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Synthetic Studies toward Penitrem E: Enantiocontrolled Construction of B–E Rings

Yu Yoshii,† Takanori Otsu,† Norihiko Hosokawa,† Kiyosei Takasu,‡ Kentaro Okano,† and Hidetoshi Tokuyama*†

Enantiocontrolled construction of B–E rings of penitrem E was accomplished from 4-iodoindole in 13 steps with an overall yield of 1.7%. Diastereoselective Tf$_2$NH-catalyzed (2 + 2)-cycloaddition between silyl enol ether and methyl acrylate furnished a tetracyclic product possessing the characteristic cyclobutane ring bearing a hydroxyl group.

A family of indole diterpene alkaloids has attracted a great deal of interest from the synthetic community because of their biological activity and unique structure. Penitrems, isolated from Penicillium cyclopium and Penicillium crustosum by the Wilson and Steyn groups, possess strong neurotoxicity1 (Fig. 1). Compared with the structurally related indole diterpenes, such as paspalicine,2 paspalinine,2c,2d,3 and paspaline,2a,2b,4 penitrems have a characteristic cyclobutane ring (B ring) and an eight-membered cyclic ether (A ring). Due to its highly fused cyclic structure, only Smith et al. have so far achieved the enantiocontrolled total synthesis of (–)-penitrem D (2) via [2 + 2]-photo-cycloaddition for the formation of the B ring.5 Curran et al. also reported construction of B–D rings of penitrem D (2) using a SmI$_2$-mediated intermolecular radical cascade reaction.6 On the other hand, synthetic studies toward penitrem A (1) and E (3) having a hydroxy group at the bridgehead of the B and C rings have not yet been reported. Recently, we developed a bis(triflic imide) (Tf$_2$NH)-catalyzed smooth (2 + 2)-cycloaddition reaction of silyl enol ether to provide a fused-cyclobutane ring bearing a silyloxy group at the bridgehead position (Scheme 1).7 The major diastereomer of the bicyclic compounds has the opposite relative configuration at the α-position of the methyl ester to those of the B/C ring in penitrem A and E; however, we anticipated that the stereochemistry of this position could be isomerized and initiated synthetic studies toward penitrem E utilizing our (2 + 2)-cycloaddition. Herein, we describe a novel strategy for an enantiocontrolled synthesis of the left segment 4 including B–E rings of penitrem E (3) featuring a palladium-catalyzed Catellani reaction8 and Tf$_2$NH-catalyzed (2 + 2)-cycloaddition reaction.7

The retrosynthetic sequence in Scheme 2 demonstrates a stereocontrolled construction of the B and C rings, having a hydroxy group at the bridgehead position. To control the facial selectivity in the C–C bond formation of a silyl enol ether and methyl acrylate, we planned to use the stereochemistry of a hydroxymethyl moiety, which is a synthetic equivalent of exo-methylene according to Smith’s synthesis9 utilizing Grieco–Nishizawa elimination.9 The tertiary alcohol attached to the B ring would be derived from ester 6 and two equivalents of methyl Grignard reagent, and the indole

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Fig. 1  Penitrems and related alkaloids.

Scheme 1  Tf$_2$NH-catalyzed (2 + 2)-cycloaddition of silyl enol ether and methyl acrylate.7c

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could be synthesized from the protected indoline through deprotection and subsequent oxidation. The cyclobutane ring bearing the hydroxyl group would be constructed by the Tf$_2$NH-catalyzed (2+2)-cycloaddition of silyl enol ether and methyl acrylate. In this reaction, we expected that the hydroxymethyl side chain in the C ring should control the facial selectivity. Silyl enol ether 7 would be derived from the corresponding ketone, which should be prepared from unsaturated ester 8 through oxidative cleavage of the C=C. We planned to construct the C ring from 4-iodoindoline derivative 9 and optically active ε-iodo-unsaturated ester 10 by Catellani reaction, a one-pot palladium-catalyzed ring formation in the presence of norbornene.

Scheme 2  Retrosynthetic analysis of left segment 4.

First, we prepared optically active ester 16 from readily available 1,3-diol 11, a coupling partner for Catellani reaction (Scheme 3). The synthesis commenced with lipase-mediated desymmetrization of meso-1,3-diol 11 at -15 °C to give monoacetate 12. Manipulation of oxygen functionalities provided mono-TIPS ether 14 in 90% ee. Appel iodination of the alcohol and subsequent olefin cross metathesis with ethyl acrylate yielded ester 16.

Scheme 3  Preparation of unsaturated ester 16.

With the ε-iodo-unsaturated ester 16 in hand, we then examined Catellani reaction for the construction of the C ring (Scheme 4). The known 4-iodoindole 17 was converted to the corresponding N-mesy1-4-iodoindoline (18) in a two-step sequence. Gratifyingly, subjection of the indoline 18 and the optically active ester 16 to the standard Catellani conditions provided the desired tricyclic compound 19 in 96% yield. Oxidative cleavage of the trisubstituted electron-deficient olefin was effected by the combination of OsO$_4$ and NaIO$_4$ to give tetralone 20 in good yield, which was converted to TBS enol ether 21a for the construction of the cyclobutane ring.

Scheme 4  Synthesis of C ring by Catellani reaction.

Having synthesized the requisite silyl enol ether, we then investigated construction of the B ring using Tf$_2$NH-catalyzed (2+2)-cycloaddition (Table 1). An aliquot of 80 mM solution of Tf$_2$NH in toluene was added to a mixture of 21a and excess methyl acrylate (5 equiv) in CH$_2$Cl$_2$ at -78 °C. After 3 days, the reaction was quenched with Et$_3$N, and the mixture was concentrated in vacuo, which was then purified to provide a mixture of cyclobutane cis-22a and trans-22a. Interestingly, unlike the previous report using the simple substrate (Scheme 1), the reaction of 21a gave the desired tricyclic products in high yield.

Table 1  Substituent effects on Tf$_2$NH-catalyzed (2+2)-cycloaddition.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'</th>
<th>Substituent</th>
<th>X (equiv)</th>
<th>Time (d)</th>
<th>cis-22 (%)</th>
<th>trans-22 (%)</th>
<th>21 (%)</th>
<th>20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBS</td>
<td>21a</td>
<td>5</td>
<td>3</td>
<td>43 (22a)</td>
<td>2.1 (10)</td>
<td>3.8</td>
<td>27.8</td>
</tr>
<tr>
<td>2</td>
<td>TBS</td>
<td>21a</td>
<td>3</td>
<td>7</td>
<td>54 (22a)</td>
<td>2.0 (10)</td>
<td>-</td>
<td>30.8</td>
</tr>
<tr>
<td>3</td>
<td>TMS</td>
<td>21b</td>
<td>5</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>19.9</td>
<td>53.4</td>
</tr>
<tr>
<td>4</td>
<td>TES</td>
<td>21c</td>
<td>5</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>65.7</td>
<td>16.8</td>
</tr>
</tbody>
</table>

a Combined yield of cis- and trans-isomers. b Isolated yield. c Not isolated. d Not determined. e Calculated by 1H NMR.
diastereomer cis-22a as a major product even under the previously established conditions (Table 1, entry 1). Reduction of the catalytic amount of the triflic imide required a prolonged reaction time but gave 22a in better yield with concomitant generation of tetralone 20 (Table 1, entry 2). TMS enol ether 21b was more prone to form tetralone 20, and none of the desired cyclobutane was isolated (Table 1, entry 3). On the other hand, TES enol ether 21c was robust but less reactive under the conditions, resulting in recovery of 65% of the starting material 21c (Table 1, entry 4). We also found that the choice of a protecting group on the nitrogen was also important for the diastereoselectivity. Thus, tosyl amide 21d and Cbz carbamate 21e were converted to the corresponding products cis-22b (cis-22b: trans-22b = 1.1:1.0) and cis-22c (cis-22c: trans-22c = 2.4:1.0), (Table 2, entries 1 and 2).  

Table 2 Effects of protective group on indoline nitrogen.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R²</th>
<th>Substrate</th>
<th>X</th>
<th>T/L (h)</th>
<th>cis-22 (22a)</th>
<th>trans-22 (22b)</th>
<th>cis-22:trans-22</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ts</td>
<td>21d</td>
<td>5</td>
<td>3</td>
<td>56 (22b)</td>
<td>44</td>
<td>1.1:1.0</td>
</tr>
<tr>
<td>2</td>
<td>Cbz</td>
<td>21c</td>
<td>5</td>
<td>3</td>
<td>46 (22c)</td>
<td>54</td>
<td>2.4:1.0</td>
</tr>
</tbody>
</table>

*a Combined yield of cis- and trans-isomers. b Isolated yield. c Not detected. d Calculated by 1H NMR.

A plausible mechanism depicted in Scheme 5 would explain the observed diastereoselectivity, which was opposite to that of the former (2 + 2) cycloaddition.  

First, Tf₂N–TBS, generated from Tf₂N, reacted as a Lewis acid to promote Mukaiyama-type Michael addition of the silyl enol ether to methyl acrylate on the less hindered face. The possible conformers A and B in the second aldol reaction provided the corresponding cyclobutanes trans-22a and cis-22a. Steric repulsion of the methyl ester and the aromatic ring disfavored chair-like conformer A, thus providing cis-22a (via the favored boat-like conformer B) as a major product. We attempted epimerization of trans-22a to obtain cis-22a; however, the treatment of the undesired trans-22a with either DBU in refluxing toluene or NaOMe in refluxing MeOH did not afford the desired cis-22a.

We then turned our attention toward the synthesis of the left segment 4 (Scheme 6). Addition of excess methyl Grignard reagent followed by protection of the resulting alcohol as its TMS ether provided the trisilylated compound 23. Deprotection of the mesyl group using LDA smoothly proceeded to give the desired unprotected indoline 24 in high yields, which was then treated with MnO₂ to afford the indole 25. Synthesis of the left segment 4 was completed in a three-step sequence through Grieco–Nishizawa elimination. Thus, after removal of three silyl groups under basic conditions, the resultant triol 5, whose structure was confirmed by X-ray crystallographic analysis in Fig. 2, was subjected to selenation followed by oxidative elimination to provide the left segment 4 while leaving the unprotected indole intact.

Scheme 5 A plausible mechanism for the diastereoselectivity in (2 + 2)-cycloaddition.

Scheme 6 Synthesis of the left segment 4.

In conclusion, we have established an enantiocontrolled construction of B–E rings in penitrem (3). Catellani reaction facilitated the one-step formation of the C ring. The B ring bearing a hydroxyl group was successfully constructed by our Tf₂N-catalyzed (2 + 2)-cycloaddition, in which the desired diastereomer was obtained as a major product.

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† Experimental procedures, compound characterization data, and copies of 1H and 13C-NMR spectra for all new compounds. [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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