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Diastereodivergent Strategies for the Synthesis of Homochiral Aculeatins

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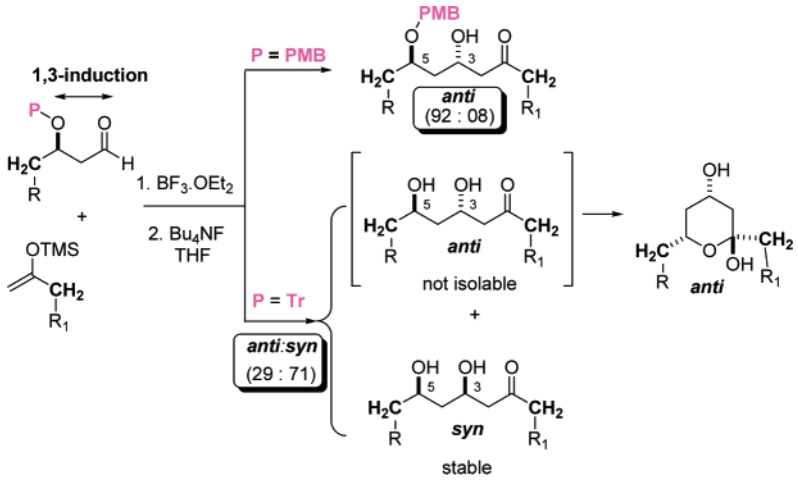

We report concise and stereocontrolled syntheses of aculeatins (−)-A, (+)-B, (+)-D, and (+)-6-*epi*-D. Diastereodivergent 1,3-inductions in Mukaiyama aldol coupling contribute to reduce steps and to increase flexibility with reactants having sterically restricted proximal substituents (i.e., CH_2), involving either a good anti or a moderate syn 1,3-induction, depending on the nature of protecting group (P). In addition, the 3,5-*syn*-diol-ketone resulting from concomitant deprotection of the β-alkoxy (Tr = trityl) group proves to be remarkably stable whereas the 3,5-anti diastereoisomer cyclizes spontaneously to the corresponding tetrahydropyran hemiketal, thus enabling a useful and facile separation. The second part of our study is devoted to improving the yield and the diastereoselectivity of the final phenolic oxidation reaction leading to aculeatins.

Introduction

Development of diastereodivergent approaches can impact the flexibility and the efficiency in the synthesis of stereochemically diverse members of natural compounds by facilitating direct access to each diastereoisomer from common intermediates. In our search for new bioactive molecules using natural products as templates, we set out to explore a novel and simple approach for the facile production of new analogues from aculeatins (Scheme 1), a new family of biologically active compounds isolated from *Amomun aculeatum* by Heilmann and co-workers in 2000.[1] Very recently, new natural and bioactive derivatives of aculeatins, the aculeatols, were characterized.[2] These compounds have gained attention because of their antiprotozoal and antibacterial properties and because of the synthetic challenge in elaborating well-defined three-dimensional structures inherent to their polyspiroketal skeleton. Several years ago we described the first synthesis of the (±)-aculeatins A and B, disclosing that these products can arise from the phenolic oxidation of an identical precursor equivalent to the 3,5-*syn*-diol-ketone **1**.[3] Later, Bulger and co-workers synthesized (±)-

(1) (a) Heilmann, J.; Mayr, S.; Brun, R.; Rali, T.; Sticher, O. *Helv. Chim. Acta* **2000**, *83*, 2939−2945. (b) Heilmann, J.; Brun, R.; Mayr, S.; Rali, T.; Sticher, O. *Phytochemistry* **2001**, *57*, 1281−1285. The relative configurations assigned for aculeatins A and B were erroneously assigned from the initial paper (see ref 1a) and have been corrected by Marco and co-workers (see ref 5a).

(2) Salim, A. A.; Su, B.-N.; Chai, H.-B.; Riswan, S.; Kardono, L. B. S.; Ruskandi, A.; Farnsworth, N. R.; Swanson, S. M.; Kinghorn, A. D. *Tetrahedron Lett.* **2007**, *48*, 1849−1853.

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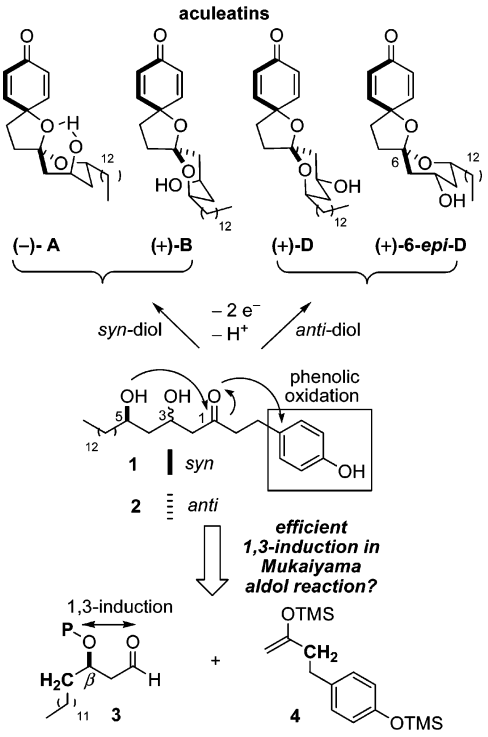
SCHEME 1. Retrosynthesis of Key Precursors 1 and 2 Giving Rise to Aculeatins by Phenolic Oxidation

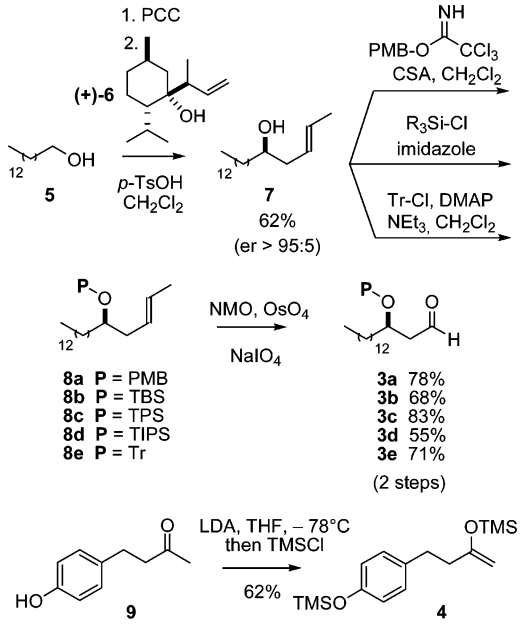


aculeatin D along with a new epimer, the (±)-6-*epi*-aculeatin D, by the oxidation of a cyclic conformer of the 3,5-*anti*-diol-ketone **2**.[4] Applying this phenolic oxidation approach, the enantioselective syntheses and the assignment of absolute configurations of aculeatins (−)-A, (+)-B, (+)-D, and (+)-6-*epi* D have been achieved recently by Marco and co-workers.[5]

A more straightforward approach was envisioned. Assembling two easily accessible fragments, the homochiral β-alkoxy aldehyde **3** and the enolsilane **4**, in a diastereodivergent process should directly lead to each individual key precursor **1** or **2**. This prospect relies on the pivotal efficiency of the acyclic stereocontrolled 1,3-induction in Mukaiyama aldol addition.[6,7] Indeed, using $BF_3{\cdot}OEt_2$ as monodentate Lewis acid, a good 1,3-anti diastereoselectivity can be achieved depending on the protecting group carried by the β-alkoxy group.[7,8] In this Mukaiyama coupling, polar substituents such as *p*-methoxybenzyl (PMB) and, to a lesser extent, *tert*-butyldimethylsilyl (TBS) ethers proved effective.[9,10] Minimization of electrostatic and steric effects has been invoked to account for the preferred transition state.[7b] However, at least one of the two reactants involved in the aldol couplings studied so far carries a proximal and bulky polysubstituted[6] or unsaturated[6,9b,9c] carbon, presumably acting to sterically differentiate the diastereomeric transition states. No example lacking a β-alkoxy group on the enolate partner while both components display a proximal methylene group (CH_2, see Scheme 1) has been reported.

Herein, we wish to report a convenient reversal of diastereoselectivity in the Mukaiyama aldol reaction. This approach, combined with our efforts to optimize the yield and the orientation of the diastereoselectivity during the phenolic oxidation from **1**, and new derivatives of **1** and **2**, offers a simple and adaptable method for the selective synthesis of homochiral aculeatins.

SCHEME 2. General Syntheses of 3a−e and 4



Results and Discussion

We started our study by synthesizing different β-alkoxy aldehydes **3a−e** according to a general route (Scheme 2). We have selected Nokami's enantioselective crotylation[11] because once made, this organic reagent **6** was shown to be stable for months and is easy to handle (no strict anhydrous condition was required during the enantioselective reaction). McDonald and co-workers had already reported the synthesis of the homochiral alcohol **7** with a good enantioselectivity (er = 93:7).[12] In our hands, oxidation of 1-tetradecanol **5** with PCC followed by treatment of the corresponding aldehyde with the Nokami's reagent **(+)-6** gave the alcohol **7** in 62% overall yield with an excellent enantioselectivity (er > 95:5).[13] A two-step

(3) Wong, Y.-S. *Chem. Commun.* **2002**, 686−687.
(4) Baldwin, J. E.; Adlington, R. M.; Sham, V. W.-W.; Márquez, R.; Bulger, P. G. *Tetrahedron* **2005**, *61*, 2353−2363.
(5) (a) Falomir, E.; Álvarez-Bercedo, P.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2005**, *46*, 8407−8410. (b) Álvarez-Bercedo, P.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2006**, *62*, 9641−9649.
(6) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729−732.
(7) (a) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537−8540. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.
(8) (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120. (b) Schetter, B.; Mahrwald, R. *Angew. Chem., Int Ed.* **2006**, *45*, 7506−7525.
(9) For examples of acyclic 1,3-anti induction in Mukaiyama aldol coupling using $BF_3{\cdot}OEt_2$ as Lewis acid, see (a) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671−8726. (b) Yokokawa, F.; Asano, T.; Shioiri, T. *Org. Lett.* **2000**, *2*, 4169−4172. (c) Yokokawa, F.; Asano, T.; Shioiri, T. *Tetrahedron* **2001**, *57*, 6311−6327. (d) Keck, G. E.; Welch, D. S.; Vivian, P. K. *Org. Lett.* **2006**, *8*, 3667−3670.
(10) For a recent example of diastereodivergent aldol addition catalyzed by $BF_3{\cdot}OEt_2$ involving a merge 1,2 and 1,3-induction, see Restorp, P.; Somfai, P. *Org. Lett.* **2005**, *7*, 893−895.
(11) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168−9169.
(12) Wiseman, J. M.; McDonald, F. E.; Liotta, D. C. *Org. Lett.* **2005**, *7*, 3155−3157.
(13) Alcohol **7** was derivatived by (−)-(*R*)-Mosher's acyl chloride, and the ratio (er) was established by ^1H and ^{19}F NMR spectra (500 MHz and 472 MHz, respectively). In our hands and with both NMR techniques, only one isomer can be detected (see Supporting Information).

SCHEME 3. 1,3-*Anti* Diastereoselectivity with PMB Ether

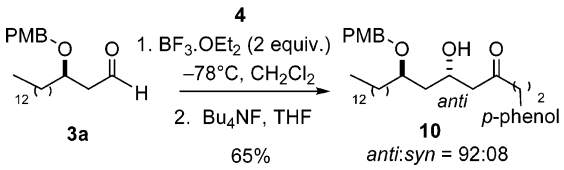
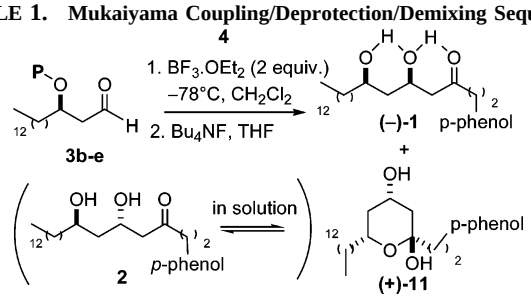


TABLE 1. Mukaiyama Coupling/Deprotection/Demixing Sequence



entry	**3** (P)	**1** (%)[a]	**11** (%)[a]	anti:syn[b]
1[c]	**3b** (TBS)	26	39	60:40
2[c]	**3c** (TPS)	35	35	50:50
3[c]	**3d** (TIPS)	32	36	53:47
4[c]	**3e** (Tr)	41	27	40:60
5[d]	**3e** (Tr)	51	21	29:71
6[e]	**3e** (Tr)	29	40	58:42
7[f]	**3e** (Tr)	-	-	-

[a] Isolated yield. [b] Ratio determined from yields of purified products **1** and **11**. [c] $BF_3{\cdot}OEt_2$ was added to a mixture of β-alkoxy aldehyde **3** and enolsilane **4**. [d] $BF_3{\cdot}OEt_2$ was added to a solution of **3** followed 2 min later by the addition of **4**. [e] $BF_3{\cdot}OEt_2$ was added to a solution of **3** and anisol followed 2 min later by the addition of **4**. [f] Instead of $BF_3{\cdot}OEt_2$, $Tr^+BF_4^-$ (1.2 equiv) was used as catalyst leading to a complex mixture. No expected products were obtained.

sequence, i.e., protection of alcohol group yielding PMB, TBS, *tert*-butyldiphenylsilyl (TPS), triisopropylsilyl (TIPS), or trityl (Tr) ethers, and an oxidative cleavage of the double bond, gave the desired protected β-alkoxy aldehydes **3a**−**e**. The enolsilane nucleophile **4** was readily prepared in one step (62%) from the commercially available 4-hydroxyphenyl-2-butanone **9**.

The aldol addition of enolsilane **4** to aldehyde **3a** (P = PMB) at −78 °C in CH_2Cl_2 by slow addition of $BF_3{\cdot}OEt_2$ (Scheme 3), followed by hydrolysis and TMS groups deprotection with Bu_4NF in THF, proceeded with a good 1,3-anti induction (dr = 92:08)[14] to give the 3,5-anti product **10** (65%). The addition of less than 2 equiv of $BF_3{\cdot}OEt_2$ gave lower yields, presumably because of the sensitive TMS groups carried by the enolsilane **4**.

In contrast, the 1,3-anti induction of aldol coupling dramatically dropped with β-alkoxy aldehydes protected by bulky silyl ethers (**3b**−**d**, Table 1). With the TBS ether (entry 1), the anti/syn ratio was only 60:40, and almost no 1,3-induction was observed with TPS and TIPS ethers (entries 2 and 3).

At this stage, isolation of products **1** and **11**, which are indeed the syn and anti products, respectively, needs some comments. The TMS protecting group was unstable during extraction and purification, and Bu_4NF/THF treatment which led to the removal of the silyl groups was thus necessary to get a reliable ratio of syn/anti induction. Interestingly, we have observed a convenient demixing of 3,5-diol-ketone diastereomers **1** and **2** that occurs during a simple chromatographic separation (silica gel, ethyl acetate/cyclohexane). The purified 3,5-*syn*-diol-ketone **1** turned out to be stable as linear isomer with a retention factor R_f = 0.45. We hypothesize that this stability should arise from the favorable intramolecular hydrogen bond formation. Conversely, the 3,5-*anti*-diol-ketone **2** was prone to cyclize to form tetrahydropyran hemiketal **11** with R_f = 0.30.

To evaluate a new protecting group, trityl ether was tested in the Mukaiyama coupling/deprotection/demixing step (Table 1, entries 4−6). This acid-labile protecting group, which can be compared to a bulky PMB ether, offers the opportunity to undergo simultaneous deprotection with $BF_3{\cdot}OEt_2$. Thus, using the same experimental conditions, 2 equiv of $BF_3{\cdot}OEt_2$ was added to a mixture of β-alkoxy aldehyde **3e** and enolsilane **4** at −78 °C (Table 1, entry 4). Unexpectedly, after treatment with Bu_4NF/THF, a weak syn 1,3-induction was observed, giving **1** (41%) and **11** (27%) with a syn/anti ratio of 60:40 (entry 4). When $BF_3{\cdot}OEt_2$ was added to the aldehyde **3e**, prior to the addition of the enolsilane **4**, an improved 1,3-syn induction was obtained yielding **1** (51%) and **11** (21%) with a syn/anti ratio of 71:29 (entry 5). We speculated that the released trityl carbenium ion may be involved in this novel 1,3-syn induction. It was reported that trityl salts can be an efficient catalyst in the Mukaiyama aldol additions.[15] Using $Tr^+ClO_4^-$ instead of $BF_3{\cdot}OEt_2$, Evans reported a reversion of anti-induction in favor of syn selectivity within the scope of merge 1,2 and 1,3-induction in Mukaiyama aldol coupling.[7b] We first performed the reaction with anisole in order to trap the trityl carbenium ion generated in situ. Loss of preferential 1,3-syn induction was observed (entry 6). When we ran the Mukaiyama aldol reaction with the aldehyde **3e** (Tr) and the enolsilane **4** using triphenylcarbenium tetrafluoroborate ($Tr^+BF_4^-$) as sole catalyst, a complex mixture of products was obtained (entry 7). In contrast, with the aldehyde **3b** (PMB) and the enolsilane **4**, the corresponding aldol product **10** was isolated in 47% yield with the same selectivity (anti/syn = 92:08) previously observed under $BF_3{\cdot}OEt_2$ catalysis (Scheme 3). In situ generation of trityl carbenium with a deprotected alcohol in presence of $BF_3{\cdot}OEt_2$ seem to be key features for the reversal of 1,3-induction in Mukaiyama aldol addition. However, the exact mechanism remains unclear.

The second part of our approach focuses on the formation of bis-spiroketal[16] induced by phenolic oxidation. Our preliminary work has demonstrated that phenyliodine(III) bis-(trifluoroacetate) (PIFA) is the reagent of choice for constructing the bis-spiroketal moiety of aculeatins through phenolic oxidation with a concomitant liberation of the ketone from a dithiane protecting group.[3] With the same reagent, Bulger and co-workers[4] reported that (±)-**11** gave the best yield of (±)-6-*epi*-aculeatin D (43%) and (±)-aculeatin D (19%) using acetone/H_2O (9:1) as solvents. These authors found, however, that the cyclic precursor (±)-**11** reopens toward the linear isomer 3,5-*anti*-diol-ketone **2** in deuterated acetone to reach an equilibrium mixture **11**/**2** of 2:1. The investigation of the key oxidative spiro-annelation by using a mixture of precursors **11** and **2** makes it difficult to clearly analyze effects involved in the diastereoselectivity. We anticipated that the tetrahydropyran methoxy ketals **12** and **13**[17] (Scheme 4) would be more stable precursors. To obtain cyclic analogues **12** and **13**, we found that simply refluxing the linear

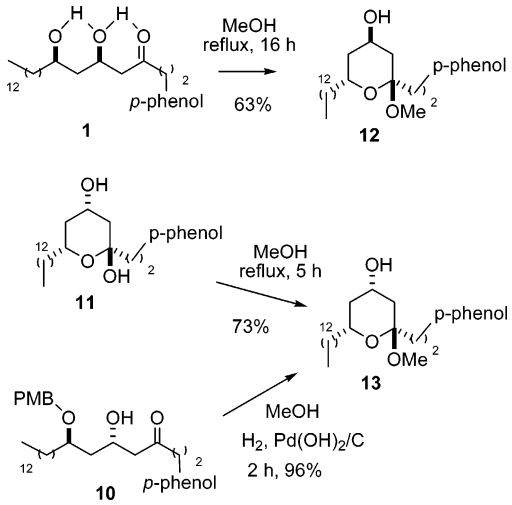
(14) Determined by ^1H NMR of the crude mixture.

(15) (a) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, 1759−1762. (b) Denmark, S. E.; Chen, C.-T. *Tetrahedron Lett.* **1994**, *35*, 4327−4330. (c) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570−4581.

(16) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617−1661.

(17) Ahmed, F.; Forsyth, C. J. *Tetrahedron Lett.* **1998**, *39*, 183−186.

SCHEME 4. Syntheses of Two New Precursors 12 and 13 for the Phenolic Oxidative Cyclization



3,5-*syn*-diol-ketone **1** and the tetrahydropyran hemiketal **11** in methanol (Scheme 4) generated the cyclic products **12** (73%) and **13** (63%), respectively. It is important to point out that the use of ether/cyclohexane as an eluent for the chromatographic purification on silica gel was crucial. Other eluent systems led to a significant decomposition during purification on the column. An alternative way to obtain **13** was the PMB deprotection of the 3,5-anti adduct **10** with $Pd(OH)_2/C$ in MeOH for 2 h. This approach directly afforded the crude product **13** (96%), which was pure enough to be used for the next step without any chromatography. The ^1H NMR analysis at 400 MHz of **12** and **13** in deuterated acetone confirmed that only one product was detectable from each precursor and that no change was observed even after 1 month. Finally, we found that dissolving **11** in deuterated acetone within 5 min gave a mixture of **11**/**2** with a ratio of 8:1, different from the equilibrium ratio of 2:1 that was reached only after 3 h in solution.[4] In this context, all our experiments with **11** were performed by quickly dissolving the reactant in the solvent and by adding the PIFA oxidant immediately (Table 2, entries 5−7).

Starting from these structurally distinct precursors **1** and **11**−**13**, we investigated their effects on the stereochemistry during the oxidative phenolic spiroannelation using conditions that ensured good yields of products. For instance, presence of water in the medium was necessary to get high yield of aculeatins.[4] In addition, we have found that running the reaction at higher concentration (0.04 M) using PIFA in acetone/H_2O (10:1) at room temperature in darkness for only 15 min allows the corresponding aculeatins to be isolated in good yields (Table 2). The yield was improved by adding additional TFA (CF_3CO_2H, optimized at 0.4 equiv) beyond that generated in situ from the PIFA reagent (entries 2 and 6).

Concerning the stereocontrol in the syntheses of aculeatins (−)-A and (+)-B, typically 3:2 selectivity in favor of (−)-aculeatin A was observed with the linear 3,5-*syn*-diol-ketone **1** as precursor (Table 2, entries 1−3), whereas with the cyclic tetrahydropyran methoxy ketal **12**, a ratio of about 1:1 was obtained (entry 4). Similarly, the product distribution of (+)-6-*epi*-aculeatin D and (+)-aculeatin D starting from the tetrahydropyran hemiketal **11** as precursor led to a preference in the formation of (+)-6-*epi*-aculeatin D (ratio of 6-*epi*-D/D 3:2, entries 5−7). In contrast, the use of the tetrahydropyran-methoxy ketal **13** gave a ratio of 1:1 (entries 8−10). Addition of the Lewis acid $ZnCl_2$ as the chelating agent had no influence over the diastereoselectivity of the resulting bis-spiroketal structure (entries 3, 7, and 10).

From these results, several points deserve to be highlighted. Because the 3,5-*syn*-diol-ketone **1** is a stable linear molecule, we postulate that generation of the reactive phenoxonium cation **14**[18] by PIFA oxidation (Scheme 5) triggers the polyspiroannelation process by prerequisite formation of a spiro-oxocarbenium cation intermediate **15**.[19] This highly electrophilic intermediate **15** is essential to initiate the second and final annelation to give aculeatins A and B. As some water is present, formation of *p*-quinol, which would initiate the polyspiroannelation process as well, cannot be excluded.[5]

A simple rationalization for preferential formation of aculeatin A compared to B (3:2) involving the intermediate **15** is not obvious. On the other hand, considering that the cyclic precursors **11**−**13** exist almost exclusive as cyclic species (vide supra) when PIFA is added, we propose that the higher proportion of aculeatins B and D obtained with the tetrahydropyran methoxy ketals **12** and **13** compared to their corresponding analogues **1** and **11** during the phenolic oxidation could lie in the affinity in quenching the phenoxonium cation **16** by nucleophiles according to two pathways (paths 1 and 2, Scheme 6). The phenoxonium cation **16** would be trapped by an intramolecular OR group **16a** (R = H, path 1) rather than a less nucleophilic oxygen atom from a methoxy group **16b** (R = Me, path 2),[20] therefore leading to the preferential formation of aculeatins A or 6-*epi*-D. Conversely, to form aculeatins B or D, a competitive intermolecular addition of water could occur, resulting in the formation of *p*-quinols **17a**,**b** (path 2) which could displace the OR group according to a SN_2 process. Finally, to interpret the beneficial effect of additional TFA on the yield, we suggest that an excess of TFA acting as a non-nucleophilic counteranion would help to stabilize the intermediate phenoxonium cations **14** and **16**, and spiro-oxocarbenium cation **15** (Schemes 5 and 6).

Conclusion

We have demonstrated that diastereodivergent approaches can be conducted to easily access new enantioselective syntheses of aculeatins (−)-A, (+)-B, (+)-D, and (+)-6-*epi*-D, within a handful of steps (six or seven steps). A useful diastereodivergent 1,3-induction in the nucleophilic addition of enolsilane to β-alkoxy aldehyde has been developed, coupled with a practical protocol for differentiating of 3,5-diol-ketone diastereoisomers. Our efforts to influence the diastereodivergent formation of bis-spiroketals by using the novel precursors **1**, **12**, and **13** for the phenolic oxidative cyclization has led to a selectivity ranging from 1:1 to 3:2. Within the scope of target-oriented syntheses, aculeatins (−)-A and (+)-B are obtained in 10.8% and 7.7% overall yields starting from Tr ether aldehyde **8e**. With another combination, aculeatins (+)-D and (+)-6-*epi*-D were synthesized in 10.7% and 9.7% yields from PMB ether aldehyde **8a**

(18) For a recent characterization of a stable phenoxonium cation by crystal structure, see Lee, S. B.; Willis, A. C.; Webster, R. D. *J. Am. Chem. Soc.* **2006**, *128*, 9332−9333.

(19) For interesting nitrogen versions of phenolic oxidation involving trapping of phenoxonium cation by sp^2 or sp heteroatoms, see (a) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397−4408. (b) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175−177.

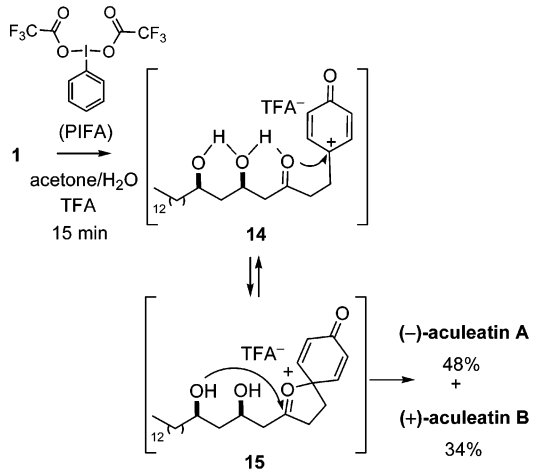
(20) For the participation of a methoxy group as nucleophile for the synthesis of bis-spiroketal by trapping ring oxocarbenium species, see Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 279−282.

TABLE 2. Synthesis of Aculeatins (−)-A, (+)-B, (+)-6-epi-D, and D from Different Precursors by PIFA Oxidation

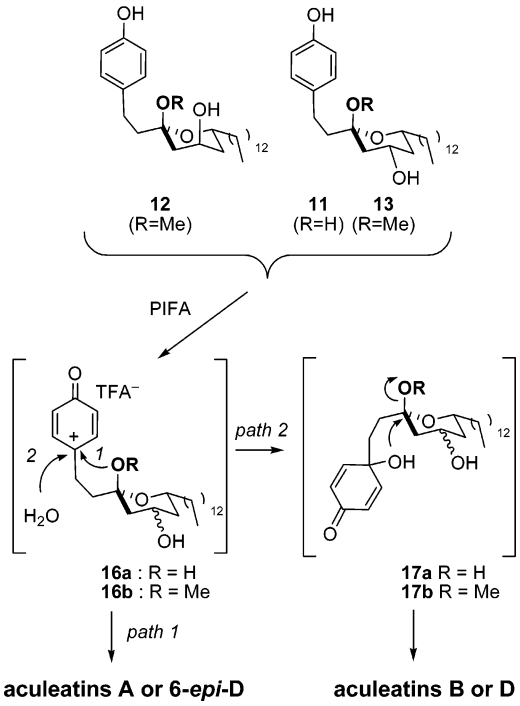
entry[a]	reactant	additive	(−)-A (%)	(+)-B (%)	(+)-6-*epi* -D (%)	(+)-D (%)	ratio	total yield (%)
1	**1**		44	27			62:38	71
2	**1**	TFA[b]	48	34			58:42	82
3	**1**	$ZnCl_2$[c]	32	25			57:43	57
4	**12**		36	32			53:47	68
5	**11**				38	26	59:41	64
6	**11**	TFA[b]			40	31	56:44	71
7	**11**	$ZnCl_2$[c]			40	29	58:42	69
8	**13**				34	35	49:51	69
9	crude **13**				31	34	48:52	65[d]
10	crude **13**	$ZnCl_2$[c]			26	25	51:49	51[d]

[a] All reactions were carried out in acetone/H_2O (10:1) with PIFA (1.2 equiv) for 15 min in darkness at 25 °C. [b] 0.4 equiv. [c] 1.1 equiv. [d] Yield over two steps.

SCHEME 5. Polyspiroannelation Process Involving a Spiro-oxocarbenium Cation Intermediate 15



SCHEME 6. Two Possible Pathways in the Phenolic Oxidation Cyclization



and by the use of **13** as precursor. Ongoing efforts are devoted to extend the production to new bioactive and potent analogues of aculeatins, and these results will be reported soon.

Experimental Section

(−)-(3*R*)-Trityloxyhexadecanal (3e). To a stirred solution of trityl chloride (411 mg, 1.47 mmol), triethylamine (0.24 mL, 1.70 mmol), and 4-dimethylaminopyridine (36 mg, 0.29 mmol) in dry CH_2Cl_2 (0.8 mL) was added a solution of alcohol **7** (198 mg, 0.74 mmol) in dry CH_2Cl_2 (0.4 mL) at rt. After stirring for 24 h at reflux, the reaction mixture was cooled to rt. The reaction was quenched with H_2O (1 mL), and the mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. After simple filtration on silica gel (cyclohexane/Et_3N 99:1), the filtrate was concentrated. The product was then dissolved in THF (5 mL). *N*-Methylmorpholine *N*-oxide (50% water, 346 mg, 1.47 mmol) and osmium(VIII) oxide (4% water, 469 mg, 0.07 mmol) were added at rt. After 2 h, sodium bisulfite (153 mg, 1.47 mmol) was added to the reaction mixture. After stirring for 5 min, the mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was then dissolved in 10 mL of THF/H_2O (1:1) and treated with sodium metaperiodate (631 mg, 2.95 mmol). After 15 min, the reaction mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on alumina (cyclohexane) to afford the aldehyde **3e** (261 mg, 0.52 mmol, 71%) as a colorless oil; $R_f = 0.26$ (cyclohexane/EtOAc 99:1) on alumina; $[\alpha]_D^{27}$ −12.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.8$ Hz, 3H), 1.05−1.30 (m, 22H), 1.35−1.45 (m, 2H), 2.47 (ddd, $J = 16.4$, 4.4, 2.8 Hz, 1H), 2.48 (ddd, $J = 16.4$, 6.4, 2.4 Hz, 1H), 3.87−3.93 (m, 1H), 7.25−7.35 (m, 9H), 7.52 (d, $J = 8.0$ Hz, 6H), 9.57 (t, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 22.9, 24.9, 29.6−29.9, 32.1, 35.8, 48.4, 69.9, 87.3, 127.3, 128.0, 129.1, 145.0, 202.3; IR ν_{max} (neat) 3439, 2925, 2853, 1693, 1643, 1448, 705 cm^{-1}; UV (MeOH) 257, 225, 212 nm; MS (DCI, NH_3 + isobutane) *m/z (%)* 499 $[M + H]^+$ (1), 243 (100); HRMS (ESI+) *m/z* calcd for $C_{35}H_{46}O_2Na$ 521.3396, found 521.3391.

1-Trimethylsilanyloxy-4-(3-trimethylsilanyloxybut-3-enyl)-benzene (4). To a stirred solution of diisopropylamine (4.10 mL, 29.2 mmol) in dry THF (30 mL) was added dropwise *n*-BuLi (2.5 M in hexane, 11.7 mL, 29.2 mmol) at 0 °C. The reaction mixture was stirred 20 min and then cooled to −78 °C, and a solution of 4-(4-hydroxyphenyl)-2-butanone (2.0 g, 12.2 mmol) in dry THF (30 mL) was added dropwise. After stirring for 20 min, trimethylsilyl chloride (3.9 mL, 30.5 mmol) was slowly added. The reaction mixture was stirred for 1.5 h, warmed to ambient temperature, and concentrated in vacuo. The crude product was dissolved in minimum dry THF and filtered over cotton wool. The filtrate was concentrated in vacuo and then distilled at 10 mmHg and 130−140 °C to provide the enolsilane **4** (2.34 g, 7.58 mmol, 62%) as a colorless oil. This product contains 7% of its regioisomer; $R_f = 0.71$ (cyclohexane/EtOAc 47:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21 (s, 9H), 0.24 (s, 9H), 2.30 (t, $J = 8.0$ Hz, 2H), 2.71 (t, $J = 8.0$ Hz, 2H), 4.05 (d, $J = 3.6$ Hz, 2H), 6.75 (d, $J = 8.2$ Hz, 2H), 7.04 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.3,

32.6, 38.5, 90.2, 119.8, 129.2, 134.7, 153.1, 158.8; IR ν_{max} (neat) 2959, 1511, 1253, 1100, 919, 846 cm^{-1}; UV (MeOH) 279, 224, 207 nm; MS (DCI, NH_3 + isobutane) *m/z (%)* 309 $[M + H]^+$ (39), 293 (25), 179 (100).

(−)-(5*R*,7*R*)-Dihydroxy-1-(4-hydroxyphenyl)icosan-3-one (1) and (+)-(2*S*,4*S*,6*R*)-2-[2-(4-hydroxyphenyl)ethyl]-6-tetrahydropyran-2,4-diol (11). To a stirred solution of aldehyde **3e** (19 mg, 0.04 mmol) in dry CH_2Cl_2 (0.7 mL) was added dropwise $BF_3{\cdot}OEt_2$ (10 μL) at −78 °C. After stirring for 2 min, enolsilane **4** (19 mg, 0.06 mmol) in dry CH_2Cl_2 (0.2 mL) was added. After stirring for 1.5 h at −78 °C, the reaction was quenched by a addition of saturated aqueous solution of $NaHCO_3$ (1 mL) and the mixture was warmed to rt. The product was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude products were then dissolved in THF (8 mL) and treated with TBAF (1 M in THF, 0.08 mL) at 0 °C. After stirring for 1 h at rt, a saturated aqueous solution of NH_4Cl (6 mL) was added. The mixture was extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/ EtOAc 4:1 then 3:2) to afford the (−)-3,5-*syn*-diol ketone **1** (8.2 mg, 0.02 mmol, 51%) and the (+)-tetrahydropyran-hemiketal **11** (3.4 mg, 0.01 mmol, 21%).

(−)-1. R_f = 0.45 (cyclohexane/EtOAc 1:1); $[\alpha]_D^{25}$ − 3.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 0.91 (t, *J* = 6.8 Hz, 3H), 1.26−1.38 (m, 22H), 1.38−1.50 (m, 3H), 1.53−1.58 (m, 1H), 2.58 (d, *J* = 6.4 Hz, 2H), 2.73−2.82 (m, 4H), 3.67−3.77 (m, 1H), 4.19−4.29 (m, 1H), 6.69 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 14.6, 23.9, 26.7, 29.9, 30.6−30.9, 33.2, 38.8, 44.9, 46.6, 51.3, 68.0, 71.2, 116.3, 130.4, 133.4, 156.8, 211.9; IR ν_{max} (thin film, CH_2Cl_2) 3477, 3388, 2918, 2848, 1703, 1682, 1518, 1470, 1120, 815 cm^{-1}; UV (MeOH) 280, 225, 204 nm; MS (ESI+) *m/z (%)* 443 $[M + Na]^+$ (100), 421 $[M + H]^+$ (4), 107 (56); HRMS (ESI+) *m/z* calcd for $C_{26}H_{44}O_4Na$ 443.3137, found 443.3134.

(+)-11: R_f = 0.30 (cyclohexane/EtOAc 1:1); $[\alpha]_D^{25}$ + 6.7 (*c* 1.0, EtOH); ^{1}H NMR (400 MHz, CD_3OD) δ 0.90 (t, *J* = 6.8 Hz, 3H), 1.03−1.13 (m, 1H), 1.24−1.38 (m, 23H), 1.39−1.58 (m, 2H), 1.82−1.89 (m, 2H), 1.89−1.96 (m, 1H), 2.01−2.08 (m, 1H), 2.61−2.68 (m, 2H), 3.85−3.93 (m, 1H), 3.99−4.09 (m, 1H), 6.69 (d, *J* = 8.2 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 14.6, 23.9, 26.8, 30.2, 30.6−30.9, 33.2, 37.2, 42.1, 43.6, 46.6, 65.9, 69.9, 99.0, 116.3, 130.4, 134.6, 156.5; IR ν_{max} (thin film, CH_2Cl_2) 3349, 2849, 1516, 1468, 1451, 1247, 823 cm^{-1}; UV (MeOH) 280, 225, 206 nm; MS (ESI+) *m/z (%)* 443 $[M + Na]^+$ (100), 421 $[M + H]^+$ (1), 107 (94); HRMS (ESI+) *m/z* calcd for $C_{26}H_{44}O_4Na$ 443.3137, found 443.3141.

(+)-(2*S*,4*R*,6*R*)-2-[2-(4-Hydroxyphenyl)ethyl]-2-methoxy-6-tridecyltetrahydropyran-4-ol (12). The (−)-3,5-*syn*-diol ketone **1** (50 mg, 0.10 mmol) was solubilized in 5 mL of anhydrous MeOH. The reaction mixture was refluxed 16 h and then concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/ether 6:4) to afford (+)-**12** (32.5 mg, 0.05 mmol, 63%) as a colorless oil; R_f = 0.15 (cyclohexane/ether 6:4); $[\alpha]_D^{27}$ + 41.1 (*c* 0.4, EtOH); ^{1}H NMR (400 MHz, CD_3OD) δ 0.90 (t, *J* = 7.0 Hz, 3H), 1.25−1.56 (m, 25H), 1.66−1.76 (m, 3H), 1.89−2.02 (m, 2H), 2.43−2.60 (m, 2H), 3.23 (s, 3H), 3.86−3.94 (m, 1H), 4.03−4.07 (m, 1H), 6.69 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 14.7, 23.9, 26.8, 30.1, 30.7−31.0, 33.3, 37.2, 38.7, 39.0, 39.9, 47.9, 65.9, 102.4, 116.3, 130.2, 134.1, 156.6; IR ν_{max} (thin film, CH_2Cl_2) 3347, 2980, 1590, 1261, 723 cm^{-1}; UV (MeOH) 280, 224, 206 nm; MS (ESI+) *m/z (%)* 473 $[M + K]^+$ (4), 457 $[M + Na]^+$ (100), 425 $[MCH_3OH + Na]^+$ (74); HRMS (ESI+) *m/z* calcd for $C_{27}H_{46}O_4Na$ 457.3294, found 457.3283.

(−)-(2*R*,4*R*,6*R*)-4-Hydroxy-2-tridecyl-1,7-dioxadispiro[5.1.5.2]-pentadeca-9,12-dien-11-one [(−)-aculeatin A] and (+)-(2*R*,4*R*,6*S*)-4-Hydroxy-2-tridecyl-1,7-dioxadispiro[5.1.5.2]pentadeca-9,12-dien-11-one [(+)-aculeatin B]. To a stirred solution of (−)-3,5-*syn*-diol ketone **1** (75 mg, 0.18 mmol) in acetone/H_2O (4.4 mL of a 10:1 v/v solution) were added TFA (5 μL, 0.07 mmol) and PIFA (86 mg, 0.20 mmol) in one portion at rt in darkness. After 15 min, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added, and the products were extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude products were purified by flash chromatography on silica gel (cyclohexane/EtOAc 4:1) to afford (−)-aculeatin A (36 mg, 86 μmol, 48%) and (+)-aculeatin B (25 mg, 60 μmol, 34%).

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for **1**, **3a**−**d**, **4**, **7**, **8a**−**d**, **13**, and aculeatins. This material is available free of charge via the Internet at http://pubs.acs.org.

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