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Direct Kinetic Formation of Nonanomeric [6.5]-Spiroketals in Aqueous Media

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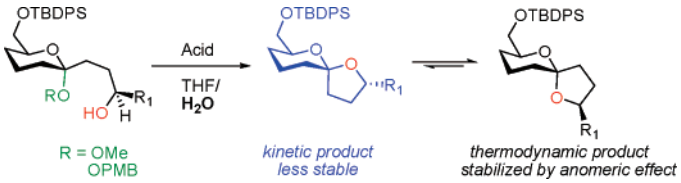

The direct kinetic formation of spiroketals from mixed ketal-alcohol precursors under acid catalysis was studied using four differently substituted systems. In all cases, the exclusive formation of the anomeric isomer was observed under equilibrating conditions. However, the formation of the nonanomeric spiroketal isomer was observed if the reaction was performed under kinetic conditions using an appropriately tuned acid. Water had a dramatic accelerating effect on the spiroketalization reactions that were performed in THF, and the highest yields of the nonanomeric products were obtained in aqueous THF. The nonanomeric/anomeric product ratio was also strongly affected by the substituents and the stereochemistry of the starting alcohol.

Introduction

The spiroketal unit forms an important structural motif of many biologically active natural products including pheromones, marine and fungal toxins, pesticides, ionophore compounds, and polyether antibiotics.[1] A diverse array of methods has been developed for the synthesis of spiroketals. Ultimately, most of them rely on Brønsted or Lewis acid catalyzed spirocyclizations that typically results in the formation of the thermodynamically more stable isomer, typically the anomeric spiroketal. For the synthesis of the unstable nonanomeric spiroketals, several groups have published ingenuous approaches to overcome the thermodynamic tendency to form the more stable anomerically stabilized spiroketal.[2] These methods typically rely either on the reversal of the thermodynamic stability of the spiroketal by additional stabilizing groups (e.g., by hydroxyl groups capable of hydrogen bonding) or on the kinetic formation of the nonanomeric spiroketal using suitably reactive activating groups.[2h,i]

In view of the natural origin of many nonanomeric spiroketals, it is surprising that their generation under mild acid catalysis has received only scant attention. These reactions may closely resemble biosynthetic pathways for their formation since there are many reported cases of biogenesis of spiroketals from hemiketal-type precursors.[3] In this vein, we recently reported the synthesis of the nonanomeric [6.5]-spiroketal ring system (the AB ring system) of the pectenotoxins.[4] In this case, we were able to form the nonanomeric [6.5]-spiroketal present in the natural product by employing kinetic control in the acid catalyzed spiroketalization step. In a continuation of our previous

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(1) For reviews of spiroketals, see: (a) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617−1661. (b) Francke, W.; Kitching, W. *Curr. Org. Chem.* **2001**, *5*, 233−251. (c) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227−256. (d) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406−4440.

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(3) (a) Schwartz, B. D.; McErlean, C. S. P.; Fletcher, M. T.; Mazomenos, B. E.; Konstantopoulou, M. A.; Kitching, W.; De Voss, J. J. *Org. Lett.* **2005**, *7*, 1173−1176. (b) McErlean, C. S. P.; Fletcher, M. T.; Wood, B. J.; De Voss, J. J.; Kitching, W. *Org. Lett.* **2002**, *4*, 2775−2778. (c) Stok, J. E.; Lang, C.-S.; Schwartz, B. D.; Fletcher, M. T.; Kitching, W.; De Voss, J. J. *Org. Lett.* **2001**, *3*, 397−400. (d) Li, A.; Piel, J. *Chem. Biol.* **2002**, *9*, 1017−1026.

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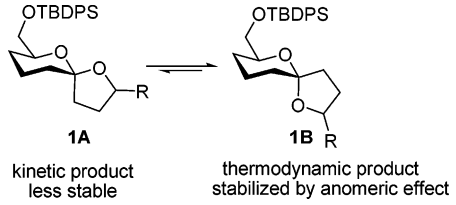
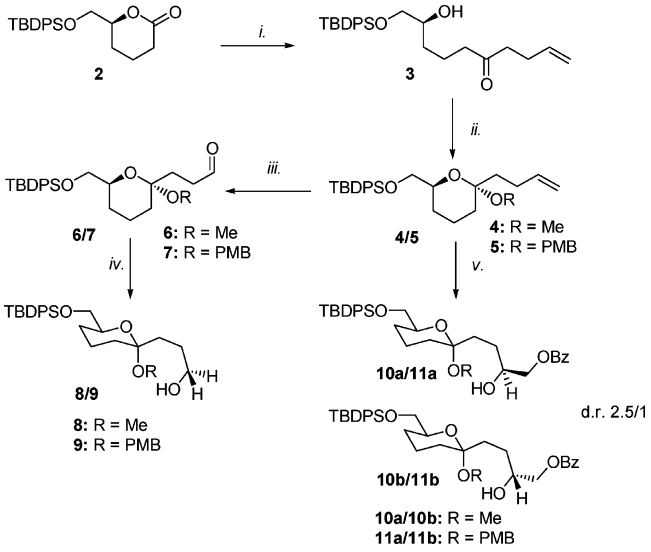


FIGURE 1. Nonanomeric and anomeric [6.5]-spiroketals.

SCHEME 1. Synthesis of Spiroketalization Precursors[a]



[a] (i) CH_2=$CHCH_2CH_2MgBr$, THF, −78 °C (49%). (ii) MeOH, PPTS (100%) or PMBOH, PPTS (62%). (iii) (a) OsO_4, NMO, ^{t}BuOH/THF/H_2O and (b) $NaIO_4$, pH 7 buffer, THF, 0 °C (52% for **6** and 45% for **7**). (iv) DIBAL-H, THF, −78 °C, (67% for **8** and 81% for **9**). (v) (a) AD-mix α, $MeSO_2NH_2$, H_2O/^{t}ButOH and (b) BzCl, pyridine, 0 °C, (76% for **10** and 63% for **11**).

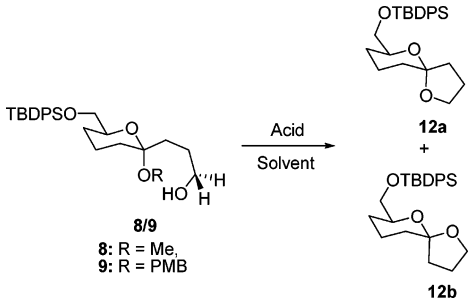
work,[4] we focused our attention on the synthesis of simplified [6.5]-spiroketal units of general structure **1A-B**, which presents a different side chain on the five-membered ring (Figure 1). The aim of this work was the development of a general and direct approach for the synthesis of minimally substituted[5] nonanomeric [6.5]-spiroketals with a minimum amount of protecting and/or activating groups. Herein, we report that water plays a key role in accelerating the spiroketalization reaction.

Results and Discussion

We decided to synthesize a variety of precursors with different substitution patterns and to test their behavior in the acid catalyzed spiroketalization reaction in the presence of different solvents.

The synthesis of precursors for the spiroketalization reactions is outlined in Scheme 1. The lactone **2**[6] was reacted with the Grignard reagent 1-butenylmagnesium bromide to afford alkene **3**, which was converted into the mixed ketal (**4** or **5**) under

SCHEME 2. Spiroketalization with Primary Alcohol Precursors



PPTS catalysis. Two different leaving groups were introduced, namely, the methoxy and *p*-methoxybenzyloxy groups (MeO and PMBO), to evaluate a possible correlation between their nature and the selectivity in the spiroketalization reaction. Alkenes **4** and **5** were converted into aldehydes **6** and **7** via a mild Lemieux−Johnson protocol (OsO_4/NMO; $NaIO_4$). Finally, DIBAL-H reduction of **6** and **7** afforded primary alcohols **8** and **9**.[7] The intermediates **4** and **5** were also dihydroxylated with AD-mix α and then benzoylated at the primary alcohol affording derivatives **10** and **11**. These benzoates were obtained as a mixture of diastereomers (**10a**/**10b** and **11a**/**11b**) in a 2.5:1 ratio.[8] Although less than desirable from a synthetic viewpoint, the lack of selectivity in the dihydroxylation reaction gave us access to two different diastereomers of the cyclization precursors, whose fate we could then observe separately.

The key spiroketalization reactions were initially explored with the primary alcohols **8** and **9** (Scheme 2). On the basis of our previous results,[4] weak acid catalysts such as $ClCH_2COOH$ and HCOOH were selected as starting points for exploration. To study the effect of the medium, three solvents with increasing hydrogen bonding acceptor ability and polarity were selected: CH_2Cl_2, CH_3CN, and THF. The first reactions were carried out in anhydrous CH_2Cl_2. As shown in Table 1, the anomeric spiroketal **12a** was isolated as the major isomer, along with the nonanomeric **12b** (Table 1, entries 1−4).[9] The use of a stronger acid catalyst such as TsOH (20 mol %) or PPTS (20 mol %) led to the rapid formation of the anomeric spiroketal **12a** as the major isomer, while the use of a weaker acid such as AcOH (80 mol %) did not afford the desired spiroketal products even after several hours (Table 1, entries 5−7). The choice of MeO (Table 1, entries 1− and 2) or PMBO (Table 1, entries 3− and 4) as leaving groups did not appear to influence the ratio of the two isomers.[10] The reactivity of **9** was then investigated in dry THF (Table 1, entries 8−10). No spiroketalization was observed under these conditions, and only starting material was recovered after several hours, even when the stronger acids such as Cl_2-CHCOOH and Cl_3CCOOH were used as the catalyst.

(5) Equatorially disposed substituent in the six-membered ring is necessary to prevent conformational flipping in the nonanomeric spiroketal. All other substituents are dispensable, although they may of course influence the kinetic anomeric/nonanomeric ratio. For further discussion, see ref 1d.

(6) (a) Prepared from (*R*)-glycidol using the method of Forsyth and coworkers: Dounay, A. B.; Urbanek, R. A.; Frydrychowski, V. A.; Forsyth, C. J. *J. Org. Chem.* **2001**, *66*, 925−938. See also: (b) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970−2972. (c) Dounay, A. B.; Forsyth, C. J. *Org. Lett.* **1999**, *1*, 451−454.

(7) Interestingly, sodium borohydride reduction of aldehyde **6** occasionally led to concomitant premature spiroketalization, in spite of the basicity of the medium. These problems were neatly avoided by the use of DIBAL-H.

(8) Observed poor selectivity is in accord with our previous results, where a similarly protected mixed ketal afforded only moderate selectivities under various AD conditions screened. See ref 4.

(9) In all cases, the configurations of the spiroketals were assigned by NOESY experiments. See the Supporting Information for details.

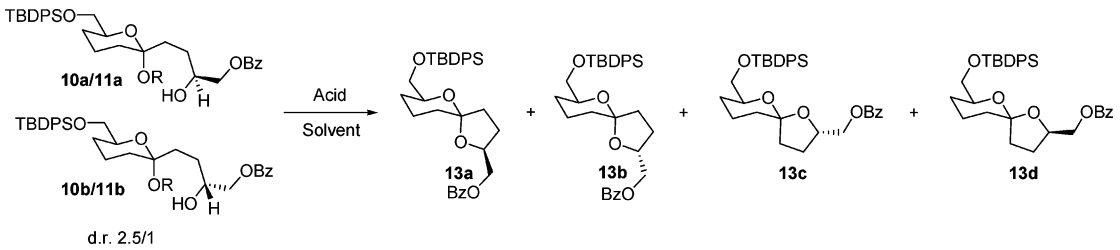
(10) Spiroketalization reactions using *p*-TsOH (20 mol %), PPTS (20 mol %), and AcOH (80 mol %) were also performed with the PMB derivative. Results were comparable to those obtained with the methoxy derivative.

TABLE 1. Spiroketalization with Primary Alcohol Precursors 8 and 9

entry	R	acid catalyst[a] (60 mol %)	pK_a in H_2O (DMSO)	solvent	time (h)	alcohol (%)[b,c]	**12a**[c] (%)	**12b**[c] (%)
1	Me	$ClCH_2COOH$[d]	2.86	CH_2Cl_2	5		67[e]	33[e]
2	Me	HCOOH	3.77	CH_2Cl_2	5.5		64[e]	28[e]
3	PMB	$ClCH_2COOH$[d]	2.86	CH_2Cl_2	4		66	32
4	PMB	HCOOH	3.77	CH_2Cl_2	3		62	38
5	Me	TsOH	−1.3	CH_2Cl_2	0.3		76	24[f]
6	Me	PPTS	5.21 (3.4)	CH_2Cl_2	0.5		64	35
7	Me	AcOH	4.76 (12.3)	CH_2Cl_2	48	99		
8	PMB	$ClCH_2COOH$	2.86	THF	24	99		
9	PMB	$Cl_2CHCOOH$	1.29	THF	24	99		
10	PMB	Cl_3CCOOH	0.65	THF	24	95	traces	traces
11	PMB	$ClCH_2COOH$	2.86	THF/H_2O 4:1	24	62	23	14
12	PMB	$Cl_2CHCOOH$	1.29	THF/H_2O 4:1	5		56	43
13	PMB	Cl_3CCOOH	0.65	THF/H_2O 4:1	2.5		59	40
14[f]		CF_3COOH[g]	−0.25	THF/H_2O 4:1	1		99	

[a] All reactions were carried out at room temperature. [b] Recovered starting material. [c] Ratios were determined by HPTLC. [d] 80 mol % of catalyst was used. [e] Isolated yields. [f] With longer reaction times, the nonanomeric product **12b** rapidly isomerized into the anomeric spiroketal **12a**. [g] Control experiment to probe the position of the thermodynamic equilibrium, starting from the pure, isolated nonanomeric spiroketal **12b**. 120 mol % of acid catalyst was used.

SCHEME 3. Spiroketalization with Secondary Alcohol Precursors 10/11



Finally, when the spiroketalization reactions were performed in 4:1 THF/water (Table 1, entries 11−13) instead of dry THF, a rapid and smooth formation of the spiroketal products could be observed. Interestingly, the ratio of nonanomeric to anomeric products was also slightly improved, particularly with stronger acids (from ca. 1:2 to ca. 1:1.5; Table 1, entry 3 vs entries 11−13). It is well-known that the magnitude of the anomeric effect decreases with increasing dielectric constant of the medium.[11] Although there are reports of spiroketalizations in wet media, especially when accompanied by a hydrolysis or an oxidation step,[12] the effect of water on the rates of acid catalyzed spiroketalization reactions and the anomeric/nonanomeric ratios has not been investigated.

We suspected that higher selectivities toward the nonanomeric spiroketal might be obtained with secondary alcohols, and as such, we then turned to the spiroketalization reactions with benzoates **10** and **11** (Scheme 3). The results are reported in Table 2.

When the spiroketalization reactions were carried out in dry CH_2Cl_2 using $ClCH_2COOH$ or HCOOH (Table 2, entries 1−2), a mixture of spiroketal isomers **13a**−**c** was obtained after a few hours. In both cases, the anomeric spiroketal **13a** predominated over the corresponding nonanomeric isomer **13c**. The diastereomeric anomeric spiroketal **13b** was also isolated from the reaction mixture, while only traces of the nonanomeric isomer could be detected. Spiroketalization of **10** in dry THF and dry CH_3CN with $ClCH_2COOH$ as the catalyst was also performed. In both solvents, only the starting material was recovered (Table 2, entries 3−6).[13] Catalysis with stronger acids, namely, dichloro- and trichloroacetic acid, in both THF and CH_3CN resulted in the formation of desired spiroketals. In CH_3CN, the anomeric spiroketal **13a** was isolated as major isomer (Table 2, entries 7− and 8). The use of dichloroacetic acid in THF resulted in no reaction at all (Table 2, entry 4), while in the presence of trichloroacetic acid in THF, the formation of both anomeric **13a** and nonanomeric **13c** spiroketals (ca. 1:1 ratio) was observed (Table 2, entry 5).

To our delight, when the spiroketalization reactions were carried out in 4:1 THF/water, the nonanomeric spiroketal **13c** was isolated as the major isomer. In particular, the use of trichloroacetic acid (Table 2, entry 11) afforded 49% of the nonanomeric spiroketal and 23% of the anomeric isomer. In aqueous media, weaker acids resulted in no reaction or a very slow conversion (Table 2, entries 9− and 10). However, the nonanomeric spiroketal was still obtained as the major isomer. Spiroketalization of the PMB precursor **11** was performed in THF/water with Cl_3CCOOH as the catalyst, affording the nonanomeric spiroketal **13c** and anomeric **13a** in a 2:1 ratio and confirming that the nature of the leaving group did not influence the stereochemical outcome (Table 2, entry 12).

In aqueous CH_3CN, the spiroketalization reactions were considerably faster and were typically completed in a few minutes. However, in all cases, the anomeric spiroketal **13a** was isolated as the major isomer (Table 2, entries 13−15). Interestingly, when the reaction was carried out at 0 °C in CH_3CN/water in the presence of a weak acid ($ClCH_2COOH$), after 5 h,

(11) Wiberg, K. B.; Marquez, M. *J. Am. Chem. Soc.* **1994**, *116*, 2197−2198.

(12) (a) Wong, Y.-S. *Chem. Commun.* **2002**, 686−687. (b) Zhou, X.-T.; Carter, R. G. *Chem. Commun.* **2004**, 2138−2140. (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.

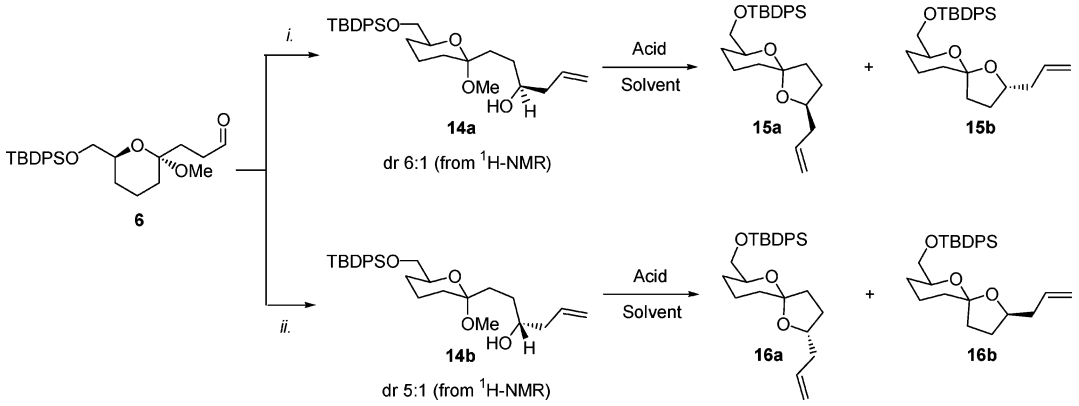
(13) In addition to these screens, we also performed the spiroketalization reactions in apolar solvents such as hexane and benzene using 80% HCOOH as acid catalyst. However, even after 24 h, no spiroketal products were detected, and the starting material was quantitatively recovered.

TABLE 2. Spiroketalizations with the Secondary Alcohol Precursors 10/11

entry	R	acid catalyst (60 mol %)	pK_a	solvent[a]	time (h)	alcohol[b,c]	**13a**[c]	**13b**[c]	**13c**[c]
1	Me	$ClCH_2COOH$[d]	2.86	CH_2Cl_2	4		40[e]	24[e]	26[e]
2	Me	HCOOH	3.77	CH_2Cl_2	3		41	20	28
3	Me	$ClCH_2COOH$	2.86	THF	24	99			
4	Me	$Cl_2CHCOOH$	1.29	THF	28	99			
5	Me	Cl_3CCOOH	0.65	THF	28	32	23	19	25
6	Me	$ClCH_2COOH$	2.86	CH_3CN	24	99			
7	Me	$Cl_2CHCOOH$	1.29	CH_3CN	5.5		53	32	14
8	Me	Cl_3CCOOH	0.65	CH_3CN	2.5		43	33	19
9	Me	$ClCH_2COOH$	2.86	THF/H_2O 4:1	16	99			
10	Me	$Cl_2CHCOOH$	1.29	THF/H_2O 4:1	28	29	19	21	28
11	Me	Cl_3CCOOH	0.65	THF/H_2O 4:1	5.5		23[e]	23[e]	49[e]
12	PMB	Cl_3CCOOH	0.65	THF/H_2O 4:1	5		24	21	46
13	Me	$ClCH_2COOH$	2.86	CH_3CN/H_2O 4:1	1		44	29	26
14	Me	$Cl_2CHCOOH$	1.29	CH_3CN/H_2O 4:1	0.5		42	30	26
15	Me	Cl_3CCOOH	0.65	CH_3CN/H_2O 4:1	0.25		50	33	16
16	Me	$ClCH_2COOH$	2.86	CH_3CN/H_2O 4:1 0 °C	5		29	26	43
17	Me	$ClCH_2COOH$[d]	2.86	CH_2Cl_2 + 30 equiv of H_2O	1		38	28	31
18[f]		CF_3COOH[g]	−0.25	THF/H_2O 4:1	2		99		

[a] All reactions were carried out at room temperature. [b] Recovered starting material. [c] Product ratios were determined by HPTLC. [d] 80 mol % of catalyst was used. [e] Isolated yields. [f] Control experiment to probe the position of the thermodynamic equilibrium, starting from the pure, isolated nonanomeric spiroketal **13b**. [g] 120 mol % of acid catalyst was used.

SCHEME 4. Synthesis of Allyl-Substituted Spiroketalization Precursors[a]



[a] (i) Allyl-*B*(Ipc)$_2$ from (+)-MeO-*B*(Ipc)$_2$, Et_2O, −100 °C (82%). (ii) Allyl-*B*(Ipc)$_2$ from (−)-MeO-*B*(Ipc)$_2$, Et_2O, −100 °C (78%).

the nonanomeric spiroketal **13c** could again be obtained as the major isomer (Table 2, entry 16). Finally, the spiroketalization of **10** in aqueous CH_2Cl_2 was explored (Table 2, entry 17). In the presence of water, the reaction was appreciably accelerated as compared to dry CH_2Cl_2. The reactions were typically completed in only 1 h. The anomeric (**13a**) and nonanomeric (**13c**) spiroketals were obtained in a 1:1 ratio.

In all of the previous spiroketalization reactions, the diastereomeric nonanomeric spiroketal isomer **13d** could be detected only in trace amounts. These results are in line with our earlier results on the pectenotoxin spiroketal system, where a similar reactivity pattern was observed: the natural C10 epimer gave rise to both nonanomeric and anomeric spiroketals, whereas the unnatural C10 epimer afforded only the anomeric spiroketal.

To explore the effect of the substitution patterns on the spiroketalization reaction, the allylic alcohol precursors **14a**,**b** were synthesized. Aldehyde **6** was treated with both enantiomers of Brown's reagent, leading to allylic alcohols **14a**,**b**;[14] **14a** was isolated as a 6:1 mixture of diastereomers, and **14b** was likewise obtained as a 5:1 diastereomeric mixture. Spiroketalization reactions of the allylic alcohols **14a**,**b** using different solvents and acid catalyst were then investigated (Scheme 4). The results are reported in Tables 3 and 4. Reaction of **14a** with weak acids in CH_2Cl_2 (Table 3, entries 1 and 2) afforded a mixture of desired spiroketals **15a** and **15b** in a 3:2 ratio. Similarly, in CH_3CN (Table 3, entries 6−8) or CH_3CN/water (Table 3, entries 12−14), the anomeric spiroketal **15a** was always obtained as the major isomer. However, by conducting the reaction in CH_3CN/water at 0 °C using $ClCH_2COOH$ led to the formation of a 1:1 mixture of **15a** and **15b** (Table 3, entry 15). Finally, the reactions were explored in THF and THF/water mixtures. In the absence of water, only a very sluggish reaction was observed even with the strongest acid (Cl_3CCOOH). The addition of water allowed the reaction to proceed to completion in a reasonable time. Although the preponderance of the nonanomeric spiroketal **15b** was not as pronounced as with the benzoates **13a**−**c**, the nonanomeric **15b** could nevertheless be isolated as the major product under our optimal conditions (4:1 THF/water, Cl_3CCOOH; Table 3, entry 11).

The same reactions were also investigated with alcohol **14b**. The results are reported in Table 4. On the basis of the results obtained in the benzoate series (Table 2), we expected that **14b** would also represent a mismatched case. Surprisingly, under

(14) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401−404.

TABLE 3. Spiroketalizations with Allyl-Substituted Spiroketalization Precursor 14a

entry	acid catalyst[a]	pK_a	solvent	time (h)	**14a**[b,c] (%)	**15a**[c] (%)	**15b**[c] (%)
1	$ClCH_2COOH$[d]	2.86	CH_2Cl_2	5		64	35
2	HCOOH	3.77	CH_2Cl_2	3		60	40
3	$ClCH_2COOH$	2.86	THF	24	99		
4	$Cl_2CHCOOH$	1.29	THF	24	99		
5	Cl_3CCOOH	0.65	THF	24	90	traces	
6	$ClCH_2COOH$	2.86	CH_3CN	48	50	36	12
7	$Cl_2CHCOOH$	1.29	CH_3CN	3		73	26
8	Cl_3CCOOH	0.65	CH_3CN	1		78	22
9	$ClCH_2COOH$	2.86	THF/H_2O 4:1	28	99		
10	$Cl_2CHCOOH$	1.29	THF/H_2O 4:1	24		49	51
11	Cl_3CCOOH	0.65	THF/H_2O 4:1	3		35[e]	46[e]
12	$ClCH_2COOH$	2.86	CH_3CN/H_2O 4:1	0.3		68	31
13	$Cl_2CHCOOH$	1.29	CH_3CN/H_2O 4:1	0.2		>95	traces
14	Cl_3CCOOH	0.65	CH_3CN/H_2O 4:1	0.2		>95	traces
15	$ClCH_2COOH$	2.86	CH_3CN/H_2O 4:1 0 °C	3.5		49	50
16[f]	CF_3COOH[g]	−0.25	THF/H_2O 4:1	2		99	

[a] All reactions were carried out at room temperature. [b] Recovered starting material. [c] Ratios were determined by HPTLC. [d] 80 mol % of catalyst was used. [e] Isolated yields. [f] Control experiment to probe the position of the thermodynamic equilibrium, starting from the pure, isolated nonanomeric spiroketal **15b**. [g] 120 mol % of catalyst was used.

TABLE 4. Spiroketalizations with Allyl-Substituted Spiroketalization Precursor 14b

entry	acid catalyst[a]	pK_a in H_2O	solvent	time (h)	**14b**[b,c] (%)	**16a**[c] (%)	**16b**[c] (%)
1	$ClCH_2COOH$[d]	2.86	CH_2Cl_2	5		90	10
2	HCOOH	3.77	CH_2Cl_2	3		>90	traces
3	$ClCH_2COOH$	2.86	THF	24	99		
4	$Cl_2CHCOOH$	1.29	THF	24	99		
5	Cl_3CCOOH	0.65	THF	24	95	traces	
6	$ClCH_2COOH$	2.86	CH_3CN	24	99		
7	$Cl_2CHCOOH$	1.29	CH_3CN	2		85	14
8	Cl_3CCOOH	0.65	CH_3CN	0.8		86	12
9	$ClCH_2COOH$	2.86	THF/H_2O 4:1	48	99		
10	$Cl_2CHCOOH$	1.29	THF/H_2O 4:1	20		53	46
11	Cl_3CCOOH	0.65	THF/H_2O 4:1	3		43[e]	40[e]
12	$ClCH_2COOH$	2.86	CH_3CN/H_2O 4:1	0.3		69	30
13	$Cl_2CHCOOH$	1.29	CH_3CN/H_2O 4:1	0.2		>95	trace
14	Cl_3CCOOH	0.65	CH_3CN/H_2O 4:1	0.2		>95	trace
15	$ClCH_2COOH$	2.86	CH_3CN/H_2O 4:1 0 °C			53	46
16[f]	CF_3COOH[g]	−0.25	THF/H_2O 4:1	2		99	

[a] All reactions were carried out at room temperature. [b] Recovered starting material. [c] Ratios were determined by HPTLC. [d] 80 mol % of catalyst was used. [e] Isolated yields. [f] Control experiment to probe the position of the thermodynamic equilibrium, starting from the pure, isolated nonanomeric spiroketal **16b**. [g] 120 mol % of catalyst was used.

our optimal conditions, the anomeric **16a** and the nonanomeric isomer **16b** were obtained in practically a 1:1 ratio (Table 4, entry 11).

The formation and hydrolysis of ketals under acidic conditions is generally believed to take place via oxycarbenium ions.[15] In the context of this study, the formation of the oxycarbenium ion requires conformational changes in the six-membered ring. To study the effect of restricted conformational flexibility of the six-membered ring in the spiroketalization precursors, we prepared the mixed acetal-ketal **22** starting from **17**[16] (Scheme 5). As expected, the bicyclic precursor **22** was much more resistant to the spiroketalization conditions than any of the monocyclic precursors (Table 5). In THF/water, the formation of spiroketal products **23a**−**d** was not observed even when a strong acid, Cl_3COOH, was used. Only in the presence of CF_3-COOH did a very slow reaction ensue. In CH_3CN/water, both Cl_3CCOOH and CF_3COOH were able to promote the spiroketalization, but at a markedly reduced rate as compared to the monocyclic series (cf. Table 2, entry 15). Interestingly, in all cases, only the anomeric spiroketal isomers could be isolated.

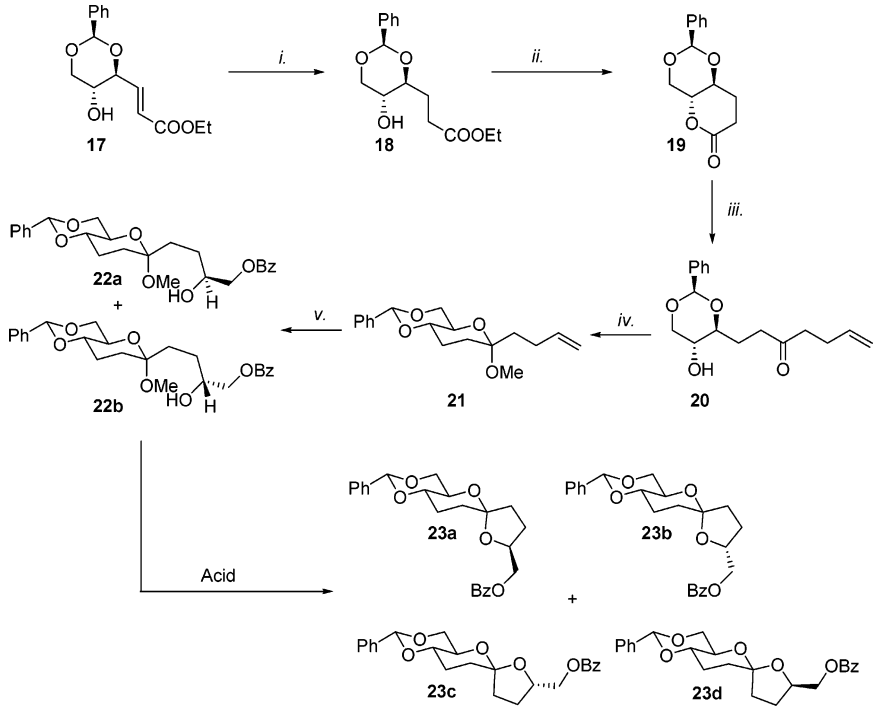
To summarize our results, we have demonstrated that by the judicious choice of solvent, preferably aqueous THF, and a relatively strong acid, the nonanomeric/anomeric ratio of acid catalyzed spiroketalizations can be considerably improved. In favorable cases, the nonanomeric spiroketal can be reliably isolated as the major product.

The nonanomeric/anomeric ratio appears to be almost independent of the leaving group on the mixed ketal precursor but strongly dependent on the substituent pattern on the cyclizing chain. These results are in line with the hypothesis that the cyclization might take place via an oxycarbenium ion or a transition state that closely resembles an oxycarbenium ion. An early transition state model for the kinetically controlled spirocyclization reaction has been suggested by Deslongchamps et al.[17] According to this model, the initially formed oxycarbenium ion is attacked by the alcohol either pseudo-equatorially

(15) For discussions, see: (a) McClelland, R. A.; Ahmad, M. *J. Am. Chem. Soc.* **1978**, *100*, 7027−7031. (b) Eliason, R.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1978**, *100*, 7037−7041. See also ref 17.

(16) Prepared according to: (a) Evanno, L.; Deville, A.; Dubost, L.; Chiaroni, A.; Bodo, B.; Nay, B. *Tetrahedron Lett.* **2007**, *48*, 2893−2896. (b) Rhee, J. U.; Bliss, B. I.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2003**, *125*, 1492−1493.

SCHEME 5. Synthesis of Bicyclic Spiroketalization Precursors[a]



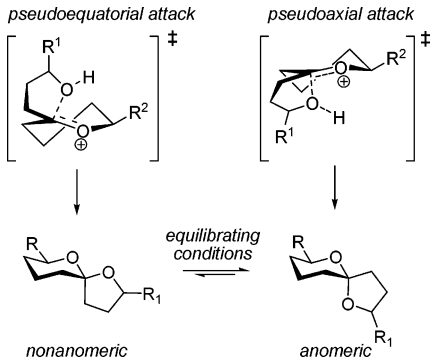
[a] (i) H_2, Pd/C (99%). (ii) (a) 1 M NaOH and (b) DCC, pyridine, DMAP (73%). (iii) $CH_2{=}CHCH_2CH_2MgBr$, THF, −78 °C (65%). (iv) MeOH, PPTS (22%). (v) (a) AD-mix α, $MeSO_2NH_2$, H_2O/^{t}BuOH and (b) BzCl, pyridine, 0 °C (52%).

TABLE 5. Spiroketalization with Bicyclic Secondary Alcohol Precursors 22

entry	acid catalyst[a] (60 mol %)	pK_a in H_2O	solvent	time (h)	alcohol (%)[b,c]	**23a**[c] (%)	**23b**[c] (%)	**23c**[c] (%)	**23d**[c] (%)
1	Cl_3CCOOH	0.65	THF/H_2O 4:1	72	99				
2	F_3CCOOH	−0.25	THF/H_2O 4:1	12	10	62	25		
3	Cl_3CCOOH	0.65	CH_3CN/H_2O 4:1	2	40	40	16	traces	traces
4	Cl_3CCOOH	0.65	CH_3CN/H_2O 4:1	5		54[d]	22[d]		
5	F_3CCOOH	−0.25	CH_3CN/H_2O 4:1	3		70	28		

[a] All reactions were carried out at room temperature. [b] Recovered starting material. [c] Ratios were determined by HPTLC. [d] Isolated yields.

SCHEME 6. Formation of Nonanomeric and Anomeric Spiroketal Isomers from Oxycarbenium Ion Intermediate



or pseudo-axially (Scheme 6). A late transition state was ruled out since this would have resulted in a high energy twist-boat-like transition state for the pseudo-equatorial attack. As a result, no nonanomeric product should have been formed. To explain the experimentally observed formation of the nonanomeric products, an early transition state was proposed where the energy difference between the two transition states should be smaller. The pseudo-axial attack leading to the anomeric isomer should still be slightly favored because the transition state should be slightly more chair-like.[15] Accordingly, the anomeric isomers should always predominate over the nonanomeric isomers.

Our results indicate that the kinetic predominance of the anomeric over nonanomeric spiroketal is not universal, and the Deslongchamps et al. rule may only apply when there are no substituents in the forming spiroketal ring. The observed substituent effects on the stereochemical outcome suggest the possibility of preassociation of the internal alcohol nucleophile. On the other hand, conformational locking of the six-membered ring with an acetal group remarkably slows down the spiroketalization reaction and appears to prevent the formation of the nonanomeric products (Scheme 5).[18] However, other suitably substituted spiroketal precursors will give rise to the formation

(17) Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75*, 604−620.

(18) Our results with the acetal series (Scheme 5) are in full agreement with the results observed by Bols and co-workers on disarmed 4,6-di-*O*-acetal glycosyl donors. Bols suggests that these donors suffer from both stereoelectronic and torsional disarmament, explaining their low reactivity. See: Jensen, H. H.; Nordstrøm, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205−9213.

of nonanomeric spiroketals as the major products when the reaction is performed under kinetic conditions. We are tempted to speculate that these kinetic spiroketalizations may be sufficient to explain the formation of most nonanomeric spiroketals in nature, especially in view of the fact that nearly all thermodynamically unstable nonanomeric [6.5]-spiroketals in natural products appear to be accompanied by their anomeric congeners. As such, the presence of nonanomeric spiroketals in natural products may simply reflect the kinetic preference to form the nonanomeric spiroketal rather than a specifically directed spirocyclization reaction.

Further studies are in progress to apply these methods to the synthesis of nonanomeric natural products, such as pectenotoxins.

Experimental Section

General methods and the synthesis of **3**−**7**, **9**−**11**, and **17**−**23** are described in the Supporting Information.

Primary Alcohol 8. A solution of the crude aldehyde **6** (33 mg, 0.076 mmol) in THF (3.0 mL) was cooled to −78 °C, and DIBAL-H (0.15 mL of a 1 M solution in toluene, 0.153 mmol) was added dropwise over a period of 10 min. The resulting solution was stirred at −78 °C for an additional 20 min and then warmed to 0 °C. After another 20 min, the reaction was quenched with aqueous saturated Rochelle's salt (1 mL). The mixture was warmed to room temperature and stirred for an additional 20 min before the solution was extracted with EtOAc (3 × 40 mL). The combined organic phases were washed pH 7 buffer, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (SiO_2) using 2:1 Et_2O/hexanes as the eluent to yield the primary alcohol **8** (23 mg, 67%) as a viscous bright yellow oil. $R_f = 0.29$ (2:1 Et_2O/hexanes, UV/vanillin stain); $[\alpha]^{20}_D = +19.9$ ($c = 1.39$, CH_2Cl_2); IR (thin film, cm^{-1}) 3401, 3071, 2931, 2858, 1472, 1462, 1113, 1082, 1010, 824, 702; ^1H NMR (acetonitrile-d_3, 400 MHz) δ 7.75−7.69 (m, 4 H), 7.48−7.38 (m, 6 H), 3.71−3.64 (m, 1H), 3.61 (dd, 2H, $J = 5.1$, 1.2 Hz), 3.49 (br m, 2 H), 3.13 (s, 3 H), 2.58 (br s, 1 H), 1.81−1.41 (m, 10 H), 1.03 (s, 9 H) ppm; ^{13}C NMR (acetonitrile-d_3, 100 MHz) δ 135.9, 135.9, 134.1, 130.1, 128.1, 128.0, 99.6, 71.4, 67.8, 62.1, 46.8, 33.0, 32.5, 27.0, 26.5, 19.2, 18.8 ppm. HRMS (ESI) calcd for $C_{26}H_{38}O_4NaSi$ 465.2437, found 465.2435, Δ 0.4 ppm.

Allyl Alcohol 14a. Brown's reagent (+)-*B*-allyldiisopinocamphenylborane was prepared according to a literature procedure.[3] A solution of (+)-Brown's reagent freshly prepared (0.16 mmol) in dry Et_2O (1 mL) was cooled at −100 °C. A solution of the aldehyde **6** (74 mg, 0.16 mmol) in dry Et_2O (2 mL) was added dropwise to the previous solution via a syringe. The resulting mixture was further stirred at the same temperature for 5 h. The reaction mixture was then quenched through the addition of MeOH (3 mL), 3 M NaOH solution (5 mL), and H_2O_2 30% (5 mL). After being stirred overnight, the mixture was poured into saturated aqueous $NaHCO_3$, extracted with Et_2O (3 × 10 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by flash column chromatography (SiO_2) using 1:5 Et_2O/hexanes as the eluent to yield alcohol **14a** (82%, 66 mg) as a 6:1 mixture of diastereomers as revealed by ^1H NMR data. Spectroscopic data of the major diastereomer are reported. Spectroscopic data of the minor diastereomer are reported in the Supporting Information. $R_f = 0.26$ (1:1 Et_2O/hexanes, UV/vanillin stain), $[\alpha]^{20}_D = +15.1$ ($c = 0.55$, CH_2Cl_2); IR (thin film, cm^{-1}) 3691, 3054, 2987, 1422, 1264; ^1H NMR (acetonitrile-d_3, 400 MHz) δ 7.77−7.73 (m, 4H), 7.48−7.43 (m, 6H), 5.87 (m, 1H), 5.10 (dd, 1H, $J = 1.2$ Hz, 17.2 Hz), 5.05 (dd, 1H, $J = 1.2$ Hz, 9.2 Hz), 3.72 (m, 1H), 3.64 (m, 2H), 3.56 (m, 1H), 3.15 (s, 3H), 2.68 (d, 1H, $J = 5.2$ Hz), 2.20 (m, 2H), 1.76−1.23 (m, 10H), 1.06 (s, 9H) ppm; ^{13}C NMR (acetonitrile-d_3, 400 MHz) δ 136.2, 135.9, 134.1, 130.1, 128.1, 116.5, 99.6, 71.4, 70.9, 67.8, 46.8, 42.2, 32.7, 32.5, 30.9, 27.0, 26.6, 19.2, 18.8 ppm. HRMS (ESI) calcd for $C_{29}H_{42}O_4NaSi$ 505.2750, found 505.2759, Δ 1.8 ppm.

The allyl alcohol **14b** was prepared similarly (see Supporting Information).

General Procedure for the Spiroketalizations. To a solution of the alcohol **8**, **9**, **10**, **11**, **14a**, **14b**, **22a**, or **22b** (0.03−0.06 mmol in 2−3 mL of solvent, see Supporting Information for details) was added the appropriate amount of acid catalyst at room temperature. The resulting solution was stirred at room temperature until the reaction was completed as indicated by TLC. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL) and H_2O (2 mL). The separated aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column chromatography (SiO_2) using 1:4 Et_2O/hexanes as the eluent.

Anomeric Spiroketal 13a. $R_f = 0.88$ (1:1 Et_2O/hexanes, vanillin stain), $[\alpha]^{20}_D = +1.4$ ($c = 0.5$, CH_2Cl_2); IR (thin film, cm^{-1}) 3054, 2987, 1718, 1424, 1266; ^1H NMR (acetonitrile-d_3, 400 MHz) δ 8.06−8.03 (d, 2H, $J = 7.8$ Hz), 7.75−7.71 (m, 4H), 7.66−7.64 (m, 1H), 7.55−7.51 (m, 2H), 7.47−7.40 (m, 6H), 4.41−4.38 (m, 2H), 4.31−4.26 (dd, 1H, $J = 6.4$ Hz, 12.4 Hz), 3.94−3.90 (ddt, 1H, $J = 2.2$, 5.1, 11.7 Hz), 3.64−3.63 (d, 2H, $J = 5.2$ Hz), 2.17 (m, 1H), 1.95−1.96 (m, 7H), 1.31−1.22 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (acetonitrile-d_3, 400 MHz) δ 166.7, 135.8, 134.1, 133.4, 130.3, 129.7, 128.9, 128.1, 128.0, 119.5, 107.0, 75.9, 71.7, 67.9, 67.0, 37.4, 33.0, 27.1, 26.1, 20.0, 19.1 ppm. HRMS (ESI) calcd for $C_{33}H_{40}O_5NaSi$ 567.2543, found 567.2535, Δ 1.4 ppm.

Anomeric Spiroketal 13b. $R_f = 0.73$ (1:1 Et_2O/hexanes, vanillin stain), $[\alpha]^{20}_D = -5.8$ ($c = 0.8$, CH_2Cl_2); IR (thin film, cm^{-1}) 3054, 2987, 1712, 1421, 1265; ^1H NMR (acetonitrile-d_3, 400 MHz) δ 8.04−8.01 (d, 2H, $J = 7.8$ Hz), 7.75−7.71 (m, 4H), 7.64−7.60 (m, 1H), 7.49−7.39 (m, 8H), 4.45−4.28 (m, 2H), 4.02 (m, 1H), 3.94−3.90 (m, 1H), 3.64−3.56 (m, 2H), 2.12 (m, 1H), 1.84−1.58 (m, 7H), 1.32−1.28 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (acetonitrile-d_3, 400 MHz) δ 166.2, 135.9, 134.1, 133.4, 130.7, 130.1, 129.6, 128.9, 128.0, 117.7, 106.8, 78.0, 71.3, 68.8, 67.8, 38.4, 33.2, 27.0, 26.6, 20.2, 19.2 ppm. HRMS (ESI) calcd for $C_{33}H_{40}O_5NaSi$ 567.2543, found 567.2546, Δ 0.5 ppm.

Nonanomeric Spiroketal 13c. $R_f = 0.63$ (1:1 Et_2O/hexanes, vanillin stain), $[\alpha]^{20}_D = +2.8$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3054, 2987, 1712, 1420, 1265; ^1H NMR (acetonitrile-d_3, 400 MHz) δ 8.01−7.98 (d, 2H, $J = 7.8$ Hz), 7.72−7.69 (m, 4H), 7.64−7.57 (m, 3H), 7.47−7.40 (m, 6H), 4.36−4-32 (m, 2H), 4.27−4.22 (m, 1H), 3.68−3.63 (m, 3H), 2.38 (ddd, 1H, $J = 1.3$, 7.1, 12.6 Hz), 2.12−2.02 (m, 1H), 1.81−1.79 (m, 2H), 1.68−1.57 (m, 6H), 1.04 (s, 9H); ^{13}C NMR (acetonitrile-d_3, 400 MHz) δ 160.4, 135.8, 134.0, 133.4, 130.6, 130.1, 129.6, 128.9, 128.1, 117.7, 108.5, 77.8, 75.3, 68.6, 67.4, 34.4, 32.6, 27.1, 26.6, 21.0, 19.1 ppm. HRMS (ESI) calcd for $C_{33}H_{40}O_5NaSi$ 567.2543, found 567.2537, Δ 1.1 ppm.

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Supporting Information Available: Full experimental procedures, compound characterization, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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