User-friendly stereoselective one-pot access to 1,4-diazepane derivatives by a cyclodehydrative three-component reaction with 1,3-dicarbonyls†

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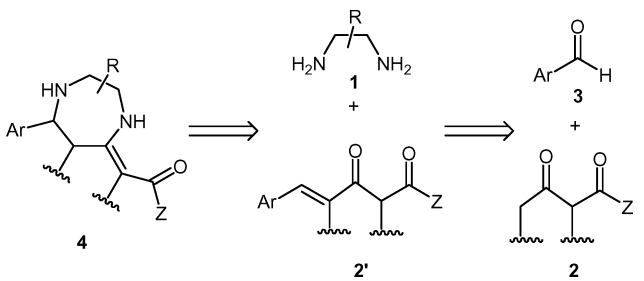
A multicomponent reaction of 1,3-dicarbonyls with 1,2-diamines and aromatic aldehydes is described for the direct stereoselective synthesis of 1,4-diazepane derivatives. Various reaction conditions were tested, including an efficient, user-friendly solvent- and catalyst-free procedure.

Introduction

Heterocycles constitute the most common structural motif in numerous natural and synthetic bioactive agents. As a result, inventing new synthetic ways to access these compounds still remains a central academic and industrial field of investigation. In this context, domino[1] multicomponent reactions[2] (MCRs), able to generate new chemical entities in a programmed and efficient manner from at least three different substrates, have emerged as powerful strategies in modern organic chemistry. Moreover, MCRs combine classical concerns such as efficiency, selectivity, molecular complexity and diversity,[3] with current preoccupations such as atom- and step-economy,[4,5] and environmentally benign reactions.[6]

Although isocyanide-based MCRs generally predominate nowadays for the construction of a wide diversity of heterocycles,[7] our ongoing interest for the specific reactivity of 1,3-dicarbonyl compounds led us to focus our attention on the development of new MCRs from these easily available substrates.[8] In this context, we have recently reported multicomponent domino transformations of β-ketoesters, β-diketones and β-ketoamides in the presence of unsaturated aldehydes and functionalised primary amines for the stereoselective synthesis of polycyclic heterocycles, promoted by molecular sieves and initiated by Michael addition.[9] At the same time, part of our efforts have been directed towards the development of the synthetic potential of 1,3-dicarbonyls using both the α- and γ-reactive sites, leading regio-, chemo- and stereoselectively to valuable α,γ-difunctionalised α-ketoesters and amides.[10] By combining these two aspects of the reactivity of such substrates, we expected that the multicomponent reaction between 1,3-dicarbonyls, 1,2-diamines and aromatic aldehydes might lead to the formation of seven-membered ring systems with 1,4-diazepane skeleton **4**, which are scaffolds of high biological interest[11] (Scheme 1). The expected heterocycle **4** may result from an aza-Michael addition–dehydrative cyclization sequence between 1,2-diamine **1** and γ-arylidene **2′**, obtained through *in situ* γ-functionalization of 1,3-dicarbonyl **2** as previously reported.[12]



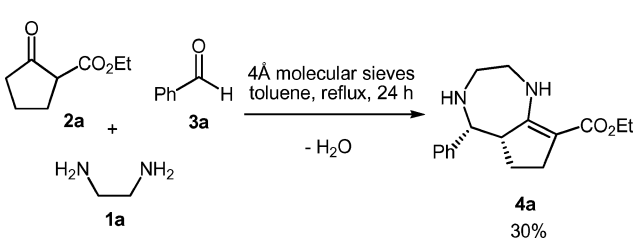
Scheme 1 Retrosynthetic analysis of 1,4-diazepane derivatives **4**.

As recently reported by Kita's team[13] and by our own group[14] in preliminary communications, this synthetic approach was validated by the obtention of the desired products. In this paper, we report the full details of these investigations, including further optimization of the reaction conditions and a brief study of the mechanism. Determination of the stereochemistry of the products will also be discussed, as well as the scope and limitations of this multicomponent sequence.

Results and discussion

Preliminary results

We initiated our study with a test experiment involving 1,2-ethylenediamine (**1a**), Dieckmann ester **2a** and benzaldehyde (**3a**) under our standard MCR conditions, *i.e.* refluxing toluene in the presence of 4 Å molecular sieves (Scheme 2).[9] After 24 hours, we were pleased to find that the desired product was formed and isolated with 30% yield. Moreover, it was obtained as a single diastereomer, identified as the *cis* isomer. However, in view of the moderate yield of this first experiment, we decided to screen various reaction conditions, in order to improve the efficiency of this multicomponent reaction.



Scheme 2 Test experiment for the synthesis of compound **4a**.

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Table 1 Optimisation of the reaction conditions for the synthesis of **4a**

Entry	Solvent	Catalyst	Yield of **4a** (%)
1	Toluene	4 Å MS	30[a]
2	Acetonitrile	4 Å MS	0
3	Dichloromethane	4 Å MS	<15[b]
4	Chloroform	4 Å MS	<15[b]
5	Dichloroethane	4 Å MS	57[a]
6	Dichloroethane	None	nd[c]
7	Dichloroethane	Montmorillonite K10	0[d]
8	Neat	None	40[a,e]

[a] Isolated yield after purification by flash chromatography. [b] Estimated in the crude. [c] Yield not determined (complex mixture). [d] Starting materials were recovered. [e] The reaction was conducted at 120 °C, and total conversion was observed after only 4 hours.

Optimisation of the reaction conditions

Variables such as the nature of the solvent, the role and the amount of the catalyst were investigated for the test reaction. Significant results are summarised in Table 1.

Concerning the nature of the solvent, we observed that the desired product was not formed in acetonitrile (entry 2), while halogenated solvents gave better results. In dichloromethane or chloroform, the 1,4-diazepane derivative **4a** was present, but in a complex mixture of non identified by-products (entries 3 and 4). Finally, dichloroethane resulted to be the solvent of choice, leading to **4a** in 57% isolated yield (entry 5). We then turned our attention to the role of 4 Å molecular sieves and found their crucial effects since refluxing in DCE alone did not result in the formation of **4a** (entry 6), but led to a complex mixture. Replacing molecular sieves by montmorillonite was unsuccessful since no conversion was observed (entry 7). Nevertheless, the result obtained in the absence of solvent and catalyst (entry 8) was of particular interest since the desired product was obtained with a yield higher than under more classical conditions, and reaction time was significantly reduced from 24 hours to 4 hours. On the basis of these preliminary observations, we examined the scope and limitations of this three-component transformation.

Scope and limitations

The general applicability of the MCR was studied using 1,2-ethylenediamine (**1a**) in combination with various cyclic and acyclic 1,3-dicarbonyls **2a–e** or β-ketosulfone **2f** and various aromatic aldehydes **3a–d** (Fig. 1).

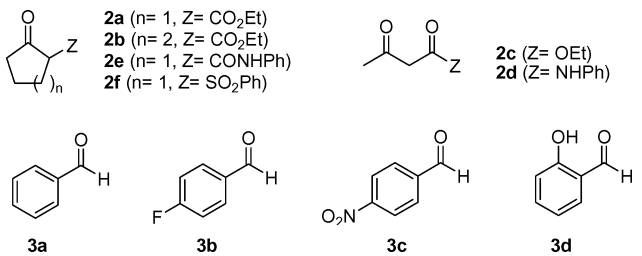
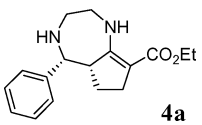
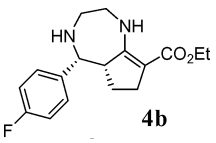
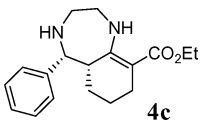
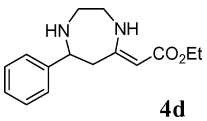
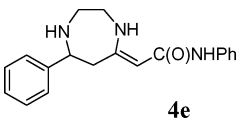
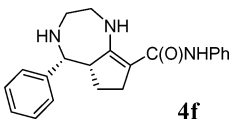
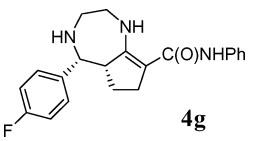
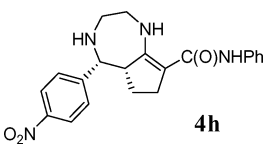
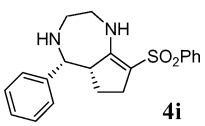
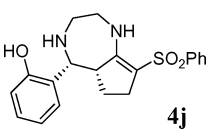


Fig. 1 Various substrates for the MCR.

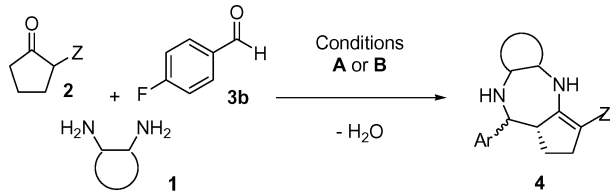
All reactions were systematically conducted both under standard (use of 4 Å MS in refluxing solvent, method **A**) and green (solvent- and catalyst-free, method **B**) conditions (Table 2). Thus, the desired products **4** were obtained in moderate yields from Dieckmann ester **2a** (entries 1, 2) while six-membered cyclic β-ketoester **2b** (entry 3) and acyclic β-ketoester **2c** (entry 4)

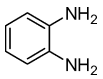
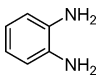
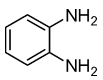
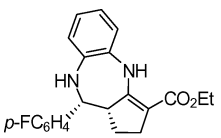
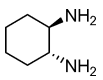
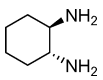
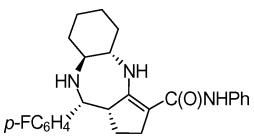
Table 2 Scope and limitations of the MCR

Entry	2	3	Product **4**	Yield[a] (%) Method **A**[b]	Method **B**[c]
1	**2a**	**3a**	 **4a**	57	40
2	**2a**	**3b**	 **4b**	40	56
3	**2b**	**3a**	 **4c**	10	14
4	**2c**	**3a**	 **4d**	35	23
5	**2d**	**3a**	 **4e**	18	0
6	**2e**	**3a**	 **4f**	37	19
7	**2e**	**3b**	 **4g**	64	77
8	**2e**	**3c**	 **4h**	26	31
9	**2f**	**3a**	 **4i**	38	21
10	**2f**	**3d**	 **4j**	23	0

[a] Isolated yield after flash chromatography. [b] 4 Å molecular sieves, 1,2-dichloroethane, reflux, 24 h. [c] Neat, 120 °C, 4 h.

Table 3 MCR from cyclic 1,2-diamines



Entry	1	2	4	Yield (%) Method **A**	Method **B**
1		**2a** (Z = OEt)	Complex mixture	—[a]	—[a]
2		**2e** (Z = NHPh)	Complex mixture	—[a]	—[a]
3		**2a** (Z = OEt)	 **4k**	45[b]	—
4		**2a** (Z = OEt)	No product	—[c]	—[c]
5		**2e** (Z = NHPh)	 **4l**	99[d]	99[d]

[a] Yield not determined – complex mixture of unidentified products obtained. [b] 4 Å MS activated with TFA prior to use. [c] Yield not determined – starting materials were recovered. [d] yield of crude product.

proved to be less efficient. Interestingly enough, the sequence was successfully extended to the use of β-ketoamides **2d–e** (entries 5–8) and β-ketosulfone **2f** (entries 9, 10). Moreover, cyclic substrates led systematically to the formation of a single diastereomer, identified as the *cis* isomer. However, no conclusion could be clearly formulated concerning the efficiency of one method (**A** or **B**) over the other.

In all cases, crude products could be obtained by simple filtration through a short pad of Celite, with purities generally higher than 80%, as estimated by NMR and HPLC analysis. However, flash chromatography purification resulted in a significant loss of pure product, probably due to unexplained degradation on silica gel. As a result, isolated yields remained moderate.

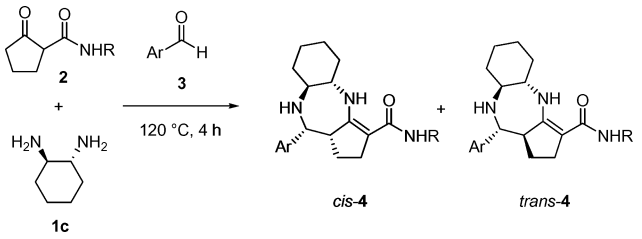
To further demonstrate the generality of this methodology, we introduced aromatic **1b** and cyclic aliphatic **1c** diamines into the sequence, in combination with *p*-fluorobenzaldehyde (**3b**) and 1,3-dicarbonyls **2a** and **2e** (Table 3).

Using *o*-phenylenediamine (**1b**) under conditions **A** or **B** did not lead to the expected 1,4-benzodiazepine in either case, whatever the 1,3-dicarbonyl used (entries 1 and 2), since a complex mixture of unidentified products was obtained, probably due to the degradation of starting materials. Nevertheless, a positive result was obtained with the formation of the benzodiazepine derivative **4k**, using 4 Å MS activated with trifluoroacetic acid prior to use (entry 3).[15] Unfortunately, this experiment was difficult to reproduce, and generalisation to other aromatic aldehydes and 1,3-dicarbonyls systematically failed.[16] In contrast, both under catalysed (method **A**) and uncatalysed (method **B**) conditions, the reaction of β-ketoamide **2e** with *trans*-cyclohexane-1,2-diamine (**1c**) resulted in quantitative formation of the corresponding 1,4-diazepane derivative **4l** as a single diastereomer (entry 5). Moreover, the product of method **B** was isolated with high purity by simple dilution of the reaction mixture with ethyl acetate, filtration through a short pad of Celite and evaporation of volatiles. This result particularly highlights the specific reactivity of β-ketoamides in this MCR, since no formation of the desired product was observed starting from Dieckmann ester **2a** under similar reaction conditions (entry 4).

Development of the MCR under solvent- and catalyst-free conditions

The excellent result obtained from β-ketoamide **2e** in the absence of solvent and catalyst led us to investigate the scope of this green

procedure.[17] Thus, *trans*-cyclohexane-1,2-diamine (**1c**) was reacted with various β-ketoamides and aromatic aldehydes (Scheme 3). In all cases, the 1,4-diazepane derivatives were formed in moderate to quantitative yields, starting either from secondary or tertiary amides (Fig. 2).



Scheme 3 Solvent- and catalyst-free MCR from β-ketoamides.

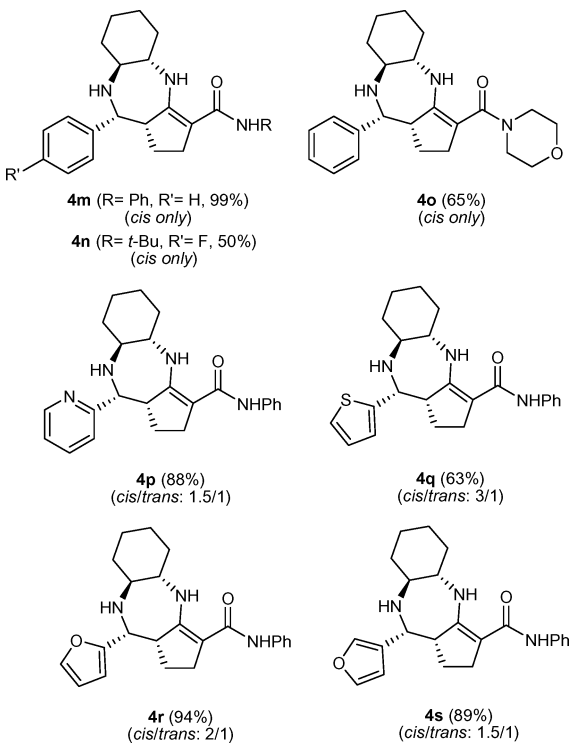
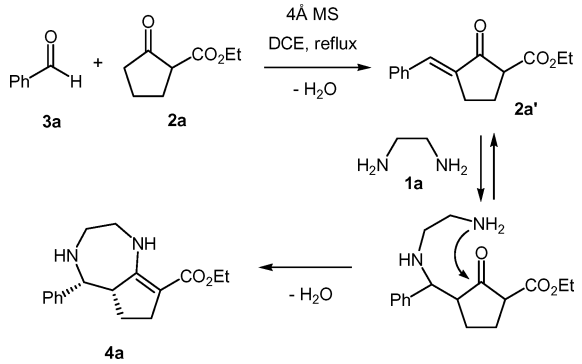


Fig. 2 Various products of the green MCR.

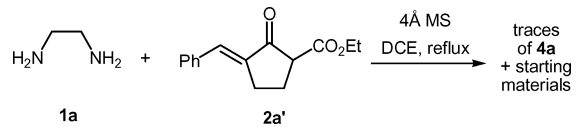
Aromatic aldehydes led exclusively to the *cis*-diastereomer, while heteroaromatic ones led to the desired products without any loss of efficiency, but as a 1.5:1 to 3:1 mixture of *cis*- and *trans*-stereoisomers. However, although it is not clear why we observed this loss of stereoselectivity, the two diastereomers were easily separable by flash chromatography. In conclusion, this environmentally friendly procedure constitutes a good substrate-directed alternative to other previously known methodologies for the synthesis of these heterocycles.[18]

Insights into the reaction mechanism

From a mechanistic point of view, various reaction pathways are possible by mixing the three starting materials. However, on the basis of our experience in the reactivity of 1,3-dicarbonyls, we initially postulated that the first step of the sequence may be the MS-promoted γ-functionalisation of the starting β-ketoester, followed by a sequence of aza-Michael addition and intramolecular dehydrative cyclisation (Scheme 4). Unfortunately, we were unable to isolate the γ-benzylidene ketoester **2a′** from an equimolar mixture of β-ketoester **2a** and benzaldehyde (**3a**) after 24 hours in refluxing DCE containing 4 Å MS. Moreover, when **2a′**, independently prepared according to a modified procedure,[10] was reacted with ethylenediamine **1a** in refluxing DCE in the presence of 4 Å MS, only traces of compound **4a** were encountered in a mixture with the starting materials, even after 24 hours (Scheme 5).

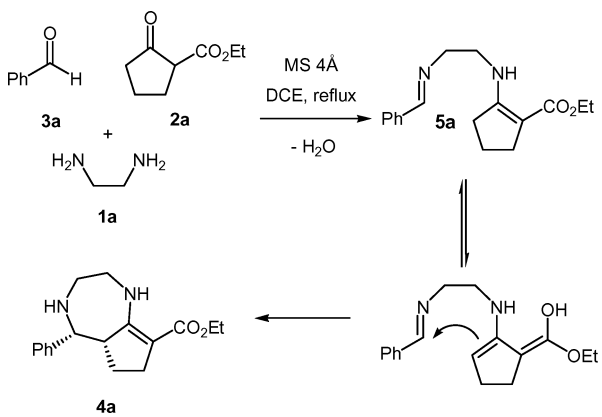


Scheme 4 Possible pathway for the synthesis of **4a** from γ-benzylidene ketoester **2a′**.



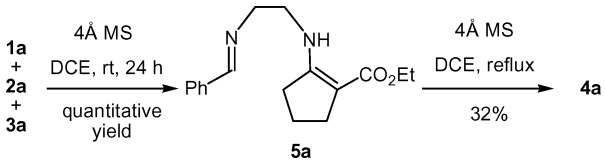
Scheme 5 Reaction of γ-benzylidene ketoester **2a′** with 1,2-ethylenediamine (**1a**) in the presence of 4 Å MS.

Alternatively, as recently suggested by Fujioka and Kita on the basis of NMR studies, another possible mechanistic pathway could involve the formation of an intermediate with imine and enamino ester functionalities **5a**, which may lead to the final product *via* an intramolecular Mannich-type condensation (Scheme 6). As a validation of this second hypothesis, we were able to isolate and fully characterise the crucial postulated intermediate



Scheme 6 Possible pathway for the synthesis of **4a** from an enamino imine intermediate.

5a by mixing the three partners in DCE containing 4 Å MS at room temperature for 24 hours (Scheme 7). Interestingly enough, heating **5a** under our standard MCR conditions gave a 32% isolated yield of **4a**. Thus, this result confirms the mechanistic proposal by Fujioka and Kita.



Scheme 7 Synthesis of enamino imine intermediate **5a** and conversion to product **4a** under standard reaction conditions.

Stereochemistry determination for the products 4

The three-component sequence gave predominantly, or exclusively in most cases, the 5,6-*cis* diastereomers of compounds **4**. This stereochemistry has been confirmed by NMR experiments, especially two-dimensional analysis. Thus, ^{1}H NMR spectra analysis revealed that all compounds **4** exhibit a doublet around 3.8 ppm with an integration of one proton, corresponding to the benzylic proton on carbon **b** (Fig. 3). For compounds of type **4A**, in which proton at **b** could couple theoretically with two other protons at **a**, this doublet means that one of the protons at **a** must form a dihedral angle of 90° with the proton at **b**, so they cannot couple. This proton's signal has the same multiplicity for both compounds of type **4B**, in which proton at **b** can only couple with one proton at **a**. Moreover, the coupling constant for the proton at **b** stays at 9.8 Hz for all compounds, so the dihedral angle of both coupling protons at **a** and **b** must be constant for all cases. To ensure this coupling constant for compounds of type **4B** and analogues, this dihedral angle should take values of 30° or 150° (Fig. 4). The NOESY spectrum of compound **4m** shows an NOE effect between protons at **a** and **b**, so this probably means that these protons are spatially close, meaning a *cis* disposition. Hence the only possible dihedral angle value is 30°, and the main stereoisomers have a 5,6-*cis* stereochemistry.

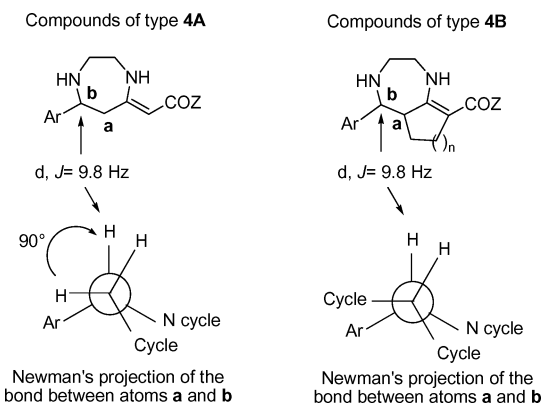


Fig. 3 Newman projections of compounds of type **4A** and **4B**.

The cyclohexane ring of compounds **4m** and analogues arises from *trans*-1,2-diaminocyclohexane, so protons **c** and **d** are placed at different faces of the molecule. The NOESY spectrum shows

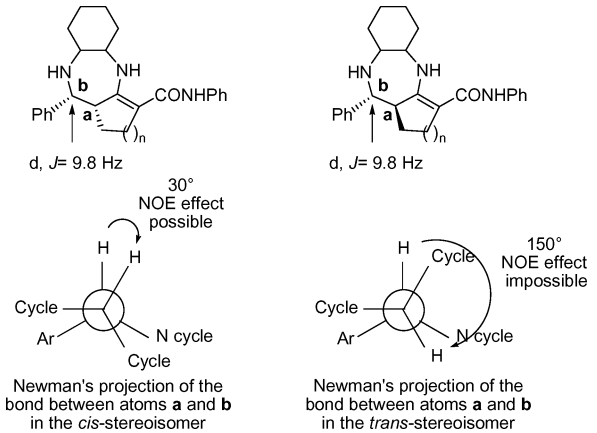


Fig. 4 Newman projection of the bond between atoms **a** and **b** in *cis*- and *trans*-stereoisomers of **4m**.

an NOE effect between protons **a** and **d** – the spatial distribution is illustrated in Fig. 5.

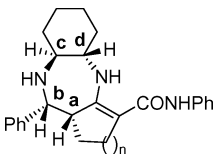


Fig. 5 Spatial distribution in *cis*-**4m**.

Conclusions

In conclusion, we report an experimentally simple multicomponent domino sequence for the synthesis of 1,4-diazepane derivatives from easily accessible starting materials. The sequence does not require any harmful reagents, and liberates water as the only by-product. We also demonstrate the mechanistic outcome by isolation of the postulated imino-enamino ester intermediate **5a**. Due to its high tolerance to substrates such as β-ketoesters, β-ketoamides or β-ketosulfones, this environmentally friendly procedure, involving heterogeneous catalysis by 4 Å molecular sieves, should be a good substrate-directed alternative to other previously published methodologies for the synthesis of 1,4-diazepanes.

Experimental section

General comments

Melting points (mp) were determined with a Büchi Melting-point B-450 apparatus and were not corrected. ^{1}H and ^{13}C NMR spectra were recorded in solution respectively at 300.13 MHz and 75.47 MHz on a Bruker AC 300 spectrometer. NMR data were collected at ambient temperature, and chemical shifts were given in ppm referenced to the appropriate solvent peak. Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet). Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Series FTIR spectrometer. Low and high-resolution mass spectra were recorded on an API 111 Plus Triple Quadripole spectrometer (Sciex), and on a

Bruker-Daltonics MALDI-ToF Autoflex spectrometer. Analytical thin layer chromatography was performed using 0.20 mm silica gel 60 plates. Flash chromatography was performed using 70–230 mesh silica gel 60 (Merck).

Typical procedure for the synthesis of compounds 4 with catalyst and solvent (Method A)

To a 50 mL two-necked round-bottomed flask flushed with Ar, equipped with a magnetic stirring bar and a reflux condenser, were added 1,2-dichloroethane freshly distilled over $CaCl_2$ (25 mL), commercially available non-activated 4 Å MS (6 g), β-ketoester, β-ketoamide or β-ketosulfone (1.28 mmol), aldehyde (1.5 mmol), and diamine (1.28 mmol). The heterogeneous mixture was stirred at reflux under Ar for 24 h. The solution was filtered through a short pad of Celite, which was thoroughly washed with DCE. The solvent was evaporated under reduced pressure to afford the crude compound, which was purified by flash chromatography over silica gel.

Typical solvent- and catalyst-free procedure for the synthesis of compounds 4 (Method B)

To a 50 mL two-necked round-bottomed flask flushed with Ar, equipped with a magnetic stirring bar and a reflux condenser, were added 1,3-dicarbonyl **2** (1.28 mmol), aldehyde **3** (1.5 mmol), and diamine **1** (1.28 mmol). The mixture was stirred at 120 °C under Ar for 4 h, diluted with AcOEt (20 mL) after cooling, and filtered through a short pad of Celite. Evaporation of the volatiles afforded a crude slurry. An analytical sample was obtained by flash chromatography over silica gel.

4a. Yield (**Method A**): 57%; Yield (Method B): 40% (145.3 mg, 0.51 mmol); brown oil; $R_f = 0.41$ (petroleum ether-AcOEt, 1:3); IR (NaCl, cm^{-1}): ν = 3296, 2954, 2837, 1746, 1642, 1590, 1481, 1436, 1392, 1248, 1089, 709, 750, 731, 696; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.2–1.3 (m, 1H) 1.22 (t, $J = 7.2$ Hz, 3H), 1.4 (m, 1H), 2.0 (br s, 1H), 2.2–2.4 (m, 2H), 2.88 (t, $J = 7.1$ Hz, 1H), 3.11 (dd, $J_1 = 12.9$ Hz, $J_2 = 4.5$ Hz, 1H), 3.2–3.3 (m, 2H), 3.45 (d, $J = 12.6$ Hz, 1H), 3.51 (d, $J = 9.6$ Hz, 1H), 4.10 (dq, $J_1 = 7.2$ Hz, $J_2 = 1.2$ Hz, 2H), 7.2–7.3 (m, 5H), 8.00 (d, $J = 5.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.7, 27.2, 27.4, 47.6, 51.4, 54.2, 58.5, 68.7, 93.6, 127.5, 127.6, 128.5, 143.3, 167.4, 168.7; MS (ESI): *m/z* (%) = 287 (100) $[M + H]^+$, 309 (95) $[M + Na]^+$; HRMS (ESI) for $[M + H]^+$: expected: 287.1754, found: 287.1752.

4b. Yield (Method A): 40% (156 mg, 0.51 mmol); Yield (**Method B**): 56% (218 mg, 0.72 mmol); amber oil; $R_f = 0.46$ (petroleum ether-AcOEt, 1:3); IR (NaCl): ν_{max} = 3600–3000, 2936, 2839, 1745, 1640, 1591, 1498,1459, 1359, 1248, 1165, 1092, 1059, 1032, 926, 825, 770, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23 (t, $J = 7.2$ Hz, 3H), 1.2–1.3 (m, 1H), 1.3–1.5 (m, 1H), 2.2–2.4 (m, 2H), 2.5–2.7 (br s, 1H), 2.89 (t, $J = 11.8$ Hz, 1H), 3.11 (dd, $J_1 = 13.2$ Hz, $J_2 = 4.8$ Hz, 1H), 3.2–3.4 (m, 2H), 3.45 (d, $J = 12.3$ Hz, 1H), 3.52 (d, $J = 9.6$ Hz, 1H), 4.12 (q, $J = 7.2$ Hz, 2H), 6.99 (t, $J = 8.7$ Hz, 2H), 7.28 (t, $J = 7.5$ Hz, 2H), 8.00 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.6, 27.1, 27.3, 47.3, 51.2, 54.2, 58.5, 67.9, 93.6, 115.2 (d, $^2J_{CF} = 21.5$ Hz), 129.1, 139.1 (d, $^3J_{CF} = 7.4$ Hz), 161.9 (d, $^1J_{CF} = 244.3$ Hz), 167.0, 168.6; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −115.2 (s); MS (ESI): *m/z* (%) = 327 (14) $[M + Na]^+$, 305 (100) $[M + H]^+$.

4c. Yield (Method A): 10% (39.4 mg, 0.13 mmol); Yield (**Method B**): 14% (55.2 mg, 0.18 mmol); yellow oil; $R_f = 0.47$ (AcOEt); IR (NaCl): ν_{max} = 3000–2600, 2910, 1711, 1632, 1582, 1440, 1355, 1305, 1267, 1219, 1174, 1159, 1086, 741, 732, 698, 632 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.28 (t, $J = 7.2$ Hz, 3H), 1.2–1.4 (m, 4H, 2H-7, 2H-8), 2.0 (br s, 1H), 2.11 (dd, $J_1 = 15.6$ Hz, $J_2 = 8.0$ Hz, 1H), 2.37 (br d, $J = 15.6$ Hz, 1H), 2.76 (td, $J = 12.9$ Hz, $J = 2.7$ Hz, 1H), 3.0 (m, 2H, H-2), 3.3 (m, 1H), 3.6 (m, 1H), 3.76 (d, $J = 8.4$ Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 7.2–7.4 (m, 5H), 9.57 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.6, 18.9, 24.1, 27.2, 42.4, 44.4, 48.8, 58.8, 65.6, 89.9, 127.4, 128.2, 128.4, 142.5, 163.3, 171.1; MS (EI): *m/z* (%) = 301 (9) $[M + H]^+$, 323 (100) $[M + Na]^+$, 339 (15) $[M + K]^+$.

4d. Yield (**Method A**): 35% (116.5 mg, 0.448 mmol); Yield (Method B): 23% (76.5 mg, 0.294 mmol); amber oil; $R_f = 0.58$ (petroleum ether-MeOH, 7:3); IR (NaCl): ν_{max} = 3600–3000, 2957, 1717, 1638, 1592, 1494, 1441, 1361, 1291, 1238, 1163, 1108, 1047, 779, 749, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25 (t, $J = 7.2$ Hz, 3H), 1.7–1.8 (br s, 1H), 2.34 (d, $J = 14.4$ Hz, 1H), 2.8–3.0 (m, 2H), 3.16 (dd, $J = 13.5$ Hz, $J = 5.1$ Hz, 1H), 3.4–3.5 (m, 1H), 3.6–3.7 (m, 1H), 3.76 (d, $J = 9.9$ Hz, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 4.46 (s, 1H), 7.0–7.5 (m, 5H), 8.92 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.6, 46.0, 46.3, 50.7, 58.4, 62.7, 82.4, 126.3, 127.6, 128.7, 145.0, 165.4, 170.6; MS (EI): *m/z* (%) = 261 (100) $[M + H]^+$, 283 (25) $[M + Na]^+$; HRMS (ESI) for $[M + H]^+$: expected: 261.1598, found: 261.1603.

4e. Yield (**Method A**): 18% (70.7 mg, 0.230 mmol); Yield (Method B): 0%; brown oil; $R_f = 0.26$ (CH_2Cl_2-AcOEt, 1:3); IR (NaCl): ν_{max} = 3800–3000, 1683, 1624, 1583, 1487, 1301, 749, 690, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.0–2.2 (br s, 1H), 2.30 (d, $J = 14.1$ Hz, 1H), 2.87 (t, $J = 11.7$ Hz, 1H), 2.95 (dd, $J = 9.4$ Hz, $J = 4.5$ Hz, 1H), 3.15 (dd, $J = 12.9$ Hz, $J = 4.8$ Hz, 1H), 3.3–3.4 (m, 1H), 3.5–3.6 (m, 1H), 3.77 (d, $J = 9.6$ Hz, 1H), 4.24 (s, 1H), 6.76 (s, 1H), 6.9–7.6 (m, 9H), 9.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.1, 46.2, 50.8, 62.7, 84.8, 119.7, 122.8, 126.3, 127.6, 128.6, 128.7, 139.1, 145.1, 164.0, 169.1; MS (EI): *m/z* (%) = 308 (100) $[M + H]^+$.

4f. Yield (**Method A**): 37% (157.7 mg, 0.47 mmol); Yield (Method B): 19% (80.5 mg, 0.24 mmol); amber oil; $R_f = 0.71$ (AcOEt); IR (NaCl): ν_{max} = 3500–2600, 3361, 1704, 1582, 1427, 1304, 1243, 1099, 701, 749, 729, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.1–1.4 (m, 1H), 1.4–1.6 (m, 1H), 2.1 (br s, 1H), 2.3–2.4 (m, 2H), 2.87 (dd, $J_1 = 15.0$ Hz, $J_2 = 6.0$ Hz 1H), 3.10 (dd, $J_1 = 15.0$ Hz, $J_2 = 6.0$ Hz, 1H), 3.2–3.3 (m, 2H, H-2), 3.42 (d, $J = 12.0$ Hz, 1H), 3.51 (d, $J = 12.0$ Hz, 1H), 6.6 (br s, 1H), 6.95 (t, $J = 9.0$ Hz, 1H), 7.1–7.3 (m, 7H), 7.42 (d, $J = 9.0$ Hz, 2H), 8.71 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.9, 27.4, 47.4, 51.4, 54.1, 68.7, 94.4, 119.6 (2C), 123.0, 127.6, 127.7 (2C), 128.5 (2C), 128.7 (2C), 138.8, 143.3, 166.4, 167.0; MS (EI): *m/z* (%) = 241 (43) $[M - Ph]^+$, 334 (100) $[M + H]^+$.

4g. Yield (Method A): 64% (288.4 mg, 0.82 mmol); Yield (**Method B**): 77% (346.4 mg, 0.99 mmol); amber oil; $R_f = 0.40$ (petroleum ether-AcOEt, 1:3); IR (NaCl): ν_{max} = 3700–3000, 1690, 1626, 1585, 1499, 1457, 1432, 1417, 1302, 1225, 825, 732, 690, 599 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.4–1.5 (m, 1H), 1.5–1.6 (m, 1H), 2.3–2.5 (m, 3H), 2.88 (t, $J = 10.5$ Hz, 1H), 3.11 (dd, $J_1 = 12.9$ Hz, $J_2 = 4.5$ Hz, 1H), 3.2–3.3 (m, 2H, H-2), 3.43

(d, $J = 12.3$ Hz, 1H), 3.54 (d, $J = 9.4$ Hz, 1H), 6.79 (s, 1H), 7.00 (t, $J = 8.7$ Hz, 4H), 7.2–7.4 (m, 3H), 7.49 (d, $J = 7.6$ Hz, 2H), 8.75 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.8, 27.3, 47.2, 51.2, 54.1, 67.8, 94.4, 115.1 (d, $^2J_{CF} = 21.0$ Hz), 119.6, 122.9, 128.9, 129.1 (d, $^3J_{CF} = 7.7$ Hz), 138.7, 139.1, 161.9 (d, $^1J_{CF} = 244.3$ Hz), 165.9, 166.9; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −115.0 (s); MS (EI): m/z (%) = 259 (37) $[M - Ph]^+$, 352 (100) $[M + H]^+$; HRMS (ESI) for $[M + H]^+$: expected: 352.1820, found: 352.1822.

4h. Yield (Method A): 26% (125.8 mg, 0.33 mmol); Yield (**Method B**): 31% (153.9 mg, 0.41 mmol); amber oil; $R_f = 0.27$ (petroleum ether-AcOEt, 1:3); IR (NaCl): $\nu_{max} = 3500–3000, 3394, 1676, 1625, 1584, 1507, 1417, 1337, 1301, 1226, 1083, 794, 740, 689$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.0–1.1 (m, 2H), 1.1–1.3 (m, 1H), 2.1–2.2 (m, 2H, H-6), 2.68 (t, $J = 12.6$ Hz, 1H), 2.93 (dd, $J_1 = 12.9$ Hz, $J_2 = 4.2$ Hz, 1H), 3.0–3.1 (m, 2H), 3.23 (d, $J = 12.6$ Hz, 1H), 3.45 (d, $J = 9.6$ Hz, 1H), 6.47 (s, 1H), 6.77 (t, $J = 7.6$ Hz, 1H), 7.00 (t, $J = 7.26$ Hz, 2H), 7.26 (m, 4H), 7.93 (d, $J = 8.5$ Hz, 2H), 8.49 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.7, 27.4, 47.2, 51.3, 53.9, 67.9, 94.6, 119.6, 123.0, 123.7, 128.5, 128.7, 138.6, 147.2, 150.4, 165.3, 166.8; MS (EI): m/z (%) = 379 (100) $[M + H]^+$, 401 (90) $[M + Na]^+$.

4i. Yield (**Method A**): 38% (172 mg, 0.486 mmol); Yield (Method B): 21% (95.1 mg, 0.269 mmol); brown oil; $R_f = 0.40$ (petroleum ether-AcOEt, 1:1); IR (NaCl): $\nu_{max} = 3350, 3035, 2918, 2839, 1601, 1482, 1435, 1364, 1257, 1125, 733, 698$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.3 (m, 1H), 1.4 (m, 1H), 1.8 (br s, 2H), 2.2 (m, 1H), 2.3 (m, 1H), 2.9 (m, 1H), 3.13 (dd, $J_1 = 12.9$ Hz, $J_2 = 4.5$ Hz, 1H), 3.3–3.4 (m, 2H, H-2), 3.44 (d, $J = 12.0$ Hz, 1H), 3.54 (d, $J = 9.6$ Hz, 1H), 7.3 (m, 4H), 7.4 (m, 1H), 7.5 (m, 3H), 7.84 (d, $J = 6.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.6, 27.9, 47.6, 51.2, 54.9, 68.2, 95.2, 126.2, 127.5, 127.6, 128.5, 128.8, 132.1,142.6, 142.9, 162.5; MS (EI): m/z (%) = 355 (100) $[M + H]^+$, 377 (13) $[M + Na]^+$; HRMS (ESI) for $[M + H]^+$: expected: 355.1475, found: 355.1474.

4j. Yield (**Method A**): 23% (108.9 mg, 0.294 mmol); Yield (Method B): 0%; black oil; $R_f = 0.25$ (petroleum ether-AcOEt, 1:1); IR (NaCl): $\nu_{max} = 3400–2700, 3343, 1601, 1435, 1264, 1129, 1060, 751, 724, 685, 663$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.3–1.5 (m, 1H), 1.6–1.9 (m, 1H), 2.0–2.2 (m, 1H), 2.3–2.5 (m, 2H, H-7), 2.5–2.6 (m, 1H), 2.93 (t, $J = 1.1$ Hz), 3.2–3.4 (m, 2H), 3.4–3.5 (m, 2H), 3.74 (d, $J = 9.3$ Hz, 1H), 6.76 (t, $J = 6.0$ Hz, 1H), 6.84 (d, $J = 8.1$ Hz, 1H), 6.92 (d, $J = 6.9$ Hz, 1H), 7.14 (t, $J = 7.2$ Hz, 1H), 7.4 (m, 1H), 7.5 (m, 2H), 7.83 (d, $J = 6.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.7, 28.0, 45.2, 46.0, 50.5, 60.4, 96.3, 117.5, 119.2, 126.2, 126.3, 128.9, 129.3, 132.3, 142.4, 156.2, 161.4; MS (EI): m/z (%) = 371 (100) $[M + H]^+$, 393 (13) $[M + Na]^+$.

4k. Yield : 45%; brown oil; $R_f = 0.28$ (petroleum ether-AcOEt, 1:7); IR (NaCl): $\nu_{max} = 3400–2900, 2909, 2844, 1687, 1599, 1421, 1284, 1234, 1167, 832, 739, 701$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23–1.38 (m, 1H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.51–1.63 (m, 1H), 2.38–2.48 (m, 1H), 2.53–2.62 (m, 1H), 3.25 (br q, $J = 8.4$ Hz, 1H), 3.78 (br s, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 4.27 (d, $J = 9.6$ Hz, 1H), 6.59–6.62 (m, 1H), 6.81–6.85 (m, 2H), 6.89–6.92 (m, 1H), 7.03–7.09 (m, 2H), 7.28–7.33 (m, 2H), 9.63 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.6, 26.4, 27.0, 51.6, 59.0, 64.3, 95.8, 116.2 (d, $^2J_{CF} = 20.7$ Hz), 120.8, 121.4, 121.6, 123.8, 129.3 (d, $^3J_{CF} = 7.7$ Hz), 129.7, 136.6, 139.5 (d, $^4J_{CF} = 3.2$ Hz), 160.3, 162.8 (d, $^1J_{CF} = 245.8$ Hz), 168.8; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −114.2 (s); MS (EI): m/z (%) = 353 (62) $[M + H]^+$, 375 (100) $[M + Na]^+$, 391 (12) $[M + K]^+$.

4l. Yield (**Method A**): 99% (181.4 mg, 0.45 mmol); Yield (**Method B**): 99% (517.1 mg, 1.28 mmol); brown crystals (mp = 100.7–101.5 °C); $R_f = 0.40$ (petroleum ether-AcOEt, 1:3); IR (NaCl): $\nu_{max} = 3400–3000, 2910, 2837, 1689, 1622, 1585, 1498, 1432, 1302, 1226, 1149, 832, 748, 687$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.2–1.3 (m, 4H), 1.3–1.5 (m, 2H), 1.6–1.9 (m, 4H), 2.02 (br d, $J = 11.0$ Hz, 1H), 2.37 (dd, $J = 8.7$ Hz, $J = 4.9$ Hz, 2H), 2.56 (m, 2H), 3.1–3.2 (m, 1H), 3.24 (q, $J = 9.3$ Hz, 1H), 3.67 (d, $J = 9.3$ Hz, 1H), 6.69 (s, 1H), 7.00 (br t, $J = 7.4$ Hz, 4H), 7.2–7.4 (m, 3H), 7.47 (d, $J = 7.5$ Hz, 2H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.1, 24.2, 26.9, 27.3, 32.0, 32.7, 54.2, 60.0, 63.0, 66.9, 93.9, 115.2 (d, $^2J_{CF} = 21.5$ Hz), 119.8, 122.9, 128.7, 129.1 (d, $^3J_{CF} = 7.6$ Hz), 138.7, 139.3 (d, $^4J_{CF} = 3.4$ Hz), 161.9 (d, $^1J_{CF} = 244.4$ Hz), 165.4, 166.9; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −115.2 (s); MS (EI): m/z (%) = 313 (14) $[M - Ph]^+$, 406 (100) $[M + H]^+$.

4m. Yield (**Method A**): 99% (495.2 mg, 1.28 mmol); Yield (**Method B**): 99% (495.2 mg, 1.28 mmol); amber oil; $R_f = 0.80$ (Petroleum ethers/AcOEt, 1:1); IR (NaCl): $\nu_{max} = 3500–2700, 3340, 3037, 2912, 2838, 1687, 1620, 1509, 1437, 1365, 1302, 1141, 1079, 730, 686, 635, 590$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.1–1.2 (m, 5H), 1.3–1.4 (m, 2H), 1.5–1.7 (m, 4H), 1.93 (br d, $J = 10.8$ Hz, 1H), 2.2–2.3 (m, 2H), 2.47 (br s, 1H), 3.07 (br s, 1H), 3.22 (q, $J = 9.0$ Hz, 1H), 3.59 (d, $J = 9.3$ Hz, 1H), 6.73 (br s, 1H), 6.91 (t, $J = 7.4$ Hz, 1H), 7.1–7.3 (m, 6H), 7.43 (d, $J = 7.5$ Hz, 2H), 8.42 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.9, 24.0, 26.7, 27.0, 31.8, 32.4, 54.0, 59.6, 62.7, 67.4, 93.7, 119.6, 122.5, 127.2, 127.3, 128.1, 128.4, 138.5, 143.3, 165.4, 166.7; MS (EI): m/z (%) = 295 (20) $[M - Ph]^+$, 388 (100) $[M + H]^+$; HRMS (ESI) for $[M + H]^+$: expected: 388.2383, found: 388.2387.

4n. Yield (Method B): 50% (246.1 mg, 0.64 mmol); orange solid (mp = 151.4–152.8 °C); $R_f = 0.47$ (Petroleum Ethers-AcOEt, 3/1); IR (NaCl): $\nu_{max} = 3600–2800, 3420, 2909, 2838, 1694, 1618, 1588, 1497, 1437, 1380, 1353, 1273, 1202, 1148, 1123, 1090, 833, 795, 760, 731, 697, 594, 554$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.0–1.2 (m, 3H), 1.2–1.4 (m, 3H), 1.35 (s, 9H), 1.5–1.7 (m, 4H), 2.0–2.2 (m, 1H), 2.2–2.3 (m, 2H), 2.4–2.5 (m, 1H), 3.1–3.2 (m, 1H), 3.18 (q, $J = 9.6$ Hz, 1H), 3.66 (d, $J = 9.6$ Hz, 1H), 4.73 (br s, 1H), 6.97 (t, $J = 8.7$ Hz, 2H), 7.27 (t, $J = 6.6$ Hz, 2H), 8.21 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.2, 24.2, 26.9, 27.7, 29.2, 32.2, 32.7, 50.3, 54.2, 59.5, 63.2, 66.9, 94.8, 115.2 (d, $^2J_{CF} = 21.1$ Hz), 129.0 (d, $^3J_{CF} = 7.6$ Hz), 139.6 (d, $^4J_{CF} = 3.5$ Hz), 161.8 (d, $^1J_{CF} = 244.4$ Hz), 162.7, 169.0; ^{19}F NMR ($CDCl_3$, 282 MHz): δ −115.4 (s); MS (EI): m/z (%) = 386 (82) $[M + H]^+$, 408 (100) $[M + Na]^+$, 424 (19) $[M + K]^+$.

4o. Yield (Method B): 65% (316.4 mg, 0.83 mmol); brown crystals (mp = 123.4–124.6 °C); $R_f = 0.38$ (Petroleum Ethers-AcOEt, 2:1); IR (NaCl): $\nu_{max} = 3600–3100, 3443, 2906, 2836, 1691, 1589, 1440, 1364, 1290, 1262, 1238, 1200, 1106, 729, 697$ cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.1–1.4 (m, 6H), 1.5–1.7 (m, 4H), 2.0 (m, 1H), 2.3 (m, 1H), 2.4 (m, 1H), 2.6 (m, 1H), 3.0 (m, 1H), 3.15 (q, $J = 9.0$ Hz, 1H), 3.2–3.5 (m, 2H), 3.5–3.7 (m, 7H), 7.2–7.3 (m, 5H), 8.39 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.1, 24.3, 29.3, 30.7, 32.2, 32.7, 44.8, 53.8, 59.9, 63.2, 67.0, 67.6, 95.3, 127.4,

127.5, 128.4, 143.7, 167.7, 171.2; MS (EI): m/z (%) = 382 (32) $[M + H]^+$, 404 (100) $[M + Na]^+$, 420 (23) $[M + K]^+$.

***Cis*-4p.** Yield (Method B): 53% (262.3 mg, 0.68 mmol); amber oil; R_f = 0.30 (AcOEt); IR (NaCl): ν_{max} = 2909, 2836, 1679, 1623, 1583, 1509, 1424, 1302, 1227, 1095, 740, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.1–1.3 (m, 3H), 1.3–1.6 (m, 3H), 1.6–1.8 (m, 3H), 1.8–1.9 (m, 2H, H-5), 2.40 (q, J = 7.1 Hz, 2H), 2.6 (m, 1H), 3.2 (m, 1H), 3.46 (q, J = 9.9 Hz, 1H), 3.87 (d, J = 9.9 Hz, 1H), 6.68 (s, 1H), 7.00 (t, J = 7.1 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 7.25 (d.t., J_1 = 7.7 Hz, J_2 = 3.6 Hz, 3H), 7.46 (d, J = 8.1 Hz, 2H), 7.63 (d.t., J_1 = 7.7 Hz, J_2 = 1.2 Hz, 1H), 8.42 (br s, 1H), 8.57 (d, J = 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.2, 24.5, 26.4, 27.5, 32.3, 33.0, 54.0, 60.8, 62.3, 67.7, 93.8, 119.8, 122.4, 122.7, 122.9, 128.7, 136.5, 138.7, 149.5, 161.7, 165.7, 166.9; MS (EI): m/z (%) = 411 (100) $[M + Na]^+$, 427 (27) $[M + K]^+$; HRMS (ESI) for $[M + H]^+$: expected: 389.2336, found: 389.2339.

***Trans*-4p.** Yield (Method B): 35% (173.5 mg, 0.45 mmol); brown oil; R_f = 0.49 (AcOEt-Acetone, 2:1); IR (NaCl): ν_{max} = 3600–3000, 1680, 1624, 1584, 1509, 1424, 1302, 1227 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.1–1.4 (m, 5H), 1.4- 1.7 (m, 4H), 2.0–2.1 (m, 1H), 2.2 (m, 1H), 2.3–2.4 (m, 2H), 2.5 (m, 1H), 3.2–3.3 (m, 1H), 3.7–3.8 (m, 1H), 4.35 (d. J = 4.5 Hz, 1H), 6.64 (br s, 1H), 7.01 (t, J = 7.3 Hz, 1H), 7.15 (dd, J_1 = 7.2 Hz, J_2 = 4.8 Hz, 1H), 7.28 (t., J = 7.5 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 7.8 Hz, 1H), 7.60 (d.t., J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 8.26 (br s, 1H), 8.55 (d, J = 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.0, 24.2, 24.7, 27.6, 31.9, 32.9, 50.3, 56.9, 59.7, 63.5, 94.7, 119.7, 122.0, 122.9, 123.0, 128.6, 135.9, 138.6, 149.4, 159.4, 164.1, 166.7; MS (EI): m/z (%) = 389 (100) $[M + H]^+$, 411 (37) $[M + Na]^+$, 427 (13) $[M + K]^+$.

***Cis*-4q.** Yield (Method B): 47% (237.3 mg, 0.60 mmol); light brown solid (mp = 109.8–110.4 °C); R_f = 0.49 (Petroleum Ethers-AcOEt, 3:1); IR (NaCl): ν_{max} = 2909, 2836, 1684, 1623, 1583, 1509, 1424, 1302, 1227, 1095, 740, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.1–1.3 (m, 3H), 1.3–1.5 (m, 2H), 1.6–1.8 (m, 5H), 2.0–2.1 (m, 1H), 2.42 (dd, J_1 = 9.0 Hz, J_2 = 5.1 Hz, 2H), 2.6 (m, 1H), 3.2 (m, 1H), 3.21 (q, J = 9.3 Hz, 1H), 4.05 (d, J = 9.3 Hz, 1H), 6.71 (s, 1H), 6.9–7.0 (m, 1H), 6.96 (t, J = 3.6 Hz, 1H), 7.03 (t, J = 7.4 Hz, 1H), 7.29 (t., J = 7.4 Hz, 2H), 7.2–7.3 (m, 1H), 7.49 (d, J = 7.4 Hz, 2H), 8.46 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.1, 24.1, 26.6, 27.1, 32.0, 32.6, 55.7, 59.5, 62.9, 63.0, 94.1, 119.8, 122.9, 124.3, 124.5, 125.8, 128.6, 138.7, 146.7, 164.7, 166.7; MS (EI): m/z (%) = 394 (15) $[M + H]^+$, 416 (100) $[M + Na]^+$.

***Trans*-4q.** Yield (Method B): 16% (80.4 mg, 0.20 mmol); brown oil; R_f = 0.46 (AcOEt); IR (NaCl): ν_{max} = 3600–3000, 2909, 1687, 1620, 1585, 1509, 1421, 1302, 1227, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.1–1.3 (m, 4H), 1.6–1.8 (m, 4H), 2.0–2.3 (m, 4H), 2.4 (m, 1H), 2.6 (m, 1H), 3.2 (m, 1H), 3.7 (m, 1H), 4.46 (d, J = 4.8 Hz, 1H), 6.57 (s, 1H), 6.96 (dd, J_1 = 4.8 Hz, J_2 = 3.6 Hz, 1H), 7.0–7.1 (m, 2H), 7.20 (d.d, J_1 = 4.8 Hz, J_2 = 1.2 Hz, 1H), 7.28 (t., J = 7.5 Hz, 2H), 7.48 (d, J = 7.5 Hz, 2H), 8.18 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.1, 24.4, 24.8, 28.0, 32.1, 33.1, 51.9, 56.7, 59.0, 59.9, 95.6, 119.7, 123.0, 124.7, 126.6, 126.8, 128.7, 138.7, 141.5, 163.2, 166.7; MS (EI): m/z (%) = 394 (41) $[M + H]^+$, 416 (100) $[M + Na]^+$.

***Cis*-4r.** Yield (Method B): 60% (286.2 mg, 0.76 mmol); amber oil; R_f = 0.62 (AcOEt-CH_2Cl_2,1:4); IR (NaCl): ν_{max} = 3031, 2909, 2837, 1683, 1623, 1584, 1509, 1433, 1364, 1302, 1227, 1141, 1093, 1004, 731, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.2 (m, 3H), 1.3–1.4 (m, 3H), 1.6–1.7 (m, 4H), 2.0 (m, 1H), 2.40 (m, 2H), 2.6 (m, 1H), 3.1 (m, 1H), 3.35 (q, J = 9.6 Hz, 1H), 3.84 (d, J = 9.6 Hz, 1H), 6.18 (d, J = 3.2 Hz, 1H), 6.30 (dd, J_1 = 3.2 Hz, J_2 = 1.8 Hz, 1H), 6.67 (br s, 1H), 7.00 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 7.5 Hz, 2H), 7.35 (br s, 1H), 7.46 (d, J = 7.5 Hz, 2H), 8.39 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.1, 24.2, 25.9, 27.3, 32.1, 32.7, 53.1, 59.9, 60.5, 62.6, 94.0, 106.5, 109.8, 119.8, 123.0, 128.7, 138.6, 141.6, 155.9, 164.9, 166.9; MS (EI): m/z (%) = 378 (25) $[M + H]^+$, 400 (100) $[M + Na]^+$; HRMS (ESI) for $[M + H]^+$: expected: 378.2176, found: 378.2175.

***Trans*-4r.** Yield (Method B): 34% (163.2 mg, 0.43 mmol); brown oil; R_f = 0.37 (AcOEt-CH_2Cl_2, 1:4); IR (NaCl): ν_{max} = 3279, 3033, 2911, 2837, 1691, 1629, 1585, 1509, 1433, 1363, 1304, 1228, 1136, 1088, 1009, 732, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.3–1.4 (m, 4H), 1.5–1.7 (m, 4H), 2.0–2.1 (m, 1H), 2.1–2.2 (m, 2H), 2.4–2.6 (m, 3H), 3.2 (m, 1H), 3.6 (m, 1H), 4.25 (d, J = 3.6 Hz, 1H), 6.28 (br s, 2H), 6.62 (br s, 1H), 7.03 (t, J = 7.5 Hz, 1H), 7.29 (t., J = 7.5 Hz, 2H), 7.33 (br s, 1H), 7.49 (d, J = 7.5 Hz, 2H), 8.15 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.1, 24.3, 24.5, 28.0, 32.0, 33.0, 50.9, 56.8, 57.0, 60.1, 94.5, 108.3, 110.3, 119.8, 123.1, 128.8, 138.7, 141.1, 152.3, 163.7, 166.7; MS (EI): m/z (%) = 400 (100) $[M + Na]^+$.

***Cis*-4s.** Yield (Method B): 56% (272.3 mg, 0.72 mmol); amber oil; R_f = 0.38 (AcOEt-CH_2Cl_2, 1:4); IR (NaCl): ν_{max} = 3600–3000, 3406, 2909, 2840, 1694, 1623, 1585, 1508, 1489, 1419, 1302, 1227, 867, 730, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.2–1.3 (m, 2H), 1.3–1.5 (m, 3H), 1.6–1.8 (m, 5H), 2.0 (m, 1H), 2.40 (m, 2H), 2.6 (m, 1H), 3.1–3.2 (m, 1H), 3.17 (q, J = 9.3 Hz, 1H), 3.72 (d, J = 9.3 Hz, 1H), 6.47 (t, J = 1.2 Hz, 1H), 6.65 (br s, 1H), 7.02 (t, J = 7.5 Hz, 1H), 7.28 (t., J = 7.5 Hz, 2H), 7.38 (d, J = 1.2 Hz, 2H), 7.47 (d, J = 7.5 Hz, 2H), 8.45 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 24.2, 24.2, 27.0, 27.3, 32.1, 32.8, 54.1, 58.7, 59.9, 63.0, 94.0, 109.0, 119.9, 123.0, 127.3, 128.8, 138.7, 139.5, 143.2, 165.5, 167.0; MS (EI): m/z (%) = 378 (100) $[M + H]^+$, 400 (41) $[M + Na]^+$, 416 (12) $[M + K]^+$.

***Trans*-4s.** Yield (Method B): 22% (110.6 mg, 0.29 mmol); brown oil; R_f = 0.26 (AcOEt-CH_2Cl_2, 3:1); IR (NaCl): ν_{max} = 3600–3000, 3360, 2923, 1688, 1625, 1585, 1509, 1489, 1433, 1303, 1227, 902, 866, 726, 688, 641 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.2–2.6 (m,14H), 3.2 (m, 1H), 3.6 (m, 1H), 4.08 (d, J = 3.9 Hz, 1H), 6.42 (d, J = 1.7 Hz, 1H), 6.58 (br s, 1H), 7.03 (t, J = 7.5 Hz, 1H), 7.29 (t., J = 7.5 Hz, 2H), 7.34 (t, J = 1.7 Hz, 1H), 7.40 (br s, 1H), 7.47 (d, J = 7.5 Hz, 2H), 8.17 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.1, 24.4, 24.8, 28.0, 31.7, 33.4, 52.0, 55.5, 56.6, 60.2, 95.0, 111.9, 119.8, 122.6, 123.1, 128.8, 138.7, 140.9, 142.4, 164.1, 166.7; MS (EI): m/z (%) = 378 (68) $[M + H]^+$, 400 (100) $[M + Na]^+$, 416 (15) $[M + K]^+$.

Synthesis of possible intermediates

Synthesis of enamino-imine compound 5a. To a 50 mL two-necked round-bottomed flask flushed with Ar, equipped with a magnetic stirring bar and a reflux condenser, were added 1,2-dichloroethane freshly distilled over $CaCl_2$ (25 mL), commercially

available inactivated 4 Å MS (6 g), β-ketoester (200 mg, 1.28 mmol), benzaldehyde (159 mg, 1.5 mmol), and ethylenediamine (77 mg, 1.28 mmol). The heterogeneous mixture was stirred at room temperature under Ar for 24 h. The solution was filtered through a short pad of Celite, which was thoroughly washed with DCE. The solvent was evaporated under reduced pressure to afford crude compound **5a**, which was purified by flash chromatography over silica gel.

5a. Yield : 99% (362.6 mg, 1.26 mmol); brown oil; IR (NaCl): ν_{max} = 3296, 2950–2700, 2930, 2827, 1749, 1643, 1592, 1456, 1440, 1355, 1297, 1215, 1162, 1100, 1035, 960, 770, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.17 (t, J = 7.2 Hz, 3H), 1.67 (quint., J = 7.4 Hz, 2H), 2.41 (t, J = 7.5 Hz, 2H), 2.50 (t, J = 7.5 Hz, 2H), 3.46 (q, J = 5.9 Hz, 2H), 3.66 (t, J = 5.9 Hz, 2H), 4.06 (q, J = 7.2 Hz, 2H), 7.3–7.4 (m, 3H), 7.43 (br s, 1H), 7.65 (t, J = 3.8 Hz, 2H), 8.18 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 20.6, 28.9, 32.0, 45.0, 58.1, 62.0, 92.7, 127.8, 128.3, 130.5, 135.7, 162.5, 164.2, 168.0; MS (EI): m/z (%) = 287 (100) $[M + H]^+$, 309 (91) $[M + Na]^+$, 325 (10) $[M + K]^+$.

Synthesis of "gamma" intermediate 2a′

To a 25 mL two-necked round-bottomed flask flushed with Ar, equipped with a magnetic stirring bar and a reflux condenser, were added β-ketoester (468 mg, 3 mmol), benzaldehyde (318 mg, 3 mmol), and 8-diazabicyclo[5.4.0]undec-7-ene (456 mg, 3 mmol). The mixture was stirred at 110 °C under Ar for 4 h. The resulting viscous slurry was purified by flash chromatography over silica gel.

2a′. Yield : 33% (241.0 mg, 0.987 mmol); white crystals (mp = 91.1–93.2 °C); R_f = 0.66 (petroleum ether-AcOEt, 1:1); IR (NaCl): νmax = 2979, 2959, 2931, 1631, 1602, 1405, 1232, 1196, 1163, 1084, 764, 684 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (t, J = 7.2 Hz, 3H), 2.64 (t, J = 5.4 Hz, 2H), 2.8–2.9 (m, 2H), 4.28 (q, J = 7.2 Hz, 2H), 6.93 (br s, 1H), 7.2–7.6 (m, 5H), 10.3 (s, 1H); ^{13}C NMR (CDCl3, 75 MHz): δ 14.2, 25.0, 26.1, 60.0, 105.9, 123.8, 128.3, 129.5, 130.5, 134.5, 138.1, 169.3, 169.8; MS (EI): m/z (%) = 267 (100) $[M + Na]^+$, 283 (25) $[M + K]^+$.

Mechanistic experiments

Conversion of enamino-imine compound 5a to 4a. To a 50 mL two-necked round-bottomed flask flushed with Ar, equipped with a magnetic stirring bar and a reflux condenser, were added 1,2-dichloroethane freshly distilled over $CaCl_2$ (11 mL), commercially available inactivated 4 Å MS (2.5 g), and enamino-imine compound **5a** (157.7 mg, 0.54 mmol). The heterogeneous mixture was stirred at reflux under Ar for 24 h. The solution was filtered through a short pad of Celite, which was thoroughly washed with DCE. The solvent was evaporated under reduced pressure to afford crude compound **4a**, which was purified by flash chromatography over silica gel. Yield: 32% (46.0 mg, 0.171 mmol).

From gamma compound 2a′ to product 4a. To a 50 mL two-necked round-bottomed flask flushed with Ar, equipped with a magnetic stirring bar and a reflux condenser, were added 1,2-dichloroethane freshly distilled over $CaCl_2$ (15 mL), diamine (3 mmol) and "gamma" compound **2a′** (182.1 mg, 0.75 mmol). The heterogeneous mixture was stirred at reflux under Ar for 42 h. The solution was filtered through a short pad of Celite, which was thoroughly washed with DCE. The solvent was evaporated under reduced pressure to afford traces of **4a**.

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18 For recent contributions in this field, see for example: (*a*) H. S. Iden and W. D. Lubell, *Org. Lett.*, 2006, **8**, 3425; (*b*) W. Van Brabandt, M. Vanwalleghem, M. D'hooghe and N. De Kimpe, *J. Org. Chem.*, 2006, **71**, 7083; (*c*) N. Wlodarczyk, P. Gilleron, R. Millet, R. Houssin and J.-P. Hénichart, *Tetrahedron Lett.*, 2007, **48**, 2583; (*d*) H. Maruoka, T. Muto, T. Tanaka, S. Imajo, Y. Tomimori, Y. Fukuda and T. Nakatsuka, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3435; (*e*) M. Limbach, V. S. Korotkov, M. Es-Sayed and A. de Meijere, *Org. Biomol. Chem.*, 2008, **6**, 3816.

