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Diastereoselective, Three-Component Cascade Synthesis of Tetrahydrofurans and Tetrahydropyrans Employing the Tandem Mukaiyama Aldol−Lactonization Process†

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A full account of studies leading to the development of a cascade sequence that generates as many as two C−C bonds, one C−O bond, and three new stereocenters providing substituted tetrahydrofurans (THFs) from simple γ-ketoaldehydes and thiopyridyl ketene acetals is described. The process involves a tandem Mukaiyama aldol−lactonization (TMAL) and accumulated evidence suggests the intermediacy of a silylated β-lactone that is intercepted by the pendant ketone. Formation of a cyclic oxocarbenium is followed by reduction with silicon-based nucleophiles leading to a highly diastereoselective synthesis of tetrahydrofurans. This cascade process has now been extended to the synthesis of tetrahydropyrans from simple δ-ketoaldehydes. The stereochemical outcome of the cascade processes described was determined by NOE correlations, coupling constant analysis, and X-ray crystallography of the derived oxygen heterocycles and is in accord with established and recently proposed models for nucleophilic additions to cyclic 5- and 6-membered oxocarbenium ions. The utility of this process was demonstrated by the synthesis of the tetrahydrofuran fragment of colopsinol B.

Introduction

The synthesis of saturated cyclic ethers represents one of the most vibrant research areas in organic chemistry and has a rich history within the realm of natural products. The synthesis of epoxides, oxetanes, tetrahydrofurans (THFs), tetrahydropyrans (THPs), and medium-ring ethers have all played important roles in the total synthesis of natural products and are common moieties in some of the most bioactive natural products discovered thus far including the epothilones,[1] taxanes,[2] haterumalides,[3] altohyrtins,[4] and brevetoxins.[5] Perhaps since they are the most commonly encountered of the cyclic ethers, THFs[6] and THPs[7] have received extensive attention from the synthetic community, and approaches to these heterocycles can be divided into three major strategies (Figure 1). Furthermore, multicomponent cascade, tandem, or domino processes that form

† In memory of Prof. A. I. Meyers: mentor, friend, and a father of asymmetric synthesis.

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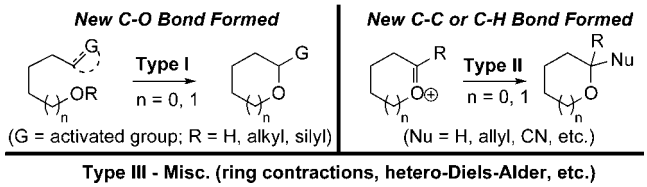
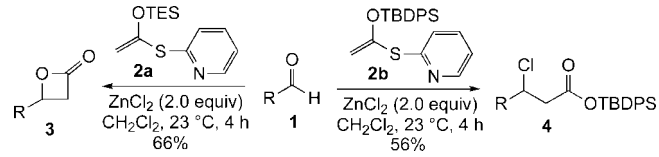


FIGURE 1. General strategies toward tetrahydrofurans and tetrahydropyrans.

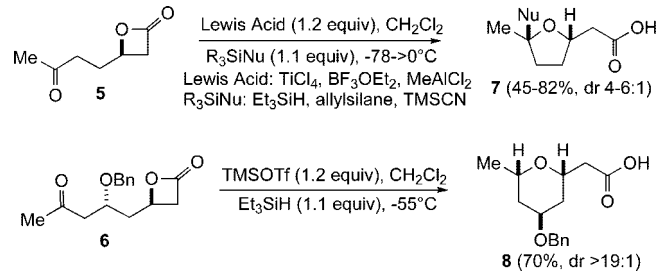
complex THFs and THPs from simple starting materials in a single reaction mixture have become more prevalent in recent years.[8]

We have previously described both diastereo- and enatioselective methods for β-lactone synthesis and their utility as strained heterocycles toward a variety of other useful moieties.[9] In the course of optimizing the $ZnCl_2$-mediated tandem Mukaiyama[10] aldol−lactonization (TMAL),[11] we observed divergent product distributions based solely on the size of the silyl group of the thiopyridyl ketene acetal leading to either β-lactones **3** or β-chloro acids **4** (Scheme 1).[12] This and other observations led us to propose the intermediacy of a silylated β-lactone in these reactions.[13] Related to the reductive cyclization of

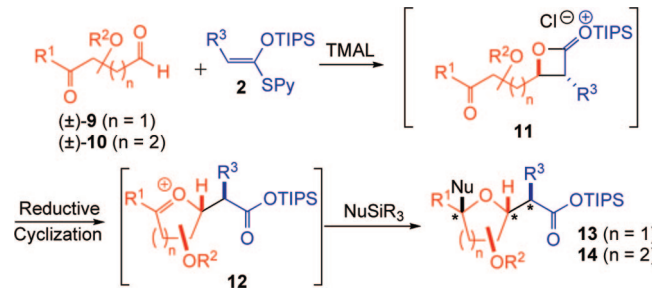
SCHEME 1. Divergent Product Distribution in the $ZnCl_2$-Mediated Tandem Mukaiyama Aldol−Lactonization (TMAL) Process



SCHEME 2. Mead Reductive Cyclization of Keto-β-lactones 5/6 toward THFs 7 and THP 8



SCHEME 3. Tandem Three-Component Synthesis of THFs 13 and THPs 14



epoxyketones leading to THFs reported by Chamberlin,[14] Mead reported an entry to THFs **7**[15] from keto-β-lactones **5** and a single example of a THP **8**[16] from benzyloxy-substituted keto-β-lactone **6** (Scheme 2). We envisioned the possibility of combining the TMAL process with a subsequent Mead-type reductive cyclization of the presumed silylated-β-lactone intermediate **11** toward a highly diastereoselective, three-component, cascade synthesis of THFs **13** and THPs **14** from ketoaldehydes (±)-**9**−**10**, thiopyridyl ketene acetals **2**, and silicon-based nucleophiles (Scheme 3). High diastereoselectivity was expected based on stereoelectronic models recently developed by Woerpel for nucleophilic additions to 5-membered cyclic oxocarbeniums[17] and established and recently refined models for 6-membered oxocarbeniums.[18] The development of such a cascade

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(13) For a related proposed silylated β-lactone in a $SnCl_4$-mediated synthesis of *cis*-β-lactones, see: Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* **1999**, *1*, 1197.

(14) (a) Mulholland, R. L.; Chamberlin, A. R. *J. Org. Chem.* **1988**, *53*, 1082. (b) Fotsh, C. H.; Chamberlin, A. R. *J. Org. Chem.* **1991**, *56*, 4141.

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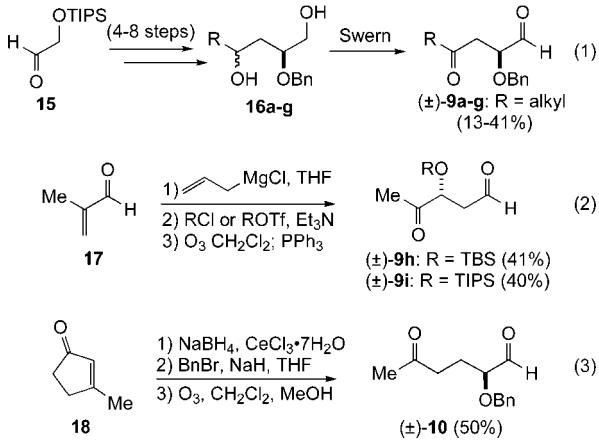
SCHEME 4. Preparation of Ketoaldehyde Substrates (±)-9 and 10 for the Cascade Process

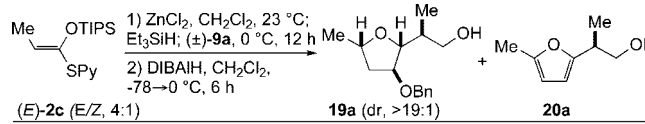


process was attractive since overall it could lead to the generation of up to two C−C bonds, one C−O bond, and three additional stereocenters. In a preliminary communication, we recently reported the realization of this three-component cascade sequence for THF synthesis, and herein, we provide a full account of our development of this process and its application to a colopsinol B fragment.[12] In addition, we describe an extension of this cascade process to the synthesis of tetrahydropyrans, which in fact are found to proceed with greater efficiency.

Results and Discussion

Preparation of Ketoaldehyde Substrates (±)-9 and 10. The preparation of racemic ketoaldehydes (±)-**9** and **10** was performed using straightforward known procedures (Scheme 4). Initial attempts to rapidly access α-benzyloxy-γ-ketoaldehyde (±)-**9a** via ozonolysis of the corresponding bis-olefin (not shown)[19] were thwarted by difficulties in purification following ozonolysis. Our second approach involving a double Swern oxidation of a diol was more tractable, albeit significantly longer (Scheme 4, eq 1). Beginning with aldehyde **15**, standard procedures were utilized[20] to access diols **16a**−**g** and following Swern oxidation provided ketoaldehydes (±)-**9a**−**g**.[21] In contrast to the difficulty in obtaining pure α-benzyloxy-γ-ketoaldehyde (±)-**9a** via ozonolysis, β-silyloxy-γ-ketoaldehydes (±)-**9h**,**i** derived from methacrolein **17** could be accessed via this procedure (Scheme 4, eq 2). Successful ozonolysis in these cases is in part due to the fact that the ketoaldehydes bearing bulky silicon protecting groups were found to be more stable than α-benzyloxy-γ-ketoaldehydes (±)-**9a**−**g** and less susceptible to the formation of inseparable byproduct. α-Benzyloxy-δ-ketoaldehyde (±)-**10** was prepared from cyclic enone **18** by a three-step sequence involving Luche reduction,[22] benzyl protection, and ozonolysis (Scheme 4, eq 3). Although ketoaldehydes (±)-**9** and **10** could be stored neat at ∼10 °C for several weeks without degradation, we typically stored larger quantities of the more stable, immediate precursors and performed the final oxidations to deliver substrates for the cascade process immediately prior to use. Finally, triisopropylsilyl (TIPS) thiopyridyl ketene acetals **2**, prepared according to known procedures,[11] were utilized instead of the corresponding *tert*-butyldiphenylsilyl (TBDPS) thiopyridyl ketene acetals (i.e., **2b**, Scheme 1) due to the relative ease of preparation and initial success in the tandem process as described below.[23]

TABLE 1. Optimization of the Cascade, Three-Component Process with α-Benzyloxy-γ-Ketoaldehyde (±)-9a Leading to Tetrahydrofuran 19a



(*E*)-**2c** (E/Z, 4:1) **19a** (dr, >19:1) **20a**

entry	$ZnCl_2$ (equiv)	(*E*)-**2c** (equiv)	Et_3SiH (equiv)	*T* (°C)	ratio **19a/20a**[a] (% yield of **19a**)[b]
1	2.0	2.0	10.0	23	1.0/3.5 (9)
2	2.0	2.0	0.0	23	**20a** only (0)
3	2.0	2.0	10.0	0 → 23	1.0/2.0 (24)
4	2.0	1.2	10.0	23	1.2/1.0 (ND)[c]
5	4.0	1.2	10.0	0 → 23	2.0/1.0 (42)
6	4.0	1.2	50.0	23	6.7/1.0 (40)
7	4.0	1.2	50.0	0 → 23	6.2/1.0 (50)
8	4.0	1.2	50.0	0 → 23	1.0/3.5 (10)[d]
9	8.0	1.2	100.0	0 → 23	9.0/1.0 (38)
10	4.0	1.2	50.0	0	6.2/1.0 (54)

[a] Estimated by crude ^1H NMR (300 MHz) analysis of the corresponding silyl esters. [b] Isolated yield over two steps. [c] Not determined. [d] No precoordination between ketene acetal (*E*)-**2a** and $ZnCl_2$ was utilized in this reaction.

Synthesis of Tetrahydrofurans via the Tandem Mukaiyama Aldol−Lactonization/Mead Reductive Cyclization Cascade Process. We began our studies of the cascade process using ketene acetal (*E*)-**2c** (4:1), Et_3SiH, and α-benzyloxy-β-ketoaldehyde (±)-**9a**, a substrate we predicted would give high diastereoselectivity for both the TMAL process and subsequent reductive cyclization (Table 1).[12] Building on our previous studies of the TMAL process with aldehydes bearing pendant nucleophiles, a solution of ketene acetal (*E*)-**2c** in CH_2Cl_2 was added to freshly fused $ZnCl_2$ and stirred for 4 h until a homogeneous solution resulted, in order to modulate the Lewis acidity and increase the rate of the desired TMAL process.[24] Initial results with these "precoordination" conditions provided a complex reaction mixture that included silyl esters (i.e., **13**, Scheme 3) as minor products (as judged by crude ^1H NMR). However, several attempts to separate these silyl esters[25] or the corresponding carboxylic acids following desilylation proved challenging.[13] Eventually, we determined that isolation was best accomplished following reduction of the crude reaction mixture with DIBAl-H which simplified isolation of THF alcohol **19a**, albeit in only 9% yield under these initial conditions accompanied by the volatile furan **20a** (Table 1, entry 1). Regardless of the relative amount of Et_3SiH added (2−50 equiv), no improvement in the ratio of THF **19a** to furan **20a** could be obtained, and a control experiment revealed that not adding triethylsilane led to exclusive formation of the furan **20a** as expected (entry 2). This suggested that the TMAL process was proceeding efficiently but an intervening, competitive aromatization process was decreasing the yield of the desired THF. Lowering the reaction temperature to 0 °C led to an increase in

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(23) Early comparisons between TIPS ketene acetal (*E*)-**2c** and the corresponding TBDPS ketene acetal indicated that optimal yields were obtained with the former reagent.
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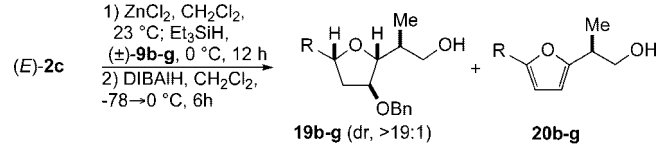
the relative amount of THF **19a**, although furan **20a** remained the major product (entry 3). This was unexpected since the TMAL process does not typically proceed below 23 °C, and this may be due to the increased electrophilicity of the aldehyde due to either inductive effects of the benzyloxy substituent or bidentate chelation with the aldehyde.[15b] Increasing the ratio of Lewis acid to ketene acetal had the most profound effect and finally delivered THF **19a** as the major product (entries 4 and 5). When these conditions were combined with a large excess of Et_3SiH at ambient temperature, crude ^1H NMR analysis indicated an improved ratio, but the isolated yield of THF **19a** did not improve (entry 6). Upon lowering the temperature with a large excess of both $ZnCl_2$ and Et_3SiH, the desired THF **19a** could be isolated in 50% yield (entry 7). As expected, if "precoordination" conditions were not used, the ratio decreased dramatically (entry 8). Utilizing 8.0 equiv of $ZnCl_2$ and 100 equiv of Et_3SiH provided the best ratio but lower isolated yield of THF **19a** (entry 9). In several conditions wherein an improved ratio (**19a/20a**) was obtained as determined by crude ^1H NMR analysis (i.e., entries 6 and 9), several minor and unidentified byproducts were also produced. Finally, optimal conditions were achieved by maintaining the reaction temperature at 0 °C for 12 h to deliver THF **19a** in 54% yield, and this corresponds to an average of ~86% yield per step over the four steps involving aldol reaction, lactonization, reductive cyclization, and DIBAlH reduction (entry 10).

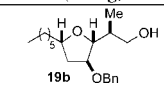
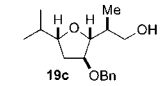
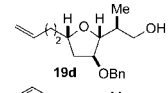
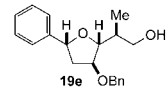
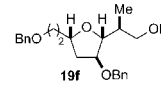
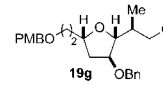
Applying the cascade process to α-benzyloxy-γ-ketoaldehydes (±)-**9b**−**g** and ketene acetal (*E*)-**2c** delivered THFs **19b**−**g** with consistently high diastereoselectivity (>19:1) and generally in moderate (42−54%) yields with one exception (entry 4) accompanied by lesser amounts of furans **20b**−**g** (Table 2).[26] In general, greater steric bulk of the ketone substituent appears to inhibit the production of the desired THF and increase formation of the furan. This observation is consistent with increased steric interactions with Et_3SiH during the reduction step with larger substituents enabling presumed elimination processes, which led to furan byproduct, to become more competitive. In the case of the phenyl substituted ketoaldehyde (±)-**9e**, the desired THF **19e** was obtained in only 13% yield along with 48% of furan **20e** (entry 4). While steric interactions may also lead to reduced yields in this case, stabilization of the oxocarbenium intermediate and greater conjugation achieved during elimination in route to furan **20e** likely also contribute to diminished yields.

Employing β-silyloxy-γ-ketoaldehydes (±)-**9 h**,**i** as substrates in the cascade process led to lower yields of THFs **19h**,**i** and isolation of new byproducts, THFs **21a**,**b** (Scheme 5). Ketoaldehyde (±)-**9h** and ketene acetal (*E*)-**2c** (*E*/*Z*, >19:1)[27] under slightly modified reaction conditions delivered the desired THF **19h** in low yield but good diastereoselectivity (dr, 9:1) and THF **21a**. When the bulky, α-oxygenated ketene acetal (*Z*)-**2d** (>19:1) was utilized, only 5% yield of the desired THF **19i** was isolated along with 40% of THF **21b**. These byproducts presumably arise from self-condensation and reduction of the ketoaldehyde substrates **9h**,**i** without incorporation of ketene acetals (*E*)-**2c** and (*Z*)-**2d**, respectively.

Variations of the ketene acetal were also explored with a desire to incorporate an acetate aldol into the cascade process.

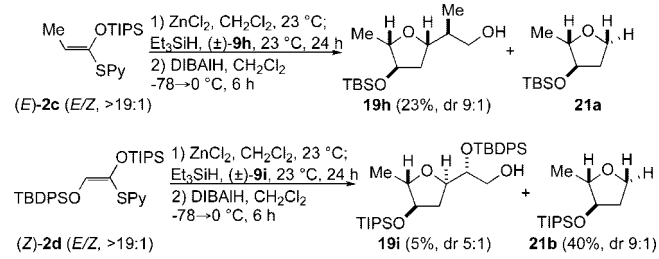
TABLE 2. Three-Component Synthesis of THFs 19b−g from α-Benzyloxy-γ-ketoaldehydes (±)-9b−g



entry	ketoaldehyde (±)-**9**	THFs (**19b-g**)	ratio **19**/**20**[a]	% yield **19** (**20**)[b]
1	(±)-**9b** (R = *n*-hexyl)	 **19b**	1.3:1	42(20)
2	(±)-**9c** (R = *i*-propyl)	 **19c**	2.3:1	52(20)
3	(±)-**9d** (R=$CH_2CH(CH_2)_2$)	 **19d**	3.0:1	49(14)
4	(±)-**9e** (R = phenyl)	 **19e**	1:5.0	13(48)
5	(±)-**9f** (R = $BnO(CH_2)_2$)	 **19f**	3.5:1	54(ND)[c]
6	(±)-**9g** (R = $PMBO(CH_2)_3$)	 **19g**	2.2:1	49(27)[d]

[a] Determined by crude ^1H NMR (300 MHz) analysis. [b] Isolated yield over two steps including the cascade process and DIBAlH reduction. Yields in parentheses correspond to estimated yields of volatile furans **20**. [c] Not determined. [d] In this case, it was necessary to maintain the DIBAlH reduction at −78 °C and slowly warm to −30 °C to prevent cleavage of the PMB group.

SCHEME 5. Synthesis of THFs 19h,i from β-Silyloxy-γ-ketoaldehydes (±)-9h,i via the Cascade Process



Use of the acetate ketene acetal **2e** provided THF **19j** in good yield but with poor diastereoselectivity as expected.[11c] Related to the strategy of Evans,[28] a masked acetate aldol in the form of thiophenyl ketene acetal (*E*)-**2f** (*E*/*Z*, 2:1) delivered THF **19k** in excellent diastereoselectivity but with diminished yield (Scheme 6). The low yield in this case and also with several other α-heteroatom substituted ketene acetals (i.e., α-SMe, OMe, OTBS, OTBDPS) is likely due to rate-retardation of the TMAL process enabling the side-reaction leading to production of simple THFs (i.e., **21c**) to be more competitive. Thus, we observed an inverse relationship between the size of the α-substituent of the ketene acetal and the yield of THF, which is consistent with our previous studies of the TMAL process.[11e]

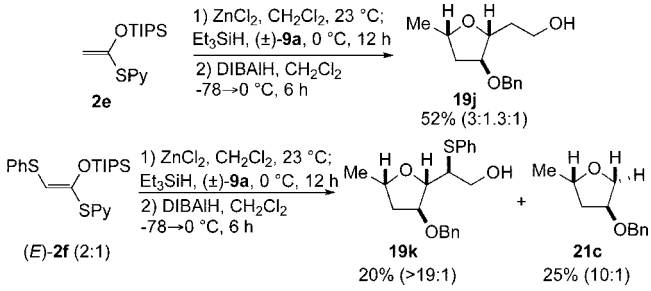
Allyltrimethylsilane was also studied as a nucleophile, and under standard conditions, THF **19l** was isolated as a single

(26) Due to difficulties arising from either volatility or purification of furans **20b**−**g**, the yields are reported as estimates.

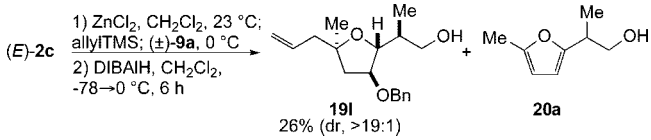
(27) Pure (*E*)-**2c** (>19:1) is required with β-silyloxy aldehydes in order to obtain maximum diastereoselectivity in the TMAL; see refs 11a and 11b.

(28) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

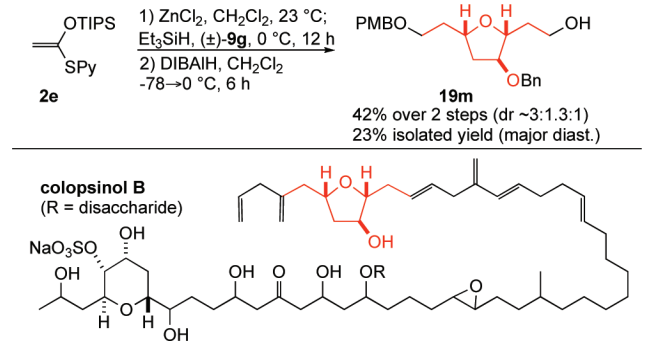
SCHEME 6. Variation of the the Ketene Acetal 2 with Ketoaldehyde (±)-9 in the Cascade Process



SCHEME 7. Use of Allyltrimethylsilane as Nucleophile in the Cascade Process Leading to Allyl THF 19l



SCHEME 8. Synthesis of the Tetrahydrofuran Fragment 19m of Colopsinol B via the Cascade Process

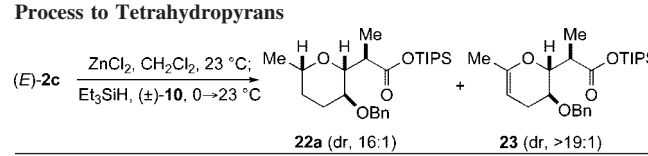


diastereomer, albeit in reduced yield (Scheme 7). Greater quantities of the typical side-product, furan **20a**, are produced and this likely reflects the slower addition of this nucleophile to the oxocarbenium. However it is important to note that an additional C−C bond is constructed with high stereocontrol of the resulting quaternary center. TMSCN was also studied briefly but gave a complex reaction mixture.

To highlight the utility of this methodology, we targeted the THF fragment of the DNA polymerase inhibitor, colopsinol B, isolated from the dinoflagellate *Amphidinium* and structurally related to the amphidinolides (Scheme 8).[29] To date, only the relative stereochemistry of the THF and THP rings has been determined by NOE and ROESY correlations and $^1H-^1H$ coupling constants, and given that no previous synthetic studies toward this natural product have been reported, this became an interesting target for application of the cascade process. Under typical conditions with ketene acetal **2e** and α-benzyloxy-γ-ketoaldehyde (±)-**9g**, alcohols **19m** were obtained following DIBALH reduction as a mixture of diastereomers as observed previously with ketene acetal **2e** (Scheme 7). The major diastereomer was separable and was isolated in 23% yield (two steps). The relative stereochemistry was deduced from coupling constant and NOE analysis and correlated well with THF **19j** (Scheme 6) and with data reported for colopsinol B.[20]

(29) Kubota, T.; Tsuda, M.; Takahashi, M.; Ishibashi, M.; Naoki, H.; Kobayashi, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3483.

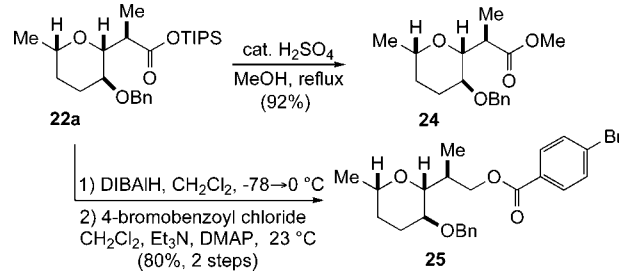
TABLE 3. Optimization of the Cascade, Three-Component Process to Tetrahydropyrans



entry	$ZnCl_2$ (equiv)	Et_3SiH (equiv)	ratio **22a/23**[a]	% yield of **22a**[b]
1	4.0	50.0	4:1	ND[c]
2	1.5	0.0		34
3	1.5	1.5	3:1	68[d]
4	2.0	2.0	20:1	75
5	2.0	10.0	>20:1	~75[e]

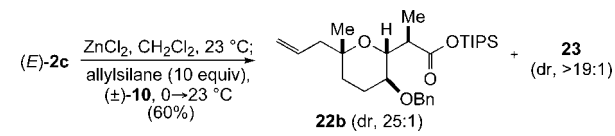
[a] Determined by crude ^1H NMR (500 MHz) analysis. [b] Isolated yield after flash column chromatography. [c] Not determined. [d] Combined yield of **22a** and **23**. [e] Contaminated with minor inseparable byproduct.

SCHEME 9. Conversion of THP 22a to Methyl Ester 24 and *p*-Bromobenzoate 25

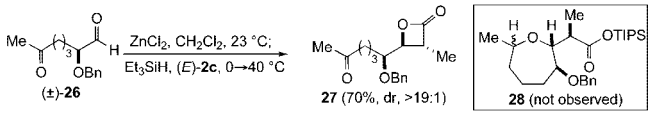


Synthesis of Tetrahydropyrans via the Tandem Mukaiyama Aldol−Lactonization/Mead Reductive Cyclization. Brief studies with α-benzyloxy-δ-ketoaldehyde (±)-**10** indicate that this cascade process is also applicable toward THP synthesis and is, in fact, more efficient (Table 3). Minimal optimization was required due to our previous extensive investigations toward THFs (cf. Table 1). Application of optimal conditions identified for THF synthesis gave a 4:1 ratio (entry 1) of THP **22a** and a dihydropyran (DHP) byproduct **23**. A control experiment without addition of Et_3SiH produced the DHP **23** in 34% yield (entry 2). Upon reducing the equivalents of $ZnCl_2$ and Et_3SiH, low selectivity was again observed; however, the total yield of the inseparable THP and DHP was 68% (entry 3). Optimal conditions were eventually found and gave the desired THP **22a** in 75% yield as the major product in a highly diastereoselective fashion (dr, 16:1) with minimal DHP **23** (entry 4). Increasing the amount of Et_3SiH to 10 equiv did not improve the yield further and led to trace amounts of inseparable byproduct. Due to the efficiency of this process, it was possible to isolate the initially formed TIPS esters in contrast to the THF synthesis. While triisopropylsilyl esters are known to be stable to silica gel,[25] we found that rapid purification was necessary to prevent desilylation. The TIPS ester **22a** is readily converted to the corresponding methyl ester **24** by standard Fisher esterification (Scheme 9). In an attempt to further verify the relative stereochemistry of THP **22a** via X-ray crystallographic analysis, DIBALH reduction and acylation delivered the *p*-bromobenzoate **25** in good yield. Unfortunately, this derivative was not crystalline. Allyltrimethylsilane (10 equiv) was also explored and gave a partially separable mixture of THP **22b** and DHP **23** (60%, combined yield) (Scheme 10).[20] Use of fewer equivalents of allyltrimethylsilane gave approximately equimolar quantities of THP **22b** to DHP **23**, while alternative allyl transfer reagents and nucleophiles including allyltriph-

SCHEME 10. Synthesis of Allyl Tetrahydropyran 22b via the Cascade Process from Ketoaldehyde (±)-10



SCHEME 11. Attempted Synthesis of an Oxepane from Ketoaldehyde (±)-26 via the Cascade Process



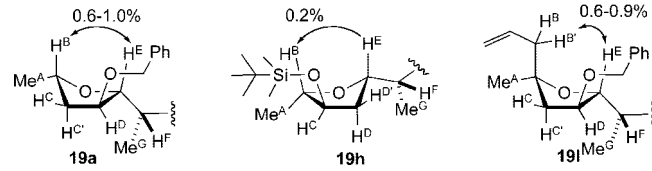
enylsilane, allyltributylstannane, and 1,3-dimethoxybenzene produced complex reaction mixtures.

Finally, in efforts to define the limits of this cascade process, we targeted a substrate (±)-**26** that would lead to an oxepane if successful.[30] As expected, even after gentle warming, oxepane **28** was not observed, however, the keto-β-lactone **27** could be isolated in useful yields (70%) resulting from only the TMAL portion of this cascade process (Scheme 11).

Stereochemical Determination of Tetrahydrofurans and Tetrahydropyrans Synthesized via the Tandem, Three-Component Process. The stereochemical outcome of the TMAL portion of this cascade process is in accord with previous diastereoselectivities observed with α-benzyloxy and β-silyloxy substrates,[11] while that of the subsequent reductive cyclization[15] sequence is in accord with that previously observed in our stepwise THF synthesis[11g] and is consistent with established and recent models for additions to cyclic oxocarbenium ions.[17,18] Extensive NOE enhancements, coupling constant analysis, and X-ray crystallography were used to assign the relative stereochemistry of the tetrahydrofurans and tetrahydropyrans obtained via the cascade process. Whereas THPs adopt readily predictable low energy chair conformations simplifying coupling constant analysis, the greater conformational mobility of THF rings makes the most stable envelope conformation more challenging to predict. Coupling constant analysis supports the relative stereochemistry shown for representative THFs **19a**, **19h**, and **19l** and NOE enhancements provided further evidence for the assigned relative stereochemistry (Table 4).[31] For example, $J_{HB,HC'}$ exhibited a diagnostic coupling constant (J = 10 Hz) in THF **19a** corresponding to a 1,2-diaxial relationship as expected.[32] However, as expected, the corresponding coupling constant was not present in THF **19l**, yet other relevant coupling constants maintained a similar range. THF **19h** showed a similar coupling constant ($J_{HD,HE}$ = 9.5 Hz), and the relative stereochemistry was also supported by NOE enhancements. In addition, single-crystal X-ray analysis of a *p*-bromobenzoate derivative (not shown) derived from acylation of alcohol **19a** provided further evidence for the relative stereochemistry of this THF.[20] Finally, the relative stereochemistry also provides evidence for the proposed mechanistic pathway (vide infra).

Coupling constant analysis provided evidence for the proposed relative stereochemistry of THPs **22a**, **24**, and **22b** and

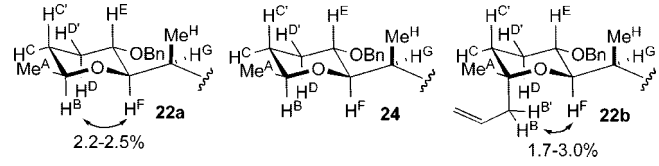
TABLE 4. Representative NOE Enhancements and Coupling Constants for Representative Tetrahydrofurans



proton(s)	**19a**: mult (J (Hz))[a]	**19h**: mult (J (Hz))[a]	**19l**: mult (J (Hz))[a]
A	d (6.0)	d (6.5)	s (NA)[b]
B	ddq (5.5, 6.0, 10.0)	dq (6.5,6.5)	dd[c] (7.5, 13.5)
C	ddd (2.0, 5.5, 13.0)	ddd (3.5, 6.5, 7.0)	dd (4.5, 13.0)
C′	ddd (7.0, 10.0, 13.0)	NA[b]	dd (7.0, 13.0)
D	ddd (2.0, 4.0, 7.0)	ddd (7.0, 9.5, 13.0)	ddd (4.5, 5.5, 7.0)
D′	NA[b]	ddd (3.5, 6.5, 13.0)	NA[b]
E	dd (4.0, 5.0)	ddd (5.0, 6.5, 9.5)	dd (5.0, 5.5)
F	m (NA)[b]	m (NA)[b]	m (NA)[b]
G	d (7.0)	d (7.0)	d (7.5)

[a] Determined by ^{1}H NMR (500 MHz) analysis. [b] Not applicable. [c] Only one dd is provided here.[20]

TABLE 5. NOE Correlations and Coupling Constants for Representative Tetrahydropyrans



proton(s)	**22a**: mult (J (Hz))[a]	**24**: mult (J (Hz))[a]	**22b**: mult (J (Hz))[a]
A	d (6.0)	d (6.0)	s (NA)[b]
B	ddq (2.0, 6.0, 8.0)	ddq (2.5,6.0,8.5)	dd[c] (8.5,13.5)
C	m	m	m
C′	m	m	m
D	m	m	m
D′	m	m	m
E	ddd (4.5, 9.3, 10.5)	ddd (4.5, 9.0, 10.5)	ddd (4.5, 9.5, 10.5)
F	dd (2.8, 9.3)	dd (5.0, 9.0)	dd (3.0, 9.5)
G	dq (2.8, 7.0)	dq (5.0, 7.5)	dq (3.0, 7.0)
H	d (7.0)	d (7.5)	d (7.0)

[a] Determined by ^{1}H NMR (500 MHz) analysis. [b] Not applicable. [c] Only one dd is provided here.[20]

NOE enhancements gave further confirmation (Table 5). For example, typical 1,2-diaxial coupling constants were observed for several key protons including $J_{HB,HC'}$ (8.0 Hz) and $J_{HD,HE'}$, $J_{HE,HF}$ (10.5 and 9.3 Hz, respectively), pointing to the expected favored chair conformation adopted by THP **22a**. A similar coupling constant trend was observed for the methyl ester THP **24**. Finally, the relative stereochemistry of THP **22b** was also confirmed by typical 1,2-diaxial coupling constants observed for $J_{HD,HE}$, $J_{HE,HF}$ (10.5 and 9.5 Hz, respectively) and also NOE enhancements ($H^F \rightarrow H^{B,B'}$). In the case of THPs, the newly generated stereocenter external to the ring is assigned on the basis of ample precedent from the TMAL and previous syntheses of THFs.

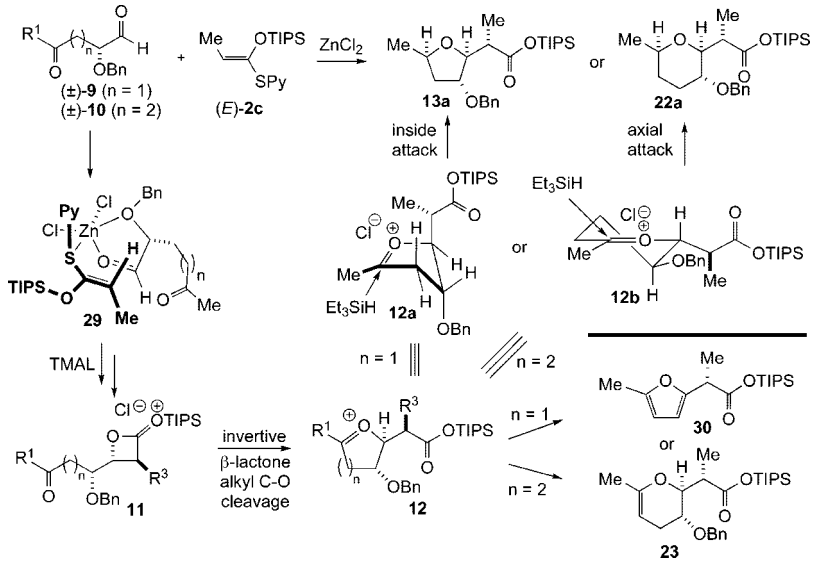
A plausible mechanism for the synthesis of both THFs and THPs can be rationalized based on the formation of silylated β-lactone **11** from a boat-like transition state arrangement **29** derived from a chelation-controlled TMAL process (Scheme 12, enantiomeric series shown which simplifies drawing of transition state arrangements).[11c,d,g] Upon invertive alkyl C−O cleavage of the silylated β-lactone **11** by the pendant ketone, oxocarbenium intermediate **12** is formed and adopts the favored

(30) α-Benzyloxy-ϵ-ketoaldehyde (±)-**26** was prepared in an analogous fashion as α-benzyloxy-δ-ketoaldehyde (±)-**10**. See the Supporting Information for details.

(31) The relative stereochemistry of other THFs reported herein followed similar trends; see the Supporting Information for details.

(32) Calculations (MM2) lend support to the proposal that the envelope conformations displayed in Table 4 are low energy conformations.

SCHEME 12. Mechanistic Proposals for the Cascade, Three-Component Synthesis of Tetrahydrofurans and Tetrahydropyrans



envelope or half-chair conformation. In the case of THFs (n = 1), envelope conformation **12a** is favored as a result of through-space stabilization of the oxocarbenium by the pseudoaxial benzyloxy substituent.[17a,b] THF **13a** is obtained via inside attack of Et_3SiH on the favored envelope conformation **12a**. In the case of THPs (n = 2), nucleophilic addition proceeds through the stereoelectronically favored half-chair conformation **12b** via axial attack.[18] Isolation of byproduct such as furan **30** or DHP **23** is rationalized by E1 elimination via α-deprotonation of the oxocarbenium likely by the pyridyl moiety of ketene acetal (*E*)-**2c**. Excess $ZnCl_2$ would be expected to deactivate the pyridyl nitrogen and thereby greatly lower the rate of elimination leading to increased yields of THF **13a** and THP **22a**. Isolation of DHP **23** provides evidence for a corresponding dihydrofuran (not isolated or shown), which undergoes further elimination, driven by aromaticity, to provide furan **30**.

Conclusions

The development of a diastereoselective, three-component cascade sequence involving the TMAL process is described and provides an expedient route to tetrahydrofurans and tetrahydropyrans from simple ketoaldehydes, thiopyridyl ketene acetals, and silyl nucleophiles. This complexity-building process provides further evidence for silylated β-lactone intermediates in the TMAL process and provides further impetus to explore different nucleophiles to trap this intermediate and access additional products from these versatile intermediates. The described process incorporates the TMAL process and Mead's reductive cyclization of isolated keto-β-lactones. The stereochemical outcome of this process is consistent with observed selectivities of the TMAL process and both established and recently refined models for nucleophilic additions to 5- and 6-membered oxocarbenium ions. The utility of this method was demonstrated by a single-step synthesis of the tetrahydrofuran fragment of colopsinol B from a simple ketoaldehyde. This methodology should find application in the total synthesis of THF and THP-containing natural products and diversity-oriented synthesis. Studies in this direction are ongoing in our laboratories and will be reported in due course.

Experimental Section

Representative Procedure for the Swern Oxidation of Diols As Described for α-Benzyloxy-γ-ketoaldehyde (±)-9a. To a solution of oxalyl chloride (2.6 mL, 29.88 mmol) in CH_2Cl_2 (50 mL) was added DMSO (4.2 mL, 59.76 mmol) dropwise at −78 °C, and the mixture was stirred for 5 min. To this solution was added diol **16a** (1.57 g, 7.47 mmol) in CH_2Cl_2 (50 mL), and the solution was stirred for 15 min, at which time Et_3N (16.7 mL, 119.52 mmol) was added and the resulting solution stirred for 2 h at −78 °C. The reaction was quenched with pH 7 buffer, and the mixture was stirred vigorously for 30 min and allowed to warm to 23 °C. The mixture was diluted with ether (250 mL), separated from the aqueous layer, washed with water (3 × 50 mL) and brine (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/ethyl acetate 75:25) delivered ketoaldehyde (±)-**9a** (1.28 g, 83%) as a pale yellow oil: R_f = 0.46 (hexanes/ethyl acetate 30:70); IR (thin film) 3029, 2719, 1715, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.84 (dd, J = 6.6, 17.4 Hz, 1H), 2.91 (dd, J = 4.8, 17.4 Hz, 1H), 4.26 (ddd, J = 0.9, 4.8, 6.6 Hz, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.73 (d, J = 11.7 Hz, 1H), 7.30−7.39 (m, 5H), 9.78 (d, J = 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.1, 44.3, 73.0, 79.3, 127.9 (2), 128.0, 128.4 (2), 137.1, 202.4, 204.5; ESI-HRMS calcd for $C_{12}H_{14}O_3Na$ [M + Na] 229.0841, found 229.0860.

Representative Procedure for the Tandem, Three-Component Synthesis of α-Benzyloxy-γ-ketoaldehydes, Thiopyridyl Ketene Acetals, and Silyl Nucleophiles As Described for Tetrahydrofuran 19a. $ZnCl_2$ (423 mg, 3.10 mmol) was freshly fused at ~0.5 mmHg and subsequently cooled to ambient temperature. The ketene acetal (*E*)-**2c** (301 mg, 0.93 mmol) was added as a solution in CH_2Cl_2 (5 mL) and stirred for 4 h at 23 °C. The heterogeneous mixture was cooled to 0 °C, Et_3SiH (6.3 mL, 38.80 mmol) and α-benzyloxy-γ-ketoaldehyde (±)-**9a** (160 mg, 0.78 mmol) in CH_2Cl_2 (5 mL) were added sequentially, and the reaction was stirred for 12 h at 0 °C. The reaction was quenched with pH 7 buffer, stirred vigorously for 30 min, poured over Celite with additional CH_2Cl_2, and dried with Na_2SO_4. Crude ^1H NMR (300 MHz) analysis revealed a 6.2:1 ratio of a single diastereomer (>19:1) of THF to furan silyl esters. Upon concentration under reduced pressure, the residue was dissolved in CH_2Cl_2 (20 mL). The resulting solution was treated with DIBAlH (830 μL, 4.66 mmol) at −78 °C, warmed to 0 °C quickly, and stirred for 6 h. The reaction quenched with MeOH (5 mL) at 0 °C *dropwise*, treated with

Rochelle's salt (10 mL), and stirred vigorously for 12 h. The resulting suspension was poured over Celite and washed with ether (200 mL). The combined organic solution was washed with satd aq NH_4Cl (2 × 20 mL), water (2 × 20 mL), and brine (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by gradient flash column chromatography (hexanes/ethyl acetate 85:15 to 80:20) delivered THF **19a** (104 mg, 54%) as a colorless oil and furan **20a** as a pale yellow oil. Characterization data for THF **19a**: $R_f = 0.56$ (hexanes/ethyl acetate 60:40); IR (thin film) 3443, 1096, 1058 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, $J = 7.0$ Hz, 3H), 1.27 (d, $J = 6.0$ Hz, 3H), 1.54 (ddd, $J = 7.0$, 10.0, 13.0 Hz, 1H), 1.95−2.03 (m, 1H), 2.11 (ddd, $J = 2.0$, 5.5, 13.0 Hz, 1H), 3.58 (dd, $J = 6.5$, 11.0 Hz, 1H), 3.64 (dd, $J = 4.5$, 11.0 Hz, 1H), 3.93 (dd, $J = 4.0$, 4.5 Hz, 1H), 3.98 (ddd, $J = 2.0$, 4.0, 7.0 Hz, 1H), 4.16 (ddq, $J = 5.5$, 6.0, 10.0 Hz, 1H), 4.45 (d, $J = 12.0$ Hz, 1H), 4.55 (d, $J = 12.0$ Hz, 1H), 7.29−7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4, 20.4, 37.8, 40.4, 66.6, 71.6, 74.5, 81.6, 87.9, 127.96 (3), 128.00 (2), 138.0; ESI-HRMS calcd for $C_{15}H_{22}O_3Li$ [M + Li] 251.1647, found 251.1686. Partial characterization data for furan **20a**: $R_f = 0.75$ (hexanes/ethyl acetate 60:40); ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, $J = 6.9$ Hz, 3H), 1.57−1.61 (m, 1H), 2.27 (d, $J = 0.9$ Hz, 3H), 2.99 (app sext, $J = 6.6$, 1H), 3.71 (dd, $J = 5.7$, 6.3 Hz, 1H), 5.88−5.89 (m, 1H), 5.97−5.98 (m, 1H).

Representative Procedure for the Tandem, Three-Component Synthesis of α-Benzyloxy-δ-ketoaldehydes, Thiopyridyl Ketene Acetals, and Silyl Nucleophiles As Described for Tetrahydropyran 22a. $ZnCl_2$ (203 mg, 1.49 mmol) was freshly fused at ~0.5 mmHg and subsequently cooled to ambient temperature. The ketene acetal (*E*)-**2c** (289 mg, 0.89 mmol) was added as a solution in CH_2Cl_2 (5 mL) and stirred for 4 h at 23 °C. The heterogeneous mixture was cooled to 0 °C, Et_3SiH (241 μL, 1.48 mmol) and α-benzyloxy-δ-ketoaldehyde (±)-**10** (164 mg, 0.74 mmol) in CH_2Cl_2 (5 mL) were added sequentially, and the reaction mixture was subsequently warmed from 0 to 23 °C over 24 h. The reaction was quenched with pH 7 buffer, stirred vigorously for 30 min, poured over Celite with additional CH_2Cl_2, and dried with Na_2SO_4. Crude ^1H NMR (500 MHz) analysis revealed a 20:1 ratio of THP **22a** (dr 16:1) to DHP **23** (dr >19:1). Purification by flash column chromatography (hexanes/ethyl acetate 98:2) delivered THP **22a** (243 mg, 75%) as a pale yellow oil: $R_f = 0.56$ (hexanes/ethyl acetate 90:10); IR (thin film) 3029, 1717, 1088, 745, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, $J = 7.0$ Hz, 3H), 1.07 (d, $J = 6.0$ Hz, 3H), 1.09 (d, $J = 7.0$ Hz, 9H), 1.10 (d, $J = 7.5$ Hz, 9H), 1.20−1.32 (m, 1H), 1.31 (qq, $J = 7.0$, 7.5 Hz, 1H), 1.42−1.52 (m, 1H), 1.68−1.74 (m, 1H), 2.26−2.32 (m, 1H), 3.00 (dq, $J = 2.8$, 7.0 Hz, 1H), 3.24 (ddd, $J = 4.5$, 9.3, 10.5 Hz, 1H), 3.43 (ddq, $J = 2.0$, 6.0, 8.0 Hz, 1H), 3.86 (dd, $J = 2.8$, 9.3 Hz, 1H), 4.44 (d, $J = 11.8$ Hz, 1H), 4.66 (d, $J = 11.8$ Hz, 1H), 7.28−7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.3, 12.2(3), 18.0(3), 18.1(3), 21.4, 29.3, 32.9, 41.4, 70.4, 73.76, 73.85, 81.1, 127.9, 128.1(2), 128.6(2), 138.5, 175.4; ESI-HRMS calcd for $C_{25}H_{42}O_4SiLi$ [M + Li] 441.3012, found 441.3014.

Keto-β-lactone 27 was prepared according to the representative procedure for the tandem, three-component synthesis of THPs using $ZnCl_2$ (136 mg, 0.50 mmol), ketene acetal (*E*)-**2c** (194 mg, 0.60 mmol), Et_3SiH (162 μL, 1.00 mmol), and α-benzyloxy-ϵ-ketoaldehyde (±)-**26** (117 mg, 0.45 mmol) in CH_2Cl_2 (10 mL) and warmed from 0 to 23 °C over 18 h. Aliquot ^1H NMR (500 MHz) analysis revealed keto-β-lactone **27** (>19:1) as the only detectable product. The reaction was gently warmed to 40 °C for 8 h, but no further reaction was observed. Representative workup and crude ^1H NMR (500 MHz) analysis also revealed keto-β-lactone **27** (>19:1) as the only detectable product. Purification by flash column chromatography (hexanes/ethyl acetate 80:20) delivered keto-β-lactone **27** (102 mg, 70%) as a pale yellow oil: $R_f = 0.46$ (hexanes/ethyl acetate 60:40); IR (thin film) 3029, 1826, 1714, 1119, 739, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (d, $J = 7.5$ Hz, 3H), 1.45−1.80 (m, 4H), 2.44 (t, $J = 7.0$ Hz, 2H), 3.38 (dq, $J = 4.0$, 7.5 Hz, 1H), 3.58 (ddd, $J = 4.5$, 6.5, 7.5 Hz, 1H), 4.22 (dd, $J = 4.0$, 6.5 Hz, 1H), 4.63 (d, $J = 11.5$ Hz, 1H), 4.74 (d, $J = 11.5$ Hz, 1H), 7.29−7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 19.3, 29.6, 30.0, 43.1, 48.2, 72.9, 78.5, 81.2, 127.9, 128.0(2), 128.5(2), 138.0, 171.4, 208.4; ESI-HRMS calcd for $C_{17}H_{24}O_4Li$ [M + Li] 297.1678, found 297.1683.

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Supporting Information Available: Experimental details and characterization data for thiopyridyl ketene acetal **2b**, β-chlorosilyl ester **4b**, α-benzyloxy-γ-ketoaldehydes (±)-**9**, **10**, and (±)-**26**, tetrahydrofurans **19a**−**m** and **21b**,**c**, furans **20a**−**g**, tetrahydropyrans **22a**, **b**, dihydropyran **23**, methyl ester **24**, *p*-bromobenzoate **25**, and keto-β-lactone **27**. Key NOE enhancements for selected tetrahydrofurans and single-crystal X-ray data for the *p*-bromobenzoate derived from THF **19a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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