Asymmetric Synthesis of Chiral 1,3-Dimethyl Units Through a Double Michael Reaction of Nitromethane and Crotonaldehyde Catalyzed by Diphenylprolinol Silyl Ether

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Abstract An efficient synthetic route to install chiral 1,3-dimethyl units through a double Michael reaction of crotonaldehyde and nitromethane catalyzed by diphenylprolinol silyl ether is developed. Either 1,3-anti- or 1,3-syn-dimethyl units are obtained selectively depending on the enantiomer of the diphenylprolinol silyl ether catalyst used. The side chain of pneumocandin B₈ is synthesized enantioselectively by using the present method as a key step.

Key words organocatalyst, Michael reaction, asymmetric synthesis, diastereoselective reaction, diphenylprolinol silyl ether

The 1,3-dimethyl unit is found in many natural products, including siphonarienal,¹ ionomycin,² scyphostatin,³ and borrelidin (Figure 1),⁴ and the stereoselective synthesis of chiral 1,3-dimethyl units is considered an important synthetic topic.⁵ There are many methods available for the diastereo- and enantioselective synthesis of anti- and syn-1,3-dimethyl units. The iterative Michael reaction of methyl groups under reagent control is a widely employed method,⁶ and iterative allylic substitution and alklylation of chiral enolates is also used.⁷ Negishi’s Zr-catalyzed carboalumination (ZACA) reaction is a powerful method for the preparation of 1,3-dimethyl units,⁸ and Aggarwal recently reported an assembly-line synthesis that proceeds through iterative homologation of boronic esters with chiral lithiated benzoate esters and chloromethyl lithium.⁹ Some of the methods use asymmetric catalytic reactions.¹⁰ In spite of these elegant methods, a procedure which is suitable for the large-scale preparation of 1,3-dimethyl units is needed.

We have already reported the asymmetric Michael reaction of an α,β-unsaturated aldehyde with nitromethane catalyzed by diphenylprolinol silyl ether¹⁰ as an effective organocatalyst (Scheme 1).¹¹ The sequential use of this Michael reaction would afford either the syn- or anti-1,3-dimethyl unit stereoselectively (Scheme 2). The Michael reaction of nitromethane and crotonaldehyde catalyzed by (S)-diphenylprolinol silyl ether (S)-1a,¹² followed by acetalization would provide 2. A second Michael reaction of the generated nitroalkane 2 and crotonaldehyde, catalyzed by either (S)- or (R)-diphenylprolinol silyl ether, would then afford the desired anti- or syn-1,3-dimethyl unit, respectively. The realization of this scenario is described herein.

Figure 1 Natural products with a 1,3-dimethyl unit

Scheme 1 An asymmetric Michael reaction catalyzed by a diphenylprolinol silyl ether
The first Michael reaction of crotonaldehyde and nitromethane was carried out using 5 mol% of (S)-diphenylprolinol diphenylmethylsilyl ether (S)-1a as the catalyst in MeOH in the presence of 10 equivalents of H₂O to afford the Michael product, which was treated with HC(OMe)₃ and a catalytic amount of TsOH in the same vessel to provide nitroacetal 2 in 94% yield and 90% ee (Scheme 3). This reaction required four days to reach completion when THF was employed as the solvent, as described previously, but was complete within two days in MeOH and proceeded with excellent enantioselectivity.

The second Michael reaction of 2 and crotonaldehyde was then investigated using diphenylprolinol trimethylsilyl ether (S)-1b as the catalyst (Table 1). Alcohol 3 was obtained in 43% yield as a diastereomeric mixture after treatment of the Michael product with NaBH₄ (entry 1). To improve this yield, four days to reach completion when THF was employed as the solvent, as described previously, but was complete within two days in MeOH and proceeded with excellent enantioselectivity.

When the reaction was conducted in MeOH with 10 equivalents of water, the product was obtained in 43% yield after 7.5 hours (Table 1, entry 1); no reaction occurred without water (entry 2). Addition of an acid was not effective in the present reaction (entry 3). The use of either THF or neat conditions were also not suitable (entries 4–7). In these reactions, nitroalkane 2 was recovered in good yield, while crotonaldehyde was consumed. One of the side products of crotonaldehyde was found to be the self-aldol product, presumably formed via the dienamine intermediate generated from crotonaldehyde and the catalyst. To suppress this side reaction, slow addition of a solution of crotonaldehyde was added slowly. However, the desired reaction did not occur because of a further side reaction involving the formation of 1-methoxybut-2-en-1-ol, which would be generated by the reaction of MeOH and crotonaldehyde (entry 8). To also suppress this side reaction, slow addition of a solution of crotonaldehyde in THF was examined, which afforded the desired product in 62% yield (entry 9).

![Scheme 2](image1)  The idea for the synthesis of anti- and syn-dimethyl units

![Scheme 3](image2)  The initial Michael reaction of crotonaldehyde and nitromethane

Table 1  The Effect of Solvent, Additive and Addition Time on the Asymmetric Michael Reaction of Nitroalkane 2 and Crotonaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>H₂O (equiv)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>10</td>
<td>7.5</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>0</td>
<td>7.5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>10</td>
<td>2</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>10</td>
<td>28</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>0</td>
<td>28</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td>neat</td>
<td>10</td>
<td>28</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7</td>
<td>neat</td>
<td>0</td>
<td>28</td>
<td>&lt;5</td>
</tr>
<tr>
<td>8</td>
<td>MeOH</td>
<td>10</td>
<td>11</td>
<td>&lt;5</td>
</tr>
<tr>
<td>9</td>
<td>MeOH</td>
<td>10</td>
<td>11</td>
<td>62</td>
</tr>
</tbody>
</table>

* Unless noted otherwise, the reaction was performed by employing 2 (0.6 mmol), crotonaldehyde (1.2 mmol), and (S)-1b (0.12 mmol) in solvent (1.2 mL) with H₂O (6.0 mmol) (or without H₂O) at room temperature for the indicated time.

* Yield of purified product.

* Benzyl alcohol (20 mol%) was added.

* A MeOH solution of crotonaldehyde was added after 10 h.

* A THF solution of crotonaldehyde was added after 10 h.
The product, which contains three chiral centers, was obtained as a mixture of several diastereomers. Denitration was then investigated. Alcohol 3 was converted into its benzoyl ester 4. After optimization of the denitration conditions, it was found that the reaction of 4 with n-Bu3SnH proceeded at 150 °C to afford alcohol 5 in 68% yield with 2:2:1 diastereoselectivity (Scheme 4a). To increase the diastereoselectivity, we further optimized the second Michael reaction using an organocatalyst with a different silyl substituent. An improved result was obtained when di-phenylmethylsilyl ether (OTBS) was converted into its benzyloxycarbonyl (Boc) derivative 6 with 3.7:1 diastereoselectivity (Scheme 4b). As shown in Table 2, it was found that the reaction of 1,3,5-trimethoxybenzene (entries 6 and 7). Table 2 indicates that the diastereoselectivities are moderate to good and that they depend on the substituents. However, the enantioselectivities of the final products are found to be excellent (>95% ee) for both 1,3-anti- and 1,3-syn-isomers. It should be noted that the enantioselectivity increased in all the cases, although that of the first Michael product 2 was 90%.

The double Michael product could also be transformed into the 1,3-disubstituted-2-oxo derivative through a Nef reaction. When anti-7 and syn-7 were treated with NaOMe and dimethyldioxirane (DMDO) 1,3-anti- and 1,3-syn-dimethylketones (anti-8 and syn-8), respectively, were obtained in good yields, albeit with a slight decrease of the diastereoselectivity and enantioselectivity (Scheme 5).

Although the enantiomeric excess of the first Michael product was 90%, the double Michael product was formed with an excellent enantioselectivity that was much higher than that of the first Michael reaction. The origin of this enhanced enantioselectivity can be explained as follows (Scheme 6). In the first Michael reaction, 2 and ent-2 were generated in a 95:5 ratio, in which 2 was formed predominantly rather than ent-2. When 2 reacted with crotonaldehyde catalyzed by (S)-1a, in which the (R)-isomer of the newly generated methyl group would be predominantly generated, anti-3 was formed predominantly, while the generation of (S)-isomers such as syn-3 and anti-ent-3 would be minor. As ent-2 is generated in a small amount in the first reaction and the generation of anti-ent-3 is also a minor reaction path in the second Michael reaction, the amount of anti-ent-3 would be very little. If the stereoselec-

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**Scheme 4** (a) Denitration of alcohol 3. (b) Optimized conditions for the second Michael reaction and subsequent denitration.
The newly generated stereocenter in the second Michael reaction is 95:5, the ratio of anti-3 and anti-ent-3 would be 90.25:0.25. Thus, the ee in the final product 3 is much higher than that of the first Michael product 2.

The present method was applied to the asymmetric synthesis of the side chain of pneumocandin B0 (9) (Figure 2).21 Pneumocandin B0 was isolated from the fermentation broth of the fungus Glarea lozoyensis by Merck & Co. Its fungal-specific mode of action is inhibition of the biosynthesis of β-(1,3)-D-glucan, which is an essential cell wall component of many pathogenic fungi. The stereoselective synthesis of the (10R,12S)-dimethylmyristoyl side chain 10 of this compound through the use of Enders’ RAMP method and diastereoselective alkylation of the chiral enolate has previously been reported.21c

Table 2 The Two-Pot Synthesis of 1,3-Disubstituted Alkanols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Cat.</th>
<th>Michael reaction yield (%)</th>
<th>dr*</th>
<th>Denitration yield (%)</th>
<th>anti</th>
<th>syn</th>
<th>ee*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>S</td>
<td>60</td>
<td>nd</td>
<td>49</td>
<td>3:7:1</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>R</td>
<td>63</td>
<td>nd</td>
<td>51</td>
<td>1:10</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>3*</td>
<td></td>
<td>R</td>
<td>60</td>
<td>nd</td>
<td>44</td>
<td>1:20</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>S</td>
<td>80</td>
<td>63:28:7:2</td>
<td>54</td>
<td>13:1</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>R</td>
<td>78</td>
<td>59:30:6:5</td>
<td>48</td>
<td>1:15</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>S</td>
<td>91</td>
<td>53:42:5:0</td>
<td>62</td>
<td>&gt;20:1</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>S</td>
<td>80</td>
<td>62:26:9:3</td>
<td>65</td>
<td>5:9:1</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

*First step (Michael reaction): Unless noted otherwise, the reactions were performed by employing 2 (0.6 mmol), α,β-unsaturated aldehyde (1.2 mmol), (S)-1a or (R)-1a (0.12 mmol), and H2O (1.2 mL) at room temperature via slow addition of the aldehyde over 20 h and further stirring of the reaction mixture for 1 h. Second step (denitration reaction): Unless noted otherwise, the reactions were performed by employing the Michael adduct (0.4 mmol), n-Bu3SnH (2.0 mmol), AIBN (0.32 mmol), and 1,3,5-trimethoxybenzene (14.0 mmol) at 250 °C for 5 min.

b Yield of purified product.

dr = diastereomer ratio in the Michael reaction determined by 1H NMR spectroscopy; nd = not determined.

diastereomer ratio and enantiomeric excess were determined by HPLC analysis on a chiral column.

Figure 2 The structure of pneumocandin B0 (9) and its side chain 10
Our synthesis of the side chain 10 started with the Michael reaction of nitromethane and crotonaldehyde catalyzed by diphenylprolinol silyl ether (S)-1a. Subsequent acetalization provided 2 in 94% yield with 90% ee. The second Michael reaction with crotonaldehyde proceeded in the presence of (R)-1a, followed by treatment with NaBH4 to afford alcohol syn-3 in 63% yield. The enantioselectivity of syn-3 is 98%, which was determined after denitration (see Table 2, entry 2). Alcohol syn-3 was converted into haloalkane 11 in 69% yield by reaction with Ph3P and I2. Dehalogenation and denitration occurred in the same pot by treatment with n-Bu3SnH and AIBN at 150 °C to afford acetal 12 in 73% yield. Treatment of acetal 12 with aqueous HCl gave aldehyde 13, which was used in the next step without purification. The Julia–Kocienski reaction with 14 proceeded smoothly to afford (E)-alkene 15 in 56% yield over two steps. Hydrogenation followed by hydrolysis using aqueous NaOH afforded the side chain of pneumocandin B0 10 in 72% yield over two steps (Scheme 7). The physical properties of synthetic 10 were identical in all respects to the reported data.
In conclusion, we have developed an efficient method for the synthesis of chiral 1,3-dimethyl units through a double Michael reaction of an aldehyde and nitroalkane catalyzed by a diphenylprolinol silyl ether. There are several noteworthy features of this reaction. Either 1,3-syn- or 1,3-anti-dimethyl units can be selectively synthesized depending on the appropriate choice of enantiomer of the diphenylprolinol silyl ether catalyst. The excellent optical purity of the double Michael product was much higher than that of the first Michael reaction because of the ‘meso-trick’. In addition to the 1,3-dimethyl unit, both 1,3-methyl alkyl and 1,3-methyl aryl units can be prepared. Finally, the side chain of pneumocandin B\textsubscript{0} was enantioselectively synthesized by using the present method as a key step.

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**Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611644.

**References and Notes**

15. In the reactions of entries 2–8 in Table 1, nitroalkane 2 was recovered in good yield (>90%).
16. The diastereoselectivity and enantioselectivity of 3 (Table 1, entry 9) were not determined. The dr after denitration is 2.2:1, see Scheme 4.
17. The diastereoselectivity and enantioselectivity of 4 (Table 1, entry 2) were not determined. The dr after denitration is 2.2:1, see Scheme 4.
19. The enantioselectivity of compound 5 is determined according to the scheme below.


