BF2OBn∙OEt2: A Novel Lewis Acid and its use in a Regio- and Stereo-selective Opening of Trisubstituted Epoxides and its Application Towards Amphidinolide C

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BF₂OBn·OEt₂: A Novel Lewis Acid and its use in a Regio- and Stereo-selective Opening of Trisubstituted Epoxides and its Application Towards Amphidinolide C and F

Nicholas A. Morra,[a] Brian L. Pagenkopf*[a]

Keywords: Lewis Acid / Epoxide Opening / Shi Epoxidation / BF₂OBn·OEt₂ / amphidinolide

The generation of a novel Lewis acid (BF₂OBn·OEt₂) has been reported and its usefulness has been demonstrated in the regio- and stereo-selective opening of trisubstituted epoxides. This Lewis acid is one in a series of novel Lewis acids generated from BF₃·OEt₂ displaying varying levels of Lewis acidity. When paired with a modified Shi epoxidation protocol highly functionalized propionate units such as those found in a wide variety of natural products can be accessed. This procedure, in conjunction with the Mukaiyama oxidative cyclization employing our second generation catalyst, Co(nmp)₂, ultimately culminated in the shortest and highest yielding route towards the methyl substituted trans-THF fragment present in amphidinolide C, C₂, and F.

Introduction

The synthesis of amphidinolide C (1, Figure 1) has been approached by many groups, resulting in the completion of several fragments, but no total synthesis has been reported to date. In particular, the C(1)-C(9) fragment has attracted considerable synthetic attention due to its stereochemical complexity. It contains a methyl substituted trans-THF ring, an anti-diol and an exocyclic olefin that is part of an unusual diene system. An efficient and concise synthesis of the methyl substituted trans-THF ring will be central to the total synthesis of amphidinolide C. Herein we describe a short synthesis of the C(1)-C(7) fragment of amphidinolide C featuring a novel Lewis acid and an aerobic oxidative cyclization to form the trans-THF ring.

Figure 1. Amphidinolide C

Our recent work on the Mukaiyama oxidative cyclization and development of a second generation catalyst, Co(nmp)₂, has resulted in a general and high yielding synthesis of trans-THF rings from their corresponding 4-pentenols. With that in mind, the initial retrosynthetic disconnection was the formation of the trans-THF ring 2 via cyclization of the methyl substituted pentenol 3 (Scheme 1). This key synthetic intermediate was proposed to be secured by a regio- and stereo-selective ring opening of epoxide 4, which would be accessed using a Shi epoxidation of diene 5.

Results and Discussion

The synthesis began with unsaturated alcohol 5, which was prepared via a 1,2-metallate rearrangement of dihydrofuran in a one pot procedure (Scheme 2). The resulting alcohol (5) was functionalized with a variety of protecting groups, followed by epoxidation using mCPBA, generating a set of racemic epoxides to evaluate the subsequent ring opening.

Scheme 2. Synthesis of trisubstituted epoxides rac-7a, rac-7b, and rac-7c

The conversion of the mono-epoxides (7a-7c) to the desired alcohols required a regioselective hydride delivery at the more hindered carbon. Initially, the Hutchins protocol, which has been reported to proceed via apparent Sn2 reaction with inversion of...
stereochemistry, was explored. Unfortunately, treatment of epoxide 7a under the standard conditions (BF₃·OEt₂, NaCNBH₃) gave results consistent with premature epoxide opening, with reactions of the presumed carbocation intermediate giving rise to an unfavorable mixture of diastereomers from Sn1 hydride delivery (rac-8, Table 1, entry 1), elimination (rac-9, Table 1, entry 2) or a pinacol-like hydride shift (rac-10, Table 1, entries 3-4). Reactions run in diethyl ether with slow addition of the Lewis acid resulted in an increase in yield but no further improvement in the diastereomeric ratio (Table 1, entries 5-8). A variety of Lewis acids were screened to achieve the desired transformation, without success (Table 1, entries 9-10). Ultimately, it was decided to modify BF₃·OEt₂ by attenuating its Lewis acidity through anionic redistribution wherein one of the fluorines would be replaced with a less electronegative group. We had previously seen success with this strategy with the more Lewis acidic species BF₃·OTf·OEt₂ and BF₃·OMs·OEt₂ (Scheme 3), which were used in the direct reduction of esters to ethers. Thus, treatment of BF₃·OEt₂ with TMSOEt generated the modified Lewis acid BF₃·OEt₂·OEt₂ (11) that displayed a ¹⁹F NMR signal at −151.5 ppm that is indicative of decreased Lewis acidity compared to the BF₃·OEt₂ (Scheme 3).

Previously:<ref>
BF₃ + TMSOTf \rightarrow \text{anionic redistribution} \rightarrow F₂BOTf + TMSF

This work:<ref>
BF₃ + TMSOEt \rightarrow \text{anionic redistribution} \rightarrow F₂BOEt + TMSF

Scheme 3. Generation of two novel Lewis acids by anionic redistribution of BF₃·OEt₂

Gratifyingly, 11 displayed sufficient Lewis acidity to efficiently facilitate the desired Sn2 conversion of racemic epoxide rac-7c to alcohol rac-8, without promoting the troublesome side reactions encountered with the use of BF₃·OEt₂ (Table 1, entry 11). The PMB protected epoxide rac-7c gave the most consistent results during the epoxide opening reaction.

The Shi epoxidation protocol appeared to be an ideal candidate for securing an enantioselective route to epoxide 7c, as it generally shows excellent preference for unactivated tri-substituted over mono-substituted olefins. While the enantiomer of the Shi catalyst (12) derived from L-fructose would be required for this application, it is accessible from inexpensive L-sorbose in 5 steps. Unfortunately, initial reactions resulted in a disappointing yield (61%) and selectivity (3:1 ratio) of the monooxepoxide 7c to the bis-epoxide 13 (Table 2, entry 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Epoxide</th>
<th>Lewis Acid (4 eq)</th>
<th>Solvent</th>
<th>Addition Time (h)</th>
<th>Yield of 8 (%)</th>
<th>Yield of 9 (%)</th>
<th>Yield of 10 (%)</th>
<th>d.r of 8 (anti:syn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a</td>
<td>BF₃·OEt₂</td>
<td>THF</td>
<td></td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>2:1</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>BF₃·OEt₂</td>
<td>THF</td>
<td></td>
<td>50</td>
<td>25</td>
<td>15</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>7a</td>
<td>BF₃·OEt₂</td>
<td>Et₂O</td>
<td>0.5</td>
<td>65</td>
<td>-</td>
<td>-</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>7a</td>
<td>BF₃·OEt₂</td>
<td>Et₂O</td>
<td>3</td>
<td>66</td>
<td>-</td>
<td>-</td>
<td>2:1</td>
</tr>
<tr>
<td>5</td>
<td>7c</td>
<td>BF₃·OEt₂</td>
<td>Et₂O</td>
<td>4</td>
<td>90</td>
<td>-</td>
<td>-</td>
<td>2:1</td>
</tr>
<tr>
<td>6</td>
<td>7c</td>
<td>InB₁₃</td>
<td>Et₂O</td>
<td>0.5</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>7c</td>
<td>BE₁₃</td>
<td>Et₂O</td>
<td>4</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>7c</td>
<td>BF₃·OEt₂·OEt₂(11)</td>
<td>Et₂O</td>
<td>4</td>
<td>91</td>
<td>-</td>
<td>20:1</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Epoxide opening results

Attempts were made to improve selectivity by increasing the addition time of the base and Oxone® to 4 or 6 hours, which led to increases in selectivity but a decrease in overall yield (Table 2, entries 2-3), while a lower reaction temperature resulted in a decrease in both yield and selectivity (Table 2, entry 4). It is known that the Shi catalyst decomposes during the course of the reaction, therefore the catalyst was added portion-wise. At higher catalyst loadings, complete conversion was finally achieved (Table 2, entries 5-6) with selectivities of approximately 7:1 of the desired product 7c to the bis-epoxide 13. Further attempts to decrease the amount of catalyst used resulted in incomplete conversions (Table 2, entry 7).

With a concise route towards pentenol 8 secured, attention was focused on the oxidative cyclization to form the trans-THF ring (Table 3). The first generation catalyst Co(modp): (14) has been previously shown to be incompatible with the easily oxidized PMB group, and attempts to cyclize 8 were unsuccessful (Table 3, entry 1). Using the standard oxidation conditions, the second generation Co(nmp): (15) also afforded little success in forming trans-THF.
ring 16 (Table 3, entry 2). In an attempt to reduce the amount of over-oxidation byproducts formed during the course of the reaction, lower reaction temperatures were examined and an optimal yield of 81% was obtained at 35 °C (Table 3, entries 3-5). It is noteworthy that even at room temperature a comparable yield of 85% BORSM was observed. Upon scale-up of the lower temperature cyclizations, yields were found to be uncharacteristically erratic (Table 3, entry 6) and it was speculated that the peroxide used during catalysis activation could be contributing to the over-oxidation byproducts.

Thus, an alternative protocol was performed whereby the catalyst was activated prior to introduction of the pentenol and the catalyst loading of 10 mol % resulted in the highest yield of 16 (94%) and the cleanest reactions, while lower catalyst loadings led to incomplete conversions (Table 3, entries 9-10). These optimized conditions proved reproducible on multi-gram scale.

Table 3. Optimization of oxidative cyclization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Loading (mol %)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield of 16 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>15</td>
<td>55</td>
<td>16</td>
<td>0</td>
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<tr>
<td>2</td>
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<td>55</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>45</td>
<td>16</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>35</td>
<td>16</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>35</td>
<td>16</td>
<td>67 (85%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>35</td>
<td>16</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>35</td>
<td>16</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>5</td>
<td>55</td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>5</td>
<td>55</td>
<td>1</td>
<td>94</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>5</td>
<td>55</td>
<td>16</td>
<td>77 (92%)</td>
</tr>
</tbody>
</table>

a) yields based on recovered starting material b) catalyst was pre-activated c) reaction performed on a 15 mmol scale

Conclusions

In summary, we have reported a highly selective Shi epoxidation of a skipped diene followed by a reductive epoxide opening mediated by the novel Lewis acid BF₃OBN-ØE₆ that can provide compounds containing useful propionate units. Implementation of these procedures for the synthesis of the C(1)-C(9) fragment of amphimidine C and F and will be disclosed elsewhere.

Experimental Section

(Z)-1-Methoxy-4-((4-methylhepta-3,6-dienyloxy)methyl)benzene (6c) To a suspension of NaH (780 mg, 32.5 mmol, 1.3 eq) in THF (150 mL) at 0 °C was added freshly prepared PMBBr (6.53 g, 32.5 mmol, 1.3 eq), followed by alcohol 5 (2.15 g, 25 mmol, 1.0 eq). The ice-bath was removed and after ca. 16 h the reaction was poured into a half-saturated solution of NH₄Cl (100 mL) in water ice (200 mL) and stirred for 5 min, after which the aqueous layer was extracted with EtOAc (150 mL × 3). The combined organics were washed with brine, dried over MgSO₄, and filtered through a thin pad of packed celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (10% EtOAc/Hex) to yield the PMB ether (6c) as a colorless oil (5.54 g, 22.5 mmol, 90%). Rf 0.42 (10% EtOAc/Hex); 1H NMR (600 MHz, CDCl₃) δ 7.25 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.72 (ddt, J = 16.7, 10.1, 6.4 Hz, 1H), 5.22 (t, J = 6.7 Hz, 1H), 5.03-4.96 (m, 1H), 4.44 (s, 2H), 3.78 (s, 3H), 3.42 (t, J = 7.0 Hz, 2H), 2.76 (d, J = 6.4 Hz, 2H), 2.31 (q, J = 7.0 Hz, 2H), 1.68 (s, 3H); 13C NMR (100 MHz, CDCl₃) δ 159.1, 135.9, 131.0, 130.6, 129.2, 121.8, 115.2, 113.7, 72.5, 69.8, 55.3, 36.5, 28.5, 23.4. HRMS m/z 246.1615 (calcd for C₁₉H₂₀O₂, 246.1619).

(2R,3S)-2- Allyl-3-(2-(4-methoxybenzoyloxy)ethyl)-2-methyloxirane (7e)

To a flask charged with diene 6c (2.46 g, 10 mmol, 1.0 eq) was added dimethyloxymethane (100 mL), acetonitrile (50 mL), buffer II (100 mL), 12 (10 mg), and Bu₃N-HSO₃ (50 mg, catalytic) and the flask was cooled to 0 °C. A syringe pump was fitted with two 60 mL syringes, one charged with K₂CO₃ (6.90 g) in water (60 mL) and the other with Oxone® (6.90 g) in water (60 mL). The K₂CO₃ and Oxone® solutions were added to the vigorously stirred solution over 4 h, and 12 was added portion-wise at the 1 h, 2 h and 3 h time mark (157 mg per addition, 630 mg total, 2.50 mmol, 0.25 eq). The reaction was stirred for 15 min after additions of the base and Oxone® were complete, at which point hexanes (200 mL) was added. The solution was transferred to a separatory funnel and the aqueous layer was extracted with hexanes (100 mL × 4). The combined organics were washed with brine, dried over MgSO₄, and filtered through a thin pad of packed celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (20% EtOAc/Hex) to yield the mono-epoxide 7e (1.93 g, 7.40 mmol, 74%) and the di-epoxide 13 (305 mg, 1.10 mmol, 11%) as yellow oils. Rf 0.17 (10% EtOAc/Hex); 1H NMR (400 MHz, CDCl₃) δ 7.24 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.77 (ddt, J = 17.2, 10.2, 7.0 Hz, 1H), 5.10-5.05 (m, 2H), 4.43 (ABd, J = 11.7 Hz, 2H), 3.59-3.56 (m, 2H), 2.86 (dd, J = 7.4, 4.7 Hz, 1H), 2.30 (dd, J = 7.7, 7.0 Hz, 1H), 2.18 (dd, J = 7.0, 7.0 Hz, 1H), 1.98-1.89 (m, 1H), 1.77-1.68 (m, 1H), 1.25 (s, 3H); 13C NMR (100 MHz, CDCl₃) δ 159.2, 133.5, 130.4, 129.3, 117.8, 113.8, 72.8, 67.3, 61.9, 60.1, 55.3, 37.9, 29.4, 22.1. HRMS m/z 262.1576 (calcd for C₁₉H₂₂O₂, 262.1569).

Benzylxoydifluoroborane etherate (11)

To a round-bottomed flask charged with TMSOBn (1.90 g, 10.5 mmol, 1.05 eq) in diethyl ether (100 mL) and fitted with a rubber septum and an argon filled balloon (20 gauge needle) was added BF₃·OEt₂ (1.26 mL, 10 mmol, 1.0 eq). To facilitate the evaporation of the TMSF the septa was pierced with another 20 gauge needle. The argon balloon was replaced as necessary, and the solution evaporates to a viscous oil in about 1 h, and argon was flushed before for an additional 10 min. To the residue was added an additional portion of diethyl ether (8 mL) to give an approximately 1.0 M solution of BF₃·OEt₂ (11). It may be necessary to repeat the evaporation process. If well sealed the BF₃·OEt₂ solution is stable for several weeks at rt or refrigerated. Solvents other than diethyl ether caused decomposition; therefore it was used for characterization and reactions. 11F NMR (375 MHz, Et₂O) δ -151.5 ppm. Trifluorotoluene (-63.9 ppm) was used as an internal standard.

(3S,4R)-1-(4-Methoxybenzoyloxy)-4-methylhept-6-en-3-ol (8)

To a flask charged with NaCNBH₃ (255 mg, 4.0 mmol, 4.0 eq) in diethyl ether (15 mL) was added epoxide 7c (262 mg, 1.0 mmol, 1.0 eq). A solution of BF₃·OEt₂ (1.0 M, 4.0 mL, 4.0 mmol, 4.0 eq) was added to the vigorously stirred solution via syringe pump over 4 h. After the addition was complete, the reaction was stirred for 15 min before being poured into a half-saturated aqueous sodium bicarbonate (100 mL). The mixture was transferred to a separatory funnel and the aqueous layer was extracted with
EtOAc (50 mL x 3). The combined organics were washed with brine, dried over MgSO4, and filtered through a thin pad of packed celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (30% EtOAc/Hex) to yield alcohol B (240 mg, 0.91 mmol, 91%) as a yellow oil. Rf 0.50 (40% EtOAc/Hex); 1H NMR (600 MHz, CDCl3) δ 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.79 (ddt, J = 17.3, 10.0, 7.1 Hz, 1H), 5.04-4.97 (m, 2H), 4.45 (m, 2H), 4.45 (s, 2H), 3.79 (s, 3H), 3.71 (dt, J = 9.5, 4.9 Hz, 1H), 3.61 (q, J = 6.4 Hz, 2H), 3.00 (d, J = 2.3 Hz, 1H), 2.30-2.26 (m, 1H), 1.90 (dt, J = 13.9, 8.3 Hz, 1H), 1.73-1.70 (m, 2H), 1.64-1.59 (m, 1H), 0.86 (d, J = 6.4 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 159.3, 137.6, 130.0, 129.3, 115.8, 113.8, 79.5, 73.0, 69.4, 55.3, 38.6, 36.9, 32.8, 15.1. HRMS m/z 264.1725 (calcd for C18H20O2, 264.1725). [α]D = +1.73° (c 1.0, CHCl3). The ee was determined to be 85% by (R)-Mosher’s analysis. (1R,2R,4R,5S)-5-(2-(4-Methoxybenzyl)oxy)ethyl-4-methyltetrahydrofuran-2-yl)methanol (16)

Procedure to pre-activate Co(nmp)2: To a flask charged with Co(nmp)2 (15) (452 mg, 0.8 mmol, 0.1 eq) and iPrOH (100 mL) was added BuOCH3 (5.33 M, 0.2 mL, 1.08 mmol, 0.14 eq). The reaction was heated to 55 °C under an oxygen atmosphere for 1 h, and solvent was removed under reduced pressure. The activated Co(nmp)2 was diluted under high vacuum (0.1 mmHg) for 5 min to ensure that any remaining peroxide was removed.

Cyclization: The pre-activated Co(nmp)2 (15) (prepared above, 0.8 mmol, 0.1 eq) was diluted with 100 mL iPrOH, and alcohol (8) was added (2.06 g, 7.8 mmol, 1 eq). The reaction was heated to 55 °C under an oxygen atmosphere for exactly 1 h, and allowed to cool to rt. Solvent was removed under reduced pressure, followed by high vacuum (0.1 mmHg) to remove all traces of iPrOH. The crude mixture was diluted with EtOAc (40 mL) and filtered through a thin pad of silica (<1 cm) over packed celite to remove the catalyst. The pad was washed with EtOAc (400 mL) and the filtrate was concentrated under reduced pressure to give THF-alcohol (16) (2.05 g, 7.34 mmol, 94%) as a yellow oil, which was used without further purification. The product rapidly decomposes, and the decomposition product leads to the loss of fine splitting and peaks are reported as multiplets. 1H NMR (600 MHz, CDCl3) δ 7.25 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.43 (d, J = 2.0 Hz, 2H), 4.06 (ddt, J = 9.4, 6.2, 3.1 Hz), 3.79 (s, 3H), 3.62 – 3.48 (m, 4H), 2.09-2.03 (m, 1H), 1.94-1.85 (m, 2H), 1.73-1.65 (m, 1H), 1.37-1.29 (m, 1H), 1.01 (d, J = 6.6 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ 159.1, 131.6, 129.2, 113.7, 82.4, 78.3, 72.6, 67.4, 65.2, 55.3, 40.1, 36.6, 34.3, 16.4. HRMS m/z 280.1667 (calcd for C18H20O2, 280.1675).

Supporting Information (see footnote on the first page of this article):

Acknowledgments

We thank the University of Western Ontario and the National Sciences and Engineering Research Council of Canada (NSERC) for financial assistance. N.M. thanks NSERC for a graduate fellowship (CGS-D3).

Submitted to the European Journal of Organic Chemistry
The novel Lewis acid BF$_3$OBn∙OEt$_2$ has been developed via anionic distribution between BF$_3$OEt$_2$ and TMSOBn. This compound demonstrates slightly lower Lewis acidity when compared to the parent Lewis acid, and was used in a regio- and stereo-selective reductive epoxide opening. The utility of this reaction was demonstrated by the conversion of commercially available and inexpensive 2,3-dihydrofuran to the C(1)-C(9) fragment of Amphidinolide C and F in 5 steps and 49% overall yield.
Supporting Information