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5-Aminopenta-2,4-dienals: Synthesis, Activation towards Nucleophiles, Molecular Modeling and Biosynthetic Implications in Relation to the Manzamine Alkaloids

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Substituted 5-aminopentadienals and glutaconaldehydes are key elements postulated in the biosynthesis of the diverse class of manzamine-type alkaloids. The activation of 5-aminopentadienals into electrophilic iminium salts and their subsequent reactivity towards various nucleophiles has permitted the synthesis of a series of unsaturated compounds sometimes accompanied by cascades of rearrangements. Molecular modeling of these systems carried out using DFT calculations of HOMO/LUMO was in agreement with the experimental results indicating that strong electrophilic agents, such as $POCl_3$ are required to turn 5-aminopentadienals into electrophiles. New examples of glutaconaldehyde reactivity, especially towards pyridinium salts, are presented and biosynthetic considerations are kept in mind throughout this study.

Introduction

Highly complex and intriguing alkaloids (as represented by **1**–**5** in Figure 1) belonging to the "manzamine family" have stimulated an impressive amount of scientific research over the last 25 years following the isolation and structure determination of manzamine A (**1**) from *Haliclona* sp. sponges by Higa in 1986 (Figure 1).[1]

Although little is known about their true biosynthetic pathway[2] and, in fact, their real origin (symbiotic bacteria within the sponges),[3] manzamine alkaloids have been the focal point of state of the art efforts directed toward their total synthesis especially when biosynthetically inspired. Indeed, two complementary biosynthetic models were put forward in the 1990s, following the Baldwin and Whitehead acrolein and dihydropyridinium hypothesis.[4] The Marazano malonaldehyde and pyridinium hypothesis[5] further enriched a fruitful debate. Both models enabled great achievements in biomimetic synthesis and were finalized in late 2000 by way of a unified model.[6]

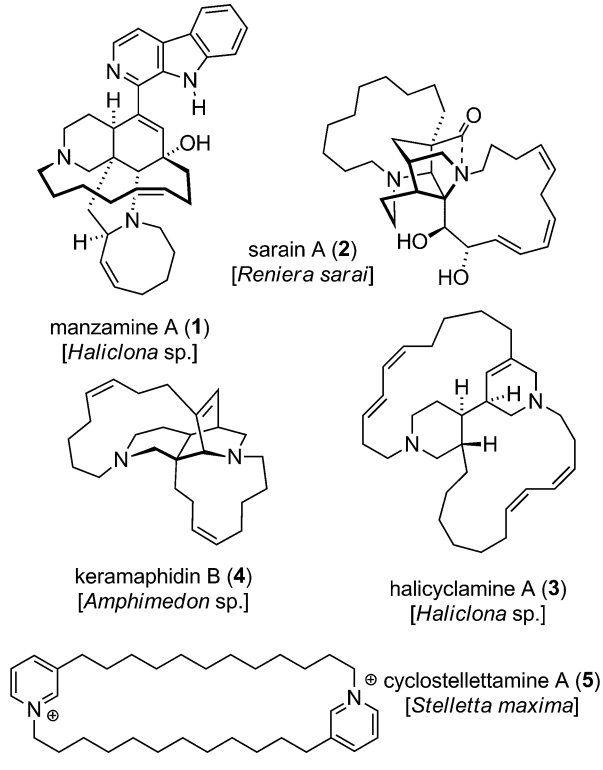

Figure 1. Representative examples of manzamine alkaloids.

Biosynthetically speaking, the key formation of pyridinium salts could be explained by a three-component reaction between a long-chain fatty primary amine, a similar aldehyde and a C_3 unit such as malonaldehyde **6**.[5a] Three types of acyclic C_5 reactive intermediates may be involved in the process: two different types of aminopentadienals (**7′**) and

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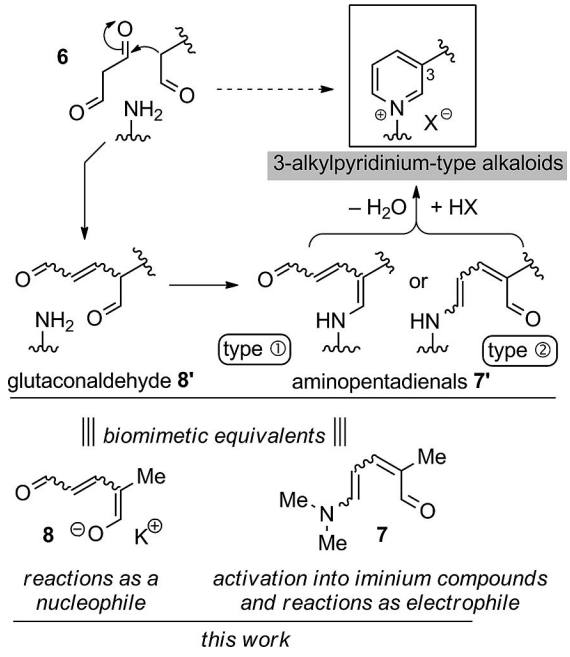
a glutaconaldehyde entity (**8′**) as represented in Scheme 1. Thus, the reactivity of such intermediates constitutes a central question when dealing with the intimate mechanisms governing the formation of manzamine-type alkaloids.



Scheme 1. Key C_5 intermediates involved in the possible biosynthesis of pyridinium rings, and their biomimetic equivalents.

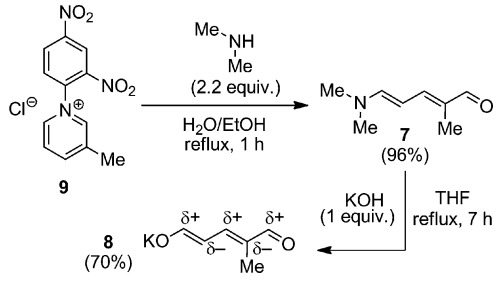
In the present work, 5-aminopentadienal **7** and glutaconaldehyde salt **8**, relevant to the above-mentioned intermediates postulated in the biosynthesis of manzamine alkaloids (they both display a lateral methyl group in place of the long fatty unsaturated side chains), have been prepared and their reactivity studied primarily following activation towards nucleophiles.[7] Biosynthetic considerations are also put forward.

To be more specific, 5-(dimethylamino)penta-2,4-dienals (**7′**), also called "Zincke aldehydes", are the focus of this work. These species readily result from ring opening of pyridinium salts such as "Zincke salts". 5-(Dialkylamino)-penta-2,4-dienals (**7′**) are more stable than the *N*-alkyl counterparts since they cannot cyclize to pyridinium salts.

Results and Discussion

Synthesis of Substrates

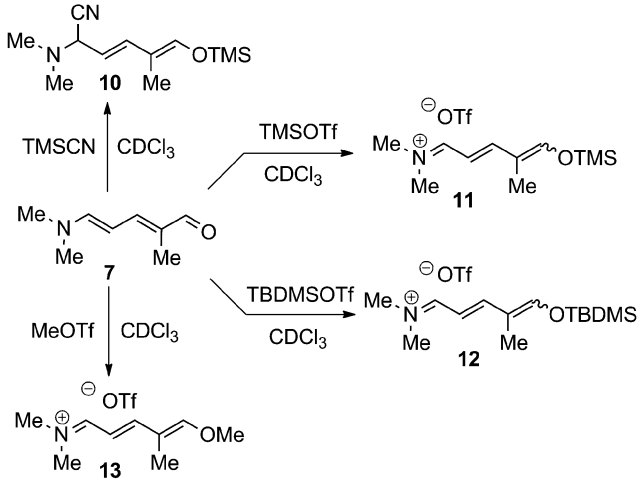
Aminopentadienal **7** was prepared in a one-step procedure by ring-opening of Zincke salt **9** by dimethylamine in a mixture of ethanol and water at reflux.[8] Removal of dinitroaniline by filtration afforded aminopentadienal **7**, which could be used without further purification. An alkaline hydrolysis of **7** in THF at reflux then allowed the preparation of glutaconaldehyde salt **8**, as detailed in Scheme 2.



Scheme 2. Preparation of aminopentadienal **7** and glutaconaldehyde potassium enolate **8**.

Activation to Iminium Salts

Aminopentadienal **7** was first treated with different activation agents and converted into the corresponding iminium salts or masked forms. Compounds **10**–**13** were quantitatively formed (as the major diastereomers >90%) upon reaction of **7** with trimethylsilyl cyanide (TMSCN), trimethylsilyl trifluoromethanesulfonate (TMSOTf), *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) and methyl trifluoromethanesulfonate (MeOTf), respectively. These iminium species (or their equivalents) could be observed by ^{1}H NMR spectroscopy when reactions were conducted in NMR tubes (Scheme 3). Nevertheless, reactions of **10**–**13** with nucleophiles appeared to be disappointing as they led mainly to the recovery of **7** or the formation of inconclusive complex mixtures thereby making recourse to other activating agents indispensable.

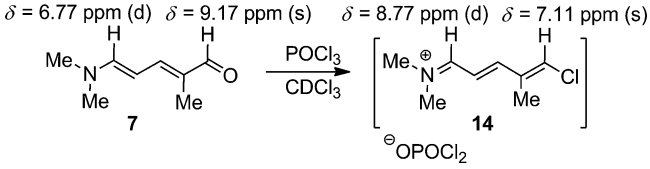


Scheme 3. Structure of iminium salts (or masked forms) **10**–**13** quantitatively obtained from compound **7** with different activating agents in $CDCl_3$.

Activation with Phosphorus Oxychloride and Reaction with Various Nucleophiles

Reaction of **7** with phosphorus oxychloride ($POCl_3$) (Scheme 4) was then investigated and found to generate chloropentadiene iminium compound **14** as the reactive

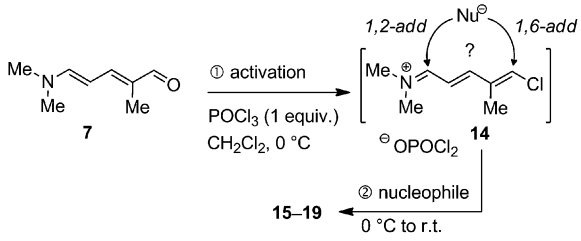
electrophilic entity that can, in fact, be considered as a double vinylogous Vilsmeier reagent.[9]

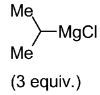
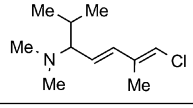
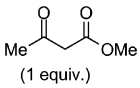
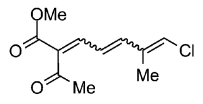
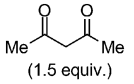
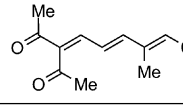
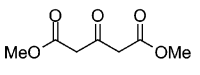
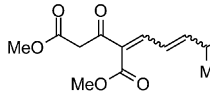
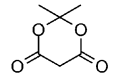
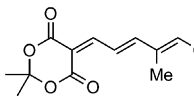


Scheme 4. Structure of chloropentadiene iminium compound **14** obtained by reaction of aminopentadienal **7** with phosphorus oxychloride in $CDCl_3$.

The reactivity of various nucleophiles towards **14** was then evaluated. The ensuing reactions led to isolation of mainly 1,2-addition compounds in moderate yields as summarized in Table 1. This was the case with isopropylmagnesium chloride (Table 1, Entry 1), methyl acetoacetate (Table 1, Entry 2), 2,4-pentanedione (Table 1, Entry 3) both in the presence of sodium methoxide, dimethyl 1,3-acetonedicarboxylate (Table 1, Entry 4) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and finally, Meldrum's acid (Table 1, Entry 5), which led respectively to compounds **15**–**19**.

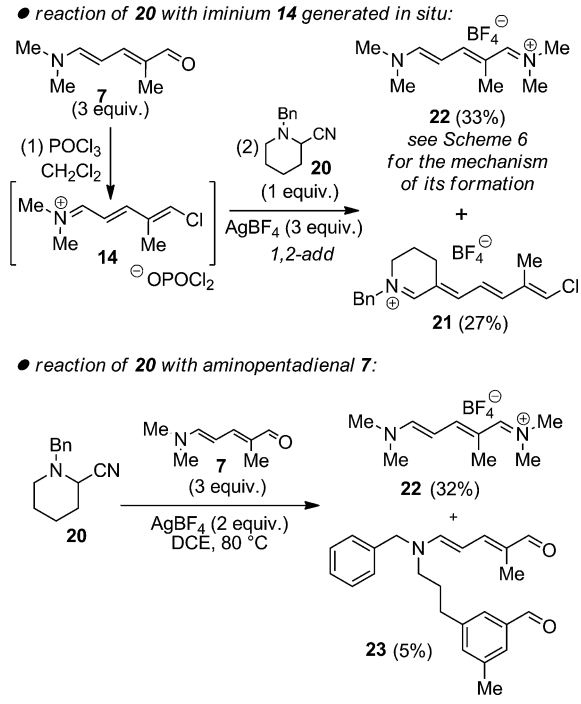
Table 1. Reactivity studies of aminopentadienal **7** activated by phosphorus oxychloride.



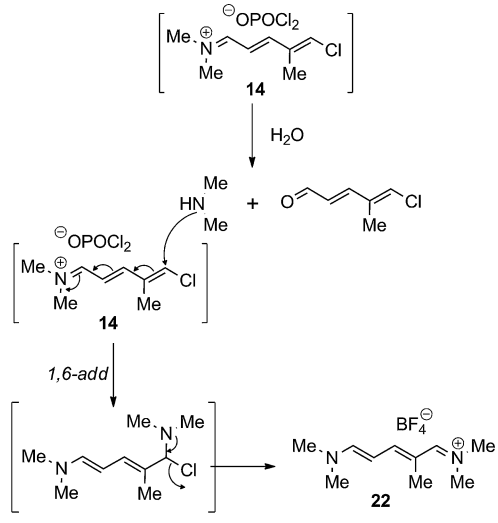
Entry	Nucleophile	Product	Yield (%)[a]
1	 (3 equiv.)	 **15**	18
2[b]	 (1 equiv.)	 **16**	36
3[b]	 (1.5 equiv.)	 **17**	37
4[c]		 **18**	12
5	 (2 equiv.)	 **19**	62

[a] Isolated yield. [b] A mixture of nucleophile and sodium methoxide (1.5 equiv.) was added to the iminium compound **14**; 22 h later, a mixture of nucleophile (2 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2 equiv.) was added to the reaction mixture. [c] Dimethyl 1,3-acetonedicarboxylate (1.2 equiv.) was added. After 23 h, additional nucleophile (1.2 equiv.) with DBU (1.2 equiv.) was added.

Appearing as pivotal functionalities in alkaloid biosynthesis, enamines were also tested as nucleophiles, as detailed in Scheme 5. An endocyclic enamine, masked as its aminonitrile form **20** was used. Reaction of **20** with iminium compound **14**, in the presence of $AgBF_4$, led to isolation of

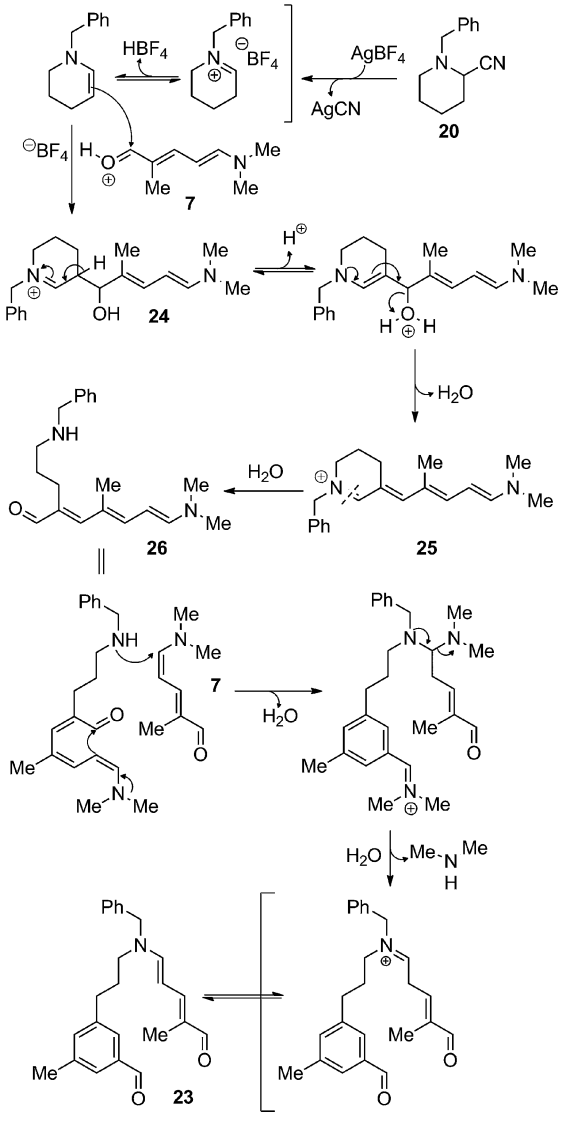


Scheme 5. Reaction of masked enamine **20** with iminium compound **14** and aminopentadienal **7** in the presence of $AgBF_4$.



Scheme 6. Hypothesized mechanism for formation of compound **22**.

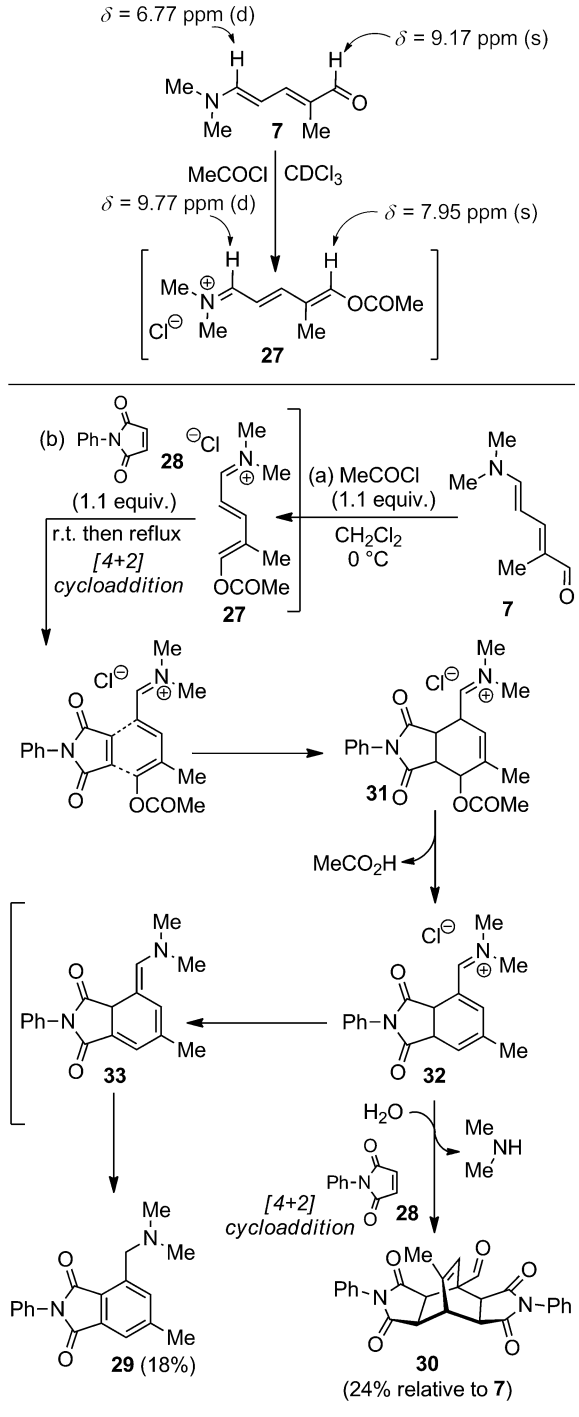
1,2-addition adduct **21** along with aminopentadiene iminium salt **22**.[10] The formation of **22** may involve the hydrolysis of chloro iminium compound **14**. As silver tetrafluoroborate is highly hygroscopic, the hydrolysis of **14** might lead to the release of dimethylamine, which could undergo a 1,6-addition to afford compound **22**.[11] (Scheme 6). When **20** reacted directly with unactivated aminopentadienal **7**, in the presence of $AgBF_4$, aminopentadiene iminium salt **22** could be isolated together with minor product **23**. The latter may result from an impressive cascade of reactions and rearrangements leading to, among other processes, formation of a disubstituted benzaldehyde aromatic ring as proposed in Scheme 7. Indeed, awaited compound **25** underwent hydrolysis providing a secondary amine and free aldehyde **26**. Compound **26** reacted with another molecule of **7** and with cyclization of the newly formed aminoheptatrienal (a vinylogous analogue of aminopentadienals evoked so far in this paper).



Scheme 7. Hypothesized mechanism for formation of compound **23**.

Activation with Acetyl Chloride and Reaction as a Diene

The *O*-acetylation of **7** by acetyl chloride in dichloromethane was achieved leading to iminium compound **27** (see selected NMR spectroscopic data in Scheme 8).[12] Whereas the addition of some nucleophiles evaluated above (such as 2,4-pentanedione, methyl acetoacetate) failed to provide new compounds and led to the recovery of starting



Scheme 8. Formation of compounds **29** and **30** by reaction of acetoxy iminium compound **27** with *N*-phenylmaleimide (**28**).

7, acetoxy iminium compound **27** could be involved as a diene in a Diels–Alder reaction with *N*-phenylmaleimide (**28**). Two rearranged compounds **29** and **30** were isolated, resulting from one and two cycloaddition reactions in 18 and 24% yields, respectively, according to the proposed mechanism (Scheme 8). In fact, a first cycloaddition reaction with *N*-phenylmaleimide (**28**), followed by in situ elimination of acetic acid, could generate intermediate **32** which, in turn, may aromatize to **29** or undergo a second cycloaddition affording compound **30**.

Molecular Modeling

As observed experimentally, aminopentadienal **7** does not appear to be aggressive enough to react efficiently with mild nucleophiles. This species needs to be activated by means of the strong electrophilic agent $POCl_3$. The resulting chloro iminium compound **14** is then able to act as an electrophile with a plethora of nucleophiles (Table 1). The addition reactions predominantly afforded 1,2 adducts with C-nucleophiles (Table 1, Entries 1–5). Alternatively, acetoxy iminium compound **27**, equivalent of **14**, seems to react at its carbonyl carbon atom with anionic nucleophiles. However, **27** also behaves as a good diene partner in the Diels–Alder reaction with *N*-phenylmaleimide (**28**) as the dienophile (Scheme 8).

To shed light on our experimental results, we carried out a modeling study of these systems on the B98 DFT level of theory[13] as implemented within GAMESS.[14] The 6-31++G(dp) criterion was selected as the basis set throughout all the modeling experiments to give a fair representation of glutaconaldehyde as its enolate form **8** (Figure 2).[15] The C_s symmetry was imposed on the four studied molecules **7**, **8**, **14** and **27** with all-*trans* configurations to ease the reading of orbital coefficients, particularly those of the LUMO and HOMO Pz orbitals.[16]

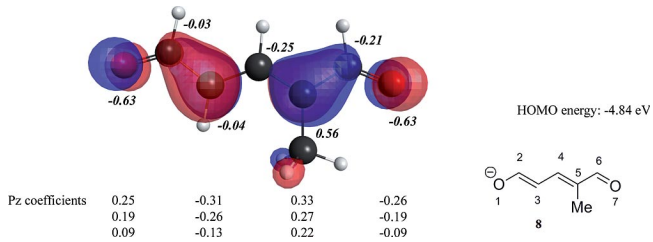


Figure 2. HOMO orbital of glutaconaldehyde as its enolate form **8**. Mulliken charges are shown in bold/italics. Calculations were carried out with ethanol as a solvent.

In good agreement with the experimental data, chloro iminium compound **14** was found to be the most reactive since its LUMO energy was as low as –3.54 eV (Figure 3). Then came acetoxy iminium compound **27** at –3.35 eV and finally, aminopentadienal **7**, whose LUMO energy was found to be only –1.52 eV.

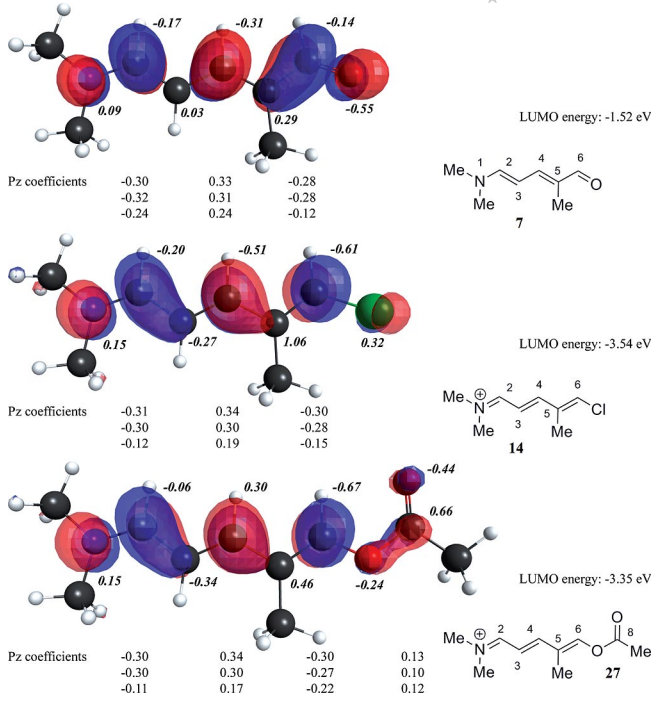


Figure 3. LUMO orbitals of **7**, **14** and **27** (from top to bottom). Mulliken charges are shown in bold/italics. Calculations were carried out with dichloromethane as a solvent. (Number 1 has been given to the nitrogen atom for compounds **7**, **14** and **27**).

Accordingly, **7** is not a good electrophile. These figures obtained from calculations with dichloromethane as a solvent, are very similar to those resulting from gas-phase computations.[17] To account for the selectivity of addition, the shapes of LUMO orbitals were examined. In all cases, the empty orbital is highly delocalized mainly over three carbon atoms (C-2, C-4 and C-6). The Pz orbitals are decomposed into three constituents, describing internal, intermediate and external contributions. The delocalization is so well dispatched that it is difficult to pinpoint precisely which carbon centre constitutes the preferred electrophilic site. It is then necessary to consider another important feature of these molecules, their electronic distribution. Being electrophiles, they are destined to react with electron-rich molecules, like anions (Table 1). Consequently, electron-deficient regions will be preferentially attacked by nucleophiles. By considering both orbital coefficients as well as charges over the carbon atoms of interest (C-2, C-4 and C-6), we could ascertain the following trends. First, chloro iminium compound **14** definitely reacts through its C-2 position. Additionally, acetoxy iminium compound **27** could undergo addition at the C-4 position. However, the ester carbonyl carbon atom (C-8) is so positively charged (0.66) that this property could overwhelm the impact of all other parameters. Attack at this position would induce cleavage of the enol acetate. This is indeed confirmed experimentally, since **27** consistently reverts back to its aldehyde precursor **7** when treated with various nucleophiles.

On the other hand, **27** reacts with *N*-phenylmaleimide (**28**) to give the Diels–Alder adduct **31**. The pathway of this transformation was entirely reconstructed by means of an intrinsic reaction coordinate (IRC) protocol using dichloromethane as a solvent (Figure 4)[18] Its activation energy is rather low at 20.5 kcal mol^{-1} (from the *s-cis* conformer of **27′**). Accordingly, the reaction is rather facile since it requires only a temperature as low as that of boiling dichloromethane. Only the *endo* trajectory was considered as it usually leads to the primary experimental adduct.[19] The *exo* adduct, normally less favoured, is formed following a very similar path. The main goal of the study was predominantly to estimate the energy profile of the reaction and its mechanism. Thus, the mechanism is concerted and asynchronous. At the transition state, the shortest bond located at the acetate end of the diene is 2.16 Å long, whereas the length of the longest bond undergoing formation is 2.29 Å.

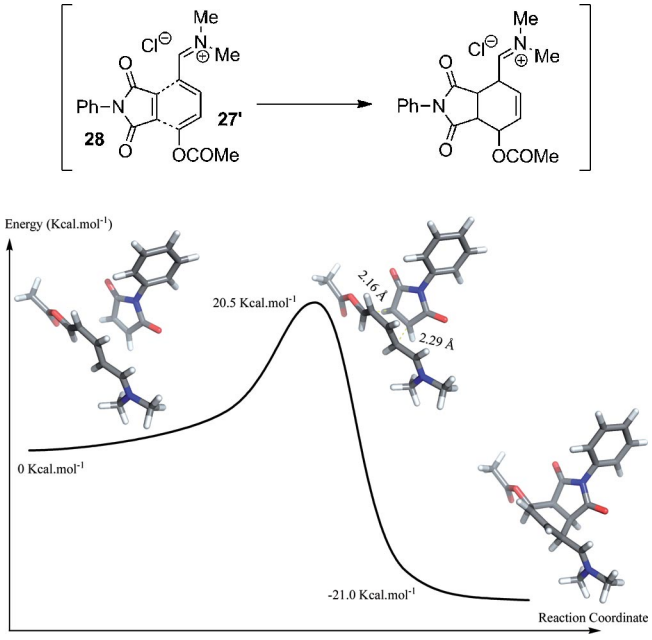
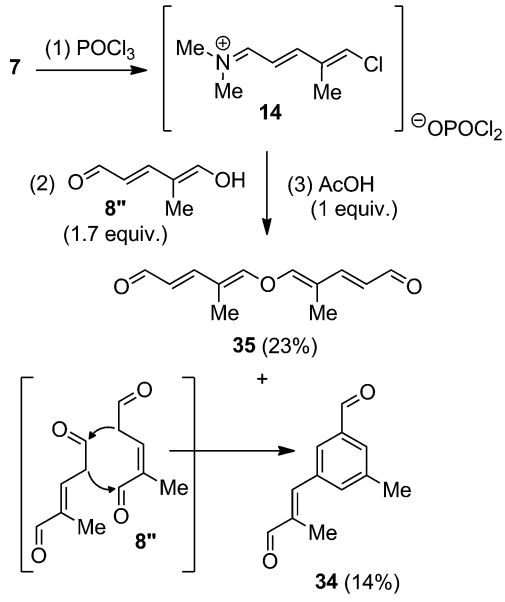


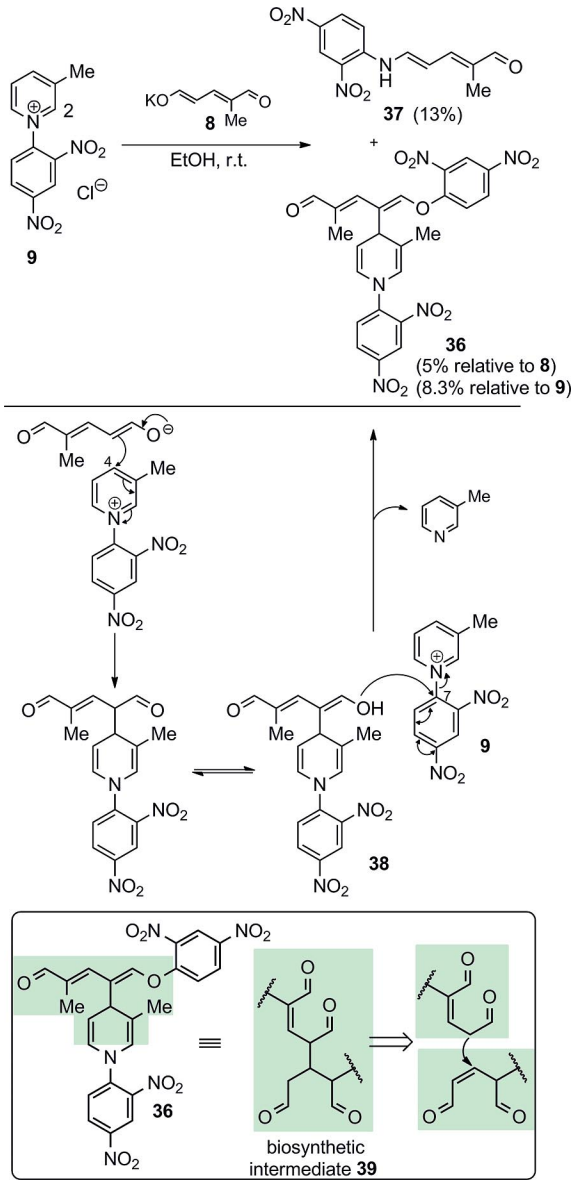
Figure 4. Summary of IRC calculations of the Diels–Alder reaction with **27′** as diene and **28** as dienophile (*endo* approach). Calculations were carried out using dichloromethane as a solvent.

Combining Aminopentadienal 7 and Glutaconaldehyde Salt 8 and Beyond

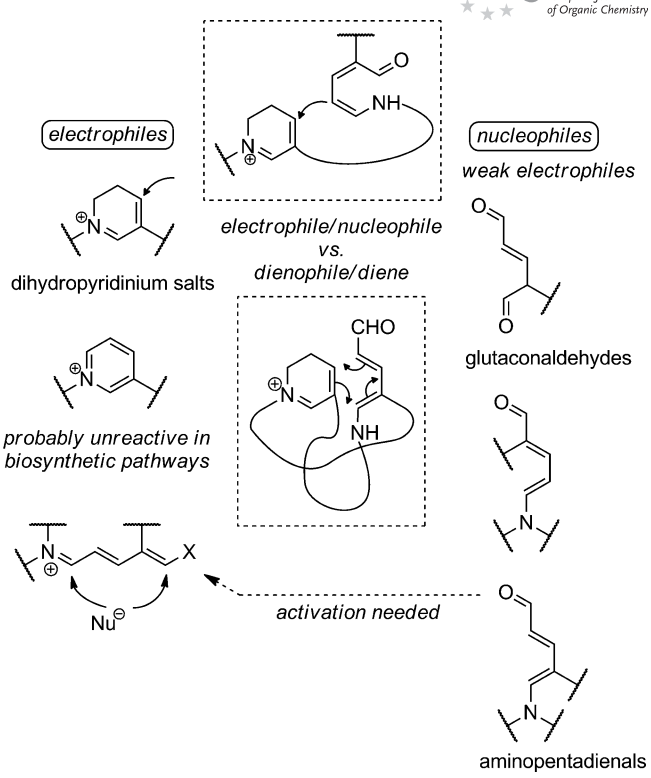
The self- and cross-condensations of substituted C_5 units such as aminopentadienals and glutaconaldehydes are, among others, crucial points in biomimetic approaches to the manzamine alkaloid group.[6] Whereas both types of units may react with electrophilic dihydropyridinium salts (corresponding to a cyclized and partially reduced form of aminopentadienals), the condensation of such units remains a challenge. In our hands, reaction of chloro iminium compound **14** (prepared with phosphorus oxychloride) with glutaconaldehyde **8″** did not yield any characterizable cross-coupling-derived compounds. Instead, substituted benzaldehyde **34** corresponding per se to dimerization of **8″** according to the proposed mechanism (Scheme 9) was isolated.[20] Compound **35**, a 1,6-addition adduct (see frame in Scheme 9) of **8″** with iminium compound **14** was also isolated from the reaction mixture. However, a crucial C–C bond formation was also observed when one of the C_5 units was replaced by Zincke salt **9**. After standing at room temperature, compound **36** was isolated with some difficulty[21] and was characterized as the adduct of two molecules of **9** and one molecule of **8**. Furthermore, generation of **36** was accompanied by compound **37**,[22] resulting from ring opening of pyridinium salt **9** after the addition of a hydroxide ion at C-2. Compound **36** may be formed and explained according to the mechanism presented in Scheme 10. Usually, the pyridinium ring of the Zincke salt is attacked at the C-2 or C-6 positions by nucleophiles with concomitant expulsion of 2,4-dinitroaniline. However, in our case, glutaconaldehyde salt **8**, as a soft nucleophile, reacted at the C-4 position of the pyridinium ring. We then envision that the enol oxygen atom of intermediate **38** attacked a second molecule of **9** since its two nucleophilic carbon atoms were substituted.[23] This type of nucleophilic substitution of the pyridinium ring of the Zincke salt is uncommon with the release of picoline instead of the 2,4-dinitroaniline. In itself and as represented in the frame of Scheme 10, compound **36** displays the key C–C bond found in most complex manzamine alkaloids. However, its low rate of formation also casts doubt on the implication of pyridinium salts acting as electrophiles during the biosynthesis of manzamine-type alkaloids.



Scheme 9. Reactivity of glutaconaldehyde **8″** with chloro iminium compound **14**.



Scheme 10. Reactivity of glutaconaldehyde potassium enolate **8** with Zincke salt **9**.



Scheme 11. Reactive tool box.

Conclusions

From the numerous and informative biomimetic studies[4–6] and from the present results of our work, it is possible to distinguish several reactive entities plausibly implicated in the biosynthesis of manzamine-type alkaloids. A selection of key elements allows us to highlight the following points (Scheme 11) and more generally to demonstrate the usefulness of biomimetic strategies in comprehending potential mechanistic steps at play during the biosynthesis of natural substances.

(i) The entities acting predominantly as strong electrophiles in biosynthetic pathways should be dihydropyridinium salts: general reactivity constraints should allow easy functionalization in vivo.

(ii) Glutaconaldehydes and aminopentadienals appear to serve as good nucleophiles. Strong activation is needed to turn the latter into electrophiles as demonstrated in the present work. Dihydropyridinium salts may also act as dienophiles and aminopentadienals (or their activated form) may serve as dienes.

(iii) Self-condensation of glutaconaldehyde-type entities is possible in the laboratory (see formation of compound **34**) but has no obvious biosynthetic consequences to the best of our knowledge.

The extensive tool box of reactivities generated over the years should now be applied to in vivo studies to help illuminate the biosynthetic pathways responsible for such complex alkaloids.

Experimental Section

General: Reactions were monitored by thin-layer chromatography carried out on silica gel plates (Merck TLC Silicagel 60_{F254}) using UV light as visualizing agent and sulfuric vanillin and heat and Draggendorff reagent and heat as developing agents. Merck Silicagel Geduran® Si 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 are used to explain the multiplicities: s = singlet; d = doublet, t = triplet; q = quartet; quint = quintet; m = multiplet; br. = broad. IR spectra were recorded with a 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).

(2*E*,4*E*)-5-(Dimethylamino)-2-methylpenta-2,4-dienal (7): Adapted from Michel et al.[8] To a stirred solution of Zincke salt **9** (10.0 g,

33.8 mmol) in a mixture of EtOH/H_2O (1:1) (100 mL) at reflux, dimethylamine (9.30 mL, 40% in H_2O, 73.8 mmol) was added dropwise. After 1 h of stirring at reflux, the mixture was concentrated under reduced pressure, and water (150 mL) was added. The precipitated brown 2,4-dinitroaniline was then removed by filtration through a pad of Celite®. The filtrate was extracted with CH_2Cl_2 (4× 60 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to give aminopentadienal **7** (4.24 g, 90%) as an orange solid. M.p. 56 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.17 (s, 1 H, CHO), 6.84 (d, $^3J_{H,H}$ = 11.6 Hz, 1 H, CH), 6.77 (d, $^3J_{H,H}$ = 12.4 Hz, 1 H, =CHN), 5.25 (dd, $^3J_{H,H}$ = 12.4, 12.0 Hz, 1 H, *CH*), 2.96 (s, 6 H, 2 CH_3), 1.76 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7 (CHO), 153.4 (CH), 151.2 (=CHN), 126.2 (C_{IV}), 95.0 (CH), 9.1 (CH_3) ppm. IR (film, CH_2Cl_2): $\tilde{\nu}_{max}$ = 1543 (ν C=O) cm^{-1}. MS (APCI): *m*/*z* = 140 [M + H]$^+$. HRMS (ESI): calcd. for $C_8H_{14}NO$ 140.1075 [M + H]$^+$; found 140.1078. R_f = 0.62 (CH_2Cl_2/MeOH, 9:1).

(2*E*,4*E*)-5-Hydroxy-2-methylpenta-2,4-dienal Potassium Salt (8):[8] Potassium hydroxide (2.01 g, 30 mmol) was dissolved in a minimum of MeOH under N_2; then dry THF (75 mL) and aminopentadienal **7** (4.24 g, 30 mmol) were added. The mixture was stirred at reflux for 6 h, then cooled in an ice bath (–5 °C), and Et_2O (130 mL) was added. After 30 min of stirring, the brown precipitate was filtered and rinsed with CH_2Cl_2. The solid was dissolved in absolute EtOH (200 mL), cooled to –10 °C for 30 min and filtered through a pad of Celite®. The filtrate was concentrated in vacuo to give the potassium salt of glutaconaldehyde **8** (3.20 g, 70%) as a beige powder. M.p. >400 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.65 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, =CHO), 8.55 (s, 1 H, CHO), 6.90 (d, $^3J_{H,H}$ = 13.0 Hz, 1 H, CH), 5.07 (dd, $^3J_{H,H}$ = 13.0, 9.2 Hz, 1 H, CH), 1.48 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 183.3 (CHO), 183.2 (CHO), 158.6 (CH), 110.8 (C_{IV}), 103.6 (CH), 9.5 (CH_3) ppm. IR (solid): $\tilde{\nu}_{max}$ = 1504 (ν C=O) cm^{-1}. HRMS (ESI): calcd. for $C_6H_7O_2$ 111.0446 [M – K]; found 111.0437.

1-(2,4-dinitrophenyl)-3-methylpyridinium Chloride (Zincke Salt 9):[24] To a solution of 1-chloro-2,4-dinitrobenzene (21.7 g, 107 mmol) in acetone (100 mL), 3-picoline (10.5 mL, 107 mmol) was added, and the reaction mixture was stirred at reflux for 12 h. After cooling at room temperature, filtration and rinsing with acetone gave the expected compound (27.8 g, 87%) as a purple powder. M.p. 206–207 °C. ^{1}H NMR (400 MHz, D_2O): δ = 9.40 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, CH), 9.03 (s, 1 H, CH), 8.98 (d, $^3J_{H,H}$ = 6.6 Hz, 1 H, CH), 8.94 (dd, $^3J_{H,H}$ = 8.8, $^4J_{H,H}$ = 2.4 Hz, 1 H, CH), 8.76 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, CH), 8.25 (dd, $^3J_{H,H}$ = 8.0, 6.6 Hz, 1 H, CH), 8.22 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, CH), 2.67 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 149.6 (CH), 149.5 (CNO_2), 144.5 (CH), 142.9 (CNO_2), 142.5 (CH), 140.5 (CMe), 138.7 (C_{IV}), 131.1 (CH), 130.5 (CH), 127.6 (CH), 122.7 (CH), 17.8 (CH_3) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1531 (NO_2), 1345 (NO_2) cm^{-1}. MS (ESI): *m*/*z* = 259 [M]$^+$.

(3*E*,5*E*)-2-(Dimethylamino)-5-methyl-6-(trimethylsilyloxy)hexa-3,5-dienenitrile (10): To a solution of aminopentadienal **7** in $CDCl_3$ (previously filtered through K_2CO_3) was added one drop of TMSCN in an NMR tube. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.49 (s, 1 H, C*H*OSiMe$_3$), 6.44 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, CH), 5.32 (dd, $^3J_{H,H}$ = 16.0, 4.5 Hz, 1 H, CH), 4.31 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, CHCN), 2.31 [s, 6 H, $(CH_3)_2$N], 1.70 (s, 3 H, CH_3), 0.21 (s, 9 H, $SiMe_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.2 (C*H*OSiMe$_3$), 135.5 (CH), 116.7 (C_{IV}), 116.2 (CH), 115.1 (CN), 60.8 (*CH*CN), 41.5 [$(CH_3)_2$N], 9.3 (CH_3), –0.5 ($SiMe_3$) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1255, 1183 cm^{-1}. MS (APCI): *m*/*z* = 239 [M + H]$^+$, 212 [M – CN]$^+$.

***N*-Methyl-*N*-[(2*E*)-4-methyl-5-(trimethylsilyloxy)penta-2,4-dienylidene]methanaminium Trifluoromethanesulfonate (11):** To a solution of aminopentadienal **7** in $CDCl_3$ (previously filtered through K_2CO_3) was added one drop of TMSOTf in an NMR tube. Two isomers **A** and **B** were observed (ratio 60:40). Isomer **A** (major): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, $^3J_{H,H}$ = 11.1 Hz, 1 H, CH=N), 7.78 (d, $^3J_{H,H}$ = 13.8 Hz, 1 H, CH), 7.29 (s, 1 H, C*H*OSiMe$_3$), 6.14 (dd, $^3J_{H,H}$ = 13.8, 11.1 Hz, 1 H, CH), 3.59 (s, 3 H, CH_3N), 3.38 (s, 3 H, CH_3N), 1.79 (s, 3 H, CH_3), 0.05 (s, 9 H, $SiMe_3$) ppm. Isomer **B**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, $^3J_{H,H}$ = 11.1 Hz, 1 H, CH=N), 7.61 (d, $^3J_{H,H}$ = 13.8 Hz, 1 H, CH), 7.54 (s, 1 H, CHO), 6.03 (dd, $^3J_{H,H}$ = 13.8, 11.1 Hz, 1 H, CH), 3.53 (s, 3 H, CH_3N), 3.33 (s, 3 H, CH_3N), 1.78 (s, 3 H, CH_3), 0.31 (s, 9 H, $SiMe_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.7 (CH), 167.6 (CH), 167.5 (CH), 166.6 (CH), 165.0 (CH), 161.7 (CH), 121.0 (C_{IV}), 116.9 (C_{IV}), 109.6 (CH, **A**), 107.7 (CH, **B**), 48.1 (CH_3N, **A**), 47.7 (CH_3N, **B**), 39.9 (CH_3N, **A**), 39.5 (CH_3N, **B**), 8.6 (CH_3, **A**), 8.3 (CH_3, **B**), 1.9 (CH_3Si, **A**), –0.6 (CH_3Si, **B**) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1616, 1576 (C=N), 1280, 1164 cm^{-1}. MS (ESI): *m*/*z* = 154 [M – OTf – OSiMe$_3$ + OMe]$^+$.

***N*-[(2*E*)-5-(*tert*-Butyldimethylsilyloxy)-4-methylpenta-2,4-dienylidene]-*N*-methylmethanaminium Trifluoromethanesulfonate (12):** To a solution of aminopentadienal **7** in $CDCl_3$ (previously filtered through K_2CO_3) was added one drop of TBDMSOTf in an NMR tube. Two isomers **A** and **B** were observed (ratio 67:33). Isomer **A**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (d, $^3J_{H,H}$ = 11.1 Hz, 1 H, CH=N), 7.83 (d, $^3J_{H,H}$ = 13.8 Hz, 1 H, CH), 7.32 (s, 1 H, CH), 6.13 (dd, $^3J_{H,H}$ = 13.8, 11.1 Hz, 1 H, CH), 3.61 (s, 3 H, CH_3N), 3.39 (s, 3 H, CH_3N), 1.81 (s, 3 H, CH_3), 0.95 [s, 9 H, $C(CH_3)_3$], 0.28 [s, 6 H, $Si(CH_3)_2$] ppm. Isomer **B**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, $^3J_{H,H}$ = 10.8 Hz, 1 H, CH=N), 7.65 (d, $^3J_{H,H}$ = 13.8 Hz, 1 H, CH), 7.59 (s, 1 H, CH), 6.01 (dd, $^3J_{H,H}$ = 13.8, 10.8 Hz, 1 H, CH), 3.54 (s, 3 H, CH_3N), 3.33 (s, 3 H, CH_3N), 1.79 (s, 3 H, CH_3), 0.86 [s, 9 H, $C(CH_3)_3$], 0.01 [s, 6 H, $Si(CH_3)_2$] ppm. Isomers **A** and **B**: ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8 (CH), 167.0 (CH), 162.2 (CH), 122.6 (C_{IV}, **A** or **B**), 120.8 (C_{IV}, **A** or **B**), 109.6 (CH), 48.1 (CH_3N), 39.9 (CH_3N), 25.7 and 25.2 [$(CH_3)_3$C-Si], 18.0 [$C(CH_3)_3$], 8.6 (CH_3), –3.0 (CH_3Si), –5.4 (CH_3Si) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1615, 1582 (C=N), 1193, 1163 cm^{-1}. MS (ESI): *m*/*z* = 154 [M – OTf – OTBDMS + OMe]$^+$.

***N*-[(2*E*,4*E*)-5-Methoxy-4-methylpenta-2,4-dienylidene]-*N*-methylmethanaminium Trifluoromethanesulfonate (13):** To a solution of aminopentadienal **7** in $CDCl_3$ (previously treated with K_2CO_3) was added one drop of MeOTf in an NMR tube. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.34 (d, $^3J_{H,H}$ = 10.8 Hz, 1 H, CH=N), 7.74 (d, $^3J_{H,H}$ = 14.0 Hz, 1 H, CH), 7.17 (s, 1 H, *CH*OCH$_3$), 6.11 (dd, $^3J_{H,H}$ = 14.0, 10.8 Hz, 1 H, CH), 3.79 (s, 3 H, OCH_3), 3.56 (s, 3 H, CH_3N), 3.37 (s, 3 H, CH_3N), 1.77 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4 (CH), 168.0 (*CH*OCH$_3$), 166.2 (CH), 117.1 (C_{IV}), 109.3 (CH), 62.7 (OCH_3), 48.0 (CH_3N), 39.8 (CH_3N), 8.7 (CH_3) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1605, 1572 (C=N), 1193, 1142 (C=C–OCH_3) cm^{-1}. MS (APCI): *m*/*z* = 154 [M – OTf]$^+$.

***N*-[(2*E*,4*E*)-5-Chloro-4-methylpenta-2,4-dienylidene]-*N*-methylmethanaminium Dichlorophosphate (14):** To a solution of aminopentadienal **7** in $CDCl_3$ was added one drop of phosphorus oxychloride ($POCl_3$) in an NMR tube. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, CH=N), 7.78 (d, $^3J_{H,H}$ = 14.4 Hz, 1 H, CH), 7.11 (s, 1 H, CHCl), 6.53 (dd, $^3J_{H,H}$ = 14.4, 10.5 Hz, 1 H, CH), 3.76 (s, 3 H, CH_3N), 3.58 (s, 3 H, CH_3N), 2.07 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7 (CH=N), 161.3 (CH), 138.2 (CHCl), 137.4 (C_{IV}), 115.9 (CH), 49.5 (CH_3N), 41.5 (CH_3N), 12.4 (CH_3) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ =

1657, 1599 (C=N), 1227, 1069 (C–Cl) cm^{-1}. HRMS (ESI): calcd. for $C_8H_{13}ClN$ 158.0731 $[M - OPOCl_2]^+$; found 158.0731.

Compound 15: To a solution of aminopentadienal **7** (100 mg, 0.719 mmol) in dry dichloromethane (5 mL) was added phosphorus oxychloride (0.07 mL, 0.719 mmol) at 0 °C under N_2. After stirring for 10 min, a 2 M isopropylmagnesium chloride solution in THF (0.36 mL, 0.720 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h after which additional isopropylmagnesium chloride (0.72 mL, 1.44 mmol) was added. After 2 d of stirring, water (5 mL) and brine (5 mL) were slowly added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2× 20 mL). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The oily residue was then purified by flash chromatography on silica gel with a gradient solvent system (CH_2Cl_2 to CH_2Cl_2/MeOH, 95:5 to 90:10) to afford compound **15** (26 mg, 18%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.32 (d, $^3J_{H,H}$ = 15.6 Hz, 1 H, CH), 6.29 (s, 1 H, CHCl), 5.62 (dd, $^3J_{H,H}$ = 15.2, 9.6 Hz, 1 H, CH), 3.26 (dd, $^3J_{H,H}$ = 10.0, 6.4 Hz, *i*Pr*CH*CH=), 2.73 [s, 6 H, $(CH_3)_2N$], 2.20 [m, 1 H, *CH*$(CH_3)_2$], 1.94 (s, 3 H, CH_3), 1.10 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, *CH*$_3$CH), 1.04 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, *CH*$_3$CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.6 (CH), 135.3 (C_{IV}), 123.5 (CHCl), 118.2 (CH), 75.1 (*i*Pr*CH*CH=), 41.2 [$(CH_3)_2N$], 28.8 [*CH*$(CH_3)_2$], 20.7 (*CH*$_3$CH), 18.1 (*CH*$_3$CH), 12.9 (CH_3) ppm. HRMS (ESI): calcd. for $C_{11}H_{21}ClN$ 202.1363 $[M + H]^+$; found 202.1363. R_f = 0.45 (CH_2Cl_2/MeOH, 9:1).

Compound 16: To a solution of aminopentadienal **7** (100 mg, 0.719 mmol) in dry dichloromethane (5 mL) was added phosphorus oxychloride (0.07 mL, 0.719 mmol) at 0 °C under N_2. After stirring for 10 min, a mixture of methyl acetoacetate (0.08 mL, 0.741 mmol) and a 30% (w/w) sodium methoxide solution in methanol (0.20 mL, 1.08 mmol) was added, and the reaction mixture was stirred at room temperature for 22 h after which a mixture of methyl acetoacetate (0.16 mL, 1.44 mmol) and DBU (0.22 mL, 1.44 mmol) in CH_2Cl_2 was added. After 4 d of stirring, the reaction mixture was concentrated in vacuo. The oily residue was then purified by flash chromatography on silica gel with a gradient solvent system (cyclohexane/ethyl acetate, 9:1 to 7:3) to afford compound **16** (59 mg, 36%) as a yellow oil. A mixture of 2 isomers **A** and **B** with a ratio 70:30 in favour of isomer **A** and for each isomer, two forms are observed by NMR spectroscopy, leading to a mixture of 4 geometric isomers in a ratio of 0.35:0.35:0.15:0.15. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.44 (m, 0.3 H, CH, **B**), 7.29–7.35 (m, 0.7 H, CH, **A**), 7.26–7.35 (m, 0.3 H, CH, **B**), 6.66–6.74 (m, 0.7 H, CH, **A**), 6.66–6.87 (m, 1 H, CH, **A** and **B**), 6.44 (s, 0.35 H, CHCl, **A**), 6.42 (s, 0.35 H, CHCl, **A**), 6.21 (s, 0.15 H, CHCl, **B**), 6.19 (s, 0.15 H, CHCl, **B**), 3.88 (s, 3 H, OMe, **A**), 3.83 (s, 0.9 H, OMe, **B**), 3.82 (s, 2.1 H, OMe, **B**), 2.43 (s, 3 H, CH_3CO, **A**), 2.39 (s, 0.9 H, CH_3CO, **B**) 2.37 (s, 2.1 H, CH_3CO, **B**), 1.97 (s, 1.05 H, CH_3, **A**), 1.96 (s, 1.05 H, CH_3, **A**), 1.94 (s, 0.45 H, CH_3, **B**), 1.92 (s, 0.45 H, CH_3, **B**) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1 (*CO*Me), 195.4 (*CO*Me), 166.6 (*CO*OMe), 165.7 (*CO*OMe), 145.1 (CH), 144.9 (CH), 137.3 (C_{IV}), 134.0 (C_{IV}), 132.4 (C_{IV}), 131.7 (C_{IV}), 126.2 (CHCl), 123.8 (CH), 121.7 (CHCl) 55.2 (MeO), 31.1 (MeCO), 12.7 (CH_3) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1716, 1234 cm^{-1}. MS (APCI): *m*/*z* = 229 $[M + H]^+$, 197 $[M - OMe]^+$. R_f = 0.51 and 0.38 (cyclohexane/ethyl acetate, 7:3).

Compound 17: To a solution of aminopentadienal **7** (100 mg, 0.719 mmol) in dry dichloromethane (5 mL) was added phosphorus oxychloride (0.07 mL, 0.719 mmol) at 0 °C under N_2. After stirring for 10 min, a mixture of 2,4-pentanedione (0.11 mL, 1.08 mmol) and a 30% (w/w) sodium methoxide solution in methanol (0.2 mL, 1.08 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h after which a mixture of 2,4-pentanedione (0.15 mL, 1.44 mmol) and DBU (0.22 mL, 1.44 mmol) in CH_2Cl_2 was added. After 6 d of stirring, the reaction mixture was concentrated in vacuo. The oily residue was then purified by flash chromatography on silica gel with a gradient solvent system (cyclohexane/ethyl acetate, 9:1 to 7:3) to afford compound **17** (56 mg, 37%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (d, $^3J_{H,H}$ = 10.8 Hz, 1 H, CH), 6.69 (d, $^3J_{H,H}$ = 15.2 Hz, 1 H, CH), 6.61 (dd, $^3J_{H,H}$ = 15.2, 10.8 Hz, 1 H, CH), 6.43 (s, 1 H, CCl), 2.37 (s, 3 H, MeCO), 2.36 (s, 3 H, MeCO), 1.95 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.8 (*CO*Me), 197.0 (*CO*Me), 144.1 (CH), 142.3 (CH), 141.8 (C_{IV}), 137.2 (C_{IV}), 126.3 (CHCl), 123.7 (CH), 31.7 (MeCO), 26.4 (MeCO), 12.7 (CH_3) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1698, 1656, 1602, 1558, 1229 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{13}ClNaO_2$ 235.0502 $[M + Na]^+$; found 235.0493. R_f = 0.27 (cyclohexane/ethyl acetate, 7:3).

Compound 18: To a solution of aminopentadienal **7** (100 mg, 0.719 mmol) in dry dichloromethane (5 mL) was added phosphorus oxychloride (0.067 mL, 0.719 mmol) at 0 °C under N_2. After stirring for 10 min, dimethyl 1,3-acetonedicarboxylate (150 mg, 0.863 mmol) was added, and the reaction mixture was stirred at room temperature for 23 h after which a mixture of dimethyl 1,3-acetonedicarboxylate (150 mg, 0.863 mmol) and DBU (0.130 mL, 0.863 mmol) was added. After 6 d of stirring, the reaction mixture was concentrated in vacuo. The oily residue was then purified by flash chromatography on silica gel with a gradient solvent system (cyclohexane/ethyl acetate, 9:1 to 8:2) to afford compound **18** (24 mg, 12%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, $^3J_{H,H}$ = 11.6 Hz, 1 H, CH), 7.01 (dd, $^3J_{H,H}$ = 14.8, 11.6 Hz, 1 H, CH), 6.77 (d, $^3J_{H,H}$ = 14.8 Hz, 1 H, CH), 6.50 (s, 1 H, CHCl), 3.86 (s, 3 H, OMe), 3.81 (s, 2 H, CH_2), 3.72 (s, 3 H, OMe), 1.98 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.8 (CO), 167.9 (2 *CO*OMe), 148.2 (CH), 146.8 (CH), 137.5 (C_{IV}), 137.4 (C_{IV}), 127.0 (CHCl), 124.2 (CH), 52.2 (MeO), 49.3 (MeO), 47.5 (CH_2), 12.7 (CH_3) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1712 (C=O), 1593 (C=O), 1548, 1237 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{15}O_5ClNa$ 309.0506 $[M + Na]^+$; found 309.0503. R_f = 0.72 (cyclohexane/AcOEt, 5:5).

Compound 19: To a solution of aminopentadienal **7** (100 mg, 0.719 mmol) in dry dichloromethane (5 mL) was added phosphorus oxychloride (0.067 mL, 0.719 mmol) at 0 °C under N_2. After stirring for 10 min, Meldrum's acid (124 mg, 0.863 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h after which additional Meldrum's acid (124 mg, 0.863 mmol) was added. After 6 d of stirring, the reaction mixture was concentrated in vacuo. The oily residue was then purified by flash chromatography on silica gel with a gradient solvent system (cyclohexane/ethyl acetate, 9:1 to 7:3) to afford compound **19** (115 mg, 62%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, $^3J_{H,H}$ = 12.0 Hz, 1 H, CH), 7.77 (dd, $^3J_{H,H}$ = 14.8, 12.0 Hz, 1 H, CH), 7.02 (d, $^3J_{H,H}$ = 15.2 Hz, 1 H, CH), 6.68 (s, 1 H, CHCl), 2.07 (s, 3 H, CH_3), 1.74 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8 (CO), 160.5 (CO), 157.3 (CH), 152.8 (CH), 138.0 (C_{IV}), 131.0 (CHCl), 125.0 (CH), 112.0 (C_{IV}), 104.8 (C_{IV}), 27.7 (2 CH_3), 12.8 (CH_3) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1724 (C=O), 1587, 1550, 1172 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{26}Cl_2NaO_8$ 535.0902 $[2M + Na]^+$; found 535.0908. R_f = 0.80 (cyclohexane/ethyl acetate, 9:1).

Compound 21: To a solution of aminopentadienal **7** (208.5 mg, 1.5 mmol) in dry CH_2Cl_2 (2 mL) was added $POCl_3$ (0.14 mL, 1.5 mmol) at 0 °C under N_2. After stirring for 10 min, *N*-benzyl-α-

cyanopiperidine **20** (100 mg, 0.5 mmol) and silver tetrafluoroborate (97 mg, 0.5 mmol) were successively added. The reaction mixture was stirred at room temperature for 20 h without any change observed by TLC. Silver tetrafluoroborate (97 mg, 0.5 mmol) was then added again, and the reaction mixture was stirred at 80 °C for 7 h after which additional silver tetrafluoroborate (97 mg, 0.5 mmol) was added. The reaction mixture was stirred at 80 °C for additional 17 h. After cooling to room temperature, the silver tetrafluoroborate excess and silver nitrate were removed through a pad of Celite®. The filtrate was concentrated under reduced pressure. The oily residue was then purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 99:1 to 90:10) to afford compound **21** (51 mg, 27%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (s, 1 H, CH=N), 7.46 (d, $^3J_{H,H}$ = 12.0 Hz, 1 H, CH), 7.38–7.48 (m, 5 H, CH Ph), 6.88 (d, $^3J_{H,H}$ = 14.7 Hz, 1 H, CH), 6.53 (dd, $^3J_{H,H}$ = 14.7, 12.0 Hz, 1 H, CH), 6.53 (s, 1 H, CHCl), 4.99 (s, 2 H, CH_2Ph), 3.59 (t, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2N), 2.55 (quint, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2CH_2N), 1.92–1.96 (m, 2 H, CH_2C_{IV}), 1.94 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8 (*CH*=N), 155.4 (CH), 148.2 (CH), 137.3 (C_{IV}), 131.3 (C_{IV} Ph), 129.7 (CHCl), 129.6 (CH, Ph), 129.5 (CH, Ph), 129.4 (CH, Ph), 127.6 (C_{IV}), 122.7 (CH), 64.0 (CH_2Ph), 48.7 (CH_2N), 20.2 (CH_2CH_2N), 19.0 (CH_2C_{IV}), 12.5 (CH_3) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1584 (C=N) cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{21}ClN$ 286.1363 [M – BF_4]$^+$; found 286.1364. R_f = 0.39 (CH_2Cl_2/MeOH, 9:1).

Compound 23: To a solution of *N*-benzyl-α-cyanopiperidine (**20**) (100 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) were successively added aminopentadienal **7** (208 mg, 1.5 mmol) and silver tetrafluoroborate (195 mg, 1 mmol). The reaction mixture was stirred at 80 °C for 20 h. After filtration through a pad of Celite®, the filtrate was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH, 99:1 to 95:5) followed by a second flash chromatography (CH_2Cl_2/AcOEt, 95:5) to afford compound **23** (9 mg, 5%) as an orange residue and aminopentadiene iuminum compound **22** (41 mg, 32%).[25] **23**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.94 (s, 1 H, CHO), 9.18 (s, 1 H, CHO), 7.53 (s, 1 H, CH Ar), 7.45 (s, 1 H, CH Ar), 7.31–7.38 (m, 5 H, CH Ph), 7.21 (br. s, 1 H, CH Ar), 6.88 (d, $^3J_{H,H}$ = 13.2 Hz, 1 H, =*CH*N), 6.84 (d, $^3J_{H,H}$ = 13.2 Hz, 1 H, CH), 5.31 (t, $^3J_{H,H}$ = 13.2 Hz, 1 H, CH), 4.39 (s, 2 H, CH_2Ph), 3.22 (t, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2N), 2.65 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, CH_2Ar), 2.40 (s, 3 H, CH_3Ar), 1.92 (quint, $^3J_{H,H}$ = 7.6 Hz, 2 H, CH_2), 1.68 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7 (CHO), 192.4 (CHO), 153.2 (CH), 150.1 (NCH), 141.7 (C_{IV}, Ar), 139.2 (C_{IV}, Ar), 136.8 (C_{IV}, Ar), 136.2 (C_{IV}, Ph), 135.3 (CH, Ar), 128.9 (2 CH), 128.0 (CH, Ph), 127.3 (CH, Ph), 126.7 (C_{IV}), 126.2 (CH, Ar), 95.4 (CH), 55.0 (CH_2Ph), 50.0 (CH_2N), 32.6 (CH_2), 28.0 (CH_2), 21.1 (CH_3), 9.1 (CH_3) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1573 (C=O) cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{28}NO_2$ 362.2120 [M + H]$^+$; found 362.2132. R_f = 0.36 (cyclohexane/AcOEt, 5:5).

***N*-[(2*E*,4*E*)-5-Acetoxy-4-methylpenta-2,4-dienylidene]-*N*-methylmethanaminium Chloride (27):** To a solution of aminopentadienal **7** (100 mg, 0.72 mmol) in a mixture of CH_2Cl_2/Et_2O (0.6 mL/4 mL) was slowly added acetyl chloride (56 μL, 0.79 mmol) at 0 °C. The reaction mixture was stirred for 30 min and placed in a freezer overnight. Filtration followed by rinsing with Et_2O gave iminium chloride **27** (116 mg, 89%) as a yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$ basified with K_2CO_3): δ = 9.77 (d, $^3J_{H,H}$ = 10.2 Hz, 1 H, *CH*=N), 8.05 (d, $^3J_{H,H}$ = 14.4 Hz, 1 H, CH), 7.95 (s, 1 H, CHO), 6.52 (dd, $^3J_{H,H}$ = 14.4, 10.2 Hz, 1 H, CH), 3.88 (s, 3 H, CH_3N), 3.58 (s, 3 H, CH_3N), 2.26 (s, 3 H, CH_3CO), 1.94 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ basified with K_2CO_3): δ = 170.5 (CH=N), 166.0 (C=O), 163.2 (CH), 148.7 (=CHO), 120.4 (C_{IV}), 115.1 (CH), 48.8 (CH_3N), 41.0 (CH_3N), 20.4 (CH_3CO), 9.8 (CH_3) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1763 (C=O), 1661, 1617 (C=N), 1170, 1137 (C–O) cm^{-1}. MS (ESI): *m*/*z* = 182 [M – Cl]$^+$. HRMS (ESI): calcd. for $C_{10}H_{16}NO_2$ 182.1176 [M]$^+$; found 182.1177.

Compounds 29 and 30: To a solution of aminopentadienal **7** (200 mg, 1.44 mmol) in dry CH_2Cl_2 (4 mL) was added acetyl chloride (0.11 mL, 1.58 mmol) at 0 °C under N_2. After 25 min, *N*-phenylmaleimide (**28**) (274 mg, 1.58 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h and then at reflux for 26 h without any change observed on TLC. The reaction mixture was then stirred at room temperature until disappearance of the iminium compound and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH, 99:1 to 90:10) to afford compound **30** (151 mg, 43% relative to **28**) as a beige powder and compound **29** (78 mg, 18%) as a brown residue. **30**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.1 (s, 1 H, CHO), 7.38–7.45 (m, 6 H, Ph), 7.10–7.14 (m, 4 H, Ph), 6.37 (s, 1 H, *CH*=C), 3.83 (m, 1 H, CH), 3.55 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 2 *CH*C=O), 3.29 (dd, $^3J_{H,H}$ = 8.4, 3.2 Hz, 2 H, 2 *CH*C=O), 1.92 (d, $^3J_{H,H}$ = 1.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5 (CHO), 174.8 (2 NC=O), 174.0 (2 NC=O), 142.2 (=*C*Me), 131.1 (C_{IV}, Ph), 129.2 (CH, Ph), 129.0 (CH, Ph), 126.1 (CH, Ph), 119.8 (=*CH*CH), 52.4 (CCHO), 46.1 (2 *CH*C=O), 43.0 (2 *CH*C=O), 40.2 (CH), 21.7 (CH_3) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1707 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 479 [M + K]$^+$. R_f = 0.69 (CH_2Cl_2/MeOH, 9:1). **29**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (s, 1 H, CH), 7.83 (s, 1 H, CH), 7.40–7.53 (m, 5 H, Ph), 4.71 (s, 2 H, CH_2N), 2.85 [s, 6 H, $(CH_3)_2$N], 2.56 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8 (C=O), 166.1 (C=O), 147.5 (*C*Me), 138.4 (CH), 132.7 (*C*C=O), 131.1 (C_{IV}, Ph), 129.2 (CH, Ph), 128.4 (CH, Ph), 128.3 (C_{IV}), 127.6 (*C*C=O), 126.4 (CH), 54.3 (CH_2N), 42.8 [$(CH_3)_2$N], 22.1 (CH_3) ppm. IR (film, $CHCl_3$): $\tilde{\nu}_{max}$ = 1713 (ν C=O) cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{19}N_2O_2$ 295.1441 [M + H]$^+$; found 295.1443. R_f = 0.49 (CH_2Cl_2/MeOH, 9:1).

(2*E*,2′*E*,4*E*,4′*E*)-5,5′-Oxybis(4-methylpenta-2,4-dienal) (35). Preparation of Glutaconaldehyde (8′′): To a solution of potassium glutaconaldehyde enolate (**8**) (200 mg, 1.33 mmol) in a biphasic mixture AcOEt/H_2O (1:1) (6 mL) was added dropwise, under vigorous stirring, an aqueous solution of HCl (5 N) until pH was 1 reached. After additional stirring at room temperature for 15 min, the organic phase was collected, dried with $MgSO_4$ and concentrated in vacuo to yield glutaconaldehyde (**8′′**) (135 mg, 90%) as an orange solid. **Preparation of Iminium Compound 14**: To a solution of aminopentadienal **7** (100 mg, 0.719 mmol) in dry CH_2Cl_2 (5 mL) was added $POCl_3$ (0.067 mL, 0.719 mmol) at 0 °C under N_2. After stirring for 20 min, a solution of glutaconaldehyde (**8′′**) (135 mg, 1.21 mmol) in dry CH_2Cl_2 (0.5 mL) was added, and the reaction mixture was stirred at room temperature for 5 d. Acetic acid (0.041 mL, 0.719 mmol) was added, and, after stirring for an additional 26 h, a basic medium was obtained by addition of a saturated aqueous K_2CO_3 solution followed by water (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2× 10 mL). The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The oily residue was then purified by flash chromatography on silica gel (cyclohexane/CH_2Cl_2, 5:5 to 3:7) then CH_2Cl_2 and CH_2Cl_2/MeOH, 98:2) to afford "dimeric" glutaconaldehyde **35** (34 mg, 23%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.58 (d, $^3J_{H,H}$ = 7.6 Hz, 2 H, 2 CHO), 7.09 (d, $^3J_{H,H}$ = 15.6 Hz, 2 H, 2 CH), 6.64 (s, 2 H, 2 = *CH*O), 6.21 (dd, $^3J_{H,H}$ = 15.6, 7.6 Hz, 2 H, 2 *CH*CHO), 1.98 (s, 6 H, 2 CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.2 (2 CHO), 151.2 (2 CH),

136.3 (2 C_{IV}), 128.8 (4 CH), 12.7 (2 CH_3) ppm. R_f = 0.43 (cyclohexane/CH_2Cl_2, 3:7).

Compound 36: To a solution of Zincke salt **9** (1.2 g, 4.06 mmol) in EtOH (20 mL) was added in one portion potassium glutaconaldehyde enolate (**8**) (610 mg, 4.06 mmol). The reaction mixture was stirred for 24 h after which additional **8** (305 mg, 2.03 mmol) was added. After stirring for 4 d, the solution was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3× 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The oily residue was then purified by flash chromatography on silica gel (cyclohexane/CH_2Cl_2/Et_2O, 7:3:5) followed by a second flash chromatography with CH_2Cl_2 as eluent to afford pure compound **36** (55 mg, 5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1 H, CHO), 8.88 (d, $^4J_{H,H}$ = 2.8 Hz, 1 H, CH Ar), 8.77 (d, $^4J_{H,H}$ = 2.8 Hz, 1 H, CH, Ar), 8.53 (dd, $^3J_{H,H}$ = 9.2, $^4J_{H,H}$ = 2.8 Hz, 1 H, CH Ar), 8.37 (dd, $^3J_{H,H}$ = 9.2, $^4J_{H,H}$ = 2.8 Hz, 1 H, CH Ar), 7.44 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, CH, Ar), 7.40 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, CH, Ar), 7.14 (s, 1 H, CH), 6.92 (s, 1 H, =CHO), 6.27 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, NCH=), 6.09 (s, 1 H, NCH=), 4.92 (dd, $^3J_{H,H}$ = 8.0, 4.0 Hz, 1 H, *CH*=CHN), 4.67 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, CH), 2.00 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9 (CHO), 153.7 (C_{IV}, Ar), 143.2 (CH), 142.3 (C_{IV}, Ar), 142.1 (C_{IV}, Ar), 141.6 (C_{IV}, Ar), 139.9 (2 C_{IV}, Ar), 139.8 (C_{IV}), 139.2 (CHO), 129.4 (CH, Ar), 128.2 (CH, Ar), 127.7 (CH), 126.1 (C_{IV}), 123.5 (CH), 123.2 (CH, Ar), 122.9 (CH, Ar), 122.4 (CH, Ar), 117.0 (CH, Ar), 115.2 (C_{IV}), 106.4 (CH), 37.0 (CH), 18.8 (CH_3), 11.8 (CH_3) ppm. IR (film, CH_2Cl_2): $\tilde{\nu}_{max}$ = 1676, 1600, 1536, 1331 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{19}N_5NaO_{10}$ 560.1024 [M + Na]$^+$; found 560.1006. R_f = 0.26 (CH_2Cl_2).

Supporting Information (see footnote on the first page of this article): NMR spectra of compounds **10**–**19**, **21**, **23**, **27**, **29**, **30**, **35** and **36**.

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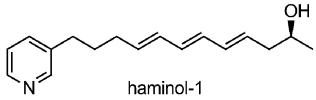

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