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The intramolecular tandem Michael/Mannich-type reaction of α,β-unsaturated carbonyl compounds with acyliminium ions provides access to chiral indolizidines

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Abstract—The intramolecular tandem Michael/Mannich-type (Michael addition/halo-Mannich-type) reaction using $TiCl_4$/*n*-Bu_4NI system between the α,β-unsaturated carbonyl compounds possessing an Evans oxazolidinone as a chiral auxiliary and *N*-acyliminium ion intermediates is described. The reaction was promoted in a mixed solvent of AcOEt–CH_2Cl_2 to afford indolizidine compounds with three stereogenic centers.

1. Introduction

The three-component tandem Michael-halo aldol type reaction has become an active topic of research because the resulting halo aldols can be converted into Morita–Baylis–Hillman (MBH) adducts by treatment with tertiary amines or other organic bases.[1–4] In particular, intramolecular coupling reactions between α,β-unsaturated carbonyl compounds and aldehydes via a sequential Michael addition–aldol reaction with the use of halides as nucleophiles are useful strategies.[5] Recently, the synthesis of aza Morita–Baylis–Hillman adducts using an intermolecular tandem Michael/Mannich-type reaction of acetylenic ketones or esters with imines in the presence of nucleophilic halides has been reported by Li et al.[6] However, few examples of a tandem Michael/Mannich-type reaction between α,β-unsaturated carbonyl compounds and *N*-acyliminium ion intermediates have been reported,[7] and such a method has not been applied to asymmetric cyclization.[8,9]

Herein we report the intramolecular tandem Michael/Mannich-type reaction of α,β-unsaturated carbonyl compounds **1** possessing an Evans oxazolidinone as the chiral auxiliary via an *N*-acyliminium ion intermediate.

2. Results and discussion

Preparation of the requisite α,β-unsaturated carbonyl compounds **1** possessing an Evans oxazolidinone involves a straightforward, high-yield, four-step synthesis starting with succinimide, as shown in Scheme 1.

N-Butenylsuccinimide **3** was prepared from the reaction of succinimide with but-3-enol under Mitsunobu conditions, according to a previously reported procedure.[10] The partial reduction of the imide carbonyl group of **3** followed by ethoxylation afforded the acyliminium ion precursor **4**, which was subjected to ozone oxidation to give aldehyde **5**. In this oxidation step, only the reaction in the presence of ozonizable dye (sudan III) as an indicator[11] and the use of EtOH as a solvent afforded a satisfactory yield. A subsequent Wittig reaction with phosphonate **6** gave the α,β-unsaturated carbonyl compound **1** possessing the Evans oxazolidinone.[12]

The resulting α,β-unsaturated carbonyl compounds **1** were then applied to the intramolecular cyclization utilizing the Michael/Mannich-type reaction via an *N*-acyliminium ion intermediate. Reaction conditions were optimized by varying the solvents, and the results are shown in Table 1.

Compound **1a** was initially applied to the $TiCl_4$/*n*-Bu_4NI system (in CH_2Cl_2)[5] as reported by Oshima et al. However, this resulted in formation of an insoluble complex of **1a**

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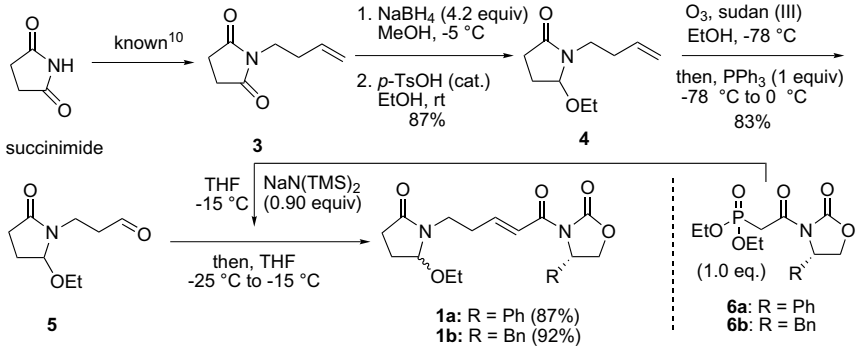
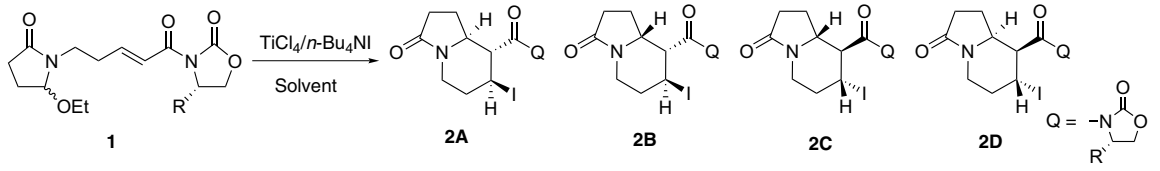


Scheme 1. Preparation of α,β-unsaturated carbonyl compounds **1.**

Table 1. Cyclization of compounds **1** to indolizidine **2** via an *N*-acyliminium ion intermediate by $TiCl_4/n\text{-}Bu_4NI$[a]



Run	Substrate	Solvent	Product **2**					
			2	Yield[b]	Diastereomer ratio[c]			
					A	**B**	**C**	**D**
1	**1a**: R = Ph	CH_2Cl_2	**2a**	0	—	—	—	—
2	**1a**: R = Ph	MeCN	**2a**	10	—	—	—	—
3	**1a**: R = Ph	$AcOEt/CH_2Cl_2$	**2a**	60	65	28	7	—[d]
4	**1b**: R = Bn	$AcOEt/CH_2Cl_2$	**2b**	58	90	10	Trace	—[d]

[a] Reactions were carried out using $TiCl_4$ (3 equiv) and $n\text{-}Bu_4NI$ (1.5 equiv) at −20 °C to 40 °C.
[b] Isolated yield of a mixture of **2A**, **2B**, and **2C**, after purification by column chromatography on silica gel.
[c] Determined by ^1H NMR integration of a mixture of **2A**, **2B**, and **2C**, after passage through a short column of silica gel ($CHCl_3$) to remove the tetrabutyl ammonium salt.
[d] No formation of **2aD** or **2bD** was observed.

possessing an oxazolidine with a titanium species (run 1). Attempts at using reported halo aldol conditions (e.g., $SnCl_4$,[7c] Et_2AlI[8a]) were also ineffective. We then investigated the use of other solvents in place of CH_2Cl_2. When MeCN was used, the cyclization of **1a** proceeded in low yield (run 2). Further attempts to find the most suitable solvent for this reaction continued; the mixed solvents of AcOEt and CH_2Cl_2 (4:1) afforded the cyclized product **2a** (R = Ph) in 60% yield, as a 65:28:7 mixture of three diastereomers (run 3). Application of compound **1b** possessing a benzyl oxazolidinone with $TiCl_4/n\text{-}Bu_4NI$ resulted in a high diastereomer ratio of **2bA** (**2b**: R = Bn, **A**/**B**/**C** = 90:10:trace) (run 4).

The stereostructure of **2** was determined on the basis of NOESY correlations. The presence of a NOESY correlation between the C7 and C8a protons of compounds **2A** and **2C** established the *cis*-relationship. No such correlation was observed for compound **2B**, thus supporting our stereochemical assignment (Fig. 1). The absolute configurations of the major isomer, 7,8a-*cis*-**2bA** (R = Bn), and the next major isomer, 7,8a-*trans*-**2aB** (R = Ph), were determined by single-crystal X-ray diffraction analysis (Fig. 2).

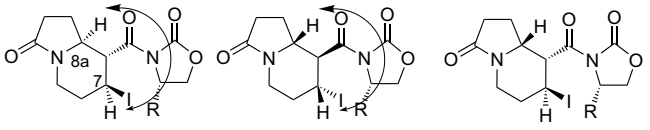


Figure 1. NOESY correlations of **2A**, **2B** and **2C**.

Unfortunately, current attempts at both the conversion of **2** to Baylis–Hillman adducts by elimination of the iodine and the removal of oxazolidinone from *N*-acyloxazolidinones **2** proved unsuccessful.[13]

The stereochemical course of these cyclized products can be explained by considering the required transition states for the ring closure from iodo titanium enolate to the indolizidine skeleton (Fig. 3).

The process of intramolecular cyclization of the titanium enolate with an (*S*)-configured iodo-substituted carbon atom might take place via two types of the chelated

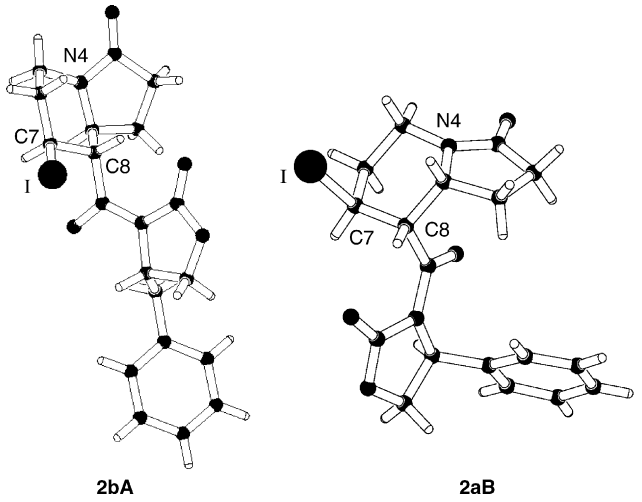


Figure 2. Crystal structures of **2bA** and **2aB**; the latter, shows the *trans* diaxial configuration at the C7 and C8 positions.

chair-like form transition structures: T***a*** or T***b***. It was considered that the former transition structure T***a*** caused a *re*-face attack of the titanium enolate on an iminium ion, leading to the major product **2A**. The latter transition structure, in which Ti coordinated to the pyrrolidinone oxygen, oxazolidine oxygen, and enolate oxygen,[14a,b] led to **2B** having the *trans*-diaxial configuration at the C7 and C8 positions (Fig. 2). Conversely, the titanium enolate with an *R*-configured iodo-substituted carbon atom resulted in *si*-face attack on an iminium ion via the transition state represented by T***c***. This led to the formation of a minor diastereomer **2C**, because large steric repulsion between the iodo-substituent and the titanium enolate is present in the chelated chair-like form, represented by T***a***′.[14c] Thus, it seems that the process of 1,4-addition of the iodine anion[15] might be an important factor in determining the transition state for enhanced diastereofacial selectivity in such a cyclization. However, we believe that enantioselectivity is probably not determined during formation of the iodo titanium enolates, because of interconversion between (*S*)- and (*R*)-iodo titanium enolates, which are in rapid (dynamic) equilibrium.[16] Subsequently, the cyclization process occurred throughout the reaction sequence via the most favored transition state, T***a***, to afford the major cyclized product **2A**.[17]

3. Conclusion

In conclusion, the first tandem Michael addition/Mannich-type reaction using a $TiCl_4$/*n*-Bu_4NI system between the α,β-unsaturated carbonyl compounds possessing an Evans oxazolidinone as chiral auxiliary and *N*-acyliminium ion intermediates was developed. Also, the use of mixed solvents, AcOEt and CH_2Cl_2, in substrates possessing Evans oxazolidinones, was shown to be effective in this study. Although the diastereofacial selectivity involved in the process of the 1,4-addition of iodine anions in this reaction is indefinable, the reaction predominately afforded three stereogenic centers to one diastereomer among the indolizidine compounds **2**. The use of chiral products **2** is currently under investigation for the synthesis of indolizidine alkaloids.

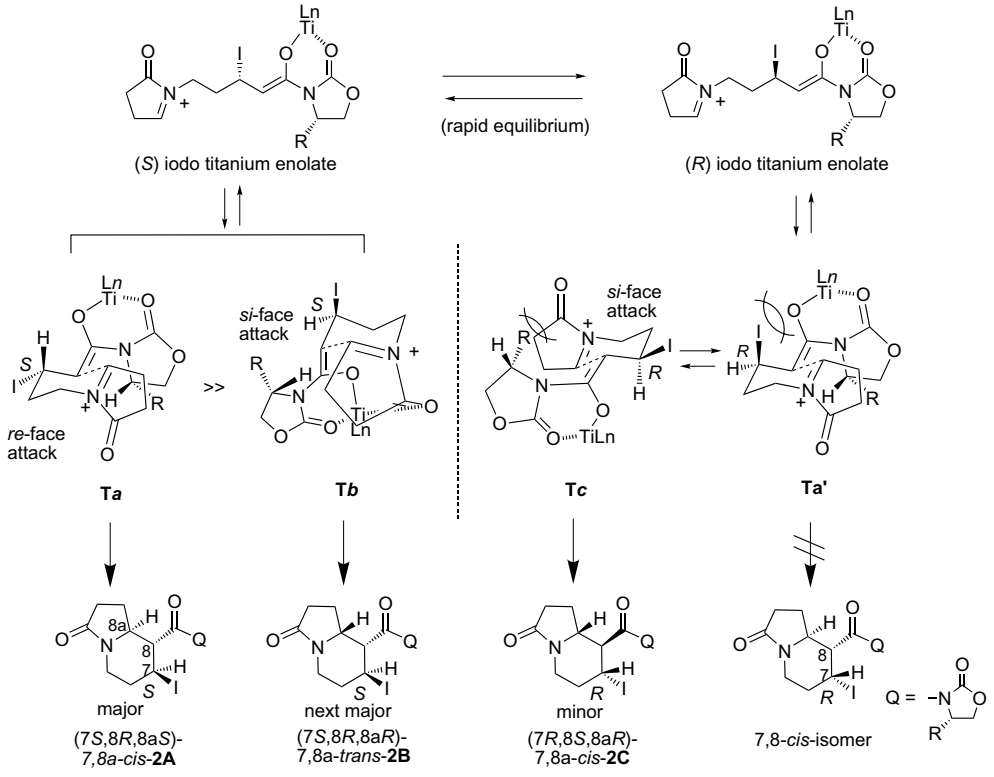


Figure 3. Plausible transition structures involving the reaction mechanism for the formation of **2**.

4. Experimental

4.1. General

Melting points were determined on a Yanagimoto MP-S3 microscope plate and are uncorrected. Optical rotations were measured with a JASCO P1030 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-300 spectrometer, Bruker DPX-400 spectrometer, Bruker DRX-500 and Bruker AV-600. Chemical shifts (δ) are given from TMS (0 ppm) as internal standard for ^{1}H NMR, and $^{13}CDCl_3$ (77.0 ppm) for ^{13}C NMR. IR spectra were measured on a JASCO IR Report-100 and Mass spectra on a Finigan TSQ-700 or Fisons VG Auto Spec instrument. Elemental analysis was recorded on an Elemental Vavio EL. Column chromatography was performed with Silica Gel BW-200 (Fuji Silysia Chemical, Ltd, 150–350 mesh). Medium-pressure liquid chromatography (MPLC) was carried out with a UV detector using prepacked silica gel cartridges with Yamazen Si-40 (Yamazen, Ltd, silica gel SiOH, 40 μm).

4.2. 1-(But-3-enyl)-5-ethoxypyrrolidin-2-one 4

Modification of Holmes's procedure, as follows, provided the desired material in higher yield.[10] To a solution of **3** (4.99 g, 32.6 mmol) in abs MeOH (170 mL) under Ar was added $NaBH_4$ (5.17 g, 136.8 mmol) in one portion at −10 °C. The mixture was then stirred for 3.5 h at −5 °C. The reaction was quenched with satd $NaHCO_3$ solution (80 mL) and water (80 mL), and the mixture extracted with $CHCl_3$ (4 times). The organic layer was washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. This crude product was used in the next step without purification. To a solution of the crude product in abs EtOH (60 mL) was added *p*-TsOH · H_2O (76 mg, 0.4 mmol) under Ar, and the mixture stirred at rt for 3.5 h. After the reaction was complete, satd $NaHCO_3$ solution (80 mL) and water (100 mL) were added to the reaction mixture at 0 °C and the mixture extracted with $CHCl_3$ (3 times). The organic layer was washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/acetone, 12:1–8:1) to give **4** (5.22 g, 87%) as a colorless liquid. The spectral data were in accord with those reported by Holmes.[10]

4.3. 3-(2-Ethoxy-5-oxopyrrolidin-1-yl)propanal 5

To a solution of **4** (1.90 g, 10.4 mmol) in abs EtOH (50 mL) containing a trace amount of sudan III (as an indicator) was bubbled ozonized O_2 at −78 °C for 3 h (until the solution showed a red discoloration). The reaction was purged of excess O_3 with a stream of Ar, after which a solution of PPh_3 (2.72 g, 10.4 mmol) in toluene (25 mL) was added gradually. The reaction mixture was stirred at −78 °C for 0.5 h, warmed to 0 °C, and stirred at the same temperature overnight. The solvent was removed in vacuo to give the residue, which was dissolved with *t*-BuOMe. After cooling the solution at −30 °C, the resulting solid (PPh_3=O) was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/*t*-BuOMe/hexane, 3:2:1 followed by $CHCl_3$/*t*-BuOMe, 2:1) to give 1.6 g (83%) of semi-pure aldehyde **5** as a colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, $J = 1.2$ Hz, 1H), 4.97 (dd, $J = 1.3$, 6.0 Hz, 1H), 3.62 (uneven t, $J \cong 6.6$ Hz, 2H), 3.48 (uneven dq, $J \cong 6.6$, $J = 1.5$ Hz, 2H), 2.87 (m, 1H), 2.72 (m, 1H), 2.52 (m, 1H), 2.28 (dd, $J = 3.3$, 9.6 Hz, 1H), 2.13 (m, 1H), 1.97 (m, 1H), 1.22 (uneven t, $J \cong 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 175.1, 90.02, 61.72, 42.53, 34.63, 28.64, 24.84, 15.14; IR (neat) 1720, 1700 cm^{-1}; MS (EI) 156 (M^+−Et), 140 (M^+−OEt).

4.4. [5(2*RS*),4*S*]-3-[(*E*)-5-(2-Ethoxy-5-oxopyrrolydin-1-yl)pent-2-enoyl]-4-phenyloxazolidin-2-one 1a

To a solution of phosphonate **6a**[12] (1.02 g, 2.99 mmol) in THF (20 mL) was added NaN $(TMS)_2$ (2.67 mL, 2.67 mmol, 1.0 M in hexane) at −15 °C under Ar. After being stirred for 1 h, a solution of **5** (550 mg, 2.97 mmol) in THF (3.5 mL) was added dropwise over 20 min at −25 °C. The reaction mixture was stirred at −25 °C for 1 h, and at −15 °C for 3 h. The reaction was quenched with a 10% citric acid solution (2.6 mL) and pH 6.86 phosphate buffer (35 mL), after which the mixture was extracted with AcOEt. The organic layer was washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by MPLC (hexane/*i*-PrOH, 20–40%) to give **1a** (960 mg, 87%) as a colorless viscous oil and nonseparable mixture of epimers (1:1); ^{1}H NMR (300 MHz, $CDCl_3$; 1:1* ratio of diastereomers) δ 7.40–7.21 (m, 5H+1H), 5.47 (dd, $J = 8.7$, 3.9 Hz, 1H), 4.93 (m, 1H), 4.70 (uneven t, $J \cong 8.9$ Hz, 1H), 4.28 (uneven dd, $J \cong 8.9$, 4.0 Hz, 1H), 3.44 and 3.43* (q, $J = 7.8$ Hz, 2H), 3.27 (m, H), 2.60–2.44 (m, 4H), 2.30 (m, 1H), 2.14 (m, 1H), 1.96 (m, 1H) 1.21 and 1.20* (t, $J = 7.8$ Hz, 3H); ^{13}C NMR (75 MHz, 1:1* ratio of diastereomers) δ 174.6, 163.82, 163.79*, 153.4, 147.32, 147.26*, 138.71, 138.67*, 128.9, 128.4, 125.73, 125.70*, 121.93, 121.87*, 89.36, 89.24*, 69.98, 61.48, 57.75, 57.74*, 39.34, 39.22*, 31.23, 31.17*, 29.03, 24.93, 15.44; IR (neat) 1780, 1690 cm^{-1}; MS (ESI) *m*/*z* 327 (M^+−OEt); HRMS (ESI): (M^+−OEt) calcd for $C_{18}H_{19}N_2O_4$, 327.1345; found, 327.1316.

4.5. [5(2*RS*),4*S*]-4-Benzyl-3-[(*E*)-5-(2-ethoxy-5-oxo-pyrrolydin-1-yl)pent-2-enoyl]oxazolidin-2-one 1b

The above procedure was carried out using phosphonate **6b**[12] (2.0 g, 5.63 mmol), **5** (938 mg, 5.06 mmol), NaN$(TMS)_2$ (5.06 mL, 5.06 mmol, 1.0 M in hexane) to give **1b** (1.81 g, 92%) as a colorless viscous oil and nonseparable mixture of epimers (1:1); ^{1}H NMR (400 MHz, $CDCl_3$; all signals belong to both diastereomers) δ 7.35–7.20 (m, 5H+1H), 7.13 (m, 1H), 4.97 (d, $J = 6.3$ Hz, 1H), 4.72 (m, 1H), 4.20 (m, 2H), 3.66 (m, 1H), 3.47 (q, $J = 7.0$ Hz, 2H), 3.33 (dd, $J = 3.2$, 13.4 Hz, 1H), 3.32 (m, 1H), 2,80 (dd, $J = 9.5$, 13.4 Hz, 1H), 2.64–2.48 (m, 3H), 2.33 (dd, $J = 3.0$, 9.9 Hz 1H), 2.17 (m, 1H), 1.99 (m, 1H), 1.24 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, 1:1* ratio of diastereomers) δ 175.0, 164.60, 153.4, 147.32, 147.30*, 135.2, 129.4, 128.9, 127.3, 122.22, 122.20*, 89.35, 89.30*, 66.14, 61.42, 55.22, 55.20*, 39.18, 39.12*, 37.79, 31.09, 31.06*, 28.88, 24.72, 15.24; IR (neat) 1780, 1690 cm^{-1}; MS (ESI)

m/*z* 341 (M^+−OEt); HRMS (ESI): (M^+−OEt) calcd for $C_{19}H_{21}N_2O_4$, 341.1501; found, 341.1478.

4.6. (4*S*)-7-Iodo-8-(2-oxo-4-phenyloxazolidine-3-carbonyl)-hexahydroindolizin-3-one 2a

To a solution of *n*-Bu_4NI (893 mg, 2.41 mmol) in CH_2Cl_2 (3 mL) was added dropwise $TiCl_4$ (4.83 mL, 4.83 mmol, 1 M inCH_2Cl_2) at −10 °C. After being stirred for 20 min at −15 °C, a solution of **1a** (600 mg, 1.61 mmol) in abs AcOEt (12 mL) was added. The mixture was stirred for 20 min at −10 °C, then allowed to warm to rt by removal from the ice cooling bath, and then stirred again for 2 h. The resulting black suspension was placed in a water bath at 40 °C and stirred for 15 h. The reaction mixture was re-cooled to 0 °C, quenched with satd NH_4Cl solution and water, then extracted with CH_2Cl_2. The organic layer was washed with 10% $Na_2S_2O_3$, saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$) to afford 436 mg (60%) of a mixture (65/28/7) of **2aA** (major component), **2aB** (next major component) and **2aC** (minor component) as a yellow solid, which was recrystallized from AcOEt to afford pure **2aA** (212 mg, recrystallized yield: 29%) as a white solid. The parent liquor was purified by MPLC (toluene/acetone, 15%) to afford the first fraction of semi-pure **2aB** (90 mg, isolated yield: 12%) and the second fraction of enriched **2aC**.

4.6.1. [7*S*,8*R*,8(4*S*),8a*S*]-7-Iodo-8-(2-oxo-4-phenyloxazolidine-3-carbonyl)hexahydroindolizin-3-one 2aA. The white solid of **2aA** obtained by the above procedure was recrystallized from *t*-BuOMe to give an analytically pure sample of **2aA** as colorless crystals: mp 184–185 °C; $[\alpha]_D^{25} = +42.3$ (*c* 1.01 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.35 (m, 3H), 7.32–7.30 (m, 2H), 5.51 (dd, $J = 3.2$, 8.6 Hz, 1H), 4.76 (t, $J = 8.8$ Hz, 1H), 4.54 (t, $J = 10.5$ Hz, 1H), 4.35 (dd, $J = 3.1$, 9.0 Hz, 1H), 4.26 (dt, $J = 3.9$, 12.5 Hz, 1H), 3.97 (ddd, $J = 1.5$, 5.1, 13.5 Hz, 1H), 3.49 (m, 1H), 2.68 (m, 1H), 2.47–2.41 (m, 2H), 2.30 (m, 1H), 2.13 (ddd, $J = 5.2$, 13.1, 26.2 Hz, 1H), 1.81 (m, 2H); ^{13}C NMR (100 MHz) δ 173.3, 171.3, 153.4, 138.8, 129.3, 129.0, 125.9, 69.99, 60.64, 57.94, 54.92, 41.13, 36.48, 29.54, 23.34 (*C*HI), 22.09; IR (KBr) 1770, 1705, 1680 cm^{-1}; MS (ESI) *m*/*z* 455 (MH^+); HRMS (ESI): (MH^+) calcd for $C_{18}H_{20}IN_2O_4$, 455.0468; found, 455.0444. Anal. Calcd for $C_{18}H_{19}IN_2O_4$: C, 47.59; H, 4.22; N, 6.17. Found: C, 47.80; H, 4.23; N, 6.35.

4.6.2. [7*S*,8*R*,8(4*S*),8a*R*]-7-Iodo-8-(2-oxo-4-phenyloxazolidine-3-carbonyl)hexahydroindolizin-3-one 2aB. The semi-pure sample of **2aB** derived from the first fraction obtained by the above procedure was recrystallized from AcOEt to give an analytically pure sample of **2aB** as colorless crystals: mp 168–170 °C; $[\alpha]_D^{26.8} = +209.4$ (*c* 1.01 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.4–7.31 (m, 5H), 5.40 (dd, $J = 4.1$, 8.8 Hz, 1H), 4.83 (br d, $J = 2.3$ Hz, 1H), 4.72 (t, $J = 9.0$ Hz, 1H), 4.38 (dd, $J = 4.2$, 9.1 Hz, 1H), 4.25 (m, 1H), 4.21 (m, 1H), 4.12 (dd, $J = 4.7$, 13.5 Hz, 1H), 3.01 (dt, $J = 2.9$, 12.5 Hz, 1H), 2.12–1.90 (m, 2H), 1.82 (m, 1H), 1.51 (ddd, $J = 6.4$, 11.0, 17.0 Hz, 1H), 1.12 (m, 1H); ^{13}C NMR (100 MHz) δ 173.6, 168.6, 153.3, 138.2, 129.18, 129.14, 126.5, 69.59, 57.78, 54.23, 47.40, 36.64, 29.44, 28.94, 26.39 (*C*HI), 20.37; IR (KBr) 1780, 1705, 1680 cm^{-1}; MS (ESI) *m*/*z* 455 (MH^+); HRMS (ESI): (MH^+) calcd for $C_{18}H_{20}IN_2O_4$, 455.0468; found, 455.0445. Anal. Calcd for $C_{18}H_{19}IN_2O_4$: C, 47.59; H, 4.22; N, 6.17. Found: C, 47.64; H, 4.32; N, 6.12.

4.6.3. [7*R*,8*S*,8(4*S*),8a*R*]-7-Iodo-8-(2-oxo-4-phenyloxazolidine-3-carbonyl)hexahydroindolizin-3-one 2aC. The second fraction of an enriched **2aC** obtained by the above procedure was purified by MPLC ($CHCl_3$) to afford a semi-pure sample of **2aC** (19 mg, isolated yield: 2.7%) as a white paste: ^1H NMR (600 MHz, $CDCl_3$) δ 7.41–7.33 (m, 5H), 5.53 (dd, $J = 2.9$, 8.6 Hz, 1H), 4.93, (t, $J = 4.7$ Hz, 1H), 4.75 (t, $J = 8.8$ Hz, 1H), 4.41 (dd, $J = 3.0$, 9.0 Hz, 1H), 4.33 (m, 1H), 4.08 (m, 1H), 3.80 (m, 1H), 2.79–2.69 (m, 2H), 2.10–2.03 (m, 2H), 1.84 (m, 1H), 1.33 (m, 1H), 1.15 (m, 1H); ^{13}C NMR (100 MHz) δ 173.4, 170.0, 153.5, 138.8, 129.2, 129.1, 126.4, 69.65, 59.19, 57.72, 46.43, 41.05, 32.11, 28.22, 21.21 (*C*HI), 20.91; MS (ESI) *m*/*z* 455 (MH^+); HRMS (ESI): (MH^+) calcd for $C_{18}H_{20}IN_2O_4$, 455.0468; found, 455.0481.

4.7. 8(4*S*)-8-(4-Benzyl-2-oxooxazolidine-3-carbonyl)-7-iodo-hexahydroindolizin-3-one 2b

The same procedure used in the preparation of **2a** was carried out using **1b** (535 mg, 1.38 mmol), *n*-Bu_4NI (767 mg, 2.08 mmol), and $TiCl_4$ (4.15 mL, 4.15 mmol, 1 M in CH_2Cl_2) to give **2b** (374 mg, 58%) as a mixture (90/10/trace) of **2bA** (major component), **2bB** (minor component), and **2bC** (not detected) as a yellow paste, which was recrystallized from AcOEt to afford pure **2bA** (288 mg, recrystallized yield: 45%) as colorless crystals. The parent liquor was concentrated in vacuo to give an enriched sample of **2bB**.

4.7.1. [7*S*,8*R*,8(4*S*),8a*S*]-8-(4-Benzyl-2-oxooxazolidine-3-carbonyl)-7-iodohexahydroindorizin-3-one 2bA. Mp 190–192 °C; $[\alpha]_D^{26.4} = +52.2$ (*c* 1.01 $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.36–7.28 (m, 3H), 7.24–7.23 (m, 2H), 4.76 (m, 1H), 4.46 (uneven t, $J \cong 10.5$ Hz, 1H), 4.33 (m, 1H), 4.28 (uneven t, $J \cong 8.3$ Hz, 1H), 4.22 (dd, $J = 2.4$, 9.1 Hz, 1H), 4.02 (ddd, $J = 1.6$, 5.1, 6.6 Hz, 1H), 3.74 (ddd, $J = 4.2$, 7.7, 7.8 Hz, 1H), 3.30 (dd, $J = 3.4$, 13.3 Hz, 1H), 2.80 (dd, $J = 9.9$, 13.3 Hz, 1H), 2.76 (dd, $J = 2.2$ Hz, $J \cong 7.6$ Hz, 1H), 2.52–2.44 (m, 2H), 2.39 (m, 1H), 2.18–2.09 (m, 2H), 1.92 (m, 1H); ^{13}C NMR (75 MHz) δ 173.7, 172.2, 153.5, 135.0, 129.6, 129.3, 127.8, 66.75, 60.84, 56.07, 55.01, 41.45, 38.46, 36.84, 29.78, 24.04 (*C*HI), 22.40; IR (KBr) 1780, 1690 cm^{-1}; MS (ESI) *m*/*z* 469 (MH^+); HRMS (ESI): (MH^+) calcd for $C_{19}H_{22}IN_2O_4$, 469.0624; found, 469.0662. Anal. Calcd for $C_{19}H_{21}IN_2O_4$: C, 48.73; H, 4.52; N, 5.98. Found: C, 48.67; H, 4.69; N, 5.83.

4.7.2. [7*S*,8*R*,8(4*S*),8a*R*]-8-(4-Benzyl-2-oxooxazolidine-3-carbonyl)-7-iodohexahydroindolizin-3-one 2bB. The enriched sample of **2bB** was purified by MPLC (toluene/acetone, 15%) to afford semipure **2bB** (28 mg, isolated yield: 4%) as a white paste accompanied by a nonseparable mixture of by-products. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.20 (m, 5H),

4.66 (ddd, $J = 3.6$, 6.6, 10.0 Hz, 1H), 4.56 (br q, $J = 2.7$ Hz, 1H), 4.40–4.33 (m, 2H), 4.23–4.15 (m, 3H), 3.34 (dd, $J = 3.5$, 10.1 Hz, 1H), 3.20 (dt, $J = 3.3$, 13.0 Hz, 1H), 2.69 (dd, $J = 10.1$, 13.0 Hz, 1H), 2.47–2.26 (m, 3H), 1.87 (m, 1H), 1.67 (m, 1H), 1.26 (m, 1H).

4.8. X-ray crystallographic study

4.8.1. Crystal structure data for 2bA. $C_{19}H_{21}IN_2O_4$, $M_r = 468.28$, monoclinic, $P2_1$, $a = 11.105(5)$ Å, $b = 8.329(4)$ Å, $c = 11.777(7)$ Å, $V = 979.35(9)$ Å^3, $T = 297(2)$ K, $Z = 2$, $D_x = 1.588$ Mg m^{-3}, μ(Mo Kα) = 1.660 mm^{-1}, 4286 measured reflections, 4286 unique reflections, 3281 observed reflections, $[I > 2\sigma(I)]$ $R_{(all)} = 0.0447$, $R_{(gt)} = 0.0358$, $wR_{(ref)} = 0.1038$, $wR_{(gt)} = 0.0995$, $S_{(ref)} = 0.848$.

4.8.2. Crystal structure data for 2aB. $C_{18}H_{19}IN_2O_4$, $M_r = 454.25$, monoclinic, $P2_1$, $a = 10.198(13)$ Å, $b = 9.728(6)$ Å, $c = 18.814(3)$ Å, $V = 1819.3(9)$ Å^3, $T = 297$ (2)K, $Z = 4$, $D_x = 1.658$ Mg m^{-3}, μ(Mo Kα) = 1.785 mm^{-1}, 7122 measured reflections, 7122 unique reflections, 3872 observed reflections $[I > 2\sigma(I)]$, $R_{(all)} = 0.0653$, $R_{(gt)} = 0.0369$, $wR_{(ref)} = 0.0897$, $wR_{(gt)} = 0.0858$, $S_{(ref)} = 0.770$.

All diagrams and calculations were performed using MAXUS crystallographic software package,[18] and the refinement was performed using SHELXL97.[19] CCDC 641914 (for **2bA**) and CCDC 641915 (for **2aB**) contain the supplementary crystallographic data for compounds **2bA** and **2aB**, respectively, studied in this article. These data can be obtained free of charge via http://www.ccdc.cam.au.ac.uk/deta_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or from The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; deposit@ccdc.cam.au.uk.

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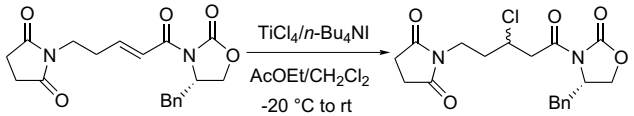
16. The conjugated addition of halide to optically active α,β-unsaturated *N*-acyloxazolidinone **7** under the same condi-

tions afforded chloride adduct **8** as a diastereomer mixture (1:1) in 75% yield, while iodide adducts were not detected (see the scheme below). This result suggests that the (*R*)- and (*S*)-iodo Ti-enolate were formed reversibly and were in rapid (dynamic) equilibrium with the starting material. Thus, enantioselectivity was not observed, and a more stable chloride adduct **8** was formed. However, exposure of substrates possessing *N*-acyloxazolozolidinones to such reaction conditions did not result in the formation of the iodide adducts. The reason for this is not understood at present (see Ref. 5). Compound **8**: Colorless paste as a nonseparable mixture of diastereomer (1:1); MS (ESI) *m*/*z* 393 (MH^+, Cl^{35}), 395 (MH^+, Cl^{37}); HRMS (ESI): (MH^+) calcd for $C_{19}H_{22}ClN_2O_5$, 393.1217; found, 393.1096.



7 **8** (1:1)

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