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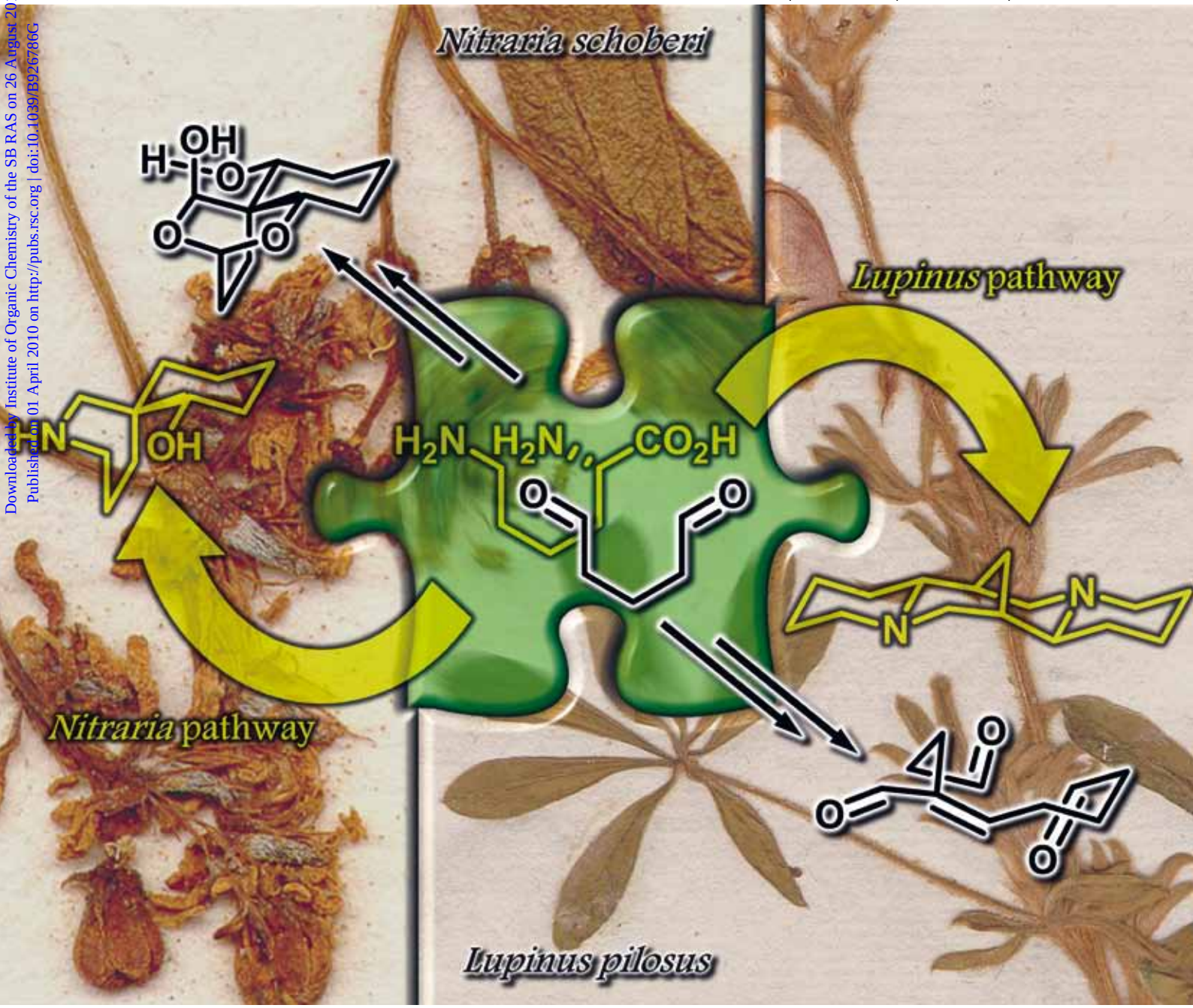

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Biomimetically relevant self-condensations of C_5 units derived from lysine†

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In various conditions, dimerization of pentanedial-derived units gives rise to interesting skeletons, which are reminiscent of alkaloids known to be biosynthesized in Nature *via* lysine metabolism.

Introduction

Throughout the last century, lysine was demonstrated to be at the origin of the incorporation of an intact 5-carbon chain into many alkaloids.[1] Some of them, like sparteine, highlight the creation of highly condensed nitrogen heterocycles from simple precursors (the alkaloid is exclusively built from lysine).[2]

Biochemically speaking, L-lysine first undergoes decarboxylation and yields cadaverine, a C_5 linear symmetric diamine (Scheme 1).[2,3] After an oxidative deamination process at one of its extremities, cadaverine gives rise to 5-aminopentanal, which is unstable and cyclizes into Δ^2-piperidine (**1**) that exists as an equilibrium between the enamine (Δ^2-piperidine) and the imine (Δ^1-piperidine) depending on the acidity of the medium. Another oxidative deamination could in principle give rise to the formation of glutaraldehyde (**2**).[4] At physiological pH, Δ^2-piperidine (**1**) can dimerize spontaneously into tetrahydroanabasine (**3**) (though stereospecific coupling involves an appropriate enzymic intervention[3]), a central molecule in the metabolism of numerous alkaloids. The first and most common evolution, "the *Lupinus* pathway" (① in Scheme 1), presumably involves hydrolysis of the imine followed by oxidation of the amine into dialdehyde **4**, at the origin of the important group of lupine alkaloids. The second pathway (② in Scheme 1) has been postulated in the *Nitraria* genus to explain the biosynthesis of a range of diverse and sometimes complex structures (*e.g.* nitraramine, nitrarine).[5,6] More recently, new secondary metabolites closely related to the *Nitraria* alkaloids have been isolated in the *Myrioneuron* genus and may involve similar biosynthetic pathways from **3** (*e.g.* myrioneurinol).[7] As a cornerstone of this scenario, intermediate **5** could arise from a retro-Michael mechanism followed by an oxidative deamination step.

Over the last few years, our laboratory has focused its efforts on biomimetic strategies and especially on the manipulation of lysine-derived units.[5] In this article we report some observations demonstrating that, in appropriate conditions, the self-condensation of glutaraldehyde (pentanedial) units constitutes a convenient access to biomimetic building blocks reminiscent of natural products derived from L-lysine. Starting from costless glutaraldehyde, several types of condensations have been studied that parallel general Scheme 1.

Results and discussion

Self condensations of glutaraldehyde

We wanted to investigate the behaviour of free **2** itself in various conditions. Glutaraldehyde in solution is known to be a mixture of several molecules.[8] Diluted in water and depending on the concentration, pH *etc.*, **2** undergoes rapid hydration to give an equilibrium of 3 hydrates, with slow formation of oligomers and polymers (Scheme 2) resulting in a chemical heterogeneity of the solutions.[9] Different types of polymers may be formed at different pH values and it is considered that polymers in the basic range are unable to revert to monomers, whereas those in the neutral or acidic range revert easily. When looking at the literature, very few compounds resulting from self-condensations of **2** have been fully characterized.

"Tangutorine-type" condensations

Products formed during the treatment of **2** at pH 8.5 in an aqueous solution of $NaHCO_3$ at 60 °C for 2 h were investigated (Scheme 3). First, dimeric structure **6** was easily isolated as the result of a double homoaldolization followed by the crotonization of one of the aldol adducts. Compound **6** was known[10] but no information was available concerning its stereochemistry. Nakagawa *et al.* determined the structure of **6** by isolating its bis-*O*-pentafluorobenzyloxime adduct, whereas we isolated pure **6** by column chromatography on silica gel.[11] It appeared by NMR as a mixture of 4 diastereomers (46 : 38 : 7 : 9), no traces of opened counterpart **7** could be detected. Oxidation of **6** with Dess–Martin periodinane in CH_2Cl_2 afforded a mixture of two diastereomers from which lactone **8** was easily crystallized as the major product. NMR analysis of **8** established a *trans* C-4a/C-8a ring fusion ($J_{H\text{-}4a–H\text{-}8a}$ = 12.4 Hz). An X-ray crystallographic analysis (see ORTEP drawing, Fig. 1) confirmed the assigned stereochemical relationship.[12,13]

Through the straightforward total synthesis of tangutorine from **6** that we disclosed earlier, we postulated **9** as a possible key-biosynthetic intermediate in the biosynthesis of various alkaloids along the above mentioned **4** or **5**. Indeed, **9** can be put forward

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† Electronic supplementary information (ESI) available: NMR spectra for compounds **6**, **8**, **10–18**. CCDC reference numbers 753047–753049. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b926786g

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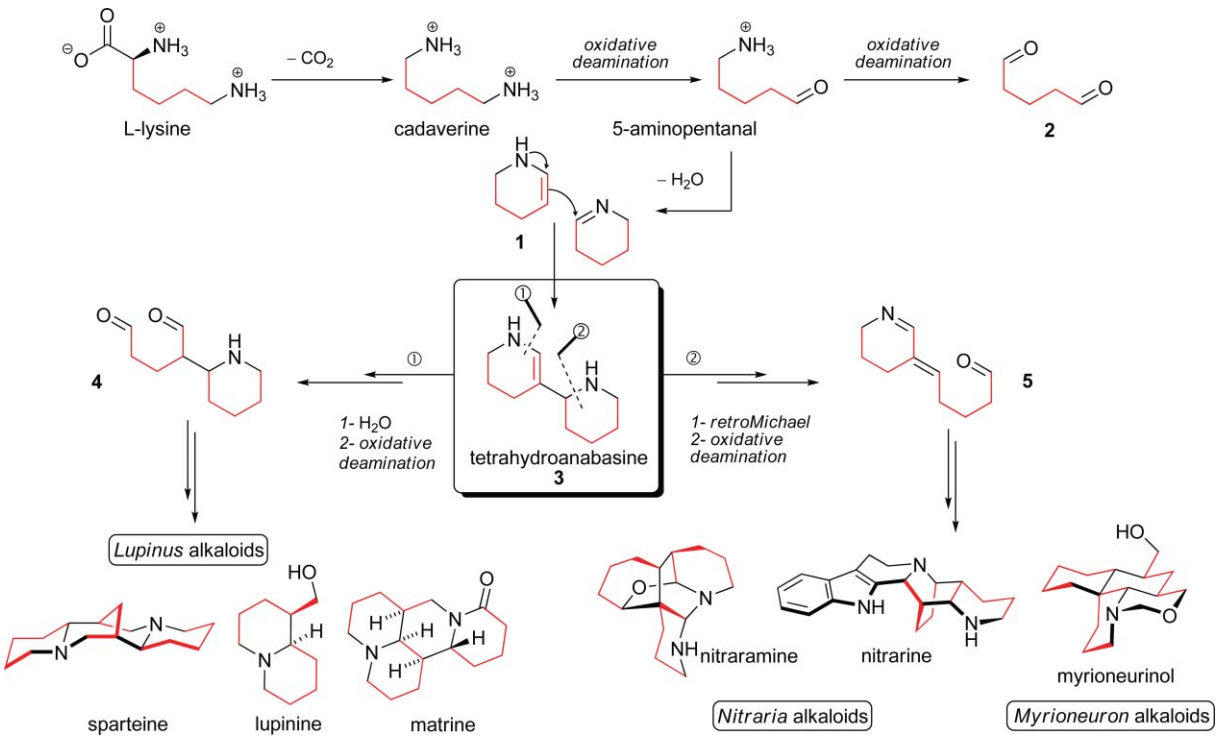
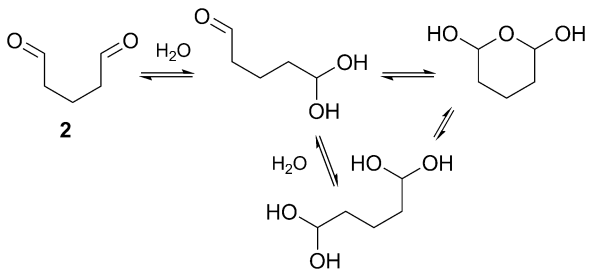


Scheme 1 Lysine and tetrahydroanabasine metabolisms.



Scheme 2 Behaviour of glutaraldehyde in water.

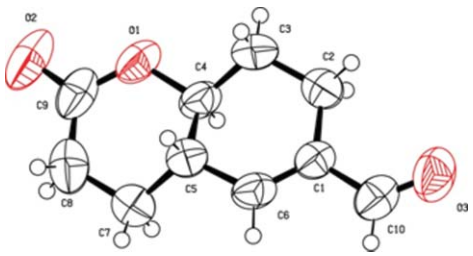


Fig. 1 ORTEP drawing of the racemic compound **8** with ellipsoids drawn at the 50% level.

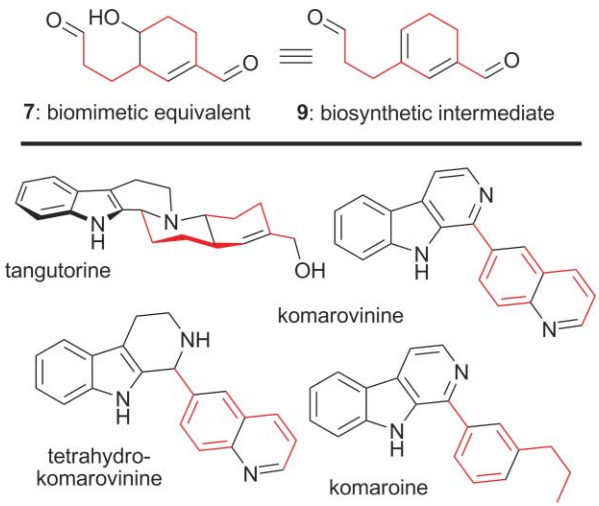


Fig. 2 A possible biosynthetic intermediate.

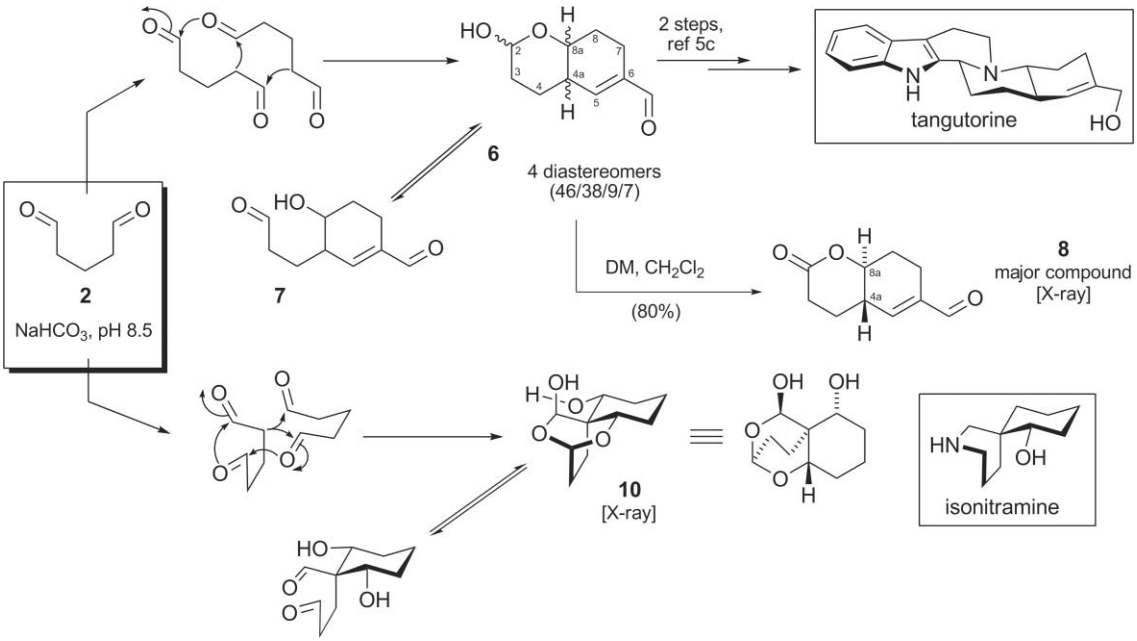
not only in the biosynthetic hypotheses of tangutorine but also in the ones of aromatic β-carbolines such as komarovinine, tetrahydrokomarovinine or komaroine (Fig. 2).[14]

Spiranic "nitramine-type" condensations

From the same reaction mixture, we were able to isolate a second crystalline compound **10**, the structure of which was difficult to establish (Scheme 3). Fortunately, X-ray analysis of a single crystal revealed a tricyclic structure with a spiranic quaternary carbon, and contiguous acetal and hemiacetal functions (Fig. 3).[15,16] This intriguing structure has a striking analogy with known *Nitraria* alkaloids such as nitramine. In addition, the plausible mechanism of formation of **10** that we suggest (Scheme 3), is totally in line with the proposed biosynthetic hypothesis of *Nitraria* spirocyclic alkaloids.[6a,e]

"Tetrahydroanabasine-type" condensations

Diethoxypentanal (**11**), a monoprotected form of **2**, was easily prepared in acidic catalytic conditions (Scheme 4).[17] Three different compounds were formed and easily separated at the multigram scale by flash chromatography including **11** (~10%



Scheme 3 Self-condensations of free glutaraldehyde in mild basic conditions.

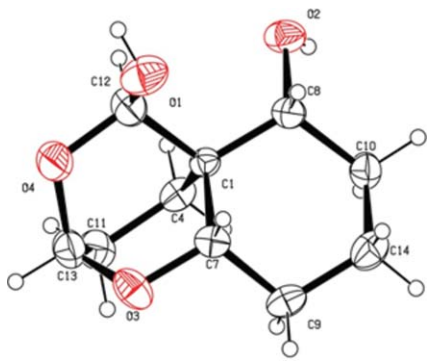
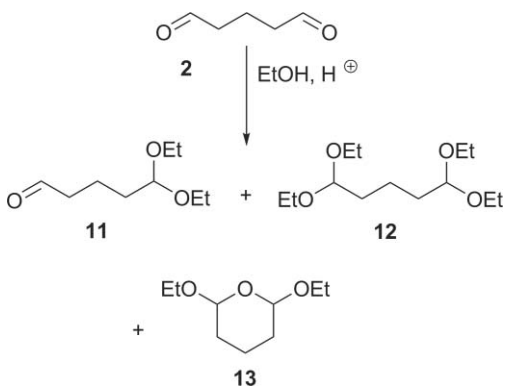


Fig. 3 ORTEP drawing of the racemic compound **10** with ellipsoids drawn at the 30% level.

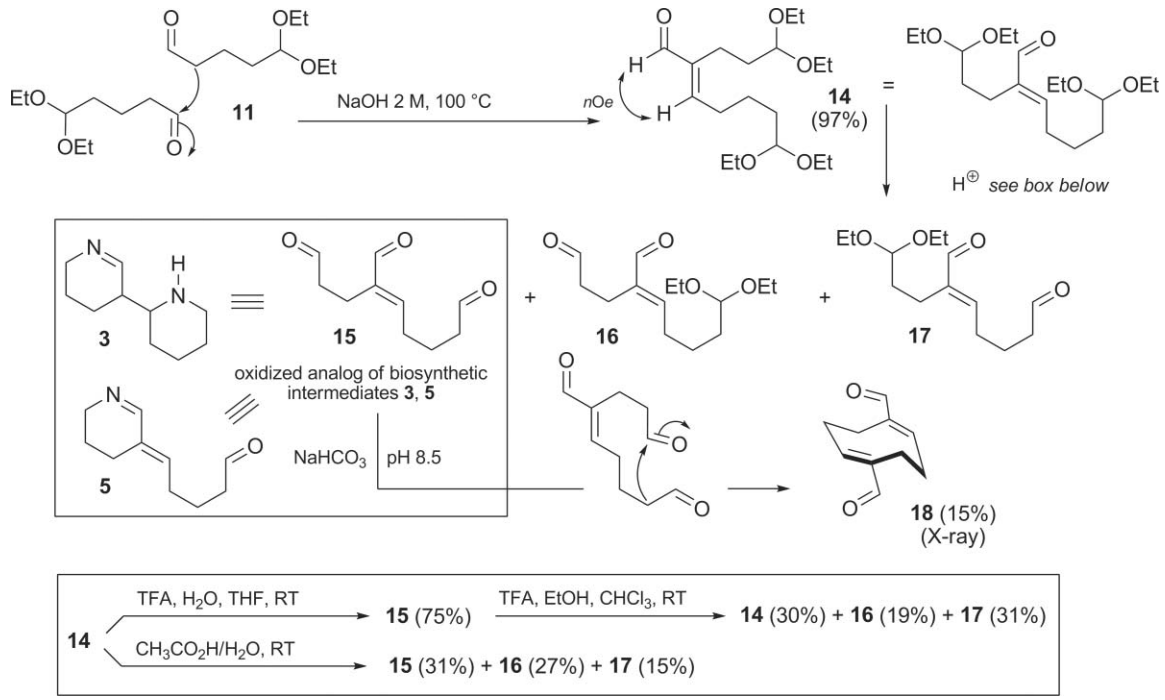


Scheme 4 Protection of glutaraldehyde.

yield) but also diprotected **12** and acetal **13**. When **11** was treated in a boiling 2 M solution of sodium hydroxide, compound **14**, resulting from homoaldolization/crotonization, was obtained in almost quantitative yield (Scheme 5). NMR studies permitted the establishment of an *E*-stereochemistry of the central Michael acceptor. As already observed in similar cases by Erkkilä and Pihko, the stereochemistry is in favour of the *E*-stereomers.[18] The deprotection of the masked aldehydes was then studied. Acidic conditions such as TFA in H_2O–THF or acidic ion exchange resins in THF–H_2O, both at room temperature, afforded trialdehyde **15** in 85% yield. Milder conditions, *i.e.* acetic acid in water with TLC control, permitted the obtainment of monoprotected **16** and **17**. These latter were separable by careful silica gel chromatography and NMR studies clearly permitted both structures to be distinguished between. Reprotection of the free aldehyde functions of **15** in chloroform with 10 equiv. of ethanol and a catalytic amount of trifluroacetic acid afforded **16** and **17** with a ratio different from the protocol used for the deprotection of **14** (see box in Scheme 5). These compounds with their C_{10} skeleton are interestingly reminiscent of biosynthetic intermediate tetrahydroanabasine (**3**) or pivotal intermediate **5** and could be considered as oxidized analogs thereof. They constitute an interesting tool box from which access to several natural products may be envisioned. Treatment of **15** with an aqueous solution of $NaHCO_3$ (pH 8.5) at 60 °C also permitted the synthesis of cyclooctadiene **18** (the structure of which was confirmed by X-ray crystallographic analysis; see Fig. 4) in low yield.

Conclusion

We have demonstrated, through simple reactions, that dialdehydes presumably derived from L-lysine intrinsically contain enough "chemical information" to give rise (without the need for nitrogen atoms) to biosynthetically related acyclic and cyclic architectures found in various alkaloids. The described synthetic schemes expand the use of C_5 dialdehydes (see the general skeletons accessed on Fig. 5) and clearly demonstrate a striking link between



Scheme 5 Manipulation of monoprotected glutaraldehyde.

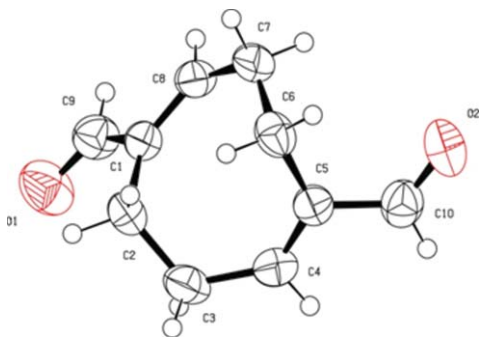


Fig. 4 ORTEP drawing of the racemic compound **18** with ellipsoids drawn at the 50% level.

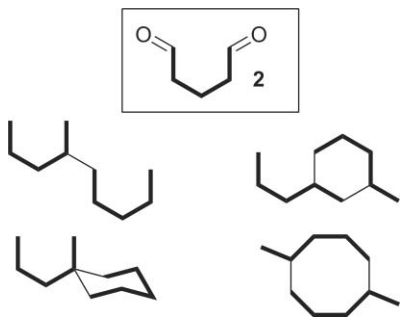


Fig. 5 Various skeletons described in this work.

alkaloids in the *Nitraria* genus. The ability of these catalyst and metal-free processes from costless reagents to give potentially valuable biomimetic equivalents recommends them as interesting tools for total synthesis.

Experimental

General

Reactions were monitored by thin-layer chromatography carried out on Merck Kieselgel silica gel plates (60F-254) using UV light as visualizing agent if required and sulfuric vanillin reagent and heat as developing agent. Merck Kieselgel silica gel (60, particle size 40–63 μm) was used for flash chromatography. NMR spectra were recorded in deuterated chloroform on AM-300 (300 MHz) or AM-400 (400 MHz) Bruker spectrometers and calibrated using undeuterated chloroform as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet; d = doublet, t = triplet; q = quartet; qu = quintet; m = multiplet; br = broad. Assignments were made on the basis of *J*Mod, COSY, HMQC, HMBC and NOESY experiments. IR spectra were recorded on Vector 22 Bruker spectrometer and values are reported in cm^{-1} units. Mass spectra were recorded at the "Service d'Analyse des Médicaments et des Métabolites" (Université Paris-Sud).

The NMR spectroscopic data for compounds **6**, **8**, **11**, **14–18** are assigned using the conventional numbering or (compound **10**) arbitrarily given numbering (see the ESI for numbered structures†).

Self-condensation of glutaraldehyde

Glutaraldehyde (**2**) (15 g, 0.15 mol, 30 mL of a 50% aqueous solution) was diluted 5 times with water and basicified to pH 8.5 by slow addition of $NaHCO_3$. The mixture was stirred at 60 °C for 2 h, cooled to room temperature and extracted with CH_2Cl_2 (3 × 250 mL). The combined organic layers were dried ($MgSO_4$)

and concentrated under reduced pressure. The oily residue was purified by flash chromatography (CH_2Cl_2–EtOAc 8 : 2 to 7 : 3) to afford successively **6** (3–4 g, 22–28%) and **10**, which was crystallized from $CHCl_3$ (1–1.5 g, 3.3–5%).

2-Hydroxy-3,4,4a,7,8,8a-hexahydro-2*H*-chromene-6-carbaldehyde (6)

Colorless oil, R_f 0.56 ($CHCl_3$–MeOH 9 : 1); MS (TOF, ESI): m/z 181 $[M-H]^+$; ^{1}H-NMR (400 MHz; $CDCl_3$) δ, the 2 major diastereomers are described (**6**, **6′**) 9.34 (2H, s, HC=O), 6.39, 6.38 (2H, 2 s, H-5, H-5′), 5.27 (1H, br s, H-2′), 4.78 (1H, d, J = 12 Hz, H-2), 3.82 (1H, ddd, J = 3.2, 9.2, 12.4 Hz, H-8a), 3.21 (ddd, 1H, J = 3.2, 9.2, 12.4 Hz, H-8′a), 2.42 (2H, dd, J = 6.4, 17.6), 2.15 (4H, m), 1.96 (3H, m), 1.93-1.46 (7H, m), 1.38 ppm (2H, dq, J = 3.2, 12.4 Hz); ^{13}C-NMR (100 MHz; $CDCl_3$) δ 193.55, 193.41 (2 × HC=O), 151.20, 150.05 (C-5, C-5′), 140.37, 140.17 (C-6, C-6′), 96.41 (C-2), 91.63 (C-2′), 76.17 (C-8′a), 69.25 (C-8a), 41.21, 40.39 (C-4a, C-4′a), 33.13, 30.70, 27.10, 23.05, 21.29, 21.11 ppm; IR: υ_{max}(film): 3630, 1695, 1640 cm^{-1}; HRMS m/z calcd for $C_{10}H_{13}O_3$ 181.0861 $[M-H]^+$; found 181.0873.

(4a*S*,8a*S*)-2-Oxo-3,4,4a,7,8,8a-hexahydro-2*H*-chromene-6-carbaldehyde (8)

To a solution of **6** (340 mg, 1.8 mmol) in CH_2Cl_2 (15 mL) was added a solution of Dess–Martin periodinane (0.792 g, 1.8 mmol, 1 equiv., 3.8 mL of a 15% solution in CH_2Cl_2). The mixture was stirred at room temperature for 10 min and then quenched by the addition of saturated solutions of $Na_2S_2O_3$ (10 mL) and $NaHCO_3$ (10 mL) and Et_2O (30 mL) and 10 min of stirring. The two resulting phases were separated and the organic layer was washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was purified by flash chromatography (C_6H_{12}–EtOAc 8 : 2 to 7 : 3) to afford **8** (0.27 g, 80%). Colorless crystals; mp = 119–123 °C (from C_6H_{12}); R_f 0.47 ($CHCl_3$–EtOAc 1 : 1); MS (ESI) m/z 181 $[M+H]^+$; ^{1}H-NMR (300 MHz; $CDCl_3$) δ 9.46 (1H, s, HC=O), 6.49 (1H, s, H-5), 4.10 (1H, ddd, J = 3.2, 9.6, 12.6 Hz, H-8a), 2.83-2.70 (m, 2H), 2.70-2.48 (m, 2H), 2.34-2.12 (m, 3H), 1.74 ppm (m, 2H); ^{13}C-NMR (100 MHz; $CDCl_3$) δ 192.7 (HC=O), 170.6 (C-2), 146.9 (C-5), 140.8 (C-6), 79.0 (C-8a), 38.2 (C-4a), 29.3 (C-4), 26.8 (C-3), 24.0 (C-8), 20.5 ppm (C-7); IR: υ_{max}(film): 1730, 1678 cm^{-1}; HRMS m/z calcd for $C_{10}H_{12}O_3Na$ 203.0684 $[M+Na]^+$; found 203.0677.

Spiranic compound (10)

Colorless crystals, mp = 108–110 °C (from $CHCl_3$); R_f 0.48 ($CHCl_3$–MeOH 9 : 1); MS (TOF, ESI): m/z 223 $[M+Na]^+$; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 6.42 (1H, d, J = 5.2 Hz, OH), 5.15 (1H, d, J = 5.2 Hz, H-4), 4.83 (1H, s, H-2), 4.41 (1H, d, J = 5.2 Hz, OH), 3.87 (1H, dd, J = 11.8, 3.9 Hz, H-1a), 3.51 (1H, ddd, J = 5.2, 5.2, 11.6 Hz, H-5), 1.88-1.79 (1H, m), 1.73-1.66 (2H, m), 1.61-1.46 (4H, m), 1.44-1.26 (2H, m), 1.17-1.03 ppm (1H, m); ^{13}C-NMR (100 MHz; DMSO-d_6) δ 93.8 (C-4), 89.6 (C-2), 69.2 (C-1a), 66.9 (C-5), 40.7 (C-4a), 29.4, 27.4, 27.1, 19.5, 14.1 ppm; IR: υ_{max}(film): 3363, 2939, 40.7 (1118 cm^{-1}; HRMS m/z calcd for $C_{10}H_{16}O_4Na$ 223.0946 $[M+Na]^+$ found 223.0942.

Monoprotection of glutaraldehyde

An aqueous solution of glutaraldehyde (50 g, 500 mmol, 100 mL of a 50% solution in H_2O) was diluted with ethanol (1 L), Amberlyst® 15 ion-exchange resin (5 g) was added. The mixture was stirred for 18 h at room temperature, the resin was eliminated by filtration. The filtrate was stirred with $NaHCO_3$ (10 g) for 2 h and then filtrated. The filtrate was evaporated under reduced pressure and the residue purified by flash chromatography (C_6H_{12}–EtOAc 8 : 2) as eluent to give successively **12** (yield not determined), **13** (yield not determined) and **11** (9 g, 10%).

5,5-Diethoxypentanal (11)

Colorless oil; R_f 0.5 (C_6H_{12}–AcOEt 5 : 5); MS (ESI) m/z 175 $[M+H]^+$; ^{1}H-NMR (400 MHz; $CDCl_3$) δ 9.63 (1H, s, H-1), 4.36, (1H, t, J = 5.5 Hz, H-5), 3.56–3.30 (4H, m, 2 H-6, 2 H-8), 2.34 (2H, t, J = 7.0 Hz, 2 H-2), 1.61–1.48 (4H, m, 2 H-3, 2 H-4), 1.07 ppm (6H, t, J = 7.1 Hz, 3 H-7, 3 H-9); ^{13}C-NMR (100 MHz; $CDCl_3$) δ 201.9 (C-1), 102.9 (C-5), 60.9 (C-6, C-8), 43.3 (C-2), 32.7 (C-4), 17.1 (C-3), 15.0 ppm (C-7, C-9); IR: υ_{max}(film): 1755, 1056 cm^{-1}.

Products of dimerization

(*E*)-2-(3,3-Diethoxypropyl)-7,7-diethoxyhept-2-enal (14). A 2 M aqueous solution of NaOH (0.1 mL) was heated at 80 °C, **11** (500 mg, 2.9 mmol) was added. The mixture was heated under reflux for 1 h, after which it was cooled and quenched by the addition of H_2O (10 mL) and extracted by CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give **14** (465 mg, 97%). Colorless oil; R_f 0.75 (C_6H_{12}/AcOEt 1 : 1); MS (ESI) m/z 331 $[M+H]^+$; ^{1}H-NMR (400 MHz; $CDCl_3$) δ 9.35 (1H, s, H-1), 6.44 (1H, t, J = 7.4 Hz, H-3), 4.48 (1H, t, J = 5.4 Hz, H-7), 4.43 (1H, t, J = 5.7 Hz, H-3′), 3.70–3.57 (4H, m), 3.52–3.40 (4H, m), 2.38 (2H, q, J = 7.4 Hz, 2 H-4), 2.28 (2H, m, 2 H-1′), 1.71–1.50 (6H, m), 1.22-1.15 ppm (12H, m); ^{13}C-NMR (100 MHz; $CDCl_3$) δ 194.7 (C-1), 154.6 (C-3), 143.2 (C-2), 102.5 (C-7), 102.2 (C-3′), 61.1 (2 × CH_2–O), 60.8 (2 × CH_2–O), 33.3 (C-6), 32.9 (C-2′), 28.4 (C-4), 24.7 (C-5), 19.3 (C-1), 15.2 ppm (4 × CH_3); IR: υ_{max}(film): 1730, 1678, 1639 cm^{-1}.

Deprotection of 14

Protocol 1: a solution of **14** (1 g, 3 mmol) in a mixture of THF–H_2O–TFA 3 : 1 : 3 (10 mL) was stirred for 1 h. The reaction was quenched with a saturated solution of aqueous $NaHCO_3$ (10 mL) and extracted by CH_2Cl_2 (3 × 20 mL). The organic extract was dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow oil, which was purified by flash chromatography (C_6H_{12}–EtOAc 6 : 4) to give **15** (413 mg, 75%).

Protocol 2: compound **14** (10 g, 30 mmol) was dissolved in a mixture of AcOH–H_2O 95 : 5 (100 mL). The mixture was stirred at room temperature and the formation of **15**, **16** and **17** was monitored by TLC (C_6H_{12}–EtOAc 1 : 1). The solvents were evaporated under reduced pressure after the disappearance of **14** to yield a crude mixture which was purified by flash chromatography (C_6H_{12}–EtOAc 8 : 2) giving successively **16** (2.10 g, 27%), **17** (1.15 g, 15%) and **15** (1.69 g, 31%).

(*E*)-Hept-3-ene-1,3,7-tricarbaldehyde (15)

Colorless oil; R_f 0.2 (C_6H_{12}–EtOAc 1 : 1); MS (ESI) *m/z* 183 $[M+H]^+$; ^{1}H-NMR (400 MHz; $CDCl_3$) δ 9.79 (1H, s, H-3′), 9.72 (1H, s, H-7), 9.35 (1H, s, H-1), 6.48 (1H, t, J = 7.4 Hz, H-3), 2.59-2.49 (6H, m, 2 H-2′, 2 H-1′, 2 H-6), 2.44 (2H, q, J = 7,4 Hz, 2 H-4), 1.83 ppm (2H, qu, J = 7.4 Hz, 2 H-5); ^{13}C-NMR (100 MHz; $CDCl_3$) δ 201.2(C-7), 200.8 (C-3′), 194.2 (C-1), 154.3 (C-3), 141.7 (C-2), 42.6 (C-6), 41.7 (C-2′), 27.6 (C-4), 20.4 (C-5), 16.4 ppm (C-1′); IR: υ_{max}(film): 1725, 1685 cm^{-1}.

(*E*)-2-(5,5-Diethoxypentylidene)pentanedial (16)

Colorless oil; R_f 0.55 (C_6H_{12}–EtOAc 1 : 1); MS (ESI) *m/z* 257 $[M+H]^+$; ^{1}H-NMR (400 MHz; $CDCl_3$) δ 9.70 (1H, s, H-5), 9.32 (1H, s, H-1), 6.49 (1H, t, J = 7.4 Hz, H-1′), 4.54 (1H, t, J = 5.3, H-5′), 3.65-3.55 (2H, m, CH_2O), 3.50-3.40 (2H, m, CH_2O), 2.50 (4H, s, 2 H-4, 2*H*-3), 2.38 (2H, q, J = 7.4 Hz, 2 H-2′), 1.68-1.50 (4H, m, 2*H*-4′, 2*H*-3′), 1.16 ppm (6H, t, J = 7.0 Hz, 2 × CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$) δ 201.2 (C-5), 194.8 (C-1), 155.8 (C-1′), 141.8 (C-2), 102.5 (C-5′), 61.3 (CH_2O), 61.1 (CH_2O), 42.3 (C-4), 32.3 (C-4′), 28.7 (C-2′), 23.8 (C-3′), 17.0 (C-3), 15.6 ppm (2 × CH_3).

(*E*)-2-(3,3-Diethoxypropyl)hept-2-enedial (17)

Colorless oil; R_f 0.54 (C_6H_{12}–Et_2O 8 : 2); MS (ESI) *m/z* 257 $[M+H]^+$; ^{1}H-NMR (400 MHz; $CDCl_3$) δ 9.76 (1H, s, H-7), 9.30 (1H, s, H-1), 6.43 (1H, t, J = 7.4 Hz, H-3), 4.40 (1H, t, J = 5.7, H-3′), 3.70-3.60 (2H, m, CH_2O), 3.52-3.40 (2H, m, CH_2O), 2,50 (2H, m, 2 H-6), 2.43 (2H, q, J = 7.4 Hz, 2 H-4), 2.25 (2H, m, 2*H*-1′), 1.87 (2H, m, 2 H-5), 1.60 (2H, m, 2*H*-2′), 1.22-1.10 ppm (6H, m, 2 × CH_3); ^{13}C-NMR (100 MHz; $CDCl_3$) δ 201.4 (C-7), 194.8 (C-1), 153.3 (C-3), 143.8 (C-2), 102.3 (C-3′), 61.3 (CH_2O), 61.1 (CH_2O), 43.2 (C-6), 32.2 (C-2′), 28.2 (C-4), 21.0 (C-5), 19.4 (C-1′), 15.3 ppm (2 × CH_3); IR: υ_{max}(film): 1721, 1680 cm^{-1}.

Protection of trialdehyde 15

Compound **15** (2 g, 11 mmol) was diluted in a mixture of $CHCl_3$–THF–EtOH, 10 : 3 : 0.1 (20 mL). The formation of **14**, **16** and **17** was controlled by TLC (C_6H_{12}–EtOAc 1 : 1). After 6 h the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (C_6H_{12}–EtOAc 8 : 2), to give successively **14** (1.09 g, 30%), **16** (536 mg, 19%) and **17** (874 mg, 31%).

Reactivity of trialdehyde 15

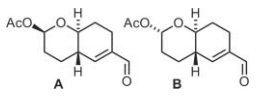
Trialdehyde **15** (150 mg, 0.82 mmol) was dissolved in H_2O (4 mL) and basicified to pH 8.5 with $NaHCO_3$. The basicified solution was heated at 60 °C for 3 h, cooled to room temperature and extracted with CH_2Cl_2 (3 × 7 mL). The concentration under reduced pressure of the dried ($MgSO_4$) combined organic layers gave a crude product that was purified by flash chromatography (CH_2Cl_2–Et_2O 9 : 1) to afford **18** (20 mg, 15%).

(1*E*,5*E*)-Cycloocta-1,5-diene-1,5-dicarbaldehyde (18)

Colorless crystals; R_f 0.71 ($CHCl_3$–EtOAc 1 : 1); MS (ESI) *m/z* 187 $[M+23]^+$; ^{1}H-NMR (400 MHz; $CDCl_3$) δ 9.36 (2H, s, HC=O), 6.61 (2H, t, J = 4.9, H-2), 2.87 (4H, t, J = 6.6 Hz, H-3), 2.69 ppm (4H, dd, J = 11.9, 6.0 Hz, H-4); ^{13}C-NMR (100 MHz; $CDCl_3$) δ 195.0 (HC=O), 154.3 (C-2), 142.0 (C-1), 30.2 (C-3), 20.8 ppm (C-4); IR: υ_{max}(film):, 1675 cm^{-1}; HRMS *m/z* calcd for $C_{10}H_{12}O_2Na$ 187.0735 $[M+Na]^+$; found 187.0737.

Notes and references

1 R. A. Azevedo and P. J. Lea, *Amino Acids*, 2001, **20**, 261–279.
2 See for example: (*a*) W. M. Golebiewski and I. D. Spenser, *Can. J. Chem.*, 1985, **63**, 2707–2718; (*b*) W. M. Golebiewski and I. D. Spenser, *J. Am. Chem. Soc.*, 1984, **106**, 7925–7927.
3 See among many others: A. M. Brown, D. J. Robins, L. Witte and M. Wink, *Plant Physiol. (Life Sci. Adv.)*, 1991, **10**, 179–185 and references cited therein.
4 One needs to keep in mind that in the plants, reactive functional groups such as aldehydes will most likely be masked in a transitory way. In this article, in order to simplify schemes and figures, these functional groups will be shown in their reactive form. In the case of glutaraldehyde, it is a known protein-reticulating agent and its presence as a free molecule in a living cell is of course unlikely but we will see that equivalents in terms of oxidation state can be put forward (*vide infra*).
5 (*a*) E. Gravel, E. Poupon and R. Hocquemiller, *Org. Lett.*, 2005, **7**, 2497–2499; (*b*) E. Gravel, E. Poupon and R. Hocquemiller, *Tetrahedron*, 2006, **62**, 5248–5253; (*c*) R. Salame, E. Gravel, K. Leblanc and E. Poupon, *Org. Lett.*, 2009, **11**, 1891–1894; (*d*) E. Gravel and E. Poupon, *Nat. Prod. Rep.*, 2010, **27**, 32–56.
6 (*a*) M. J. Wanner and G. J. Koomen, in *Studies in Natural Products-Chemistry: Stereoselectivity in Synthesis and Biosynthesis of Lupine and Nitraria Alkaloids*, ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1994; vol. 14, pp 731–768 and references therein; (*b*) M. J. Wanner and G. J. Koomen, *J. Org. Chem.*, 1994, **59**, 7479–7484; (*c*) M. J. Wanner and G. J. Koomen, *J. Org. Chem.*, 1995, **60**, 5634–5637; (*d*) D. François, M.-C. Lallemand, M. Selkti, A. Tomas, N. Kunesch and H.-P. Husson, *J. Org. Chem.*, 1997, **62**, 8914–8916; (*e*) D. François, M.-C. Lallemand, M. Selkti, A. Tomas, N. Kunesch and H.-P. Husson, *Angew. Chem., Int. Ed.*, 1998, **37**, 104–105.
7 See for example: (*a*) V. C. Pham, A. Jossang, T. Sévenet, V. H. Nguyen and B. Bodo, *Tetrahedron*, 2007, **63**, 11244–11249; (*b*) V. C. Pham, A. Jossang, T. Sévenet, V. H. Nguyen and B. Bodo, *Eur. J. Org. Chem.*, 2009, 1412–1416 and references cited therein. See also, ref. 5*d*.
8 Glutaraldehyde **2** is quite stable as an aqueous solution whereas it undergoes rapid polymerization in neat conditions with catalytic amount of water. The numerous applications of **2** have been extensively reviewed over the years as a cross-linking agent in biochemistry or histology or as a biocide: see among others, Types of Antimicrobials Agents, in *Russel, Hugo & Ayliffe's Principle and Practice of Disinfection, Preservation and Sterilization*, ed. A. P. Fraise, P. A. Lambert and J.-Y. Maillard, 4th edn, Blackwell Publishing, Oxford, 2004, pp. 8–97; M. A. Hayat, Glutaraldehyde, in *Principles and Techniques of Electron Microscopy, Biological Applications*, Cambridge University Press, Cambridge, 2000, pp. 28–42; H.-P. Husson, J. Royer, Glutaraldehyde, in *e-EROS Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Chichester, 2001.
9 See *inter alia*: (*a*) P. M. Hardy, A. C. Nicholls and H. N. Rydon, *J. Chem. Soc., Chem. Commun.*, 1969, 565–566; (*b*) T. Tashima, U. Kawakami, M. Harada, T. Sakata, N. Satoh, T. Nakagawa and H. Tanaka, *Chem. Pharm. Bull.*, 1987, **35**, 4169–4180; (*c*) G. Goissis, S. A. Yoshioka, D. M. Braile and V. D. A. Ramirez, *Artif. Organs*, 1998, **22**, 210–214.
10 T. Tashima, M. Imai, Y. Kuroda, S. Yagi and T. Nakagawa, *J. Org. Chem.*, 1991, **56**, 694–697.
11 The yield is of course low, but experimentally speaking, glutaraldehyde **2** is a cheap reagent and **6** is the most nonpolar compound of the reaction based on silica gel TLC profile which renders its purification by chomatography easy. In practise, 15 g of **2** give 3–4 g of **6** in a reproducible manner.
12 No information concerning the stereochemistry of **6** was disclosed in ref. 10. A complete study is given for the first time in the present work..
13 Acetylation of **6** permitted the chromatographic resolution of **A** and **B** resulting from the 2 major diastereomers of **6**—see the ESI†.



14 Komarovinine: T. S. Tulyaganov, A. A. Ibragimov and S. Yu. Yunusov, *Chem. Nat. Compd.*, 1982, **18**, 604–606 komaroine: T. S. Tulyaganov, A. A. Ibragimov and S. Yu. Yunusov, *Chem. Nat. Compd.*, 1984, **20**, 378–379 tetrahydrokomarovinine: T. S. Tulyaganov and S. Yu. Yunusov, *Chem. Nat. Compd.*, 1990, **26**, 49–53.
15 Experimentally speaking, 15 g of **2** can furnished 1–1.5 g of crystalline **10**.
16 Various solvents were used to register NMR spectra. In $CDCl_3$, **10** was not soluble, the addition of a few drops of MeOD resulted in a rapid degradation. Correct spectra were recorded using acetone-d_6, or better, DMSO-d_6, but prolonged standing in solution resulted in an equilibrium with its opened free aldehyde counterpart (δ 9.5 ppm, DMSO-d_6) assignment was therefore difficult.
17 Syntheses and synthetic applications of **11** as well as other dialdehyde monoacetals have been reviewed, see: C. Botteghi and F. Soccolini, *Synthesis*, 1985, 592–604; see also ref. 4*c*. Another convenient procedure is given in the experimental section of the present paper.
18 A. Erkkilä and P. M. Pihko, *Eur. J. Org. Chem.*, 2007, 4205–4216.

