Knoevenagel Adducts from Reactions between Glutaconate Moieties and Aldehydes and Their Adducts with Primary Amines and Enamines

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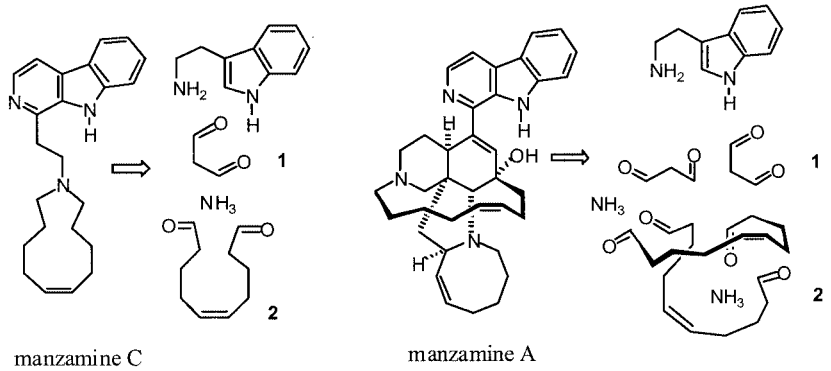
Evaluation of an hypothesis regarding the biomimetic synthesis of manzamine alkaloids from the stepwise condensation of malonate, aldehydes and primary amine derivatives is presented. The first part of this study was concentrated on the Knoevenagel reaction, with various aldehydes, of glutaconaldehydes **7** and their ester analogues **17** and **23**, in order to prepare stable derivatives of dienes **8**. This reaction, previously reported to work only with salicylaldehyde and glutaconic esters, appeared to be difficult to control in the case of the glutaconaldehyde derivative **7a**, but was successful when starting from esters **17** and **23**. This result allowed the preparation of new dienes **21**, **22a–c**, and **25**. The second part of this paper reports preliminary results concerning the reactivity of diene **21** towards primary amines and aldehyde equivalents. Dienals such as **21** were found to react with primary amines to afford 1,2-dihydropyridines such as **26** or **27**. Diene **21** was also shown to give diastereoisomeric cycloadducts **30** or **32** with enamines or oxazolidine derivatives. The cycloadducts **30** were finally shown to react with *n*-butylamine in acidic medium to give rearranged cyclopentenes **36** and **37**. Although the synthesis of derivatives such as **9** or **10**, corresponding to the AB ring system of manzamine A, by this approach have yet to be successful, the reported results reveal some new aspects of this multicomponent chemistry, some features of which are related to polyketide-type condensations.

Introduction

Research, based on model reactions, into plausible scenarios for explaining the biosynthetic origin of manzamine A (Scheme 1) and related alkaloids[1] has been a topic of much interest during the last few years.[2,3] A reasonable starting point for this research is the likelihood that manzamine A is produced by condensation of two three-carbon units (such as malonaldehyde, **1**) and two identical aldehydes **2** with tryptamine and ammonia. A striking analogy with the plausible origin of manzamine C strongly supports this hypothesis.



Scheme 1

From this scheme it can be inferred that aldehydes **2** are evidently derived from fatty acid derivatives. The origin of the three-carbon unit, in contrast, is less evident. Baldwin

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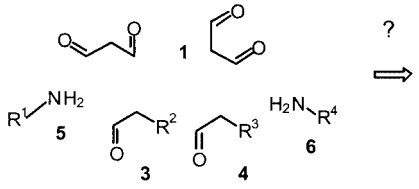
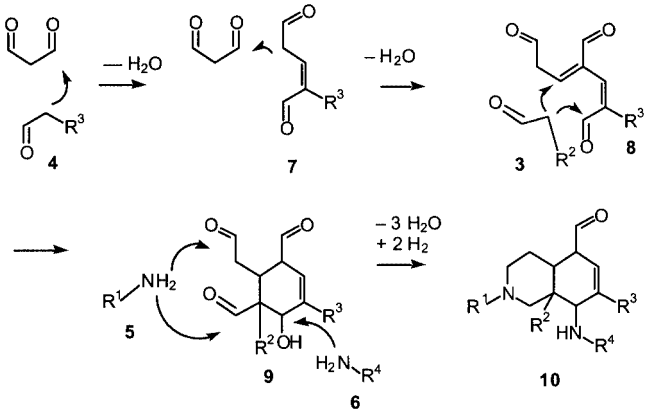
and Whitehead initially proposed acrolein as a candidate,[2] while we later suggested malonaldehyde (**1**), produced by oxidation of fatty acids.[3] Malonate derivatives, precursors of natural polyketide biosynthesis, might also be considered.

In connection with these hypotheses, we also anticipated that control over multicomponent condensation reactions of malonaldehyde (**1**) derivatives (or ester equivalents), aldehydes **3**−**4**, and primary amines **5**−**6** (Scheme 2) would be of high synthetic value, not only for the generation of natural manzamine alkaloids, but also for synthesis of new, nonnatural molecular scaffolds.



Scheme 2

There are multiple ways to assemble these molecules. In initial studies in this field we reported that a stepwise multicomponent condensation, starting from a Knoevenagel adduct of malondialdehyde, offered a new route to the core skeleton of natural alkaloid halicyclamine A.[4] This paper now reports the first results concerning the evaluation of the sequence depicted in Scheme 3.



Scheme 3

Accordingly, the first part of this paper describes new results concerning general aspects of the successful preparation of new Knoevenagel adducts equivalent to **8** from aldehydes and glutaconate-like derivatives **7** (possessing aldehyde or ester groups). Such preparations had previously been reported to be successful only in the case of reactions between glutaconate esters and salicylaldehyde.[5,6]

The second part of this study presents results concerning the reactions of these Knoevenagel adducts with primary amines and aldehyde synthetic equivalents, with the objective of finding a route to bicyclic derivatives possessing the essential features of the AB ring of manzamine A. Although Knoevenagel adducts **8** did not provide access to the desired derivatives corresponding to **9** or **10**, it is shown that they can react with primary amines and enamines to give dihydropyridine intermediates or new cycloadducts, respectively.

Results and Discussion

1. Knoevenagel Adducts from the Reactions between Glutaconate Moieties and Aldehydes

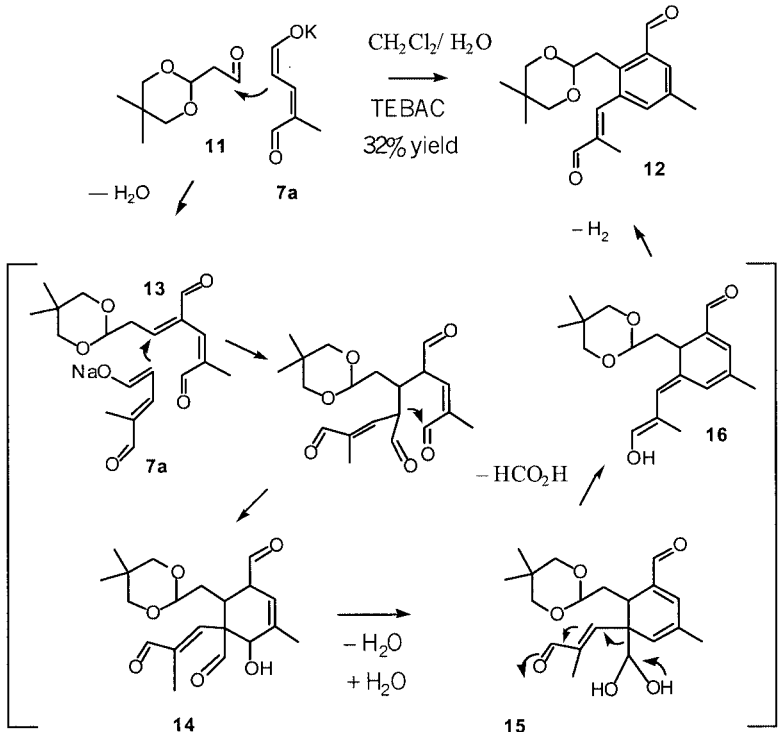
The study started with an investigation (Scheme 4) of the Knoevenagel reaction between glutaconaldehyde potassium salt **7a** and aldehyde **11**, a stable derivative of malonaldehyde (**1**), which had been reported to react in similar Knoevenagel processes.[7]

Because of the insolubility of salt **7a** in organic solvents, the reaction was conducted in the presence of a phase-transfer catalyst. Surprisingly, the main product − obtained in 32% yield from aldehyde **11** (at 50% conversion) − was identified as the substituted benzene derivative **12**. A proposed mechanism for this reaction is depicted in Scheme 4. There is initial formation of the desired Knoevenagel adduct **13**, but this is followed by the addition of a second equivalent of **7a** to give alcohol **14**. A similar observation has been reported in the case of the trimerization of malondialdehyde.[8] The next step could be a decomposition of the hydrated species **15**, which is likely to occur in alkaline medium, and this step is finally followed by aromatization. The formation of the hypothetical intermediate **14** has similarities with the chemistry resulting in the desired adduct **9** (cf. Scheme 3), suggesting that such an approach is feasible. However, the rapid addition of a second molecule **7** precluded further studies concerning the addition of another aldehyde (**3** in Scheme 3). For these reasons we next turned our attention to the more stable 5-oxopent-3-enoate derivative **17**.[3b] The results of this study are summarized in Scheme 5.

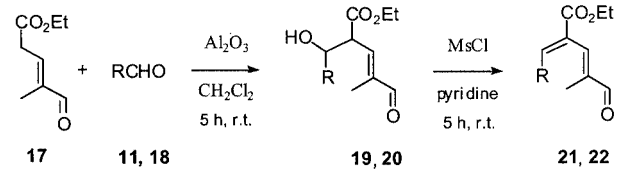
The use of normal Knoevenagel reaction conditions[9] was unsuccessful. However, use of alumina[10] allowed us to prepare the corresponding alcohols **19** and **20a**−**c** under very practical conditions and in appreciable yields (56−60%). These alcohols were all obtained as mixtures of two diastereomers in 50:50 ratios. The corresponding elimination products − the dienals **21** and **22a**−**c** − were formed by addition of mesyl chloride in pyridine. The double bond geometries of these dienals were deduced from NOE experiments.

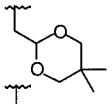
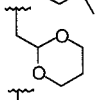
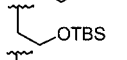
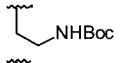
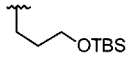
Surprisingly, no adducts were observed from the aldehydes **18d**−**f**. The interpretation of such subtle differences in reactivity is not clear. A possible explanation may be stabilization of the alcohol group, possibly through hydrogen bonding, in products **19** and **20a**−**c**, precluding the reversibility of the reaction.

From methyl-substituted glutaconate **23** (Scheme 6), in contrast, similar derivatives **24** (mixtures of diastereoisomers in 50:50 ratios) were easily obtained by the use of LDA as a base, in the presence of DMPU. The use of 2 equiv. of aldehyde significantly increased the yield.

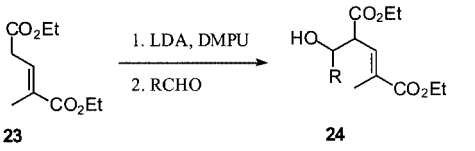


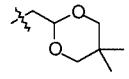
Scheme 4



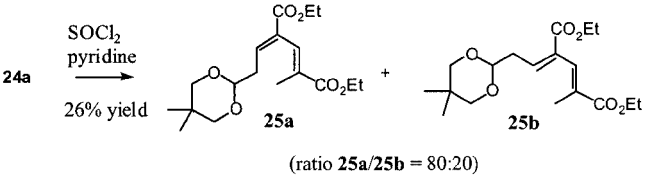
RCHO		product (% yield)	product (% yield)
11	R = 	**19** (56)	**21** (49)
18a	R = 	**20a** (60)	**22a**(40)
18b	R = 	**20b** (—)	**22b** (17, overall)
18c	R = 	**20c** (56)	**22c** (40)
18d	R = 	**20d** (0)	—
18e	R = *n*Bu	**20e** (0)	—
18f	R = Ph	**20f** (0)	—

Scheme 5



RCHO		product (% yield)
11	R = 	**24a** (35, 83 with 2 equiv. of **11**)
18e	R = *n*Bu	**24b** (66)
18f	R = Ph	**24c** (20)

Scheme 6

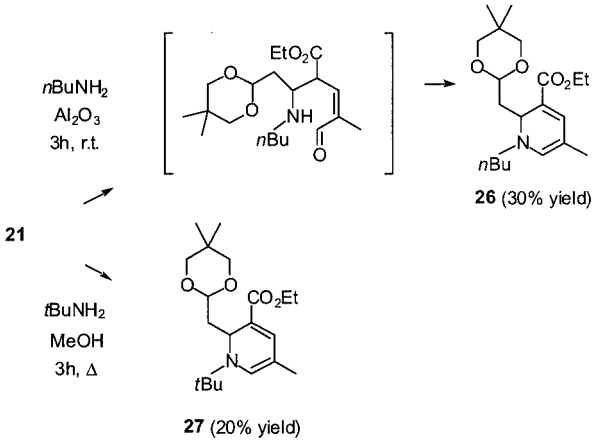


Scheme 7

A brief investigation showed that dienes such as **25** are obtainable by this method (Scheme 7). In this case thionyl chloride was used instead of mesyl chloride, and the corresponding diene **25** was obtained as a mixture of two regioisomers **25a** and **25b** in a 80:20 ratio. Again, the structures of these inseparable isomers were deduced from NOE experiments.

2. Reactivity of Dienal 21 towards Primary Amines and Aldehyde Equivalents

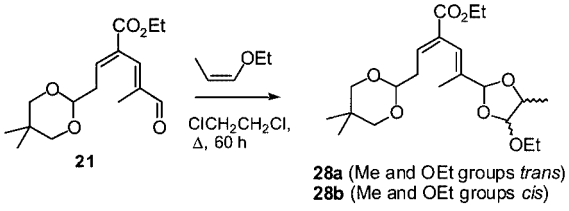
The next step in the evaluation of the route depicted in Scheme 3 was the investigation of reactions between equivalents of dienes **8** and aldehydes and primary amines. Reactions between dienal **21** and primary amines were first bri-



Scheme 8

efly studied (Scheme 8). The initial goal of this study was to examine the preparation of imino derivatives from the intermediates. In all experiments, dihydropyridines such as **26** or **27** were obtained in moderate (not optimized) yields.

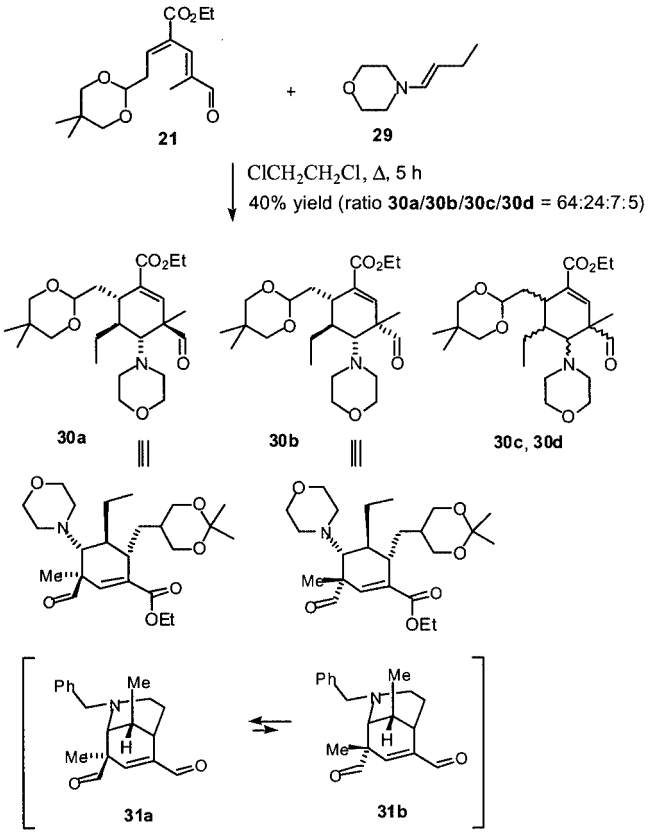
We then focused our attention on reactions between dienal **21** and aldehyde equivalents (models for the reaction **3** + **8** → **9**, see Scheme 3). Treatment of **21** (Scheme 9) with ethyl propenyl ether, used previously for similar reactions on Knoevenagel adducts,[4,7] disappointingly resulted in the formation of degradation products, along with recovery of 20% of the starting material. The only isolated products (13% yield) were the oxidized diastereoisomeric acetals **28a** and **28b** (70:30 ratio, the structures derived from NOE experiments). The vinyl ether is probably not reactive enough towards dienal **21**, so the acetals **28** would be the result of a reaction between **21** and an oxidized form of this derivative due to long contact times (60 h).



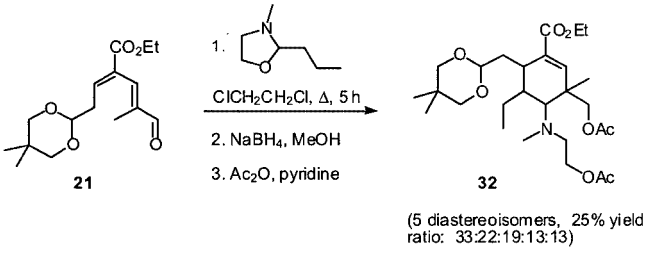
Scheme 9

In contrast, treatment with enamines gave cycloaddition products as depicted in Scheme 10. Thus, morpholine enamine **29** reacted with the dienal **21** to give a mixture of cycloadducts **30**. In principle there are eight possible diastereoisomers, but only four (**30a**−**d**) were obtained, in a 64:24:7:5 ratio. The structures of the two minor isomers **30c**−**d** could not be resolved, while those of the two major derivatives were found to be **30a** and **30b** from extensive NMR spectroscopy studies of a mixture of these two products obtained after chromatography on silica gel.

At this point it should be noted that adducts **30a** and **30b** display strong structural similarities with derivatives **31a** and **31b**. It is quite remarkable that these last derivatives, resulting from the addition of methyl-substituted glutaconaldehyde to methyl-substituted dihydropyridinium salts, were obtained from previous model studies.[3b] From this comparison it is also likely that adducts **30a** and **30b** are in an equilibrium comparable to that found in the case of bicyclic derivatives **31a** and **31b**. Not only enamines, but also oxazolidine derivatives gave cycloaddition products with diene **21**, affording adducts **32** under the same conditions (Scheme 11).

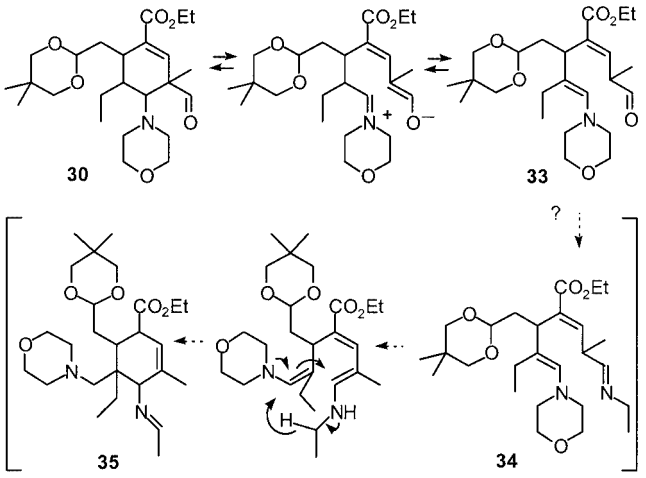


Scheme 10



Scheme 11

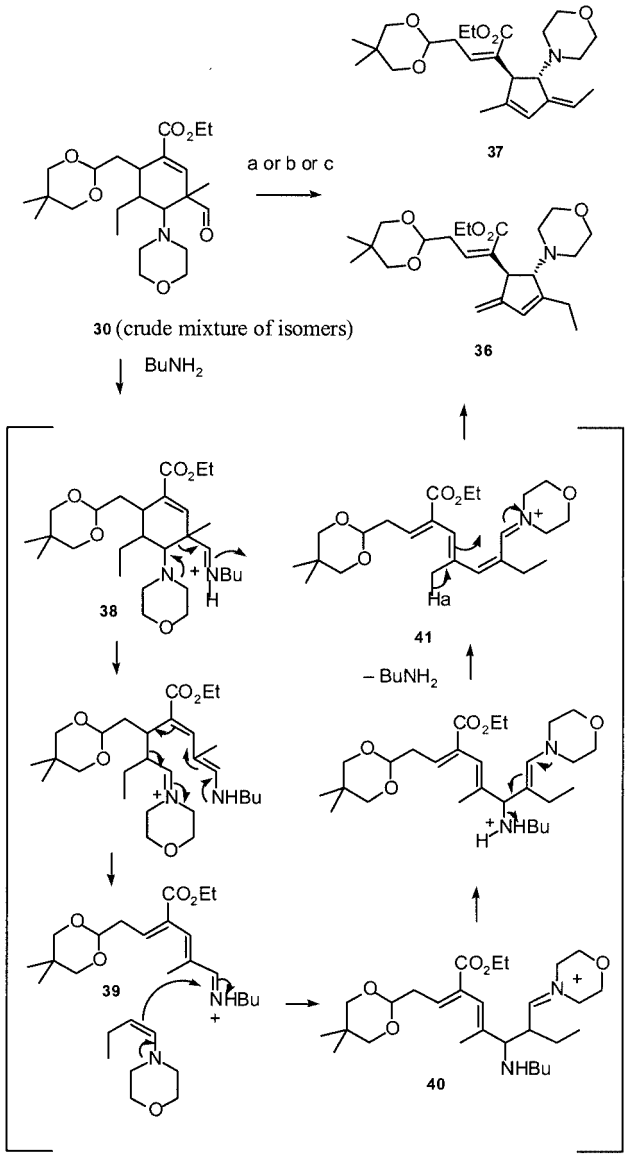
The equilibration mechanism of adducts **30** can be regarded as a retro-Mannich process involving an iminium salt and enamine intermediate **33** (Scheme 12). Therefore, and by analogy with previous results from our synthesis of the AB ring of manzamine A,[3b,3c] it was expected that formation of an intermediate imine **34** should afford the cyclized derivative **35** by a similar cyclization-oxidation-reduction process.



Scheme 12

We then prepared the corresponding imine derivatives from crude isomeric derivatives **30** and treated the resulting mixtures in acidic media (Scheme 13). We did not observe formation of derivative **35**, but, unexpectedly, the only isolated products from the reaction were cyclopentenes **36** and **37**. Depending on the conditions (see Exp. Sect.), these products could be isolated in 27 and 11% yields, respectively, or product **36** could be formed alone in 25% yield. Their structures and stereochemistries were deduced from intensive NMR experiments.

A mechanism to explain the formation of such cyclopentenes is proposed. The protonated imine **38** could rearrange to the opened compound **39** and the enamine, with successive breaking of two carbon−carbon bonds. The following step would be a readdition of enamine to give the iminium salt **40**. After elimination of butylamine to give **41**, an elimination-cyclization process would occur. Elimination of H_a in **41** would provide cyclopentene **36**, while elimination of H_b would give **37**.



Scheme 13. (a) (i) $BuNH_2$, MeOH, molecular sieves (3 Å); (ii) $MeSO_3H$, Δ, 1 h (**36**: 27% yield, **37**: 11% yield); (b) (i) $BuNH_2$, pentane, Al_2O_3, 2 h; (ii) PTSA, toluene, Δ (**36**: 21% yield, **37**: 8% yield); (c) (i) $BuNH_2$, MeOH, molecular sieves (3 Å), Δ, 1 h; (ii) CSA, Δ, overnight (**36**: 25% yield)

Conclusion

Evaluation of the route summarized in Scheme 3 gave encouraging results. In particular, it was shown from these studies that it is possible to obtain equivalents of previously unknown dienes **8**. These intermediates presumably formed the desired Michael adducts with enamines (see **33**), but this was followed by an intramolecular Mannich reaction to give cycloadducts **30**. This two-step reaction is also likely to be concerted. Attempts to form the imino intermediate **34** did not result in the desired formation of "manzamine-like" derivative **35** but in the unexpected isolation of rearrangement products **36** and **37**.

Despite this somewhat negative result, the above observations illustrate some aspects of the subtle chemistry of the new reported intermediates. We hope that these results will give some insight into such chemistry, closely related in some ways to polyketide synthesis and transformations. Other ways to assemble the molecules depicted in Scheme 3 are also possible and are currently under investigation in our laboratory.

Experimental Section

General Remarks: IR spectra were recorded with a Perkin−Elmer Spectrum BX FT-IR apparatus, as films on NaCl. NMR spectra were recorded with Bruker AC 200, AC 250, AM 300, or AM 400 machines. Mass spectra were obtained with an AQA Navigator ThermoQuest® instrument. Microanalyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France. Merck silica gel 60 (40−63 μm) was used for flash chromatography. High-Resolution Mass Spectrometry (HRMS) was performed with an MALDI-TOF machine (Voyager).

Substituted Benzene 12: 2-Methylglutacondialdehyde potassium salt **7a** (0.15 g, 1 mmol)[3b] was added to a solution of aldehyde **11** (0.16 g, 1 mmol) in CH_2Cl_2 (4 mL). A catalytic amount of tetrabutylammonium chloride (TEBAC) was added, and the solution was heated at 45 °C for 1 h and then stirred overnight. The mixture was then quenched with H_2O and extracted with CH_2Cl_2. GC analysis of the crude product on a capillary column showed 50% unchanged aldehyde **11**. Chromatography on alumina (EtOAc/heptane, 0:10 to 1:9) gave pure substituted benzene derivative **12** as an oil (50 mg, 32% yield from reacted aldehyde **11**). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.69 (s, 3 H), 1.06 (s, 3 H), 1.82 (s, 3 H), 2.42 (s, 3 H), 3.35 (d, ^2J = 11 Hz, 2 H), 3.40 (m, 2 H), 3.44 (d, ^2J = 11 Hz, 2 H), 4.59 (t, ^3J = 4.8 Hz, 1 H), 7.28 (s, 1 H), 7.7 (s, 2 H), 9.66 (s, 1 H), 10.32 (s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.2 (CH_3), 18.4, 19.1, 20.2 (CH_3) (× 3), 27.5 (C), 30.7 (CH_2), 74.5 (CH_2) (× 2), 98.3 (CH), 128.7 (CH), 131.6 (C), 131.9 (CH), 132.9, 134.2, 138.1 (3 C), 146.7 (CH), 189.9 (CH), 192.7 (CH) ppm. MS (EI, 70 eV): *m*/*z* (%) = 316 [M^+], 286, 186; (FAB): *m*/*z* (%) = 317 [MH^+].

General Procedure for the Synthesis of Alcohols 19 and 20: A mixture of glutaconate derivative **17** (1 mmol), aldehydes **11** or **18** (1 mmol), and alumina (5 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 5 h. The mixture was then filtered and the resulting solution was concentrated in vacuo. The residue was purified by flash chromatography on alumina (EtOAc/heptane, 2:8).

Alcohol 19: This compound was prepared from **17** (2.0 g, 12.8 mmol), **11** (2.0 g, 12.8 mmol), and alumina (6.5 g, 64 mmol); colorless oil, mixture of two diastereomers, 50:50 (2.25 g, 56%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.73 (s, 3 H), 1.19 (s, 3 H), 1.27 (t, ^3J = 7.0 Hz, 1.5 H), 1.28 (t, ^3J = 7.0 Hz, 1.5 H), 1.74−1.82 (m, 2 H), 1.80 (d, ^4J = 1.5 Hz, 1.5 H), 1.82 (d, ^4J = 1.5 Hz, 1.5 H), 3.42−3.68 (m, 5 H), 4.10−4.25 (m, 2 H), 4.30 (dt, ^3J = 7.7, ^3J = 6.0 Hz, 0.5 H), 4.50 (ddd, ^3J = 9.0, ^3J = 4.5, ^3J = 3.0 Hz, 0.5 H), 4.70 (t, ^3J = 4.5 Hz, 1 H), 6.50 (dq, ^3J = 10.0, ^4J = 1.5 Hz, 0.5 H), 6.80 (dq, ^3J = 10.0, ^4J = 1.5 Hz, 0.5 H), 9.38 (s, 0.5 H), 9.43 (s, 0.5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.6, 9.7 (CH_3), 14.0 (CH_3), 21.6 (CH_3), 22.8 (CH_3), 30.0 (C_{quat}), 38.6, 38.8 (CH_2), 50.9, 52.2 (CH), 61.3 (CH_2), 68.3, 69.1 (CH), 77.0 (CH_2) (× 2), 100.3, 100.4 (CH), 142.0, 142.2 (C_{quat}), 146.0 (CH), 170.8, 170.9 (C_{quat}), 194.4, 194.6 (C_{quat}) ppm. IR (neat): $\tilde{\nu}$ = 3429 cm^{-1}, 2958, 2855, 1731, 1690. MS (EI, 70 eV): *m*/*z* (%) = 314 (75) [$M^{\cdot+}$], 297 (78), 225 (79), 115 (97), 69 (100).

Alcohol 20a: This compound was prepared from **17** (552 mg, 3.0 mmol), **18a** (482 mg, 3.6 mmol), and alumina (1.5 g, 15 mmol); colorless oil, mixture of two diastereomers, 50:50 (515 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, ^3J = 5.0 Hz, 1.5 H), 1.28 (t, ^3J = 5.0 Hz, 1.5 H), 1.30 (m, 1 H), 1.77 (d, ^4J = 1.5 Hz, 1.5 H), 1.80 (m, 2 H), 1.80 (d, ^4J = 1.5 Hz, 1.5 H), 2.10 (m, 1 H), 3.50 (br. s, 1 H), 3.61 (^3J = 10.0, ^3J = 6.5 Hz, 0.5 H), 3.63 (dd, ^3J = 10.0, ^3J = 8.0 Hz, 0.5 H), 3.80 (m, 2 H), 4.15 (m, 2 H), 4.19 (q, ^3J = 5.0 Hz, 1 H), 4.20 (q, ^3J = 5.0 Hz, 1 H), 4.32 (br. q, ^3J = 6.5 Hz, 0.5 H), 4.50 (ddd, ^3J = 8.0, ^3J = 4.5, ^3J = 3.0 Hz, 0.5 H), 4.80 (t, ^3J = 3.8 Hz, 1 H), 6.46 (dq, ^3J = 10.0, ^4J = 1.0 Hz, 0.5 H), 6.70 (dq, ^3J = 10.0, ^4J = 1.5 Hz, 0.5 H), 9.45 (s, 0.5 H), 9.50 (s, 0.5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.8, 9.9 (CH_3), 14.2 (CH_3), 25.7 (CH_2), 39.2, 39.3 (CH_2), 51.1, 52.4 (CH), 61.6 (CH_2), 67.0 (CH_2) (× 2), 68.5, 69.3 (CH), 100.7 (CH), 142.3, 142.5 (C_{quat}), 146.3 (CH), 171.0, 171.1 (C_{quat}), 194.6, 194.8 (C_{quat}) ppm. IR (neat): $\tilde{\nu}$ = 3487 cm^{-1}, 2965, 2858, 1732, 1690. MS (EI, 70 eV): *m*/*z* (%) = 286 (4) [$M^{\cdot+}$], 267 (20), 87 (100). HRMS: calculated for $C_{14}H_{22}O_6$ + Na 309.13141; found 309.13061.

Alcohol 20b: Analytical sample (mixture of two diastereomers, 50:50). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.90 (s, 9 H), 1.27 (t, ^3J = 7.3 Hz, 1.5 H), 1.28 (t, ^3J = 7.3 Hz, 1.5 H), 1.60−1.70 (m, 2 H), 1.82 (d, ^4J = 1.0 Hz, 1.5 H), 1.83 (d, ^4J = 1.0 Hz, 1.5 H), 3.65 (dd, ^3J = 10.0, ^3J = 6.5 Hz, 0.5 H), 3.66 (dd, ^3J = 20.0, ^3J = 10.0 Hz, 0.5 H), 3.75−4.00 (m, 2 H), 4.20 (q, ^3J = 7.3 Hz, 1 H), 4.22 (q, ^3J = 7.3 Hz, 1 H), 4.30 (m, 0.5 H), 4.40 (m, 0.5 H), 6.46 (dq, ^3J = 10.4, ^4J = 1.0 Hz, 0.5 H), 6.72 (dq, ^3J = 9.8, ^4J = 1.0 Hz, 0.5 H), 9.46 (s, 0.5 H), 9.51 (s, 0.5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.2, −5.4 (CH_3) (× 2), 9.9, 10.0 (CH_3), 14.2 (CH_3), 18.3 (C_{quat}), 26.0 (CH_3) (× 2), 36.0, 36.2 (CH_2), 51.6, 52.7 (CH), 61.6 (CH_2), 61.9, 62.1 (CH_2), 72.0, 72.9 (CH), 142.2, 142.4 (C_{quat}), 146.5, 146.7 (CH), 171.2 (C_{quat}), 194.7, 195.0 (C_{quat}) ppm.

Alcohol 20c: This compound was prepared from **17** (300 mg, 1.62 mmol), **18c** (280 mg, 1.62 mmol) and alumina (825 mg, 8.1 mmol); colorless oil, mixture of two diastereomers, 50:50 (300 mg, 56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, ^3J = 6.5 Hz, 3 H), 1.37 (s, 9 H), 1.73 (s, 1.5 H), 1.75 (s, 1.5 H), 3.15 (m, 2 H), 3.35 (m, 2 H), 3.53 (dd, ^3J = 10.5, ^3J = 6.0 Hz, 0.5 H), 3.60 (dd, ^3J = 10.5, ^3J = 9.0 Hz, 0.5 H), 4.00 (m, 1 H), 4.13 (q, ^3J = 6.5 Hz, 2 H), 4.92 (br. s, 1 H), 6.39 (d, ^3J = 10.5 Hz, 0.5 H), 6.63 (d, ^3J = 10.5 Hz, 0.5 H), 9.38 (s, 0.5 H), 9.43 (s, 0.5 H) ppm. IR (neat): $\tilde{\nu}$ = 3401 cm^{-1}, 2980, 1719, 1692. MS (ESI): *m*/*z* (%) = 352 (100) [M + Na^+], 368 (30) [M + K^+]. HRMS: calculated for $C_{16}H_{27}NO_6$ + Na 352.17361; found 352.17344.

General Procedure for the Preparation of Dienals 21 and 22a−c from Alcohols 19 and 20: Mesyl chloride (3 mmol) was added to a cooled solution (0 °C) of the alcohol (1 mmol) in pyridine (0.2 mL). The mixture was stirred at room temperature for 3 h. After dilution with H_2O, the mixture was extracted with CH_2Cl_2. The resulting organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/heptane, 2:8).

Dienal 21: This compound was prepared from alcohol **19** (1.0 g, 3.4 mmol) and mesyl chloride (790 μL, 10.2 mmol) in pyridine (6 mL); colorless oil (493 mg, 49%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.68 (m, 3 H), 1.14 (s, 3 H), 1.26 (t, ^3J = 7.3 Hz, 3 H), 1.62 (d, ^3J = 1.3 Hz, 3 H), 2.37 (dd, ^3J = 4.5, ^3J = 1.3 Hz, 2 H), 3.37 (td, ^2J = 11.0 Hz, 2 H), 3.56 (d, ^2J = 11.0 Hz, 2 H), 4.19 (q, ^3J = 7.3 Hz, 2 H), 4.53 (t, ^3J = 4.8 Hz, 1 H), 6.98 (s, 1 H), 7.07 (t, ^3J = 7.3 Hz, 1 H), 9.53 (s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 11.2 (CH_3), 14.0 (CH_3), 21.5 (CH_3), 22.7 (CH_3), 29.8 (C_{quat}), 35.4 (CH_2), 60.9 (CH_2), 76.9 (CH_2) (× 2), 99.7 (CH), 129.7 (C_{quat}), 140.5 (CH), 141.7 (C_{quat}), 143.0 (CH), 165.2 (C_{quat}), 194.5 (C_{quat}) ppm. IR (neat): $\tilde{\nu}$ = 2957 cm^{-1}, 2850, 1735, 1690. MS (CI): *m*/*z* (%) = 297 (100) [M + H], 167 (40), 115 (86). HRMS: calculated for $C_{24}H_{37}NO_5$+Na 319.15214; found 319.15337.

Dienal 22a: This compound was prepared from alcohol **20a** (400 mg, 1.4 mmol) and mesyl chloride (320 μL, 4.2 mmol) in pyridine (6 mL): colorless oil (150 mg, 40%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31 (t, ^3J = 7.2 Hz, 3 H), 1.39 (m, 1 H), 1.67 (d, ^3J = 1.0 Hz, 3 H), 2.09 (m, 1 H), 2.39 (dd, ^3J = 7.4, ^3J = 4.8, ^3J = 1.0 Hz, 2 H), 3.77 (td, ^2J = 12.0, ^3J = 2.5 Hz, 2 H), 4.11 (ddd, ^2J = 12.0, ^3J = 4.9, ^3J = 1.0 Hz, 2 H), 4.24 (q, ^3J = 7.2 Hz, 2 H), 4.68 (t, ^3J = 4.8 Hz, 1 H), 7.01 (s, 1 H), 7.08 (t, ^3J = 7.4 Hz, 1 H), 9.67 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3 (CH_3), 14.3 (CH_3), 25.6 (CH_2), 36.1 (CH_2), 61.3 (CH_2), 67.1 (CH_2) (× 2), 100.1 (CH), 130.1 (C_{quat}), 140.7 (C_{quat}), 142.1 (CH), 143.4 (CH), 165.6 (C_{quat}), 194.8 (C_{quat}) ppm. IR (neat): $\tilde{\nu}$ = 2976 cm^{-1}, 2854, 1717, 1689. $C_{14}H_{20}O_5$ (268.3): calcd. C 62.67, H 7.51; found C 62.73, H 7.63.

Dienal 22b: The reaction between the glutaconate derivative **17** (1.7 g, 11 mmol), aldehyde **18b** (2 g, 11 mmol), and alumina (5.61 g,

55 mmol) furnished a crude material. This material was treated with mesyl chloride (2.55 mL, 33 mmol) to furnish dienal **22b** (620 mg, 17% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.89 (s, 9 H), 1.31 (t, ^3J = 7.0 Hz, 3 H), 1.68 (s, 3 H), 2.30 (q, ^3J = 6.0 Hz, 2 H), 3.73 (t, ^3J = 6.0 Hz, 2 H), 4.24 (q, ^3J = 7.0 Hz, 2 H), 7.02 (s, 1 H), 7.07 (t, ^3J = 6.0 Hz, 1 H), 9.58 (s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = −3.0 (CH_3), 11.3 (CH_3), 14.1 (CH_3), 18.2 (C_{quat}), 25.8 (CH_3), 33.4 (CH_2), 61.1 (CH_2), 61.2 (CH_2), 129.2 (C_{quat}), 141.7 (C_{quat}), 143.5 (CH), 144.0 (CH), 165.5 (C_{quat}), 194.7 (C_{quat}) ppm. MS (EI, 70 eV): *m*/*z* (%) = 326 (5) [$M^{\cdot+}$], 269 (30), 195 (40), 75 (100).

Dienal 22c: This compound was prepared from alcohol **20c** (300 mg, 0.91 mmol) and mesyl chloride (210 μL, 2.73 mmol) in pyridine (4 mL); colorless oil (110 mg, 40%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.29 (t, ^3J = 6.5 Hz, 3 H), 1.41 (s, 9 H), 1.65 (s, 3 H), 2.27 (q, ^3J = 6.5 Hz, 2 H), 3.25 (q, ^3J = 6.2 Hz, 2 H), 4.22 (q, ^3J = 6.5 Hz, 2 H), 4.65 (br. s, 1 H), 6.94 (t, ^3J = 7.5 Hz, 1 H), 6.97 (s, 1 H), 9.55 (s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 11.2 (CH_3), 14.0 (CH_3), 28.2 (CH_3), 30.7 (CH_2), 39.0 (CH_2), 61.2 (CH_2), 79.4 (C_{quat}), 129.8 (C_{quat}), 141.9 (C_{quat}), 142.9 (CH), 143.2 (CH), 155.7 (C_{quat}), 165.3 (C_{quat}), 194.5 (C_{quat}) ppm. IR (neat): $\tilde{\nu}$ = 2979 cm^{-1}, 2933, 1716, 1693. MS (ESI): *m*/*z* (%) = 334 (100) [M + Na^+], 350 (30) [M + K^+]. HRMS: calculated for $C_{16}H_{25}NO_5$ + Na 334.16304; found 334.16166.

General Procedure for the Synthesis of Alcohols 24: DMPU (2 mmol) was added at −78 °C to a solution of lithium diisopropylamide (1.5 mmol) in THF (20 mL). The resulting mixture was stirred at −78 °C for 30 min, and diethyl glutaconate (1 mmol) was then added. The resulting mixture was stirred at −78 °C for 30 min, and aldehyde (2 mmol) was then added. After 30 min at −78 °C, the solution was treated with an NH_4Cl solution. The organic phase was dried with $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by flash chromatography.

Alcohol 24a: LDA [prepared from diisopropylamine (720 μL, 5.1 mmol) and *n*-butyllithium (3 mL, 1.6 M)] in 45 mL of THF, DMPU (720 μL, 6 mmol), **23** (600 mg, 3 mmol), and **11** (1.05 g, 6.7 mmol) furnished **24a**; colorless oil, mixture of two diastereomers, 50:50 (892 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.73 (s, 3 H), 1.19 (s, 3 H), 1.27 (t, ^3J = 7.0 Hz, 3 H), 1.30 (t, ^3J = 7.0 Hz, 3 H), 1.70−1.90 (m, 2 H), 1.91 (d, ^4J = 1.5 Hz, 1.5 H), 1.92 (d, ^4J = 1.5 Hz, 1.5 H), 3.45 (m, 3 H), 3.62 (d, ^2J = 11.1 Hz, 2 H), 4.19 (m, 4 H), 4.31 (tt, ^3J = 9.0, ^3J = ^4J = 2.5 Hz, 0.5 H), 4.40 (ddt, ^3J = 9.5, ^3J = 4.8, ^3J = ^4J = 2.4 Hz, 0.5 H), 4.68 (t, ^3J = 4.8 Hz, 0.5 H), 4.69 (t, ^3J = 4.8 Hz, 0.5 H), 6.67 (dq, ^3J = 10.7, ^4J = 1.5 Hz, 0.5 H), 6.90 (dq, ^3J = 10.3, ^4J = 1.5 Hz, 0.5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.1, 13.2 (CH_3), 14.1 (CH_3), 14.2 (CH_3), 21.8 (CH_3), 23.0 (CH_3), 30.2 (C_{quat}), 38.5, 38.8 (CH_2), 51.0, 52.5 (CH), 60.8, 60.9 (CH_2), 61.2 (CH_2), 68.4, 69.3 (CH), 77.2 (CH_2) (× 2), 100.5, 100.8 (CH), 132.2 (C_{quat}), 134.5, 134.2 (CH), 167.4 (C_{quat}), 171.5, 172.7 (C_{quat}) ppm. IR (neat): $\tilde{\nu}$ = 3505 cm^{-1}, 2957, 2869, 1712. MS (ESI): *m*/*z* (%) = 359 (2) [M + H^+], 381 (70) [M + Na^+], 397 (100) [M + K^+].

Alcohol 24b: LDA [prepared from diisopropylamine (120 μL, 0.85 mmol) and *n*-butyllithium (500 μL, 1.6 M)] in 7 mL of THF, DMPU (120 μL, 1 mmol), **23** (100 mg, 0.5 mmol), and **18e** (50 μL, 0.5 mmol) furnished **24b**; colorless oil, mixture of two diastereomers, 50:50 (90 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 6.5 Hz, 3 H), 1.24 (t, ^3J = 7.0 Hz, 1.5 H), 1.25 (t, ^3J = 7.0 Hz, 1.5 H), 1.29 (t, ^3J = 7.0 Hz, 3 H), 1.30−1.55 (m, 4 H), 1.90 (d, ^4J = 1.5 Hz, 1.5 H), 1.91 (d, ^4J = 1.5 Hz, 1.5 H), 2.73 (d, ^3J = 5.8 Hz, 0.5 H), 2.86 (d, ^3J = 3.3 Hz, 0.5 H), 3.40 (dd, ^3J = 10.5, ^3J = 1.0 Hz, 0.5 H), 3.42 (dd, ^3J = 10.5, ^3J = 2.5 Hz, 0.5 H), 3.92 (m, 0.5 H), 4.03 (m, 0.5 H), 4.16 (q, ^3J = 7.2 Hz, 2 H), 4.19 (q, ^3J = 7.2 Hz, 2 H), 6.66 (dq, ^3J = 10.5, ^4J = 1.5 Hz, 0.5 H), 6.86 (dq, ^3J = 10.5, ^4J = 1.5 Hz, 0.5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 12.2 (CH_3), 13.1 (CH_3), 13.2 (CH_3), 14.1 (CH_3), 17.7, 17.9 (CH_2), 35.4, 35.8 (CH_2), 49.9, 51.4 (CH), 59.8 (CH_2), 60.3 (CH_2), 70.5, 71.2 (CH), 130.8, 131.5 (C_{quat}), 133.0, 133.8 (CH), 166.5 (C_{quat}), 171.2, 171.4 (C_{quat}), ppm. IR (neat): $\tilde{\nu}$ = 3502 cm^{-1}, 2961, 2935, 1713. MS (ESI): *m*/*z* (%) = 273 (2) [M + H^+], 295 (100) [M + Na^+], 311 (30) [M + K^+].

Alcohol 24c: LDA [prepared from diisopropylamine (120 μL, 0.85 mmol) and *n*-butyllithium (500 μL, 1.6 M)] in 7 mL of THF, DMPU (120 μL, 1 mmol), **23** (100 mg, 0.5 mmol), and **18f** (60 μL, 0.6 mmol) furnished **24c**; colorless oil, mixture of two diastereomers, 50:50 (30 mg, 20%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (t, ^3J = 7.1 Hz, 1.5 H), 1.18 (t, ^3J = 7.1 Hz, 1.5 H), 1.19 (t, ^3J = 7.1 Hz, 1.5 H), 1.23 (t, ^3J = 7.1 Hz, 1.5 H), 1.48 (d, ^4J = 1.5 Hz, 1.5 H), 1.57 (d, ^4J = 1.5 Hz, 1.5 H), 3.59 (dd, ^3J = 10.3, ^3J = 5.3 Hz, 0.5 H), 3.65 (dd, ^3J = 10.5, ^3J = 7.4 Hz, 0.5 H), 4.02 (t, ^3J = 7.1 Hz, 1 H), 4.05 (q, ^3J = 7.1 Hz, 2 H), 4.12 (q, ^3J = 7.1 Hz, 2 H), 4.92 (d, ^3J = 8.4 Hz, 0.5 H), 5.11 (d, ^3J = 5.3 Hz, 0.5 H), 6.59 (dq, ^3J = 10.5, ^4J = 1.5 Hz, 0.5 H), 6.85 (dq, ^3J = 10.3, ^4J = 1.5 Hz, 0.5 H), 7.15−7.30 (m, 5 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.0, 13.2 (CH_3), 14.5 (CH_3), 14.6 (CH_3), 53.8, 54.2 (CH), 61.2 (CH_2), 61.7, 61.8 (CH_2), 74.9, 75.4 (CH), 126.6 (CH), 126.8 (CH), 128.4, 128.6 (CH), 128.7 (CH), 128.8 (CH), 133.2, 132.5 (C_{quat}), 134.2 (CH), 141.0, 141.1 (C_{quat}), 167.7, 167.8 (C_{quat}), 172.1, 172.5 (C_{quat}) ppm. IR (neat): $\tilde{\nu}$ = 3463 cm^{-1}, 2982, 2934, 1737, 1712. MS (ESI): *m*/*z* (%) = 329 (100) [M + Na^+], 345 (8) [M + K^+]. HRMS: calculated for $C_{17}H_{22}O_5$ + Na 329.13649; found 329.13583.

Dienals 25: Compound **24a** (120 mg, 0.34 mmol) and thionyl chloride (75 μL, 10 mmol) in 2 mL of pyridine furnished a mixture of **25a** and **25b** as a mixture of two diastereoisomers, 80:20 (30 mg, 26%). IR (neat): $\tilde{\nu}$ = 2957 cm^{-1}, 2851, 1712. MS (ESI): *m*/*z* (%) = 341 (4) [M + H^+], 363 (100) [M + Na^+], 379 (20) [M + K^+]. HRMS: calculated for $C_{18}H_{28}O_6$ + Na 363.17836; found 363.17766. **25a:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.66 (s, 3 H), 1.12 (s, 3 H), 1.22 (t, ^3J = 7.1 Hz, 3 H), 1.25 (t, ^3J = 7.1 Hz, 3 H), 1.68 (d, ^4J = 1.0 Hz, 3 H), 2.35 (ddd, ^3J = 7.0, ^3J = 5.0, ^4J = 1.0 Hz, 2 H), 3.36 (d, ^2J = 11.0 Hz, 2 H), 3.54 (d, ^2J = 11.0 Hz, 2 H), 4.14 (q, ^3J = 7.1 Hz, 2 H), 4.16 (q, ^3J = 7.1 Hz, 2 H), 4.48 (t, ^3J = 5.0 Hz, 1 H), 6.96 (t, ^3J = 7.0 Hz, 1 H), 7.21 (q, ^4J = 1.0 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.6 (CH_3) (× 2), 14.9 (CH_3), 22.2 (CH_3), 23.3 (CH_3), 30.5 (C_{quat}), 35.8 (CH_2), 61.2 (CH_2), 61.3 (CH_2), 77.5 (CH_2) (× 2), 100.5 (CH), 131.0 (C_{quat}), 132.4 (C_{quat}), 133.2 (CH), 140.1 (CH), 166.3 (C_{quat}), 167.8 (C_{quat}) ppm. **25b:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.66 (s, 3 H), 1.12 (s, 3 H), 1.22 (t, ^3J = 7.1 Hz, 3 H), 1.25 (t, ^3J = 7.1 Hz, 3 H), 1.91 (d, ^4J = 1.0 Hz, 3 H), 2.91 (ddd, ^3J = 7.0, ^3J = 5.0, ^4J = 1.0 Hz, 2 H), 3.36 (d, ^2J = 11.0 Hz, 2 H), 3.54 (d, ^2J = 11.0 Hz, 2 H), 4.14 (q, ^3J = 7.1 Hz, 2 H), 4.16 (q, ^3J = 7.1 Hz, 2 H), 4.50 (t, ^3J = 5.0 Hz, 1 H), 6.29 (t, ^3J = 7.0 Hz, 1 H), 7.26 (q, ^4J = 1.0 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.2 (CH_3), 14.6 (CH_3), 14.9 (CH_3), 22.2 (CH_3), 23.3 (CH_3), 30.5 (C_{quat}), 35.8 (CH_2), 61.2 (CH_2), 61.3 (CH_2), 77.5 (CH_2) (× 2), 101.0 (CH), 129.3 (C_{quat}), 131.4 (C_{quat}), 136.4 (CH), 141.7 (CH), 166.9 (C_{quat}), 168.7 (C_{quat}) ppm.

Dihydropyridine 26: *n*-Butylamine (33 μL, 0.34 mmol) was added dropwise to a solution of **21** (100 mg, 0.34 mmol) in pentane (10 mL). Alumina (173 mg, 1.7 mmol) was added to the resulting solution. The mixture was stirred at room temperature for 2 h and

then filtered through Celite. Yellow oil (36 mg, 30%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.70 (s, 3 H), 0.89 (t, ^3J = 7.0 Hz, 3 H), 1.18 (s, 3 H), 1.29 (m, 5 H), 1.51 (m, 2 H), 1.74 (m, 2 H), 1.78 (s, 3 H), 3.15 (m, 2 H), 3.56 (m, 2 H), 3.61 (m, 2 H), 4.19 (q, ^3J = 7.0 Hz, 2 H), 4.40 (t, ^3J = 5.0 Hz, 1 H), 4.64 (t, ^3J = 6.7 Hz, 1 H), 6.13 (s, 1 H), 7.01 (s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.8 (CH_3), 14.5 (CH_3), 16.9 (CH_3), 19.7 (CH_2), 21.9 (CH_3), 23.2 (CH_3), 30.1 (C_{quat}), 32.5 (CH_2), 36.7 (CH_2), 51.5 (CH), 54.2 (CH_2), 59.6 (CH_2), 77.2 (CH) (× 2), 99.8 (CH), 103.4 (C_{quat}), 129.0 (C_{quat}), 137.2 (CH), 138.5 (CH), 166.6 (C_{quat}) ppm. IR (neat): $\tilde{\nu}$ = 3420 cm^{-1}, 2932, 2854, 1721, 1668. MS (EI, 70 eV): *m*/*z* (%) = 351 (20) [M$^{\cdot+}$], 222 (70), 138 (100).

Compounds 28: Ethyl propenyl ether (110 μL, 1.02 mmol) in 5 mL of 1,2-dichloroethane was added to a solution of **21** (100 mg, 0.34 mmol) in 20 mL of 1,2-dichloroethane. The mixture was heated at reflux for 5 h and then concentrated in vacuo. The residue was chromatographed on silica gel (EtOAc/heptane, 2:8) to afford **28a** and **28b** as a mixture of two diastereoisomers, 70:30 (18 mg, 13%). IR (neat): $\tilde{\nu}$ = 2977 cm^{-1}, 2933, 1724, 1710, 1120. MS (ESI): *m*/*z* (%) = 421 (100) [M + Na$^+$], 437 (50) [M + K$^+$]. HRMS: calculated for $C_{21}H_{34}O_7$ + Na 421.22022; found 421.22158. **28a:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71 (s, 3 H), 1.18 (s, 3 H), 1.22 (t, ^3J = 7.0 Hz, 3 H), 1.27 (t, ^3J = 6.0 Hz, 3 H), 1.31 (d, ^3J = 7.5 Hz, 3 H), 1.55 (d, ^3J = 7.0 Hz, 3 H), 2.44 (dd, ^3J = 7.0, ^3J = 5.0 Hz, 2 H), 3.41 (d, ^2J = 10.0 Hz, 2 H), 3.52 (dq, ^2J = 10.0, ^3J = 7.0 Hz, 1 H), 3.60 (d, ^2J = 10.0 Hz, 2 H), 3.83 (dq, ^2J = 10.0, ^3J = 7.0 Hz, 1 H), 4.01 (qd, ^3J = 7.5, ^3J = 3.0 Hz, 1 H), 4.18 (q, ^3J = 6.0 Hz, 2 H), 4.53 (t, ^3J = 5.0 Hz, 1 H), 4.80 (d, ^3J = 3.0 Hz, 1 H), 5.44 (s, 1 H), 6.26 (br. s, 1 H), 6.94 (td, ^3J = 7.0, ^4J = 1.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0 (CH_3), 14.2 (CH_3), 15.1 (CH_3), 18.0 (CH_3), 21.8 (CH_3), 22.9 (CH_3), 30.1 (C_{quat}), 35.3 (CH_2), 60.7 (CH_2), 63.9 (CH_2), 77.2 (CH_2) (× 2), 100.4 (CH), 105.4 (CH), 106.3 (CH), 124.3 (CH), 130.7 (C_{quat}), 136.9 (C_{quat}), 138.5 (CH), 166.6 (C_{quat}) ppm. **28b:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71 (s, 3 H), 1.18 (s, 3 H), 1.22 (t, ^3J = 7.0 Hz, 3 H), 1.27 (t, ^3J = 6.0 Hz, 3 H), 1.31 (d, ^3J = 7.5 Hz, 3 H), 1.52 (d, ^3J = 7.0 Hz, 3 H), 2.44 (dd, ^3J = 7.0, ^3J = 5.0 Hz, 2 H), 3.41 (d, ^2J = 10.0 Hz, 2 H), 3.52 (dq, ^2J = 10.0, ^3J = 7.0 Hz, 1 H), 3.60 (d, ^2J = 10.0 Hz, 2 H), 3.83 (dq, ^2J = 10.0, ^3J = 7.0 Hz, 1 H), 4.18 (m, 3 H), 4.53 (t, ^3J = 5.0 Hz, 1 H), 5.11 (d, ^3J = 4.0 Hz, 1 H), 5.55 (s, 1 H), 6.22 (br. s, 1 H), 6.94 (td, ^3J = 7.0, ^4J = 1.0 Hz, 1 H), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2 (CH_3), 13.8 (CH_3), 15.1 (CH_3), 18.0 (CH_3), 21.8 (CH_3), 22.9 (CH_3), 30.1 (C_{quat}), 35.3 (CH_2), 60.7 (CH_2), 63.5 (CH_2), 76.0 (CH), 77.2 (CH_2) (× 2), 100.4 (CH), 101.2 (CH), 104.7 (CH), 122.9 (CH), 130.7 (C_{quat}), 138.4 (C_{quat}), 138.5 (CH), 166.6 (C_{quat}) ppm.

Cyclized Compounds 30: 4-(But-1-enyl)morpholine (719 mg, 5.1 mmol) in 5 mL of 1,2-dichloroethane was added to a solution of **21** (500 mg, 1.7 mmol) in 20 mL of 1,2-dichloroethane. The mixture was heated at reflux for 5 h and was then concentrated in vacuo. The residue was chromatographed on silica gel (EtOAc/heptane, 2:8) to afford **30** as a mixture of four diastereoisomers, 64:24:7:5 (298 mg, 40%). A mixture of the two major isomers **30a** and **30b** was isolated. IR (neat): $\tilde{\nu}$ = 2943 cm^{-1}, 2936, 1714. MS (ESI): *m*/*z* (%) = 438 (5) [M + H$^+$], 460 (100) [M + Na$^+$], 476 (55) [M + K$^+$]. HRMS: calculated for $C_{24}H_{39}NO_6$ + H 438.28556; found 438.28391. **30a:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.69 (s, 3 H), 0.88 (t, ^3J = 7.5 Hz, 3 H), 1.15 (s, 3 H), 1.27 (t, ^3J = 7.5 Hz, 3 H), 1.40 (s, 3 H), 1.61 (m, 2 H), 1.80−2.00 (m, 1 H), 2.00−2.20 (m, 1 H), 2.68 (t, ^3J = 7.5 Hz, 2 H), 2.80−2.90 (m, 4 H), 3.30−3.40 (m, 2 H), 3.50−3.60 (m, 6 H), 4.18 (q, ^3J = 7.5 Hz, 2 H), 4.44 (dd, ^3J = 7.5, ^3J = 2.5 Hz, 1 H), 6.20 (s, 1 H), 9.78 (s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 8.2 (CH_3), 14.2 (CH_3), 21.7 (CH_3), 21.9 (CH_3), 23.2 (CH_3), 23.7 (CH_2), 29.7 (C_{quat}), 35.5 (CH), 36.9 (CH), 38.7 (CH_2), 39.8 (CH_2) (× 2), 56.0 (C_{quat}), 60.7 (CH_2), 67.8 (CH_2) (× 2), 71.4 (CH), 77.1 (CH_2) (× 2), 101.0 (CH), 135.5 (C_{quat}), 137.4 (CH), 166.8 (C_{quat}), 200.9 (CH) ppm. **30b:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.69 (s, 3 H), 0.95 (t, ^3J = 7.5 Hz, 3 H), 1.15 (s, 3 H), 1.30 (t, ^3J = 7.5 Hz, 3 H), 1.40 (s, 3 H), 1.61 (m, 2 H), 2.00−1.80 (m, 1 H), 2.00−2.20 (m, 1 H), 2.74 (t, ^3J = 7.5 Hz, 2 H), 2.80−2.90 (m, 5 H), 3.30−3.40 (m, 2 H), 3.50−3.60 (m, 6 H), 4.20 (q, ^3J = 7.5 Hz, 2 H), 4.38 (dd, ^3J = 7.5, ^3J = 2.5 Hz, 1 H), 6.56 (s, 1 H), 9.67 (s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 8.6 (CH_3), 14.2 (CH_3), 21.7 (CH_3), 21.9 (CH_3), 23.2 (CH_3), 24.3 (CH_2), 30.1 (C_{quat}), 35.6 (CH), 36.2 (CH), 38.7 (CH_2), 39.8 (CH_2) (× 2), 54.0 (C_{quat}), 60.8 (CH_2), 65.0 (CH), 67.9 (CH_2) (× 2), 77.1 (CH_2) (× 2), 101.1 (CH), 135.5 (C_{quat}), 137.7 (CH), 166.8 (C_{quat}), 205.1 (C_{quat}) ppm.

Rearranged Compounds 36 and 37

Procedure 1: Butylamine (47 μL, 0.48 mmol) was added dropwise to a solution of **30** (140 mg, 0.32 mmol) in anhydrous methanol (5 mL) in the presence of molecular sieves (3 Å). The mixture was heated at reflux for 1 h and was then allowed to cool to room temperature. Methanesulfonic acid (31 μL, 0.48 mmol) was added and the resulting mixture was heated at reflux overnight. The reaction mixture was then allowed to cool to room temperature and filtered through Celite. The residue was concentrated in vacuo and chromatographed on silica gel (EtOAc/heptane, 1:3) to afford **36** (36 mg, 27%) and **37** (15 mg, 11%).

Procedure 2: Butylamine (35 μL, 0.35 mmol) was added dropwise to a solution of **30** (100 mg, 0.23 mmol) in pentane (5 mL) in the presence of alumina. The mixture was stirred for 2 h and was then filtered through Celite and concentrated in vacuo. The residue was dissolved in toluene (5 mL), and *p*-toluenesulfonic acid (67 mg, 0.35 mmol) was added. The resulting mixture was heated at reflux under Dean−Stark conditions. The residue was concentrated and chromatographed on silica gel (EtOAc/heptane, 1:3) to afford **36** (21 mg, 21%) and **37** (8 mg, 8%).

Procedure 3: Butylamine (67 μL, 0.68 mmol) was added dropwise to a solution of **30** (197 mg, 0.45 mmol) in anhydrous methanol (10 mL) in the presence of molecular sieves (3 Å). The mixture was heated at reflux for 1 h and was then allowed to cool to room temperature. Camphorsulfonic acid (158 mg, 0.68 mmol) was added and the resulting mixture was heated at reflux overnight. The reaction mixture was then allowed to cool to room temperature and filtered through Celite. The residue was concentrated in vacuo and chromatographed on silica gel (EtOAc/heptane, 1:3) to afford **36** (47 mg, 25%).

36: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.73 (s, 3 H), 1.12 (t, ^3J = 7.5 Hz, 3 H), 1.20 (s, 3 H), 1.24 (t, ^3J = 7.5 Hz, 3 H), 2.20 (q, ^3J = 7.5 Hz, 2 H), 2.44 (q, ^3J = 5.0 Hz, 4 H), 2.60 (t, ^3J = 7.5 Hz, 2 H), 3.44 (d, ^2J = 9.5 Hz, 2 H), 3.60 (m, 2 H), 3.64 (m, 4 H), 3.90 (br. s, 1 H), 4.13 (s, 1 H), 4.17 (q, ^3J = 7.5 Hz, 2 H), 4.44 (s, 1 H), 4.59 (t, ^3J = 5.0 Hz, 1 H), 4.72 (s, 1 H), 6.07 (s, 1 H), 6.94 (t, ^3J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 11.8 (CH_3), 14.2 (CH_3), 21.9 (CH_3), 22.0 (CH_2), 22.7 (CH_3), 30.2 (C_{quat}), 34.7 (CH_2), 39.7 (CH), 48.9 (CH_2) (× 2), 60.5 (CH_2), 67.7 (CH_2) (× 2), 77.3 (CH_2) (× 2), 77.7 (CH), 100.6 (CH), 101.2 (CH_2), 129.3 (CH), 136.1 (C_{quat}), 137.3 (CH), 154.3 (C_{quat}) (× 2), 167.0 (C_{quat}) ppm. IR (neat): $\tilde{\nu}$ = 1737 cm^{-1}, 1700, 1682. MS (ESI): *m*/*z* (%) = 420 (35) [M + H$^+$], 442 (38) [M + Na$^+$]. HRMS: calculated for $C_{24}H_{37}NO_5$ + H 420.27500; found 420.27479.

37: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.73 (s, 3 H), 0.88 (t, ^3J = 7.5 Hz, 3 H), 1.26 (s, 3 H), 1.68 (s, 3 H), 1.75 (d, ^3J = 7.0 Hz, 3 H), 2.44 (m, 4 H), 2.58 (m, 2 H), 3.44 (d, ^2J = 9.5 Hz, 2 H), 3.60−3.64 (m, 6 H), 3.94 (br. s, 1 H), 4.13 (s, 1 H), 4.17 (q, ^3J = 7.5 Hz, 2 H), 4.55 (t, ^3J = 5.0 Hz, 1 H), 5.27 (q, ^3J = 7.0 Hz, 1 H), 6.16 (s, 1 H), 6.93 (t, ^3J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 14.4 (CH_3), 15.8 (CH_3), 21.8 (CH_3), 22.9 (CH_3), 31.9 (C_{quat}), 34.5 (CH_2), 39.7 (CH), 48.8 (CH_2) (× 2), 60.5 (CH_2), 67.4 (CH_2) (× 2), 77.1 (CH_2) (× 2), 77.4 (CH), 100.4 (CH), 117.3 (CH), 125.8 (CH), 136.1 (C_{quat}), 139.7 (C_{quat}), 140.5 (C_{quat}), 146.0 (CH), 167.0 (C_{quat}) ppm. IR (neat): $\tilde{\nu}$ = 1737 cm^{-1}, 1700, 1682. MS (ESI): *m/z* (%) = 420 (35) [M + H^+], 442 (38) [M + Na^+].

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