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Multicomponent domino process to oxa-bridged polyheterocycles and pyrrolopyridines, structural diversity derived from work-up procedure

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Dedicated to Professor Kishi on the occasion of his receipt of the Tetrahedron Prize

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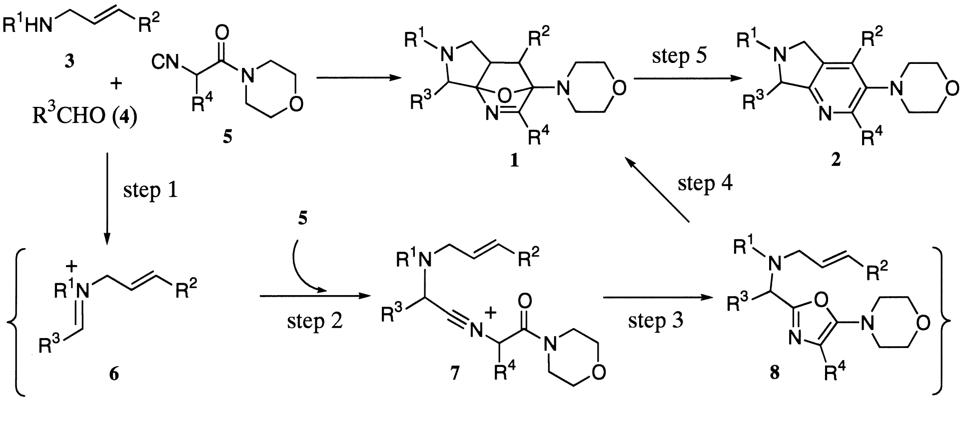
Abstract—Novel three-component domino processes to polyheterocycles are developed. Reaction of an allylamine (**3**), an aldehyde (**4**) and an α-isocyanoacetamide (**5**) in methanol at room temperature provides an efficient access to oxa-bridged tricycle (**1**) as a single diastereoisomer. In this one-pot process, one C–N, one C–O and three C–C bonds are formed with concomitant creation of five asymmetric centers. While isolable, the oxa-bridged tricycles (**1**) can be cleanly in-situ fragmented to pyrrolopyridines (**2**) under acidic conditions (trifluoroacetic acid, −78°C), providing thus an unusual work-up derived structural diversity. The operational simplicity and excellent chemical yield make these novel heterocycle syntheses valuable in diversity-oriented high throughput synthesis. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

With the advent of functional genomics and proteomics, more information about the structures and functions of biologically active macromolecules is becoming available.[1] Indeed, there will be at least 10 times as many molecular targets that can be exploited for future drug therapy than are being used today.[2] To match and to some extent, to validate such a formidable advance in biological research, the identification and optimization of small molecules that can specifically interact with therapeutical targets are of utmost importance[3] and constitute actually the bottleneck in medicinal chemistry.[4] To accelerate the creation of bioactive compounds, various synthetic technologies have been developed. Among them, multicomponent reaction[5] and domino



Scheme 1. Three-component domino process to polyheterocycles, a mechanistic working hypothesis.

Keywords: multi-component reaction; isonitrile; polyheterocycle; pyrrolopyridine; high throughput synthesis.

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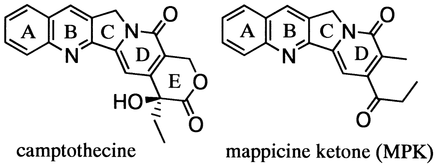
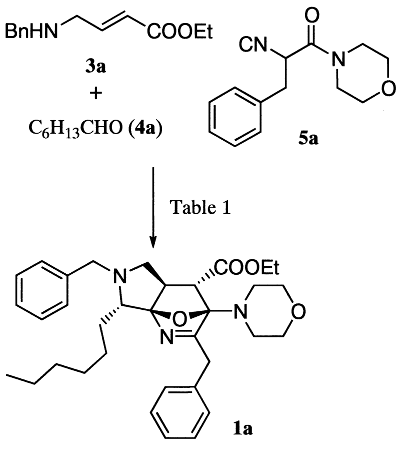


Figure 1.

process[6] are recognized to be highly valuable in combinatorial synthesis.

Within this context, we initiated a research program aimed at the development of highly efficient synthesis of polyheterocycles by a combined use of multi-component reaction (MCR) and domino processes. Consequently, we developed novel three-component syntheses of 5-aminooxazole,[7] polycyclic tetrahydroisoquinoline,[8] a four-component synthesis of pyrrolo[3,4-*b*] pyridin-5-one[9] and a two step synthesis of macrocycles[10,11] from readily available starting materials. Impelled by an interest in providing a rapid construction of polyheterocyclic scaffolds, we were led to consider a novel three-component synthesis of oxa-bridged polyheterocycle and pyrrolo[3,4-*b*] pyridine according to the sequence of event outlined in Scheme 1. Thus, reaction of an allylamine (**3**), an aldehyde (**4**) and an α-isocyano acetamide (**5**) should give the aminooxazole via an iminium, then a nitrilium intermediate. Cycloaddition of oxazole as an aza-diene with a properly predisposed dienophile would then produce an oxa-bridged heterocycle (**1**), which under appropriate conditions would undergo further fragmentation to provide pyrrolopyridine (**2**). We report herein the realization of this multi-component domino process and document that structural diversity can be derived from simple modification of work-up procedures. Pyrrolopyridines **2** has attracted increased attention as biologically active scaffold in searching of CNS active agents,[12] herbicides[13] and anti-diabetic agents.[14] This skeleton has also been found in medicinally important natural products such as camptothecine and mappicine ketone (Fig. 1).[15,16] With few notable exceptions,[9,17] most of the reported syntheses were based on the functionalization of azaphthalimide and were thus limited in scope.[18]



Scheme 2. A three component synthesis of oxa-bridged heterocycle.

Table 1. Three-component synthesis of **1a**—survey of reaction conditions

Entry	Solvent	*T* (°C)	Concentration (M)	Additive[a]	Yield(%)[b]
1	Toluene	60	0.5	LiBr	44
2	Toluene	rt	0.5	LiBr	56
3	MeOH	rt	0.5	LiBr	66
4	Toluene	rt	0.5	NH_4Cl	57
5	MeOH	rt	0.5	NH_4Cl	55
6	MeOH	rt	0.5	No	92
7	MeOH	rt	0.5	SiO_2	72
8	MeOH	rt	0.1	SiO_2	94

Reaction time: 2 h.

[a] Abbreviations: LiBr=lithium bromide, NH_4Cl=ammonium chloride, SiO_2=silica gel.

[b] Isolated yield.

2. Results and discussion

2.1. Three-component synthesis of oxa-bridged tricyclic ring system

In analogy to our previous work on the three-component synthesis of oxa-bridged tetracyclic tetrahydroisoquinoline,[8] three-component condensation of 4-benzylamino crotonate (**3a**), heptanal (**4a**) and α-isocyanoacetamide (**5a**) was carried out in toluene in the presence of lithium

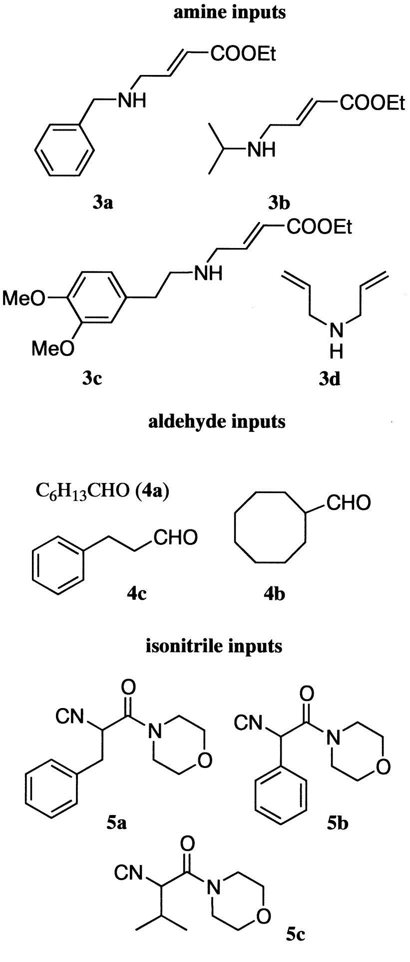


Figure 2. Structure of starting materials.

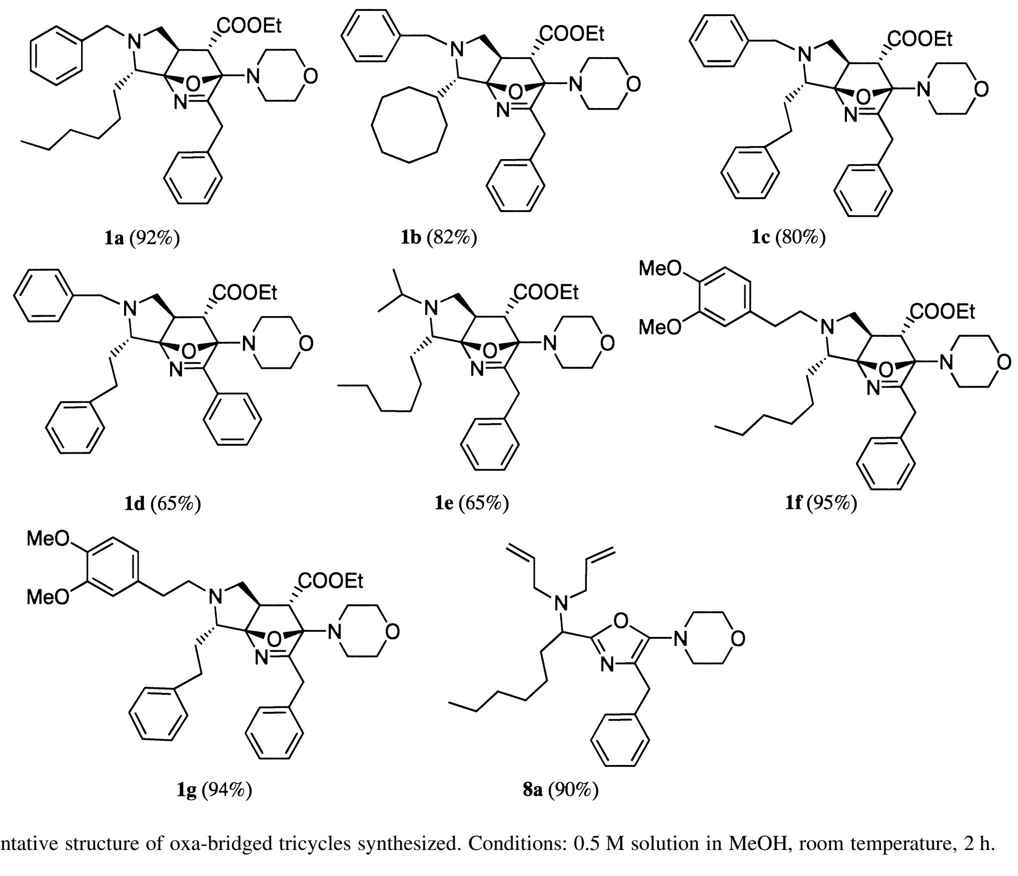
bromide. Under these conditions, the desired oxa-bridged tricycle **1a** was indeed isolated in 44% yield (Scheme 2). To improve the efficiency of this reaction, conditions varying solvents, reaction temperatures, additives and concentrations were surveyed using **3a**, **4a**, and **5a** as inputs (Table 1). Under optimum conditions (MeOH, room temperature, 2 h) we found, the tricycle **1a** was isolated in 92% yield as a single diastereomer (entry 6). Neither lithium bromide[8] nor ammonium chloride[9] showed beneficial effects to the desired reaction manifold due probably to the low stability of oxa-bridged tricycle. It is worthy noting that one C–N, one C–O and three C–C bonds were formed with concomitant creation of five asymmetric centers in this one-pot multicomponent domino process. The efficiency of this reaction was thus truly remarkable if one looked at the yield per bond formation.[19]

The scope of this novel multicomponent domino process is examined using four allylamines (**3a**–**3d**), three aldehydes (**4a**–**4c**) and three isocyanoacetamides (**5a**–**5c**) as inputs (Fig. 2). Some representative oxa-bridged tricyclic compounds synthesized (MeOH, room temperature) were enlisted in Fig. 3. In most cases, the reaction was performed with approximately equimolar amount of the three components and was completed within two hours. Examination of the ^{1}H NMR spectra of the crude reaction mixture indicated that the purity of compound **1** exceeded 80% after simple evaporation of methanol.

At least four distinct reaction processes, namely: (a) condensation between amine and aldehyde, (b) nucleophilic addition of isonitrile to imine, (c) ring-chain tautomerization and (d) intramolecular Diels–Alder cycloaddition were involved in this one-pot process. Considering the excellent chemical yield of the final product, these steps might proceed in a highly ordered fashion at the expense of other non-productive manifolds. It is interesting to note that the formation of oxazole (step 3) is the only irreversible step, while all other reactions including the intramolecular Diels–Alder cycloaddition are reversible. Indeed, small percentage of 5-aminooxazole **8**, the direct precursor of polycycle **1**, was frequently observed as the only discernable by-product in the crude reaction mixture. That intramolecular cycloaddition of 5-aminooxazole (**8**) leading to oxa-briged tricycle (**1**) occurred at room temperature is intriguing.[20–22] On the other hand, the mild conditions are certainly also responsible for the high isolated yield of tricycle **1**.

That the reaction proceeded through oxazole intermediate was evidenced by the isolation of compound **8a**. In fact, when *N*,*N*-diallylamine was used as input, the reaction stopped at the oxazole step under the identical conditions (MeOH, room temperature). Apparently, it is necessary to use electron-poor dienophile in order for the whole sequence to tricycle being realized *at room temperature*.

The free rotation of C–C bond at the peripheral of the tricyclic ring system is highly hindered owing to the steric hinderance and is reflected in the ^{1}H NMR spectra of these compounds. Thus, each of the two methine-protons of carboethoxy function (COOCH_2CH$_3$) appeared as a multiple ABX3 system (δ=4 ppm or so). From both



1a (92%)
1b (82%)
1c (80%)
1d (65%)
1e (65%)
1f (95%)
1g (94%)
8a (90%)

Figure 3. Representative structure of oxa-bridged tricycles synthesized. Conditions: 0.5 M solution in MeOH, room temperature, 2 h.

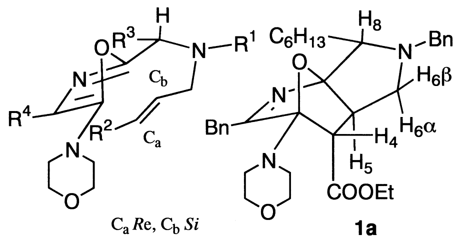
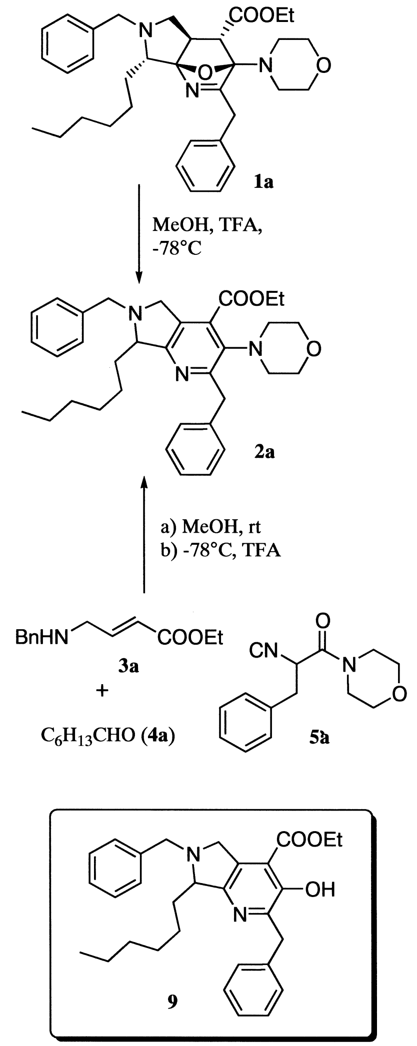


Figure 4. Stereochemistry.

mechanistic consideration and NMR studies, the stereochemistry of the cycloadduct **1** was tentatively assigned as shown in Scheme 2. The proton H4 of compound **1a** (Fig. 4) resonanced at δ=2.93 ppm has the coupling constant of 4.0 Hz (J_{H4-H5}), indicative of a gauche relationship with proton H5. Since the C5–C6 bond has to be *exo*-oriented for the inherent ring strain imposed by the connecting bridge, the observed coupling constant indicated an *endo* position of the ester group. Hence, the stereochemistry of the *trans* double bond of allyl amine was transmitted to the final cycloadduct.[21] This model of ring formation is indicative of a concerted rather than a stepwise process, since one could expect the formation of *exo*, *exo* diastereomers if the latter mechanism was operating. The relative stereochemistry of the major adduct **1a** with a R$_1$ substituent *trans* to the oxygen bridge was deduced from the observation of strong NOE cross peaks between H8–H6β, H6α–H5 and H4–H6β in its NOESY spectrum (Fig. 4). The face-selectivity (C$_a$/*re*, C$_b$/*si* of dienophile, Fig. 4) of the intramolecular Diels–Alder cycloaddition must be controlled by the stereochemistry of C-8 and should be accounted for on both kinetic and thermodynamic ground. The same selectivity has been observed in the related process.[8,19,23]



Scheme 3. Synthesis of pyrrolopyridine.

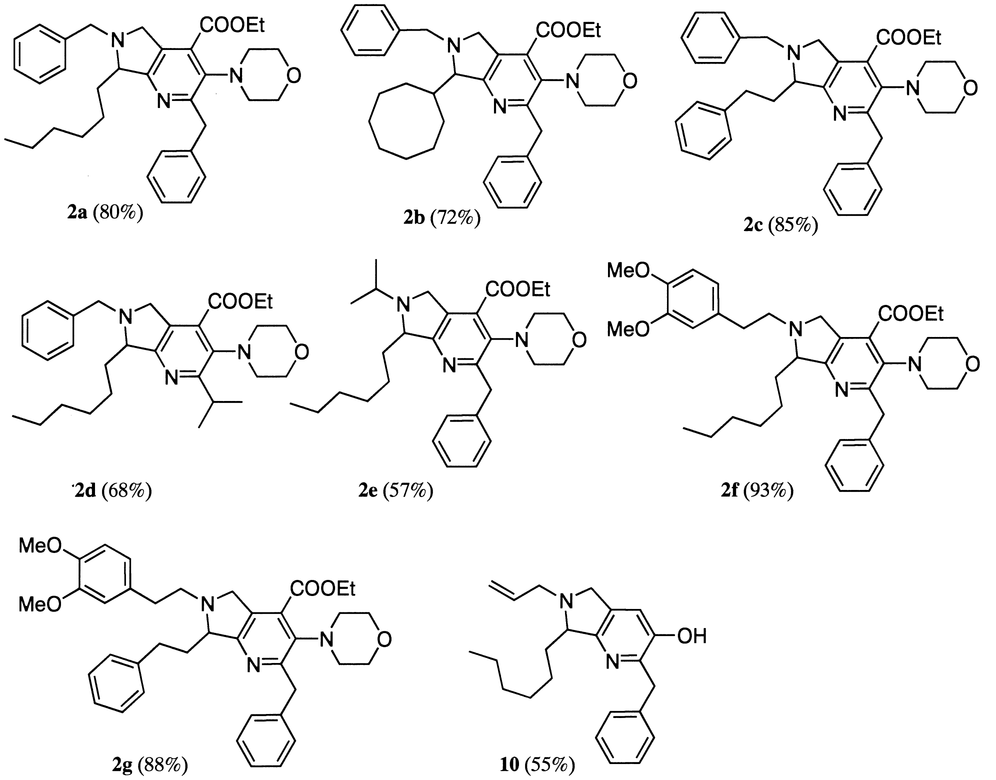
2.2. Fragmentation of oxa-bridged heterocycle and three-component synthesis of pyrrolopyridine

Using **1a** as model compound, conditions for performing the fragmentation of bridged α-amino ether function were surveyed varying solvents (MeOH, toluene), acids (TFA, AcOH, *p*-TsOH) and temperatures (room temperature, 0, −30, −78°C). Under optimum conditions (methanol, TFA, −78°C), the fragmentation assisted by the lone-pair electron of nitrogen occurred rapidly (20 min) to provide pyrrolopyridine (**2a**) in 85% yield. When acetic acid or pTsOH was used instead of TFA, a variable amount of phenol **9** was obtained as a side-product (Scheme 3).

It is evident that conditions for the three-component synthesis of *oxa*-bridged tricycle **1** and its subsequent fragmentation to **2** are compatible. This consideration prompted us to examine the one-pot synthesis of pyrrolopyridine. In the event, stirring a solution of amine (**3a**), aldehyde (**4a**), and isocyanoacetamide (**5a**) at room temperature for 2 hrs followed by addition of TFA at −78°C provided directly the pyrrolopyridine **2a** in 80% yield. Fig. 5 listed some of the pyrrolopyridines synthesized by this one-pot procedure. On the other hand, refluxing a toluene solution of oxazole **8a** led directed to pyrrolopyridine **10** in 55% yield.

3. Conclusion

In conclusion, we have developed a novel three-component synthesis of oxa-bridged tricycle (**1**) and pyrrolopyridines (**2**) starting from easily available allylamine (**3**), aldehyde (**4**) and isocyanoacetamide (**5**). The process is atom economic and ecologically benign since only molecular water was lost in this rather complicated bond-forming process. Indeed five and four chemical bonds were produced, respectively, en route to the production of compounds **1** and **2**. It is interesting to note that two families of structurally distinct heterocycles have been produced from the same inputs under identical conditions except for the work-up procedures. While the reaction itself allowed the incorporation of at least four diversity points, an additional diversity was provided by modifying the work-up procedure. The operational simplicity and excellent chemical yield made these novel heterocycle syntheses highly attractive in diversity-oriented parallel synthesis.



2a (80%) **2b** (72%) **2c** (85%) **2d** (68%) **2e** (57%) **2f** (93%) **2g** (88%) **10** (55%)

Figure 5. Representative structure of pyrrolopyridine synthesized. Conditions: 0.5 M solution in MeOH, room temperature, 2 h, then −78°C, TFA, 20 min.

4. Experimental

4.1. General procedure for the three component synthesis of oxa-brigded tricycles (1)

A solution of allylamine (**3**) (1.2 mmol) and aldehyde (**4**) (1.2 mmol) in dry methanol (0.5 M) was stirred at room temperature for 1 h. The α-isocyanoacetamide (**5**) (1.0 mmol) was then added. After being stirred at room temperature for 2 h (monitored by TLC), the volatile was removed under reduced pressure and the residue was purified by flash chromatograph (SiO_2) to give the corresponding oxa-brigded tricycles **1**.

4.1.1. Compound 1a. Yield 92%. R_f=0.39 (Hept/AcOEt (7/3)); IR ($CHCl_3$) ν 2959, 2928, 2858, 1730, 1601, 1495, 1454, 1271, 1235, 1118, 1071, 1042, 1029, 901 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.29 (m, 10H), 4.18 (m, 1H), 4.06 (d, J=13.0 Hz, 1H), 4.05 (m, 1H), 3.80 (d, J=16.0 Hz, 1H), 3.69 (m, 4H), 3.60 (d, J=16.0 Hz, 1H), 3.42 (d, J=13.0 Hz, 1H), 3.14 (dd, J=8.0, 7.5 Hz, 1H), 2.98 (m, 2H), 2.93 (d, J=4.0 Hz, 1H), 2.73 (dd, J=9.0, 3.0 Hz, 1H), 2.55 (m, 2H), 2.42 (ddd, J=10.5, 7.0, 4.0 1H), 2.04 (dd, J=10.0, 8.0 Hz, 1H), 2.03 (m, 1H), 1.72 (m, 1H), 1.33 (m, 8H), 1.23 (t, J=7.5 Hz, 3H), 0.9 (t, J=6.6 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.0, 170.0, 139.4, 136.3, 129.1, 128.7, 128.4, 128.3, 127.1, 126.6, 108.2, 107.5, 67.0, 65.4, 61.1, 58.9, 57.0, 51.1, 49.6, 48.6, 45.3, 35.3, 31.9, 31.7, 29.6, 26.2, 22.6, 14.2, 14.1; MS (EI): m/z 559 (M^+, 17%).

4.1.2. Compound 1b. Yield 82%. R_f=0.65 (Hept/AcOEt (7/3)); IR ($CHCl_3$) ν 2922, 2855, 1728, 1602, 1495, 1454, 1117 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.5–7.23 (m, 10H), 4.19 (m, 1H), 4.12 (d, J=13.0 Hz, 1H), 4.03 (m, 1H), 3.80 (d, J=16.0 Hz, 1H), 3.74 (m, 4H), 3.59 (d, J=16.0 Hz, 1H), 3.40 (d, J=13.0 Hz, 1H), 3.22 (dd, J=8.0, 7.5 Hz, 1H), 3.0 (m, 3H), 2.92 (d, J=4.0 Hz, 1H), 2.75 (d, J=3.0 Hz, 1H), 2.60 (m, 2H), 2.42 (ddd, J=10.5, 7.0, 4.0 Hz, 1H), 2.05 (m, 1H), 2.05 (dd, J=10.0, 8.0 Hz, 1H), 1.85–1.53 (m, 14H), 1.28 (t, J=7.0 Hz, 1H). MS (EI): m/z 585 ($M+H^+$, 1%).

4.1.3. Compound 1c. Yield 80%. R_f=0.45 (Hept/AcOEt (7/3)); IR ($CHCl_3$) ν 2921, 2858, 1730, 1602, 1495, 1454, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.4–7.12 (m, 15H), 4.20 (m, 1H), 4.05 (m, 1H), 4.0 (d, J=13.0 Hz, 1H), 3.80 (d, J=16.0 Hz, 1H), 3.72 (m, 4H), 3.64 (d, J=16.0 Hz, 1H), 3.44 (d, J=13.0 Hz, 1H), 3.16 (dd, J=8.0, 7.5 Hz, 1H), 3.00 (m, 2H), 2.96 (d, J=4.0 Hz, 1H), 2.80 (dd, J=9.5, 3.0 Hz, 1H), 2.66 (m, 2H), 2.46 (ddd, J=10.5, 7.0, 4.0 Hz, 1H), 2.26 (m, 2H), 2.06 (dd, J=10.0, 8.0 Hz, 1H), 1.95 (m, 2H), 1.25 (t, J=7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 176.5, 169.9, 143.0, 139.3, 136.0, 129.4, 128.7, 128.6, 128.3, 128.2, 128.1, 127.0, 126.7, 126.6, 108.1, 107.4, 67.1, 64.5, 61.2, 58.6, 56.9, 53.5, 49.8, 48.7, 45.3, 35.7, 32.4, 31.0, 14.3; MS (EI): m/z 580 ($M+H^+$, 4%).

4.1.4. Compound 1d. Yield 65%. R_f=0.43 (Hept/AcOEt (7/3)); IR ($CHCl_3$) ν 2957, 2927, 2856, 1719, 1602, 1494, 1454, 1272, 1251, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.21 (m, 1H), 7.45–7.23 (m, 9H), 4.09 (d, J=13.0 Hz, 1H), 3.93–3.63 (m, 2H), 3.72 (m, 4H), 3.48 (d, J=13.0 Hz, 1H), 3.20–3.11 (m, 3H), 3.12 (d, J=4.0 Hz, 1H), 2.83 (dd, J=9.0, 3.0 Hz, 1H), 2.78 (m, 2H), 2.62 (ddd, *J*=10.5, 7.0, 4.0 1H), 2.10 (m, 1H), 2.07 (dd, *J*=10.0, 8.0 Hz, 1H), 1.73 (m, 1H), 1.47–1,25 (m, 8H), 0.95–0.89 (m, 6H); ^{13}C NMR (62.5 MHz, CDCl$_3$) δ (ppm): 169.2, 169.7, 139.4, 132.5, 130.8, 128.7, 128.2, 128.1, 127.0, 126.0, 108.3, 107.3, 66.9, 65.4, 61.0, 59.0, 57.1, 50.5, 48.9, 48.2, 45.4, 31.8, 29.5, 26.1, 22.7, 14.1, 13.5; MS (ES+): *m/z* 546 (M+H$^+$, 63%).

4.1.5. Compound 1e. Yield 65%. R_f=0.35 (Hept/AcOEt (7/3)); IR (CHCl$_3$) ν 2964, 2929, 2859, 1731, 1602, 1495, 1455, 1271, 1240, 1118 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 7.48–7.15 (m, 5H), 4.20 (m, 1H), 4.07 (m, 1H), 3.75 (d, *J*=16.0 Hz, 1H), 3.66 (m, 4H), 3.60 (d, *J*=16.0 Hz, 1H), 3.26 (dd, *J*=8.0, 7.5 Hz, 1H), 2.98 (d, *J*=4.0 Hz, 1H), 2.95 (m, 3H), 2.81 (m, 1H), 2.66–2.43 (m, 3H), 2.22 (dd, *J*=10.0, 8.0 Hz, 1H), 1.99 (m, 1H), 1.58 (m, 2H), 1.28 (m, 7H), 1.27 (t, *J*=7.0 Hz, 3H), 1.14–0.96 (m, 6H), 0.87 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$) δ (ppm): 176.0, 170.0, 136.4, 129.3, 128.6, 126.6, 108.3, 107.5, 67.1, 62.1, 61.2, 51.1, 50.9, 49.2, 48.7, 45.9, 35.3, 33.4, 32.1, 29.7, 26.5, 22.7, 22.2, 17.2, 14.4, 14.1; MS (EI): *m/z* 511 (M+H$^+$, 9%).

4.1.6. Compound 1f. Yield 95%. R_f=0.31 (Hept/AcOEt (7/3)); IR (CHCl$_3$) ν 2933, 2858, 1731, 1602, 1515, 1455, 1219, 1118 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 7.39–7.21 (m, 5H), 6.78 (m, 3H), 4.29–4.05 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.79 (d, *J*=16.0 Hz, 1H), 3.69 (m, 4H), 3.60 (d, *J*=16.0 Hz, 1H), 3.47 (dd, *J*=8.0, 7.5 Hz, 1H), 3.05 (d, *J*=4.0 Hz, 1H), 3.04–2.93 (m, 3H), 2.83–2.48 (m, 7H), 2.15 (m, 1H), 2.14 (dd, *J*=10.0, 8.0 Hz, 1H), 1.63 (m, 1H), 1.29 (t, *J*=7.0 Hz, 3H), 1.35–1.25 (m, 8H), 0.87 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$) δ (ppm): 176.1, 170.0, 148.9, 147.3, 136.2, 133.1, 129.2, 128.2, 126.6, 120.6, 112.1, 111.3, 108.3, 107.3, 67.0, 66.9, 65.8, 61.2, 57.2, 56.9, 56.0, 55.9, 55.8, 49.6, 48.6, 45.5, 35.3, 34.6, 32.0, 32,1, 29.6, 26.4, 22.7, 14.3, 14.2; MS(ES+): *m/z* 634 (M+H$^+$, 79%).

4.1.7. Compound 1g. Yield 94%. R_f=0.33 (Hept/AcOEt (7/3)); IR (CHCl$_3$) ν 2938, 2859, 1731, 1602, 1515, 1455, 1262, 1238, 1118 cm^{-1}; ^{1}H NMR (300 MHz, CD$_3$COCD$_3$) δ (ppm): 7.43–7.05 (m, 10H), 6.87–6.73 (m, 3H), 4.27 (m, 1H), 4.11 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.81–3.62 (m, 6H), 3.47 (dd, *J*=8.0, 7.5 Hz, 1H), 3.20 (d, *J*=4.0 Hz, 1H), 3.07 (m, 2H), 2.96 (m, 1H), 2.8–2.5 (m, 8H), 2.42 (ddd, *J*=10.5, 7.0, 4.0 Hz, 1H), 2.16 (dd, *J*=10.0, 8.0 Hz, 1H), 2.02 (m, 1H), 1.88 (m, 1H), 1.30 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$) δ (ppm): 176.5, 169.9, 148.9, 147.4, 142.8, 136.2, 133.1, 129.4, 128.5, 128.3, 128.0, 126.7, 125.5, 120.6, 112.1, 111.3, 108.3, 107.2, 67.1, 64.8, 61.2, 57.1, 56.6, 55.8, 55.7, 49.7, 48.7, 45.4, 35.7, 34.5, 32.4, 31.0, 14.4; MS (ES+): *m/z* 676 (M+23, 65%).

4.2. General procedure for the three component synthesis of pyrrolo[3,4-*b*]pyridine (2)

A solution of allylamine (**3**) (1.2 mmol) and aldehyde (**4**) (1.2 mmol) in dry methanol (0.5 M) was stirred at room temperature for 1 h. The α-isocyanoacetamide (**5**) (1.0 mmol) was then added. After being stirred at room temperature for 1 h (monitored by TLC), the reaction mixture was cooled to −78°C and trifluoroacetic acid (7.0 mmol) was added. After the disappearance of oxa-brigded tricycle (**1**), the reaction mixture was diluted with aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic phases were dried (Na$_2$SO$_4$), and evaporated under reduced pressure. The crude product was purified by flash chromatograph or preparative TLC (silica gel, eluent: Hept/AcOEt=9/1) to give the corresponding pyrrolopyridines (**2**).

4.2.1. Compound 2a. Yield 80%. R_f=0.47 (Hept/AcOEt (7/3)); IR (CHCl$_3$) ν 2930, 2858, 1730, 1495, 1454, 1375, 1265, 1112, 1019 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 7.4–7.21 (m, 10H), 4.38 (d, *J*=14.0 Hz, 1H), 4.32 (q, *J*=7.0 Hz, 2H), 4.22 (d, *J*=14.0 Hz, 1H), 4.21, (*J*=13.0 Hz, 1H), 4.05 (dd, *J*=14.5, 1.0 Hz, 1H), 3.98 (s large, 1H), 3.65–3.60 (m, 5H), 3.57 (d, *J*=13.0 Hz, 1H), 2.92 (m, 4H), 2.04 (m, 1H), 1.85 (m, 1H), 1.62 (m, 1H), 1.30 (t, *J*=7.0 Hz, 3H), 1.29 (m, 7H), 0.88 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$) δ (ppm): 167.3, 159.6, 159.5, 140.6, 140.3, 139.2, 133.9, 130.0, 128.6, 128.5, 128.4, 128.1, 127.0, 125.9, 68.1, 67.6, 61.9, 58.6, 51.0, 40.3, 31.9, 29.8, 24.6, 22.7, 14.2, 14.1; MS (ES+): *m/z* 542 (M+H$^+$, 100%).

4.2.2. Compound 2b. Yield 72%. R_f=0.65 (Hept/AcOEt (7/3)); IR (CHCl$_3$) ν 2924, 2856, 1723, 1602, 1494, 1453, 1374, 1265, 1112, 1019 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 7.39–7.25 (m, 10H), 4.40 (d, *J*=14.0 Hz, 1H), 4.32 (q, *J*=7.0 Hz, 2H), 4.24 (d, *J*=13.5 Hz, 1H), 4.16 (d, *J*=14.0 Hz, 1H), 4.10 (dd, *J*=14.0, 1.3 Hz, 1H), 3.96 (m, 1H), 3.68–3.66 (m, 5H), 3.56 (dd, *J*=14.0, 1.5 Hz, 1H), 2.96 (m, 4H), 2.10 (m, 2H), 1.56 (m, 14H), 1.30 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$) δ (ppm): 167.3, 159.7, 159.4, 140.4, 140.3, 139.8, 133.6, 130.2, 128.8, 128.4, 128.1, 126.9, 125.9, 75.3, 67.7, 61.9, 59.9, 55.9, 51.1, 41.5, 40.2, 30.2, 30.0, 27.2, 26.8, 26.6, 26.3, 26.2, 14.2; MS (ES+): *m/z* 568 (M+H$^+$, 100%).

4.2.3. Compound 2c. Yield 85%. R_f=0.5 (Hept/AcOEt (7/3)); IR (CHCl$_3$) ν 2925, 2856, 1724, 1602, 1495, 1454, 1374, 1263 1111, 1019 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 7.4–7.12 (m, 15H); 4.33 (d, *J*=14.0 Hz, 1H), 4.27 (q, *J*=7.0 Hz, 2H), 4.17 (d, *J*=14.0 Hz, 1H), 4.14 (d, *J*=14.0 Hz, 1H), 4.03 (dd, *J*=14.0, 1.5 Hz), 3.97 (m, 1H), 3.61 (m, 4H), 3.6 (d, *J*=14.0 Hz, 1H), 3.55 (dd, *J*=14.0, 2.2 Hz, 1H), 2.87–3.00 (m, 5H), 2.45 (m, 1H), 2.29 (m, 1H), 2.04 (m, 1H), 1.24 (t, *J*=7.0 Hz, 3H), ^{13}C NMR (62.5 MHz, CDCl$_3$) δ (ppm): 167.2, 159.8, 159.7, 143.0, 140.7, 140.3, 138.0, 133.9, 130.0, 128.7, 128.6, 128.4, 128.2, 127.1, 126.0, 125.5, 67.6, 67.5, 61.9, 58.4, 55.2, 51.0, 40.2, 33.7, 30.8, 29.7, 14.2; EM (ES+): *m/z* 562 (M+1, 100%).

4.2.4. Compound 2d. Yield 68%. R_f=0.4 (Hept/AcOEt (7/3)); IR (CHCl$_3$) ν 2930, 2857, 1775, 1726, 1494, 1454, 1375, 1264, 1111, 1027, 1017 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 7.48–7.23 (m, 5H), 4.34 (q, *J*=7.0 Hz, 1H), 4.25 (d, *J*=13.2 Hz, 1H), 4.02 (dd, *J*=14.2, 1.5 Hz, 1H), 3.91 (m, 1H), 3.76 (m, 4H), 3.6 (d, *J*=13.2 Hz, 1H), 3.54 (dd, *J*=14.2, 2.5 Hz, 1H), 3.0 (m, 4H), 1.98 (m, 1H), 1.9–1,65 (m, 2H), 1.32 (t, *J*=7.0 Hz, 1H), 1.27 (m, 8H), 1.25 (d, *J*=6.6 Hz, 3H), 1.23 (d, *J*=6.6 Hz, 3H), 0.89 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$) δ (ppm):

165.8, 160.7, 139.3, 138.7, 138.4, 134.4, 128.6, 128.3, 127.0, 68.1, 67.9, 61.6, 58.6, 55.0, 51.3, 32.1, 31.8, 30.1, 29.7, 24.7, 22.7, 22.6, 22.5, 22.4, 14.4, 14.2; MS (ES+): *m/z* 494 ($M+H^+$, 100%).

4.2.5. Compound 2e. Yield 57%. R_f=0.47 (Hept/AcOEt (7/3)); IR ($CHCl_3$) ν 2929, 2856, 1723, 1602, 1494, 1453, 1374, 1263, 1111, 1018 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.5–7.35 (m, 5H), 4.41 (q, J=7.0 Hz, 2H), 4.38 (d, J=14.7 Hz, 1H), 4.21 (d, J=14.7 Hz, 1H), 4.11–4.04 (m, 2H), 3.92 (d, J=13.2 Hz, 1H), 3.66 (m, 4H), 3.17 (m, 1H), 3.0–2.86 (m, 4H), 1.87 (m, 1H), 1.74 (m, 2H), 1.55 (m, 1H), 1.40 (t, J=7.0 Hz, 3H), 1.26 (m, 6H), 1.16 (d, J=6.60 Hz, 3H), 1.04 (d, J=6.60 Hz, 3H), 0.87 (t, J=6.60 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 167.5, 160.9, 159.6, 140.7, 140.4, 134.0, 130.1, 128.7, 128.2, 126.0, 67.7, 64.6, 62.0, 53.5, 51.1, 49.2, 40.5, 33.1, 32.0, 29.9, 24.9, 22.8 16.5, 14.4, 14.2; MS (ES+): *m/z* 494 ($M+H^+$, 100%).

4.2.6. Compound 2f. Yield 93%. R_f=0.5 (Hept/AcOEt (7/3)); IR ($CHCl_3$) ν 2927, 2855, 1722, 1602, 1515, 1494, 1464, 1454, 1374, 1264, 1156, 1141, 1111 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 7.24–7.14 (m, 5H), 6.77–6.88 (m, 3H), 4.41 (q, J=7.0 Hz, 2H), 4.37 (d, J=14.7 Hz, 1H), 4.28 (dd, J=14.3, 1.5 Hz), 4.24 (d, J=14.7 Hz, 1H), 3.89 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.70 (dd, J=14.3, 1.8 Hz), 3.60 (m, 4H), 3.15 (m, 1H), 2.6–2.9 (m, 7H), 1.89 (m, 1H), 1.75 (m, 1H), 1.39 (t, J=7.0 Hz, 3H), 1.24 (m, 8H), 0.86 (t, J=6.6 Hz, 3H), ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 167.3, 160.0, 148.9, 147.4, 140.7, 140.2, 133.7, 132.9, 129.8, 128.5, 128.1, 125.9, 120.5, 112.0, 111.2, 67.9, 67.6, 61.9, 56.6, 55.9, 55.4, 51.0, 40.3, 32.5, 31.9, 29.7, 24.7, 22.7, 14.3, 14.1; EM (ES+): *m/z* 616 ($M+H^+$, 100%).

4.2.7. Compound 2g. Yield 88%. R_f=0.45 (Hept/AcOEt (7/3)); IR ($CHCl_3$) ν 1718, 1602, 1265, 1111, 1029 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 7.26–7.07 (m, 8H), 6.97–6.8 (m, 5H), 4.44 (q, J=7.0 Hz, 2H), 4.38 (d, J=14.0 Hz, 1H), 4.35 (dd, J=14.5, 1.8 Hz, 1H), 4.25 (d, J=14.0 Hz, H), 3.93 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.71 (dd, J=14.5, 2.2 Hz, 1H), 3.65 (m, 4H), 3.16 (m, 1H), 3.0–2.75 (m, 7H), 2.57 (m, 1H), 2.23 (m, 2H), 1.96 (m, 1H), 1.42 (t, J=7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 167.4, 159.8, 159.7, 149.0, 147.5, 143.0, 140.7, 140.2, 133.7, 132.9, 130.0, 128.6, 128.5, 128.2, 128.1, 126.0, 125.4, 120.6, 112.2, 111.3, 67.6, 66.9, 61.2, 56.3, 56.0, 55.4, 51.1, 40.3, 34.8, 34.1, 30.8, 14.4; EM (ES+): *m/z* 636 ($M+H^+$, 18%).

4.2.8. Compound 8a. Yield 90%. R_f=0.7 (Hept/AcOEt (7/3)); IR ($CHCl_3$) ν 2957, 2928, 2859, 2360, 1602, 1495, 1454, 1115, 995, 923 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.27–7.20 (m, 5H), 5,73 (m, 2H), 5,12 (m, 4H), 3.83 (s, 2H), 3.81 (t, J=8.0 Hz, 1H), 3.73 (m, 4H), 3.34 (dd, J=14.7, 5.2 Hz, 1H), 2.96 (m, 4H), 2,86 (dd, J=14.7, 7.4 Hz; 1H), 1.9 (m, 2H), 1.26 (m, 8H), 0.87 (t, J=6,6 Hz, 3H), ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 159.3, 151.5, 139.8, 136.5, 128.5, 128.3, 126.0, 124.1, 116.9, 66.9, 53.5, 51.1, 31.7, 30.4, 29.0, 26.3, 22.6, 14.1; MS (ES+): *m/z* 438 ($M+H^+$, 100%).

4.2.9. Compound 10. Yield 55%. R_f=0.42 (Hept/AcOEt (7/3)); IR ($CHCl_{3)}$ ν 2956, 2929, 2857, 2796, 1693, 1956, 1951, 1599, 1357, 1320, 1223, 1208, 1139, 994, 899 cm^{-1}; ^{1}H NMR (300 MHz,) CD_3COCD_3) δ (ppm): 8.10 (m, 2H), 7.37 (m, 3H), 5.94 (m, 1H), 5.23 (m, 2H), 3.61 (dd, J=14.0, 5.0 Hz, 1H), 3.55 (m, 1H), 3,17 (m, 1H), 2,94 (dd, J=14.0, 8.0 Hz, 1H), 2.75 (dd, J=16.0, 7.0 Hz, 1H), 2.33 (dd, J=16.0, 12.5 Hz, 1H), 2.19 (m, 1H), 2.10–1.65 (m, 3H), 1,34 (m, 5H), 0.89 (t, J=6.6 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm): 137.4, 134.7, 134.6, 133.0, 129.6, 128.4, 127.9, 118.0, 67.6, 57.8, 56.8, 38.0, 39.1, 31.9, 30.6, 29.9, 25.0, 22.8, 14.0; MS (ES+): *m/z* 351.5 ($M+H^+$, 100%)

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