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Syn−Anti Isomerization of Aldols by Enolization

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A variety of aldol adducts are shown to undergo efficient syn−anti isomerization in the presence of imidazole by an enolization mechanism. Isomerizations are high yielding and occur with little or none of the usual byproducts arising from competing elimination or retroaldol reactions. Most substrates reach equilibrium within 0.3−3 days at ambient temperature in chloroform, benzene, or dichloromethane containing 0.3−1 M imidazole. The process is particularly facile for aldols derived from tetrahydro-4*H*-thiopyran-4-one with rate constants for equilibration varying over ca. 1 order of magnitude for the adducts studied; structurally related aldols derived from cyclohexanone isomerized ca. 3−4 times slower. Isomerization of the acyclic aldol 5-hydroxy-4-methyl-5-phenyl-3-pentanone required heating to 60 °C but was achieved with minimal (<5%) retroaldol or elimination. A methoxymethyl ether derivative isomerized 30−40 times slower than the parent aldol. Isomerization of α,α′-disubstituted aldols and α,α′-bisaldols indicated low regioselectivity in the enolization. The synthetic utility of the process was demonstrated with the effective preparation of aldol stereoisomers unobtainable by direct methods.

Introduction

The aldol addition of a ketone enol or enolate derivative to an aldehyde can produce up to two new stereogenic centers, and several stereoisomeric products are generally possible.[1] The development of methods for stereoselective aldol reactions has been intensively investigated for more than 20 years, and this reaction is now among the most powerful in the synthetic chemist's arsenal for stereocontrolled carbon−carbon bond formation.[2] Aldol reactions have been used extensively in total syntheses of numerous stereochemically complex natural products.[3] Nonetheless, retrosynthetic disconnections involving stereoselective aldol transforms must be made carefully because the ability to produce any specific aldol stereoisomer selectively,[2c,4] especially when both substrates are chiral,[5,6] remains a significant challenge.[7]

Isomerization of aldol adducts is an alternative strategy to access stereoisomers that cannot be obtained directly. A β-hydroxy ketone (or aldehyde) can isomerize by keto−enol tautomerism or retroaldol−aldol mechanisms.[8] The aldol reaction is readily reversible (i.e., retroaldol), and when mediated by weak bases (e.g., hydroxide, alkoxide, amine), product distribution is generally under thermodynamic control.[9,10] The "directed" aldol reaction[11] using preformed enol(ate) derivatives typically gives products under kinetic control;[2] however,

(1) Up to 16 stereoisomeric products (eight diastereomers) are possible if both substrates are racemic.

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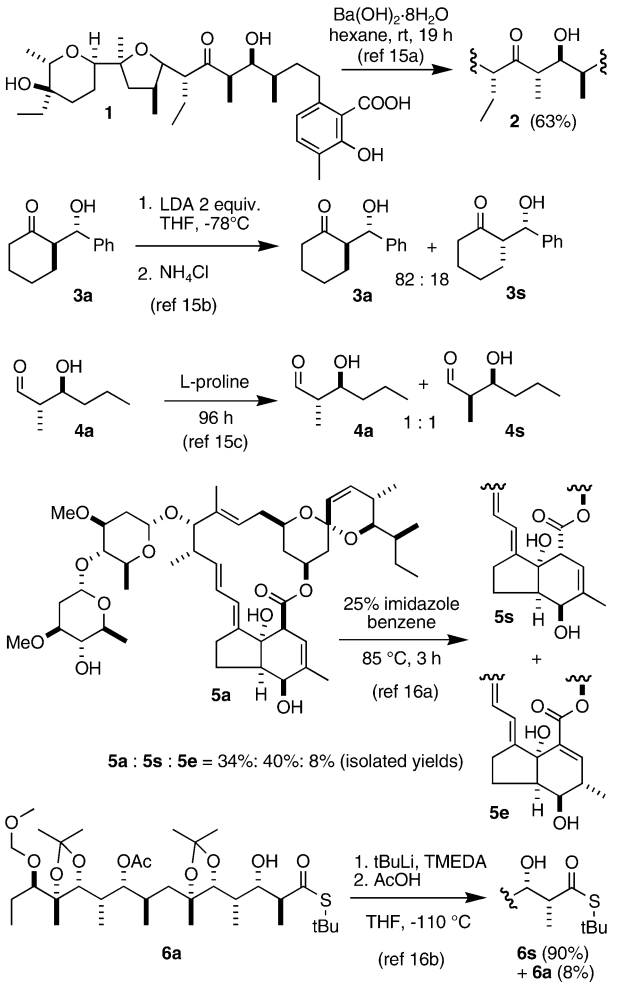
isomerization of metal aldolate intermediates via retroaldol can be facile under certain conditions.[12] A retroaldol mechanism has been implicated in several reports of isomerization of cyclic[9a,13] and acyclic[12e,14] aldols under basic conditions. By contrast, examples of isomerization of aldols consistent with an enolization mechanism are rare,[15] and even in these cases, the possibility of a retroaldol mechanism cannot be ruled out. Similarly, only scattered reports of related isomerizations of 3-hydroxycarboxylic acid derivatives via enol(ate) intermediates have appeared.[16] Several pertinent examples from the literature are summarized in Scheme 1. Although the syn−anti isomerization of aldols is clearly a useful process, there are few examples presumably because the basic conditions necessary to generate the required enol(ate) often induce retroaldol or elimination reactions. We previously reported that imidazole efficiently catalyzes syn−anti isomerization of various β-hydroxy ketones by an enolization mechanism with negligible retroaldol or elimination.[17] In this paper, the results of our study of the scope and limitations of this process are presented.

Results and Discussion

We have been exploring the stereoselectivities of sequential aldol reactions of **8** and **10** as the foundation of a thiopyran-based synthetic route to polypropionates.[18,19] The propensity of imidazole to isomerize tetrahydrothiopyranone-derived aldols was first observed during a failed attempt to protect the hydroxyl group in

SCHEME 1



7a[18] by reaction[20] with TBDMSCl in the presence of an excess of imidazole in CH_2Cl_2; after 5 days, approximately 30% of **7s**[18] was detected and isolated from the reaction mixture. That imidazole was responsible for the isomerization was readily demonstrated by monitoring a $CDCl_3$ solution of **7a** containing 10 equiv of imidazole (ca. 0.4 M) by ^{1}H NMR; a 1.5:1 equilibrium mixture of **7s** and **7a**, respectively, resulted within 4 d. Equilibrium was confirmed by obtaining the same mixture under the identical conditions but starting from **7s**. These solutions were stable for several weeks with negligible retroaldol (as judged by the absence of **10**) or elimination products being detected. Subjecting **11a**[18] or **11s**[18] to the same conditions resulted in a 1.8:1 equilibrium mixture of **11s** and **11a**, respectively. In all cases, aqueous workup of the isomerization reaction provided the mixture of aldols in >95% yield. Possible isomerization pathways for aldols **7** and **11** are illustrated in Scheme 2. Whereas all possible stereoisomers can result from a retroaldol−aldol pathway, keto−enol tautomerism can interconvert only 2 stereoisomers. We conclude that the above isomerizations of **7** and **11** proceed via imidazole catalyzed enolization[21]

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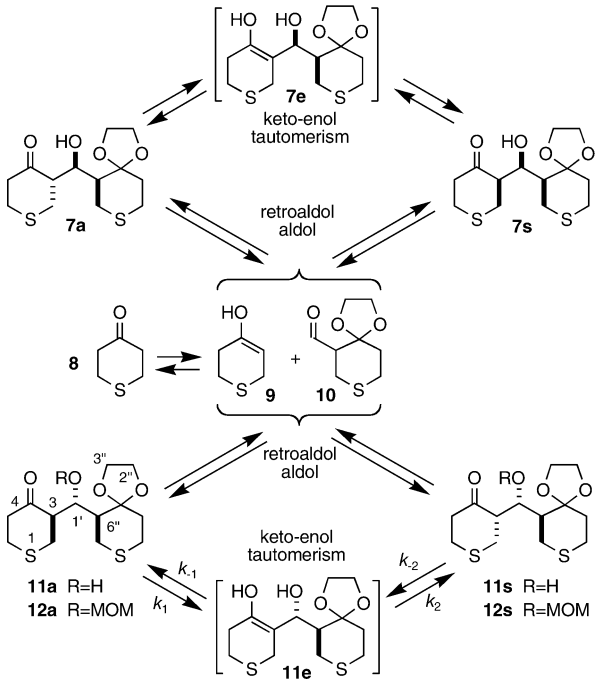
SCHEME 2



because: i) **11** was not detected in the isomerization of **7**; ii) **7** was not detected in the isomerization of **11**; iii) imidazole does not catalyze an aldol reaction between **8** and **10** under the same conditions.

Table 1 presents the effect of solvent on the rate[22] and equilibrium ratio for isomerizations of **11** and **7**. The rates of isomerization of **11** in $CDCl_3$ and benzene were ca. twice those in CD_2Cl_2 or CH_3OH and ca. 10 times greater than in acetone-d_6 or DMF-d_7. Reactions in CD_3OD were complicated by the isotope effects resulting from deuterium incorporation; however, significant diastereoselectivity in the ketonization of **11e** was revealed (i.e., $k_{-1} \gg k_2$) under these conditions. Starting from **11s**, the formation of 3-deuterio **11a** was much faster than the formation of 3-deuterio **11s**, and starting with **11a**, deuteration at C-3 in **11a** was almost complete (>90%) before the presence of **11s** could be detected (5%). Together, these results imply that the enolization of **11a** is much faster than the enolization of **11s**, at least in methanol solution.[23] The isomerization of **7** was ca. 3 times slower than **11** (cf. entries 2 and 8);[24] however, qualitatively similar

TABLE 1. Effect of Solvent on the Rate and Equilibrium Ratio for Isomerizations of 11 and 7[a]

entry	starting aldol	solvent	K_{eq} (syn/anti)	k_{obs}[b] (10^{-2} h^{-1})	$t_{1/2}$[c]
1	**11a**	$CDCl_3$	1.8:1 (**11s**/**11a**)	6[d]	0.5 d
2	**11s**	$CDCl_3$	1.8:1 (**11s**/**11a**)	5.9	12 h
3		CD_2Cl_2	1.9:1	2.9	24 h
4		C_6D_6	1.5:1	5.3	13 h
5		acetone-d_6	1.6:1	0.55	130 h
6		DMF-d_7	2.1:1	0.43	160 h
7		CH_3OH	2.0:1	3[d]	1 d
8	**7a**	$CDCl_3$	1.5:1 (**7s**/**7a**)[e]	2.1	33 h
9		CD_2Cl_2	1.6:1[e]	*f*	*f*
10		acetone-d_6	2.0:1	*f*	*f*
11		C_6D_6	1.4:1	*f*	*f*
12		CH_3OH	1.7:1	*f*	*f*

[a] Room temperature; [imidazole] = 0.3 M; [aldol] = 0.03 M. [b] The slope of the line obtained by plotting $-\ln[(R_t - R_e)/(R_t + 1)]$ vs t where R_t is the ratio of aldols (e.g., [**11s**]/[**11a**]; measured by ^{1}H NMR) at time t and R_e is the ratio at equilibrium (≥8 data points over the initial 2 half-lives; $R^2 > 0.99$); see the Supporting Information for details. Relative error estimated at ±10%. [c] Half-life = $t_{1/2} = (\ln 2)/k_{obs}$. [d] Determined as above but from only three data points. [e] Equilibrium confirmed by obtaining the same ratio starting from **7s**. [f] Not determined.

solvent effects on the rate and equilibrium ratio were observed (entries 8−12). For both **7** and **11**, the syn diastereomers (**7s** and **11s**) were predominant at equilibrium in all solvents examined. Relatively more of the anti diastereomers (**7a** and **11a**) were present at equilibrium in less polar solvents (e.g., C_6D_6) compared to polar solvents (e.g., CH_3OH) but this effect was modest.

The effect of the base and concentration on the rate of isomerization of **11s** in $CDCl_3$ was also investigated (Table 2). Isomerizations in the presence of 4-(dimethylamino)pyridine (DMAP) were 1.5−2.5 times more facile than with imidazole at the same concentration (cf. entry pairs 1/8, 3/10, 4/11, 7/14). As expected, the rates of isomerization were independent of the initial concentration of **11s** (cf. entry sets 4/5/6 or 11/12/13) but increased with increasing concentration of base (cf. entry sets 3/4/7 or 10/11/14). The reaction order in imidazole was determined to be 1.3 from the slope of the line obtained by plotting $\ln(k_{obs})$ versus ln([imidazole]) using the data from entries 1, 3, 4, and 7 in Table 1.[25] This noninteger value implies a complex mechanism for enolization perhaps involving more than one imidazole molecule.[21] Similarly, the reaction order in DMAP was determined to be near 1 (as expected)[21] from the data in entries 9, 10, 11, and 14 in Table 2.[26] Although DMAP is somewhat more effective as an isomerization catalyst, the lower basicity, lower molecular weight, and much lower cost per mole of imidazole justify its preferential use.[27] By contrast, reactions were markedly slower in the presence of Et_3N or *N*-methylimidazole (Table 2, entries 15 and 16) and isomerization was not observed in the presence of pyridine or 1,2,4-triazole. Attempted isomerization of **11s** via retroaldol under Holt's conditions ($Ti(O^iPr)_4$, CH_2Cl_2)[14b] only gave an elimination product (77%).

We have previous shown that **7a**, **7s**, and **11s** can each be prepared stereoselectively by aldol reactions of **8** and

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(22) See the Supporting Information for details on the determination of rate constants. The rate for reversible isomerization of two aldols via their common unstable enol is characterized by k_{obs} which is the equivalent pseudo-first-order rate constant for equilibration of a nonequilibrium system (e.g., the rate at which an excess concentration of **11a** reaches its equilibrium value) and is the sum of the rate constants for the forward and reverse reactions. The forward and reverse reactions each comprise two steps, enolization (slow) and ketonization (fast), whose pseudo-first-order rate constants are given by the product of the rate constant for enolization and the partition for ketonization. For example, in the isomerization of **11a** to **11s** via **11e** (Scheme 2), $k_{obs} = (k_1k_2 + k_{-1}k_{-2})/(k_2 + k_{-1})$.

(23) If ketonization favors **11a** ($k_{-1} \gg k_2$) and equilibrium favors **11s** ($K_{eq} = (k_1k_2)/(k_{-2}k_{-1}) = 1.8$), then $k_1 \gg k_{-2}$ (Scheme 2).

(24) The data does not allow one to distinguish whether these observed differences are due to different rates of enolization, different partitions for ketonization, or both.

(25) Linear regression of the four data points used yielded a slope of 1.28 ± 0.13 (95% confidence interval).

(26) Linear regression of the four data points used yielded a slope of 0.96 ± 0.23 (95% confidence interval).

TABLE 2. Effect of Base and Concentration on the Rate of Isomerization of 11s[a]

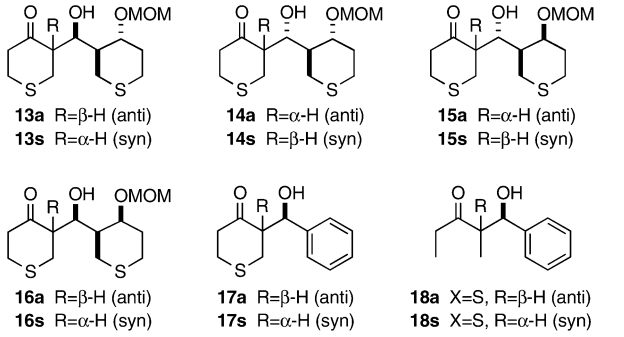
entry	base	[base] (M)	[**11s**]$_0$ (M)	k_{obs}[b] (10^{-2} h^{-1})	$t_{1/2}$ (h)
1	imidazole	0.10	0.015	1.5	48
2		0.20	0.016	3.6	19
3		0.20	0.030	3.6	19
4		0.40	0.030	8.1	8.6
5		0.40	0.060	7.7	9.0
6		0.40	0.120	7.8	8.9
7		0.80	0.030	21	3.2
8	DMAP	0.10	0.015	3.7	19
9		0.10	0.030	4.4	16
10		0.20	0.030	8.7	8.0
11		0.40	0.030	19	3.6
12		0.40	0.060	18	3.9
13		0.40	0.120	19	3.6
14		0.80	0.030	32	2.2
15	Et_3N	0.40	0.016	0.63	110
16	*N*-methylimidazole	0.40	0.040	0.24	289
17	pyridine	0.22	0.016	d	
18	1,2,4-triazole	0.05[e]	0.04	f	
19	$Ti(O^iPr)_4$	0.036	0.018	g	

[a] Room temperature in $CDCl_3$. [b] The slope of the line obtained by plotting $-\ln[(R_t - R_e)/(R_t + 1)]$ vs t where R_t is the ratio of [**11s**]/[**11a**] at time t (measured by ^{1}H NMR) and R_e (= 1.8) is the ratio at equilibrium (≥8 data points over the initial 2 half-lives; $R^2 > 0.99$); see the Supporting Information for details. Relative error estimated at ±10%. [c] Half-life = $t_{1/2} = (\ln 2)/k_{obs}$. [d] Only **11s** (>95%) after 200 h. [e] The observed solubility in $CDCl_3$ (ca. 3 mg/mL) as determined by ^{1}H NMR with **11s** as internal standard. [f] Only **11s** (>95%) after 140 h. [g] Reaction in CH_2Cl_2 at 0 °C for 5 h gave an elimination product in 77% yield (cf. ref 14b).

10 under appropriate conditions.[18] Isomerization of **11s** provides a useful route to the elusive anti−anti diastereoisomer **11a**, a process that is viable on preparative scale because these diastereomers can be separated by fractional crystallization. Thus, $MgBr_2$-mediated aldol reaction of the trimethylsilyl enol ether of **9** with **10** gave a 3:1 mixture of **11s** and **11a**, respectively, after workup.[18] Crystallization of the crude mixture from methanol gave **11s** in 61% overall yield.[28] Isomerization of the so-obtained **11s** with 1 M imidazole in CH_2Cl_2 for 24 h gave a 2:1 mixture of **11s** and **11a**, respectively, in >95% yield. Crystallization of this mixture gave **11s** (ca. 60%) and a mother liquor highly enriched in **11a** (4−8:1). After subjecting **11s** to a second round of isomerization and crystallization, fractionation of the combined mother liquors gave **11a** in >50% overall yield from **10**.

The scope of the imidazole-catalyzed syn−anti isomerization of aldols was examined by treating **3**,[18] **12**−**17**,[18] and **18**[29] with imidazole in $CDCl_3$ solution (Table 3). Isomerizations of the diastereoisomeric aldols **13**−**16** gave mutually exclusive products, thereby clearly ruling out a retroaldol mechanism. The syn diastereomer predominated at equilibrium for three of the four syn−anti diastereomer pairs (entries 1−4). The rates of isomerization were not determined accurately for this series of aldols but were qualitatively similar[30] to those for **7** and **11** under similar conditions although the rate of isomerization of **16** was considerably slower. To explore the importance of the thiopyranone moiety on the isomerization, the structurally related aldols **3**, **17**, and **18** were examined (entries 5−10). The isomerization of **17a** with 0.3 M imidazole was faster than that of the cyclohexanone analogue **3a** suggesting that the presence of sulfur facilitates enolization by a factor of ca. 3. By contrast, isomerization of the acyclic analogue **18** was exceedingly slow under these conditions. As expected, the reactions were faster at higher imidazole concentrations but isomerization of **18s** was still very slow at room temperature. However, heating a solution of **18s** in benzene-d_6[31] containing 1.0 M imidazole at 60 °C for 9 days produced 1.1:1 equilibrium[32] mixture of **18a** and **18s**, respectively. Despite these much harsher conditions, elimination was negligible and only a small amount of retroaldol occurred (as indicated by the presence of benzaldehyde, ca. 4%). Finally, isomerization of the methoxymethyl (MOM) ether derivative **12s** was 30−40 times less facile than **11s** (cf. entries 4 and 7 in Table 2 with entries 11 and 12 in Table 3) demonstrating the importance of the hydroxyl

TABLE 3. Imidazole-Catalyzed Syn−Anti Isomerizations of Aldols 3 and 13−19 in $CDCl_3$ Solution[a]



entry	starting aldol	K_{eq} (syn/anti)	k_{obs}[b] (10^{-2} h^{-1})	$t_{1/2}$[c]
1	**13a**	1:1.1 (**13s**/**13a**) [d]	8[e]	0.4 d
2	**14s**	1.5:1 (**14s**/**14a**)	8[e]	0.4 d
3	**15a**	3.1:1 (**15s**/**15a**) [d]	8[e]	0.4 d
4	**16a**	2.0:1 (**16s**/**16a**) [d]	1[e]	3 d
5	**17a**	1:1.6 (**17s**/**17a**)	2[e]	1.5 d
6	**3a**	1:2.0 (**3s**/**3a**)	0.7[e]	4 d
7	**18s**[f]	*g*	*g*	≫10 d[h]
8	**17a**[i]	1:1.6 (**17s**/**17a**)	4.8	14 h
9	**3a**[i]	1:2.0 (**3s**/**3a**)	1.6	43 h
10	**18s**[f,j]	1:1.1 (**18s**/**18a**)	1.7	41 h
11	**12s**[k]	3.7:1 (**12s**/**12a**)[d]	0.20	340 h
12	**12s**[l]	3.9:1 (**12s**/**12a**)[d]	0.66	110 h

[a] At room temperature; [imidazole] = 0.3 M; [aldol] = 0.03 M. [b] The slope of the line obtained by plotting $-\ln[(R_t - R_e)/(R_t + 1)]$ vs t where R_t is the ratio of [**11s**]/[**11a**] at time t (measured by ^{1}H NMR) and R_e (= 1.8) is the ratio at equilibrium (≥8 data points over the initial 2 half-lives; $R^2 > 0.99$); see the Supporting Information for details. [c] Half-life = $t_{1/2} = (\ln 2)/k_{obs}$. [d] Equilibrium confirmed by obtaining the same ratio starting from the syn diastereomer. [e] Estimated from two to three intermediate data points and the time required to reach equilibrium (ref 30). [f] A 9:1 mixture of **18s**/**18a** was used. [g] Not determined. [h] >80% **18s** after 10 days. [i] [Imidazole] = 0.7 M. [j] At 60 °C in benzene-d_6; [imidazole] = 1 M. [k] [Imidazole] = 0.4 M. [l] [Imidazole] = 0.8 M.

(27) For some substrates, DMAP was found to be much more effective than imidazole: Akinnusi, O. T. Unpublished results.

(28) Silica gel chromatography (25−50% ethyl acetate in hexane) of the mother liquor at this stage gave **11s** (6%) and **11a** (22%).

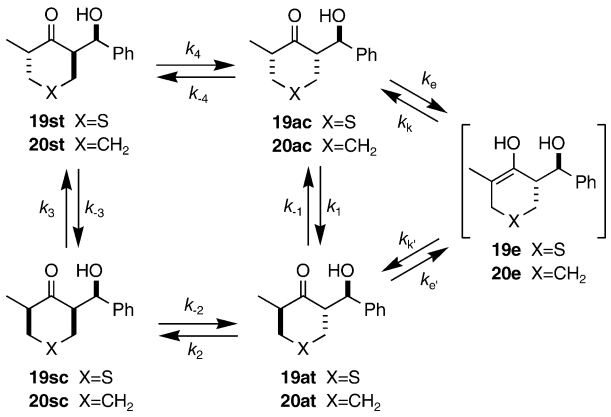
(29) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027−3037.

(30) Assuming a pseudo-first-order process and at least 5 half-lives required to reach equilibrium.

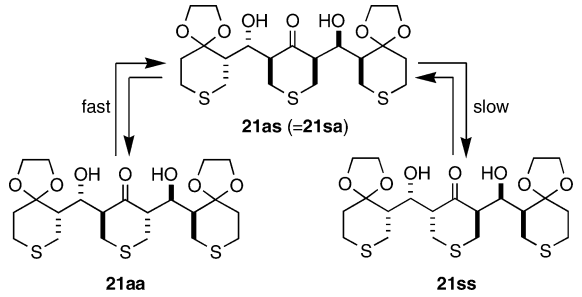
(31) Chloroform solutions of imidazole were not stable to prolonged heating.

(32) The ratio was unchanged after 13 days. Holt et al. (ref 14b) obtained a 5:4 mixture of **18a** and **18s** by isomerization in the presence of Ti(O-*i*-Pr)$_4$ (retroaldol mechanism).

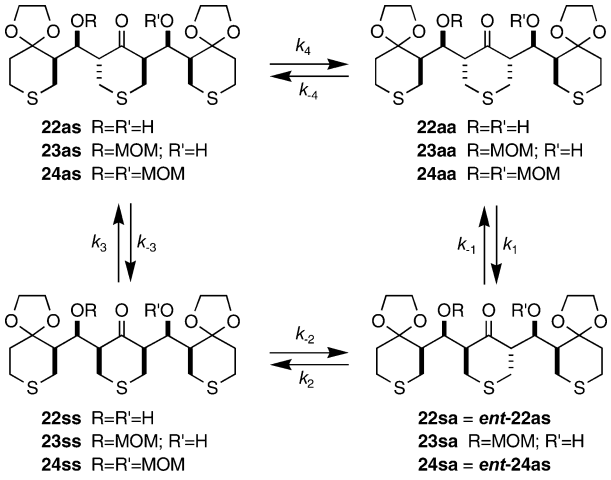
SCHEME 3



SCHEME 4



SCHEME 5



group to the facility of reaction and suggesting the possibility of intramolecular catalysis,[21] perhaps via hydrogen bonding to the carbonyl group.

To further explore the generality of process and the effects of structure on reactivity, isomerizations of the α-methyl aldols **19** and **20**[33] (Scheme 3)[34] and the bisaldol derivatives **21**−**24**[19] (Schemes 4 and 5) were investigated. In these cases, isomerization can occur through regioisomeric enols producing a four-component equilibration. The diastereomers **19st**, **19ac**, and **19at** were individually isomerized in $CDCl_3$ solution in the presence of imidazole (0.4 M), and the relative concentration of the components as a function of time was monitored by ^1H NMR. In each case, the same equilibrium ratio of 36:31:22:11 of **19ac**, **19sc**, **19at**, and **19st**, respectively, was obtained within 5−7 days. Isomerizations of the four diastereomers of **20** under the same conditions were much slower than with **19**. An equilibrium mixture of 62:28:7.5:2.5 of **20ac**, **20sc**, **20at**, and **20st**, respectively, was obtained from **20st** within 3 weeks; however, more than 6 weeks were required to achieve the same mixture starting from **20sc** or **20at** and **20ac** had not reached equilibrium after 2 months. For both **19** and **20**, the 1,3-cis diastereomers (i.e., **ac** and **sc**) predominated over the 1,3-trans diastereomers (i.e., **at** and **st**) with the anti diastereomer predominating over the syn diastereomer (i.e., **ac** > **sc** and **at** > **st**) at equilibrium. Comparing the equilibrium ratios reveals a greater difference in thermodynamic stability among the diastereomers of **20** than among those of **19** presumably because of the reduced steric interaction of the axial substituent in the 1,3-trans diastereomers **19at** and **19st** compared to **20at** and **20st** due to presence of the sulfur atom.

Exposure of individual diastereomers of **21**−**24** to imidazole led in each case to an equilibrium mixture containing only those diastereomers that could result from keto−enol tautomerism (Table 4).[35] These isomerizations proceeded without significant elimination or retroaldol even after prolonged reaction (>100 days in some cases).[36] A number of synthetically useful aspects were noted from the effect of structure and reaction conditions on the process.

The isomerization of **21aa** with 1 M imidazole in $CDCl_3$ gave an equilibrium mixture within 10 days where the **21ss** diastereomer predominated (Table 4, entry 1).[37] However, monitoring the progress of the reaction by ^1H NMR revealed that **21as** comprised >65% of the mixture after 1 day indicating that isomerization of **21aa** to **21as** was much faster than from **21as** to **21ss** (Scheme 4). This observation was exploited by stopping the reaction after 1 day whereby **21as** could be obtained in good yield from **21aa** (Table 4, entry 2). Isomerization of **22aa** in several solvents revealed that the ratio of the C_s-symmetrical aldols (**22ss**, **22aa**) at equilibrium was solvent dependent (1.3−3.8:1) but the unsymmetrical bisaldol **22as** consistently comprised 60−65% of the mixture (Table 4, entries 3−7).[38] Optimization of the conditions resulted in a convenient preparation of **22ss** from **22aa** (Table 4, entry 7). Sequential two-directional aldol reactions of **8** with **10** allows for rapid (two to four steps) and stereoselective syntheses of **21aa**, **21ss**, **22aa**, and **22as**.[39] Although we have been unable to obtain **21as** or **22ss** directly by this approach, isomerizations of the readily available **21aa**

(33) Duhamel, P.; Cahard, D.; Quesnel, Y.; Poirier, J.-M. *J. Org. Chem.* **1996**, *61*, 2232−2235.

(34) Aldols prepared by reactions of benzaldehyde with the LDA generated Li enolates from 2-methylcyclohexanone and from tetrahydro-3-methylthiopyran-4-one. The individual diastereomers were separated by chromatography. The relative configurations of **20at** and **20st** were incorrectly assigned in the literature; see the Supporting Information for details.

(35) A retroaldol mechanism is clearly ruled out. For example, there are a total of 20 diastereomers possible for bisadol **21** (or **22**). In principle, all diastereomers could be produced from **21** or **22** via a retroaldol-aldol mechanism whereas enolization can only interconvert the three diastereomers shown in Schemes 4 and 5 (note: **21as** is identical to **21sa** and **22as** is the enantiomer of **22sa**).

(36) In some cases, 1−5% of benzaldehyde (signifying retroaldol) was observed after prolonged reaction.

(37) Entropy of symmetry favors **21as** (C_1) by a factor of 2 over **21aa** and **21ss** (C_2); thus. neglecting differences in enthalpy among the diastereomers, a 1:2:1 mixture of **21aa**/**21as**/**21ss** would be expected.

(38) Neglecting differences in enthalpy among the diastereomers, a 1:2:1 mixture of **22aa**/(±)-**22as**/**22ss** would be expected.

TABLE 4. Imidazole-Catalyzed Syn−Anti Isomerizations of Bisaldols 21−24[a]

entry	starting aldol	[imidazole] (M)	solvent	ratio of aldols at equilibrum[b]	*t* (d)[c]
1	**21aa**	1.0	$CDCl_3$	6:39:55 (**21aa**/**21as**/**21ss**)	10
2	**21aa**	1.0	CH_2Cl_2	29:60:11 (**21aa**/**21as**/**21ss**)[d]	1
3	**22aa**	0.8	$CDCl_3$	18:60:22 (**22aa**/(±)-**22as**/**22ss**)[e]	4
4		0.4	$CDCl_3$	18:61:21 (**22aa**/(±)-**22as**/**22ss**)[e]	8
5		0.8	CH_2Cl_2	14:66:20 (**22aa**/(±)-**22as**/**22ss**)	10
6		0.4	C_6D_6	12:61:27 (**22aa**/(±)-**22as**/**22ss**)	10
7		1.0	acetone	9:63:28 (**22aa**/(±)-**22as**/**22ss**)[f]	8
8	**23aa**	0.4	$CDCl_3$	13:24:23:40 (**23aa**/**23as**/**23sa**/**23ss**)[e]	35
9	**24aa**	0.4	$CDCl_3$	7:47:46 (**24aa**/(±)-**24as**/**24ss**)[e]	120

[a] At room temperature. [b] Measured by ^{1}H NMR. [c] The approximate time required to reach equilibrium. [d] A nonequilibrium mixture. Isolated yields (13 mg scale): **21aa** (25%), **21as** (45%), **21ss** (10%). [e] Equilibrium confirmed by obtaining the same ratio starting from the **as** or **ss** diastereomers. [f] Isolated yields (46 mg scale): **21aa** (8%), **21as** (63%), **21ss** (26%).

and **22aa** constitute synthetically viable routes to these diastereomers. Thus, the combination of stereoselective aldol reactions and isomerization allows the synthesis of any the six diastereomers **21** and **22** in only a few steps from common building blocks.

Comparing the isomerizations of **22**−**24** with 0.4 M imidazole in $CDCl_3$ showed that the proportion of the syn−syn diastereomer at equilibrium increased with increasing MOM protection (**22ss**, 21%; **23ss**, 40%; **24ss**, 46%) suggesting that manipulation of the hydroxy group could be a useful synthetic tool in these processes. However, the isomerizations of the MOM-protected derivatives **23** and **24** were much slower than **22**. These trends are consistent with those observed in the isomerizations of **11** and **12**. We were interested in determining if the hydroxy groups in **19**−**23** imparted any kinetically significant regioselectivity or stereoselectivity to the isomerizations because such effects could be exploited synthetically. Obtaining the pseudo-first-order rate constants for isomerization (i.e., k_n, k_{-n}; $n = 1-4$) for the four-component systems **19**−**24** is much more difficult than for the two-component systems (e.g., **11**−**18**).[40] Although these rate constants must be interpreted with caution,[24] the data suggest that enolizations of **19**, **20**, and **23** occur with only modest regioselectivity (<2.5:1).

Our data firmly establish that isomerization proceeds by an enolization mechanism; however, the mechanistic details of the enolization step are uncertain. Acid- and base-catalyzed enolization of ketones has been extensively studied for more than a century, and various mechanistic subtleties have been revealed.[21] Comparatively few mechanistic studies of enolization of β-oxy ketones (i.e., hydroxy, alkoxy, acyloxy) have appeared, and most of these are concerned with the ensuing elimination reaction.[41] Our results clearly suggest that enolization is facilitated by a β-hydroxy group, and this is most easily accommodated by assuming hydrogen bonding to the carbonyl group. Similarly, the enhanced enolization observed for anti aldol **11a** relative to syn aldol **11s** can be rationalized by "tighter" hydrogen bonding in the anti diastereomer.[42] Although intramolecular acid- and base-catalyzed enolization of β-keto acids and *o*-hydroxyacetophenones have been studied,[21,43] we are unaware of any reports of similar catalysis by a β-hydroxy group. However, base-catalyzed enolization of hydroxyacetone (at the CH_3 group)[44] is 3.4 times faster than acetone[45] which, in turn, is 10−20 times faster than methoxyacetone[46] establishing the beneficial effect of an α-hydroxy group. The order of reactivity observed for isomerizations of **18**, **3**, and **17** (relative rates ca. 0.1, 1, and 3, respectively) can be explained by consideration of the rates for base-catalyzed enolization of 3-pentanone, cyclohexanone, and cyclohexanones with polar substituents at the 4 position (e.g., −OH, −OMe, −OCOMe, etc.).[47] An interesting question concerns the requirements for isomerization in preference to retroaldol or elimination. Base-catalyzed retroaldol requires abstraction of the proton from the hydroxy group and is facilitated by stronger bases and in protic solvents.[9] Specific base-catalyzed eliminations from β-oxy ketones with poor

(39) The chiral bisaldols used in this study were racemic (ref 19). The stereoselective syntheses of **21aa**, **21ss**, **22as**, and **22sa** require the use of enantiomerically pure **10**. This work will be reported separately.

(40) See the Supporting Information for details on the determination of rate constants. The kinetic model (Scheme 3 or 5) assumes each isomerization reaction is first order with respect to the particular "starting" aldol concentration at a fixed concentration of imidazole, as shown. The forward and reverse reactions each comprise two steps, enolization (slow) and ketonization (fast), whose pseudo-first-order rate constants are given by the product of the rate constant for enolization and the partition for ketonization. For example, in the isomerization of **19at** to **19ac** via **19e** (Scheme 3), $k_1 = (k_e k_{k'})/(k_k + k_{k'})$. The ratios k_n/k_{-n} ($n = 1-4$) are governed by the corresponding equilibrium ratios for the component pair of aldols. The sums $k_n + k_{-n}$ ($n = 1-4$) can be used to compare the ease of the isomerization between two components within a four-component equilibration or to compare with the rate of isomerization in a two-component equilibration (i.e., k_{obs}) (ref 22). In contrast to a two-component system, the rate that equilibrium is achieved in a four-component system depends on the initial distribution of the components. The average of $k_n + k_{-n}$ ($n = 1-4$) can be used as an overall indication of the facility of equilibration in a four-component system and can be compared to the rate of isomerization in a two-component equilibration (i.e., k_{obs}) (ref 22).

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leaving groups (e.g., methoxy, hydroxy) with rate-limiting breakdown of an equilibrium concentration of the enolate have been observed.[48] For these compounds, keto−enol tautomerism is enhanced under conditions that minimize the equilibrium concentration of enolate (i.e., use of weak bases). Further, the rate of elimination from enolates of intramolecularly hydrogen bonded aldols should be attenuated because of poor $\pi-\sigma^*$ orbital overlap. Finally, the observed influence of the base on the rates of isomerization is difficult to accommodate. The rates of general base-catalyzed enolization (rate-limiting abstraction of the α-C−H proton) typically increase with increasing pK_a of the base.[21] Low basicity and steric arguments can be invoked to account for the low reactivities of pyridine (pK_a 5.21) and Et_3N (pK_a 10.75) with **11s** (Table 2), respectively. This approach seems less appropriate to explain the much lower reactivity of *N*-methylimidazole (pK_a 7.06) compared to imidazole (pK_a 6.95)[49,50] and the reactivity of DMAP (pK_a 9.2) seems to rule out a requirement for a hydrogen bond donor. Although imidazole and DMAP may catalyze enolization by different mechanisms, their unique ability to catalyze isomerization of aldols raises the possibility of nucleophilic catalysis.[51]

Conclusion

In conclusion, imidazole has been shown to be a very effective catalyst for syn−anti isomerization of aldols via an enolization mechanism. DMAP is also effective isomerization catalyst but the lower basicity, molecular weight, and cost per mole of imidazole justify its preferential use for most substrates. The process is applicable to a broad range of substrates[52] and is particularly facile for tetrahydro-4*H*-thiopyran-4-on-derived aldols. The presence of the aldol hydroxy group greatly facilitates isomerization but has only a small effect on enolization regioselectivity. Most substrates reach equilibrium within 0.3−3 days at ambient temperature in chloroform or benzene containing 0.3−1 M imidazole. A more rapid equilibration can be achieved with gentle warming but the generality of this approach was not examined. Isomerizations are high yielding and occur with little or none of the usual byproducts arising from competing elimination or retroaldol reactions even after prolonged reaction. Consequently, this isomerization process can provide convenient synthetic access to diastereomers unavailable by direct methods (e.g., **11a**, **21as**, and **22ss**). Although the equilibrium ratios are typically modest, synthetically useful amounts of material can be obtained by recycling if necessary.

Experimental Section[53]

(3*S*)-*rel*-3-[(*R*)-(6*R*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(hydroxy)methyl]tetrahydro-4*H*-thiopyran-4-one (11a). Crystallization of the crude product from aldol reaction of **10** (3.47 g, 18.5 mmol) and the trimethylsilyl enol ether of **8** (7.00 g, 37.0 mmol) in the presence of $MgBr_2{\cdot}OEt_2$ (14.3 g, 55.4 mmol) as previously described[18] gave solid **11s** (3.49 g, 62%) and a mother liquor containing a ca. 5:1 mixture of **11a**/**11s**. A solution of the solid **11s** (3.49 g, 11.5 mmol) and imidazole (6.8 g, 0.10 mol) in CH_2Cl_2 (100 mL) was allowed to stand for 24 h. The mixture was washed with aqueous citric acid (0.2 M) and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give a 2:1 mixture of **11s**/**11a** (3.40 g, 98%). Crystallization of the mixture from methanol gave solid **11s** (2.08 g, 61%) and a mother liquor containing a ca. 8:1 mixture of **11a**/**11s**. The solid **11s** (2.08 g) was subjected to isomerization as above to give solid **11s** (1.22 g, 58%) and a mother liquor containing a ca. 6:1 mixture of **11a**/**11s**. The combined mother liquors from the above crystallizations (3) (4.1 g; a 6:1 mixture of **11a**/**11s**) were fractionated by MPC (25−50% ethyl acetate in hexane) to give **11s** (437 mg; a total of 1.66 g of **11s** isolated, 30% overall from **10**) and **11a** (2.88 g, 51% from **10**). Spectral data was identical to that reported previously.[18]

(3*R*,5*S*)-*rel*-3,5-Bis[(*S*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]-dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (21as). Bisaldol **21aa** (13 mg, 0.026 mmol) was added to a solution of imidazole (136 mg, 2.00 mmol) in CH_2Cl_2 (2.0 mL). After 20 h at room temperature, the mixture was diluted with aqueous citric acid (0.1 M) and extracted with CH_2Cl_2 (×3). The combined organic layers were dried over Na_2SO_4 and concentrated to give a 6.2:3:1 mixture (12 mg) of **21as**, **21aa**, and **21ss**, respectively. Fractionation of the mixture by PTLC (2% MeOH in CH_2Cl_2; multiple elution) gave **21ss** (1.5 mg, 12%), **21aa** (3.5 mg, 27%), and the titled compound (6 mg, 46%): IR (DRIFT) ν_{max} 3518, 2917, 1694, 1427, 1153, 1131, 1101, 1042 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 4.69 (1H, ddd, J = 1.5, 3.5, 6 Hz, HC-1′), 4.17 (1H, ddd, J = 3.5, 7.5, 10 Hz, HC-1″), 3.45−3.24 (6H, m, H_2CO × 4), 3.24−3.02 (9H, m, H_2CO, HC-2, HC-3, HC-5, HC-6, HC-7′, H_2C-7″), 3.13 (1H, d, J = 1.5 Hz, HOC-1′), 2.85 (1H, dd, J = 11.5, 13 Hz, HC-2 or HC-6), 2.77 (1H, d, J = 10 Hz, HOC-1″), 2.72 (1H, br d, J = 13.5 Hz, HC-7), 2.58 (1H, m, J = 4, 8, 13 Hz, HC-9″), 2.52 (1H, ddd, J = 3.5, 3.5, 13 Hz, HC-2 or HC-6), 2.49 (1H, ddd, J = 3, 10.5, 13.5 Hz, HC-9′), 2.25−2.24 (2H, m, HC-9′, HC-9″), 2.21 (1H, ddd, J = 3.5, 4, 9.5 Hz, HC-6′), 2.16 (1H, ddd, J = 3.5, 7, 7.5 Hz, HC-6″), 1.63 (1H, ddd, J = 3, 6, 13.5 Hz, HC-10′), 1.48 (1H, ddd, J = 3.5, 10.5, 13.5 Hz, HC-10′), 1.45−1.36 (2H, m, H_2C-10″); (500 MHz, $CDCl_3$) δ 4.53 (1H, br d, J = 8.5 Hz, HC-1′), 4.17−3.89 (9H, m, HC-1″, H_2CO ×4), 3.33 (1H, ddd, J = 3.5, 4, 13.5 Hz, HC-2), 3.27 (1H, ddd, J = 3.5, 3.5, 12 Hz, HC-5), 3.21 (1H, dd, J = 12, 13 Hz, HC-6), 3.10 (1H, d, J = 1 Hz, HOC-1′), 3.09−2.50 (9H, m, HC-3, H_2C-7′, H_2C-7″, H_2C-9′, H_2C-9″), 2.97 (1H, d, J = 9.5 Hz, HOC-1″), 2.91 (1H, ddd, J = 3, 3.5, 13 Hz, HC-6), 2.85 (1H, dd, J = 11.5, 13.5 Hz, HC-2), 2.22 (1H, ddd, J = 3, 7.5, 7.5 Hz, HC-6″), 2.16−2.07 (2H, m, HC-6′, HC-10′ or HC-10″), 1.88 (1H, ddd, J = 3, 8.5, 13.5 Hz, HC-10′ or HC-10″), 1.78−1.71 (2H, m, HC-10′, HC-10″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5 (s), 110.2 (s), 109.0 (s), 70.9 (d, C-1′), 66.9 (d, C-1″), 64.9 (t), 64.8 (t), 64.3 (t), 64.0 (t), 57.5 (d), 57.0 (d), 47.5 (d), 46. (d), 37.1 (t), 35.8 (t), 35.5 (t), 34.6 (t), 29.3 (t), 26.8 (t), 26.7 (t), 26.6 (t); LRMS (EI) m/z (relative intensity) 492 ([M]$^+$, 1), 304 (8), 188 (15), 159

(48) Methoxy-2-butanone,[41d] *cis*-octahydro-8a-hydroxy-4a-methyl-2(1*H*)-naphthalenone,[41h] and prostaglandin E_2[41k] (note: intramolecular hydrogen bonding is not possible for these aldols).

(49) The rate constants for imidazole- and *N*-methylimidazole-catalyzed enolizations of β-oxy ketones were very similar (see ref 41g and h).

(50) For imidazole-catalyzed enolization of acetone, see: (a) Mel'nichenko, I. V.; Yasnikov, A. A. *Ukr. Khim. Zh.* **1964**, *30*, 723−728. (b) Bender, M. L.; Williams, A. *J. Am. Chem. Soc.* **1966**, *88*, 2502−2508. For a discussion of the possibility of imidazole acting as a bifunctional enolization catalyst, see refs 41g, 51a, and: (c) Banks, B. E. C. *J. Chem. Soc.* **1962**, 63−71. (d) Breslow, R.; Graff, A. *J. Am. Chem. Soc.* **1993**, *115*, 10988−10989.

(51) (a) Bruice, P. Y.; Bruice, T. C. *J. Am. Chem. Soc.* **1978**, *100*, 4793−4801. (b) Bruice, P. Y. *J. Am. Chem. Soc.* **1983**, *105*, 4982−4996. (c) Bruice, P. Y. *J. Am. Chem. Soc.* **1990**, *112*, 7361−7368.

(52) For other examples, see: (a) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F. *J. Org. Chem.* **2003**, *68*, 9624−9634. (b) Williamson, R. T.; Marquez, B. L.; Sosa, A. C. B.; Koehn, F. E. *Magn. Reson. Chem.* **2003**, *41*, 379−385.

(53) See the Supporting Information for general methods and procedures.

(12), 132 (73), 99 (100), 86 (24), 55 (21); HRMS *m*/*z* calcd for $C_{21}H_{32}O_7S_3$ 492.1310, found 492.1310.

(3*R*,5*S*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]-dec-6-ylhydroxymethyl]-5-[(*S*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (22ss). Bisaldol **22aa** (46 mg, 0.093 mmol) was added to a solution of imidazole (680 mg, 10.0 mmol) in acetone (10 mL) at room temperature. After 8 days, the mixture was diluted with aqueous citric acid (0.1 M) and extracted with CH_2Cl_2 (×3). The combined organic layers organic were dried over Na_2SO_4 and concentrated to give a 6.2:3.0:1 mixture of **22as**, **22ss**, and **22aa**, respectively. Fractionation of the mixture by PTLC (2% MeOH in CH_2Cl_2; multiple elution) gave **22as** (29 mg, 63%), **22aa** (4 mg, 8%), and the titled compound **22ss** (12 mg, 26%): IR (DRIFT) ν_{max} 3511, 2916, 1702, 1427, 1153, 1102, 1038, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.57 (2H, ddd, J = 2.5, 4.5, 6.5 Hz, HC-1′, HC-1″), 4.09−3.96 (8H, m, H_2CO × 4), 3.25 (2H, br d, J = 13.5 Hz, HC-2, HC-6), 3.09 (2H, ddd, J = 4.5, 6.5, 11.5 Hz, HC-3, HC-5 [$J_{HC-2-HC-3}$ = 4.5, 11.5 Hz]), 3.06 (2H, d, J = 2.5 Hz, HO × 2), 2.98 (2H, dd, J = 9.5, 14 Hz, HC-7′, HC-7″), 2.91 (2H, dd, J = 11.5, 13.5 Hz, HC-2, HC-6), 2.78−2.71 (4H, m, HC-7′, HC-7″, HC-9′, HC-9″), 2.64 (2H, m, HC-9′, HC-9″), 2.11 (2H, ddd, J = 3.5, 4.5, 9.5 Hz, HC-6′, HC-6″), 2.09 (2H, ddd, J = 3, 6.5, 14 Hz, HC-10′, HC-10″), 1.77 (2H, ddd, J = 3.5, 10, 14 Hz, HC-10′, HC-10″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9 (s, C-4), 109.9 (s × 2, C-5′, C-5″), 66.9 (d × 2, C-1′, C-1″), 64.6 (t × 2, CH_2O), 64.5 (t × 2, CH_2O), 57.8 (d × 2, C-3, C-5), 46.6 (d × 2, C-6′, C-6″), 35.5 (t × 2, C-10′, C-10″), 34.3 (t × 2, C-2, C-6), 27.5 (t × 2, C-7′, C-7″), 26.8 (t × 2, C-9′, C-9″); LRMS (EI) *m*/*z* (relative intensity) 492 ($[M]^+$, 1), 188 (14), 159 (11), 132 (73), 100 (10), 99 (100), 86 (24), 55 (8); HRMS *m*/*z* calcd for $C_{21}H_{32}O_7S_3$ 492.1310, found 492.1311 (EI).

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Supporting Information Available: General experimental and procedures for **12**, **19**, **20**, **23**, and **24**, determination of relative configurations, determination of rate constants, and ^1H NMR spectra for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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