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Design and synthesis of novel oxa-bridged isoxazolidines and 1,3-aminoalcohols

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Dedicated to Professor G. S. R. Subba Rao, Indian Institute of Science, Bangalore, India

Abstract—An expedient intramolecular olefin–nitrone cycloaddition (INC) route is reported for the synthesis of a series of novel oxa-bridged isoxazolidines and 1,3-aminoalcohols starting from D-(+)-mannose-derived nitrones.

Optically pure 1,2- and 1,3-aminoalcohols have found wide applications as chiral ligands in asymmetric synthesis.[1] These ligands have primarily been used in enantioselective additions of dialkylzinc to α,β-unsaturated ketones[2] and for the enantioselective reduction of prochiral ketones.[1a,3] Though 1,2-aminoalcohols can be readily obtained by the reduction of commercially available naturally occurring amino acids, 1,3-aminoalcohols usually need to be generated from isoxazolidines by N–O bond cleavage. There are many reports of the synthesis of isoxazolidines from various olefinic aldehydes. These isoxazolidines (obtained from 1,3-dipolar cycloaddition reactions)[4] have long been regarded as important key intermediates for the synthesis of a wide variety of natural and unnatural products, particularly alkaloids,[5] amino acids[6] and amino sugars.[7] The more demanding nonracemic isoxazolidines can be prepared using chiral pool derived precursors for intramolecular olefin–nitrone cycloaddition.[8] Sugar templates have also been used elegantly in INC[9] to generate enantiomerically pure heterocycles such as tetrahydropyrans, pyrans and oxepanes.

In view of the importance of 1,3-aminoalcohols in asymmetric synthesis and in continuation of our interest in utilizing carbohydrates in natural product synthesis, we became interested in designing and synthesizing new types of oxa-bridged bicyclic chiral 1,3-aminoalcohols and isoxazolidines. We chose D-(+)-mannose as a suitable starting material as it has the appropriate stereochemistry to provide the desired tricyclic isoxazolidines by INC (Scheme 1). In addition, the acetonide group directs the formation of one of the possible diastereomers and also offers an opportunity for temporarily appending a range of noncarbohydrate ligands. To the best of our knowledge, this is the first successful approach to oxa-bridged tricyclic isoxazolidines via intramolecular nitrone cycloaddition (INC) and to their corresponding optically active chiral 1,3-aminoalcohols.

According to our retrosynthetic analysis, as shown in Scheme 2, the isoxazolidine **2**, the key intermediate for the 1,3-aminoalcohol, can be prepared from naturally occurring, easily available and optically pure D-(+)-mannose in a few steps.

Our synthesis (Scheme 3) starts with the addition of an excess of vinylmagnesium bromide in THF to D-(+)-mannose diacetonide **4** to afford a mixture of two diastereomers **5**[10] in 90% yield. Selective oxidation of this diastereomeric allylic alcohol was carried out with MnO_2 in CH_2Cl_2 to provide an allylic ketone, which spontaneously underwent cyclization to give the lactol **6** in 92% yield. Under mild acidic condition (PPTS in methanol), *O*-methylation of the alcohol as well as deprotection of more exposed 5,6-*O*-isopropylidene group was accomplished to afford the diol **7** in 88% yield. Though the lactol **6** was obtained as a mixture of diastereomers, we

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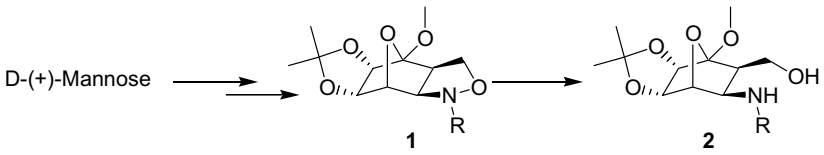
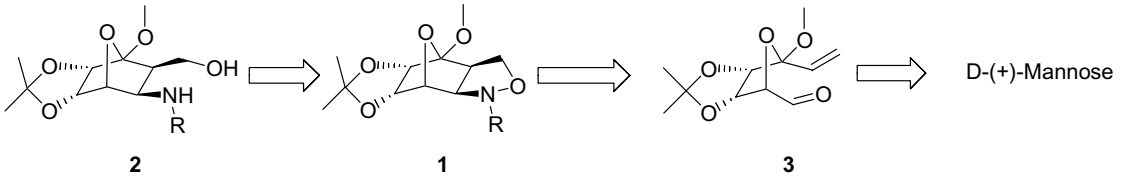
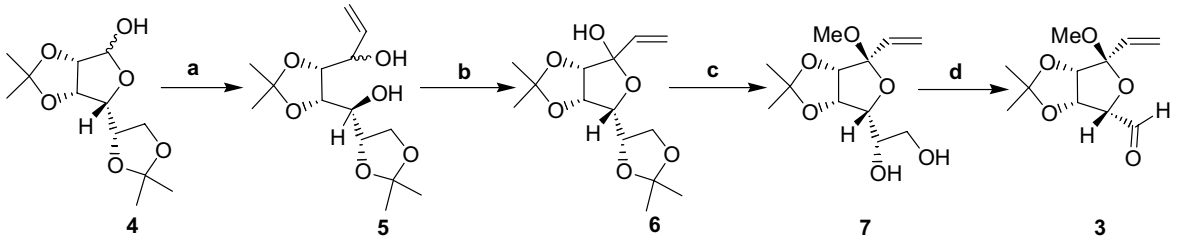


Scheme 1.



Scheme 2.

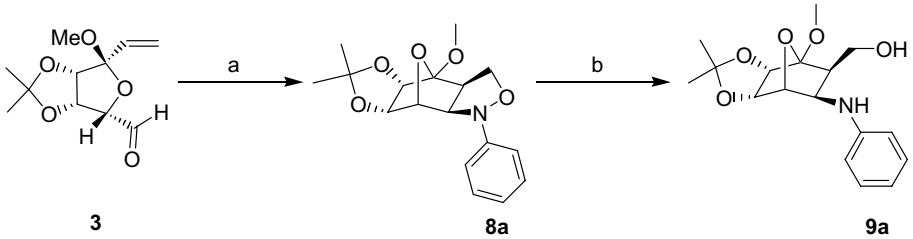


Scheme 3. Reagents and conditions: (a) CH_2=$CHMgBr$, THF, 0 °C–rt, 12 h, 90%; (b) MnO_2, CH_2Cl_2, rt, 12 h, 92%; (c) PPTS, MeOH, rt, 10 h, 88%; (d) silica gel supported $NaIO_4$, CH_2Cl_2, rt, 2 h, 87%.

were gratified to find that the methanolysis of **6** to **7** was highly stereoselective as anticipated. The stereochemistry of the quaternary carbon was tentatively assigned as shown in Scheme 3 since the OMe group is expected to approach the substrate from the least hindered β-face. The requisite aldehyde **3** for the key INC, was subsequently obtained by cleaving the diol **7** with silica gel supported $NaIO_4$[11] in 87% yield. The aldehyde **3**, thus obtained, was sufficiently pure to proceed to the next step.

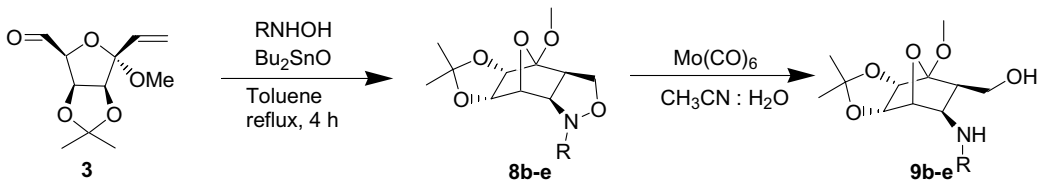
With abundant quantities of aldehyde **3**, we were suitably placed for the execution of the key intramolecular nitrone olefin cycloaddition reaction. To check the feasibility of this key INC, initially an equimolar mixture of aldehyde **3** and *N*-phenylhydroxylamine in toluene was refluxed in the presence of a catalytic amount of dibutyltin oxide (2 mol %) for several hours using a Dean–Stark apparatus. The successful formation of the desired isoxazolidine **8a**[12] in 70% yield[13] prompted us to proceed to cleave the N–O bond and extend this route to a range of novel isoxazolidines and 1,3-aminoalcohols. Though there are several methods (reductive and oxidative cleavage)[14] reported for the cleavage of N–O bonds, in our hands, our acid sensitive isoxazolidines were reductively cleaved by reacting with $Mo(CO)_6$[15] and water to afford 1,3-aminoalcohols with complete retention of configuration of the stereocentres (Scheme 4).

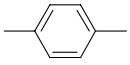
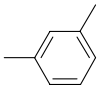
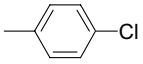
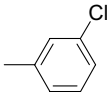
After successfully synthesizing chiral 1,3-aminoalcohol[16] **9a** in diastereomerically pure form, we extended this methodology to the synthesis of a series of *N*-substituted isoxazolidines by using different *N*-arylhydroxylamines followed by reductive cleavage to afford a range of *N*-substituted chiral 1,3-aminoalcohols. In all cases, the *N*-monosubstituted hydroxylamines were prepared[17] by reduction of the corresponding substituted nitrobenzene with zinc and ammonium chloride (Table 1).



Scheme 4. Reagents and conditions: (a) PhNHOH, Bu_2SnO, toluene, reflux, 4 h, 70%; (b) $Mo(CO)_6$, CH_3CN–H_2O, reflux, 2–3 h, 85%.

Table 1.



Entry	R	Yield (%)	
		8	**9**
a		70	85
b		65	90
c		74	91
d		71	89
e		71	93

In conclusion, this paper illustrates the potential of commercially available sugars as starting materials for the synthesis of a wide range of tricyclic oxa-bridged chiral isoxazolidines and bicyclic oxa-bridged chiral 1,3-aminoalcohols via intramolecular nitrone cycloaddition reactions. The utility of these aminoalcohols and isoxazolidines in various asymmetric reactions is currently being studied in our laboratory and the results will be reported elsewhere.

Acknowledgements

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13. All compounds reported here were duly characterized. Selected data: Compound **8a**: $R_f = 0.53$ [ethyl acetate–hexanes (3:7)]; $[\alpha]_D^{25}$ +127.61 (*c* 1.05, $CHCl_3$); IR (film)

2930, 2859, 1596, 1489, 1382, 1265, 1200, 1158, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.25 (2H, m), 7.05–6.93 (3H, m), 4.78–4.70 (2H, m), 4.55–4.51 (2H, m), 4.35 (1H, dd, J = 8.7, 3.3 Hz), 3.89 (1H, dd, J = 8.7, 7.8 Hz), 3.55 (3H, s), 3.49 (1H, dt, J = 7.2, 3.0 Hz), 1.55 (3H, s), 1.39 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.6, 129.1, 121.8, 118.6, 114.7, 110.8, 78.2, 75.0, 68.1, 65.8, 52.8, 48.6, 26.0, 25.1; LRMS (EI) $(M+Na)^+$ 342.1690; HRMS (EI) calcd for $C_{17}H_{21}NO_5Na$ $(M+Na)^+$ *m/z* 342.1317. Found *m/z* 342.1315. Compound **8c**: R_f = 0.40 [ethyl acetate–hexanes (1:4)]; $[\alpha]_D^{25}$ +122.77 (*c* 1.01, $CHCl_3$); IR (film) 2925, 2859, 1609, 1449, 1366, 1258, 1200, 1158, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.19–7.14 (1H, m), 6.87 (1H, s), 6.83–6.76 (2H, m), 4.78–4.73 (2H, m), 4.54–4.50 (2H, m), 4.34 (1H, dd, J = 8.7, 3.3 Hz), 3.88 (1H, dd, J = 8.7, 7.7 Hz), 3.55 (3H, s), 3.51–3.45 (1H, m), 2.33 (3H, s), 1.55 (3H, s), 1.39 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.3, 139.1, 129.0, 123.0, 118.7, 115.5, 112.0, 110.8, 78.3, 78.1, 75.1, 68.1, 66.0, 52.8, 48.5, 26.0, 25.1, 21.7; LRMS (EI) $(M+Na)^+$ 356.1599; HRMS (EI) calcd for $C_{18}H_{24}NO_5$ $(M+H)^+$ *m/z* 334.1654. Found *m/z* 334.1662. Compound **8d**: R_f = 0.60 [ethyl acetate–hexanes (1:4)]; $[\alpha]_D^{25}$ +123.01 (*c* 1.26, $CHCl_3$); IR (film) 2920, 2859, 1585, 1493, 1377, 1258, 1159, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.23 (2H, d, J = 9.0 Hz), 6.95 (2H, d, J = 9.0 Hz), 4.77–4.69 (2H, m), 4.50–4.45 (2H, m), 4.34 (1H, dd, J = 8.7, 3.0 Hz), 3.86 (1H, dd, J = 8.7, 7.8 Hz), 3.55 (3H, s), 3.52–3.46 (1H, m), 1.55 (3H, s), 1.39 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1, 129.0, 127.0, 118.7, 116.0, 110.8, 78.2, 78.0, 75.0, 68.2, 66.0, 52.9, 48.6, 26.0, 25.1; LRMS (EI) $(M+Na)^+$ 376.1233; HRMS (EI) calcd for $C_{17}H_{21}NO_5Cl$ $(M+H)^+$ *m/z* 354.1108. Found *m/z* 354.1113.

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16. All compounds reported here were duly characterized. Selected data: Compound **9a**: R_f = 0.64 [ethyl acetate–hexanes (1:4)]; mp 139–141 °C; $[\alpha]_D^{25}$ +19.84 (*c* 1.26, $CHCl_3$); IR (KBr) 3541, 3400, 2920, 2859, 1600, 1508, 1382, 1266, 1200, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22–7.16 (2H, m), 6.74 (1H, t, J = 7.2 Hz), 6.67 (2H, d, J = 8.1 Hz) 4.73–4.65 (2H, m), 4.52 (1H, d, J = 8.4 Hz), 4.17 (1H, d, J = 4.8 Hz), 4.00 (1H, dd, J = 12.0, 4.5 Hz), 3.91 (1H, dd, J = 12.0, 3.6 Hz), 3.59 (3H, s), 2.99–2.94 (1H, m), 1.61 (3H, s), 1.39 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.5, 118.7, 118.3, 113.9, 112.1, 77.9, 77.6, 74.6, 59.3, 53.9, 52.8, 41.7, 26.1, 25.2. Compound **9c**: R_f = 0.56 [ethyl acetate–hexanes (1:4)]; mp 164–165 °C; $[\alpha]_D^{25}$ +16.07 (*c* 1.12, $CHCl_3$); IR (KBr) 3558, 3409, 2986, 2950, 2920, 2854, 1611, 1474, 1265, 1200, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.09 (1H, t, J = 7.8 Hz), 6.60 (1H, d, J = 7.2 Hz), 6.54–6.51 (2H, m), 4.73–4.64 (2H, m), 4.50 (1H, d, J = 8.8 Hz), 4.17 (1H, dd, J = 4.8, 1.2 Hz), 4.00 (1H, dd, J = 12.0, 4.5 Hz), 3.94 (1H, dd, J = 12.3, 4.0 Hz), 3.60 (3H, s), 2.99–2.94 (1H, m), 2.28 (3H, s), 1.61 (3H, s), 1.39 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4, 129.4, 119.6, 118.7, 115.2, 112.1, 111.0, 77.9, 77.6, 74.6, 59.4, 54.3, 52.8, 41.7, 29.8, 26.2, 25.2, 21.7. Compound **9d**: R_f = 0.33 [ethyl acetate–hexanes (1:4)]; mp 125–126 °C; $[\alpha]_D^{25}$ +16.83 (*c* 1.01, $CHCl_3$); IR (KBr) 3562, 3409, 2920, 2859, 1598, 1505, 1265, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.16 (2H, d, J = 8.4 Hz), 6.66 (2H, d, J = 8.4 Hz), 4.74–4.65 (2H, m), 4.46 (1H, d, J = 8.4 Hz), 4.16 (1H, d, J = 4.8 Hz), 4.05 (1H, dd, J = 12.0, 3.6 Hz), 3.94 (1H, dd, J = 12.0, 3.0 Hz), 3.6 (3H, s), 2.97–2.92 (1H, m), 1.59 (3H, s), 1.39 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.5, 129.5, 123.7, 118.8, 115.5, 112.1, 74.5, 59.3, 54.9, 52.9, 41.5, 32.0, 29.8, 26.2, 25.2.
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