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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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Abstract

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 developed¹ including ring contractions of various six-membered rings such as tetrahydropyrans⁶ and δ -lactones.⁷

Some of the most elegant and efficient approaches to THFs fall into the last category (Type III). Overman developed the Prins-pinacol route to THFs⁸ that has been applied to *trans*-kumausyne and other members of the *Laurencia* family of marine natural products,⁹ as well as (-)-citroviral¹⁰ and briarellin E.¹¹ Roush and Micalizio¹² 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 THFs²⁰ 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 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).

Results and Discussion

Synthesis of Keto- β -Lactones **12a–f** *via* the Tandem Mukaiyama Aldol Lactonization

The required aldehydes ($\pm$)-**10a–c**, possessing both α - and β -oxygenation, were prepared in racemic fashion by standard procedures (Scheme 4).³¹ Application of the TMAL process to α -benzyloxy aldehyde ($\pm$)-**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). It is worth noting that 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 ($\pm$)-**10b–c**, β -lactones **11d–f** were obtained with moderate diastereoselectivity and the stereochemical outcome is consistent with Evans' model³² and our previous studies²⁷ (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 ($\pm$)-**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 (Scheme 6). The use of PPh₃ to reduce the ozonides proved to be more efficient leading to fewer by-products 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 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* ($J_{4,5} = 2.7\text{--}3.6$ 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 the direct 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 $\text{BF}_3\cdot\text{OEt}_2$ as Lewis acid led to the desired THF **13a** along with significant quantities of an unexpected by-product, 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 ("pre-cooled") 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 62% 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 67% 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 by-products 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). It is interesting to note that 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, while $\text{BF}_3\cdot\text{OEt}_2$ 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 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 equivalents 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 $\text{S}_{\text{N}}2$ 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 Et₃SiH.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 work-up.

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 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 pseudoaxial 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 moiety⁴⁰ leads to lower electron donation compared to a benzyloxy substituent. Thus, compared to the hydrogen atom, the pseudoequatorial 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 Et₃SiH (*cf.* **28**, Scheme 8). These effects combine with the preferred “inside 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**

ZnCl₂ (273 mg, 2.00 mmol) was freshly fused at ~0.5 mm Hg and subsequently cooled to ambient temperature. Ketene acetal **6a** (384 mg, 1.20 mmol) and then aldehyde ($\pm$)-**10a** (204 mg, 1.00 mmol) were each added as a solution in 5 mL of CH₂Cl₂ (final concentration of aldehyde in CH₂Cl₂ ~0.1 M). This suspension was stirred for 14 h at 23 °C then quenched with pH 7 buffer, stirred vigorously for 30 min, and poured over Celite with additional CH₂Cl₂. After concentration under reduced pressure, the residue was redissolved in CH₂Cl₂ (final concentration of β -lactone in CH₂Cl₂ ~0.15 M) and treated with CuBr₂ (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 ^1H 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} ; ^1H 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 $\text{C}_{16}\text{H}_{20}\text{O}_3\text{Li}$ [$\text{M} + \text{Li}$] 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 ^1H 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} ; ^1H 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 $\text{C}_{15}\text{H}_{19}\text{O}_4$ [$\text{M} - \text{H}$] 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 $\text{BF}_3 \cdot \text{OEt}_2$ (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 $\text{BF}_3 \cdot \text{OEt}_2$, the solution was allowed to warm to 0°C slowly over 5 h, and then stirred at 0 – 10°C for 3 d. 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, concentrated under reduced pressure to deliver crude THF **13c** as a mixture of diastereomers (~18:1, ~50% conversion) as judged by analysis of crude ^1H 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} ; ^1H 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 $\text{C}_{30}\text{H}_{35}\text{O}_5\text{Si}$ [$\text{M} - \text{H}$] 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 ^1H 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} ; ^1H 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, $J = 4.0, 6.5$ Hz, 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 $\text{C}_{14}\text{H}_{27}\text{O}_4\text{Si}$ [$\text{M} - \text{H}$] 287.1679, found 287.1611.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
General Routes to Tetrahydrofurans

SCHEME 1.

Tandem Mukaiyama Aldol-Lactonization (TMAL) Process

SCHEME 2.

Mead Reductive Cyclization to Tetrahydrofurans

SCHEME 3.
Three-step Strategy Toward Tetrahydrofurans

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

SCHEME 5.

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

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

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**

SCHEME 8.

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

TABLE 1
Alkenyl β -Lactones **11a-f** via the TMAL Process from Aldehydes ($\pm$)-**10a-c**

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

^aWith 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 (SiO₂) of both diastereomers.
- ^d Refers to relative stereochemistry and was determined by analysis of crude reaction mixture by ¹H 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).

TABLE 2
Stereochemical Assignment of γ -benzyloxy- β -lactones **11a–c** and **12a–c**

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

^aDetermined by analysis of chromatographically pure β -lactones by ¹H NMR (300 MHz).

^bMinor diastereomers were carried directly to ozonolysis step and thus not fully characterized.

^cNot available.

This keto- β -lactone was not prepared.

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

entry	Lewis Acid	conc. (M) ^a	method ^b	Et ₃ SiH (equiv)	ratio THF 13a /furan 19 ^c	% yield ^d

1	TiCl ₄	0.05	A	1.2	1/5	ND
2	BF ₃ •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

^aRefers to the final concentration of keto- β -lactone in CH₂Cl₂.

^b1.2 equiv of Lewis acid was added to a solution of keto- β -lactone and Et₃SiH in CH₂Cl₂ at -78 °C. Method A: TiCl₄ in CH₂Cl₂ (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 CH₂Cl₂ (0.03 M) was added down the side of the flask and allowed to warm to 0 °C over 6 h.

^cRatio determined by crude ¹H NMR (500 MHz).

^dRefers to isolated yield of inseparable mixture of THF and furan.

^eSignificant 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 ^d	dr ^b
1	<i>anti</i> - 12b (>19:1)	TESOTf ^c	<i>anti</i> - 13b OBn	82	14:1
2	<i>syn</i> - 12b (>19:1)	TESOTf ^c	<i>syn</i> - 13b OBn	78	>19:1
3	<i>anti</i> - 12c (18:1)	BF ₃ •OEt ₂ ^d	<i>anti</i> - 13c OTBDPS	51(35) ^f	18:1
4	12d (9:1)	TiCl ₄ ^e	13c OBn	84	9:1
5	12e (2:1)	TiCl ₄ ^e	13d TBSO	68	2:1
6	12f (5:1)	TiCl ₄ ^e	13e TBSO	55	5:1
			13f TIPSO		

^a Isolated yields of the mixture of diastereomers.

^b Determined by analysis of crude reaction mixtures by ¹H NMR (500 MHz).

^c TESOTf in CH₂Cl₂ (0.03 M solution) was added to a solution of keto- β -lactone and Et₃SiH (20 equiv) in CH₂Cl₂ at -78 °C and allowed to warm to 0 °C over 5 h.

^d BF₃•OEt₂ (0.03 M solution) was added to a solution of keto- β -lactone and Et₃SiH (20 equiv) in CH₂Cl₂ at -78 °C and allowed to warm to 0 °C over 5 h. This reaction was then stirred for 3 d at 0–10 °C.

^e TiCl₄ in CH₂Cl₂ (1.0 M) was added to a solution of keto- β -lactone and Et₃SiH (20 equiv) in CH₂Cl₂ for 4 h at -78 °C.

^fYield in parentheses refers to recovered keto- β -lactone **12c**.