

EPIMERIZATION OF TRANS-3-ARYLAZIRIDINE-2-CARBOXYLATES AT THE C3 POSITION †

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Abstract – We describe here effective epimerization of trans to cis isomer of 1-benzyl-3-arylaziridine-2-carboxylates. The combination of samarium metal, iodine and N,N-dimethylaminoethanol promoted the epimerization of trans isomer to a ca. 1 : 1 mixture of cis and trans ones. Investigating more effective catalyst, indium chloride was found to afford a ca. 2 : 1 mixture of cis and trans isomers. Epimerization at benzylic position in the aziridines is suggested from the result with optically active ones. Preparation of cis-2-indolylaziridine towards construction of aziridinomitosene skeleton was achieved in this epimerization reaction.

INTRODUCTION

Aziridines are one of the versatile synthetic intermediates for the preparation of N-containing biologically active compounds.1,2 Among them, synthesis and utilization of aziridine-2-carboxylates 1 are much focused because they are convertible to α- 2 or β-amino acid derivatives 3 by regioselective ring-opening reactions at C3-N and C2-N bond, respectively (Scheme 1).1,3,4 We have reported an atom-economical synthesis of 3-arylaiziridine-2-carboxylates 1 from guanidinium salt 4 (derived from ureas 5) and aromatic aldehydes 6 mediated by a base such as 1,1,3,3-tetramethylguanidine (TMG).5 Synthesis of optically active 1 was also achieved with employing chiral guanidinium salt 7 in high ee. In this process, trans isomers mainly formed when electron-rich aromatic aldehydes such as piperonal and p-anisaldehyde were used and were successfully applied to the synthesis of β-aminoalcohols.6,7 However, corresponding cis-aziridines, applicable to the synthesis of natural products containing cis-aziridines such as mitomycin C,8 were minor products in this process, whereas the ratio of cis isomer was increased up to 3 : 1 when aromatic aldehydes with non-substituted or electron-withdrawing group are used.9 Epimerization of
trans-aziridines is one of the candidates for preparation of the corresponding cis isomers. During our trials for reductive ring opening of trans-3-arylaziridine-2-carboxylates to amino acid derivatives, we observed the epimerization of trans isomer to cis one. We describe here the new method for the synthesis of cis-aziridinecarboxylates cis-1 by epimerization of the corresponding trans isomer trans-1 and its application for the synthesis of cis-indolylaziridine derivative, the useful synthetic intermediate for the construction of aziridinomitosene skeleton.10

RESULTS

Synthesis of Aziridines
The trans isomers of aziridine substrates trans-1 employed in this study were synthesized according to the reported procedure from guanidinium salt 4 or chiral one 7 and aldehydes 6 (Scheme 1). The N-tosylindole-2-carboxyaldehyde (6c), the substrate for the synthesis of indolylaziridine 1c, was prepared through LiAlH4 reduction and MnO2 oxidation of commercially available indole-2-carboxylate 8 followed by tosylation (Scheme 2).
Trials for regioselective ring opening of trans-1a

Aziridines (11 in Figure 1) are classified into two groups, “activated” and “unactivated” (or nonactivated) aziridines, dependent on their substituents on the nitrogen atom, in which the former category includes electron-withdrawing substituents such as tosyl, tert-butoxycarbonyl or acyl functions, whereas a hydrogen atom and alkyl substituents are typical for the latter one. Although the reactivity of “activated” aziridines were well investigated, there are only limited reports on the utilization of “unactivated” aziridines for organic synthesis. For example, β-aminoester synthesis via regioselective reductive ring opening of aziridinecarboxylates by the reductions with magnesium metal in methanol and with samarium (II) iodide (SmI₂) had been reported. In the former condition, only “activated” aziridines gave the corresponding β-aminoesters. On the other hand, the latter SmI₂ afforded the corresponding β-aminoesters and from “activated” 2-acylaziridine (R = H in Figure 1), respectively, in the presence of N,N-dimethylaminoethanol.

"Activated" aziridines: R = Ts, Boc, Ac, etc.
"Unactivated" aziridines: R = H, alkyl, etc.

Figure 1 “Activated” and “unactivated” aziridines

Scheme 3 Reported synthesis of β-aminoesters 13 and 15 via reductive ring-opening of “activated” 12 and “unactivated” aziridines 14 by SmI₂/DMEA system.
(DMEA) as a proton source and a Lewis acid scavenger (Scheme 3). The selective formation of \( \beta \)-aminoesters 13 and 15 could be explained by the regioselective C2-N bond cleavage of ketyl radicals 16.

Thus, we attempted reductive ring opening of “unactivated” aziridinecarboxylate (±)-\( \text{trans-1a} \) (R = benzyl in Figure 1) with SmI\(_2\) for the synthesis of \( \beta \)-aminoester 17. However, most of the starting material was recovered and only small amount of desired \( \beta \)-aminoester 17 was obtained on the reaction with SmI\(_2\), prepared from samarium metal (Sm) and diiodomethane (CH\(_2\)I\(_2\)), in the presence of DMEA at -78 °C (run 1, Table 1). The reaction was sluggish even at -40 °C to give \( \alpha \)-18 and \( \beta \)-aminoesters 17 in low yields (run 2). Therefore, we turned to utilize molecular iodine (I\(_2\)) for the activation of Sm.\(^{16}\) This reaction system has the following advantages towards conventional Sm/CH\(_2\)I\(_2\) system for the preparation of SmI\(_2\): 1) Sm has higher reductive potential compared to SmI\(_2\) (Sm\(^{2+}/\text{Sm} = -2.68 \text{ V}, \text{Sm}^{3+}/\text{Sm}^{2+} = -1.55 \text{ V});\(^{17}\) 2) iodide anion could be reusable in Sm(0)-Sm(II) and Sm(II)-Sm(III) conversions.

Two procedures for the preparation of SmI\(_2\) from Sm and I\(_2\) reported by Yanada \textit{et al.} were Table 1 Trials for ring-opening reaction of aziridine (±)-\( \text{trans-1a} \) with “SmI\(_2\)”

![Diagram](image-url)

<table>
<thead>
<tr>
<th>run</th>
<th>method</th>
<th>I(_2) (eq)</th>
<th>conditions</th>
<th>crude (%)</th>
<th>trans-1a</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>cis-1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1( ^b )</td>
<td>-</td>
<td>-</td>
<td>-78 °C, 30 min</td>
<td>57</td>
<td>88</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2( ^b )</td>
<td>-</td>
<td>-</td>
<td>-40 °C, 30 min</td>
<td>77</td>
<td>70</td>
<td>8</td>
<td>22</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>0.4</td>
<td>50 °C, 30 min</td>
<td>quant.</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>4.0</td>
<td>rt, 30 min</td>
<td>80</td>
<td>7</td>
<td>-</td>
<td>26</td>
<td>29</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>0.4</td>
<td>50 °C, 30 min</td>
<td>77</td>
<td>91</td>
<td>-</td>
<td>trace</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6( ^c )</td>
<td>B</td>
<td>0.4</td>
<td>rt, 30 min</td>
<td>91</td>
<td>91</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>4.0</td>
<td>50 °C, 30 min</td>
<td>63</td>
<td>-</td>
<td>-</td>
<td>38</td>
<td>62</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\( ^a \) The ratio was determined by the \(^1\)H-NMR analysis. \( ^b \) SmI\(_2\) (4 equivalents), prepared from Sm metal and CH\(_2\)I\(_2\), was used. \( ^c \) HMPA (2 equivalents) was added.
tested: THF was added to a mixture of Sm, I₂ and aziridine substrate followed by addition of DMEA as described in the literature (method A);¹⁸ᵃᵇ a mixture of Sm and I₂ in THF was roughly degassed and sonicated. Confirmed the blue color in the reaction mixture, a solution of aziridine and DMEA in THF was added (method B).¹⁸ᶜ At first, the effect of the equivalency of I₂ was examined in method A. When 0.4 equivalent of I₂ was used, the epimerization product (±)-cis-1a was obtained instead of the desired β-aminoester 17 (run 3). In this case, the ratio of cis and trans isomers in crude product was ca. 1 : 1. Increment of I₂ to 4.0 equivalents lead to the non-selective formation of α-aminoester 18, dihydrocinnamate 19, cinnamate 20,¹⁹ and (±)-cis-1a (run 4). The indicative blue color of SmI₂ was not observed in each trials in method A. On the other hand, the reaction was retarded in method B with 0.4 equivalent of I₂, even in the presence of HMPA (runs 5, 6). Dihydrocinnamate 19 and α-aminoester 18 were mainly generated with excess amount of I₂ (run 7). In these trials, desired β-aminoester 17 was not obtained as a major product, however, the epimerization of trans-aziridine to cis-one was observed with 0.4 equivalent of I₂ in method A. To our knowledge, only the epimerization reaction of aziridines in basic,²⁰ thermal²¹,²² and photochemical conditions²² and that of vinyl aziridines with palladium catalysts²³ were reported.²⁴ Thus, we explored the epimerization reactions of trans-1a.²⁵

Table 2 Effects of reagents on the epimerization of aziridine (±)-trans-1a

<table>
<thead>
<tr>
<th>run</th>
<th>Sm (4 eq)</th>
<th>I₂ (0.4 eq)</th>
<th>DMEA (4.0 eq)</th>
<th>product ratio ¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>trans-1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>24 (13)</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>40 (24)</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>40 (24)</td>
</tr>
</tbody>
</table>

¹ The ratio was determined by the ¹H-NMR analysis. The value in parenthesis shows isolated yield after column chromatography (hexane - AcOEt = 20 : 1 to 5 : 1). ² Run 3 in Table 1. ³ Small amount of unidentified byproducts was contaminated. ⁴ Anti : syn = 1.0 : 0.2.
Epimerization reaction of trans- to cis-aziridinocarboxylates

We next examined the role of reagents in method A (Table 2). Epimerization is predominant in the absence of DMEA, however, amide cis-21 was isolated as a byproduct, which would be derived from (±)-cis-1a and benzylamine, presumably generated on decomposition of 1a (run 2). Corresponding trans-isomer of 21 was not observed in this experiment. Surprisingly, even in lacking Sm and both of Sm and DMEA, 1 : 1 mixtures of (±)-cis- and (±)-trans-1a were obtained (runs 3, 4). A small amount of unidentified byproducts was contaminated in the former, and ring-opening product 22 was generated as a mixture of diastereoisomers in the latter condition. No reaction was observed in the absence of I2 (run 5). These results showed that I2 is crucial for this epimerization.

To identify the epimerized chiral center of trans-1a, optically active aziridine trans-1a was subjected to the reaction in method A (Scheme 4). Treatment of (2R,3S)-trans-1a (71% ee) with Sm/I2 system afforded a 1 : 1 mixture of cis- and trans-1a. After the separation, absolute configuration of each diastereoisomer was determined as (2R,3S) for trans and (2R,3R) for cis isomer by chiral HPLC analysis, respectively, which shows that the epimerization occurs at benzylic C3 position of trans-1a.

Next, the effect of the aryl groups at C3 of aziridines was investigated (Table 3). Reactions of trans-aziridines with electron-rich aromatics such as 3,4-methylenedioxy- trans-1a and 3,4-dimethoxyphenyl derivatives trans-1b gave a 1 : 1 mixture of diastereoisomers (runs 1, 2). Disappointingly, epimerization of 2-indolyl derivative trans-1c to cis-one, a synthon for the aziridinomitosene skeleton, was sluggish (run 3) and phenyl trans-1d and 4-chlorophenyl derivatives trans-1e gave no isomerization product (runs 4, 5). These results clearly showed that the electron-donating character of aryl group is important in this epimerization reaction.

Thus, more powerful catalysts were explored with using several Lewis acids (Table 4). Epimerization of (±)-trans-1a with boron trifluoride etherate (BF3·OEt2) at -60 °C produced a trans-major mixture (cis : trans = ca. 1 : 2.3) (run 2). Stronger Lewis acid, such as tin (IV) chloride (SnCl4) was not so effective to give a mixture in the same ratio as the reaction with BF3·OEt2 (run 3). Milder Lewis acid such as zinc iodide (ZnI2) gave cis-major mixture, however, ring opening product 22 was contaminated as a major

![Scheme 4 Epimerization reaction of optically active aziridine (2R,3S)-trans-1a with Sm/I2 system](image-url)
Table 3 Effects of aryl group at C3 on the epimerization of aziridine (±)-trans-1

<table>
<thead>
<tr>
<th>run</th>
<th>aziridine</th>
<th>product ratio</th>
<th>run</th>
<th>aziridine</th>
<th>product ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>50 : 50</td>
<td>4</td>
<td>1d</td>
<td>100 : 0</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>52 : 48</td>
<td>5</td>
<td>1e</td>
<td>100 : 0</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>83 : 17</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Ar in aziridines 1 correspond to those in Scheme 1. b The ratio was determined by the 1H-NMR analysis. c Run 3 in Table 1.

Table 4 Effects of reagents on the epimerization of aziridine trans-1

<table>
<thead>
<tr>
<th>run</th>
<th>aziridine</th>
<th>reagents</th>
<th>solvent</th>
<th>condition</th>
<th>crude yield (%)</th>
<th>product ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Sm (4), I2 (0.4), DMEA (4)</td>
<td>THF</td>
<td>50 °C, 30 min</td>
<td>quant.</td>
<td>50 50 -</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>BF3·OEt2 (1.0)</td>
<td>CH2Cl2</td>
<td>-60 °C, 3.5 h</td>
<td>quant.</td>
<td>70 (60) 30 (25) -</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>SnCl4 (1.0)</td>
<td>CH2Cl2</td>
<td>-60 °C, 1 h</td>
<td>95</td>
<td>70 30 -</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>ZnI2 (0.8)</td>
<td>CH2Cl2</td>
<td>0 °C, 2 h</td>
<td>97</td>
<td>29 14 57</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>InCl3 (0.7)</td>
<td>CH2Cl2</td>
<td>rt, 30 min</td>
<td>98</td>
<td>36 64 -</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>InCl3 (0.2)</td>
<td>CH2Cl2</td>
<td>rt, 30 min</td>
<td>quant.</td>
<td>30 70 -</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>InCl3 (0.2)</td>
<td>CH2Cl2</td>
<td>rt, 1 d</td>
<td>quant.</td>
<td>30 70 -</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>InCl3 (0.3)</td>
<td>CH2Cl2</td>
<td>rt, 20 min</td>
<td>quant.</td>
<td>30 70</td>
</tr>
<tr>
<td>9</td>
<td>1c</td>
<td>InCl3 (0.2)</td>
<td>CH2Cl2</td>
<td>rt, 1 h</td>
<td>quant.</td>
<td>48 (44) 52 (43) -</td>
</tr>
</tbody>
</table>

a Ar in aziridines 1 correspond to those in Scheme 1. b The ratio was determined by the 1H-NMR analysis. The value in parenthesis shows isolated yields after column chromatography. c Run 3 in Table 1. d Anti : syn = 1.0 : 0.1. e (2R,3S)-isomer (76% ee). f (2R,3R)-isomer (76% ee).
product (cis-1a : trans-1a : 22 = ca. 2 : 1 : 4) (run 4). Next, indium chloride (InCl₃), effective catalyst for the ring opening of “activated” and “unactivated” aziridines, was applied. As a result, cis-major mixture (cis : trans = ca. 1.8 : 1) of 1a was obtained without any formation of byproduct (run 5). The ratio of the epimeric products was not affected by the decrease of the reagent from 0.7 to 0.2 equivalent (run 6) or longer reaction period to 1 day (run 7). Epimerization at C-3 position of 1a was confirmed by conversion of (2R,3S)-trans to (2R,3R)-cis isomer (run 8). The epimerization of trans-indolylaziridine 1c with InCl₃ gave a ca. 1 : 1 mixture of cis- and trans-1c (run 9).

**DISCUSSION**

The epimerization of trans-1a with Sm/I₂ system could be proceeded in mainly two steps: 1) ring opening, 2) re-cyclization, and via four pathways (Scheme 5): cationic cleavage of aziridine trans-1a at C2-N (to 23, path A) and C3-N bonds (to 24, path B), and single-electron reduction on the carbonyl group to ketyl radical 27 and cleavage at C2-N (to 25, path C) and C2-C3 bonds (to 26, path D). The result with optically active trans-aziridine (2R,3S)-trans-1a to cis-one (2R,3R)-1a (Scheme 4) supports path B. The results of runs 2-4 in Table 2 showed the important role of I₂. Furthermore, the epimerization was not observed when I₂ was completely consumed for the preparation of SmI₂ in method B (run 5 in Table

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**Scheme 5 Possible pathways of the epimerization of trans- to cis-aziridine 1a**
Scheme 6 Proposed mechanisms of epimerization of trans-1a via C3-N bond cleavage

1). From these results, the selective cleavage of benzylic C3-N bond mediated by I2 (path E in Scheme 6) to iodide 28 and S_N1-type re-cyclization were proposed as a reaction mechanism. Sm species could act as Lewis acid towards 1a to promote the ring-opening step via aziridinium 29 to iodide 30 (path F). Reaction with other Lewis acids such as InCl3 is considered to proceed through C3-N bond cleavage of trans-1a to cationic intermediate 31 followed by re-cyclization (path G). For the moment, the reason why InCl3 gave the best result is not clear.

Scheme 7 Proposed mechanism for the generation of hydrogenated products 18 and 19
On the other hand, the main products of the reaction with excess mount of I₂ are hydrogenated products such as 18 and 19 (runs 4 and 7 in Table 1). Selective C3-N bond cleavage of aziridine trans-1a with I₂ and reduction of corresponding iodide 28 with SmI₂ would furnish organosamarium species 32, which would be protonated to α-aminoester 18. Elimination of samarium amide 33 from 32 to cinnamate 20 followed by reduction with SmI₂ would give dihydrocinnamate 19 (Scheme 7).

CONCLUSION
In conclusion, we found the epimerization conditions of trans to cis isomer of 3-arylaziridine-2-carboxylates. In the preliminary trials, a combination of Sm, I₂, and DMEA was found to be effective, in which I₂ is crucial in this epimerization. The reaction with optically active aziridine suggested the epimerization at benzylic C3 position. InCl₃ was found to be the most effective Lewis acid for the epimerization of aziridines with electron-rich aromatics as well as indolyl group.²⁸ Application of this system to the synthesis of cis-aziridine-containing natural products such as mitomycins is under investigation.

EXPERIMENTAL
General: All melting points were measured on Yanagimoto MPSI melting point apparatus and are uncorrected. IR spectra were recorded in neat or with Attenuated Total Reflectance (ATR) system on a JASCO FT / IR-300E spectrophotometer. ¹H and ¹³C NMR spectra were recorded in CDCl₃ on a JEOL JNM-GSX-400α, JNM-ECP-400, JNM-GSX-500α, JNM-ECP-600 unless otherwise stated. MS spectra were measured on JEOL JNM MS-GCMATE for EIMS, and JEOL JMS-HX110 or JEOL JMS-AX505 for FABMS. Ultrasonic stirrer, a Nihonseiki Youkai-kun, USS-1, was used for sonication. For column chromatography was used Kanto Chemical silica gel 60 spherical. For TLC were used Merck Art 5715 DC-Fertigplatten Kieselgel 60 F₂₅₄. Anhydrous CH₂Cl₂ and THF were purchased from Kanto Chemical and Wako Chemical, respectively. Samarium metal (Sm) was purchased from Nippon Yttrium Co. Ltd. as ingot and was used after grind and washing with hexane and methanol, successively, and dried.

1H-Indole-2-carboxyaldehyde (10)
A solution of ethyl indole-2-carboxylate (3.00 g, 15.9 mmol) in THF (18 mL) was added to a suspension of LiAlH₄ (3.03 g, 79.8 mmol) in THF (18 mL) at 0 °C and the whole was stirred at 0 °C for 30 min. H₂O (5 mL), 20% NaOH (5 mL), and H₂O (20 mL) was added successively at 0 °C. The whole was diluted with CH₂Cl₂-CH₃OH (8 : 1, 50 mL) and was stirred at rt for 1 h. The mixture was filtered off through a pad of Celite pad and the filtrate was washed with brine (3 x 40 mL) and dried over MgSO₄. The solvent was evaporated in vacuo to leave alcohol 9 as pale yellow solids (2.32 g, 99%). The crude 9
was dissolved in CH₂Cl₂ (75 mL) and MnO₂ (13.2 g, 152 mmol) was added. After stirring at rt for 14 h, the whole was filtered off through a pad of Celite® and the precipitate was washed with CH₂Cl₂. The filtrate and the washing was combined and evaporated in vacuo to give aldehyde 10 as brown solid (1.77 g, 79%), which was used for next step without further purification.

1-(p-Toluenesulfonyl)-1H-indole-2-carboxyaldehyde
A solution of aldehyde 10 (2.35 g, 16.2 mmol) in DMF (9 mL) was added to a suspension of NaH (60%, 976 mg, 24.4 mmol) in DMF (15 mL) at 0 °C and the whole was stirred at rt for 30 min. A solution of p-toluenesulfonyl chloride (4.32 g, 22.7 mmol) in DMF (7 mL) was added at 0 °C and the whole was stirred at 0 °C for 2 h. H₂O (25 mL) was added at 0 °C and the whole was extracted with AcOEt (5 x 40 mL). The combined organic layer was washed with H₂O (10 x 1.5 mL) and brine (5 x 1.5 mL) and was dried over MgSO₄. The solvent was evaporated in vacuo and the residue was purified by silica gel (SiO₂) column chromatography (CC) (hexane : benzene = 1 : 2) to give pale yellow solids (2.95 g, 61%). mp 136.5 - 137.5 °C. IR (ATR, cm⁻¹) 1674 (C=O). ¹H-NMR (400 MHz) δ (ppm): 2.33 (3H, s, CH₃), 7.20 (2H, d, J = 8.3 Hz, Ts-meta-H₂), 7.32 (1H, t, J = 7.6 Hz, H-6), 7.47 (1H, s, H-3), 7.53 (1H, t, J = 7.3 Hz, H-5), 7.63 (1H, d, J = 8.1 Hz, H-7), 7.66 (2H, d, J = 8.3 Hz, Ts-ortho-H₂), 8.24 (1H, d, J = 8.6 Hz, H-4), 10.54 (1H, s, CHO). ¹³C-NMR (100 MHz) δ (ppm): 21.5, 115.3, 118.8, 123.6, 124.8, 126.6, 128.1, 128.89, 129.9, 134.6, 137.7, 138.4, 145.6, 183.3. HREIMS m/z 299.0641 (Calcd for C₁₆H₁₃NO₃S: 299.0616).

Synthesis of indolylaziridinecarboxylates 1c
A mixture of aldehyde 6c (150 mg, 0.50 mmol) and guanidinium salt 4 (240 mg, 0.60 mmol) in THF (0.5 mL) was sonicated until complete dissolution of 6a and 4. Freshly distilled TMG (0.08 mL, 0.64 mmol) was added at rt and the whole was stirred at rt for 23 h. The whole was dissolved in MeCN (10 mL) and SiO₂ (Fuji silicia, FL100D, 3.0 g) was added. The mixture was stirred at rt for 1 day. After the suction filtration of the SiO₂, the residue was washed with CHCl₃. The filtrate and the washings were combined and the whole was evaporated in vacuo. The residue was purified by CC (hexane - AcOEt = 15 : 1) to give trans-1c as a yellow oil (169 mg, 67%) and cis-1c as a yellow oil (13 mg, 5%).
(2RS,3RS)-tert-Butyl [1-benzyl-3-(1-p-toluenesulfonyl-1H-indol-2-yl)aziridine-2-carboxylate (trans-1c)
IR (ATR, cm⁻¹) 1722 (C=O). ¹H-NMR (400 MHz) δ (ppm): 1.46 [9H, s, C(CH₃)₃], 2.32 (3H, s, CH₃), 2.76 (1H, br s, C2H), 3.83 (1H, br s, C3H), 4.16, 4.40 (each 1H, d, J = 13.9 Hz, PhCH₂), 6.54 (1H, s, indole C3H), 7.14-7.44 (total 10H, m, Ar), 7.76 (2H, d, J = 8.1 Hz, Ts-ortho-H₂), 8.11 (1H, d, J = 8.2 Hz, indole C4H). ¹³C-NMR (100 MHz) δ (ppm): 21.5, 28.0, 42.9, 44.1, 54.6, 82.0, 109.5, 114.3, 120.9,
123.6, 124.5, 126.6, 126.9, 128.21, 128.25, 129.1, 129.8, 135.8, 136.9, 138.6, 139.2, 144.8, 167.4.

HREIMS m/z 502.1923 (Calcd for C_{29}H_{30}N_{2}O_{4}S: 502.1926).

(2RS,3SR)-**tert**-Butyl [1-benzyl-3-(1-p-toluenesulfonyl-1H-indol-2-yl)aziridine-2-carboxylate (cis-1c)

IR (ATR, cm^{-1}) 1738 (C=O).  ^1H-NMR (400 MHz) δ (ppm): 1.19 [9H, s, C(CH$_3$)$_3$], 2.31 (3H, s, CH$_3$),

2.69 (1H, d, $J$ = 6.4 Hz, C2H), 3.58 (1H, d, $J$ = 6.4 Hz, C3H), 3.82, 3.90 (each 1H, d, $J$ = 13.9 Hz, PhCH$_2$),

6.74 (1H, s, indole C3H), 7.14-7.36 (total 7H, m, Ar), 7.42 (2H, diffused t, $J$ = 7.6 Hz, Ar), 7.74 (2H, d, $J$ = 8.4 Hz, Ts-ortho-H$_2$), 8.00 (1H, d, $J$ = 8.2 Hz, indole C4H).  ^13C-NMR (100 MHz) δ (ppm):

21.5, 27.7, 42.1, 47.2, 63.3, 81.3, 111.7, 114.1, 120.9, 123.4, 12435, 126.7, 127.2, 127.9, 128.4, 129.1, 129.8, 135.5, 135.8, 136.7, 137.9, 144.7, 167.2.  HREIMS m/z 502.1934 (Calcd for C$_{29}$H$_{30}$N$_{2}$O$_{4}$S: 502.1926).

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**General procedure for the trials towards reductive ring opening of trans-1a with Sm/I$_2$ system**

(method A, run 3 in Table 1)

To a mixture of Sm (92 mg, 0.61 mmol), I$_2$ (16 mg, 0.06 mmol) and trans-1a (53 mg, 0.15 mmol) under Ar atmosphere, THF (1 mL) and DMEA (0.06 mL, 0.60 mmol) were added at rt and the whole was stirred vigorously at 50 °C for 30 min. After cooling, 10% aq. Na$_2$S$_2$O$_3$ (5 mL) was added and the whole was filtered through a pad of Celite. The filtrate was extracted with AcOEt (2 x 20 mL). The combined organic layers were combined and was washed with saturated aq. NaHCO$_3$ (2 x 5 mL), H$_2$O (2 x 5 mL), and brine (2 x 5 mL), successively, and dried over MgSO$_4$. The solvent was evaporated *in vacuo* and the residue was analyzed by ^1H-NMR to be a 1 : 1 mixture of *trans-* and *cis-*1a.

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**General procedure for the trials towards reductive ring opening of trans-1a with Sm/I$_2$ system**

(method B, run 6 in Table 1)

To a mixture of Sm (92 mg, 0.61 mmol), I$_2$ (16 mg, 0.06 mmol), THF (1.0 mL) was added and the whole was roughly vacuumed with stirring and sonication at rt. After 20 min, color of the mixture changed to dark blue. HMPA (0.05 mL, 0.29 mmol) was added and the color of the mixture changed to purple. After stirring for 15 min, a solution of trans-1a (50 mg, 0.14 mmol) and DMEA (0.06 mL, 0.60 mmol) in THF (1.0 mL) was added at rt and the whole was stirred at rt for 30 min. 10% aq. Na$_2$S$_2$O$_3$ (5 mL) was added and the whole was filtered through a pad of Celite. The filtrate was extracted with AcOEt (2 x 20 mL). The combined organic layers were combined and was washed with saturated aq. NaHCO$_3$ (2 x 5 mL), H$_2$O (2 x 5 mL), and brine (2 x 5 mL), successively, and dried over MgSO$_4$. The solvent was evaporated *in vacuo* and the residue was analyzed by ^1H-NMR to be a mixture of trans-1a and 17 (91 : 9).
(±)-tert-Butyl 3-benzylamino-3-(3,4-methylenedioxyphenyl)propionate (17)
A colorless oil. IR (neat, cm⁻¹) 3332 (N-H), 1719 (C=O). ¹H-NMR (400 MHz) δ (ppm): 1.38 [9H, s, \(\text{C(CH}_3\text{)}_3\)], 2.48 (1H, dd, \(J = 15.3, 5.2\) Hz, one of \(\text{CH}_2\text{CO}\)), 2.58 (1H, dd, \(J = 15.3, 8.7\) Hz, one of \(\text{CH}_2\text{CO}\)), 3.53, 3.64 (each 1H, d, \(J = 13.2\) Hz, Ph\(\text{CH}_2\)), 4.00 (1H, dd, \(J = 8.7, 5.2\) Hz, CH), 5.95 (2H, s, OCH₂O), 6.75-6.81 (2H, m, Ar), 6.91 [1H, d, \(J = 1.5\) Hz, Ar(2)-H], 7.21-7.32 (5H, m, Ar). ¹³C-NMR (100 MHz) δ (ppm): 28.0, 44.4, 51.3, 58.9, 80.7, 100.9, 107.2, 108.0, 120.6, 126.8, 128.1, 128.3, 136.8, 140.3, 146.7, 147.8, 171.0. HRFABMS \(m/z\) 356.1829 (Calcd for C₂₁H₂₆NO₄: 356.1862).

(±)-tert-Butyl 2-benzylamino-3-(3,4-methylenedioxyphenyl)propionate (18)
A colorless oil. IR (neat, cm⁻¹) 3334 (N-H), 1722 (C=O). ¹H-NMR (400 MHz) δ (ppm): 1.40 [9H, s, \(\text{C(CH}_3\text{)}_3\)], 2.82 (1H, dd, \(J = 13.7, 7.1\) Hz, one of \(\text{CH}_2\text{Ar}\)), 2.86 (1H, dd, \(J = 13.7, 6.6\) Hz, one of \(\text{CH}_2\text{Ar}\)), 3.35 (1H, dd, \(J = 7.1, 6.6\) Hz, CH), 3.64, 3.81 (each 1H, d, \(J = 12.9\) Hz, Ph\(\text{CH}_2\)), 5.92 (2H, s, OCH₂O), 6.64 [1H, dd, \(J = 7.8, 1.7\) Hz, Ar(6)-H], 6.70 [1H, d, \(J = 1.7\) Hz, Ar(2)-H], 6.71 [1H, d, \(J = 7.8\) Hz, Ar(6)-H], 7.21-7.32 (5H, m, Ar). ¹³C-NMR (100 MHz) δ (ppm): 28.1, 39.5, 52.0, 62.7, 81.2, 100.8, 108.0, 109.8, 122.4, 127.0, 128.2, 128.4, 131.3, 146.2, 147.4, 173.9. HRFABMS \(m/z\) 356.1886 (Calcd for C₂₁H₂₆NO₄: 356.1862).

tert-Butyl 3-(3,4-methylenedioxyphenyl)propionate (19)
A colorless oil. IR (neat, cm⁻¹) 1724 (C=O). ¹H-NMR (400 MHz) δ (ppm): 1.43 [9H, s, \(\text{C(CH}_3\text{)}_3\)], 2.49 (2H, t, \(J = 8.0\) Hz, CH₂CO), 2.82 (2H, t, \(J = 8.0\) Hz, CH₂Ar), 5.92 (2H, s, OCH₂O), 6.65 [1H, dd, \(J = 8.0, 2.0\) Hz, Ar(6)-H], 6.69 [1H, d, \(J = 2.0\) Hz, Ar(2)-H], 6.72 [1H, d, \(J = 8.0\) Hz, Ar(5)-H]. ¹³C-NMR (100 MHz, CDCl₃) δ (ppm): 28.2, 30.9, 37.4, 80.4, 100.8, 108.1, 121.1, 134.6, 145.8, 147.6, 172.2. HREIMS \(m/z\) 250.1199 (Calcd for C₁₄H₁₈O₄: 250.1205).

(E)-tert-Butyl 3-(3,4-methylenedioxyphenyl)acrylate (20)
Colorless needles. mp 79-81 °C (lit., 79-80 °C). IR (neat, cm⁻¹) 1739 (C=O). ¹H-NMR (400 MHz) δ (ppm): 1.53 [9H, s, \(\text{C(CH}_3\text{)}_3\)], 6.00 (2H, d like, \(J = 1.1\) Hz, OCH₂O), 6.19 (1H, d, \(J = 15.9\) Hz, C₂-H), 6.80 [1H, d, \(J = 8.1\) Hz, Ar(5)-H], 6.67 [1H, diffused dd, \(J = 8.1, 1.5\) Hz, Ar(6)-H], 6.99 [1H, diffused d, \(J = 1.5\) Hz, Ar(2)-H], 7.49 (1H, d, \(J = 15.9\) Hz, C₃-H).

(2RS,3RS)-N,N'-Dibenzyl-3-(3,4-methylenedioxyphenyl)aziridine-2-carboxamide (cis-21)
A yellow oil. IR (ATR, cm⁻¹) 3376 (N-H), 1664 (C=O). ¹H-NMR (400 MHz) δ (ppm): 2.26 (1H, d, \(J = 7.0\) Hz, C₂H), 3.11 (1H, d, \(J = 7.0\) Hz, C₃H), 3.61, 3.81 (each 1H, d, \(J = 13.0\) Hz, PhCH₃), 4.00 (1H, dd, \(J = 15.0, 7.3\) Hz, one of PhCH₃), 4.38 (1H, dd, \(J = 15.0, 4.9\) Hz, one of PhCH₃), 5.90, 5.91 (each 1H, d, \(J = 15.0, 7.3\) Hz, one of PhCH₃).
= 1.5 Hz, one of OCH$_2$O), 6.53 (1H, brt, $J = 5.8$ Hz, NH), 6.64 [1H, d, $J = 8.1$ Hz, Ar(5)-H], 6.69 [1H, d, $J = 1.5$ Hz, Ar(2)-H], 6.72-6.74 (3H, m, Ar), 7.15-7.18 (3H, m, Ar), 7.31-7.36 (5H, m, Ar).  $^{13}$C-NMR (100 MHz) $\delta$ (ppm): 42.6, 46.6, 47.5, 63.3, 101.0, 108.2, 108.3, 121.1, 127.0, 127.2, 127.7, 128.3, 128.4, 128.7, 128.9, 137.7, 137.8, 147.0, 147.5, 167.6.  HRFABMS $m/z$ 387.1729 (Calcd for C$_{24}$H$_{23}$N$_2$O$_3$: 387.1709).

General procedure for the isomerization of aziridine trans-1a with InCl$_3$ (run 7 in Table 4)

To a mixture of trans-1a (41 mg, 0.12 mmol) and InCl$_3$ (6 mg, 0.027 mmol), CH$_2$Cl$_2$ (1.5 mL) was added and the whole was stirred at rt for 25 min. Sat. aq. NaHCO$_3$ (5 mL) was added and the whole was extracted with CH$_2$Cl$_2$ (4 x 6 mL). The organic layers were combined and the whole was washed with H$_2$O (2 x 6 mL) and brine (2 x 6 mL), successively, and dried over K$_2$CO$_3$. The solvent was evaporated in vacuo and the residue was analyzed by $^1$H-NMR to be a mixture of trans- and cis-1a (30 : 70).

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REFERENCES AND NOTES

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7. Synthesis of vinylaziridines from $\alpha$, $\beta$-unsaturated aldehydes and the application towards synthesis of sphingosine were also reported: W. Disadee and T. Ishikawa, J. Org. Chem., 2005, 70, 9399.


26. The absolute configuration of the product *cis-*1a was tentatively determined by the comparison on chiral HPLC analysis of known (2R,3R)-*cis*-1d.\(^5\) Conditions: column: DAICEL CHIRALCEL AD-H, solvent: hexane : 2-propanol = 50 : 1, rate: 1.0 mL/min, detection: 254 nm. Retention time: (2R,3R)-*cis*-1d: 6.5 min (major), 11.6 min (minor); *cis-*1a in this experiment: 11.4 min (major), 15.2 min (minor).


28. Preliminary trial for the treatment of (±)-*trans-*1a in basic condition (LDA, THF, -15 °C, 1 h then H\(_2\)O or acetic acid at -78 °C) showed no epimerization.