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STEREOSELECTIVE FORMATION OF FUNCTIONALIZED 2-ARYL-TETRAHYDROFURANS FROM AROMATIC ALDEHYDES VIA INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS (INOC AND IOOC).[1a]

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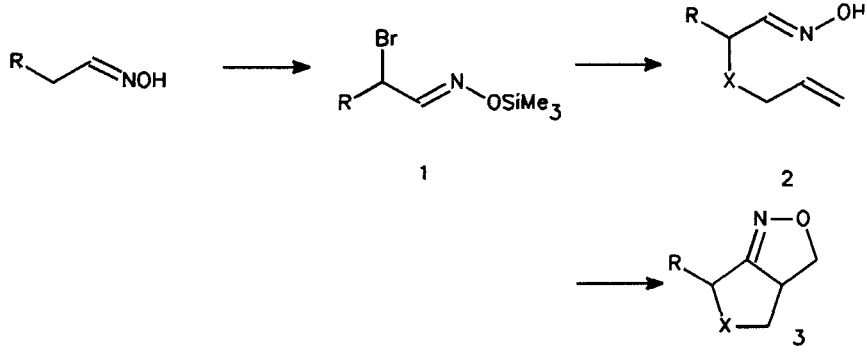
Abstract: α-Allyloxyaldoximes **8**, formed by the reduction of β-nitrostyrenes **5** with $SnCl_2$-$2H_2O$ in the presence of an unsaturated alcohol, undergo either thermally induced intramolecular oxime olefin cycloaddition (IOOC) to bicyclic isoxazolidines **7**, with stereospecific introduction of three stereocenters, or nitrile oxide olefin cycloadditions (INOC) to bicyclic isoxazolines **6**. This provides an entry into functionalized tetrahydrofurans and tetrahydropyrans.

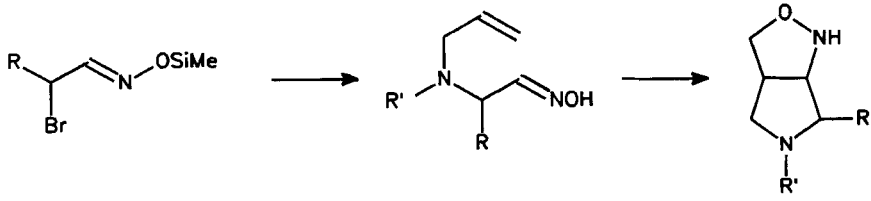
Stereoselectively substituted and functionalized tetrahydrofurans and pyrans are of interest as analogs of carbohydrates[2] We have recently shown that allyl alcohols or allyl amines can be converted in a two carbon chain extension by means of O-silyl-α-bromoaldoximes **1**[3], into α-allyloxy or α-allylamino substituted aldoximes **2**.[4] Since these oximes were easily oxidized to nitrile oxides, they were



*Author to whom correspondence should be addressed

suitable precursors for intramolecular nitrile oxide olefin cycloadditions (INOC). The isoxazolines **3** resulting from such INOC reactions can serve as a precursor to hydroxyketones.[5] or to other functional groups,[6] thus leading to functionalized tetrahydrofurans or pyrrolidines.

We also found that certain unsaturated α-aminoaldoximes can undergo a thermally induced ring closure to isoxazolidines.[7] These novel intramolecular oxime-olefin cycloadditions (IOOC) appear to proceed via an H-nitrone tautomer[8] of the oxime and often take place with a high degree of stereoselectivity.[9] For instance, simple heating of the oxime 2 (R^1:Ph, R:Et) at 80° in benzene led to cycloaddition product **4** as a single diastereomer.[7]



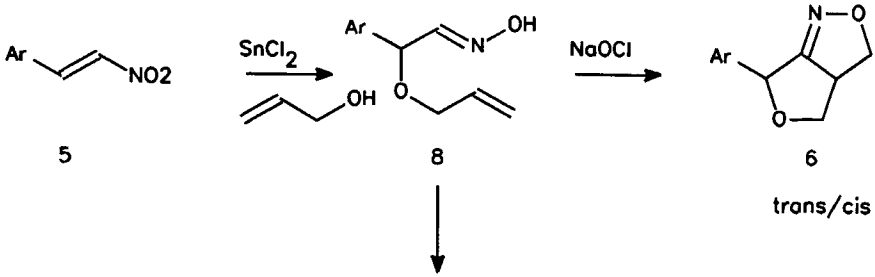
1 2 (X = N) 4

In some cases, as in arylacetaldehydes, the precursors to **1** are not easily accessible. We now report a convenient alternative approach to oximes **8** via nitroolefins **5** which in turn are readily available from aromatic aldehydes. Oximes **8** which possess a properly situated unsaturated ether chain were converted either in an INOC or an IOOC reaction into fused cyclic ethers. The method involves the reaction of β-nitrostyrenes **5** with allyl alcohol (or homoallyl alcohol) in the presence of $SnCl_2$-$2H_2O$ to produce unsaturated ether oximes **8a-g**. Apparently, the first step of the reaction involves reduction of **5** to an unsaturated nitroso compound which readily adds the unsaturated alcohol *in situ* in a Michael fashion, as has been shown for the reduction of β-nitrostyrene with $SnCl_2$-$2H_2O$ in

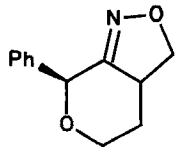
alcoholic medium by Kabalka *et. al.*[10] The resultant oximes were transformed by means of NaOCl or chloramine-T[11] into nitrile oxide intermediates, which underwent spontaneous cyclization to isoxazolines **6a-g** in 40-70% yield.

The method is especially convenient for the synthesis of aryl substituted cyclic ethers of type **6**, since the starting nitrostyrenes **5** are readily available by condensation of aromatic aldehydes with nitromethane, while the lengthier path via the α-bromooxime synthon **1** requires the more difficulty accessible arylacetaldehydes. In all cases studied, we observed two isomers of **6** in which the *trans* compound predominates 4:1.

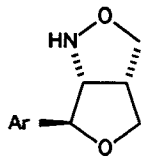
We found that aldoxime **8b**, when heated in benzene in a sealed tube at 110-120°C, underwent smooth intramolecular cycloaddition to the tetrahydrofurano isoxazolidine



5 8 6



6g



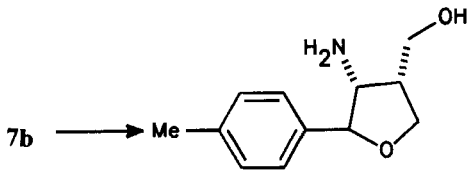
7

Ar = a) Ph; b) 4-Me-C_6H_4; c) 4-MeO-C_6H_4;
d) 3,4-(OCH_2)-C_6H_3; e) 3,4-$(MeO)_2$-C_6H_3; f) 3,4,5-$(MeO)_3$-C_6H_2

7b in 77% yield. This ring closure proceeded stereospecifically to generate three adjacent stereochemical centers. Lithium aluminum hydride (LAH) reduction of **7b**

resulted in isolation of stereoselectively functionalized tetrahydrofuran derivative **9b** in 75% yield.

In order to establish the generality of the IOOC reaction and its applicability to the synthesis of tetrahydrofuran derivatives, we investigated a number of examples. Heating of the unsaturated aldoximes **8a-f** at 100-120°C in benzene in a sealed tube for 6 h led via intramolecular cycloaddition to tetrahydrofuran derivatives **7a-f** as oils in 60-80% yield. Only one isomer was isolated in all cases studied. Earlier attempts to cyclize **8a** by heating at 80°C had led to **7a** in only 25% yield.[4b] Both H^1 and ^{13}C NMR spectra of the tetrahydrofuran **7a** obtained in the current study were superimposable with the spectra of material previously reported. While the homologous **8g** failed to undergo ring closure to a perhydropyran derivative even at higher temperature, it was converted to **6g** as the major isomer via INOC reaction.



9b

In all cases the basic structure of the products was apparent from ^1H- and ^{13}C-correlated NMR and mass spectra (see experimental). It is interesting to note that the mass spectra of the isoxazolines (**6a-f**) and the isoxazolidines (**7a-f**) showed a very similar fragmentation pattern.[12] For example, in both cases the base peak is MH^+ and often there are fragments corresponding to MH^+-CH_2OH and MH^+-Ar.

EXPERIMENTAL

General: ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on a Bruker 300 MHz spectrometer using $CDCl_3$ solutions with tetramethylsilane as internal reference are expressed as δ values. The chemical shifts were expressed in δ, coupling constants J are given in hertz. Mass spectra were obtained on a Finnigan 4021 mass spectrometer at an ionizing energy of 35 ev. Chromatographic separation was carried out on a silica gel column (70-230 mesh, Merck). Thin layer chromatography (TLC) was done with pre-coated silica gel plates (Kieselgel 60, F_{254} Merck) using chloroform as eluent.

General procedure for the preparation of the unsaturated oximes. 2-Allyloxy-2-phenylacetaldoxime 8a. Allyl alcohol (50 mL) was added to a mixture of β-nitrostyrene **5a** (0.447 g, 3 mmol) and stannous chloride dihydrate (0.9 g, 4 mmol) and the reaction mixture was stirred for 4 h at room temperature. Most of the allyl alcohol was removed under reduced pressure and the residue was extracted with benzene (3 x 5 mL). The organic phases were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed over silica gel with CH_2Cl_2:EtOAC as the eluent to yield 59% of oxime **8a** (oil, E:Z=6:1 isomers). **8a** was identical by spectral comparison with the authentic oxime prepared via 1.[4b]

8b: (53% yield, oil, Z:E=1:2). ^1H NMR E-Isomer: δ 2.35 (s, 3H, CH_3), 4.01 (m, 2H, CH_2O), 4.94 (d, J = 7 Hz, 1H, CH-O), 5.20 and 5.29 (dq, 1H, vinyl), 5.92 (ddt, 1H, vinyl), 7.17 and 7.25 (dt, J = 9, 1 Hz, 2H, Ar), 7.44 (d, J = 7 Hz, 1H, CH=N), 7.85 (br, 1H, OH) superimposed on Z-Isomer: δ 2.35 (s, 3H, CH_3), 4.01 (m, 2H, CH_2O, 5.20 and 5.29 (dq, 1H, vinyl), 5.65 (d, J = 6 Hz, 1H, CH-O), 5.93 (ddt, 1H, vinyl), 6.94 (d, J = 6 Hz, 1H, CH=N), 7.16 and 7.30 (dt, J = 9, 1 Hz, 2H, Ar), 8.15 (br s, 1H, OH). ^{13}C NMR E-isomer: δ 21.50 (CH_3), 69.46 (CH_2O),

77.84 (CH-O), 117.44 (vinyl CH_2), 126.75, 129.34 (Ar), 134.08 (vinyl CH), 135.06 and 138.03 (Ar), 151.50 (CH=N) together with Z-isomer: δ 21.50, 69.62, 72.87, 117.44. 126.99, 129.21, 134.08, 134.92, 137.88 and 152.17. MS (m/z, relative intensity, EI) 205 ($MH^{\bullet+}$, S), 188 ($MH^{\bullet+}$ - OH, 100), 161 ($MH^{\bullet+}$ -CH=N-OH, 61), 160 ($MH^{\bullet+}$- CH_2=NOH_2, 25), 148 ($MH^{\bullet+}$- C_3H_5O), 199 (Ar C=O^+, 49). Anal. Calcd. for $C_{12}H_{15}O$, 59), 119 (Ar-C=O, 49. Anal. Calcd. for $C_{12}H_{15}NO_2$ C 70.24; H 7.32. Found C 69.93; H 7.44.

8c: (68% yield, oil, Z:E=1:2), ^1H NMR E isomer: δ 3.79 (s, 3H, CH_3O), 4.00 (m, 2H, CH_2O), 4.92 (d, J = 7 Hz, 1H, CH-O), 5.19 and 5.28 (dq, 1H, vinyl), 5.90 (ddt, 1H, vinyl), 6.89 and 7.28 (dt, J = 9, 2 Hz, 2H Ar), 7.41 (d, J = 7 Hz, 1H, CH=N), 8.64 (br s, 1H, OH) together with Z-isomer: δ 3.78 (s, 3H, CH_3O), 4.00 (m, 2H, CH_2O), 5.19 and 5.28 (dq, 1H, vinyl), 5.63 (d, J = 6 Hz, 1H, CH-O), 5.91 (ddt, 1H, vinyl), 6.88 and 7.34 (dt, 2H, Ar), 6.94 (d, J = 6 Hz, CH=N), 8.92 (br s, 1H, OH). ^{13}C NMR E isomer: δ 55.24 (CH_3O), 69.37 (CH_2O), 77.61 (CH-O), 114.12 (Ar), 117.40 (vinyl), 128.09, 130.24 (Ar), 134.12 (vinyl), 151.46 (CH=N), 159.55 (Ar) together with Z isomer: δ 55.25, 69.55, 72.61, 113.98, 117.40, 128.32, 130.11, 134.16, 152.21, 159.44. MS (m/z, relative intensity, EI) 221 ($MH^{\bullet+}$, 28), 204($MH^{\bullet+}$ - OH, 55), 177 ($MH^{\bullet+}$ - CH=N-OH, 88), 164 ($MH^{\bullet+}$ - C_3H_5O. 100), 135 (Ar-C=O^+, 90). Anal. Calcd. for $C_{12}H_{15}NO_3$ C 65.16; H 6.78. Found C 65.40; H 6.62.

8d: (69% yield, oil, Z:E=2:3). ^1H NMR E isomer: δ 4.00 (m, 2H, CH_2O), 4.88 (d, J = 7 Hz, 1H, CH-O), 5.20 and 5.30 (dq, 1H, vinyl), 5.91 (ddt, 1H, vinyl), 5.94 (s, 2H, CH_2O_2), 6.72-6.92 (m, 3H, Ar), 7.41 (d, 7 Hz, 1H, CH=N), 7.83 (br s, 1H, OH) together with Z-isomer: δ 4.00 (m, 2H, CH_2O), 5.20 and 5.30 (dq, 1H, vinyl), 5.60 (d, J = 6 Hz, 1H, CH-O), 5.91 (ddt, 1H, vinyl), 5.93 (s, 2H, CH_2O_2), 6.73 - 6.92 (m, 3H, Ar), 6.90 (d, J = 6 Hz, 1H, CH=N), 8.15 (br s, 1H, OH). ^{13}C NMR E-isomer: δ 69.44 (CH_2O), 77.77 (CH-O), 101.12 (CH_2O_2), 107.22, 108.34 (Ar),

117.52 (vinyl), 120.45, 132.06 (Ar), 134.03 (vinyl), 147.44, 147.84 (Ar), 152.03, together with Z-isomer: δ 69.60, 72.70, 101.06, 107.50, 108.28, 117.52, 120.68, 131.83, 134.03, 147.58, 148.03, 151.39. MS (m/z, relative intensity, EI) 235 ($MH^{\bullet+}$ - 53), 218 ($MH^{\bullet+}$ - OH, 18), 191 ($MH^{\bullet+}$ - CH=N-OH, 129), 178 ($MH^{\bullet+}$ - C_3H_5O, 14), 149 (178 - CHO, 100).

8e: (54% yield, oil, Z:E 1:10). ^1H NMR E-isomer: δ 3.83 and 3.80 (s, 3H, CH_3O), 3.98 (m, 2H, CH_2O), 4.88 (d, J = 7 Hz, 1H, CH-O), 5.16 and 5.26 (dq, 1H, vinyl), 5.89 (ddt, 1H, vinyl), 6.76-6.94 (m, 3H, Ar), 7.41 (d, J = 7 Hz, 1H, CH=N), 8.38 (br s, 1H, OH), together with Z-isomer: δ 3.80 (s, 3H, CH_3O), 3.98 (m, 2H, CH_2O), 5.16 and 5.26 (dq, 1H, vinyl), 5.60 (d, J = 6 Hz, 1H, CH-O), 5.89 (ddt, 1H, vinyl), 6.76-6.94 (m, 3H, Ar), 6.88 (d, J = 6 Hz, 1H, CH=N), 8.40 (br s, 1H, OH). ^{13}C NMR E-isomer: δ 56.03 (CH_3O), 69.51 (CH_2O), 77.89 (CH-O), 110.08, 111.53 (Ar), 117.43 (vinyl), 119.42, 130.89 (Ar), 134.22 (vinyl), 149.24, 149.51 (Ar), 151.65 (CH=N) together with Z-isomer: δ 56.03, 69.70, 72.72, 110.37, 111.53, 117.43, 119.67, 130.89, 134.22, 149.24, 149.51, 152.34. MS (m/z, relative intensity, EI), 251 ($M^{\bullet+}$, 100), 234 ($M^{\bullet+}$ - OH, 24), 207 ($M^{\bullet+}$ - CH=N-OH, 48), 194 ($M^{\bullet+}$ - C_3H_5O, 35), 165 ($Ar\text{-}C{=}O^+$, 83), 138 (Ar^+, 51). Anal. Calcd. for $C_{13}H_{17}NO_4$ C 62.15: H 6.77. Found C 61.80; H 6.78.

8f: (64% yield, oil, Z:E 4:5). ^1H NMR E isomer: δ 3.84 (s, 3H, CH_3O), 4.03 (m, 2H, CH_2O), 4.90 (d, J = 7 Hz, 1H, CH-O), 5.23 and 5.32 (dq, 1H, vinyl), 5.93 (ddt, 1H, vinyl), 6.60 (s, 2H, Ar), 7.43 (d, J = 7 Hz, CH=N), 7.73 (br s, 1H, OH) together with Z isomer: δ 3.84 (s, 3H, CH_3O), 3.86 (s, 6H, CH_3O), 4.03 (m, 2H, CH_2O), 5.23 and 5.32 (dq, 1H, vinyl), 5.64 (d, J = 6 Hz, 1H, 1H, CH=N), 8.08 (br s, 1H, OH). ^{13}C NMR E isomer: δ 56.05 (CH_3O), 60.70 (CH_3O), 69.46 (CH_2O), 77.97 (CH-O), 103.62, 117.53 (vinyl), 133.02 (vinyl), 133.66, 137.80 (Ar), 151.50 (CH=N), 153.26 (Ar) together with Z-isomer: δ 56.05, 60.70, 69.72, 72.62, 103.88, 117.53, 133.47, 137.72, 150.98, 153.41. MS (m/z relative intensity, EI),

281 ($M^{\bullet+}$, 100), 264 ($M^{\bullet+}$ -OH, 2), 237 ($M^{\bullet+}$ - CH=N-OH, 13), 224 ($M^{\bullet+}$ - C_3H_5O, 53), 208, 196 (Ar-CH=$O^{\bullet+}$, 40).

General procedure for the INOC cyclization.[13] 2-Phenyltetrahydrofurano [3,4-c]isoxazoline (6a). To a solution of 0.191 g (1 mmol) of oxime **8a** in 10 mL dichloromethane, containing a few drops of triethylamine and stirred at 0°C, was added 3 mL of 11% NaOCl solutions\ (5 mmol) over 5 min. The reaction was allowed to come to room temperature and was further stirred for 8 h. The two phases were separated and the aqueous phase was extracted with two portions of 10 mL dichloromethane. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated to yield a crude oil which on flash chromatography over SiO_2 with CH_2Cl_2:EtOAC 4:1 as the eluent gave 0.163 g **6a** (86%) as a 4:1 *trans*:*cis* mixture of isomers (oil). The spectral data were completely in agreement with those reported.[14]

6b: (90% yield, oil as a 4:1 *trans*:*cis* mixture of isomers). δ *trans*-**6b**: ^1H NMR 2.35 (s, 3H, CH_3), 3.81 (dd, J = 9, 8 Hz, 1H, THF - CH_2O), 4.08 (dd, J = 12, 8 Hz, 1H, isox. CH_2O), 4.24 (m, 1H, bridgehead CH), 4.42 (t, J = 8 Hz, 1H, THF CH_2O), 4.59 (dd, J = 9, 8 Hz, 1H, isox. CH_2O), 5.58 (br s, 1H, CH-O), 7.18 and 7.29 (dm, J = 9 Hz, 2H, Ar). ^{13}C NMR δ 21.12 (CH_2), 54.66 (CH bridgehead), 69.87 (CH_2O THF), 73.00 (CH-O), 73.64 (CH_2O isox.), 125.70, 129.37, 134.53, 138.26 (Ar), 170.31 (C=N). ***cis*-6b:** ^1H NMR δ 2.35 (s, 3H, CH_3), 3.89 (m, 1H, THF CH_2O), 4.06 (m, 1H, isox. CH_2O), 4.25 - 4.40 (m, 2H, bridgehead + CH_2O THF), 4.61 (m, 1H, CH_2O isox.), 5.58 (br s, 1H, CH-O), 7.18 and 7.32 (dm, 2H, Ar). ^{13}C NMR δ 21.12 (CH_3), 56.08 (CH bridgehead), 69.13 (CH_2O THF), 73.11 (CH-O), 73.99 (CH_2O isox.), 126.47, 129.25, 134.36, 138.36, 138.26 (Ar), 170.57 (C=N). MS (m/z relative intensity, mixture of isomers, EI) 203 ($M^{\bullet+}$, 51), 202 ($M^{\bullet+}$ - H, 100), 188 ($M^{\bullet+}$ - CH_3, 84), 173 ($M^{\bullet+}$ - CH_3O, 31), 119 (Ar-C=O^+, 98).

6c: (87% yield, solid as 4:1 *trans:cis* mixture of isomers). The spectral data were completely in agreement with those reported.[13b]

6d: (88% yield, oil, 4:1 *trans:cis* isomer mixture) ***trans*-6d**: ^{1}H NMR δ 3.79 (dd, J = 9, 8 Hz, 1H, THF-CH_2O), 4.07 (dd, J = 12, 8 Hz, 1H, isox. - CH_2O), 4.24 (m, 1H, bridgehead-CH), 4.42 (t, J = 8 Hz, 1H, CH_2O THF), 4.60 (dd, J = 9, 8 Hz, 1H, CH_2O isox.), 5.51 (br s, 1H, CH-O), 5.91 (s, 2H, CH_2O_2), 6.78 - 6.93 (m, 3H, Ar). ^{13}C NMR δ 54.56 (CH bridgehead), 69.87 (CH_2O THF), 72.84 (CH-O), 73.70 (CH_2O isox.), 101.23 (CH_2O). 106.43, 108.25, 119.34, 131.26, 148.07 (Ar), 170.33 (C=N). ***cis*-6d:** ^{1}H NMR δ 3.89 (m, 1H, CH_2O THF), 4.09 (m, 1H, CH_2O isox.), 4.32-4.40 (m, 2H, CH_2O THF + bridgehead), 4.65 (m, 1H, CH_2O isox.), 5.51 (br s, 1H, CH-O), 5.91 (s, 2H, CH_2O_2), 6.78-6.93 (m, 3H, Ar.). ^{13}C NMR δ 55.83 (CH bridgehead), 69.21 (CH_2O THF), 73.08 (CH-O), 74.17 (CH_2O isox.), 101.23 (CH_2O_2), 107.15, 108.39, 120.35, 130.95, 147.78 (Ar), 170.51 (C=N). MS (m/z relative intensity, mixture of isomers, EI) 234 ($MH^{\cdot+}$, 100), 233 ($MH^{\cdot+}$, 30), 204 ($MH^{\cdot+}$ - CHO, 14), 203 ($MH^{\cdot+}$ - CH2O, 13). Anal. Calcd. for $C_{12}H_{11}NO_4$ C 61.80; H 4.72. Found C 61.56; H 4.81.

6e: (84% yield). The two isomers were separated on careful chromatography over silica gel with 4:1 CH_2Cl_2: EtOAC as the eluent. ***trans*-6e:** crystals from methanol, mp 97-98°C. ^{1}H NMR δ 3.79 (dd, J = 8, 8 Hz, 1H, CH_2O THF), 3.86 and 3.88 (s, 3H, CH_2O), 4.06 (dd, J = 12, 8 Hz, 1H), CH_2O isox.), 4.23 (m, 1H, CH bridgehead), 4.41 (t, J = 8 Hz, 1H, CH_2O THF), 4.59 (dd, J = 9, 8 Hz, 1H, CH_2O isox.), 5.54 (br s, 1H, CH-O), 6.82 - 6.95 (m, 3H, Ar); ^{13}C NMR δ 54.66 (CH bridgehead), 55.99 (CH_3O), 69.88 (CH_2O THF), 72.85 (CH-O), 73.69 (CH_2O isox.), 109.04, 111.34, 118.00, 129.85, 149.36 (Ar), 170.30 (C=N). Anal. Calcd. for $C_{13}H_{13}NO_4$ C 62.15; H 6.77. Found C 61.80; H 6.79. ***cis*-6e** oil: ^{1}H NMR δ 3.86 and 3.88 (s, 3H, CH_3O), 3.89 (m, 1H, CH_2O THF), 4.05 (m, 1H, CH_2O isox.), 4.32 - 4.48 (m, 2H, CH_2O THF + CH bridgehead), 4.62 (m, 1H, CH_2O

isox.), 5.54 (br s, 1H, CH-O), 6.84-7.02 (m, 3H, Ar). ^{13}C NMR δ 55.95 (CH_3O), 56.03 (CH bridgehead), 69.03 (CH_2O THF), 72.96 (CH-O), 73.97 (CH_2O isox.), 109.96, 111.30, 119.02, 129.53, 149.19 (Ar), 170.37 (C=N). MS (m/z relative intensity, mixture of isomers, CI, CH_4) 250 (MH^+, 100), 219 ($MH^{\cdot+}$ - CH_2O, 6).

6f: (82% yield). The two isomers were separated on careful chromatography over silica gel with 3:1 CH_2Cl_2:EtOAc as the eluent. ***trans*-6f**, crystals from methanol, mp 112°C: ^1H NMR δ 3.84 (dd, J = 9, 8 Hz, 1H, CH_2O THF), 3.84 (s, 3H, CH_3O), 3.88 (s, 6H, CH_3O), 4.09 (dd, J = 12, 8 Hz, 1H, CH_2O isox.), 4.25 (m, 1H, CH bridgehead), 4.45 (t, = 8 Hz, 1H, CH_2O THF), 4.61 (dd, J = 9, 8 Hz, 1H, CH_2O isox.), 5.55 (br s, 1H, CH-O), 6.64 (s, 2H, Ar). ^{13}C NMR δ 54.39 (CH bridgehead), 56.22 (CH_3O), 60.82 (CH_3O), 69.98 (CH_2O THF), 72.85 (CH-O), 73.76 (CH_2O isox.), 102.56, 132.80, 138.02, 153.56 (Ar), 170.06 (C=N). Anal. Calcd. for $C_{14}H_{17}NO_5$ C 60.22; H 6.10. Found C 59.90; H 6.08. ***cis*-6f**, oil, ^1H NMR δ 3.84 (s, 3H, CH_3O), 3.88 (s+m, 7H, CH_3O + CH_2O THF), 4.07 (m, 1H, CH_2O isox.), 4.28 - 4.48 (m, 2H, CH_2O THF + CH bridgehead), 4.62 (m, 1H, CH_2O isox.), 5.55 (br s, 1H, CH-O), 6.70 (s, 2H, Ar). ^{13}C NMR δ 56.12 (CH bridgehead), 56.21 (CH_3O), 60.80 (CH_3O), 69.23 (CH_2O THF), 73.00 (CH-O), 73.90 (CH_2O isox.), 103.45, 132.56, 138.32, 153.12 (Ar), 170.21 (C=N). MS (m/z relative intensity, mixture of isomers, CI, CH_4) 280 (MH^+, 100), 112 (MH^+ - Ar, 12).

6g: (50% yield, oil). ^1H NMR ($CDCl_3$) δ 1.95 (dq, 1H, CH_2), 2.23 (tq, 1H, CH_2), 3.54 (m, 1H, CH), 3.75 (dt, 1H, J = 10 Hz, CH_2O), 3.85 (dd, 1H, J = 6 Hz, 5′ - H), 4.23 (dq, 1H, CH_2O), 4.66 (dd, 1H, J = 6 Hz, 5′ - 4), 5.12 (s, 1H, CH), 7.38 (m, 5H,, Ar-H); MS (m/z relative intensity), $C_{12}H_{13}NO_2$ 204 (MH^+, 100), 173 (5), 125 (5).

General procedure for the thermal cyclization of oximes 8. 2-Phenyltetrahydrofurano [3,4-c] isoxazolidine 7a. Oxime **8a** (0.1 g, 0.5 mmol0

dissolved in benzene (5 mL) was heated for 6 h in a sealed tube in a 120-140°C oil bath. Alternatively, the oxime was heated in chlorobenzene at the same temperature under atmospheric pressure without affecting the yield. Evaporation of the solvent yielded the product, which showed the presence of trace amounts of starting material. Purification by column chromatography (SiO_2, 3:1 CH_2Cl_2:EtOAc) yielded 0.070 g (70%) of **7a** as an oil. The product was spectroscopically identical to **7a** previously reported.[4b]

7b: (72% yield, oil). ^1H NMR δ 2.34 (s, 3H, CH_3), 3.33 (m, 1H, bridgehead CH), 3.58 (br, 1H, CH_2O isox.), 3.61 (dd, J = 9, 8 Hz, 1H, CH_2O THF), 3.95 (ddd, J = 8, 5 Hz, 1H, CH-N), 4.01 (d, J = 6 Hz, 1H, CH_2O isox.), 4.39 (t, J = 8, Hz, 1H, CH_2O THF), 4.48 (d, J = 6 Hz, 1H, CH-O), 5.21 (d, J = 5 Hz, 1H, N-H), 7.16 and 7.31 (dm. J = 9 Hz, 2H, Ar). ^{13}C NMR δ 21.11 (CH_3), 49.83 (CH-CH_2), 73.01 (CH_2O THF), 74.24 (CH-N), 76.02 (CH_2O isox.), 85.26 (CH-O), 125.82, 129.14, 137.33 (Ar). MS (m/z relative intensity, CI, CH_4) 206 (MH^+, 100), 175 (MH^+ - CH_2O, 67) 114 (MH^+ - Ar, 31).

7c: (77% yield, mp 87°C), ^1H NMR δ 3.34 (m, 1H, CH-CH_2), 3.58 (br, 1H, CH_2O isox.), 3.61 (dd, J = 9, 8 Hz, 1H, CH_2O THF), 3.81 (s, 3H, CH_3O), 3.95 (dd, J = 8, 6.5 Hz, 1H, CH-N), 4.02 (d, J = 8 Hz, 1H, CH_2O isox.), 4.40 (t, J = 9 Hz, 1H, CH_2O THF), 4.44 (d, J = 6.5 Hz, 1H, CH-O), 5.2 (br, 1H, NH), 6.89 and 7.35 (dt, J = 9, 2 Hz, 2H, Ar). ^{13}C NMR δ 49.93 (<u>CH</u>CH_2), 55.34 (CH_3O), 73.01 (CH_2O THF, 74.24 (CH-N), 76.11 (CH_2O isox.), 85.18 (CH-O), 114.02, 127.24, 132.11, 159.36 (Ar). MS (m/z relative intensity, CI, CH_4) 222 (MH^+, 100), 181 (M^+ - CH_2O, 10), 136 (Ar - $C{=}O^+$, 9), 114 (M^+ - Ar, 8).

7d: (70% yield, mp 101°C), ^1H NMR δ 3.32 (m, 1H, CH-CH_2), 3.57 (br, 1H, CH_2O isox.), 3.59 (t, J = 8.5, 1H, CH_2O THF), 3.91 (dd, J = 8, 7 Hz, 1H, CH-N), 4.02 (d, J = 9 Hz, CH_2O isox.), 4.37 (d, J = 7 Hz, 1H, CH-O), 4.39 (t, J = 8 Hz, 1H, CH_2O THF), 5.20 (br, 1H, NH), 5.94 (s, 2H, CH_2O_2), 6.78 (d, J = 8 Hz, 1H,

Ar), 6.90 (m, 2H, Ar). ^{13}C NMR δ 49.75 (CH-CH_2), 73.02 (CH_2O THF), 74.25 (CH-N), 76.02 (CH_2O isox.), 85.29 (CH-O), 100.98 (CH_2O_2), 106.41, 108.20, 119.39, 134.18, 147.12, 147.84 (Ar). MS (m/z relative intensity, CI, CH_4) 236 (MH^+, 100), 206 (MH^+ - CH_2O, 13), 205 (M^+ - CH_2O, 12), 114 (MH^+ - Ar, 12).

7e: (83% yield, mp 144°C). ^1H NMR δ 3.32 (m, 1H, CH-CH_2), 3.54 (br, 1H, CH_2O isox.), 3.58 (t, J = 8.5 Hz, 1H, CH_2O THF), 3.86 and 3.88 (s, 3H, CH_3O), 3.94 (dd, J = 8, 7 Hz, 1H, CH-N), 4.02 (d, J = 9, Hz, 1H, CH_2O isox.), 4.41 (t, J = 9 Hz, 1H, CH_2O THF), 4.43 (d, J = 7 Hz, 1H, CH-O), 5.22 (br, 1H, N-H), 6.84 (d, J = 8 Hz, 1H, Ar), 6.98 (m, 2H, Ar). ^{13}C NMR δ 49.78 (CHCH_2), 55.90, 55.95 (CH_3O), 73.00 (CH_2O THF), 74.19 (CH-N), 75.97 (CH_2O isox.), 85.18 (CH-O). 109.08, 111.22, 118.09, 132.85, 148.57, 149.07 (Ar). MS (m/z relative intensity,CI, CH_4) 252 (MH^+, 100), 207 (MH^+- CH_2NOH, 5), 114 (MH^+ -Ar, 51). Anal. Calcd. for $C_{13}H_{17}NO_4$: C 62.15; H 6.77. Found C 62.12; H 6.79.

7f: (74% yield, mp 125°C). ^1H NMR δ 3.35 (m, 1H, CH-CH_2), 3.59 (br, 1H, CH_2O isox.), 3.61 (t, J = 8.5 Hz, 1H, CH_2O THF), 3.84 (s, 3H, CH_3O), 3.86 (s, 6H, CH_3O), 3.94 (dd, J = 9, 7 Hz, 1H, CH-N), 4.05 (d, J = 9 Hz, 1H, CH_2O isox.), 4.41 (d, J = 7 Hz, 1H, CH-O), 4.45 (t, J = 9 Hz, 1H, CH_2O THF), 5.22 (br, 1H, NH), 6.68 (s, 2H, Ar). ^{13}C NMR δ 49.70 (CH-CH_2), 56.13 and 60.78 (CH_3O), 73.05 (CH_2O THF), 74.26 (CH-N), 75.97 (CH_2O isox.), 85.28 (CH-O), 102.58, 135.37, 153.30 (Ar). MS (m/z relative intensity, CI, CH_4) 282 (M^+, 100), 281 (M^+, 27), 114 (MH^+ - Ar, 9). Anal. Calcd. for $C_{14}H_{19}NO_5$ C 59.78; H 6.76. Found C 59.61: H 6.57.

2-p-Tolyl-*trans*-3-amino-*trans*-4-hydroxymethyltetrahydrofuran (9b). Reduction of **7b** (0.07 g) with LAH in diethyl ether gave **9b** in 75% yield as a colorless oil. ^1H NMR ($CDCl_3$):δ 2.57 (m, 1H, 4-H), 3.48 (bt, 1H, 3-H), 3.81 (m, 6H, OMe, OCH_2, 5-H), 4.25 (bdd, 1H, 5-H), 4.40 (d, 1H, 1-H), 4.62 (bs, 1H, OH), 6.90 (d, 2H, 3′, 5′-H), 7.28 (d, 2H, 2′, 6′-H); ^{13}C NMR ($CDCl_3$): δ 28.67

(d), 41.78 (d), 54.29 (q), 60.73 (dd), 68.35 (dd), 86.09 (d), 113.02 (d), 126.61 (d), 131.61 (s), 158.49 (s); MS (m/z relative intensity, $C_{12}H_{17}NO_3$. (MH^+, 100), 206 (MH^+ -H_2O, 8.4), 176 (11), 150 (11), 116,(24).

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