Tetrahedron: *Asymmetry* 20 (2009) 2014–2020

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Highly diastereoselective synthesis of pyrido[2,1-*b*][1,3]oxazin-4(6*H*)-one by intramolecular anodic oxidation

Dong-Sheng Lee *

Department of Chemistry, National Chung-Hsing University, Taichung 402, Taiwan

ARTICLE INFO

Article history:
Received 3 July 2009
Accepted 14 August 2009
Available online 14 September 2009

ABSTRACT

This paper describes a method for the intramolecular anodic oxidation of ω-hydroxyl amides. Products were obtained in acceptable yields from different starting materials using various applied currents, charge, and reactant concentrations. Compounds **1a** and **1d** afforded a single diastereomer in 67% yield when the applied current and reactant concentration were 100 mA and 0.04 M.

1. Introduction

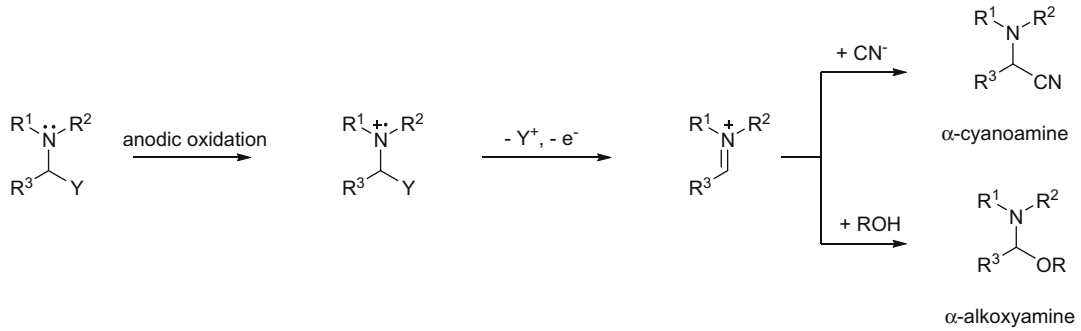
The use of electrochemical oxidation for the synthesis of heterocyclic compounds has recently attracted the interest of various research groups.[1] This technique is advantageous as it can be used to oxidize various functional groups, generate highly reactive intermediates, and reverse the polarity of a given functionality. Many researchers in the past had carried out anodic cyanation[2] of tertiary amines. The products of this reaction, α-cyanoamines, are very important synthons that are used for synthesizing various aminoacids and alkaloids. Anodic oxidation of tertiary amines affords a highly reactive iminium ion, which is subsequently attacked by the cyanide to form the corresponding α-cyanoamines (Scheme 1). Yang et al. have developed an anodic cyanation method for synthesizing gephyrotoxin 223AB.[3] Anodic oxidation of amines[4] and their derivatives such as amides,[5] sulfonamides,[6] amidophosphates,[6b] and carbamates[7] is a reliable method for introducing an alkoxy group onto the carbon atom that is in the α-position with respect to the nitrogen. The resulting α-methoxylated amides and carbamates are versatile intermediates that can be used for further functionalization at the aforementioned α-position. For example, treatment of the α-methoxylated carbamates with a Lewis acid generates *N*-acyliminium ions, which can be trapped with a broad variety of nucleophiles to yield *trans*-2,5-disubstituted pyrrolidine,[8] (−)-pseudoconhydrine,[9] bulgecinine, and bulgecin C.[10] Pilli et al. illustrated the synthesis of chiral 2-allylpiperidine from *N*-acyliminium ions using chiral carbamates derived from (*S*)-(+)-mandelic acid as the chiral auxiliary.[11] Yudin et al. have developed a method for the intramolecular cyclization of *N*-acyliminium ions obtained from pyrrolidine- and piperidine-based carbamates.[12] Royer et al. used an anodic amide oxidation to synthesize metabolites of ifosfamide and cyclophophamide (anticancer drugs).[13] To the best of our knowledge, the diastereoselectivity of anodic oxidations was poor regardless of using a chiral auxiliary[11] or chiral pool approach.[8–10,12,13] We are interested in developing a highly diastereoselective anodic oxidation for the preparation of chiral tertiary amido alcohols which are a versatile starting material for alkaloid synthesis. Moreover, many reports[14] illustrated that ketopinic acid derivatives, used as a chiral auxiliary, achieved excellent diastereoselectivity in asymmetric synthesis. Herein, we report the electrochemical oxidation of a chiral amide obtained using (1*S*)-ketopinic acid as the chiral auxiliary and compare the diastereoselectivity observed in this reaction with that observed in intramolecular cyclization.

2. Results and discussion

With the purpose of optimizing the reaction conditions for intramolecular cyclization, a model study was first performed on tertiary amido alcohol **1a** (Scheme 2).[15] Anodic oxidation was carried out in a beaker-type undivided cell containing two platinum plate-type electrodes. In a typical electrolysis, a solution of **1a** and Et_4NBF_4 in EtOH/CH_3CN (1:1) was placed in a 50 mL beaker and electrolyzed by passing a constant current between the anode (3.0 cm × 5.0 cm) and the cathode (3.0 cm × 5.0 cm). The results of this reaction are summarized in Table 1. Only one diastereomer of the intramolecular cyclization product **7a*S*** was obtained. No intermolecular product **8a** was detected in the reaction as 2.0 and 3.0 Faraday electric charges were used and compound **1a** was recovered in 36% and 10% yield, respectively (entries 1 and 2). The electrolyte could be recovered from the reaction mixture in 80–90% yield. Our results illustrate that intramolecular cyclization was faster than intermolecular cyclization. The chemical yields of the products were unaffected by increasing the concentration of **1a** and the number of equivalents of the electrolyte

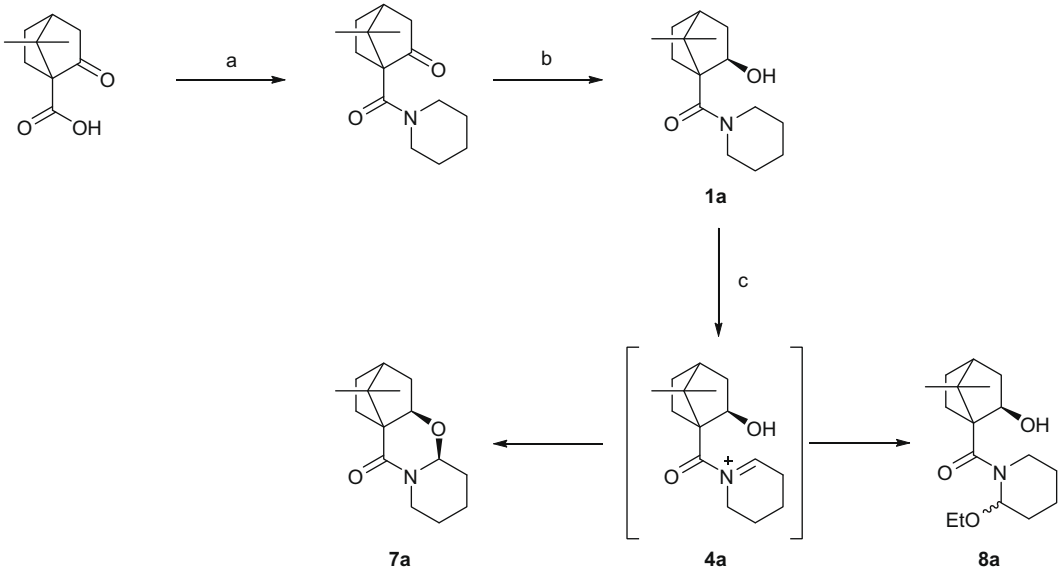
* Tel.: +886 4 22840412; fax: +886 4 22862547.
E-mail address: dslee@mail.nchu.edu.tw

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.08.017



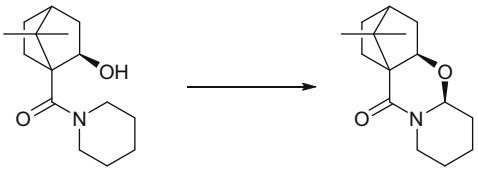
Scheme 1.

(entries 4, 6 8, and 9). However, with an increase in the charge, the yield decreased (entries 3–5) as the cyclization product **7a*S*** was further oxidized when the reaction time was increased. The use of the recovered electrolyte in this reaction did not affect the yield of the product (entries 3 and 7). Ojima et al.[16] reported an example of Rh-catalyzed CO insertion to Boc-(*S*)-Ser-(allyl)Gly-OMe which subsequently underwent a diastereoselective cyclization to form the bicyclic dipeptide. The cyclization step was considered to be a kinetically controlled process by molecular mechanics calculation. According to the mechanism, the *si*-face attack was favored over *re*-face attack in the intramolecular nucleophilic addition of the hydroxyl group to the iminium bond. We have proposed the transition state of intramolecular cyclization of compound **1a** as shown in Scheme 3. The hydroxyl group attacked from the *si* face of the ion because a *re*-face attack has larger steric hindrance between the camphor moiety and the hydrogen of the iminium moiety. The X-ray structure of **7a*S***[17] revealed that the absolute configuration of the piperidine ring has an (*S*) structure (Fig. 1). Encouraged by the above results, various tertiary amido alcohols **1** were synthesized by reacting (1*S*)-ketopinic acid with cyclic amines or dialkylamines. The anodic oxidation results obtained for **1** are provided in Table 2. Excellent yields and high diastereomeric excess of the products were achieved by the intramolecular cyclization of tertiary amido alcohols presumably via intermediate **4**. The diastereoselectivity was higher when **1a** and **1d** were employed as the starting materials than when **1b** and **1c** were utilized. In the case of **1a** or **1d**, only one diastereomer of the intramolecular cyclization products **7a*S*** or **7d*S*** was obtained. In the acyclic amines system, two possible transition states, **4E** and **4Z**, were formed by anodic oxidation (Scheme 4). As mentioned above, *si*-face attack was favored than *re*-face attack in the intramolecular nucleophilic addition of the hydroxyl group to the iminium bond. The major product **7*S*** was afforded by attacking the *si*-face from the transition state **4E**. However, the energy difference between transition states **4E** and **4Z** was small when a larger alkyl group was used as in the case of open chain amine **1b** or **1c** by means of MM2 calculation (Fig. 3). Therefore, the diastereomeric excess of anodic oxidation products decreased (entries 2 and 3). X-ray crystallographic studies[18] of **7c*R***, shown in Figure 2, confirmed our assignments of the absolute configuration of the α-amino carbon. A different product was obtained when the cheaper chiral compounds, ethyl (*S*)-lactate and ethyl (*S*)-3-hydroxybutyrate, were used as the chiral auxiliary instead of (1*S*)-ketopinic acid (Scheme 5). Table 3 shows the results of the anodic oxidation reaction. The intermolecular product **10** was formed predominantly when **2** was used as the starting material. On the contrary, the intramolecular product **11** was obtained when the electrolysis was performed using **3**. In the six-membered ring system, compounds **3** and **1**, the intramolecular attack by a hydroxyl group was much faster than intermolecular EtOH attack onto the *N*-acyliminium cation. However, for the five-membered ring system, compound **2**, intramolecular hydro-



Scheme 2. The electrolysis of **1a**. Reagents, conditions, and yield: (a) (i) $SOCl_2$, rt; (ii) piperidine; (b) $NaBH_4$, EtOH, −20 °C, two steps 95%; (c) Et_4NBF_4, EtOH/CH_3CN, Pt, I = 100 mA.

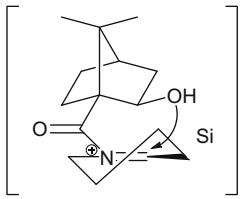
Table 1
Electrolysis of tertiary amido alcohol **1a**[a]



1a **7a*S***

Entry	Et_4NBF_4 (equiv)	Concn (M)	Electric charge (Faraday)	**1a** Yield (%)	**7a*S*** Yield (%)
1	2.00	0.040	2.00	36	44
2	2.00	0.040	3.00	10	63
3	2.00	0.040	3.50	0	67
4	2.00	0.040	5.00	0	45
5	2.00	0.040	7.00	0	21
6	2.00	0.080	3.50	0	67
7	2.00[b]	0.040	3.50	0	62
8	1.00	0.040	3.50	0	66
9	3.00	0.040	3.50	0	65

[a] The reaction was carried out under constant current ampere, 100 mA. All yields were obtained after purification.
[b] The recovered electrolyte was used repeatedly in the reaction.



4a

Scheme 3. Possible transition states of intramolecular cyclization in the case of a cyclic amine.

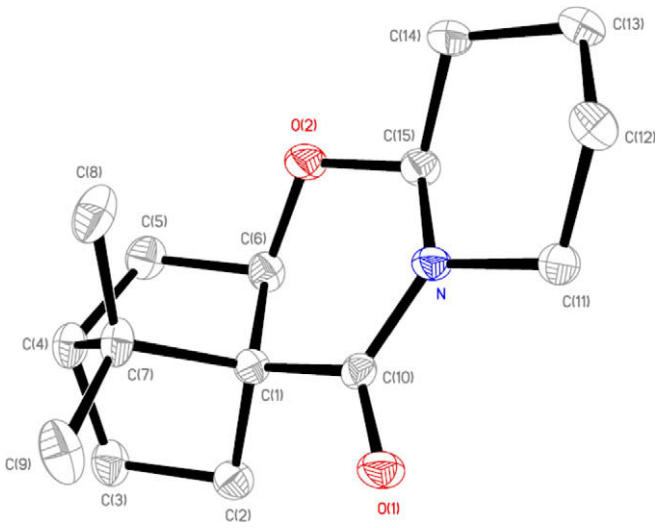


Figure 1. ORTEP diagram of **7a*S***.

xyl attack is much slower than intermolecular EtOH attack onto the *N*-acyliminium cation. We assume that the five-membered amido hydroxyl group is pointing away from the *N*-acyliminium ion and the five-membered ring is too short to get around to the back of the α-carbon of *N*-acyliminium ion. For stoichiometric conversion, the applied electric charge had to be greater when using **3** as the starting material than when using compound **2** (entries 4 and 8). Compound **10** was isolated as a mixture of two diastereomers (3:1 ratio), whose separation was difficult. The diastereomeric ratio of **11** was greater than 3:1 as determined by NMR spectroscopy. The yields of the products increased with the applied electric charge (entries 1–4). With a decrease in the applied current, the yield of the product decreased, but 21% of the starting material was recovered (entry 5). A lower yield was obtained when the current was reduced. The yield showed a slight decrease with an increase in the applied current.

3. Conclusion

In conclusion, piperidines and pyrrolidines with an isoborneol-based chiral auxiliary could be electrochemically cyclized at the α-carbon to a single diastereomer. We observed the optimum conditions for the electrolysis of **1** by performing experiments at room temperature under a constant current (100 mA) and an applied charge of 3.5 F/mol. In addition, we have established a method for substrates with hydroxyl groups to undergo intramolecular cyclization with various degrees of ease depending on their chain length. In our future research, we plan to achieve carbon–carbon bond formation by treating the intramolecular products **7** with a nucleophile in the presence of a Lewis acid.

4. Experimental

4.1. General aspects

Melting points were determined with a Buchi 535 digital melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer Model 241 polarimeter using a 1.0 dm cell at specific temperatures. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury-400 spectrometer in a solution of $CDCl_3$ with chemical shifts (δ) given in ppm from internal TMS; *J*-values are in hertz. High-resolution mass spectra were recorded on a Jeol Jms-SX/SX 102A mass spectrometer and HRMS was measured by a Finnigan MA+ mass spectrometer. Merck 5715 glass-backed TLC plates were used for the analysis of reactions with detection by 0.5% phosphomolybdic acid solution in 95% EtOH. Merck Silica Gel 60 (70–230 mesh) was used for chromatography. The melting points were determined with a Fargo MP–2D digital melting point apparatus and are uncorrected.

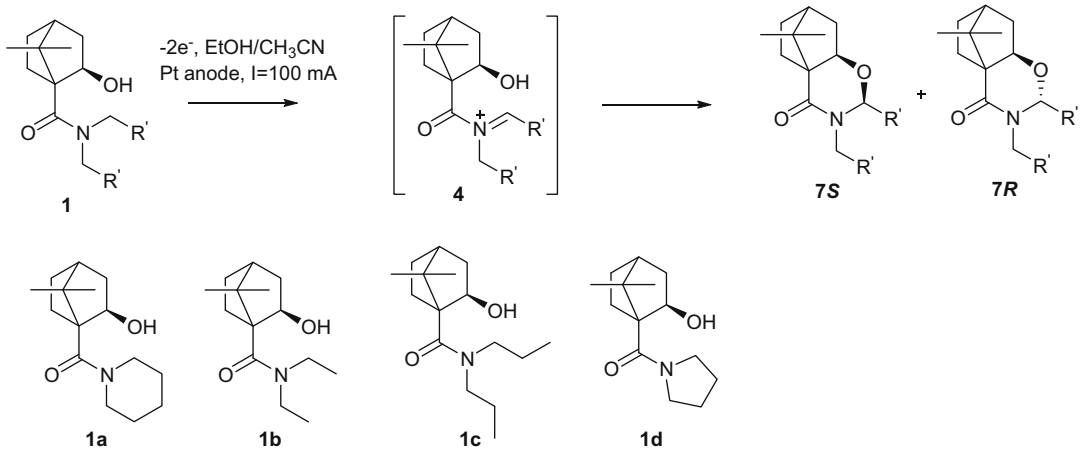
4.2. General procedure for the preparation of compound 1

To a flask containing (1*S*)-ketopinic acid (3778.0 mg, 20.73 mmol), thionyl chloride (5.00 mL, 68.84 mmol) was added at 24 °C. The mixture was stirred at 24 °C for 20 h. The excess thionyl chloride was removed under reduced pressure to give the crude acid chloride. The crude product in THF (20 mL) was added to piperidine (10.00 mL, 59.342 mmol) at 0 °C. The mixture was stirred for 3 h at 24 °C and diluted with EtOAc (20 mL). The white salt was removed and the filtrate was concentrated in vacuo to afford a colorless oil. To a flask containing 1-[(1*S*)-ketopinyl]piperidine in absolute EtOH (60 mL) was added $NaBH_4$ (3655.7 mg, 96.635 mmol) at −20 °C until the reaction was complete. After the solvent was removed in vacuo, 2 M NaOH (30 mL) was added and the solution was extracted with EtOAc (30 mL × 3). Evaporation of the solvent afforded white solids.

4.2.1. ((1*S*,2*R*,4*R*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)(piperidin-1-yl)methanone 1a[15b]

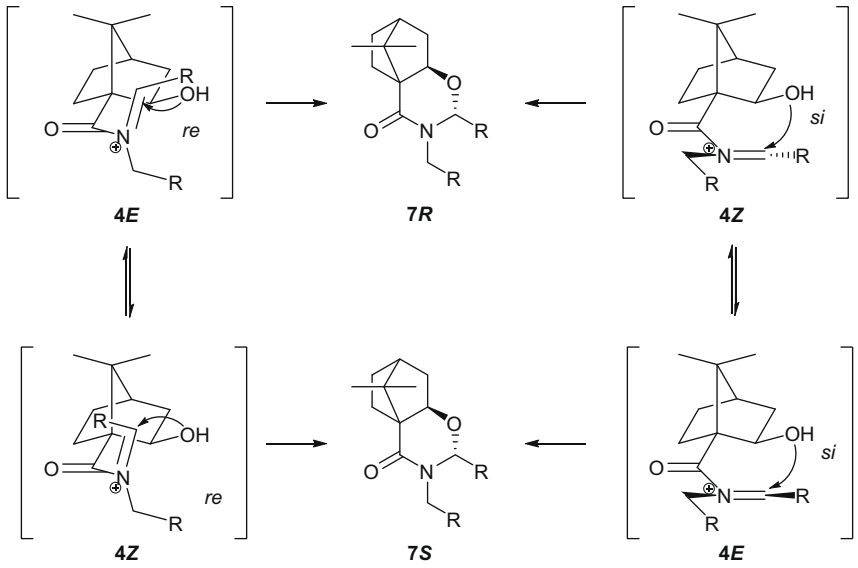
Yield 95%; white solid; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.21 (s, 3H), 1.23 (s, 3H), 1.39–1.63 (m, 7H), 1.91 (d, *J* = 18.0 Hz, 1H), 2.24–2.34 (m, 1H), 2.49 (ddd, *J* = 18.0, 5.0, 3.0 Hz), 3.43 (br, 4H).

Table 2
Electrolysis of compound **1**[a]



Entry	Substrate **1**	Electric charge (Faraday)	**7** Yield (%)	Recovery yield **1** (%)	Ratio[b] **7S**/**7R**
1	**1a**	3.50	67	0	100/0
2	**1b**	3.50	86	0	74/26
3	**1c**	3.50	74	14	58/42
4	**1d**	3.50	62	0	100/0

[a] A solution of 1 (1 equiv) and Et_4NBF_4 (2 equiv) in EtOH/CH_3CN (1:1) was electrolyzed under constant current ampere, 100 mA.
[b] The ratio was analyzed by 400 MHz NMR spectrum.



Scheme 4. Possible transition states for intramolecular cyclization in the case of open chain amines.

4.2.2. (1*S*,2*R*,4*R*)-2-Hydroxy-7,7-dimethyl-*N*,*N*-diethylbicyclo-[2.2.1]heptane-1-carboxamide 1b

Yield 94%; white solid; mp = 151–152 °C; $[\alpha]_D = -18.7$ (*c* 1.38, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) $\delta = 1.11$ (s, 3H), 1.16 (t, $J = 7.2$ Hz, 6H), 1.39 (s, 3H), 1.46–1.53 (m, 1H), 1.61–1.64 (m, 2H), 1.78–1.85 (m, 2H), 1.91–2.05 (m, 2H), 2.12 (d, $J = 5.2$ Hz, 1H), 3.27–3.36 (m, 2H), 3.49–3.57 (m, 2H), 4.13–4.17 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 13.69$, 21.90, 22.03, 27.08, 30.14, 40.79, 41.48, 44.73, 50.80, 60.73, 77.87, 171.94. MS (EI) *m*/*z* (%): 239.2 (11.0); 221.2 (45.9); 149.1 (91.8); 100.1 (51.8); 95.1 (90.7); 72.1 (94.6); 58.1 (100.0). HRMS (EI): *m*/*z* calcd for $C_{14}H_{25}NO_2$: 239.1893; found: 239.1889.

4.2.3. (1*S*,2*R*,4*R*)-2-Hydroxy-7,7-dimethyl-*N*,*N*-dipropylbicyclo-[2.2.1]heptane-1-carboxamide 1c

Yield 94%; white solid; mp = 108–109 °C; $[\alpha]_D = -0.3$ (*c* 2.84, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) $\delta = 0.90$ (t, $J = 7.2$ Hz, 6H), 1.11 (s, 3H), 1.39 (s, 3H), 1.41–1.63 (m, 7H), 1.77–1.85 (m, 2H), 1.92–2.04 (m, 2H), 2.18 (br, 1H), 3.15–3.22 (m, 2H), 3.38–3.45 (m, 2H), 4.14 (dd, $J = 7.6$, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 11.29$, 21.53, 21.92, 22.05, 27.10, 30.25, 41.46, 44.74, 48.58, 50.83, 60.86, 77.92, 172.27. MS (EI) *m*/*z* (%): 267.3 (8.1); 167.1 (42.2); 149.1 (63.7); 95.1 (43.5); 72.1 (100.0). HRMS (EI): *m*/*z* calcd for $C_{16}H_{29}NO_2$: 267.2217; found: 267.2208.

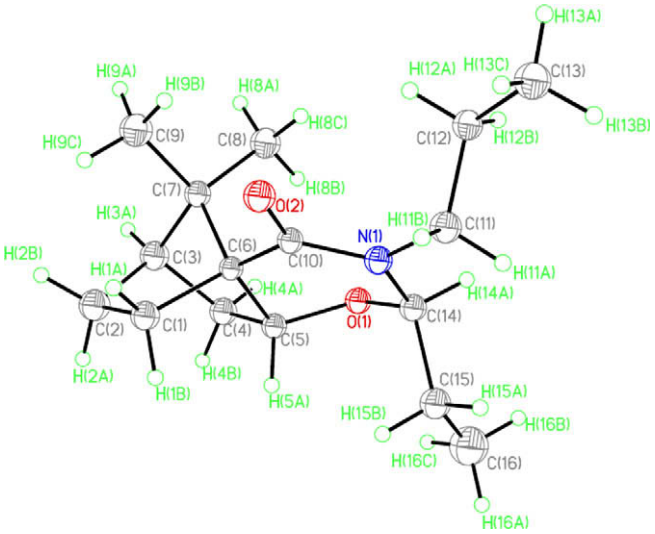


Figure 2. ORTEP diagram of 7c***R***.

4.2.4. ((1*S*,2*R*,4*R*)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)(pyrrolidin-1-yl)methanone 1d[15b]

Yield 96%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.12 (s, 3H), 1.38 (s, 3H), 1.51–1.58 (m, 1H), 1.65 (t, J = 4.0 Hz, 1H), 1.74–2.05 (m, 9H), 2.64 (br, 1H), 3.57 (br, 4H), 4.16 (dd, J = 8.0, 3.6 Hz, 1H).

4.3. Typical procedure for the preparation of compounds 2 and 3

A solution of ethyl (*S*)-lactate (5.0 mL, 43.85 mmol) and piperidine (22.0 mL, 222.4 mmol) was refluxed for 19 h. The excess piperidine was removed by distillation to afford brown oil. The crude product was purified by distillation in vacuo to afford pale yellow oil.

4.3.1. (*S*)-2-Hydroxy-1-(piperidin-1-yl)propan-1-one 2

Yield 66%; pale yellow oil; $[\alpha]_D$ = −1.4 (c 7.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.32 (d, J = 6.8 Hz, 3H), 1.58–1.70 (m, 6H), 3.34 (t, J = 5.6 Hz, 2H), 3.59–3.62 (m, 2H), 4.46 (q, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.45, 24.37, 25.45, 26.15, 43.63, 45.80, 63.98, 173.36. MS (EI) m/z (%): 157.1 (9.0); 112.1 (100.0) 69.1 (65.8). HRMS (EI): m/z calcd for $C_8H_{15}NO_2$: 157.1089; found: 157.1096.

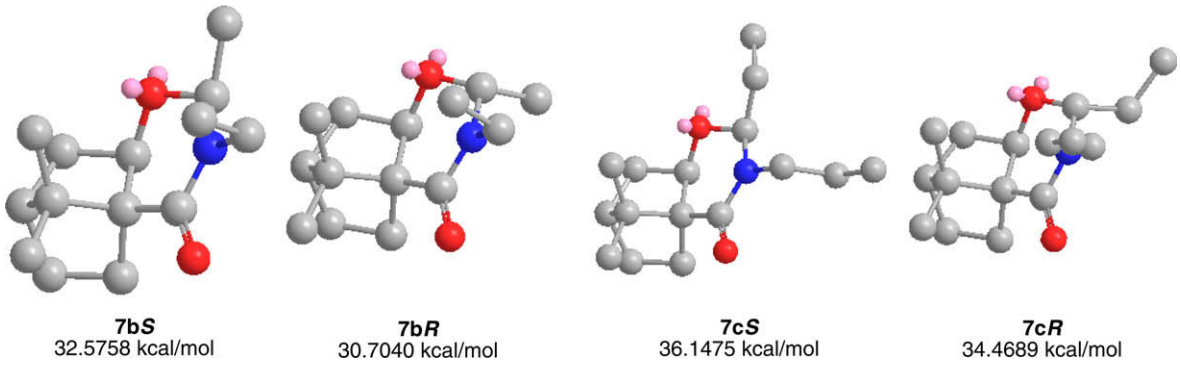
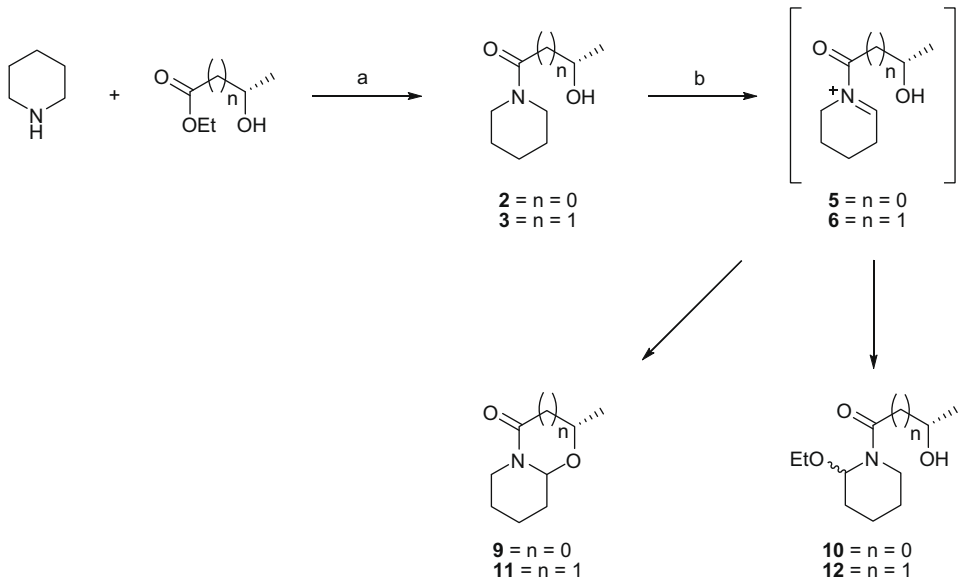
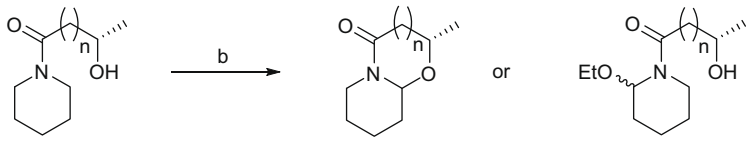


Figure 3. The energy of intramolecular cyclization was obtained by MM2 calculation.



Scheme 5. The electrolysis of **2** and **3**. Reagents, conditions, and yield: (a) heating, 19 h, 66%; (b) Et_4NBF_4, EtOH/CH_3CN, Pt, I = 100 mA.

Table 3
The electrolysis of compounds **2** and **3**



2 = n = 0
3 = n = 1

9 = n = 0
11 = n = 1

10 = n = 0
12 = n = 1

Entry	Substrate	Current ampere (A)	Electric charge (Faraday)	Product (Yield%)	Recovery yield (%)	Ratio[a] ***R*/*S***
1	**2**	0.100	5.00	**10** (50)	**2** (32)	25/75
2	**2**	0.100	6.00	**10** (49)	**2** (11)	25/75
3	**2**	0.100	6.50	**10** (56)	**2** (9)	25/75
4	**2**	0.100	7.00	**10** (74)	**2** (0)	25/75
5	**2**	0.075	7.00	**10** (32)	**2** (21)	25/75
6	**2**	0.150	7.00	**10** (58)	**2** (0)	25/75
7	**2**	0.200	7.00	**10** (60)	**2** (0)	30/70
8	**3**	0.100	3.50	**11** (0)	**3** (93)	—
9	**3**	0.100	7.00	**11** (40)	**3** (50)	40/60

[a] The ratio was analyzed by 400 MHz NMR spectrum.

4.3.2. (*S*)-3-Hydroxy-1-(piperidin-1-yl)butan-1-one 3

Yield 62%; pale orange oil; $[\alpha]_D$ = +61.6 (*c* 2.87, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 1.22 (d, *J* = 6.4 Hz, 3H), 1.52–1.71 (m, 6H), 2.29 (dd, *J* = 16.4, 9.6 Hz, 1H), 2.48 (dd, *J* = 16.4, 2.4 Hz, 1H), 3.36–3.39 (m, 2H), 3.50–3.62 (m, 2H), 4.18–4.23 (m, 1H), 4.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.12, 24.38, 25.44, 26.25, 40.64, 42.41, 46.27, 64.18, 170.70. MS (EI) *m*/*z* (%): 171.1 (39.2); 126.1 (57.6); 112.1 (45.1); 84.1 (100.0). HRMS (EI): *m*/*z* calcd for $C_9H_{17}NO_2$: 171.1252; found: 171.1255.

4.4. General procedure for anodic oxidation

A solution of tertiary amido alcohol **1** (1 equiv) and Et_4NBF_4 (2 equiv) in EtOH/CH_3CN (1:1, 50 mL) was placed in a 50 mL beaker. This mixture was electrolyzed under constant current ampere through a platinum plate anode (3.0 cm × 5.0 cm) and platinum cathode (3.0 cm × 5.0 cm). The solvent was removed under reduced pressure. The electrolyte was filtered out and rinsed with EtOAc. The filtrate was concentrated under reduced pressure to afford the crude product which was purified by column chromatography.

4.4.1. Compound 7a*S*

Yield 67%; white solid; mp = 112–114 °C; $[\alpha]_D$ = −47.7 (*c* 2.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 1.10 (s, 3H), 1.12 (s, 3H), 1.37–1.42 (m, 2H), 1.69–1.99 (m, 10H), 2.29–2.46 (m, 2H), 3.78 (dd, *J* = 8.0, 3.2 Hz, 1H), 4.62 (dd, *J* = 8.0, 3.2 Hz, 1H), 4.71 (d, *J* = 14 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.95, 21.51, 22.38, 24.82, 27.71, 28.62, 33.08, 37.62, 39.91, 44.81, 50.17, 53.76, 80.76, 86.25, 169.71. MS (EI) *m*/*z* (%): 249.2 (44.2); 221.2 (28.6); 207.1 (34.5); 84.1 (100.0); 55.0 (35.5). HRMS (EI): *m*/*z* calcd for $C_{15}H_{23}NO_2$: 249.1725; found: 249.1727.

4.4.2. (1*S*,4*S*,6*R*,8*R*)-3-Ethyl-4,11,11-trimethyl-5-oxa-3-aza-tricyclo[6.2.1.0^{1,6}]undecan-2-one 7b*S*

Yield 64%; colorless oil; $[\alpha]_D$ = −23.8 (*c* 3.53, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 1.00 (s, 3H), 1.10 (s, 3H), 1.14 (t, *J* = 6.8 Hz, 3H), 1.45 (d, *J* = 5.6 Hz, 3H), 1.72–1.98 (m, 6H), 2.26–2.32 (m, 1H), 3.42 (nonet, *J* = 6.8 Hz, 2H), 3.77 (dd, *J* = 8.0, 3.2 Hz, 1H), 4.95 (q, *J* = 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.25, 20.92, 21.42, 21.57, 27.80, 28.69, 36.63, 37.57, 44.83, 50.24, 53.13, 81.45, 84.41, 170.21. MS (EI) *m*/*z* (%): 237.2 (91.6); 222.2 (53.1); 193.2 (59.3); 164.1 (50.5); 149.1 (52.6); 121.1 (100.0); 72.1 (51.4). HRMS (EI): *m*/*z* calcd for $C_{14}H_{23}NO_2$: 237.1719; found: 237.1724.

4.4.3. (1*S*,4*R*,6*R*,8*R*)-3-Ethyl-4,11,11-trimethyl-5-oxa-3-aza-tricyclo[6.2.1.0^{1,6}]undecan-2-one 7b*R*

Yield 22%; colorless oil; $[\alpha]_D$ = −10.3 (*c* 1.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 1.04 (s, 3H), 1.05 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H), 1.41 (d, *J* = 5.6 Hz, 3H), 1.66–1.91 (m, 6H), 2.20–2.26 (m, 1H), 2.73 (sextet, *J* = 6.8 Hz, 2H), 3.84 (sextet, *J* = 6.8 Hz, 1H), 4.14 (dd, *J* = 8.0, 3.2 Hz, 1H), 4.99 (q, *J* = 5.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.12, 19.26, 20.49, 21.63, 27.75, 28.28, 37.27, 38.04, 44.83, 50.79, 52.63, 75.64, 83.29, 168.72. MS (EI) *m*/*z* (%): 237.2 (37.8); 222.2 (100.0); 149.1 (76.9); 121.1 (70.8). HRMS (EI): *m*/*z* calcd for $C_{14}H_{23}NO_2$: 237.1717; found: 237.1723.

4.4.4. (1*S*,4*S*,6*R*,8*R*)-3-Propyl-4-ethyl-11,11-dimethyl-5-oxa-3-aza-tricyclo[6.2.1.0^{1,6}]undecan-2-one 7c*S*

Yield 43%; colorless oil. $[\alpha]_D$ = -46.45 (*c* 2.28, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.88 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H), 1.11 (s, 6H), 1.44–1.99 (m, 10H), 2.24–2.32 (m, 1H), 2.99–3.06 (m, 1H), 3.68–3.76 (m, 2H), 4.81 (dd, *J* = 5.6, 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 7.39, 11.40, 21.12, 21.45, 21.52, 26.56, 27.79, 29.18, 37.50, 43.00, 44.82, 50.18, 53.37, 81.46, 87.58, 171.15. MS (EI) *m*/*z* (%): 265.2 (9.8); 236.2 (100.0); 149.1 (45.3); 121.1 (58.1). HRMS (EI): *m*/*z* calcd for $C_{16}H_{27}NO_2$: 265.2030; found: 265.2036.

4.4.5. (1*S*,4*R*,6*R*,8*R*)-3-Propyl-4-ethyl-11,11-dimethyl-5-oxa-3-aza-tricyclo[6.2.1.0^{1,6}]undecan-2-one 7c*R*

Yield 31%; white solid; mp = 84–86 °C; $[\alpha]_D$ = +23.5 (*c* 2.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 0.92 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H), 1.10 (s, 3H), 1.11 (s, 3H), 1.56–1.97 (m, 10H), 2.22–2.32 (m, 1H), 2.54–2.61 (m, 1H), 3.81–3.88 (m, 1H), 4.03 (dd, *J* = 8.0, 3.2 Hz, 1H), 4.66 (dd, *J* = 10.4, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.16, 11.44, 20.63, 21.26, 21.69, 24.97, 27.81, 28.36, 37.21, 44.99, 45.30, 50.91, 52.74, 75.33, 88.58, 169.14. MS (EI) *m*/*z* (%): 265.2 (0.7); 236.2 (100.0); 149.1 (64.0); 121.1 (72.0). HRMS (EI): *m*/*z* calcd for $C_{16}H_{27}NO_2$: 265.2047; found: 265.2044.

4.4.6. Compound 7d*S*

Yield 62%; colorless oil; $[\alpha]_D$ = +12.0 (*c* 2.18, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 1.10 (s, 3H), 1.12 (s, 3H), 1.75–2.29 (m, 11H), 3.42–3.48 (m, 1H), 3.63–3.70 (m, 1H), 3.88 (dd, *J* = 8.0,

3.6 Hz, 1H), 5.01 (dd, J = 8.0, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.62, 20.42, 21.80, 28.01, 28.31, 31.86, 36.84, 42.85, 45.05, 50.71, 53.24, 84.60, 89.19, 169.58. MS (EI) m/z (%): 235.2 (41.1); 207.1 (41.1); 70.1 (100.0). HRMS (EI): m/z calcd for $C_{14}H_{21}NO_2$: 235.1561; found: 235.1567.

4.4.7. (2*S*)-1-(2-Ethoxypiperidin-1-yl)-2-hydroxypropan-1-one 10

Yield 74%; pale yellow oil; Two conformational isomers, approx. 3:1 ratio of isomers **10*S***:**10*R***: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.19 and 1.21 (two sets of doublet, J = 7.2 Hz, 3H), 1.32 and 1.34 (two sets of triplet, J = 6.8 Hz, 3H), 1.43–1.94 (m, 7H), 2.88–3.32 (two sets of multiplet, 1H), 3.37–3.45 (two sets of multiplet, 2H), 4.45 and 4.53 (two sets of quartet, J = 6.8 Hz, 1H), 4.94–5.86 (two sets of multiplet, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.97, 18.49, 21.16, 21.57, 22.24, 24.93, 25.38, 25.72, 30.28, 30.64, 37.47, 39.73, 40.34, 62.04, 62.74, 64.30, 78.36, 81.16, 174.66, 174.74. MS (EI) m/z (%): 201.2 (0.3); 156.1 (100.0); 128.1 (46.0); 82.1 (69.3). HRMS (EI): m/z calcd for $C_{10}H_{19}NO_3$: 201.1359; found: 201.1362.

4.4.8. (2*S*)-2-Methylhexahydropyrido[2,1-*b*][1,3]oxazin-4(6*H*)-one 11

Yield 40%; pale yellow oil; Two conformational isomers, approx. 3:2 ratio of isomers **11*S***:**11*R***: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.28 (d, J = 6.0, Hz, 3H), 1.33–2.01 (m, 6H), 2.21–2.57 (m, 3H), 3.84–3.92 and 4.18–4.28 (two sets of multiplet, 1H), 4.59–4.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.21, 21.47, 23.09, 23.89, 25.06, 25.26, 32.46, 33.32, 39.63, 40.30, 40.61, 41.63, 66.29, 70.01, 84.37, 86.74, 165.64, 166.78. MS (EI) m/z (%): 169.1 (100.0); 128.1 (46.1); 100.1 (54.9); 85.1 (58.8); 69.1 (75.7); 55.1 (45.0). HRMS (EI): m/z calcd for $C_9H_{15}NO_2$: 169.1113; found: 169.1108.

Acknowledgments

The author would like to thank the Department of Chemistry of NCHU for financial support of this work and be grateful to the National Center for High-performance Computing for computer time and facilities. Professors Ta-Tung Lu, Chu-Chieh Lin, Han-Mou Gau, and Teng-Kuei Yang are also acknowledged for their helpful discussion.

References

1. (a) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265; (b) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527.
2. (a) Andresdes, S.; Zahnow, E. W. *J. Am. Chem. Soc.* **1969**, *91*, 4181; (b) Eberson, L.; Helgee, B. *Acta Chem. Scand.* **1975**, *11329*, 451; (c) Chiba, T.; Takata, Y. *J. Org. Chem.* **1977**, *42*, 2973; (d) Konho, A.; Fuchigami, T.; Fujita, Y.; Nonaka, T. *J. Org. Chem.* **1990**, *55*, 1952; (e) Zhao, P.; Yin, Y.-W. *J. Heterocycl. Chem.* **2004**, *41*, 157.
3. Yang, T.-K.; Yeh, S.-T.; Lay, Y.-Y. *Heterocycles* **1994**, *38*, 1711.
4. (a) Weinberg, N. L.; Brown, E. A. *J. Org. Chem.* **1966**, *31*, 4058; (b) Smith, P. J.; Mann, C. K. *J. Org. Chem.* **1968**, *33*, 316; (c) Weinberg, N. L. *J. Org. Chem.* **1968**, *33*, 4326.
5. (a) Ross, S. D.; Finkelstein, M.; Petersen, R. C. *J. Am. Chem. Soc.* **1964**, *86*, 2745; (b) Ross, S. D.; Finkelstein, M.; Petersen, R. C. *J. Org. Chem.* **1966**, *31*, 128; (c) Rudd, E. J.; Finkelstein, M.; Ross, S. D. *J. Org. Chem.* **1972**, *37*, 1763; (d) Nyberg, K.; Servin, R. *Acta. Chem. Scand., Ser. B* **1976**, *30*, 640; (e) Mitzlaff, M.; Warning, K.; Rehling, H. *Synthesis* **1980**, 315; (f) Shono, T. *Top. Curr. Chem.* **1988**, *148*, 131.
6. (a) Ross, S. D.; Finkelstein, M.; Rudd, E. J. *J. Org. Chem.* **1972**, *37*, 2387; (b) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K.; Kanazawa, T.; Tsuda, K. *J. Org. Chem.* **1984**, *49*, 3711.
7. (a) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264; (b) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172.
8. Wistrand, L.-G.; Skrinjar, M. *Tetrahedron* **1991**, *47*, 573.
9. Cossy, J.; Dumas, C.; Pardo, D. G. *Synlett* **1997**, 905.
10. Barrett, A. G. M. *J. Org. Chem.* **1991**, *56*, 2787.
11. D'Oca, M. G. M.; Pilli, R. A.; Pardini, V. L.; Curi, D.; Comninos, F. C. M. *J. Braz. Chem. Soc.* **2001**, *12*, 507.
12. Siu, T.; Li, W.; Yudin, A. K. *J. Comb. Chem.* **2000**, *2*, 545.
13. Paci, A.; Martens, T.; Royer, J. *Biorg. Med. Chem. Lett.* **2001**, *11*, 1347.
14. (a) Chu, Y.-Y.; Yu, C.-S.; Chen, C.-J.; Yang, K.-S.; Lian, J.-C.; Lin, C.-H.; Chen, K. *J. Org. Chem.* **1999**, *64*, 6993; (b) Lin, C.-C.; Wang, Y.-C.; Hsu, J.-L.; Chiang, C.-C.; Su, D.-W.; Yan, T.-H. *J. Org. Chem.* **1997**, *62*, 3806; (c) Bertrand, M. P.; Crich, D.; Nouguier, R.; Samy, R.; Stien, D. *J. Org. Chem.* **1996**, *61*, 3588; (d) Yan, T. S.; Tan, C. W.; Lee, H. C.; Lo, H. C.; Huang, T. Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613.
15. (a) Hari, Y.; Aoyama, T. *Synthesis* **2005**, 583; (b) Engel, T. d. l. C.; Maroto, B. L.; Martinez, A. G.; Cerero, S. d. l. M. *Tetrahedron: Asymmetry* **2008**, *19*, 646.
16. Chiou, W.-H.; Mizutani, N.; Ojima, I. *J. Org. Chem.* **2007**, *72*, 1871.
17. Details of the X-ray structure of **7a*S*** can be obtained from the Cambridge Crystallographic Data Centre (CCDC 738833).
18. Details of the X-ray structure of **7c*R*** can be obtained from the Cambridge Crystallographic Data Centre (CCDC 738834).