First Model Reactions towards the Synthesis of Sarain A Core Skeleton Based upon a Biogenetic Scenario

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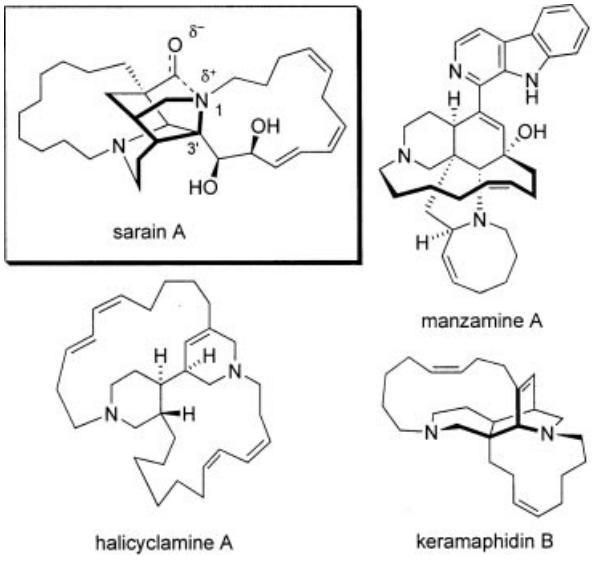
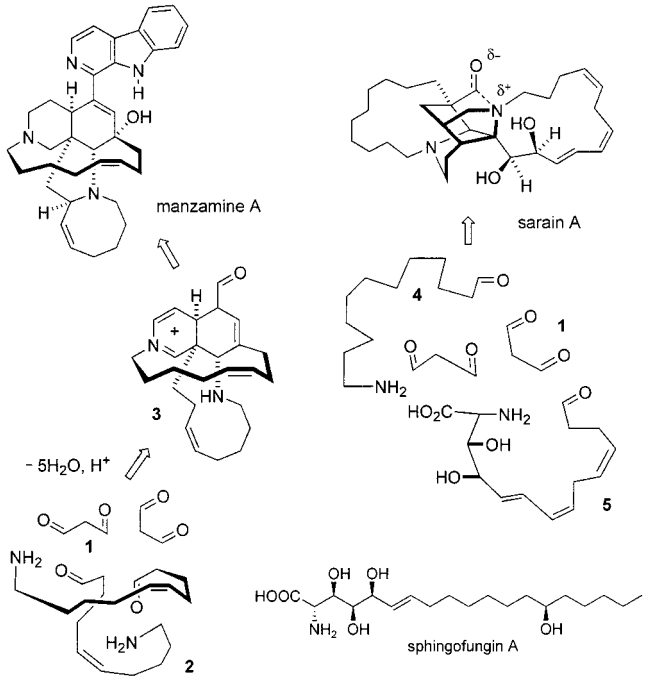
Sarain A is a complex macrocyclic marine alkaloid extracted from sponges of the order *Haplosclerida*. It is likely that this alkaloid shares a common origin with manzamine alkaloids, also extracted from sponges of the same order. In this paper, new concepts concerning this origin are presented and constitute the basis for a synthetic strategy. A preliminary evaluation of this strategy is presented and leads, as a first result, to a five-step access to the bicyclic intermediate **43**.

Sarain A is a complex alkaloid isolated from the sponge *Reniera Sarai*.[1] Despite its unique skeleton, it is believed to have the same biogenetic origin as other macrocyclic alkaloids extracted from sponges of the same order (*Haplosclerida*) such as, inter alia, manzamine A, halicyclamine A, keramaphidin B.[2] The basis for an understanding of this origin were initially formulated by Baldwin and Whitehead who proposed an original pathway for explaining the origin of keramaphidin B and manzamine A. This pathway involved formation of dihydropyridine intermediates from long-chain aminoaldehydes and acrolein, followed by intramolecular cyclization reactions.[3] This theory was further-extended to others alkaloids in these series.[2a] With regard to sarain A, we initially suggested a related route, involving the same dihydropyridine pathway, in which an additional oxidative cyclization was necessary to form the 1–3′ carbon–nitrogen bond.[4]

From the results of model experiments in our laboratory, a modification of the Baldwin and Whitehead hypothesis was proposed.[5] In this new proposal, two molecules of malondialdehyde **1** and two unsaturated long-chain aminoaldehydes **2** condense to give key intermediate **3** (Scheme 1).





Scheme 1.

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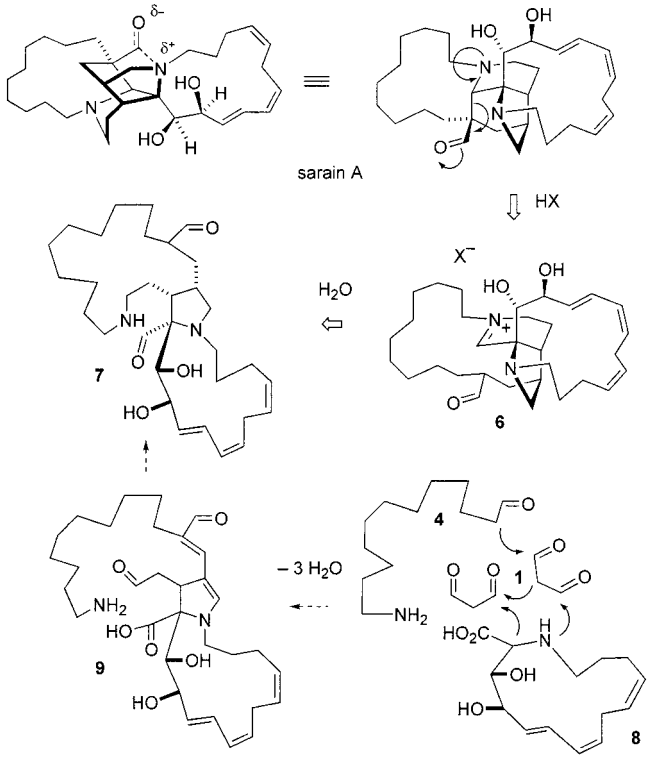
This chemistry does not necessarily involve the formation of dihydropyridine species, which are prone to undesired oxido-reduction reactions. Another advantage of this modification is that, if malondialdehyde has the right degree of oxidation, the real precursors can be malonate units. In this case, the biosyntheses of this new family of natural products could be viewed as closely related to the polyketide pathway. This last biosynthetic process is, in particular, characteristic of bacterial metabolism, and it is quite remarkable that manzamine A and its 8-hydroxy congener have recently been shown to be, in fact, produced by an actinomycete bacteria associated with the sponge.[6]

In this paper we present a new proposal for the origin of sarain A, which is closely related to our modified hypothesis involving manzamine A. The hypothesis involves reductive condensation of malondialdehyde **1** (malonate?) units with a long-chain aminoaldehyde **4** but, as a third partner, a sphingolipid derivative **5**. Thus, this proposal would have the advantage of connecting the origin of sarain A with the well-known family of sphingolipid secondary metabolites (compare, for example, the structure of intermediate **5** with the structure of sphingofungin A).[7] If this proposal is speculative, considering the lack of biogenic experiments, it constitutes what we believe to be a useful disconnection for the synthesis of this complex molecule. In this way, preliminary encouraging model experiments are presented.



Scheme 2.

Results and Discussion

The Biogenetic Scenario

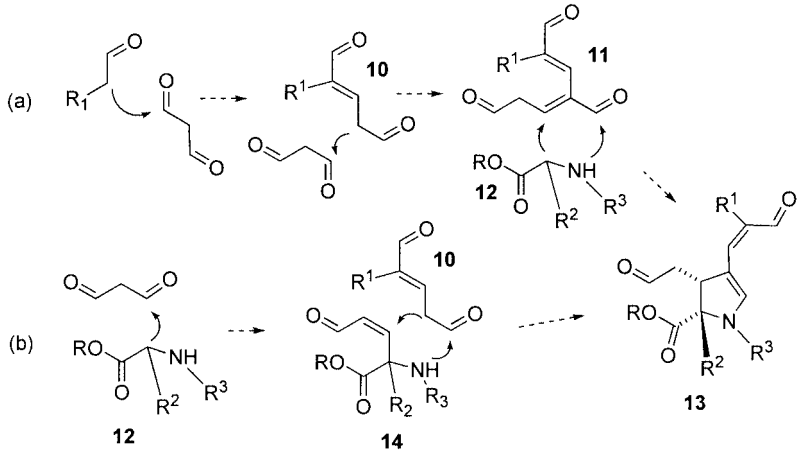
The first step in the retrosynthetic analysis of sarain A involves a retro-Mannich process, which leads to iminium salt **6** (Scheme 2). Earlier results from our laboratory suggest that this carbon–nitrogen bond should arise from a Mannich reaction.[5b] In addition, most of the syntheses under investigation to date use similar bond formation as a final step for the construction of the core polycyclic system of sarain A.[8] Hydrolysis of the iminium intermediate **6** results in the formation of aldehyde **7**. We propose that such an intermediate can be the result of condensation of an amino aldehyde **4** and the macrocycle **8** (resulting from reductive amination of the sphingolipide derivative **5**) with two three-carbon units such as malondialdehyde **1**. Derivative **9** can be obtained as a neat result of this condensation. Reductive amination, reduction of the carboxylic acid function, and reduction of two double bonds are then required to give the polycyclic molecule **7**. There are evidently a number of different possibilities for both the initial multicomponent condensation and the reduction steps. We decided to evaluate them experimentally.

Model Experiments

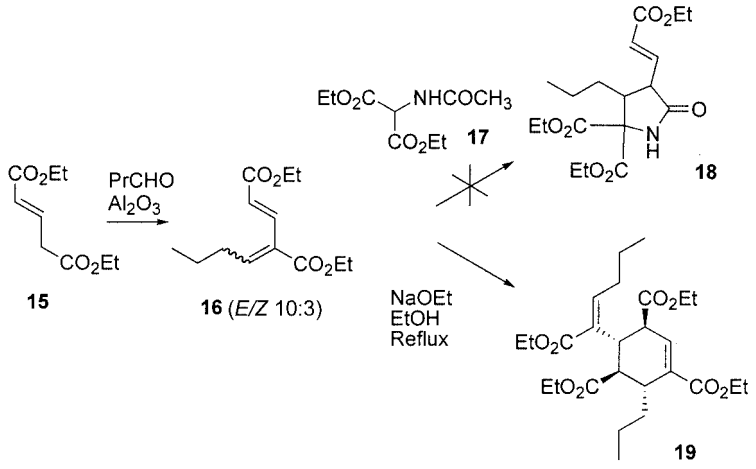
If we assume that the glutacondialdehyde derivative **10** (Scheme 3) is formed first (but this can be done at the end of the synthesis, vide infra), there are two different ways to assemble it with malondialdehyde and the amino acid derivative **12**. A first route (a) could involve a Knoevenagel addition to give adduct **11**, followed by addition of the amino acid **12** to give sarain A precursor **13** (see postulated intermediate **9** in Scheme 2). An alternate route (b) begins with the formation of the α,β-unsaturated aldehyde **14**, followed by the addition of glutacondialdehyde derivative **10**. In this paper, we report the results of model studies involving route (a).[9]

The Knoevenagel adducts of glutacondialdehyde, analogous to **11**, were recently shown to be unstable due to the addition of a second molecule of glutacondialdehyde, which resulted in the formation of substituted aromatic derivatives.[9a] By contrast, the corresponding glutaconate derivatives were found to be more stable and were used in this study. Thus, diethyl glutaconate **15** was reacted with butyraldehyde by using conditions described earlier[9a] (Scheme 4) to give isomeric adducts **16**. Ethyl acetamidomalonate **17** was chosen as the amino acid equivalent since the conjugate addition of this derivative to α,β-unsaturated esters is well documented.[10] The reaction between **16** and **17** was expected to give, in alkaline conditions, the pyrrolidone **18** according to our model. However, no trace of the desired product **18** could be detected, and the only product isolated was the cyclohexene **19** which was recovered in 36% yield as a single isomer.

The dimerization product **19** is the result of a cycloaddition process between two molecules of diene **16**. This cycloaddition is most likely to proceed through a tandem



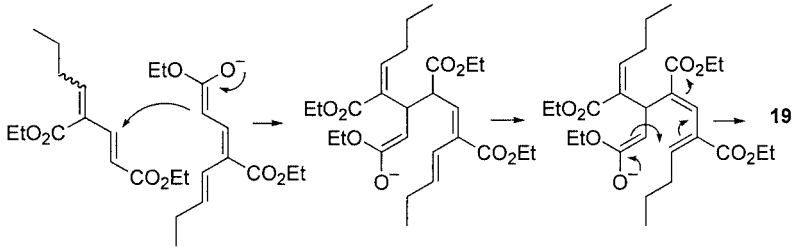
Scheme 3. Two possible pathways towards model intermediate **13**.



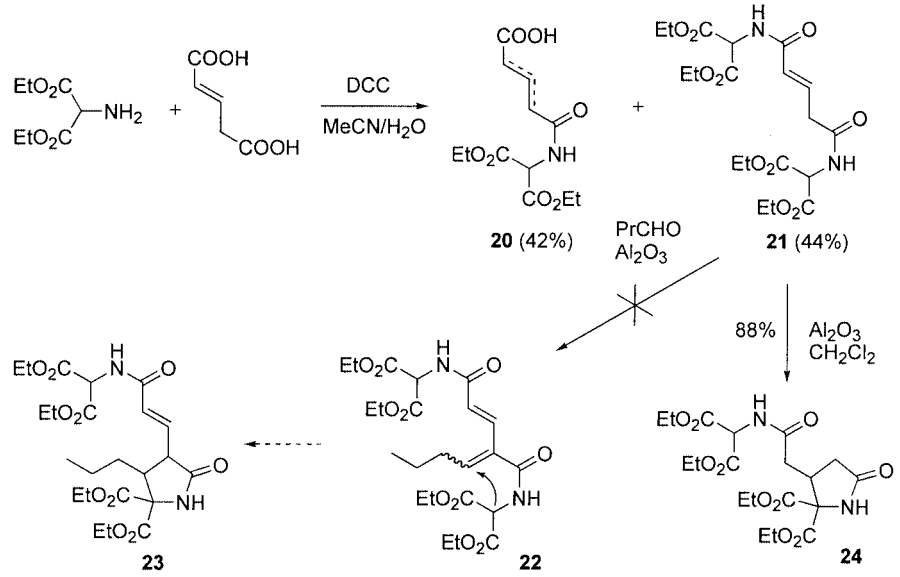
Scheme 4.

Michael–Michael reaction, since sodium ethoxide proved to be necessary for the reaction to take place (Scheme 5). The relative stereochemistry of the four asymmetric centers was determined by NOESY experiments. The complete diastereoselectivity of the reaction is quite remarkable and is likely to be the result of thermodynamic control.

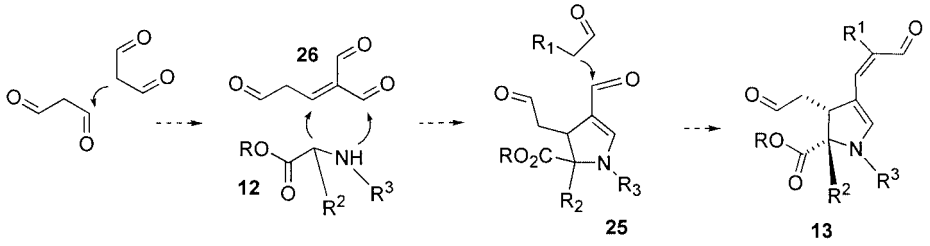
Because the dimerization process of **16** is too fast to allow the desired intermolecular Michael addition to take place, the addition was attempted intramolecularly (Scheme 6). For this purpose, diethyl aminomalonate was coupled with glutaconic acid to give a mixture of the two isomeric monoamides **20** and the diamide **21**. This diamide was isolated and subjected to conditions described above for the preparation of **16**, to prepare the Knoevenagel adduct **22**, which could eventually cyclized to **23**. Such a ring formation process is of the type 5-*endo*-trig, which is usually unfavorable though still possible (vide infra Scheme 9), but it was hoped that the double activation of the new double bond in **22** would compensate for this lack of reactivity. However, the vinylogous Knoevenagel reaction of **21** with butyraldehyde did not occur at all and only the pyrrolidinone **24**, arising from a favorable 5-*exo*-trig cyclization, was



Scheme 5.



Scheme 6.

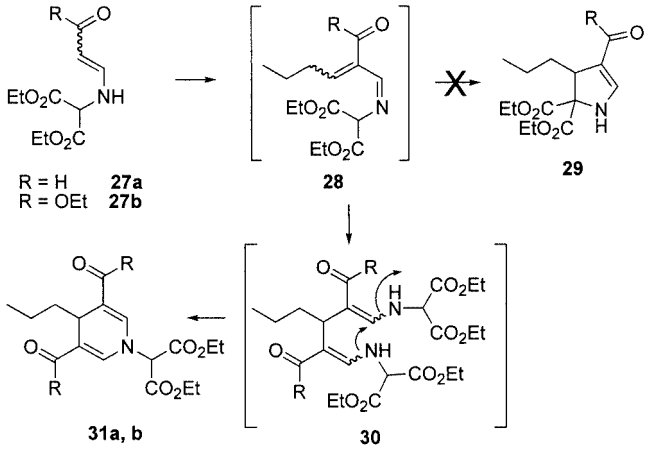


Scheme 7.

isolated. This product can be easily obtained in 88% yield by using simple alumina catalysis.

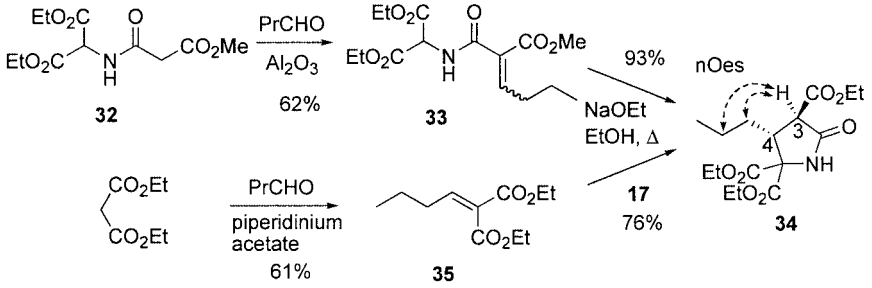
Since the use of glutaconates derivatives turned out to be difficult, we targeted intermediate **25** as a precursor of **13** by using the Knoevenagel chemistry of malondialdehyde (Scheme 7).

Malonaldehyde is known to form the dimer **26**[11] (Scheme 7) but, even with suitable protection, the presence of an amine invariably led to 1,4-dihydropyridines through the Hantzsch reaction.[12] An attempt was then made to modify the reaction pathway through the use of enaminal **27a** or aminoacrylate **27b** with the hope that a stepwise approach would allow the corresponding pyrrolines **29** to be obtained. Compounds **27a** and **27b** were obtained in very good yield from ethyl aminomalonate by reaction with malonaldehyde and ethyl propiolate, respectively, (Scheme 8). Acid derivative **27a** was mixed with propanal or butanal under various conditions, but either no reaction was observed (LiBr/DBU, K_2CO_3, TEA, Na_2SO_4) or the reagents degraded (NaH, $ZnCl_2$, AcO^-pyH^+). Reaction with *para*-toluenesulfonic acid or camphorsulfonic acid afforded the 1,4-dihydropyridine **31a** in 90% yield. The same reactivity was observed with aminoacrylate **27b** but the dihydropyridine **31b** was obtained in only 52% yield.



Scheme 8.

It became obvious that the extremely favored Hantzsch reactivity prevents other transformations to take place, which means that enamines should be avoided. For this purpose, β-carboxyamide **32** (Scheme 9) was used as a synthetic equivalent of **27a**. It cleanly reacted with butanal on alumina to afford the Knoevenagel adduct **33** as a mixture of *E*/*Z* isomers. Finally, **33** underwent the long-awaited 5-



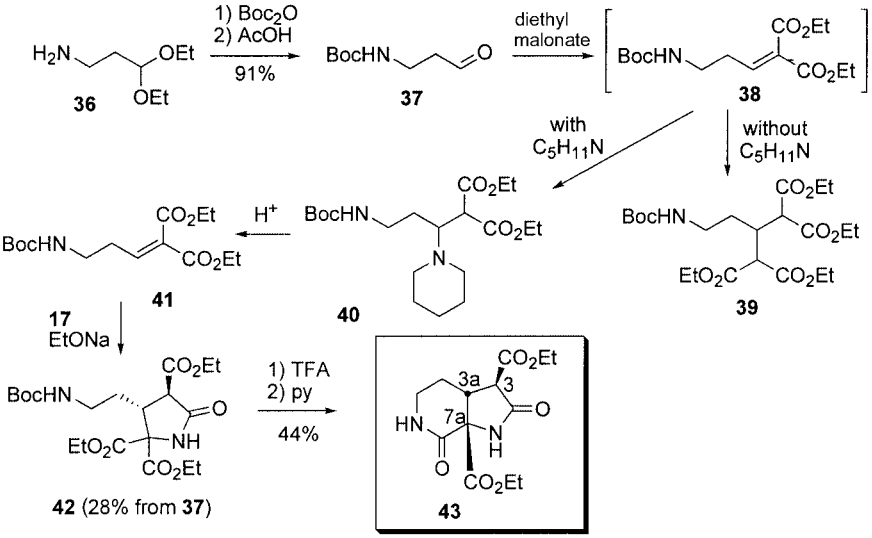
Scheme 9.

endo-trig cyclization to form pyrrolidone **34** in excellent yield. Such a sequence was then attempted intermolecularly. The Knoevenagel compound **35** was prepared from ethyl malonate and butyraldehyde, and it reacted with ethyl acetamidomalonate under the same conditions as above to give again pyrrolidone **34** in 76% yield. This closely matches the biogenetic pathway depicted in Scheme 2. However, NOESY experiments show that proton H-3 has a nOe with the propyl group at C-4, so protons H-3 and H-4 are *trans*, a stereochemistry opposite to that required for sarain A (see **7**, Scheme 2).

In order to prepare a more advanced model, the same methodology was applied to the β-aminoaldehyde **37** obtained in two steps from acetal **36** (Scheme 10).[13] By contrast, Knoevenagel reaction of **37** with ethyl malonate was not as easy as for the formation of intermediate **35**. Either no reaction was observed or the desired Knoevenagel product **38** was formed, but it reacted immediately with another molecule of ethyl malonate to give adduct **39**. Some methods are described in order to circumvent that kind of over-reactivity of Knoevenagel adducts.[14] They usually involve trapping the adduct by a nucleophile (methoxide,[15] secondary amines,[16] thiols[17]) and regenerating it after all the malonate has been consumed. Sodium ethoxide failed to give the desired adduct and even increased the yield of tetraester **39**, whereas reaction with piperidine afforded **40**, which could be satisfactorily transformed back to the unstable Knoevenagel compound **41**. Reaction of the crude product with ethyl acetamidomalonate **17** led to the pyrrolidinone **42** in 28% yield from **37**. Deprotection of the amine moiety, followed by spontaneous cyclization, finally afforded pyrrolidinone **43** in 44% nonoptimized yield. An X-ray analysis of this compound, depicted in Figure 1, shows that the ring junction in **43** is *cis* as in sarain A. However the stereochemistry at C-3 is opposite to that required for the synthesis of the natural alkaloid.

Conclusions

In conclusion, we have shown, through preliminary experiments, that the hypothetical multicomponent chemistry, leading to plausible sarain A precursors depicted in Scheme 2, can be modeled in the laboratory. This chemistry leads, in particular, to highly functionalized five-membered nitrogen heterocycles such as **24**, **34** or **43**. Intermediate **43** can be viewed as a possible synthon for further work that involves the synthesis of sarain A, since it possesses the same ring junction as the natural alkaloid. The main difficulty that is associated with this strategy is the inappropriate β stereochemistry of the C-3 substituent, a pattern which is evidently thermodynamically favored. Access to



Scheme 10.

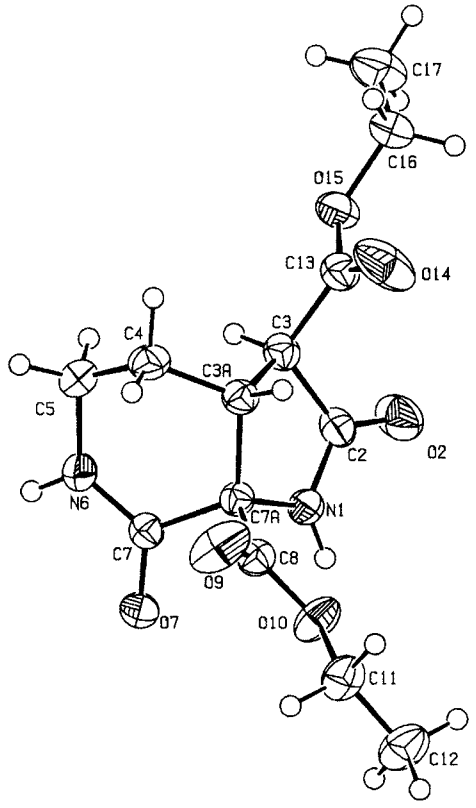


Figure 1. The molecular structure of pyrrolidinone **43**; the displacement ellipsoids are plotted at the 50% probability level.

the H-3,H-3a *cis* derivatives, along with a study of route (b) (Scheme 3), will be reported in a future paper.

Experimental Section

Knoevenagel Adducts 16: Ethyl glutaconate (2.00 mL, 11.3 mmol) was added to a suspension of alumina (38.0 g, 373 mmol) in DCM (75 mL). A solution of butyraldehyde (1.00 mL, 11.3 mmol) in DCM (10 mL) was added dropwise over 90 min. After 72 h, alumina was filtered off and washed thoroughly with DCM (6 × 50 mL). The solvent was evaporated under vacuum, and the yellow oily residue was purified by column chromatography over silica gel (heptanes/EtOAc, 95:5) to afford the title compound (1.63 g, 6.78 mmol, 60% yield) as a mixture of 4-*E*/*Z* isomers (*E*/*Z* ratio 10:3 as determined by NMR spectroscopy and GC). ^{1}H NMR (mixture of *E*/*Z* isomers, 250 MHz, $CDCl_3$): δ = 0.96 (0.9 H, t, *J* = 7.3 Hz), 0.97 (t, 3 H, *J* = 7.3 Hz), 1.30 and 1.34 (1.8 H, t, *J* = 7.2 Hz), 1.31 and 1.33 (t, 6 H, *J* = 7.2 Hz), 1.52 (0.6 H, m), 1.54 (m, 2 H), 2.37 (0.6 H, m), 2.39 (m, 2 H), 4.19 and 4.29 (q, 4 H, *J* = 7.2 Hz), 4.23 and 4.32 (1.2 H, q, *J* = 7.2 Hz), 6.02 (0.3 H, d, *J* = 15.9 Hz), 6.30 (0.3 H, t, *J* = 7.8 Hz), 6.50 (d, 1 H, *J* = 15.9 Hz), 7.02 (t, 1 H, *J* = 7.8 Hz), 7.26 (0.3 H, d, *J* = 15.9 Hz), 7.53 (d, 1 H, *J* = 15.9 Hz) ppm. ^{13}C NMR (mixture of *E*/*Z* isomers, 62.5 MHz, $CDCl_3$): δ = 13.8, 14.2, 22.0, 22.1, 30.8, 32.1, 60.4, 60.9, 119.1, 122.9, 128.4, 135.6, 142.3, 147.9, 150.3, 166.0, 167.3 ppm. IR (film): $\tilde{\nu}$ = 2963, 1718, 1632, 1464, 1289, 1179 cm^{-1}. MS (EI): *m*/*z* = 240 $[M]^+$.

Cycloadduct 19: Sodium ethoxide (38 mg, 0.56 mmol) was added to a solution of adducts **16** (300 mg, 1.25 mmol) in absolute ethanol (2 mL), and the mixture was stirred at reflux for 14 h then cooled down to room temperature. Acetic acid (60 μL, 1.05 mmol) was added, followed by DCM (100 mL). The organic layer was washed with water (3 × 100 mL), dried with $MgSO_4$, and the solvents were evaporated under vacuum. The yellow oily residue (403 mg) was purified by column chromatography on silica gel (pentane/ether, 8:2) to afford the title compound (114 mg, 0.24 mmol, 38% yield). ^{1}H NMR (400 MHz, C_6D_6): δ = 0.94 (t, 3 H, *J* = 7.4 Hz), 0.97 (t, 3 H, *J* = 7.3 Hz), 0.98 (t, 3 H, *J* = 7.1 Hz), 1.04 (t, 3 H, *J* = 7.1 Hz), 1.07 (t, 3 H, *J* = 7.1 Hz), 1.13 (t, 3 H, *J* = 7.1 Hz), 1.42–1.52 (m, 3 H), 1.61 (m, 1 H), 1.78 (m, 1 H), 2.10 (m, 1 H), 2.46 (m, 2 H), 3.76 (t, 1 H, *J* = 10.7 Hz), 3.80 (m, 1 H), 3.83 (t, 1 H, *J* = 11.2 Hz), 3.90–4.21 (m, 8 H), 4.61 (dt, 1 H, *J* = 10.9, 1.9 Hz), 7.24 (t, 1 H, *J* = 7.2 Hz), 7.33 (t, 1 H, *J* = 1.9 Hz) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 14.0, 14.2, 14.3, 14.6, 18.9, 22.4, 30.9, 35.4, 38.7, 40.2, 46.1, 48.3, 60.3, 60.4, 60.5, 60.8, 130.7, 135.6, 135.8, 148.2, 166.6, 166.8, 172.6, 177.1 ppm. IR (film): $\tilde{\nu}$ = 2964, 1719, 1707, 1632, 1464, 1289, 1183 cm^{-1}. HRMS (ESI$^+$): *m*/*z* = 503.26219 $[M + Na]^+$ ($C_{16}H_{40}O_8Na$: calcd. 503.26209).

Derivatives 20 and 21: Ethyl aminomalonate hydrochloride (1.95 g, 9.21 mmol) was dissolved in DCM (100 mL) and washed with a saturated calcium carbonate solution (100 mL). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The colorless oil obtained (1.61 g, 9.20 mmol) was dissolved in MeCN/water (1:1, 10 mL) and cooled down to –5 °C under argon. Glutaconic acid (598 mg, 4.60 mmol) was added. A solution of DCC (1.89 g, 9.20 mmol) in acetonitrile (5 mL) was then added dropwise. After 16 h at room temperature, the mixture was filtered, and the filtrate evaporated under vacuum. The solid residue was taken up in DCM (50 mL), stirred for 15 min, and the persistent precipitate filtered off. The filtrate was evaporated, and the operation was repeated until no precipitate was formed. The white solid obtained was purified by column chromatography on silica gel (DCM/MeOH, 99:1 to 95:5) to afford a mixture of the two regioisomers **20** (564 mg, 1.97 mmol, 42%) in ratio 4:1 and the diamide **21** (897 mg, 2.02 mmol, 44%).

***(E)*-*N*-Bis(ethoxycarbonyl)methyl-2*H*- and –4*H*-Glutaconic Acids (20):** ^{1}H NMR (250 MHz, [D_6]acetone): δ = 1.25 (7.5 H, t, *J* = 7.1 Hz), 3.27 (dd, 2 H, *J* = 7.1, 1.5 Hz), 3.34 (0.5 H, dd, *J* = 7.1, 1.5 Hz), 4.21 (m, 5 H), 5.14 (d, 1 H, *J* = 7.3 Hz), 5.25 (0.25 H, d, *J* = 7.6 Hz), 5.97 (d, 1 H, *J* = 15.6 Hz), 6.25 (0.25 H, d, *J* = 15.4 Hz), 6.92 (dt, 1 H, *J* = 15.4, 7.1 Hz), 7.00 (0.25 H, dt, *J* = 15.6, 7.1 Hz), 7.91 (1.25 H, br. s) ppm. ^{13}C NMR (62.5 MHz, [D_6]acetone): δ = 14.3, 37.2, 38.9, 57.3, 62.7, 124.7 126.6, 137.9, 142.9, 165.3, 167.1, 167.3, 171.6 ppm. MS (ESI$^+$): *m*/*z* = 288 $[M + H]^+$, 310 $[M + Na]^+$, 326 $[M + K]^+$.

(*E*)-*N*,*N*′-Bis[bis(ethoxycarbonyl)methyl]glutaconamide (21): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.29 (t, 12 H, *J* = 7.1 Hz), 3.23 (dd, 2 H, *J* = 7.1, 1.3 Hz), 4.26 and 4.27 (q, 8 H, *J* = 7.1 Hz), 5.11 and 5.23 (d, 2 H, *J* = 7.0 Hz), 6.12 (dt, 1 H, *J* = 15.4, 1.3 Hz), 6.70 and 6.71 (d, 2 H, *J* = 7.4 Hz), 6.95 (dt, 1 H, *J* = 15.4, 7.1 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 38.8, 56.5, 62.7, 126.2, 137.1, 164.4, 166.1, 166.3, 168.7 ppm. IR (film): $\tilde{\nu}$ = 3419, 3052, 2987, 1757, 1742, 1686, 1622, 1502, 1422, 1276, 1253, 1019 cm^{-1}. MS (ESI$^+$): *m*/*z* = 445 $[M + H]^+$, 467 $[M + Na]^+$, 483 $[M + K]^+$.

Substituted Pyrrolidinone 24: Diamide **21** (145 mg, 0.33 mmol) was added to a suspension of alumina (330 mg, 3.23 mmol) in DCM (3 mL) at room temperature. After 72 h, alumina was filtered off and washed thoroughly with DCM (5 × 20 mL). The solvent was evaporated under reduced pressure, and the solid residue (132 mg) was purified by column chromatography over silica gel (heptanes/EtOAc, 9:1) to afford the title pyrrolidinone (127 mg, 0.29 mmol, 88%) as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t,

12 H, J = 7.1 Hz), 2.25 (dd, 1 H, J = 17.1, 8.1 Hz), 2.31 (dd, 1 H, J = 14.7, 11.8 Hz), 2.68 (dd, 1 H, J = 17.1, 8.4 Hz), 2.76 (dd, 1 H, J = 14.7, 3.4 Hz), 3.42 (dddd, 1 H, J = 11.8, 8.4, 8.1, 3.4 Hz), 4.20–4.32 (m, 8 H), 5.14 (d, 1 H, J = 7.0 Hz), 6.76 (s, 1 H), 6.99 (d, 1 H, J = 7.3 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.8, 13.9, 14.0, 35.6, 36.3, 37.5, 56.4, 62.5, 62.6, 62.7, 70.6, 166.2, 167.6, 168,0, 169.8, 175.1 ppm. IR (film): $\tilde{\nu}$ = 3418, 3055, 2986, 2916, 1741, 1712, 1505, 1371, 1281, 1217, 1095, 1032, 859 cm^{-1}. MS (ESI$^+$): m/z = 445 [M + H]$^+$, 467 [M + Na]$^+$, 483 [M + K]$^+$.

Ethyl 2-(3-Oxypropenyl)aminomalonates 27a (*E*/*Z* Isomers): Ethyl aminomalonate hydrochloride (2.11 g, 10.0 mmol) was added to a suspension of the sodium salt of malonaldehyde[18] (1.12 g, 10.0 mmol) in DCM (50 mL) under argon. The mixture was stirred for 4 h at room temperature, then filtered, and the solid washed with DCM (3 × 50 mL). The combined filtrates were evaporated under vacuum, and the orange residue (2.82 g) was purified by column chromatography over silica gel (heptanes/EtOAc, 1:1) to afford the title aminoacroleine (2.06 g, 9.00 mmol, 90%) as a mixture isomers in a *E*/*Z* ratio of 85:15 as determined by NMR spectroscopy. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22 (t, 7 H, J = 7.1 Hz), 4.05–4.35 (4.72 H, m), 4.55 (0.18 H, d, J = 6.9 Hz), 4.57 (d, 1 H, J = 6.2 Hz), 5.15 (0.18 H, dd, J = 7.7, 2.1 Hz), 5.17 (dd, 1 H, J = 13.2, 8.5 Hz), 6.46 (t, 1 H, J = 6.6 Hz), 6.72 (0.18 H, m), 7.20 (dd, 1 H, J = 13.2, 7.7 Hz), 9.11 (d, 1 H, J = 8.1 Hz), 9.21 (0.18 H, dd, J = 4.8, 2.1 Hz), 10.12 (0.18 H, m) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.8, 59.7, 62.6, 61.8, 61.9, 97.1, 104.0, 150.6, 154.4, 165.4, 165.7, 189.4, 190.5 ppm. IR (film): $\tilde{\nu}$ = 2984, 2916, 1740, 1618, 1371,1166, 1021, 858 cm^{-1}. MS (CI, isobutane): m/z = 230 [M + H]$^+$.

Ethyl 2-(2-Ethoxycarbonylvinylamino)malonate 27b (*E*/*Z* Isomers): Ethyl aminomalonate (2.07 g, 11.82 mmol) and ethyl propiolate (1.2 mL, 11.84 mmol) were mixed in absolute ethanol (25 mL), and the solution was heated at reflux for 4 h. The solvent was removed under vacuum, and the yellow oily residue (3.20 g) was purified by column chromatography over silica gel (DCM/EtOAc, 9:1) to afford the title aminoacrylate (2.92 g, 10.7 mmol, 90%) as an equimolar mixture of *E*- and *Z* isomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.30 (m, 18 H), 4.13 (m, 4 H), 4.27 (m, 8 H), 4.50 (d, 1 H, J = 8.5 Hz), 4.54 (d, 1 H, J = 7.0 Hz), 4.66 (d, 1 H, J = 8.1 Hz), 4.77 (d, 1 H, J = 13.6 Hz), 5.49 (d, 1 H, J = 6.8 Hz), 6.58 (dd, 1 H, J = 12.5, 8.1 Hz), 7.49 (dd, 1 H, J = 13.6, 7.3 Hz), 8.33 (dd, 1 H, J = 11.8, 8.8 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.4, 59.0, 59.3, 59.9, 62.5, 62.8, 63.3, 86.8, 89.6, 146.0, 148.8, 166.0, 166.4, 168.6, 196.9 ppm. IR (film): $\tilde{\nu}$ = 3336, 2982, 2936, 1748,1740, 1673, 1622, 1477, 1369, 1301, 1200, 1095, 858, 788 cm^{-1}. MS (EI): m/z = 273 [M]$^+$.

Ethyl 2-(3,5-Diformyl-4-propyl-1,4-dihydropyridin-1-yl)malonate (31a): A solution of aminoacroleine (216 mg, 0.94 mmol) in 1,2-dichloroethane (5 mL) was added to a solution of butyraldehyde (0.20 mL, 2.27 mmol) in 1,2-dichloroethane (10 mL). *p*-Toluenesulfonic acid (100 mg, 0.58 mmol) was added, and the mixture was heated at reflux for 1 h. After evaporation of the solvent under vacuum, the red oily residue (600 mg) was purified by column chromatography over silica gel (heptanes/EtOAc, 1:1) to afford the title dihydropyridine (143 mg, 0.42 mmol, 90%) as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83 (t, 3 H, J = 7.2 Hz), 1.13 (m, 2 H), 1.35 (t, 6 H, J = 7.1 Hz), 1.47 (m, 2 H), 3.92 (t, 1 H, J = 4.8 Hz), 4.25–4.45 (m, 4 H), 4.90 (s, 1 H), 6.94 (s, 2 H), 9.29 (s, 2 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.9, 14.0, 17.9, 27.4, 36.1, 63.3, 67.1, 122.6, 146.4, 164.6, 189.0 ppm. IR (film): $\tilde{\nu}$ = 2959, 2935, 2873, 1744, 1667, 1580, 1421, 1393, 1369, 1225, 1156, 1111, 1028, 917, 707 cm^{-1}. MS (EI): m/z = 337 [M]$^+$.

1,4-Dihydropyridine-3,5-dicarboxylate 31b: Aminoacrylate **27b** (240 mg, 87 mmol) and butyraldehyde (0.10 mL, 1.13 mml) were dissolved in 1,2-dichloroethane (5 mL). *p*-Toluenesulfonic acid (50 mg, 0.29 mmol) was added, and the mixture was heated at reflux for 4 h. The solvent was evaporated under vacuum, and the resulting yellow oil (378 mg) was purified by column chromatography over silica gel (heptanes/EtOAc, 8:2) to afford the title dihydropyridine (96 mg, 0.23 mmol, 51%) as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83 (t, 3 H, J = 7.2 Hz), 0.94 (m, 2 H), 1.30 (t, 14 H, J = 7.1 Hz), 1.31 (m, 2 H), 3.87 (t, 1 H, J = 4.8 Hz), 4.10–4.35 (m, 8 H), 4.68 (s, 1 H), 7.20 (s, 2 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.9, 14.0, 14.2, 14.3, 17.6, 30.6, 38.0, 60.1, 62.9, 67.5, 109.3, 137.8, 165.1, 166.9 ppm. IR (film): $\tilde{\nu}$ = 2959, 2936, 1748,1741, 1705, 1592, 1369, 1203, 1185, 1094, 1023, 860 cm^{-1}. MS (EI): m/z = 425 [M]$^+$.

Ethyl 2-(2-Methoxycarbonylacetamido)malonate 32: Ethyl aminomalonate hydrochloride (2.11 g, 9.87 mmol) and sodium methoxycarbonylacetate (1.56 g, 9.78 mmol) were dissolved in acetonitrile/water (3:1, 60 mL) at –5 °C. DCC (2.06 g, 10.0 mmol) was added, and the mixture was stirred at –5 °C for 2 h and then for additional 4 h at room temperature. The white precipitate was filtered off and washed with DCM (3 × 50 mL). The filtrate was diluted with DCM (200 mL) and washed with water (3 × 150 mL). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The residue (3.07 g) was purified by column chromatography over silica gel (DCM/EtOAc, 9:1) to afford the title amide (2.59 g, 9.41 mmol, 96%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26 (t, 6 H, J = 7.2 Hz), 3.38 (s, 2 H), 3.73 (s, 3 H), 4.24 (m, 4 H), 5.13 (d, 1 H, J = 6.8 Hz), 8.02 (d, 1 H, J = 6.6 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.8, 40.6, 52.4, 56.4, 62.5, 164.8, 165.8, 168.9 ppm. IR (film): $\tilde{\nu}$ = 3413, 3353, 2956, 1754, 1742, 1682, 1517, 1373, 1344, 1218, 1178, 1019, 858 cm^{-1}. MS (ESI$^+$): m/z = 276 [M + H]$^+$, 298 [M + Na]$^+$, 314 [M + K]$^+$.

Ethyl 2-((2*E* and 2*Z*)-2-Methoxycarbonylhex-2-enoylamino)malonate 33: Amide **32** (350 mg, 1.27 mmol) and butyraldehyde (0.168 mL, 1.90 mmol) were added under argon to a suspension of alumina (872 mg, 8.55 mmol) in DCM (0.50 mL). The mixture was stirred at room temperature for 96 h, then filtered through Celite, and the solid was washed with DCM (5 × 10 mL). The combined filtrates were evaporated under vacuum, and the resulting oil (323 mg) was purified by column chromatography over silica gel (heptanes/DCM/EtOAc 65:25:10) to afford the two isomeric amides (192 mg, 0.58 mmol, 46%) and (2*E*) (68 mg, 0.21 mmol, 16%). **(*Z*)-Isomer:** ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.94 (t, 3 H, J = 7.3 Hz), 1.29 (t, 6 H, J = 7.3 Hz), 1.52 (h, 2 H, J = 7.3 Hz), 2.52 (q, 2 H, J = 7.3 Hz), 3.86 (s, 3 H), 4.26 (m, 4 H), 5.17 (d, 1 H, J = 6.6 Hz), 7.59 (t, 1 H, J = 7.3 Hz), 8.97 (d, 1 H, J = 6.6 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.8, 13.9, 21.8, 32.5, 52.1, 57.1, 62.4, 125.0, 157.8, 165.0, 166.1, 167.2 ppm. IR (film): $\tilde{\nu}$ = 3352, 2961, 2874, 1759, 1743, 1710, 1665, 1512, 1440, 1372, 1281, 1223, 1151, 1023, 808 cm^{-1}. MS (ESI$^+$): m/z = 330 [M + H]$^+$, 352 [M + Na]$^+$, 368 [M + K]$^+$. **(*E*)-Isomer:** ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.95 (t, 3 H, J = 7.3 Hz), 1.31 (t, 6 H, J = 7.3 Hz), 1.53 (h, 2 H, J = 7.3 Hz), 2.61 (q, 2 H, J = 7.3 Hz), 3.80 (s, 3 H), 4.26 (m, 4 H), 5.21 (d, 1 H, J = 6.6 Hz), 7.29 (t, 1 H, J = 7.3 Hz), 8.20 (d, 1 H, J = 6.6 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.8, 14.0, 22.0, 31.9, 52.5, 56.7, 62.6, 126.6, 156.5, 163.9, 166.0, 166.1 ppm. IR (film): $\tilde{\nu}$ = 3344, 2961, 2874, 1759, 1742, 1711, 1678, 1511, 1438, 1372, 1251, 1157, 1024, 860, 807 cm^{-1}. MS (ESI$^-$): m/z = 328 [M – H]$^-$.

Pyrrolidinone 34. From Amide 33: Amide **33** (*E*- or *Z*-isomer, 304 mg, 0.92 mmol) was dissolved in absolute ethanol (10 mL). So-

dium ethoxide (31 mg, 0.46 mmol) was added, and the solution was heated to reflux for 1 h. After cooling to room temperature, the mixture was neutralized with glacial acetic acid (0.035 mL, 0.77 mmol), then diluted with DCM (100 mL) and washed with brine (100 mL). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The yellowish solid obtained (330 mg) was recrystallized from 95% ethanol to afford the title pyrrolidinone (294 mg, 0.86 mmol, 93%) as a white solid. **From Knoevenagel Adduct 35:** Ethyl acetamidomalonate (277 mg, 1.27 mmol) and diester **35** (300 mg, 1.40 mmol) were dissolved in absolute ethanol (2 mL). Sodium ethoxide (41 mg, 0.60 mmol) was added, and the mixture was heated to reflux for 14 h. After cooling to room temperature, glacial acetic acid (0.040 mL, 0.89 mmol) was added, and the solvents were evaporated from the mixture under reduced pressure. The resulting orange oil was taken up in water (3 mL) and stirred for 30 min. The precipitate was filtered off, washed with water (3×10 mL) and dried under vacuum. Recrystallization from 95% ethanol afforded the title pyrrolidinone (332 mg, 0.97 mmol, 76%) as a white solid. M.p. (MeOH) 74 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, J = 7.1 Hz), 1.26 and 1.28 (t, 9 H, J = 7.1 Hz), 1.12–1.32 (m, 3 H), 1.79 (m, 1 H), 3.28 (m, 2 H), 4.26 (m, 6 H), 7.06 (br. s, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 13.7, 13.9, 20.5, 32.6, 44.4, 53.8, 61.7, 62.4, 62.6, 69.8, 167.3, 168.3, 169.1, 171.5 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3413, 2966, 2935, 1742, 1727, 1466, 1370, 1221, 1042, 860 cm^{-1}. MS (EI): m/z = 343 $[M]^+$. Calcd. C 55.97, H 7.34, N 4.08; found C 56.04, H 7.62, N 4.17.

Ethyl 2-Butylidenemalonate 35: Ethyl malonate (1.52 mL, 10.0 mmol), butyraldehyde (0.882 mL, 10.0 mmol), and piperidinium acetate (290 mg, 2.00 mmol) were dissolved in DCM (30 mL). The mixture was stirred for 15 h at room temperature, then diluted with DCM (150 mL) and washed successively with 0.1 N hydrochloric acid (150 mL), saturated $NaHCO_3$ solution (150 mL) followed by brine (150 mL). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (heptanes/EtOAc, 9:1) to afford the title Knoevenagel adduct (1.31 g, 6.10 mmol, 61%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, 3 H, J = 7.3 Hz), 1.26 and 1.30 (t, 6 H, J = 7.3 Hz), 1.49 (q, 2 H, J = 7.3 Hz), 2.25 (dd, 2 H, J = 7.7, 7.3 Hz), 4.20 and 4.27 (q, 4 H, J = 7.3 Hz), 6.96 (t, 1 H, J = 7.7 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 14.1, 21.6, 31.7, 61.1, 128.8, 142.1, 163.9, 165.5 ppm. IR (film): $\tilde{\nu}$ = 2964, 2935, 2874, 1734, 1727, 1646, 1465, 1375, 1251, 1212, 1060, 865 cm^{-1}. MS (EI): m/z = 214 $[M]^+$.

3-*tert*-Butoxycarbonylaminopropanal 37: The title compound was obtained in 91% yield from 3-aminopropanal diethylacetal following a known procedure[13] and was used without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 2.71 (t, 2 H, J = 5.6 Hz), 3.42 (q, 2 H, J = 6.3 Hz), 4.90 (br. s, 1 H), 9.81 (s, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl3): δ = 28.2, 34.0, 44.1, 85.0, 155.8, 201.3 ppm. IR (film): $\tilde{\nu}$ = 3356, 2927, 2934, 1697 (large), 1522, 1393, 1367, 1277, 1252, 1170, 1006, 862 cm^{-1}. HRMS (ESI$^+$): m/z = 228.1216 $[M + MeOH + Na]^+$ ($C_9H_{19}NNaO_4$: calcd. 228.1212).

Pyrrolidinone 42: A solution of aldehyde **37** (1.15g, 0.66 mmol) in DCM (0.5 mL) and ether (2 mL) was added over 2.5 h to a solution of piperidine (0.55 mL, 0.56 mmol) and diethyl malonate (0.70 mL, 0.46 mmol) in diethyl ether (10 mL) at –5 °C. The mixture was stirred for 1.5 h and then dried with Na_2SO_4. The salt was filtered and washed with DCM. The filtrate was evaporated and taken up with DCM (4 mL). *p*-Toluenesulfonic acid (1 g) and Na_2SO_4 were added to the mixture at 0 °C, and the mixture was stirred at this temperature for 3 h. The salt was filtered, and the filtrate was taken up with ether to give a milky mixture which was washed with water. The organic layer was dried (Na_2SO_4), and the solvent evaporated under vacuum to give a mixture of aldehyde, diethyl malonate, and the expected Knoevenagel adduct **41** (1.63 g). This mixture was added to a solution of acetamidomalonate (1.01 g, 0.47 mmol) in absolute ethanol (25 mL). The mixture was stirred at room temperature for 40 min and then heated to reflux for 19 h. The yellowish mixture was acidified with acetic acid (2.4 mL), and ethanol was azeotropically removed with toluene under reduced pressure. The mixture was taken up with DCM, washed with a saturated $NaHCO_3$ solution and brine, and dried with $MgSO_4$. After removal of the solvents, the resulting oil was chromatographed on silica gel (heptanes/EtOAc, 6:4 to 5:5) to afford the title pyrrolidinone (840 mg, 28% from **37**). ^{1}H NMR (600 MHz, C_6D_6): δ = 0.76 (t, J = 6.9 Hz, 3 H, CH_3), 0.84 (t, J = 6.9 Hz, 3 H, CH_3), 1.00 (t, J = 6.9 Hz, 3 H, CH3), 1.39–1.43 (m, 1 H, H6), 1.44 (s, 9 H, *t*Bu), 2.016–2.048 (m, 1 H, H6), 2.98–2.99 (m, 1 H, H7), 3.23–3.25 (m, 1 H, H7), 3.49 (d, J = 11.4 Hz, H4) 4.68 (br. s, 1 H, NHBoc), 6.62 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.1, 28.4, 30.7, 38.1, 41.8, 53.2, 62.4, 62.8, 63.0, 69.3, 79.3, 155.7, 167.3, 168.2, 169.0, 170.4 ppm. IR (film): $\tilde{\nu}$ = 3341, 2980, 2937, 1741, 1715, 1510, 1367, 1254, 1217, 1169, 1014, 860 cm^{-1}. HRMS (ESI$^+$): m/z = 467.1998 $[M + Na]^+$. $C_{20}H_{32}N_2O_9Na$ (467.2006): calcd. C 54.04, H 7.26, N 6.30; found C 54.11, H 7.36, N 6.35.

Pyrrolidinone 43: Trifluoroacetic acid (0.56 mL, 7.54 mmol) was added to a solution of carbamate **42** (334 mg, 0.75 mmol) in DCM (3.2 mL). The mixture was heated to reflux for 4.5 h. The solvent was removed, and residual TFA was co-evaporated with toluene. The residue was dissolved in a mixture of pyridine/DCM (1:3) and washed with water. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was stirred in methanol, and the precipitate filtered off and dried under vacuum to give the title compound (106 mg, 0.33 mmol, 44%) as a white solid. M.p. (MeOH) 178 °C. ^{1}H NMR (300 MHz, [D_5]pyridine): δ = 1.24 (t, 3 H, J = 6.9 Hz), 1.26 (t, 3 H, J = 6.9 Hz), 1.86–1.94 (m, 1 H), 2.31–2.39 (m, 1 H), 3.59–3.64 (m, 2 H), 3.80–3.87 (m, 1 H), 3.91 (d, 1 H, J = 4.8 Hz), 4.31 (q, 2 H, J = 6.9 Hz), 4.33 (dq, 1 H, J = 10.9, J = 6.9 Hz), 4.44 (dq, 1 H, J = 10.9, J = 6.9 Hz), 9.57 (s, 1 H, NH), 11.56 (1 H, NH) ppm. ^{13}C NMR (75 MHz, [D_5]pyridine): δ = 13.8 (CH3), 26.5 (C-4), 39.1 (C-5), 41.9 (C-3a), 53.8 (C-3), 61.5 (OCH_2), 62.0 (OCH_2), 67.5 (C-7a), 167.5 (C-7), 169.2 (*C*(O)-C-3), 170.6 (C-2), 171.4 [*C*(O)-C-7a] ppm. IR (nujol): $\tilde{\nu}$ = 3266, 3201, 2924, 2854, 1728, 1678, 1637, 1457, 1377, 1260, 1184, 1019, 816 cm^{-1}. HRMS (ESI$^+$): m/z = 321.1057 $[M + Na]^+$. $C_{13}H_{18}N_2O_6Na$ (321.1063): calcd. C 52.34, H 6.08, N 9.39; found C 52.23, H 5.91, N 9.13.

X-ray Crystallographic Study of Pyrrolidinone 43: Suitable crystals for the X-ray crystallographic studies of **43** were obtained as colorless prisms by crystallization from methanol. The crystals were mounted on the tip of a glass fiber with epoxy glue. The X-ray data were collected at 298 K with a Nonius Kappa-CCD diffractometer equipped with a graphite monochromator and Mo-K_α radiation (λ = 0.71073 Å). A total of 321 60-s frames were collected in three sets with a 1.1° ω-scan. Data reduction was carried out with the DENZO program from the HKL suite.[19] The structure was solved by direct methods with SHELXS and refined by least-squares methods on F^2, using SHELXL, both programs from the SHELX-97 package.[20] All non-hydrogen atoms were refined anisotropically, and the H atoms were located from difference-Fourier syntheses, but their positional parameters were recalculated geometrically and treated as riding, with *U*iso(H) = 1.15 *U*eq(parent atom) or 1.2 *U*eq(-CH_3). CCDC-249235 contains the supplementary crystallographic data for this paper. These data can be obtained free of

charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data for 43: $C_{13}H_{18}N_2O_6$, *Mr*= 298.29, space group orthorhombic, *Pbca* (No. 61). Unit cell parameters: *a*= 7.823(4) Å, *b*= 13.586(3) Å, *c*= 26.095(4) Å, *V*= 2773.5(16) Å^3, *Z* = 8, $\rho_{calcd.}$ = 1.429 Mg m^{-3}, *F*(000) = 1264, μ(Mo-K_α) = 0.114 mm^{-1}. Crystal dimensions 0.18 × 0.13 × 0.13 mm. A total of 5180 reflections collected, 2809 independent reflections (R_{int} = 0.0287), final R_{int} [$I > 2\sigma(I)$]: R_1 = 0.0432, wR_2 = 0.1116 for 192 variable parameters {$w = 1/[\sigma^2F_o^2 + (0.0718P)^2 + 0.3488P]$, where $P = (F_o^2 + 2F_c^2)/3$}. $(\Delta/\sigma)_{max} < 0.001$, $\Delta\rho_{max}$ = 0.28 e Å^3, $\Delta\rho_{min}$ = –0.19 e Å^3, GOF = 1.037.

[1] a) Y. Guo, A. Madaio, E. Trivellone, G. Scognamiglio, G. Cimino, *Tetrahedron* **1996**, *52*, 8341–8348; b) G. Cimino, C. A. Mattia, L. Mazzarella, R. Puliti, G. Scognamiglio, A. Spinella, E. Trivellone, *Tetrahedron* **1989**, *45*, 3863–3872.

[2] For comprehensive reviews see: a) N. Matzanke, R. J. Gregg, S. M. Weinreb, *Org. Prep. Proc. Int.* **1998**, *30*, 3–51; b) M. Tsuda, J. Kobayashi, *Heterocycles* **1997**, *46*, 765–794; c) R. J. Andersen, R. W. M. Van Soest, F. Kong, *Alkaloids: Chemical and Biological Perspectives*, vol. 10 (Ed.: S. W. Pelletier), Pergamon Press, Elsevier Science, **1996**, p. 301–355; d) P. Crews, X.-C. Cheng, M. Adamczeski, J. Rodriguez, M. Jaspar, F. J. Schmitz, S. C. Traeger, E. O. Pordesimo, *Tetrahedron* **1994**, *50*, 13567–13574.

[3] a) J. E. Baldwin, R. C. Whitehead, *Tetrahedron Lett.* **1992**, *33*, 2059–2062; For the latest results in this field and previous references see: b) J.-M. Gomez, L. Gil, C. Ferroud, A. Gateau-Olesker, M.-T. Martin, C. Marazano, *J. Org. Chem.* **2001**, *66*, 4898–4903; c) J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, V. Lee, D. R. Spring, R. C. Whitehead, *Chem. Eur. J.* **1999**, *5*, 3154–3161.

[4] L. Gil, A. Gateau-Olesker, C. Marazano, B. C. Das, *Tetrahedron Lett.* **1995**, *36*, 707–710.

[5] a) M. Herdemann, A. Al-Mourabit, M.-T. Martin, C. Marazano, *J. Org. Chem.* **2002**, *67*, 1890–1897; b) K. Jakubowicz, K. Ben Abdeljelil, M. Herdemann, M.-T. Martin, A. Gateau-Olesker, A. Almourabit, C. Marazano, B. C. Das, *J. Org. Chem.* **1999**, *64*, 7381–7387; c) A. Kaiser, X. Billot, A. Gateau-Olesker, C. Marazano, B. C. Das, *J. Am. Chem. Soc.* **1998**, *120*,8026–8034.

[6] R. T. Hill, M. T. Hamann, O. Peraud, N. Kasanah "*Manzamine-producing actinomycetes";* Worldwide patent WO 2004/013297 (US, 2003/024238), 12 February **2004**, pp. 49.

[7] F. VanMiddlesworth, C. Dufresne, F. E. Wincott, R. T. Mosley, K. E. Wilson, *Tetrahedron Lett.* **1992**, *33*, 297–301.

[8] Sarain A synthetic studies; a) M. J. Sung, H. I. Lee, H. B. Lee, J. K. Cha, *J. Org. Chem.* **2003**, *68;* 2205–2208; b) O. Irie, K. Samizu, J. R. Henry, S. M. Weinreb, *J. Org. Chem.* **1999**, *64*, 587–595; c) S. Jaroch, R. T. Matsuoka, L. E. Overman, *Tetrahedron Lett.* **1999**, *40*, 1273–1276; d) D. J. Denhart, D. A. Griffith, C. H. Heathcock, *J. Org. Chem.* **1998**, *63*, 9616–9617.

[9] For other studies from our laboratory concerning the Knoevenagel approach to manzamine alkaloids see: a) A. Lopez Giral, F. Mahuteau-Betzer, A. Gateau-Olesker, C. Marazano, *Eur. J. Org. Chem.* **2003**, 1859–1867; b) M. Sanchez Salvatori, C. Marazano, *J. Org. Chem.* **2003**, *68*, 8883–8889.

[10] For exemples see: a) R. B. Silverman, S. M. Nanavati *J. Med. Chem.* **1990**, *33*, 931–936; b) A. Barco, S. Beneti, G. P. Pollini, P. G. Baraldi, M. Guarneri, C. Gandolfi, R. Ceserani, D. J. Longiave *J. Med. Chem.* **1981**, *24*, 625–628; c) Y. C. Kim, G. H. Cocolas *J. Med. Chem.* **1965**, *8*, 509–512.

[11] L. F. Tietze, K.-H. Glüsenkamp, W. Holla, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 793.

[12] U. Eisner, J. Kuthan, J. *Chem. Rev.* **1972**, *72*, 1–42.

[13] I. Levchine, P. Rajan, M. Borloo, W. Bollaert, A. Haemers, *Synthesis* **1994**, 37–39.

[14] L. F. Tietze, U. Beifuss, in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 9, pp. 341–394.

[15] P. Margaretha, O. E. Polansky, *Tetrahedron Lett.* **1969**, *10*, 4983–4986.

[16] B. R. Chhabra, M. L. Bolte, W. D. Crow *Aust. J. Chem.* **1984**, *37*, 1795–1797.

[17] M. Eberle, R. G. Lawton, *Helv. Chim. Acta* **1988**, *71*, 1974–1982.

[18] A. Gómez-Sánchez, I. Hermosín, J.-M. Lassaletta, I. Maya, *Tetrahedron* **1993**, *49*, 1237–1250.

[19] Z. Otwinovski, W. Minor, "Macromolecular Crystallography, Part A", in *Methods in Enzymology*, Academic Press, **1997**, pp. 307–326.

[20] G. M. Sheldrick, *SHELXL-97 Program for crystal structure refinement*, University of Göttingen, Germany, **1997**.

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