

# FIRST FORMATION OF THIEPINO[2,3-*b*]- AND THIEPINO[3,2-*a*]-INDOLIZINE DERIVATIVES<sup>1</sup>

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**Abstract** – The reactions of potassium 1,3-bis(ethoxycarbonyl)indolizine-2-thiolates with ethyl 4-bromocrotonate afforded the corresponding indolizine derivatives having (*E*)-(3-ethoxycarbonyl-2-propenyl)thio, (*E*- and (*Z*)-(3-ethoxycarbonyl-1-propenyl)thio group at the 2-position. The alkaline treatment of these *S*-alkylated indolizines gave the title compounds in good yields.

We previously reported that potassium indolizine-2-thiolates bearing electron-withdrawing groups at the 1-, and 3-positions were useful precursors for the preparation of some novel nitrogen-bridged heterocycles such as thieno[2,3-*b*]-, thieno[3,2-*a*]-,<sup>2,3</sup> and thiino[2,3-*b*]indolizine derivatives.<sup>4</sup> The key step in above reactions was the intramolecular nucleophilic addition of the carbanion species generated in the 2-substituent onto a cyano or an acyl carbonyl group at the 1- or 3-position. Subsequent hydrogen transfer or elimination from the primary cycloadducts provided the corresponding heterocycles. As an extension of this reaction, we were interested in the behavior of indolizine derivatives having a vinylogous carbanion (allyl anion) in the 2-substituent, because species such as **Ia** should form 2-vinylthiophenes **II**, but those such as **Ib** should provide thiepins **III** which are not readily accessible (see Figure 1). In general, the route leading to five-membered heterocycles such as **II** is more favorable than that to provide seven-membered heterocycles such as **III** because of the smooth approach of the reaction sites in the transition state and of ready stabilization (aromatization) of the primary adducts. However, an example in which seven-membered products were exclusively formed is also known.<sup>5</sup> Here we describe the first formations of thiepino[2,3-*b*]- and thiepino[3,2-*a*]indolizine derivatives from the alkaline treatment of diethyl 1,3-indolizinedicarboxylates having an (*E*)-(3-ethoxycarbonyl-2-propenyl)thio, (*E*- and (*Z*)-(3-ethoxycarbonyl-1-propenyl)thio group at the 2-position.

When potassium 1,3-bis(ethoxycarbonyl)indolizine-2-thiolate (**2a**), generated in situ by the reactions of diethyl 2-[(2-ethoxycarbonyl)thio]indolizine-1,3-dicarboxylate (**1a**) with potassium *tert*-butoxide in

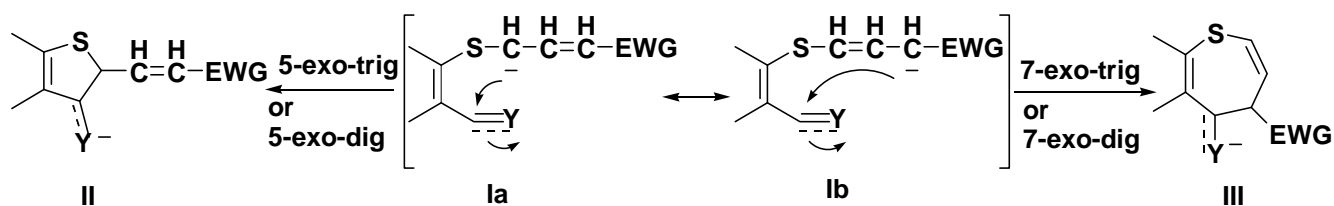
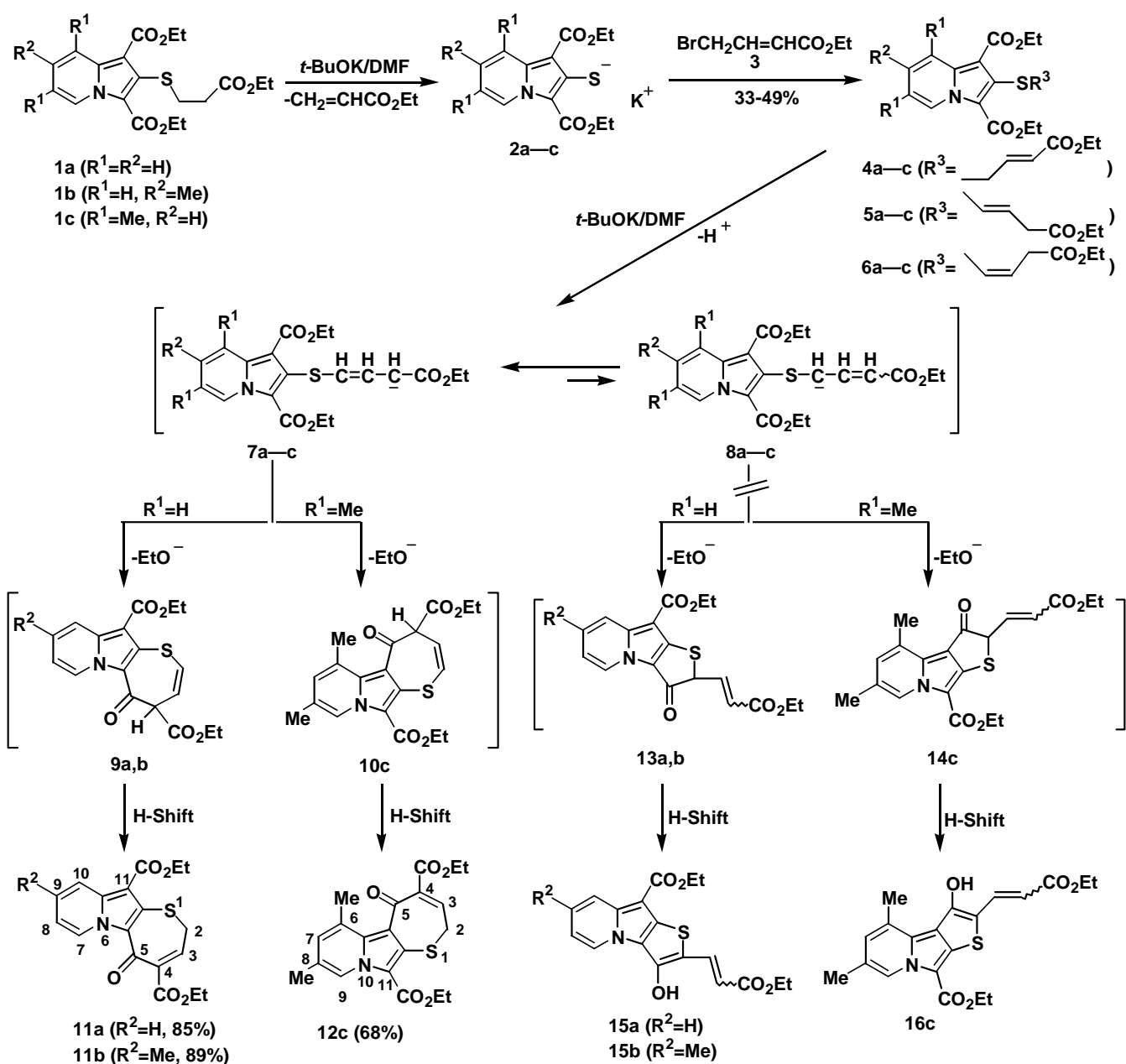


Figure 1

DMF, was treated with ethyl 4-bromocrotonate (**3**), a mixture of diethyl 2-[(*E*)-(3-ethoxycarbonyl-2-propenyl)thio]- (**4a**), diethyl 2-[(*E*)-(3-ethoxycarbonyl-1-propenyl)thio]- (**5a**), and diethyl 2-[(*Z*)-(3-ethoxycarbonyl-1-propenyl)thio]indolizine-1,3-dicarboxylates (**6a**) was obtained in a 49% yield as a pale yellow oil, and its ratio was 100:6:3.<sup>6,7</sup> Similar treatment of *S*-protected indolizines **1b,c** with **3** afforded the mixtures of the corresponding *S*-alkylated indolizines **4b+5b+6b** (its ratio is 100:4:2) and **4c+5c+6c** (its ratio is 50:11:9) in 40% and 33% yields.<sup>6,7</sup> Since all of indolizines **4a—c**, **5a—c**, and **6a—c** thus obtained are potential precursors for vinylogous carbanions such as **7a—c** and/or **8a—c**, we next examined their deprotonation. The reactions of **4a+5a+6a** and **4b+5b+6b** with potassium *tert*-butoxide in DMF at room temperature proceeded smoothly to give the corresponding products **11a,b** as unstable yellow powders in 85% and 89% yields.<sup>8,9</sup> These compounds were not diethyl 5-oxo-4,5-dihydrothiepine[2,3-*b*]indolizine-4,11-dicarboxylates (**9a,b**) which were initially expected from the nucleophilic attack of the carbanions **7a,b** on the ester carbonyl group at the 3-position of the indolizine ring followed by the elimination of an ethoxide ion, but were diethyl 5-oxo-2,5-dihydrothiepine[2,3-*b*]indolizine-4,11-dicarboxylates (**11a**) and its 9-methyl derivatives **11b** which were derived from the proton transfer of the cycloadducts **9a,b**. Similar reaction of **4c+5c+6c** provided diethyl 6,8-dimethyl-5-oxo-2,5-dihydrothiepine[3,2-*a*]indolizine-4,11-dicarboxylate (**12c**) in a 68% yield as an unstable yellow powder.<sup>8,9</sup> In these reactions, however, the alternative 2-vinylthieno[2,3-*b*]- (**9a,b**) or 2-vinylthieno[3,2-*a*]indolizine derivative (**10c**) which can be formed via the intermediate **8a—c** could not be obtained at all. These results are shown in Scheme 1.

The structural assignments for products **4a—c**, **5a—c**, **6a—c**, **11a,b**, and **12c** were performed mainly by <sup>1</sup>H-NMR spectral analyses. In particular, the structures of major *S*-alkylated indolizines **4a—c** could readily be determined by the presence of the *S*-methylene triplet ( $J=7.6$  Hz) at  $\delta$  3.63—3.75 ppm and of the vinyl protons with a trans-coupling constant (15.4 Hz) near  $\delta$  5.7 and 6.9 ppm respectively, together with the signals of three ethoxycarbonyl and indolizine ring protons. Similarly, the structures of minor products **5a—c** and **6a—c** were assigned as the *E*- and *Z*-isomers of the 2-[(3-ethoxycarbonyl-1-propenyl)thio] group by the appearances of the methylene triplet ( $J=6.8—7.2$  Hz) at higher magnetic regions ( $\delta$  3.08 (trans) and 3.32 or 3.33 (cis) ppm) and of the *S*-vinyl protons with a trans- (15.2—15.4 Hz) or cis-coupling constant (9.4—9.6 Hz) near  $\delta$  5.8 and 6.2 ppm. On the other hand, <sup>1</sup>H-NMR



Scheme 1

spectra of thienopyridines **11a,b** and thienopyridines **12c** exhibited the presence of only two ethoxy groups and the loss of an ethoxy group at lower magnetic regions. This is assignable to the ethoxycarbonyl group at the 1- or 3-position of the indolizine ring. This fact strongly suggested that carbanion **7** or **8** interacted with the ethoxycarbonyl group at the 1- or 3-position with the elimination of an ethoxide ion during these reactions. The absence of the AB type signals due to the exocyclic vinyl group as shown in 2-vinylthienopyridines **15a,b** and **16c** and the presence of the AX<sub>2</sub> type signals ( $\delta$  3.39-3.43 (d, SCH<sub>2</sub>) and 7.07-9.19 ppm (t, 3-H)) with a vicinal coupling constant (7.3 Hz) supported the thienopyridine structure for **11a,b** and **12c**. Furthermore, the comparisons of the chemical shifts of the protons on the indolizine ring in **11a,b** and **12c** with those in *S*-alkylated indolizines **4a-c** disclosed the orientation of these cyclizations. That is, the chemical shifts for each 7-proton in **11a,b** were shifted to a

higher magnetic region (ca.  $\delta$  0.5 ppm) in comparison with those of **4a,b**, while the chemical shifts of each 10-proton in **11a,b** and of the 9-proton in **12c** were grossly similar to those in **4a—c**. These facts indicate that the nucleophilic attacks of the anions on the 3-ester carbonyl carbon in **7a,b** and on the 1-ester one in **7c** occurred. The same orientation of the cyclization on the indolizine ring have already been observed in the transformation reactions from diethyl 2-(acylmethylthio)indolizine-1,3-dicarboxylates to the corresponding 2-acylthieno[2,3-*b*]- and 2-acylthieno[3,2-*a*]indolizine derivatives, and the electronic and steric effects leading to such orientations have been also described.<sup>3</sup> The reason for the exclusive formation of thiepino[2,3-*b*]- **11a,b** and thiepino[3,2-*a*]indolizine **12c** from the alkaline treatment of *S*-alkylated indolizines **4a—c**, **5a—c**, and **6a—c** is unclear, but the larger contribution of the allyl anions **7a—c**, which are stabilized by resonance and inductive effects, over the alternative anions **8a—c** may be considered. Further investigation of this reaction is now in progress.

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6. **4a**, <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.22, 1.46, and 1.47 (each 3H, t,  $J=7.1$  or  $7.2$  Hz,  $3\times\text{OCH}_2\text{CH}_3$ ), 3.75 (2H, dd,  $J=7.6$ , and  $1.2$  Hz,  $\text{SCH}_2$ ), 4.11, 4.44, and 4.47 (each 2H, q,  $J=7.1$  or  $7.2$  Hz,  $3\times\text{OCH}_2\text{CH}_3$ ), 5.68 (1H, dt,  $J=15.4$ ,  $1.3$ , and  $1.3$  Hz,  $=\text{CHCO}_2\text{Et}$ ), 6.91 (1H, dt,  $J=15.4$ ,  $7.6$ , and  $7.6$  Hz,  $\text{SCH}_2\text{CH}=\text{CH}$ ), 6.93 (1H, dt,  $J=7.1$ ,  $7.1$ , and  $1.2$  Hz, 6-H), 7.27 (1H, ddd,  $J=9.2$ ,  $6.8$ , and  $1.1$  Hz, 7-H), 8.26 (1H, dt,  $J=9.3$ ,  $1.1$ , and  $1.1$  Hz, 8-H), and 9.42 (1H, dt,  $J=7.1$ ,  $1.1$ , and  $1.1$  Hz, 5-H).  
**4b**, <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.23, 1.46, and 1.47 (each 3H, t,  $J=7.1$  Hz,  $3\times\text{OCH}_2\text{CH}_3$ ), 2.43 (3H, d,  $J=1.0$  Hz, 7-Me), 3.74 (2H, dd,  $J=7.6$  and  $1.2$  Hz,  $\text{SCH}_2$ ), 4.12, 4.44, and 4.46 (each 2H, q,  $J=7.1$  or  $7.2$  Hz,  $3\times\text{OCH}_2\text{CH}_3$ ), 5.67 (1H, dt,  $J=15.4$ ,  $1.3$ , and  $1.3$  Hz,  $=\text{CHCO}_2\text{Et}$ ), 6.77 (1H, dd,  $J=7.3$  and  $1.9$  Hz, 6-H), 6.91 (1H, dt,  $J=15.4$ ,  $7.6$ , and  $7.6$  Hz,  $\text{SCH}_2\text{CH}=\text{CH}$ ), 8.06 (1H, quint,  $J=1.0$  Hz, 8-H), and 9.32 (1H, d,  $J=7.2$  Hz, 5-H).  
**4c**, <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 1.24, 1.42, and 1.47 (each 3H, t,  $J=7.1$  Hz,  $3\times\text{OCH}_2\text{CH}_3$ ), 2.30 (3H, s, 6-Me), 2.42 (3H, s, 8-Me), 3.63 (2H, dd,  $J=7.6$  and  $1.2$  Hz,  $\text{SCH}_2$ ), 4.14, 4.42, and 4.45 (each 2H, q,  $J=7.2$  Hz,  $3\times\text{OCH}_2\text{CH}_3$ ), 5.66 (1H, dt,  $J=15.4$ ,  $1.2$ , and  $1.2$  Hz,  $=\text{CHCO}_2\text{Et}$ ), 6.80 (1H, br s, 7-Me), 6.93 (dt,  $J=15.4$ ,  $7.7$ , and  $7.7$  Hz,  $\text{SCH}_2\text{CH}=\text{CH}$ ), 9.19 (1H, br s, 5-H).  
**5a**, <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 3.08 (2H, dd,  $J=7.2$  and  $1.3$  Hz,  $\text{CH}_2\text{CO}_2\text{Et}$ ), 5.80 (1H, dt,  $J=15.3$ ,  $7.2$ , and

7.2 Hz, SCH=CHCH<sub>2</sub>), and 6.20 (1H, dt, *J*=15.3, 1.4, and 1.4 Hz, SCH=CH).<sup>10</sup>

**5b**, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 3.08 (2H, dd, *J*=7.2 and 1.3 Hz, CH<sub>2</sub>CO<sub>2</sub>Et), 5.79 (1H, dt, *J*=15.2, 7.2, and 7.2 Hz, SCH=CHCH<sub>2</sub>), and 6.20 (1H, dt, *J*=15.2, 1.3, and 1.3 Hz, SCH=CH).<sup>10</sup>

**5c**, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.25, 1.39, and 1.41 (each 3H, t, *J*=7.1 or 7.2 Hz, 3xCO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3.08 (2H, dd, *J*=7.1 and 1.5 Hz, CH<sub>2</sub>CO<sub>2</sub>Et), 4.13 and 4.35 (each 2H, q, *J*=7.2 Hz, 2xCO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 5.82 (1H, dt, *J*=15.3, 7.1, and 7.1 Hz, SCH=CHCH<sub>2</sub>), and 6.21 (1H, dt, *J*=15.4, 1.2, and 1.2 Hz, SCH=CH).<sup>10</sup>

**6a**, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 3.33 (2H, dd, *J*=6.8 and 1.7 Hz, CH<sub>2</sub>CO<sub>2</sub>Et), 5.79 (1H, dt, *J*=9.5, 6.8, and 6.8 Hz, SCH=CHCH<sub>2</sub>), and 6.21 (1H, dt, *J*=9.5, 1.6, and 1.6 Hz, SCH=CH).<sup>10</sup>

**6b**, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 3.33 (2H, dd, *J*=6.8 and 1.7 Hz, CH<sub>2</sub>CO<sub>2</sub>Et), 5.78 (1H, dt, *J*=9.6, 6.8, and 6.8 Hz, SCH=CHCH<sub>2</sub>), and 6.21 (1H, dt, *J*=9.5, 1.7, and 1.7 Hz, SCH=CH).<sup>10</sup>

**6c**, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.29, 1.37, and 1.40 (each 3H, t, *J*=7.0 or 7.1 Hz, 3xCO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 3.32 (2H, dd, *J*=6.9 and 1.7 Hz, CH<sub>2</sub>CO<sub>2</sub>Et), 4.18 and 4.34 (each 2H, q, *J*=7.2 Hz, 2xCO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 5.82 (1H, dt, *J*=9.4, 6.8, and 6.8 Hz, SCH=CHCH<sub>2</sub>), and 6.26 (1H, dt, *J*=9.5, 1.6, and 1.6 Hz, SCH=CH).<sup>10</sup>

7. The separation of these indolizine mixtures **4a+5a+6a**, **4b+5b+6b**, and **4c+5c+6c** were unsuccessful, but they gave satisfactory elemental analyses.

**4a+5a+6a** (pale yellow oil). *Anal.* Calcd for C<sub>20</sub>H<sub>23</sub>NO<sub>6</sub>S: C, 59.25; H, 5.72; N, 3.45. Found: C, 59.41; H, 5.66; N, 3.35.

**4b+5b+6b** (pale yellow oil). *Anal.* Calcd for C<sub>21</sub>H<sub>25</sub>NO<sub>6</sub>S: C, 60.13; H, 6.01; N, 3.34. Found: C, 60.28; H, 5.98; N, 3.22.

**4c+5c+6c** (pale yellow oil). *Anal.* Calcd for C<sub>22</sub>H<sub>27</sub>NO<sub>6</sub>S: C, 60.95; H, 6.28; N, 3.23. Found: C, 60.95; H, 6.35; N, 3.16.

8. **11a**: mp 134—137 °C, *v* (KBr) cm<sup>-1</sup> 1698 and 1747. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.31 and 1.44 (each 3H, t, *J*=7.1 or 7.2 Hz, 2xOCH<sub>2</sub>CH<sub>3</sub>), 3.43 (2H, d, *J*=7.3 Hz, 2-H), 4.22 and 4.40 (each 2H, q, *J*=7.1 or 7.2 Hz, 2xOCH<sub>2</sub>CH<sub>3</sub>), 7.04 (1H, dt, *J*=6.8, 1.2, and 1.2 Hz, 8-H), 7.19 (1H, t, *J*=7.3 Hz, 3-H), 7.46 (1H, ddd, *J*=9.1, 7.0, and 1.2 Hz, 9-H), 8.23 (1H, dt, *J*=9.0, 1.2, and 1.2 Hz, 10-H), 8.95 (1H, dt, *J*=6.7, 1.2, and 1.2 Hz, 7-H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 14.19, 14.55, 35.86, 60.42, 61.45, 100.90, 114.92, 119.24, 121.41, 127.24, 127.59, 128.96, 141.50, 143.79, 145.50, 162.99, 169.17, 171.78. HRMS *m/z* calcd for C<sub>18</sub>H<sub>18</sub>NO<sub>5</sub>S (M<sup>+</sup>+H): 360.0900, found: 360.0898.

**11b**: mp 121—124 °C, *v* (KBr) cm<sup>-1</sup> 1664, 1701, 1748. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 1.30 and 1.43 (each 3H, t, *J*=7.1 or 7.2 Hz, 2xOCH<sub>2</sub>CH<sub>3</sub>), 2.48 (3H, s, 9-Me), 3.41 (2H, d, *J*=7.3 Hz, 2-H), 4.22 and 4.39 (each 2H, q, *J*=7.1 or 7.2 Hz, 2xOCH<sub>2</sub>CH<sub>3</sub>), 8.00 (1H, br s, 10-H), 8.79 (1H, d, *J*=6.8 Hz, 7-H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ: 14.19, 14.57, 21.93, 35.87, 60.32, 61.43, 99.94, 117.23, 118.21, 121.02,

126.63, 127.18, 141.19, 141.69, 144.26, 145.90, 163.15, 169.24, 171.32. HRMS  $m/z$  calcd for  $C_{19}H_{20}NO_5S$  ( $M^+ + H$ ): 374.1057, found: 374.1025.

**12c**, mp 117—120 °C,  $\nu$  (KBr)  $cm^{-1}$  1668, 1692, and 1736.  $^1H$  NMR ( $CDCl_3$ )  $\delta$ : 1.30 and 1.45 (each 3H, t,  $J=7.1$  or  $7.2$  Hz,  $2 \times OCH_2CH_3$ ), 2.35 (3H, s, 8-Me), 2.89 (3H, s, 6-Me), 3.39 (2H, d,  $J=7.3$  Hz, 2-H), 4.21 and 4.41 (each 2H, q,  $J=7.0$  or  $7.1$  Hz,  $2 \times OCH_2CH_3$ ), 7.03 (1H, br s, 9-H), 7.07 (1H, t,  $J=7.3$  Hz, 3-H), 9.19 (1H, br s, 9-H).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$ : 14.20, 14.55, 18.32, 20.00, 36.17, 60.64, 61.34, 107.99, 113.60, 124.69, 125.57, 125.82, 129.55, 131.54, 135.47, 142.45, 144.73, 160.39, 169.47, 178.12. HRMS  $m/z$  calcd for  $C_{20}H_{22}NO_5S$  ( $M^+ + H$ ): 388.1232, found: 388.1191.

- 9 Because thiepiñoindolizines **11a,b** and **12c** were considerably unstable, their compositions were confirmed by high resolution mass spectra.
- 10 Other proton signals were overlapped with those of major products **4a—c**.