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Cyclization in situ of enose-/ynose-nitrilimines: an expedient approach to the synthesis of chiral glycopyrazoles and pyrazolonucleosides

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Abstract—Intramolecular [3+2] nitrilimine cycloaddition reactions on carbohydrate-derived substrates proceed in a regioselective fashion, affording structurally novel chiral glycopyrazoles (**4–6** and **10a–c**) in good yields. The products can be subsequently transformed to bicyclic pyrazoles (viz. **11** from **4**) or nucleoside analogues (viz. **12** from **4**).

1. Introduction

The pyrazole moiety is present in a large number of biologically active compounds,[1] which find wide application in the pharmaceutical[2] and agrochemical industries.[3] Numerous synthetic routes to pyrazole heterocycles have been developed based on (i) the condensation of hydrazines with β-dicarbonyl compounds[4] or with α, β-unsaturated carbonyl compounds followed by appropriate transformations,[5] and (ii) inter-, intra-, or sequential inter-intramolecular [3+2] cycloaddition reaction of diazo compounds[6] or nitrilimines[7] to alkynes or alkenes followed by oxidation. The 1,3-dipolar cycloaddition reactions of nitrilimines to obtain pyrazoles appears to have tremendous potential for the development of structurally novel synthetic entities, particularly when the nitrilimine is generated[8,9] through oxidation of aldehyde hydrazones with chloramine T or lead tetraacetate; judicious manipulation of the aldehyde and the olefin moieties allows a lot of flexibility in achieving the target structure. Although the synthesis of enantiomerically pure pyrazole derivatives employing chiral dipolarophiles and homochiral nitrilimines has been reported,[10] reports on the intramolecular version of this methodology on a carbohydrate backbone are rare.[11] For our research programme directed towards the synthesis of enantiomerically pure pyrazole derivatives, we opted to use this reaction on appropriately designed carbohydrate-derived precursors. We realized that introduction of a *C*-/*O*-allyl or propargyl group at C-3 of the glucose ring and generation of an aldehyde group at C-5 through simple functional group manipulations followed by conversion of the aldehyde to nitrilimine could lead to spontaneous [3+2] cycloaddition, furnishing optically active and structurally unique pyrazoles or pyrazolines (Fig. 1). Opening of the furanose ring in the addition products was expected to furnish fused pyrazoles/pyrazolines. Besides, introduction of various nucleobases directly onto the anomeric center of the furanose ring could lead to nucleoside analogues with

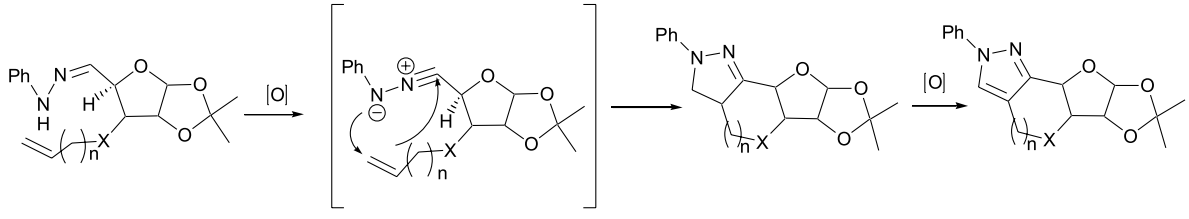

Figure 1. A general method for the synthesis of glycopyrazoles.

Keywords: Nitrilimine cycloaddition reaction; Synthesis; Glycopyrazoles; Pyrazolonucleosides; D-Glucose.
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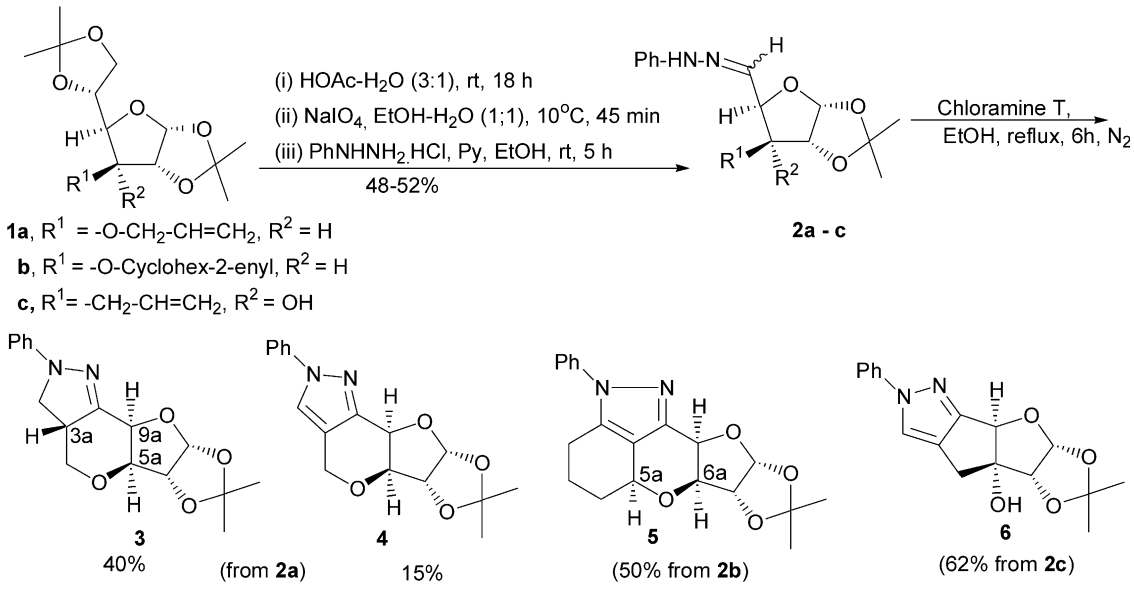


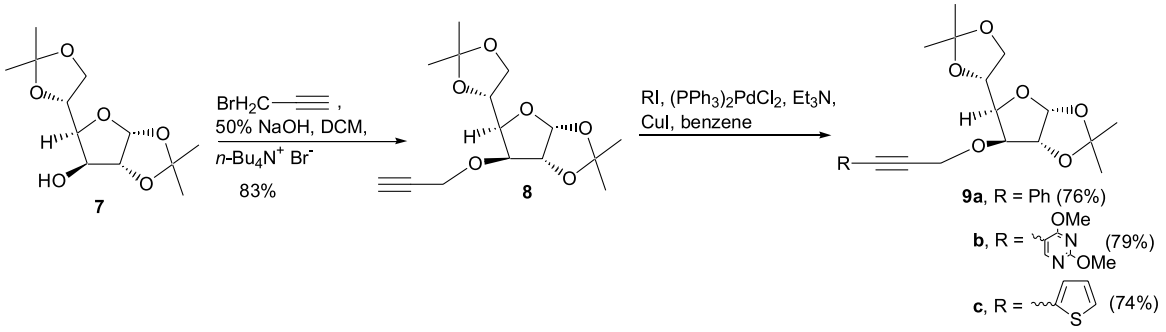
Scheme 1. Synthesis of pyrazoline **3** and pyrazoles **4–6** through INIC reaction.

pyrazole/pyrazoline ring in the structures. The present communication deals with the scope of this reaction for developing functionalized chiral glycopyrazoles and pyrazolonucleosides.

2. Results and discussion

Selective opening of the 5,6-*O*-isopropylidene group of the D-glucose-derived precursors **1a–c**[12] by acid treatment followed by vicinal diol cleavage with sodium periodate and reaction with phenyl hydrazine furnished the corresponding hydrazones **2a–c** (as a mixture of *cis* and *trans* isomers as evident from the duplicity of peaks in the ^{1}H NMR). Oxidation with chloramine T thereafter was expected to furnish the respective pyrazolines as the intramolecular nitrilimine cycloaddition (INIC) products. However, the initially formed pyrazolines appear to have undergone in situ oxidation to form the pyrazoles (Scheme 1); only **2a** yielded the pyrazoline **3** (40%) as the major product along with the pyrazole **4** (15%), while **2b** and **2c** gave **5** and **6**, respectively. Formation of **3** was indicated by the disappearance of vinylic proton signals of **1a** in the δ 5.20–5.30 and 5.80–6.00 regions along with appearance of peaks for methylene protons at δ 3.25–3.34 (m, 2H) and for a methine proton at δ 3.55–3.62 (m, 1H) in the ^{1}H NMR spectrum. This was confirmed by the presence of three quaternary (δ 112.6, 145.6 and 147.0) and two methylene (δ 49.9 and 71.5) carbon signals in its ^{13}C NMR spectrum. The absence of similar proton signals in the NMR of **4** and the appearance instead of a 1H singlet at δ 7.63 confirmed its formation through the oxidation of **3**. Regarding the identification of the other products, the appearance of a double doublet for H-5a at δ 4.54 (J=5.3, 10.2 Hz) in the ^{1}H NMR spectrum of **5** and of five quaternary carbon signals in its ^{13}C NMR spectrum indicated its formation. Similarly, the absence of signals in the olefinic proton region (δ 5.18–6.03) coupled with the presence of two singlets at δ 5.09 and 7.63 in the ^{1}H NMR spectrum and of five quaternary carbons in the ^{13}C NMR spectrum of **6** indicated the structure shown. The *trans* relationship of H-3a (δ 3.59) with H-9a (δ 4.98) (and hence with H-5a at δ 4.02) in **3** was borne out by the absence of correlation in the NOESY spectrum. However, the presence of distinct cross-peaks between the signals for the H-6a (δ 4.36) and the H-5a (δ 4.54) in the NOESY spectrum of **5** signified their *cis* relationship.

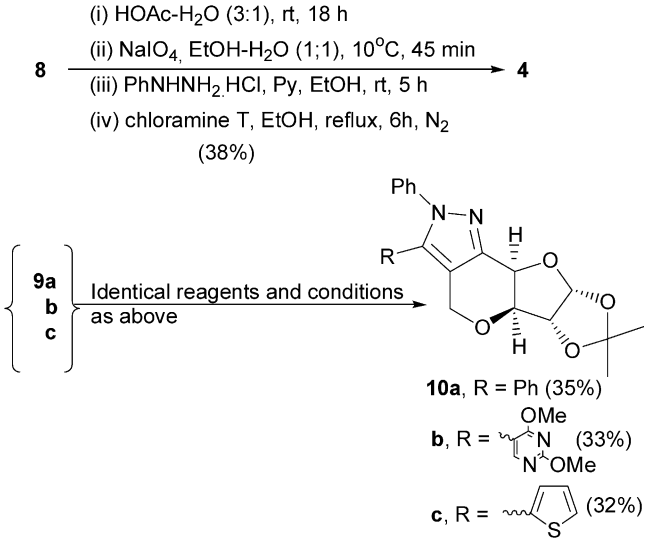
The INIC reaction was also attempted on the substrates carrying an *O*-propargyl or substituted propargyl group at *C*-3 of the carbohydrate precursor. Starting with **7** (Scheme 2), the 3-*O*-propargyl-α-D-glucofuranose



Scheme 2. Preparation of 3-*O*-alkynyl-1,2:5,6-diacetone-D-glucose derivatives **8**, **9a–c**.

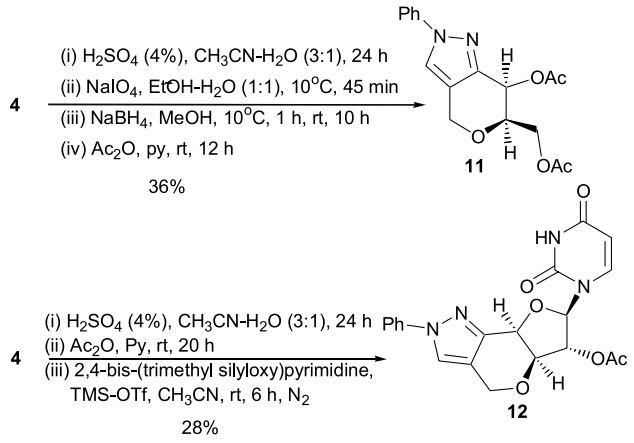
derivative **8** was prepared through propargylation (propargyl bromide, CH_2Cl_2, 50% aq NaOH, n-$Bu_4N^+Br^-$, rt, 12 h) of C-3–OH group. Compounds **9a–c** were, however, synthesized by incorporating phenyl, 2,4-dimethoxyuracil-5-yl and thiophen-2-yl groups at the terminal carbon of the triple bond of **8** though Sonogashira coupling[13] with the corresponding iodides in the presence of a catalytic amount of bis(triphenylphosphine)dichloro palladium(II) and copper (I) iodide. The formation of the desired product in each case was tested by NMR spectroscopy. Thus, the acetylenic proton signal at δ 2.48 in the ^{1}H NMR of **8** was found absent in those of the products **9a–c**. Instead the characteristic signals for protons of the substituent were observed.

When the acetylenic compounds **8** and **9a–c** were subjected to dil acetic acid treatment, they afforded the respective 5,6-dihydroxy derivatives. The products were subjected to vicinal diol cleavage with $NaIO_4$ and reaction with phenyl hydrazine to furnish the corresponding hydrazones. Oxidation of these hydrazones with chloramine T followed by cycloaddition reactions of the generated nitrilimines furnished the corresponding pyrazoles **4** and **10a–c** in 32–38% overall yields (Scheme 3). The structures of the products were deduced from spectral analyses.



Scheme 3. Conversion of **8** and **9a–c** to pyrazoles **4** and **10a–c**.

The derived INIC products could be further transformed into new varieties of bicyclic pyrazoles and nucleoside analogues (Scheme 4). Thus, **4** was converted to pyranopyrazole **11** through a sequence of reactions involving removal of the 1,2-*O*-isopropylidene group with 4% H_2SO_4 in CH_3CN–H_2O (3:1), $NaIO_4$ cleavage of the masked aldehyde, $NaBH_4$ reduction, and acetylation of the diol with acetic anhydride in pyridine. Besides, nucleobases could be successfully installed on **4** by cleavage of the acetonide group, acetylation to form a mixture of the diacetates and reaction with 2,4-bis-(trimethylsilyloxy)pyramidine in presence of TMS–OTf in CH_3CN at room temperature to furnish the nucleoside derivative **12**. Anchimeric assistance



Scheme 4. Conversion of **4** to bicyclic pyrazole **11** and modified nucleoside **12**.

by the neighbouring acetoxy group directs the incoming nucleobase to the β-face.

The formation of **11** was deduced from the appearance of an acetoxy peak at δ 2.11 (s, 6H) and of two methylene carbon signals at δ 62.8 and 63.1 in its ^{1}H and ^{13}C NMR spectra. The presence of a 3H singlet at δ 2.19 (OAc) and two doublets at δ 5.63 and 7.70 (olefin protons of uracil) in the ^{1}H NMR of **12** confirmed the presence of the nucleoside base at the anomeric carbon of the ribose ring.

In summary, it appears that intramolecular [3+2] nitrilimine cycloaddition reaction could be applied to D-glucose derived substrates to synthesize chiral pyrazoles of diverse structures and also pyrazolonucleoside analogues. The method is very simple and capable of extension to many other carbohydrate based precursors.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 L spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were obtained using either JEOL AX-500 or Micromass Q-Tof micro™ spectrometers. IR spectra were measured on a JASCO 700 spectrophotometer. Elemental analyses were carried out with a C, H, N-analyzer. Specific rotations were measured at 589 nm on a JASCO P-1020 polarimeter. TLC was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}).

3.1.1. 1,2-*O*-Isopropylidene-3-*O*-allyl-5-aldoglucofuranose phenylhydrazones (2a *cis/trans* mixture). *Typical procedure*. Compound **1a** (3.0 g, 10.0 mmol) was dissolved in dil HOAc (75%, 50 mL) and stirred at rt for 18 h. The solvent was evaporated in vacuo and the last trace of HOAc was removed through coevaporation with toluene (3× 50 mL) to afford a crude residue, which was purified by column chromatography over silica gel using $CHCl_3$–MeOH (49:1) to afford the corresponding 5,6-dihydroxy glucose derivative (2.08 g). The material was dissolved in EtOH (40 mL); the solution was cooled to 10 °C and treated

with an aqueous solution (40 mL) of $NaIO_4$ (2.05 g, 9.6 mmol) dropwise while stirring (45 min). The reaction mixture was filtered, the filtrate was concentrated and the product was extracted with $CHCl_3$ (2×40 mL). The $CHCl_3$ solution was washed with H_2O (2×50 mL), dried (Na_2SO_4) and evaporated to give a crude aldehyde (1.37 g). Without further purification, it was treated with phenylhydrazine hydrochloride (900 mg, 6.18 mmol) and pyridine (1.0 mL), and the mixture was stirred at rt for 5 h. The solvent was evaporated and the product was extracted with $CHCl_3$ (3×25 mL). The $CHCl_3$ solution was washed with H_2O (2×25 mL), dried (Na_2SO_4) and the solvent was evaporated to yield the hydrazone mixture **2a** (1.62 g, 51%) as a sticky mass; [found: C, 64.02; H, 6.82; N, 8.58. $C_{17}H_{22}N_2O_4$ requires C, 64.13; H, 6.97; N, 8.80]; IR (KBr): ν_{max} 3305, 1648, 1601, 1585, 1318, 1257, 1100, 1004, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s), 1.49 (s), 1.51 (s), 1.55 (s), 3.97–4.14 (m), 4.30 (br s), 4.59 (m), 4.85 (br s), 5.18–5.30 (m), 5.97–6.07 (m), 6.87 (m), 7.01 (d), 7.06 (d), 7.23 (m), 7.46 (br s); ESIMS, *m*/*z*: 319 (M^++H), 341 (M^++Na).

3.1.2. 1,2-*O*-Isopropylidene-3-*O*-cyclohex-2-enyl-5-aldo-glucofuranose phenylhydrazone (2b *cis*/*trans* mixture). Sticky mass; [found: C, 66.88; H, 7.08; N, 7.59. $C_{20}H_{26}N_2O_4$ requires C, 67.02; H, 7.31; N, 7.82]; IR (KBr): ν_{max} 3330, 1645, 1601, 1321, 1262, 1072, 998, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34 (s), 1.50 (s), 1.55 (s), 1.63-2.10 (m), 3.96–4.39 (m), 4.58 (d), 4.85 (t-like), 5.70–6.06 (m, merged with a d at δ 5.97), 6.82–6.91 (m), 6.99–7.11 (m), 7.21 (t-like), 7.61 (br s); ESIMS, *m*/*z*: 359 (M^++H), 381 (M^++Na).

3.1.3. 1,2-*O*-Isopropylidene-3-*C*-allyl-5-aldoallofuranose-phenylhydrazone (2c *cis*/*trans* mixture). Gum; [found: C, 63.90; H, 6.77; N, 8.60. $C_{17}H_{22}N_2O_4$ requires C, 64.13; H, 6.97; N, 8.80]; IR (neat): ν_{max} 3472, 3312, 1640, 1600, 1256, 1079, 1007, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s), 1.40 (s), 1.63 (s), 2.14–2.29 (m), 2.39–2.48 (m), 3.60 (br s), 4.36 (d), 4.39 (d), 4.48 (d), 4.75 (d), 5.12–5.21 (m), 5.78–5.93 (m), 6.47 (d), 6.86 (t), 6.94 (d), 7.03 (t-like), 7.22 (d), 7.27 (d), 7.65 (s), 9.12 (s); ESIMS, *m*/*z*: 319 (M^++H), 341 (M^++Na).

3.1.4. (3a*R*,5a*S*,5b*R*,8a*R*,9a*R*)-7,7-Dimethyl-2-phenyl-2,3,3a,4,5a,5b,8a,9a-octahydro-5,6,8,9-tetraoxa-1,2-diaza-cyclopenta[*b*]-*as*-indacene (3); (5a*S*,5b*R*,8a*R*,9a*R*)-7,7-dimethyl-2-phenyl-2,4,5a,5b,8a,9a-hexahydro-5,6,8,9-tetraoxa-1,2-diaza-cyclopenta[*b*]-*as*-indacene (4). *Typical procedure*. To the hydrazone **2a** (636 mg, 2.0 mmol) dissolved in ethanol (40 mL) was added chloramine T (843 mg, 3.0 mmol) and the mixture was heated at reflux under N_2 for 6 h. The solvent was evaporated in vacuo and the residual mass was extracted with $CHCl_3$ (2×30 mL). The $CHCl_3$ solution was washed successively with water (2×25 mL), 1 M NaOH (20 mL), and brine (2×20 mL), and then dried (Na_2SO_4). Evaporation of the solvent furnished a reddish gummy material, which was purified by chromatography on silica gel using $CHCl_3$ as eluent to afford **3** (253 mg, 40%) and **4** (94 mg, 15%).

3.1.5. Compound 3. Gummy mass; [found: C, 64.34; H, 6.18; N, 8.58. $C_{17}H_{20}N_2O_4$ requires C, 64.54; H, 6.37; N, 8.86]; $[\alpha]_D^{25}$ = +117.4 (*c* 0.56, $CHCl_3$); IR (neat): ν_{max} 1598, 1500, 1377, 1214, 1161, 1093, 1013, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (s, 3H), 1.56 (s, 3H), 3.25–3.34 (m, 2H), 3.54–3.66 (m, 1H), 3.98 (dd, 1H, *J*=10.1, 11.5 Hz), 4.02 (d, 1H, *J*=1.9 Hz), 4.21 (dd, 1H, *J*=6.3, 10.5 Hz), 4.58 (d, 1H, *J*=3.5 Hz), 4.98 (d, 1H, *J*=1.9 Hz), 6.01 (d, 1H, *J*=3.5 Hz), 6.85 (dt, 1H, *J*=0.6, 7.3 Hz), 6.99 (dd, 2H, *J*=0.6, 7.8 Hz), 7.25–7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.7 (CH_3), 27.2 (CH_3), 41.7 (CH), 49.9 (CH_2), 71.5 (CH_2), 74.1 (CH), 83.6 (CH), 84.0 (CH), 106.4 (CH), 112.6 (C), 113.2 (2×CH), 120.0 (CH), 129.6 (2×CH), 145.6 (C), 147.0 (C); EIMS, *m*/*z*: 316 (M^+).

3.1.6. Compound 4. Sticky material; [found: C, 64.95; H, 5.73; N, 8.72. $C_{17}H_{18}N_2O_4$ requires C, 64.96; H, 5.77; N, 8.91]; $[\alpha]_D^{25}$ = +23.1 (*c* 0.4, $CHCl_3$); IR (neat): ν_{max} 1597, 1503, 1389, 1213, 1162, 1084, 1015, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 3H), 1.59 (s, 3H), 4.17 (d, 1H, *J*=2.0 Hz), 4.65 (d, 1H, *J*=13.9 Hz), 4.71 (d, 1H, *J*=3.6 Hz), 4.92 (d, 1H, *J*=13.9 Hz), 5.20 (d, 1H, *J*=2.1 Hz), 6.05 (d, 1H, *J*=3.6 Hz), 7.30 (t, 1H, *J*=7.3 Hz), 7.43 (t, 2H, *J*=8.1 Hz), 7.67 (d, 2H, *J*=7.2 Hz), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.8 (CH_3), 27.3 (CH_3), 62.7 (CH_2), 70.8 (CH), 81.2 (CH), 84.3 (CH), 106.4 (CH), 112.5 (C), 117.1 (C), 119.8 (2×CH), 121.6 (CH), 127.2 (CH), 129.8 (2×CH), 140.4 (C), 145.1 (C); FABMS, *m*/*z*: 315 (M^++1).

3.1.7. (5a*S*,6a*S*,7*R*,8*R*,9a*R*)-7,8-Isopropylidene-dioxy-3,4,5,5a,6a,7,8,9a-octahydro-2*H*-6,9-dioxa-1,2-diaza-cyclopenta[*d*]acenaphthalene (5). Foam; [found: C, 67.69; H, 6.18; N, 7.63. $C_{20}H_{22}N_2O_4$ requires C, 67.78; H, 6.26; N, 7.90]; $[\alpha]_D^{25}$ = −7.1 (*c* 0.33, $CHCl_3$); IR (KBr): ν_{max} 1597, 1503, 1380, 1217, 1162, 1077, 1017, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.37 (s, 3H), 1.58 (s, 3H), 1.81–1.90 (m, 2H), 2.15–2.24 (m, 2H), 2.68 (m, 1H), 3.00 (dd, 1H, *J*=6.0, 16.8 Hz), 4.36 (d, 1H, *J*=2.2 Hz), 4.54 (dd, 1H, *J*=5.3, 10.2 Hz), 4.69 (d, 1H, *J*=3.6 Hz), 5.28 (d, 1H, *J*=2.2 Hz), 6.02 (d, 1H, *J*=3.6 Hz), 7.30 (t, 1H, *J*=7.4 Hz), 7.42 (t, 2H, *J*=7.9 Hz), 7.62 (d, 2H, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.7 (CH_2), 24.2 (CH_2), 26.8 (CH_3), 27.4 (CH_3), 29.2 (CH_2), 71.4 (CH), 72.3 (CH), 82.7 (CH), 84.1 (CH), 106.5 (CH), 112.2 (C), 120.7 (C), 122.3 (2×CH), 127.1 (CH), 129.5 (2×CH), 136.9 (C), 140.7 (C), 143.8 (C); FABMS, *m*/*z*: 355 (M^++H).

3.1.8. (3a*R*,3b*R*,4a*R*,7b*R*)-2,2-Dimethyl-6-phenyl-3a,6,7b,8a-tetrahydro-4*H*-1,3,8-trioxa-6,7-diaza-dicyclopenta[*a*,*e*]pentalen-3b-ol (6). Foamy mass; [found: C, 64.79; H, 5.65; N, 8.87. $C_{17}H_{18}N_2O_4$ requires C, 64.96; H, 5.77; N, 8.91]; $[\alpha]_D^{25}$ = +112.7 (*c* 0.25, $CHCl_3$); IR (neat): ν_{max} 3449, 1598, 1504, 1380, 1218, 1162, 1080, 1030, 999, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.44 (s, 3H), 1.67 (s, 3H), 2.93 (d, 1H, *J*=16.2 Hz), 3.01 (d, 1H, *J*=16.2 Hz), 4.51 (d, 1H, *J*=3.6 Hz), 5.09 (s, 1H), 6.01 (d, 1H, *J*=3.6 Hz), 7.29 (1H merged signal), 7.42 (t, 2H, *J*=7.8 Hz), 7.63 (s, 1H), 7.64 (d, 2H, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.4 (CH_3), 27.8 (CH_3), 34.7 (CH_2), 82.6 (CH), 83.5 (CH), 94.6 (C), 107.2 (CH), 113.7 (C), 119.9 (2×CH), 122.4 (CH), 125.9 (C), 126.9 (CH), 129.8 (2×CH), 141.1 (C), 158.6 (C); EIMS, *m*/*z*: 314 (M^+).

3.1.9. (3a*R*,4*S*,5*R*,6a*R*)-5-(2,2-Dimethyl-[1,3]dioxolan-4*R*-yl)-2,2-dimethyl-6-prop-2-ynyloxy-tetrahydro-furo[2,3-*d*][1,3]dioxole (8). To a stirred heterogeneous

solution of **7** (1.30 g, 5.0 mmol) in dichloromethane (70 mL) and 50% NaOH (70 mL) containing *n*-tetrabutylammonium bromide (160 mg), was added propargyl bromide (893 mg, 7.5 mmol) and the mixture was stirred at rt for 12 h. The organic layer was taken out, washed with H_2O until neutral and then dried (Na_2SO_4). The solvent was evaporated and the resulting product was purified by silica gel column chromatography using $CHCl_3$–pet. ether (1:9) as the eluent to obtain **8** (1.25 g, 83%) as a thick liquid; [found: C, 60.37; H, 7.28. $C_{15}H_{22}O_6$ requires C, 60.39; H, 7.43]; IR (neat): ν_{max} 3275, 2117, 1378, 1216, 1076, 1022, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.35 (s, 3H), 1.43 (s, 3H), 1.50 (s, 3H), 2.48 (t, 1H, $J=2.3$ Hz), 3.99 (dd, 1H, $J=5.4$, 8.6 Hz), 4.07–4.11 (m, 2H), 4.14 (dd, 1H, $J=3.0$, 7.6 Hz), 4.25–4.31 (m, 3H), 4.63 (d, 1H, $J=3.6$ Hz), 5.88 (d, 1H, $J=3.6$ Hz); EIMS, *m/z*: 298 (M^+).

3.1.10. (3a*R*,4*S*,5*R*,6a*R*)-5-(2,2-Dimethyl-[1,3]dioxolan-4*R*-yl)-2,2-dimethyl-6-(3-phenyl-prop-2-ynyloxy)-tetrahydro-furo[2,3-*d*][1,3]dioxole (9a). *Typical procedure*. To a solution of **8** (2.00 g, 6.71 mmol) in dry benzene (50 mL) was added bis(triphenylphosphine)palladium dichloride (93 mg, 0.13 mmol), cuprous iodide (13 mg, 0.06 mmol), triethyl amine (4.6 mL) and iodobenzene (1.63 g, 0.9 mL), and the mixture was stirred under N_2 for 20 h at rt. After removal of the solvent under reduced pressure, the residue obtained was extracted with $CHCl_3$ (3×30 mL). The $CHCl_3$ solution was washed with water (2×20 mL), dried (Na_2SO_4) and evaporated to give a crude product, which was purified by column chromatography on silica gel. Elution with pet. ether–$CHCl_3$ (1:1) furnished **9a** (1.91 g, 76%) as a light yellowish oil; [found: C, 67.15; H, 6.90. $C_{21}H_{26}O_6$ requires C, 67.36; H, 7.00]; $[\alpha]_D^{25}=-10.5$ (*c* 0.43, $CHCl_3$); IR (neat): ν_{max} 2237, 1498, 1448, 1375, 1254, 1215, 1163, 1077, 1026, 847, 758, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.35 (s, 3H). 1.42 (s, 3H), 1.51 (s, 3H), 4.02 (dd, 1H, $J=5.6$, 8.4 Hz), 4.11 (dd, 1H, $J=6.1$, 8.4 Hz), 4.18 (m, 2H), 4.34 (dd, 1H, $J=5.8$, 11.8 Hz), 4.50 (s, 2H), 4.69 (d, 1H, $J=3.4$ Hz), 5.90 (d, 1H, $J=3.4$ Hz), 7.32 (m, 3H), 7.45 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 25.2 (CH_3), 26.1 (CH_3), 26.7 ($2\times CH_3$), 58.6 (CH_2), 67.0 (CH_2), 72.4 (CH), 80.9 (CH), 81.2 (CH), 82.6 (CH), 84.4 (C), 86.4 (C), 105.1 (CH), 108.9 (C), 111.7 (C), 128.1 ($2\times$CH), 128.4 (CH), 130.1 (C), 131.6 ($2\times$CH); FABMS, *m/z*: 375 ($M^+ +H$).

3.1.11. (3a*R*,4*S*,5*R*,6a*R*)-5-{3-[5-(2,2-Dimethyl-[1,3]dioxolan-4*R*-yl)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-6-yloxy]-prop-1-ynyl}-2,4-dimethoxy-pyrimidine (9b). Gummy material; [found: C, 57.68; H, 6.33; N, 6.19. $C_{21}H_{28}N_2O_8$ requires C, 57.79; H, 6.47; N, 6.42]; $[\alpha]_D^{25}=-5.5$ (*c* 1.5, $CHCl_3$); IR (neat): ν_{max} 2226, 1594, 1551, 1472, 1388, 1077, 1017, 848, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.36 (s, 3H), 1.46 (s, 3H), 1.51 (s, 3H), 4.02 (s, 3H), 4.05 (s, 3H), 4.09–4.18 (m, 4H), 4.32 (m, 1H), 4.53 (s, 2H), 4.70 (d, 1H, $J=3.6$ Hz), 5.90 (d, 1H, $J=3.6$ Hz), 8.34 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.8 (CH_3), 26.6 (CH_3), 27.2 ($2\times CH_3$), 54.9 (CH_3), 55.5 (CH_3), 59.3 (CH_2), 67.6 (CH_2), 73.0 (CH), 78.5 (C), 81.4 (CH), 82.0 (CH), 83.2 (CH), 91.5 (C), 105.6 (CH), 109.4 (C), 112.2 (C), 162.0 (CH), 164.7 (C), 2 quaternary C signals not observed; FABMS, *m/z*: 437 ($M^+ +H$), 459 ($M^+ +Na$).

3.1.12. (3a*R*,4*S*,5*R*,6a*R*)-5-(2,2-Dimethyl-[1,3] dioxolan-4*R*-yl)-2,2-dimethyl-6-(3-thiophen-2-yl-prop-2-ynyloxy)-tetrahydro-furo[2,3-*d*][1,3]dioxole (9c). Gum; [found: C, 59.67; H, 6.38. $C_{19}H_{24}O_6S$ requires C, 59.98; H, 6.36]; $[\alpha]_D^{25}=-5.53$ (*c* 0.75, $CHCl_3$); IR (neat): ν_{max} 2222, 1375, 1253, 1214, 1163, 1077, 1024, 847, 706 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.50 (s, 3H), 4.01 (dd, 1H, $J=5.4$, 8.5 Hz), 4.10 (dd, 1H, $J=6.1$, 8.4 Hz), 4.15 (m, 2H), 4.29–4.35 (m, 1H), 4.51 (s, 2H), 4.67 (d, 1H, $J=3.6$ Hz), 5.90 (d, 1H, $J=3.6$ Hz), 6.98 (dd, 1H, $J=3.7$, 4.9 Hz), 7.23 (d,1H, $J=3.4$ Hz), 7.27 (d, 1H, $J=4.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.8 (CH_3), 26.6 (CH_3), 27.2 ($2\times CH_3$), 59.3 (CH_2), 67.6 (CH_2), 72.9 (CH), 80.2 (C), 81.5 (CH), 81.9 (CH), 83.2 (CH), 89.0 (C), 105.6 (CH), 109.4 (C), 112.2 (C), 122.7 (C), 127.3 (CH), 127.9 (CH), 132.9 (CH). FABMS, *m/z*: 381 ($M^+ +H$), 403 ($M^+ +Na$).

3.1.13. (5a*S*,5b*R*,8a*R*,9a*R*)-7,7-Dimethyl-2,3-diphenyl-2,4,5a,5b,8a,9a-hexahydro-5,6,8,9-tetraoxa-1,2-diaza-cyclopenta[*b*]-*as*-indacene (10a). The reaction was carried out according to the method adopted for **3**. Thus, the hydrazone (392 mg, 1.0 mmol) derived from **9a** as described was dissolved in ethanol (40 mL), treated with chloramine T (418 mg, 1.5 mmol) and heated at reflux for 6 h under N_2. Usual work-up followed by purification using silica gel column chromatography and $CHCl_3$–MeOH (99.5:0.5) as eluent afforded **10a** (273 mg, 70%) as a thick gum; [found: C, 70.69; H, 5.55; N, 6.91. $C_{23}H_{22}N_2O_4$ requires C, 70.75; H, 5.68; N, 7.17]; $[\alpha]_D^{25}=-4.0$ (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 1596, 1498, 1448, 1373, 1216, 1162, 1081, 1015, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 3H), 1.59 (s, 3H), 4.24 (d, 1H, $J=1.8$ Hz), 4.72 (d, 1H, $J=3.6$ Hz), 4.77 (s, 2H), 5.24 (d, 1H, $J=1.9$ Hz), 6.08 (d, 1H, $J=3.6$ Hz), 7.07 (m, 2H), 7.31 (br s, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.9 (CH_3), 27.3 (CH_3), 63.1 (CH_2), 71.1 (CH), 81.3 (CH), 84.3 (CH), 106.5 (CH), 112.5 (C), 115.7 (C), 125.5 ($2\times$CH), 127.9 (CH), 128.9 (CH), 129.1 ($2\times$CH), 129.3 ($4\times$CH), 129.9 (C), 137.2 (C), 140.1 (C), 144.2 (C); ESIMS, *m/z*: 413 ($M^+ +Na$), 803 ($2M^+ +Na$).

3.1.14. (5a*S*,5b*R*,8a*R*,9a*R*)-3-(2,4-Dimethoxypyrimidin-5-yl)-7,7-dimethyl-2-phenyl-2,4,5a,5b,8a,9a-hexahydro-5,6,8,9-tetraoxa-1,2-diaza-cyclopenta[*b*]-*as*-indacene (10b). Foamy solid; [found: C, 60.88; H, 5.32; N, 12.19. $C_{23}H_{24}N_4O_6$ requires C, 61.05; H, 5.35; N, 12.38]; $[\alpha]_D^{25}=+3.5$ (*c* 1.38, $CHCl_3$); IR (KBr): ν_{max} 1735, 1613, 1572, 1552, 1480, 1455, 1391, 1082, 1015, 758, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 3H), 1.58 (s, 3H), 3.78 (s, 3H), 3.99 (s, 3H), 4.23 (d, 1H, $J=2.0$ Hz), 4.66–4.72 (m, 3H), 5.23 (d, 1H, $J=2.1$ Hz), 6.07 (d, 1H, $J=3.5$ Hz), 7.28–7.36 (m, 5H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.8 (CH_3), 27.3 (CH_3), 54.4 (CH_3), 55.5 (CH_3), 62.9 (CH_2), 70.9 (CH), 81.3 (CH), 84.3 (CH), 105.6 (C), 106.5 (CH), 112.5 (C), 117.2 (C), 124.7 ($2\times$CH), 128.2 (CH), 129.2 (C), 129.4 ($2\times$CH), 140.3 (C), 144.2 (C), 159.4 (CH), 165.9 (C), 168.3 (C); ESIMS, *m/z*: 475 ($M^+ +Na$).

3.1.15. (5a*S*,5b*R*,8a*R*,9a*R*)-7,7-Dimethyl-2-phenyl-3-thiophen-2-yl-2,4,5a,5b,8a,9a-hexahydro-5,6,8,9-tetraoxa-1,2-diaza-cyclopenta[*b*]-*as*-indacene (10c). Foamy solid; [found: C, 63.68; H, 5.05; N, 6.94. $C_{21}H_{20}N_2O_4S$ requires C, 63.62; H, 5.08; N, 7.07]; $[\alpha]_D^{25}=+5.27$ (*c* 0.56,

$CHCl_3$); IR (KBr): ν_{max} 1736, 1596, 1498, 1455, 1376, 1219, 1162, 1085, 1016, 759, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 3H), 1.58 (s, 3H), 4.22 (d, 1H, J= 1.6 Hz), 4.72 (d, 1H, J=3.8 Hz), 4.73 (d, 1H, J=13.4 Hz), 4.90 (d, 1H, J=14.1 Hz), 5.21 (d, 1H, J=1.9 Hz), 6.07 (d, 1H, J=3.5 Hz), 6.72 (dd, 1H, J=0.9, 3.5 Hz), 6.97 (dd, 1H, J=3.7, 5.0 Hz), 7.31–7.37 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.9 (CH_3), 27.3 (CH_3), 63.1 (CH_2), 70.9 (CH), 81.1 (CH), 84.2 (CH), 106.5 (CH), 112.5 (C), 115.9 (C), 126.3 (2×CH), 127.6 (CH), 127.9 (CH), 128.2 (CH), 128.7 (CH), 129.3 (CH), 129.5 (CH), 130.4 (C), 131.5 (C), 140.0 (C), 144.1 (C); ESIMS, *m/z*: 419 (M^++Na), 815 ($2M^+$+Na).

3.1.16. (6*R*,7*R*)-Acetic acid-6-acetoxymethyl-2-phenyl-2,4,6,7-tetrahydro-pyrano [4,3-*c*] pyrazol-7-yl ester (11). Compound **4** (314 mg, 1.0 mmol) was dissolved in 4% H_2SO_4 in CH_3CN–H_2O (3:1) (25 mL) and kept at rt for 24 h. The acidic solution was neutralized with solid $CaCO_3$, filtered, and the filtrate was evaporated in vacuo. The residue was dissolved in EtOH (20 mL) and treated dropwise at 10 °C with an aqueous solution (20 mL) of $NaIO_4$ (314 mg, 1.0 mmol) with stirring for 45 min. Usual work-up followed by $NaBH_4$ reduction in MeOH (30 mL) afforded an alcohol, which was acetylated with Ac_2O (0.5 mL) in pyridine (1.5 mL) at rt for 12 h to furnish a crude product. The product was purified by silica gel column chromatography using pure $CHCl_3$ as an eluent to afford **11** (119 mg, 36%) as a thick gum; [found: C, 61.68; H, 5.28; N, 8.30. $C_{17}H_{18}N_2O_5$ requires C, 61.81; H, 5.49; N, 8.48]; $[\alpha]_D^{25}=-74.5$ (*c* 0.52, $CHCl_3$); IR (neat): ν_{max} 1743, 1598, 1503, 1371, 1225, 1049, 958, 758, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.11 (s, 6H), 4.01–4.06 (m, 1H), 4.27 (dd, 1H, J=7.2, 11.5 Hz), 4.36 (dd, 1H, J=5.3, 11.5 Hz), 4.75 (d, 1H, J=14.0 Hz), 5.05 (d, 1H, J= 14.0 Hz), 6.16 (d, 1H, J=1.9 Hz), 7.29 (t, 1H, J=7.6 Hz), 7.44 (t, 2H, J=8.1 Hz), 7.66 (d, 2H, J=7.9 Hz), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.6 (CH_3), 20.8 (CH_3), 62.6 (CH), 62.8 (CH_2), 63.1 (CH_2), 75.6 (CH), 116.9 (C), 119.3 (2×CH), 121.2 (CH), 126.8 (CH), 129.3 (2×CH), 139.8 (C), 145.5 (C), 169.9 (C), 170.5 (C); ESIMS, *m/z*: 353 (M^++Na).

3.1.17. (5a*S*,6*R*,7*R*,8a*R*)-Acetic acid-7-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-2-phenyl-2,4,5a,6,7,8a-hexahydro-5,8-dioxa-1,2-diaza-*as*-indacen-6-yl ester (12). 2,4-Bis-(trimethyl silyloxy)pyramidine was prepared by refluxing a mixture of uracil (336 mg, 3.0 mmol) and trimethylsilyl chloride (2 drops) dissolved in hexamethyl disilazane (7 mL) under N_2 for 10 h. The residue obtained after evaporation of the solvent in vacuo was dissolved in acetonitrile (5 mL) and added to a solution of the diacetate mixture (358 mg, 1.0 mmol) in acetonitrile (5 mL) [generated from **4** through opening of 1,2-*O*-isopropylidene group followed by acetylation] and TMS–OTf (0.5 mL). The mixture was stirred for 6 h at rt under N_2. TLC showed complete disappearance of the starting material. The solution was neutralized with solid $NaHCO_3$, treated with water (3 drops), and the solvent was evaporated in rotary evaporator. The gummy material was extracted with $CHCl_3$ (2×25 mL), the $CHCl_3$ solution was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by silica gel column chromatography eluting with $CHCl_3$–MeOH mixture (49.5:0.5) to afford **12** (193 mg, 47%) as a foamy solid; [found C, 58.60; H, 4.38; N, 13.40. $C_{20}H_{18}N_4O_6$ requires C, 58.53; H, 4.42; N, 13.65]; $[\alpha]_D^{25}=+73.7$ (*c* 0.95, $CHCl_3$); IR (KBr): ν_{max} 3408, 1747, 1688, 1503, 1459, 1391, 1221, 1060, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.19 (s, 3H), 4.20 (d, 1H, J= 2.2 Hz), 4.71 (d, 1H, J=14.1 Hz), 4.98 (d, 1H, J=14.1 Hz), 5.18 (d, 1H, J=2.2 Hz), 5.27 (br s, 1H), 5.63 (d, 1H, J= 8.0 Hz), 6.21 (d, 1H, J=1.1 Hz), 7.33 (t, 1H, J=7.4 Hz), 7.44–7.49 (m, 3H), 7.70 (d, 2H, J=7.8 Hz), 7.77 (s, 1H), 8.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.2 (CH_3), 62.9 (CH_2), 72.9 (CH), 79.9 (CH), 81.5 (CH), 90.5 (CH), 102.7 (CH), 116.7 (C), 119.8 (2×CH), 121.9 (CH), 127.6 (CH), 129.9 (2×CH), 140.2 (C), 141.0 (CH), 143.5 (C), 150.3 (C), 163.2 (C), 169.7 (C); ESIMS, *m/z*: 433 (M^++Na), 843 ($2M^+$+Na).

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