Efficient synthesis of heterocyclic compounds using ethenetricarboxylic acid diesters†

Shoko Yamazaki,* Yuko Iwata and Yugo Fukushima

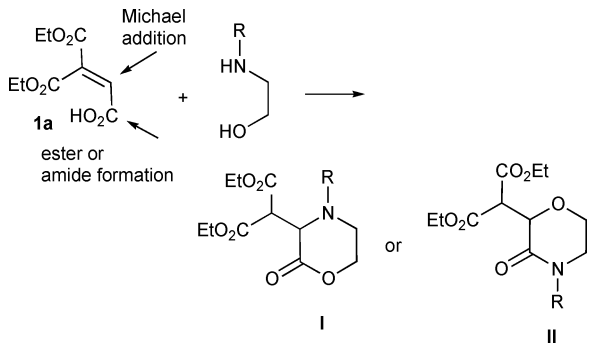
Received 24th October 2008, Accepted 24th November 2008
First published as an Advance Article on the web 8th January 2009
DOI: 10.1039/b818878e

Ethenetricarboxylic acid diester **1a** is a useful compound bearing two reactive sites, a CO_2H 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 CO_2H group and a Michael acceptor (Scheme 1).[5d,f] We envisioned that heterocycles 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.

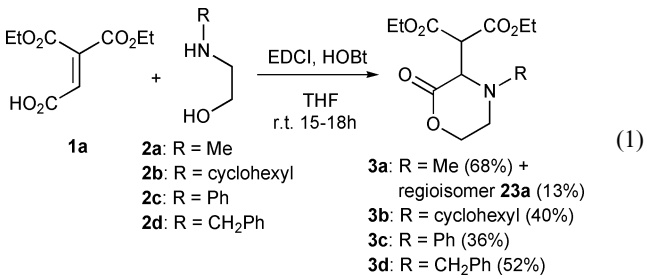


Scheme 1

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]



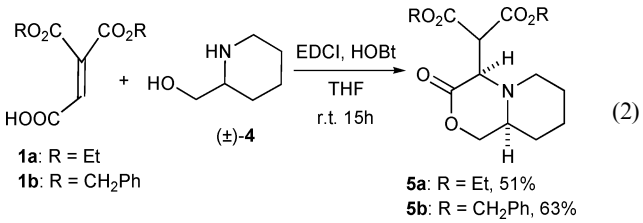
(1)

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

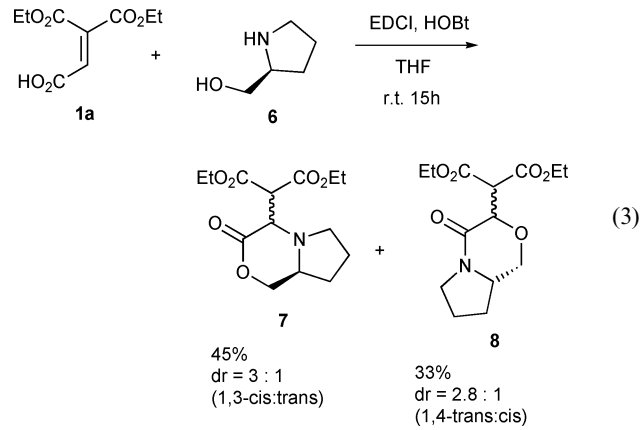
Department of Chemistry, Nara University of Education, Takabatake-cho, Nara 630-8528, Japan. E-mail: yamazaks@nara-edu.ac.jp
† Electronic supplementary information (ESI) available: Additional experimental procedures and spectral data. See DOI: 10.1039/b818878e

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 (~1660 cm^{-1}), which appears in the regioisomers, and NOE and HMBC correlations.

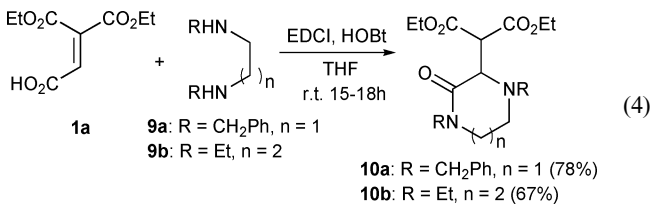


(2)



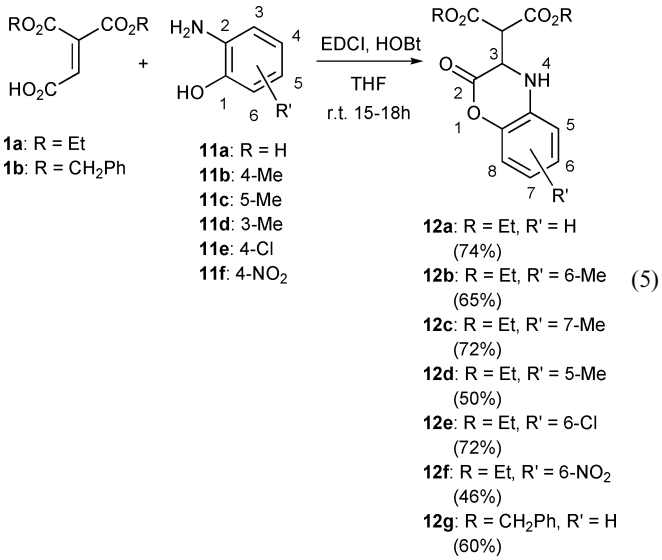
(3)

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-diazaheptane **10b** in good yields (eqn 4).



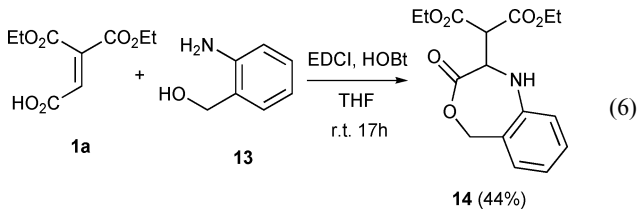
(4)

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.



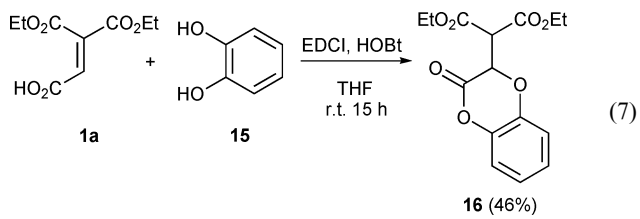
(5)

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).



(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).



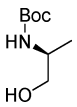
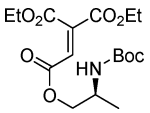
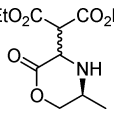
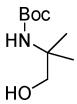
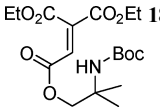
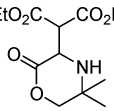
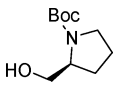
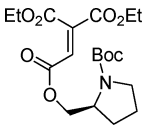
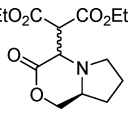
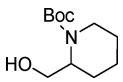
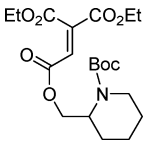
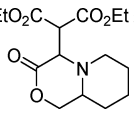
(7)

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.

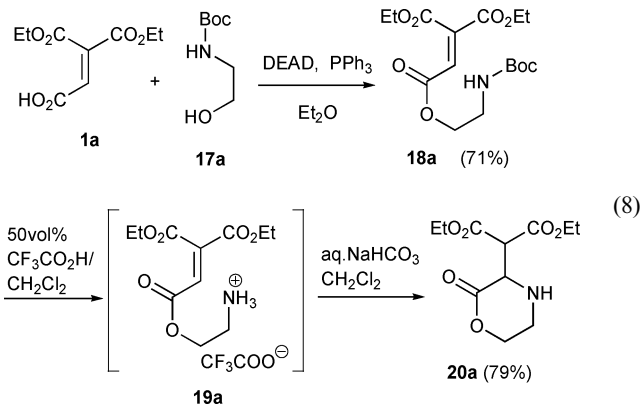
B. Stepwise cyclization *via* *N*-Boc aminoesters

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. $NaHCO_3$), 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.

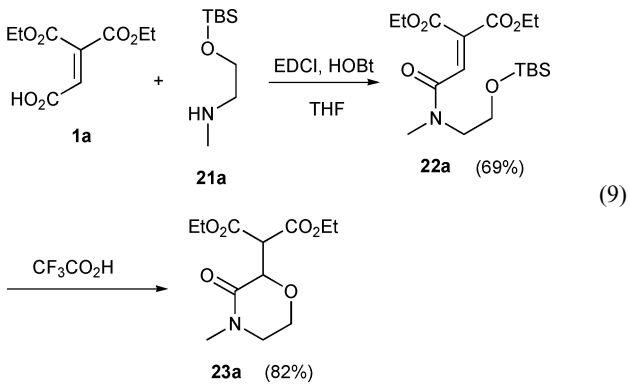
Table 1 Preparation of esters **18** and their cyclization reactions

Aminoalcohol **17**	Condensation method	*N*-Boc aminoester **18**	Yield	Product **20**	Yield
 **17b**	DEAD, PPh_3 Et_2O	 **18b**	71%	 **20b**	86% dr = 1.7:1~1:0[a] (1,3-cis:trans)[b]
 **17c**	EDCI, HOBt THF	 **18c**	50%	 **20c**	53%
 **17d**	DEAD, PPh_3 Et_2O	 **18d**	45%	 **7**	79% dr = 3:5 (1,3-cis:trans)[b]
 **17e**	EDCI, DMAP CH_2Cl_2	 **18e**	30%	 **5a**	78%

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



(8)



(9)

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 ($OSiMe_2{}^tBu$) 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]

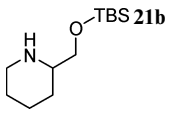
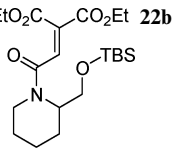
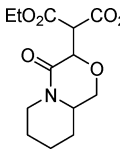
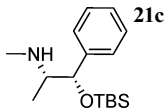
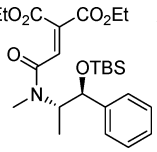
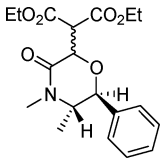
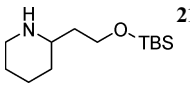
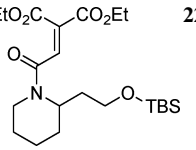
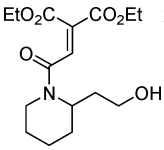
In summary, the reaction of ethenetricarboxylic acid diester **1** with secondary 2-aminoalcohols in the presence of EDCI and HOBt in one pot gave *N*,*O*-containing heterocyclic compounds regioselectively, with a preference for 1,4-addition of amines. The stepwise methods involving *N*-Boc protected 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 CF_3CO_2H)[5d] in THF (4 mL) were added HOBt (1-hydroxybenzotriazole) (135 mg,

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

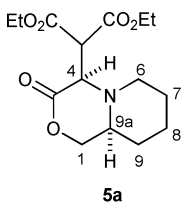
O-TBS amine **21**	*O*-TBS amide **22**	Yield	Deprotection method	Product **23**	Yield
 **21b**	 **22b**	55%	TFA TBAF	 **23b**	91% dr = 1.3:1 (1,4-trans:cis) 89% dr = 1:1
 **21c**	 **22c**	63%	TFA	 **23c**	89% dr = 3:1 (1,3-trans:cis)
 **21d**	 **22d**	45%	TFA	 **24d**	100%

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 CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, 2M aqueous citric acid, saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_4), 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%).

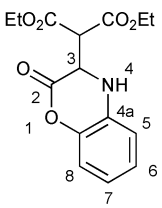
3a. R_f = 0.3 (ether); Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.30 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.31 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.43 (s, 3H, NCH_3), 2.72 (ddd, J = 12.8, 11.2, 2.9 Hz, 1H, NCHH), 2.90 (ddd, J = 12.8, 2.4, 2.4 Hz, 1H, NCHH), 3.64 (d, J = 3.8 Hz, 1H, NCH), 3.89 (d, J = 3.8 Hz, 1H, $CH(CO_2Et)_2$), 4.18–4.37 (m, 5H, CH_2CH_3, 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; ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 (NCH_2), 65.75 (NCH), and between δ 3.64 and δ 43.38 (NCH_3); 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 $C_{12}H_{19}NO_6$ 273.1212).

23a. R_f = 0.1 (ether); Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.28 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.29 (t, J = 7.0 Hz, 3H, CH_2CH_3), 3.01 (s, 3H, NCH_3), 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, $CH(CO_2Et)_2$), 4.19–4.29 (m, 4H, CH_2CH_3), 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; ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 $C_{12}H_{19}NO_6$ 273.1212).

5a. R_f = 0.5 (hexane : ether = 1 : 4); Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.11 (dddd, J = 12.8, 12.8, 11.2, 4.0 Hz, 1H, H_9), 1.25–1.39 (m, 1H, H_8), 1.29 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.31 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.47 (dddd, J = 13.2, 13.2, 3.8, 3.8 Hz, 1H, H_7), 1.57–1.62 (m, 1H, H_9), 1.67–1.72 (m, 1H, H_7), 1.78–1.82 (m, 1H, H_8), 2.09 (ddd, J = 11.7, 11.7, 2.5 Hz, 1H, H_6), 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, H_6), 3.66 (d, J = 3.8 Hz, 1H, H_4), 3.87 (d, J = 3.8 Hz, 1H, $CH(CO_2Et)_2$), 4.07 (dd, J = 10.8, 3.1 Hz, 1H, H_1), 4.12 (dd, J = 10.3, 10.3 Hz, 1H, H_1), 4.20–4.35 (m, 4H, CH_2CH_3). Selected NOEs are between δ 2.51 and δ 3.66; ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 (C_4), between δ 3.66 and δ 52.51 (C_6), 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 $C_{15}H_{23}NO_6$ 313.1525).



5a



12a

12a. R_f = 0.7 (hexane : ether = 1 : 4); Pale yellow crystals; mp 67–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.18 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.33 (t, J = 7.1 Hz, 3H, CH_2CH_3), 4.06–4.17 (m, 2H, CH_2CH_3), 4.23 (d, J = 4.4 Hz, 1H, $CH(CO_2Et)_2$), 4.25–4.37 (m, 2H, CH_2CH_3), 4.64 (d, J = 4.4 Hz, 1H, H_3), 4.94 (bs, 1H, H_4), 6.74–6.76 (m, 1H, H_5), 6.81 (td, J = 7.8, 1.5 Hz, 1H, H_7), 6.96–7.01 (m, 2H, $H_{6,8}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 × 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

This work was supported by the Ministry of Education, Culture, Sports, Science, and Technology of the Japanese Government. We thank Ms. A. Sumi, Ms. A. Matsubara and Mr. M. Matsubara (Nara University of Education) for experimental help. We thank Nara Institute of Science and Technology (NAIST) and Prof. K. Kakiuchi (NAIST) for mass spectra. We also thank Prof. S. Umetani (Kyoto University) for mass spectra and elemental analyses.

References

1 (*a*) A. E. A. Porter, *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky, and C. W. Rees, eds.; Pergamon Press, Oxford, 1984; Vol. 3, pp. 157–197; (*b*) M. Sainsburg, *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky, and C. W. Rees, eds.; Pergamon Press, Oxford, 1984; Vol. 3, pp. 995–1038; (*c*) J. T. Sharp, *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky, and C. W. Rees, eds.; Pergamon Press, Oxford, 1984; Vol. 7, pp. 593–651.

2 For some recent examples of biologically active 1,4-oxazine derivatives: (*a*) W. Yang, Y. Wang, Z. Ma, R. Golla, T. Stouch, R. Seethala, S. Johnson, R. Zhou, T. Güngör, J. H. M. Feyen and J. K. Dickson, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2327; (*b*) Y.-J. Wu, C. G. Boissard, J. Chen, W. Fitzpatrick, Q. Gao, V. K. Gribkoff, D. G. Harden, H. He, R. J. Knox, J. Natale, R. L. Pieschl, J. E. Starrett, Jr, L.-Q. Sun, M. Thompson, D. Weaver, D. Wu and S. I. Sworetzky, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1991; (*c*) K. Torisu, K. Kobayashi, M. Iwahashi, Y. Nakai, T. Onoda, T. Nagase, I. Sugimoto, Y. Okada, R. Matsumoto, F. Nanbu, S. Ohuchida, H. Nakai and M. Toda, *Bioorg. Med. Chem.*, 2004, **12**, 5361; (*d*) X. Chen, D. J. Kempf, L. Li, H. L. Sham, S. Vasavanonda, N. E. Wideburg, A. Saldivar, K. C. Marsh, E. MacDonald and D. W. Norbeck, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3657.

3 (*a*) Six-membered hetarenes with two unlike or more than two heteroatoms and fully unsaturated larger-ring heterocycles, *Science of Synthesis, Houben-Weyl Method of Molecular Transformation*, Vol. 17, S. M. Weinreb, ed. George Tieme, Sttutgart, 2004; (*b*) J. Ilaš, P. Š. Anderluh, M. S. Dolenc and D. Kikelj, *Tetrahedron*, 2005, **61**, 7325; (*c*) For recent examples of the synthesis of 1,4-oxazines, see: M. Vasylyev and H. Alper, *Org. Lett.*, 2008, **10**, 1357; (*d*) B. Gabriele, G. Salerno, L. Veltri, R. Mancuso, Z. Li, A. Crispini and A. Bellusci, *J. Org. Chem.*, 2006, **71**, 7895; (*e*) E. Claveau, I. Gillaizeau, J. Blu, A. Bruel and G. Coudert, *J. Org. Chem.*, 2007, **72**, 4832; (*f*) S.-C. Yang, H.-C. Lai and Y.-C. Tsai, *Tetrahedron Lett.*, 2004, **45**, 2693; (*g*) P. Stefanic, K. Turnsek and D. Kikelj, *Tetrahedron*, 2003, **59**, 7123.

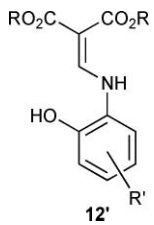
4 For examples: (*a*) Y. Fukudome, H. Naito, T. Hata and H. Urabe, *J. Am. Chem. Soc.*, 2008, **130**, 1820; (*b*) T. P. Zabawa and S. R. Chemler, *Org. Lett.*, 2007, **9**, 2035; (*c*) D. Xu, A. Chiaroni, M.-B. Fleury and M. Largeron, *J. Org. Chem.*, 2006, **71**, 6374; (*d*) C. S. Cho and S. G. Oh, *Tetrahedron Lett*, 2006, **47**, 5633; (*e*) C. O. Okafor and M. U. Akpuaka, *J. Chem. Soc. Perkin Trans. 1*, 1993, 159.

5 (*a*) S. Yamazaki, H. Kumagai, T. Takada and S. Yamabe, *J. Org. Chem.*, 1997, **62**, 2968; (*b*) S. Yamazaki, K. Yamada, S. Yamabe and K. Yamamoto, *J. Org. Chem.*, 2002, **67**, 2889; (*c*) S. Yamazaki, S. Morikawa, Y. Iwata, M. Yamamoto and K. Kuramoto, *Org. Biomol. Chem.*, 2004, **2**, 3134; (*d*) S. Yamazaki, K. Ohmitsu, K. Ohi, T. Otsubo and K. Moriyama, *Org. Lett.*, 2005, **7**, 759; (*e*) S. Yamazaki and Y. Iwata, *J. Org. Chem*, 2006, **71**, 739; (*f*) S. Yamazaki, M. Yamamoto and A. Sumi, *Tetrahedron*, 2007, **63**, 2320.

6 The aqueous workup described in the Experimental section gave only the major products usually.

7 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.

8 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.



12′

9 The yields of condensation of **1a** and **17** vary sometimes, therefore the optimized conditions were used.

10 Similar amine deprotection and subsequent cyclization was also reported: B. J. Turunen and G. I. Georg, *J. Am. Chem. Soc.*, 2006, **128**, 8702.

11 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.

12 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**.

13 (*a*) A. P. Krapcho, *Synthesis*, 1982, 805 and 893; (*b*) V. Wascholowski, K. R. Knudsen, C. E. T. Mitchell and S. V. Ley, *Chem. Eur. J.*, 2008, **14**, 6155.