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Synthesis of Chiral Pyranocyclohexane, Oxepanocyclohexane, and Furylpyran and -oxepane Systems by the Application of Intramolecular Nitrone and Nitrile Oxide Cycloaddition of Carbohydrate Derivatives

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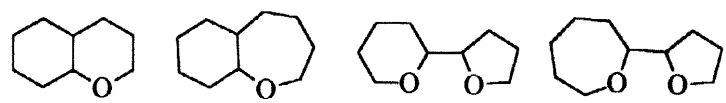
Abstract: Chiral nonracemic pyranocyclohexanes 7 and 8 and oxepanocyclohexane 11 and 12 were obtained from a single 1,2-isopropylidene-3-*O*-cyclohexenyl carbohydrate aldehyde 4 via intramolecular nitrile oxide cycloaddition, and were converted to 2-(2'-tetrahydrofuryl)pyran 28, which incorporates the lasalocid skeleton, and the related oxepane derivative 32 respectively, through modification of the furanoside ring by applying 2-*O*-allyl carbohydrate nitrone cycloaddition. © 1999 Elsevier Science Ltd. All rights reserved.

The supremacy of carbohydrates as a chiral pool in the synthesis of enantiomerically pure compounds is unquestionable.[1] Reactions involving such precursors lead to diverse classes of chiral molecules. In this regard the potential of intramolecular nitrone and nitrile oxide cycloadditions has been demonstrated through their application in natural product synthesis and synthesis of complex ring systems,[2,3] and recent application of these reactions involving nitrones and nitrile oxides derived from *O*-allyl ethers of carbohydrates has made possible the synthesis of various ring sizes of chiral nonracemic cyclic ether derivatives.[3] In fact, enantiomerically pure chiral pyran and oxepane derivatives could easily be prepared by these methods.[3] As pyranocyclohexane (**A**), oxepanocyclohexane (**B**) and 2-(2'-tetrahydrofuryl)pyran (**C**) systems constitute the skeletal frameworks of



A **B** **C** **D**

natural products such as forskolin,[4] sipophenol A[5] and lasalocid[6] respectively, it appeared worthwhile to apply the *O*-allyl nitrone and nitrile oxide cycloaddition strategy to the construction of the above cyclic ether systems. We describe herein the synthesis of the pyranocyclohexane (**A**), oxepanocyclohexane (**B**) and 2-(2'-tetrahydrofuryl)pyran (**C**) as well as the related 2-(2'-tetrahydrofuryl)oxepane (**D**) systems from D-glucose by the judicious application of *O*-cyclohexenyl carbohydrate nitrile oxide and *O*-allyl carbohydrate nitrone cycloaddition.

The starting material for this synthetic study was the well-known 1,2:5,6-diisopropylidene-α-D-glucose (**1**). Apart from being one of the most readily available carbohydrate derivatives, **1** proved to be a very useful precursor by affording products with a 1,2-isopropylidene furanoside ring fused to cyclic ether systems.[3,7] The protected furanoside ring is amenable to modifications by way of degradations and various transformations, thereby leading to other useful compounds. Reaction of **1** with racemic cyclohexenyl bromide in the presence of NaH in THF led to the *O*-cyclohexenyl ether **2** as an inseparable mixture of two diastereomers in nearly quantitative yield (Scheme 1). Treatment of **2** with 75% aqueous HOAc at 25 °C smoothly removed the 5,6-isopropylidene group selectively to give a diastereomeric mixture of diols **3**, as evident from IR and ^{1}H NMR spectra. The oxidative cleavage of the vicinal diol system in **3** could easily be effected with $NaIO_4$ giving rise to

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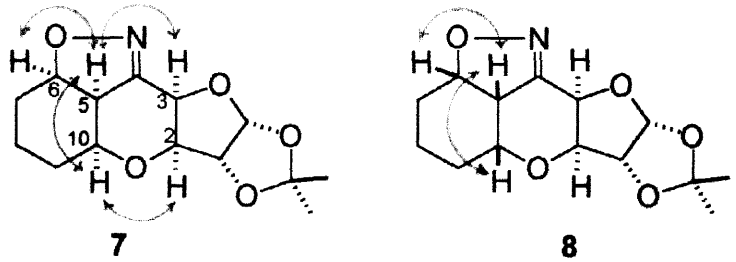
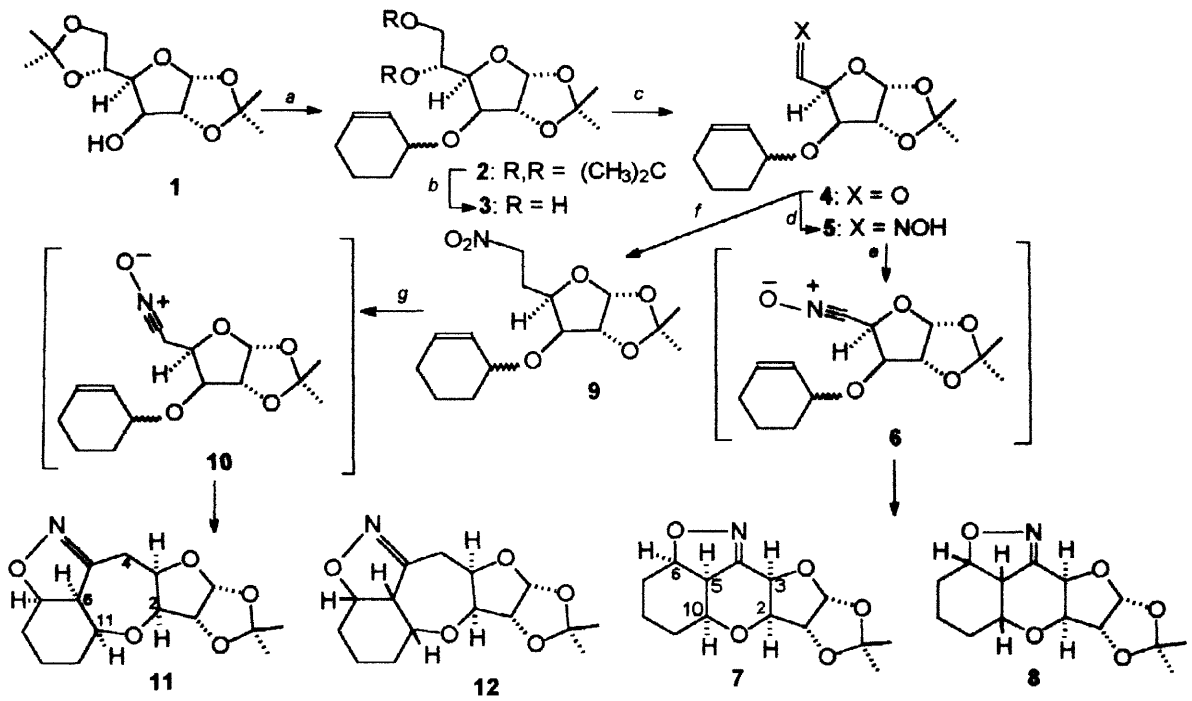
the diastereomeric aldehydes **4**, which constituted a common precursor of both pyran and oxepane derivatives. Thus, the diastereomeric mixture of the oxime **5** prepared from **4**, on treatment with chloramine T [8] in ethanol led to the formation of the pyranocyclohexane derivatives **7** (44 %) and **8** (20 %) via the cycloaddition of the diastereomeric nitrile oxides **6**. The structures of **7** and **8** were established by mass, ^1H and ^{13}C NMR spectral data. The conspicuous feature of the ^1H NMR spectra of both **7** and **8** was the appearance of the 5-H as a clean doublet of doublets and the 6-H and 10-H as two well separated multiplets, as indicated by decoupling experiments. The stereochemistry of the newly formed chiral centres *viz*. 5-C, 6-C and 10-C in **7** and **8** was established by NOESY experiments. Apart from the appearance of distinct cross peaks between 5-H and 6-H, 5-H and 10-H in **7**, which confirmed the *cis*, *syn*-6-C - 5-C - 10-C fusion, the appearance of cross peaks between 5-H and 3-H, and 10-H and 2-H (both 2-H and 3-H having D-glucose configurations) clearly indicated the assigned stereochemistry in **7**. The similar feature involving 5-H and 3-H correlation was found absent in the NOESY spectrum of **8**, which was commensurate with the β-configuration of the 5-H, 6-H and 10-H in **8** (Fig 1). It is thus apparent that the faciality of approach of the nitrile oxide dipole is determined by



7 **8**

Fig 1. Salient NOE correlations of **7** and **8**



a (±)-3-bromocyclohexene, NaH, THF, reflux, 6 h, 96 % *b* 75 % aq. HOAc, 25°C, 12 h, 98 % *c* $NaIO_4$, MeOH - H_2O, 25°C, 2h *d* $NH_2OH.HCl$, pyridine, MeOH, reflux, 6 h *e* Chloramine-T, MeOH, reflux, 8 h, 64 % *f* (i) CH_3NO_2, KF, i-PrOH, 25°C (ii) Ac_2O, DMAP, CH_2Cl_2, 25°C, 12 h, (iii) $NaBH_4$, EtOH, 25°C, 12 h *g* PhNCO, benzene, Et_3N, reflux, 20 h, 41 %

Scheme 1

the orientation of the *O*-cyclohexenyl moiety. Thus for the diastereomer of **6** in which the ether moiety at the cyclohexenyl carbon has β orientation (Fig 2), the product is represented by **7**, and similarly the other

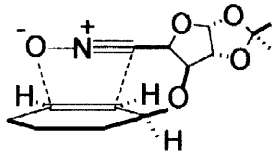
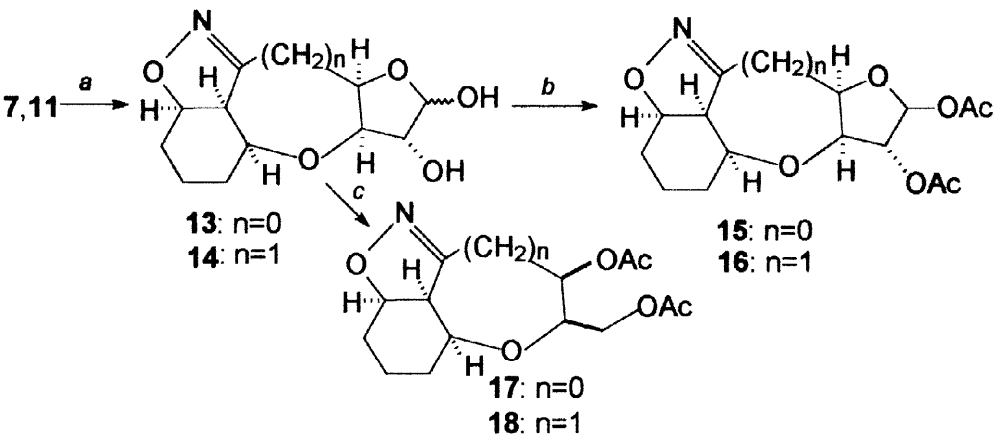


Fig 2

diastereomer leads to **8**. The pyranocyclohexane derivatives bear some resemblance to the pyranone system present in forskolin. Preliminary experiments involving transformation of **7** to a pyranone skeleton indicates the possibility of application of this strategy to the synthesis of forskolin or its analogues.[9]

As mentioned earlier, the aldehyde **4** also served as the precursor for the oxepanocyclohexane derivatives (Scheme 1). Thus, **4** was converted to the diastereomeric nitro compounds **9** following a known[10] protocol involving reaction of **4** with nitromethane followed by dehydration with acetic anhydride and reduction with sodium borohydride. Treatment of **9** with phenyl isocyanate resulted in the formation of the diastereomeric nitrile oxides **10**, which underwent cycloaddition in situ to form the oxepanocyclohexane derivatives **11** (22 %) and **12** (19 %). As expected the purification of these compounds posed problems due to the difficulty in separation of the urea derivatives formed in the reaction. The ^{1}H NMR spectra of both **11** and **12** were very similar to those of **7** and **8**, except that the protons of the extra methylene group in **11** or **12** appeared as two sets of doublet of doublets with high geminal coupling constants (~15 Hz). The stereochemistry of the newly formed chiral centres in **11** and **12** was assigned on the basis of analogy with that in **7** and **8**. The pyranocyclohexane derivatives **7/8** and their homologues *viz.* the oxepane derivatives **11/12** are homochiral. The specific rotations of **7** and **11** as well as **8** and **12** not only have the same signs, they are also very close in magnitude. So on the basis of this isorotation relationship **11** and **12** were assigned the same stereochemistry at 6-C, 7-C and 11-C as that at 5-C, 6-C and 10-C in **7** and **8**.

The isopropylidene furanoside moiety in pyranocyclohexane and oxepanocyclohexane derivatives **7**, **8**, **11** and **12** serve as a useful site for modification of the skeletal framework. By means of simple degradations or transformations the above derivatives could be converted to other useful products. As a demonstration, simple removal of the isopropylidene group followed by acetylation converted **7** and **11** to the diacetates **15** and **16** respectively (Scheme 2). It is worthy of mention that 1,2-diacetates of carbohydrates are useful intermediates

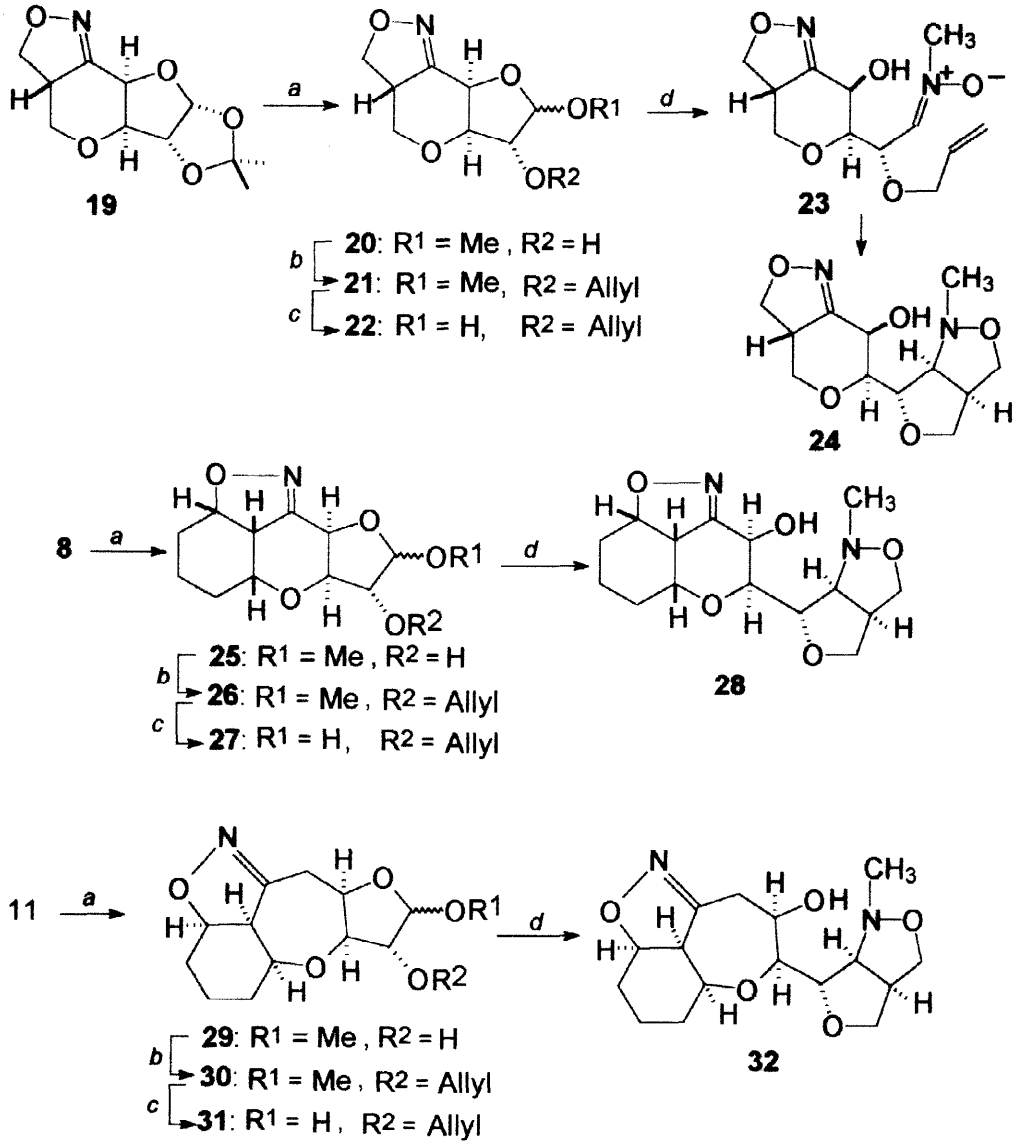


a 1 M aq. HCl, dioxane, 80°C, 2 h *b* Ac_2O, DMAP, pyridine, 25°C, 12 h, 70 % (**15**), 61 % (**16**), *c* (i) $NaIO_4$, MeOH-H_2O, 25°C, 2 h (ii) $NaBH_4$, EtOH, 25°C, 12 h (iii) *b*, 55 % (**17**), 63 % (**18**).

Scheme 2

in the synthesis of nucleosides.[11] The intermediate diols **13** and **14** could smoothly be degraded to the simpler pyranocyclohexane and pyranooxepane derivatives **17** and **18** respectively by way of oxidation with $NaIO_4$, reduction with $NaBH_4$ followed by acetylation (Scheme 2).[7]

However, a more important and useful transformation of the above cyclic ether derivatives was realised through the conversion of the furanoside ring to a tetrahydrofuran ring leading to a novel construction of the 2-(2'-tetrahydrofuryl)pyran skeleton found in lasalocid[6], an antibiotic isolated from *Streptomyces lasaliensis*. The strategy for this conversion rested on our earlier reported 2-*O*-allyl carbohydrate nitrone cycloaddition leading to tetrahydrofuran derivatives.[12] The feasibility of the strategy was established through the conversion of the known[13] pyran derivative **19** to **24** (Scheme 3). Treatment of **19** with methanol in presence of *p*-TsOH



a p-TsOH, MeOH, reflux, 5 h *b* Allyl bromide, Bu_4NBr, 50 % aq. NaOH, CH_2Cl_2, 6 h *c* 50 % aq. TFA, reflux, 3 h *d* MeNHOH.HCl, $NaHCO_3$, 80 % aq. EtOH, reflux, 20 h, 15 % (**24**), 29 % (**28**), 52 % (**32**).

Scheme 3

smoothly gave rise to **20** as a mixture of diastereomers. Allylation[14] of **20** with allyl bromide in the presence of tetrabutyl ammonium bromide in 50% aqueous NaOH-CH_2Cl_2 led to the *O*-allyl derivative **21**, which on being treated with 50% aqueous trifluoroacetic acid led to **22**.Treatment of **22** with *N*-methylhydroxylamine generated the nitrone **23**, which underwent cycloaddition *in situ* giving the 2-(2'-tetrahydrofuryl)pyran derivative **24** in 15% overall yield from **19**. The occurrence of cycloaddition was indicated by the absence of peaks due to the vinyl groups and the appearance of a peak due to the methyl group at δ 2.68 in the ^1H NMR

spectrum of **24**.Otherwise the ^{1}H NMR spectrum was not very informative due to overlapping of signals. However the ^{13}C spectrum of **24** revealed the presence of the C=N (δ 156.9) as well as doublets due to the high field methine carbon atoms, (δ 44.3, 46.8). The stereoechemistry of the newly formed chiral centres *viz.* of the tetrahydrofuran moiety in **24** was based on the analogy with similar systems prepared in our previous work.[13] In addition to the molecular ion, the mass spectrum of **24** also exhibited peaks due to ($M^+ - H_2O$) and ions resulting from the fragmentation of the bond joining the furan and the pyran rings.

It is worthwhile to mention that **24** incorporates the 2-(2'-tetrahydrofuryl)pyran skeleton, which is present in lasalocids.[6] Similarly **8** and **11** were converted to the 2-(2'-tetrahydrofuryl)pyran and the 2-(2'-tetrahydrofuryl)oxepane derivatives **28** (29 %) and **32** (52 %) respectively following the same sequence of reactions as mentioned for the conversion of **19** to **24**. The ^{13}C NMR spectra of both **28** and **32** exhibited the salient features of the isoxazolidine fused tetrahydrofuran moiety of **24**. The mass spectrum of **28** revealed a similar fragmentation pattern to **24**, whereas that for **32** did not show any significant peak due to the loss of H_2O. The intermediates invoved in the sequences **19** to **24**, **8** to **28** and **11** to **32** were syrupy mixtures of diastereomers, and rigorous purification of these intermediates was not attempted. Instead, they were carried to the final cycloaddition step, and the cycloadducts were fully characterised. A notable aspect of the above transformation is that **24**, **28** and **32** retained all the carbon atoms of the precursor aldehyde and three chiral centres of the carbohydrate backbone. In conclusion, the above work demonstrates the potential of the intramolecular nitrone and nitrile oxide cycloaddition of *O*-allyl derivatives of carbohydrate for the construction of complex cyclic ether ring systems. In fact the strategy described above for the construction of the furylpyran systems represents a novel entry into the lasalocid skeleton.[15,16] The furyl cyclic ether derivatives, which could be expediently prepared from the above mentioned pyranocyclohexane and oxepanocyclohexane derivatives represent suitable precursors of lasalocid analogues. Work on this is in progress.

EXPERIMENTAL

Melting points are uncorrected. Unless otherwise noted, ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively in $CDCl_3$. Silica gel of 60-120 mesh was used for chromatography unless otherwise mentioned. Organic extracts were dried over anhydrous Na_2SO_4 and solvent was removed in a rotary evaporator under reduced pressure. Petroleum ether refers to that fraction having bp. 60 - 80 °C.

Pyranocyclohexanes 7 and 8 : To a suspension of NaH (400 mg, 16.6 mmol) in THF (30 ml) was added 1,2:5,6-diisopropylidene-α-D-glucose (**1**) (2 g , 7.69 mmol) in portions at 0 °C with stirring. After the addition was over , the reaction mixture was stirred at 25 °C for 40 min. (±)-3-Bromocyclohexene (1.5 ml , 12.5 mmol) was then added to the above reaction mixture at 0 ° C and stirring was continued for 30 min, after which it was heated under reflux for 15 h. The reaction mixture was then poured into crushed ice (200 g) and extracted with CH_2Cl_2 (3 x 30 ml). The combined organic extracts were washed with water (2x 25 ml). Removal of solvent furnished **2** as a light yellow syrupy liquid; (2.5 g , 96 %); $[\alpha]_D^{25}$ – 20.2 (c 0.1 , $CHCl_3$); MS : m/z 340 (M^+; very weak), 325 (M^+ - 15, 60 %); I.R. (neat): 2982, 2932, 1648, 1453, 1377, 1322, 1216, 1163, 1072, 1018, 849, 754 cm^{-1} ; ^{1}H NMR (100 MHz) (diastereomeric mixture) : δ 1.20 - 2.20 (m, 6 H), 1.32 (s, 3 H), 1.36 (s, 3 H), 1.44 (s, 3 H), 1.48 (s, 3 H), 3.88-4.68 (m, 6H), 4.52 (d, J = 4.0 Hz, 1H), 5.60-6.20 (m, 2H), 5.92 (d, J = 4 Hz, 1H); ^{13}C (25 MHz) : 18.7, 18.8, 25.0, 25.3, 26.2, 26.5, 26.7, 27.9, 29.0, 67.2, 72.4, 72.6, 73.7, 79.9, 80.5, 81.2, 81.3, 83.8, 84.1, 105.2, 108.6, 111.5, 127.0, 127.2, 131.1, 131.4.

The above material was taken in up 75 % aq. HOAc (20 ml) and stirred at 25 °C for 15 h. The solution was distilled with toluene repeatedly for azeotropic removal of HOAc and water yielding the diol **3** as a syrupy liquid (2.15 g , 98 %); $[\alpha]_D^{25}$ – 19.5 (0.07, $CHCl_3$); MS : m/z 300 (M^+; 10 %), 239 (15 %); IR (neat) : 3410 cm^{-1} ; ^{1}H NMR (100 MHz) (diastereomeric mixture) : δ 1.36 (s, 3H), 1.48 (s, 3H), 1.36-2.40 (m, 13H, one proton exchangeable with D_2O), 2.88 (m, 1H, exchangeable with D_2O), 3.56- 4.40 (m, 6H), 4.56 (d, J = 4 Hz, 1H), 5.60-6.20 (m, 2H), 6.20 (d, J = 4 Hz, 1H); ^{13}C NMR (diastereomeric mixture): δ 18.7 (CH_2), 18.8 (CH_2), 25.01 (CH_2), 25.05 (CH_2), 26.1 (CH_3), 26.6 (CH_3), 27.9 (CH_2), 29.2 (CH_2), 64.3 (CH_2), 69.2 (CH), 69.4 (CH), 72.3 (CH), 72.4 (CH), 79.6 (CH), 79.8 (CH), 80.2 (CH), 80.3 (CH), 83.2 (CH), 83.3 (CH), 104.9 (CH), 105.0 (CH), 111.6 (quaternary C), 125.9 (CH), 127.0 (CH), 131.8

(CH), 132.4 (CH). Calcd. for $C_{15}H_{24}O_6.0.5\ H_2O$, C, 58.23 %; H, 7.82 %; Found, C, 58.47 %; H, 7.87 %.

To a solution of this diol in MeOH (55 ml) was added with stirring a solution of $NaIO_4$ (2.38 g , 11 mmol) in water (25 ml) dropwise at 0 °C. Stirring was continued at 0 °C for 30 min and at 25 °C for 2 h. After the reaction was concentrated and water was added, it was extracted with $CHCl_3$ (3 x 25 ml) , washed with water and dried. Removal of solvent furnished the aldehyde **4** (1.87 g) as a light yellow syrupy liquid which was used immediately for the next step; MS : m/z 268 (M^+ ; very weak), 253 ($M^+ - 15$; 11 %); IR (neat) : 1736 cm^{-1}; ^1H NMR (100 MHz): δ 1.36 (s, 3H), 1.48 (s, 3H), 6.16 (d, $J = 4$ Hz, 1H), and 9.72 (d, $J = 2$ Hz, 1H).

A mixture of **4** (3.5 g , 13 mmol), prepared as described above, pyridine (7 ml) , MeOH (48 ml) and $NH_2OH.HCl$ (1.4 g , 20 mmol) was heated under reflux for 8 h. After removal of solvent the residue was extracted with $CHCl_3$ and the organic layer was washed with water (3 x 50 ml) and dried giving the oxime **5** as a light yellow syrup (3 g); IR (neat) : 3264, 1669 cm^{-1}; ^1H NMR (100 MHz) (diastereomeric mixture of *syn* and *anti* isomers) : δ 1.32 (s, 3H), 1.48 (s, 3H), 1.20-2.24 (m, 6H), 3.80-4.20 (m, 2H), 4.40 (d, $J = 4$ Hz), 4.60 (m), 4.64- 4.84 (m), 5.24 (m), 5.60-6.08 (m), 6.92 (d, $J = 4$ Hz), 7.44 (d, $J = 8$ Hz), 7.46 (d, $J = 8$ Hz), 8.28 (broad hump), 8.60 (broad hump); Calcd. for $C_{14}H_{21}NO_5$, N % 4.94; Found, N % 4.75. Chloramine T (3.2 g) was added to a solution of the above oxime **5** (3 g , 10 mmol) in MeOH (35 ml) , and the mixture was heated under reflux for 6 h. After removal of solvent, the residue was treated with water (200 ml) and extracted with CH_2Cl_2 (3 x 75 ml). The organic layer was washed successively with water, 1M NaOH solution and finally water. The organic extract was then dried and removal of solvent afforded a yellow syrupy residue. Chromatography of the material over silica gel using ethyl acetate-petroleum ether (1 : 4) as eluent yielded **8** (0.82 g , 20 %) as colourless needles, m.p. 151-152 °C ($CHCl_3$ - petroleum ether); $[\alpha]_D^{28}$ + 72.9 (c 1.24, $CHCl_3$); MS : m/z 281 (M^+ ; 70 %), 266 ($M^+ - 15$; 100 %); I.R. (KBr): 2984, 2940, 1632, 1450, 1378, 917, 844 cm^{-1}; ^1H NMR : δ 0.92-1.97 (m, 6H), 1.30 (s, 3H), 1.49 (s, 3H), 3.49 (dd, $J = 7.8$, 9.5 Hz, 1H), 4.12 (d, $J = 2$ Hz, 1H), 4.20 (m, 1H), 4.56 (d, $J = 3.7$ Hz, 1H), 4.84 (m, 1H), 4.90 (d, $J =$ 1.9 Hz, 1H), 5.91 (d, $J = 3.6$ Hz, 1 H); ^{13}C NMR : 17.4 (CH_2), 24.7 (CH_2), 26.2 (CH_3), 26.8 (CH_3), 27.0 (CH_2), 44.0 (CH), 70.5 (CH), 72.6 (CH), 75.0 (CH), 79.5 (CH), 84.2 (CH), 106.0 (CH), 112.2 (quaternary C) , 151.8 (quaternary C); Calcd. for $C_{14}H_{19}NO_5$, C, 59.77 % ; H, 6.80 % ; N, 4.97 % . Found , C, 59.71 % ; H, 6.79 % ; N, 4.93 % .

Further elution with ethyl acetate-petroleum ether (3 : 7) afforded **7** as colourless needles (1.32g, 44 %), m.p. 154-155 °C ; $[\alpha]_D^{28}$ - 68.7 (c 0.77, $CHCl_3$) ; MS : m/z 281 (M^+ ; 100 %), 266 ($M^+ - 15$; 37 %); I.R. (KBr) : 2928, 1634, 1441, 1379, 1272, 1168, 1112, 1075, 920 cm^{-1}; ^1H NMR : δ 1.36 (s, 3H), 1.52 (s, 3H), 1.47-1.81 (m, 6H), 3.42 (ddd, $J = 10.6$, 9.5, 0.8 Hz, 1H), 3.99 (m, 1H), 4.15 (d, $J = 4.3$ Hz, 1H), 4.59 (d, $J = 3.6$ Hz, 1H), 4.77 (m, 1H), 5.21 (dd, $J = 4.2$, 1.4 Hz, 1H), 6.03 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR : δ 15.4 (CH_2), 26.6 (CH_3), 27.4 (CH_3), 27.4 (CH_2), 29.3 (CH_2), 45.2 (CH), 72.6 (CH), 75.8 (CH), 78.6 (CH), 82.2 (CH), 84.3 (CH), 106.1 (CH), 112.7 (quaternary C), 153.8 (quaternary C) ; Calcd. for $C_{14}H_{19}NO_5$, C, 59.77 % ; H, 6.80 % ; N, 4.97 % . Found , C, 59.76 % ; H, 6.81 % ; N, 4.95 %.

Oxepanocyclohexane derivatives 11 and 12: A mixture of the aldehyde **4** (1.87 g , 7 mmol), prepared as described before, nitromethane (5 ml, 92 mmol) anhydrous KF (640 mg, 14 mmol) and 2- propanol (25 ml) was stirred at 25 °C for 15 h . The reaction mixture was filtered and the filtrate was concentrated to afford a syrupy liquid. To a solution of this material in CH_2Cl_2 (5 ml) at 0°C, Ac_2O (1 ml) and 4-dimethylaminopyridine (DMAP) (66 mg) were added , and the mixture was kept at 25 °C for 12 h. It was then washed with a cold, saturated aqueous NaCl solution, dried, and concentrated to yield a yellow oil. The latter was dissolved in ethanol (10 ml) and added dropwise to a stirred suspension of $NaBH_4$ (600 mg) in EtOH (50 ml) at 0 °C . The reaction was stirred for 15 h at 25 °C and then treated carefully with HOAc at 0°C. After evaporation of solvent from the mixture, water (50 ml) was added to the residue. It was then extracted with $CHCl_3$ (3 x 50 ml) and the combined extracts were washed with water (2 x 50 ml) and dried. Removal of solvent yielded a yellow oil , which was chromatographed over neutral alumina using ethyl acetate-petroleum ether (1 : 1) as eluent giving **9** (1.57 g , 72 %) as a light yellow syrupy liquid; IR (neat) : 1554 cm^{-1} ; MS : m/z 313 (M+ ; 9 %), 298 ($M^+ - 15$; 74 %) ; ^1H NMR (diastereomeric mixture) : δ 1.31 (s, 3H), 1.48 (s, 3H), 1.00-2.50 (m, 8H), 3.90-4.26 (m, 3H), 4.56 (m, 3H), 5.53-5.87 (m, 3H); ^{13}C NMR : δ 18.8 (CH_2), 18.9 (CH_2), 25.0 (CH_2), 25.1 (CH_2), 26.2 (CH_3), 26.5 (CH_3), 26.7 (CH), 28.1 (CH_2), 29.5 (CH_2),

72.3 (CH), 72.56 (CH), 72.60 (CH), 72.7 (CH), 76.6 (CH), 76.8 (CH), 80.7 (CH), 80.8 (CH), 83.6 (CH), 104.8 (CH), 111.6 (quaternary C), 125.9 (CH), 127.1 (CH), 131.9 (CH), 132.3 (CH); Calcd. for $C_{15}H_{23}NO_6$, C, 57.49 %; H, 7.39 %, N, 4.47 %; Found, C, 57.95 %, H, 7.06 %, N, 4.31 %.

To a solution of **9** (1 g, 3 mmol) in benzene (130 ml) were added PhNCO (3 ml, 3 mmol) and Et_3N (4.6 ml , 33 mmol), and the mixture was heated under reflux for 30 h. Water (100 ml) was added and the mixture stirred 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 (2 x 50 ml). The combined organic extracts were washed with water and dried. Removal of solvent yielded a dark brown oil which was chromatographed over silica gel (100 - 200 mesh). Elution with ethyl acetate-petroleum ether (1 : 4) yielded **12** (0.18 g , 19 %) as a colourless needles, m.p. 122 °C ($CHCl_3$-petroleum ether); $[\alpha]_D^{26}$ + 89.2 (c 0.39, $CHCl_3$); MS : m/z 295 (M^+ ; 50 %), 294 (90%), 280 (M^+ –15; 50 %), 279 (100%); I.R. (KBr): 2938, 1621, 1445, 1379, 1213, 1164, 1079, 1023, 882 cm^{-1}; ^1H NMR : δ 1.32 (s, 3H), 1.49 (s, 3H), 1.45-1.78 (m, 6H), 2.79 (dd, J = 15.7, 3.7 Hz, 1H), 3.24 (dd, J = 15.7, 6.3 Hz, 1H), 3.45 (dd, J = 9.4, 7.6 Hz, 1H), 3.85 (m, 1H), 4.26 (d, J = 3.7 Hz, 1H), 4.40 (m, 1H), 4.55 (d, J = 4.0 Hz, 1H), 4.58 (m, 1H), 5.88 (d, J = 4.0 Hz, 1H); ^{13}C NMR : 15.3 (CH_2), 24.7 (CH_2), 26.0 (CH_3), 26.5 (CH_3), 28.17 (CH_2), 28.22 (CH_2), 52.1 (CH), 69.0 (CH), 75.7 (CH), 79.1 (CH), 81.2 (CH), 85.9 (CH), 104.2 (CH), 111.2 (quaternary C), 156.2 (quaternary C); Calcd. for $C_{15}H_{21}NO_5$: N, 4.74 %; Found N, 5.02 %.

Further elution with ethyl acetate - petroleum ether (3 : 7) gave **11** (0.20 g , 22 %) as colourless needles, m.p. 203 °C ($CHCl_3$-petroleum ether); $[\alpha]_D^{26}$ - 68.6 ° (c 0.42, $CHCl_3$); MS : m/z 295 (M^+ ; 40 %), 294 (80 %), 280 (M^+ – 15; 50 %), 279 (100 %); I.R. (KBr): 2932, 1620, 1378, 1345, 1212, 1166, 1083, 1021, 877 cm^{-1}; ^1H NMR : δ 1.30 (s, 3H), 1.49 (s, 3H), 1.30-1.79 (m, 6H), 2.25 (dd, J = 14.7, 4.0 Hz, 1H), 3.13 (dd, J = 14.7, 5.0 Hz,1H), 3.46 (dd, J = 9.9, 6.6 Hz, 1H), 3.90 (m, 1H), 4.02 (d, J = 2.5 Hz, 1H), 4.36 (m, 1H), 4.53 (d, J = 3.6 Hz,1H), 4.57 (m, 1H), 5.91 (d, J = 3.6 Hz, 1H); ^{13}C NMR : 14.9 (CH_2), 25.1 (CH_2), 26.2 (CH_3), 26.8 (CH_3), 28.0 (CH_2), 28.3 (CH_2), 53.8 (CH), 74.3 (CH), 76.2 (CH), 78.3 (CH), 85.3 (CH), 85.4 (CH), 104.5 (CH), 111.4 (quaternary C), 154.5 (quaternary C); Calcd. for $C_{15}H_{21}NO_5$: C, 61.0 %; H, 7.17 %; N, 4.74 %; Found C, 60.87 %; H, 7.16 %; N, 4.35 %.

General procedure for the preparation of the diacetates 15 and 16 : The general procedure is illustrated by the preparation of **15**. A solution of **7** (0.40 g , 1.42 mmol) in a mixture of dioxane (8 ml) and 1M aq. HCl (3 ml) was heated at 80 ° C for 2 h. Completion of the reaction was monitored by TLC. The reaction mixture was then neutralised by careful addition of solid $NaHCO_3$. Solvent was then removed until a solid residue appeared which was extracted with ethyl acetate repeatedly. The combined organic extracts were dried and removal of solvent afforded the diol **13** as a colourless syrup, which was used immediately for the next step. The above material (180 mg) was up taken in pyridine (1 ml) containing DMAP (5 mg) , cooled to 0 °C and Ac_2O (0.3 ml) added with stirring. The reaction mixture was kept at 25 ° C for 24 h, poured into crushed ice and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic extracts were washed with water, dried and concentrated. The residue was azeotropically distilled with toluene repeatedly to remove pyridine when a syrupy liquid was obtained. Chromatography of the material over silica gel using ethyl acetate-petroleum ether (3 : 1) afforded the diacetate **15** (0.15 g , 70 %) as colourless needles, m.p. 198-199 ° C ($CHCl_3$-petroleum ether) ; $[\alpha]_D^{26}$ + 22.8 (c 0.28, $CHCl_3$); I.R. (KBr): 1741 cm^{-1}; MS: m/z 325 (M^+ ; very weak), 266 (M+ – 59; 60 %), 265 (60 %), 223 (100 %) ; ^1H NMR: δ 1.57 (m, 4H), 1.96 (m, 2H), 2.09 (s, 6H), 3.37 (dd, J = 10.8, 8.8 Hz, 1H), 3.88 (m, 1H), 4.42 (dd, J = 6.7, 5.0 Hz, 1H), 4.76 (dd, J = 11.2, 4.1 Hz, 1H), 5.17 (d, J = 6.9 Hz, 1H), 5.20 (d, J = 4.7 Hz, 1H), 6.55 (d, J = 4.4 Hz, 1H); ^{13}C NMR : δ 14.2 (CH_2), 20.3 (CH_3), 20.8 (CH_3), 26.2 (CH_2), 28.0 (CH_2), 46.0 (CH), 72.1 (CH), 74.3 (CH), 77.0 (CH), 78.2 (CH), 80.8 (CH), 93.6 (CH), 153.6 (quaternary C), 168.8 (quaternary C), 169.4 (quaternary C); Calcd. for $C_{15}H_{19}NO_7$: C, 55.38 %; H, 5.89 %; N, 4.30 %; found C, 55.19 %; H, 5.84 %; N, 3.92 %.

16: The same procedure starting from **11** (200 mg , 0.68 mmol) yielded the diol **14** (172 mg) which was acetylated to give the diacetate **16** (0.14 g , 61 %) as colourless needles, m.p. 95-96 ° C ($CHCl_3$-petroleum ether) ; $[\alpha]_D^{26}$ + 35.5 (c 0.45, $CHCl_3$); I.R. (KBr): 1743 cm^{-1}; MS: m/z 339 (M^+ ; 25 %), 280 (M^+ – 59; 100 %); ^1H NMR : δ 1.31 (m, 2H), 1.70 (m, 2H), 1.90 (m, 2H), 2.81 (m, 1H), 3.04 (dd, J =

14.5, 4.1 Hz, 1H), 3.51 (t, J = 8.6 Hz, 1H), 4.00 (m, 1H), 4.40 (m, 2H), 4.73 (m, 1H), 5.10 (t, J = 4.5 Hz, 1H), 6.40 (d, J = 4.5 Hz, 1H); ^{13}C NMR: δ 17.5 (CH_2), 20.4 (CH_3), 20.8 (CH_3), 27.3 (CH_2), 28.1 (CH_2), 29.6 (CH_2), 51.5 (CH), 74.5 (CH), 76.6 (CH), 78.2 (CH), 78.8 (CH), 79.3 (CH), 93.2 (CH), 154.5 (quaternary C), 169.3 (quaternary C); 169.7 (quaternary C); Calcd. for $C_{16}H_{21}NO_7$: C, 56.63 %; H, 6.24 %; N, 4.13 %; Found C, 56.39 %; H, 6.17 %; N, 3.95 %.

General procedure for the preparation of 17 and 18 :The general procedure is illustrated by the preparation of **17**. To a solution of the diol (210 mg) in MeOH (11 ml) at 0°C was added with stirring $NaIO_4$ (280 mg , 1.3 mmol) in water (4 ml) dropwise. After completion of addition stirring was continued at 25 °C for 2 h, the mixture filtered and the filtrate concentrated. The residue was extracted with $CHCl_3$ (3 x 25 ml) and the combined organic extracts were washed with water (3 x 20 ml), dried and removal of solvent yielded a syrupy liquid which was immediately used for the next reaction. To a solution of the above material in EtOH (7 ml) at 0°C was added with stirring $NaBH_4$ (30 mg) in portions, and stirring was continued for further 12 h at 25 °C. The reaction mixture was then treated with 50% aq. HOAc and after removal of solvent the residue obtained was extracted with ethyl acetate (5 x 10 ml).The combined organic extracts were dried and removal of solvent gave a syrupy liquid.The latter was taken in pyridine (1 ml) containing DMAP (5 mg), and Ac_2O (0.5 ml) was added dropwise at 0 °C.The reaction mixture was kept at 25 °C for 24 h after which it was poured into crushed ice and extracted with $CHCl_3$ (3 x 25 ml). The combined organic extracts were washed with water, dried and concentrated. The residue was azeotropically distilled with toluene repeatedly to remove pyridine when a syrupy liquid was obtained. Chromatography of the material over silica gel using ethyl acetate-petroleum ether (3 : 1) afforded the diacetate **17** (125 mg , 55 %) as colourless needles, m.p. 89-90°C ($CHCl_3$-petroleum ether) ; $[\alpha]_D^{26}$ - 149.5 (c, .95, $CHCl_3$); I.R. (KBr): 1741 cm^{-1} ; MS : m/z 297 (M^+ ; 8 %), 254 (77 %),237 (77 %), 195 (100 %); ^{1}H NMR: δ 1.32 (m, 1H), 1.59 (m, 1H), 1.80 (m, 4H), 2.07 (s, 3H), 2.11 (s, 3H), 3.57 (t, J = 9.8 Hz, 1H), 4.06-4.28 (m, 4H), 4.86 (m, 1H), 5.97 (m, 1H); ^{13}C NMR : 15.9 (CH_2), 20.6 (CH_3), 20.7 (CH_3), 27.8 (CH_2), 29.6 (CH_2), 44.8 (CH), 62.0 (CH_2), 66.5 (CH), 72.8 (CH), 74.0 (CH), 79.5 (CH), 153.3 (quaternary C), 169.8 (quaternary C), 170.5 (quaternary C); Calcd. for $C_{14}H_{19}NO_6$: C, 56.56 %; H, 6.40 %; N, 4.71 %; Found C, 56.23 %, H, 6.35 %; N, 4.31 %.

18: The same procedure starting from the diol **14** (250 mg) yielded the diacetate **18** (210 mg , 62.5 %) as colourless needles, m.p. 82-83 °C ; $[\alpha]_D^{26}$ + 112.1 (c 0.48, $CHCl_3$); I.R. (KBr): 1736 cm^{-1} ; MS: m/z 311 (M^+ ; 63 %), 242 (M+ – 59; 100 %); ^{1}H NMR: δ 1.45 (m, 2H), 1.69 (m, 2H), 1.95 (m, 2H), 2.05 (s, 3H), 2.12 (s, 3H), 2.49 (dd, J = 14.5, 2.3 Hz, 1H), 3.25 (dd, J = 14.4, 4.6 Hz, 1H), 3.49 (dd, J = 10.3, 6.7 Hz, 1H), 3.79 (dt, J = 7.5, 1.2 Hz, 1H), 3.94 (m,1H), 4.01 (dd, J = 11.2, 6.2 Hz, 1H), 4.12 (dd, J = 11.3, 7.3 Hz, 1H), 4.57 (m, 1H), 5.04 (m, 1H); ^{13}C NMR: δ 14.2 (CH_2), 20.8 (CH_3), 21.0 (CH_3), 23.7 (CH_2), 27.2 (CH_2), 30.3 (CH_2), 55.1 (CH), 63.3 (CH_2), 68.3 (CH), 76.1 (CH), 78.6 (CH), 82.7 (CH), 153.9 (quaternary C), 170.5 (quaternary C), 170.6 (quaternary C); Calcd. for $C_{15}H_{21}NO_6$: C, 57.87 %; H, 6.79 %; N, 4.49 %; found C, 57.81 %; H, 6.75 %; N, 4.46 %.

General procedure for the preparation of 2-(2'-tetrahydrofuryl)pyran and -oxepane derivatives 24, 28 and 32 : The general procedure for the preparation of **24**, **28** and **32** is illustrated by the preparation of **24**. A solution of **19**[13] (600 mg , 2.5 mmol) in dry MeOH (25 ml) containing TsOH (60 mg) was heated at reflux for 5 h. The reaction mixture was neutralised with saturated $NaHCO_3$ solution and solvent was removed until a syrupy residue was obtained. Extraction with CH_2Cl_2 (5 x 25 ml) followed by drying of the combined organic extracts gave **20** (500 mg) as a light yellow viscous oil. ^{1}H NMR (diastereomeric mixture): δ 3.04 (d, J = 2.7 Hz), 3.34 (m), 3.45, 3.57 (both singlets, CH_3), 3.70 (m), 3.80-4.00 (m), 4.26 (m), 4.56 (m), 5.01 (m), 5.25 (d, J = 4.2 Hz).

A solution of the above material in CH_2Cl_2 (8 ml) was treated with allyl bromide (0.31 ml), 50 % aq. NaOH (8 ml) and Bu_4NBr (84 mg) and the reaction mixture was stirred at 25 °C for 6 h. The organic layer was separated, washed with water, dried and concentrated. The syrupy liquid obtained was chromatographed over neutral alumina using $CHCl_3$-petroleum ether (1 : 9) giving **21** (500 mg) as a light yellow oil ; MS : m/z 255 (M^+ ; 10 %); IR (neat): 2926, 1631, 1463, 1198, 1121cm^{-1}; ^{1}H NMR (diastereomeric mixture): δ 3.31

(m), 3.45, 3.51 (both s), 3.60 - 4.30 (m), 4.53 (m), 4.90-4.96 (m), 5.10-5.34 (m), 5.60, .5.90 (both multiplets). A solution of the above material in 50 % aq.TFA was heated at reflux for 3 h. Azeotropic removal of the aq. TFA with benzene left a syrupy residue, which was extracted with CH_2Cl_2 (3 x 25 ml). The combined organic extracts were washed with saturated $NaHCO_3$ solution, dried and evaporated yielding **22** (300 mg) as a light yellow syrup, which was used without purification for the next step . A solution of the above material in 80 % aq. EtOH (20 ml) was treated with MeNHOH.HCl (170 mg, 2.05 mmol) and $NaHCO_3$ (170 mg, 2.05 mmol), and the reaction was heated under reflux for 20 h. Removal of solvent left a sticky residue, which was extracted with CH_2Cl_2 (4 x 25 ml). The combined organic extracts were washed with water, dried and removal of solvent afforded a sticky material, which was chromatographed over neutral alumina using ethyl acetate-petroleum ether (3 : 1) yielding **24** (100 mg, 14.8 %) as white granules, m.p. 134-135 °C ($CHCl_3$-petroleum ether); [α]$_D^{26}$ + 182.4 (c 0.76, $CHCl_3$); I.R. (KBr): 3140 cm^{-1} ; MS: m/z 270 (M^+ ; 100 %), 252 (M^+ – 18; 50 %); ^{1}H NMR: δ 2.68 (s, 3H), 3.30- 3.44 (m, 3H), 3.60-3.68 (m, 2H), 3.75-3.92 (m, 4H), 4.17 (m, 1H), 4.37- 4.48 (m, 2H), 4.54 (d, J = 2.1 Hz, 1H), 4.73 (bs, 1H); ^{13}C NMR: 43.3 (CH_3), 44.3 (CH), 46.8 (CH), 65.0 (CH), 69.6 (CH_2), 69.8 (CH_2), 72.0 (CH_2), 74.5 (CH_2), 74.8 (CH), 81.8 (CH), 83.1 (CH), 156.9 (quaternary C); Calcd. for $C_{12}H_{18}N_2O_5$: C, 53.32 %; H, 6.71 %; N, 10.37 %; found C, 53.42; H, 6.57; N, 10.24 %.

28: The same procedure starting from **8** (250 mg , 0.89 mmol) yielded, *via* **25** which was used without purification, **26** (260 mg); MS : m/z 295 (M^+ ;10 %); IR (neat): 3472, 2928, 2864, 2356, 1624, 1456, 1449, 1376, 1032, 849 cm^{-1}; ^{1}H NMR (diastereomeric mixture) : δ 1.25 – 1.89 (m), 3.42 (s), 3.57 (m), 3.96 (s), 4.12 (m), 4.31 (m), 4.87 (m), 4.99 (s), 5.21- 5.35 (m), 5.89 (m). **26** was converted without purification *via* **27** to **28** (80 mg, 29 %) as colourless needles, m.p. 166-167 ° C ($CHCl_3$-petroleum ether); [α]$_D^{26}$ + 90.9 (c 0.68, $CHCl_3$); I.R. (KBr): 3224 cm^{-1} ; MS: m/z 310 (M^+; 100 %), 292 (M^+ – 18; 50 %); ^{1}H NMR: 1.24 (m, 2H), 1.53 (m, 1H), 1.74 (m, 2H), 1.92 (m, 1H), 2.67 (s, 3H), 3.38 (m, 1H), 3.64 (m, 2H), 3.78 (m, 4H), 4.17 (dd, J = 9.1, 7.1 Hz., 1H), 4.40 (m, 2H), 4.51 (d, J = 2.2 Hz., 1H), 4.66 (s, 1H), 4.85 (m, 1H).^{13}C NMR: δ 17.7 (CH_2), 24.7 (CH_2), 27.6 (CH_2), 43.4 (CH_3), 44.1 (CH), 46.9 (CH), 64.2 (CH), 69.6 (CH_2), 72.4 (CH), 72.8 (CH), 74.7 (CH_2), 75.0 (CH), 79.3 (CH), 83.3 (CH), 155.1 (quaternary C); Calcd. for $C_{15}H_{22}N_2O_5$: C, 58.05 %; H, 7.15 %; N, 9.03 %; found C, 58.03 %; H, 7.15 %; N, 8.95 %.

32: The same procedure starting from **11** (140 mg, 0.47 mmol) yielded, via **29** , which was used without purification, **30** (136 mg) as a brown oil; MS : m/z 309 (M^+ ; 25 %); IR (neat): 2926, 2858, 1648, 1454, 1257, 1233, 1184 cm^{-1}; ^{1}H NMR (anomeric mixture): δ 1.30 (m), 1.70 (m), 1.80 (m), 2.04 (m), 2.58, 3.00 (both multiplets), 3.40, 3.42 (both singlets), 3.52 (m), 3.93-4.40 (m), 4.70 (m, 1H), 4.86 (m), 5.21-5.34 (m), 5.92 (m).

30 was converted without purification *via* **31** to **32** (80 mg, 52.2 %) as white needles, m.p. 154-155 °C ($CHCl_3$-petroleum ether) ; [α]$_D^{26}$ - 55.0 (c 0.2, $CHCl_3$); I.R. (KBr): 3300 cm^{-1} ; MS: m/z 324 (M^+ ; 100 %); ^{1}H NMR : δ 1.49 (m, 2H), 1.68 (m, 2H), 1.96 (m, 2H), 2.52 (dd, J = 13.8, 2.4 Hz, 1H), 2.65 (s, 3H), 3.05 (dd, J = 13.8, 4.7 Hz, 1H), 3.35 (m, 1H), 3.46 (m, 2H), 3.56 (m, 1H), 3.69 (m, 2H), 3.86 (m, 1H), 3.93 (m, 1H), 4.12-4.24 (m, 3H), 4.56 (m,1H); ^{13}C NMR: δ 14.5 (CH_2), 24.3 (CH_2), 28.1 (CH_2), 33.5 (CH_2), 44.0 (CH_3), 48.5 (CH), 54.6 (CH), 67.8 (CH), 70.2 (CH), 74.0 (CH_2), 76.2 (CH_2), 77.4 (CH), 78.3 (CH), 84.7 (CH), 86.0 (CH), 155.3 (quaternary C); Calcd. for $C_{16}H_{24}N_2O_5$: C, 59.24 %; H, 7.46 %; N, 8.64 %; found C, 59.32 %; H, 7.29 %; N, 8.50 %.

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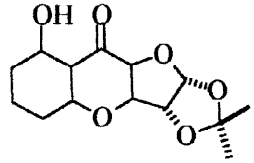
9. As an example, treatment of **7** with H_2 in the presence of Raney Ni led to a product, which was assigned the following structure on the basis of IR, ^1H and ^{13}C NMR spectral data. The structure bears a close resemblance to the pyranone skeleton of forskolin, and the isopropylidene furanoside moiety present in the above skeleton can be subjected to modification giving rise to the substituents e.g. vinyl present in forskolin.



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