Towards the Total Synthesis of Actinoranone: Unexpected Domino Retro Friedel-Crafts Acylation and Esterification.

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Abstract

We report herein an unprecedented domino retro Friedel Crafts (FC) acylation and esterification of electron-rich tetralones, an indanone and a benzo-suberone.

Introduction

Actinoranone (1) is a natural meroterpenoid with an unique scaffold, which displays cytotoxic activity.¹ This natural product was isolated from marine bacterium and there is no synthesis reported so far. In order to confirm the proposed structure of 1 and elucidate its stereochemistry, we designed a bioinspired retrosynthetic approach, which includes as a key fragment the ketal 2. For our surprise, after a concise synthesis of tetralone 6 (5 steps, 40% overall yield), a conventional protocol to synthesize a dioxolane ring induced completely a domino retro FC acylation and esterification to furnish ester 8 in 97% yield, an unprecedented transformation.

Scheme 1. Unexpected domino retro-FC acylation and esterification en route to actinoranone (1).

Results and Discussion

After this unexpected outcome, we decided to explore the synthetic potential of this domino reaction. Firstly, the degree of methoxylation was investigated and tetralones 8, 10 and 12 were evaluated. Compounds 8 and 10 containing less electron-rich aromatic rings did not undergo the retro FC reaction nor the ketalization. On the other hand, tetralone 12, containing three methoxy groups, furnished the domino reaction product in 60% yield along 32% of the demethoxylated product 14, which did not suffer the retro FC reaction. The size of the ring fused to the aromatic system was also evaluated: the bicycles containing a 5 and a 7 membered-ring (compounds 15 and 17) were able to participate in a domino retro FC and esterification in high yields.

Table 1. Domino retro FC acylation and esterification.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Products</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>9</td>
<td>N.R.²</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>N.R.²</td>
</tr>
<tr>
<td>12</td>
<td>13: 60%</td>
<td>14: 32%</td>
</tr>
<tr>
<td>15</td>
<td>16</td>
<td>93%</td>
</tr>
<tr>
<td>17</td>
<td>18</td>
<td>89%</td>
</tr>
</tbody>
</table>

Compounds 8 and 10 were obtained from commercial source, and compounds 6, 12, 15 and 17 were synthesized in 4-5 steps. Isolated yield. No reaction, recovery of starting material.

Conclusions

We observed a new domino reaction en route to the total synthesis of actinoranone (1), involving a retro FC acylation and esterification. This reaction was studied with different bicycles, and work is now in progress to evaluate different alcohols and other nucleophiles.

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