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Stereoselective synthesis of polyoxygenated linear diaza-triquinanes via intramolecular 1,3-dipolar cycloaddition of sugar-derived hex-5-enals

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ABSTRACT

An efficient and stereoselective synthesis of diaza-triquinanes, the skeleton structures of many natural products, has been accomplished by intramolecular 1,3-dipolar cycloaddition of azomethine imine generated from sugar-derived hex-5-enal and pyrazolidin-3-one.

1. Introduction

The polyquinane natural products have generated a great deal of interest among synthetic chemists in the last two decades, because of their wide distribution in nature, their unique and fascinating molecular architecture, and their interesting biological activities.[1] Among the isolated polyquinanes, the ones with triquinane framework are more abundant and some linearly fused triquinanes (Fig. 1) show interesting biological activities. For example, hirsutic acid (**B**) has antibiotic activity and coriolin (**C**) shows antibacterial and antitumor activities.[2] (+)-Connatusin A (**E**) is a newly isolated compound from the culture broth of fungus *Lentinus connatus* BCC 8996.[3] It has been suggested that the linear triquinane-based compounds could act as serotonin 5-HT_6 receptor antagonists for the treatment of Alzheimer's disease.[4] As shown in Fig. 1, most of the linear triquinane natural products have hydroxyl substitutions (compounds **B**–**E**); in addition, natural compounds (**C**) and (**E**) have a carbonyl group in one of the five-membered rings.

Several strategies, especially the cascade radical methods,[5] have been employed in the synthesis of this family of natural products. And despite the wealth of literature available for the isolation of carbocyclic triquinanes, there are only a few reports on the isolation or syntheses of the structurally novel and biologically potent siblings, such as oxa-, dioxatriquinanes,[6] aza- and diazatriquinanes.[7]

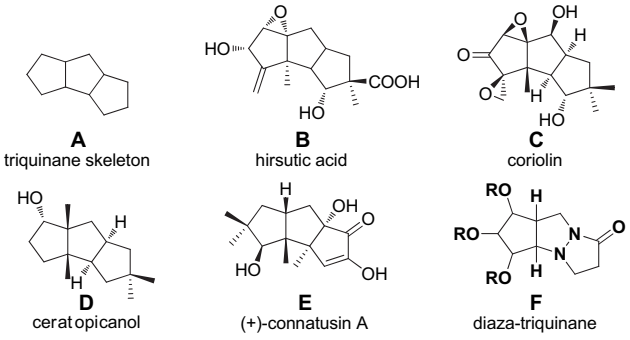

Fig. 1. Structures of some triquinane natural products and derivatives.

Carbohydrates have been used as synthetic chiral auxiliaries or chiral building blocks in asymmetric transformations because of their known absolute stereochemistry and availability.[8] 1,3-Dipolar cycloaddition reaction of azomethine imine is an important tool for the preparation of diazacyclic ring compounds or nitrogen substituted compounds. For instance, stereocontrolled or stereoselective 1,3-dipolar cycloaddition of azomethine imine derived from pyrazolidin-3-one have been investigated extensively.[9] Although several sugar templates have been selected for the construction of oxa-, dioxatriquinanes by cascade radical reaction recently,[10] and 1,3-dipolar cycloaddition of sugar-derived azomethine imine has been used to construct bicyclic compounds,[11] there

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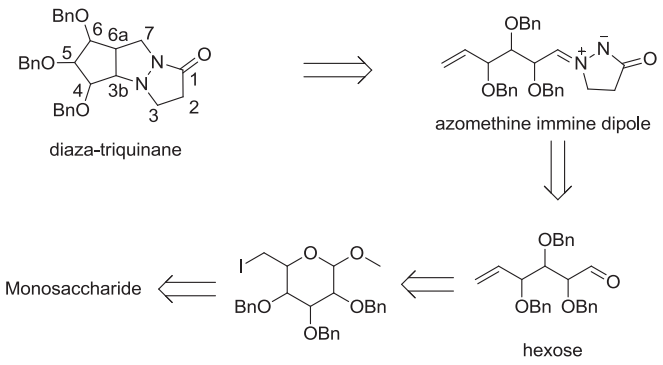
is still no published report on the synthesis of diaza-triquinanes via intramolecular cycloaddition of azomethine imine derived from carbohydrates.

Hex-5-enals derived from carbohydrates were most valuable synthons, used in total synthesis of natural products and asymmetric synthesis,[12] as well as pyrazolidin-3-ones, which were good substances for constructing aza-cycloskeletons, were now just only used in the intermolecular cycloaddition reactions.[13] Herein we report an efficient and stereoselective synthesis of a series of multifunctional diaza-triquinanes (**E** in Fig. 1) as triquinane skeleton mimics using intramolecular 1,3-dipolar cycloaddition of sugar-derived hex-5-enals with various pyrazolidin-3-ones, and the prediction model of the asymmetric reaction is of great value for further research.

2. Results and discussion

As shown in Scheme 1, the construction of a linear diaza-triquinane ring system was envisaged through a 1,3-dipolar cycloaddition reaction involving an azomethine imine dipole and an internal olefin. The templates for such reaction could be obtained from methyl 6-deoxy-6-iodo-hexosides through one-step reductive reaction, which were useful synthons and could be conveniently realized from monosaccharides.



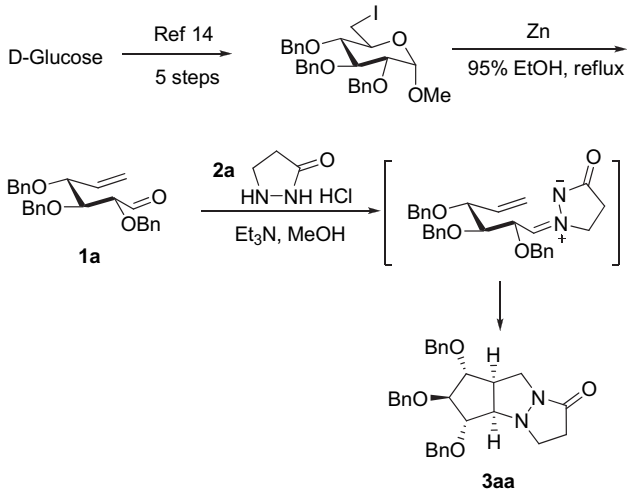
Scheme 1. Retrosynthesis of linear diaza-triquinanes.

The reaction of (2*R*,3*S*,4*R*)-2,3,4-tris(benzyloxy)hex-5-enal (**1a**)[12b,14] with pyrazolidin-3-one hydrochloride (**2a**) in MeOH at room temperature with Et_3N as base furnished 3b*S*,6a*R*-cis cycloadduct (**3aa**) as the single isomer in 83% yield. The generation of the azomethine imine dipolar intermediate by the condensation of hex-5-enal with pyrazolidin-3-one was rapid. The subsequent intramolecular cycloaddition proceeded smoothly and stereoselectively and completed in 2 h as indicated by TLC (Scheme 2).

In order to optimize the reaction conditions, we initially examined the reaction of 4 M hex-5-enal (**1a**) with pyrazolidin-3-one hydrochloride (**2a**) in MeOH at room temperature (Table 1: entries 1–5), and found that the choice of base has some impact on the reaction. Cycloadduct **3aa** was obtained in higher yield using Et_3N and pyridine (83% yield, entry 1 and 84% yield, entry 5) comparing with other bases used (entries 1–4). Et_3N was chosen because of its easier removal than pyridine.

Afterward, we examined the reaction in MeOH using Et_3N as base at room temperature (Table 1: entries 1, 6, 7) and found that 0.1 M hex-5-enal concentration (88% yield; entry 7) was slightly better than other concentrations (entries 1, 6). Comparing with the reported conditions of the two-step reactions,[9] our optimized reaction conditions were milder and the yields were higher.

We suspect that the stereoselectivity was introduced by the two chiral centers at the adjacent positions of aldehyde and olefin. Cycloaddition reactions of five different hex-5-enals (**1a**–**1e**)[13] with pyrazolidin-3-one hydrochloride (**2a**) in the presence of Et_3N were



Scheme 2. Synthesis of linear diaza-triquinane from D-glucose.

Table 1
Reaction of (2*R*,3*S*,4*R*)-2,3,4-tris(benzyloxy)hex-5-enal (**1a**) with pyrazolidin-3-one hydrochloride (**2a**)[a]

Entry	Solvent	Concentration (M)	Base	Yield[b] (%)
1	MeOH	4	Et_3N	83
2	MeOH	4	DBU	74
3	MeOH	4	DBN	79
4	MeOH	4	DIPEA	58
5	MeOH	4	Py	84
6	MeOH	1	Et_3N	82
7	MeOH	0.1	Et_3N	88

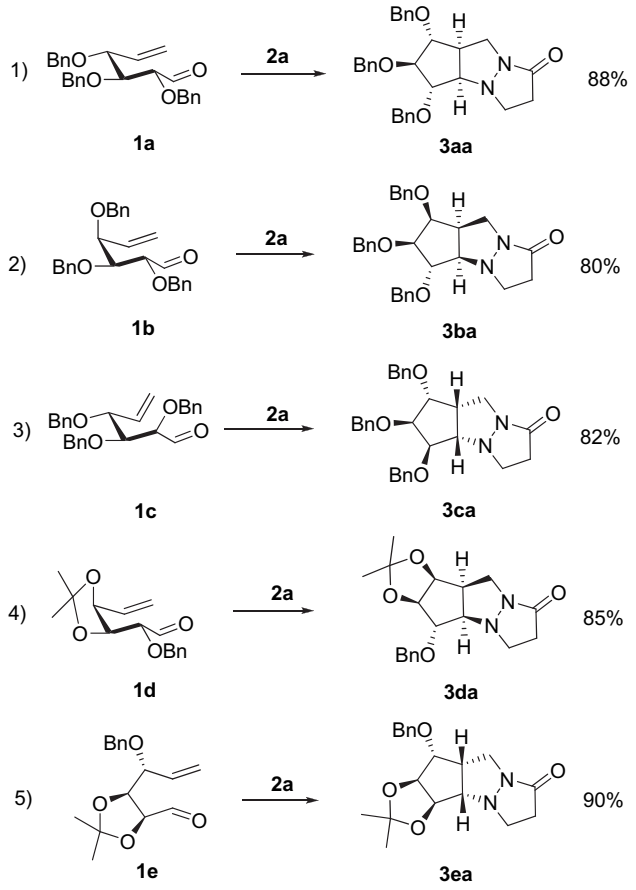
[a] Standard reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), base (2.2 mmol), rt, 2 h.
[b] Isolated yields.

carried out to verify this hypothesis (Scheme 3). The cycloadduct with the (3b*S*,6a*R*)-cis-configuration was characterized as the only respective isomer of the reactions of **1a**, **1b**, **1d** with **2a**, whereas the reactions of **1c**, **1e** with **2a** produced the (3b*R*,6a*R*)-cis-configurational cycloadducts. These results indicate that the chiral center next to the aldehyde controls the stereoselectivity of the cyclization product.

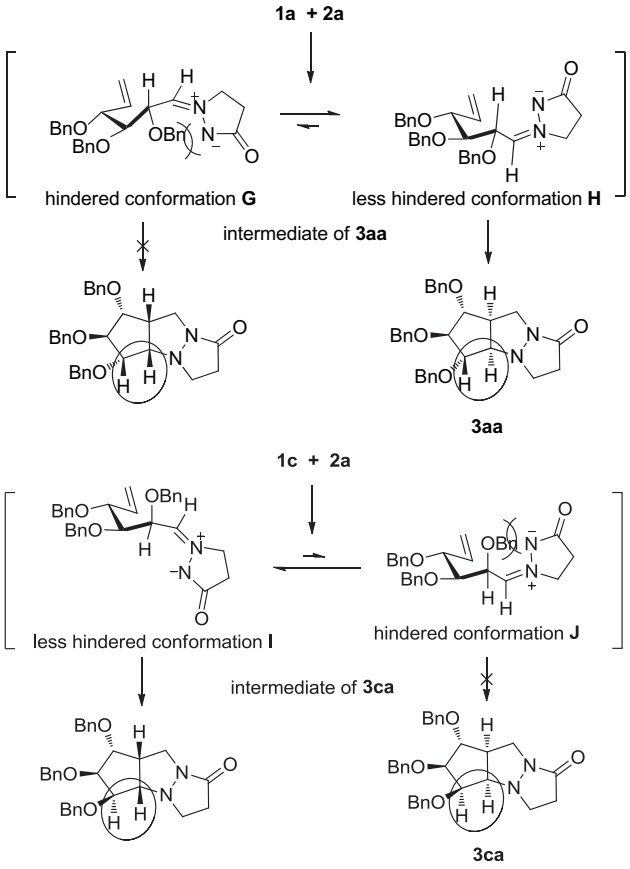
A plausible pathway was proposed to explain the specific cycloaddition stereochemistry (Scheme 4). Conformation **H** of the azomethine imine intermediate of **1a** with H-1 and H-2 at *anti*-positions was preferred for its less steric hindrance, and the (3b*S*,6a*R*)-cis product **3aa** was formed predominantly. The C1–C2 staggered conformation **G** is disfavored because of the steric hindrance from the dipole and 2-OBn. Despite the different stereochemistry and substitutions at 3-, 4-positions, **1a**, **1b**, **1d** with 2*S* configuration all formed the H-3b, H-4 *trans* diaza-triquinanes. In contrast, the cycloaddition of **1c** (or **1e**) with **2a** formed (3b*R*,6a*R*)-*cis* diaza-triquinane **3ca** (or **3ea**). Less hindered conformation **I** with *anti*-H-1 and H-2 was preferred and produced the final product **3ca** (or **3ea**) with cis-H-3b and H-6a, and trans-H-3b and H-4.

As listed in Schemes 3 and 4, the unique obtained cycloadducts have the similar configuration in which H-3b and H-4 is trans, that was owed to the chiral center of C-2. And the model substances could be used in other reactions to control the stereoselectivity.

When the same reaction was carried out with racemic 4-methylpyrazolidin-3-one, 5-methylpyrazolidin-3-one, and 5-phenylpyrazolidin-3-one, a series of diaza-triquinane derivatives were obtained in good yields (Scheme 5). The additional chiral centers on pyrazolidin-3-ones did not affect the stereoselectivity of ring junction. Two diastereoisomers were isolated readily by column chromatography for each reaction.



Scheme 3. Stereocontrolled cycloaddition of hex-5-enals (**1a**–**1e**) with pyrazolidin-3-one hydrochloride (**2a**).



Scheme 4. Proposed conformations of azomethine imine intermediates.

The reaction of 5-phenylpyrazolidin-3-one with hex-5-enals (**1a**, **1d**, **1e**) showed moderate selectivity with the *R*-configuration (see Scheme 5), which could be explained by the steric hindrance between 3-Ph and the formed cyclopentane ring. And 3*S*-conformation of isomer **3ed** became the major product as the temperature increased (Table 2).

3. Structural determination

The structure and the stereochemistry of all the diaza-triquinane products were determined by analysis of their ^{1}H, ^{13}C, $^{1}H-^{1}H$-COSY and NOE NMR spectra. The absolute configurations of the diaza-triquinane compounds were determined by establishing the relative stereochemistry of the two newly formed stereocenters to those already known in the starting materials. The configurations of the three secondary carbons of hex-5-enals should remain the same during the dehydration-dipolar cycloaddition reactions. The two protons H-3b and H-6a at the ring junction positions should be in a cis-configuration, which was supported by the significant NOE enhancements between them. A trans configuration would be unstable because of the high ring constrain.

Using compound **3ca** as one example, we assigned the NMR peaks at 4.23 ppm to H-6, 4.09 ppm to H-5, 3.69 ppm to H-4, 3.13 ppm to H-6a, and 2.97 ppm to H-3b (Fig. 2). And we used NOE experiments to confirm the stereochemical assignments. The selective irradiation of H-6a resulted in the loss of coupling in the signal of H-6, H-3b, and H-7, indicating that these protons are spatially close to each other and H-6, H-6a, and H-3b are cis to each other. NOE enhancement between H-4 and H-3b was also observed but it is weaker than that of H-6a and H-3b. These NOE results demonstrate that the configurations of the two newly formed chiral carbons were 3b*R* and 6a*R*, respectively.

The configurations of 2- or 3-substituted diaza-triquinane compounds were also determined by the NOE experiments. For example, cis-H-3 and H-4 was found in compound **3dd**-*R* since they show 5.0% NOE enhancement; on the contrary, trans-H-3 and H-4 was found in compound **3dd**-*S* because no NOE enhancement was observed.

Because the signal peaks of **3aa** overlapped with each other and a definite assignment of the configuration was not possible, compound **3aa** was transformed into (4*R*,5*S*,6*S*)-4,5,6-tribenzoyloxy-octahydrocyclopenta[*c*]pyrazol[1,2-*a*]pyrazolidin-1-one (**5aa**) by catalytic hydrogenation and benzoylation. The configuration of compound **5aa** was determined to be 3b*S*,6a*R*-cis using the method described above (Scheme 6).

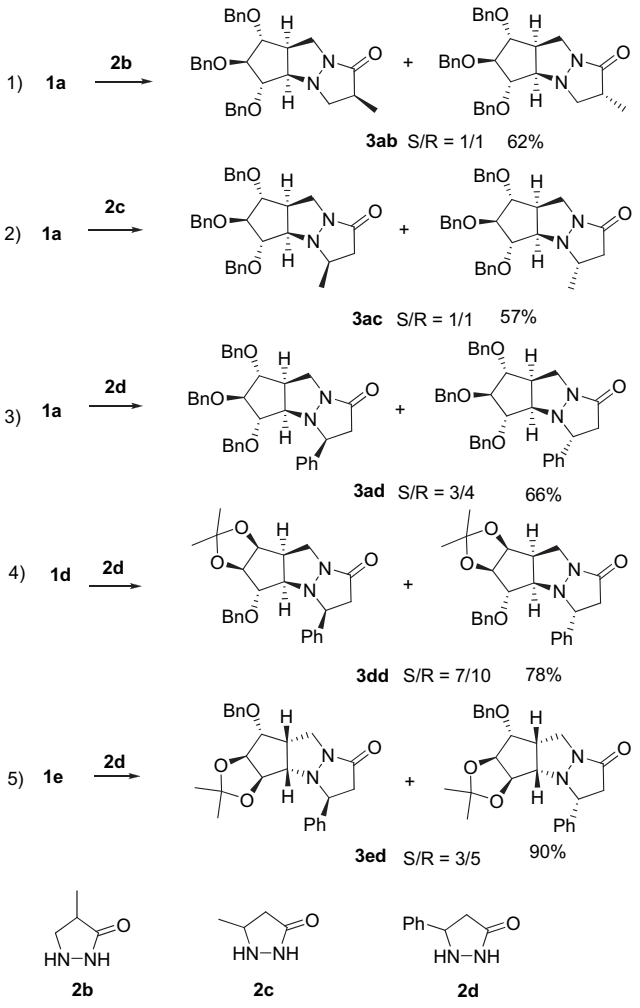
4. Conclusion

We have developed a novel, highly efficient and stereocontrolled method for the synthesis of diaza-triquinane derivatives through 1,3-dipolar cycloaddition using sugar-derived hex-5-enals as chiral synthons. The bioactivities of these multifunctional natural product-like molecules will be assayed in a high content screening process.

5. Experimental

5.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 instrument using TMS as the internal standard. Mass spectra were



Scheme 5. Synthesis of diaza-triquinane using pyrozolidin-3-one derivatives.

Table 2
Influence of temperature on substrate-selectivity

Entry	Hex-5-enal	Pyrazolidin-3-one	T (°C)	S/R[a]	Yield[b]
1	**1e**	**2d**	−40[c]	3/4	68
2	**1e**	**2d**	20	3/5	90
3	**1e**	**2d**	60	7/5	94

[a] Determined by ^{1}H NMR experiment.
[b] Isolated yield.
[c] There was azomethine imine intermediate left in the reaction solution.

obtained on an IBIMDS Sciex QStar mass spectrometer. Optical rotations were measured at 25 °C using an Optical Activity AA10R automatic polarimeter. TLC was performed on glass plates coated with Silica Gel GF_{254} (Merck). Column chromatography was performed on Silica Gel H60 (Haiyang Chemical Factory, Qingdao, Shandong, China). Solvents were purified by standard procedures.

5.2. General procedure for the preparation of 1a–1e[12b,14a–d]

To a solution of 6-iodide (1 mmol) in 95% EtOH (10 mL) activated Zn (654 mg, 10 mmol) was added and the mixture was refluxed with vigorous stirring until complete disappearance of 6-iodide (0.5–2 h). The mixture was cooled to room temperature, the solids were filtered off, and the solvent was evaporated and the crude product was subjected to chromatography on silica gel using petroleum/acetoacetate (20:1) as eluent to give pure aldehydes **1a**–**1e**.

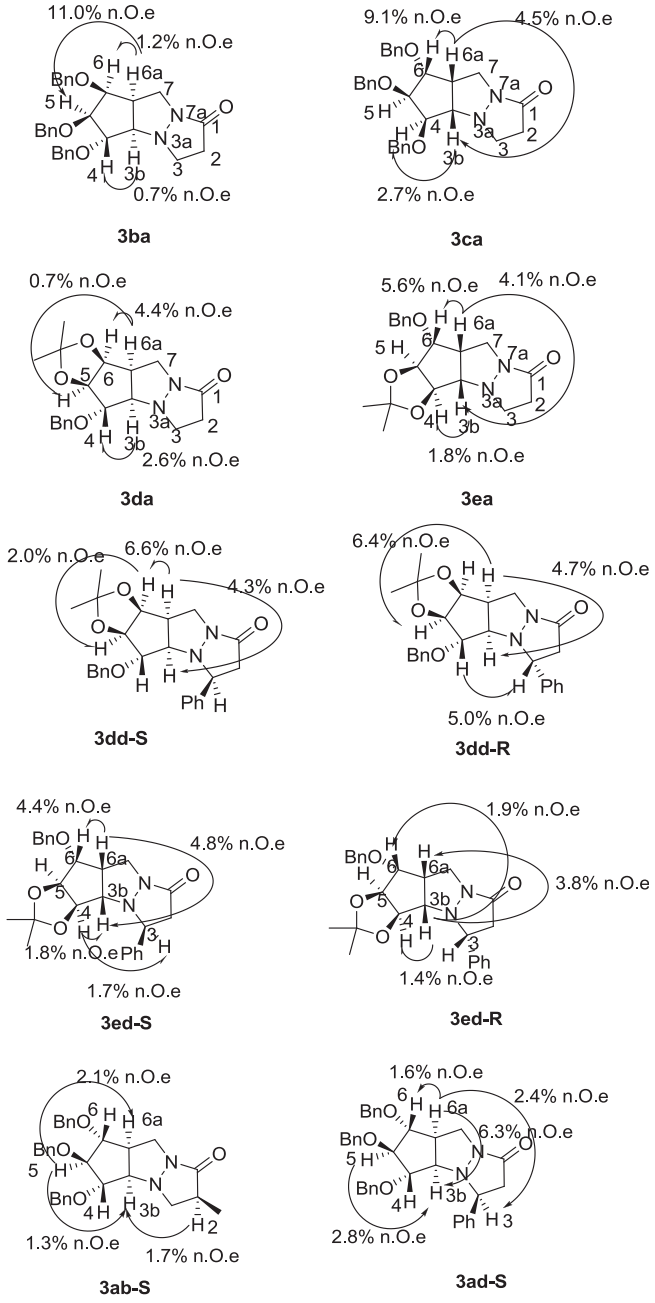
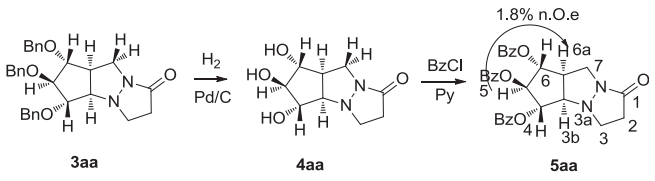


Fig. 2. NOE enhancement in diaza-quinane compounds.



Scheme 6. Configuration determination of compound **3aa** after derivation.

5.2.1. (2R,3S,4R)-2,3,4-Tris(benzyloxy)hex-5-enal[14b] ***1a***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H, H-1), 7.69–6.95 (m, 15H), 5.82 (ddd, J=16.6, 11.0, 7.7 Hz, 1H, H-5), 5.54–5.08 (m, 2H, H-6, 6′), 4.71 (dd, J=11.7, 1.7 Hz, 2H), 4.58 (d, J=11.7 Hz, 1H), 4.53 (d, J=11.5 Hz, 1H), 4.48 (d, J=11.8 Hz, 1H), 4.36 (d, J=11.5 Hz, 1H), 4.15 (dd, J=7.5, 5.0 Hz, 1H), 3.93–3.61 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.71, 138.00, 137.85, 137.38, 134.96, 128.65, 128.52, 128.49, 128.46, 128.40,

128.32, 128.27, 128.06, 127.75, 119.54, 82.56, 81.92, 80.09, 77.55, 77.23, 76.91, 74.65, 73.40, 71.09.

5.2.2. (2R,3S,4S)-2,3,4-Tri(benzyloxy)hex-5-enal[12b,14c] ***1b***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75–9.50 (m, 1H, H-1), 7.44–7.06 (m, 15H), 5.98–5.81 (m, 1H, H-5), 5.49–5.39 (m, 2H, H-6, 6′), 4.70–4.44 (m, 5H), 4.18 (dd, J=11.4, 4.7 Hz, 1H), 4.08 (dd, J=7.6, 6.1 Hz, 2H), 3.87 (dd, J=7.5, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.81, 138.08, 137.73, 137.42, 135.76, 128.65, 128.53, 128.47, 128.39, 128.28, 128.04, 127.83, 120.51, 84.14, 81.41, 79.46, 77.55, 77.23, 76.91, 74.51, 73.64, 70.31.

5.2.3. (2S,3S,4R)-2,3,4-tris(benzyloxy)hex-5-enal[14b] ***1c***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, J=1.5 Hz, 1H, H-1), 7.45–7.14 (m, 15H), 5.87 (ddd, J=18.0, 10.3, 7.8 Hz, 1H, H-5), 5.35 (ddd, J=10.4, 8.5, 1.0 Hz, 2H, H-6, 6′), 4.75–4.57 (m, 4H), 4.48 (d, J=11.7 Hz, 1H), 4.36 (d, J=11.8 Hz, 1H), 4.15–4.03 (m, 2H), 3.88 (dd, J=5.6, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.84, 138.28, 138.05, 137.51, 135.30, 128.62, 128.52, 128.48, 128.21, 128.13, 128.08, 127.91, 127.79, 120.07, 83.81, 83.01, 80.71, 77.55, 77.23, 76.91, 74.30, 72.98, 70.94.

5.2.4. (2R,3S,4S)-3,4-O-Isopropylidenedioxy-2-benzyloxyhex-5-enal[14c,d] ***1d***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, J=1.4 Hz, 1H, H-1), 7.60–7.10 (m, 6H), 5.93 (ddd, J=17.5, 10.4, 7.3 Hz, 1H, H-5), 5.36 (dt, J=17.3, 1.3 Hz, 1H, H-6), 5.30–5.18 (m, 1H, H-6′), 4.46 (dd, J=6.8, 4.0 Hz, 1H), 3.77 (dd, J=4.0, 1.4 Hz, 1H), 1.54 (s, 4H), 1.36 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.63, 137.30, 133.83, 128.64, 128.19, 128.06, 119.50, 109.83, 82.85, 78.92, 78.52, 77.55, 77.23, 76.91, 73.29, 26.94, 25.42.

5.2.5. (2S,3S,4R)-2,3-O-Isopropylidenedioxy-4-benzyloxyhex-5-enal ***1e***. $[\alpha]_D^{25}$ −20.0 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, J=1.9 Hz, 1H, H-1), 7.77–6.93 (m, 5H), 5.94 (ddd, J=17.2, 10.4, 8.1 Hz, 1H, H-5), 5.62–4.97 (m, 2H, H-6, 6′), 4.51–4.48 (m, 1H), 4.46 (d, J=11.1 Hz, 1H), 4.38 (dd, J=8.1, 1.9 Hz, 1H), 4.08 (d, J=11.4 Hz, 1H), 3.79 (dd, J=8.1, 2.3 Hz, 1H), 1.59 (s, 4H), 1.37 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.38, 137.97, 134.34, 128.39, 127.56, 127.53, 120.10, 111.33, 82.93, 80.64, 77.98, 77.55, 77.23, 76.91, 69.80, 26.68, 25.21; HRMS (ES) m/z calcd for $C_{16}H_{20}O_4$ $[M+H]^+$: 276.1362, found: 277.14456.

5.3. General procedure for the preparation of cycloadducts 3aa–3ea

A solution of **1a**–**e** (1.0 mmol), 3-pyrazolidinone hydrochloride **2a** (1.2 mmol), and Et_3N (2.2 mmol) in MeOH (10 mL) was stirred at room temperature for 2 h. The solvent and Et_3N were removed in vacuo and the crude product was subjected to chromatography on silica gel using DCM/MeOH (100:1) as the eluting solvent.

5.3.1. (3bS,4R,5S,6S,6aR)-4,5,6-Tris(benzyloxy)octahydrocyclopenta[c]pyrazol[1,2-a]pyrazolidin-1-one ***3aa***. $[\alpha]_D^{25}$ −6.0 (c 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.10 (m, 15H), 4.80–4.51 (m, 6H), 4.13 (t, J=7.2 Hz, 1H, H-5), 3.97–3.88 (m, 2H, H-4, 7), 3.86 (dd, J=6.6, 1.9 Hz, 1H, H-6), 3.53 (ddd, J=10.8, 8.8, 6.5 Hz, 1H, H-3), 3.03–2.86 (m, 4H, H-6a, 7′, 3b, 3′), 2.68–2.49 (m, 2H, H-2, 2′); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.79, 138.29, 137.92, 137.77, 128.59, 128.45, 128.03, 128.00, 127.87, 127.84, 127.80, 127.74, 90.56, 86.25, 84.28, 72.74, 72.37, 70.98, 48.31, 48.15, 45.47, 32.75; HRMS (ES) m/z calcd for $C_{30}H_{32}N_2O_4$ $[M+H]^+$: 485.2440, found: 485.2454.

5.3.2. (3bS,4R,5S,6R,6aR)-4,5,6-Tris(benzyloxy)octahydrocyclopenta[c]pyrazol[1,2-a]pyrazolidin-1-one ***3ba***. $[\alpha]_D^{25}$ −25.3 (c 1.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–6.83 (m, 15H), 4.81 (d, J=12.3 Hz, 1H), 4.69–4.55 (m, 5H), 4.17 (dd, J=5.9, 3.0 Hz, 1H, H-4), 3.96–3.87 (m, 2H, H-5, 6), 3.75 (dd, J=11.2, 9.7 Hz, 1H, H-7), 3.65 (ddd, J=10.3, 9.2, 5.5 Hz, 1H, H-3), 3.48 (dd, J=10.6, 6.3 Hz, 1H, H-7′), 3.07 (ddd, J=15.9, 7.8, 4.8 Hz, 1H, H-6a), 2.97 (dd, J=9.8, 2.9 Hz, 1H, H-3b), 2.93 (dd, J=17.8, 7.6 Hz, 1H, H-3′), 2.73 (dt, J=17.6, 8.9 Hz, 1H, H-2), 2.60 (ddd, J=16.6, 9.3, 5.5 Hz, 1H, H-2′); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.96, 138.32, 138.26, 138.13, 128.71, 128.65, 128.62, 128.17, 128.09, 128.01, 127.92, 127.77, 86.52, 85.42, 77.55, 77.23, 76.91, 76.31, 73.47, 73.07, 72.99, 72.70, 50.28, 46.00, 39.93, 33.60; HRMS (ES) m/z calcd for $C_{30}H_{32}N_2O_4$ $[M+H]^+$: 485.2440, found: 485.2452.

5.3.3. (3bR,4R,5S,6R,6aS)-4,5,6-Tris(benzyloxy)octahydrocyclopenta[c]pyrazol[1,2-a]pyrazolidin-1-one ***3ca***. $[\alpha]_D^{25}$ −11.3 (c 2.49, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.12 (m, 15H), 4.69 (d, J=12.0 Hz, 1H), 4.68 (d, J=12.0 Hz, 1H), 4.63 (d, J=12.0 Hz, 1H), 4.61 (d, J=12.0 Hz, 1H), 4.52 (d, J=12.0 Hz, 1H), 4.48 (d, J=11.9 Hz, 1H), 4.23 (t, J=8.4 Hz, 1H, H-6), 4.09 (dd, J=8.3, 4.2 Hz, 1H, H-5), 3.74 (dd, J=11.9, 9.9 Hz, 1H, H-7), 3.69 (d, J=4.1 Hz, 1H, H-4), 3.48 (dt, J=11.2, 8.2 Hz, 1H, H-3), 3.30 (dd, J=11.9, 6.7 Hz, 1H, H-7′), 3.13 (ddd, J=18.1, 9.3, 7.0 Hz, 1H, H-6a), 2.97 (d, J=9.2 Hz, 1H, H-3b), 2.83 (dt, J=11.2, 7.8 Hz, 1H, H-3′), 2.56 (t, J=8.0 Hz, 1H, H-2, 2′); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.61, 138.53, 138.18, 138.13, 128.62, 128.59, 128.50, 128.12, 128.09, 127.95, 127.83, 127.75, 127.71, 83.31, 81.02, 77.45, 73.03, 72.86, 72.71, 71.03, 48.13, 43.50, 40.60, 32.07; HRMS (ES) m/z calcd for $C_{30}H_{32}N_2O_4$ $[M+H]^+$: 485.2440, found: 485.2452.

5.3.4. (3bS,4R,5S,6R,6aR)-5,6-Di-O-isopropylidene-4-benzyloxy-octahydrocyclopenta[c]pyrazol[1,2-a]pyrazolidin-1-one ***3da***. $[\alpha]_D^{25}$ −36.0 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.02 (m, 5H), 4.76 (d, J=6.1 Hz, 1H, H-5), 4.71–4.65 (m, 2H, H-6, $-CH_2OPh$), 4.53 (d, J=11.8 Hz, 1H, $-CH_2OPh$), 3.85 (s, 1H, H-4), 3.78–3.68 (m, 1H, H-7), 3.61–3.49 (m, 2H, H-7′, 3), 3.26 (ddd, J=10.8, 7.4, 3.9 Hz, 1H, H-6a), 3.14 (d, J=7.6 Hz, 1H, H-3b), 2.92–2.81 (m, 1H, H-3′), 2.75–2.52 (m, 2H, H-2, 2′), 1.49 (s, 3H, $-CH_3$), 1.31 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.12, 137.52, 128.74, 128.24, 128.03, 112.67, 88.45, 83.73, 79.77, 77.55, 77.23, 76.91, 76.48, 71.96, 49.13, 49.00, 40.37, 33.62, 26.61, 25.05; HRMS (ES) m/z calcd for $C_{19}H_{24}N_2O_4$ $[M+H]^+$: 345.1814, found: 345.1825.

5.3.5. (3bR,4S,5S,6S,6aS)-4,5-Di-O-isopropylidene-6-benzyloxy-octahydrocyclopenta[c]pyrazol[1,2-a]pyrazolidin-1-one ***3ea***. $[\alpha]_D^{25}$ +61.1 (c 2.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.11 (m, 5H), 4.86–4.78 (m, 2H, H-5, $-CH_2OPh$), 4.58 (d, J=5.4 Hz, 1H, H-4), 4.49 (d, J=12.4 Hz, 1H, $-CH_2OPh$), 3.90 (d, J=7.2 Hz, 1H, H-6), 3.72 (ddd, J=11.4, 7.4, 3.5 Hz, 2H, H-3, 7), 3.48 (dd, J=11.4, 3.2 Hz, 1H, H-7′), 3.39 (ddd, J=16.4, 7.6, 3.6 Hz, 1H, H-6a), 3.09 (d, J=7.6 Hz, 1H, H-3b), 3.03 (dd, J=19.6, 9.2 Hz, 1H, H-3′), 2.79 (dt, J=17.6, 8.8 Hz, 1H, H-2), 2.65 (ddd, J=16.8, 9.2, 5.6 Hz, 1H, H-2′), 1.41 (s, 3H, $-CH_3$), 1.31 (s, 3H, $-CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.62, 137.55, 128.68, 128.17, 128.12, 111.13, 86.67, 82.44, 82.39, 81.18, 72.46, 49.59, 48.97, 40.03, 33.25, 26.96, 24.65; HRMS (ES) m/z calcd for $C_{19}H_{24}N_2O_4$ $[M+H]^+$: 345.1814, found: 345.1823.

5.4. General procedure for the preparation of cycloadducts 3ab/3ac/3ad/3dd/3ed

A solution of 1 (1.0 mmol), 3-pyrazolidinone (2.5 mmol) and Et_3N (1.0 mmol) in MeOH (10 mL) was stirred at room temperature until the completion of the reaction as evidenced by TLC analysis. The solvent and Et_3N were removed in vacuo and the crude product was subjected to chromatography on silica gel using DCM/MeOH (100:1) as the eluting solvent.

5.4.1. (2S,3bS,4R,5S,6S,6aR)-4,5,6-Tris(benzyloxy)octahydrocyclopenta[c]pyrazol[1,2-a]-2-methylpyrazolidin-1-one ***3ab****-S*. $[\alpha]_D^{25}$ −14.2 (c 1.41, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–6.80 (m, 15H), 4.75 (dd, J=27.9, 11.7 Hz, 2H, $-CH_2OPh$), 4.60 (qd, J=11.7, 5.7 Hz, 4H, $-CH_2OPh$), 4.19–4.11 (m, 1H, H-5), 4.01–3.91 (m, 2H, H-6, 7), 3.88

(dd, *J*=6.7, 3.0 Hz, 1H, H-4), 3.23 (dd, *J*=11.4, 8.9 Hz, 1H, H-3), 3.16–3.07 (m, 1H, H-3′), 3.00 (dd, *J*=9.2, 2.7 Hz, 1H, H-3b), 2.92 (dt, *J*=14.7, 4.4 Hz, 2H, H-6a, 7′), 2.76–2.64 (m, 1H, H-2), 1.23 (d, *J*=7.1 Hz, 3H, $-CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.28, 138.54, 138.12, 138.07, 128.73, 128.71, 128.57, 128.24, 128.11, 128.01, 127.95, 127.90, 127.85, 127.76, 90.89, 86.58, 84.52, 77.55, 77.23, 76.91, 72.90, 72.61, 72.50, 70.34, 54.67, 48.29, 46.61, 37.25, 15.27; HRMS (ES) *m*/*z* calcd for $C_{31}H_{34}N_2O_4$ $[M+H]^+$: 499.2597, found: 499.2594.

5.4.2. (2R,3bS,4R,5S,6S,6aR)-4,5,6-Tris(benzyloxy)octahydrocyclopenta[c]pyrazol[1,2-a]-2-methylpyrazolidin-1-one ***3ab****-R.* $[\alpha]_D^{25}$ +17.4 (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–6.97 (m, 15H), 4.76–4.52 (m, 6H, 3×$-CH_2OPh$), 4.17–4.09 (m, 1H, H-4), 3.90 (ddd, *J*=11.1, 9.9, 5.5 Hz, 3H, H-5, 6, 7), 3.77 (t, *J*=8.7 Hz, 1H, H-3), 3.05 (ddd, *J*=17.4, 10.5, 4.3 Hz, 2H, H-3b, 7′), 2.99–2.87 (m, 2H, H-3′, 6a), 2.40 (dd, *J*=11.9, 9.1 Hz, 1H, H-2), 1.20 (d, *J*=7.1 Hz, 3H, $-CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.85, 138.46, 138.07, 137.89, 128.72, 128.56, 128.23, 128.11, 127.99, 127.85, 127.75, 90.47, 85.98, 84.73, 77.55, 77.23, 76.91, 72.87, 72.72, 72.54, 72.40, 60.00, 48.14, 44.32, 41.32, 14.43; HRMS (ES) *m*/*z* calcd for $C_{31}H_{34}N_2O_4$ $[M+H]^+$: 499.2597, found: 499.2594.

5.4.3. (3R/S,3bS,4R,5S,6S,6aR)-4,5,6-Tris(benzyloxy)octahydrocyclopenta[c]pyrazol[1,2-a]-3-methylpyrazolidin-1-one ***3ac****-RS.* Mixture of **3ac**-*R* and **3ac**-*S*. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–6.95 (m, 30H), 4.87–4.52 (m, 12H), 4.13 (t, *J*=7.3 Hz, 1H), 4.08 (t, *J*=7.4 Hz, 1H), 4.00 (dd, *J*=10.6, 7.7 Hz, 1H), 3.94 (t, *J*=7.3 Hz, 1H), 3.90 (dd, *J*=7.0, 3.9 Hz, 1H), 3.88–3.84 (m, 1H), 3.81 (t, *J*=6.4 Hz, 1H), 3.65–3.50 (m, 3H), 3.24–3.13 (m, 2H), 3.05 (dd, *J*=9.6, 3.8 Hz, 1H), 3.00–2.86 (m, 2H), 2.66 (dd, *J*=16.5, 8.0 Hz, 1H), 2.52 (dd, *J*=16.7, 7.9 Hz, 1H), 2.40 (dd, *J*=16.5, 9.3 Hz, 1H), 2.28 (dd, *J*=16.7, 9.6 Hz, 1H), 1.25 (d, *J*=6.4 Hz, 3H), 1.21 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.98, 138.32, 138.20, 137.98, 137.81, 137.60, 128.76, 128.71, 128.60, 128.56, 128.28, 128.13, 128.02, 127.96, 127.86, 90.42, 89.18, 87.21, 86.43, 84.84, 77.55, 77.23, 76.91, 72.88, 72.83, 72.63, 72.40, 72.33, 72.26, 71.42, 63.89, 59.64, 51.83, 47.87, 47.58, 45.36, 41.06, 40.93, 20.41, 17.95; (*R*/*S*=1:1).

5.4.4. (3S,3bS,4R,5S,6S,6aR)-4,5,6-Tris(benzyloxy)octahydrocyclopenta[c]pyrazol[1,2-a]-3-phenylpyrazolidin-1-one ***3ad****-S.* $[\alpha]_D^{25}$ +28.6 (*c* 1.12, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–6.81 (m, 20H), 4.77 (d, *J*=11.6 Hz, 1H, $-CH_2OPh$), 4.67 (d, *J*=11.6 Hz, 1H, $-CH_2OPh$), 4.64 (d, *J*=11.7 Hz, 1H, $-CH_2OPh$), 4.58–4.52 (m, 3H, H-3, $-CH_2OPh$), 4.50 (d, *J*=11.6 Hz, 1H, $-CH_2OPh$), 4.01 (t, *J*=7.0 Hz, 1H, H-5), 3.87 (t, *J*=7.2 Hz, 1H, H-4), 3.78 (dd, *J*=6.2, 5.0 Hz, 1H, H-6), 3.63 (dd, *J*=8.9, 7.1 Hz, 1H, H-3b), 3.49–3.37 (m, 2H, H-7, 7′), 2.94 (dt, *J*=13.5, 4.6 Hz, 1H, H-6a), 2.82 (dd, *J*=16.8, 9.1 Hz, 1H, H-2), 2.69 (dd, *J*=16.8, 8.5 Hz, 1H, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.07, 137.89, 137.46, 137.33, 129.35, 129.35, 128.85, 128.69, 128.69, 128.49, 128.39, 128.39, 128.24, 128.15, 128.00, 127.75, 88.11, 86.11, 86.06, 77.55, 77.23, 76.91, 72.90, 72.42, 71.96, 66.43, 47.59, 46.13, 46.10, 39.25; HRMS (ES) *m*/*z* calcd for $C_{36}H_{36}N_2O_4$ $[M+H]^+$: 561.2753, found: 561.2747.

5.4.5. (3R,3bS,4R,5S,6S,6aR)-4,5,6-Tris(benzyloxy)octahydrocyclopenta[c]pyrazol[1,2-a]-3-phenylpyrazolidin-1-one ***3ad****-R.* $[\alpha]_D^{25}$ −65.0 (*c* 0.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J*=7.8, 1.5 Hz, 2H), 7.38–7.14 (m, 17H), 6.96 (dd, *J*=6.6, 3.0 Hz, 2H), 4.59 (ddd, *J*=29.9, 21.8, 11.7 Hz, 4H, 2×$-CH_2OPh$), 4.15 (dd, *J*=11.0, 8.4 Hz, 1H, H-3), 4.08–3.93 (m, 5H, H-4, 5, 6, $-CH_2OPh$), 3.67 (dd, *J*=5.6, 2.5 Hz, 1H, H-7), 3.19–3.07 (m, 3H, H-3b, 6a, 7′), 2.96 (dd, *J*=16.4, 8.4 Hz, 1H, H-2), 2.85 (dd, *J*=16.3, 11.1 Hz, 1H, H-2′); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.55, 138.25, 138.07, 137.91, 129.06, 128.76, 128.57, 128.48, 128.16, 127.97, 127.92, 127.70, 127.46, 90.99, 86.49, 84.80, 77.55, 77.23, 76.91, 72.77, 72.59, 72.34, 69.43, 53.62, 48.65, 44.50; HRMS (ES) *m*/*z* calcd for $C_{36}H_{36}N_2O_4$ $[M+H]^+$: 561.2753, found: 561.2740.

5.4.6. (3S,3bS,4R,5S,6R,6aR)-5,6-Di-O-isopropylidene-4-benzyloxyoctahydrocyclopenta[c]pyrazol[1,2-a]-3-phenylpyrazolidin-1-one ***3dd****-S.* $[\alpha]_D^{25}$ +73.6 (*c* 3.81, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.02 (m, 10H), 4.76 (d, *J*=12.3 Hz, 1H, $-CH_2OPh$), 4.68 (d, *J*=5.4 Hz, 1H, H-5), 4.54 (d, *J*=12.3 Hz, 1H, $-CH_2OPh$), 4.21 (d, *J*=9.9 Hz, 1H, 3), 4.17 (d, *J*=5.4 Hz, 1H, H-4), 3.92 (d, *J*=6.9 Hz, 1H, H-6), 3.87–3.76 (m, 1H, H-7), 3.56 (dd, *J*=11.4, 3.6 Hz, 1H, H-7′), 3.48 (dt, *J*=16.1, 5.8 Hz, 1H, H-6a), 3.27 (d, *J*=7.4 Hz, 1H, H-3b), 2.99 (dd, *J*=16.4, 8.6 Hz, 1H, H-2), 2.86 (dd, *J*=16.3, 10.6 Hz, 1H, H-2′), 1.37 (s, 3H, $-CH_3$), 1.15 (s, 3H, $-CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.33, 139.98, 138.01, 128.88, 128.55, 128.17, 127.83, 127.52, 127.13, 110.97, 85.97, 83.10, 81.49, 77.55, 77.23, 76.91, 76.64, 71.94, 68.53, 48.92, 44.08, 39.48, 26.98, 24.61; HRMS (ES) *m*/*z* calcd for $C_{25}H_{28}N_2O_4$ $[M+H]^+$: 421.2127, found: 421.2124.

5.4.7. (3R,3bS,4R,5S,6R,6aR)-5,6-Di-O-isopropylidene-4-benzyloxyoctahydrocyclopenta[c]pyrazol[1,2-a]-3-phenylpyrazolidin-1-one ***3dd****-R.* $[\alpha]_D^{25}$ −40.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.08 (m, 10H), 4.63 (tt, *J*=7.0, 5.7 Hz, 3H, H-5, 6, $-CH_2OPh$), 4.52 (t, *J*=9.1 Hz, 1H, H-3), 4.41 (d, *J*=11.6 Hz, 1H, $-CH_2OPh$), 3.89 (dd, *J*=11.3, 4.8 Hz, 1H, H-7), 3.79 (dd, *J*=6.5, 4.3 Hz, 1H, H-4), 3.60 (t, *J*=7.0 Hz, 1H, H-3b), 3.35 (t, *J*=10.7 Hz, 1H, H-7), 3.27 (ddd, *J*=12.3, 11.1, 7.2 Hz, 1H, H-6a), 2.74 (dd, *J*=9.1, 1.8 Hz, 2H, H-2, 2′), 1.57 (s, 3H, $-CH_3$), 1.33 (s, 3H, $-CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.13, 139.58, 137.34, 128.89, 128.69, 128.52, 128.30, 128.20, 127.45, 113.47, 86.75, 81.31, 77.55, 77.23, 76.99, 76.91, 71.65, 69.34, 59.80, 46.95, 42.75, 39.40, 26.95, 25.10; HRMS (ES) *m*/*z* calcd for $C_{25}H_{28}N_2O_4$ $[M+H]^+$: 421.2127, found: 421.2126.

5.4.8. (3S,3bS,4R,5S,6R,6aR)-5,6-Di-O-isopropylidene-4-benzyloxyoctahydrocyclopenta[c]pyrazol[1,2-a]-3-phenylpyrazolidin-1-one ***3ed****-S.* $[\alpha]_D^{25}$ −8.2 (*c* 1.47, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7.05 (m, 10H), 4.72 (dd, *J*=15.0, 7.1 Hz, 2H, H-3, $-CH_2OPh$), 4.63 (dd, *J*=6.5, 3.4 Hz, 1H, H-4), 4.47 (d, *J*=12.1 Hz, 1H, $-CH_2OPh$), 4.44 (d, *J*=6.7 Hz, 1H, H-5), 3.95 (dd, *J*=6.5, 3.3 Hz, 1H, H-3b), 3.66 (dd, *J*=11.8, 5.3 Hz, 1H, H-7), 3.54–3.41 (m, 1H, H-7′), 3.38 (d, *J*=6.9 Hz, 1H, H-6), 3.36–3.30 (m, 1H, H-6a), 3.13 (dd, *J*=16.6, 8.7 Hz, 1H, H-2), 2.94 (dd, *J*=16.7, 8.7 Hz, 1H, H-2′), 1.37 (s, 3H, $-CH_3$), 1.24 (s, 3H, $-CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.49, 137.74, 129.09, 128.63, 128.05, 127.99, 127.85, 112.37, 85.39, 83.08, 78.73, 77.55, 77.23, 76.91, 72.22, 67.82, 61.10, 50.06, 41.94, 39.81, 27.12, 24.85; HRMS (ES) *m*/*z* calcd for $C_{25}H_{28}N_2O_4$ $[M+H]^+$: 421.2127, found: 421.2124.

5.4.9. (3R,3bS,4R,5S,6R,6aR)-5,6-Di-O-isopropylidene-4-benzyloxyoctahydrocyclopenta[c]pyrazol[1,2-a]-3-phenylpyrazolidin-1-one ***3ed****-R.* $[\alpha]_D^{25}$ +115.3 (*c* 2.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.57–7.21 (m, 10H), 4.76 (d, *J*=12.3 Hz, 1H, $-CH_2OPh$), 4.69 (dd, *J*=5.4, 1.2 Hz, 1H, H-4), 4.54 (d, *J*=12.3 Hz, 1H, $-CH_2OPh$), 4.24–4.16 (m, 2H, H-3, 5), 3.92 (dd, *J*=6.9, 1.3 Hz, 1H, H-3b), 3.81 (dd, *J*=11.3, 9.1 Hz, 1H, H-7), 3.56 (dd, *J*=11.4, 3.6 Hz, 1H, H-7′), 3.49 (ddd, *J*=16.1, 7.3, 3.9 Hz, 1H, H-6a), 3.27 (d, *J*=7.4 Hz, 1H, H-6), 2.99 (dd, *J*=16.4, 8.6 Hz, 1H, H-2), 2.87 (dd, *J*=16.4, 10.5 Hz, 1H, H-2′), 1.38 (s, 3H, $-CH_3$), 1.16 (s, 3H, $-CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.73, 140.16, 138.09, 128.94, 128.61, 128.22, 127.89, 127.58, 127.18, 111.05, 86.08, 83.25, 81.60, 77.55, 77.23, 76.91, 76.69, 72.04, 68.48, 48.98, 44.06, 39.58, 27.05, 24.68; HRMS (ES) *m*/*z* calcd for $C_{25}H_{28}N_2O_4$ $[M+H]^+$: 421.2127, found: 421.2126.

5.5. Preparation of compound (3b*S*,4*R*,5*S*,6*S*,6a*R*)-4,5,6-tris(hydroxy)octahydrocyclopenta[*c*]pyrazol[1,2-*a*]pyrazolidin-1-one 4aa

A suspension of **3aa** (0.2 mmol, 97 mg) and Pd/C (10 mg) in MeOH (2 mL) was stirred at rt under 0.4 MPa H_2 atmosphere for 2 h. The reaction mixture was filtered and concentrated to give the crude **4aa** (42 mg). Then the crude product was subjected to chromatography on

silica gel using DCM/MeOH (5:1) as the eluting solvent, yielding pure **4aa** quantitively. $[\alpha]_D^{25}$ −7.9 (*c* 1.52, MeOH); ^{1}H NMR (400 MHz, CD_3OD/$CDCl_3$ (3:1)) δ 4.09–4.02 (m, 1H), 3.95–3.89 (m, 1H), 3.89–3.84 (m, 1H), 3.80 (dt, *J*=10.8, 8.0 Hz, 1H), 3.43 (d, *J*=8.8 Hz, 1H), 3.34–3.24 (m, 1H), 3.22 (dd, *J*=11.6, 4.0 Hz, 1H), 3.09 (dd, *J*=9.7, 3.1 Hz, 1H), 3.01 (td, *J*=8.6, 4.4 Hz, 1H), 2.84 (t, *J*=8.1 Hz, 2H); ^{13}C NMR (101 MHz, CD_3OD/$CDCl_3$ (3:1)) δ 172.14, 85.11, 80.12, 79.22, 78.90, 78.57, 72.96, 49.79, 49.58, 49.36, 49.15, 48.94, 48.72, 48.51, 45.87, 33.97; HRMS (ES) *m*/*z* calcd for $C_9H_{14}N_2O_4$ $[M+H]^+$: 215.1032, found: 215.1026.

5.6. Preparation of compound (3b*S*,4*R*,5*S*,6*S*,6a*R*) octahydrocyclopenta[*c*]pyrazol[1,2-*a*]pyrazolidin-1-one-4,5,6-triyl tribenzoate 5aa

To a stirred solution of compound **4aa** (0.2 mmol, 42 mg) in pyridine (3 mL) was added benzoyl chloride (0.8 mmol, 93 μL) at 0 °C. After stirring at rt overnight, the reaction mixture was concentrated and purified by chromatography to yield **5aa** (84 mg, 80% yield). $[\alpha]_D^{25}$ −5.1 (*c* 3.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28–7.98 (m, 6H), 7.57 (dt, *J*=9.3, 7.5 Hz, 3H), 7.49–7.38 (m, 6H), 6.29–6.05 (m, 1H), 5.66 (t, *J*=6.7 Hz, 1H), 5.45 (dd, *J*=5.2, 1.4 Hz, 1H), 4.19 (dd, *J*=12.0, 8.7 Hz, 1H), 3.83 (dt, *J*=11.8, 8.5 Hz, 1H), 3.55 (dd, *J*=12.1, 4.5 Hz, 1H), 3.46 (ddd, *J*=11.9, 8.8, 6.7 Hz, 1H), 3.40–3.31 (m, 1H), 3.28 (d, *J*=9.2 Hz, 1H), 2.72–2.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.38, 166.04, 166.02, 165.54, 133.83, 133.69, 130.15, 130.09, 129.35, 128.76, 128.69, 127.05, 81.47, 80.82, 78.57, 77.55, 77.23, 76.91, 72.36, 50.02, 47.70, 45.57, 31.73; HRMS (ES) *m*/*z* calcd for $C_{30}H_{26}N_2O_7$ $[M+H]^+$: 527.1818, found: 527.1802.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.04.031. These data include MOL files and InChIKeys of the most important compounds described in this article.

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