# Tandem Aldol-Cyclization Sequence for the Construction of Cyclic Ethers. The Formation of Substituted Tetrahydrofurans[1]

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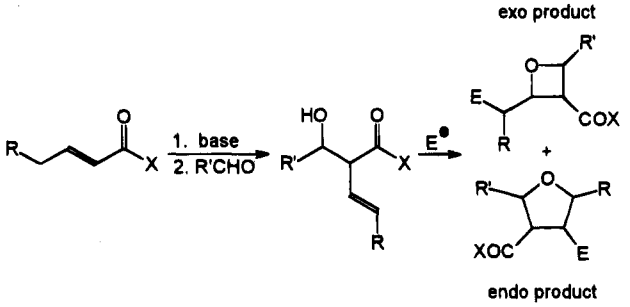
The application of a tandem deconjugative aldol-cyclization sequence for the construction of substituted tetrahydrofurans was examined. The aldol condensation of alkenoates proceeded with alkylation at the α-position to generate homoallylic alcohol moieties. These compounds could be induced to cyclize under the influence of iodine via an endo mode. The stereoselectivity for the cyclization occurred in good to excellent fashion. X-ray crystal structure analysis of three of the tetrahydrofurans established unambiguously the product stereochemistry. This was used to propose a transition structure for the cyclization which correctly predicts the observed product stereochemistry. By this method, virtually all the possible stereoisomers for the substituted tetrahydrofurans can be constructed by judicious choice of aldol product and/or olefin geometry.

## Introduction

There has been a recent resurgence in the synthesis of tetrahydrofurans through an electrophile-catalyzed cyclization of unsaturated alcohols.[2] While initial efforts in this area[3] examined the 5-*exo-trig* mode of ring closure, the more recent studies[2] have investigated the 5-*endo-trig* mode. The advantage of the endo mode of cyclization over the exo mode is that construction of the cyclic ether results in the introduction of functionality internal to the ring and not on pendent side chains. This attribute can be exploited in the synthesis of natural products that contain highly functionalized cyclic ethers, e.g., polyether antibiotics.[4] In the majority of cases studied, tetrahydrofurans have been the sole product isolated. However, the formation of oxetanes,[2a] by an exo mode of cyclization, has been reported. In the previous work,[2] rather elaborate, multistep sequences were required to assemble the desired cyclization precursor. We wished to develop a one-step approach to this compound with the ability to vary substituents and control relative and absolute sterochemistry.[5] With this goal in mind, we embarked upon the application of a tandem aldol-cyclization sequence for the synthesis of substituted cyclic ethers (see Scheme 1). We envisioned the sequence to occur as follows. The deconjugative aldol condensation[6] of crotyl derivatives with aldehydes or ketones would lead to an aldol product with a homoallylic substructure. This portion of the molecule could then undergo an electrophile-mediated cyclization. In principle, two potential reaction manifolds are possible. An exo-mode of cyclization would result in the formation of an oxetane, while an endo-mode of cyclization would result in a tetrahydrofuran. According to Baldwin's rules the exo product would be the predicted result; however, there are reports in the literature that show products derived from endo cyclizations are possible. We now wish to present our initial findings from our investigation of this aldol-cyclization sequence.

**Scheme 1**




## Results and Discussion

The deconjugative α-alkylation of crotyl systems has been studied[6] in simple systems, and we have expanded upon this work in our systems. Thus, treatment of ethyl crotonate **1** with LDA/HMPA at −78 °C resulted in formation of the dienolate which upon exposure to a carbonyl compound and quenching of the reaction at −78 °C with saturated $NH_4Cl$ solution resulted in isolation of the corresponding homoallylic alcohol ester **2**. Table 1 shows that the only product isolated was the one derived from α-alkylation. In those cases where diastereoisomers were generated, approximately a 1:1 mixture of aldols was observed.

With the homoallylic alcohols **2** in hand, we investigated the electrophile-mediated cyclization to form the cyclic ether. Two of the standard conditions for cyclization were examined ($I_2$, $NaHCO_3$, and PhSeCl). The use

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(1) Presented, in part, at the 33rd National Organic Chemistry Symposium, Montana State University, Bozeman, Montana, 1993, Abstract A-84.

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(4) (a) Robinson, J. A. *Prog. Chem. Org. Nat. Prod.* **1991**, *58*, 1. (b) *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982; Vols. 1–2. (c) Wierenga, W. *Total Synth. Nat. Prod.* **1981**, *4*, 263.

(5) Evans, D. A.; Sjogren, E. B.; Bartoli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957.

(6) (a) Rathke, M. W.; Sullivan, D. *Tetrahedron Lett.* **1972**, *4249*. (b) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1972**, 4249. (b) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433. (c) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163.

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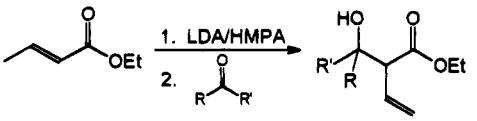
**Table 1. Products from the Aldol Step of Reaction Sequence**

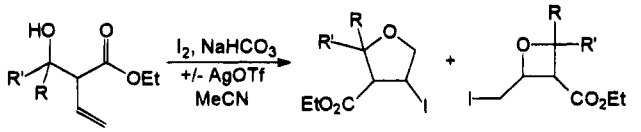



1 2

| entry | product (2) R, R′ | yield[a] (%) |
|---|---|---|
| 1 | **a**, Me, Me | 70 |
| 2 | **b**, $-(CH_2)_4-$ | 56 |
| 3 | **c**, $-(CH_2)_5-$ | 65 |
| 4 | **d**, Me, H | 91 (1:1)[b] |
| 5 | **e**, Ph, H | 88 (1.4:1)[b] |

[a] Based on isolated, chromatographically pure compound. [b] Ratio determined by $^1H$ NMR integration.

**Table 2. Products from the Electrophile-Mediated Cyclization Step of Sequence**




2 3 4

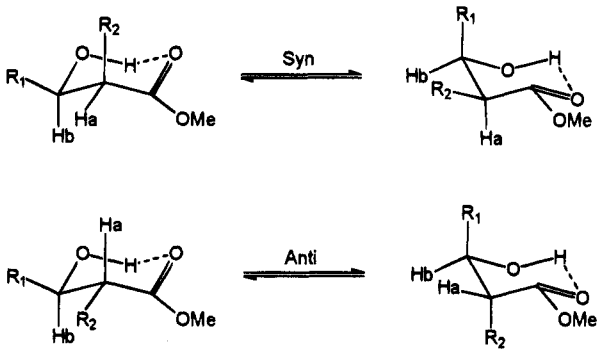
| | | products | | |
|---|---|---|---|---|
| entry | R, R′ | reaction condns | yield[a] (%) | ratio[b] (3:4) |
| 1 | Me, Me | −AgOTf | 81 | 1:1.7 |
| | | +AgOTf | 65 | 1:1.1 |
| 2 | $(CH_2)_4$ | −AgOTf | 61 | 1:1.5 |
| | | +AgOTf | 59 | 1.5:1 |
| 3 | $(CH_2)_5$ | −AgOTf | 81 | 1:3.8 |
| | | +AgOTf | 54 | 1:1.7 |
| 4 | Me, H | −AgOTf | 71 | 1.7:1 |
| | | +AgOTf | 65 | 1.7:1 |
| 5 | Ph, H | −AgOTf | 41 | irreproducible |
| | | +AgOTf | 34 | |

[a] Based on isolated, chromatographically pure compound. [b] Ratio determined by weight of isolated product after chromatography.

of silver triflate in conjunction with iodine was also investigated (see Table 2). Contrary to the previous results,[2] PhSeCl resulted in little if any product formation. In these systems, iodine appears to be the electrophile of choice. The use of iodine resulted in a reaction that did not appear to go to completion even after 3 days. Maximal product formation occurred after 24 h, and as a result reactions were routinely worked up after this time. The addition of silver triflate along with the iodine provided for a great rate enhancement. This resulted in complete reaction in 1-2 h.

As one can see from Table 2, a mixture of tetrahydrofuran **3** and oxetane **4** was obtained. Only one diastereomer was observed for Table 2, entries 1−3. This provided initial evidence that the electrophile-mediated cyclizations in these systems could proceed with excellent stereocontrol. For Table 2, entry 4, a 1:1 mixture of diastereomers was observed. This result is a consequence of the fact the aldol reaction afforded a mixture of *syn* and *anti* aldol products. The fact that only two isomers were formed provided further evidence for the control of stereoselectivity in the cyclization step. The relative stereochemistry of these diastereoisomers was not determined (*vide infra*). From Table 2, entry 5, it would appear that aromatic substituents are not compatible with this system at this position (*vide infra*). While the reactions with the phenyl-substituted system (Table 2, entry 5) proved to be very messy and irreproducible,

**Scheme 2**

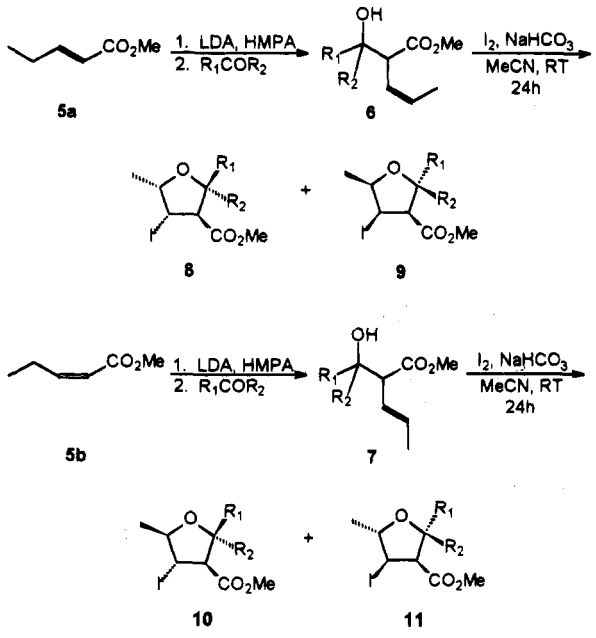



tetrahydrofuran **3** appeared to be the sole product. Two factors stand out from these results that may provide further insight into the mechanistic details of this cyclization reaction. First, the formation of oxetanes had not been observed in the reported examples for simple iodine-mediated cyclizations. Second, a trend, most notable in Table 2, entry 2, appears to indicate that in the absence of silver triflate 4-membered ring formation is favored, while in the presence of silver triflate 5-membered ring formation is favored. One could view this product distribution as follows. Without silver triflate the slow reaction rates tend to favor closure onto the more stable carbocation, secondary versus primary (4-membered over 5-membered), i.e., "pseudo-thermodynamic conditions", while in the presence of silver triflate, the faster reaction rates favor closure to the less strained ring system (5-membered over 4-membered), i.e., "pseudo-kinetic conditions". The potential for the interconversion of **4** to the more stable **3** under the reaction conditions exists. However, when **3** and **4** were individually subjected to the reaction conditions, iodine and silver triflate, recovered starting material was isolated; *i.e.*, no interconversion was witnessed. This dichotomy in product formation may be a reflection of greater carbocationic character in the intermediate, an indication of an asymmetric iodonium ion or a combination of both. Indeed, in a theoretical treatment of bromonium ion intermediates, a bromine asymmetrically disposed over the alkene was calculated to be the optimal geometry.[7] In the well-studied exo mode of cyclization,[3] both of these factors act in concert and could not be dissected apart. Our system has set these effects in direct competition and, in principle, would allow one to probe the nature of the iodonium intermediate.

On the basis of our and others'[2b-g] work, we believed that the placement of a methyl group on the olefinic end of a homoallylic alcohol would direct the 5-*endo-trig* cyclization toward the formation of 5-membered rings. The internal olefin would give rise to a selection of two secondary carbenium ions; therefore, one would predict closure to a 5-membered ring would be favored over closure to a 4-membered ring. In order to make use of our methodology, we required access to 2-pentenoic acid methyl ester (**5**). Since it is known that inversion of geometry of the olefin occurs in the deconjugative alkylation,[6] access to both the (*E*), **5a**,[8] and the (*Z*)-, **5b**,[9] forms of the ester were required in order to fully probe the

(7) Yamabe, S.; Minato, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3339.
(8) Prepared by condensing the anion of trimethyl phosphonoacetate with propanal.
(9) Prepared by diazomethane esterification of the corresponding acid which was prepared as described: Rappe, C. *Org. Synth.* **1973**, *53*, 123.

stereochemical effects of the olefin geometry on the cyclization step.




Formation of homoallylic alcohols **6** and **7** by deconjugative alkylation of **5** was carried out as described (*vide supra*). The products were obtained in 47–91% yields with the reactions of **5a** occurring in upper half of this range. The use of acetaldehyde and benzaldehyde resulted in the formation of *syn* and *anti* aldol products **6** and **7** in a roughly 1:1 ratio, and these compounds could be separated by chromatography.

It had been observed[10] that systems, such as these, adopt an intramolecular H-bonded form in nonpolar solvents (see Scheme 2). The resultant chair conformation allowed one to assign stereochemistry based on the magnitude of the vicinal coupling constants for the $H_a$–$H_b$ protons (syn isomer 0–4 Hz; anti isomer 6–12 Hz).

In their paper, Heathcock and co-workers[11] noted a problem with this method when other resonances overlapped with the ones of interest. As a result they investigated the use of $^{13}C$ NMR to rectify this problem. It was observed that the carbinol and methine carbons experienced an upfield shift for the *syn* isomer relative to the *anti* isomer and that this shift was smaller for the methine carbon. While the difference in the chemical shifts could be zero, in none of the examples was there an inversion of the shifts.

From an examination of Table 3 the observations of House[10] and Heathcock,[11] in general, are true but there are some caveats. While in the majority of cases, when the proton resonances are resolved, one can use the vicinal coupling constants to determine stereochemistry; however, the ranges of coupling constants are greater than had been noted.[10] Our results show that the *syn* isomer can have coupling constants as high as 8.0 Hz.[12] In all cases the *syn* isomer exhibited a coupling constant less than the *anti* isomer. When one examines our $^{13}C$ NMR resonances, we observe trends similar to those of Heathcock[11] for our aldol products when one notes the resonances for the carbinol carbons. The same cannot be said for the methine carbon resonances. For example, compounds **6d** and **7e** show an upfield shift of the *anti* isomer relative to the *syn* isomer; *i.e.*, for the methine carbon an inversion of the resonances is possible. Therefore, one should ideally have both isomers in order to compare values for unambiguous use this spectroscopic method.

With these compounds in hand, each was subjected to the cyclization reaction conditions, and the results for **6** are presented in Table 4 and the results for **7** are presented in Table 5. Appropriate control reactions were conducted to show that no product isomerization occurred under these reaction conditions and that olefin geometry was maintained during the reaction.

As one can see from the tables, tetrahydrofurans were the exclusive product isolated in good to excellent yields. The formation of oxetanes were ruled out using two methods. For three of the compounds, crystal structures were obtained and only showed tetrahydrofuran formation (see Figure 1). NMR data also proved to be useful. In addition to high field $^1H$ and $^{13}C$ NMR, HMQC spectra indicated, for example in **8a**, that the signal at $\delta$ 4.8 was bonded to a carbon with resonance of $\delta$ 30. If this had been the resonance for the ether methine hydrogen of the corresponding oxetane, then the carbon resonance for this

**Table 3. NMR Data for Selected Atoms of β-Hydroxy Esters**

| | syn diastereomer | | | anti diastereomer | | |
|---|---|---|---|---|---|---|
| | $^1H$ | $^{13}C$ (ppm) | | $^1H$ | $^{13}C$ (ppm) | |
| compd | $J_{ab}$ (Hz) | CH | COH | $J_{ab}$ (Hz) | CH | COH |
| 2d | 6.2 | 60.90 | 67.56 | 8.4 | 60.90 | 68.43 |
| 2e | 6.4 | 60.83 | 73.88 | 8.0 | 60.96 | 75.20 |
| 6d | 4.8 | 51.87 | 67.93 | 9.2 | 51.81 | 68.82 |
| 6e | 2.8 | 51.62 | 74.25 | 9.2 | 52.09 | 75.43 |
| 7d | 5.2 | 56.22 | 67.73 | 8.4 | 57.28 | 68.70 |
| 7e | 6.8 | 57.54 | 74.10 | 8.0 | 56.84 | 75.48 |

**Table 4. Product Distribution from Tandem Aldol-Cyclization Sequence with Ester 5a**

| entry | aldol product | yield[a] (%) | THF product | yield[a] (%) |
|---|---|---|---|---|
| 1 | **6a** | 77 | **8a**:**9a** (10:1) | 76 |
| 2 | **6b** | 64 | **8b**:**9b** (11:1) | 78 |
| 3 | **6c** | 60 | **8c**:**9c** (3.6:1) | 88 |
| 4 | *syn*-**6d** | 91 | *anti*-**8d**:*anti*-**9d** (42:1) | 76 |
| 5 | *anti*-**6d** | | *syn*-**8d**:*syn*-**9d** (12:1) | 68 |
| 6 | *syn*-**6e** | 85 | *anti*-**8e**:*anti*-**9e** (4.5:1) | 69 |
| 7 | *anti*-**6e** | | *syn*-**8e**:*syn*-**9e** (3.1:1) | 55 |

[a] Based on isolated, chromatographically pure compound.

**Table 5. Product Distribution from Tandem Aldol-Cyclization Sequence with Ester 5b**

| entry | aldol product | yield[a] (%) | THF product | yield[a] (%) |
|---|---|---|---|---|
| 1 | **7a** | 65 | **10a**:**11a** (16:1) | 94 |
| 2 | **7b** | 47 | **10b**:**11b** (3.2:1) | 89 |
| 3 | **7c** | 56 | **10c**:**11c** (3.3:1) | 89 |
| 4 | *syn*-**7d** | 50 | *anti*-**10d**[b] | 70 |
| 5 | *anti*-**7d** | | *syn*-**10d**[b] | 57 |
| 6 | *syn*-**7e** | 67 | *anti*-**10e**[b] | 85 |
| 7 | *anti*-**7e** | | *syn*-**10e**:*syn*-**11e** (7.2:1) | 79 |

[a] Based on isolated, chromatographically pure compound. [b] Only compound isolated.

(10) (a) Stiles, M.; Winkler, R.; Chang, Y.; Traynor, L. *J. Am. Chem. Soc.* **1964**, *86*, 3337. (b) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(11) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294. For a recent application of this method see: Martin, S. F.; Lee, W.-C. *Tetrahedron Lett.* **1993**, *34*, 2711.

(12) Galatsis, P. University of Guelph, unpublished results.

(13) Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Spectral Data for Structure Determination of Organic Compounds*, 2nd ed.; Springer-Verlag: New York, 1989.

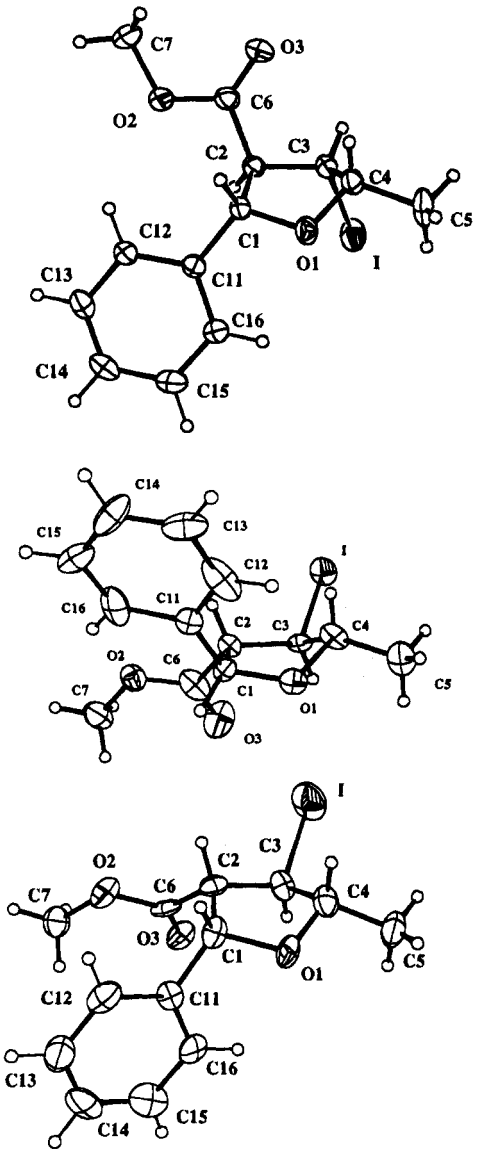
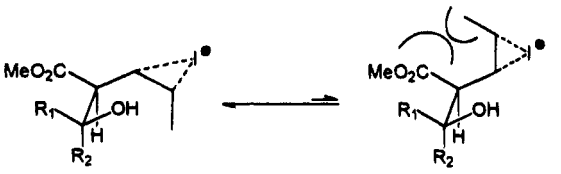


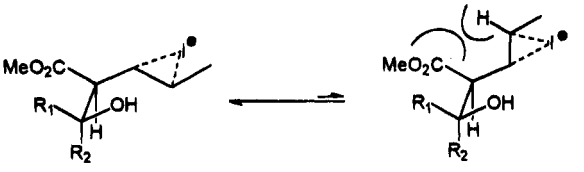

**Figure 1.** Ortep structures for tetrahydrofurans: *anti*-**8e** (top), *anti*-**10e** (middle), and *syn*-**10e** (bottom).

compound should have been on the order of $\delta$ 73.[13] Furthermore, we have shown that a shift of the methyl group to the internal position of the alkene favors exclusive formation of the oxetanes.[14] This would tend to support the idea that there is some degree of carbocationic character in the transition state for the cyclization reaction. These reactions exhibited good to excellent stereocontrol. Also in these systems, cyclization of the phenyl derivatives now occurs in good to excellent yield. In the previous system, which contained a terminal olefin, this cyclization was very problematic and could not be consistently observed. The relative stereochemistry of the products was determined from a combination of NOE measurements and a comparison of trends in the NMR data. The stereochemical assignments were unambiguously determined, in the cases *anti*-**8e**, *anti*-**10e**, and *syn*-**10e**, by X-ray crystallographic analysis (Figure 1). For the three compounds, the molecular dimensions are entirely in accord with accepted values and have been deposited.[15] In *anti*-**10e**, the unit cell contains four molecules in enantiomorphic pairs related by a crystallographic glide plane.




**12** **13**

With this data and what is known[2,3] about the cyclization reaction, one can propose a model that may be a good representation of the transition state. The fusion of this information is consistent with transition structures **12** and **14**. Structures **12** and **13** are the possible conformations for the transition state for products derived from aldol product **6**. The allylic strain depicted in **13** would destabilize this conformation relative to **12**. The observed stereochemistry is correctly predicted by structure **12**. For the products derived from aldol product **7**, the two possible transition structures are **14** and **15**. As in the previous analysis, the allylic strain in **15** would render **14** the more stable conformation. Again, as before, structure **14** correctly predicts the observed stereochemistry for this system.




**14** **15**

## Conclusions

In summary, we have shown the viability of a tandem aldol-cyclization sequence for the assembly of cyclic ethers with the ability to control substitution pattern. Furthermore, we have extended the utility of the tandem aldol-cyclization sequence for the construction of substituted tetrahydrofurans. By the appropriate choice of olefin geometry and/or aldol stereochemistry, one can selectively obtain virtually all the possible stereoisomers. The application of this methodology in chiral form, with a chiral auxiliary at the ester position, is currently in progress. Also, we have augmented the observations of House and Heathcock as to the use of NMR resonances in the determination of aldol stereochemistry.

## Experimental Section

**General Procedures and Materials.** Melting points were taken on a Fischer-Johns melting point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively, unless specified otherwise.

All solvents used for chromatography were distilled prior to use. Reactions were monitored by TLC using E. Merck precoated silica gel 60 F-250 (0.25 mm thickness) aluminum-backed plates. The plates were visualized by immersion in *p*-anisaldehyde solution and warming on a hotplate. E. Merck

(14) Galatsis, P.; Parks, D. J. *Tetrahedron Lett.*, in press.

(15) The author has deposited atomic coordinates for *anti*-**8e**, *anti*-**10e**, and *syn*-**10e** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

silica gel 60 (70–230 mesh) was used for column chromatography. All solvents were reagent grade, and anhydrous solvents were dried prior to use as follows: HMPA and $CH_2Cl_2$ was distilled from $CaH_2$, while ether and THF were distilled from benzophenone ketyl. Compounds obtained from commercial sources were used directly as received.

**General Procedure for Deconjugative Aldol Reactions.** To a solution of diisopropylamine (DIPA) (1.7 eqiv) in 10 mL of THF at 0 °C was added *n*-BuLi (1.5 equiv). After stirring for 15 min the reaction was cooled to −78 °C and HMPA (1.5 equiv) was added. This mixture was stirred for 30 min before adding a solution of the unsaturated ester in 4 mL of THF via cannula. The dienolate was allowed to form for 30 min, and then a solution of the electrophile in 4 mL of THF was added via cannula. The reaction was quenched after 30 min at −78 °C with 5 mL of saturated $NH_4Cl$ solution and warmed to rt, the aqueous phase was extracted three times with ether, the combined organic phases were then washed with brine, dried with anhydrous $Na_2SO_4$, and filtered, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography eluting with ethyl acetate/hexanes.

**Ethyl 2-(Hydroxy-2-propyl)-3-butenoate (2a).** The dienolate of ethyl crotonate (2.19 mmol, 0.25 g), generated from LDA (prepared from DIPA (3.72 mmol, 0.52 mL) and *n*-BuLi (3.29 mmol, 1.40 mL), 2.3 M solution in hexanes) and HMPA (3.29 mmol, 0.57 mL), was reacted with acetone (2.85 mmol, 0.21 mL) to afford the deconjugated aldol product in 70% yield (0.264 g): IR (film) 3474, 3082, 2979, 2937, 1721, 1637, 1462, 1379, 1325, 1171, 1032, 997, 933, 891, 631 $cm^{-1}$; $^1H$ NMR $\delta$ 5.94 (ddd, 1H, $J$ = 16.8, 10.4, 10.4 Hz), 5.23 (dd, 1H, $J$ = 10.0, 1.2 Hz), 5.18 (d, 1H, $J$ = 17.2 Hz), 4.17 (m, 2H), 3.29 (brs, 1H), 2.99 (d, 1H, $J$ = 9.2 Hz), 1.26 (t, 3H, $J$ = 7.2 Hz), 1.23 (s, 3H), 1.17 (s, 3H); $^{13}C$ NMR $\delta$ 173.67, 132.76, 119.80, 71.15, 60.84, 60.42, 28.60, 26.46, 14.08.

**Ethyl 2-(1-Hydroxy-1-cyclopentyl)-3-butenoate (2b).** The dienolate of ethyl crotonate (2.19 mmol, 0.25 g), generated from LDA (prepared from DIPA (3.72 mmol, 0.52 mL) and *n*-BuLi (3.29 mmol, 1.40 mL), 2.3 M solution in hexanes) and HMPA (3.29 mmol, 0.57 mL), was reacted with cyclopentanone (2.63 mmol, 0.23 mL) to afford the deconjugated aldol product in 56% yield (0.223 g): IR (film) 3521, 3084, 2963, 2908, 2875, 1715, 1640, 1454, 1371, 1330, 1182, 1099, 1037, 996, 921, 738, 650 $cm^{-1}$; $^1H$ NMR $\delta$ 6.01 (ddd, 1H, $J$ = 17.2, 10.4, 8.8 Hz), 5.23 (dd, 1H, $J$ = 10.4, 1.2 Hz), 5.20 (ddd, 1H, $J$ = 17.2, 1.2, 1.2 Hz), 4.19 (m, 2H), 3.24 (d, 1H, $J$ = 1.3 Hz), 3.06 (d, 1H, $J$ = 8.8 Hz), 1.83 (m, 2H), 1.70–1.50 (m, 6H), 1.28 (t, 3H, $J$ = 7.2 Hz); $^{13}C$ NMR $\delta$ 174.02, 132.98, 119.19, 82.14, 60.85, 58.82, 39.37, 37.32, 23.83, 23.66, 14.11.

**Ethyl 2-(1-Hydroxy-1-cyclohexyl)-3-butenoate (2c).** The dienolate of ethyl crotonate (2.19 mmol, 0.25 g), generated from LDA (prepared from DIPA (3.72 mmol, 0.52 mL) and *n*-BiLi (3.29 mmol, 1.40 mL), 2.3 M solution in hexanes) and HMPA (3.29 mmol, 0.57 mL), was reacted with cyclohexanone (2.41 mmol, 0.25 mL) to afford the deconjugated aldol product in 65% yield (0.303 g): IR (film) 3500, 3080, 2932, 2859, 1719, 1637, 1449, 1393, 1370, 1321, 1167, 1095, 1030, 982, 923, 850, 830, 670 $cm^{-1}$; $^1H$ NMR $\delta$ 5.98 (ddd, 1H, $J$ = 17.2, 9.2, 9.2 Hz), 5.25 (dd, 1H, $J$ = 10.0, 1.2 Hz), 5.20 (brd, 1H, $J$ = 17.2 Hz), 4.18 (m, 2H), 3.20 (brs, 1H), 3.06 (d, 1H, $J$ = 9.2 Hz), 1.75–1.40 (m, 10H), 1.28 (t, 3H, $J$ = 6.8 Hz); $^{13}C$ NMR $\delta$ 173.89, 132.38, 119.67, 71.88, 60.80, 59.28, 36.85, 34.56, 25.57, 21.88, 21.50, 14.12.

**Ethyl 2-(1-Hydroxy-1-ethyl)-3-butenoate (2d).** The dienolate of ethyl crotonate (6.57 mmol, 0.75 g), generated from LDA (prepared from DIPA (7.88 mmol, 1.10 mL) and *n*-BuLi (7.22 mmol, 2.89 mL), 2.5 M solution in hexanes) and HMPA (7.22 mmol, 1.26 mL), was reacted with acetaldehyde (9.20 mmol, 0.50 mL) to afford the deconjugated aldol product in 91% yield (0.947 g) as an inseparable 1:1 mixture of diastereomers: IR (film) 3443, 3082, 2979, 2935, 1723, 1639, 1454, 1372, 1273, 1177, 1104, 1030, 996, 627 $cm^{-1}$; $^1H$ NMR $\delta$ 5.94 (ddd, 1H, $J$ = 17.2, 10.4, 9.6 Hz), 5.83 (ddd, 1H, $J$ = 16.8, 10.4, 9.2 Hz), 5.32 (dd, 1H, $J$ = 10.4, 1.6 Hz), 5.26 (ddd, 1H, $J$ = 6.0, 1.2, 0.4 Hz), 5.23 (m, 1H), 5.21 (s, 1H), 4.26–4.14 (m, 4H), 4.09 (dq, 1H, $J$ = 6.4, 6.4 Hz), 4.07 (dq, 1H, $J$ = 6.4, 6.4 Hz), 3.03 (dd, 1H, $J$ = 8.4, 8.4 Hz), 3.00 (dd, 1H, $J$ = 9.2, 4.8 Hz), 2.74 (brs, 1H), 1.28 (t, 3H, $J$ = 7.2 Hz), 1.28 (t, 3H, $J$ = 7.2 Hz), 1.21 (d, 3H, $J$ = 6.0 Hz), 1.19 (d, 3H, $J$ = 6.0 Hz); $^{13}C$ NMR $\delta$ 173.13, 173.08, 132.80, 131.87, 120.41, 119.34, 68.44, 67.56, 60.90, 58.31, 57.23, 20.72, 20.00, 14.08.

**Ethyl 2-(1-Hydroxy-1-benzyl)-3-butenoate (2e).** The dienolate of ethyl crotonate (6.57 mmol, 0.75 g), generated from LDA (prepared from DIPA (7.88 mmol, 1.10 mL) and *n*-BiLi (7.22 mmol, 2.89 mL), 2.5 M solution in hexanes) and HMPA (7.22 mmol, 1.26 mL), was reacted with benzaldehyde (7.88 mmol, 0.74 mL) to afford the deconjugated aldol product in 88% yield (1.29 g) as an inseparable 1.4:1 mixture of diastereomers: IR (film) 3445, 3084, 3069, 3030, 2982, 2936, 1719, 1639, 1494, 1452, 1378, 1230, 1089, 1034, 925, 862, 763, 701, 633 $cm^{-1}$; $^1H$ NMR $\delta$ 7.38–7.22 (m, 10H), 5.96 (ddd, 1H, $J$ = 17.2, 10.4, 8.8 Hz), 5.68 (ddd, 1H, $J$ = 17.2, 10.0, 8.4 Hz), 5.25 (dd, 1H, $J$ = 10.0, 0.8 Hz), 5.16 (ddd, 1H, 17.2 0.8, 0.8 Hz), 5.06 (brd, 1H, $J$ = 10.0 Hz), 5.02 (dt, 1H, $J$ = 17.2, 1.2 Hz), 4.98 (d, 1H, $J$ = 6.8 Hz), 4.91 (d, 1H, $J$ = 8.0 Hz), 4.17 (q, 2H, $J$ = 7.2 Hz), 4.03 (q, 2H, $J$ = 6.8 Hz), 3.42 (t, 1H, $J$ = 8.0 Hz), 3.32 (dd, 1H, $J$ = 8.8, 6.0 Hz), 3.11 (brs, 1H), 3.04 (brs, 1H), 1.23 (t, 3H, $J$ = 7.2 Hz), 1.10 (t, 3H, $J$ = 7.2 Hz); $^{13}C$ NMR $\delta$ 172.85, 172.35, 141.14, 140.68, 132.19, 131.94, 128.24, 128.13, 127.89, 127.77, 126.60, 126.40, 120.36, 119.30, 75.20, 73.88, 60.96, 60.83, 58.29, 57.82, 14.02, 13.87.

**Methyl (Z)-2-(2-Hydroxy-2-propyl)-3-pentenoate (6a).** The dienolate of methyl (*E*)-pentenoate (2.63 mmol, 0.30 g), generated from LDA (prepared from DIPA (3.15 mmol, 0.44 mL) and *n*-BuLi (2.89 mmol, 1.15 mL), 2.5 M solution in hexanes) and HMPA (2.89 mmol, 0.50 mL), was reacted with acetone (3.68 mmol, 0.27 mL) to afford the deconjugated aldol product in 77% yield (0.349 g): IR (film) 3675–3190, 3032, 2980, 2953, 2886, 1728, 1440, 1379, 1330, 1249, 1198, 1159, 1040, 1020, 962, 915, 835, 815, 769, 732, 693 $cm^{-1}$; $^1H$ NMR $\delta$ 5.77 (dq, 1H, $J$ = 11.2, 6.8 Hz), 5.60 (m, 1H), 3.72 (s, 3H), 3.41 (d, 1H, $J$ = 10.0 Hz), 3.33 (s, 1H), 1.69 (dd, 3H, $J$ = 6.8, 1.6 Hz), 1.26 (s, 3H), 1.19 (s, 3H); $^{13}C$ NMR $\delta$ 174.59, 128.91, 124.55, 71.78, 53.06, 51.82, 28.66, 26.19, 13.21.

**Methyl (Z)-2-(2-Hydroxyl-2-cyclopentyl)-3-pentenoate (6b).** The dienolate of methyl (*E*)-pentenoate (2.63 mmol, 0.30 g), generated from LDA (prepared from DIPA (3.15 mmol, 0.44 mL) and *n*-BuLi (2.89 mmol, 1.15 mL), 2.5 M solution in hexanes) and HMPA (2.89 mmol, 0.50 mL), was reacted with cyclopentanone (2.66 mmol, 0.24 mL) to afford the deconjugated aldol product in 64% yield (0.335 g): IR (film) 3700–3200, 3028, 2961, 2875, 1720, 1437, 1379, 1332, 1245, 1198, 1162, 1030, 1003, 913, 835, 771, 708 $cm^{-1}$; $^1H$ NMR $\delta$ 5.71 (dq, 1H, $J$ = 10.4, 6.4 Hz), 5.62 (m, 1H), 3.68 (s, 3H), 3.43 (d, 1H, $J$ = 10.0 Hz), 3.21 (s, 1H), 1.89–1.72 (m, 2H), 1.70–1.39 (m, 6H), 1.68 (dd, 3H, $J$ = 6.8, 1.2 Hz); $^{13}C$ NMR $\delta$ 174.82, 128.42, 124.69, 82.64, 51.80, 51.66, 39.28, 37.14, 23.82, 23.65, 13.24.

**Methyl (Z)-2-(2-Hydroxy-2-cyclohexyl)-3-pentenoate (6c).** The dienolate of methyl (*E*)-pentenoate (2.63 mmol, 0.30 g), generated from LDA (prepared from DIPA (3.15 mmol, 0.44 mL) and *n*-BuLi (2.89 mmol, 1.15 mL), 2.5 M solution in hexanes) and HMPA (2.89 mmol, 0.50 mL), was reacted with cyclohexanone (3.63 mmol, 0.27 mL) to afford the deconjugated aldol product in 60% yield (0.341 g): IR (film) 3700–3250, 3028, 2938, 2860, 1718, 1442, 1401, 1332, 1262, 1198, 1164, 1071, 1035, 981, 947, 923, 840, 767, 735, 698 $cm^{-1}$; $^1H$ NMR $\delta$ 5.76 (dq, 1H, $J$ = 10.4, 6.4 Hz), 5.62 (tq, 1H, $J$ = 10.0, 2.0 Hz), 3.70 (s, 3H), 3.43 (d, 1H, $J$ = 10.0 Hz), 3.16 (s, 1H), 1.75–1.40 (m, 8H), 1.68 (dd, 3H, $J$ = 6.8, 1.6 Hz), 1.30–1.15 (m, 2H); $^{13}C$ NMR $\delta$ 174.68, 128.85, 124.12, 72.41, 52.24, 51.77, 36.86, 34.32, 25.61, 21.84, 21.57, 13.31.

**Methyl (Z)-2-(1-Hydroxy-1-ethyl)-3-pentenoate (6d).** The dienolate of methyl (*E*)-pentenoate (4.38 mmol, 0.50 g), generated from LDA (prepared from DIPA (5.26 mmol, 0.74 mL) and *n*-BuLi (4.82 mmol, 1.9 mL), 2.5 M solution in hexanes) and HMPA (4.82 mmol, 0.84 mL), was reacted with acetaldehyde (6.13 mmol, 0.34 mL) to afford the deconjugated aldol product in 91% yield (0.628 g) as a seperable 1.2:1/syn:anti mixture of diastereomers. ***Syn* diastereomer**: IR (film) 3725–3150, 3028, 2979, 2956, 2929, 1738, 1436, 1402, 1376, 1259, 1238, 1199, 1168, 1137, 1103, 1028, 936, 921, 856, 780, 733, 702 $cm^{-1}$; $^1H$ NMR $\delta$ 5.81 (dq, 1H, $J$ = 10.8, 6.8 Hz), 5.53

(tq, 1H, $J$ = 10.8, 1.2 Hz), 4.08 (m, 1H), 3.68 (s, 3H), 3.36 (dd, 1H, $J$ = 10.0, 4.8 Hz), 2.76 (brs 1H), 1.68 (dd, 3H, $J$ = 6.8, 1.6 Hz), 1.14 (d, 3H, $J$ = 6.4 Hz); $^{13}$C NMR $\delta$ 173.96, 129.80, 123.44, 67.93, 51.87, 50.19, 19.88, 13.22. ***Anti* diastereomer**: IR (film) 3725–3150, 3025, 2976, 2957, 1741, 1438, 1401, 1374, 1314, 1246, 1199, 1166, 1115, 1024, 997, 920, 873, 782, 731, 698 cm$^{-1}$; $^1$H NMR $\delta$ 5.72 (dq, 1H, $J$ = 11.2, 1.2 Hz), 5.36 (tq, 1H, $J$ = 10.8, 1.6 Hz), 4.04 (m, 1H), 3.71 (s, 3H), 3.39 (dd, 1H, $J$ = 9.6, 9.2 Hz), 2.75 (brs, 1H), 1.71 (dd, 3H, $J$ = 6.8, 1.6 Hz), 1.18 (d, 3H, $J$ = 6.0 Hz); $^{13}$C NMR $\delta$ 174.06, 128.88, 124.55, 68.82, 51.81, 20.55, 13.34.

**Methyl (*Z*)-2-(1-Hydroxy-1-benzyl)-3-pentenoate (6e).** The dienolate of methyl (*E*)-pentenoate (2.63 mmol, 0.30 g), generated from LDA (prepared from DIPA (3.15 mmol, 0.44 mL) and *n*-BuLi (2.89 mmol, 1.2 mL), 2.5 M solution in hexanes) and HMPA (2.89 mmol, 0.50 mL), was reacted with benzaldehyde (2.63 mmol, 0.27 mL) to afford the deconjugated aldol product in 85% yield (0.490 g) as a separable 1:1.4/syn: anti mixture of diastereomers. ***Syn* diastereomer**: IR (film) 3700–3200, 3094, 3068, 3039, 2954, 2919, 2856, 1736, 1605, 1495, 1457, 1437, 1404, 1372, 1324, 1256, 1198, 1168, 1121, 1088, 1028, 972, 920, 834, 771, 739, 704 cm$^{-1}$; $^1$H NMR $\delta$ 7.37–7.23 (m, 5H), 5.77 (dq, 1H, $J$ = 11.2, 6.8 Hz), 5.61 (m, 1H), 5.06 (dd, 1H, $J$ = 5.6, 2.4 Hz), 3.67 (dd, 1H, $J$ = 10.4, 6.0 Hz), 3.61 (s, 3H), 2.94 (d, 1H, $J$ = 2.8 Hz), 1.15 (dd, 3H, $J$ = 6.8, 2.0 Hz); $^{13}$C NMR $\delta$ 173.44, 140.86, 130.44, 128.15, 127.72, 126.26, 123.14, 74.25, 51.96, 51.62, 13.02. ***Anti* diastereomer**: IR (film) 3700–3200, 3091, 3065, 3031, 2951, 2919, 2859, 1739, 1605, 1497, 1452, 1437, 1402, 1372, 1334, 1271, 1236, 1201, 1166, 1033, 975, 917, 847, 784, 764, 734, 696, 631 cm$^{-1}$; $^1$H NMR $\delta$ 7.36–7.24 (m, 5H), 5.52 (dq, 1H, $J$ = 10.8, 6.8 Hz), 5.34 (tq, 1H, J = 10.8, 1.6 Hz), 4.89 (d, 1H, $J$ = 8.8 Hz), 3.75 (m, 1H), 3.73 (s, 3H), 2.91 (brs, 1H), 1.33 (dd, 3H, $J$ = 6.4, 1.6 Hz); $^{13}$C NMR $\delta$ 173.96, 141.18, 129.32, 128.20, 127.92, 126.66, 123.76, 75.43, 52.09, 51.95, 12.84.

**Methyl (*E*)-2-(2-Hydroxy-2-propyl)-3-pentenoate (7a).** The dienolate of methyl (*Z*)-pentenoate (2.20 mmol, 0.25 g), generated from LDA (prepared from DIPA (3.70 mmol, 0.52 mL) and *n*-BuLi (3.30 mmol, 1.3 mL), 2.5 M solution in hexanes) and HMPA (3.30 mmol, 0.57 mL), was reacted with acetone (3.30 mmol, 0.24 mL) to afford the deconjugated aldol product in 65% yield (0.246 g): IR (film) 3494, 3033, 2976, 2952, 2917, 2885, 2858, 1727, 1664, 1439, 1383, 1355, 1253, 1200, 1169, 1021, 972, 933, 912, 824, 786, 733 cm$^{-1}$; $^1$H NMR $\delta$ 5.61 (m, 2H), 3.71 (s, 3H), 2.97 (d, 1H, $J$ = 8.4 Hz), 1.72 (d, 3H, $J$ = 4.8 Hz), 1.22 (s, 3H), 1.17 (s, 3H); $^{13}$C NMR $\delta$ 174.66, 131.09, 125.20, 71.33, 59.27, 51.81, 28.63, 26.47, 18.03.

**Methyl (*E*)-2-(2-Hydroxy-2-cyclopentyl)-3-pentenoate (7b).** The dienolate of methyl (*Z*)-pentenoate (2.20 mmol, 0.25 g), generated from LDA (prepared from DIPA (3.70 mmol, 0.52 mL) and *n*-BuLi (3.30 mmol, 1.3 mL), 2.5 M solution in hexanes) and HMPA (3.30 mmol, 0.57 mL), was reacted with cyclopentanone (2.22 mmol, 0.20 mL) to afford the deconjugated aldol product in 47% yield (0.203 g): IR (film) 3521, 3031, 2958, 2875, 1738, 1718, 1666, 1437, 137, 1350, 1321, 1243, 1197, 1162, 1029, 1003, 974 cm$^{-1}$; $^1$H NMR $\delta$ 5.63 (m, 2H), 3.71 (s, 3H), 3.02 (m, 1H), 1.89–1.73 (m, 2H), 1.70 (d, 3H, $J$ = 4.8 Hz), 1.69–1.44 (m, 6H); $^{13}$C NMR $\delta$ 174.99, 130.44, 125.45, 82.39, 57.65, 51.83, 39.35, 37.29, 23.86, 23.69, 18.02.

**Methyl (*E*)-2-(2-Hydroxy-2-cyclohexyl)-3-pentenoate (7c).** The dienolate of methyl (*Z*)-pentenoate (2.20 mmol, 0.25 g), generated from LDA (prepared from DIPA (3.70 mmol, 0.52 mL) and *n*-BuLi (3.30 mmol, 1.3 mL), 2.5 M solution in hexanes) and HMPA (3.30 mmol, 0.57 mL), was reacted with cyclohexanone (2.22 mmol, 0.23 mL) to afford the deconjugated aldol product in 56% yield (0.259 g): mp = 35–36 °C; IR (film) 3517, 3031, 2937, 2859, 1735, 1716, 1667, 1450, 1436, 1401, 1379, 1351, 1264, 1198, 1168, 1140, 1069, 1042, 1006, 970, 841 cm$^{-1}$; $^1$H NMR $\delta$ 5.64–5.58 (m, 2H), 3.70 (s, 3H), 3.09 (s, 1H), 3.02 (m, 1H), 1.72 (d, 3H, $J$ = 4.4 Hz), 1.69–1.35 (m, 10H); $^{13}$C NMR $\delta$ 174.82, 130.82, 124.76, 71.97, 58.14, 51.75, 36.86, 34.54, 25.59, 21.89, 21.52, 18.04.

**Methyl (*E*)-2-(1-Hydroxyl-1-ethyl)-3-pentenoate (7d).** The dienolate of methyl (*Z*)-pentenoate (3.07 mmol, 0.35 g), generated from LDA (prepared from DIPA (5.20 mmol, 0.73 mL) and *n*-BuLi (4.60 mmol, 1.5 mL), 2.5 M solution in hexanes) and HMPA (4.60 mmol, 0.50 mL), was reacted with acetaldehyde (4.60 mmol, 0.26 mL) to afford the deconjugated aldol product in 50% yield (0.238 g) as a separable 1:1.3/syn: anti mixture of diastereomers. ***Syn* diastereomer**: IR ($CCl_4$) 3675–3425, 3033, 2981, 2951, 2935, 2918, 2886, 2853, 1741, 1723, 1439, 1284, 1231, 1192, 1168, 1105, 1004, 971, 944, 927, 912 cm$^{-1}$; $^1$H NMR $\delta$ 5.68 (dq, 1H, $J$ = 15.2, 6.4 Hz), 5.54 (ddd, 1H, $J$ = 15.2, 9.2, 1.2 Hz), 4.04 (dq, 1H, $J$ = 6.4, 6.4 Hz), 3.71 (s, 3H), 2.95 (dd, 1H, $J$ = 8.8, 5.2 Hz), 2.00 (brs, 1H), 1.74 (dd, 3H, $J$ = 6.4, 1.6 Hz), 1.16 (d, 3H, $J$ = 6.0 Hz); $^{13}$C NMR $\delta$ 174.07, 131.91, 124.28, 67.73, 56.22, 51.92, 19.98, 18.10. ***Anti* diastereomer**: IR ($CCl_4$) 3650–3225, 3030, 2972, 2952, 2929, 2855, 1739, 1433, 1374, 1349, 1279, 1243, 1198, 1167, 1116, 1007, 968, 945 cm$^{-1}$; $^1$H NMR $\delta$ 5.65 (dq, 1H, $J$ = 14.8, 6.8 Hz), 5.42 (m, 1H), 4.00 (dq, 1H, $J$ = 7.6, 6.4 Hz), 3.71 (s, 3H), 2.98 (t, 1H, $J$ = 8.4 Hz), 2.12 (brs, 1H), 1.70 (d, 3H, $J$ = 5.2 Hz), 1.18 (d, 3H, $J$ = 6.0 Hz); $^{13}$C NMR $\delta$ 174.09, 130.62, 125.34, 68.70, 57.28, 51.92, 20.80, 18.04.

**Methyl (*E*)-2-(1-Hydroxyl-1-benzyl)-3-pentenoate (7e).** The dienolate of methyl (*Z*)-pentenoate (3.07 mmol, 0.35 g), generated from LDA (prepared from DIPA (5.20 mmol, 0.73 mL) and *n*-BuLi (4.60 mmol, 1.5 mL), 2.5 M solution in hexanes) and HMPA (4.60 mmol, 0.50 mL), was reacted with benzaldehyde (3.10 mmol, 0.32 mL) to afford the deconjugated aldol product in 67% yield (0.452 g) as a separable 1.8:1/syn: anti mixture of diastereomers. ***Syn* diastereomer**: IR ($CCl_4$) 3613, 3531, 3092, 3067, 3035, 3002, 2955, 2920, 2885, 2855, 1734, 1719, 1667, 1608, 1499, 1454, 1437, 1380, 1318, 1288, 1195, 1165, 1088, 1049, 1026, 969, 700, 601 cm$^{-1}$; $^1$H NMR $\delta$ 7.35-7.23 (m, 5H), 5.60 (m, 2H), 4.95 (d, 1H, $J$ = 6.8 Hz), 3.57 (s, 3H), 3.27 (m, 1H), 2.83 (brs, 1H), 1.71 (d, 3H, $J$ = 4.8 Hz); $^{13}$C NMR $\delta$ 173.24, 140.81, 132.12, 128.18, 127.81, 126.41, 124.34, 74.10, 57.54, 51.86, 18.10. ***Anti* diastereomer**: IR ($CCl_4$) 3618, 3512, 3091, 3067, 3033, 2954, 2921, 2857, 1739, 1722, 1603, 1496, 1455, 1438, 1380, 1354, 1267, 1197, 1165, 1041, 1026, 968, 702 cm$^{-1}$; $^1$H NMR $\delta$ 7.36–7.24 (m, 5H), 5.42 (dq, 1H, $J$ = 15.6, 6.4 Hz), 5.34 (dd, 1H, $J$ = 15.6, 8.4 Hz), 4.88 (dd, 1H, $J$ = 8.4, 4.0 Hz), 3.71 (s, 3H), 3.37 (t, 1H, $J$ = 8.0 Hz), 2.92 (d, 1H, $J$ = 4.8 Hz), 1.57 (d, 3H, $J$ = 5.6 Hz); $^{13}$C NMR $\delta$ 173.91, 141.35, 130.70, 128.26, 127.86, 126.56, 124.69, 75.48, 56.84, 52.00, 17.92.

**General Procedure for the Iodine–Silver Triflate Mediated Cyclizations.** To a solution of iodine (3 eqiv) in 5 mL of acetonitrile was added sodium bicarbonate (3 eqiv), silver triflate (3 eqiv), and the allylic alcohol (1 eqiv). The reaction was allowed to stir at rt for 1–2 h before filtering through a pad of Celite and washing with $CH_2Cl_2$. The filtrate was washed once with 0.2 M $Na_2S_2O_3$, dried ($Na_2SO_4$), and filtered and the solvent removed in vacuo. The crude product mixture was purified by chromatography eluting with ether: pentane = 1:9.

**Cyclization of 2a.** A mixture of iodine (3.48 mmol, 0.884 g), $NaHCO_3$ (3.48 mmol, 0.293 g), and silver triflate (3.48 mmol, 0.895 g) was used to cyclize aldol product **2a** (1.16 mmol, 0.200 g) in 1 h. After chromatography, **3a** (0.118 g, 34%) and **4a** (0.108 g, 31%) were isolated. Cyclization without silver triflate required 27 h at rt. Thus, treatment of **2a** (0.581 mmol, 0.100 g) with iodine (1.74 mmol, 0.442 g) and $NaHCO_3$ (1.74 mmol, 0.146 g) afforded, after chromatography, **3a** (0.043 g, 30%) and **4a** (0.074 g, 51%) based on recovered **2a** (0.016 g). **2,2-Dimethyl-3-carbethoxy-4-iodotetrahydrofuran (3a)**: IR (film) 2980, 2936, 2872, 1735, 1463, 1371, 1354, 1291, 1264, 1219, 1154, 1099, 1050, 1030, 860, 808, 733 cm$^{-1}$; $^1$H NMR $\delta$ 4.51 (dt, 1H, $J$ = 9.2, 6.8 Hz), 4.23 (m, 3H), 3.96 (t, 1H, $J$ = 9.6 Hz), 3.12 (d, 1H, $J$ = 9.6 Hz), 1.47 (s, 3H), 1.30 (t, 3H, $J$ = 7.2 Hz), 1.14 (s, 3H); $^{13}$C NMR $\delta$ 169.71, 82.64, 74.63, 64.89, 61.22, 28.84, 24.13, 16.98, 14.21. **2,2-Dimethyl-3-carbethoxy-4-iodomethyloxetane (4a)**: IR (film) 2980, 2933, 2872, 1722, 1463, 1401, 1384, 1369, 1329, 1261, 1232, 1194, 1159, 1094, 1042, 965, 863, 733, 651 cm$^{-1}$; $^1$H NMR $\delta$ 4.83 (dt, 1H, $J$ = 7.2, 5.6 Hz), 4.21 (m, 2H), 3.35 (AB portion of ABX, 2H, $J_{ab}$ = 10.0, $J_{ax}$ = 5.6, $J_{bx}$ = 7.2, $\Delta\nu_{ab}$ = 25.7 Hz), 3.17 (d, 1H, $J$ = 7.2 Hz), 1.55 (s, 3H), 1.40 (s, 3H), 1.30 (t, 3H, $J$ = 6.8 Hz); $^{13}$C NMR $\delta$ 169.30, 80.54, 73.99, 60.88, 54.21, 31.13, 24.17, 14.26, 9.80.

**Cyclization of 2b.** A mixture of iodine (3.31 mmol, 0.841

g), $NaHCO_3$ (3.31 mmol, 0.278 g), and silver triflate (3.31 mmol, 0.851 g) was used to cyclize aldol product **2b** (1.10 mmol, 0.200 g) in 1.5 h. After chromatography, **3b** (0.125 g, 35%) and **4b** (0.086 g, 24%) were isolated. Cyclization without silver triflate required 24 h at rt. Thus, treatment of **2b** (0.552 mmol, 0.100 g) with iodine (1.66 mmol, 0.420 g) and $NaHCO_3$ (1.66 mmol, 0.139 g) afforded, after chromatography, **3b** (0.039 g, 24%) and **4b** (0.059 g, 37%) based on recovered **2b** (0.012 g). **2-Oxa-4-iodo-5-carbethoxyspiro[4.4]nonane (3b)**: IR (film) 2965, 2875, 1735, 1466, 1446, 1396, 1371, 1349, 1329, 1257, 1219, 1187, 1152, 1097, 1045, 1032, 980, 920, 860, 738 $cm^{-1}$; $^1H$ NMR $\delta$ 4.49 (dt, 1H, $J$ = 8.8, 7.2 Hz), 4.22 (m, 3H), 3.92 (t, 1H, $J$ = 9.2 Hz), 3.32 (d, 1H, $J$ = 8.8 Hz), 2.03–1.95 (m, 1H), 1.93–1.83 (m, 1H), 1.80–1.55 (m, 5H), 1.49–1.40 (m, 1H), 1.30 (t, 3H, $J$ = 7.2 Hz); $^{13}C$ NMR $\delta$ 170.18, 92.82, 74.67, 62.39, 61.21, 38.57, 34.40, 23.82, 23.31, 17.44, 14.24; HRMS $C_{11}H_{17}O_3I$ calcd 324.0222, found 324.02291. **2-Oxa-3-(iodomethyl)-4-carbethoxyspiro[3.4]octane (4b)**: IR (film) 2965, 2875, 1733, 1466, 1449, 1426, 1384, 1334, 1301, 1257, 1184, 1117, 1079, 1042, 960, 860, 750, 621 $cm^{-1}$; $^1H$ NMR $\delta$ 4.82 (ddd, 1H, $J$ = 7.6, 6.8, 5.2 Hz), 4.21 (m, 2H), 3.34 (AB portion of ABX, 2H, $J_{ab}$ = 10.0, $J_{ax}$ = 5.2, $J_{bx}$ = 7.6, $\Delta\nu_{ab}$ = 30.0 Hz), 2.14 (m, 1H), 1.96 (m, 1H), 1.87 (m, 1H), 1.80–1.55 (m, 5H), 1.29 (t, 3H, $J$ = 7.2 Hz); $^{13}C$ NMR $\delta$ 169.56, 90.18, 74.62, 60.92, 52.63, 41.21, 34.94, 22.93, 22.59, 14.27, 9.66; HRMS $C_{11}H_{17}O_3I$ calcd 197.1177 (M - I) found 197.1185.

**Cyclization of 2c.** A mixture of iodine (2.40 mmol, 0.610 g), $NaHCO_3$ (2.40 mmol, 0.202 g), and silver triflate (2.41 mmol, 0.617 g) was used to cyclize aldol product **2c** (0.80 mmol, 0.170 g) in 2 h. After chromatography, **3c** (0.056 g, 20%) and **4c** (0.096 g, 34%) were isolated. Cyclization without silver triflate required 72 h at rt. Thus, treatment of **2c** (0.471 mmol, 0.100 g) with iodine (1.41 mmol, 0.359 g) and $NaHCO_3$ (1.41 mmol, 0.119 g) afforded, after chromatography, **3c** (0.084 g, 65%) and **4c** (0.022 g, 17%) based on recovered **2c** (0.021 g). **2-Oxa-4-iodo-5-carbethoxyspiro[4.5]decane (3c)**: IR (film) 2985, 2935, 2861, 1735, 1447, 1371, 1349, 1254, 1221, 1178, 1141, 1114, 1047, 1025, 924, 903, 848, 823, 735 $cm^{-1}$; $^1H$ NMR $\delta$ 4.48 (dt, 1H, $J$ = 9.6, 7.2 Hz), 4.23 (m, 3H), 3.92 (t, 1H, $J$ = 9.6 Hz), 3.20 (d, 1H, $J$ = 9.2 Hz), 1.85–1.46 (m, 8H), 1.31 (t, 3H, $J$ = 6.4 Hz), 1.16 (m, 2H); $^{13}C$ NMR $\delta$ 169.89, 84.06, 74.39, 65.71, 61.18, 37.13, 32.85, 25.18, 22.75, 21.86, 17.38, 14.26; HRMS $C_{12}H_{19}O_3I$ calcd 211.1334 (M - I), found 211.1336. **2-Oxa-3-(iodomethyl)-4-carbethoxyspiro[3.5]nonane (4c)**: IR (film) 2982, 2935, 2861, 1732, 1450, 1404, 1383, 1368, 1325, 1291, 1264, 1239, 1193, 1169, 1092, 1047, 970, 918, 903, 839, 732, 625 $cm^{-1}$; $^1H$ NMR $\delta$ 4.83 (ddd, 1H, $J$ = 8.4, 6.8, 5.2 Hz), 4.20 (m, 2H), 3.33 (AB portion of ABX, 2H, $J_{ab}$ = 10.0, $J_{ax}$ = 5.2, $J_{bx}$ = 8.8, $\Delta\nu_{ab}$ = 52.9 Hz), 3.04 (d, 1H, $J$ = 6.4 Hz), 1.92–1.34 (m, 10H), 1.30 (t, 3H, $J$ = 7.2 Hz); $^{13}C$ NMR $\delta$ 169.30, 81.99, 74.60, 60.84, 54.20, 40.83, 32.90, 24.82, 21.82, 21.77, 14.22, 9.89; HRMS $C_{12}H_{19}O_3I$ calcd 211.1334 (M - I), found 211.1338.

**Cyclization of 2d.** A mixture of iodine (1.90 mmol, 0.481 g), $NaHCO_3$ (1.90 mmol, 0.519 g), and silver triflate (1.90 mmol, 0.488 g) was used to cyclize aldol product **2d** (0.632 mmol, 0.100 g) in 1 h. After chromatography, **3d** (0.071 g, 38%) and **4d** (0.49 g, 26%) were isolated. Cyclization without silver triflate required 45 h at rt. Thus, treatment of **2d** (0.632 mmol, 0.100 g) with iodine (1.90 mmol, 0.481 g) and $NaHCO_3$ (1.90 mmol, 0.519 g) afforded, after chromatography, **3d** (0.061 g, 45%) and **4d** (0.036 g, 26%) based on recovered **2d** (0.027 g). **2-Methyl-3-carbethoxy-4-iodotetrahydrofuran (3d)**: IR (film) 2978, 2929, 2873, 1735, 1450, 1383, 1279, 1193, 1154, 1095, 1034, 881, 860, 741 $cm^{-1}$; $^1H$ NMR $\delta$ 4.55–4.37 (m, 4H), 4.28–4.14 (m, 5H), 4.10–3.99 (m, 2H), 3.94 (t, 1H, $J$ = 8.0 Hz), 3.36 (dd, 1H, $J$ = 8.0, 8.0 Hz), 2.99 (t, 1H, $J$ = 8.0 Hz), 1.44 (d, 3H, $J$ = 6.4 Hz), 1.30 (t, 6H, $J$ = 6.8 Hz), 1.22 (d, 3H, $J$ = 6.4 Hz); $^{13}C$ NMR $\delta$ 170.68, 170.28, 78.76, 76.95, 76.83, 76.00, 62.78, 61.40, 61.19, 59.13, 20.50, 17.77, 17.37, 16.92, 14.22, 14.19; HRMS $C_8H_{13}O_3$ calcd 157.0864 (M - I), found 157.0858. **2-(Iodomethyl)-3-carbethoxy-4-methyloxetane (4d)**: IR (film) 2976, 2930, 2871, 1732, 1448, 1409, 1376, 1335, 1273, 1240, 1193, 1142, 1099, 1078, 1042, 957, 888, 685 $cm^{-1}$; $^1H$ NMR $\delta$ 4.98 (m, 1H), 4.77 (m, 3H), 4.30–4.16 (m, 4H), 3.52 (dd, 1H, $J$ = 9.6, 6.4 Hz), 3.41 (d, 2H, $J$ = 6.4 Hz), 3.36 (AB portion of ABX, 2H, $J_{ab}$ = 10.4, $J_{ax}$ = 5.2, $J_{bx}$ = 7.2, $\Delta\nu_{ab}$ = 23.5 Hz), 3.03 (t, 1H, $J$ = 6.8 Hz), 1.49 (d, 3H, $J$ = 6.0 Hz), 1.40 (d, 3H, $J$ = 6.0 Hz), 1.30 (t, 3H, $J$ = 7.2 Hz), 1.29 (t, 3H, $J$ = 7.2 Hz); $^{13}C$ NMR $\delta$ 170.22, 169.50, 81.09, 77.65, 77.23, 75.42, 74.55, 73.94, 61.12, 52.13, 48.05, 33.37, 18.50, 14.15, 9.80, 9.62; HRMS $C_8H_{13}O_3$ calcd 157.0864 (M - I), found 157.0864.

**General Procedure for the Iodine-Mediated Cyclization.** To a solution of iodine (3.0 eq) in 5 mL of dry acetonitrile was added $NaHCO_3$ (3.0 eq) followed by the aldol product (1.0 eq, 100–300 mg). The reaction was stirred at rt for 12–38 h protected from light before being poured into a 0.2 M solution of $Na_2S_2O_3$. The aqueous phase was extracted three times with ether, the combined extracts were washed once with brine, dried (anhydrous $Na_2SO_4$), and filtered, and the solvent was removed *in vacuo*. The crude product was purified by column chromatography by eluting with either an ethyl acetate/hexanes or an ether/pentane mixture in order to separate the major and minor products.

**Cyclization of 6a.** A mixture of iodine (1.74 mmol, 0.442 g) and $NaHCO_3$ (1.74 mmol, 0.146 g) was used to cyclize aldol product **6a** (0.581 mmol, 0.100 g). After chromatography, **8a** (0.120 g) and **9a** (0.012 g) were isolated in a combined yield of 76%. **(3*S*,4*S*,5*S*)-2,2,5-Trimethyl-3-carbethoxy-4-(iodomethyl)tetrahydrofuran (8a)**: IR (film) 2980, 2950, 2937, 2867, 1741, 1438, 1389, 1371, 1337, 1314, 1249, 1205, 1156, 1110, 1071, 1040, 994, 955, 919, 859, 761, 725 $cm^{-1}$; $^1H$ NMR $\delta$ 4.79 (dd, 1H, $J$ = 7.2, 6.0 Hz), 3.76 (dq, 1H, $J$ = 6.0, 6.0 Hz), 3.75 (s, 3H), 3.41 (d, 1H, $J$ = 7.2 Hz), 1.52 (s, 3H), 1.36 (d, 3H, $J$ = 6.0 Hz), 1.11 (s, 3H); $^{13}C$ NMR $\delta$ 171.01, 81.79, 74.91, 65.42, 52.18, 30.27, 24.42, 23.40; HRMS $C_9H_{15}O_3I$ calcd 171.1021 (M - I), found 171.1057. **(3*S*,4*R*,5*R*)-2,2,5-Trimethyl-3-carbethoxy-4-ioditetrahydrofuran (9a)**: IR (film) 2974, 2954, 2864, 1741, 1438, 1386, 1371, 1348, 1317, 1260, 1234, 1203, 1167, 1071, 1050, 1022, 970, 955, 929, 859, 815, 771 $cm^{-1}$; $^1H$ NMR $\delta$ 4.68 (t, 1H, $J$ = 7.2 Hz), 4.16 (dq, 1H, $J$ = 7.2, 7.2 Hz), 3.74 (s, 3H), 3.20 (d, 1H, $J$ = 7.6 Hz), 1.84 (d, 3H, $J$ = 6.8 Hz), 1.53 (s, 3H), 1.40 (s, 3H); $^{13}C$ NMR $\delta$ 169.71, 79.95, 79.00, 52.10, 51.94, 30.46, 29.85, 24.26, 21.80; HRMS $C_9H_{15}O_3I$ calcd 171.1021 (M - I), found 170.0999.

**Cyclization of 6b.** A mixture of iodine (1.51 mmol, 0.374 g) and $NaHCO_3$ (1.51 mmol, 0.127 g) was used to cyclize aldol product **6b** (0.504 mmol, 0.100 g). After chromatography, **8b** (0.109 g) and **9b** (0.010 g) were isolated in a combined yield of 78% based on recovered **6b** (0.006 g). **(3*S*,4*S*,5*S*)-2-Oxa-3-methyl-4-iodo-5-carbethoxyspiro[4.4]nonane (8b)**: IR (film) 2954, 2874, 2846, 1738, 1435, 1378, 1335, 1268, 1253, 1214, 1196, 1178, 1152, 1104, 1070, 1045, 1027, 993, 978, 955, 921, 868, 760 $cm^{-1}$; $^1H$ NMR $\delta$ 4.75 (dd, 1H, $J$ = 6.4, 6.4 Hz), 3.74 (s, 3H), 3.63 (dq, 1H, $J$ = 6.0, 6.0 Hz), 3.60 (d, 1H, $J$ = 6.8 Hz), 2.08–1.92 (m, 2H), 1.82–1.49 (m, 6H), 1.34 (d, 3H, $J$ = 6.4 Hz); $^{13}C$ NMR $\delta$ 171.33, 91.82, 74.85, 63.44, 52.11, 39.65, 34.12, 31.37, 24.17, 23.98, 23.39; HRMS $C_{11}H_{17}O_3I$ calcd 324.0222, found 324.02116. **(3*R*,4*R*,5*S*)-2-Oxa-3-methyl-4-iodo-5-carbethoxyspiro[4.4]nonane (9b)**: IR (film) 2962, 2955, 2927, 2871, 1741, 1437, 1389, 1377, 1334, 1243, 1197, 1159, 1076, 1022, 979, 952 $cm^{-1}$; $^1H$ NMR $\delta$ 4.70 (t, 1H, $J$ = 6.8 Hz), 4.18 (dq, 1H, $J$ = 7.2, 7.2 Hz), 3.74 (s, 3H), 3.43 (d, 1H, $J$ = 7.2 Hz), 2.15 (m, 1H), 1.98 (m, 1H), 1.85 (d, 3H, $J$ = 7.2 Hz), 1.77–1.55 (m, 6H); $^{13}C$ NMR $\delta$ 170.00, 89.54, 79.37, 51.95, 50.29, 40.61, 35.16, 29.54, 23.06, 22.71, 21.70; HRMS $C_{11}H_{17}O_3I$ calcd 197.1178 (M - I), found 197.1180.

**Cyclization of 6c.** A mixture of iodine (1.39 mmol, 0.354 g) and $NaHCO_3$ (1.39 mmol, 0.117 g) was used to cyclize aldol product **6c** (0.465 mmol, 0.100 g). After chromatography, **8c** (0.100 g) and **9c** (0.029 g) were isolated in a combined yield of 88% based on recovered **6c** (0.007 g). **(3*S*,4*S*,5*S*)-2-Oxa-3-methyl-4-iodo-5-carbethoxyspiro[4.5]decane (8c)**: IR (film) 2976, 2934, 2860, 1738, 1450, 1440, 1369, 1346, 1263, 1243, 1210, 1172, 1149, 1111, 1070, 1030, 979, 924, 845, 828, 759, 731 $cm^{-1}$; $^1H$ NMR $\delta$ 4.73 (dd, 1H, $J$ = 6.8, 5.6 Hz), 3.75 (s, 3H), 3.31 (d, 1H, $J$ = 7.2 Hz), 1.89–1.44 (m, 8H), 1.36 (d, 3H, $J$ = 6.4 Hz), 1.17 (m, 1H), 1.02 (dt, 1H, $J$ = 13.2, 4.4 Hz); $^{13}C$ NMR $\delta$ 171.06, 83.14, 74.77, 65.94, 52.08, 39.37, 31.57, 30.57, 25.19, 24.27, 22.84, 21.85; HRMS $C_{12}H_{19}O_3I$ calcd 338.0379, found 338.0383. **(3*R*,4*R*,5*S*)-2-Oxa-3-methyl-4-iodo-5-**

**carbethoxyspiro[4.5]decane (9c)**: IR (film) 2937, 2860, 1736, 1442, 1394, 1372, 1346, 1288, 1260, 1235, 1197, 1167, 1065, 1020, 979, 962, 921, 853, 833 $cm^{-1}$; $^1H$ NMR $\delta$ 4.76 (t, 1H, $J$ = 7.2 Hz), 4.17 (dq, 1H, $J$ = 7.2, 7.2 Hz), 3.74 (s, 3H), 3.10 (d, 1H, $J$ = 7.6 Hz), 1.84 (d, 3H, $J$ = 6.7 Hz), 1.85−1.20 (m, 10H); $^{13}C$ NMR $\delta$ 169.84, 81.39, 79.31, 51.92, 51.19, 40.06, 33.02, 29.37, 24.86, 21.98, 21.78, 21.46; HRMS $C_{12}H_{19}O_3I$ calcd 338.0379, found 338.0364.

**Cyclization of *syn*-6d.** A mixture of iodine (1.90 mmol, 0.481 g) and $NaHCO_3$ (1.90 mmol, 0.160 g) was used to cyclize aldol product ***syn*-6d** (0.632 mmol, 0.100 g). After chromatography, ***anti*-8d** (0.126 g) and ***anti*-9d** (0.003 g) were isolated in a combined yield of 76% based on recovered ***syn*-6d** (0.005 g). **(2*R*,3*S*,4*S*,5*S*)-2,5-Dimethyl-3-carbethoxy-4-iodotetrahydrofuran (*anti*-8d)**: IR (film) 2976, 2952, 2932, 2867, 1738, 1438, 1376, 1320, 1268, 1203, 1150, 1119, 1033, 986, 949, 912, 875, 835 $cm^{-1}$; $^1H$ NMR $\delta$ 4.71 (t, 1H, $J$ = 4.4 Hz), 4.00 (dq, 1H, $J$ = 6.4, 6.4 Hz), 3.75 (s, 3H), 3.28 (dd, 1H, $J$ = 6.8, 4.4 Hz), 3.26 (dq, 1H, $J$ = 5.6, 5.6 Hz), 1.49 (d, 3H, $J$ = 6.4 Hz), 1.34 (d, 3H, $J$ = 5.6, Hz); $^{13}C$ NMR $\delta$ 172.24, 78.01, 77.24, 63.85, 52.42, 32.50, 23.42, 21.16; HRMS $C_8H_{13}O_3I$ calcd 283.9909, found 283.9898. **(2*R*,3*S*,4*R*,5*R*)-2,5-Dimethyl-3-carbethoxy-4-iodotetrahydrofuran (*anti*-9d)**: IR (film) 2972, 2956, 2927, 2856, 1743, 1438, 1404, 1372, 1342, 1268, 1196, 1175, 1162, 1101, 1058, 1037, 1016, 995, 976, 952, 910, 859 $cm^{-1}$; $^1H$ NMR $\delta$ 4.81 (dq, 1H, $J$ = 6.0, 6.0 Hz), 4.62 (t, 1H, $J$ = 7.2 Hz), 4.17 (dq, 1H, $J$ = 7.2, 7.2 Hz), 3.74 (s, 3H), 3.06 (t, 1H, $J$ = 6.8 Hz), 1.87 (d, 3H, $J$ = 6.8 Hz), 1.47 (d, 3H, $J$ = 6.0 Hz); $^{13}C$ NMR $\delta$ 170.75, 82.08, 74.60, 52.22, 49.89, 29.47, 22.79, 21.43; HRMS $C_8H_{13}O_3I$ calcd 157.0864 (M - I), found 157.0865.

**Cyclization of *anti*-6d.** A mixture of iodine (1.90 mmol. 0.481 g) and $NaHCO_3$ (1.90 mmol, 0.160 g) was used to cyclize aldol product ***anti*-6d** (0.632 mmol, 0.100 g). After chromatography, ***syn*-8d** (0.096 g) and ***syn*-9d** (0.008 g) were isolated in a combined yield of 68% based on recovered ***anti*-6d** (0.016 g). **(2*S*,3*S*,4*S*,5*S*)-2,5-Dimethyl-3-carbethoxy-4-iodotetrahydrofuran (*syn*-8d)**: IR (film) 2980, 2949, 2932, 2891, 1735, 1438, 1385, 1324, 1302, 1268, 1206, 1156, 1107, 1054, 961, 909, 866, 819, 773, 736 $cm^{-1}$; $^1H$ NMR $\delta$ 4.66 (t, 1H, $J$ = 4.8 Hz), 4.64 (dq, 1H, $J$ = 8.4, 6.4 Hz), 3.99 (dq, 1H, $J$ = 6.0, 6.0 Hz), 3.74 (s, 3H), 3.57 (dd, 1H, $J$ = 8.0, 4.8 Hz), 1.33 (d, 3H, $J$ = 6.0 Hz), 1.17 (d, 3H, $J$ = 6.8 Hz); $^{13}C$ NMR $\delta$ 171.20, 76.61, 74.05, 59.76, 52.05, 30.75, 23.04, 17.28; HRMS $C_8H_{13}O_3I$ calcd 157.0864 (M - I), found 157.0869. **(2*S*,3*S*,4*R*,5*R*)-2,5-Dimethyl-3-carbethoxy-4-iodotetrahydrofuran (*syn*-9d)**: IR (film) 2976, 2953, 2929, 2869, 2856, 1743, 1439, 1382, 1358, 1304, 1233, 1202, 1176, 1076, 1017, 994, 973, 952, 882 $cm^{-1}$; $^1H$ NMR $\delta$ 4.93 (dq, 1H, $J$ = 9.2, 6.4 Hz), 4.78 (t, 1H, $J$ = 6.0 Hz), 4.35 (dq, 1H, $J$ = 6.4, 5.6 Hz), 3.77 (s, 3H), 3.56 (dd, 1H, $J$ = 8.8, 6.4 Hz), 1.89 (d, 3H, $J$ = 7.2 Hz), 1.40 (d, 3H, $J$ = 6.4 Hz); $^{13}C$ NMR $\delta$ 170.15, 82.54, 74.80, 56.72, 51.64, 30.70, 21.67, 17.92.

**Cyclization of *syn*-6e.** A mixture of iodine (1.36 mmol, 0.346 g) and $NaHCO_3$ (1.36 mmol, 0.114 g) was used to cyclize aldol product ***syn*-6e** (0.454 mmol, 0.100 g). After chromatography, ***anti*-8e** (0.085 g) and ***anti*-9e** (0.019 g) were isolated in a combined yield of 69% based on recovered ***syn*-6e** (0.004 g). **(2*R*,3*S*,4*S*,5*S*)-2-Phenyl-3-carbethoxy-4-iodo-5-methyltetrahydrofuran (*anti*-8e)**: IR (film) 3090, 3070, 3040, 2984, 2950, 2924, 2850, 1738, 1495, 1454, 1436, 1373, 1340, 1314, 1268, 1208, 1177, 1110, 1027, 973, 926, 851, 761, 701 $cm^{-1}$; $^1H$ NMR $\delta$ 7.52−7.28 (m, 5H), 4.95 (d, 1H, $J$ = 7.6 Hz), 4.81 (t, 1H, $J$ = 4.4 Hz), 3.76 (s, 3H), 3.58 (dd, 1H, $J$ = 7.2, 4.0 Hz), 3.53 (dq, 1H, $J$ = 5.6, 5.6 Hz), 1.46 (d, 3H, $J$ = 6.0 Hz); $^{13}C$ NMR $\delta$ 172.22, 139.54, 128.52, 128.26, 126.38, 83.60, 77.70, 64.48, 52.53, 32.11, 23.28; HRMS $C_{13}H_{15}O_3I$ calcd 346.0066, found 346.0071. A sample suitable for X-ray analysis was obtained by recrystallization from ethyl acetate/hexanes, mp = 55−56 °C. Details of the crystal structure analysis (cell data, data collection, processing, and refinement) are concisely summarized in Table 1 of the supplementary material. **(2*R*,3*S*,4*R*,5*R*)-2-Phenyl-3-carbethoxy-4-iodo-5-methyltetrahydrofuran (*anti*-9e)**: IR (film) 3093, 3070, 3032, 2982, 2955, 2928, 2867, 1740, 1501, 1459, 1438, 1389, 1374, 1271, 1202, 1178, 1154, 1081, 1024, 909, 864, 697 $cm^{-1}$; $^1H$ NMR $\delta$ 7.40−7.28 (m, 5H), 5.14 (d, 1H, $J$ = 8.0 Hz), 4.41 (dq, 1H, $J$ = 9.6, 6.0 Hz), 4.12 (t, 1H, $J$ = 10.0 Hz), 3.77 (s, 3H), 3.40 (dd, 1H, $J$ = 10.4, 8.0 Hz), 1.46 (d, 3H, $J$ = 6.0 Hz); $^{13}C$ NMR $\delta$ 171.13, 140.76, 128.67, 128.11, 125.44, 84.02, 82.31, 63.87, 52.60, 25.87, 17.35; HRMS $C_{13}H_{15}O_3I$ calcd 346.0066, found 346.0072.

**Cyclization of *anti*-6e.** A mixture of iodine (1.36 mmol, 0.346 g) and $NaHCO_3$ (1.36 mmol, 0.114 g) was used to cyclize aldol product ***anti*-6e** (0.454 mmol, 0.100 g). After chromatography, ***syn*-8e** (0.037 g) and ***syn*-9e** (0.013 g) were isolated in a combined yield of 55% based on recovered ***anti*-6e** (0.042 g). **(2*S*,3*S*,4*S*,5*S*)-2-Phenyl-3-carbethoxy-4-iodo-5-methyltetrahydrofuran (*syn*-8e)**: IR (film) 3086, 3065, 3035, 2995, 2984, 2946, 2930, 2874, 1727, 1689, 1607, 1494, 1455, 1437, 1368, 1347, 1317, 1278, 1247, 1206, 1181, 1145, 1096, 1024, 945, 916, 886, 798, 701, 675 $cm^{-1}$; $^1H$ NMR $\delta$ 7.33−7.21 (m, 5H), 5.60 (d, 1H, $J$ = 8.0 Hz), 4.77 (t, 1H, $J$ = 5.2 Hz), 4.39 (dq, 1H, $J$ = 5.2, 5.2 Hz), 3.82 (dd, 1H, $J$ = 8.0, 4.4 Hz), 3.16 (s, 3H), 1.46 (d, 3H, $J$ = 6.4 Hz); $^{13}C$ NMR $\delta$ 170.40, 138.35, 128.01, 127.95, 126.12, 80.25, 78.65, 61.74, 51.62, 30.29, 23.01; HRMS $C_{13}H_{13}O_3I$ calcd 346.0066, found 346.0071. **(2*S*,3*S*,4*R*,5*R*)-2-Phenyl-3-carbethoxy-4-iodo-5-methyltetrahydrofuran (*syn*-9e)**: IR ($CCl_4$) 3091, 3071, 3034, 2952, 2925, 2853, 1743, 1493, 1453, 1437, 1385, 1313, 1274, 1226, 1200, 1179, 1144, 1078, 1057, 1023, 989, 965, 941, 698 $cm^{-1}$; $^1H$ NMR $\delta$ 7.41−7.24 (m, 5H), 5.83 (d, 1H, $J$ = 9.2 Hz), 5.03 (5, 1H, $J$ = 6.0 Hz), 4.40 (dq, 1H, $J$ = 6.8, 6.8 Hz), 3.88 (dd, 1H, $J$ = 9.2, 6.8 Hz), 3.27 (s, 3H), 2.00 (d, 3H, $J$ = 6.4 Hz); $^{13}C$ NMR $\delta$ 169.08, 137.72, 128.37, 128.16, 125.88, 82.81, 78.94, 51.69, 48.54, 29.09, 21.74; HRMS $C_{13}H_{15}O_3I$ calcd 346.0066, found 346.0079.

**Cyclization of 7a.** A mixture of iodine (1.70 mmol, 0.442 g) and $NaHCO_3$ (1.70 mmol, 0.146 g) was used to cyclize aldol product **7a** (0.580 mmol, 0.100 g). After chromatography, **10a** (0.144 g) and **11a** (0.019 g) were isolated in a combined yield of 94%. **(3*S*,4*S*,5*R*)-2,2,5-Trimethyl-3-carbethoxyl-4-iodotetrahydrofuran (10a)**: IR ($CCl_4$) 2977, 2955, 2927, 2867, 1739, 1438, 1383, 1365, 1245, 1198, 1163, 1117, 1073, 997, 953, 918, 856, 763, 728, $cm^{-1}$; $^1H$ NMR $\delta$ 4.10 (dq, 1H, $J$ = 10.0, 5.6 Hz), 4.01 (t, 1H, $J$ = 10.4 Hz), 3.74 (s, 3H), 3.18 (d, 1H, $J$ = 10.8 Hz), 1.41 (s, 3H), 1.33 (d, 3H, $J$ = 6.0 Hz), 1.13 (s, 3H); $^{13}C$ NMR $\delta$ 170.35, 81.65, 80.55, 65.42, 52.16, 29.38, 25.93, 25.64, 17.30; HRMS $C_9H_{15}O_3I$ calcd 171.1021 (M - I), found 171.1036. **(3*S*,4*R*,5*S*)-2,2,5-Trimethyl-3-carbethoxy-4-iodotetrahydrofuran (11a)**: IR ($CCl_4$) 2975, 2953, 2928, 2869, 1742, 1438, 1374, 1242, 1198, 1166, 1096, 1073, 1046, 994, 967, 947, 921, 877, 859, 818, 757, 728, 704 $cm^{-1}$; $^1H$ NMR $\delta$ 4.56 (dq, 1H, $J$ = 10.0, 6.4 Hz), 4.02 (dd, 1H, $J$ = 9.6, 7.6 Hz), 3.76 (s, 3H), 3.11 (d, 1H, $J$ = 7.2 Hz), 1.38 (s, 3H), 1.35 (d, 3H, $J$ = 6.8 Hz), 1.34 (s, 3H); $^{13}C$ NMR $\delta$ 170.65, 81.32, 80.60, 60.69, 51.59, 31.33, 25.27, 25.15, 18.48; HRMS $C_9H_{15}O_3I$ calcd 171.1021 (M - I), found 171.1039.

**Cyclization of 7b.** A mixture of iodine (1.50 mmol, 0.384 g) and $NaHCO_3$ (1.50 mmol, 0.127 g) was used to cyclize aldol product **7b** (0.504 mmol, 0.100 g). After chromatography, **10b** (0.111 g) and **11b** (0.035 g) were isolated in a combined yield of 89%. **(3*R*,4*S*,5*S*)-2-Oxa-3-methyl-4-iodo-5-carbethoxyspiro[4.4]nonane (10b)**: IR ($CCl_4$) 2970, 2953, 2933, 2872, 1739, 1435, 1390, 1369, 1336, 1275, 1233, 1197, 1158, 1089, 983, 947, 923, 724 $cm^{-1}$; $^1H$ NMR $\delta$ 4.02 (m, 2H), 3.74 (s, 3H), 3.37 (d, 1H, $J$ = 9.6 Hz), 2.02−1.91 (m, 1H), 1.82−1.40 (m, 7H), 1.34 (d, 3H, $J$ = 5.6 Hz); $^{13}C$ NMR $\delta$ 170.99, 91.88, 80.80, 63.28, 52.13, 39.53, 36.08, 26.41 23.69, 23.19, 17.25; HRMS $C_{11}H_{17}O_3I$ calcd 324.0222, found 324.0204. **(3*S*,4*R*,5*S*)-2-Oxa-3-methyl-4-iodo-5-carbethoxyspiro[4.4]nonane (11b)**: IR ($CCl_4$) 2970, 2952, 2928, 2869, 2845, 1740, 1433, 1374, 1354, 1334, 1303, 1190, 1168, 1140, 1097, 1046, 987, 880, 818, 767, 730 $cm^{-1}$; $^1H$ NMR $\delta$ 4.56 (dq, 1H, $J$ = 9.6, 6.0 Hz), 3.99 (dd, 1H, $J$ = 9.6, 7.6 Hz), 3.75 (s, 3H), 3.20 (d, 1H, $J$ = 7.2 Hz), 1.90−1.55 (m, 8H), 1.31 (d, 3H, $J$ = 6.4 Hz); $^{13}C$ NMR $\delta$ 170.94, 91.71, 81.42, 59.91, 51.62, 41.67, 35.77, 25.64, 23.66, 23.52, 18.68; HRMS $C_{11}H_{17}O_3I$ calcd 324.0222, found 324.0199.

**Cyclization of 7c.** A mixture of iodine (1.40 mmol, 0.359 g) and $NaHCO_3$ (1.40 mmol, 0.119 g) was used to cyclize aldol product **7c** (0.470 mmol, 0.100 g). After chromatography, **10c** (0.108 g) and **11c** (0.033 g) were isolated in a combined yield

of 89%. **(3*R*,4*S*,5*S*)-2-Oxa-3-methyl-4-iodo-5-carbethoxyspiro[4.5]decane (10c)**: IR (film) 2976, 2935, 2862, 1739, 1442, 1376, 1332, 1267, 1237, 1196, 1177, 1147, 1106, 1076, 1040, 1018, 999, 969, 928, 904, 849, 830, 754, 729, 688 $cm^{-1}$; $^1H$ NMR $\delta$ 4.07 (dq, 1H, $J$ = 10.0, 6.0 Hz), 3.99 (t, 1H, $J$ = 10.4 Hz), 3.74 (s, 3H), 3.07 (d, 1H, $J$ = 10.0 Hz), 1.80–1.42 (m, 8H), 1.34 (d, 3H, $J$ = 5.6 Hz), 1.26-1.08 (m, 2H); $^{13}C$ NMR $\delta$ 170.59, 82.99, 80.28, 66.23, 52.10, 37.46, 34.53, 26.52, 25.09, 22.61, 21.87, 17.32; HRMS $C_{12}H_{19}O_3I$ calcd 338.0379, found 338.0385. **(3*S*,4*R*,5*S*)-2-Oxa-3-methyl-4-iodo-5-carbethoxyspiro[4.5]decane (11c)**: IR (film) 2974, 2931, 2861, 1740, 1438, 1368, 1331, 1282, 1236, 1196, 1174, 1139, 1102, 1075, 1040, 994, 962, 924, 902, 870, 848, 827, 762, 727 $cm^{-1}$; $^1H$ NMR $\delta$ 4.55 (dq, 1H, $J$ = 9.6, 6.4 Hz), 3.98 (dd, 1H, $J$ = 9.6, 6.8 Hz), 3.75 (s, 3H), 3.15 (d, 1H, $J$ = 7.2 Hz), 1.80–1.25 (m, 10H), 1.32 (d, 3H, $J$ = 6.4 Hz); $^{13}C$ NMR $\delta$ 170.69, 83.74, 80.64, 66.27, 52.14, 37.50, 34.57, 25.67, 25.13, 23.37, 21.91, 18.55; HRMS $C_{12}H_{19}O_3I$ calcd 338.0379, found 338.0368.

**Cyclization of *syn*-7d.** A mixture of iodine (1.90 mmol, 0.481 g) and $NaHCO_3$ (1.90 mmol, 0.159 g) was used to cyclize aldol product ***syn*-7a** (0.630 mmol, 0.100 g). After chromatography, ***anti*-10a** (0.126 g) was isolated in a 70% yield. **(2*R*,3*S*,4*S*,5*R*)-2,5-Dimethyl-3-carbethoxy-4-iodotetrahydrofuran (*anti*-10d)**: IR (film) 2977, 2950, 2931, 2870, 1740, 1439, 1387, 1369, 1262, 1222, 1198, 1146, 1104, 1052, 979, 954, 918, 872, 738, 637 $cm^{-1}$; $^1H$ NMR $\delta$ 4.32 (dq, 1H, $J$ = 9.2, 6.8 Hz), 4.02 (m, 2H), 3.74 (s, 3H), 3.42 (dd, 1H, $J$ = 8.4, 8.4 Hz), 1.37 (d, 3H, $J$ = 5.2 Hz), 1.18 (d, 3H, $J$ = 6.8 Hz); $^{13}C$ NMR $\delta$ 171.07, 83.30, 75.32, 59.68, 52.09, 25.45, 17.31, 16.76; HRMS $C_8H_{13}O_3I$ calcd 283.9910, found 283.9890.

**Cyclization of *anti*-7d.** A mixture of iodine (1.90 mmol, 0.481 g) and $NaHCO_3$ (1.90 mmol, 0.159 g) was used to cyclize aldol product ***anti*-7a** (0.630 mmol, 0.100 g). After chromatography, ***syn*-10a** (0.103 g) was isolated in a 57% yield. **(2*S*,3*S*,4*S*,5*R*)-2,5-Dimethyl-3-carbethoxy-4-iodotetrahydrofuran (*syn*-10d)**: IR (film) 2974, 2953, 2928, 2869, 1741, 1439, 1383, 1273, 1201, 1164, 1094, 1049, 993, 951, 923, 901, 836, 730 $cm^{-1}$; $^1H$ NMR $\delta$ 4.20 (m, 2H), 3.99 t, 1H, $J$ = 9.6 Hz), 3.76 (s, 3H), 3.02 (dd, 1H, $J$ = 10.0, 8.0 Hz), 1.36 (d, 3H, $J$ = 6.4 Hz), 1.34 (d, 3H, $J$ = 6.0 Hz); $^{13}C$ NMR $\delta$ 171.12, 82.39, 76.68, 63.06, 52.46, 25.74, 21.21, 17.25; HRMS $C_8H_{13}O_3I$ calcd 283.9910, found 283.9910.

**Cyclization of *syn*-7e.** A mixture of iodine (1.36 mmol, 0.346 g) and $NaHCO_3$ (1.36 mmol, 0.114 g) was used to cyclize aldol product ***syn*-7e** (0.450 mmol, 0.100 g). After chromatography, ***anti*-10e** (0.133 g) was isolated in a 85% yield. **(2*R*,3*S*,4*S*,5*R*)-2-phenyl-3-carbethoxy-4-iodo-5-methyltetrahydrofuran (*anti*-10e)**: IR ($CCl_4$) 3092, 3067, 3032, 2979, 2952, 2932, 2874, 1743, 1495, 1460, 1443, 1388, 1371, 1267, 1198, 1175, 1149, 1080, 1022, 916, 867, 699 $cm^{-1}$; $^1H$ NMR $\delta$ 7.40–7.27 (m, 5H), 5.14 (d, 1H, $J$ = 8.4 Hz), 4.41 (dq, 1H, $J$ = 9.6, 6.0 Hz), 4.12 (t, 1H, $J$ = 10.4 Hz), 3.77 (s, 3H), 3.40 (dd, 1H, $J$ = 10.4, 8.0 Hz), 1.46 (d, 3H, $J$ = 6.0 Hz); $^{13}C$ NMR $\delta$ 171.15, 140.78, 128.68, 128.12, 125.46, 84.05, 82.32, 63.89, 52.59, 25.88, 17.36; HRMS $C_{13}H_{15}O_3I$ calcd 346.0066, found 346.0063. A sample suitable for X-ray analysis was obtained by recrystallization from isooctane, mp = 56.5–57.5 °C. Details of the crystal structure analysis (cell data, data collection, processing, and refinement) are concisely summarized in Table 1 of the supplementary material.

**Cyclization of *anti*-7e.** A mixture of iodine (1.36 mmol, 0.346 g) and $NaHCO_3$ (1.36 mmol, 0.114 g) was used to cyclize aldol product ***anti*-7e** (0.450 mmol, 0.100 g). After chromatography, ***syn*-10e** (0.108 g) and ***syn*-11e** (0.015 g) were isolated in a combined yield of 79%. **(2*S*,3*S*,4*S*,5*R*)-2-Phenyl-3-carbethoxy-4-iodo-5-methyltetrahydrofuran (*syn*-10e)**: IR ($CCl_4$) 3094, 3068, 3032, 2979, 2951, 2931, 2873, 2847, 1747, 1493, 1458, 1439, 1381, 1362, 1248, 1201, 1182, 1152, 1092, 1021, 991, 956, 923, 901, 874, 825, 696, 650 $cm^{-1}$; $^1H$ NMR $\delta$ 7.25–7.15 (m, 5H), 5.18 (d, 1H, $J$ = 9.6 Hz), 4.16 (dq, 1H, $J$ = 9.6, 6.0 Hz), 4.10 (t, 1H, $J$ = 9.2 Hz), 3.66 (t, 1H, $J$ = 9.6 Hz), 3.09 (s, 3H), 1.46 (d, 3H, $J$ = 5.6 Hz); $^{13}C$ NMR $\delta$ 170.03, 137.47, 128.24, 127.96, 126.61, 83.62, 81.49, 61.77, 51.63, 24.56, 16.53; HRMS $C_{13}H_{15}O_3I$ calcd 219.1022 (M - I), found 219.1027. A sample suitable for X-ray analysis was obtained by recrystallization from isooctane, mp = 65–66 °C. Details of the crystal structure analysis (cell data, data collection, processing, and refinement) are concisely summarised in Table 1 of the supplementary material. **(2*S*,3*S*,4*R*,5*S*)-2-Phenyl-3-carbethoxy-4-iodo-5-methyltetrahydrofuran (*syn*-11e)**: IR ($CCl_4$) 3091, 3069, 3031, 2980, 2950, 2926, 2869, 1746, 1497, 1457, 1438, 1381, 1303, 1251, 1222, 1203, 1173, 1138, 1092, 1057, 1016, 979, 960, 908, 865, 700 $cm^{-1}$; $^1H$ NMR $\delta$ 7.28–7.14 (m, 5H), 5.29 (d, 1H, $J$ = 6.4 Hz), 4.81 (dq, 1H, $J$ = 10.0, 6.4 Hz), 3.98 (dd, 1H, $J$ = 10.0, 6.4 Hz), 3.59 (t, 1H, $J$ = 6.0 Hz), 3.22 (s, 3H), 1.38 (d, 3H, $J$ = 6.0 Hz); $^{13}C$ NMR $\delta$ 128.04, 127.82, 125.51, 82.38, 80.52, 58.59, 51.31, 23.98, 17.98; HRMS $C_{13}H_{15}O_3I$ calcd 219.1022 (M - I), found 219.1022.

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**Supplementary Material Available:** Summary of data collection details and copies of $^1H$ NMR spectra of all compounds (53 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfiche version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.