JOC Article

Diastereoselective Synthesis of Tetrahydrofurans via Mead Reductive Cyclization of Keto-β-Lactones Derived from the Tandem Mukaiyama Aldol Lactonization (TMAL) Process

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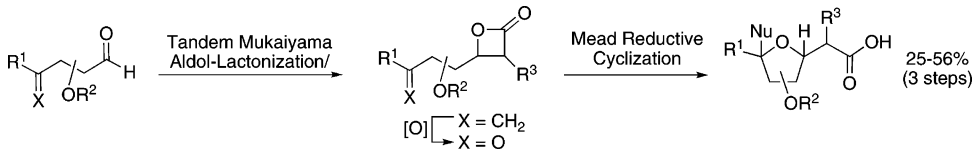

The development of a diastereoselective, three-step strategy for the construction of substituted tetrahydrofurans from alkenyl aldehydes based on the tandem Mukaiyama aldol-lactonization process and Mead reductive cyclization of keto β-lactones is reported. Stereochemical outcomes of the TMAL process are consistent with models established for Lewis acid-mediated additions to α-benzyloxy and β-silyloxy aldehydes while reductions of the five-membered oxocarbenium ions are consistent with Woerpel's models. Further rationalization for observed high diastereoselectivity in reductions of α-silyloxy 5-membered oxocarbenium ions based on stereoelectronic effects are posited. A diagnostic trend for coupling constants of γ-benzyloxy β-lactones was observed that should enable assignment of the relative configuration of these systems.

Introduction

Tetrahydrofurans (THFs) are common heterocyclic motifs in natural products, and thus, many routes have been developed to access these moieties.[1] These approaches can be divided into three major synthetic strategies (Figure 1). In one strategy, an oxygen nucleophile displaces, adds to, or opens an activated group (G) such as a leaving group (e.g., mesylate),[2] an olefin (e.g., iodoetherification),[3] or a strained ring (e.g., epoxide)[4] to form a new C−O bond (Type I). In another strategy, a nucleophile adds to an oxocarbenium intermediate and a new C−C or C−H bond is formed (Type II).[5] Finally, several miscellaneous strategies have been developed[1] including ring contractions of various six-membered rings such as tetrahydropyrans[6] and δ-lactones.[7]

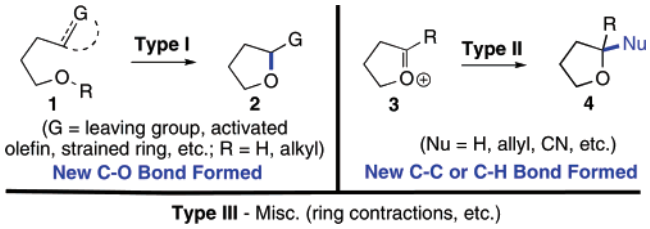

FIGURE 1. General Routes to Tetrahydrofurans.

Some of the most elegant and efficient approaches to THFs fall into the last category (Type III). Overman developed the Prins-pinacol route to THFs[8] that has been applied to *trans*-kumausyne and other members of the *Laurencia* family of marine natural products,[9] as well as (−)-citreoviral[10] and

(1) For reviews on the synthesis of THFs, see: (a) Kang, J. E.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348. (b) Norcross, R.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. (c) Harmange, J.-C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711. (d) Boivin, T. *Tetrahedron* **1987**, *43*, 3309.

(2) (a) Buchanan, J. G.; Dunn, A. D.; Edgar, A. R. *J. Chem. Soc., Perkin 1* **1974**, 1943. (b) Buchanan, J. G.; Dunn, A. D.; Edgar, A. R. *J. Chem. Soc., Perkin 1* **1975**, 1191.

(3) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.

(4) Chamberlin previously reported a similar route to THFs as Mead, but utilizing epoxides instead of β-lactones: (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.

(5) Ogawa, T.; Pernet, A. G.; Hanessian, S. *Tetrahedron Lett.* **1973**, *37*, 3543.

(6) Michael, P.; Ting, P. C.; Bartlett, P. A. *J. Org. Chem.* **1985**, *50*, 2416.

(7) Mantell, S. J.; Ford, P. S.; Watkin, D. J.; Fleet, G. W. J.; Brown, D. *Tetrahedron Lett.* **1992**, *33*, 4503.

(8) For initial disclosure, see: Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748. For a Perspective, see: Pennington, L. D.; Overman, L. E. *J. Org. Chem.* **2003**, *68*, 7143.

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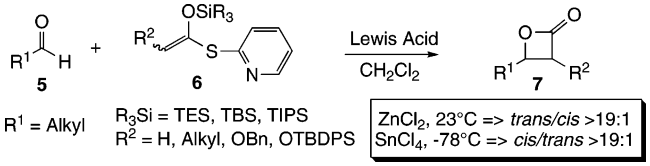
briarellin E.[11] Roush and Micalizio[12] refined and expanded the [3+2] annulation of aldehydes and allylsilanes toward THFs first reported by Panek.[13] This strategy had been applied to pectenotoxin II,[14] amphidinolide F,[15] asimicin,[16] (+)-bullatacin,[17] angelmicin B,[18] and haterumalide ND.[19] Lee developed a radical cyclization approach to THFs[20] and utilized this method in the total synthesis of pamamycin 607,[21] (+)-methyl nonactate,[22] kumausallene,[23] and kumausyne.[24] Herein, we report a hybrid of Type I and Type II strategies that involves a Mead reductive cyclization of keto-β-lactones prepared by the tandem Mukaiyama aldol-lactonization (TMAL) process.

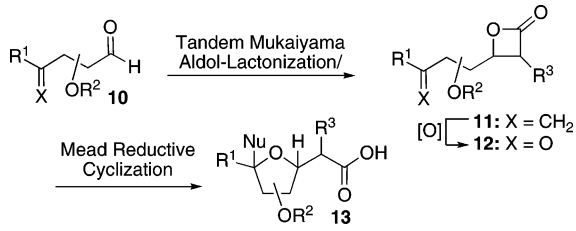
β-Lactones continue to gain prominence as versatile intermediates in synthesis,[25] to be found as integral components in bioactive natural products,[26] and to demonstrate their utility as enzyme inhibitors with therapeutic potential.[27] We previously reported stereoselective routes to both *cis*[28] and *trans*[29] β-lactones via tandem Mukaiyama aldol-lactonization (TMAL) processes employing substrate control (Scheme 1).[28,29] This methodology was applied to total syntheses of (−)-panclicin D,[27a] tetrahydrolipstatin/orlistat,[27b] okinonellin B,[27c] and brefeldin A.[27d] Mead previously demonstrated the utility of simple keto-β-lactones **8** for the synthesis of THFs **9** by a Lewis acid-mediated, reductive cyclization process (Scheme 2).[30] Building on these precedents, we envisioned a highly diastereoselective synthesis of substituted tetrahydrofurans by combining the TMAL process and Mead reductive cyclization of substituted keto-β-lactones (Scheme 3).

SCHEME 1. Tandem Mukaiyama Aldol-Lactonization (TMAL) Process

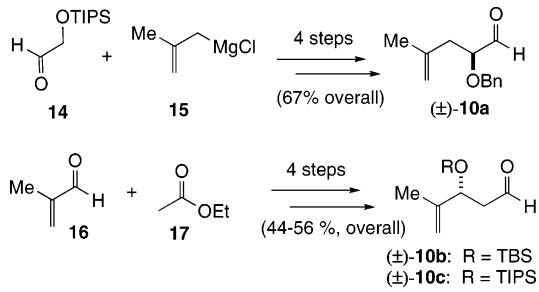


SCHEME 2. Mead Reductive Cyclization toward Tetrahydrofurans

SCHEME 3. Three-Step Strategy toward Tetrahydrofurans



SCHEME 4. Synthesis of Aldehydes (±)-10a−c

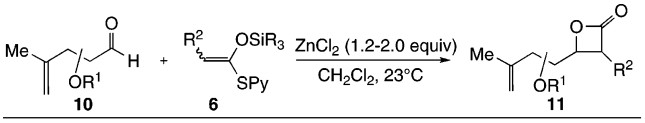


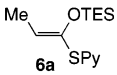
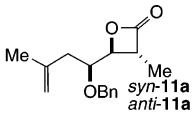
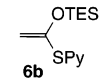
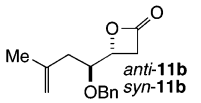
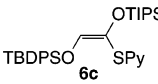
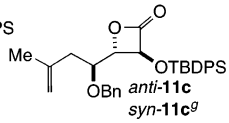
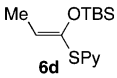
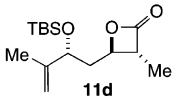
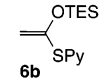
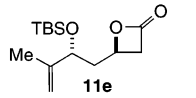
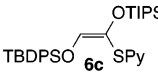
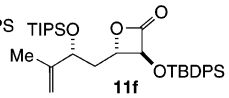
Results and Discussion

Synthesis of Keto-β-Lactones 12a-f via the Tandem Mukaiyama Aldol Lactonization. The required aldehydes (±)-**10a−c**, possessing both α- and β-oxygenation, were prepared by standard procedures (Scheme 4).[31] Application of the TMAL process to α-benzyloxy aldehyde (±)-**10a** employing propionate ketene acetal **6a** proceeded with high diastereoselectivity to give β-lactone **11a** based on chelation control (Table 1, entry 1). However, acetate ketene acetal **6b** gave low diastereoselectivity as expected with only a slight preference for the Felkin-Ahn-derived β-lactone *anti*-**11b** (Table 1, entry 2). Both of these TMAL reactions proceeded in comparable yield and diastereoselectivity at 0 °C under slightly prolonged reaction times. The sterically demanding, oxygenated ketene acetal **6c** delivered moderate yield of *anti*-**11c** after prolonged reaction times and proceeded with moderate diastereoselectivity (Table 1, entry 3). In the case of β-silyloxy aldehydes (±)-**10b−c**, β-lactones **11d−f** were obtained with moderate diastereoselectivity and the

(9) (a) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378. (b) Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468.
(10) Hanaki, N.; Link, J. T.; MacMillan, D. W. C.; Overman, L. E.; Trankle, W. G.; Wurster, J. A. *Org. Lett.* **2000**, *2*, 223.
(11) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650.
(12) (a) Roush, W. R.; Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41*, 9413. (b) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461.
(13) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868.
(14) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949.
(15) Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3865.
(16) Tinsley, J. M.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 10818.
(17) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R-A. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245.
(18) Lambert, W. T.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5501.
(19) Hoye, T. R.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 6950.
(20) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831.
(21) (a) Lee, E.; Jeong, E. J.; Kang, E. J.; Sung, L, T.; Hong, S. K. *J. Am. Chem. Soc.* **2001**, *123*, 10131. (b) Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K.; Lee, E. *J. Am. Chem. Soc.* **2002**, *124*, 14655.
(22) Lee, E.; Choi, S. J. *Org. Lett.* **1999**, *1*, 1127.
(23) Lee, E.; Yoo, S-K.; Choo, H.; Song, H. Y. *Tetrahedron Lett.* **1998**, *39*, 317.
(24) Lee, E.; Yoo, S-K.; Cho, Y-S.; Cheon, H-S.; Chong, Y. H. *Tetrahedron Lett.* **1997**, *38*, 7757.
(25) (a) Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729. (b) Wang, Y.; Tennyson, R. L.; Romo, D. *Heterocycles* **2004**, *64*, 605. For selected recent examples, see: (c) Donohoe, T. J.; Sintim, H. O.; Sisangia, L.; Harling, J. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 2293. (d) Getzle, Y. D. Y. L.; Kundnani, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2004**, *126*, 6842. (e) Calter, M. A.; Tretyak, O. A.; Flaschenriem, C. *Org. Lett.* **2005**, *7*, 1809. (f) Mitchell, T. A.; Romo, D. *Heterocycles* **2005**, *66*, 627. (g) Shen, X.; Wasmuth, A. S.; Zhao, J.; Zhu, C.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 7438. (h) Henry-Riyad, H.; Lee, C.; Purohit, V. C.; Romo, D. *Org. Lett.* **2006**, *8*, 4363. (i) Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 1717.
(26) Lowe, C.; Vederas, J. C. *Org. Prep. Proced. Int.* **1995**, *27*, 305.
(27) (a) Yang, H. W.; Zhao, C.; Romo, D. *Tetrahedron* **1997**, *53*, 16471. (b) Ma, G.; Zancanella, M.; Oyola, Y.; Richardson, R. D.; Smith, J. W.; Romo, D. *Org. Lett.* **2006**, *8*, 4497. (c) Schmitz, W. D.; Messerschmidt, B.; Romo, D. *J. Org. Chem.* **1998**, *63*, 2058. (d) Wang, Y.; Romo, D. *Org. Lett.* **2002**, *4*, 3231.
(28) Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* **1999**, *1*, 1197.
(29) Yang, H. W.; Romo, D.; *J. Org. Chem.* **1997**, *62*, 4.
(30) Mead, K. T.; Pillai, S. K. *Tetrahedron Lett.* **1993**, *34*, 6997.
(31) See Supporting Information for details.

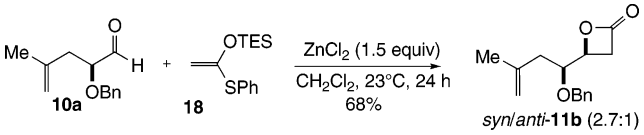
TABLE 1. Alkenyl β-Lactones 11a−f via the TMAL Process from Aldehydes (±)-10a−c



entry	aldehyde	ketene acetal	alkenyl-β-lactone[a]	time[b]	% yield[c]	dr[d]
1	**10a**	 **6a** *E*:*Z* (4:1)	 *syn*-**11a** *anti*-**11a**	14 h	83	>19:1[e]
2	**10a**	 **6b**	 *anti*-**11b** *syn*-**11b**	9 h	80	1.5:1[e]
3	**10a**	 **6c** *Z*:*E* (>19:1)	 *anti*-**11c** *syn*-**11c**[g]	12 d	56[f]	4:1[e]
4	**10b**	 **6d** *E*:*Z* (>19:1)	 **11d**	28 h	59	9:1
5	**10b**	 **6b**	 **11e**	20 h	69[f]	2:1
6	**10c**	 **6c** *Z*:*E* (>19:1)	 **11f**	10 d	75	5:1

[a] With the exception of *syn*-**11c**, only trans β-lactones were produced and the major diastereomer is displayed. [b] Entries 1−2 proceeded efficiently at 0 °C with increased reaction times and delivered comparable yield and diastereoselectivity. [c] Refers to isolated, purified yield (SiO_2) of both diastereomers. [d] Refers to relative stereochemistry and was determined by analysis of crude reaction mixture by ^{1}H NMR (300 MHz). [e] Diastereomers were separable by flash column chromatography. [f] This yield includes the subsequent ozonolysis step. [g] The minor diastereomer is tentatively assigned as a *cis*-β-lactone arising from chelation control based on coupling constant analysis (see Table 2).

SCHEME 5. Reversal of Relative Stereochemistry of Alkenyl-β-Lactone 11b via the TMAL Process with Thiophenyl Ketene Acetal 18



stereochemical outcome is consistent with Evans' model[32] and our previous studies[27] (Table 1, entries 4 and 6). Once again, acetate ketene acetal **6b** gave low diastereoselectivity as expected (Table 1, entry 5). Our previous studies suggested that use of thiophenyl acetate ketene acetal **18** with α-benzyloxy aldehyde (±)-**10a** may lead to a reversal of selectivity toward the chelation controlled adduct, which could be attributed to greater possibility for chelation control due to the monodentate thiophenyl ligand.[33] Indeed, this reversal was observed for α-unsubstituted-β-lactones **11b**, albeit in diminished ratio (Scheme 5).

Ozonolysis of alkenyl-β-lactones **11** proceeded smoothly to deliver the required keto-β-lactones **12** for reductive cyclization

(32) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

SCHEME 6. Synthesis of Keto-β-Lactones 12a-f via Ozonolysis

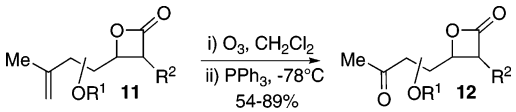
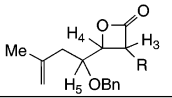
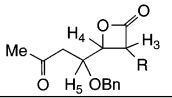


TABLE 2. Stereochemical Assignment of γ-Benzyloxy-β-lactones 11a−c and 12a−c Based on Coupling Constants

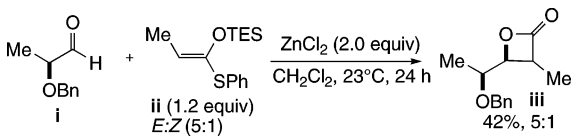
entry		$J_{4,5}$ (Hz)[a]	entry		$J_{4,5}$ (Hz)[a]
1	*syn*-**11a**	6.0	7	*syn*-**12a**	5.1
2	*anti*-**11a**[b]	3.0	8	*anti*-**12a**	NA[c]
3	*anti*-**11b**	2.7	9	*anti*-**12b**	3.3
4	*syn*-**11b**	5.1	10	*syn*-**12b**	4.5
5	*anti*-**11c**[b]	3.0	11	*anti*-**12c**	3.6
6	*syn*-**11c**[b]	5.7	12	*syn*-**12c**	6.0

[a] Determined by analysis of chromatographically pure β-lactones by ^{1}H NMR (300 MHz). [b] Minor diastereomers were carried directly to ozonolysis step and thus not fully characterized. [c] Not available. This keto-β-lactone was not prepared.

(Scheme 6). The use of PPh_3 to reduce the ozonides proved to be more efficient, leading to fewer byproducts compared to dimethyl sulfide and therefore simplified purification. Due to some instability noted for keto-β-lactones **12**, they were typically rapidly purified and used immediately in subsequent Mead reductive cyclizations.

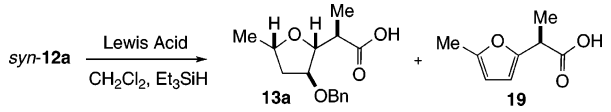
Stereochemical Assignment of β-Lactones 11−12. With the exception of β-lactones **11c**, bearing a bulky TBDPS group, stereochemical assignment of β-lactones **11a−f** obtained via the TMAL process corresponded to previous reports and were subsequently confirmed by NOE analysis of the corresponding THFs **13a−f** (*vide infra*).[31] However, the γ-benzyloxy-β-lactones **11a−c** and **12a−c** displayed a significant trend in coupling constants that may be a predictive tool for assignment of relative (i.e., *syn* vs *anti*) stereochemistry of these systems (Table 2). It is well-established that the internal stereochemistry (i.e., *cis* vs *trans*) of β-lactones can be assigned based on coupling constant analysis, and this is observed for β-lactones **11−12** (*cis*: $J_{3,4} = 5.7-6.0$ Hz; *trans*: $J_{3,4} = 3.3-4.5$ Hz).[34]

(33) Zhao, C. Ph.D. Thesis, Texas A&M University, 1999.



(34) Abraham, R. J. *J. Chem. Soc. B* **1968**, 173.

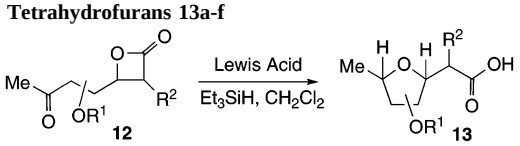
TABLE 3. Optimization of the Reductive Cyclization of Keto-β-Lactone *syn*-12a



entry	Lewis Acid	conc. (M)[a]	method[b]	Et_3SiH (equiv)	ratio THF **13a**/ furan **19**[c]	% yield[d]
1	$TiCl_4$	0.05	A	1.2	1/5	ND
2	$BF_3{\cdot}OEt_2$	0.05	B	1.2	1/1	ND
3	TESOTf	0.05	B	1.2	2/1	60
4	TESOTf	0.01	C	1.2	10/1	68
5	TESOTf	0.01	C	20.0	68/1	67
6	TESOTf	0.01	C	0	0/1	28 (98)[e]

[a] Refers to the final concentration of keto-β-lactone in CH_2Cl_2. [b] Lewis acid (1.2 equiv) was added to a solution of keto-β-lactone and Et_3SiH in CH_2Cl_2 at −78 °C. Method A: $TiCl_4$ in CH_2Cl_2 (1.0 M) was added down the side of the flask and stirred for 4 h at −78 °C. Method B: Neat Lewis acid was added dropwise at −78 °C, quickly warmed to 0 °C, and stirred for 4 h. Method C: Lewis acid in CH_2Cl_2 (0.03 M) was added down the side of the flask and allowed to warm to 0 °C over 6 h. [c] Ratio determined by crude ^1H NMR (500 MHz). [d] Refers to isolated yield of inseparable mixture of THF and furan. [e] Significant loss of the furan occurred during purification leading to diminished yields. However, estimated yield based on crude weight and ^1H NMR analysis indicated nearly quantitative conversion.

TABLE 4. Mead Reductive Cyclization of Keto-β-Lactones 12 toward Tetrahydrofurans 13a-f



entry	keto-β-lactone	Lewis Acid	tetrahydrofuran	% yield[a]	dr[b]
1	*anti*-**12b** (>19:1)	TESOTf[c]	*anti*-**13b**	82	14:1
2	*syn*-**12b** (>19:1)	TESOTf[c]	*syn*-**13b**	78	>19:1
3	*anti*-**12c** (18:1)	$BF_3{\bullet}OEt_2$[d]	**13c**	51(35)[f]	18:1
4	**12d** (9:1)	$TiCl_4$[e]	**13d**	84	9:1
5	**12e** (2:1)	$TiCl_4$[e]	**13e**	68	2:1
6	**12f** (5:1)	$TiCl_4$[e]	**13f**	55	5:1

[a] Isolated yields of the mixture of diastereomers. [b] Determined by analysis of crude reaction mixtures by ^1H NMR (500 MHz). [c] TESOTf in CH_2Cl_2 (0.03 M solution) was added to a solution of keto-β-lactone and Et_3SiH (20 equiv) in CH_2Cl_2 at −78 °C and allowed to warm to 0 °C over 5 h. [d] $BF_3{\bullet}OEt_2$ in CH_2Cl_2 (0.03 M solution) was added to a solution of keto-β-lactone and Et_3SiH (20 equiv) in CH_2Cl_2 at −78 °C and allowed to warm to 0 °C over 5 h. This reaction was then stirred for 3 days at 0−10 °C. [e] $TiCl_4$ in CH_2Cl_2 (1.0 M) was added to a solution of keto-β-lactone and Et_3SiH (20 equiv) in CH_2Cl_2 for 4 h at −78 °C. [f] Yield in parentheses refers to recovered keto-β-lactone **12c**.

However, to the best of our knowledge, the determination of relative stereochemistry of these systems has not previously been based solely on coupling constant analysis. In the case of γ-benzyloxy-β-lactones **11a**−**c** and **12a**−**c**, the coupling constants for *syn* ($J_{4,5}$ = 4.5−6.0 Hz) and *anti* ($J_{4,5}$ = 2.7−3.6 Hz) diastereomers followed a clear trend that is also consistent with our previous studies.[27] This is likely due to the conformational rigidity of these systems resulting from torsional strain.[35] Although subsequent NOE data for stereochemical assignment of THF **13c** was inconclusive, a tentative assignment of the precursor β-lactones *anti*-**11c** and *anti*-**12c** based on this diagnostic coupling constant trend is plausible.

Optimization of Mead Reductive Cyclization. Initial studies of the reductive cyclization of keto-β-lactone *syn*-**12a** employing conditions reported by Mead with $TiCl_4$ or $BF_3{\bullet}OEt_2$ as Lewis acid led to the desired THF **13a** along with significant quantities of an unexpected byproduct, furan **19** (Table 3, entries 1−2). Mead found that silyl triflates also promoted cyclization of keto β-lactones to THFs.[36] When triethylsilyl triflate (TESOTf) was added dropwise at −78 °C and then warmed quickly to 0 °C, the ratio of THF to furan did not improve significantly, but this provided the desired THF **13a** as the major product (Table 3, entry 3). After extensive experimentation, we found that when TESOTf was added down the side of the flask at −78 °C ("precooled") as a dilute solution in CH_2Cl_2, and the reaction was allowed to warm to 0 °C slowly over 6 h; this provided the desired THF **13a** in 68% yield with only 6% of furan **19** (Table 3, entry 4). Further improvements resulted when a large excess of Et_3SiH (20.0 equiv) was employed and THF **13a** was isolated in 68% yield as a single diastereomer with only trace amounts of furan **19** (Table 3, entry 5). Finally, a control experiment revealed that furan **19** was the only product formed in the absence of Et_3SiH (Table 3, entry 6). Indeed, furan byproducts have been observed previously during reductions of 5-membered oxocarbenium ions.[37]

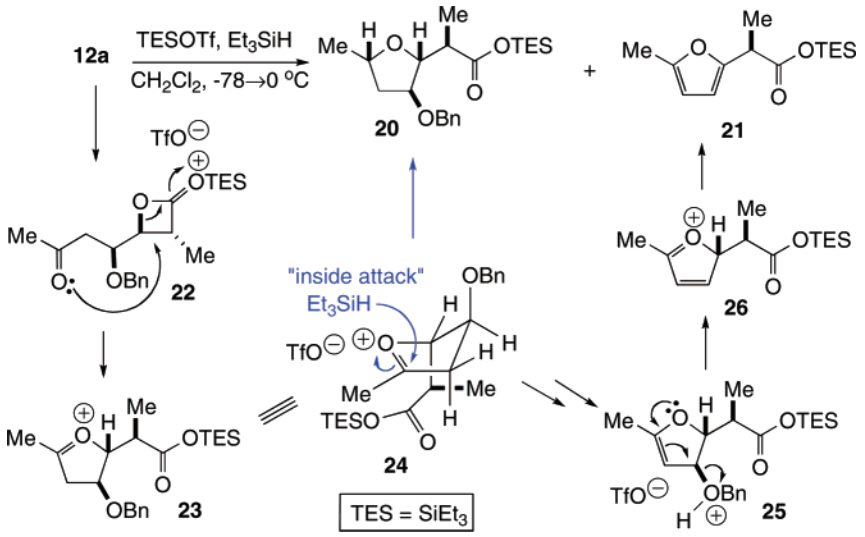
Scope of Mead Reductive Cyclization. Using the optimized conditions, various γ-benzyloxy-keto-β-lactones **12** were converted to THFs **13** with efficient transfer of stereochemistry and only trace quantities of furan were observed (Table 4, entries 1−2). A possible stereoreinforcing effect is operative with *anti*- and *syn*-β-lactones **12b** (dr, 14:1 vs 19:1, respectively), which may be due to a developing 1,3-diaxial interaction of the oxocarbenium intermediate (*cf.* **24**, Scheme 7) leading to greater selectivity for "inside attack." In the case of keto-β-lactone **12c**, TESOTf delivered a complex mixture of products, whereas $BF_3{\bullet}OEt_2$ provided a cleaner, albeit slower, reaction to provide THF **13c** (Table 4, entry 3). In the case of δ-silyloxy-keto-β-lactones **12d**−**f**, there was less concern of furan formation based on our proposed mechanism (*vide infra*). Thus, the strong Lewis

(35) Analysis of molecular models for these γ-benzyloxy-β-lactones suggests that there should be a conformational preference due to unfavorable gauche interactions and cancellation of dipoles.

(36) White, D.; Zemribo, R.; Mead, K. T. *Tetrahedron Lett.* **1997**, *38*, 2223.

(37) In the course of the total synthesis of (−)-azaspiracid, a similar byproduct was observed: Evans, D. A.; Kvaerno, L.; Mulder, J. A.; Raymer, B.; Dunn, T. B.; Beauchemin, A.; Olhava, E.; Juhl, M.; Kagechika, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4693. Similar furans were obtained from the corresponding dihydrofurans: Katagiri, N.; Tabei, N.; Atsuumi, S.; Haneda, T.; Kato, T. *Chem. Pharm. Bull.* **1985**, *33*, 102.

SCHEME 7. Model for Diastereoselectivity in Reductive Cyclization with γ-Benzyloxy-β-Lactones Based on Woerpel's Model and a Proposed Mechanism for Formation of Furan 21

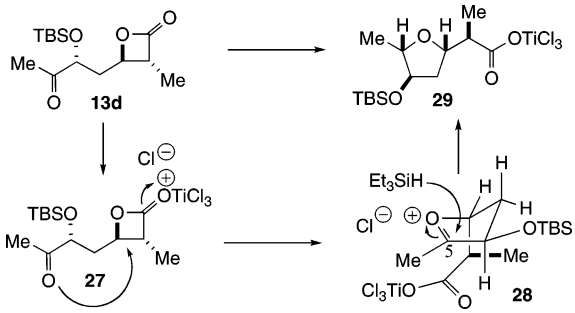


acid $TiCl_4$ previously utilized by Mead promoted the reductive cyclization in moderate to good yields with excellent levels of stereochemical transfer using only 1.2 equiv of Et_3SiH (Table 4, entries 4−6). The relative stereochemistry of all ring stereocenters of THFs **13a**−**f** was confirmed by NOE analysis observed for multiple protons of the THF rings,[31] which also confirmed invertive ring cleavage during cyclization. The relative stereochemistry between the α-stereocenter and the THF rings is premised on stereochemical invertive cyclization of the *trans*-substituted (vs *cis*) β-lactones, which in turn is based on coupling constants. An exception was THF **13c** for which NOE data were inconclusive, and thus, relative stereochemistry was tentatively assigned based on coupling constants (cf. Table 2). Thus, the stereochemical outcome in each case is consistent with stereochemical invertive alkyl C−O ring cleavage by the pendant ketone followed by reduction of the oxocarbenium to the tetrahydrofuran as predicted by the Woerpel model.[38]

Mechanistic Rationale for Mead Reductive Cyclization. Regarding the mechanism of this process for benzyloxy-substituted systems, the reductive cyclization leading to THF **20** and furan **21** is presented as an example (Scheme 7). Ketone cleavage of a silyl activated β-lactone intermediate **22** via alkyl C−O scission in an S_N2 fashion delivers the oxocarbenium **23** in line with previous proposals by Mead.[30] The stereoelectronically favored envelope conformation **24** places the benzyloxy substituent in the pseudoaxial orientation as proposed by Woerpel and reduction occurs via "inside attack" of Et_3SiH.[38] Alternatively, a competing pathway leading to furan **21** could involve elimination leading to enol ether **25** which then undergoes acid-mediated elimination of benzyl alcohol to provide oxocarbenium **26**. This is followed by rapid aromatization to furan **21** by loss of a second proton, which may occur upon reaction workup.

In the case of δ-silyloxy-keto-β-lactones **12d**−**f**, based on Woerpel's findings with related benzyloxy systems which provided diastereomeric ratios of 5−6:1, we expected only moderate selectivity for the reduction of oxocarbeniums **28** (Scheme 8).[38b] However, we found that the diastereoselectivity

SCHEME 8. Model for Diastereoselectivity in Reductive Cyclization with δ-Silyloxy-β-lactones Based on Woerpel's Model



of the reduction was >19:1 since the diastereomeric ratio of the THFs **13d**−**f** matched well with the diastereomeric ratio of the substrate β-lactones **12d**−**f**, respectively. There appear to be several factors governing this increase in selectivity. Woerpel has shown that hydrogen atoms prefer to reside in the pseudo-axial position adjacent to an oxocarbenium in both five and six-membered rings for favorable hyperconjugation between the C−H bond and the 2p orbital of the oxocarbenium.[38b,39] Less studied by Woerpel were the effects of α-silyloxy oxocarbeniums and both steric and electronic effects could influence the stereochemical outcome. The decreased electron density of the oxygen due to the silyloxy moiety[40] leads to lower electron donation compared to a benzyloxy substituent. Thus, compared to the hydrogen atom, the pseudequatorial orientation of the silyloxy substituent is preferred to a greater extent. Steric considerations would also dictate that the more bulky silyloxy group reside in the pseudoequatorial position to a greater degree than a benzyloxy substituent. Additionally, developing gauche interactions between the C5 methyl and the pseudoequatorial silyloxy substituent also favors "inside attack" of Et_3SiH (*cf.* **28**, Scheme 8). These effects combine with the preferred "inside

(38) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208. (b) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879.

(39) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521.

(40) (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. (b) Kahn, S. D.; Keck, G. E.; Henre, W. J. *Tetrahedron Lett.* **1987**, *28*, 279. (c) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281. (d) Shambayati, S.; Blake, J.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697.

attack" leading to high diastereoselectivity for α-silyloxy substituted-oxocarbenium ions.

In summary, we developed a three-step strategy for the diastereoselective synthesis of THFs from alkenyl aldehydes proceeding through β-lactone intermediates. The strategy involves the TMAL process and Mead's reductive cyclization of keto-β-lactones. The stereoselectivity of the latter process is rationalized by Woerpel's model for "inside attack" of oxocarbeniums. An increase in selectivity for certain α-silyloxy oxocarbenium ions was observed and is rationalized based on stereoelectronic effects building on Woerpel's findings. The stereoselectivity of the TMAL process for α-benzyloxy and β-silyloxy aldehydes with several thiopyridyl ketene acetals was defined including a reversal in selectivity when a thiophenyl ketene acetal was employed. A correlation between relative stereochemistry and coupling constants was observed that provides a predictive method for the stereochemical assignment of γ-benzyloxy-β-lactones. This strategy should prove useful for the synthesis of tetrahydrofurans found in natural products and the results of these studies will be reported in due course.

Experimental Section

Representative Procedure for the TMAL Reaction as Described for γ-Benzyloxy-alkenyl-β-lactone *syn*-11a. $ZnCl_2$ (273 mg, 2.00 mmol) was freshly fused at ~0.5 mmHg and subsequently cooled to ambient temperature. Ketene acetal **6a** (384 mg, 1.20 mmol) and then aldehyde (±)-**10a** (204 mg, 1.00 mmol) were each added as a solution in 5 mL of CH_2Cl_2 (final concentration of aldehyde in CH_2Cl_2 ~0.1 M). This suspension was stirred for 14 h at 23 °C and then quenched with pH 7 buffer, stirred vigorously for 30 min, and poured over Celite with additional CH_2Cl_2. After concentration under reduced pressure, the residue was redissolved in CH_2Cl_2 (final concentration of β-lactone in CH_2Cl_2 ~0.15 M) and treated with $CuBr_2$ (357 mg, 1.60 mmol). After stirring for 2.5 h, the crude β-lactone *syn*-**11a** was again poured over Celite and washed with ether (200 mL). The combined organic layers were washed with 10% aq K_2CO_3 (3 × 50 mL), H_2O (2 × 50 mL), and brine (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to deliver crude β-lactone *syn*-**11a** as a single diastereomer (>19:1) as judged by analysis of crude ^{1}H NMR (300 MHz). Purification by flash column chromatography (hexanes/ethyl acetate 95:5) delivered pure *syn*-**11a** (216 mg, 83%) as a colorless oil: R_f = 0.42 (80:20 hexanes/ethyl acetate); IR (thin film) 3071, 3031, 1827, 1119 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (d, J = 7.5 Hz, 3H), 1.78 (dd, J = 0.9, 1.2 Hz, 3H), 2.25 (ddd, J = 0.9, 6.3, 14.1 Hz, 1H), 2.40 (ddd, J = 1.2, 6.9, 14.1 Hz, 1H), 3.43 (dq, J = 4.2, 7.5 Hz, 1H), 3.74 (ddd, J = 6.0, 6.3, 6.9 Hz, 1H), 4.22 (dd, J = 4.2, 6.0 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 4.83−4.86 (m, 1H), 4.88−4.91 (m, 1H), 7.29−7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 22.7, 38.7, 47.5, 72.5, 76.8, 80.5, 114.2, 127.78, 127.82(2), 128.4(2), 137.9, 140.9, 171.5; ESI-HRMS calcd for $C_{16}H_{20}O_3Li$ [M + Li] 267.1572, found 267.1591.

Representative Procedure for Mead Reductive Cyclization of γ-Benzyloxy-keto-β-lactones as Described for THF 13a (Procedure A). To a solution of γ-benzyloxy-keto-β-lactone *syn*-**12a** (262 mg, 1.00 mmol) in CH_2Cl_2 (50 mL) was added Et_3SiH (3.2 mL, 20.0 mmol) slowly at −78 °C followed by TESOTf (274 μL, 1.20 mmol in 40 mL CH_2Cl_2) down the side of the flask at −78 °C over 10 min to ensure cooling. Upon addition of 10 mL of CH_2Cl_2 to rinse down any remaining TESOTf, the solution was allowed to warm to 0 °C slowly over 5 h, quenched with pH 4 buffer (50 mL), and warmed to 23 °C with vigorous stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to deliver crude THF **13a** as a single diastereomer (>19:1) with only trace amounts of furan **19** (68:1) as judged by analysis of crude ^{1}H NMR (500 MHz). Gradient flash column chromatography (hexanes/ethyl acetate 80:20 to 60:40) delivered THF **13a** (178 mg, 67%) as a colorless oil. A center fraction from the column was used for characterization: R_f = 0.46 (60:40 hexanes/ethyl acetate); IR (thin film) 3500−2300, 1708, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (d, J = 7.0 Hz, 3H), 1.29 (d, J = 6.0 Hz, 3H), 1.54 (ddd, J = 6.5, 10.5, 13.5 Hz, 1H), 2.11 (ddd, J = 1.0, 5.0, 13.5 Hz, 1H), 2.68 (dq, J = 6.0, 7.0 Hz, 1H), 4.01 (ddd, J = 1.0, 3.0, 6.5 Hz, 1H), 4.12 (dd, J = 3.0, 6.0 Hz, 1H), 4.21−4.28 (m, 1H), 4.49 (d, J = 11.5 Hz, 1H), 4.52 (d, J = 11.5 Hz, 1H), 7.27−7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.8, 20.5, 40.1, 42.8, 71.4, 75.3, 81.9, 85.4, 127.88(2), 127.95, 128.6(2), 138.1, 178.7; ESI-HRMS calcd for $C_{15}H_{19}O_4$ [M − H] 263.1283, found 263.1271.

Representative Procedure for Mead Reductive Cyclization of γ-Benzyloxy-keto-β-lactones as Described for THF 13c (Procedure B). To a solution of γ-benzyloxy-keto-β-lactone **12c** (199 mg, 0.40 mmol) in CH_2Cl_2 (20 mL) was added Et_3SiH (1.3 mL, 8.00 mmol) slowly at −78 °C followed by BF_3•OEt_2 (61 μL, 0.48 mmol in 16 mL CH_2Cl_2) down the side of the flask at −78 °C over 10 min to ensure cooling. Upon addition of 10 mL of CH_2Cl_2 to rinse down any remaining BF_3•OEt_2, the solution was allowed to warm to 0 °C slowly over 5 h and then stirred at 0−10 °C for 3 days. The reaction was quenched with pH 4 buffer (50 mL) and warmed to 23 °C with vigorous stirring. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to deliver crude THF **13c** as a mixture of diastereomers (~18:1, ~50% conversion) as judged by analysis of crude ^{1}H NMR (500 MHz). Gradient flash column chromatography (hexanes/ethyl acetate 90:10 to 60:40) delivered recovered **12c** (70 mg, 35%, dr 18:1) as a pale-yellow oil and THF **13c** (102 mg, 51%, dr 18:1) as a pale yellow oil. A center fraction of THF **13c** from the column was used for characterization. Characterization data for the major (anti) diastereomer **13c**: R_f = 0.30 (70:30 hexanes/ethyl acetate); IR (thin film) 3437−2404, 1731, 1108 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 9H), 1.27 (d, J = 6.0 Hz, 3H), 1.48 (ddd, J = 6.5, 11.0, 13.5 Hz, 1H), 2.03 (dd, J = 5.0, 13.5 Hz, 1H), 4.07 (dd, J = 2.5, 6.5 Hz, 1H), 4.16 (dd, J = 2.5, 4.5 Hz, 1H), 4.18−4.24 (m, 1H), 4.32 (s, 2H), 4.43 (d, J = 4.5 Hz, 1H), 7.23−7.70 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.7, 20.0, 27.2(3), 40.3, 71.5, 72.8, 75.8, 81.0, 86.1, 127.8(2), 127.9, 128.00(2), 128.04(2), 128.6(2), 130.36, 130.40, 132.3, 132.8, 136.0(2), 136.2(2), 138.1, 173.0; ESI-HRMS calcd for $C_{30}H_{35}O_5Si$ [M − H] 503.2254, found 503.2241.

Representative Procedure for Mead Reductive Cyclization of δ-Silyloxy-keto-β-lactones as Described for THF 13d (Procedure C). To a solution of δ-silyloxy-keto-β-lactone **12d** (202 mg, 0.71 mmol) in CH_2Cl_2 (15 mL) was added Et_3SiH (137 μL, 0.85 mmol) dropwise at −78 °C followed by $TiCl_4$ (846 μL, 1.0 M in CH_2Cl_2) down the side of the flask at −78 °C over 5 min to ensure cooling. Upon addition of 5 mL of CH_2Cl_2 to rinse down any remaining $TiCl_4$, the solution was stirred at −78 °C for 3 h, quenched with pH 7 buffer (50 mL), and warmed to 23 °C with vigorous stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated under reduced pressure to deliver crude THF **13d** as a mixture of diastereomers (9:1) as judged by analysis of crude ^{1}H NMR (500 MHz). Gradient flash column chromatography (hexanes/ethyl acetate 90:10 to 60:40) delivered THF **13d** (170 mg, 84%, dr 9:1) as a pale-yellow oil: Characterization data for the major (*syn*) diastereomer **13d**: R_f 0.49 (hexanes/ethyl acetate 60:40); IR (thin film) 3475−2460, 1707, 1250 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ −0.04 (s, 6H), 0.90 (s, 9H), 1.07 (d, J = 6.5 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H), 1.74 (ddd, J = 6.5, 8.5, 13.0 Hz, 1H), 1.78 (ddd, J = 3.5, 6.5, 13.0 Hz, 1H), 2.47 (dq, J = 7.0, 7.0 Hz, 1H), 3.67 (ddd, J = 3.5, 4.0, 6.5 Hz, 1H), 3.79 (dq, J = 4.0, 6.5 1H), 4.24 (ddd, J

= 3.5, 7.0, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ −4.8, −4.6, 13.3, 18.1, 19.1, 25.9(3), 39.0, 45.0, 78.3, 78.7, 82.5, 180.6; ESI-HRMS calcd for $C_{14}H_{27}O_4Si$ [M− H] 287.1679, found 287.1611.

Acknowledgment. We thank the NIH (GM-069784) and the Welch Foundation (A-1280) for generous support of this work. We thank Dr. Ziad Moussa (TAMU) for helpful discussions and Dr. Shane Tichy of the Laboratory for Biological Mass Spectrometry supported by the Office of the Vice President for Research (TAMU) for acquiring mass spectral data and helpful discussions.

Supporting Information Available: Experimental details and characterization data (including ^{1}H and ^{13}C NMR spectra) for aldehydes (±)-**10a**−**c** and their precursors, alkenyl-β-lactones **11a**−**b**, **11d**, and **11f**, keto-β-lactones **12a**−**f**, tetrahydrofurans **13a**−**f** (with NOE data), and furan **19**. A comparison of key coupling constants for THFs **13a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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