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$BF_2OBn{\cdot}OEt_2$: A Lewis Acid, Its Use in a Regio- and Stereoselective Opening of Trisubstituted Epoxides, and Its Application towards Amphidinolide C and F

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The generation of a new Lewis acid ($BF_2OBn{\cdot}OEt_2$) has been reported, and its usefulness has been demonstrated in the regio- and stereoselective ring-opening of trisubstituted epoxides. This Lewis acid is one in a series of new Lewis acids generated from $BF_3{\cdot}OEt_2$ that display 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. In conjunction with a Mukaiyama oxidative cyclization employing our second generation catalyst $Co(nmp)_2$, this procedure ultimately culminated in the shortest and highest yielding route towards the methyl-substituted *trans*-tetrahydrofuran (*trans*-THF) fragment present in amphidinolide C, C2, and F.

Introduction

The synthesis of amphidinolide C (**1**, see Figure 1) has been approached by many groups, and although this has resulted in the completion of several fragments, no total synthesis has been reported to date.[1,2] In particular, the C-1–C-9 fragment has attracted considerable synthetic attention because of its stereochemical complexity. It contains a methyl-substituted *trans*-tetrahydrofuran (*trans*-THF) ring, an *anti*-diol moiety, and an exocyclic olefin that is part of an unusual diene system. An efficient and concise synthesis of the methyl-substituted *trans*-THF ring is central to the total synthesis of amphidinolide C. Herein, we describe a short synthesis for the C-1–C-7 fragment of amphidinolide C, which features a new Lewis acid and an aerobic oxidative cyclization to form the *trans*-THF ring.

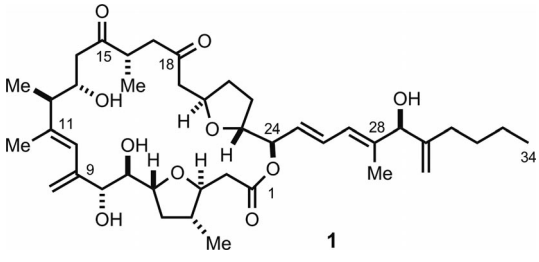
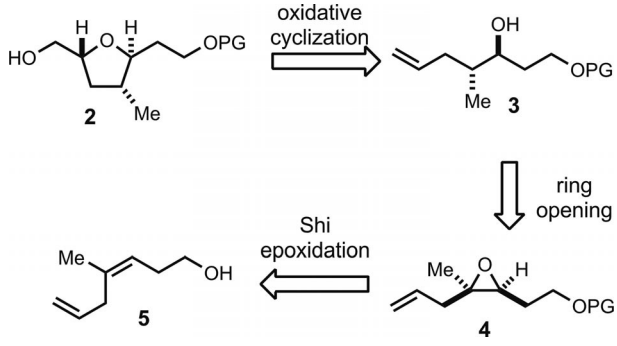


Figure 1. Amphidinolide C.

Our recent work on the Mukaiyama oxidative cyclization reaction and the development of the second generation catalyst $Co(nmp)_2$ has resulted in a general and high-yielding synthesis of the *trans*-THF rings starting from their corresponding 4-pentenols.[3] With that in mind, the initial retrosynthetic disconnection involves the formation of the *trans*-THF ring in **2** through the cyclization of the methyl-substituted pentenol **3** (see Scheme 1). This key synthetic intermediate would be secured by a regio- and stereoselective ring opening of epoxide **4**, which would be accessed through a Shi epoxidation of diene **5**.



Scheme 1. Retrosynthetic analysis.

Results and Discussion

The synthesis began with unsaturated alcohol **5**, which was prepared by a 1,2-metallate rearrangement of dihydrofuran in a one-pot procedure (see Scheme 2).[4] The resulting alcohol **5** was functionalized with a variety of protecting groups to give **6a**–**6c**, which underwent epoxidation by treatment with *meta*-chloroperoxybenzoic acid (*m*CPBA) to generate a set of racemic epoxides that were used to evaluate the subsequent ring-opening reaction.

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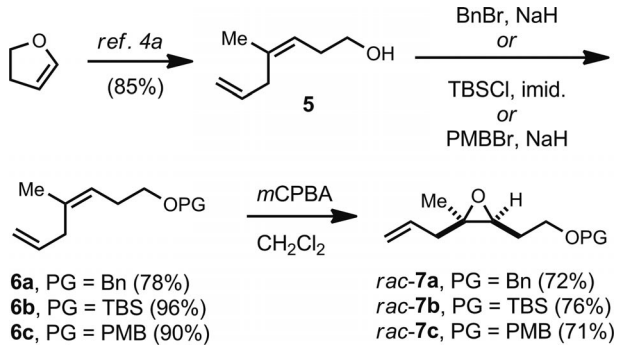
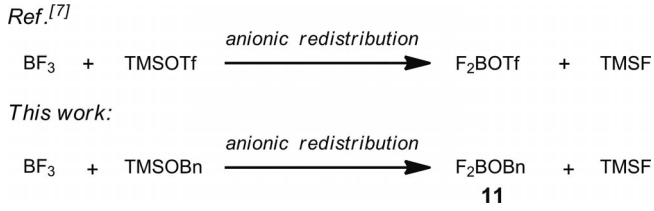


Scheme 2. Synthesis of trisubstituted epoxides *rac*-**7a**, *rac*-**7b**, and *rac*-**7c** (TBS = *tert*-butyldimethylsilyl).

The conversion of the monoepoxides **7a**–**7c** to the desired alcohols required a regioselective hydride delivery to the more hindered carbon. Initially, we explored the Hutchins protocol, which proceeds by an apparent S_N2 reaction and occurs with the inversion of stereochemistry.[5] Unfortunately, treatment of epoxide **7a** under the standard conditions ($BF_3{\cdot}OEt_2$, $NaCNBH_3$) gave results consistent with a premature epoxide ring opening, and reactions of the presumed carbocation intermediate gave rise to an unfavorable mixture of diastereomers through either S_N1 hydride delivery to give *rac*-**8** (see Table 1, Entry 1), elimination to give *rac*-**9** (see Table 1, Entry 2), or a pinacol-like hydride shift to give *rac*-**10** (see Table 1, Entries 3 and 4). Reactions carried out in diethyl ether with a slow addition of the Lewis acid resulted in an increase in yield, but there was no further improvement in the diastereomeric ratio (*dr*, see Table 1, Entries 5–8). A variety of Lewis acids were screened to achieve the desired transformation, but these attempts were unsuccessful (see Table 1, Entries 9 and 10).[6] Ultimately, we was decided to modify the $BF_3{\cdot}OEt_2$ by attenuating its Lewis acidity through an anionic redistribution, in which one of the fluorines was replaced with a less electronegative group. We had previously achieved success with this strategy, when applied to the more Lewis acidic species $BF_2OTf{\cdot}OEt_2$ and $BF_2OMs{\cdot}OEt_2$ (see Scheme 3), which were used in the direct reduction of esters to ethers.[7] Thus, the treatment of $BF_3{\cdot}OEt_2$ with (benzyloxy)trimethylsilane (TMSOBn) generated the modified Lewis acid $BF_2OBn{\cdot}OEt_2$ (**11**), which displayed a ^{19}F NMR signal at –151.5 ppm that is indicative of decreased Lewis acidity in comparison to $BF_3{\cdot}OEt_2$ (see Scheme 3).[8]

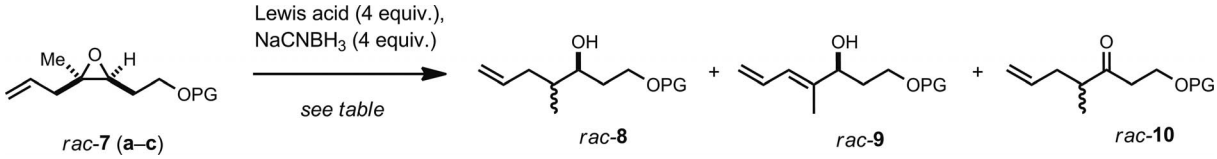


Scheme 3. Generation of two new Lewis acids by anionic redistribution of $BF_3{\cdot}OEt_2$.

Gratifyingly, **11** displayed sufficient Lewis acidity to facilitate efficiently the desired S_N2 conversion of racemic epoxide *rac*-**7c** to alcohol *rac*-**8**, without promoting the troublesome side reactions encountered by using $BF_3{\cdot}OEt_2$ (see Table 1, Entry 11). The *p*-methoxybenzyl-protected (PMB-protected) epoxide *rac*-**7c** gave the most consistent results for the epoxide ring-opening reaction.

The Shi epoxidation protocol appeared to be an ideal candidate for securing an enantioselective route to epoxide **7c**, as this reaction generally shows a strong preference for unactivated trisubstituted olefins over monosubstituted ones.[9] Although the enantiomer of the Shi catalyst (**12**), which is derived from L-fructose, would be required for this application, it is accessible in five steps from inexpensive L-sorbose.[10] Unfortunately, initial attempts at the enantiose-

Table 1. Epoxide opening results.

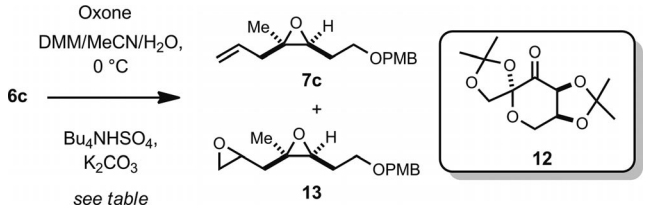


Entry	Epoxide	Lewis acid [4 equiv.]	Solvent	Addition time [h]	Yield **8** %	Yield **9** %	Yield **10** %	*dr* of **8** (*anti*/*syn*)
1	**7a**	$BF_3{\cdot}OEt_2$	THF	–	20	–	–	2:1
2	**7b**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	3	–	99	–	–
3	**7a**	$BF_3{\cdot}OEt_2$	THF	0.5	50	–	25	2:1
4	**7a**	$BF_3{\cdot}OEt_2$	THF	3	65	–	15	2:1
5	**7c**	$BF_3{\cdot}OEt_2$	Et_2O	–	23	–	–	2:1
6	**7c**	$BF_3{\cdot}OEt_2$	Et_2O	0.5	51	–	–	2:1
7	**7c**	$BF_3{\cdot}OEt_2$	Et_2O	3	66	–	–	2:1
8	**7c**	$BF_3{\cdot}OEt_2$	Et_2O	4	90	–	–	2:1
9	**7c**	$InBr_3$	Et_2O	–	0[a]	–	–	–
10	**7c**	BEt_3	Et_2O	4	0[a]	–	–	–
11	**7c**	$BF_2OBn{\cdot}OEt_2$ (**11**)	Et_2O	4	91	–	–	>20:1

[a] Starting material recovered.

lective synthesis of epoxide **7c** resulted in a disappointing yield (61%) and selectivity, giving a 3:1 ratio of monoepoxide **7c** to bis(epoxide) **13** (see Table 2, Entry 1).

Table 2. Synthesis of epoxide **7c**.



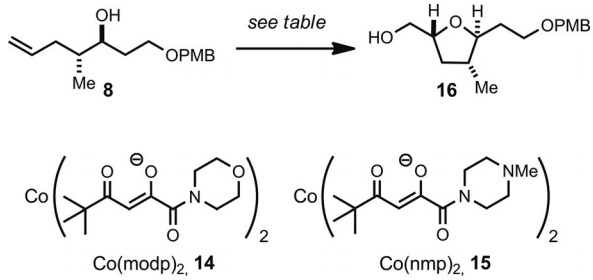
Entry	Addition time [h]	**12** [mol-%]	Recovered **6c** [%]	**7c** [%]	**13** [%]
1	2	20	14	61	20
2	4	20	32	50	11
3	6	20	45	40	7
4[a]	4	20	62	23	8
5[b]	4	35	0	75	13
6[b]	4	25	0	74	11
7[b]	4	20	11	60	8

[a] Reaction conducted at –10 °C. [b] Catalyst added in four portions over 4 h.

Attempts were made to improve the selectivity by increasing the addition time of the base and Oxone® to 4 or 6 h. This did lead to an increase in the selectivity, but there was a decrease in overall yield (see Table 2, Entries 2 and 3). A lower reaction temperature resulted in a decrease in both the yield and selectivity (see Table 2, Entry 4). Because the Shi catalyst could decompose during the course of the reaction,[11] it was added portionwise. At higher catalyst loadings, complete conversion was finally achieved (see Table 2, Entries 5 and 6) with selectivities of an approximate 7:1 ratio of the desired product **7c** to bis(epoxide) **13**. Further attempts to decrease the amount of catalyst resulted in incomplete conversions (see Table 2, Entry 7).

With a concise route towards pentenol **8** secured, we focused our attention on the oxidative cyclization to form the *trans*-THF ring (see Table 3). The first generation catalyst Co(modp)$_2$ (**14**) had previously been shown to be incompatible with the easily oxidized PMB group,[3] and attempts to cyclize **8** with this catalyst were unsuccessful (see Table 3, Entry 1). Using the standard oxidation conditions, the second generation catalyst Co(nmp)$_2$ (**15**) also afforded little success in forming *trans*-THF ring **16** (see Table 3, Entry 2). To reduce the amount of overoxidation byproducts formed during the course of the reaction, lower reaction temperatures were examined, and as a result, an optimal yield of 81% was obtained when the reaction was conducted at 35 °C (see Table 3, Entries 3–5). It is noteworthy that even at room temperature a comparable yield based on recovered starting material (BORSM) of 85% was observed. Upon scale-up of the cyclization at a lower temperature, the yields were uncharacteristically erratic (see Table 3, Entry 6), and we speculated that the peroxide used during the activation of the catalyst could be contributing to the overoxidation byproducts.

Table 3. Optimization of oxidative cyclization.



Entry	Catalyst	Loading [mol-%]	Temp. [°C]	Time [h]	% Yield **16**
1	**14**	15	55	16	0
2	**15**	15	55	16	10
3	**15**	15	45	16	55
4	**15**	15	35	16	81
5	**15**	15	22	16	67 (85[a])
6	**15**	15	35	16	65[b]
7	**15**	15[c]	35	16	80[b]
8	**15**	15[c]	55	1	91
9	**15**	10[c]	55	1	94[b]
10	**15**	5[c]	55	16	77 (92[a])

[a] Yields based on recovered starting material. [b] Reaction performed on a 15 mmol scale. [c] Catalyst was preactivated.

Thus, an alternative protocol was performed, whereby the catalyst was activated prior to the introduction of the pentenol to ensure that no peroxides were present. Initial reactions using the preactivated Co(nmp)$_2$ (**15**) provided significant advantages in terms of the reproducibility of the yield (see Table 3, Entry 7), but overoxidation remained problematic. Eventually, careful monitoring of the reaction by TLC resulted in a surprising finding, that is, the reaction went to completion after just 1 h (see Table 3, Entry 8). Similar reactions typically require more than 12 h. Further optimization of the reaction conditions showed that a catalyst loading of 10 mol-% resulted in the highest yield of **16** (94%) and the cleanest reaction, whereas lower catalyst loadings led to incomplete conversions (see Table 3, Entries 9 and 10). These optimized conditions proved reproducible on a multigram scale.

Conclusions

In summary, we have reported on a highly selective Shi epoxidation of a skipped diene. This was followed by a reductive epoxide ring-opening reaction that was mediated by the new Lewis acid $BF_2OBn{\cdot}OEt_2$ to provide a compound containing a useful propionate unit. Implementation of these procedures for the synthesis of the C-1–C-9 fragment of amphidinolide C and F 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 equiv.) in THF (150 mL) at 0 °C was added freshly prepared *p*-meth-

oxybenzyl bromide (PMBBr, 6.53 g, 32.5 mmol, 1.3 equiv.) followed by the addition of alcohol **5** (2.15 g, 25 mmol, 1.0 equiv.). The ice bath was removed, and after approximately 16 h, the reaction was poured into a half-saturated solution of NH_4Cl (100 mL) in ice water (200 mL). The resulting mixture was stirred for 5 min, and then the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and then filtered through a thin pad of packed Celite. The solvent was removed under reduced pressure, and the crude oil was purified by flash chromatography (10% EtOAc/hexane) to yield PMB ether **6c** (5.54 g, 22.5 mmol, 90%) as a colorless oil; R_f = 0.42 (10% EtOAc/hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.8 Hz, 2 H), 6.87 (d, J = 8.8 Hz, 2 H), 5.72 (ddt, J = 16.7, 10.1, 6.4 Hz, 1 H), 5.22 (t, J = 6.7 Hz, 1 H), 5.03–4.96 (m, 1 H), 4.44 (s, 2 H), 3.78 (s, 3 H), 3.42 (t, J = 7.0 Hz, 2 H), 2.76 (d, J = 6.4 Hz, 2 H), 2.31 (q, J = 7.0 Hz, 2 H), 1.68 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 135.9, 135.1, 130.6, 129.2, 121.8, 115.2, 113.7, 72.5, 69.8, 55.3, 36.5, 28.5, 23.4 ppm. HRMS: calcd. for $C_{16}H_{22}O_2$ 246.1619; found 246.1615.

(2*R*,3*S*)-2-Allyl-3-[2-(4-methoxybenzyloxy)ethyl]-2-methyloxirane (7c): To a flask charged with diene **6c** (2.46 g, 10 mmol, 1.0 equiv.) was added dimethoxymethane (DMM, 100 mL), acetonitrile (50 mL), buffer[12] (100 mL), **12** (157 mg), and $Bu_4N{\cdot}HSO_4$ (50 mg, catalytic), and the resulting mixture was cooled to 0 °C. A syringe pump was fitted with two 60 mL syringes. One was charged with K_2CO_3 (6.90 g) in water (60 mL), and the second was charged with Oxone® (6.90 g) in water (60 mL). The K_2CO_3 and Oxone® solutions were added to the vigorously stirred solution over 4 h, and during this time to the reaction mixture were also added additional amounts of **12** portionwise at the 1 h, 2 h, and 3 h timepoints (157 mg per addition, 630 mg total for 4 additions, 2.50 mmol, 0.25 equiv.). After the additions of the base and Oxone® were complete, the reaction was stirred for 15 min, and then hexanes (200 mL) were added. The solution was transferred to a separatory funnel, and the aqueous layer was extracted with hexanes (4 × 100 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and filtered through a thin pad of packed Celite. The solvent was removed under reduced pressure, and the crude oil was purified by flash chromatography (20% EtOAc/hexane) to yield monoepoxide **7c** (1.93 g, 7.40 mmol, 74%) and bis(epoxide) **13** (305 mg, 1.10 mmol, 11%) as yellow oils; R_f = 0.17 (10% EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.6 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 5.77 (ddt, J = 17.2, 10.2, 7.0 Hz, 1 H), 5.10–5.05 (m, 2 H), 4.43 (ABd, J = 11.7 Hz, 2 H), 3.59–3.56 (m, 2 H), 2.86 (dd, J = 7.4, 4.7 Hz, 1 H), 2.30 (dd, J = 7.0, 7.0 Hz, 1 H), 2.18 (dd, J = 7.0, 7.0 Hz, 1 H), 1.98–1.89 (m, 1 H), 1.77–1.68 (m, 1 H), 1.25 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 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 ppm. HRMS: calcd. for $C_{16}H_{22}O_3$ 262.1569; found 262.1576.

(Benzyloxy)difluoroborane–Diethyl Ether (11): To a round-bottomed flask charged with TMSOBn (1.90 g, 10.5 mmol, 1.05 equiv.) in diethyl ether (100 mL) and fitted with a rubber septum and a balloon filled with argon (20.5 gauge needle) was added $BF_3{\cdot}OEt_2$ (1.26 mL, 10 mmol, 1.0 equiv.). To facilitate the evaporation of the TMSF, the septum was pierced with another 20.5 gauge needle. The argon balloon was replaced as necessary, and the solution evaporated to a viscous oil in about 1 h. The argon flow was maintained for an additional 10 min.[13] To the residue was added an additional portion of diethyl ether (8 mL) to give an approximately 1.0 M solution of $BF_2OBn{\cdot}OEt_2$ (**11**).[14] It may be necessary to repeat the evaporation process.[14] If well sealed, the $BF_2OBn{\cdot}OEt_2$ solution was stable at room temp., or it was refrigerated for several weeks. Solvents other than diethyl ether caused decomposition, and, therefore, diethyl ether was used for the characterization and reactions. ^{19}F NMR (375 MHz, Et_2O): δ = –151.5 ppm. Trifluorotoluene (–63.9 ppm) was used as an internal standard.

(3*S*,4*R*)-1-(4-Methoxybenzyloxy)-4-methylhept-6-en-3-ol (8): To a flask charged with $NaCNBH_3$ (255 mg, 4.0 mmol, 4.0 equiv.) in diethyl ether (15 mL) was added epoxide **7c** (262 mg, 1.0 mmol, 1.0 equiv.). To the vigorously stirred solution was added a solution of $BF_2OBn{\cdot}OEt_2$ (ca. 1.0 M, 4.0 mL, 4.0 mmol, 4.0 equiv.) by syringe pump over 4 h. After the addition was complete, the reaction was stirred for 15 min and then was poured into a half-saturated solution of aqueous sodium hydrogen carbonate (100 mL). The mixture was transferred to a separatory funnel, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and filtered through a thin pad of packed Celite. The solvent was removed under reduced pressure, and the crude oil was purified by flash chromatography (30% EtOAc/hexane) to yield alcohol **8** (240 mg, 0.91 mmol, 91%) as a yellow oil; R_f = 0.50 (40% EtOAc/hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 5.79 (ddt, J = 17.3, 10.0, 7.1 Hz, 1 H), 5.04–4.97 (m, 2 H), 4.45 (m, 2 H), 4.45 (s, 2 H), 3.79 (s, 3 H), 3.71 (dt, J = 9.5, 4.9 Hz, 1 H), 3.61 (q, J = 6.4 Hz, 2 H), 3.00 (d, J = 2.3 Hz, 1 H), 2.30–2.26 (m, 1 H), 1.90 (dt, J = 13.9, 8.3 Hz, 1 H), 1.73–1.70 (m, 2 H), 1.64–1.59 (m, 1 H), 0.86 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.3, 137.6, 130.0, 129.3, 115.8, 113.8, 75.2, 73.0, 69.4, 55.3, 38.6, 36.9, 32.8, 15.1 ppm. HRMS: calcd. for $C_{16}H_{24}O_3$ 264.1725; found 264.1725. $[\alpha]_D^{20}$ = +1.73 (c = 1.0, $CHCl_3$). The enantiomeric excess (*ee*) was determined by using (*R*)-Mosher's analysis to be 85%.

{(2*R*,4*R*,5*S*)-5-[2-(4-Methoxybenzyloxy)ethyl]-4-methyltetrahydrofuran-2-yl}methanol (16)

Procedure to Preactivate Co(nmp)$_2$: To a flask charged with $Co(nmp)_2$ (**15**, 452 mg, 0.8 mmol, 0.1 equiv.) and *i*PrOH (100 mL) was added *t*BuOOH (5.33 M solution, 0.2 mL, 1.08 mmol, 0.14 equiv.). The reaction was heated to 55 °C under oxygen for 1 h, and then the solvent was removed under reduced pressure. The activated $Co(nmp)_2$ was dried under high vacuum (0.1 Torr) for 5 min to ensure that any remaining peroxide was removed.

Cyclization: The preactivated $Co(nmp)_2$ (**15**, 0.8 mmol, 0.1 equiv.) was diluted with *i*PrOH (100 mL), to this mixture was added alcohol **8** (2.06 g, 7.8 mmol, 1 equiv.). The reaction was heated to 55 °C under oxygen for exactly 1 h and then allowed to cool to room temp. The solvent was removed under reduced pressure and then under high vacuum (0.1 Torr) to remove all trace amounts of *i*PrOH. 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 that was used without further purification. (The product rapidly decomposes, and the decomposition product gives characteristically broad peaks at δ = 3.65 and 3.45 ppm. The presence of the decomposition product also results in the loss of the fine-splitting patterns, and the peaks are reported as multiplets.) ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 4.43 (d, J = 2.0 Hz, 2 H), 4.06 (ddt, J = 9.4, 6.2, 3.1 Hz, 1 H), 3.79 (s, 3 H), 3.62–3.48 (m, 4 H), 2.09–2.03 (m, 1 H), 1.94–1.85 (m, 2 H), 1.73–1.65 (m, 1 H), 1.37–1.29 (m, 1 H), 1.01 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.1, 130.6, 129.2, 113.7, 82.4,

78.3, 72.6, 67.4, 65.2, 55.3, 40.1, 36.6, 34.3, 16.4 ppm. HRMS: calcd. for $C_{16}H_{24}O_4$ 280.1675; found 280.1667.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra.

Acknowledgments

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[1] a) N. A. Morra, B. L. Pagenkopf, *Org. Lett.* **2011**, *13*, 572–575; b) for C-18–C-34, see: S. Roy, C. D. Spilling, *Org. Lett.* **2010**, *12*, 5326–5329; c) for C-1–C-5, see: M. P. Paudyal, N. P. Rath, C. D. Spilling, *Org. Lett.* **2010**, *12*, 2954–2957; d) for C-1–C-9, see: L. Ferrié, B. Figadére, *Org. Lett.* **2010**, *12*, 4976–4979; e) for C-7–C-20, see: S. Mahapatra, R. G. Carter, *Org. Biomol. Chem.* **2009**, *7*, 4582–4585; f) for C-18–C-29, see: A. Armstrong, C. Pyrkotis, *Tetrahedron Lett.* **2009**, *50*, 3325–3328; g) for C-1–C-9, see: R. H. Bates, J. B. Shotwell, W. R. Roush, *Org. Lett.* **2008**, *10*, 4343–4346; h) for C-19–C-34, see: D. K. Mohapatra, H. Rahaman, M. S. Chorghade, M. K. Gurjar, *Synlett* **2007**, 567–570; i) for C-11–C-29, see: J. B. Shotwell, W. R. Roush, *Org. Lett.* **2004**, *6*, 3865–3868; j) for C-1–C-10 and C-17–C-29, see: T. Kubota, M. Tsuda, J. Kobayashi, *Tetrahedron* **2003**, *59*, 1613–1625; k) for C-1–C-9, see: H. Ishiyama, M. Ishibashi, J. Kobayashi, *Chem. Pharm. Bull.* **1996**, *44*, 1819–1822.

[2] For the synthesis of amphidinolide F, which was recently reported, see: S. Mahaparta, R. G. Carter, *Angew. Chem. Int. Ed.* **2012**, *32*, 7948–7951.

[3] a) C. Palmer, N. A. Morra, A. C. Stevens, B. Bajtos, B. P. Machin, B. L. Pagenkopf, *Org. Lett.* **2009**, *11*, 5614–5617; b) J. Wang, N. A. Morra, H. Zhao, J. S. T. Gorman, V. Lynch, R. McDonald, J. F. Reichwein, B. L. Pagenkopf, *Can. J. Chem.* **2009**, *87*, 328–334.

[4] a) K. Jarowicki, P. J. Kocienski, L. Qun, *Org. Synth.* **2002**, *79*, 11–13; b) K. Jarowicki, P. J. Kocienski, *Synlett* **2005**, 167–169.

[5] R. O. Hutchins, I. M. Taffer, W. Burgoyne, *J. Org. Chem.* **1981**, *46*, 5214–5215.

[6] The other Lewis acids screened are $MgBr_2$, $ZnCl_2$, $TiCl_4$, $SnCl_4$, $Yb(OTf)_3$, and $Sc(OTf)_3$.

[7] N. A. Morra, B. L. Pagenkopf, *Synthesis* **2008**, 511–514.

[8] The ^{19}F NMR peak shift can be correlated to the strength of the Lewis acid. The order of the strongest to weakest is $BF_2OTf{\cdot}OEt_2$ (–146.9 ppm), $BF_2OMs{\cdot}OEt_2$ (–148.3 ppm), and $BF_2OBn{\cdot}OEt_2$ (–151.5 ppm). Trifluorotoluene (–63.9 ppm) was used as an internal standard.

[9] Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.

[10] M.-X. Zhao, Y. Shi, *J. Org. Chem.* **2006**, *71*, 5377–5379.

[11] The catalyst can be deactivated by a competing Baeyer–Villiger oxidation, which is disfavored at a higher pH.

[12] The buffer is a 0.05 M solution of $Na_2B_2O_7{\cdot}H_2O$ in 1×10^{-4} M aqueous Na_2EDTA.

[13] This setup was found to be optimal for production of $BF_2OBn{\cdot}OEt_2$ without the formation of $BF(OBn)_2{\cdot}OEt_2$. Alternative procedures were examined including heating, reduced pressure, and nitrogen flow through a Schlenk line, but they were less effective.

[14] If the solution contains significant amounts of $BF_3{\cdot}OEt_2$, the evaporation procedure can be repeated as needed until the ^{19}F NMR shows only product. The concentration of the solution can be more accurately determined by adding an internal standard (e.g., trifluorotoluene) and comparing peak integration using No-D (no-deuterium) ^{19}F NMR spectroscopy. For further details, see: T. R. Hoye, B. M. Eklov, M. Voloshin, *J. Am. Chem. Soc.* **2004**, *126*, 2567–2570.

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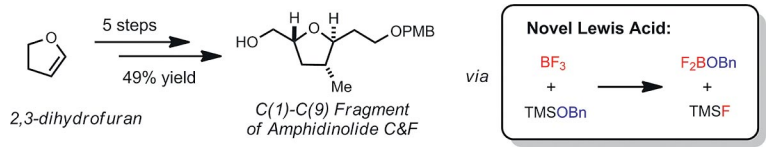
Studies Toward Amphidinolides



The new Lewis acid $BF_2OBn{\cdot}OEt_2$ was generated by an anionic redistribution between $BF_3{\cdot}OEt_2$ and benzyloxytrimethylsilane and used in a regio- and stereoselective epoxide ring-opening reaction. The utility of this reaction was demonstrated by the conversion of commercially available 2,3-dihydrofuran into the C-1–C-9 fragment of amphidinolide C and F in five steps and 49% overall yield.

Keywords: Natural products / Asymmetric catalysis / Regioselectivity / Cyclization / Lewis acids / Epoxidation

