32.50 mmol) as the alkylating agent yielded after chromatography of the crude product (EtOAc–petroleum ether, 1:19) **9** (2.20 g, 88%) as a pale yellow liquid, $[\alpha]_D^{25}$ −12.0 (*c* 0.76, $CHCl_3$); IR (Neat): 3291, 2117, 1449 cm$^{-1}$; MS (EI): *m/z* 476 (M), 415 (M−SEt); $^1$H NMR: $\delta$ 4.51 (t, 2H, *J*=2.4 Hz), 4.49 (d, 2H, *J*=2.1 Hz), 4.41 (d, 2H, *J*=2.2 Hz), 4.36 (t, 2H, *J*=2.4 Hz), 4.22–4.21 (m, 2H), 4.11 (t, 2H, *J*=4.5 Hz), 4.00–3.96 (m, 3H), 3.88 (t, 1H, *J*=4.3 Hz), 3.73 (dd, 1H, *J*=11.3, 6.1 Hz), 2.81–2.68 (m, 4H), 2.47–2.45 (m, 5H), 1.28 (t, 6H, *J*=7.4 Hz); $^{13}$C NMR: $\delta$ 81.9 (CH), 80.0 (CH), 79.7 (CH), 79.6 (2×CH), 79.3 (CH), 79.2 (CH), 78.2 (CH), 77.4 (CH), 74.8 (q), 74.6 (q), 74.5 (2×q), 74.4 (q), 68.5 ($CH_2$), 60.0 ($CH_2$), 59.8 ($CH_2$), 58.8 ($CH_2$), 58.1 ($CH_2$), 57.2 ($CH_2$), 52.5 (CH), 25.1 ($CH_2$), 24.8 ($CH_2$), 14.2 ($CH_3$), 14.1 ($CH_3$). Anal. Calcd for $C_{25}H_{32}O_5S_2$: C, 63.00; H, 6.77. Found: C, 63.24; H, 6.68.

### 3.2. General procedure for the cleavage of diethyl dithioacetals by $HgCl_2$

Preparation of the aldehydes **10**, **30** and **34**. The general procedure for the cleavage of the dithioacetals by $HgCl_2$ is illustrated by the preparation of **10**.

A mixture of **8** (1.00 g, 2.00 mmol) in 80% aq $CH_3CN$ (30 mL), $HgCl_2$ (1.20 g, 4.40 mmol) and $CaCO_3$ (0.45 g, 4.40 mmol) were added and stirred at 25 °C for 6 h. After completion of the reaction as revealed by TLC, the resulting precipitate was filtered and washed with $CH_3CN$. The combined filtrate and washings were evaporated under reduced pressure. The residue obtained was extracted with $CH_2Cl_2$ and the combined organic extracts were washed

with water and dried. Removal of solvent yielded **10** (0.76 g, 96%) as a light yellow liquid, which was used without purification for the next step.

The aldehydes **30** and **34** prepared by this method were also used without purification.

### 3.3. General procedure for the cleavage of diethyl dithioacetals by $NaIO_4$–$H_2SO_4$

Preparation of the aldehydes **13**, **32** and **36**. The general procedure for the cleavage of the dithioacetals is illustrated by the preparation of **13**.

To a solution of **9** (1.00 g, 2.10 mmol) in EtOH (40 mL) was added with stirring a solution of $NaIO_4$ (1.12 g, 5.23 mmol) in water (10 mL) and the mixture was stirred at 25 °C for 10 h. It was then filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with $CH_2Cl_2$ and the combined organic extracts were washed with water, dried and removal of solvent afforded a syrupy material. A solution of the above material in THF (20 mL) containing a catalytic amount of conc $H_2SO_4$ was stirred at 25 °C for 12 h. The reaction mixture was neutralised with saturated $NaHCO_3$ solution and solvent was removed until a syrupy residue was obtained. The residue was extracted with $CH_2Cl_2$ and the combined organic layers were washed with water, dried and concentrated to give **13** (0.56 g, 72%) as a colorless liquid, which was immediately used without purification for the next step.

The aldehydes **32** and **36** prepared by the above method was also used without purification.

### 3.4. General procedure for the preparation of aldoximes 11, 14, 31, 33, 35 and 37

The general procedure is illustrated by the preparation of **11**.

A mixture of **10** (0.80 g, 2.10 mmol), pyridine (0.4 mL, 5.00 mmol), $NH_2OH.HCl$ (0.22 g, 3.15 mmol) and MeOH (20 mL) was heated under reflux for 8 h. After removal of solvent, the residue was extracted with $CH_2Cl_2$. The organic extract was washed with water, dried and evaporated under reduced pressure. The residue was repeatedly co-evaporated with dry toluene, and then chromatographed (EtOAc–petroleum ether, 1:16–1:12) to give the oxime **11** (0.60 g, 72%, mixture of *syn* and *anti* isomers) as a pale yellow syrup, IR (Neat): 3363, 3081, 3014, 1646, 1457, 1424 $cm^{-1}$; MS (FAB): *m/z* 396 (M+H); $^1H$ NMR: $\delta$ 7.48 (d, 0.75H, $J$=7.5 Hz), 6.95 (d, 0.25H, $J$=6.5 Hz), 5.96–5.83 (m, 5H), 5.30–5.10 (m, 10H), 4.88 (dd, 0.25H, $J$=6.4, 4.6 Hz), 4.33–3.54 (m, 15.75H); $^{13}C$ NMR: $\delta$ 150.9 (CH), 149.4 (CH), 135.2 (CH), 134.9 (2×CH), 134.8 (CH), 134.7 (CH), 134.6 (CH), 134.5 (CH), 134.3 (CH), 134.0 (CH), 133.9 (CH), 117.4 ($CH_2$), 117.2 ($CH_2$), 117.0 ($CH_2$), 116.9 ($CH_2$), 116.8 ($CH_2$), 116.7 ($CH_2$), 116.5 ($CH_2$), 116.4 ($CH_2$), 116.3 ($CH_2$), 116.2 ($CH_2$), 80.3 (CH), 79.5 (CH), 79.1 (CH), 78.5 (CH), 78.2 (CH), 77.8 (2×CH), 76.8 (CH), 74.2 ($CH_2$), 73.9 ($CH_2$), 73.6 ($CH_2$), 73.2 ($CH_2$), 72.1 ($CH_2$), 71.4 ($CH_2$), 71.0 ($CH_2$), 70.7 ($CH_2$), 70.1 ($CH_2$), 68.8 ($CH_2$), 68.4 ($CH_2$), 68.3 ($CH_2$). Anal. Calcd for $C_{21}H_{33}NO_6$: C, 63.78; H, 8.41; N, 3.54. Found: C, 63.59; H, 8.47; N, 3.42.

**3.4.1. Aldoxime 14.** Pale yellow syrup; yield: 66%; mixture of *syn* and *anti* isomers; IR (Neat): 3362, 3293, 2119, 1445 $cm^{-1}$; MS (FAB): *m/z* 386 (M+H), 330 (M−$OCH_2CCH$); $^1H$ NMR: $\delta$ 7.97 (br s, 1H), 7.54 (d, 0.8H, $J$=7.6 Hz), 6.99 (d, 0.2H, $J$=6.5 Hz), 5.09 (dd, 0.2H, $J$=6.4, 3.7 Hz), 4.46–4.12 (m, 10.8H), 4.01–3.86 (m, 4H), 3.77–3.73 (m, 1H), 2.49–2.44 (m, 5H); $^{13}C$ NMR: $\delta$ 149.8 (CH), 148.6 (CH), 79.8 (CH), 79.7 (CH), 79.6 (2×CH), 79.5 (CH), 79.3 (CH), 79.2 (CH), 79.0 (CH), 78.9 (CH), 78.3 (CH), 77.9 (CH), 77.7 (CH), 77.3 (CH), 75.8 (CH), 75.4 (q), 75.3 (q), 75.0 (q), 74.9 (q), 74.8 (q), 74.7 (q), 74.6 (q), 74.4 (q), 70.6 (CH), 67.8 ($CH_2$), 67.7 ($CH_2$), 59.8 ($CH_2$), 59.7 ($CH_2$), 59.6 ($CH_2$), 59.5 ($CH_2$), 58.2 ($CH_2$), 57.4 ($CH_2$), 57.2 ($CH_2$), 56.3 ($CH_2$). Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.57; H, 6.23; N, 3.53.

**3.4.2. Aldoxime 31.** Colorless syrup; yield: 59%; mixture of *syn* and *anti* isomers; IR (Neat): 3354, 3062, 3031, 1644, 1603, 1494, 1454 $cm^{-1}$; MS (FAB): *m/z* 596 (M+H); $^1H$ NMR: $\delta$ 7.41 (d, 0.75H, $J$=7.6 Hz), 7.31–7.26 (m, 20H), 6.89 (d, 0.25H, $J$=6.2 Hz), 5.89–5.76 (m, 1H), 5.24 (dd, 1H, $J$=17.2, 1.4 Hz), 5.14 (dd, 1H, $J$=10.3, 1.4 Hz), 4.88 (dd, 0.25H, $J$=6.2, 4.5 Hz), 4.74–4.43 (m, 7.75H), 4.24 (dd, 1H, $J$=7.4, 6.3 Hz), 4.11–4.05 (m, 1H), 4.00–3.96 (m, 1H), 3.91–3.82 (m, 4H), 3.70–3.66 (m, 1H); $^{13}C$ NMR: $\delta$ 151.3 (CH), 149.6 (CH), 138.4 (q), 138.36 (q), 138.2 (q), 138.0 (q), 134.0 (CH), 133.9 (CH), 128.3 (CH), 128.2 (CH), 128.16 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.36 (CH), 117.7 ($CH_2$), 117.5 ($CH_2$), 79.8 (CH), 78.4 (CH), 78.3 (CH), 76.9 (CH), 75.0 ($CH_2$), 74.6 ($CH_2$), 74.1 ($CH_2$), 73.2 ($CH_2$), 71.9 ($CH_2$), 71.7 ($CH_2$), 71.1 ($CH_2$), 70.3 ($CH_2$), 69.3 ($CH_2$), 68.8 ($CH_2$). Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.60; H, 6.94; N, 2.35. Found: C, 74.82; H, 6.97; N, 2.21.

**3.4.3. Aldoxime 33.** Colorless syrup; yield: 64%; mixture of *syn* and *anti* isomers; IR (Neat): 3362, 3292, 3062, 3031, 2117, 1604, 1495, 1453 $cm^{-1}$; MS (FAB): *m/z* 616 (M+Na), 594 (M+H), 576 (M−OH), 538 (M−$OCH_2CCH$), 486 (M−OBn); $^1H$ NMR: $\delta$ 7.40 (d, 0.8H, $J$=7.4 Hz), 7.31–7.25 (m, 20H), 6.91 (d, 0.2H, $J$=6.0 Hz), 5.07 (dd, 0.2H, $J$=5.9, 3.8 Hz), 4.76–4.59 (m, 5H), 4.57–4.41 (m, 3.8H), 4.26–3.99 (m, 3H), 3.92–3.83 (m, 3H), 3.75 (dd, 0.2H, $J$=10.3, 5.8 Hz), 3.69 (dd, 0.8H, $J$=10.1, 4.6 Hz), 2.36 (t, 1H, $J$=2.2 Hz); $^{13}C$ NMR: $\delta$ 149.0 (CH), 138.5 (q), 138.3 (q), 138.1 (q), 128.3 (CH), 128.24 (CH), 128.22 (CH), 128.19 (CH), 128.16 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.44 (CH), 127.39 (CH), 79.7 (CH), 79.5 (CH), 79.2 (CH), 78.7 (CH), 78.3 (CH), 76.1 (CH), 75.1 (q), 74.8 ($CH_2$), 74.3 ($CH_2$), 73.2 ($CH_2$), 71.9 ($CH_2$), 68.9 ($CH_2$), 56.3 ($CH_2$). Anal. Calcd for $C_{37}H_{39}NO_6$: C, 74.85; H, 6.62; N, 2.36. Found: C, 74.77; H, 6.87; N, 2.16.

**3.4.4. Aldoxime 35.** Colorless syrup; yield: 82%; mixture of *syn* and *anti* isomers; IR (Neat): 3354, 3063, 3031, 1644, 1604, 1495, 1454 $cm^{-1}$; MS (FAB): *m/z* 634 (M+K), 618 (M+Na), 596 (M+H); $^1H$ NMR: $\delta$ 7.49 (d, 0.75H, $J$=7.6 Hz), 7.31–7.25 (m, 20H), 6.93 (d, 0.25H, $J$=6.6 Hz), 5.94–5.81 (m, 1H), 5.18 (dd, 1H, $J$=17.2, 1.4 Hz), 5.08 (dd, 1H, $J$=10.2, 1.4 Hz), 4.98 (dd, 0.25H, $J$=6.2, 4.0 Hz), 4.72 (d, 1H, $J$=11.5 Hz), 4.65–4.46 (m, 4.75H), 4.43–4.27 (m, 3H), 4.19–4.11 (m, 2H), 3.91–3.76 (m, 4H), 3.67–3.60 (m, 1H); $^{13}C$ NMR: $\delta$ 150.8 (CH), 149.4 (CH), 138.4 (q), 138.3

(q), 138.2 (q), 138.1 (q), 138.0 (q), 137.5 (q), 137.4 (q), 135.1 (CH), 134.8 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 116.5 ($CH_2$), 116.3 ($CH_2$), 79.3 (CH), 79.1 (CH), 78.7 (CH), 78.5 (CH), 78.0 (CH), 77.9 (CH), 76.8 (CH), 74.8 ($CH_2$), 74.3 ($CH_2$), 73.5 ($CH_2$), 73.2 ($CH_2$), 73.1 ($CH_2$), 72.0 ($CH_2$), 71.7 ($CH_2$), 71.6 ($CH_2$), 71.2 ($CH_2$), 69.0 ($CH_2$), 68.4 ($CH_2$). Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.60; H, 6.94; N, 2.35. Found: C, 74.46; H, 7.12; N, 2.16.

**3.4.5. Aldoxime 37.** Colorless syrup; yield: 67%; mixture of *syn* and *anti* isomers; IR (Neat): 3363, 3292, 3061, 3032, 2119, 1604, 1495, 1453 $cm^{-1}$; MS (FAB): *m/z* 594 (M+H), 576 (M−OH), 486 (M−OBn); $^1H$ NMR: $\delta$ 7.54 (d, 0.7H, $J$=7.6 Hz), 7.31–7.26 (m, 20H), 6.98 (d, 0.3H, $J$=6.2 Hz), 4.95 (dd, 0.3H, $J$=6.4, 4.4 Hz), 4.71–4.46 (m, 6H), 4.43–4.27 (m, 4.7H), 4.03 (dd, 0.3H, $J$=5.6, 4.3 Hz), 3.96–3.81 (m, 2.7H), 3.77–3.72 (m, 1H), 3.67–3.62 (m, 1H), 2.39 (t, 1H, $J$=2.3 Hz). Anal. Calcd for $C_{37}H_{39}NO_6$: C, 74.85; H, 6.62; N, 2.36. Found: C, 74.69; H, 6.59; N, 2.32.

**3.4.6. (3*S*,4*R*,5*R*,6*R*)-3,4,5,6,7-Pentaallyloxy-1-nitroheptane (12).** A mixture of the aldehyde **10** (1.76 g, 4.63 mmol) prepared as described above, nitromethane (5.1 mL, 92.60 mmol), anhydrous KF (0.40 g, 6.90 mmol) and isopropanol (20 mL) was stirred at 25 °C for 15 h. The mixture was then filtered and the filtrate was concentrated to afford a syrupy liquid. To a solution of this material in $CH_2Cl_2$ (20 mL) at 0 °C, $Ac_2O$ (1 mL) and 4-dimethylaminopyridine (DMAP) (50 mg) were added, and the mixture was kept at 25 °C for 12 h. After addition of water (25 mL), the mixture was extracted with $CH_2Cl_2$, and the combined organic layers were washed with 10% HCl (5 mL), water, dried and concentrated to yield an oil. The latter was dissolved in ethanol (10 mL) and added dropwise to a stirred suspension of $NaBH_4$ (1.00 g) in EtOH (30 mL) at 0 °C and the resulting mixture was stirred for 6 h at 25 °C. Excess $NaBH_4$ was destroyed by the addition of 10% aqueous AcOH, and the residue obtained after removal of solvent was extracted with $CH_2Cl_2$. The combined organic layers were washed with water, dried and concentrated under reduced pressure to give a syrupy residue, which was chromatographed (EtOAc–petroleum ether, 1:12) to give **12** (1.40 g, 71%) as a light yellow syrupy liquid, $[\alpha]_D^{25}$ −16.7 (*c* 0.86, $CHCl_3$); IR (Neat): 3081, 1646, 1553 $cm^{-1}$; MS (FAB): *m/z* 426 (M+H); $^1H$ NMR: $\delta$ 5.98–5.82 (m, 5H), 5.30–5.13 (m, 10H), 4.55 (dd, 1H, $J$=13.3, 7.4 Hz), 4.46 (dd, 1H, $J$=13.3, 6.4 Hz), 4.23–3.96 (m, 10H), 3.78–3.53 (m, 6H), 2.47–2.39 (m, 1H), 2.17–2.09 (m, 1H); $^{13}C$ NMR: $\delta$ 134.7 (CH), 134.64 (CH), 134.62 (CH), 134.4 (CH), 134.2 (CH), 117.0 ($CH_2$), 116.7 (2×$CH_2$), 116.5 ($CH_2$), 116.2 ($CH_2$), 79.5 (CH), 77.8 (CH), 77.5 (CH), 75.4 (CH), 73.5 ($CH_2$), 72.8 ($CH_2$), 72.2 ($CH_2$), 72.0 ($CH_2$), 71.9 ($CH_2$), 70.5 ($CH_2$), 68.0 ($CH_2$), 28.6 ($CH_2$). Anal. Calcd for $C_{22}H_{35}NO_7$: C, 62.10; H, 8.29; N, 3.29. Found: C, 62.02; H, 8.14; N, 3.35.

**3.4.7. (α,β)-Methyl-3,5,6-tri-*O*-benzylglucofuranoside (16).** A solution of **15** (4.5 g, 9.18 mmol) in dry MeOH (75 mL) containing TsOH (0.22 g, 1.41 mmol) was heated at reflux for 6 h. The reaction mixture was neutralised with saturated $NaHCO_3$ solution and solvent was removed until a syrupy residue was obtained. The residue was extracted with $CH_2Cl_2$ and the combined organic layers were washed with water, dried and concentrated to give **16** (4.2 g, 98%) as a light yellow viscous oil, which was a mixture of the α and β anomers and used as such for the next steps. The mixture was separated by chromatography (100–200 mesh; EtOAc–petroleum ether, 1:9) to give the α-**16** as a colorless syrup, $[\alpha]_D^{28}$ +28.9 (*c* 0.32, $CHCl_3$); IR (Neat): 3517, 3062, 3031, 1604 $cm^{-1}$; MS (FAB): *m/z* 487 (M+Na), 465 (M+H), 447 (M−OH), 433 (M−$OCH_3$); $^1H$ NMR: $\delta$ 7.33–7.25 (m, 15H), 5.02 (d, 1H, $J$=4.5 Hz), 4.78 (d, 1H, $J$=11.5 Hz), 4.69 (d, 1H, $J$=11.7 Hz), 4.61–4.57 (m, 2H), 4.54 (d, 1H, $J$=11.5 Hz), 4.51 (d, 1H, $J$=11.7 Hz), 4.30 (dd, 1H, $J$=8.2, 4.4 Hz), 4.24 (dd, 1H, $J$=4.1, 1.4 Hz), 4.06–4.00 (m, 2H), 3.86 (dd, 1H, $J$=10.5, 1.9 Hz), 3.69 (dd, 1H, $J$=10.6, 5.8 Hz), 3.46 (s, 3H).

Further elution with EtOAc–petroleum ether (1:7) afforded the β-**16** as a colorless syrup, $[\alpha]_D^{28}$ −54.9 (*c* 0.25, $CHCl_3$); IR (Neat): 3431, 3062, 3031, 1604 $cm^{-1}$; MS (FAB): *m/z* 487 (M+Na), 465 (M+H), 447 (M−OH), 433 (M−$OCH_3$); $^1H$ NMR: $\delta$ 7.36–7.25 (m, 15H), 4.79 (s, 1H), 4.75 (d, 1H, $J$=11.4 Hz), 4.62–4.58 (m, 3H), 4.53 (d, 1H, $J$=11.9 Hz), 4.50 (d, 1H, $J$=11.4 Hz), 4.39 (dd, 1H, $J$=8.9, 4.9 Hz), 4.18 (s, 1H), 4.06 (ddd, 1H, $J$=8.7, 5.1, 1.9 Hz), 3.96 (dd, 1H, $J$=4.8, 1.1 Hz), 3.89 (dd, 1H, $J$=10.7, 1.9 Hz), 3.72 (dd, 1H, $J$=10.7, 5.2 Hz), 3.36 (s, 3H).

### 3.5. General procedure for the alkylation of 16

The procedure is illustrated by the preparation of methyl-2-*O*-allyl-3,5,6-tri-*O*-benzylglucofuranoside (**17**).

**3.5.1. Methyl-2-*O*-allyl-3,5,6-tri-*O*-benzylglucofuranoside (17).** A mixture of **16** (3.3 g, 7.11 mmol) in $CH_2Cl_2$ (50 mL), 50% aq NaOH solution (40 mL), tetrabutylammoniumbromide (15 mol%) and allyl bromide (0.92 mL, 10.66 mmol) was vigorously stirred for 12 h at 25 °C. Water (50 mL) was added and the mixture was extracted with $CH_2Cl_2$. The combined organic layer was washed with water, dried and the solvent was removed under reduced pressure to afford **17** (3.26 g, 91%) as a colorless syrup, which was a mixture of the α and β anomers and used as such for the next steps. The mixture was separated by chromatography (EtOAc–petroleum ether, 1:19) to give the β-**17** as a colorless syrup, $[\alpha]_D^{25}$ −39.1 (*c* 2.15, $CHCl_3$); IR (Neat): 3063, 3031, 1644, 1603 $cm^{-1}$; MS (FAB): *m/z* 527 (M+Na), 505 (M+H), 473 (M−$OCH_3$); $^1H$ NMR: $\delta$ 7.37–7.24 (m, 15H), 5.87–5.76 (m, 1H), 5.26–5.14 (m, 2H), 4.85 (s, 1H), 4.78 (d, 1H, $J$=11.4 Hz), 4.59–4.57 (m, 4H), 4.51 (d, 1H, $J$=11.4 Hz), 4.31 (dd, 1H, $J$=9.0, 4.6 Hz), 4.08 (ddd, 1H, $J$=9.0, 5.3, 2.0 Hz), 4.02 (dd, 1H, $J$=4.5, 0.7 Hz), 3.92–3.87 (m, 4H), 3.72 (dd, 1H, $J$=10.7, 5.3 Hz), 3.38 (s, 3H); $^{13}C$ NMR: $\delta$ 138.8 (q), 138.5 (q), 137.8 (q), 133.9 (CH), 128.2 (2×CH), 128.16 (2×CH), 128.1 (2×CH), 127.8 (2×CH), 127.6 (CH), 127.5 (2×CH), 127.4 (2×CH), 127.3 (CH), 127.2 (CH), 117.3 ($CH_2$), 108.5 (CH), 85.4 (CH), 80.4 (CH), 80.1 (CH), 76.5 (CH), 73.2 ($CH_2$), 72.2 ($CH_2$), 72.1 ($CH_2$), 70.7 ($CH_2$), 70.5 ($CH_2$), 55.8 ($CH_3$). Anal. Calcd for $C_{31}H_{36}O_6$: C, 73.79; H, 7.19. Found: C, 73.56; H, 7.28.

Further elution with EtOAc–petroleum ether (1:16) afforded the α-**17** as a colorless syrup, $[\alpha]_D^{25}$ +43.2 (*c* 1.20, $CHCl_3$);

IR (Neat): 3063, 3031, 1644, 1602 $cm^{-1}$; MS (FAB): *m/z* 505 (M+H); $^1H$ NMR: $\delta$ 7.33–7.27 (m, 15H), 5.97–5.84 (m, 1H), 5.27 (d, 1H, $J$=17.3 Hz), 5.20 (d, 1H, $J$=10.3 Hz), 4.95 (d, 1H, $J$=4.2 Hz), 4.79 (d, 1H, $J$=11.6 Hz), 4.63 (d, 1H, $J$=11.8 Hz), 4.56 (s, 2H), 4.55 (d, 1H, $J$=11.5 Hz), 4.54 (d, 1H, $J$=11.3 Hz), 4.33 (t, 1H, $J$=6.4 Hz), 4.21 (dd, 1H, $J$=5.7, 4.0 Hz), 4.12–3.98 (m, 3H), 3.94 (t, 1H, $J$=4.0 Hz), 3.86 (dd, 1H, $J$=10.6, 1.7 Hz), 3.71 (dd, 1H, $J$=10.5, 6.1 Hz), 3.41 (s, 3H); $^{13}C$ NMR: $\delta$ 138.8 (q), 138.5 (q), 138.0 (q), 134.4 (CH), 129.7 (CH), 128.9 (CH), 126.8 (CH), 117.7 ($CH_2$), 101.4 (CH), 83.6 (CH), 81.9 (CH), 76.8 (CH), 76.7 (CH), 73.3 ($CH_2$), 72.5 ($CH_2$), 72.2 ($CH_2$), 71.7 ($CH_2$), 71.2 ($CH_2$), 55.4 ($CH_3$). Anal. Calcd for $C_{31}H_{36}O_6$: C, 73.79; H, 7.19. Found: C, 73.68; H, 7.36.

**3.5.2. Methyl-2-*O*-propargyl-3,5,6-tri-*O*-benzylglucofuranoside (18).** The above procedure using propargyl bromide as the alkylating agent gave **18** (88%) as a mixture of anomers, which was used without separation for the next step. The mixture was separated by chromatography (EtOAc–petroleum ether, 1:19) to give the β-**18** as a colorless syrup, $[\alpha]_D^{25}$ −54.0 (*c* 1.49, $CHCl_3$); IR (Neat): 3285, 3062, 3031, 2117, 1602 $cm^{-1}$; MS (FAB): *m/z* 525 (M+Na), 503 (M+H), 471 (M−$OCH_3$); $^1H$ NMR: $\delta$ 7.37–7.25 (m, 15H), 4.87 (s, 1H), 4.77 (d, 1H, $J$=11.4 Hz), 4.64 (d, 1H, $J$=12.0 Hz), 4.59 (s, 2H), 4.57 (d, 1H, $J$=12.0 Hz), 4.51 (d, 1H, $J$=11.4 Hz), 4.29 (dd, 1H, $J$=9.0, 4.7 Hz), 4.15–4.01 (m, 5H), 3.89 (dd, 1H, $J$=10.7, 2.0 Hz), 3.71 (dd, 1H, $J$=10.7, 5.3 Hz), 3.39 (s, 3H), 2.44 (t, 1H, $J$=2.5 Hz); $^{13}C$ NMR: $\delta$ 138.8 (q), 138.5 (q), 137.7 (q), 128.3 (2×CH), 128.2 (2×CH), 128.1 (2×CH), 127.8 (2×CH), 127.6 (CH), 127.5 (4×CH), 127.3 (CH), 127.2 (CH), 108.3 (CH), 84.9 (CH), 80.0 (CH), 79.9 (CH), 79.0 (CH), 76.4 (CH), 75.1 (q), 73.3 ($CH_2$), 72.3 ($CH_2$), 72.0 ($CH_2$), 70.6 ($CH_2$), 57.0 ($CH_2$), 55.9 ($CH_3$). Anal. Calcd for $C_{31}H_{34}O_6$: C, 74.08; H, 6.82. Found: C, 73.84; H, 6.73.

Further elution with EtOAc–petroleum ether (1:16) afforded the α-**18** as a colorless syrup, $[\alpha]_D^{25}$ +39.5 (*c* 1.04, $CHCl_3$); IR (Neat): 3285, 3063, 3032, 2119, 1602 $cm^{-1}$; MS (FAB): *m/z* 525 (M+Na), 503 (M+H), 471 (M−$OCH_3$); $^1H$ NMR: $\delta$ 7.35–7.21 (m, 15H), 5.02 (d, 1H, $J$=3.9 Hz), 4.79 (d, 1H, $J$=11.6 Hz), 4.68 (d, 1H, $J$=11.7 Hz), 4.56 (s, 2H), 4.55 (d, 1H, $J$=11.6 Hz), 4.53 (d, 1H, $J$=11.7 Hz), 4.35–4.16 (m, 5H), 4.03 (ddd, 1H, $J$=8.2, 6.1, 2.2 Hz), 3.86 (dd, 1H, $J$=10.6, 2.2 Hz), 3.70 (dd, 1H, $J$=10.6, 6.1 Hz), 3.41 (s, 3H), 2.46 (t, 1H, $J$=2.5 Hz); $^{13}C$ NMR: $\delta$ 138.8 (q), 138.5 (q), 137.9 (q), 128.4 (CH), 128.3 (2×CH), 128.2 (2×CH), 128.1 (2×CH), 127.6 (2×CH), 127.5 (2×CH), 127.4 (2×CH), 127.3 (CH), 127.2 (CH), 101.3 (CH), 82.7 (CH), 81.6 (CH), 79.2 (CH), 76.8 (CH), 76.5 (CH), 75.3 (q), 73.3 ($CH_2$), 72.5 ($CH_2$), 72.0 ($CH_2$), 71.1 ($CH_2$), 57.6 ($CH_2$), 55.4 ($CH_3$). Anal. Calcd for $C_{31}H_{34}O_6$: C, 74.08; H, 6.82. Found: C, 74.26; H, 6.68.

**3.5.3. Methyl-2,3,5,6-tetra-*O*-benzylglucofuranoside (19).** The above procedure using benzyl bromide as the alkylating agent gave **19** (90%) as a mixture of anomers, which was used without separation for the next step. The mixture was separated by chromatography (EtOAc–petroleum ether, 1:16) to give the β-**19** as a colorless syrup, $[\alpha]_D^{25}$ −30.4 (*c* 1.35, $CHCl_3$); IR (Neat): 3062, 3031, 1603 $cm^{-1}$; MS (EI): *m/z* 554 (M); $^1H$ NMR: $\delta$ 7.36–7.26 (m, 20H), 4.90 (s, 1H), 4.77 (d, 1H, $J$=11.4 Hz), 4.59 (s, 2H), 4.52 (s, 2H), 4.51 (d, 1H, $J$=11.2 Hz), 4.43 (s, 2H), 4.35 (dd, 1H, $J$=9.0, 4.6 Hz), 4.11–4.06 (m, 2H), 3.92 (s, 1H), 3.88 (d, 1H, $J$=1.7 Hz), 3.72 (dd, 1H, $J$=10.7, 5.3 Hz), 3.37 (s, 3H); $^{13}C$ NMR: $\delta$ 138.8 (q), 138.6 (q), 137.8 (q), 137.4 (q), 128.4 (2×CH), 128.3 (2×CH), 128.2 (2×CH), 128.1 (2×CH), 127.9 (2×CH), 127.8 (CH), 127.6 (CH), 127.5 (6×CH), 127.3 (CH), 127.2 (CH), 108.6 (CH), 85.6 (CH), 80.5 (CH), 80.1 (CH), 76.5 (CH), 73.3 ($CH_2$), 72.3 ($CH_2$), 72.1 ($CH_2$), 71.7 ($CH_2$), 70.7 ($CH_2$), 55.8 ($CH_3$). Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91. Found: C, 75.91; H, 6.83.

Further elution with EtOAc–petroleum ether (1:14) afforded the α-**19** as a colorless syrup, $[\alpha]_D^{25}$ +40.6 (*c* 1.19, $CHCl_3$); IR (Neat): 3062, 3031, 1603 $cm^{-1}$; MS (EI): *m/z* 554 (M); $^1H$ NMR: $\delta$ 7.34–7.19 (m, 20H), 4.87 (d, 1H, $J$=4.2 Hz), 4.77 (d, 1H, $J$=11.6 Hz), 4.63 (d, 1H, $J$=12.0 Hz), 4.55–4.45 (m, 6H), 4.35 (t, 1H, $J$=6.2 Hz), 4.23 (dd, 1H, $J$=5.7, 3.9 Hz), 4.02–3.95 (m, 2H), 3.85 (dd, 1H, $J$=10.5, 2.0 Hz), 3.69 (dd, 1H, $J$=10.5, 6.1 Hz), 3.39 (s, 3H); $^{13}C$ NMR: $\delta$ 138.8 (q), 138.5 (q), 137.9 (q), 137.5 (q), 128.3 (2×CH), 128.2 (2×CH), 128.1 (2×CH), 128.0 (2×CH), 127.9 (2×CH), 127.8 (CH), 127.5 (3×CH), 127.4 (2×CH), 127.3 (2×CH), 127.2 (CH), 127.1 (CH), 101.3 (CH), 83.5 (CH), 81.9 (CH), 76.7 (CH), 76.5 (CH), 73.2 ($CH_2$), 72.5 ($CH_2$), 72.4 ($CH_2$), 72.0 ($CH_2$), 71.1 ($CH_2$), 55.3 ($CH_3$). Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91. Found: C, 75.72; H, 6.74.

### 3.6. General procedure for the deglycosylation of the methylfuranosides 20, 21, 22

The general deglycosylation procedure is illustrated by the preparation of **20**.

**3.6.1. 2-*O*-Allyl-3,5,6-tri-*O*-benzylglucofuranose (20).** A solution of the α/β mixture **17** (2.60 g) in 50% aq TFA (30 mL) was stirred at 25 °C for 24 h. The reaction mixture was neutralized with solid $NaHCO_3$. The resulting mixture was extracted with $CH_2Cl_2$ and the combined organic extract was washed with water, dried and concentrated to give a syrupy liquid, which on chromatography (EtOAc–petroleum ether, 1:9) gave an anomeric mixture of **20** (2.42 g, 96%) as a colorless syrup, IR (Neat): 3508, 3062, 3031, 1644, 1603 $cm^{-1}$; MS (FAB): *m/z* 513 (M+Na), 491 (M+H), 473 (M−OH); $^1H$ NMR: $\delta$ 7.36–7.21 (m, 15H), 5.88–5.77 (m, 1H), 5.48 (d, 0.4H, $J$=3.3 Hz), 5.28–5.17 (m, 2.6H), 4.84 (d, 0.6H, $J$=11.4 Hz), 4.83 (d, 0.4H, $J$=11.4 Hz), 4.63–4.47 (m, 5H), 4.31 (dd, 0.6H, $J$=9.4, 3.7 Hz), 4.23 (dd, 0.4H, $J$=9.1, 3.3 Hz), 4.12–3.89 (m, 5.6H), 3.78 (d, 0.4H, $J$=3.7 Hz), 3.72 (dd, 0.6H, $J$=10.6, 5.5 Hz), 3.70 (dd, 0.4H, $J$=10.6, 5.8 Hz).

**3.6.2. 2-*O*-Propargyl-3,5,6-tri-*O*-benzylglucofuranose (21).** The same procedure starting from the α/β mixture of **18** (2.95 g) yielded an anomeric mixture of **21** (2.70 g, 94%) as a colorless syrup, IR (Neat): 3435, 3287, 3062, 3031, 2117, 1603 $cm^{-1}$; MS (FAB): *m/z* 511 (M+Na), 471 (M−OH), 411 (M−Ph); $^1H$ NMR: $\delta$ 7.35–7.25 (m, 15H), 5.50 (d, 0.35H, $J$=3.4 Hz), 5.22 (s, 0.65H), 4.82 (d, 0.65H, $J$=11.5 Hz), 4.81 (d, 0.35H, $J$=11.4 Hz), 4.64–4.47 (m, 6H), 4.30–4.22 (m, 1H), 4.18–4.12 (m, 3H), 4.07–3.99 (m, 1H),

3.94–3.88 (m, 1H), 3.72 (dd, 0.65H, $J=10.7$, 5.4 Hz), 3.69 (dd, 0.35H, $J=10.7$, 5.9 Hz), 2.45 (t, 1H, $J=2.5$ Hz).

**3.6.3. 2,3,5,6-Tetra-*O*-benzylglucofuranose (22).** The same procedure starting from the α/β mixture of **19** (2.00 g) yielded an anomeric mixture of **22** (1.73 g, 89%) as a colorless syrup, IR (Neat): 3508, 3062, 3031, 1603 $cm^{-1}$; MS (FAB): *m/z* 563 (M+Na), 523 (M−OH); $^1H$ NMR: δ 7.36–7.17 (m, 20H), 5.48 (br s, 0.4H), 5.25 (br s, 0.6H), 4.83 (d, 0.6H, $J=11.4$ Hz), 4.81 (d, 0.4H, $J=11.3$ Hz), 4.63–4.41 (m, 7H), 4.34 (dd, 0.6H, $J=9.4$, 3.7 Hz), 4.26 (dd, 0.4H, $J=9.1$, 3.3 Hz), 4.12–3.83 (m, 4H), 3.73 (dd, 0.6H, $J=10.5$, 5.4 Hz), 3.69 (dd, 0.4H, $J=10.5$, 5.5 Hz).

### 3.7. General procedure for the preparation of the diethyl dithioacetal derivatives 24, 26, 28 and 29

The general procedure for the preparation of the above compounds is illustrated by the preparation of **24**.

A solution of **20** (2.40 g) in conc HCl (18 mL) was cooled to 0 °C with stirring for 15 min. To the mixture was added EtSH (9 mL) dropwise and the resulting solution was stirred for another 4 h at 0 °C. The solution was kept in a freezer for 16 h. The reaction mixture was neutralised with solid $NaHCO_3$ and then extracted with $CH_2Cl_2$. The combined organic layers were washed with water, dried and evaporated under reduced pressure yielding a light yellow syrup, which was chromatographed (EtOAc–petroleum ether, 1:11) to give **23** (2.37 g, 81%) as a colorless syrup, $[\alpha]_D^{25}-46.7$ (*c* 0.14, $CHCl_3$); IR (Neat): 3539, 3063, 3030, 1604, 1496, 1453 $cm^{-1}$; MS (FAB): *m/z* 619 (M+Na), 597 (M+H), 535 (M−SEt); $^1H$ NMR: δ 7.34–7.26 (m, 15H), 6.01–5.88 (m, 1H), 5.25 (dd, 1H, $J=17.2$, 1.6 Hz), 5.12 (dd, 1H, $J=10.5$, 1.4 Hz), 4.83 (d, 1H, $J=11.2$ Hz), 4.72 (d, 1H, $J=11.6$ Hz), 4.57 (s, 2H), 4.43 (d, 1H, $J=11.2$ Hz), 4.34–4.28 (m, 3H), 4.19 (d, 1H, $J=7.5$ Hz), 3.98–3.87 (m, 3H), 3.75–3.62 (m, 3H), 2.76–2.61 (m, 4H), 1.25 (t, 3H, $J=7.4$ Hz), 1.23 (t, 3H, $J=7.4$ Hz).

A solution of **23** (2.30 g, 3.86 mmol) in THF (20 mL) was added dropwise to a stirred suspension of NaH (60% suspension in mineral oil; 0.232 g, 5.79 mmol) in THF (20 mL) at 0 °C. After the addition was over, the mixture was stirred at 25 °C for 1 h. To this mixture was added dropwise with stirring a solution of benzyl bromide (0.70 mL, 5.79 mmol) in THF (20 mL) at 0 °C and stirring was continued for 30 min. The mixture was heated at 25 °C for 12 h. It was then cooled to 0 °C and few drops of water were added to destroy excess NaH. After concentration of the mixture, the residue was extracted with $CH_2Cl_2$. The combined organic layers were washed with water, dried, concentrated and the residue was chromatographed (EtOAc–petroleum ether, 1:10) to give **24** (1.72 g, 65%) as a colorless syrup, $[\alpha]_D^{25}-2.4$ (*c* 0.11, $CHCl_3$); IR (Neat): 3062, 3030, 1644, 1604, 1495, 1453 $cm^{-1}$; MS (FAB): *m/z* 709 (M+Na), 625 (M−SEt), 579 (M−OBn); $^1H$ NMR: δ 7.33–7.25 (m, 20H), 5.99–5.87 (m, 1H), 5.22 (d, 1H, $J=17.2$ Hz), 5.08 (d, 1H, $J=10.3$ Hz), 4.82–4.61 (m, 5H), 4.51–4.48 (m, 3H), 4.29–4.26 (m, 2H), 4.17–4.14 (m, 1H), 3.95–3.83 (m, 5H), 3.76–3.73 (m, 1H), 2.66 (q, 2H, $J=7.4$ Hz), 2.56–2.48 (m, 2H), 1.20 (t, 3H, $J=7.4$ Hz), 1.14 (t, 3H, $J=7.4$ Hz); $^{13}C$ NMR: δ 138.6 (q), 138.5 (q), 138.2 (q), 135.0 (CH), 128.1 (CH), 128.08 (CH), 128.03 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 127.44 (CH), 127.4 (CH), 127.36 (CH), 127.2 (CH), 116.1 ($CH_2$), 82.9 (CH), 80.7 (CH), 79.4 (CH), 78.6 (CH), 75.2 ($CH_2$), 73.8 ($CH_2$), 73.4 ($CH_2$), 73.1 ($CH_2$), 71.8 ($CH_2$), 70.0 ($CH_2$), 53.3 (CH), 24.9 ($CH_2$), 24.7 ($CH_2$), 14.3 ($CH_3$), 14.2 ($CH_3$). Anal. Calcd for $C_{41}H_{50}O_5S_2$: C, 71.68; H, 7.34. Found: C, 71.57; H, 7.17.

**3.7.1. Dithioacetal 26.** The same procedure starting from **21** (2.69 g) yielded after chromatography (EtOAc–petroleum ether, 1:10) **25** (2.48 g, 76%) as a light yellow syrup, $[\alpha]_D^{25}-33.2$ (*c* 0.64, $CHCl_3$); IR (Neat): 3536, 3288, 3062, 3031, 2120, 1603, 1496, 1452 $cm^{-1}$; MS (FAB): *m/z* 633 (M+K), 617 (M+Na), 595 (M+H), 533 (M−SEt); $^1H$ NMR: δ 7.34–7.26 (m, 15H), 4.86 (d, 1H, $J=11.1$ Hz), 4.73 (d, 1H, $J=11.7$ Hz), 4.57 (s, 2H), 4.48 (d, 2H, $J=1.7$ Hz), 4.43 (d, 1H, $J=11.1$ Hz), 4.34 (d, 1H, $J=11.7$ Hz), 4.22–4.20 (m, 1H), 4.09 (dd, 1H, $J=7.4$, 2.9 Hz), 3.97 (d, 1H, $J=2.9$ Hz), 3.89 (dd, 1H, $J=10.4$, 2.4 Hz), 3.75–3.70 (m, 2H), 3.66–3.62 (m, 1H), 2.72 (q, 2H, $J=7.3$ Hz), 2.70 (q, 2H, $J=7.3$ Hz), 2.40 (t, 1H, $J=2.4$ Hz), 1.26 (t, 3H, $J=7.3$ Hz), 1.23 (t, 3H, $J=7.3$ Hz); $^{13}C$ NMR: δ 138.2 (q), 138.1 (q), 138.0 (q), 128.2 (CH), 128.15 (CH), 128.11 (CH), 128.0 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 83.0 (CH), 79.8 (CH), 78.0 (CH), 77.8 (CH), 74.6 (q), 74.6 ($CH_2$), 73.3 ($CH_2$), 71.4 ($CH_2$), 70.6 (CH), 69.8 ($CH_2$), 60.1 ($CH_2$), 52.7 (CH), 25.6 ($CH_2$), 25.5 ($CH_2$), 14.3 (2×$CH_3$).

Alkylation of **25** (1.07 g, 1.80 mmol) with benzyl bromide (0.32 mL, 2.70 mmol) using the procedure described for the convertion of **23** to **24** gave after chromatography (EtOAc–petroleum ether, 1:16) **26** (0.93 g, 76%) as a colorless syrup, $[\alpha]_D^{25}+1.0$ (*c* 0.20, $CHCl_3$); IR (Neat): 3289, 3062, 3031, 2120, 1603, 1495, 1452 $cm^{-1}$; MS (FAB): *m/z* 685 (M+H), 623 (M−SEt), 577 (M−OBn); $^1H$ NMR: δ 7.36–7.23 (m, 20H), 4.81 (d, 1H, $J=11.2$ Hz), 4.76 (d, 1H, $J=11.3$ Hz), 4.72 (d, 1H, $J=11.2$ Hz), 4.68 (d, 1H, $J=11.2$ Hz), 4.66 (d, 1H, $J=11.4$ Hz), 4.55–4.51 (m, 3H), 4.47–4.45 (m, 2H), 4.20–4.17 (m, 1H), 3.96–3.87 (m, 5H), 3.76–3.70 (m, 1H), 2.64 (q, 2H, $J=7.4$ Hz), 2.59–2.50 (m, 2H), 2.37 (t, 1H, $J=2.2$ Hz), 1.20 (t, 3H, $J=7.4$ Hz), 1.15 (t, 3H, $J=7.4$ Hz); $^{13}C$ NMR: δ 138.5 (2×q), 138.2 (q), 138.1 (q), 128.2 (3×CH), 128.1 (3×CH), 128.0 (4×CH), 127.9 (2×CH), 127.5 (2×CH), 127.4 (3×CH), 127.3 (CH), 127.27 (CH), 127.2 (CH), 82.0 (CH), 80.2 (CH), 80.0 (CH), 79.2 (CH), 78.8 (CH), 75.1 ($CH_2$), 74.5 (q), 73.6 ($CH_2$), 73.1 ($CH_2$), 71.8 ($CH_2$), 69.8 ($CH_2$), 59.5 ($CH_2$), 52.8 (CH), 25.1 ($CH_2$), 24.7 ($CH_2$), 14.3 ($CH_3$), 14.1 ($CH_3$). Anal. Calcd for $C_{41}H_{48}O_5S_2$: C, 71.89; H, 7.06. Found: C, 71.82; H, 7.24.

**3.7.2. Dithioacetal 28.** Dithioacetylation of **22** (1.54 g) afforded after chromatography (EtOAc–petroleum ether, 1:11) **27** (1.34 g, 73%) as a colorless syrup, $[\alpha]_D^{28}-18.9$ (*c* 0.23, $CHCl_3$); IR (Neat): 3538, 3062, 3031, 1604, 1496, 1452 $cm^{-1}$; MS (FAB): *m/z* 669 (M+Na), 585 (M−SEt); $^1H$ NMR: δ 7.37–7.18 (m, 20H), 4.86 (d, 1H, $J=11.1$ Hz), 4.80 (d, 1H, $J=11.2$ Hz), 4.78 (d, 1H, $J=11.1$ Hz), 4.71 (d, 1H, $J=11.6$ Hz), 4.57 (s, 2H), 4.42 (d, 1H, $J=11.1$ Hz), 4.30 (d, 1H, $J=11.6$ Hz), 4.22 (d, 1H, $J=7.7$ Hz), 4.09 (dd, 1H, $J=7.7$, 2.7 Hz), 3.96 (d, 1H, $J=2.7$ Hz), 3.90 (dd, 1H, $J=10.7$, 2.8 Hz), 3.76–3.71 (m, 2H), 3.66–3.61 (m, 1H), 2.74–2.59 (m, 4H), 1.24 (t, 3H, $J=7.4$ Hz), 1.20 (t, 3H,

$J=7.4$ Hz); $^{13}$C NMR: $\delta$ 138.2 (3×q), 138.0 (q), 128.1 (CH), 128.03 (CH), 127.99 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 83.3 (CH), 78.1 (CH), 77.9 (CH), 75.1 ($CH_2$), 74.4 ($CH_2$), 73.2 ($CH_2$), 71.3 ($CH_2$), 70.5 (CH), 69.8 ($CH_2$), 53.3 (CH), 25.6 ($CH_2$), 25.2 ($CH_2$), 14.2 (2×$CH_3$).

Alkylation of **27** (1.70 g, 2.63 mmol) with allyl bromide (0.34 mL, 3.95 mmol) gave after chromatography (EtOAc–Petroleum ether, 1:16) **28** (1.10 g, 61%) as a colorless syrup, $[\alpha]_D^{25}+3.8$ (*c* 0.39, $CHCl_3$); IR (Neat): 3063, 3030, 1644, 1604, 1496, 1453 cm$^{-1}$; MS (FAB): *m/z* 685 (M−H), 625 (M−SEt), 579 (M−OBn); $^1$H NMR: $\delta$ 7.44–7.26 (m, 20H), 5.95–5.82 (m, 1H), 5.20 (d, 1H, $J=17.2$ Hz), 5.12 (d, 1H, $J=10.3$ Hz), 4.86 (d, 1H, $J=11.0$ Hz), 4.80 (d, 1H, $J=11.2$ Hz), 4.79 (d, 1H, $J=10.8$ Hz), 4.66 (d, 1H, $J=11.1$ Hz), 4.62 (d, 1H, $J=11.6$ Hz), 4.51 (s, 2H), 4.37 (d, 1H, $J=11.8$ Hz), 4.24–4.20 (m, 2H), 4.13–4.04 (m, 3H), 3.91–3.83 (m, 2H), 3.77 (t, 1H, $J=4.4$ Hz), 3.67 (dd, 1H, $J=9.9$, 4.7 Hz), 2.77–2.59 (m, 4H), 1.22 (t, 3H, $J=7.3$ Hz), 1.20 (t, 3H, $J=7.3$ Hz); $^{13}$C NMR: $\delta$ 138.6 (q), 138.5 (q), 138.4 (q), 138.2 (q), 134.8 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 116.8 ($CH_2$), 82.7 (CH), 80.5 (CH), 78.9 (CH), 78.7 (CH), 75.1 ($CH_2$), 74.5 ($CH_2$), 73.1 ($CH_2$), 72.8 ($CH_2$), 71.6 ($CH_2$), 69.5 ($CH_2$), 53.4 (CH), 24.8 (2×$CH_2$), 14.3 (2×$CH_3$). Anal. Calcd for $C_{41}H_{50}O_5S_2$: C, 71.68; H, 7.34. Found: C, 71.52; H, 7.32.

**3.7.3. Dithioacetal 29.** Alkylation of **27** (1.30 g, 2.01 mmol) with propargyl bromide (0.45 mL, 3.02 mmol) yielded after chromatography (EtOAc–Petroleum ether, 1:16) **29** (1.00 g, 73%) as a colorless syrup, $[\alpha]_D^{28}-11.2$ (*c* 0.27, $CHCl_3$); IR (Neat): 3289, 3062, 3031, 2120, 1604, 1496, 1452 cm$^{-1}$; MS (FAB): *m/z* 707 (M+Na), 684 (M), 623 (M−SEt), 577 (M−OBn); $^1$H NMR: $\delta$ 7.38–7.22 (m, 20H), 4.89 (d, 1H, $J=11.0$ Hz), 4.80 (d, 1H, $J=11.1$ Hz), 4.79 (d, 1H, $J=11.4$ Hz), 4.66 (d, 1H, $J=11.3$ Hz), 4.61 (d, 1H, $J=11.8$ Hz), 4.50 (s, 2H), 4.42–4.37 (m, 3H), 4.21–4.08 (m, 3H), 3.97–3.90 (m, 2H), 3.84–3.79 (m, 1H), 3.65 (dd, 1H, $J=10.5$, 5.4 Hz), 2.77–2.63 (m, 4H), 2.44 (t, 1H, $J=2.3$ Hz), 1.23 (t, 3H, $J=7.4$ Hz), 1.22 (t, 3H, $J=7.4$ Hz); $^{13}$C NMR: $\delta$ 138.3 (q), 138.2 (q), 138.1 (q), 137.9 (q), 127.9 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 82.5 (CH), 80.3 (CH), 79.9 (CH), 79.0 (CH), 77.8 (CH), 75.0 ($CH_2$), 74.7 (q), 74.5 ($CH_2$), 72.9 ($CH_2$), 71.5 ($CH_2$), 69.3 ($CH_2$), 58.5 ($CH_2$), 53.2 (CH), 24.7 ($CH_2$), 24.5 ($CH_2$), 14.2 (2×$CH_3$). Anal. Calcd for $C_{41}H_{48}O_5S_2$: C, 71.89; H, 7.06. Found: C, 71.97; H, 7.12.

### 3.8. General procedure for the preparation of the *N*-benzyl nitrones 38 and 39 and their cycloaddition to (1′*R*,2′*R*,3′*R*,3a*R*,6*S*,6a*S*)-6-(2′-hydroxy-1′,3′,4′-tribenzyloxy)butyltetrahydrofuro[3,4-*c*]isoxazole (41) and (1′*R*,2′*R*,3′*R*,3a*R*,6*S*,6a*S*)-1-benzyl-6-(1′,2′,3′,4′-tetraallyloxy)butyltetrahydrofuro[3,4-*c*]isoxazole (42)

The general procedure is illustrated by the preparation of **39** and its cycloaddition to **42**.

A solution of the aldehyde **10** (0.38 g, 1.00 mmol) and BnNHOH (0.19 g, 1.54 mmol) in benzene (10 mL) was heated under reflux in the presence of 3 Å molecular sieves (0.21 g) for 8 h. It was then filtered and washed with benzene. The combined filtrate and the washings were evaporated to afford a syrupy residue, which on chromatography (EtOAc–petroleum ether, 1:7) gave **42** (0.36 g, 75%) as a colorless syrup, $[\alpha]_D^{25}+21.8$ (*c* 1.42, $CHCl_3$); IR (Neat): 3079, 3013, 1645 cm$^{-1}$; MS (EI): *m/z* 485 (M), 204; $^1$H NMR: $\delta$ 7.39–7.24 (m, 5H), 6.00–5.83 (m, 3H), 5.77–5.64 (m, 1H), 5.33–5.00 (m, 8H), 4.30–4.24 (m, 1H), 4.18–4.00 (m, 9H), 3.82–3.48 (m, 9H), 3.38–3.28 (m, 3H); $^{13}$C NMR: $\delta$ 136.6 (q), 135.3 (CH), 135.0 (CH), 134.8 (CH), 134.7 (CH), 129.0 (2×CH), 128.3 (2×CH), 127.4 (CH), 116.4 ($CH_2$), 116.3 ($CH_2$), 116.0 ($CH_2$), 115.9 ($CH_2$), 83.2 (CH), 80.5 (CH), 78.5 (CH), 78.2 (CH), 73.9 ($CH_2$), 73.4 ($CH_2$), 73.2 ($CH_2$), 72.0 ($CH_2$), 71.9 (CH), 70.6 ($CH_2$), 69.7 ($CH_2$), 69.2 ($CH_2$), 59.9 ($CH_2$), 48.4 (CH). Anal. Calcd for $C_{28}H_{39}NO_6$: C, 69.25; H, 8.09; N, 2.88. Found: C, 68.95; H, 7.99; N, 2.72.

*Compound* **41**. The same procedure starting from **20** (0.42 g, 0.86 mmol) with BnNHOH (0.16 g, 1.30 mmol) yielded after chromatography (EtOAc–petroleum ether, 1:5) **41** (0.36 g, 70%) as a white solid, mp 98–99 °C, $[\alpha]_D^{25}-16.4$ (*c* 1.40, $CHCl_3$); IR (KBr): 3508, 3061, 3031, 1604 cm$^{-1}$; MS (EI): *m/z* 595 (M), 204; $^1$H NMR (100 MHz): $\delta$ 7.36–7.28 (m, 20H), 4.74 (d, 1H, $J=12.0$ Hz), 4.58 (s, 2H), 4.42 (s, 2H), 4.32–4.08 (m, 2H), 3.96–3.52 (m, 12H), 3.36 (m, 1H), 1.64 (br s, 1H); $^{13}$C NMR (25 MHz): $\delta$ 138.6 (2×q), 138.4 (q), 136.2 (q), 129.2 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 85.4 (CH), 77.7 (CH), 77.4 (CH), 73.7 ($CH_2$), 73.6 ($CH_2$), 73.3 ($CH_2$), 72.7 (CH), 71.7 ($CH_2$), 71.3 (CH), 70.0 (2×$CH_2$), 59.8 ($CH_2$), 47.5 (CH). Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.60; H, 6.94; N, 2.35. Found: C, 74.48; H, 7.23; N, 2.18.

**3.8.1. Preparation of the *N*-methyl nitrone 40 and its cycloaddition to (1′*R*,2′*R*,3′*R*,3a*R*,6*S*,6a*S*)-1-methyl-6-(1′,2′,3′,4′-tetraallyloxy)butyltetrahydrofuro[3,4-*c*]-isoxazole (43).** A solution of **10** (1.16 g, 3.05 mmol), MeNHOH.HCl (0.33 g, 3.95 mmol) and $NaHCO_3$ (0.39 g, 4.64 mmol) in 80% aqueous EtOH (40 mL) was heated under reflux for 12 h. After it was cooled to 25 °C, the mixture was concentrated under reduced pressure to give a residue, which was extracted with $CH_2Cl_2$. The organic layer was washed with water, dried and concentrated to give a reddish yellow syrupy residue, which on chromatography (EtOAc–petroleum ether, 1:6) gave **43** (0.94 g, 75%) as a pale yellow syrup. $[\alpha]_D^{25}+19.8$ (*c* 0.65, $CHCl_3$); IR (Neat): 3079, 1645 cm$^{-1}$; MS (FAB): *m/z* 410 (M+H), 128; $^1$H NMR: $\delta$ 6.00–5.85 (m, 4H), 5.30–5.09 (m, 8H), 4.35–3.99 (m, 10H), 3.84–3.81 (m, 2H), 3.72–3.51 (m, 7H), 3.34–3.29 (m, 1H), 2.63 (s, 3H); $^{13}$C NMR: $\delta$ 135.0 (CH), 134.7 (CH), 134.6 (CH), 134.4 (CH), 116.3 ($CH_2$), 116.1 ($CH_2$), 116.0 ($CH_2$), 115.5 ($CH_2$), 82.6 (CH), 79.7 (CH), 78.7 (CH), 77.9 (CH), 75.1 (CH), 73.5 ($CH_2$), 73.0 (2×$CH_2$), 71.7 ($CH_2$), 70.4 ($CH_2$), 69.1 ($CH_2$), 68.8 ($CH_2$), 48.4 (CH), 43.4 ($CH_3$). Anal. Calcd for $C_{22}H_{35}NO_6$: C, 64.52; H, 8.61; N, 3.42. Found: C, 64.53; H, 8.77; N, 3.22.

**3.8.2. (1′*R*,2′*R*,3′*R*,2*S*,3*S*,4*S*)-3-Methylamino-4-hydroxymethyl-2-(1′,2′,3′,4′-tetraallyloxy)butyltetrahydrofuran (50).** A mixture of the isoxazolidine **43** (2.06 g, 5.01 mmol) and Zn dust (1.31 g, 20.04 mmol) in 60% aqueous AcOH (35 mL) was heated under reflux for 7 h. After completion

of the reaction as revealed by TLC, the mixture was concentrated under reduced pressure. The residue was extracted with $CH_2Cl_2$ and the combined organic extracts were washed with $NaHCO_3$, water, dried and concentrated under reduced pressure to give a syrupy residue, which was chromatographed (MeOH–$CH_2Cl_2$, 1:49) to give **50** (1.40 g, 75%) as a colorless syrup, $[\alpha]_D^{28}+2.1$ (*c* 0.81, $CHCl_3$); IR (Neat): 3331, 3080, 3012, 1645 $cm^{-1}$; MS (EI): *m/z* 412 (M+H), 130; $^1H$ NMR: $\delta$ 6.01–5.84 (m, 4H), 5.30–5.11 (m, 8H), 4.34–4.25 (m, 2H), 4.18–4.05 (m, 4H), 4.01–3.96 (m, 3H), 3.85–3.66 (m, 8H), 3.58–3.51 (m, 2H), 3.29 (t, 1H, *J*=7.3 Hz), 2.85 (br s, 2H, exchangeable with $D_2O$), 2.49 (s, 3H); $^{13}C$ NMR: $\delta$ 135.1 (CH), 134.9 (CH), 134.6 (CH), 134.4 (CH), 116.7 ($CH_2$), 116.4 (2×$CH_2$), 115.8 ($CH_2$), 82.6 (CH), 79.9 (CH), 79.2 (CH), 77.7 (CH), 74.0 ($CH_2$), 72.5 ($CH_2$), 71.9 ($CH_2$), 70.7 ($CH_2$), 69.5 ($CH_2$), 69.1 ($CH_2$), 64.0 (CH), 61.4 ($CH_2$), 42.0 (CH), 35.7 ($CH_3$). Anal. Calcd for $C_{22}H_{37}NO_6$: C, 64.21; H, 9.06; N, 3.40. Found: C, 63.96; H, 8.78; N, 3.13.

### 3.9. General procedure for the generation of *O*-allyl and *O*-propargyl nitrile oxides from oximes and their cycloaddition

A mixture of chloramine-T hydrate (0.64 mmol) and the oxime (0.25 mmol) in EtOH (10 mL) was heated under reflux for 9 h. After completion of the reaction as revealed by TLC, the resulting precipitate was filtered and the filtrate was evaporated under reduced pressure. The residue was extracted with $CH_2Cl_2$ and the combined organic layer was washed successively with water, 1 M aq NaOH solution and water. The organic extract was then dried, and removal of solvent afforded a syrupy residue, which on chromatography over silicagel (100–200 mesh; EtOAc–petroleum ether) gave the dihydroisoxazoline as a mixture of 3a-epimers or the isoxazole. The yields of the mixture of 3a-epimeric dihydroisoxazolines are presented in Table 2. The individual epimers **55**, **56**, **60** and **61** could be isolated by column chromatography. The mixture of **57** and **58** on preparative TLC gave enriched fractions of the two compounds.

**3.9.1. (1′*R*,2′*R*,3′*R*,3a*R*,6*S*)-6-(1′,2′,3′,4′-Tetraallyloxy)-butyl-3a,4-dihydro-3*H*,6*H*-furo[3,4-*c*]isoxazole (55).** $[\alpha]_D^{25}-39.7$ (*c* 0.21, $CHCl_3$); IR (Neat): 3080, 1645 $cm^{-1}$; MS (EI): *m/z* 393 (M), 112; $^1H$ NMR: $\delta$ 6.02–5.81 (m, 4H), 5.34–5.11 (m, 8H), 4.51 (dd, 1H, *J*=10.2, 8.3 Hz), 4.41 (s, 1H), 4.38 (dd, 1H, *J*=10.6, 6.7 Hz), 4.29 (dd, 1H, *J*=12.5, 5.8 Hz), 4.21 (dd, 1H, *J*=12.5, 5.8 Hz), 4.10–3.97 (m, 6H), 3.89–3.81 (m, 2H), 3.74–3.64 (m, 3H), 3.59–3.55 (m, 1H), 3.50 (dd, 1H, *J*=7.8, 1.3 Hz), 3.34 (t, 1H, *J*=10.8 Hz); $^{13}C$ NMR: $\delta$ 156.1 (q), 135.6 (CH), 134.8 (CH), 134.5 (CH), 133.3 (CH), 118.4 ($CH_2$), 116.8 ($CH_2$), 116.6 ($CH_2$), 116.4 ($CH_2$), 82.5 (CH), 78.7 (CH), 77.4 (CH), 74.3 ($CH_2$), 72.2 ($CH_2$), 71.9 ($CH_2$), 70.7 ($CH_2$), 70.0 ($CH_2$), 69.9 ($CH_2$), 69.9 (CH), 68.9 ($CH_2$), 44.7 (CH). Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 63.87; H, 7.93; N, 3.43.

**3.9.2. (1′*R*,2′*R*,3′*R*,3a*S*,6*S*)-6-(1′,2′,3′,4′-Tetraallyloxy)-butyl-3a,4-dihydro-3*H*,6*H*-furo[3,4-*c*]isoxazole (56).** $[\alpha]_D^{25}-69.4$ (*c* 0.46, $CHCl_3$); IR (Neat): 3081, 1646 $cm^{-1}$; MS (EI): *m/z* 393 (M), 112; $^1H$ NMR: $\delta$ 6.01–5.81 (m, 4H), 5.32–5.14 (m, 8H), 4.75 (d, 1H, *J*=4.7 Hz), 4.59 (dd, 1H, *J*=10.7, 8.1 Hz), 4.28–4.20 (m, 2H), 4.11–3.82 (m, 10H), 3.76–3.59 (m, 5H); $^{13}C$ NMR: $\delta$ 157.7 (q), 135.0 (CH), 134.9 (CH), 134.6 (CH), 133.7 (CH), 117.6 ($CH_2$), 117.5 ($CH_2$), 116.8 ($CH_2$), 116.6 ($CH_2$), 80.5 (CH), 76.3 (CH), 75.4 (CH), 73.6 ($CH_2$), 72.3 ($CH_2$), 72.2 (CH), 71.4 ($CH_2$), 71.2 ($CH_2$), 70.8 ($CH_2$), 69.8 ($CH_2$), 68.3 ($CH_2$), 50.4 (CH). Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 63.87; H, 7.88; N, 3.63.

**3.9.3. (1′*R*,2′*R*,3′*R*,3a*R*,6*S*)-6-(1′,2′,3′,4′-Tetrabenzyloxy)-butyl-3a,4-dihydro-3*H*,6*H*-furo[3,4-*c*]isoxazole (57) and (1′*R*,2′*R*,3′*R*,3a*S*,6*S*)-6-(1′,2′,3′,4′-tetrabenzyloxy)butyl-3a,4-dihydro-3*H*,6*H*-furo[3,4-*c*]isoxazole (58).** NMR and mass spectra of the preparative TLC fractions enriched in either **57** or **58** were obtained. Data for the fraction enriched in the faster moving compound **57** in TLC (EtOAc–petroleum ether, 1:3): MS (FAB): *m/z* 594 (M+H); $^1H$ NMR (peaks assignable to **57** are presented): $\delta$ 7.32–7.29 (m), 4.83 (d, *J*=3.3 Hz), 4.76 (s), 4.67 (d, *J*=11.9 Hz), 4.62 (d, *J*=10.7 Hz), 4.56 (d, *J*=12.2 Hz), 4.52 (s), 4.27 (t, *J*=7.9 Hz), 4.08 (dd, *J*=6.1, 4.2 Hz), 3.67 (dd, *J*=9.6, 4.7 Hz), 3.59 (t, *J*=9.0 Hz); $^{13}C$ NMR (peaks assignable to **57** are presented): $\delta$ 170.3 (q), 138.7 (q), 138.4 (q), 138.2 (q), 138.1 (q), 128.4–127.4 (aromatic CH), 80.6 (CH), 79.8 (CH), 78.6 (CH), 75.3 ($CH_2$), 74.6 ($CH_2$), 73.43 ($CH_2$), 73.36 ($CH_2$), 73.1 (CH), 72.0 ($CH_2$), 69.8 ($CH_2$), 69.3 ($CH_2$), 56.0 (CH). Anal. Calcd for $C_{37}H_{39}NO_6$: C, 74.85; H, 6.62; N, 2.36. Found: C, 74.73; H, 6.69; N, 2.25. Data for the fraction enriched in the slower moving compound **58** in TLC (EtOAc–petroleum ether, 1:3): MS (FAB): *m/z* 594 (M+H); $^1H$ NMR (peaks assignable to **58** are presented): $\delta$ 7.32–7.28 (m), 4.86 (d, *J*=3.1 Hz), 4.76–4.68 (m), 4.58 (d, *J*=11.8 Hz), 4.52 (s), 4.23 (dd, *J*=5.9, 4.5 Hz), 4.15 (dd, *J*=5.9, 3.8 Hz), 3.70 (dd, *J*=9.9, 5.1 Hz); $^{13}C$ NMR (peaks assignable to **58** are presented): $\delta$ 170.4 (q), 138.8 (q), 138.6 (q), 138.5 (q), 138.3 (q), 128.4–127.4 (aromatic CH), 81.3 (CH), 79.6 (CH), 79.1 (CH), 75.5 ($CH_2$), 74.5 ($CH_2$), 73.4 ($CH_2$), 72.4 (CH), 72.0 ($CH_2$), 69.7 ($CH_2$), 56.6 (CH). Anal. Calcd for $C_{37}H_{39}NO_6$: C, 74.85; H, 6.62; N, 2.36. Found: C, 74.95; H, 6.53; N, 2.23.

**3.9.4. (1′*R*,3a*R*,6*R*,7*R*,8*R*)-6-(1′,2′-Dibenzyloxy)ethyl-7,8-dibenzyloxy-3a,4,7,8-tetrahydro-3*H*,6*H*-2,5-dioxa-1-azaazulene (60).** $[\alpha]_D^{25}+75.2$ (*c* 0.37, $CHCl_3$); IR (Neat): 3061, 3031, 1602 $cm^{-1}$; MS (FAB): *m/z* 594 (M+H); $^1H$ NMR: $\delta$ 7.31–7.20 (m, 18H), 7.09–7.07 (m, 2H), 4.79 (d, 1H, *J*=12.3 Hz), 4.70 (d, 1H, *J*=11.6 Hz), 4.63–4.42 (m, 6H), 4.25 (d, 1H, *J*=12.0 Hz), 4.21 (d, 1H, *J*=12.0 Hz), 4.10–4.04 (m, 2H), 3.93–3.79 (m, 3H), 3.73–3.65 (m, 3H), 3.52 (t, 1H, *J*=10.7 Hz); $^{13}C$ NMR: $\delta$ 159.7 (q), 138.5 (2×q), 137.5 (q), 137.4 (q), 128.4 (4×CH), 128.3 (2×CH), 128.2 (2×CH), 128.1 (2×CH), 128.0 (2×CH), 127.9 (CH), 127.8 (CH), 127.6 (2×CH), 127.5 (2×CH), 127.4 (2×CH), 77.7 (CH), 77.0 (CH), 75.5 (CH), 73.4 ($CH_2$), 72.5 ($CH_2$), 71.7 ($CH_2$), 71.1 ($CH_2$), 70.9 (CH), 70.4 ($CH_2$), 69.3 ($CH_2$), 69.0 ($CH_2$), 52.7 (CH). Anal. Calcd for $C_{37}H_{39}NO_6$: C, 74.85; H, 6.62; N, 2.36. Found: C, 74.62; H, 6.86; N, 1.99.

**3.9.5. (1′*R*,3a*S*,6*R*,7*R*,8*R*)-6-(1′,2′-Dibenzyloxy)ethyl-7,8-dibenzyloxy-3a,4,7,8-tetrahydro-3*H*,6*H*-2,5-dioxa-1-azaazulene (61).** $[\alpha]_D^{25}-57.9$ (*c* 0.52, $CHCl_3$); IR (Neat):

3061, 3031, 1607 $cm^{-1}$; MS (FAB): *m/z* 616 (M+Na), 594 (M+H); $^1H$ NMR: $\delta$ 7.33–7.22 (m, 20H), 4.81 (d, 1H, *J*= 4.5 Hz), 4.68–4.46 (m, 7H), 4.31 (d, 1H, *J*=3.3 Hz), 4.27 (d, 1H, *J*=3.6 Hz), 4.09–4.03 (m, 3H), 3.82–3.75 (m, 4H), 3.68–3.58 (m, 2H); $^{13}C$ NMR: $\delta$ 157.7 (q), 138.4 (q), 138.3 (q), 137.4 (q), 137.0 (q), 128.4 (2×CH), 128.3 (2×CH), 128.2 (6×CH), 127.9 (CH), 127.6 (5×CH), 127.4 (2× CH), 127.4 (CH), 127.3 (CH), 80.3 (CH), 76.4 (CH), 75.2 (CH), 73.6 ($CH_2$), 73.2 ($CH_2$), 72.0 (CH), 71.8 ($CH_2$), 71.7 (2×$CH_2$), 69.6 ($CH_2$), 68.2 ($CH_2$), 50.2 (CH). Anal. Calcd for $C_{37}H_{39}NO_6$: C, 74.85; H, 6.62; N, 2.36. Found: C, 74.54; H, 6.87; N, 2.14.

**3.9.6. (1′*R*,2′*R*,3′*R*,6*S*)-6-(1′,2′,3′,4′-Tetrapropargyloxy)-butyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (67).** 72%; $[\alpha]_D^{28}+10.4$ (*c* 0.25, $CHCl_3$); IR (Neat): 3289, 2120 $cm^{-1}$; MS (EI): *m/z* 383 (M); $^1H$ NMR: $\delta$ 8.05 (s, 1H), 5.42 (d, 1H, *J*=6.1 Hz), 4.96 (d, 1H, *J*=11.7 Hz), 4.86 (d, 1H, *J*=11.7 Hz), 4.51–4.38 (m, 4H), 4.33–4.31 (m, 2H), 4.26–4.23 (m, 2H), 4.05 (dd, 1H, *J*=6.2, 3.7 Hz), 3.99–3.96 (m, 3H), 3.79 (dd, 1H, *J*=11.4, 4.9 Hz), 2.48–2.43 (m, 4H); $^{13}C$ NMR: $\delta$ 170.5 (q), 148.0 (CH), 123.6 (q), 79.9 (CH), 79.7 (2×CH), 79.4 (CH), 78.8 (CH), 77.9 (CH), 77.3 (CH), 76.7 (CH), 74.8 (q), 74.7 (q), 74.6 (q), 74.4 (q), 67.8 ($CH_2$), 64.1 ($CH_2$), 60.1 ($CH_2$), 59.7 ($CH_2$), 58.4 ($CH_2$), 57.3 ($CH_2$). Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.58; H, 5.87; N, 3.38.

**3.9.7. (1′*R*,2′*R*,3′*R*,6*S*)-6-(1′,2′,3′,4′-Tetrabenzyloxy)-butyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (68).** 77%; $[\alpha]_D^{28}+13.5$ (*c* 0.40, $CHCl_3$); IR (Neat): 3062, 3031, 1602 $cm^{-1}$; MS (FAB): *m/z* 592 (M+H), 500 (M−Bn), 484 (M−OBn); $^1H$ NMR: $\delta$ 7.96 (s, 1H), 7.34–7.21 (m, 18H), 7.09–7.07 (m, 2H), 5.39 (d, 1H, *J*=3.8 Hz), 4.92 (d, 1H, *J*=11.5 Hz), 4.81–4.77 (m, 3H), 4.70–4.53 (m, 6H), 4.21 (t, 1H, *J*= 4.9 Hz), 4.01–3.87 (m, 3H), 3.71 (dd, 1H, *J*=10.0, 5.0 Hz); $^{13}C$ NMR: $\delta$ 171.1 (q), 147.6 (CH), 138.7 (q), 138.5 (q), 138.4 (q), 138.2 (q), 128.3 (2×CH), 128.25 (2×CH), 128.2 (2×CH), 128.1 (2×CH), 127.8 (2×CH), 127.74 (2×CH), 127.7 (2×CH), 127.6 (2×CH), 127.5 (CH), 127.4 (CH), 127.3 (2×CH), 124.0 (q), 81.2 (CH), 79.5 (CH), 78.7 (CH), 76.2 (CH), 75.1 ($CH_2$), 74.5 ($CH_2$), 73.3 ($CH_2$), 72.0 ($CH_2$), 69.4 ($CH_2$), 64.3 ($CH_2$). Anal. Calcd for $C_{37}H_{37}NO_6$: C, 75.11; H, 6.30; N, 2.37. Found: C, 74.97; H, 6.38; N, 2.26.

**3.9.8. (1′*R*,6*R*,7*R*,8*R*)-6-(1′,2′-Dibenzyloxy)ethyl-7,8-dibenzyloxy-7,8-dihydro-4*H*,6*H*-2,5-dioxa-1-aza-azulene (69).** 80%; $[\alpha]_D^{28}+6.7$ (*c* 0.24, $CHCl_3$); IR (Neat): 3061, 3031, 1603 $cm^{-1}$; MS (FAB): *m/z* 592 (M+H), 500 (M−Bn), 484 (M−OBn); $^1H$ NMR: $\delta$ 8.18 (s, 1H), 7.34–7.05 (m, 20H), 4.87 (d, 1H, *J*=5.4 Hz), 4.72 (d, 1H, *J*= 13.8 Hz), 4.69 (d, 1H, *J*=11.6 Hz), 4.64 (d, 1H, *J*= 12.3 Hz), 4.54–4.18 (m, 9H), 3.86 (dd, 1H, *J*=12.4, 4.1 Hz), 3.75–3.70 (m, 2H); $^{13}C$ NMR: $\delta$ 160.3 (q), 154.1 (CH), 138.5 (2×q), 137.3 (q), 137.2 (q), 128.5 (2×CH), 128.4 (3×CH), 128.37 (3×CH), 128.2 (2×CH), 127.9 (CH), 127.8 (2×CH), 127.74 (CH), 127.68 (2×CH), 127.6 (2×CH), 127.5 (CH), 127.4 (CH), 118.5 (q), 79.2 (CH), 77.0 (CH), 73.9 (CH), 73.3 ($CH_2$), 72.2 ($CH_2$), 71.8 ($CH_2$), 70.8 ($CH_2$), 69.8 (CH), 69.1 ($CH_2$), 62.5 ($CH_2$). Anal. Calcd for $C_{37}H_{37}NO_6$: C, 75.11; H, 6.30; N, 2.37. Found: C, 75.27; H, 6.47; N, 2.23.

**3.9.9. Preparation of the nitrile oxide 53 and its cycloaddition to (1′*R*,2′*R*,3′*R*,3a*R*,6*S*)-6-(1′,2′,3′,4′-tetra-allyloxy)butyl-3a,4,6,7-tetrahydro-3*H*-pyrano[4,3-*c*]-isoxazole (59).** To a solution of **12** (0.19 g, 0.45 mmol) in benzene (10 mL) was added 4-chlorophenyl isocyanate (0.69 g, 4.50 mmol) and $Et_3N$ (0.6 mL, 4.50 mmol), and the mixture was stirred at 25 °C for 50 h under $N_2$ atmosphere. Water (5 mL) was added and the mixture was stirred for 24 h. It was then filtered and the residue was washed repeatedly with benzene. The organic layer of the filtrate was separated and the aqueous layer was extracted with benzene. The combined organic extracts were washed with water and dried. Removal of solvent yielded a residue, which was chromatographed over silicagel (100–200 mesh; EtOAc–petroleum ether, 1:10) to afford **59** (0.12 g, 68%) as a colorless syrup, $[\alpha]_D^{25}+49.1$ (*c* 2.33, $CHCl_3$); IR (Neat): 3079, 1645 $cm^{-1}$; MS (EI): *m/z* 407 (M), 126; $^1H$ NMR (500 MHz): $\delta$ 6.01–5.83 (m, 4H), 5.28–5.12 (m, 8H), 4.47 (dd, 1H, *J*=10.3, 8.3 Hz), 4.36 (dd, 1H, *J*=10.6, 6.8 Hz), 4.30 (ddt, 1H, *J*=12.2, 5.7, 1.3 Hz), 4.24 (ddt, 1H, *J*=12.6, 5.5, 1.3 Hz), 4.20–4.14 (m, 2H), 4.13 (ddt, 1H, *J*=12.9, 5.5, 1.3 Hz), 4.05 (ddt, 1H, *J*=12.9, 5.5, 1.4 Hz), 4.00–3.99 (m, 2H), 3.88 (dd, 1H, *J*=6.2, 4.0 Hz), 3.74–3.69 (m, 3H), 3.63 (dd, 1H, *J*=8.9, 4.8 Hz), 3.57–3.52 (m, 2H), 3.45–3.38 (m, 1H), 3.26 (t, 1H, *J*=10.7 Hz), 2.68–2.59 (m, 2H); $^{13}C$ NMR (125 MHz): $\delta$ 157.3 (q), 135.2 (CH), 134.9 (2×CH), 134.5 (CH), 117.5 ($CH_2$), 116.9 ($CH_2$), 116.8 ($CH_2$), 116.5 ($CH_2$), 80.4 (CH), 79.5 (CH), 78.03 (CH), 78.0 (CH), 74.7 ($CH_2$), 73.5 ($CH_2$), 72.2 ($CH_2$), 71.6 ($CH_2$), 70.8 ($CH_2$), 69.3 ($CH_2$), 68.8 ($CH_2$), 47.3 (CH), 28.0 ($CH_2$). Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16; N, 3.44. Found: C, 64.61; H, 8.36; N, 3.32.

## Acknowledgements

S. G. is grateful to Council of Scientific and Industrial Research, India for the award of a Senior Research Fellowship. Thanks are due to Dr. V. S. Giri, Mr. A. Banerjee and Mr. S. Chowdhury for spectral analyses.

## References and notes

1. Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon: New York, 1992; pp 1069–1109.
2. Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon: New York, 1992; pp 1111–1168.
3. Torsell, K. B. G. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; New York: VCH, 1988.
4. Adams, J. P.; Paterson, J. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3695.
5. Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419.
6. Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
7. Frederickson, M. *Tetrahedron* **1997**, *53*, 403.
8. Bhattacharjee, A.; Datta, S.; Chattopadhyay, P.; Ghoshal, N.; Kundu, A. P.; Pal, A.; Mukhopadhyay, R.; Chowdhury, S.; Bhattacharjya, A.; Patra, A. *Tetrahedron* **2003**, *59*, 4623 and references cited therein.

9. Mukhopadhyay, R.; Kundu, A. P.; Bhattacharjya, A. *Tetrahedron Lett.* **1995**, *36*, 7729.
10. Torrente, S.; Noya, B.; Branchadell, V.; Alonso, R. *J. Org. Chem.* **2003**, *68*, 4772.
11. Rong, J.; Roselt, P.; Plavec, J.; Chattopadhyay, J. *Tetrahedron* **1994**, *50*, 4921.
12. Hassner, A.; Rai, K. M. L. *Synthesis* **1989**, 57.
13. Ko, S. S.; Confalone, P. N. *Tetrahedron* **1985**, *41*, 3511.
14. Wolfrom, M. L.; Thompson, A. In Whistler, R. L., Wolfrom, M. L., Eds.; Methods in Carbohydrate Chemistry; Academic: New York, 1963; Vol. II, pp 427–428.
15. Meyers, A. I.; Comins, D. L.; Ronald, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 7104.
16. Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1971**, *12*, 3151.
17. Nieuwenhuyse, H.; Louw, R. *Tetrahedron Lett.* **1971**, *12*, 4141.
18. Kozikowski, A. P.; Li, C.-S. *J. Org. Chem.* **1985**, *50*, 778.
19. Du, Y.; Kong, F. *Tetrahedron Lett.* **1995**, *36*, 427.
20. Although a fused isoxazolidine is the usual product of the cycloaddition of a 5-hexenyl nitrone system, the formation of a bridged isoxazolidine has been reported during the cycloaddition of a cyclopropenyl nitrone; Cordero, F. M.; Brandi, A. *Tetrahedron Lett.* **1995**, *36*, 1343.
21. Hassner, A.; Maurya, R.; Friedman, O.; Gottlieb, H. E.; Padwa, A.; Austin, D. *J. Org. Chem.* **1993**, *58*, 4539.
22. Hassner, A.; Maurya, R.; Mesko, E. *Tetrahedron Lett.* **1988**, *29*, 5313.
23. Yan, M.-C.; Liu, J.-Y.; Lin, W.-W.; Kao, K.-H.; Liu, J.-T.; Jang, J.-J.; Yao, C.-F. *Tetrahedron* **1999**, *55*, 12493.
24. Pal, A.; Bhattacharjee, A.; Bhattacharjya, A. *Synthesis* **1999**, 1569.
25. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 1080–1082.
26. Hecker, S. J.; Heathcock, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 4586.
27. Arnone, A.; Cavicchioli, A.; Donadelli, A.; Resnati, G. *Tetrahedron: Asymmetry* **1994**, *5*, 1019.
28. Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *Carbohydr. Res.* **1991**, *222*, 189.
29. Smith, A. L.; Pitsinos, E. N.; Hwang, C.-K.; Mizuno, Y.; Saimoto, H.; Scarlato, G. R.; Suzuki, T.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7612.
30. Duclos, O.; Dureault, A.; Depezay, J. C. *Tetrahedron Lett.* **1992**, *33*, 1059.
31. Ishikawa, T.; Shimizu, K.; Ishii, H.; Ikeda, S.; Saito, S. *J. Org. Chem.* **2001**, *66*, 3834.
32. Pal, A.; Bhattacharjya, A.; Mukhopadhyay, R. *Tetrahedron Lett.* **2000**, *41*, 10135.