Synthesis of Enantiopure Pyranoisoxazole and Oxepanoisoxazole Derivatives from *O*-Alkynyl Carbohydrate Ethers by the Application of Intramolecular Nitrile Oxide Cycloaddition

Arani Pal, Ashoke Bhattacharjee, Anup Bhattacharjya*

Indian Institue of Chemical Biology, 4, Raja S. C. Mullick Road, Calcutta- 700032, India
Fax+91(33)4730284; E-mail: iichbio@giascl01.vsnl.net.in
Received 1 April 1999; revised 19 May 1999

Abstract: A useful synthesis of enantiomerically pure pyrano- and oxepanoisoxazole derivatives by the application of intramolecular cycloaddition of 3-*O*-alkynyl carbohydrate nitrile oxides is described. One of the isoxazole derivatives was transformed to a furylpyran system having the lasalocid A skeleton using 2-*O*-allyl carbohydrate nitrone cycloaddition.

Key words: cycloaddition, 3-*O*-alkynyl carbohydrate nitrile oxides, chiral isoxazoles, lasalocid A

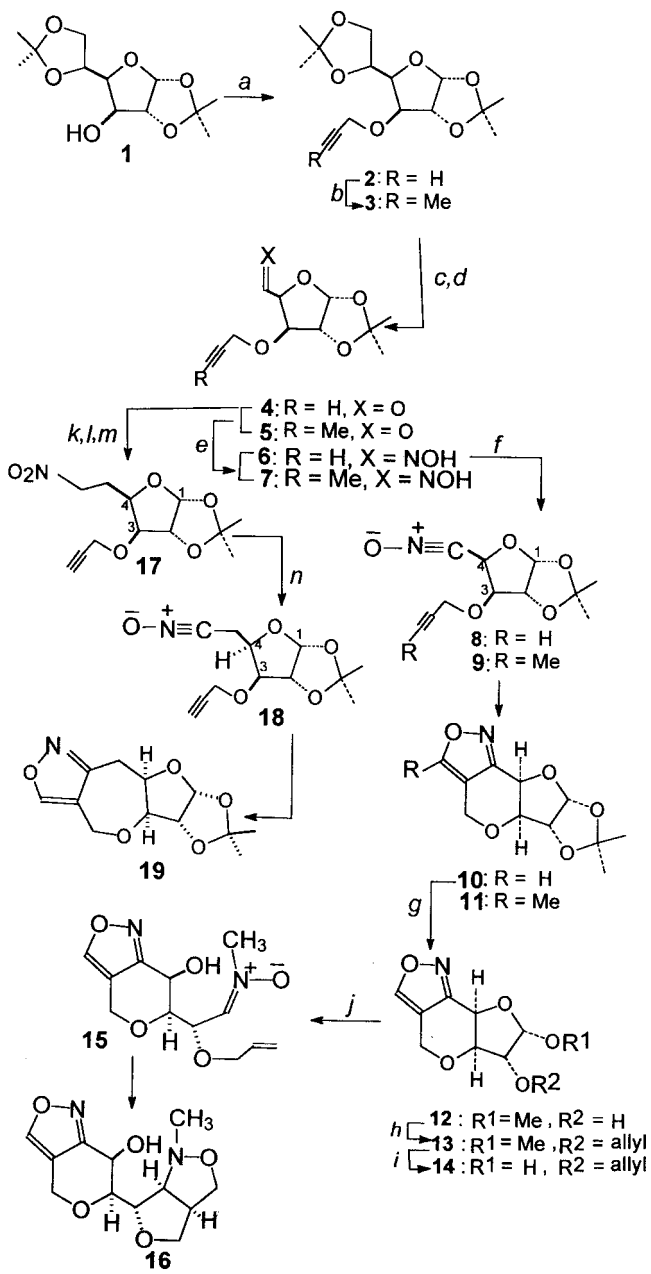
Utilization of naturally occurring chiral compounds as starting materials in the synthesis of enatiomerically pure compounds is well established.[1] Recently application of intramolecular 1,3-dipolar cycloaddition of nitrones and nitrile oxides derived from *O*-alkenyl carbohydrate derivatives has proved to be an important strategy for the synthesis of chiral cyclic ether fused isoxazolidines and isoxazolines.[2, 3] The particular importance of isoxazole derivatives as medicinally important compounds has led us to investigate the possibility of preparing the aforementioned compounds in enatiomerically pure forms through cycloaddition of nitrile oxides derived from *O*-alkynyl carbohydrate derivatives, and we describe herein the application of such a methodology to the synthesis of enantiopure pyranoisoxazoles, oxepanoisoxazoles and a compound having the furylpyran skeleton characteristic of lasalocid A and its congeners.

The well known 1,2:5,6-diisopropylidene-α-D-glucofuranoside (**1**) was converted to the corresponding *O*-propargyl ether **2** in 90% yield by alkylation[4] with propargyl bromide in the presence of tetrabutylammonium bromide in a biphasic medium consisting of dichloromethane and 50% aqueous NaOH solution (Scheme). Reaction of **2** with butyllithium followed by treatment with methyl iodide afforded the 3-*O*-butynyl ether **3** in 50% yield (Scheme). Both **2** and **3** were converted to the aldehydes **4** and **5** following standard procedures[5] involving selective deprotection by treatment with 75% aqueous acetic acid and subsequent oxidation with sodium metaperiodate (Scheme). Oximation of **4** and **5** with hydroxylammonium chloride in pyridine/methanol gave the corresponding oximes **6** and **7.** In contrast to the purification of oxime **6**, that of **7** proved to be difficult, and **7** was used without purification in the next step. Oxidation of the oxime **6** and **7** with chloramine-T in refluxing alcohol gave the isoxazole derivatives **10** (84%) and **11** (53%) respectively, via the formation of the nitrile oxides **8** and **9**, which underwent cycloaddition in situ.

The formation of the isoxazole **10** was evident from the appearance of a one-proton singlet at δ = 8.28 due to the proton attached to the isoxazole nucleus in the ^{1}H NMR spectrum as well as a quaternary carbon at δ = 154.3 and a methine carbon at δ = 150.9 in the ^{13}C NMR spectrum of **10**. Similarly appearance of singlets at δ = 155.3 and 161.8 in the ^{13}C NMR spectrun of **11** was consistent with the presence of the isoxazole nucleus. Inspite of the presence of four chiral centres in **10** and **11**, due to the presence of the isoxazole nucleus and the rigidly functionalized cyclic ether moiety, the ^{1}H NMR spectra of **10** and **11** exhibited first order spectral behaviour even in the 100 MHz field strength.

The presence of the diisopropylidene ring in the above isoxazole derivatives makes these compounds amenable to modifications giving rise to important structural skeletons. As a demonstration, the pyranoisoxazole **10** was treated with methanol in the presence of *p*-toluenesulfonic acid to give **12** as a mixture of diastereomers. A sequence of allylation with allyl bromide afforded **13** and deglycosylation by treatment with aqueous trifluoroacetic acid afforded **14**. As **14** is a hemiacetal, its reaction with *N*-methylhydroxylamine led to the formation of **16** incorporating a furylpyran system via the cycloaddition[6] of the nitrone **15**. The structure of **16** was secured from ^{1}H and ^{13}C NMR spectral analyses. The appearance of a three proton singlet due to the NCH_3 at δ = 2.73 in the ^{1}H NMR spectrum and a peak due to the NCH_3 at δ = 43.3 in the ^{13}C spectrum of **16** as well as absence of peaks due to the allyl moiety was indicative of the occurrence of cycloaddition. The stereochemistry of the ring juncture of the furoisoxazolidene system in **16** was assigned on the basis of analogy with related systems obtained from similar cycloadditions.[6] It is worthy of mention that the furylpyran skeleton present in **16** constitutes the structural framework of lasalocid A[7] and its congeners, and **16** thus represents a potentially useful molecule for developing structural analogs of the aforementioned compounds.

In a separate route, the aldehyde **4** was converted to the nitro derivative **17** according to a known protocol (Scheme).[8] Treatment of **17** with phenyl isocyanate at 25 °C resulted in the formation of the oxepanoisoxazole derivative **19** in 28% yield via the cycloaddition of the nitrile oxide **18**. A one-proton singlet at δ = 8.16 in the ^{1}H



Reagents and conditions: a) propargyl bromide/CH_2Cl_2/50% aq NaOH/Bu_4NBr, 25 °C, 15 h, 90%; b) MeI/BuLi/THF, –40 °C, 1.5 h, 50%; c) 75% aq AcOH, 25 °C, 15 h; d) $NaIO_4$/MeOH/H_2O, 0 to 25 °C, 2 h; e) NH_2OH•HCl/pyridine/MeOH, reflux, 5 h, **6**:68%, **7**:60%; f) chloramine-T/MeOH, reflux, 7 h, **10**:84%, **11**:53%; g) TsOH/MeOH, reflux, 6 h, 90%; h) allyl bromide/NaH/THF, 0 to 25 °C, 15 h, 66%; i)50% aq CF_3CO_2H, 25 °C, 24 h; j) MeNHOH•HCl/$NaHCO_3$/80% aq EtOH, reflux, 20 h, 39%; k) nitromethane/KF/propan-2-ol, 25 °C, 15 h; l) Ac_2O/CH_2Cl_2/DMAP, 25 °C, 15 h; m) $NaBH_4$/EtOH, 0 to 25 °C, 15 h, 48%; n) PhNCO/Et_3N/benzene, 25 °C, 48 h, 28%

Scheme

NMR spectrum and quaternary carbon peaks at δ = 117.0 and 158.7 and a methine carbon at δ = 153.5 in the ^{13}C NMR spectrum of **19** clearly indicated the presence of the isoxazole nucleus. Another feature of the ^1H NMR spectrum of **19** is the appearance of a set of two doublets of doublets due to the 4-CH_2**,** which is fully consistent with the assigned structure.

In conclusion, although the work described here involved alkynyl nitrile oxides generated from isopropylidenedioxy carbohydrate derivatives, the strategy is expected to be general and bears significant potential for further applications related to the synthesis of chiral isoxazoles.

Melting points were determined in open capillaries and are uncorrected. Unless otherwise mentioned all ^1H and ^{13}C NMR spectra were recorded at 100 and 25 MHz, respectively, using $CDCl_3$ as solvent and TMS as the internal standard. Mass spectra were run on EI mode at 70 ev. Elemental analysis was performed at Indian Association for the Cultivation of Science, Calcutta, India. Organic extracts were dried over anhyd Na_2SO_4 and concentrated under reduced pressure using a rotary evaporater. Unless otherwise mentioned, silica gel (60–120 mesh) was used for column chromatography. Petroleum ether refers to the fraction having bp 60–80 °C.

1,2:5.6-Diisopropylidene-3-*O*-propargyl-α-D-glucose (2)

To a solution of **1** (5g, 19 mmol) and propargyl bromide (80% in toluene, 2.5 mL) in CH_2Cl_2 (40 mL) was added 50% aq NaOH solution (40 mL) and the mixture was stirred vigorously. Bu_4NBr (0.6g, 1.9 mmol) was then added to this mixture and stirring was continued for further 15 h at 25 °C. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried and evaporated to give an oil, which was chromatographed over neutral alumina using EtOAc/petroleum ether (1:9) as eluent to give **2** (90%) as a pale yellow oil; $[\alpha]_D^{28}$ –18.6 (*c* = 0.84, $CHCl_3$).

IR (neat): ν = 3274, 2120 cm^{-1}.

^1H NMR: δ = 1.24 (s, 3H), 1.28 (s, 3 H), 1.36 (s, 3 H), 1.44 (s, 3 H), 2.40 (br s, 1 H), 3.84–4.12 (m, 5 H), 4.22 (d, *J* = 3 Hz, 2 H), 4.58 (d, *J* = 4Hz, 1 H), 5.82 (d, *J* = 4 Hz, 1 H)

MS: *m/z* = 297 (M+–1), 283 (M+–15).

1,2:5.6-Diisopropylidene-3-*O*-(buty-2-nyl) -α-D-glucose (3)

To a solution of **2** (2.3 g, 8 mmol) in THF (35 mL), cooled to –40 °C was added BuLi (15% in hexane, 10 mL), and the mixture was allowed to stir at –40 °C for 1.5 h, after which MeI (1 mL) was added and stirred for further 2 h. The mixture was then poured into H_2O and concentrated. The residual solution was extracted with Et_2O and dried. The residue obtained after removal of solvent was chromatographed using EtOAc/petroleum ether (1:9 to 2:8) affording **3** (1.2g, 50%) as a pale yellow syrupy liquid; $[\alpha]_D^{28}$+2.1 (*c* = 0.38, $CHCl_3$).

IR (neat): ν = 2230 cm^{-1}.

^1H NMR: δ = 1.32 (s, 3 H), 1.36 (s, 3 H), 1.44 (s, 3 H), 1.52 (s, 3 H), 1.88 (br s, 3 H), 4.00–4.42 (m, 7 H), 4.64 (d, *J* = 4 Hz, 1 H), 5.92 (d, *J* = 4 Hz, 1 H).

Oximes 6 and 7; General Procedure

Aldehydes **4** and **5**: A solution of **2** or **3** (27 mmol) in 75% aq HOAc (40 mL) was stirred for 15 h at 25 °C. The mixture was then concentrated and the residue was coevaporated with toluene (3 ↔ 50 mL) in order to remove AcOH. The residue was chromatographed over silica gel using EtOAc as eluent to give a colourless syrup. To a methanolic solution of the above material cooled to 0 °C was added dropwise a solution of $NaIO_4$ (19 mmol) in H_2O (50 mL) with stirring, which was continued at 0 °C for 30 min and at 25 °C for 2 h. The mixture was filtered and the filtrate was concentrated under re-

duced pressure. The residue was extracted with $CHCl_3$ and dried. Removal of solvent afforded the aldehyde **4** or **5** as a colourless syrupy liquid, which was used immediately for the next step without any purification.

Aldehyde 4
IR (neat): ν = 2120, 1738 cm^{-1}.

Aldehyde 5
IR (neat): ν = 2236, 1739 cm^{-1}.

Oximes **6** and **7**: A solution of the aldehyde **4** or **5**, $NH_2OH•HCl$ (10 mmol) and pyridine (5 mL) in MeOH (25 mL) was refluxed for 5 h. Solvent was removed and the residue was extracted with $CHCl_3$. The organic layer was washed with H_2O, dried and concentrated to give the oxime **6** or **7** as a syrup which was used directly for the next step.

Oxime 6
Yield: 68%; pale yellow syrup.
IR (neat): ν = 3400, 3286, 2120 cm^{-1}.

^{1}H NMR (mixture of *syn* and *anti* isomers): δ = 1.32 (s, 3 H), 1.48 (s, 3 H), 2.48 (m, 1 H), 4.20 (m, 2.5 H), 4.48 (d, *J* = 2 Hz, 0.5 H), 4.68 (d, *J* = 4 Hz, 1 H), 4.72–4.84 (m, 0.5 H, partly overlapped with the doublet at 4.68), 5.24 (t, *J* = 4 Hz, 0.5 H), 5.98 (d, *J* = 4 Hz, 1 H), 6.92 (d, *J* = 4 Hz, 0.5 H), 7.48 (d, *J* = 6 Hz, 0.5 H).

^{13}C NMR (75 MHz):δ = 26.10, 26.62, 26.67, 57.46, 57.55, 75.20, 75.44, 75.60, 77.54, 78.53, 81.06, 81.87, 82.01, 82.31, 83.09, 104.53, 105.00, 105.39, 111.93, 112.085, 112.19, 146.91, 148.73, 151.43.

MS: *m/z* = 241 (M^+).

Anal. calcd. for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.27; N, 5.80. Found C, 54.60; H, 6.18; N, 5.15.

Oxime 7
Yield:60%; dark red oil mixed with unidentifed impurities.

IR (neat): ν = 3400, 2230 cm^{-1}.

^{1}H NMR: δ = 1.32 (s, 3 H), 1.50 (s, 3 H), 1.84 (t, *J* = < 2 Hz, 3 H), 4.16 (m, 2.5 H), 4.46 (d, *J* = 4 Hz, 0.5 H), 4.68 (d, *J* = 4 Hz, 1 H), 4.72–4.84 (m, 0.5 H, partly overlapped with the doublet at 4.68), 5.24 (t, *J* = 4 Hz, 0.5 H), 5.98 (br d, *J* = 4 Hz, 1 H), 6.92 (d, *J* = 4 Hz, 0.5 H), 7.52 (d, *J* = 6 Hz, 0.5 H).

Isoxazoles 10 and 11; General Procedure
A mixture of the oxime **6** or **7** (1.25 mmol), MeOH (10 mL) and chloramine-T hydrate (98%, 342 mg, 1.5 mmol) was refluxed for 7 h. After removal of solvent, the residue was extracted with CH_2Cl_2. The organic extract was washed successively with aq 1 N NaOH, H_2O, brine and dried. Removal of solvent gave a syrup which was chromatographed over silica gel using EtOAc/petroleum ether (2:8) as eluent to furnish the pyranoisoxazole derivatives.

(5a*S*,6*R*,7*R*,8a*R*)-5a,6,7,8a-Tetrahydro-6,7-isopropylidenedioxy-4*H*-furo[2',3':5,6]pyrano[4,3-*c*]isoxazole (10)
Yield:84%; white needles; mp 152–153 °C; $[\alpha]_D^{28}$+42.0 (*c* = 0.7, $CHCl_3$).

^{1}H NMR: δ = 1.36 (s, 3 H), 1.56 (s, 3 H), 4.14 (d, *J* = 2 Hz, 1 H), 4.54 (dd, *J* = 14, <2 Hz, 1 H), 4.72 (d, *J* = 4 Hz, 1 H), 4.94(d, *J* = 14 Hz, 1 H), 5.24 (d, *J* = 2 Hz, 1 H), 6.02 (d, *J* = 4 Hz, 1 H), 8.24 (s, 1 H).

^{13}C NMR (50 MHz): δ = 26.3 (CH_3), 26.9 (CH_3), 60.3 (CH_2), 68.2 (CH), 80.4 (CH), 105.9 (CH), 112.1 (quaternary), 112.3 (quaternary), 150.9 (CH), 154.3 (quaternary).

Mass: *m/z* = 239 (M^+), 224 (M+– 15).

Anal. calcd. for $C_{11}H_{13}NO_5$: C, 55.22; H, 5.48; N, 5.85. Found C, 55.28; H, 5.49; N, 5.46.

(5a*S*,6*R*,7*R*,8a*R*)-3-Methyl-5a,6,7,8a-tetrahydro-6,7-isopropylidenedioxy-4*H*-furo[2',3':5,6]pyrano[4,3-*c*]isoxazole (11)
Yield:53%; white needles; mp 134–135 °C; $[\alpha]_D^{28}$+30.9 (*c* = 0.7, $CHCl_3$).

^{1}H NMR: δ = 1.36 (s, 3 H), 1.56 (s, 3 H), 2.36 (s, 3 H), 4.08 (d, *J* = < 2 Hz, 1 H), 4.46 (d, *J* = 14 Hz, 1 H), 4.68 (d, *J* = 4 Hz, 1 H), 4.82 (d, *J* = 14 Hz, 1 H), 5.16 (d, *J* = < 2 Hz, 1 H), 6.00 (d, *J* = 4 Hz, 1 H).

^{13}C NMR: δ = 11.1 (quartet), 26.2 (quartet), 26.7 (quartet), 60.6 (t), 68.8 (d), 80.2 (d), 83.4 (d), 105.9 (d), 108.3 (s), 112.2 (s), 155.3 (s), 161.8 (s).

MS: *m/z* = 253 (M^+).

Anal. Calcd. for $C_{12}H_5NO_5$: C, 56.90; H, 5.97; N, 5.53. Found C, 56.83; H, 5.88; N, 5.12.

(5a*S*,6*R*,7*R/S*,8a*R*)-5a,6,7,8a-Tetrahydro-6-hydroxy-7-methoxy-4*H*-furo[2',3':5,6]pyrano[4,3-*c*]isoxazole (12)
A solution of **10** (1.7 g, 7.1 mmol) and TsOH (0.15g) in MeOH (25 mL) was refluxed for 6 h. The mixture was cooled to 0 °C and neutralized with aq satd $NaHCO_3$ solution and then concentrated. The residue was extracted with EtOAc (5 x 20 mL) and the combined organic extracts were dried. Removal of solvent yielded a colourless oil which was chromatographed over silica gel using EtOAc as eluent giving **12** (90%) as white granules; mp 82–83 °C; $[\alpha]_D^{28}$ –14.5 (*c* = 1.59, $CHCl_3$).

IR (KBr): ν = 3984, 3728, 3580,1613 cm^{-1}.

^{1}H NMR (300 MHz, mixture of diastereomers): δ = 3.22 (d, *J* = 4.8 Hz, 0.5 H), 3.29 (s, 1.5 H), 3.55 (br m, 0.5 H), 3.59 (s, 1.5 H), 4.13 (d, *J* = 2.1 Hz, 0.5 H), 4.17 (d, *J* = 3.9 Hz, 0.5 H), 4.35 (br m, 1 H), 4.49 (t, *J* = 14.3, 10.2 Hz, 1 H), 4.92 (dd, *J* = 14.3, 10.2 Hz, 1 H), 4.99 (s, 0.5 H), 5.16 (d, *J* = 3.1 Hz, 0.5 H), 5.19 (d, *J* = 4.4 Hz, 0.5 H), 5.26 (d, *J* = 4.1Hz, 0.5 H), 8.25 (s, 0.5 H), 8.27 (s, 0.5 H).

^{13}C NMR (75 MHz, mixture of diastereomers): δ = 55.7 (CH_3), 56.4 (CH_3), 59.7 (CH_2), 59.9 (CH_2), 66.8 (CH), 69.4 (CH), 76.2 (CH), 79.4 (CH), 81.9 (CH), 82.5 (CH), 103.2 (CH), 110.9 (CH), 112.8 (quartet), 151.2 (CH), 151.4 (CH), 155.3 (quartet), 156.2 (quartet).

Anal. Calcd. for $C_9H_{11}NO_5$: C, 50.70; H, 5.20; N, 6.57. Found C, 50.70; H, 5.16; N, 6.42.

(5a*S*,6*R*,7*R/S*,8a*R*)-6-Allyloxy-5a,6,7,8a-tetrahydro-7-methoxy-4*H*-furo[2',3':5,6]pyrano[4,3-*c*]isoxazole (13)
To a suspension of oil-free NaH (74 mg, 3 mmol) in THF (5 mL) cooled to 0 °C was added a solution of **12** (440 mg, 2 mmol) with stirring followed by addition of allyl bromide (0.5 mL, 5 mmol) at 0 °C. The mixture was allowed to come to 25 °C and stirring was continued for 15 h. Excess NaH was destroyed by careful addition of ice and THF was removed under reduced pressure. The residue was extracted with CH_2Cl_2, washed with H_2O and dried. Removal of solvent yielded a colourless syrup which was chromatographed over silica gel using $CHCl_3$/petroleum ether (1:1) as eluent yielding **13** (66%) as white needles; mp 102–103 °C; $[\alpha]_D^{28}$+34.6 (*c* = 1.57, $CHCl_3$).

IR (KBr): ν = 1648, 1613, 1367 cm^{-1}.

^{1}H NMR (300 MHz, mixture of diastereomers): δ = 3.56 (s, 3 H), 4.11 (dd, *J* = 4.4, 2.8 Hz, 1 H), 4.18 (d, *J* = 5.9 Hz, 2 H), 4.32 (dd, *J* = 4.4, 2.7 Hz, 1 H), 4.49 (d, *J* = 14.2 Hz, 1 H), 4.86 (d, *J* = 14.1 Hz, 1 H), 5.11 (d, *J* = 4.7 Hz, 1 H), 5.16 (d, *J* = 4.5 Hz, 1 H), 5.26 (d, *J* = 9.0 Hz, 1 H), 5.34 (dd, *J* = 17.2, 1.2 Hz, 1 H), 5.97 (m, 1 H), 8.26 (s, 1 H).

^{13}C NMR (75 MHz): δ = 55.8 (CH_3), 59.4 (CH_2), 65.9 (CH), 72.2 (CH_2), 80.9 (CH), 83.7 (CH), 102.5 (CH), 113.1 (quartet), 118.5 (CH_2), 133.9 (CH), 151.3 (CH), 155.7 (quartet).

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found C, 56.91; H, 5.60; N, 5.36.

Furylpyran Derivative 16

A solution of **13** (530 mg, 2.09 mmol) in 50% aq TFA (5 mL) was stirred at r.t. for 24 h. After completion of reaction (24 h) as indicated by TLC, the mixture was neutralized at 0 °C by careful addition of aq $NaHCO_3$ solution, and then extracted with $CHCl_3$, washed with H_2O and dried. Removal of solvent yielded **14** as a brown syrup, which was used without purification for the next step.

Compound 14

^{1}H NMR (300 MHz, mixture of diastereomers, selected peaks): δ = 5.93 (m, 1 H), 8.24 (s, 0.5 H), 8.26 (s, 0.5 H).

^{13}C NMR (75 MHz, mixture of diastereomers): δ = 66.9 (CH), 69.5 (CH), 71.0 (CH_2), 72.3 (CH_2), 79.3 (CH), 79.7 (CH), 81.3 (CH), 85.4 (CH), 97.7 (CH), 102.4 (CH), 112.0 (q), 112.4 (q), 117.9 (CH_2), 118.6 (CH_2), 133.1 (CH), 133.5 (CH), 151.2 (CH), 151.3 (CH), 155.1 (quartet), 155.5 (quartet).

Conversion of **14** to Furylpyran Derivative **16**

A mixture of the above syrupy material (239 mg), $NaHCO_3$ (106 mg, 1.26 mmol) and MeNHOH•HCl (239 mg, 0.84 mmol) in 80% aq EtOH (20 mL) was refluxed for 20 h, and the mixture was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2, washed with H_2O and dried. Removal of solvent yielded a reddish brown oil, which was chromatographed over silica gel with MeOH/EtOAc (1:9) as eluent to give **16** as white needles (39%); mp 162–163 °C; $[\alpha]_D^{28}$+5.4 (*c* = 0.59, $CHCl_3$).

^{1}H NMR (300 MHz): δ = 2.73 (s, 3 H), 3.44 (m, 1 H), 3.57 (dd, *J* = 7.4, 1.4 Hz, 1 H), 3.65 (d, *J* = 8.0 Hz, 1 H), 3.7 (d, *J* = 6.9 Hz, 1 H), 3.82 (dd, *J* = 9.2, 1.3 Hz, 1 H), 3.91 (t, *J* = 7.8 Hz, 1 H), 4.19 (dd, *J* = 9.1, 7.1 Hz, 1 H), 4.42 (t, *J* = 8.8 Hz, 1 H), 4.64 (d, *J* = 14.3 Hz, 1 H), 4.85 (br s, 1 H), 4.97 (br s, 1 H), 5.07 (d, *J* = 14.3 Hz, 1 H), 8.24 (s, 1 H).

^{13}C NMR (75 MHz): δ = 43.3 (CH_3), 46.9 (CH), 61.2 (CH), 61.4 (CH_2), 69.7 (CH_2), 74.5 (CH_2), 75.0 (CH), 79.8 (CH), 82.3 (CH), 112.7 (quartet), 151.3 (CH), 158.0 (quartet).

Anal. Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.72; H, 6.01; N, 10.44. Found C, 53.50; H, 5.85; N, 10.39.

(2*R*,3*R*,4*S*,5*R*)-2,3-Isopropylidenedioxy-4-propargyloxy-5-(2-nitroethyl)-2,3,4,5-tetrahydrofuran (17)

A mixture of the aldehyde **4** (3.5 g, 0.02 mol), nitromethane (8.8 mL), anhyd KF (1.24 g, 27 mmol) and propan-2-ol (50 mL) was stirred at 25 °C for 15 h, after which it was filtered and the filtrate was concentrated to afford a syrupy liquid. To a solution of this material in CH_2Cl_2 (50 mL) at 0 °C, Ac_2O (2 mL) and DMAP (90 mg) were added and the mixture was kept at 25 °C for 15 h. It was then washed with a cold brine, dried and concentrated to yield a yellow oil. The latter was dissolved in EtOH (50 mL) and added dropwise to a stirred suspension of $NaBH_4$ (1.3 g, 35 mmol) in EtOH (50 mL) at 0 °C. The mixture was stirred at 25 °C for 15 h and then treated carefully with AcOH at 0 °C in order to remove excess of $NaBH_4$. After evaporation of solvent from the mixture, H_2O (50 mL) was added to the residue. It was then extracted with $CHCl_3$, washed with H_2O and dried. Removal of solvent yielded a yellow oil which was chromatographed over neutral alumina using EtOAc/petroleum ether (1:1) giving **17** (2g, 48%) as a light yellow syrupy liquid; $[\alpha]_D^{28}$ –47.6 (*c* = 0.25, $CHCl_3$).

IR (neat): ν = 1549, 1375 cm^{-1}.

^{1}H NMR (300 MHz): δ = 1.32 (s, 3 H), 1.49 (s, 3 H), 2.37 (m, 2 H), 2.52 (t, *J* = 2.2 Hz, 1 H), 4.04 (d, *J* = 3.2 Hz, 1 H), 4.16–4.33 (m, 3 H), 4.54–4.62 (m, 3 H), 5.88 (d, *J* = 3.8 Hz, 1 H).

^{13}C NMR (75 MHz): δ = 26.5 (CH_3), 26.5 (CH_2, overlapping), 27.1 (CH_3), 57.6 (CH_2), 72.7 (CH_2), 75.9 (CH), 76.9 (CH), 79.1 (quartet), 82.1 (CH), 82.4 (CH), 105.1 (CH), 112.2 (CH).

Anal. Calcd. for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32; N, 5.17. Found C, 53.20; H, 6.24; N, 4.73.

(5a*S*,6*R*,7*R*,8a*R*)-5a,6,7,8a,9-Pentahydro-6,7-isopropylidenedioxy-4*H*-furo[2',3':6,7]oxepano [4,3-*c*]isoxazole (19)

A solution of **17** (400 mg, 1.47 mmol), PhNCO (1.6 mL, 14.7 mmol) and Et_3N (2 mL, 14.3 mmol) in benzene (25 mL) was stirred at 25 °C for 48 h. H_2O (50 mL) was added to the mixture and srtirred at 25 °C for 15 h. It was then filtered through a sintered glass funnel 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 H_2O and dried. Removal of solvent yielded a dark brown oil, which was chromatographed over silica gel (100–200 mesh) using EtOAc/petroleum ether (1:4) as eluent yielding **19** (28%) as white needles; mp 98–99 °C; $[\alpha]_D^{28}$ –15.2 (*c* = 0.25, $CHCl_3$).

^{1}H (300 MHz): δ = 1.31 (s, 3 H), 1.49 (s, 3 H), 3.28 (dd, *J* = 15.0, 5.4 Hz, 1 H), 3.36 (dd, *J* = 15.0, 6.9 Hz, 1 H), 4.06 (d, *J* = 2.5 Hz, 1 H), 4.49 (m, 1 H), 4.56 (d, *J* = 13.5 Hz, 1 H), 4.57 (d, *J* = 3.6 Hz, 1 H), 4.83 (d, *J* = 13.5 Hz, 1 H), 5.90 (d, *J* = 3.6 Hz, 1 H), 8.16 (s, 1 H).

^{13}C NMR (75 MHz): δ = 26.0 (CH_2), 26.2 (CH_3), 26.7 (CH_3), 62.4 (CH_2), 77.0 (CH), 84.6 (CH), 84.7 (CH), 104.8 (CH), 111.6 (quartet), 117.0 (quartet), 153.5 (CH), 158.7 (quartet).

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found C, 57.47; H, 5.77; N, 5.41.

Acknowledgement

A.P. is grateful to I.I.C.B. for a temporary assignment. As.B. is thankful to CSIR, India for the award of a Research Associateship. A.B. acknowledges the financial help from DST, India. Thanks are due to Dr. R. Mukhopadhyay and Dr. V. S. Giri for help in NMR analysis.

References

(1) Hannesian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon Press: Oxford 1983.
(2) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
(3) Frederickson, M. *Tetrahedron* **1997**, *53*, 403.
(4) Bhattacharjee, A.; Chattopadhyay, P.; Kundu, A. P.; Mukhopadhyay, R.; Bhattacharjya, A. *Ind. J. Chem.* **1995**, *35B*, 69.
(5) Bhattacharjee, A.; Bhattacharjya, A.; Patra, A. *Tetrahedron Lett*. **1995**, *36*, 4677.
(6) Mukhopadhyay, R.; Kundu, A. P.; Bhattacharjya, A. *Tetrahedron Lett*. **1995**, *36*, 7729.
(7) Westley, J. W. *Adv. Appl. Microbiol*. **1977**, *22*, 177.
(8) Kozikowski, A.P.; Li, C.-S. *J. Org. Chem*. **1985**, *50*, 778.

Article Identifier:
1437-210X,E;1999,0,09,1569,1572,ftx,en;Z02999SS.pdf