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A Chiron Approach to the Total Synthesis of (+)-Aculeatin D

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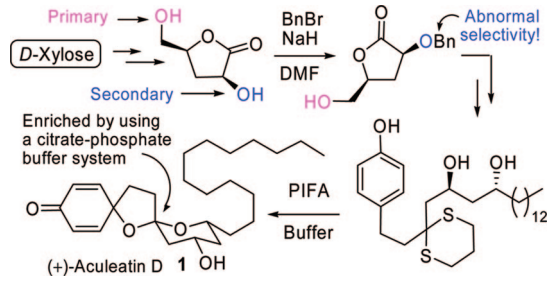
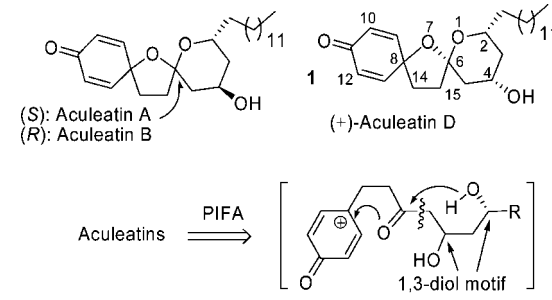


A synthesis of natural aculeatin D has been achieved, with the key stereogenic centers taken from inexpensive and readily available D-xylose. In elaboration of D-xylose into a desired form readily applicable in synthesis a previously misinterpreted and overlooked abnormal selectivity in hydroxyl protection was noticed and exploited. Protocols were developed for monotosylation of a triol insoluble in CH_2Cl_2 and "freezing" the less stable isomer (aculeatin D) at the PIFA-mediated oxidative spirocyclization, respectively. An unexplained deprotonation at a benzyl protecting group by a thermodynamically more stable dithiane carbanion in the literature was also addressed.

Introduction

Aculeatins A−D were isolated from the petroleum ether extract of the rhizomes of *Amomum aculeatum* by Heilmann in 2000−2001.[1] Because of their novel framework and significant antiprotozoal, antibacterial, and antitumoral activities, these compounds have invoked several[2] synthetic investigations. The first synthesis of this class of compounds (racemic aculeatins A and B) was reported by Wong in 2002,[2a] which established the entry into the spirocyclic framework by using a PIFA (phenyliodonium(III) bis(trifluoroacetate))-mediated cascade of reactions. This strategy (Scheme 1) later was also employed in all the subsequent approaches. As a consequence, construction of the hidden 1,3-dihydroxy unit became the major concern in designing different routes to the aculeatins. The majority of the existing

SCHEME 1



approaches utilized a stepwise manner to construct the 1,3-diol motif, with the relative configuration secured by either 1,3-induced asymmetric reduction[2a−e] of β-hydroxyl ketones or Micheal addition[2f] of an in situ formed hemiacetal. In the recent synthesis by Ramana and Srinivas[2g] this diol fragment was derived from D-glucolactone.

In a literature study we noticed an interesting compound (**6a**) encapsulated in Shurrle and Pipersberg's[3] synthesis of deoxyribose analogues, which contained a stereochemically well-defined 1,3-dihydroxy motif and appeared to be directly useable as a chiral building block for the corresponding stretch in, for

(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.

(2) (a) Wong, Y. S. *J. Chem. Soc., Chem. Commun.* **2002**, 686–687. (b) Falomir, E.; Alvarez-Bercedo, P.; Carda, M.; Marco, J. A *Tetrahedron Lett.* **2005**, *46*, 8407–8410. (c) Baldwin, J. E.; Adlington, R. M.; Sham, V. W. W.; Marquez, R.; Bulger, P. G. *Tetrahedron* **2005**, *61*, 2353–2363. (d) Alvarez-Bercedo, P.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2006**, *62*, 9641–9649. (e) Peuchmaur, M.; Wong, Y. S. *J. Org. Chem.* **2007**, *72*, 5374–5379. (f) Chandrasekhar, S.; Rambabu, C.; Shyamsunder, T. *Tetrahedron Lett.* **2007**, *48*, 4683–4685. (g) Ramana, C. V.; Srinivas, B. *J. Org. Chem.* **2008**, *73*, 3915–3918.

(3) Shurrle, K.; Piepersberg, W. *J. Carbohydr. Chem.* **1996**, *15*, 435–447.

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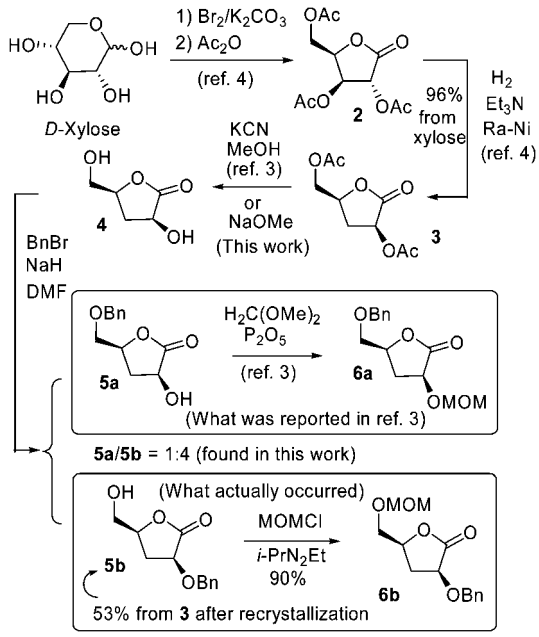
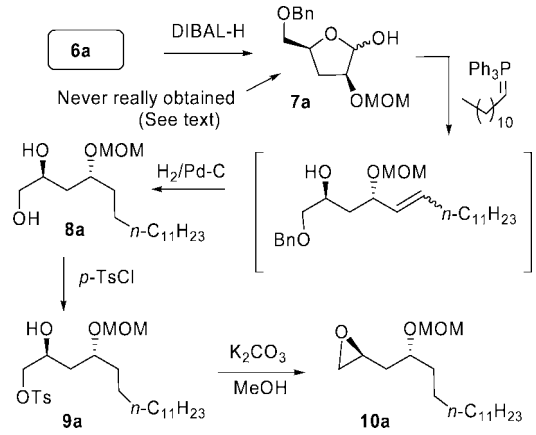
Published on Web 08/16/2008

SCHEME 2



SCHEME 3. The Initially Planned Yet Never Accomplished Route to 10a



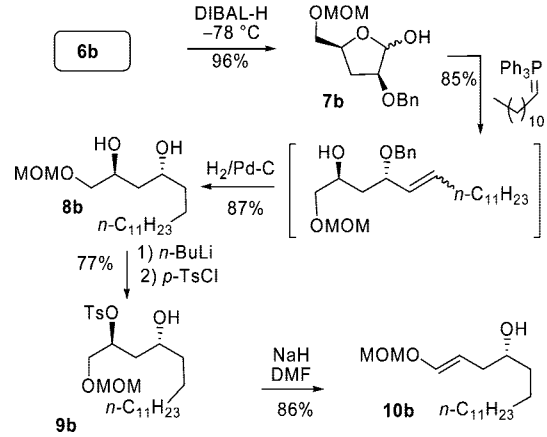
instance, aculeatin D. However, the steps leading to **3** in that synthesis were not so convenient to perform. Then we noticed that in the work by Okabe[4] and co-workers the synthesis of a precursor for nucleotides also contained an approach to the same diacetate with D-xylose as the starting material (Scheme 2). It appeared that combination of these two separate sequences would make a facile route to **6a** and thus offer a new way to acquire the 1,3-diol motif embedded in aculeatin D and many other natural products without involving any expensive/troublesome reagents. These factors prompted us to undertake the synthesis described below.

Results and Discussion

Our synthesis emerged with the preparation of **6a** via **5a** according to the literature[3,4] (Scheme 2). The **6a** was planned (Scheme 3) to be elaborated into **10a**, which on reaction with a proper dithiane species would lead to a precursor needed for the PIFA-mediated oxidative spirocyclization.

(4) (a) Okabe, M.; Sun, R. C.; Zenchoff, G. B. *J. Org. Chem.* **1991**, *56*, 4392–4397. (b) Sun, R. C.; Okabe, M. *Org. Synth.* **1995**, *72*, 48–52.

SCHEME 4. What Actually Occurred When Executing Scheme 3



In execution of Scheme 3 we encountered many unexpected difficulties because of the mis-assigned structure of **6a** in the literature (see below). The DIBAL-H reduction, Wittig reaction (with $Me(CH_2)_{10}CH{=}PPh_3$[5]), and the hydrogenation (Scheme 3) proceeded smoothly, affording a diol with the ^1H NMR, IR and mass spectra seemingly compatible with the expected structure. Then, strange phenomena began to appear. The tosylation completely failed under conventional conditions (*p*-TsCl/Et_3N/DMAP/CH_2Cl_2, *p*-TsCl/Py, or *n*-Bu_2SnO/*p*-TsCl/Et_3N/DMAP/CH_2Cl_2[6a−c]). Use of more forcing conditions (*n*-BuLi/*p*-TsCl) did give a tosylate-alcohol in 89% yield. However, it turned out to be fully resistant to K_2CO_3/MeOH in the normally rather facile epoxidation. When a clean transformation was finally realized by using NaH/DMF, the product did not contain any epoxy functionality but possessed a C−C double bond. After complete spectroscopic analyses including 2D NMR (COSY and HMQC), the compound was proven to be enol **10b**.

From **10b** deducing backward, what actually occurred when we tried to execute Scheme 3 must be as shown in Scheme 4, with the intermediate structures being **6b**−**9b**.[7] Consequently, our "**5a**" prepared according to the literature must be **5b**. Indeed, the spectroscopic data for authentic[8] **5b** (prepared via an unambiguous route) in the literature are identical with those recorded for our "**5a**". We also prepared **5a** from **11**[4] through an unambiguous route (Scheme 5). The ^1H and ^{13}C NMR spectra of this compound turned out to be incompatible with those reported[3] in the literature. Therefore, what was obtained there also must be **5b** rather than **5a**.

The abnormal selectivity leading to the predominant formation of **5b** deserves mentioning. To our knowledge, it has never been documented before that a secondary OH is more reactive than a primary one in the same diol in similar reactions.[9] Although the reason for such an unusual prefer-

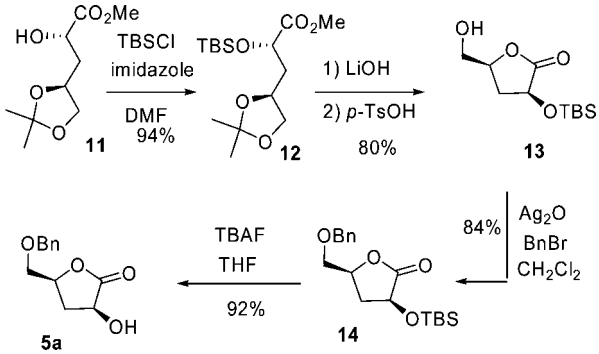
(5) Shi, M.; Xu, B. *J. Org. Chem.* **2002**, *67*, 294–297.

(6) (a) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447–450. (b) Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. M. H.; Moher, E. D.; Van Khau, V.; Kosmrlj, B. *J. Am. Chem. Soc.* **2002**, *124*, 3578–3585. (c) Martinelli, M. J.; Vaidyanathan, R.; Van Khau, V. *Tetrahedron Lett.* **2000**, *41*, 3773–3776. (d) Boons, G.-J.; Castle, G. H.; Clase, J. A.; Grice, P.; Ley, S. V.; Pinel, C. *Synlett* **1993**, 913–914.

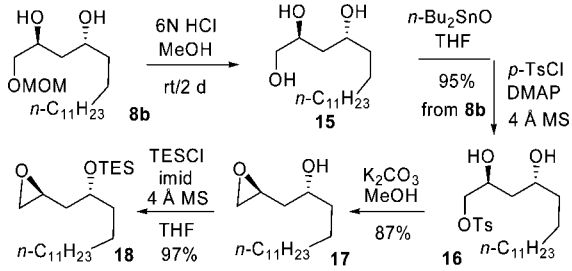
(7) Note that the regioselectivity observed in the tosylation and the subsequent elimination is of preparative significance and may be exploitable for the synthesis of other targets.

(8) Bigorra, J.; Font, J.; Echaguen, C. O.; Ortuno, R. M. *Tetrahedron* **1993**, *49*, 6717–6728: with **5b** prepared in five steps and 6.6% overall yield from D-ribolactone.

SCHEME 5



SCHEME 6



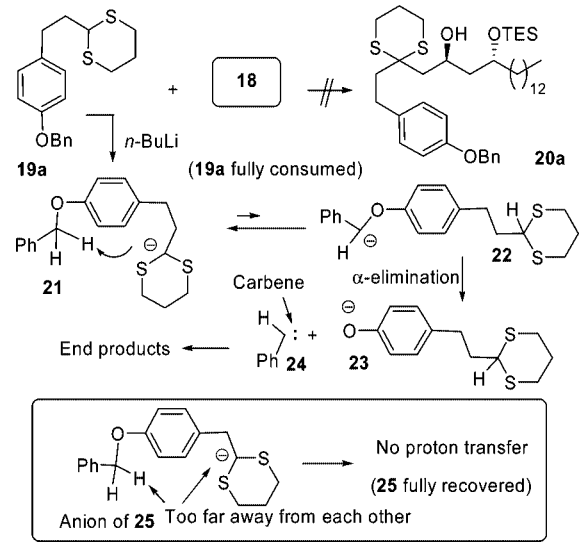
ence is not clear yet, the synthesis comprises a rapid route to **5b**, a potentially useful chiral building block that otherwise is not so easy to access.

Because of the newly recognized value of **5b** in synthesis, we next re-examined the benzyl protection of diol **4** in further detail. It was then noticed that the crude product mixture actually contained **5a** and **5b** in about a 1:4 ratio,[10] along with a small amount of dibenzyl-protected species. The major component **5b** tended to crystallize and hence was readily isolated in high purity with an overall yield of 53% from **3** under slightly modified conditions. The **5a**, however, was not able to be isolated in pure form despite our exhaustive efforts.[10]

The adjusted route to the epoxide moiety is depicted in Scheme 6. The MOM group in **8b** was hydrolyzed with 6 N HCl to give the triol **15**, with the intention to achieve **16** via selective tosylation of **15** by using Martinelli's[6a−c] n-Bu_2SnO/p-TsCl/Et_3N/CH_2Cl_2 protocol. However, because **15** turned out to be insoluble in CH_2Cl_2 direct execution of this plan was unfeasible at the tosylation step. Fortunately, after failures with many solvents we found that **15** could be reasonably dissolved in THF and therefore used this solvent as a substitute for CH_2Cl_2.

Using THF to replace the normally employed CH_2Cl_2 seemed to have a strong influence on the tosylation. At ambient temperature, with or without n-Bu_2SnO, the reaction was sluggish and nonselective when **15** was treated with Et_3N/p-TsCl/DMAP. Use[6d] of toluene to remove the H_2O (formed in reaction with n-Bu_2SnO) azeotropically remarkably facilitated the reaction but did not improve the selectivity. As

SCHEME 7



15 contained three OH groups, we suspected that the poor selectivity might result from coexistence of two cyclic stannylene acetals (the key intermediates responsible for the selectivity[6a−c]) caused by heating. To avoid this undesired factor, we switched to removing the H_2O at ambient temperature with 4 Å molecular sieves. Gratifyingly, under such conditions the anticipated **16** was formed as the only product in 95% overall yield from **8b**.

The unstable tosylate **16** was then treated with K_2CO_3/MeOH to give epoxide **17**. Subsequent protection of the remaining OH with TESCl (triethylchlorosilane) afforded **18**, setting the stage for chain extension through reaction with dithiane **19**. In preparative runs, the three steps could be carried out in 77% overall yield from **8b** with only one chromatography at the end.

Coupling of **18** with **19a** was unexpectedly difficult, always leading to a complex mixture (Scheme 7). Close examination revealed that **19a** decomposed on treatment with n-BuLi, even before introduction of **18**. Then we noticed that this phenomenon of **19a** had been studied by Whiting[11] before. They already found that the "culprit" was a deprotonation at the Bn group. However, they did not explain why the Bn group, which is normally stable[12] to n-BuLi and consequently dithiane anions, could be deprotonated.

We also examined a congener[13] (**25**) of **19a** under the otherwise identical deprotonation conditions. The starting **25** was fully recovered after workup and no decomposition product could be detected. This experiment excluded the possibility of deprotonation at the benzylic position by n-BuLi or the dithiane anion in another molecule. Because **19a** and **25** are so similar to each other, the acidity of the protons at the benzylic and dithiane positions in **25** is expected to be comparable to that of their counterparts in **19a**. Thus, it is likely that the decomposition of **19a** was caused by an intramolecular deprotonation as depicted in Scheme 7.

(9) It is interesting to note that other protecting groups may still react in a normal manner with diol **4** on the primary OH. See e.g.: Vargeese, C.; Abushanab, E. *Nucleosides Nucleotides* **1992**, *11*, 1549–1559.

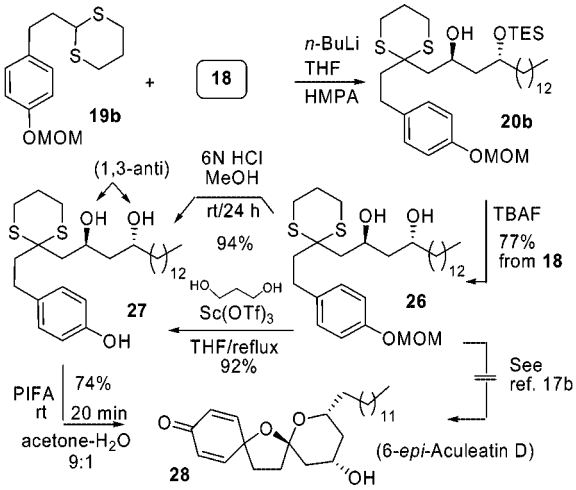
(10) These two components were inseparable by TLC, conventional flash column chromatography, or preparative HPLC, although separable by analytical HPLC. Formation of calcium salt ((a) Sharpless, K. B.; Chong, A. O.; Scott, J. A. *J. Org. Chem.* **1975**, *40*, 1252–1257) or oxidation with TEMPO ((b) Breton, T.; Bashiardes, G.; Leger, J.-M.; Kokoh, K. B. *Eur. J. Org. Chem.* **2007**, 1567–1570.) could not differentiate these two components.

(11) Henley-Smith, P.; Whiting, D. A.; Wood, A. F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 614–622.

(12) The benzyl group is frequently employed as protecting group in dithiane carbanion chemistry, see, e.g.: Smith, A. B., III; Sfouggatakis, C.; Gotchev, D. B.; Shirakami, S.; Bauer, D.; Zhu, W.; Doughty, V. A. *Org. Lett.* **2007**, *6*, 3637–3640.

(13) Battersby, A. R.; Chrystal, E. J. T.; Staunton, J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 31–42.

SCHEME 8



Although **22** is thermodynamically less favored compared with **21**, frequent intramolecular encountering may facilitate its formation to a small extent. Subsequent irreversible α-elimination leading to **23** and **24** soon consumes all the transient **22** and consequently **21** before the desired coupling with **18** takes place.

The synthesis was then continued by using the known[14] **19b** in place of **19a**. Without interference of the Bn group, **20b** formed smoothly although an excess of **19b** was needed to ensure a full conversion of **18** (Scheme 8).

An adverse effect of the excess **19b** in the coupling was its similar polarity to that of **20b**, which made isolation of pure **20b** extremely difficult. For this reason, the crude product was directly desilylated to diol **26** (83% yield from **18**). The MOM group was then cleaved with either 6 N HCl or $Sc(OTf)_3$/$HO(CH_2)_3OH$/THF[15] to yield **27**, a compound essentially the same as the precursor (a 1,3-syn diol) of Wong's synthesis of aculeatins A and B except for the relative configuration of the diol.

Bulger's[2c] work strongly suggested that 9:1 acetone−H_2O was the best solvent system for achieving the highest yield of (±)-**1**. Hence, it was also adopted in this work. Interestingly, with **27** as precursor **28** was formed as the *only* product in 74% isolated yields.[16] It is noteworthy that in all previous syntheses of aculeatins involving a free ketone/hemiketal precursor containing a 1,3-anti diol motif a mixture of **1** and **28** was obtained, while use of a thioketal precursor with a 1,3-syn diol motif also led to formation of a mixture of both epimers of the spiroketal.[2] The unique result in the present case suggests that delicate changes in the structure of the spirocyclization precursor may have unexpected yet strong influence on the outcome of the reaction. Although so far **28** has not been found in nature, judging from the fact that its relation to **1** is similar to that of aculeatin B to A such a highly selective formation of **28** should also be potentially useful.

Our attention was next directed to the acquisition of **1**. We recalled that at the start of reaction TLC showed the presence of a minor component in the mixture, which disappeared completely later. In light of Bulger's[2c] and Falomir's[2d] work, we suspected that the **1** formed might undergo spontaneous isomerization to **28** with time. Quenching the reaction at an early stage did allow for isolation of the minor component, which proved to be the desired **1**. Further treatment of **1** with F_3CCO_2H, a species bound to form in the PIFA-mediated reaction, also led to a full conversion into **28**. Apparently, an acidic medium that is strong enough to trigger off the spiroketalization while still weak enough to avoid further isomerization of **1** to **28** is needed here.

SCHEME 9

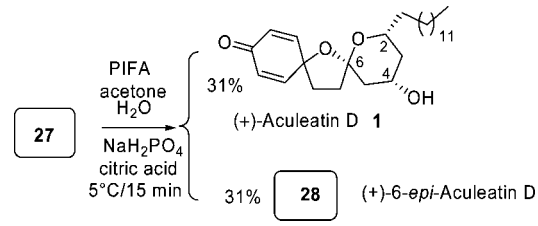


TABLE 1. Outline of the PIFA-Mediated Spirocyclization Leading to Aculeatin D (1) and 6-*epi*-Aculeatin D (28)

entry	yield of **1** (%)	yield of **28** (%)	conditions	ref
1	19	43	acetone−H_2O (9:1)/rt/20 min	2c
2	21	57	acetone−H_2O (9:1)/rt/25 min/dark	2d
3	34	31	acetone−H_2O (10:1)/25 °C/15 min/dark	2e
4	29	29	acetone−H_2O (10:1)/25 °C/15 min/dark	2g
5	31	31	acetone−H_2O (9:1)/buffer/5 °C/15 min	this work

We first tried $PhI(OAc)_2$, which was less acidic than PIFA. However, neither **1** nor **28** was formed under the otherwise identical conditions. Then we tried to add a citric acid−NaH_2PO_4 buffer pair (pH of 6)[17] to the PIFA reaction system to control the acidity. To our gratification, this strategy worked well dramatically raising the content of **1** in the product mixture from 0 to 50% (Scheme 9).[18] It should be noted that apart from controlling the acidity, introduction of the buffer pair to the reaction system may also have other so far unidentified effects because of the presence of additional species such as Na^+ ion and citrate/phosphate anions.[19]

For rapid comparison, some relevant results of PIFA-mediated oxidative spirocyclization leading to aculeatin D and its 6-epimer in the literature are listed in Table 1. It can be seen that under most circumstances **28** was formed in higher yields, indicating it is thermodynamically more favored. In entries 1−4 the immediate precursors for the cyclization were either a free ketone or a hemiketal. It appears that use of a thioketal as the precursor as in this work may have a facilitating effect, because the reaction could finish at lower temperature or within shorter time. However, the preference for formation of **28** seems also enhanced. Use of a buffer helps to limit preferential generation of the thermodynamically more favored isomer.

Conclusions

In summary, natural aculeatin D (**1**) has been synthesized from inexpensive and readily available D-xylose. En route to

(14) Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460–6471.

(15) Oriyama, T.; Watahiki, T.; Kobayashi, Y.; Hirano, H.; Suzuki, T. *Synth. Commun.* **2001**, *31*, 2305–2311.

(16) (a) Using MeCN to replace acetone did not lead to any substantial changes. (b) Treatment of **26** with PIFA did not lead to formation of any **1** or **28**.

(17) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, UK, 1996; p 43.

(18) We are not aware of any precedents of using a buffer to enhance the formation of a thermodynamically less favored isomer of a ketal in similar reactions. Such a strategy may also find use in the synthesis of the thermodynamically less favored isomers of similar spiroketals.

(19) We thank one of the referees for pointing out such possibilities.

the synthesis of **1** it was found that in protection of diol **4** with use of a literature procedure the benzyl group was, contrary to what was reported before, predominantly attached to the secondary OH rather than the primary one, disclosing the first exception to the broadly accepted notion that primary OH groups are more reactive than secondary ones. This finding also turned the previous literature route to "**5a**" to a rapid and practical access to **5b**, a potentially useful chiral building block for target molecules containing 1,3-dihydroxy motif(s), which is otherwise not so easy to prepare. Alcohol **5a**, which is considered as a known compound for more than a decade but was never actually isolated and characterized, has been synthesized through an unambiguous route. A set of conditions were developed for selective tosylation of the primary OH of a triol that is insoluble in CH_2Cl_2 (and many other solvents) thus not suitable for employing all existing protocols. A previously known yet unexplained deprotonation at the benzyl group of **19a** by a dithiane anion was shown to take place intramolecularly. Exclusive formation of **28** in the PIFA-mediated oxidative spirocyclization was observed for the first time. Finally, a citrate−phosphate buffer system was introduced in the spirocyclization, which effectively raised the content of the desired yet thermodynamically less favored **1** in the product mixture from 0 to 50%.

Experimental Section

Synthesis of 8b from 6b. DIBAL-H (1 M, in cyclohexane, 23.1 mL, 23.1 mmol) was added to a solution of **6b** (5.591 g, 21.00 mmol) in dry CH_2Cl_2 (100 mL) stirred in a −78 °C bath. After completion of the addition, the mixture was stirred at the same temperature until TLC showed completion of the reduction. EtOH (3 mL) was added to decompose the excess hydride, followed by aqueous sat. potassium sodium tartrate (10 mL). The mixture was stirred at ambient temperature until both phases were clear. The phases were separated. The aqueous phase was back extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (3:2 PE/EtOAc) on silica gel gave the hemiacetal **7b** as a colorless oil (an inseparable mixture of the α/β-OH epimers, 5.215 g, 19.44 mmol, 93%).

LiHMDS (1 M, in THF, 35 mL, 35 mmol) was added to a solution of $Br^+Ph_3P^-(CH_2)_{11}CH_3$ (18.00 g, 36.20 mmol) in dry THF (70 mL) stirred in a −78 °C bath under N_2. The resulting (red-brown) solution was stirred at the same temperature for 1.5 h. A mixture of **7b** anion (freshly prepared by addition of LiHMDS (1 M, in THF, 19 mL, 19 mmol) to a solution of **7b** (5.215 g, 19.44 mmol) in dry THF (30 mL) stirred at −78 °C under N_2) was introduced via a cannula. The mixture was stirred at −60 °C for 2 h. The cooling bath was allowed to warm to ambient temperature naturally. The stirring was continued at ambient temperature overnight. Aqueous sat. $NHCl_4$ was added to neutralize the reaction mixture. Most of the solvent was then removed on a rotary evaporator. The residue was partitioned between H_2O and EtOAc. The phases were separated. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (5:1 PE/EtOAc) on silica gel furnished the intermediate alkene as a colorless oil (an inseparable mixture of cis/trans isomers, 6.921 g, 16.45 mmol, 85%), which was used as such in the next step.

A mixture of the above obtained intermediate alkene (cis/trans mixture, 6.509 g, 15.47 mmol) and 10% Pd−C (1.3 g) in EtOAc (70 mL) was stirred under H_2 (50 atm) for 24 h. The solids were filtered off. The filtrate was concentrated on a rotary evaporator to dryness. The residue was chromatographed (1:1 PE/EtOAc) on silica gel to give **8b** as a white solid (4.478 g, 13.47 mmol, 87%): mp 52−53 °C; $[\alpha]^{27}_D$ −3.78 (*c* 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.67 (s, 2H), 4.13−4.08 (m, 1H), 3.94−3.82 (m, 1H), 3.62 (dd, *J* = 3.3, 10.1 Hz, 1H), 3.48 (dd, *J* = 7.5, 10.1 Hz, 1H), 3.39 (s, 3H), 2.97 (br s, 2H, 2 OH's), 1.69−1.27 (m, 26H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.0, 73.2, 68.8, 68.0, 55.4, 39.1, 37.6, 31.9, 29.9−29.5 (all the remaining/unresolved alkyl carbons), 29.3, 25.8, 22.7, 14.1; FT-IR (film) 3422, 2919, 2850, 1468, 1401, 1154, 1124, 1043, 942, 833, 721 cm^{-1}; ESI-MS *m*/*z* 355.2 ([M + Na]$^+$); ESI-HRMS calcd for $C_{19}H_{40}O_4Na$ ([M + Na]$^+$) 355.2824, found 355.2814.

Synthesis of 17 from 8b. A solution of **8b** (3.325 g, 10.00 mmol) in MeOH (20 mL) and 6 N HCl (5 mL) was stirred at ambient temperature for 2 d, when TLC showed completion of the reaction. The mixture was coevaporated with MeOH several times on a rotary evaporator to remove the water to give the intermediate triol **15** as a white solid (only fairly soluble in THF, slightly soluble in MeOH, almost insoluble in EtOAc, Et_2O, CH_2Cl_2, or $CHCl_3$).

From a separate run a small analytical sample was obtained at this stage by chromatography (1:1 THF/PE) on silica gel, from which the following data were acquired for **15**: mp 88−89 °C. $[\alpha]^{23}_D$ −7.76 (*c* 0.55, THF); ^{1}H NMR (300 MHz, CD_3OD) δ 3.91−3.80 (m, 2H), 3.53−3.42 (m, 2H), 2.23 (s, OH), 1.52−1.31 (m, 28H), 0.92 (t, *J* = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 68.7, 67.1, 67.0, 31.7, 29.7−29.4 (all the remaining/unresolved alkyl carbons), 29.1, 25.7, 22.5, 14.3; FT-IR (film) 3400, 2954, 2914, 2847, 1651, 1470, 1116, 1082, 1021 cm^{-1}; ESI-MS *m*/*z* 311.1 ([M + Na]$^+$); ESI-HRMS calcd for $C_{17}H_{36}O_3Na$ ([M + Na]$^+$) 311.2557, found 311.2570.

Activated 4 Å molecular sieves (5.0 g) was added to a solution of the above obtained crude triol **15** in dry THF (150 mL), followed by *n*-Bu_2SnO (2.738 g, 11.00 mmol). A lot of white precipitates formed immediately. The mixture was stirred at ambient temperature for 1 h before DMAP (122 mg, 1.00 mmol), NEt_3 (3.1 mL, 20 mmol), and *p*-TsCl (2.097 g, 11.00 mmol) were added in turn. After another 2 h of stirring, TLC showed completion of the reaction. The mixture was diluted with Et_2O (500 mL) and filtered through Celite. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed (3:1 PE/EtOAc) on silica gel to give **16** as a white solid (4.187 g, 9.459 mmol, 95% yield from **8b**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 4.21−4.11 (m, 1H), 4.04 (dd, *J* = 3.8, 10.1 Hz, 1H), 3.95 (dd, *J* = 7.1, 10.1 Hz, 1H), 3.92−3.83 (m, 1H), 2.53 (m, 3H), 2.45 (s, 3H), 1.25−1.62 (m, 24H), 0.88 (t, *J* = 6.4 Hz, 3H). This tosylate (**16**) is very unstable and must be used immediately.

Powdered K_2CO_3 (50 mg, 0.362 mmol) was added to a solution of **16** (122 mg, 0.275 mmol) in anhydrous MeOH (3 mL) stirred in a −5 °C bath. After completion of the addition the cooling bath was allowed to warm naturally to ambient temperature. The mixture was stirred for 2 h, when TLC showed completion of the reaction. Et_2O was added. The solids were filtered off through Celite. The filtrate was concentrated on a rotary evaporator to dryness. The residue was chromatographed (4:1 PE/EtOAc) on silica gel to give **17** as a white solid (66 mg, 0.24 mmol, 87% from **16**): mp 41−42 °C. $[\alpha]^{25}_D$ −14.3 (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88−3.77 (m, 1H), 3.19−3.14 (m, 1H), 2,83 (t, *J* = 5.2, 4.4 Hz, 1H), 2.62 (dd, *J* = 2.6, 4.4 Hz, 1H), 2.00 (d, *J* = 3.5 Hz, 1H, OH), 1.89−1.80 (m, 1H), 1.67−1.57 (m, 1H), 1.53−1.27 (m, 22H), 0.89 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.4, 50.3, 46.9, 39.0, 37.6, 31.9, 29.7−29.6 (all the remaining/unresolved alkyl carbons), 29.4, 25.6, 22.7, 14.1; FT-IR (film) 3397, 2955, 2916, 2848, 2361, 2345, 1472, 1464, 1327, 1135, 1098, 1064, 915, 862, 827 cm^{-1}; ESI-MS *m*/*z* 293.2 ([M + Na]$^+$); ESI-HRMS calcd for $C_{17}H_{34}O_2Na$ ([M + Na]$^+$) 293.2456, found 293.2451.

In a parallel preparative run, from **8b** (3.325 g, 10.00 mmol) without any chromatographic purification of the intermediate **15** and **16**, epoxide **17** (2.071 g, 7.658 mmol) was obtained in 77% overall yield.

TES Protection of 17 Leading to 18. TESCl (1.68 mL, 10.0 mmol) was added dropwise to a solution of **17** (1.35 g, 5.00 mmol), imidazole (1.68 g, 10.0 mmol), and activated 4 Å MS (1.5 g) in dry THF (10 mL) stirred at ambient temperature. After 5 min of stirring, TLC showed completion of the reaction. The mixture was diluted with Et_2O (200 mL) and filtered through Celite to remove the white precipitates. The filtrate was concentrated on a rotary evaporator to dryness. The residue was chromatographed (50:1 PE/EtOAc) on silica gel to afford **18** as a colorless oil (1.865 g, 4.848 mmol, 97%): $[\alpha]^{25}_D$ −15.1 (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93−3.85 (m, 1H), 3.07−3.01 (m, 1H), 2.80 (dd, J = 3.9, 5.1 Hz, 1H), 2.49 (dd, J = 2.5, 5.1 Hz, 1H), 1.71−1.56 (m, 2H), 1.46−1.54 (m, 2H), 1.30−1.24 (m, 20H), 0.97 (t, J = 7.6 Hz, 9H), 0.88 (t, J = 6.5 Hz, 3H), 0.62 (q, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.3, 49.9, 47.6, 40.4, 38.1, 31.9, 29.8, 29.70−29.65 (all the remaining/unresolved alkyl carbons), 29.61, 29.59, 29.4, 25.2, 22.7, 14.1, 6.9, 5.1; FT-IR (film) 3042, 2925, 2876, 2854, 1465, 1413, 1377, 1239, 1070, 1008, 742 cm^{-1}; EI-MS *m*/*z* (%) 355 (M^+ + 1, 33), 300 (23), 299 (78), 143 (26), 115 (100), 103 (25), 87 (33), 69 (20); EI-HRMS calcd for $C_{21}H_{43}O_2Si$ ([M + H]$^+$) 355.3032, found 355.3024.

Synthesis of 26 from 18 and 19b via 20b. *n*-BuLi (1.6 M, in hexanes, 2.86 mL, 4.6 mmol) was added to a solution of **19b** (1.300 g, 4.57 mmol) in dry THF (12 mL) stirred at −65 °C (EtOH−dry ice bath) under N_2. After completion of the addition, the mixture was stirred at temperatures between −20 and −40 °C for 3 h. The bath temperature was recooled to −65 °C. A solution of **18** (943 mg, 2.45 mmol) in dry THF (5 mL) and dry HMPA (3 mL) was then introduced. The stirring was continued at −40 °C for 1 h, when TLC showed completion of the reaction. The mixture was partitioned between H_2O and CH_2Cl_2. The phases were separated. The organic layer was washed in turn with H_2O and brine and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (15:1 PE/EtOAc) on silica gel gave an inseparable mixture of **20b** and unreacted **19b**, which was therefore used directly in the following desilylation.

A solution of *n*-Bu_4NF (1 M in THF, 5 mL, 5 mmol) was added to a solution of the above obtained mixture of **20b** and **19b** in THF (4 mL) stirred at ambient temperature. The mixture was stirred at the same temperature for 12 h before being partitioned between H_2O and CH_2Cl_2. The organic layer was washed in turn with H_2O and brine and dried over anhydrous Na_2SO_4. Removal of the solvent and chromatography (4:1 PE/EtOAc) on silica gel afforded **26** as a yellowish oil (1.051 g, 1.89 mmol, 77% from **18**): $[\alpha^{25}]_D$ +3.66 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 5.15 (s, 2H), 4.40−4.33 (m, 1H), 3.98−3.88 (m, 1H), 3.80 (br s, 1H, OH), 3.47 (s, 3H), 3.05−2.94 (m, 2H), 2.92−2.77 (m, 3H), 2.73−2.63 (m, 2H), 2.54−2.45 (dd, J = 9.8, 15.1 Hz, 1H), 2.33−2.10 (m, 2H), 2.07−1.91 (m, 3H), 1.26−1.69 (m, 28H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 134.9, 129.4, 116.5, 94.6, 69.0, 66.4, 55.9, 52.0, 44.8, 43.5, 42.1, 37.6, 31.9, 29.8, 29.7−29.5 (all the remaining/unresolved alkyl carbons), 29.4, 26.4, 26.1, 25.8, 24.9, 22.7, 14.1; FT-IR (film) 3448, 2925, 2853, 1611, 1509, 1458, 1422, 1232, 1198, 1153, 1079, 1009, 923, 830 cm^{-1}; ESI-MS *m*/*z* 577.5 ([M + Na]$^+$); ESI-HRMS calcd for $C_{31}H_{54}O_4S_2Na$ ([M + Na]$^+$) 577.3361, found 577.3344.

Removal of the MOM Group in 26 (27). Method A: A solution of **26** (20 mg, 0.036 mmol) and $Sc(OTf)_3$ (6.0 mg, 0.0018 mmol) and $HO(CH_2)_3OH$ (5.0 μL, 0.072 mmol) in CH_2Cl_2 (1 mL) was heated to reflux for 3 h. After cooling to ambient temperature, the mixture was chromatographed (3:1 PE/EtOAc) on silica gel to give **27** as a white solid (17 mg, 0.033 mmol, 92%): mp 76−77 °C; $[\alpha^{25}]_D$ +5.67 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.1 Hz, 2H), 6.76 (d, J = 8.1 Hz, 2H), 6.00−6.08 (m, 1H), 4.40−4.35 (m, 1H), 3.99 (br s, 2H, 2OH's), 2.91−3.04 (m, 3H), 2.74−2.87 (m, 3H), 2.61−2.69 (m, 1H), 2.46−2.65 (dd, J = 15.3 Hz, 1H), 1.92−2.30 (m, 5H), 1.25−1.78 (m, 26H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 133.3, 129.5, 115.4, 69.2, 66.5, 51.9, 44.6, 43.3, 42.1, 37.5, 31.9, 29.7−29.6 (all the remaining/unresolved alkyl carbons), 29.3, 26.4, 26.1, 25.8, 24.9, 22.7, 14.1; FT-IR (film) 3399, 3269, 2954, 2923, 2848, 2360, 2342, 1641, 1612, 1593, 1516, 1465, 1451, 1232, 829 cm^{-1}; ESI-MS *m*/*z* 533.5 ([M + Na]$^+$); ESI-HRMS calcd for $C_{29}H_{50}O_3S_2Na$ ([M + Na]$^+$) 533.3094, found 533.3083.

Method B: A solution of **26** (100 mg, 0.18 mmol) in MeOH (1.5 mL) containing aq. HCl (6 N, 0.1 mL) was stirred at ambient temperature for 48 h. The mixture was concentrated to dryness on a rotary evaporator. The residue was chromatographed (2:1 PE/EtOAc) on silica gel to afford **27** as a white solid (86 mg, 0.168 mmol, 94%).

Spirocyclization of 27 without Buffer (28). PIFA (42 mg, 0.098 mmol) was added to a solution of **27** (20 mg, 0.039 mmol) in acetone−H_2O (9:1 v/v, 0.5 mL) stirred at ambient temperature. The mixture was stirred for another 20 min (when TLC showed full disappearance of the starting **27**). Aqueous sat. Na_2SO_3 was added to quench the reaction. The mixture was diluted with Et_2O, then washed in turn with aq. sat. $CuSO_4$ and aq. sat. Na_2SO_4 before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and chromatography (3:2 PE/EtOAc) on silica gel afforded **28** as a colorless oil (12 mg, 0.029 mmol, 74%): $[\alpha]^{25}_D$ +11.72 (*c* 0.60, $CHCl_3$) (lit.[2d] $[\alpha]^{25}_D$ +5.7 (*c* 0.3, $CHCl_3$); lit.[2e] $[\alpha]^{26}_D$ +15.0 (*c* 1.0, $CHCl_3$)); ^{1}H NMR (300 MHz, C_6D_6) δ 6.72−6.68 (dd, J = 2.9, 10.0 Hz, 1H), 6.17−6.01 (m, 3H), 4.05−3.95 (m, 1H), 3.80−3.70 (m, 1H), 2.04−1.84 (m, 3H), 1.76−1.71 (m, 1H), 1.61−1.32 (m, 28H), 0.92 (t, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 184.7, 151.0, 149.0, 127.4, 126.7, 109.0, 79.1, 69.2, 65.1, 43.5, 41.2, 38.8, 36.4, 34.8, 32.3, 30.1−30.0 (all the remaining/unresolved alkyl carbons), 29.8, 26.0, 23.1, 14.3; FT-IR (film) 3421, 2922, 2853, 1700, 1671, 1629, 1458, 1388, 1202, 1172, 1125, 1059, 990, 934, 877, 853. ESI-MS *m*/*z* 441.3 ([M + Na]$^+$); ESI-HRMS calcd for $C_{26}H_{42}O_4Na$ ([M + Na]$^+$) 441.2975, found 441.2990.

Synthesis of 1 (and 28). PIFA (42 mg, 0.098 mmol) was added to a solution of **27** (20 mg, 0.039 mmol) in acetone−aqueous Na_2HPO_4/citric acid buffer (5:1 v/v, 0.5 mL; with the buffer stock solution prepared by mixing 63 mL of 0.2 M Na_2HPO_4 and 37 mL of 0.1 M citric acid according to the literature)[19] stirred at 5 °C (ice−H_2O bath). The mixture was stirred at the same temperature for another 15 min (when TLC showed full disappearance of the starting **27**). Aqueous sat. Na_2SO_3 was added to quench the reaction. The mixture was diluted with Et_2O, then washed in turn with aq. sat. $CuSO_4$ and aq. sat. Na_2SO_4 before being dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator and chromatography (3:2 PE/EtOAc) on silica gel gave **28** (the less polar component, 5 mg, 0.012 mmol, 31% yield) and **1** (the more polar component, 5 mg, 0.012 mmol, 31% yield) as colorless oils. Data for aculeatin D **1**: $[\alpha]^{25}_D$ +53.24 (*c* 0.57, $CHCl_3$) (lit.[1a] $[\alpha]^{25}_D$ +46.5 (*c* 1.0, $CHCl_3$); lit.[2e] $[\alpha]^{26}_D$ +48.9 (*c* 1.0, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (dd, J = 2.8, 10.3 Hz, 1H), 6.80 (dd, J = 3.1, 10.3 Hz, 1H), 6.16 (dd, J = 2.0, 10.3 Hz, 1H), 6.13 (dd, J = 1.8, 10.2 Hz, 1H), 3.91−3.80 (m, 1H), 3.40−3.34 (m, 1H), 2.43−2.39 (m, 1H), 2.33−2.23 (m, 1H), 2.16−2.04 (m, 2H), 1.99−1.94 (m, 1H), 1.89−1.60 (m, 4H), 1.52−1.44 (m, 2H), 1.34−1.24 (m, 22H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.5, 151.5, 148.8, 127.4, 127.2, 109.2, 78.1, 71.6, 66.8, 43.6, 40.8, 35.7, 34.9, 33.4, 31.9, 29.7−29.5 (all the remaining/unresolved alkyl carbons), 29.4, 29.3, 25.9, 22.7, 14.1; FT-IR (film) 3425, 2924, 2853, 1671, 1631, 1458, 1379, 1197, 1061, 1011, 953, 858 cm^{-1}; ESI-MS *m*/*z* 441.2 ([M + Na]$^+$); ESI-HRMS calcd for $C_{26}H_{42}O_4Na$ ([M + Na]$^+$) 441.2975, found 441.2980. Data for 6-*epi*-aculeatin D **28**: see the above experiment.

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Supporting Information Available: Experimental procedures for preparation of **5a**, **5b**, **6b**, **10b**, **12**, **13**, and **14**, physical and spectroscopic data for all new compounds, and ^{1}H and ^{13}C NMR spectra of **5a**, **5b**, **6b**, **8b**, **9b** (^{1}H only), **10b** (also COSY and HMQC), **12**, **13**, **14**, **15** (^{1}H only), **17**, **18**, **26**, **27**, **28**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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