

Efficient synthesis of heterocyclic compounds using ethenetricarboxylic acid diesters†

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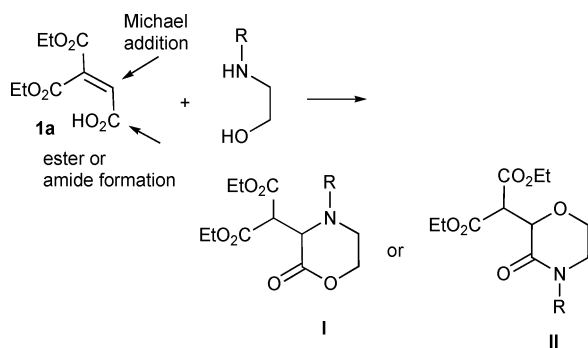
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Ethenetricarboxylic acid diester **1a** is a useful compound bearing two reactive sites, a CO₂H group and a Michael acceptor. Reactions of **1a** and reagents with oxygen and nitrogen nucleophilic moieties have been examined. The reaction of **1a** with 2-aminoalcohols in the presence of EDCI and HOBt in one pot gave *N,O*-containing heterocyclic compounds, regioselectively. The stepwise method has also been carried out. Deprotection of *N*-Boc protected aminoesters, followed by basic aqueous workup, gave various 1,4-oxazine derivatives. Deprotection of the *O*-TBS protected amides also leads to spontaneous cyclization and affords 1,4-oxazine derivatives. They have the opposite regiochemistry to those from the one-pot reaction. Thus, both ester or amide regioisomers can be prepared. These synthetic methods represent a new general strategy for the construction of diverse heterocyclic systems such as morpholine-derived heterocycles.

Introduction

Six-membered heterocyclic compounds containing nitrogen and oxygen, such as oxazine, dioxane and diazine skeletons are of considerable interest, due to their biological activity.^{1,2} Several methods have been reported for the preparation of these compounds.³ Various new synthetic strategies to construct them by the reactions of 2-aminoalcohols, 1,2-diamines, or 1,2-diols have been studied recently.⁴ Reagents bearing two nucleophilic sites and C–C components with two electrophilic sites react effectively and lead to heterocycle formation. It is desirable to find new highly functionalized acceptors with regioselective reactivity for the construction of diversely substituted heterocyclic systems.

Previously, we have shown the utility of ethenetricarboxylates for various synthetic reactions, as highly reactive Michael acceptors.⁵ Ethenetricarboxylic acid diester **1a** is considered to be a useful compound bearing two reactive sites: a CO₂H group and a Michael acceptor (Scheme 1).^{5d,f} We envisioned that heterocycles



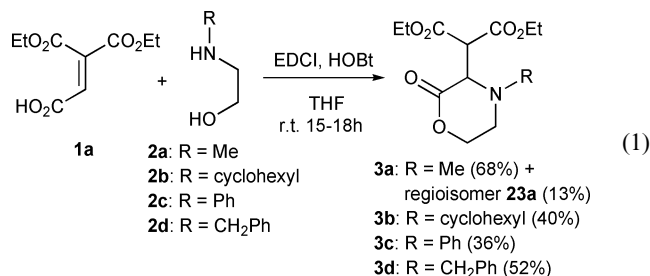
Scheme 1

may be accessible by one-pot or simple stepwise reactions of **1a** and reagents with oxygen and nitrogen nucleophilic moieties. Control of the regioselectivity for formation of oxazines **I** or **II** is also of interest. The products **I** or **II** can be valuable building blocks for the synthesis of more complex derivatives. The common condensation reaction of **1a** with reagents such as 2-aminoalcohols, 2-aminophenol, 1,2-diols, 1,2-diamines and their 1,3-analogues were examined in this study. The scope and limitations of the reaction are described.

Results and discussion

A. Cyclization of **1** in one pot

The reaction of **1a** with various 2-aminoalcohols **2** in the presence of EDCI (3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride) and HOBt (1-hydroxybenzotriazole) in THF was examined. The reaction with secondary 2-aminoethanols **2a–d** gave *N,O*-containing heterocyclic compounds **3a–d** regioselectively with preference for 1,4-addition of amines (eqn 1). For the reaction of **2a**, a minor regioisomer (**23a**, *vide post*), an amide oxazine was obtained in 13% yield. For the other derivatives, only isomers **3** were observed, even though the yields were modest.⁶



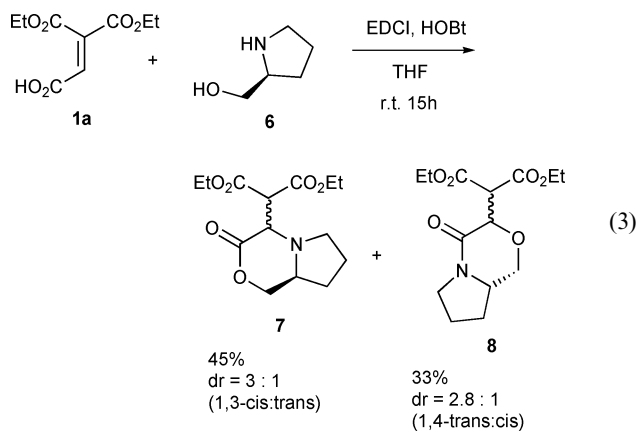
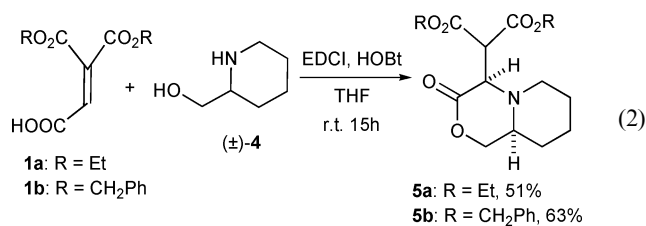
The one-pot reaction of **1a** with 2-piperidinemethanol **4** in the presence of EDCI and HOBt in THF gave a bicyclic *N,O*-containing heterocyclic compound **5a** as a single diastereomer in 51% yield, exclusively (eqn 2). Dibenzyl ester derivative **1b** also

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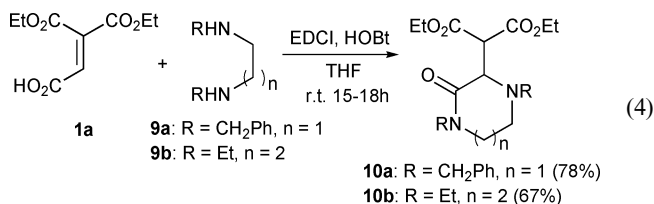
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reacted with **4** to give the heterocycle **5b** in 63% yield. On the other hand, the reaction of **1a** with (*S*)-2-pyrrolidinemethanol **6** gave a mixture of *N,O*-regioisomers **7** (45%, dr = 3:1)⁷ and **8** (33%, dr = 2.8:1) (eqn 3). In this example, the major product **7** is still a *N*-Michael adduct, however, the selectivity is low. The effect of the stereochemical factor on *N/O* selectivity is under investigation.

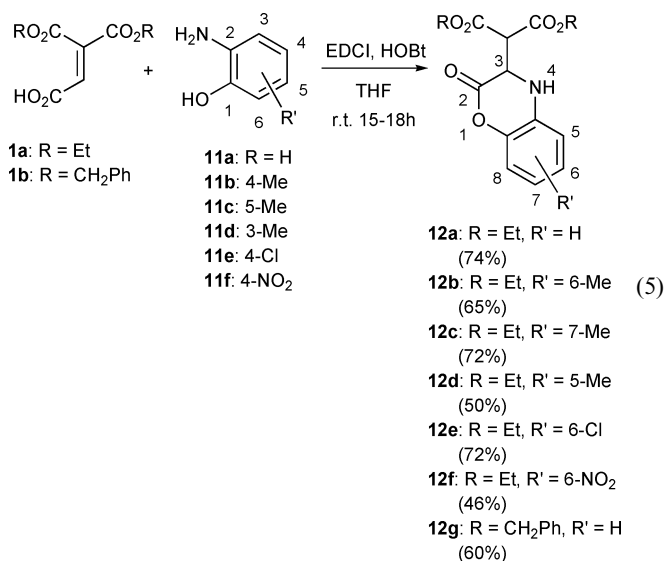
The regiochemistry of the major *N*-Michael adducts was determined by the absence of IR amide absorption ($\sim 1660\text{ cm}^{-1}$), which appears in the regioisomers, and NOE and HMBC correlations.



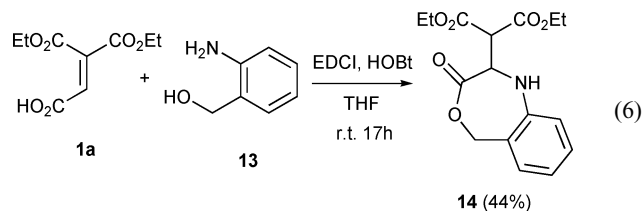
The reaction of **1a** with symmetric secondary 1,2-diamine **9a** and 1,3-diamine **9b** was examined next. The reaction in the presence of EDCI and HOBT in THF gave 1,4-pyrazine **10a** and the seven-membered 1,4-diazepane **10b** in good yields (eqn 4).



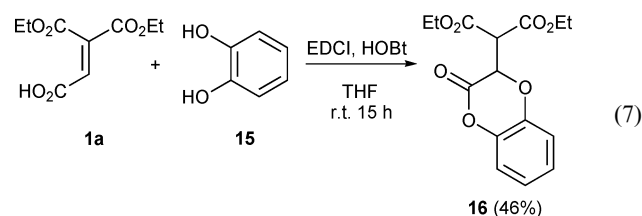
The reaction of **1a** with primary aliphatic amines, 2-aminoalcohols, gave a complex mixture. On the other hand, the reaction of **1a** with primary aromatic amines, 2-aminophenols **11**, gave cyclized products, 1,4-benzoxazines **12** efficiently in up to 74% yield (eqn 5).⁸ The products **12** arise from *N*-Michael adducts, selectively. Dibenzyl ester **1b** also gave **12g** as a major product.



The reaction of **1a** with 2-hydroxymethylaniline **13** gave a benzo[*e*][1,4]oxazepine derivative **14** in 44% yield as the major isolable product (eqn 6).



The reaction of **1a** with aliphatic 1,2-diols such as ethylene glycol, *trans*-cyclohexane-1,2-diol and *cis*-cyclohexane-1,2-diol gave complex mixtures. The reaction of **1a** with aromatic 1,2-diol, pyrocatechol **15**, gave a cyclized product **16** in 46% yield (eqn 7).

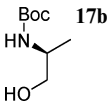
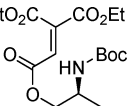
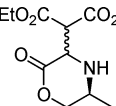
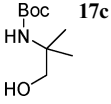
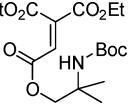
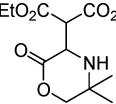
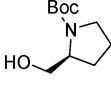
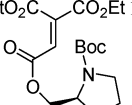
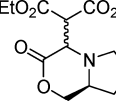
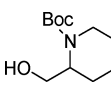
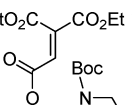
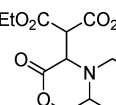


In the *N/O* one-pot reactions, determination of whether amine addition or ester formation occurs first may be complicated. The amine may react faster because of its stronger nucleophilicity. Also, the amine conjugate addition may be reversible.

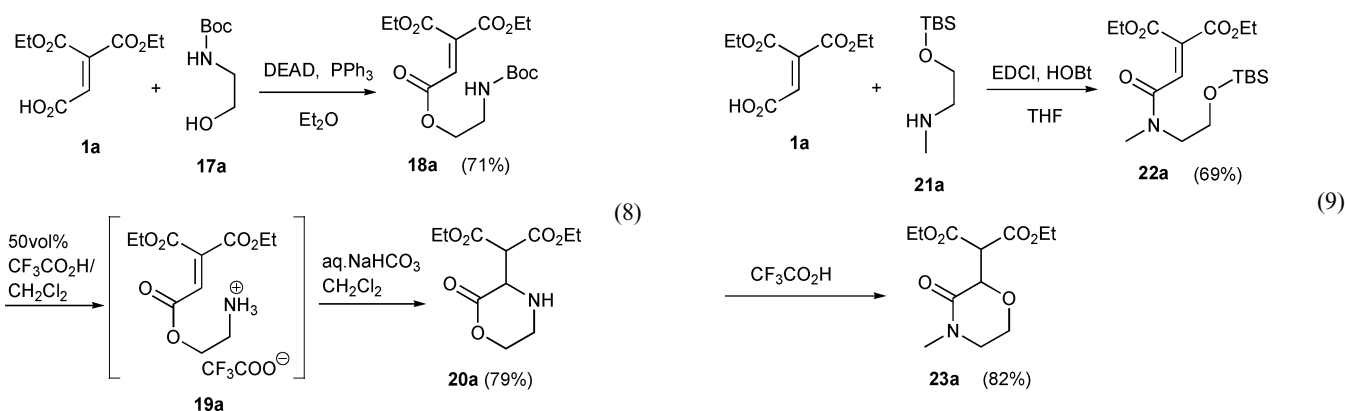
B. Stepwise cyclization via *N*-Boc aminoesters

Next, the stepwise method was carried out. *N*-Boc protected aminoesters **18** were prepared from **1a** and *N*-Boc protected amino alcohols **17** under Mitsunobu conditions or by EDCI/DMAP or EDCI/HOBT condensation (eqn 8 and Table 1).⁹ Deprotection of the *N*-Boc group by trifluoroacetic acid (TFA) to give a TFA salt **19**, followed by basic aqueous workup (aq. NaHCO₃), gave various 1,4-oxazine derivatives **20**. Intramolecular 1,4-addition of amines occurs spontaneously.¹⁰ The products have the same regiochemistry as the one-pot reaction. The *N*-Boc protected aminoesters lead to primary aliphatic amine adducts, which could not be obtained by one-pot reactions.

Table 1 Preparation of esters **18** and their cyclization reactions

Aminoalcohol 17	Condensation method	<i>N</i> -Boc aminoester 18	Yield	Product 20	Yield
	DEAD, PPh ₃ , Et ₂ O		71%		86% dr = 1.7:1–1:0 ^a (1,3-cis:trans) ^b
	EDCI, HOBT THF		50%		53%
	DEAD, PPh ₃ , Et ₂ O		45%		79% dr = 3:5 (1,3-cis:trans) ^b
	EDCI, DMAP CH ₂ Cl ₂		30%		78%

^a The diastereomer ratio changed on standing.⁷ ^b Cis:trans refers to substitution in the oxazine ring.



The use of chiral amino acid-derived aminoalcohols **17b,d** gave chiral cyclized products **20b** and **7**, although the products were obtained as diastereomer mixtures.⁷ Selective formation of **5a** from **18e** as well as the one-pot formation described above may arise from the stability of the diequatorial 1,3-cis substituents adopting a chair-like conformation for the six-membered 1,4-oxazine ring.¹¹ In the ring closed products, the amine addition and elimination may be reversible, leading to the stable isomer **5a**.

C. Stepwise cyclization via *O*-TBS amides

The stepwise method via *O*-TBS (OSiMe₂^tBu) protected amides **22** was also examined (eqn 9 and Table 2). The amides **22** were prepared from **1a** and *O*-TBS protected amines **21**. Deprotection of the *O*-TBS group of **22a,b,c** by trifluoroacetic acid or tetrabutylammonium fluoride (for **22b**) gave 1,4-oxazine derivatives **23a,b,c**. The substituted derivatives **23b,c** were also obtained as diastereomer mixtures. The products **23a,b** have the opposite regiochemistry to that of the one-pot reaction. Thus, both ester or amide regioisomers can be prepared. Attempts to obtain seven-membered rings by this deprotonation method failed. The reaction of **22d** with TFA gave deprotonated alcohol derivative **24d** in quantitative yield.¹²

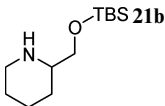
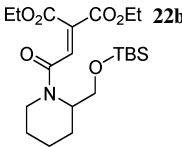
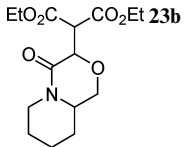
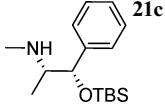
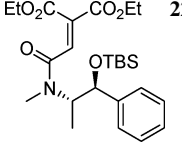
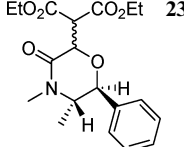
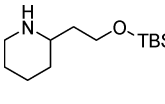
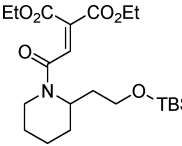
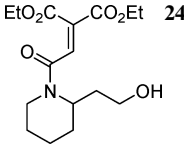
In summary, the reaction of ethenetricarboxylic acid diester **1** with secondary 2-aminoalcohols in the presence of EDCI and HOBT in one pot gave *N,O*-containing heterocyclic compounds regioselectively, with a preference for 1,4-addition of amines. The stepwise methods involving *N*-Boc protected aminoesters or *O*-TBS protected amides afforded the regioisomeric 1,4-oxazine derivatives, respectively. These metal-free synthetic methods represent a new general strategy for the construction of diverse heterocyclic systems such as morpholine-derived heterocycles. Also, the present reaction has potential with regard to other bifunctional nucleophiles *i.e.* thiophenol or other SH-containing substrates. Transformation of the products, including monodecarboxylation of the diester groups,¹³ to potentially useful compounds is under investigation.

Experimental section

Typical experimental procedure (eqn 1)

To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1a** (216 mg, 1 mmol) (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate upon treatment with CF₃CO₂H)^{5d} in THF (4 mL) were added HOBT (1-hydroxybenzotriazole) (135 mg,

Table 2 Preparation of amides **22** and the deprotection reaction

O-TBS amine 21	O-TBS amide 22	Yield	Deprotection method	Product 23	Yield
		55%	TFA TBAF		91% dr = 1.3:1 (1,4-trans:cis) 89% dr = 1:1
		63%	TFA		89% dr = 3:1 (1,3-trans:cis)
		45%	TFA		100%

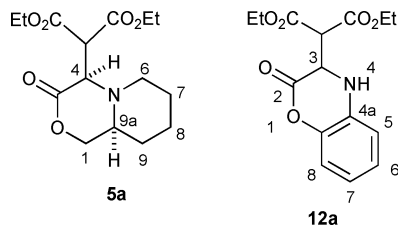
1 mmol), EDCI (1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride) (199 mg, 1.04 mmol) and 2-(methylamino)ethanol **2a** (75 mg, 1 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 13 h. The mixture was concentrated *in vacuo* and the residue was diluted with CH₂Cl₂. The organic phase was washed with saturated aqueous NaHCO₃ solution, 2M aqueous citric acid, saturated aqueous NaHCO₃ and water, dried (Na₂SO₄), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with ether to give **3a** (186 mg, 68%) and **23a** (36 mg, 13%).

3a. R_f = 0.3 (ether); Pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.30 (t, *J* = 7.1 Hz, 3H, CH₂CH₃), 1.31 (t, *J* = 7.1 Hz, 3H, CH₂CH₃), 2.43 (s, 3H, NCH₃), 2.72 (ddd, *J* = 12.8, 11.2, 2.9 Hz, 1H, NCHH), 2.90 (ddd, *J* = 12.8, 2.4, 2.4 Hz, 1H, NCHH), 3.64 (d, *J* = 3.8 Hz, 1H, NCH), 3.89 (d, *J* = 3.8 Hz, 1H, CH(CO₂Et)₂), 4.18–4.37 (m, 5H, CH₂CH₃, OCHH), 4.50 (ddd, *J* = 10.9, 10.9, 2.5 Hz, 1H, OCHH). Selected NOEs are between δ 2.43 and δ 2.72, 2.90, 3.64, 3.89; ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 13.84 (q), 13.89 (q), 43.38 (q), 50.94 (t), 53.34 (d), 61.65 (t), 61.81 (t), 65.75 (d), 67.00 (t), 166.93 (s), 167.33 (s), 167.98 (s). Selected HMBC correlations are between δ 2.43 and δ 50.94 (NCH₂), 65.75 (NCH), and between δ 3.64 and δ 43.38 (NCH₃); IR (neat) 2983, 1738, 1463, 1373, 1300, 1201, 1150 cm⁻¹; MS (EI) *m/z* 273 (M⁺, 9), 181 (17), 114 (100%); exact mass M⁺ 273.1211 (calcd for C₁₂H₁₉NO₆ 273.1212).

23a. R_f = 0.1 (ether); Pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.28 (t, *J* = 7.1 Hz, 3H, CH₂CH₃), 1.29 (t, *J* = 7.0 Hz, 3H, CH₂CH₃), 3.01 (s, 3H, NCH₃), 3.14 (bd, *J* = 11.9 Hz, 1H, NCHH), 3.71 (td, *J* = 11.7, 4.3 Hz, 1H, NCHH), 3.87 (td, *J* = 11.7, 3.0 Hz, 1H, OCHH), 4.06 (ddd, *J* = 11.9, 4.2, 1.5 Hz, 1H, OCHH), 4.11 (d, *J* = 4.3 Hz, 1H, CH(CO₂Et)₂), 4.19–4.29 (m, 4H, CH₂CH₃), 4.67 (d, *J* = 4.3 Hz, 1H, OCH). Selected NOEs are between δ 3.01 and δ 3.14, 3.71 and between δ 3.87 and δ 4.67; ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 14.00 (q), 14.02 (q), 34.44 (q), 48.41 (t), 54.20 (d), 61.58 (t), 61.67 (t), 63.37 (t), 75.52 (d), 166.69 (s), 167.01 (s), 167.21 (s). Selected HMBC correlations are between δ 3.01 and δ 167.21 (NC=O); IR (neat) 2982, 1747, 1736, 1661, 1505, 1372, 1343, 1267, 1150 cm⁻¹; MS (EI) *m/z* 273 (M⁺,

39), 228 (53), 154 (96), 86 (100%); HRMS M⁺ 273.1213 (calcd for C₁₂H₁₉NO₆ 273.1212).

5a. R_f = 0.5 (hexane : ether = 1 : 4); Pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.11 (dddd, *J* = 12.8, 12.8, 11.2, 4.0 Hz, 1H, H₉), 1.25–1.39 (m, 1H, H₈), 1.29 (t, *J* = 7.1 Hz, 3H, CH₂CH₃), 1.31 (t, *J* = 7.1 Hz, 3H, CH₂CH₃), 1.47 (dddd, *J* = 13.2, 13.2, 3.8, 3.8 Hz, 1H, H₇), 1.57–1.62 (m, 1H, H₉), 1.67–1.72 (m, 1H, H₇), 1.78–1.82 (m, 1H, H₈), 2.09 (ddd, *J* = 11.7, 11.7, 2.5 Hz, 1H, H₆), 2.51 (dddd, *J* = 10.4, 10.4, 2.8, 2.8 Hz, 1H, H_{9a}), 3.04 (ddd, *J* = 11.2, 2.7, 2.7 Hz, 1H, H₆), 3.66 (d, *J* = 3.8 Hz, 1H, H₄), 3.87 (d, *J* = 3.8 Hz, 1H, CH(CO₂Et)₂), 4.07 (dd, *J* = 10.8, 3.1 Hz, 1H, H₁), 4.12 (dd, *J* = 10.3, 10.3 Hz, 1H, H₁), 4.20–4.35 (m, 4H, CH₂CH₃). Selected NOEs are between δ 2.51 and δ 3.66; ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 13.95 (q), 14.03 (q), 23.20 (t), 25.00 (t), 26.94 (t), 52.51 (t), 53.72 (d), 56.23 (d), 61.67 (t), 61.88 (t), 64.67 (d), 71.47 (t), 167.15 (s), 167.63 (s), 168.52 (s). Selected HMBC correlations are between δ 2.09 and δ 64.67 (C₄), between δ 3.66 and δ 52.51 (C₆), and between δ 2.09, 3.04 and δ 56.23 (C_{9a}); IR (neat) 2982, 2940, 1739, 1460, 1373, 1282, 1215, 1093 cm⁻¹; MS (EI) *m/z* 313 (M⁺, 30), 221 (93), 193 (83), 154 (100%); HRMS M⁺ 313.1526 (calcd for C₁₅H₂₃NO₆ 313.1525).



12a. R_f = 0.7 (hexane : ether = 1 : 4); Pale yellow crystals; mp 67–70 °C; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.18 (t, *J* = 7.1 Hz, 3H, CH₂CH₃), 1.33 (t, *J* = 7.1 Hz, 3H, CH₂CH₃), 4.06–4.17 (m, 2H, CH₂CH₃), 4.23 (d, *J* = 4.4 Hz, 1H, CH(CO₂Et)₂), 4.25–4.37 (m, 2H, CH₂CH₃), 4.64 (d, *J* = 4.4 Hz, 1H, H₃), 4.94 (bs, 1H, H₄), 6.74–6.76 (m, 1H, H₅), 6.81 (td, *J* = 7.8, 1.5 Hz, 1H, H₇), 6.96–7.01 (m, 2H, H_{6,8}); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 13.81 (q), 13.98 (q), 53.44 (d), 54.25 (d), 62.34 (t), 62.44 (t), 115.18 (d), 116.80 (d), 120.15 (d), 125.33 (d), 131.15 (s), 140.19

(s), 164.51 (s), 166.72 (s), 167.92 (s). Selected HMBC correlations are between δ 4.64 and δ 131.15 (C_{4a}); IR (KBr) 3366, 2989, 1735, 1732, 1358, 1282, 1234, 1180 cm^{-1} ; MS (EI) m/z 307 (M^+ , 43), 187 (46), 147 (61), 120 (100%); HRMS M^+ 307.1060 (calcd for $C_{15}H_{17}NO_6$, 307.1056).

Preparation of 20a (eqn 8)

To a solution of **18a** (74 mg, 0.2 mmol) in dichloromethane (0.7 mL) was added trifluoroacetic acid (0.7 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 1 h. The mixture was concentrated *in vacuo* and the residue was diluted with CH_2Cl_2 . The organic phase was washed with saturated aqueous $NaHCO_3$ solution and water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with CH_2Cl_2 –MeOH (4 : 1) to give **20a** (42 mg, 79%).

20a. $R_f = 0.7$ (CH_2Cl_2 : MeOH = 4 : 1); Colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.30 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 1.31 (t, $J = 7.1$ Hz, 3H, CH_2CH_3), 2.71 (bs, 1H, NH), 3.08–3.18 (m, 2H, NCH_2), 4.11 (d, $J = 3.5$ Hz, 1H, NCH), 4.21–4.31 (m, 5H, CH_2CH_3 , $CH(CO_2Et)_2$), 4.39–4.51 (m, 2H, OCH_2). Selected NOEs are between δ 3.08–3.18 and δ 4.11; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.03 (q), 14.08 (q), 42.31 (t), 53.89 (d), 57.81 (d), 62.09 (2 \times t), 70.32 (t), 167.83 (s), 168.23 (s), 168.55 (s). Selected HMBC correlations are between δ 3.08–3.18 and δ 57.81 (NCH); IR (neat) 3346, 2983, 1739, 1466, 1373, 1294, 1203, 1034 cm^{-1} ; MS (FAB) m/z 260 ($M + H^+$); HRMS (FAB) ($M + H^+$)⁺ 260.1150 (calcd for $C_{11}H_{18}NO_6$ ($M + H$) 260.1134).

Preparation of 23a (eqn 9)

To **22a** (105 mg, 0.27 mmol) was added trifluoroacetic acid (1.1 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 1 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography over silica gel eluting with CH_2Cl_2 –AcOEt (1 : 4) to give **23a** (61 mg, 82%).

Acknowledgements

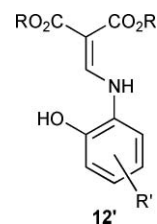
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- The aqueous workup described in the Experimental section gave only the major products usually.
- The products **7** and **20b** are somewhat unstable and the diastereomer ratios sometimes change on standing, possibly due to the reversibility of the amine elimination and addition. The product **5a** is always obtained as a single diastereomer. (a) G. Bartoli, M. Bartolacci, A. Giuliani, E. Marcantoni, M. Massaccesi and E. Torregiani, *J. Org. Chem.*, 2005, **70**, 169; (b) G. Bartoli, M. Bosco, E. Marcantoni, M. Petrini, L. Sambri and E. Torregiani, *J. Org. Chem.*, 2001, **66**, 9052; (c) F. Toda, H. Takumi, M. Nagami and K. Tanaka, *Heterocycles*, 1998, **47**, 467.
- In the reaction in eqn 5, byproducts **12'** were observed in small amounts. **12'a** ($R = Et/R' = H$, trace) and **12'g** ($R = CH_2Ph/R' = H$, 23%) were isolated and characterized. Formation of **12'** may arise from decarboxylation.



- The yields of condensation of **1a** and **17** vary sometimes, therefore the optimized conditions were used.
- Similar amine deprotection and subsequent cyclization was also reported: B. J. Turunen and G. I. Georg, *J. Am. Chem. Soc.*, 2006, **128**, 8702.
- There is 7.5 kcal/mol free energy difference between 1,3-cis and 1,3-trans stereoisomers of **5a** by B3LYP/6-31G* calculations. In comparison, the difference between 1,3-cis and trans isomers of **7** is 3.1 kcal/mol and that of **20b** is 4.5 kcal/mol.
- The cyclization of **24d** was attempted by treatment of **24d** with $ZnCl_2$ in CH_2Cl_2 . However, the reaction gave a complex mixture along with the recovered **24d**.
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