Diastereoselective construction of azetidin-2-ones by electrochemical intramolecular C-C bond forming reaction

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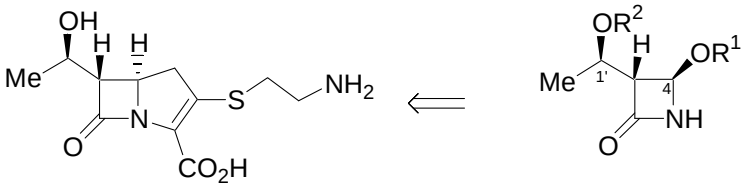
Abstract- A convenient method for synthesis of optically active azetidin-2-ones using electrochemical oxidation has been exploited. The method consists of a diastereoselective intramolecular C-C bond forming reaction between active methylene and methyne groups through an electrochemical system in which positive iodine species acted as mediators under mild conditions.

Keywords: azetidinone; electrochemical oxidation; diastereoselective; carbon-carbon bond forming reaction, cyclization

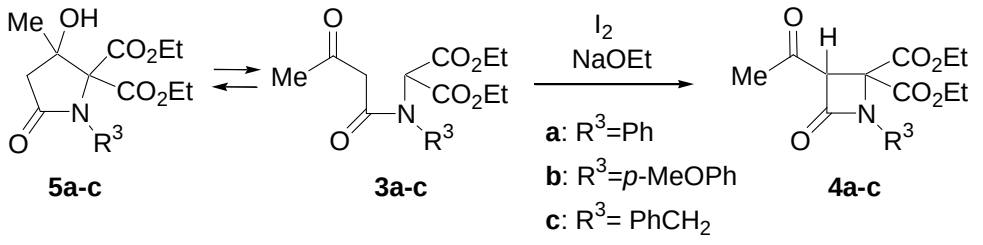
1. Introduction

Since the discovery of thienamycin (**1**),[1] a variety of synthetic methods of **1** and its precursors **2** have been exploited (Scheme 1).[2] However, new efficient synthetic methods are still of great interest because of economic reasons and the continuing need for novel β-lactamase inhibitors. In 1985, Simig and co-workers reported that the construction of *N*-protected azetidin-2-ones **4a-c** from *N*-arylated or *N*-benzylated *N*-(3-oxobutyryl)aminomalonate diethyl esters **3a-c**, which are equilibrated with pyrrolidine-2-ones **5a-c**, was achieved by I_2 in the presence of NaOEt (Eq. 1).[3]



1 thienamycin **2**

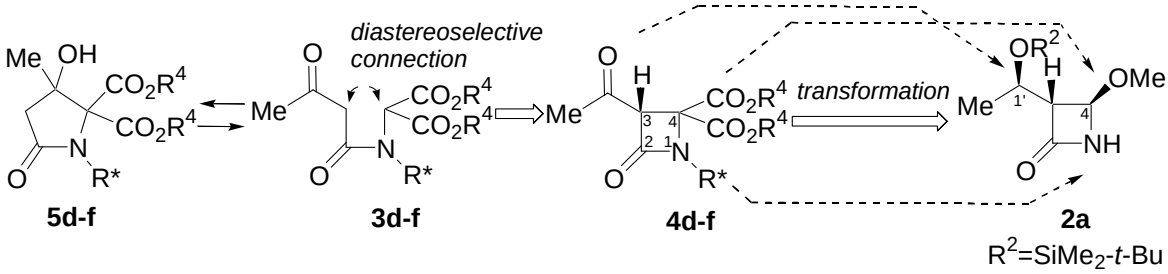
Scheme 1.



5a-c **3a-c** **4a-c** (1)

Although this reaction is very convenient for the construction of azetidin-2-one skeleton,

there has been no report for its chiral version. We report herein a convenient electrochemical diastereoselective construction of azetidin-2-ones **4d-f** possessing acetyl group at the 3-position and two alkoxylcarbonyl groups at the 4-position from easily available *N*-(3-oxobutyryl)aminomalonate esters **3d-f** possessing a chiral auxiliary on a nitrogen atom (Scheme 2). Scheme 2 also shows our strategy for the transformation of **4d-f** to enantiomerically pure 4-methoxy-3-(1'-silyloxyethyl)azetidin-2-one (**2a**)[4] which is an important key synthetic intermediate for **1**.



Scheme 2. Strategy for preparation of enantiomerically pure azetidin-2-one **4**.

2. Results and discussion

2.1 Preparation of chiral pyrrolidin-2-ones 5d-f

Pyrrolidin-2-ones **5d-f** were prepared in good to high yields using similar method for preparation of **5a-c** (Eq. 2).[3] The results are shown in Table 1.

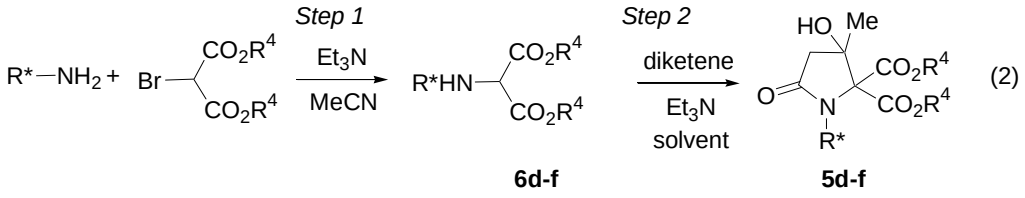
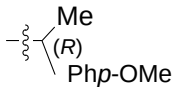


Table 1. Preparation of 2- pyrrolidinones **5d-g**.

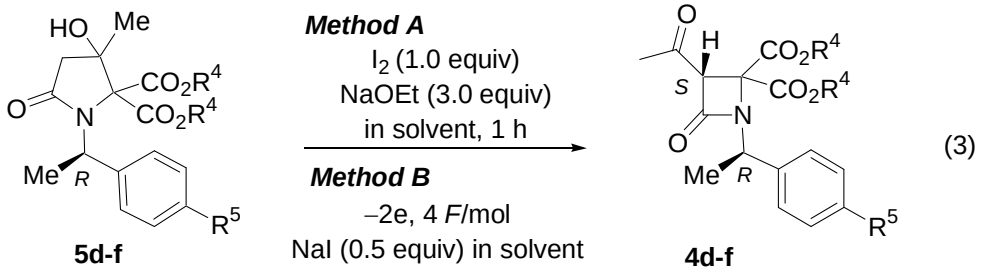
entry	R*	R^4	condition			yield (%)[b] of **6**		yield (%)[b] of **5**	
			Step 1	Step 2					
1		Et	rt	80 °C[a]	toluene	**6d**	79	**5d**	93
2		*t*-Bu	80 °C[a]	80 °C[a]	toluene	**6e**	83	**5e**	88

3		*t*-Bu	80 °C[a]	rt	CH_2Cl_2	**6f**	94	**5f**	87

[a] Temperature of bath. [b] Isolated yield.

2.2 Diastereoselective construction of azetidin-2-ones 4d-f

Chemical intramolecular C-C bond forming reaction of **5d-f** (Method A) and the corresponding electrochemical reaction (Method B) were examined under various conditions (Eq. 3). The results are summarized in Table 2.



(3)

Table 2. Diastereoselective cyclization of pyrrolidin-2-ones **5d-f**.

entry	Substrate	method[a]	conditions		product **4**		
			solvent	temp		yield (%)[b]	de (%)[c]
1	**5d**	**A**	EtOH	rt	**4d**	0	-
2	**5d**	**B**	EtOH	a.t.[d]	**4d**	23	58
3	**5d**	**A**	MeCN	rt	**4d**	0	-
4	**5d**	**B**	MeCN	a.t.[d]	**4d**	41	58
5	**5d**	**A**	EtOH	85 °C[e]	**4d**	30	48
6	**5d**	**B**	EtOH	85 °C[e]	**4d**	19	59
7	**5d**	**A**	MeCN	85 °C[e]	**4d**	12	48
8	**5d**	**B**	MeCN	85 °C[e]	**4d**	56	68
9	**5e**	**B**	MeCN	a.t.[d]	**4e**	33	79
10	**5e**	**B**	MeCN	85 °C[e]	**4e**	94	80
11	**5f**	**B**	MeCN	a.t.[d]	**4f**	67	70
12	**5f**	**B**	MeCN	85 °C[e]	**4f**	89	74

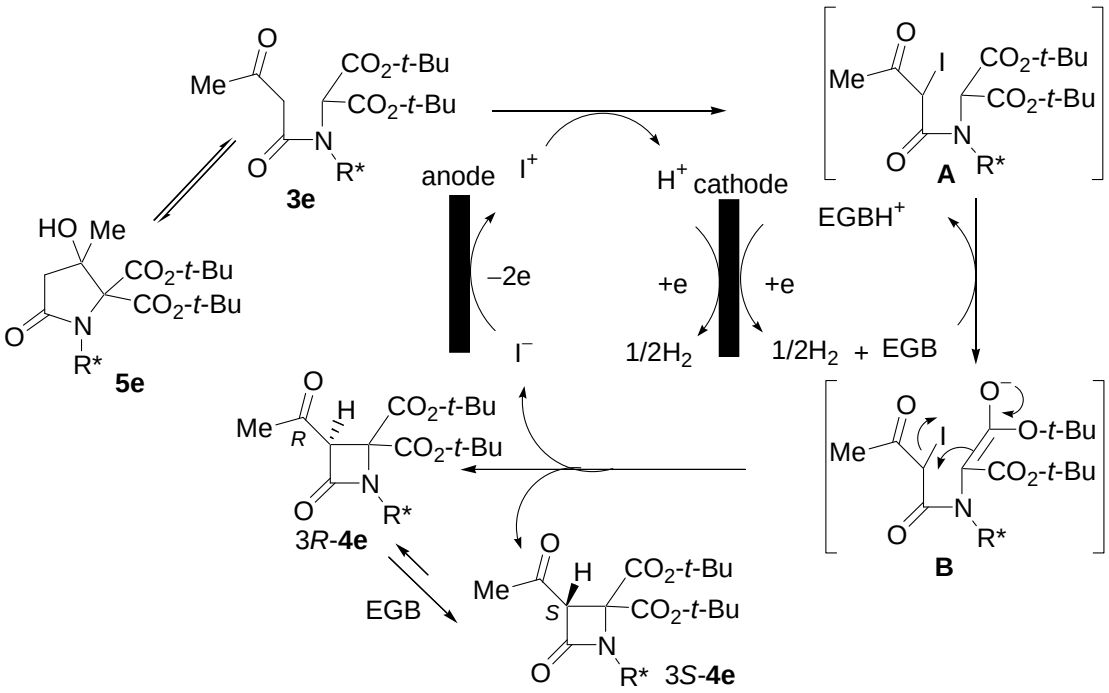
[a] Method A: A solution of **5** (0.5 mmol), I_2 (0.5 mmol), and NaOEt (1.5 mmol) in solvent (5 mL) was stirred for 1 h. Method B: 4 *F*/mol of electricity was passed through a solution of **5** (0.5 mmol) and NaI (0.5 mmol) in solvent (5 mL). [b] Isolated yield (%). [c] Determined by ^{1}H-NMR. [d] Ambient

temperature (The temperature of the reaction mixture gradually raised from rt to ca 50 ^{o}C as electricity was passed.). [e] Temperature of bath.

When chemical cyclization of diethyl ester **5d** was attempted in ethanol and acetonitrile at room temperature, azetidin-2-one **4d** was not obtained at all (entries 1 and 3), however increase of temperature to 85 ^{o}C lead to formation of **4d** in low yields with moderate diastereoselectivities (entries 5 and 7). On the other hand, electrochemical cyclization of **5d** at ambient temperature proceeded to afford **4d** in moderate yields (entries 2, 4, 9, and 11). Heat generated during electrochemical oxidation might affect the cyclization. Although the yield of **4d** by electrochemical cyclization of **5d** in ethanol was not improved at 85 ^{o}C compared with at ambient temperature (entries 2 and 6), in acetonitrile somewhat better yield was obtained than that at ambient temperature (entries 4 and 8). The best result was obtained in acetonitrile at 85 ^{o}C (entry 8). These optimized conditions were applicable to cyclization of di-*t*-butyl esters **5e** and **5f** to afford azetidin-2-ones **4e** and **4f** in high yields with good to high diastereoselectivities (entries 10 and 12). Recrystalization of **4e** from a mixture of diethyl ether and *n*-hexane (1/2 V/V) afforded 3*S*-**4e** as a single diastereoisomer.

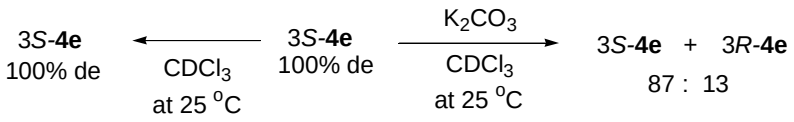
2.3. Reaction mechanism

Plausible reaction mechanism for electrochemical cyclization of **3e** is shown in Scheme 3. Briefly, anodically generated positive iodine species "I^{+}" react with **3e** to afford iodinated intermediate **A**,[5] which is transformed to enolate **B**[6] by cathodically generated base "EGB".[7] Finally cyclization of **B** affords thermodynamically stable 3*S*-**4e** diastereoselectively. The reason why electrochemical reaction in Table 2 shows higher yields and diastereoselectivity than the corresponding chemical reaction might be explainable by the characteristics of "EGB". Since "EGB" on cathode simultaneously generated along with "I^{+}" on anode in the electrochemical reaction, the electrochemical reaction holds almost neutral. On the other hand, the chemical reaction is always too basic. The strong basicity in the chemical reaction might lower the yield and daistereoselectivity of **4e**.



Scheme 3. Plausible reaction mechanism of electrochemical cyclization.

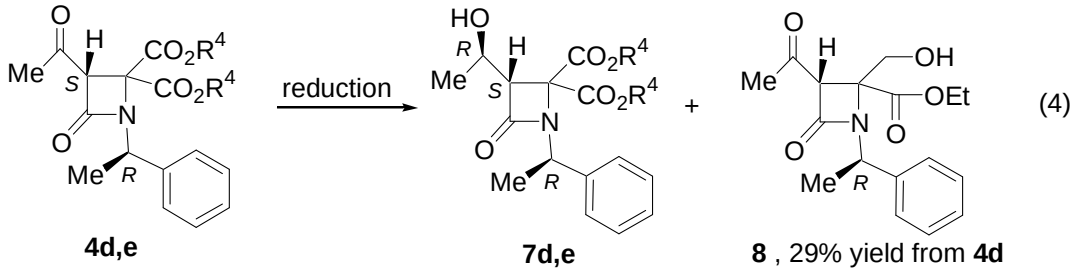
In fact, equilibration of 3*S*-**4e** and 3*R*-**4e** in the reaction conditions was confirmed by ^{1}H-NMR (Scheme 4). Although diastereomerically pure 3*S*-**4e** was not epimerized in $CDCl_3$, epimerization of 3*S*-**4e** in the presence of potassium carbonate was observed to reach to the equilibrium. Although we can not deny some effect of kinetic control on the diastereoselectivities in these cyclization, thermodynamic control could rationalize the diastereoselectivities.



Scheme 4. Equilibration of 3*S*-**4e** and 3*R*-**4e**.

2.4. Diastereoselective reduction

Diastereoselective reduction of acetyl group in **4d,e** was carried out under several reaction conditions (Eq. 4). The results are summarized in Table 3.



(4)

Although $NaBH_4$ majorly reduced ethoxycarbonyl group instead of acetyl group in diethyl ester **4d** to afford **8** (entry 1), $NaBH_4$ or DIBAH in THF reduced acetyl group in di-*t*-butyl ester **4e** to afford **7e** in good to high diastereoselectivity. Epimerization of **4e** at the 3-position was not observed under the reaction conditions.

Table 3. Diastereoselective reduction of 3-acetylazetidin-2-ones **4d**,**e**.

entry	substrate	reductant	condition		product **7**		
			solvent	temp		yield (%)[a]	de (%)[b]
1	**4d**	$NaBH_4$	MeOH	rt	**7d**	7	-
2	**4e**	$NaBH_4$	MeOH	rt	**7e**	89	12
3	**4e**	$NaBH_4$	THF	rt	**7e**	85	76
4	**4e**	$NaBH_4$	THF	–20 °C	**7e**	83	84
5	**4e**	DIBAH	THF	rt	**7e**	48	80
6	**4e**	DIBAH	THF	0 °C	**7e**	46	78

[a] Isolated yield (%). [b] Determined by ^{1}H-NMR.

2.5. Determination of absolute stereoconfiguration for 7e

Recrystalization of **7e** afforded 3*S*,1'*R*-**7e** as a single diastereoisomer, whose absolute stereoconfiguration was determined to be 1'*R* by X-ray analysis (Figure 1).[8]

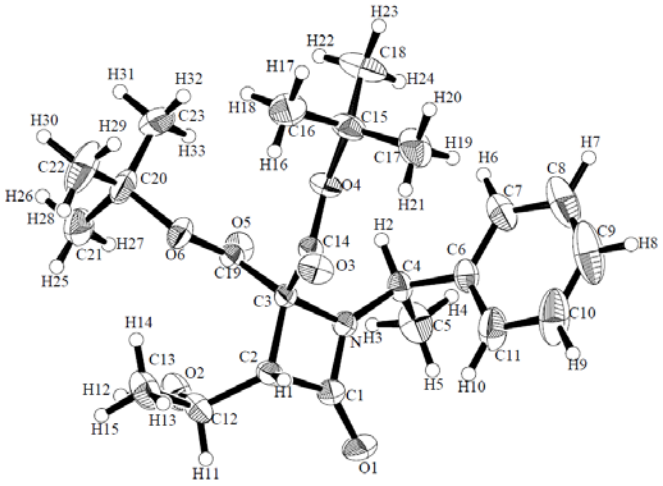


Figure 1. Absolute stereoconfiguration of **7e**.

As a result, It was deduced that major isomer of **4e** was 3*S*-**4e**.

2.6 Stereochemical course.

The diastereoselectivity might be explained by thermodynamical stability of 3*S*-**4e** compared with 3*R*-**4e**. Namely, when 1'*R*-phenylethyl group occupied the lower side of azetidine ring shown as (b) and (d) in Figure 2, there might be steric repulsion between *t*-butyl group and phenyl group. Additionally, steric repulsion between acetyl group and 1'*R*-phenylethyl group in 3*S*-**4e** might occurr ((b) in Figure 2). On the other hand, when 1'*R*-phenylethyl group occupied the upper side of azetidine ring ((a) and (c) in Figure 2), there might be steric repulsion between acetyl group and 1'*R*-phenylethyl group in 3*R*-**4e** ((c) in Figure 2). Accordingly, 3*S*-**4e** shown as (a) in Figure 2 is the most stable confomation. Also, bulkier di-*t*-butyl ester **4e** could be obtained with better diastereoselectivity than that of diethyl ester **4d**.

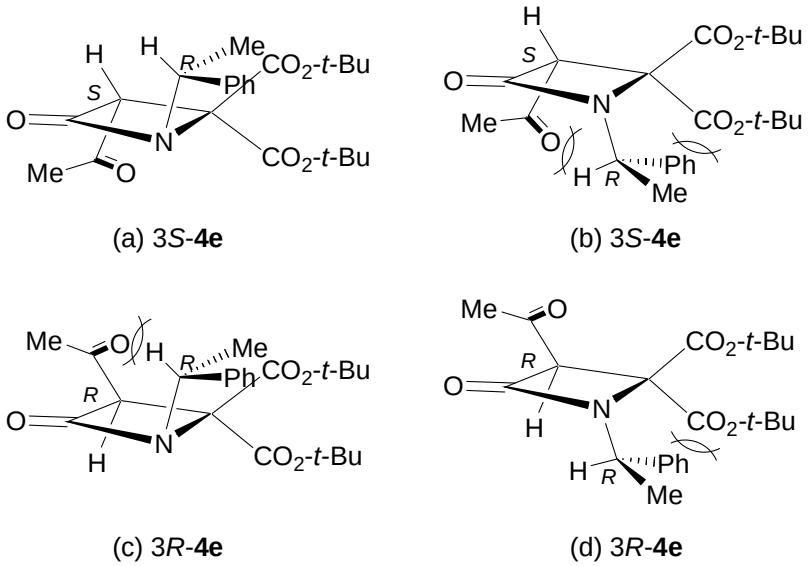
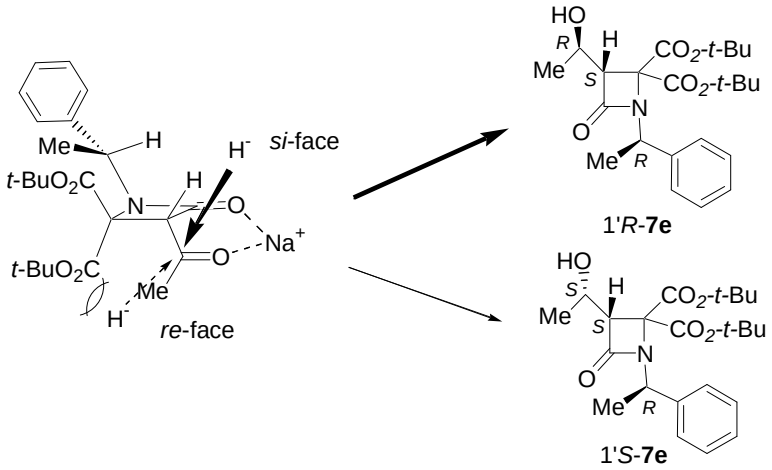


Figure 2. Steric hindrance of 3*S*-**4e** and 3*R*-**4e**.

Plausible stereochemical course for the $NaBH_4$ reduction of **4e** are shown in Scheme 5. Sodium ion chelates with the two carbonyl groups, due to this and also the steric repulsion on the *re*-face between the hydride ion and the *tert*-butyl group, the hydride attack therefore takes place on the *si*-face to afford 1'*R*-**7e** diastereoselectively. Higher diastereoselectivity in THF than MeOH seems to support chelation (entries 2 and 3 in Table 3).

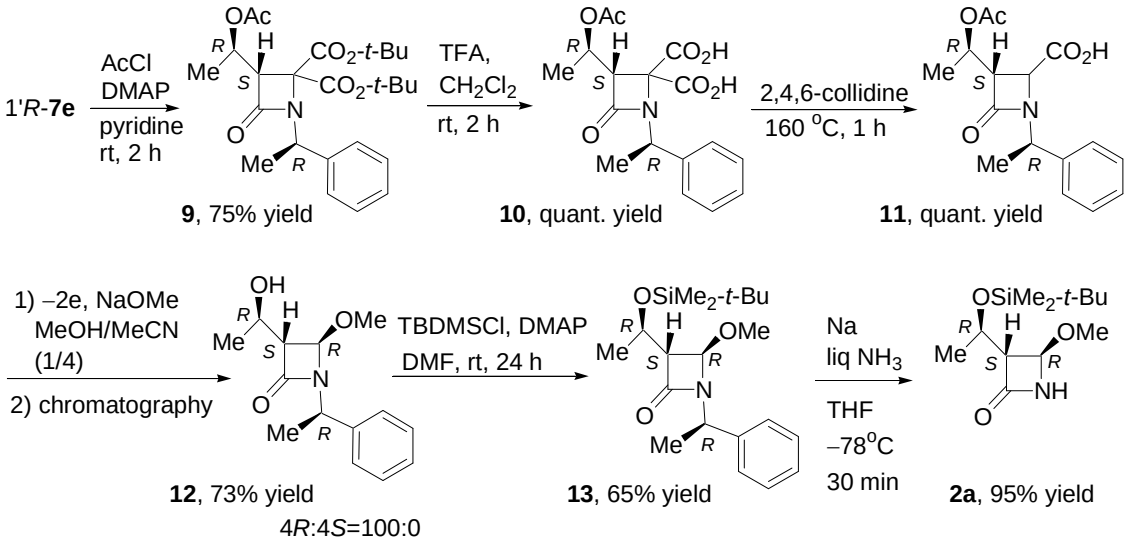


Scheme 5. Plausible stereochemical course for $NaBH_4$ reduction of 3*S*-**4e**.

2.7. Preparation of enantiomerically pure azetizin-2-one 2a from 1'*R*-7e

Enantiomerically pure 4-methoxy-3-(1'-silyloxyethyl)azetidin-2-one (**2a**) was prepared from 1'*R*-**7e** by procedure shown in Scheme 6. Namely, acetylation of 1'*R*-**7e**

afforded **9**, which was then subjected to acid catalyzed hydrolysis to give dicarboxylic acid **10** in quantitative yield. Decarboxylation of **10** afforded monocarboxylic acid **11**, which was then transformed into 4*R*-methoxylated azetidinone **12** in 73% yield by the non-Kolbe electrolysis.[9,10] Silylation of **12** and successive hydrogenolysis of chiral auxiliary of **13** afforded desired azetidinone **2a** as an enantiomerically pure form (Scheme 6).



Scheme 6. Preparation of azetidinone **2a** from 1'*R*-**7e**.

3. Conclusion

A convenient method for the synthesis of optically active azetidin-2-ones using electrochemical oxidation has been exploited. The method consists of diastereoselective intramolecular C-C bond forming reaction between active methylene and methyne groups by electrochemical mediator system in which positive iodine species act as mediators under mild conditions.

4. Experimental section

4.1. General.

Electrochemical reactions were carried out using DC Power Supply (GP 050-2) of Takasago Seisakusho, Inc. ^{1}H NMR spectra were measured on a Varian Gemini 300 and 400 spectrometer with TMS as an internal standard. ^{13}C NMR spectra were measured on a Varian Gemini 400 spectrometer with TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR-8100A. Elemental analyses were carried in Center for Instrumental Analysis, Nagasaki University. Mass spectra were obtained on a JEOL JMS-DX 303 instrument. Specific rotations were measured with Jasco

DIP-1000. All melting points were measured on MICRO MELTING POINT APPARATUS (Yanaco) and are uncorrected.

All solvents were used as supplied without further purification. Diethyl bromomalonate, 1*R*-phenylethylamine, and 1*R*-(4-methoxyphenyl)ethylamine are commercially available. Di-*t*-butyl bromomalonate was prepared from di-*t*-butyl malonate by known procedure.[11]

*4.2. Preparation of aminomalonate **6d-f**: general procedure;*

To a solution of 1*R*-phenylethylamine (3.05 g, 25 mmol) and Et_3N (2.53 g, 25 mmol) in acetonitrile (25 mL) was added diethyl bromomalonate (8.13 g, 34 mmol). After stirring for 6 h, to the resulting mixture was poured water (30 mL). Organic portion of aqueous layer was extracted with dichloromethane (3 x 25 mL) and washed with sat. aq. NaCl (25 mL). After drying the organic layer over $MgSO_4$, solvent was removed in vacuo, and residue purified by silica gel column chromatography (*n*-hexane : AcOEt = 10 : 1) to afford diethyl (1*R*-phenylethyl)aminomalonate (**6d**)[12] in 79 % yield.

Di-*tert*-butyl (1*R*-phenylethyl)aminomalonate (6e)

yellow oil; $[\alpha]_D^{28.3}$ +58.8 (c=1.0, $CHCl_3$); ^{1}H NMR (300MHz $CDCl_3$) δ 1.38 (d, *J*=6.6Hz, 3H), 1.42 (s, 9H), 1.47 (s, 9H), 2.37 (br s, NH), 3.69 (s, 1H), 3.79 (q, *J*=6.6Hz, 1H), 7.20-7.39 (m, 5H); IR (neat) 3350, 2978, 2932, 2342, 1750, 1734, 1475, 1493, 1475, 1455, 1395, 1140, 1007, 847, 702 cm^{-1}; HRMS (EI) Calcd for $C_{19}H_{28}NO_4$ (M^+) 335.2097, Found: 335.2095.

Di-*tert*-butyl [(1*R*-(4-methoxyphenyl)ethyl]aminomalonate (6f)

yellow oil; ^{1}H NMR (300MHz $CDCl_3$) δ 1.36 (d, *J*=6.6Hz, 3H) 1.42 (s, 9H), 1,47 (s, 9H), 2.38 (br s, NH), 3.75 (q, *J*=6.6Hz, 1H), 3.80 (s, 3H), 6.85 (d, *J*=8.7Hz, 2H), 7.25 (d, *J*=8.7Hz, 2H); IR(neat) cm^{-1}; HRMS (EI) Calcd for $C_{20}H_{31}NO_5$ (M^+) 365.2202, Found: 365.2214.

*4.3. Preparation of chiral pyrrolidin-2-ones **5d-f**: General Procedure*

To a solution of **6d** (5.59 g, 20 mmol) and Et_3N (2.02 g, 20 mmol) in toluene (30 mL) was slowly added dropwise diketene (1.7 mL, 22 mmol) at 0 ^oC. After the solution was stirred at 80 ^oC for 1h, the solvent was removed in vacuo at room temperature. The

residue was purified by silica gel column chromatography (*n*-hexane : AcOEt = 1 : 1) to afford diethyl 3-hydroxy-3-methyl-1-(1'*R*-phenylethyl) pyrrolidin-5-one-2,2-dicarboxylate (**5d**) in 93 % yield.

Diethyl 3-hydroxy-3-methyl-1-(1'*R*-phenylethyl) pyrrolidin-5-one-2,2-dicarboxylate (5d) (a mixture of two diastereomers)

white solid; mp 56-61 ^{o}C; ^{1}H NMR (400MHz $CDCl_3$) δ 0.93 and 0.99 (2t, *J*=7.3Hz, 3H), 1.27 and 1.31 (2t, *J*=7.3Hz, 3H), 1.49 and 1.50 (2s, 3H), 1.81 and 1.84 (2d, *J*=7.2Hz, 3H), 2.55-2.80 (m, 2H), 3.68-4.40 (m, 5H), 4.75 and 4.93 (2q, *J*=7.3Hz, 1H), 7.10-7.40 (m, 5H); IR (neat): 3400, 2984, 2940, 1736, 1707, 1686, 1410, 1269, 1231, 1079, 1098, 1053, 704 cm^{-1}; HRMS (EI) Calcd for $C_{19}H_{25}NO_6$ (M^+) 363.1682, Found: 363.1684.

Di-*tert*-butyl 3-hydroxy-3-methyl-1-(1'*R*-phenylethyl)pyrrolidin-5-one-2,2-dicarboxylate (5e) (a mixture of two diastereomers)

white solid; mp 153-160 ^{o}C; ^{1}H NMR (400MHz $CDCl_3$) δ 1.11 and 1.24 (2s, 9H), 1.41 and 1.51 (2s, 9H), 1.48 and 1.63 (2s, 3H), 1.81 and 1.84 (2d, *J*=7.3Hz, 3H), 2.52-2.74 (m, 2H), 3.54 and 4.03 (2s, 1H, OH), 4.76 and 5.02 (2q, *J*=7.3Hz, 1H), 7.15-7.40 (m, 5H); ^{13}C NMR (100MHz, $CDCl_3$) δ 19.2, 20.1, 23.5, 24.0, 27.3, 27.5, 27.8, 27.9, 46.1, 46.2, 54.5, 55.7, 76.5, 80.0, 84.0, 84.1, 84.5, 84.7, 126.2, 126.3, 126.4, 126.6, 128.1, 142.2, 142.4, 166.3, 166.6, 166.7, 167.1, 174.0, 174.1; IR(neat): 3400, 2980, 2938, 1730, 1692, 1395, 1302, 1250, 1157, 1024, 754, 696 cm^{-1}; Anal. Calcd for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N 3.34. Found: C, 66.25; H, 8.14; N 3.33.

Di-*tert*-butyl 3-hydroxy-1-[1'*R*-(4-methoxyphenyl)ethyl]-3-methylpyrrolidin-5-one-2,2-dicarboxylate (5f) (a mixture of two diastereomers)

white solid; mp 186-187 ^{o}C; ^{1}H NMR (400MHz $CDCl_3$) δ 1.19 and 1.30 (2s, 9H), 1.47 and 1.53 (2s, 9H), 1.51 and 1.60 (2d, *J*=3.0Hz, 3H), 1.80 and 1.82 (2d, *J*=6.8Hz, 3H), 2.55-2.72 (m, 2H), 3.52 and 3.90 (2s, 1H, OH), 3.74 and 3.75 (2s, 3H), 4.74 and 4.94 (2q, *J*=6.8Hz, 1H), 6.75-6.85 (m, 2H), 7.22 and 7.31 (2d, *J*=8.8Hz, 2H); ^{13}C NMR (100MHz $CDCl_3$) δ 19.4, 20.0, 23.6, 23.9, 27.4, 27.6, 27.9, 28.0, 46.2, 46.3, 54.2, 55.1, 55.2, 76.5, 76.6, 80.0, 80.2, 84.0, 84.1, 84.5, 84.6, 113.4, 113.5, 127.5, 128.0, 134.4, 134.6, 158.1, 158.3, 166.2, 166.6, 166.9, 167.0, 173.9, 174.0; IR (neat): 3400, 2980, 2038, 1750, 1732, 1720, 1700, 1868, 1615, 1559, 1514, 1474, 1395, 1370, 1339,

1302, 1248, 1156, 1030, 910, 831, 735 cm^{-1}; HRMS (EI) Calcd for $C_{24}H_{35}NO_7$ (M^+) 449.2414, Found: 449.2400.

*4.4. Preparation of chiral azetidin-2-ones **4d-f**:*

4.4.1. Typical Procedure for chemical method A (entry 5 in Table 2);

To a solution of **5d** (182 mg, 0.5 mmol) in ethanol (5 mL) was added I_2 (127 mg, 0.5 mmol) and Na (35 mg, 1.5 mmol). After stirring for 1 h at 85 ^oC, to the reaction mixture was added AcOEt (30 mL). The resulting solution was washed with 5% $Na_2S_2O_3$ (3 × 10 mL) and sat. aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to silica gel columun chromatography (*n*-hexane : AcOEt =1 : 1) to afford 3*S*-**4d** in 30% yield with 48% de.

4.4.2. Typical Procedure for electrochemical method B (entry 10 in Table 2);

In an undivided cell equipped with platinum plate electrodes (1 x 2 cm^2) was placed a solution of **5e** (210 mg, 0.5 mmol) and NaI (75 mg, 0.5 mmol) in acetonitrile (5 mL). A constant current (100 mA) was passed through the cell externally warmed in oil-bath (85 ^oC). After 4 *F*/mol of electricity was passed, to the reaction mixture was added AcOEt (30 mL). The resulting solution was washed with 5% $Na_2S_2O_3$ (3 × 10 mL) and sat. aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to silica gel columun chromatography (*n*-hexane : AcOEt =1 : 1) to afford 3*S*-**4e** in 94% yield with 80% de, which was recrystalized from a mixture of diethyl ether and *n*-hexane (1/2 V/V) to give enantiomerically pure 3*S*-**4e**.

Diethyl 3*S*-acetyl-1-(1'*R*-phenylethyl)azetidin-2-one-4,4-dicarboxylate (4d) (3*S*:3*R* = 74:26)

yellow oil; ^1H NMR (300MHz $CDCl_3$) δ 0.94 (t, *J*=7.2Hz, 2.22H), 1.06 (t, *J*=7.2Hz, 0.78H), 1.32 (t, *J*=7.2Hz, 3H), 1.74 (d, *J*=7.2Hz, 0.78H), 1.87 (d, *J*=7.2 Hz, 2.22H), 2.31 (s, 0.78H), 2.35 (s, 2.22H), 3.47-3.62 (m, 0.74H), 3.78-3.90 (m, 0.74H), 3.90-4.02 (m, 0.26H), 4.03-4.15 (m, 0.26H), 4.15-4.45 (m, 2H), 4.57-4.70 (m, 0.74H), 4.75-4.85 (m, 0.26H), 4.68 (s, 0.26H), 4.84 (s, 0.74H), 7.20-7.45 (m, 5H); IR (neat): 2984, 2938, 1779, 1455, 1393, 1300, 1280, 1240,1180, 1096, 1057, 1028, 903, 860, 762, 702 cm^{-1}; HRMS (EI) Calcd for $C_{19}H_{23}NO_6$ (M^+) 361.1525, Found: 361.1525.

Di-*tert*-butyl 3*S*-acetyl-1-(1'*R*-phenylethyl)azetidin-2-one-4,4-dicarboxylate (4e)

white solid; mp 140-142 °C; $[\alpha]_D^{26.2}$ –6.1 (c=1.0, $CHCl_3$); ^{1}H NMR (300MHz $CDCl_3$) δ 1.07 (s, 9H), 1.55 (s, 9H), 1.85 (d, *J*=7.2Hz, 3H), 2.35 (s, 3H), 4.66 (q, *J*=7.2 Hz, 1H), 4.86 (s, 1H), 7.18-7.40 (m, 5H); ^{13}C NMR (100MHz, $CDCl_3$) δ 22.8, 27.0, 27.8, 30.4, 57.0, 66.5, 67.2, 83.8, 83.9, 125.9, 127.2, 128.7, 143.0, 162.7, 164.9, 165.3, 197.8; IR (neat): 2980, 2930, 1765, 1718, 1495, 1394, 1371, 1001, 970, 900, 851, 764, 702 cm^{-1}; Anal. Calcd for $C_{23}H_{31}NO_6$: C, 66.17; H, 7.48; N, 3.35. Found: C, 65.79; H, 7.62; N, 3.31.

Di-*tert*-butyl 3*S*-acetyl-1-[1'*R*-(4-methoxyphenyl)ethyl]azetidin-2-one-4,4-dicarboxylate (4f)

white solid; mp 107 °C; $[\alpha]_D^{23.8}$ +3.0 (c=1.0, $CHCl_3$); ^{1}H NMR (300MHz $CDCl_3$) δ 1.13 (s, 9H), 1.54 (s, 9H), 1.82 (d, *J*=7.2Hz, 3H), 2.34 (s, 3H), 3.78 (s, 3H) 4.62 (q, *J*=7.2 Hz, 1H), 4.82 (s, 1H), 6.84 (d, *J*=8.7Hz, 2H), 7.22 (d, *J*=8.7Hz, 2H); IR (neat): 2980, 2936, 1771, 1734, 1615, 1559, 1541, 1514, 1474, 1395, 1370, 1302, 1248, 1159, 1032, 831 cm^{-1}; HRMS (EI) Calcd for $C_{24}H_{33}NO_7$ (M^+): 447.2257, Found: 447.2268.

*4.5. Diastereoselective reduction of 3S-**4e:***

To a solution of 3*S*-**4e** (100 mg, 0.24 mmol) in tetrahydrofuran (3 mL) was added $NaBH_4$ (18 mg, 0.48 mmol). After stirring for 4 h at –20 °C, to the reaction mixture was added AcOEt (30 mL). The resulting solution was washed with water (20 mL) and sat. aqueous NaCl (20 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to silica gel columun chromatography (*n*-hexane : AcOEt =1 : 1) to afford 1'*R*-**7e** in 83% yield with 84% de, which was recrystalized from diethyl ether to give enantiomerically pure 1'*R*-**7e**.

3*S*-(1'*R*-Hydroxyethyl)-1-(1'*R*-phenylethyl)azetidin-2-one-4,4-dicarboxylic acid di-*tert*-butyl ester (7e)

white solid; mp 151-153 °C; $[\alpha]_D^{26.2}$ +19.7 (c=1.0, $CHCl_3$); ^{1}H NMR (300MHz $CDCl_3$) δ 1.10 (s, 9H), 1.43 (d, *J*=3.0Hz, 3H), 1.58 (s, 9H), 1.85 (d, *J*=5.4Hz, 3H), 2.57 (d, *J*=2.4Hz, 1H), 3.78 (d, *J*=6.9Hz, 1H), 4.00-4.07 (m, 1H), 4.58 (q, *J*=5.4Hz, 1H), 7.18-7.30 (m, 5H); IR (neat): 3500, 2980, 2936, 1759, 1736, 1495, 1456, 1395, 1370, 1343, 1250, 1156, 835, 758, 700 cm^{-1}; HRMS (EI) Calcd for $C_{23}H_{33}NO_6$: C, 65.85; H,

7.93; N, 3.34. Found: C, 66.20; H, 8.07; N, 3.35.

*4.6. Acetylation of 1'R-**7e:***

To a solution of 1'*R*-**7e** (420 mg, 1.0 mmol) and 4-dimethylaminopyridine (12 mg, 0.1 mmol) in pyridine (5 mL) was added dropwise acetyl chloride (236 mg, 3 mmol). After stirring for 2 h at rt, to the reaction mixture was added AcOEt (50 mL). The resulting solution was washed with 3% HCl (3 x 25 mL) and sat. aqueous NaCl (25 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to silica gel columun chromatography (*n*-hexane : AcOEt =3 : 1) to afford **9** in 75% yield.

Di-*tert*-butyl 3*S*-(1'*R*-acetoxyethyl)-1-(1'*R*-phenylethyl)azetidin-2-one-4,4-dicarboxylate (9)

white solid; mp 78-81 ^{o}C; $[\alpha]_D^{27.4}$ +25.4 (c=0.9, $CHCl_3$); ^{1}H NMR(300MHz $CDCl_3$) δ 1.08 (s, 9H), 1.46 (d, *J*=6.6Hz, 3H), 1.53 (s, 9H), 1.86 (d, *J*=7.2Hz, 3H), 2.03 (s, 3H), 4.01 (d, *J*=6.6Hz, 1H), 4.57 (q, *J*=7.2Hz, 1H), 5.23 (q, *J*=6.6Hz, 1H), 7.15-7.35 (m, 5H); IR (neat): 2980, 2934, 2380, 1769, 1740, 1495, 1456, 1395, 1456, 1395, 1341, 1244, 1159, 1144, 1115, 1065, 1048, 905, 849, 834, 760, 733, 700 cm^{-1}; Anal. Calcd for $C_{25}H_{35}NO_7$: C, 65.06; H, 7.64; N, 3.03. Found: C, 64.95; H, 7.40; N, 2.90.

*4.7. Preparation of dicaroboxylic acid (**10**):*

To a solution of **9** (462 mg, 1.0 mmol) in dichloromethane (4 mL) was slowly added trifluoroacetic acid (3.7 mL, 50 mmol). After stirring for 2 h at rt, concentration of the reaction mixture under reduced pressure afforded **10** in quantitative yield.

3*S*-(1'*R*-Acetoxyethyl)-1-(1'*R*-phenylethyl)azetidin-2-one-4,4-dicarboxylic acid (10)

white solid; mp 132-136 ^{o}C; $[\alpha]_D^{28.0}$ +25.3 (c=1.0, $CHCl_3$); ^{1}H NMR (300MHz $CDCl_3$) δ 1.46 (d, *J*=6.0Hz, 3H), 1.83 (d, *J*=7.2Hz, 3H), 2.02 (s, 3H), 3.90 (d, *J*=10.8Hz, 1H), 4.63 (q, *J*=7.2Hz, 1H), 5.45 (dq, *J*=6.0Hz, *J*=10.8Hz, 1H), 7.20-7.40 (m, 5H), 8.55 (m, 2H); IR (neat): 3500, 2984, 2359, 1750, 1541, 1497, 1456, 1375, 1260, 1180, 1160, 1063, 1050, 1028, 963, 912, 760, 700 cm^{-1}; HRMS (EI) Calcd for $C_{17}H_{19}NO_7$ (M^+): 349.1162, Found: 349.1135.

*4.8. Preparation of monocarboxylic acid (**11**):*

To a solution of **10** (349 mg, 1.0 mmol) in 2,4,6-collidine (2 mL) was heated at 160

^{o}C with oil-bath. After heating for 1 h, to the reaction mixture was added AcOEt (10 mL). The resulting carboxylate ion was collected with sat. $NaHCO_3$ (3 x 10mL). Combined aqueous layer was acidified with 5% HCl. The carboxylic acid was extracted with AcOEt (3 x 20 mL). The resulting organic layer washed with sat. aqueous NaCl (25 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford **11** in quantitative yield.

3*S*-(1'*R*-Acetoxyethyl)-1-(1'*R*-phenylethyl)azetidin-2-one- 4*R*-carboxylic acid (11)
(4*R*:4*S*=72:28)

white solid; mp 86-90 ^{o}C; ^{1}H NMR (300MHz $CDCl_3$) δ 1.30 (d, *J*=6.3Hz, 0.84H), 1.42 (d, *J*=6.3Hz, 2.16H), 1.60 (d, *J*=6.9Hz, 0.84H), 1.80 (d, *J*=6.9Hz, 2.16H), 1.89 (s, 0.84H), 1.95 (s, 2.16H), 3.26 (dd, *J*=1.8Hz, *J*=10.5Hz, 0.28H), 3.55 (dd, *J*=5.4Hz, *J*=10.5Hz, 0.72H), 3.94 (d, *J*=1.8Hz, 0.28H), 4.07 (d, *J*=5.4H, 0.72H), 4.53 (q, *J*=7.2H, 0.72H), 5.57 (q, *J*=7.2Hz, 0.28H), 5.18-5.34 (m, 1H), 7.26-7.40 (m, 5H) , 7.60-7.90 (m, 1H); IR(neat): 3500, 2982, 1748, 1638, 1541, 1497, 1456, 1379, 1242, 1200, 1142, 1050, 953, 924, 853, 799, 766, 722 cm^{-1} ; HRMS (EI) Calcd for $C_{16}H_{19}NO_5$ (M^+): 305.1263, Found: 305.1277.

*4.9. Decarboxylative methoxylation of **11**:*

In an undivided cell equipped with platinum plate electrodes (1 x 2 cm^2) was placed a solution of **11** (101 mg, 0.33 mmol) and NaOMe (54 mg, 1 mmol) in a mixture of acetonitrile (4 mL) and methanol (1 mL). A constant current (50 mA) was passed through the cell externally cooled with water-bath. After 2 *F*/mol of electricity was passed, to the reaction mixture was added AcOEt (30 mL). The resulting solution was washed with sat. aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to silica gel columun chromatography (*n*-hexane : AcOEt =2 : 1) to afford **12** as a single diastereomer in 73% yield.

4*R*-Methoxy-3*R*-(1'*R*-hydroxylethyl)-1-(1'*R*-phenylethyl)azetidin-2-one (12)

colorless oil; ^{1}H NMR (400MHz $CDCl_3$) δ 1.27 (d, *J*=6.4Hz, 3H), 1.63 (d, *J*=7.3Hz, 3H), 1.80-2.50 (m, 1H), 2.99 (dd, *J*=3.6Hz, *J*=5.4Hz, 1H), 3.24 (s, 3H), 4.08 (dq, *J*=5.4Hz, *J*=6.4Hz, 1H), 4.73 (d, *J*=1.0Hz, 1H), 4.93 (q, *J*=7.3Hz, 1H), 7.26-7.36 (m, 5H); ^{13}C NMR (100MHz $CDCl_3$) δ 19.4, 21.5, 51.4, 54.2, 62.7, 64.0, 84.5, 127.2, 127.7, 128.6, 139.8, 166.5; IR(neat): 3420, 3032, 2975, 2936, 2836, 1740, 1495, 1455, 1395,

1374, 1206, 1184, 1140, 1098, 1028, 997, 951, 864, 766, 700 cm^{-1}; HRMS Calcd for $C_{14}H_{19}NO_3$: 249.1365, Found: 249.1354.

*4.10. Silylation of **12**:*

To a solution of **12** (60 mg, 0.24 mmol) and 4-dimethylaminopyridine (88 mg, 0.72 mmol) in *N*,*N*-dimethylformamide (1 mL) was added *tert*-butyldimethylsilyl chloride (109 mg, 0.72 mmol). After stirring for 24 h at rt, to the reaction mixture was added AcOEt (30 mL). The resulting solution was washed with water (10 mL) and sat. aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected on silica gel columun chromatography (*n*-hexane : AcOEt =5 : 1) to afford **13** in 65% yield.

4*R*-Methoxy-3*R*-[1'*R*-(*tert*-butyldimethylsilyloxy)ethyl]-1-(1'*R*-phenylethyl)azetidin-2-one (13)

colorless oil; ^{1}H NMR (400MHz $CDCl_3$) δ –0.02 (s, 3H), 0.02 (s, 3H), 0.80 (s, 9H), 1.21 (d, *J*=6.4Hz, 3H), 1.63 (d, *J*=7.3Hz, 3H), 2.90 (dd, *J*=0.6Hz, *J*=4.9Hz, 1H), 3.20 (s, 3H), 4.05 (dq, *J*=4.9Hz, *J*=6.4Hz, 1H), 4.71 (d, *J*=0.6Hz, 1H), 4.86 (q, *J*=7.3Hz, 1H), 7.26-7.39 (m, 5H); ^{13}C-NMR (100MHz $CDCl_3$) δ –4.7, –4.7, 17.9, 20.0, 22.7, 25.7, 51.7, 54.1, 63.2, 64.4, 84.7, 127.3, 127.6, 128.6, 139.9, 166.2; IR(neat): 3033, 2955, 2930, 2897, 2857, 1765, 1495, 1472, 1389, 1250, 1204, 1183, 1150, 1100, 1040, 1028, 1005, 934, 853, 812, 777, 700 cm^{-1}; HRMS (EI) Calcd for $C_{20}H_{33}NO_3$ (M^+): 363.2230, Found: 363.2199.

*4.11. Removal of N-protecting group of **13**:*

To anhydrous liq. ammonia (2 mL) was added Na (18 mg, 0.78 mmol) at –78 °C. Successively, a solution of **13** (47 mg, 0.13 mmol) in tetrahydrofuran (2 mL) was added to the ammonia. After stirring for 1 h at –78 °C, to the reaction mixture was added sat. aqueous NaCl (10mL). The organic portion was extracted with AcOEt (3 x 10 mL). The resulting organic layer was washed with sat. aqueous NaCl (25 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to silica gel columun chromatography (*n*-hexane : AcOEt =2 : 1) to afford **2a**[4] in 95% yield.

4*R*-Methoxy-3*R*-[1'*R*-(*tert*-butyldimethylsilyloxy)ethyl]azetidin-2-one (2a)

colorless crystal; mp 56-58 °C; $[\alpha]_D^{27.0}$ –28.9 (c=1.4, $CHCl_3$); ^{1}H NMR (400MHz

$CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.26 (d, *J*=6.4Hz, 3H), 3.00 (dd, *J*=1.0Hz, *J*=4.9Hz, 1H), 3.37 (s, 3H), 4.17 (dq, *J*=4.9Hz, *J*=6.4Hz, 1H), 5.00 (d, *J*=1.0Hz, 1H), 6.53 (s, 1H); ^{13}C NMR (100MHz $CDCl_3$) δ –5.1, –4.3, 17.9, 22.5, 25.7, 25.7, 54.9, 64.2, 65.2, 81.5, 167.7.

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References and notes

1. A representative reviews, see: (a) Kametani, T.; Ihara, M. *Yuki Gosei Kagaku Kyokaishi* **1980**, *52*, 1025–1036. (b) Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729-806. (c) Berks, A. H. *Tetrahedron,* **1996**, *52*, 331–375.
2. (a) Noyori, R.; Ikeda, T.; Ohkuma, T, Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Asito. T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc*. **1989**, *111*, 9134–9135. (b) Murahashi, S.-I.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc*. **1990**, *112*, 7820–7822. (c) Kita, Y.; Shibata, N.; Miki, T.; Takemura, Y.; Tamura, O. *J. Chem. Soc., Chem. Comm.* **1990**, 727–729. (d) Nagao, Y.; Nagase, Y.; Kumagai, T.; Mastunaga, H.; Abe, T.; Shimada, O.; Hayashi, T.; Inoue, Y. *J. Org. Chem*. **1992**, *57*, 4243–4249. (e) Lynch, J. E.; Laswell, W. L.; Volante, R. P.; Reamer, R. A.; Tschaen, D. M.; Shinkai, I. *Heterocycles* **1993**, *35*, 1029-37 (f) Cozzi, F.; Annunziata, R.; Cinquini, M.; Poletti, L.; Perboni, A.; Tamburini, B. *Chirality* **1998**, *10*, 91-94. (g) Cainelli, G.; Galletti, P.; Giacomini, D. *Tetrahedron Lett.* **1998**, *39*, 7779-7782. (h) Tatsuta, K.; Takahashi, M.; Tanaka, N.; Chikauchi, K. *J. Antibiot*. **2000**, *53*, 1231-1234. (i) Laurent, M.; Cérésiat, M.; Marchand-Brynaert, J. *J. Org. Chem.* **2004**, *69*, 3194–3197; (j) Laurent, M.; Cérésiat, M.; Marchand-Brynaert, J.*Eur. J. Org. Chem.* **2006**, 3755-3766. (k) Singh, S. K.; Singh, G. B.; Byri, V. K.; Satish, B.; Dhamjewar, R.; Gopalan, B. *Syn. Commun.* **2008**, *38*, 456-464. (l) Kuroboshi, M.; Miyada, M.; Tateyama, S.; Tanaka, H. *Heterocycles* **2008**, *76*, 1471–1484.
3. Simig, G.; Doleschall, G.; Hornyák, G.; Fetter, J.; Lempert, K.; Nyitrai, J.; Huszthy, P.; Gizur, T.; Kájtar-Peredy, M. *Tetrahedron* **1985**, *41*, 479–484.
4. (a) Kita, Y.; Shibata, N.; Yoshida, N.; Tohjo, T. *Chem. Pharm. Bull*. **1992**, *40*, 1044–1046; (b) Kita, Y.; Shibata, N.; Yoshida, N.; Kawano, M.; Matsumoto, K. *J.*

Org. Chem. **1994**, *59*, 938–939.

5. (a) Shiozaki, M.; Ishida, N.; Maruyama, H.; Hiraoka, T. *Tetrahedron* **1983**, *39*, 2399–2407. (b) Sánta, Z.; Párkányi, L.; Németh, I.; Nagy, J.; Nyitrai, J. *Tetrahedron: Asymmetry* **2001**, *12*, 89–94.
6. (a) Carelli, I.; Insei, A.; Carelli, V.; Casadei, M. A.; Liberature, F.; Moracci, F. M. *Synthesis* **1986**, 591–593. (b) Casadei, M. A.; Rienzo, B. D.; Insei, A.; Moracci, F. M. *J. Chem. Soc. Perkin Trans. 1* **1992**, 379–382. (c) Feroci, M.; Chiarotto, I.; Orsini, M.; Sotgiu, G.; Insei, A. *Adv. Synth. Catal.* **2008**, *350*, 1355–1359.
7. In this reaction "EGB" was not cleared yet but it might be the conjugated base of **3e**. Representative literatures for electrochemical reactions using "EGB", see: (a) Shono, T.; Kise, N.; Tanabe, T. *J. Org. Chem.* **1988**, *53*, 1364–1367. (b) Shono, T.; Matsumura, Y.; Katoh, S.; Takeuchi, K.; Sasaki, K.; Kamada, T.; Shimizu, R. *J. Am. Chem. Soc.* **1990**, *112*, 2368–2372. (c) Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S. *J. Org. Chem.* **1991**, *56*, 2–4. (d) Matsumura, Y.; Satoh, Y.; Shirai, K.; Onomura, O.; Maki, T. *J. Chem. Soc. Perkin Trans. 1* **1999**, 2057–2060.
8. Crystallographic data for structure of azetidin-2-one **7e** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 745174. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK; fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
9. (a) Mori, M.; Kagechika, K.; Sasai, H.; Shibasaki, M. *Tetrahedron* **1991**, *47*, 531–540. (b) Wanyoike, G. N.; Onomura, O.; Maki, T.; Matsumura, Y. *Org. Lett.* **2002**, *4*, 1875–1877. (c) Onomura, O.; Kirira, P. G.; Tanaka, T.; Tsukada, S.; Matsumura, Y.; Demizu, Y. *Tetrahedron* **2008**, *64*, 7498–7503.
10. Although the corresponding 4-acetoxylated compound **14** was prepared from **11** by electrochemical oxidation described below, the reduction of **14** with Na in liq. NH_3 did not afford the corresponding *N*-unsubstituted azetidin-2-one; see, electrochemical decarboxylative acetoxylation: In an undivided cell equipped with platinum plate electrodes (1 x 2 cm^2) was placed a solution of **11** (153 mg, 0.5 mmol) and AcOK (98 mg, 1 mmol) in a mixture of acetonitrile (4 mL) and acetic acid (1 mL). A constant current (50 mA) was passed through the cell externally cooled with water-bath. After 4 *F*/mol of electricity was passed, to the reaction mixture was added sat. $NaHCO_3$ (30 mL). Organic portion was extracted with AcOEt (3 x 15 mL). The resulting organic layer was washed with sat. aqueous

NaCl (10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was subjected to silica gel columun chromatography (*n*-hexane : AcOEt =2 : 1) to afford **14** in 60% yield.

4*R*-Acetoxy-3*R*-(1'*R*-acetoxyethyl)-1-(1'*R*-phenylethyl)azetidin-2-one (14): colorless oil; ^{1}H NMR (400MHz $CDCl_3$) δ 1.24 (d, *J*=6.3Hz, 3H), 1.55 (d, *J*=7.4Hz, 3H), 1.83 (s, 3H), 1.90 (s, 3H), 3.09 (dd, *J*=1.0Hz, *J*=5.8Hz, 1H), 4.80 (q, *J*=7.3Hz, 1H), 5.09 (quint. *J*=6.3Hz, 1H), 5.92 (d, *J*=1.0Hz, 1H), 7.20-7.40 (m, 5H); ^{13}C-NMR (100MHz, $CDCl_3$) δ 18.2, 19.1, 20.8, 20.8, 52.7, 62.3, 66.1, 78.0, 126.9, 127.9, 128.7, 140.1, 164.3, 169.9, 169.9; IR (neat): 3500, 2984, 2853, 1738, 1640, 1497, 1456, 1377, 1242, 1200, 1140, 1050, 953, 922, 851, 799, 722, 704 cm^{-1}; HRMS (EI) Calcd for $C_{17}H_{21}NO_5$ (M^+): 319.1420, Found: 319.1430.

11. Battersby, A. R.; Turner, S. P. D.; Block, M. H.; Sheng, Z.-C.; Zimmerman, S. C.; *J. Chem. Soc. Perkin Trans. 1* **1988**, 1577–1586.
12. Sugiyama, S.; Watanabe, S.; Inoue, T.; Kurihara, R.; Itou, T.; Ishi, K. *Tetrahedron* **2003**, *59*, 3417–3426.

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