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A concise highly enantioselective cascade synthesis of indolizidine alkaloids with a quaternary stereocenter

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Abstract—Enantiomerically pure indolizidinones bearing a quaternary stereocenter were obtained by Rh(II)-catalyzed decomposition of α-diazo ketodiesters through a carbenoid/spiro[5,5]ammonium ylide/Stevens [1,2]-shift with a ring-expansion cascade process. The isolation of stable chiral ammonium ylides, namely the key intermediates of the process, unambiguously confirmed the stereochemistry of the total process.

1. Introduction

The tandem metallo-carbenoid/ylide/[1,2]-Stevens rearrangement sequence is of great potential as a method for the synthesis of complex alkaloids.[1] When looking at the stereochemistry in the rearrangement of ammonium[2] or oxonium ylides,[3] a high configuration retention level, during migration of a stereogenic center, can be expected.[4] Such a cascade sequence has been proposed for a (−)-epilupinine synthesis, involving a not isolable spirocyclic [5,6]-ammonium ylide generated from a diazocarbonyl compound,[5] and achieved with remarkable diastereoselectivity, but modest enantioselectivity.[6]

As part of an ongoing program on asymmetric synthesis by intramolecular C–H activation via metal carbenes derived from diazocarbonyls,[7] we attempted to prepare chiral indolizidinones **1a** and **1b**, which bear an asymmetric quaternary carbon, by using the above sequential protocol (Fig. 1).

These compounds are immediate precursors of swansonine analogues, an important class of biologically active natural and unnatural chiral polyhydroxylated alkaloids, whose development is required to achieve more concise and competitive synthetic methods aimed at lowering their high cost (swansonine is the first glycosidase inhibitor to be selected for clinical testing as an anticancer drug; its cost has hindered clinical trials).[8]

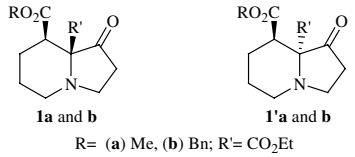
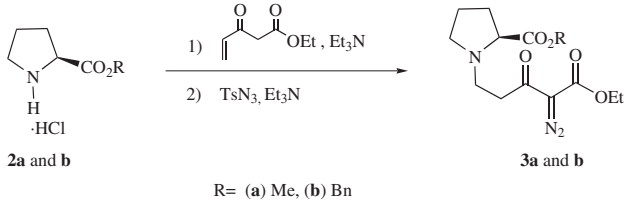


Figure 1.

2. Results and discussion

L-Prolines **2a** and **2b**, bearing the nitrogen atom tethered to an α-diazoketoester chain, were selected as the appropriate substrates for obtaining chiral alkaloids **1a** and **1b** and **1′a** and **1′b**. The starting diazocompounds **3a** and **3b** were prepared efficiently in two steps by conjugate addition of **2a** and **2b** to ethyl 3-keto-pent-4-enoate[9] followed by diazo-transfer with tosylazide (Scheme 1).



Scheme 1.

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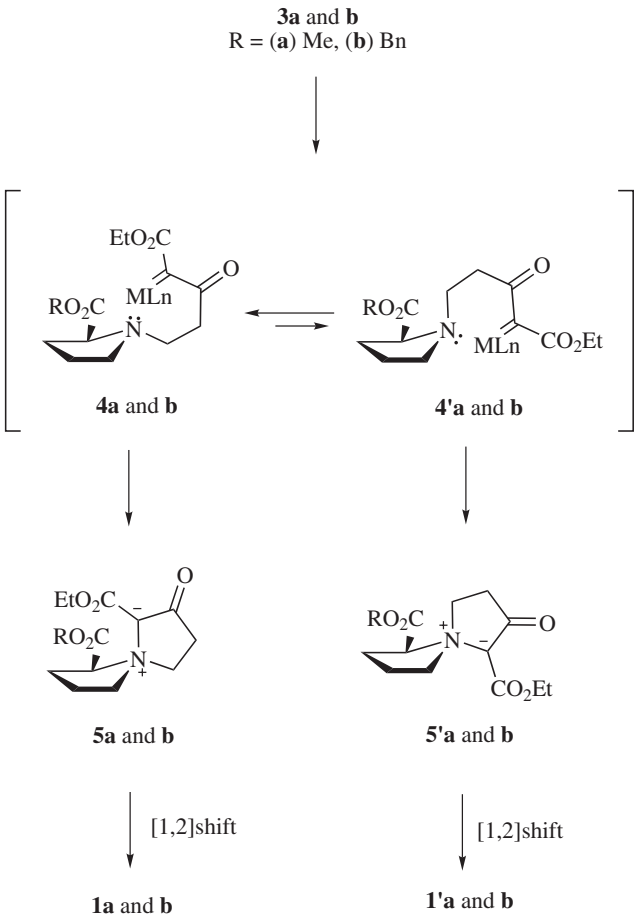


Scheme 2.

^{1}H NMR analysis of **3a** and **3b**, using the chiral reagent Eu(hfc)$_3$, indicated their enantiomeric purity, excluding racemization during the *N*-alkylation conjugate step.

The notion of using such diazocompounds as the key starting materials for a convenient approach toward the targets **1** and **1′** was attractive for the following reasons. Due to the diazo group position on the chain of **3a** and **3b**, [5,5]-spirocyclic ylides **5a** and **5b** were expected to form, by nitrogen trapping of the metallocarbene precursors **4a** and **4b**, over competitive C–H-insertion process, as depicted in Scheme 2. Moreover, the presence of a substituent on the ylide carbon could result in an improved enantioselectivity of the subsequent rearrangement step, by increasing the steric interaction to the chiral migrating group approach. Finally, the proline moiety choice of **3a** and **3b** was suggested by a probably more efficient [1,2]-shift of its carbon atom, due to the presence of a conjugative stabilizing C=O ester group.[11]

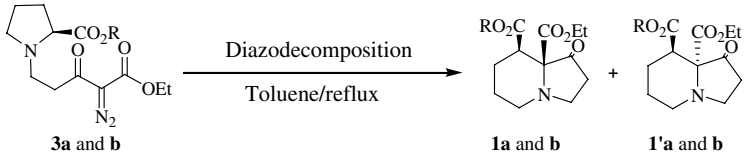
Two transition metal catalysts and various reaction conditions were studied (Table 1). When the diazo-decomposition was carried out in refluxing toluene using Rh$_2$(OAc)$_4$ as the catalyst, a 60/40 diastereomeric mixture of **1a** and **1′a** and 72/28 of **1b** and **1′b** were obtained in 84% and 85% yield, respectively. The Cu(acac)$_2$ catalyzed reaction afforded a 53/47 and 65/35 mixture with 90% yield. The diastereomers were resolved by flash chromatography. The configuration assignment to the newly formed quaternary stereocenter was deduced from 2D NOESY correlation studies. Thus, for the major **1a** and **1b** stereoisomers, the NOESY trace of the ethyl ester methylene protons showed a positive NOE effect for the proton at C-8 (3.65 and 3.66 ppm, respectively). This effect was not observed when the same experiments were performed for **1′a** and **1′b**. For compounds **1a** and **1b**, 80% and 90% ee, respectively, were measured by using the chiral reagent Eu(hfc)$_3$, and comparing the shift separations observed in the ^{1}H NMR spectra to those obtained from the racemates submitted to the same treatment.

The enantiomeric excesses of the minor stereoisomers **1′a** and **1′b** were difficult to determine, since they could not be obtained totally free of **1a** and **1b**.

Interestingly, when a CH_2Cl_2 solution of **3a** was refluxed, in the presence of Rh$_2$(OAc)$_4$ (Table 2) ylides **5a** and **5′a** (60:40) were obtained in reasonable yield and resolved by flash chromatography. Configuration assignment to the ylides was deduced from 2D NOESY correlation studies. Thus, for **5a** and **5b**, the NOESY trace of the ethyl ester methylene protons shows a positive NOE effect for the methyl and benzyl protons at 3.65 and 5.11 ppm, respectively. This effect was not observed when the same experiments were performed for **5′a** and **5′b**. ^{1}H NMR analysis of **5a** and **5b**, using the chiral reagent Eu(hfc)$_3$, indicated their enantiomeric purity, excluding racemization during the spirocyclization step.

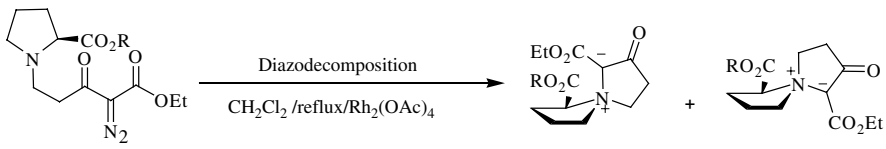
Heating of ylide **5a** in toluene at reflux (Table 3), without catalyst, afforded alkaloid **1a** cleanly as a single diastereoisomer (95% ee), in good yield. By decomposition

Table 1.



Substrate	Cat	Yield (%)	**1a** and **1b**:**1′a** and **1′b**	Ee of **1a** and **1b** (%)
3a	Rh$_2$(OAc)$_4$	84	60:40	80
3a	Cu(acac)$_2$	90	53:47	68
3b	Rh$_2$(OAc)$_4$	85	72:28	84
3b	Cu(acac)$_2$	90	65:35	90

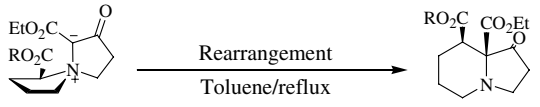
Table 2.



3a and **b** **5a** and **b** **5'a** and **b**

Substrate	Yield (%)	Diastereoselectivity (**5**:**5′**)
3a	91	60:40
3b	90	70:30

Table 3.



5a and **b** **1a** and **b**

Substrate	Yield (%)	Diastereoselectivity	Ee of **1a**,**b** (%)
5a	83	100	95
5b	85	100	95

performed under the same conditions, diazo benzylester **3b** furnished ylides **5b** and **5′b** as a 70:30 diastereomeric mixture. By heating ylide **5b** in toluene at reflux without a catalyst, alkaloid **1b**, was obtained as a single diastereomer in 95% ee.

3. Conclusion

In spite of data previously reported,[10] the rhodium-based catalysis for the generation of ammonium ylides has been shown to be more effective. It is interesting to note that in the refluxing toluene catalyzed protocol, the overall yield, diastereoselectivity, and enantioselectivity were increased for the benzyl diazoester **3b**. Rarely, during the decomposition of the diazocompounds could the ammonium ylides be isolated, only ever being obtained as achiral products.[11] The isolation of our stable ylides as pure diastereomers and enantiomers enabled us to probe the stereochemistry of the complete cascade process unambiguously. Their thermal reaction afforded the ring-expanded indolizidinones as pure diastereomers in high enantiomeric excess. These results may suggest the ylide undergoes a [1,2]-Stevens shift with retention; consequently this reaction step could still be considered intramolecular, or involving solvent caged radical pairs characterized by a very fast recombination.[2e]

The diastereomeric ratios observed for ylides **5a** and **5b** and **5′a** and **5′b**, obtained in the $CH_2Cl_2/Rh_2(OAc)_4$ reaction of **3a** and **3b**, were in line with the above conclusions: these ratios are approximately the same as those obtained for **1a** and **1b** and **1′a** and **1′b** in the refluxing toluene/$Rh_2(OAc)_4$ system, respectively.

In this cascade pathway, the stereochemical information is transferred to the newly formed stereogenic quaternary carbon of the target indolizidinones by migrating of the template proline stereocenter through the asymmetric nitrogen atom of the spirocyclic ammonium ylide intermediate.

In summary, this report represents a very rapid highly enantioselective synthetic approach to unnatural swainsonine analogues.[12] Our targets are characterized by the presence of a quaternary asymmetric carbon atom, whose construction is always of synthetic value.[13]

Finally, it is noteworthy that this protocol overall may meet the criteria of being atom-economic.[14]

4. Experimental

4.1. General

^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Varian VXR-300 spectrometer with TMS as the internal standard. COSY, NOESY, HSQC, and USQC-TOSCY spectra were recorded with a Bruker Avance 600 equipped with inverse detection probe. Infrared (IR) spectra were performed on a FT/IR-480plus JASKO spectrophotometer. The optical rotations were measured by a polarimeter P-1010 JASKO in a 1 dm tube. All reagents and solvents employed were reagent grade materials purified by standard methods and redistilled before use.

4.2. (2*S*)-1-(4-Diazo-4-ethoxycarbonyl-3-oxo-butyl)-pyrrolidine-2-carboxylic acid methyl ester 3a

To a stirred solution of L-proline methyl ester hydrochloride (1.0 g, 0.006 mol) and 3-oxo-pent-4-enoic acid ethyl ester (0.85 g, 0.006 mol) in CH_2Cl_2 (15 mL), a solution of Et_3N (0.63 mL, 0.0066 mol) in CH_2Cl_2 (10 mL)

was added dropwise and stirred for 30 min. To the reaction mixture, tosyl azide (1.20 g, 0.0066 mol) and a solution of Et_3N (2.8 mL, 0.02 mol) in CH_2Cl_2 (10 mL) were added dropwise at 0 °C . After the addition was complete, the solution was warmed to room temperature and stirred overnight. The solvent was evaporated and the residue purified by flash chromatography (Et_2O/petroleum ether/Et_3N, 8:2:0.1) to give the diazo compound **3a** (1.25 g, 70%) as a yellow oil: $[\alpha]_D^{25} = -56.1$ (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.33 (t, 3H, $J = 7.05$ Hz), 1.75–2.01 (m, 3H), 2.01–2.20 (m, 1H), 2.42 (q, 1H, $J = 7.8$ Hz), 2.70–2.85 (m, 1H), 3.00–2.15 (m, 3H), 2.15–3.25 (m, 2H), 3.73 (s, 3H), 4.29 (q, 2H, $J = 7.05$ Hz); ^{13}C NMR ($CDCl_3$): δ 14.3, 23.1, 29.3, 38.9, 49.0, 51.8, 53.3, 61.3, 65.6, 76.2, 161.2, 174.5, 191.2; IR (neat) 2955, 2835, 2135, 1717, 1653, 1301 cm^{-1}. Anal. Calcd for $C_{13}H_{19}N_3O_5$: C, 52.52; H, 6.44; N, 14.13. Found C, 52.43; H, 6.47; N, 14.09.

4.3. (2*S*)-1-(4-Diazo-4-ethoxycarbonyl-3-oxo-butyl)-pyrrolidine-2-carboxylic acid benzyl ester 3b

Following the above procedure, treatment of L-proline benzyl ester hydrochloride (1.5 g, 0.0062 mol) with 3-oxo-pent-4-enoic acid ethyl ester (0.88 g, 0.0062 mol), tosyl azide (1.34 g, 0.0068 mol), and Et_3N, gave, after flash chromatography (Et_2O/petroleum ether/Et_3N, 6:4:0.1), diazo compound **3b** (1.72 g, 75%) as a yellow oil: $[\alpha]_D^{25} = -43.3$ (*c* 1.0, $CHCl_3$); ^1H NMR: δ 1.32 (t, 3H, $J = 7.05$ Hz), 1.72–2.02 (m, 3H), 2.02–2.20 (m, 1H), 2.46 (q, 1H, $J = 8.7$ Hz), 2.73–2.90 (m, 1H), 3.00–3.23 (m, 3H), 3.31 (dd, 1H, $J = 5.6$, 8.7 Hz), 4.28 (q, 2H, $J = 7.05$ Hz), 5.16 (s, 2H), 7.29–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.2, 23.1, 29.2, 38.9, 48.8, 53.1, 61.3, 65.4, 66.2, 76.4, 128.0, 128.1, 128.4, 135.9, 161.1, 173.7, 191.1; IR (neat): 2978, 2823, 2135, 1716, 1654, 1456 and 1301 cm^{-1}. Anal. Calcd for $C_{19}H_{23}N_3O_5$: C, 61.11; H, 6.21; N, 11.25. Found C, 61.20; H, 6.20; N, 11.26.

4.4. Ylides 5a and 5′a

To a refluxing solution of $Rh_2(OAc)_4$ (0.013 g, 3 mol%) in 30 mL of dry CH_2Cl_2, a solution of **3a** (0.297 g, 0.001 mol) in dry CH_2Cl_2 (20 mL) was added dropwise over 30 min. After stirring for another 30 min at reflux, the reaction mixture was cooled and concentrated to give a 60:40 mixture of **5a** and **5′a**. Purification by flash chromatography (Et_2O/MeOH/Et_3N, 5:5:0.1) gave 0.147 g (55%) of **5a** as a yellow amorphous solid and 0.096 g (36%) of **5′a** not totally free of **5a**.

4.4.1. (5*S*,6*R*)-1-Ethoxycarbonyl-6-methoxycarbonyl-1-oxo-5-azonia[4,4]nonane-1-ylide 5a. $[\alpha]_D^{25} = -69.6$ (*c* 0.47, $CHCl_3$); ^1H NMR: δ 1.36 (t, 3H, $J = 7.1$ Hz), 2.13–2.35 (m, 2H), 2.35–2.57 (m, 2H), 2.62 (t, 2H, $J = 8.1$ Hz), 3.13–3.36 (m, 2H), 3.78 (s, 3H), 4.13–4.35 (m, 3H), 4.67 (q, 1H, $J = 10.8$ Hz), 5.61 (dd, 1H, $J = 8.6$ and 11.3 Hz); ^{13}C NMR ($CDCl_3$): δ 14.7, 19.5, 24.7, 32.9, 53.4, 55.8, 59.1, 66.0, 68.3, 99.8, 162.7, 167.2, and 178.8; IR (neat): 2961, 1739, 1592, 1441, 1263 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.90; H, 7.15; N, 5.20.

4.4.2. (5*R*,6*R*)-1-Ethoxycarbonyl-6-methoxycarbonyl-1-oxo-5-azonia[4,4]nonane-1-ylide 5′a. ^1H NMR: δ 1.31 (t, 3H, $J = 7.1$), 1.90–2.50 (m, 1H), 2.24–2.43 (m, 2H); 2.52–2.75 (m, 2H), 2.90–3.13 (m, 1H), 3.55–3.74 (m, 2H), 3.75 (s, 3H), 3.89 (q, 1H, $J = 9.3$ Hz), 4.02 (dd, 1H, $J = 6.9$ and 9.9 Hz), 4.08–4.40 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 14.9, 22.9, 27.9, 33.2, 52.9, 59.0, 65.8, 67.1, 77.5, 106.6, 162.8, 165.1, and 177.3.

4.5. Ylides 5b and 5′b

Following the above procedure, decomposition of diazoester **3b** (0.373 g, 0.001 mol) gave a 70:30 mixture of **5b** and **5′b** (0.310 g, 90%). Purification on a column of neutral alumina (CH_2Cl_2/MeOH, 95:5) gave **5b** as a pale oil and **5′b** not totally free of **5b**.

4.5.1. (5*S*,6*R*)-1-Ethoxycarbonyl-6-benzyloxycarbonyl-1-oxo-5-azonia[4,4]nonane-1-ylide 5b. $[\alpha]_D^{25} = -80.9$ (*c* 0.22, $CHCl_3$); ^1H NMR: δ 1.32 (t, 3H, $J = 7.1$ Hz), 2.09–2.61 (m, 6H), 3.20–3.43 (m, 2H), 3.95–4.09 (m, 1H), 4.23 (q, 2H, $J = 7.1$ Hz), 4.66 (q, 1H, $J = 10.8$ Hz), 5.18 (AB system, 2H), 5.69 (dd, 1H, $J = 8.4$ and 11.4 Hz), 7.29–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.7, 19.2, 24.4, 32.9, 55.6, 58.9, 65.7, 68.1, 99.7, 128.3, 128.6, 134.2, 162.6, 166.4, 178.7; IR (neat): 2977, 1739, 1645, 1594, and 1417 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.15; H, 6.68; N, 4.02.

4.5.2. (5*S*,6*R*)-1-Ethoxycarbonyl-6-benzyloxycarbonyl-1-oxo-5-azonia[4,4]nonane-1-ylide 5′b. ^1H NMR: δ 1.28 (t, 3H, $J = 7.1$ Hz); 1.92–2.11 (m, 1H), 2.26–2.42 (m, 2H), 2.50–2.80 (m, 2H), 3.00–3.18 (m, 1H), 3.60–3.82 (m, 2H), 3.91 (q, 1H, $J = 9.3$ Hz), 3.98–4.31 (m, 4H), 5.14 (AB system, 2H), 7.28–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.9, 23.1, 28.0, 32.9, 59.2, 66.0, 67.3, 68.1, 77.9, 107.3, 128.6, 128.7, 134.6, 162.8, 164.5, and 190.9.

4.6. General procedure for the diazo-decomposition in toluene

To a refluxing solution of catalyst in 30 mL of dry toluene was added dropwise a solution of diazo in 20 mL of dry toluene over 30 min. After stirring for another 30 min at reflux, the mixture was cooled, concentrated, and purified by flash chromatography.

4.6.1. Indolizidinones 1a and 1′a. (a) Following the general procedure, decomposition of **3a** (0.297 g, 0.001 mol) with of $Rh_2(OAc)_4$ (0.013 g, 3 mol%), after flash chromatography (petroleum ether/ethyl acetate, 8:2), gave 0.225 g (84%) of the product as a 60:40 resolved mixture of **1a** and **1′a**. (b) Following the general procedure, the decomposition of **3a** (0.297 g, 0.001 mol) with $Cu(acac)_2$ (0.013 g, 5 mol%) gave 0.270 g (90%) of product as 53:47 resolved mixture of **1a** and **1′a**. (c) By heating of 0.147 g of ylide **5a** in refluxing toluene for 30 min, 0.123 g (83%) of **1a** (95% ee) were obtained.

4.6.1.1. (8*R*,8*R*)-1-Oxo-hexahydro-indolizine-8,8a-dicarboxylic acid 8a-ethyl ester 8-methyl ester 1a. Colorless oil; $[\alpha]_D^{25} = -92$ (*c* 0.5, $CHCl_3$), 95% ee; ^1H NMR: δ 1.28 (t, 3H, $J = 7.1$ Hz), 1.49–1.55 (m, 3H), 2.27 (dd, 1H, $J = 2.7$ and 13.5 Hz), 2.42 (ddd, 1H, $J = 2.1$, 7.1, and 18.3 Hz), 2.78 (q, 1H, $J = 8.9$ Hz), 2.85–2.95 (m, 1H), 3.35 (dt, 1H, $J = 2.1$ and 8.7 Hz), 3.44 (q, 1H, $J = 8.1$ Hz), 3.56–3.63 (m, 1H), 3.67 (s, 3H), 4.21 (q, 2H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$): δ 14.2, 21.5, 24.7, 36.0, 44.1, 46.4, 47.4, 51.9, 61.6, 73.1, 169.2, 172.4, and 208.8; IR (neat): 2950, 2855, 2748, 1765, 1736, 1443 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 58.11; H, 7.06; N, 5.17.

4.6.1.2. (8*R*,8a*S*)-1-Oxo-hexahydro-indolizine-8,8a-dicarboxylic acid 8a-ethyl ester 8-methyl ester 1′a. Colorless oil; $[\alpha]_D^{25} = 80$ (*c* 0.6, $CHCl_3$), 90% ee; ^1H NMR: δ 1.30 (t, 3H, $J = 7.1$ Hz), 1.52–1.71 (m, 1H), 1.71–1.83 (m, 1H), 1.92–2.04 (m, 1H), 2.22–2.60 (m, 4H), 2.78 (ddd, 1H, $J = 1.8$, 5.1, and 11.7 Hz), 2.83–2.94 (m, 1H), 3.08 (dt, 1H, $J = 3.3$ and 12 Hz), 3.17 (dt, 1H, $J = 2.1$ and 9.0 Hz), 3.71 (s, 1H), 4.15–4.36 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.3, 23.5, 24.1, 34.8, 44.5, 45.5, 46.6, 51.8, 60.8, 68.4, 167.0, 172.9, and 206.3; IR (neat): 2940, 2847, 1776, 1731, 1438 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.89; H, 7.17; N, 5.15.

4.6.2. Indolizidinones 1b and 1′b. (a) Following the general procedure, the decomposition of **3a** (0.373 g, 0.001 mol) with $Rh_2(OAc)_4$ (0.013 g, 3 mol%) in toluene gave, after flash chromatography (petroleum ether/ethyl acetate, 8:2), 0.225 g (85%) of product as a resolved mixture of **1b** and **1′b** in the ratio of 72:28. (b) Following the general procedure, the decomposition of 0.373 g (0.001 mol) of **3b** with 0.013 g (5 mol%) of $Cu(acac)_2$ gave 0.310 g (90%) of product as a resolved mixture of **1b** and **1′b** in the ratio of 65:35. (c) The heating of 0.200 g of ylide **5b** in refluxing toluene for 30 min gave 0.170 g (85%) of **1a** with 95% ee.

4.6.2.1. (8*R*,8a*R*)-1-Oxo-hexahydro-indolizine-8,8a-dicarboxylic acid 8-benzyl ester 8a-ethyl ester 1b. Pale yellow oil; $[\alpha]_D^{25} = -70.1$ (*c* 1.5, $CHCl_3$), 95% ee; ^1H NMR: δ 1.27 (t, 3H, $J = 7.1$ Hz), 1.42–1.74 (m, 3H), 2.24–2.44 (m, 2H), 2.68 (q, 1H, $J = 8.7$ Hz), 2.81–2.99 (m, 2H), 3.27 (dt, 1H, $J = 2.1$ and 8.7 Hz), 3.42 (q, 1H, $J = 7.8$ Hz), 3.60–3.68 (m, 1H), 4.20 (q, 2H, $J = 7.1$ Hz), 5.11 (AB system, 2H), 7.27–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.2, 21.6, 24.9, 36.0, 44.1, 46.4, 47.4, 61.6, 66.6, 73.2, 128.1, 128.2, 128.5, 135.7, 169.2, 171.7, 209.9; IR (neat): 3033, 2939, 2855, 1764, 1725, and 1455 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.14; H, 6.75; N, 4.05.

4.6.2.2. (8*R*,8a*S*)-1-Oxo-hexahydro-indolizine-8,8a-dicarboxylic acid 8-benzyl ester 8a-ethyl ester 1′b. Yellow oil; $[\alpha]_D^{25} = 34.4$ (*c* 0.88, $CHCl_3$), 90% ee; ^1H NMR: 1.22 (t, 3H, $J = 7.1$ Hz), 1.50–1.71 (m, 3H), 1.71–1.84 (m, 1H), 1.94–2.09 (m, 1H), 2.25–2.46 (m, 2H), 2.46–2.62 (m, 2H), 2.78 (ddd, 1H, $J = 1.8$, 5.1, and 11.4 Hz), 2.82–2.93 (m, 1H), 3.07 (dt, 1H, $J = 3.3$ and 11.7 Hz), 3.12–3.22 (m, 1H), 4.13 (ddq, 2H, $J = 7.2$, 10.8, and 51 Hz), 5.15 (s, 2H), 7.26–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.0, 23.7, 24.2, 34.9, 44.8, 45.6, 46.7, 60.8, 66.6, 68.4, 128.2, 128.5, 129.6, 135.8, 166.9, 172.3, 206.3; IR (neat): 3033, 2938, 2849, 1766, 1731, 1455 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.97; H, 6.72; N, 4.09.

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References and notes

1. Curtis, E. A.; Padwa, A.; Worsencroft, K. J. *Tetrahedron Lett.* **1997**, *38*, 3319; Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Sheean, S. M. *J. Org. Chem.* **1997**, *62*, 78; Padwa, A.; Price, A. T. *J. Org. Chem.* **1998**, *63*, 5556; Padwa, A.; Snyder, J. P.; Curtis, E. A.; Sheean, S. M.; Worsencroft, K. J.; Kappe, C. O. *J. Am. Chem. Soc.* **2000**, *122*, 8155.
2. (a) Campell, A.; Huston, A. H. J.; Kenion, J. *J. Chem. Soc.* **1947**, 93; (b) Brewster, H. H.; Kline, M. W. *J. Am. Chem. Soc.* **1952**, *74*, 5179; (c) Millard, B. J.; Stevens, T. S. *J. Chem. Soc.* **1963**, 3397; (d) Schollkopf, U.; Ludwig, U.; Ostermann, G.; Patsch, M. *Tetrahedron Lett.*, **1969**, 3415; (e) Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009.
3. West, F. G.; Eberlein, T. H.; Tester, R. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2857; Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062.
4. For a general review of the Stevens rearrangement, see: Markò, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 913–973; West, F. G.; Clark, J. S. In *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Clark, J. S., Ed.; University Press Oxford: Oxford, 2002; See also: Stevens, T. S.; Creighton, E. M.; Gordon, A. B.; Macincol, M. T. *J. Chem. Soc.* **1928**, 3193.
5. For reviews of ammonium ylides generated by diazo compounds, see: Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo-Compounds*; John Wiley Sons: New York, 1997; West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *116*, 1177; Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263; Padwa, A.; Beall, L. S. In *Advances in Nitrogen Heterocycles*; JAI: Stamford, CT, 1998; Vol. 3, pp 117–158.
6. (a) West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420; (b) Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, *53*, 16565; (c) Vanecko, J. A.; West, F. G. *Org. Lett.* **2002**, *4*, 2813.
7. Chelucci, G.; Saba, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 78; Chelucci, G.; Saba, A. *Tetrahedron Lett.* **1995**, *36*, 4673; Chelucci, G.; Saba, A.; Valle, G. *Tetrahedron: Asymmetry* **1995**, *6*, 807; Chelucci, G.; Saba, A. *Tetrahedron: Asymmetry* **1997**, *8*, 699; Chelucci, G.; Culeddu, N.; Saba, A.; Valenti, R. *Tetrahedron Lett.* **1999**, *40*, 8269; Chelucci, G.; Saba, A.; Valenti, R.; Bacchi, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3449; Saba, A. *Tetrahedron Lett.* **2003**, *44*, 2895.
8. Motohiro, H.; Kunio, N.; Hiroshi, T.; Junji, H.; Masanobu K.; Hatsuo, A.; Hiroshi, I. Patent EP 104826; *Chem. Abstr.* **1984**, *101*, 28283x; White, S. L.; Schweitzer, K.;

Humpries, D.; Olden, K. *Biochem. Biophys. Res. Commun.* **1988**, *150*, 615; Yagita, M.; Saksela, E. *Scand. J. Immunnol.* **1990**, *31*, 275; Kino, T.; Inamura, N.; Nakahara, K.; Kiyoto, S.; Goto, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 936; Stegelmeier, B. L.; Snider, P. W.; James, L. F.; Panter, K. E.; Molyneux, R. J.; Gardner, D. R.; Ralphs, M. H.; Pfister, J. A. *Tox. Plants Other Nat. Toxicants* **1998**, 285; Dennis, J. W.; Shah, R. N.; Ziser, L. Patent WO 9,846,602; *Chem. Abstr*. **1998**, *129*, 306525j.

9. Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717.
10. West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892; Clark, J. S.; Krowiak, S. A.; Street, L. J.; West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6892; West, F. G.; Glaeske, K. W.; Naidu, B. N. *Synthesis* **1993**, 977.
11. Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem.* **2001**, *66*, 2414; Padwa, A.; Snyder, J. P.; Curtis, C. O.; Shechan, S. M.; Worsencroft, K. J.; Kappe, C. O. *J. Am. Chem. Soc.* **2000**, *122*, 8155.
12. El Nemr, A. *Tetrahedron* **2000**, *56*, 8579.
13. Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1688; Dehli, J. R.; Gotor, V. *J. Org. Chem.* **2002**, *67*, 1716; Kawabata, T.; Kawatami, S.; Majumdar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012; Spino, C.; Beaulieu, C. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1930; Spino, C.; Gobdout, C. *J. Am. Chem. Soc.* **2003**, *125*, 12107; Carlier, P. R.; Zhao, H.; De Guzman, J. C.-H.; Lam, P. *J. Am. Chem. Soc.* **2003**, *125*, 11483; For reviews, see: Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4591; Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 389; Fuji, K. *Chem. Rev.* **1993**, *93*, 2037; Romo, D.; Mayers, A. I. *Tetrahedron* **1991**, *47*, 5903; Martin, S. F. *Tetrahedron* **1980**, *36*, 419.
14. Trost, B. M. *Science* **1991**, *254*, 1471.