JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

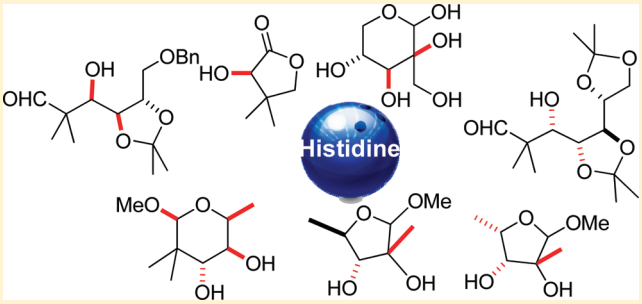
Histidine-Catalyzed Asymmetric Aldol Addition of Enolizable Aldehydes: Insights into its Mechanism

Ulf Scheffler and Rainer Mahrwald*

Institute of Chemistry, Humboldt University, Brook-Taylor Strasse 2, 12489 Berlin, Germany

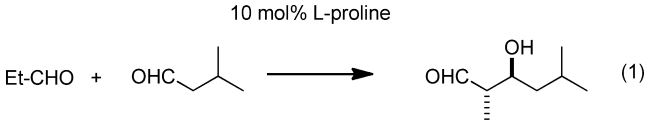
Supporting Information

ABSTRACT: Extensive studies of asymmetric cross-aldol addition between enolizable aldehydes are described and provide a deeper insight into histidine-catalyzed aldol additions. In particular, aspects of enantio- as well as diastereoselectivity of these reactions are discussed. Rules and predictions of configurative outcome are explained by using different transition-state models. These discussions are confirmed by extensive computations.



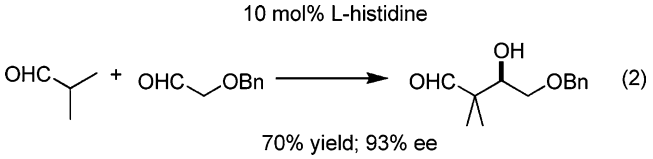
INTRODUCTION

Over the past decade, extremely valuable results and progress have been realized in organocatalyzed asymmetric aldol additions. In particular, studies by MacMillan have outlined the first examples of direct and enantioselective cross-aldol reactions of enolizable aldehydes in the presence of catalytic amounts of proline.[1] This new aldol methodology allows the direct and asymmetric coupling of different enolizable aldehydes. After the first reports of proline-catalyzed cross-aldol additions between enolizable aldehydes,[2] protocols on catalytic transformation in the presence of proline derivatives,[3] chiral imidazolinones,[4] chiral 1,2-diamines,[5] and chiral sulfonamides[6] were published. Though these transformations are extremely high enantioselective coupling processes, there are several problems that could not be solved by these reactions. Because of the instability of the intermediate enamines,[7] α-branched enolizable aldehydes exclusively react as carbonyl components in these transformations. In contrast, α-unbranched enolizable aldehydes can react as carbonyl components as well as enol components. This problem can be overcome by utilization of a syringe pump technique. A highlight of this development is shown in eq 1. Both aldehydes, propionaldehyde



as well as isovaleraldehyde, bear two α-methylene protons, but only one regioisomer could be detected by ^{1}H NMR analysis in this reaction.[1]

We have recently described preliminary results of asymmetric histidine-catalyzed cross-aldol addition of enolizable aldehydes.[8] Histidine is able to discriminate deployed aldehydes based on their electronic nature. Electron-rich aldehydes react exclusively as nucleophiles, whereas electron-deficient aldehydes react as carbonyl compounds (eq 2). Thus, when used with α-branched



electron-rich aldehydes this reaction gives access to α-quaternary carbon atoms. Artificial reaction conditions such as syringe pump techniques are not necessary because of this strict differentiation.

Herein, we describe experiments that provide a general extension of this transformation. In addition, we offer a deeper insight into the mechanism and configuration of this reaction.

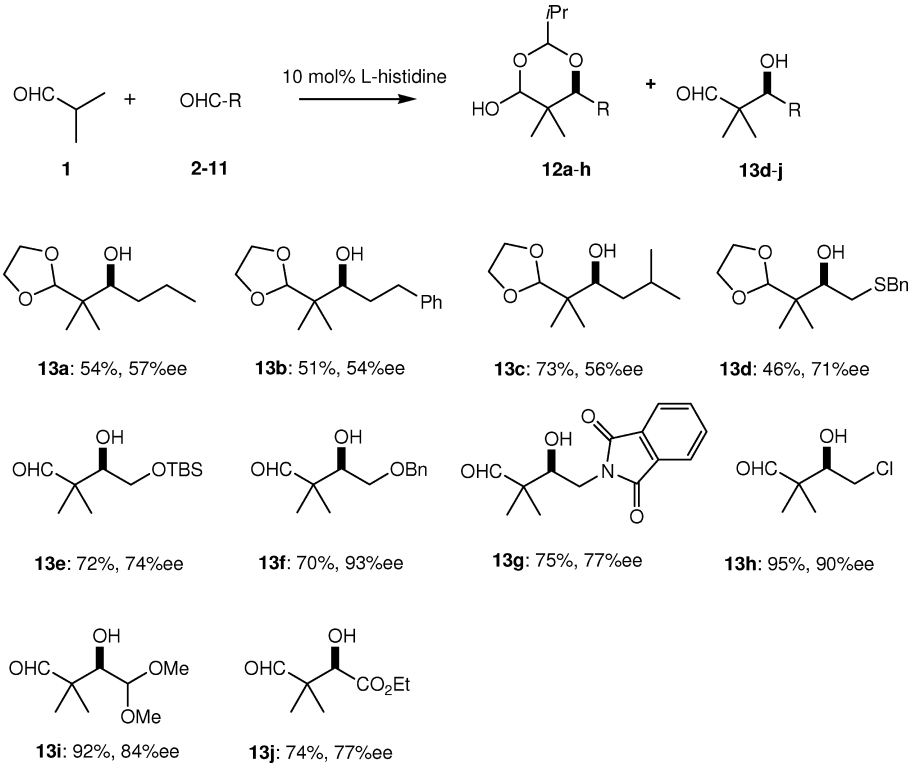
RESULTS AND DISCUSSION

Reactions of Achiral Aldehydes. In order to explore the scope and limitations of this histidine-catalyzed aldol addition, several series of different substrates have been examined. The results will be discussed in this paper to provide a more general insight into the configurative events of this histidine-catalyzed aldol addition. In a first set, isobutyraldehyde **1** was reacted as the enol component with several different aldehydes **2**−**11** as electrophiles. During these reactions, a differing ratio of aldol adducts **13e**−**j** and the corresponding isobutyracetals **12a**−**h** was detected (Scheme 1). The degree of acetalization can be influenced only to a very small degree by the stoichiometry of reactants (on that basis, the amount of isobutyraldehyde **1** was adjusted (1−2 equiv 1 relative to the electrophile)). In order to avoid troublesome separation and identification of

Received: December 20, 2011
Published: February 6, 2012

   dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310−2330

Scheme 1. Histidine-Catalyzed Aldol Additions of Isobutyraldehyde[a]

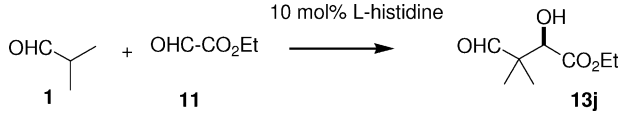


[a]Reaction conditions: 10 mol % of histidine in 0.2 mL of water, 5.5 respectively, 10 mmol of **1** and 5 mmol of **2**–**11**, rt. **13a**–**d**: yields after transformation into corresponding dioxolanes. **13e**–**j**: combined yields of acetals and aldol adducts.

stereoisomers, acetals **12a**–**d** were converted and purified as their corresponding 1,3-dioxolanes **13a**–**d**. In contrast, the corresponding hydroxy aldehydes **13e**–**j** were isolated in good to high yields when used with the more reactive aldehydes **6**–**11** as carbonyl components. The formation of acetals **12a**–**h** is mainly dictated by the electronic nature of the electrophile. Also, the formation of acetals correlates with reaction time. The longer the reaction time, the greater the degree of acetalization. (For detailed information about the degree of acetalization, see the Supporting Information.) A similar trend is observed in stereoselectivity. When used with relative electron-rich aldehydes **2**–**5**, moderate enantioselectivities were detected in aldol adducts **13a**–**d**. The more reactive carbonyl components **6**–**11** yield aldol adducts **13e**–**j** with good to high levels of enantioselectivity. Even in reactions of electron-rich aldehydes, a strong preference for the formation of quaternary centers was detected. Products **13a**–**c** were isolated without relevant amounts of homoaldol adducts of α-unbranched aldehydes **2**–**5**. Instead of that, the homo aldol adduct of isobutyraldehyde **1** was detected as the major byproduct.

An inadequate reproducibility was observed in reactions of ethyl glyoxylate **11** (toluenic solution) with isobutyraldehyde **1**. Ethyl glyoxylate **11** is known as a very reactive aldehyde, but toluene turned out to be the wrong solvent in these reactions. For that reason, several additional solvents were tested in this model reaction (Table 1). These interesting results represent an excerpt of more detailed investigation which is found in the Experimental Section. No reaction occurs when used with ethyl glyoxylate **11** in toluene and isobutyraldehyde **1** (entry 1, Table 1). A reaction is observed at varying levels by addition of different solvents.

Table 1. Influence of Solvent on Histidine-Catalyzed Aldol Addition[a]



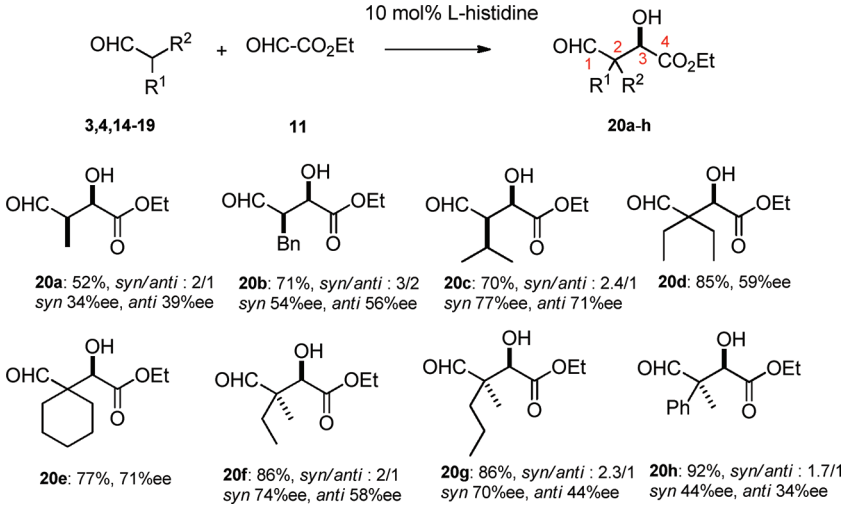
entry	solvent	yield (%)	ee (%)	time (h)
1	toluene	–	–	120
2	DMSO	7	<10	36
3	MeCN	22	41	60
4	Cl_3CCN	31	28	36
5	$HO(CH)_3–OH$	34	67	24
6	$HO(CH)_2–OH$	74	77	20
7	H_2O	23	60	20
8	H_2O	65	65	16[b]

[a]Reaction conditions: 10 mol % of histidine in 1.0 mL of solvent, 5 mmol of isobutyraldehyde, and ethyl glyoxylate, rt. [b]10 mol % of histidine in 0.2 mL of water, 5 mmol of isobutyraldehyde, and ethyl glyoxylate, rt.

The highest yields as well as enantioselectivities were observed by adding ethylene glycol. Also, water is accelerating this reaction as well. However, there is an optimum for the use of water as can be seen by comparing entries 7 and 8 in Table 1. Large amounts of water sharply decrease yields, whereas equimolar amounts of water relative to the reactants strongly increase yields. Interestingly, a very low influence on enantioselectivity was observed in both cases (compare entries 7 and 8, Table 1). By deployment of aqueous buffer systems or solutions of different salts as solvents a clear decrease in yield and selectivity was observed. A neutral pH value turned out to be essential. On the

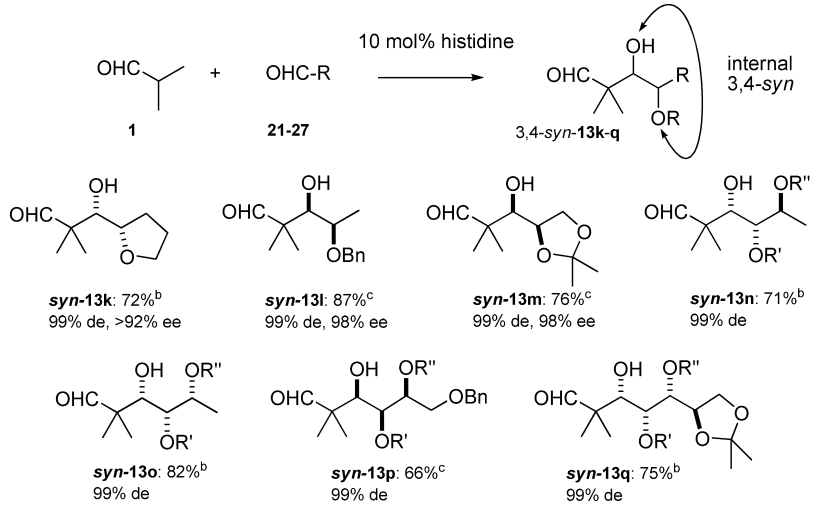
dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310–2330

Scheme 2. Histidine-Catalyzed Aldol Additions of Ethyl Glyoxylate and Enolizable Aldehydes[a]



[a]Reaction conditions: 10 mol % of histidine in 1.0 mL of solvent, 5 mmol of isobutyraldehyde and ethyl glyoxylate, rt. Numbering: for clarity and ease of comparison between results the aldehyde functionality of the aldol adducts was set as 1-position for all examples in this paper. In order to define *syn*- or *anti*-configuration of aldol products, the substituents of the aldol chain are specified by priority rules (CIP rules).

Scheme 3. Histidine-Catalyzed Diastereoselective Aldol Addition of Chiral Oxygen-Containing Aldehydes to Isobutyraldehyde (Matched Situation)[a]



[a]Reaction conditions: 10 mol % of histidine in 0.2 mL of water, 5.5 mmol of **1**, and 5 mmol of **21**−**27**, rt. [b]D-Histidine. [c]L-Histidine, R′ = R″ = CMe_2. Absolute and relative configuration as well as enantiomeric excess were determined for products **13k**−**m** to exclude a potential racemization of the electrophile. To exclude epimerization in aldol adducts **13n**−**q** simple determination of the relative configuration is necessary.

basis of these findings, ethylene glycol was used as standard solvent in further reactions of ethyl glyoxylate **11** with different aldehydes as enol components (Scheme 2).

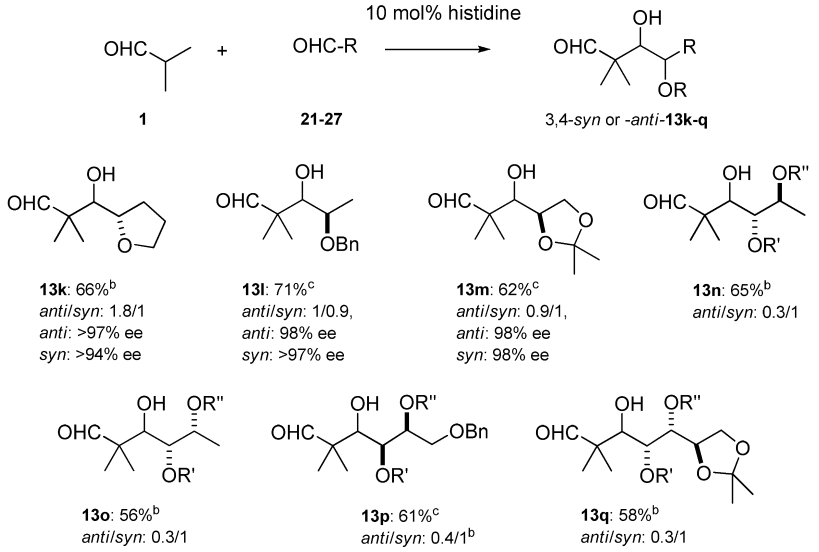
In contrast to the well-known *anti*-selective proline catalysis, the aldol adducts in this series were detected in moderate 2,3-*syn*-diastereoselectivity. When used with α-branched aldehydes an increasing of enantiomeric excess is observed. The formation of aldol adduct **20h** represents an exception with regard to enantioselectivity (44% ee). This is suspected to be attributable to the formation of conjugated enamine of hydratropaldehyde **19**. Similar results relating to yields and selectivities were obtained when used with dimethoxyacetaldehyde **10** as carbonyl component.[8a] β-Hydroxy aldehydes **20a**−**h** were transformed into the corresponding 2-hydroxy-α-lactones by reduction with $NaBH_4$ and subsequent acidic treatment in good to excellent yields. Determination of simple diastereoselectivity was determined at the stage of the corresponding γ-lactones. Absolute configuration was determined for aldehydes **20a**−**c** at the stage of the corresponding γ-lactones and directly for the aldehydes **20d**−**h** (see the Supporting Informations).

Reactions of Chiral Carbonyl Components. Inspired by these results, chiral oxygen-substituted aldehydes were tested in a next series of transformations. In order to explore the stereochemical direction, several different chiral aldehydes were reacted with isobutyraldehyde in the presence of catalytic amounts of L- and D-histidine.

A matched situation is observed when used with L-histidine and (*R*)-configured α-chiral aldehydes or D-histidine and

dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310−2330

Scheme 4. Histidine-Catalyzed Aldol Addition of Chiral Oxygen-Containing Aldehydes to Isobutyraldehyde (Mismatched Situation)[a]



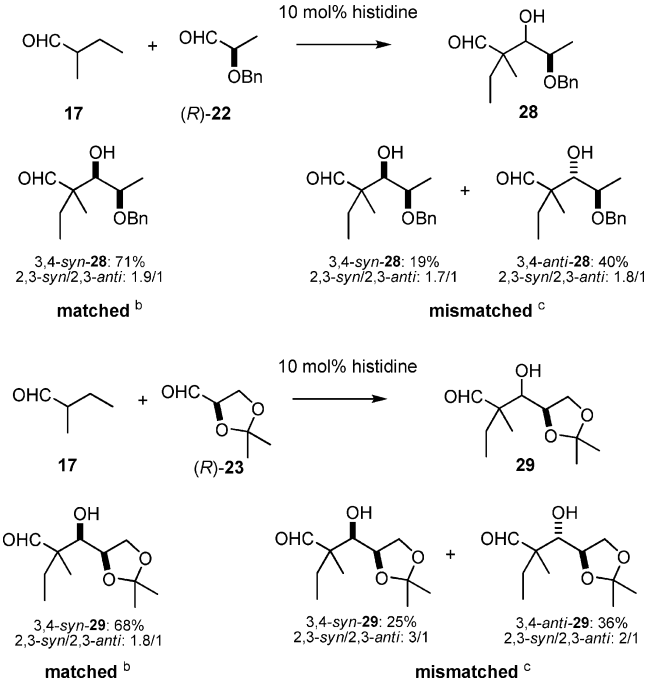
[a]Reaction conditions: 10 mol % of histidine in 0.2 mL of water, 5.5 mmol of **1**, and 5 mmol of **21**–**27**, rt. [b]L-Histidine. [c]D-Histidine. R′ = R″ = CMe_2. Absolute and relative configuration as well as enantiomeric excess were determined for products **13k**–**m** to exclude a potential racemization of the electrophile. To exclude epimerization in aldol adducts **13n**–**q** simple determination of the relative configuration is necessary.

(*S*)-configured aldehydes **21**–**27** (Scheme 3). The aldol adducts **13k**–**q** were isolated with extremely high degrees of diastereoselectivity. The formation of acetals was not detected. Racemization or epimerization of starting aldehydes were not observed under these reaction conditions. Thus, enantiopure products were isolated. Exclusively 3,4-*syn*-configured aldol adducts were detected. Both the configurational stability of chiral aldehydes **21**–**27** as well as the exceptionally high internal *syn*-diastereoselectivity dictate the configurative installation of the *β*-hydroxy group in aldol adducts **13k**–**q**.

When used with L-histidine and (*S*)-configured *α*-chiral aldehydes respectively D-histidine and (*R*)-configured *α*-chiral aldehydes the mismatched situation is observed (Scheme 4). Aldol adducts **13k**–**q** were observed with slightly lower yields (approximately 10%; compare the results of Scheme 3 with those of Scheme 4). The most outstanding feature of these transformations is the complete breakdown of diastereoselectivity compared with the matched series (Scheme 3). Both diastereoisomers, the *anti*- as well as the *syn*-configured aldol adducts, were isolated in a ratio of nearly 1:1 (**13k**–**m**). A slight increase of *syn*-diastereoselectivity is observed when used with aldehydes bearing large substituents (**13n**–**q**). It is assumed that only the *α*-chiral center of the aldehydes has a noticeable influence on the reaction. Comparison of the results of **13n** and **13o** indicates no influence of the *β*-stereocenter of the reactants on diastereoselectivity. *Syn*- as well as *anti*-configured diastereoisomers **13k**–**q** were detected in enantiopure form.

In order to gain a deeper insight into diastereocontrol of histidine-catalyzed aldol reactions, we also tested the combination of chiral electrophiles and differently substituted *α*-branched nucleophiles. To this end, racemic 2-methylbutyraldehyde **17** was reacted with *α*-chiral aldehydes **22** and **23** in the presence of D- or L-histidine (Scheme 5). Remarkable differences in 2,3-selectivity could not be detected by comparing these results with those of Scheme 2 (compare **20f** in Scheme 2 with **28** and **29** in Scheme 5). In addition, the internal 3,4-diastereoselectivity is comparable to the corresponding reactions of isobutyraldehyde **1**. In the mismatched case, an enhancement of the formation of 3,4-*anti*-configured product is detected

Scheme 5. Histidine-Catalyzed Aldol Addition of *α*-Chiral Oxygen-Containing Aldehydes to 2-Methylbutyraldehyde[a]



[a]Reaction conditions: 10 mol % of histidine in 0.2 mL of water, 5.5 mmol of **17**, and 5 mmol of **22**–**23**, rt.

[b]L-Histidine.

[c]D-Histidine. Racemization of the carbonyl component was not observed.

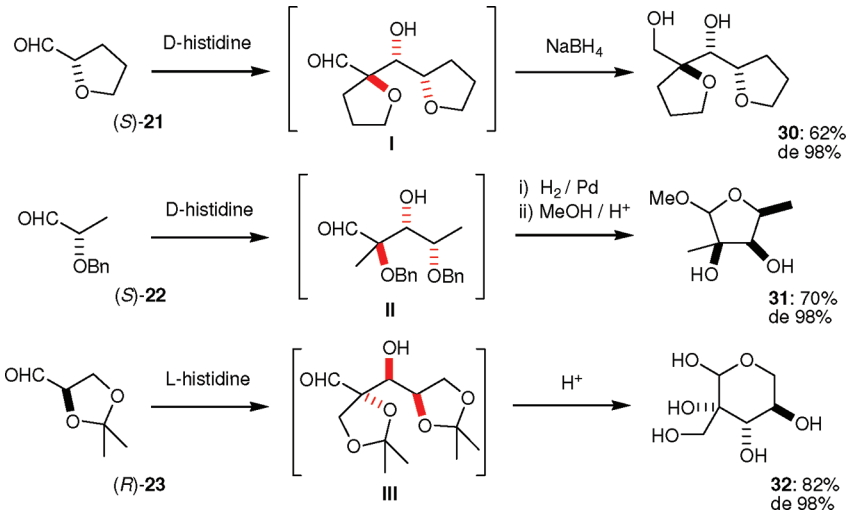
dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310–2330

(compare **13l** and **13m**, Schemes 3 and 4). These results indicate that the α-chiral center of the electrophile has a very low influence on the 2,3-diastereoselectivity.

Homodimerization Reactions of Chiral Aldehydes. In a further series of experiments, we tested chiral oxygen-containing aldehydes in homoaldol additions (Scheme 6). Once again, matched/mismatched situations were observed in these transformations but not to the extent as discussed previously (compare the results of Schemes 3 and 4 with those of Schemes 6 and 7). Similar yields, diastereoselectivities, and enantioselectivities were detected in both series. Thus, even the mismatched case becomes a valuable tool for stereoselective synthesis. Again, the matched situation is dictated by the α-chiral center of the carbonyl compound. In the matched series, only one stereoisomer was detected (Scheme 6). The internal 3,4-*syn*-configuration is observed exclusively as an outstanding feature of matched histidine-catalyzed aldol additions. In contrast to previous results bond formation proceeds quantitatively *anti*-selective (compare results of Scheme 6 with those of Scheme 2). Structures in brackets were not detected. The actual acetal structure has been omitted for a clear illustration of the configurative outcome.

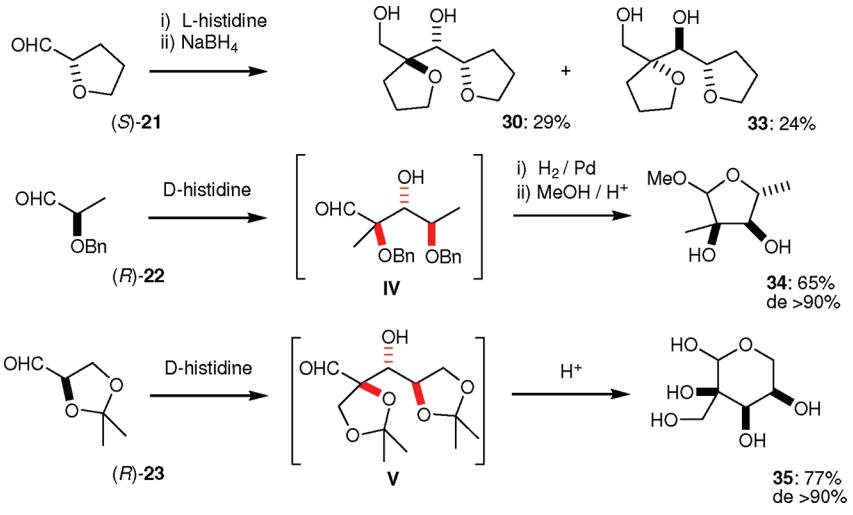
In the following series, we have realized the mismatched situation (Scheme 7). When used with (*S*)-configured aldehyde **21** in the presence of L-histidine two diastereoisomers **33** and **30** were detected in a ratio of approximately 1:1. Furthermore, aldol adducts **30** and **33** were isolated with lower yields (53% compared to 62% compound **30** in Scheme 6). When used with aldehydes **22** and **23**, aldol adducts **34** and **35** were isolated with slightly lower yields though with nearly the same high stereoselectivities as observed in the matched series (compare **31** and **32**, Scheme 6, with **34** and **35**, Scheme 7). Again the bond formation proceeds quantitatively *anti*-selective, but the outstanding feature of mismatched homodimerization reactions is a moderate to excellent internal 3,4-*anti*-configuration.

Scheme 6. Matched Homoaldol Additions of α-Chiral Aldehydes[a]



[a]Reaction conditions: 3.3 mol % of histidine in 0.1 mL of water, 6 mmol of **21**−**23**, rt. The aldol adducts form acetals quantitatively, though these acetals can be very labile. Racemization of the carbonyl component was not observed. Products **30**−**32** were isolated in enantio- and diastereopure form.

Scheme 7. Mismatched Homoaldol Additions of α-Chiral Aldehydes[a]

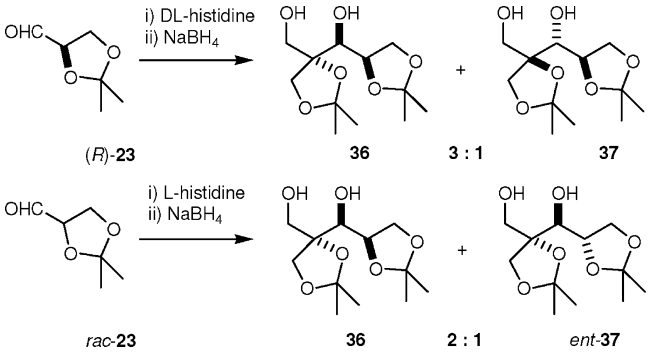


[a]Reaction conditions: 3.3 mol % of histidine in 0.1 mL of water, 6 mmol of **21**−**23**, rt. Racemization of the carbonyl component was not observed. Products **30** and **33**−**35** were isolated in enantiopure form.

dx.doi.org/10.1021/jo202558f | *J. Org. Chem.* 2012, 77, 2310−2330

The existence of a matched/mismatched situation was demonstrated conclusively by following experiments. Homodimerization of protected glyceraldehyde **23** was accomplished with catalytic amounts of racemic histidine. On the other hand racemic aldehyde **23** was reacted with L-histidine (Scheme 8).

Scheme 8. Matched and Mismatched Homodimerization of Isopropylideneglyceraldehyde under Competitive Conditions[a]



[a]Reaction conditions: (i) 3.3 mol % of histidine in 0.1 mL of water, 6 mmol of **21**–**23**, rt; (ii) $NaBH_4$, *i*-PrOH, rt.

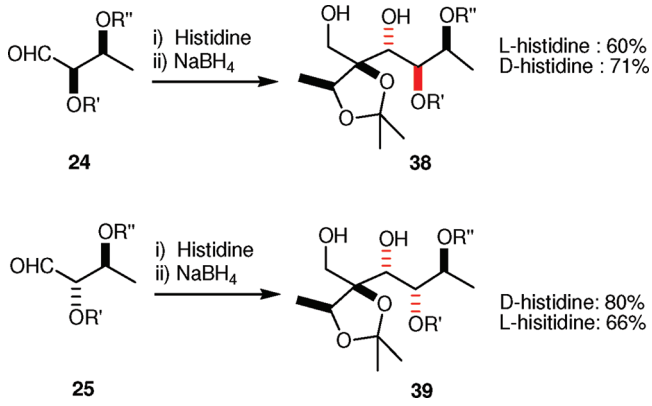
Both reactions were quenched before full conversion was observed (reaction time 30 h). For reasons of simplicity regarding the isolation as well as identification the reduction products of these reactions were analyzed. On the basis of the conditions, the matched reaction competes with the mismatched reaction. Thus, the faster reaction provides higher yield. Unambiguously, product **36** was identified as the matched product (respectively identically configured compound **32**, Scheme 6).

In summary, matched homodimerizations of oxygen-containing α-chiral aldehydes result in 2,3-*anti*-3,4-*syn*-configured aldol adducts with excellent stereoselectivities. The mismatched situation gives access to 2,3-*anti*-3,4-*anti*-configured products (with the restriction for **30**, Scheme 7). 2,3-*Syn*-configured diastereoisomers were not detected.

In contrast to homodimerization of α-chiral aldehydes (Schemes 6 and 7), homodimerizations of α,β-chiral aldehydes proceed with excellent diastereoselectivities by deployment of L- as well as D-histidine. To this end, we tested aldehydes **24** and **25** (Scheme 9). The (*S*)-configured β-chiral center of the nucleophiles alone dictates the diastereoselective outcome of these reactions. The products were isolated with an extremely high degree of 2,3-*anti*-configuration. Furthermore, the installation of the chiral center in 3-position proceeds completely (*R*)-selective independent of the deployed catalyst. Thus, neither the configuration of histidine nor the configuration of the carbonyl aldehyde have a relevant influence on the configuration during the C–C bond formation process (compare the results of **38** and **39**, Scheme 9). In addition, an optional access to 3,4-*syn*- or 3,4-*anti*-configured aldol adducts as observed by deployment of L- or D-histidine in the α-chiral aldehyde series is not possible (compare results of Scheme 6 and 7 with those of Scheme 9).

Note that other enantiomers of aldol products described in Schemes 1 and 2 are available with same yields and stereoselectivities by deployment of D-histidine. Access to both enantiomers of Schemes 3–9 is given by optional deployment of L- or D-histidine and (*R*)- or (*S*)-configured chiral aldehydes.

Scheme 9. Histidine-Catalyzed Homodimerization of α,β-Chiral Aldehydes[a]



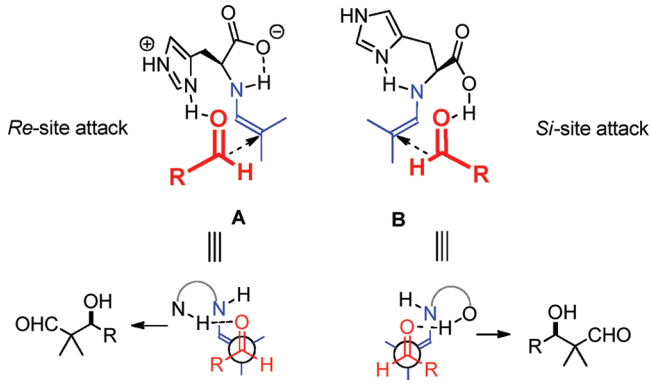
[a]Reaction conditions: 3.3 mol % of histidine in 0.1 mL of water, 6 mmol of **24**–**25**, rt. R′ = R″ = CMe_2. Epimerization of the carbonyl component was not observed. Products **38** and **39** were isolated in enantio- and diastereopure form.

This general statement has been proven by several experimental series.

Reaction Mechanism. We have described the reaction pathway in histidine catalysis in a previous paper in cooperation with Ken Houk et al. In particular, aspects of enantioselectivity as well as simple diastereoselectivity were discussed and confirmed by extensive computations.[9] The reaction proceeds via an enamine mechanism and the attraction of carbonyl aldehyde by hydrogen bonds. The enamine is formed by the primary amine of the amino acid permitting the deployment of α-branched aldehydes.

In contrast to proline, histidine contains two possible hydrogen bond donators. Thus, the two most favorable transition states lead to opposite chirality of the products (Scheme 10). The energy

Scheme 10. General Transition States for L-Histidine in Reactions of Isobutyraldehyde



difference between these two transition states determines the obtained selectivity.

The preferred zwitterionic transition state **A** results in the *Re*-attack using L-histidine. Attraction of the electrophile is realized by the imidazolium group. This situation explains the configuration of products discussed in Schemes 1 and 2. The uncharged transition state **B** is very important to understand the complex situation of diastereoselectivity in histidine catalysis. It opens another reaction pathway if **A** is disfavored because of the configuration of chiral aldehydes (mismatched

dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310–2330

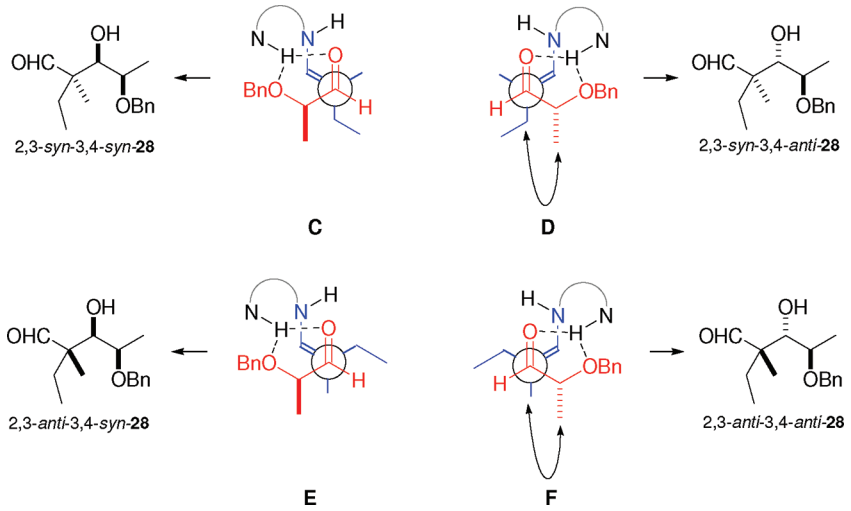
case). In transition state **B**, the attraction of the electrophile is realized by the carboxylic group.

The diastereoselective outcome of the reactions described above is determined by the structure of the particular enamine and the orientation of the carbonyl compound. Aldol reactions of aldehydes **17** and (*R*)-**22** were selected as examples (Schemes 11 and 12). These considerations can easily be transferred to aldol reactions with other aldehydes. The moiety of the carbonyl aldehyde occupies a pseudoaxial position as illustrated in transition states **A** and **B** for reactions with isobutyraldehyde. Thus, reactions of the *E*-enamine of aldehydes **17** or (*R*)-**22** gives access to 2,3-*syn*-configured aldol adducts and the *Z*-enamine to 2,3-*anti*-configured products, respectively. When used with unfunctionalized enol components, *E*-enamine will be formed predominantly resulting in a moderate *syn*-selectivity of the products (transition-state model **C** and **D** in Scheme 11). These considerations are related to the results of **20a−c**, **f−h** in Scheme 2 and **28** and **29** in Scheme 5.

When used with functionalized, chiral aldehydes the formation of the relative 3,4-configuration is dictated by a *Re*- or *Si*-site attack at the carbonyl component (Scheme 3−9). The configurative findings are in agreement with those obtained in Cram-chelate-selective reactions. α-Oxygen atoms are able to act as additional hydrogen bond acceptors for the imidazolium- as well as for the carboxylic-proton. The excellent diastereoselectivity in the matched situation is the result of the constructive influence of the catalyst. The mentioned hydrogen bond can be formed effectively if (*R*)-configured carbonyl aldehydes and L-histidine are deployed. As a consequence of that, the electrophiles are attacked at their *Re*-site. These findings match the preferred attraction of the carbonyl compound by the imidazolium group as illustrated in Scheme 11 (matched case, Schemes 3 and 6) (models **C** and **E**).

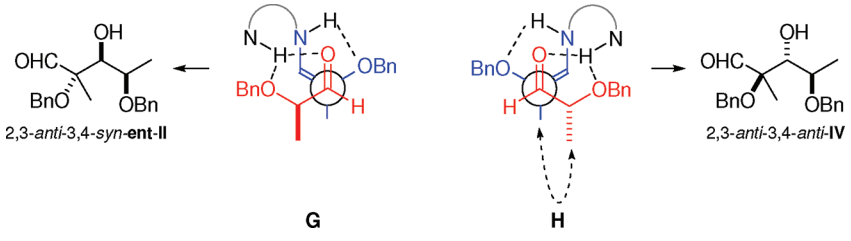
In contrast, when used with D-histidine, the imidazolium group directs the electrophile to a *Si*-site attack in the mismatched case (Scheme 4, **21** in Scheme 7). On the basis of these considerations, 3,4-*anti*-configured products should be favored. However, instead, a mixture of 3,4-*syn*- and 3,4-*anti*-configured products was detected (3/1 to 1/1). An explanation for this apparent contradiction is given by the following assumption. Because of steric interactions (demonstrated in transitions state models **D** or **F**), the reaction switches partially to transition state **B**, which is still an option to proceed with formation of the additional hydrogen bond. Following this pathway, the same *syn*-configured products as in the matched case are achieved even though the catalyst of opposite chirality is applied.

Scheme 11. Schematic Models for Reactions of 2-Methylbutyraldehyde and (*R*)-Benzyloxypropionaldehyde with Internal and External Diastereodifferentiation[a]



[a]These models are related to reactions of Schemes 2−5. For reactions in Scheme 2, no matched/mismatched situation can occur. Thus models can be simplified to *E*- and *Z*-enamine formation. For reactions of Schemes 3 and 4, configuration of the enamine is irrelevant. Thus models can be simplified considering no 2,3-selectivity. **C**: L-histidine; *E*-enamine; (*R*)-**22** (matched); **E**: L-histidine; *Z*-enamine; (*R*)-**22** (matched); **D**: D-histidine; *E*-enamine; (*R*)-**22** (mismatched); **F**: D-histidine; *Z*-enamine; (*R*)-**22** (mismatched); models for attraction of the carbonyl component by the carboxylic group (transition state **B**) are not depicted because they relate to **C**−**F** except for the directing group.

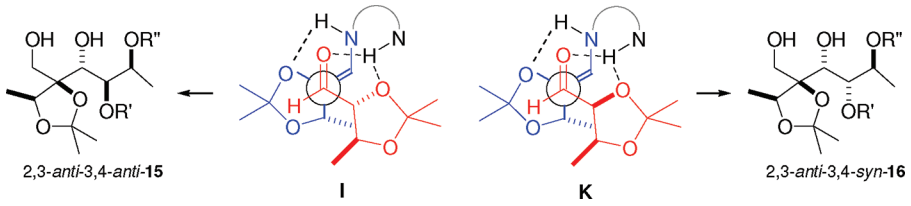
Scheme 12. Transition State Models for Homodimerization Reactions of (*R*)-Benzyloxypropionaldehyde with Internal and External Diastereodifferentiation[a]



[a]These models are related to reactions in Schemes 6−8; **G**: L-histidine; *Z*-enamine; (*R*)-**22** (matched); **H**: D-histidine; *Z*-enamine; (*R*)-**22** (mismatched).

dx.doi.org/10.1021/jo202558f | *J. Org. Chem.* 2012, 77, 2310−2330

Scheme 13. Transition State Models for Homodimerization of Aldehydes 24 and 25[a]



[a]R′ = R″ = CMe_2; these models are related to reactions in Scheme 9; **I**: D-histidine; *Z*-enamine; (*R.S*)-**24**; **K**: D-histidine; *Z*-enamine; (*S.S*)-**25**; models for L-histidine are not depicted because they relate to **I** and **K** except for the directing group.

When used with α-chiral oxygen-containing enol components in homoaldol additions, *Z*-enamine is formed exclusively due to another additional hydrogen bond with the enamine proton (**G** and **H**, Scheme 12).[10] As a result of that, the C−C bond formation process proceeds with an extremely high degree of 2,3-*anti*-diastereoselectivity. This is observed in matched as well as in mismatched series (Schemes 6 and 7). Again, the matched reaction yields 3,4-*syn*-configured products. In contrast to reactions of unfunctionalized nucleophiles, the mismatched reaction also proceeds with excellent diastereocontrol. Compared to the matched situation, the aldol adducts were isolated with a high degree of 3,4-*anti*-diastereoselectivity (Scheme 7). Because of the enamine hydrogen bond, it is assumed that steric interactions are very low between the enamine and electrophile moiety in these reactions, compared to aldol additions of isobutyraldehyde **1** or 2-methylbutyraldehyde **17** with chiral oxygen-containing aldehydes (transition-state model **H**, Scheme 12). Thus, a switch to transition state **B** is unfavored.

These considerations are impressively supported by results of homodimerizations of both diastereoisomers of α,β-chiral aldehydes **24** and **25** (Scheme 9). The β-chiral centers of the nucleophiles dictate the stereochemical outcome of these reactions. Because of the cyclic structure of the chiral enamine, the γ-methyl substituent prevents the attack at the carbonyl aldehyde by the (*Si*)-site of the enamine (Scheme 13). The formation of *Z*-enamine is strongly supported by experimental data. In reactions of *E*-enamine, different diastereoisomers would have to be obtained. Also, by deployment of both D- or L-histidine the same configured aldol adducts **38** or **39** are isolated. These results support the existence of the two reaction pathways **A** and **B** since L- as well as D-catalyst must have the possibility to assist the *Si*-attack at the electrophile to give the same products. Again, yields are slightly higher if the carbonyl attraction can be accomplished by the imidazolium group (Scheme 9).

CONCLUSION

In summary, we have given a comprehensive overview of the possibilities in histidine-catalyzed direct aldol additions between enolizable aldehydes. Rules and tendencies for the application as well as prediction of the stereochemical outcome were explained and supported by different transition state models. This insight into histidine catalysis is especially important for synthetic prediction of new compounds. These transformations are characterized by operationally simple and very mild conditions, high stereoselectivities and yields. We are convinced that histidine catalysis will prove of much value as a key tool in total synthesis. This is already demonstrated by contemplating structures in this paper. In particular this has been demonstrated by the first organocatalytic synthesis of D-hamamelose **35**[11] and the first total synthesis of 2-C-methyl-D-5-deoxyribose **34**,[12] which is the carbohydrate moiety of Trachycladines A and B.[13] 2-Hydroxypropanoates **20a−h** were transformed into the corresponding 2-hydroxy-γ-lactones.[14] This implies the total synthesis of pantolactone[15] (derivative of **13j**) and 3-hydroxy-4-ethyl-4-methyldihydrofuran-2-one (derivative of *anti*-**20f**).[16]

EXPERIMENTAL SECTION

General Methods. Commercially available aldehydes **1−4** and **14−19** were freshly distilled before use. *tert*-Butyldimethylsilyloxyacetaldehyde **6** and benzyloxyacetaldehyde **7**, chloroacetaldehyde **9** (50% aqueous solution), 2,2-dimethoxyacetaldehyde **10** (60% aqueous solution), and ethyl glyoxylate **11** (50% in toluene) were used as purchased. Additional aldehydes were prepared according to published protocols: **5**,[17] **8**,[18] **21**,[19] *R*-**22**,[20] *S*-**22**,[21] **23**,[22] **24**,[23] **25**,[24] **26**,[25] and **27**.[26] ^{1}H NMR and ^{13}C NMR spectra were recorded at 300, 400, or 500 and 75, 100, or 125 MHz, respectively. Chemical shifts are given in ppm and coupling constants in Hz. Purification of products was accomplished by flash chromatography (silica gel 60, particle size 0.04−0.063 mm). Yields were determined after column chromatography. Thin-layer chromatography was performed with silica gel 60 F_{254} TLC plates. Development was performed either with cer(IV)-sulfate/phosphomolybdic acid or $KMnO_4$ solutions. The structures were refined with SHELX97 (Sheldrick, G. M. Program for Crystal Structure Refinement, Universität Göttingen).

General Reaction Procedures. *General Aldol Procedure A (Synthesis of Compounds **13a−d**).* In these experiments, relevant amounts of the corresponding hemiacetals **12** were detected. In a typical experiment, 78 mg of L-histidine (0.5 mmol) was added to a mixture of isobutyraldehyde **1** (10 mmol) and 5 mmol of corresponding aldehydes **2−5** and 200 mg of water. The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After completion of the reaction (5−7 days), the mixture was quenched with acetone, dried ($MgSO_4$), and filtrated. The filtrate was evaporated in vacuo. The remaining residue was dissolved in 1.0 mL of glycol and 5 mL of THF, and then 0.5 mmol of toluenesulfonic acid was added. The reaction was monitored by TLC. After completion (∼12 h, rt) the reaction mixture was neutralized, filtrated, absorbed to Celite, and purified by column chromatography (hexane/acetone 19/1−4/1).

*General Aldol Procedure B (Synthesis of Compounds **13e−j**).* In these experiments, the corresponding hemiacetals **12** were detected only in minority. In a typical experiment, 78 mg of L-histidine (0.5 mmol) was added to a mixture of isobutyraldehyde **1** (5.5−6 mmol) and 5 mmol of corresponding aldehydes **6−11** and 200 mg of water (note: since aldehydes **9** and **10** are already applied as aqueous solutions no water needs to be added). The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After completion of the reaction (16 h to 4 days), the mixture was quenched with acetone, dried ($MgSO_4$), and filtrated. The filtrate was absorbed to Celite and evaporated in vacuo, and the remaining residue was purified by column chromatography (hexane/acetone 19/1−3/1).

*General Aldol Procedure C (Synthesis of Compounds **20a−h**).* L-Histidine (155 mg) was added to a mixture of ethyl glyoxylate **11** (10 mmol, 50% in toluene), 11 mmol of corresponding aldehydes **14**, **3**, **4**, and **15−19**, and 1 mL of glycol. The reaction mixture was stirred

dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310−2330

vigorously at room temperature and monitored by TLC. After completion of the reaction (12 h to 2 days), the mixture was quenched with acetone, dried ($MgSO_4$), and filtrated. The filtrate was evaporated in vacuo with toluene (three times) and absorbed to Celite, and the remaining residue was purified by column chromatography (hexane/acetone 19/1−3/1).

*General Aldol Procedure D (Synthesis of Compounds **13k−q**).* L- or D-histidine (78 mg) was added to a mixture of isobutyraldehyde **1** (5.5 mmol), 5 mmol of corresponding aldehydes **21−27**, and 200 mg of water. The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After completion of the reaction (12 h to 2 days), the mixture was quenched with acetone, dried ($MgSO_4$), and filtrated. The filtrate was absorbed to Celite and evaporated in vacuo, and the remaining residue was purified by column chromatography (hexane/acetone 19/1−5/1).

*General Aldol Procedure E (Synthesis of Compounds **28** and **29**).* L- or D-histidine (78 mg) was added to a mixture of *rac*-2-methylbutyraldehyde **17** (5.5 mmol), 5 mmol of corresponding aldehydes **22−23**, and 200 mg of water. The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After completion of the reaction (12 h to 2 days), the mixture was quenched with acetone, dried ($MgSO_4$) and filtrated. The filtrate was absorbed to Celite and evaporated in vacuo, and the remaining residue was purified by column chromatography (hexane/acetone 19/1).

*General Aldol Procedure F (Synthesis of Compounds **30−35** and **38−39**).* L- or D-histidine (31 mg) was added to a mixture of 6 mmol of corresponding aldehydes **21−25** and 100 mg of water. The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After completion of the reaction (2−4 days), the mixture was quenched with acetone, dried ($MgSO_4$), and filtrated. The filtrate was absorbed to Celite and evaporated in vacuo, and the remaining residue was purified by column chromatography (hexane/acetone 19/1−4/1).

General Procedure for Reduction of Hemiacetals and Crude Reaction Products. In a typical experiment, 3 mmol of the corresponding hemiacetals was dissolved in *i*-PrOH, and 60 mg of $NaBH_4$ was added. The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After completion of the reaction (10 min to 2 h), the mixture was slowly quenched with acetone and after 10 min with saturated aqueous NH_4Cl solution, dried ($MgSO_4$), and filtrated. The filtrate was absorbed to Celite and evaporated in vacuo, and the remaining residue was purified by column chromatography (hexane/acetone 9/1−3/1).

*(S)-2-(1,3-Dioxolan-2-yl)-2-methylhexan-3-ol (**13a**).* Colorless oil: $[\alpha]$ = −21.8 (c = 1, $CHCl_3$) (57% ee); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.87 (s, 3H), 0.92 (s, 3H), 0.92 (t, 3H, J = 7.2), 1.28−1.66 (m, 4H), 3.56 (dd, 1H, J = 2.3, 9.8), 3.81−3.89 (m, 2H), 3.94−4.00 (m, 2H), 4.65 (s, 1H); ^{13}C NMR (75 MHz) δ = 14.1, 16.5, 19.8, 20.3, 33.2, 40.7, 64.8, 65.1, 75.3, 110.0; HRMS (CI) m/z calcd for $C_{10}H_{20}O_3$ + Na^+ 11.1305, found 211.1299.

*(S)-2-(1,3-Dioxolan-2-yl)-2-methyl-5-phenylpentan-3-ol (**13b**).* Colorless oil: $[\alpha]$ = −6.2 (c = 1, $CHCl_3$) (54% ee); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.91 (s, 3H), 0.97 (s, 3H), 1.66−1.83 (m, 2H), 2.64 (ddd, 1H, J = 6.4, 10.2, 13.6), 3.00 (ddd, 1H, J = 5.0, 10.6, 13.6), 3.64 (dd, 1H, J = 1.9, 10.7), 3.85−4.04 (m, 4H), 4.67 (s, 1H), 7.19−7.33 (m, 5H); ^{13}C NMR (75 MHz) δ = 16.5, 20.4, 33.0, 33.2, 40.7, 64.8, 65.1, 75.1, 110.0, 125.6, 128.3, 128.5, 142.7; HRMS (CI) m/z calcd for $C_{15}H_{22}O_3$ + H^+ 251.1642, found 251.1641.

*(S)-2-(1,3-Dioxolan-2-yl)-2,5-dimethylhexan-3-ol (**13c**).* Colorless oil: $[\alpha]$ = −31.6 (c = 1, $CHCl_3$) (56% ee); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.85 (s, 3H), 0.88 (d, 3H, J = 6.6), 0.91 (s, 3H), 0.92 (d, 3H, J = 6.5), 1.11 (ddd, 1H, J = 1.8, 10.3, 13.7), 1.35 (ddd, 1H, J = 3.6, 10.9, 13.6), 1.84 (ddspt, 1H, J = 3.5, 6.6, 10.2), 3.63 (dd, 1H, J = 1.9, 10.8), 3.81−3.99 (m, 4H), 4.65 (s, 1H); ^{13}C NMR (75 MHz) δ = 16.5, 20.2, 21.2, 24.2, 24.4, 40.1, 40.6, 64.8, 65.1, 73.3, 110.0; HRMS (CI) m/z calcd for $C_{11}H_{22}O_3$ + H^+ 203.1642, found 203.1642.

*(R)-1-Benzylthio-3-(1,3-dioxolan-2-yl)-3-methylbutan-2-ol (**13d**).* Colorless oil: $[\alpha]$ = −45.9 (c = 1, $CHCl_3$) (71% ee); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.84 (s, 3H), 0.92 (s, 3H), 2.43 (dd, 1H, J = 8.8, 13.6), 2.60 (dd, 1H, J = 1.2, 13.7), 3.71 (dd, 1H, J = 1.3, 8.7), 3.72−3.79 (m, 2H), 3.81−3.98 (m, 4H), 4.69 (s, 1H), 7.23−7.36 (m, 5H); ^{13}C NMR (75 MHz) δ = 16.9, 19.1, 33.8, 35.9, 41.0, 64.9, 65.1, 73.7, 108.6, 127.0, 128.4, 129.0, 138.2; HRMS (CI) m/z calcd for $C_{15}H_{22}O_3S$ + H^+ 283.1362, found 283.1363.

*(R)-4-tert-Butyldimethylsilyloxy-3-hydroxy-2,2-dimethylbutanal (**13e**).* Colorless oil: $[\alpha]$ = −8.5 (c = 1, $CHCl_3$) (74% ee); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.87 (s, 3H), 0.88 (s, 9H), 0.90 (s, 3H), 1.08 (s, 3H), 1.10 (s, 3H), 3.57 (dd, 1H, J = 6.8, 10.0), 3.68 (dd, 1H, J = 3.6, 10.0), 3.73 (dd, 1H, J = 3.6, 6.8), 9.60 (s, 1H); ^{13}C NMR (75 MHz) δ = −5.5, −5.5, −3.6, 17.9, 19.0, 25.8, 48.5, 63.2, 75.8, 205.4; HRMS (CI) m/z calcd for $C_{12}H_{26}O_3Si$ + H^+ 247.1724, found 247.1726.

*(R)-4-Benzyloxy-3-hydroxy-2,2-dimethylbutanal (**13f**).* Colorless oil: $[\alpha]$ = −8.7 (c = 1, $CHCl_3$) (93% ee); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.11 (s, 3H), 1.12 (s, 3H), 3.49 (dd, 1H, J = 7.4, 9.6 Hz), 3.59 (dd, 1H, J = 3.4, 9.6), 3.94 (dd, 1H, J = 3.3, 7.4), 4.6 (s, 2H), 7.2−7.5 (m, 5H), 9.60 (s, 1H). ^{13}C NMR (75 MHz) δ = 17.7, 19.0, 48.7, 70.6, 73.5, 74.3, 127.8, 127.9, 128.5, 137.6, 206.5; HRMS (CI) m/z calcd for $C_{13}H_{18}O_3$ + H^+ 223.1329, found 223.1328

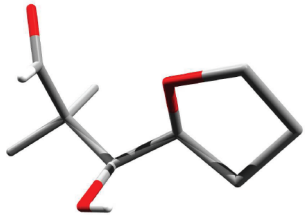
*(R)-4-(1,3-Dioxoisoindolin-2-yl)-3-hydroxy-2,2-dimethylbutanal (**13g**).* Colorless oil: $[\alpha]$ = −19.6 (c = 1, $CHCl_3$) (77% ee); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.18 (s, 3H), 1.20 (s, 3H), 3.75 (dd, 1H, J = 9.2, 14.2), 3.82 (dd, 1H, J = 2.7, 14.2), 4.03 (dd, 1H, J = 2.7, 9.2), 7.70 (m, 2H), 7.82 (m, 2H), 9.53 (s, 1H); ^{13}C NMR (75 MHz) δ = 16.5, 18.9, 40.5, 49.6, 73.6, 123.4, 134.1,168.7, 205.1; HRMS (CI) m/z calcd for $C_{14}H_{15}O_4N$ + Na^+ 284.0893, found 284.0889.

*(R)-4-Chloro-3-hydroxy-2,2-dimethylbutanal (**13h**).* Colorless oil: $[\alpha]$ = −12.2 (c = 1, $CHCl_3$) (90% ee); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.15 (s, 3H), 1.16 (s, 3H), 3.49 (dd, 1H, J = 9.6, 11.4), 3.71 (dd, 1H, J = 2.4, 11.4), 3.97 (dd, 1H, J = 2.2, 9.6), 9.57 (s, 1H); ^{13}C NMR (75 MHz) δ = 17.1, 19.1, 46.9, 49.6, 75.3, 204.7; HRMS (CI) m/z calcd for $C_{12}H_{22}Cl_2O_4$ + Na^+ 323.0787, found 323.0787.

*(R)-3-Hydroxy-4,4-dimethoxy-2,2-dimethylbutanal (**13i**).* Colorless oil: $[\alpha]$ = +5.3 (c = 1, $CHCl_3$) (84% ee); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.05 (s, 3H), 1.08 (s, 3H), 3.33 (s, 3H), 3.41 (s, 3H), 3.68 (1H, d, J = 6.2), 4.18 (1H, d, J = 6.2), 9.42 (s, 1H); ^{13}C NMR (75 MHz) δ = 16.6, 19.5, 48.4, 54.9, 55.8, 74.2, 104.8, 203.1; HRMS (CI) m/z calcd for $C_{14}H_{28}O_8$ + H^+ 325.1857, found 325.1863 2 [M − CH_2] + H^+

*2(R)-Hydroxy-3,3-dimethyl-4-oxobutyric Acid Ethyl Ester (**13j**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.06 (s, 3H), 1.14 (s, 3H), 1.27 (t, 3H, J = 7.2), 4.25 (m, 2H), 4.32 (s, 1H), 9.57 (s, 1H); ^{13}C NMR (75 MHz) δ = 14.1, 16.9, 18.2, 50.4, 62.3, 73.5, 172.8, 202.5; HRMS (CI) m/z calcd for $C_8H_{14}O_4$ + H^+ 175.0965, found 175.0963.

*(S)-3-Hydroxy-2,2-dimethyl-3(S)-tetrahydrofuran-2-yl)propanal (syn-**13k**).* Colorless oil: $[\alpha]$ = −1.3 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.10 (s, 3H), 1.13(s, 3H), 1.74−2.00 (m, 4H), 3.54 (d, 1H, J = 2.7), 3.70−3.86 (m, 2H), 3.95 (dpst, 1H, J = 2.6, 6.7), 9.61 (s, 1H); ^{13}C NMR (75 MHz) δ = 18.4, 19.6, 26.1, 29.3, 49.8, 68.9, 77.2, 77.3, 206.2; HRMS (CI) m/z calcd for $C_9H_{16}O_3^+$ 172.10999, found 172.1099.



*(R)-3-Hydroxy-2,2-dimethyl-3(S)-tetrahydrofuran-2-yl)propanal (anti-**13k**).* Colorless oil: $[\alpha]$ = −12.1 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.09 (s, 3H), 1.16 (s, 3H), 1.81−1.96 (m, 4H), 3.66−3.89 (m, 3H), 3.74 (d, 1H, J = 6.2), 9.54 (s, 1H); ^{13}C NMR (75 MHz) δ = 17.6, 19.0, 25.8, 27.7, 49.1, 67.8, 76.9, 79.2, 205.1.

*(3R,4R)-4-Benzyloxy-3-hydroxy-2,2-dimethylpentanal (syn-**13l**).* Colorless oil: $[\alpha]$ = −34.0 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.05 (s, 3H), 1.15 (s, 3H), 1.28 (d, 3H, J = 6.2), 3.39 (d, 1H, J = 2.0), 3.69 (dq, 1H, J = 2.0, 6.2), 4.33 (d, 1H, J = 11.1), 4.56 (d, 1H, J = 11.1), 7.27 - 7.37 (m, 5H), 9.62 (s, 1H); ^{13}C NMR (75 MHz) δ = 16.4, 18.9, 20.3, 49.2, 70.4, 72.5, 81.1, 127.9, 128.2, 128.4, 137.4,

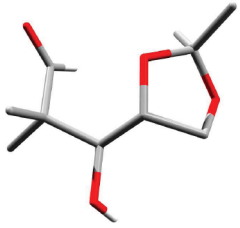
dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310−2330

205.3; HRMS (CI) m/z calcd for $C_{14}H_{20}O_3 + H^+$ 237.1485, found 237.1486.

*(3S,4R)-4-Benzyloxy-3-hydroxy-2,2-dimethylpentanal (anti-**13l**).* Colorless oil: $[\alpha] = -12.2$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.06 (s, 3H), 1.08 (s, 3H), 1.26 (d, 3H, J = 6.1), 3.45 (dq, 1H, J = 6.1, 7.2), 3.70 (d, 1H, J = 7.2), 4.36 (d, 1H, J = 11.3), 4.49 (d, 1H, J = 11.4), 7.25−7.38 (m, 5H), 9.48 (s, 1H); ^{13}C NMR (75 MHz) δ = 16.1, 16.4, 19.9, 49.1, 70.5, 75.0, 78.1, 127.7, 128.1, 128.3, 137.6, 203.3.

*(R)-3-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanal (syn-**13m**).*[8a] Colorless oil: $[\alpha] = +0.5$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.09 (s, 3H), 1.11(s, 3H), 1.32 (s, 3H), 1.38 (s, 3H), 2.62 (d, 1H, J = 7.6, OH), 3.54 (dd, 1H, J = 2.6, 7.6), 3.81 (dd, 1H, J = 7.0, 8.1), 4.01 (dd, 1H, J = 7.0, 8.1), 4.19 (dpst, 1H, J = 2.6, 7.0), 9.59 (s, 1H); ^{13}C NMR (75 MHz) δ = 18.2, 19.5, 25.3, 26.1, 49.6, 66.8, 74.3, 74.8, 109.6, 205.6; HRMS (CI) m/z calcd for $C_{10}H_{18}O_4 + NH_4^+$ 220.1543, found: 220.1543.

*(S)-3-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanal (anti-**13m**).* Colorless oil: $[\alpha] = +13.1$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.10 (s, 3H), 1.14 (s, 3H), 1.32 (s, 3H), 1.38 (s, 3H), 3.84 (dd, 1H, J = 7.1, 8.1), 3.89−3.96 (m, 1H), 4.05 (d, 1H, J = 7.4), 4.06 (dd, 1H, J = 3.3, 8.1), 9.50 (s, 1H); ^{13}C NMR (75 MHz) δ = 17.8, 18.1, 25.2, 26.4, 49.3, 66.5, 75.4, 75.7, 109.1, 204.8.



*(S)-3-Hydroxy-2,2-dimethyl-3-((4R,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)propanal (3,4-syn-**13n**).* Colorless oil: $[\alpha] = +23.5$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ = 1.11 (m, 6H), 1.33 (s, 3H), 1.39 (d, 3H, J = 6.5), 1.47 (s, 3H), 3.62 (s, 1H), 4.14 (d, 1H, J = 6.9), 4.40 (psqin, 1H, J = 6.6), 9.65 (s, 1H); ^{13}C NMR (125 MHz) δ = 15.3, 18.5, 19.5, 24.6, 26.7, 50.1, 73.6, 74.0, 75.2, 107.9, 205.8.

*(R)-3-Hydroxy-2,2-dimethyl-3-((4R,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)propanal (3,4-anti-**13n**).* Colorless oil: $[\alpha] = -8.5$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ = 1.12 (s, 3H), 1.15 (s, 3H), 1.27 (s, 3H), 1.30 (d, 3H, J = 6.5), 1.37 (s, 3H), 3.83 (d, 1H, J = 9.7), 3.93 (dd, 1H, J = 6.0, 9.7), 4.39 (psqin, 1H, J = 6.4), 9.43 (s, 1H); ^{13}C NMR (75 MHz) δ = 15.7, 16.1, 19.2, 25.2, 27.8, 50.0, 72.4, 73.7, 76.9, 108.2, 204.5.

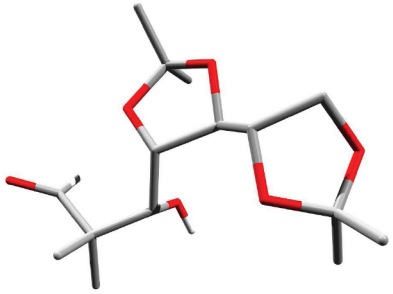
*(S)-3-Hydroxy-2,2-dimethyl-3-((4R,5R)-2,2,5-trimethyl-1,3-dioxolan-4-yl)propanal (3,4-syn-**13o**).* Colorless oil: $[\alpha] = +11.0$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.09 (s, 3H), 1.14 (s, 3H), 1.27 (d, 3H, J = 6.0), 1.37 (s, 3H), 1.39 (s, 3H), 3.49 (d, 1H, J = 0.4), 3.57 (dd, 1H, J = 0.4, 8.5), 4.08 (dq, 1H, J = 6.0, 8.6), 9.59 (s, 1H); ^{13}C NMR (75 MHz) δ = 16.8, 18.3, 19.1, 26.6, 27.6, 50.2, 71.8, 73.6, 80.3, 109.1, 205.7; HRMS (CI) m/z calcd for $C_{11}H_{20}O_4 + NH_4^+$ 234.1700, found 234.1698.

*(R)-3-Hydroxy-2,2-dimethyl-3-((4R,5R)-2,2,5-trimethyl-1,3-dioxolan-4-yl)propanal (3,4-anti-**13o**).* Colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.11 (s, 3H), 1.14 (s, 3H), 1.30 (s, 3H), 1.35 (s, 3H), 1.36 (d, 3H, J = 6.0), 3.48 (dd, 1H, J = 7.5, 8.6), 3.76 (d, 1H, J = 8.7), 4.07 (dq, 1H, J = 6.1, 7.4), 9.45 (s, 1H); ^{13}C NMR (75 MHz) δ = 16.9, 18.7, 19.5, 26.6, 27.3, 50.2, 76.8, 77.3, 81.4, 108.6, 205.1.

*(R)-3-((4S,5S)-5-Benzyloxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanal (3,4-syn-**13p**).* Colorless oil: $[\alpha] = -23.3$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.08 (s, 3H), 1.13(s, 3H), 1.40 (s, 3H),1.41 (s, 3H), 3.58 (dd, 1H, J = 5.0, 10.2), 3.63 (d, 1H, J = 0.6), 3.66 (dd, 1H, J = 4.9, 10.2), 3.97 (dd, 1H, J = 0.6, 8.4), 4.21 (dpst, 1H, J = 4.9, 8.5), 4.58 (s, 2H), 7.27−7.38 (m, 5H), 9.57 (s, 1H); ^{13}C NMR (75 MHz) δ = 18.2, 19.3, 26.7, 27.2, 50.2, 69.8, 72.7, 73.6, 76.5, 76.8, 110.0, 127.7, 127.7, 128.9, 137.7, 205.7; HRMS (CI) m/z calcd for $C_{18}H_{26}O_5 + H^+$ 323.1853, found 323.1853.

*(S)-3-((4S,5S)-5-Benzyloxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropanal (3,4-anti-**13p**).* Colorless oil: $[\alpha] = +10.1$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.12 (s, 3H), 1.13 (s, 3H),1.32 (s, 3H),1.32 (s, 3H), 3.51 (dd, 1H, J = 7.9, 9.0), 3.67 (dd, 1H, J = 7.4, 9.0), 3.77 (dd, 1H, J = 4.5, 9.0), 3.78 (d, 1H, J = 8.9), 4.06 (dpst, 1H, J = 4.5, 7.8), 4.60 (s, 2H), 7.28−7.39 (m, 5H), 9.48 (s, 1H); ^{13}C NMR (75 MHz) δ = 15.9, 19.1, 26.5, 26.7, 50.1, 70.4, 73.9, 75.6, 79.2, 80.7, 109.6, 128.0, 128.2, 128.6, 136.6, 204.2.

*(S)-3-Hydroxy-2,2-dimethyl-3-((4R,4′R,5R)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)propanal (3,4-syn-**13q**).* Colorless prisms: mp 65.7 °C: $[\alpha] = +12.5$ (c = 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.12 (s, 3H), 1.16 (s, 3H),1.32 (s, 3H),1.35 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 3.79 (d, 1H, J = 9.8), 3.89−3.95 (m, 2H), 4.00−4.07 (m, 2H), 4.13 (dd, 1H, J = 6.0, 8.4), 9.61 (s, 1H); ^{13}C NMR (75 MHz) δ = 18.2, 19.6, 25.2, 26.7, 26.7, 27.2, 50.2, 67.9, 73.4, 77.3, 77.8, 78.5, 109.8, 110.1, 205.9; HRMS (CI) m/z calcd for $C_{15}H_{26}O_6 + H^+$ 303.1802, found 303.1801.



*(R)-3-Hydroxy-2,2-dimethyl-3-((4R,4′R,5R)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)propanal (3,4-anti-**13q**).* Colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.12 (s, 3H), 1.14 (s, 3H),1.31 (m, 6H),1.36 (s, 3H),1.46 (s, 3H), 3.71−4.21 (m, 6H), 9.49 (s, 1H); ^{13}C NMR (75 MHz) δ = 15.5, 19.5, 25.0, 26.3, 26.4, 26.6, 50.1, 68.0, 75.2, 76.3, 80.9, 82.1, 109.8, 110.5, 203.8.

*2(R)-Hydroxy-3(R)-methyl-4-oxobutyric Acid Ethyl Ester (syn-**20a**).* *syn-* and *anti-***20a** were obtained as inseparable mixture of aldol adducts and different anomers of *n*-propylidene hemiacetals. Thus, exact characterization by NMR experiments was accomplished for the corresponding lactone derivatives: HRMS (CI) m/z calcd for $C_7H_{12}O_4 + H^+$ 161.0808, found 161.0806 (see the Supporting Information).

*2(R)-Hydroxy-3(R)-benzyl-4-oxobutyric Acid Ethyl Ester (syn-**20b**).* Colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.27 (t, 3H, J = 7.1), 2.99 (dd, 1H, J = 9.0, 12.8), 3.07−3.15 (m, 1H), 3.21 (dd, 1H, J = 7.3, 12.7), 4.17 (d, 1H, J = 3.1), 4.23 (q, 2H, J = 7.1), 7.18−7.36 (m, 5H), 9.67 (s, 1H); ^{13}C NMR (75 MHz) δ = 14.1, 31.4, 56.1, 62.2, 68.5, 126.7, 128.7, 129.1, 137.9, 173.5, 201.5; HRMS (CI) m/z calcd for $C_{13}H_{16}O_4 + Na^+$ 259.0941, found 259.0939.

*2(R)-Hydroxy-3(S)-benzyl-4-oxobutxyric Acid Ethyl Ester (anti-**20b**).* Colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.18 (t, 3H, J = 7.1), 2.82 (dd, 1H, J = 7.0, 13.7), 3.07−3.15 (m, 1H), 3.20 (dd, 1H, J = 8.4, 13.8), 4.26 (q, 2H, J = 7.2), 4.65 (d, 1H, J = 3.8), 7.18−7.36 (m, 5H), 9.76 (d, 1H, J = 0.9); ^{13}C NMR (75 MHz) δ = 13.9, 29.6, 56.3, 62.2, 68.5, 126.6, 128.5, 129.2, 138.0, 173.2, 201.2.

*2(R)-Hydroxy-3(R)-isopropyl-4-oxobutyric Acid Ethyl Ester (syn-**20c**).* Colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.01 (d, 3H, J = 6.9), 1.02 (d, 3H, J = 7.0), 1.29 (t, 3H, J = 7.1), 2.33 (m, 1H), 2.48 (ddd, 1H, J = 2.2, 3.0, 8.6), 4.25 (q, 2H, J = 7.1), 4.38 (d, 1H, J = 2.9), 9.72 (d, 1H, J = 2.2); ^{13}C NMR (75 MHz) δ = 14.1, 20.5, 20.8, 26.2, 60.3, 62.2, 69.2, 174.0, 204.1; HRMS (CI) m/z calcd for $C_9H_{16}O_4 + Na^+$ 211.0941, found 211.0939.

*2(R)-Hydroxy-3(S)-isopropyl-4-oxobutyric Acid Ethyl Ester (anti-**20c**).* Colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.05 (d, 3H,

dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310−2330

J = 6.5), 1.07 (d, 3H, J = 6.5), 1.29 (t, 3H, J = 7.2), 2.33 (m, 1H), 2.54 (ddd, 1H, J = 2.8, 5.2, 8.0), 4.28 (q, 2H, J = 7.2), 4.55 (d, 1H, J = 5.2), 9.78 (d, 1H, J = 2.8); ^{13}C NMR (75 MHz) δ = 14.0, 19.8, 21.1, 26.2, 60.6, 62.2, 68.8, 174.0, 203.1.

*2(R)-Hydroxy-3,3-diethyl-4-oxobutyric Acid Ethyl Ester (**20d**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.87 (t, 3H, J = 7.6), 0.88 (t, 3H, J = 7.6), 1.29 (t, 3H, J = 7.1), 1.59−1.78 (m, 4H), 4.25 (m, 2H, J = 7.2), 4.41 (s, 1H), 9.60 (s, 1H); ^{13}C NMR (75 MHz) δ = 7.9, 8.0, 14.0, 21.7, 22.6, 55.8, 62.2, 72.6, 173.6, 204.1; HRMS (CI) m/z calcd for $C_{10}H_{18}O_4$ + H^+ 203.1278, found 203.1276.

*(R)-Ethyl 2-(1-Formylcyclohexyl)-2-hydroxyacetate (**20e**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.27 (t, 3H, J = 7.1), 1.37−1.66 (m, 8H), 1.74−1.80 (m, 1H), 1.91−1.96 (m, 1H), 4.13 (s, 1H), 4.23 (m, 2H, J = 7.1), 9.57 (s, 1H); ^{13}C NMR (75 MHz) δ = 14.1, 22.0, 22.2, 25.1, 25.9, 27.8, 53.5, 62.2, 73.8, 172.8, 204.5; HRMS (CI) m/z calcd for $C_{11}H_{18}O_4$ + NH_4^+ 232.1543, found 232.1543.

*2(R)-Hydroxy-3(R)-ethyl-3-methyl-4-oxobutyric Acid Ethyl Ester (syn-**20f**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.84 (t, 3H, J = 7.6), 0.96 (s, 3H), 1.25 (t, 3H, J = 7.1), 1.63−1.83 (m, 2H), 4.22 (m, 2H, J = 7.2), 4.40 (s, 1H), 9.58 (s, 1H); ^{13}C NMR (75 MHz) δ = 8.1, 12.7, 14.1, 26.0, 53.8, 62.4, 72.8, 173.2, 203.0; HRMS (CI) m/z calcd for $C_9H_{16}O_4$ + Na^+ 211.0941, found 211.0939.

*2(R)-Hydroxy-3(S)-ethyl-3-methyl-4-oxobutyric Acid Ethyl Ester (anti-**20f**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.86 (t, 3H, J = 7.5), 1.06 (s, 3H), 1.29 (t, 3H, J = 7.2), 1.61−1.76 (m, 2H), 4.26 (m, 2H, J = 7.2), 4.34 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (75 MHz) δ = 8.2, 12.7, 14.0, 24.9, 53.4,62.1, 73.3, 172.9, 203.4.

*2(R)-Hydroxy-3(R)-methyl-3-propyl-4-oxobutyric Acid Ethyl Ester (syn-**20g**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.88 (t, 3H, J = 7.3), 0.96 (s, 3H), 1.23 (t, 3H, J = 7.1), 1.18−1.34 (m, 2H), 1.55−1.73 (m, 2H), 4.21 (m, 2H, J = 7.4), 4.38 (s, 1H), 9.58 (s, 1H); ^{13}C NMR (75 MHz) δ = 13.2, 14.0, 14.6, 16.9, 35.5, 53.7, 62.3, 73.0, 173.1, 203.1; HRMS (CI) m/z calcd for $C_{10}H_{19}O_4$ + H^+ 203.1278, found 203.1276.

*2(R)-Hydroxy-3(S)-methyl-3-propyl-4-oxobutyric Acid Ethyl Ester (anti-**20g**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.88 (t, 3H, J = 7.2), 1.06 (s, 3H), 1.29 (t, 3H, J = 7.2), 1.15−1.29 (m, 2H), 1.51−1.70 (m, 2H), 4.26 (m, 2H, J = 7.2), 4.34 (s, 1H), 9.54 (s, 1H); ^{13}C NMR (75 MHz) δ = 13.2, 14.1, 14.6, 17.1, 34.5, 53.3, 62.1, 73.4, 172.8, 203.4.

*2(R)-Hydroxy-3(R)-methyl-3-phenyl-4-oxobutyric Acid Ethyl Ester (syn-**20h**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.22 (t, 3H, J = 7.2), 1.53 (s, 3H), 4.19 (m, 2H), 4.92 (s, 1H), 7.27−7.41 (m, 5H), 9.71 (s, 1H); ^{13}C NMR (75 MHz) δ = 14.0, 15.2, 58.0, 62.3, 73.5, 127.6, 127.8, 128.8, 136.1, 172.4, 198.9; HRMS (CI) m/z calcd for $C_{13}H_{16}O_4$ + H^+ 237.1121, found 237.1117.

*2(R)-Hydroxy-3(S)-methyl-3-phenyl-4-oxobutyric Acid Ethyl Ester (anti-**20h**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.93 (t, 3H, J = 7.2), 1.58 (s, 3H), 3.95 (q, 2H, J = 7.2), 4.91 (s, 1H), 7.27−7.41 (m, 5H), 9.64 (s, 1H); ^{13}C NMR (75 MHz) δ = 13.6, 13.8, 57.7, 61.6, 73.8, 127.6, 127.9, 128.7, 135.7, 172.3, 199.4.

*(2R,3R,4R)-4-Benzyloxy-2-ethyl-3-hydroxy-2-methylpentanal (2,3-syn-3,4-syn-**28**).* Colorless oil: $[\alpha]$ = −11.8 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.84 (pst, 3H, J = 7.5), 0.98 (s, 3H), 1.31 (d, 3H, J = 6.3), 1.67 (dq, 1H, J = 7.5, 13.9), 1.79 (dq, 1H, J = 7.6, 13.9), 3.43 (d, 1H, J = 1.2), 3.70 (dq, 1H, J = 1.5, 6.3), 4.31 (d, 1H, J = 11.1), 4.53 (d, 1H, J = 11.1), 7.27−7.38 (m, 5H), 9.62 (s, 1H); ^{13}C NMR (75 MHz) δ = 7.9, 15.0, 16.4, 26.2, 52.4, 70.4, 72.2, 80.3, 127.9, 128.3, 128.4, 137.3, 205.7; HRMS (CI) m/z calcd for $C_{15}H_{22}O_3$ + H^+ 251.1642, found 251.1644.

*(2S,3R,4R)-4-Benzyloxy-2-ethyl-3-hydroxy-2-methylpentanal (2,3-anti-3,4-syn-**28**).* Colorless oil: $[\alpha]$ = −20.2 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.84 (pst, 3H, J = 7.6), 1.13 (s, 3H), 1.27 (d, 3H, J = 6.3), 1.49 (dq, 1H, J = 7.6, 14.2), 1.76 (dq, 1H, J = 7.6, 14.2), 3.49 (d, 1H, J = 2.3), 3.68 (dq, 1H, J = 2.3, 6.2), 4.35 (d, 1H, J = 11.2), 4.58 (d, 1H, J = 11.2), 7.27−7.37 (m, 5H), 9.60 (s, 1H); ^{13}C NMR (75 MHz) δ = 8.1, 15.7, 16.4, 25.8, 52.4, 70.4, 72.9, 79.3, 127.8, 128.0, 128.4, 137.5, 206.2.

*(2R,3S,4R)-4-Benzyloxy-2-ethyl-3-hydroxy-2-methylpentanal (2,3-syn-3,4-anti-**28**).* Colorless oil: 2,3-*syn*-3,4-*anti*-**28** and 2,3-*anti*-3,4-*anti*-**28** → inseparable mixture; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.85 (pst, 3H, J = 7.6), 1.02 (s, 3H), 1.30 (d, 3H, J = 6.0), 1.54 (m, 1H), 1.76 (m, 1H), (3.45 (dq, 1H, J = 6.0, 8.1), 3.76 (d, 1H, J = 8.1), 4.34 (d, 1H, J = 11.2), 4.47 (d, 1H, J = 11.2), 7.27 - 7.41 (m, 5H), 9.44 (s, 1H); ^{13}C NMR (75 MHz) δ = 8.0, 11.9, 16.6, 26.9, 52.5, 70.4, 74.8, 77.9, 127.6, 128.3, 128.3, 137.4, 202.9.

*(2S,3S,4R)-4-Benzyloxy-2-ethyl-3-hydroxy-2-methylpentanal (2,3-anti-3,4-anti-**28**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.84 (pst, 3H, J = 7.5), 1.00 (s, 3H), 1.19 (d, 3H, J = 6.2), 1.61 (dq, 1H, J = 7.5, 14.0), 1.78 (dq, 1H, J = 7.5, 14.0), (3.59 (dq, 1H, J = 4.9, 6.2), 3.86 (d, 1H, J = 4.8), 4.44 (d, 1H, J = 11.6), 4.57 (d, 1H, J = 11.6), 7.25−7.37 (m, 5H), 9.61 (s, 1H); ^{13}C NMR (75 MHz) δ = 8.2, 14.8, 15.7, 25.4, 51.9, 70.5, 75.1, 77.3, 127.7, 128.3, 128.4, 137.9, 206.1.

*(R)-2-((R)-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2-methylbutanal (2,3-syn-3,4-syn-**29**).* Colorless oil: 2,3-*syn*-3,4-*syn*-**29**, 2,3-*anti*-3,4-*syn*-**29**, 2,3-*syn*-3,4-*anti*-**29** and 2,3-*anti*-3,4-*anti*-**29** → inseparable mixture; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.85 (pst, 3H, J = 7.6), 1.10 (s, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.57 (dq, 1H, J = 7.6, 15.0), 1.86 (dq, 1H, J = 7.5, 15.0), 3.60 (d, 1H, J = 2.2), 3.81 (dd, 1H, J = 7.4, 8.0), 4.03 (dd, 1H, J = 6.6, 8.0), 4.19 (ddd, 1H, J = 2.2, 6.6, 7.3), 9.59 (s, 1H); ^{13}C NMR (75 MHz) δ = 8.3, 15.5, 25.4, 25.7, 26.1, 53.2, 67.0, 73.1, 74.6, 109.7, 206.6; HRMS (CI) m/z calcd for $C_{11}H_{20}O_4$+ NH_4^+ 234.1700, found 234.1699.

*(S)-2-((R)-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2-methylbutanal (2,3-anti-3,4-syn-**29**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.84 (pst, 3H, J = 7.5), 1.08 (s, 3H), 1.34 (s, 3H), 1.40 (s, 3H), 1.60 (dq, 1H, J = 7.5, 14.3), 1.73 (dq, 1H, J = 7.5, 14.6), 3.59 (d, 1H, J = 2.2), 3.87 (dd, 1H, J = 6.9, 8.1), 4.04 (dd, 1H, J = 6.6, 8.1), 4.19 (dpst, 1H, J = 2.6, 6.7), 9.62 (s, 1H); ^{13}C NMR (75 MHz) δ = 8.0, 14.5, 25.2, 26.1, 26.1, 52.8, 66.8, 74.2, 75.2, 109.7, 206.3.

*(S)-2-((S)-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2-methylbutanal (2,3-syn-3,4-anti-**29**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.84 (pst, 3H, J = 7.6), 1.08 (s, 3H), 1.29 (s, 3H), 1.36 (s, 3H), 1.59 (dq, 1H, J = 7.6, 14.1), 1.73 (dq, 1H, J = 7.6, 14.1), 3.84 (d, 1H, J = 4.9), 3.88−3.96 (m, 1H), 4.00−4.07 (m, 2H), 9.48 (s, 1H); ^{13}C NMR (75 MHz) δ = 8.1, 13.3, 25.0, 26.2, 26.3, 52.6, 66.7, 75.3, 75.7, 109.2, 204.7.

*(R)-2-((S)-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2-methylbutanal (2,3-anti-3,4-anti-**29**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.85 (pst, 3H, J = 7.5), 1.05 (s, 3H), 1.32 (s, 3H), 1.38 (s, 3H), 1.65 (dq, 1H, J = 7.6, 14.1), 1.81 (dq, 1H, J = 7.5, 14.2), 3.86 (dd, 1H, J = 7.2, 8.3), 3.95 (m, 1H), 3.98 (d, 1H, J = 6.2), 4.12 (m, 1H), 9.52 (s, 1H); ^{13}C NMR (75 MHz) δ = 8.2, 14.3, 25.5, 25.8, 26.3, 52.5, 65.9, 73.1, 75.6, 109.8, 206.4.

Compounds **30** and **33** were obtained by $NaBH_4$ reduction of the crude reaction products containing a mixture of acetals and aldol adducts. **30** and **33** are inseparable mixtures of diasteromers.

*1(R)-(Tetrahydro-2(S)-(hydroxymethyl)furan-2-yl)2(S)-tetrahydrofuran-2-yl)methanol (**30**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.79−2.01 (m, 8H), 3.45 (d, 1H, J = 11.6), 3.53 (d, 1H, J = 2.1), 3.63 (d, 1H, J = 11.6), 3.78−3.91 (m, 4H), 3.98 (dpst, 1H, J = 2.1, 7.2); ^{13}C NMR (75 MHz) δ = 25.8, 26.2, 29.2, 29.4, 64.6, 68.3, 69.2, 75.5, 77.2, 86.4; HRMS (CI) m/z calcd for $C_{10}H_{18}O_4$ + H^+ 203.1278, found 203.1278.

*1(S)-(Tetrahydro-2(R)-(hydroxymethyl)furan-2-yl)2(S)-tetrahydrofuran-2-yl)methanol (**33**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.76−2.07 (m, 8H), 3.44 (d, 1H, J = 7.7), 3.59 (m, 1H), 3.72−3.94 (m, 6H); ^{13}C NMR (75 MHz) δ = 25.4, 26.1, 29.4, 31.2, 64.6, 68.4, 68.9, 76.5, 78.9, 86.0.

Compounds **31** and **34** were obtained as their unprotected methylglycosides as follows: The intermediate and instable acetal was subjected to reductive deprotection. The crude product was dissolved in MeOH under hydrogen atmosphere (1 atm) and a spatula of palladium on charcoal was added. The deprotection was completed within 12 h at rt. The mixture was filtrated and acidic ion-exchanger (DOWEX-50WX2) was added to the filtrate. After 12 h at rt the mixure was filtrated (and, if needed, neutralized). The filtrate was adsorbed to Celite and evaporated in vacuo The remaining residue was purified by column chromatography (hexane/acetone 4/1).

Both anomers of compound **31** and **34** are easily separable by column chromatography (**31**: α/β 2.2:1; **34**: α/β 1:3.5).

*(2R,3R,4R,5S)-Tetrahydro-2-methoxy-3,5-dimethylfuran-3,4-diol (α-**31**).* Colorless oil: $[\alpha] = -58.9$ (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.27 (d, 3H, J = 6.6), 1.29 (s, 3H), 3.40 (s, 3H), 3.55 (d, 1H, J = 4.6), 4.27 (dq, 1H, J = 4.6, 6.6), 4.40 (1H, s); ^{13}C NMR (75 MHz) δ = 16.3, 22.3, 55.4, 77.0, 77.5, 77.7, 106.8; HRMS (CI) m/z calcd for $C_7H_{14}O_4 + Na^+$ 185.0784, found 185.0783.

*(2S,3R,4R,5S)-Tetrahydro-2-methoxy-3,5-dimethylfuran-3,4-diol (β-**31**).* Colorless oil: $[\alpha]$= +104.6 (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.23 (d, 3H, J = 7.1), 1.31 (s, 3H), 3.35 (s, 3H), 3.89 (d, 1H, J = 6.1), 4.23 (dq, 1H, J = 6.1, 7.1), 4.64 (s, 1H); ^{13}C NMR (75 MHz) δ = 15.3, 19.9, 55.2, 75.3, 76.5, 79.5, 108.1.

*(2R,3R,4R,5R)-Tetrahydro-2-methoxy-3,5-dimethylfuran-3,4-diol (β-**34**).*[12] Colorless oil: $[\alpha] = -76.8$ (c = 1.0, $CHCl_3$) ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.28 (s, 3H), 1.23 (d, 3H, J = 6.4), 3.36 (s, 3H), 3.61 (d, 1H, J = 7.0), 3.91 (psquin, 1H, J = 6.7), 4.58 (s, 1H); ^{13}C NMR (75 MHz) δ = 19.2, 20.5, 55.0, 79.0, 79.2, 81.0, 108.7.

*(2S,3R,4R,5R)-Tetrahydro-2-methoxy-3,5-dimethylfuran-3,4-diol (α-**34**).* Colorless oil: $[\alpha] = -29.4$ (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.22 (d, 3H, J = 6.6), 1.33 (s, 3H), 3.36 (s, 3H), 3.92 (d, 1H, J = 6.2), 4.24 (psquin, 1H, J = 6.4), 4.65 (s, 1H); ^{13}C NMR (75 MHz) δ = 15.4, 19.8, 55.2, 75.3, 76.4, 79.6, 108.0.

Compounds **32** and **35** were achieved by acidic treatment of the crude reaction product (acetal) with ion-exchanger (DOWEX-50WX2) in aq dioxane (5%) for 12 h. Upon completion of deprotection the mixture was filtrated, the filtrate absorbed to Celite and evaporated in vacuo The remaining residue was purified by column chromatography (CH_2Cl_2/MeOH/H_2O 13/6/1).

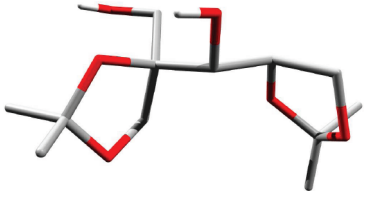
*(3S,4S,5R)-Tetrahydro-3-(hydroxymethyl)-2H-pyran-2,3,4,5-tetrol or -2-(hydroxymethyl)-D-lyxose (**32**).*[27] Colorless oil: $[\alpha] = -1.4$ (c = 0.05, $CHCl_3$); ^1H NMR (D_2O, 300 MHz) δ = [mixture of two anomers] 3.34−3.88 (m, 6H), 4.94 (s, 1H); ^{13}C NMR (75 MHz) δ = [mixture of two anomers] major anomer: 61.9, 64.1, 67.7, 71.9, 76.1, 94.9; minor anomer: 60.8, 65.5, 67.8, 72.6, 75.5, 95.3; HRMS (CI) m/z calcd for $C_6H_{12}O_6 - H^+$ 179.0561, found 179.0555.

*(3R,4R,5R)-Tetrahydro-3-(hydroxymethyl)-2H-pyran-2,3,4,5-tetraol (Hamamelose, **35**).*[28] Analytical data of this compound are in full agreement, especially with the complete NMR assignment of all anomers of furanoic and pyranoic forms in literature.

Compounds **36** and **37** were obtained by general procedure for $NaBH_4$ reduction of the crude reaction mixture of homodimerization of (*R*)-**23** (Scheme 8).

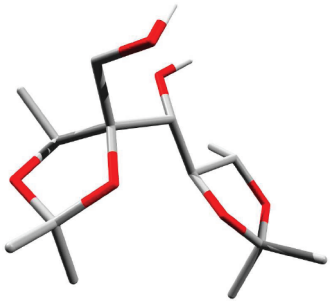
*1(S)-(4(R)-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(4(R)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**36**).*[8a] Colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.35 (s, 3H), 1.38 (s, 3H), 1.40 (s, 3H), 1.42 (s, 3H), 3.68−4.10 (m, 7H), 4.26 (dpst, 1H, J = 6.8, 3.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 25.3, 26.3, 26.5, 27.1, 65.0, 67.3, 67.4, 71.6, 74.1, 83.9, 109.6, 110.3.

*1(R)-(4(S)-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(4R)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**37**).* Colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ = 1.34 (s, 3H), 1.41 (s, 3H), 1.43 (s, 3H), 1.44 (s, 3H), 3.61 (d, 1H, J = 8.2), 3.69 (d, 1H, J = 11.5), 3.78 (d, 1H, J = 11.7), 3.94−4.11 (m, 4H), 4.17 (dd, 1H, J = 6.1, 8.1); ^{13}C NMR (75 MHz) δ = 25.2, 26.4, 26.7, 27.0, 63.2, 68.1, 68.7, 74.2, 75.1, 84.0, 109.7, 110.0.



Compounds **38** and **39** were obtained by $NaBH_4$ reduction of the crude reaction mixture of homodimerization of **24** and **25** (Scheme 9).

*1(R)-((4R,5S)-4-(Hydroxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)((4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methanol (**38**).* Colorless oil: $[\alpha] = -11.2$ (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ = 1.37−1.44 (m, 18H), 3.55−3.62 (m, 3H), 3.78 (d, 1H, J = 12.3), 4.16 (dq, 1H, J = 1.9, 5.8), 4.33 (q, 1H, J = 6.5); ^{13}C NMR (125 MHz) δ = 13.6, 19.5, 26.4, 26.7, 27.3, 28.5, 61.5, 72.6, 74.7, 77.6, 80.6, 84.6, 107.6, 108.9; HRMS (CI) m/z calcd for $C_{14}H_{26}O_6$ + H^+ 291.1802, found 291.1802.



*1(R)-((4R,5S)-4-(Hydroxymethyl)-2,2,5-trimethyl-1,3-dioxolan-4-yl)((4R,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)methanol (**39**).* Colorless oil: $[\alpha]$ = +35.0 (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ = 1.25 (d, 3H, J = 6.5), 1.33 (d, 3H, J = 6.1), 1.36 (s, 3H), 1.39 (s, 3H), 1.45 (s, 3H), 1.49 (s, 3H), 3.62 (d, 1H, J = 11.2), 3.78 (m, 1H), 3.92 (dd, 1H, J = 1.6, 7.0), 4.34−4.43 (m, 2H), 4.4.49 (q, 1H, J = 6.5); ^{13}C NMR (125 MHz) δ = 13.9, 16.0, 24.8, 26.3, 27.0, 28.7, 61.7, 68.1, 73.9, 74.0, 74.6, 83.7, 107.6, 107.7.

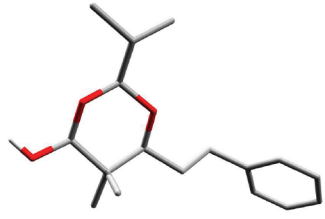
Degree of Acetalization. The ratio between aldol products and corresponding acetals **12** depends on the deployed aldehydes. A tendency to less formation of acetals for electron-poor carbonyl components was observed. This is demonstrated in Table 2.

Table 2. Degree of Acetalization of Different Aldol Adducts

product	reaction time	degree of acetalization (%)	isobutyraldehyde (equiv)
13a	7 d	>90	2
13b	7 d	>90	2
13c	7 d	>90	2
13d	5 d	90	2
13e	40 h	85	2
13f	24 h	36	1.2
13g	16 h	23	1.2
13h	16 h	<10	1.1
13i	16 h	<5	1.1
13j	16 h	<5	1.1

The acetals **12** contain two additional stereocenters, hence four corresponding diastereomers exist. In solution most of these acetals are quite labile and tend to epimerize (Table 3); thus, no analytical data for compounds **12** is given in this paper with one exception: in the crude product mixture of the reaction leading to product **13b** crystals of one diastereomer of the corresponding racemic hemiactal **12b** were found.

*rac-(S,S,S)-2-Isopropyl-5,5-dimethyl-6-phenethyl-1,3-dioxan-4-ol (**12b**).*



Enantiomeric excess of acetals **12** is according to ee detected in aldol adducts **13**. This was confirmed by separated determination of the enantiomeric excess. The isolated acetals of suitable examples were transferred into their corresponding aldol adducts **13** by acidic treatment. The ee for these aldol products was separately determined.

*General Procedure for the Formation of Lactone Derivatives of Compounds **20a−h**.* In a typical experiment 3 mmol of the corresponding aldehydes **20a−h** were solved in Et_2O and 40 mg $NaBH_4$

dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310−2330

Table 3. Influence of Solvent in Histidine-Catalyzed Aldol Addition: Yields and Selectivity of a Model Reaction with Different Solvents (Isobutyraldehyde and Ethyl Glyoxylate)[a]

entry	solvent	yield (%)	ee (%)	reaction time
1	DMSO[b]	7	<10	3 d
2	DMF[b]	10	<10	3 d
3	THF[b]	12	30	3 d
4	4-methyl-1,3-dioxolan-2-one[b]	10	46	2 d
5	1-methylpyrrolidin-2-one[b]	12	0	3 d
6	acetonitrile	22	41	5 d
7	trichloracetonitrile	31	28	3 d
8	propyloxyethanol	5	<20	2 d
9	hexafluoro-2-propanol	10	37	2 d
10	2-propanol	9	36	2 d
11	methanol	25	65	20 h
12	1,3-propanediol	34	67	24 h
13	1,4-butanediol	24	61	24 h
14	glycerol	52	60	20 h
15	glycol	74	77	20 h
16	water	23	60	20 h
17	water[c]	65	65	16 h

[a]Reaction conditions: 10 mol % of histidine in 1.0 mL of solvent, 5 mmol of isobutyraldehyde and ethyl glyoxylate (50% in toluene). [b]Reaction does not proceed unless 0.2 mL water is added. [c]10 mol % histidine in 0.2 mL water, 5 mmol of isobutyraldehyde, and ethyl glyoxylate (50% in toluene).

was added. The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After completion of the reaction (10 min to 2 h), the mixture was slowly quenched with saturated aqueous NH_4Cl solution, dried ($MgSO_4$) and filtrated. The filtrate was acidified with toluenesulfonic acid, stirred at room temperature, and monitored by TLC. After completion of the reaction (1−12 h), the mixture was neutralized, absorbed to Celite, evaporated in vacuo and the remaining residue was purified by column chromatography (hexane/acetone or pentane/diethylether).

No remarkable change in diastereomeric ratio was observed (with the exception of **20h**). Yields of transformations are given in Table 4.

*3(R)-Hydroxy-4(S)-methyldihydrofuran-2-one (Lactone of syn-**20a**).*[29] Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.21 (d, 3H, J = 6.6), 2.51 (m, 1H), 3.78 (dd, 1H, J = 9.1, 10.6), 4.03 (d, 1H, J = 10.5), 4.39 (dd, 1H, J = 7.9, 9.0); ^{13}C NMR (75 MHz) δ = 14.2, 38.7, 70.7, 73.6, 178.0; HRMS (CI) m/z calcd for $C_5H_8O_3 + Na^+$ 139.0366, found 139.0360.

*3(R)-Hydroxy-4(R)-methyldihydrofuran-2-one (lactone of anti-**20a**).*[29] Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.09 (d, 3H, J = 7.1), 2.73 (dddq, 1H, J = 2.0, 5.2, 7.1, 7.3), 4.03 (dd, 1H, J = 2.0, 9.3), 4.33 (dd, 1H, J = 5.3, 9.3), 4.51 (d, 1H, J = 7.3); ^{13}C NMR (75 MHz) δ = 11.5, 34.9, 69.9, 71.8, 177.8.

*3(R)-Hydroxy-4(S)-benzyldihydrofuran-2-one (Lactone of syn-**20b**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.41 (dd, 1H, J = 11.1, 14.1), 2.80−2.92 (m, 1H), 3.15 (dd, 1H, J = 4.6, 14.1), 4.14 (m, 2H, J = 5.6, 9.6), 4.57 (d, 1H, J = 7.1), 7.15−7.33 (m, 5H); ^{13}C NMR (75 MHz) δ = 31.1, 42.1, 68.7, 69.6, 126.6, 128.7, 129.0, 138.5, 177.5; HRMS (CI) m/z calcd for for $C_{11}H_{12}O_3 + NH_4^+$ 210.1125, found 210.1122.

*3(R)-Hydroxy-4(R)-benzyldihydrofuran-2-one (Lactone of anti-**20b**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.72 (dd, 1H, J = 9.3, 13.2), 2.73−2.82 (m, 1H), 3.18 (dd, 1H, J = 3.7, 13.2), 3.90 (dd, 1H, J = 9.3, 10.1), 4.19 (d, 1H, J = 10.1), 4.25 (dd, 1H, J = 7.5, 9.3), 7.16−7.35 (m, 5H); ^{13}C NMR (75 MHz) δ = 36.2, 45.0, 69.2, 71.9, 126.9, 128.7, 128.8, 137.3, 177.6.

*3(R)-Hydroxy-4(S)-isopropyldihydrofuran-2-one (:actone of syn-**20c**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.86 (d, 3H, J = 6.8), 0.99 (d, 3H, J = 6.8), 2.08 (psok, 1H, J = 6.9), 2.27 (psqin, 1H, J = 6.9), 4.22 (dd, 1H, J = 6.3, 9.2), 4.33 (dd, 1H, J = 7.0, 9.2), 4.38 (d, 1H, J = 7.0)M; ^{13}C NMR (75 MHz) δ = 18.8, 20.9, 24.7, 46.6, 68.3, 69.6, 178.3; HRMS (CI) m/z calcd for $C_7H_{12}O_3 + NH_4^+$ 162.1125, found 162.1122.

*3(R)-Hydroxy-4(R)-isopropyldihydrofuran-2-one (Lactone of anti-**20c**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.92 (d, 3H, J = 6.7), 1.08 (d, 3H, J = 6.7), 1.77 (dpssep, 1H, J = 5.0, 6.7), 2.16−2.32 (m, 1H), 3.88 (dd, 1H, J = 9.2, 10.6), 4.18 (d, 1H, J = 10.4), 4.38 (dd, 1H, J = 6.9, 9.2); ^{13}C NMR (75 MHz) δ = 10.0, 20.5, 30.5, 49.7, 68.8, 71.5, 178.5.

*3(R)-Hydroxy-4,4-dimethyldihydrofuran-2-one (Lactone of **13j**).*[30] Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.08 (s, 3H), 1.23 (s, 3H), 3.94 (d, 1H, J = 8.9), 4.02 (d, 1H, J = 8.9), 4.11 (s, 1H); ^{13}C NMR (75 MHz) δ = 18.8, 22.9, 40.9, 75.7, 76.4, 177.6; HRMS (CI) m/z calcd for $C_6H_{10}O_3 + Na^+$ 153.0522, found 153.0522

*3(R)-Hydroxy-4,4-diethyldihydrofuran-2-one (Lactone of **20d**).*[31] Colorless oil: $[\alpha]$ = −13.2 (c = 1, $CHCl_3$) (59% ee); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.86 (t, 3H, J = 7.5), 0.93 (t, 3H, J = 7.6), 1.37−1.64 (m, 4H), 3.85 (d, 1H, J = 9.3), 4.10 (d, 1H, J = 9.3), 4.22 (s, 1H); ^{13}C NMR (75 MHz) δ = 8.0, 8.3, 21.5, 27.9, 46.3, 73.1, 74.4, 178.8; HRMS (CI) m/z calcd for $C_8H_{14}O_3 + NH_4^+$ 176.1281, found 176.1282.

*4(R)-Hydroxy-2-oxaspiro[4.5]decan-3-one (Lactone of **20e**).*[31] Colorless oil: $[\alpha]$ = +19.4 (c = 1, $CHCl_3$) (71% ee); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.14−1.78 (m, 10H), 3.87 (d, 1H, J = 9.2), 4.07 (s, 1H), 4.33 (d, 1H, J = 9.2); ^{13}C NMR (75 MHz) δ = 21.7, 22.9, 25.3, 25.8, 33.6, 44.0, 73.7, 75.6, 178.0; HRMS (CI) m/z calcd for $C_9H_{14}O_3$ 170.09429, found 170.09429.

*3(R)-Hydroxy-4(S)-ethyl-4-methyldihydrofuran-2-one (Lactone of syn-**20f**).*[32] Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.97 (t, 3H, J = 7.6), 1.07 (s, 3H), 1.38−1.60 (m, 2H), 3.96 (d, 1H, J = 9.2), 4.01 (d, 1H, J = 9.1), 4.17 (s, 1H); ^{13}C NMR (75 MHz) δ = 8.3, 15.9, 24.1, 44.1, 75.0, 75.6, 178.0; HRMS (CI) m/z calcd for $C_7H_{12}O_3 + H^+$ 145.0859, found 145.0859.

*3(R)-Hydroxy-4(R)-ethyl-4-methyldihydrofuran-2-one (Lactone of anti-**20f**).*[32] Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.91 (t, 3H, J = 7.5), 1.18 (s, 3H), 1.48−1.72 (m, 2H), 3.86 (d, 1H, J = 9.1), 4.15 (s, 1H), 4.19 (d, 1H, J = 9.2); ^{13}C NMR (75 MHz) δ = 8.6, 20.9, 30.1, 43.5, 73.7, 75.8, 178.0.

*3(R)-Hydroxy-4(S)-methyl-4-propyldihydrofuran-2-one (Lactone of syn-**20g**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.92 (t, 3H, J = 7.0), 1.06 (s, 3H), 1.26−1.61 (m, 4H), 3.95 (d, 1H, J = 9.0), 3.99 (d, 1H, J = 8.9), 4.18 (s, 1H); ^{13}C NMR (75 MHz) δ = 14.6, 16.4, 17.5, 39.8, 43.9, 75.2, 75.8, 178.2; HRMS (CI) m/z calcd for for $C_8H_{14}O_3 + NH_4^+$ 176.1281, found: 176.1278.

*3(R)-Hydroxy-4(R)-methyl-4-propyldihydrofuran-2-one (Lactone of anti-**20g**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.91 (t, 3H, J = 6.9), 1.17 (s, 3H), 1.20−1.52 (m, 4H), 3.85 (d, 1H, J = 9.2), 4.14 (s, 1H), 4.18 (d, 1H, J = 9.2); ^{13}C NMR (75 MHz) δ = 14.6, 17.2, 21.4, 33.8, 43.3, 74.2, 75.8, 178.3.

*3(R)-Hydroxy-4(S)-methyl-4-phenyldihydrofuran-2-one (Lactone of syn-**20h**).* Colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.42 (s, 3H), 4.33 (d, 1H, J = 8.9), 4.44 (d, 1H, J = 8.9), 4.70 (s, 1H), 7.27−7.40 (m, 5H); ^{13}C NMR (75 MHz) δ = 21.1, 48.0, 74.2, 74.7, 125.2, 127.3, 128.9, 143.1, 177.0; HRMS (CI) m/z calcd for for $C_{11}H_{12}O_3 + H^+$ 193.0859, found 193.0859.

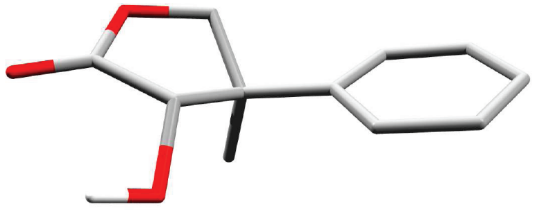
Table 4. Yields of γ-Lactone Synthesis

entry	1	2	3	4	5	6	7	8	9
starting compd	**20a**	**20b**	**20c**	**20d**	**20e**	**20f**	**20g**	**20h**	**13j**
yield (%)	50	79	59	92	90	96	93	60[a]	95

[a]Cyclization of *anti*-**20h** does not take place under these reaction conditions. Thus, the product was achieved in lower yield but diastereopure.

dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310−2330

For single-crystal X-ray structure analysis 3(*S*)-hydroxy-4(*R*)-methyl-4-phenyldihydrofuran-2-one was synthesized by using catalytic amounts of D-histidine.



Determination of Absolute Configuration and Enantiomeric Excess. The determination of the absolute configuration and the enantiomeric excess of products **20**, **13a–m**, **31**, and **34** was performed using the Mosher ester technique. In some cases, derivatives of the products had to be used, usually since chemical shifts of the diastereomeric MTPA esters were too similar for a definite determination.

Determination of Enantiomeric Excess. The aldol adducts were converted into the corresponding (*S*)-MTPA esters as follows:

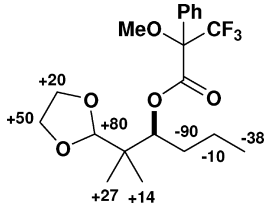
A 1.5 mL (0.01 mmol) portion of a CH_2Cl_2 solution of (*R*)-MTPA-Cl (0.015 mol/L) was added to a solution of the corresponding aldol adduct (0.01 mmol) and catalytic amounts of DMAP in 1.0 mL of abs CH_2Cl_2. After 10 h at rt, the reaction mixture was diluted with diethyle ther and extracted with aq NH_4Cl solution. The organic layer was separated, dried (Na_2SO_4), and filtrated, and the filtrate was evaporated in vacuo The remaining crude residue was used for ^1H NMR experiments.

The enantiomeric excess of the reactants was determined by integration of corresponding signals in the ^1H NMR spectra.

Proof of Absolute Configuration. The calculated differences of chemical shifts in the ^1H NMR spectra of the corresponding Mosher esters indicate the assigned configuration of aldol products.[33]

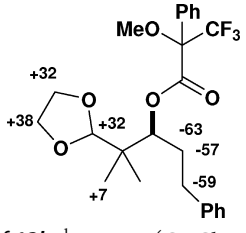
The indicated chemical shift differences ($\Delta\delta(S-R)$, ppb) established the absolute stereochemistry at the C3 for aldol adducts (stereogenic center formed by aldol addition).

For compounds **30** and **39**, the absolute configuration was also determined by single-crystal X-ray analysis of derivatives.



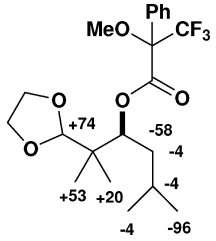
Compounds 13a–k (Scheme 1). *(S)-Mosher ester of **13a**:* ^1H NMR ($CDCl_3$, 500 MHz) δ = 0.86 (t, 3H, *J* = 7.3), 0.89 (s, 3H), 0.90 (s, 3H), 1.15–1.28 (m, 2H), 1.51–1.61 (m, 2H), 3.53 (m, 3H), 3.78–3.81 (m, 2H), 3.89–3.92 (m, 2H), 4.52 (s, 1H), 5.24 (dd, 1H, *J* = 3.4, 9.2), 7.38–7.41 (m, 3H), 7.58–7.59 (m, 2H).

*(R)-Mosher ester of **13a**:* ^1H NMR ($CDCl_3$, 500 MHz) δ = 0.88 (s, 3H), 0.88 (s, 3H), 0.90 (t, 3H, *J* = 7.3), 1.25–1.37 (m, 2H), 1.52–1.67 (m, 2H), 3.57 (m, 3H), 3.72–3.76 (m, 2H), 3.84–3.90 (m, 2H), 4.44 (s, 1H), 5.23 (dd, 1H, *J* = 2.4, 9.6), 7.37–7.41 (m, 3H), 7.58–7.61 (m, 2H).



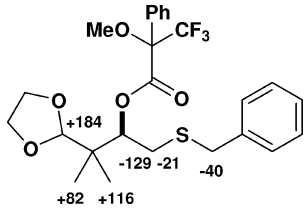
*(S)-Mosher ester of **13b**:* ^1H NMR ($CDCl_3$, 500 MHz) δ = 0.89 (s, 3H), 0.91 (s, 3H), 1.77–1.85 (m, 1H), 1.93–2.00 (m, 1H), 2.50 (pst, 2H, *J* = 8.4), 3.58 (m, 3H), 3.78 (m, 2H), 3.88 (m, 2H), 4.51 (s, 1H), 5.31 (dd, 1H, *J* = 2.2, 10.0), 7.08–7.65 (m, 10H).

*(R)-Mosher ester of **13b**:* ^1H NMR ($CDCl_3$, 500 MHz) δ = 0.89 (s, 3H), 0.90 (s, 3H), 1.82–1.91 (m, 1H), 1.99–2.06 (m, 1H), 2.56 (pst, 2H, *J* = 8.3), 3.61 (m, 3H), 3.75 (m, 2H), 3.85 (m, 2H), 4.48 (s, 1H), 5.31 (dd, 1H, *J* = 2.0, 10.0), 7.11–7.66 (m, 10H).



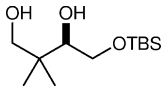
*(S)-Mosher ester of **13c**:* ^1H NMR ($CDCl_3$, 500 MHz) δ = 0.81 (d, 3H, *J* = 6.3), 0.89 (s, 3H), 0.93 (s, 3H), 0.94 (d, 3H, *J* = 6.7), 1.13 (ddd, 1H, *J* = 1.8, 10.4, 13.6), 1.52 (m, 1H), 1.86 (m, 1H), 3.52 (m, 3H), 3.74–3.99 (m, 4H), 4.51 (s, 1H), 5.30 (dd, 1H, *J* = 1.6, 10.6), 7.31–7.71 (m, 5H).

*(R)-Mosher ester of **13c**:* ^1H NMR ($CDCl_3$, 500 MHz) δ = 0.87 (s, 3H), 0.87 (s, 3H), 0.90 (d, 3H, *J* = 6.4), 0.94 (d, 3H, *J* = 6.3), 1.13 (ddd, 1H, *J* = 1.8, 10.1, 13.6), 1.58 (m, 1H), 1.86 (m, 1H), 3.57 (m, 3H), 3.74–4.01 (m, 4H), 4.44 (s, 1H), 5.31 (dd, 1H, *J* = 1.5, 10.3), 7.34–7.73 (m, 5H).

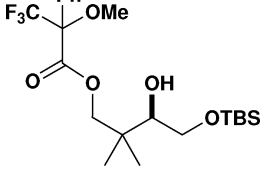


*(S)-Mosher ester of **13d**:* ^1H NMR ($CDCl_3$, 500 MHz) δ = 0.90 (s, 3H), 0.93 (s, 3H), 2.48 (dd, 1H, *J* = 10.6, 14.6), 2.78 (dd, 1H, *J* = 2.4, 14.6), 3.53 (m, 3H), 3.73 (m, 2H), 3.74–3.94 (m, 4H), 4.55 (s, 1H), 5.41 (dd, 1H, *J* = 2.4, 10.5), 7.23–7.71 (m, 10H).

*(R)-Mosher ester of **13d**:* ^1H NMR ($CDCl_3$, 500 MHz) δ = 0.81 (s, 3H), 0.82 (s, 3H), 2.50 (dd, 1H, *J* = 10.6, 14.6), 2.81 (dd, 1H, *J* = 2.3, 14.6), 3.63 (m, 3H), 3.77 (m, 2H), 3.78–3.95 (m, 4H), 4.36 (s, 1H), 5.39 (dd, 1H, *J* = 2.3, 10.5), 7.23–7.71 (m, 10H).



(*R*)-4-tert-*Butyl*-dimethylsilyloxy-2,2-dimethylbutane-1,3-diol was obtained by the general procedure for $NaBH_4$ reduction of the crude reaction product **13e** containing a mixture of acetals and aldol adducts: ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.08 (m, 6H), 0.89 (s, 3H), 0.90 (s, 9H), 0.91 (s, 3H), 3.45 (m, 2H), 3.56 (m, 2H), 3.70 (d, 1H, *J* = 6.4); ^{13}C NMR (75 MHz) δ = −5.4, −5.4, 18.2, 19.3, 22.4, 25.8, 37.3, 63.4, 71.7, 78.4. In this case, the Mosher ester can be used for determination of the enantiomeric excess only. It is assumed that the absolute configuration is in analogy to other reaction products.



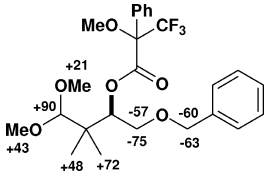
(S)-Mosher ester: ^1H NMR ($CDCl_3$, 500 MHz) δ = 0.04 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 0.91 (s, 3H), 0.94 (s, 3H), 3.42 (dd, 1H, *J* = 3.1, 8.7), 3.49 (dd, 1H, *J* = 8.7, 9.8), 3.54 (m, 3H), 3.62 (dd, 1H, *J* = 3.2, 9.8), 4.05 (d, 1H, *J* = 10.7), 4.33 (d, 1H, *J* = 10.7), 7.39–7.56 (m, 5H).

(R)-Mosher ester: ^1H NMR ($CDCl_3$, 500 MHz) δ = 0.05 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 0.92 (m, 6H), 3.48 (m, 2H), 3.54 (m, 3H), 3.65 (d, 1H, *J* = 6.5), 4.12 (d, 1H, *J* = 10.7), 4.24 (d, 1H, *J* = 10.7), 7.39–7.56 (m, 5H).

Compound **13f** was transferred into its corresponding dimethylacetal by acidic treatment of the crude reaction product with ion-exchanger

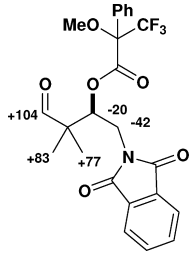
dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310–2330

(DOWEX-50WX2) in methanol for 12 h. Upon completion of deprotection the mixture was filtrated and the filtrate absorbed to Celite and evaporated in vacuo The remaining residue was purified by column chromatography (hexane/acetone 9/1).



(S)-Mosher ester of ***13f*** *(dimethyl acetal):* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.95 (s, 3H), 0.98 (s, 3H), 3.44 (m, 3H), 3.44 (s, 3H), 3.45 (s, 3H), 3.60 (dd, 1H, *J* = 8.5, 11.1), 3.73 (dd, 1H, *J* = 2.8, 11.1), 3.91 (s, 1H), 4.40 (d, 1H, *J* = 11.9), 4.53 (d, 1H, *J* = 11.9), 5.52 (dd, 1H, *J* = 2.8, 8.5), 7.22–7.70 (m, 10H).

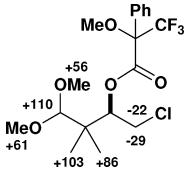
(R)-Mosher ester of ***13f*** *(dimethyl acetal):* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.90 (s, 3H), 0.91 (s, 3H), 3.40 (s, 3H), 3.43 (s, 3H), 3.56 (m, 3H), 3.65 (dd, 1H, *J* = 8.5, 11.1), 3.80 (dd, 1H, *J* = 2.7, 11.1), 3.83 (s, 1H), 4.46 (d, 1H, *J* = 11.7), 4.60 (d, 1H, *J* = 11.7), 5.51 (dd, 1H, *J* = 2.7, 8.5), 7.15–7.70 (m, 10H).



(S)-Mosher ester of ***13g****:* ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.24 (s, 3H), 1.26 (s, 3H), 3.37 (m, 3H), 3.74 (dd, 1H, *J* = 2.3, 14.6), 4.07 (dd, 1H, *J* = 9.8, 14.6), 5.78 (dd, 1H, *J* = 2.4, 9.8), 7.16–7.32 (m, 5H), 7.74 (m, 2H), 7.80 (m, 2H), 9.55 (s, 1H).

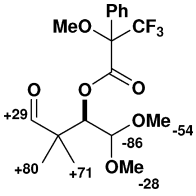
(R)-Mosher ester of ***13g****:* ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.16 (s, 3H), 1.17 (s, 3H), 3.50 (m, 3H), 3.76 (dd, 1H, *J* = 2.3, 14.7), 4.11 (dd, 1H, *J* = 9.6, 14.7), 5.73 (dd, 1H, *J* = 2.1, 9.6), 7.27–7.41 (m, 5H), 7.72 (m, 2H), 7.84 (m, 2H), 9.44 (s, 1H).

Compound **13h** was transferred into its corresponding dimethyl acetal by acidic treatment of the crude reaction product with ion-exchanger (DOWEX-50WX2) in methanol for 12 h. Upon completion of deprotection, the mixture was filtrated and the filtrate absorbed to Celite and evaporated in vacuo The remaining residue was purified by column chromatography (hexane/acetone 9/1).



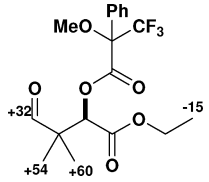
(S)-Mosher ester of ***13h*** *(dimethyl acetal):* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.94 (s, 3H), 0.97 (s, 3H), 3.51 (m, 3H), 3.52 (s, 3H), 3.53 (s, 3H), 3.59 (dd, 1H, *J* = 9.8, 12.3), 3.88 (s, 1H), 3.93 (dd, 1H, *J* = 2.3, 12.3), 5.46 (dd, 1H, *J* = 2.3, 9.8), 7.38–7.71 (m, 5H).

(R)-Mosher ester of ***13h*** *(dimethyl acetal):* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.87 (s, 3H), 0.87 (s, 3H), 3.40 (s, 3H), 3.41 (s, 3H), 3.62 (dd, 1H, *J* = 9.4, 12.3), 3.63 (m, 3H), 3.77 (s, 1H), 3.96 (dd, 1H, *J* = 2.1, 12.3), 5.44 (dd, 1H, *J* = 2.1, 9.4), 7.39–7.71 (m, 5H).



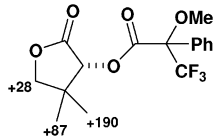
(S)-Mosher ester of ***13i****:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.04 (s, 3H), 1.10 (s, 3H), 3.27 (s, 3H), 3.33 (s, 3H), 3.51 (m, 3H), 4.32 (d, 1H, *J* = 6.8), 5.42 (d, 1H, *J* = 6.8), 7.44–7.39 (m, 3H), 7.54–7.59 (m, 2H), 9.44 (s, 1H).

(R)-Mosher ester of ***13i****:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.97 (s, 3H), 1.02 (s, 3H), 3.32 (s, 3H), 3.36 (s, 3H), 3.59 (m, 3H), 4.40 (d, 1H, *J* = 6.8), 5.46 (d, 1H, *J* = 6.8), 7.44–7.39 (m, 3H), 7.54–7.59 (m, 2H), 9.41 (s, 1H).



(S)-Mosher ester of ***13j****:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.14 (s, 3H), 1.17 (s, 3H), 1.27 (t, 3H, *J* = 7.2), 3.51 (q, 3H, *J* = 1.0), 4.20–4.29 (m, 2H), 5.33 (s, 1H), 7.38–7.66 (m, 5H), 9.51 (s, 1H).

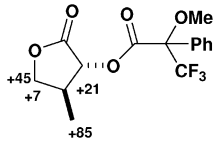
(R)-Mosher ester of ***13j****:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.09 (s, 3H), 1.11 (s, 3H), 1.28 (t, 3H, *J* = 7.2), 3.62 (q, 3H, *J* = 1.2), 4.20–4.29 (m, 2H), 5.31 (s, 1H), 7.38–7.66 (m, 5H), 9.58 (s, 1H).



(S)-Mosher ester of (R)-pantolactone: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.26 (s, 6H), 3.54 (q, 3H, *J* = 1.0), 4.09 (s, 2H), 5.55 (s, 1H), 7.32–7.63 (m, 5H).

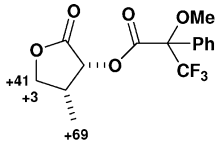
(R)-Mosher ester of (R)-pantolactone: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.95 (s, 3H), 1.17 (s, 3H), 3.63 (q, 3H, *J* = 1.1), 4.05 (s, 2H), 5.59 (s, 1H), 7.40–7.80 (m, 5H).

Compounds ***20a–h*** *(Scheme 2).* Absolute configuration and enantiomeric excess for compounds **20a–c** was determined using the corresponding lactone derivatives to avoid undesired elimination reactions.



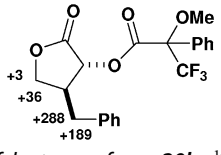
*(S)-Mosher ester of lactone of syn-****20a****:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.24 (d, 3H, *J* = 6.7), 2.81–2.98 (m, 1H), 3.56 (q, 3H, *J* = 1.5), 3.92 (dd, 1H, *J* = 9.2, 10.4), 4.51 (dd, 1H, *J* = 8.2, 9.0), 5.35 (d, 1H, *J* = 10.6), 7.37–7.64 (m, 5H).

(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.16 (d, 3H, *J* = 6.6), 2.63–2.75 (m, 1H), 3.64 (q, 3H, *J* = 1.2), 3.91 (dd, 1H, *J* = 9.2, 10.4), 4.46 (dd, 1H, *J* = 8.0, 9.0), 5.48 (d, 1H, *J* = 10.7), 7.36–7.65 (m, 5H).



*(S)-Mosher ester of lactone of anti-****20a****:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.93 (d, 3H, *J* = 7.1), 2.85–2.95 (m, 1H), 3.63 (q, 3H, *J* = 1.3), 4.06 (dd, 1H, *J* = 2.5, 9.3), 4.43 (dd, 1H, *J* = 5.0, 9.3), 5.81 (d, 1H, *J* = 7.5), 7.39–7.63 (m, 5H).

(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.13 (d, 3H, *J* = 7.1), 2.64–2.75 (m, 1H), 3.45 (q, 3H, *J* = 1.0), 4.11 (dd, 1H, *J* = 2.6, 9.3), 4.43 (dd, 1H, *J* = 5.0, 9.3), 5.76 (d, 1H, *J* = 7.5), 7.39–7.63 (m, 5H).

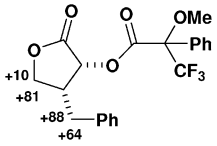


*(S)-Mosher ester of lactone of syn-****20b****:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.50 (dd, 1H, *J* = 11.4, 14.3), 2.95 (dd, 1H, *J* = 4.4, 14.1),

dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310–2330

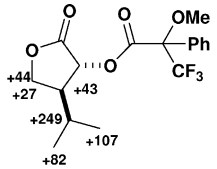
3.02−3.12 (m, 1H), 3.55 (q, 3H, *J* = 0.9), 4.18 (dd, 1H, *J* = 3.0, 12.4), 4.21 (dd, 1H, *J* = 5.4, 11.9), 5.88 (d, 1H, *J* = 7.4), 7.03−7.68 (m, 10H).

(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.31 (dd, 1H, *J* = 11.8, 14.2), 2.66 (dd, 1H, *J* = 4.2, 14.2), 2.94−3.01 (m, 1H), 3.67 (q, 3H, *J* = 1.1), 4.15 (dd, 1H, *J* = 2.9, 9.8), 4.21 (dd, 1H, *J* = 5.2, 9.6), 5.93 (d, 1H, *J* = 7.4), 7.03−7.70 (m, 10H).



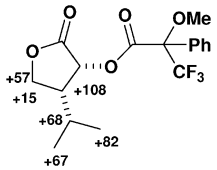
*(S)-Mosher ester of lactone of anti-**20b**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.81 (dd, 1H, *J* = 8.6, 13.9), 3.01 (dd, 1H, *J* = 5.6, 13.7), 3.01−3.11 (m, 1H), 3.44 (q, 3H, *J* = 0.9), 4.03 (pst, 1H, *J* = 9.6), 4.39 (dd, 1H, *J* = 8.2, 9.2), 5.53 (d, 1H, *J* = 10.2), 7.03−7.68 (m, 10H).

(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.72 (dd, 1H, *J* = 10.2, 15.0), 2.95 (dd, 1H, *J* = 4.7, 15.0), 2.96−3.04 (m, 1H), 3.61 (q, 3H, *J* = 1.1), 4.15 (pst, 1H, *J* = 9.4), 4.31 (dd, 1H, *J* = 7.6, 9.2), 5.64 (d, 1H, *J* = 10.2), 7.03−7.70 (m, 10H).



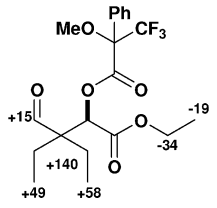
*(S)-Mosher ester of lactone of syn-**20c**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.88 (d, 3H, *J* = 6.9), 0.96 (d, 3H, *J* = 6.7), 1.86 (psokt, 1H, *J* = 6.8), 2.53 (m, 1H), 3.52 (q, 3H, *J* = 1.0), 4.23 (dd, 1H, *J* = 6.2, 9.4), 4.24 (dd, 1H, *J* = 7.0, 9.3), 5.73 (d, 1H, *J* = 7.6), 7.40−7.65 (m, 5H).

(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.77 (d, 3H, *J* = 6.8), 0.88 (d, 3H, *J* = 6.7), 1.61 (psokt, 1H, *J* = 6.8), 2.48 (m, 1H), 3.59 (q, 3H, *J* = 1.2), 4.19 (dd, 1H, *J* = 5.9, 9.4), 4.40 (dd, 1H, *J* = 7.0, 9.4), 5.81 (d, 1H, *J* = 7.5), 7.40−7.65 (m, 5H).



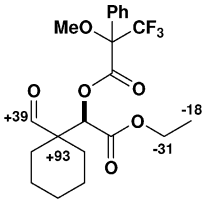
*(S)-Mosher ester of lactone of anti-**20c**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.94 (d, 3H, *J* = 6.4), 0.96 (d, 3H, *J* = 6.7), 1.81 (m, 1H), 2.61 (m, 1H), 3.55 (q, 3H, *J* = 1.0), 4.01 (dd, 1H, *J* = 9.8, 9.6), 4.54 (dd, 1H, *J* = 8.9, 9.2), 5.42 (d, 1H, *J* = 10.1), 7.40−7.65 (m, 5H).

(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.81 (d, 3H, *J* = 6.9), 0.87 (d, 3H, *J* = 6.7), 1.75 (m, 1H), 2.50 (m, 1H), 3.64 (q, 3H, *J* = 1.3), 3.99 (dd, 1H, *J* = 9.7, 9.4), 4.48 (dd, 1H, *J* = 8.9, 9.1), 5.63 (d, 1H, *J* = 10.3), 7.40−7.65 (m, 5H).



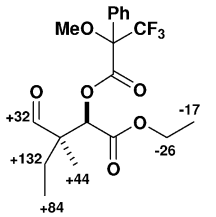
*(S)-Mosher ester of lactone of **20d**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.83 (t, 3H, *J* = 7.5), 0.85 (t, 3H, *J* = 7.5), 1.26 (t, 3H, *J* = 7.2), 1.61−1.82 (m, 4H), 3.52 (q, 3H, *J* = 1.1), 4.23 (q, 2H, *J* = 7.2), 5.41 (s, 1H), 7.40−7.65 (m, 5H), 9.53 (s, 1H).

(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.77 (t, 3H, *J* = 7.5), 0.80 (t, 3H, *J* = 7.5), 1.28 (t, 3H, *J* = 7.1), 1.47−1.67 (m, 4H), 3.63 (q, 3H, *J* = 1.3), 4.27 (q, 2H, *J* = 7.2), 5.38 (s, 1H), 7.40−7.65 (m, 5H), 9.52 (s, 1H).



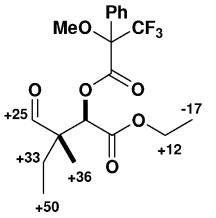
*(S)-Mosher ester of lactone of **20e**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.14−1.68 (m, 8H), 1.26 (t, 3H, *J* = 7.1), 1.93 (m, 2H), 3.51 (q, 3H, *J* = 1.0), 4.23 (q, 2H, *J* = 7.1), 5.13 (s, 1H), 7.38−7.67 (m, 5H), 9.59 (s, 1H).

(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.14−1.68 (m, 8H), 1.28 (t, 3H, *J* = 7.1), 1.83 (m, 2H), 3.62 (q, 3H, *J* = 1.2), 4.26 (q, 2H, *J* = 7.1), 5.10 (s, 1H), 7.38−7.67 (m, 5H), 9.55 (s, 1H).



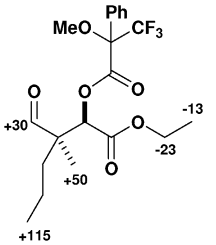
*(S)-Mosher ester of lactone of syn-**20f**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.84 (t, 3H, *J* = 7.5), 1.10 (s, 3H), 1.25 (t, 3H, *J* = 7.2), 1.57−1.74 (m, 2H), 3.52 (q, 3H, *J* = 0.9), 4.22 (q, 2H, *J* = 7.2), 5.45 (s, 1H), 7.38−7.58 (m, 5H), 9.61 (s, 1H).

(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.76 (t, 3H, *J* = 7.6), 1.05 (s, 3H), 1.26 (t, 3H, *J* = 7.1), 1.42−1.63 (m, 2H), 3.65 (q, 3H, *J* = 1.1), 4.25 (q, 2H, *J* = 7.2), 5.43 (s, 1H), 7.40−7.67 (m, 5H), 9.57 (s, 1H).



*(S)-Mosher ester of lactone of anti-**20f**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.89 (t, 3H, *J* = 7.5), 1.15 (s, 3H), 1.28 (t, 3H, *J* = 7.1), 1.60−1.72 (m, 2H), 3.51 (q, 3H, *J* = 1.1), 4.25 (q, 2H, *J* = 7.2), 5.33 (s, 1H), 7.38−7.58 (m, 5H), 9.45 (s, 1H).

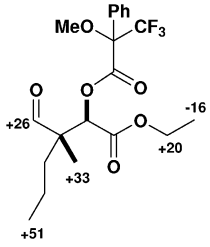
(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.84 (t, 3H, *J* = 7.6), 1.11 (s, 3H), 1.30 (t, 3H, *J* = 7.1), 1.54−1.72 (m, 2H), 3.61 (q, 3H, *J* = 1.2), 4.24 (q, 2H, *J* = 7.1), 5.29 (s, 1H), 7.40−7.67 (m, 5H), 9.42 (s, 1H).



*(S)-Mosher ester of lactone of syn-**20g**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.85 (t, 3H, *J* = 7.2), 1.10 (s, 3H), 1.18−1.53 (m, 4H), 1.25 (t, 3H, *J* = 7.1), 3.52 (q, 3H, *J* = 1.1), 4.22 (q, 2H, *J* = 7.1), 5.46 (s, 1H), 7.40−7.67 (m, 5H), 9.62 (s, 1H).

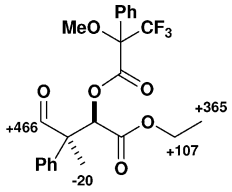
(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.74 (t, 3H, *J* = 7.1), 1.05 (s, 3H), 1.12−1.53 (m, 4H), 1.26 (t, 3H, *J* = 7.2), 3.67 (q, 3H, *J* = 1.2), 4.25 (q, 2H, *J* = 7.2), 5.43 (s, 1H), 7.39−7.67 (m, 5H), 9.59 (s, 1H).

dx.doi.org/10.1021/jo202558f | *J. Org. Chem.* 2012, 77, 2310−2330



*(S)-Mosher ester of lactone of anti-**20g**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.84 (t, 3H, J = 7.2), 1.12 (s, 3H), 1.21−1.59 (m, 4H), 1.30 (t, 3H, J = 7.1), 3.61 (q, 3H, J = 1.2), 4.23 (q, 2H, J = 7.1), 5.28 (s, 1H), 7.39−7.67 (m, 5H), 9.43 (s, 1H).

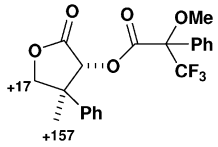
(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.89 (t, 3H, J = 7.3), 1.15 (s, 3H), 1.21−1.60 (m, 4H), 1.28 (t, 3H, J = 7.1), 3.51 (q, 3H, J = 1.1), 4.25 (q, 2H, J = 7.2), 5.33 (s, 1H), 7.40−7.67 (m, 5H), 9.45 (s, 1H).



*(S)-Mosher ester of lactone of anti-**20h**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.20 (t, 3H, J = 7.2), 1.62 (s, 3H), 3.34 (q, 3H, J = 1.2), 3.94 (m, 2H), 6.06 (s, 1H), 7.18−7.64 (m, 10H), 9.74 (s, 1H).

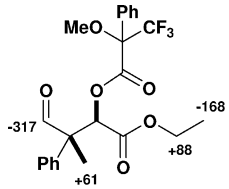
(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.83 (t, 3H, J = 7.1), 1.64 (s, 3H), 3.53 (q, 3H, J = 1.1), 3.83 (m, 2H), 5.75 (s, 1H), 7.18−7.64 (m, 10H), 9.38 (s, 1H).

Since the calculated differences of chemical shifts in the ^{1}H NMR spectra of the corresponding Mosher esters of **20h** do not explicitly indicate the configuration of aldol product, the cyclic lactone of ***syn*-20h** was used to confirm the configuration.



(S)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.54 (s, 3H), 3.53 (q, 3H, J = 1.0), 4.47 (m, 2H), 6.15 (s, 1H), 7.16−7.62 (m, 10H).

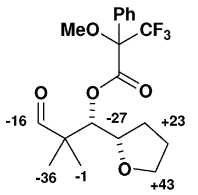
(R)-Mosher ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.38 (s, 3H), 3.68 (q, 3H, J = 1.0), 4.45 (m, 2H), 6.12 (s, 1H), 7.16−7.62 (m, 10H).



*(S)-Mosher ester of anti-**20h**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.84 (t, 3H, J = 7.1), 1.66 (s, 3H), 3.62 (q, 3H, J = 1.1), 3.89 (m, 2H), 5.80 (s, 1H), 7.18−7.64 (m, 10H), 9.33 (s, 1H).

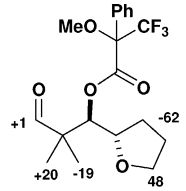
*(R)-Mosher ester of anti-**20h**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.20 (t, 3H, J = 7.2), 1.60 (s, 3H), 3.40 (q, 3H, J = 1.2), 3.80 (m, 2H), 5.99 (s, 1H), 7.18−7.64 (m, 10H), 9.65 (s, 1H).

*Compounds **13k−m** (Schemes 3 and 4).* Absolute and relative configuration as well as enantiomeric excess were determined for products **13l−n** to exclude a potential racemization of the electrophile. In order to exclude potential epimerization in aldol adducts **13o−r** only simple determination of the relative configuration is necessary (see Determination of Relative Configuration).



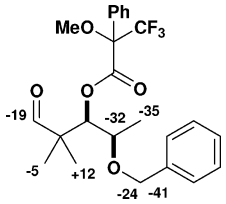
*(S)-Mosher ester of syn-**13k**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.04 (s, 3H), 1.15 (s, 3H), 1.68−2.00 (m, 4H), 3.53 (q, 3H, J = 1.3), 3.60−3.72 (m, 2H), 4.15 (dpst, 1H, J = 3.5, 7.5), 5.25 (d, 1H, J = 3.5), 7.39−7.64 (m, 5H), 9.59 (s, 1H).

*(R)-Mosher ester of syn-**13k**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.04 (s, 3H), 1.12 (s, 3H), 1.64−1.98 (m, 4H), 3.54 (q, 3H, J = 1.3), 3.56−3.68 (m, 2H), 4.18 (dpst, 1H, J = 2.9, 7.4), 5.20 (d, 1H, J = 2.9), 7.39−7.61 (m, 5H), 9.60 (s, 1H).



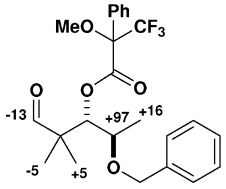
*(S)-Mosher ester of anti-**13k**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.95 (s, 3H), 1.15 (s, 3H), 1.61−1.91 (m, 4H), 3.51 (q, 3H, J = 1.2), 3.61−3.96 (m, 3H), 5.33 (d, 1H, J = 7.9), 7.39−7.56 (m, 5H), 9.46 (s, 1H).

*(R)-Mosher ester of anti-**13k**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.93 (s, 3H), 1.17 (s, 3H), 1.79−1.97 (m, 4H), 3.53 (q, 3H, J = 1.2), 3.66−4.09 (m, 3H), 5.37 (d, 1H, J = 7.6), 7.38−7.58 (m, 5H), 9.46 (s, 1H).



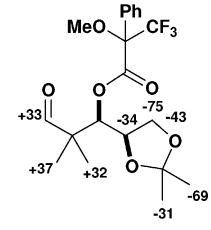
*(S)-Mosher ester of syn-**13l**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.96 (s, 3H), 1.05 (s, 3H), 1.07 (d, 3H, J = 6.4), 3.49 (m, 3H), 3.80 (dq, 1H, J = 2.1, 6.4), 4.29 (d, 1H, J = 11.7), 4.46 (d, 1H, J = 11.7), 5.15 (d, 1H, 2.1), 7.20−7.68 (m, 10H), 9.57 (s, 1H).

*(R)-Mosher ester of syn-**13l**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.94 (s, 3H), 1.06 (s, 3H), 1.11 (d, 3H, J = 6.4), 3.60 (m, 3H), 3.82 (dq, 1H, J = 2.0, 6.4), 4.32 (d, 1H, J = 11.5), 4.49 (d, 1H, 11.5), 5.15 (d, 1H, 2.0), 7.23−7.68 (m, 10H), 9.59 (s, 1H).



*(S)-Mosher ester of anti-**13l**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.97 (s, 3H), 1.04 (s, 3H), 1.09 (d, 3H, J = 6.2), 3.52 (m, 3H), 4.17 (d, 1H, J = 17.0), 4.46 (d, 1H, J = 17.3), 4.51 (dq, 1H, J = 6.2, 7.0), 5.45 (d, 1H, 6.8), 7.23−7.59 (m, 10H), 9.43 (s, 1H).

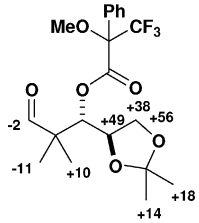
*(R)-Mosher ester of anti-**13l**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.96 (s, 3H), 1.04 (s, 3H), 1.07 (d, 3H, J = 6.2), 3.47 (q, 3H, J = 1.5), 4.36 (d, 1H, J = 11.1), 4.41 (dq, 1H, J = 6.4, 7.1), 4.51 (d, 1H, 11.2), 5.40 (d, 1H, 7.0), 7.25−7.63 (m, 10H), 9.45 (s, 1H).



dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310−2330

*(S)-Mosher ester of syn-**13m**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.06 (s, 3H), 1.19 (s, 3H), 1.26 (s, 3H), 1.27 (s, 3H), 3.50 (m, 3H), 3.54 (dd, 1H, J = 6.8, 8.5), 3.94 (dd, 1H, J = 6.8, 8.5), 4.34 (dpst, 1H, J = 3.6, 6.8), 5.27 (d, 1H, J = 3.4), 7.37−7.45 (m, 3H), 7.53−7.60 (m, 2H), 9.57 (s, 1H).

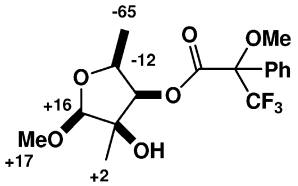
*(R)-Mosher ester of syn-**13m**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.02 (s, 3H), 1.15 (s, 3H), 1.30 (s, 3H), 1.34 (s, 3H), 3.58 (m, 3H), 3.61 (dd, 1H, J = 6.6, 8.7), 3.99 (dd, 1H, J = 6.6, 8.7), 4.37 (dpst, 1H, J = 4.0, 6.6), 5.32 (d, 1H, J = 4.0), 7.36−7.47 (m, 3H), 7.61−7.68 (m, 2H), 9.54 (s, 1H).



*(S)-Mosher ester of anti-**13m**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.97 (s, 3H), 1.15 (s, 3H), 1.29 (s, 3H), 1.37 (s, 3H), 3.52 (q, 3H, J = 1.3), 3.70 (dd, 1H, J = 6.1, 8.6), 3.88 (dd, 1H, J = 6.3, 8.5), 4.13 (dpst, 1H, J = 6.2, 7.7), 5.42 (d, 1H, J = 7.7), 7.41−7.56 (m, 3H), 7.53−7.60 (m, 2H), 9.48 (s, 1H).

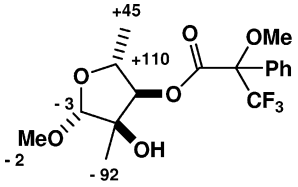
*(R)-Mosher ester of anti-**13m**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.98 (s, 3H), 1.14 (s, 3H), 1.28 (s, 3H), 1.35 (s, 3H), 3.50 (q, 3H, J = 1.2), 3.65 (dd, 1H, J = 6.1, 8.7), 3.84 (dd, 1H, J = 6.3, 8.7), 4.08 (dpst, 1H, J = 6.2, 8.1), 5.37 (d, 1H, J = 8.0), 7.41−7.55 (m, 5H) 9.48 (s, 1H).

*Compounds **28** to **39** (Schemes 5−9).* Possible racemization of the carbonyle compound could be excluded for compounds **28**−**39** (see the results of Schemes 3 and 4). Thus, determination of the absolute configuraton is not necessary. Nevertheless, the absolute configuration for compounds **31** and **34** was exemplified.



*(S)-Mosher ester of β-**31**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.14 (d, 3H, J = 6.6), 1.40 (s, 3H), 3.35 (s, 3H), 3.55 (q, 3H, J = 1.1), 4.42 (s, 1H), 4.43 (dq, 1H, J = 5.1, 6.6), 5.11 (d, 1H, J = 5.1), 7.39−7.45 (m, 3H), 7.58−7.64 (m, 2H).

*(R)-Mosher ester of β-**31**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.21 (d, 3H, J = 6.6), 1.40 (s, 3H), 3.33 (s, 3H), 3.56 (q, 3H, J = 1.1), 4.40 (s, 1H), 4.44 (dq, 1H, J = 5.1, 6.6), 5.13 (d, 1H, J = 5.1), 7.38−7.44 (m, 3H), 7.56−7.61 (m, 2H).



*(S)-Mosher ester of β-**34**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.22 (s, 3H), 1.41 (d, 3H, J = 6.4), 3.39 (s, 3H), 3.55 (q, 3H, J = 1.2), 4.19 (psquin, 1H, J = 6.5), 4.58 (s, 1H), 5.07 (d, 1H, J = 6.9), 7.40−7.54 (m, 5H).

*(R)-Mosher ester of β-**34**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.31 (s, 3H), 1.37 (d, 3H, J = 6.4), 3.40 (s, 3H), 3.55 (q, 3H, J = 1.1), 4.08 (psquin, 1H, J = 6.5), 4.58 (s, 1H), 5.06 (d, 1H, J = 6.6), 7.41−7.55 (m, 5H).

Determination of Relative Configuration. The relative configuration was determined by a combination of single-crystal X-ray structure analysis, analysis of the vicinal ^{1}H-coupling constants (^{1}H NMR), by NO experiments of corresponding cyclic derivatives of aldol adducts and reasonable analogy. In some cases, the aldol adducts could be transferred into derivatives known from literature.

Compounds of Scheme 2. Relative configuration of new compounds **20b**,**g** was determined by NO experiments of the corresponding lactone derivatives (see the Supporting Informations). Since these experiments do not explicitly indicate the relative configuration of compound **20c**, we assumed the configuration in analogy to the other reaction products.

Compounds of Scheme 3−5. The relative 3,4-configuration of products of diastereoselective reactions in Scheme 3 and 4 can be determined by the ^{1}H-coupling constants of aldol adducts. Generally, the 3,4-*anti*-configured products show higher values of coupling constants. To support this principle, single-crystal X-ray analysis and NO experiments of many products were additionally performed. In some cases, derivatives of the aldol adducts were used. For examples **13k**−**m** the absolute configuration of the new generated stereocenter was determined by Mosher-ester technique to demonstrate that no racemization of the deployed chiral reactant takes place. Since no racemization or epimerization of the reactants were observed, Mosher ester technique is also effective for determination of the relative configuration of the reaction products (compounds ***syn*-13o** and ***anti*-13p**). Table 5 shows the ^{1}H-coupling constants of compounds in Schemes 3−5, and additional methods that were used to determine the relative configuration.

Table 5. 3,4-Coupling Constants of Compounds in Schemes 3 and 4 (^{1}H NMR) (M: Mosher Ester Technique)

entry	compd	3,4-config	$J_{3,4}$ (Hz)	config confirmed by
1	**13k**	*syn*	2.7	crystal structure/M
2	**13k**	*anti*	6.2	M
3	**13l**	*syn*	2.0	M
4	**13l**	*anti*	7.2	M
5	**13m**	*syn*	2.6	crystal structure[a]/M
6	**13m**	*anti*	7.4	crystal structure/M
7	**13n**	*syn*	0.0	crystal structure/NOE of derivative
8	**13n**	*anti*	9.7	NOE of derivative
9	**13o**	*syn*	0.4	M
10	**13o**	*anti*	8.7	
11	**13p**	*syn*	0.6	
12	**13p**	*anti*	8.9	M
13	2,3-*syn*-**28**	*syn*	1.2	
14	2,3-*syn*-**28**	*anti*	4.8	
15	2,3-*anti*-**28**	*syn*	2.3	NOE of derivative/M
16	2,3-*anti*-**28**	*anti*	8.1	
17	2,3-*syn*-**29**	*syn*	2.2	crystal structure of derivative
18	2,3-*syn*-**29**	*anti*	4.9	crystal structure of derivative
19	2,3-*anti*-**29**	*syn*	2.2	
20	2,3-*anti*-**29**	*anti*	6.2	

[a]Crystal structure was reported in ref 8a.

Compounds **13n** were transferred into the corresponding unprotected methylglycosides as follows: To a mixture of 1 mmol of **13n** in 5 mL of methanol and 0.5 mL of water was added 0.1 mmol of toluenesulfonic acid. The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After completion of the reaction (~12 h), the mixture was neutralized with Na_2CO_3, dried ($MgSO_4$), and filtrated. The remaining residue was absorbed to Celite and purified by column chromatography (hexane/acetone/methanol 6/3/1). The reaction products were used in NO experiments for determination of the relative configuration (see the Supporting Informations).

(2S,3R,4S,6R)-Tetrahydro-6-methoxy-2,2,5-trimethyl-2H-pyran-3,4-diol. Colorless oil (derivative of *syn*-**13n**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 0.97 (s, 3H), 1.00 (s, 3H),1.29 (d, 3H, J = 6.2), 3.26 (pst, 1H, J = 9.4), 3.31 (s, 3H), 3.58 (d, 1H, J = 9.3), 3.61 (dq, 1H, J = 6.2,

dx.doi.org/10.1021/jo202558f | J. Org. Chem. 2012, 77, 2310−2330

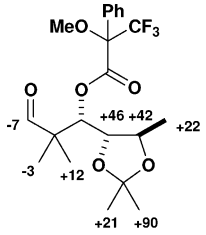
9.5), 4.16 (*s*, 1H); ^{13}C NMR (125 MHz) δ = 18.0, 19.0, 22.4, 40.8, 55.0, 67.8, 74.4, 76.1, 106.1.

(2S,3R,4S,6S)-Tetrahydro-6-methoxy-2,2,5-trimethyl-2H-pyran-3,4-diol. Colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 0.89 (s, 3H), 1.00 (s, 3H),1.34 (d, 3H, *J* = 6.0), 3.11 (d, 1H, *J* = 8.9), 3.20 (pst, 1H, *J* = 9.0), 3.26 (dq, 1H, *J* = 5.9, 9.1), 3.47 (s, 3H), 3.96 (*s*, 1H); ^{13}C NMR (125 MHz) δ = 12.7, 17.9, 22.1, 41.7, 57.4, 72.1, 74.1, 79.6, 107.3.

(2S,3R,5S)-Tetrahydro-2-((S)-1-hydroxyethyl)-5-methoxy-4,4-dimethylfuran-3-ol. Colorless oil (derivative of *anti*-**13n**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.02 (s, 3H), 1.03 (s, 3H), 1.23 (d, 3H, *J* = 6.5), 3.35 (s, 3H), 3.68 (dd, 1H, *J* = 4.8, 7.2), 3.87 (dq, 1H, *J* = 4.8, 6.5), 4.11 (*d*, 1H, *J* = 7.2), 4.39 (s, 1H); ^{13}C NMR (125 MHz) δ = 18.6, 19.3, 19.7, 46.1, 55.6, 68.8, 76.9, 86.4, 111.4.

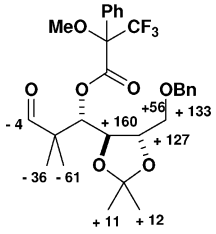
(2S,3R,5R)-Tetrahydro-2-((S)-1-hydroxyethyl)-5-methoxy-4,4-dimethylfuran-3-ol. Colorless oil: (derivative of *anti*-**13n**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.00 (s, 3H), 1.04 (s, 3H), 1.27 (d, 3H, *J* = 6.5), 3.34 (s, 3H), 3.64 (pst, 1H, *J* = 4.8), 3.68 (d, 1H, *J* = 4.4), 3.93 (dq, 1H, *J* = 5.3, 6.5), 4.45 (s, 1H); ^{13}C NMR (125 MHz) δ = 16.4, 19.3, 25.4, 45.7, 55.0, 67.8, 78.1, 89.4, 111.0.

Absolute and relative configuration as well as enantiomeric excess were determined for products **13k–m** to exclude a potential racemization of the electrophile. In order to exclude potential epimerization in aldol adducts **13n–q**, only simple determination of the relative configuration is necessary.



*(S)-Mosher ester of syn-**13o**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.05 (s, 3H), 1.19 (s, 3H), 1.21 (s, 3H), 1.27 (d, 3H, *J* = 5.9), 1.33 (s, 3H), 3.51 (q, 3H, *J* = 1.1), 3.61 (dq, 1H, *J* = 5.9, 8.6), 3.75 (dd, 1H, *J* = 1.6, 8.6), 5.25 (d, 1H, *J* = 1.6), 7.41–7.59 (m, 3H), 9.59 (s, 1H).

*(R)-Mosher ester of syn-**13o**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.03 (s, 3H), 1.12 (s, 3H), 1.19 (s, 3H), 1.24 (d, 3H, *J* = 5.9), 1.30 (s, 3H), 3.52 (q, 3H, *J* = 1.4), 3.57 (m, 1H), 3.70 (dd, 1H, *J* = 1.6, 8.7), 5.20 (d, 1H, *J* = 1.6), 7.40–7.57 (m, 5H), 9.59 (s, 1H).



*(S)-Mosher ester of anti-**13o**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.03 (s, 3H), 1.18 (s, 3H), 1.36 (s, 3H), 1.38 (s, 3H), 3.13 (dd, 1H, *J* = 5.1, 10.7), 3.31 (dd, 1H, *J* = 2.2, 10.7), 3.46 (q, 3H, *J* = 1.1), 3.99 (m, 1H), 4.00 (m, 1H), 4.34 (d, 1H, *J* = 12.2), 4.47 (d, 1H, *J* = 12.2), 5.44 (d, 1H, *J* = 8.2), 7.24–7.51 (m, 10H), 9.51 (s, 1H).

*(R)-Mosher ester of anti-**13o**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.97 (s, 3H), 1.14 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 3.29 (dd, 1H, *J* = 5.3, 10.8), 3.43 (q, 3H, *J* = 1.0), 3.44 (dd, 1H, *J* = 2.7, 10.8), 4.05 (dd, 1H, *J* = 7.7, 8.0), 4.13 (ddd, 1H, *J* = 2.6, 5.2, 7.9), 4.43 (d, 1H, *J* = 12.2), 4.53 (d, 1H, *J* = 12.2), 5.46 (d, 1H, *J* = 8.0), 7.27–7.52 (m, 10H), 9.50 (s, 1H).

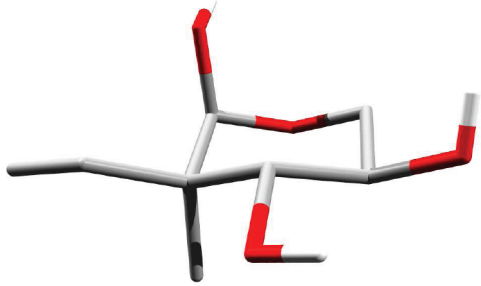
*(S)-Mosher ester of 2,3-syn-3,4-syn-**28**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.73 (t, 3H, *J* = 7.5), 0.97 (s, 3H), 1.09 (d, 3H, *J* = 6.4), 1.20–1.36 (m, 2H), 3.48 (q, 3H, *J* = 1.0), 3.77 (dq, 1H, *J* = 1.9, 6.5), 4.28 (d, 1H, *J* = 11.1), 4.45 (d, 1H, *J* = 11.1), 5.17 (d, 1H, *J* = 1.9), 7.20 - 7.62 (m, 10H), 9.49 (s, 1H).

Compound 2,3-*anti*-3,4-*syn*-**28** was transferred into the corresponding isopropylidene-derivative as follows: 2 mmol of 2,3-*anti*-3,4-*syn*-**28** was reduced to the corresponding alcohol by the general procedure for $NaBH_4$ reduction. The crude product was dissolved in methanol under a hydrogen atmosphere, and a spatula of palladium on charcoal was added. The deprotection was completed within 12 h at rt. The mixture was filtrated, and 5 mL of 2,2-dimethoxypropane and 0.2 mmol of toluenesulfonic acid were added. The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After completion of the reaction (~24 h), the mixture was diluted with acetone, neutralized with Na_2CO_3, dried ($MgSO_4$), and filtrated. The remaining residue was absorbed to Celite and purified by column chromatography (hexane/acetone 9/1).

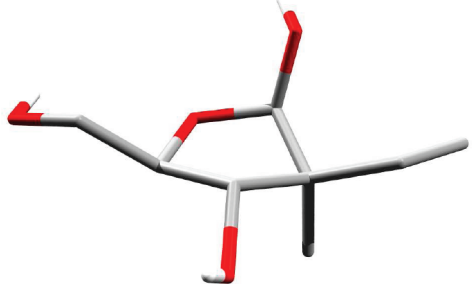
(R)-2-Methyl-2-((4R,5R)-2,2,5-trimethyl-1,3-dioxolan-4-yl)butan-1-ol. Colorless oil (derivative of 2,3-*anti*-3,4-*syn*-**28**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 0.85 (s, 3H), 0.90 (t, 3H, *J* = 7.5), 1.31 (d, 3H, *J* = 6.0), 1.38 (s, 3H), 1.38 (s, 3H), 1.54 (m, 1H), 1.67 (m, 1H), 3.43 (d, 1H, *J* = 11.2), 3.54 (d, 1H, *J* = 11.2), 3.58 (d, 1H, *J* = 8.1), 4.05 (dq, 1H, *J* = 6.0, 7.9); ^{13}C NMR (125 MHz) δ = 7.7, 18.4, 20.3, 23.8, 27.0, 27.2, 38.6, 68.9, 72.7, 90.0, 107.5.

Compounds **29** were transferred into the corresponding unprotected glycosides as follows:to a mixture of 1 mmol **29** in 5 mL dioxane and 2 mL water 0.1 mmol toluenesulfonic acid was added. The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After completion of the reaction (~12 h), the mixture was diluted with dioxane, neutralized with Na_2CO_3, dried ($MgSO_4$), and filtrated. The remaining residue was absorbed to Celite and purified by column chromatography (hexane/acetone/methanol 2/2/1).

*(3R,4R,5R)-3-Ethyl-3-methyltetrahydro-2H-pyran-2,4,5-triol (Derivative of 2,3-syn-3,4-syn-**29**).* Colorless oil: ^{1}H NMR ($OC(CD_3)_2$, 500 MHz) δ = (mixture of four anomers) 0.85–1.07 (m, 6H), 1.27–1.67 (m, 2H), 3.04–4.16 (m, 4H), (4.53 (d, *J* = 5.1 Hz), 4.76 (d, *J* = 3.7 Hz), 4.85 (d, *J* = 4.1 Hz), 5.02 (d, *J* = 3.8 Hz) 1H); ^{13}C NMR (125 MHz) δ = (mixture of four anomers) 8.8, 9.0, 9.9, 10.3, 14.1, 14.6, 16.5, 17.3, 28.6, 29.2, 30.4, 30.6, 44.5, 45.1, 51.0, 52.2, 63.8, 63.9, 68.0, 69.9, 70.0, 70.0, 77.0, 77.8, 78.6, 79.8, 80.6, 83.6, 98.8, 98.8, 100.2, 104.9; HRMS (CI) *m*/*z* calcd for $C_8H_{20}O_4$ + NH_4^+ 194.1387, found 194.1385.



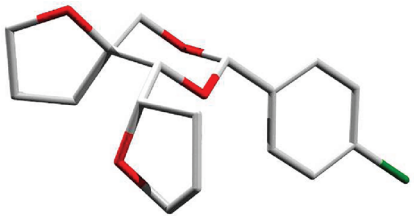
*(3S,4S,5R)-3-Ethyl-5-(hydroxymethyl)-3-methyltetrahydrofuran-2,4-diol (Derivative of 2,3-syn-3,4-anti-**29**):* ^{1}H NMR ($OC(CD_3)_2$, 500 MHz) δ = (mixture of two anomers) major anomer: 0.87 (t, 3H, *J* = 7.5), 0.93 (s, 3H), 1.45 (dq, 1H, *J* = 7.5, 13.6), 1.56 (dq, 1H, *J* = 7.5, 13.5), 3.53–3.56 (m, 1H), 3.64 (dd, 1H, *J* = 3.0, 11.6), 3.81 (ddd, 1H, *J* = 3.0, 4.4, 7.4), 3.96 (d, 1H, *J* = 7.4), 4.87 (s, 1H). minor anomer: 0.86 (t, 3H, *J* = 7.5), 0.91 (s, 3H), 1.31–1.41 (m, 2H), 3.53–3.56 (m, 1H), 3.66 (m, 1H), 3.69 (d, 1H, *J* = 7.2), 3.84 (ddd, 1H, *J* = 3.3, 5.1, 7.2), 4.96 (s, 1H); ^{13}C NMR (125 MHz) δ = (mixture of two anomers) major anomer: 9.9, 16.5, 28.7, 50.9, 63.9, 78.0, 85.7, 104.8; minor anomer: 9.7, 13.2, 32.2, 49.6, 64.2, 78.0, 84.5, 104.7.



dx.doi.org/10.1021/jo202558f | *J. Org. Chem.* 2012, 77, 2310–2330

Compounds of Scheme 6–8. Compounds **30** and **33** were transferred into the corresponding *p*-bromophenyl acetals as follows: to a mixture of 2 mmol of diol in 5 mL of DCM and 2.5 mmol of *p*-bromobenzaldehyde was added 0.1 mmol of toluenesulfonic acid. The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After completion of the reaction (~24 h), the mixture was diluted with DCM, neutralized with Na_2CO_3, dried ($MgSO_4$), and filtrated. The remaining residue was absorbed to Celite and purified by column chromatography (hexane/acetone 19/1).

*Bromophenyl acetal of **30**:* ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.79–2.08 (m, 7H), 2.52 (ddpst, 1H J = 1.2, 8.1, 12.7), 3.59 (d, 1H, J = 10.7), 3.66 (d, 1H, J = 4.2), 3.81 (d, 1H, J = 10.7), 3.76–3.90 (m, 4H), 4.13 (dpst, 1H, J = 4.2, 7.0), 5.49 (s, 1H), 7.36 (m, 2H), 7.47 (m, 2H); ^{13}C NMR (125 MHz) δ = 25.7, 25.8, 28.8, 29.3, 68.6, 68.7, 75.5, 76.3, 78.0, 84.5, 100.9, 122.8, 128.0, 131.2, 136.9.



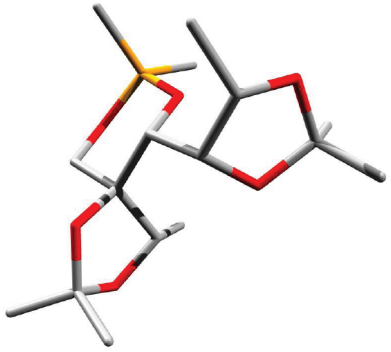
*Bromophenyl acetal of **33**.* Colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 1.83–2.06 (m, 7H), 2.09–2.17 (m, 1H), 3.64 (d, 1H, J = 10.8), 3.71 (psq, 1H, J = 7.2), 3.81 (d, 1H, J = 10.8), 3.84 (d, 1H, J = 5.2), 3.87–3.92 (m, 3H), 4.03 (dpst, 1H, J = 5.2, 6.8), 5.49 (s, 1H), 7.32–7.35 (m, 2H), 7.47–7.50 (m, 2H); ^{13}C NMR (125 MHz) δ = 25.6, 25.8, 28.1, 29.2, 68.1, 68.6, 75.2, 76.9, 77.4, 84.4, 100.3, 122.8, 127.9, 131.3, 137.0.

*(S)-Mosher ester of **33**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.65 (ddd, 1H, J = 6.5, 8.2, 12.9), 1.78–1.91 (m, 6H), 2.10 (ddd, 1H, J = 6.9, 8.4, 12.9), 3.44 (m, 1H), 3.55 (m, 3H), 3.76–3.87 (m, 4H), 3.89–3.93 (m, 1H), 4.33 (d, 1H, J = 11.3), 4.46 (d, 1H, J = 11.3), 7.38–7.41 (m, 3H), 7.54–7.56 (m, 2H).

*(S)-Mosher ester of **37**:* ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.28 (s, 3H), 1.29 (s, 3H), 1.38 (m, 6H), 3.60 (d, 1H, J = 7.3), 3.86 (m, 3H), 3.86 (d, 1H, J = 9.5), 3.91 (dd, 1H, J = 5.6, 7.8), 3.98 (dpst, 1H, J = 5.7, 7.4), 4.08 (dd, 1H, J = 5.7, 7.8), 4.10 (d, 1H, J = 9.5), 4.38 (d, 1H, J = 11.6), 4.47 (d, 1H, J = 11.6), 7.38–7.54 (m, 5H).

Compound **39** was transformed into the corresponding dimethylsilyl ether as follows: to a solution of 2 mmol of **39** in 10 mL of DCM was added 1 mmol of imidazole, 5 mmol of triethylamine, and 1.2 mmol of dimethyldichlorosilane. The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After completion of the reaction (~6 h), the mixture was diluted with DCM and filtrated. The remaining residue was absorbed to Celite and purified by column chromatography (hexane/acetone 19/1).

*Dimethylsilyl ether of **39**:* ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 0.18 (s, 3H), 0.21 (s, 3H), 1.34 (s, 3H), 1.34 (d, 3H, J = 6.2), 1.37 (s, 3H), 1.37 (s, 3H), 1.42 (d, 3H, J = 6.4), 1.47 (s, 3H), 3.57 (dd, 1H, J = 1.3, 11.4), 3.99 (s, 1H), 4.15 (d, 1H, J = 11.4), 4.36 (d, 1H, J = 6.8), 4.39 (dq, 1H, J = 6.2, 6.8), 4.88 (dq, 1H, J = 1.2, 6.4); ^{13}C NMR (125 MHz) δ = −3.8, −2.2, 14.5, 15.0, 25.9, 26.0, 26.4, 28.7, 67.0, 73.6, 73.9, 73.9, 74.8, 79.4, 106.5, 108.2.



■ ASSOCIATED CONTENT

Supporting Information

Optimization works, structure elucidations, proof of configuration, corresponding lactones, diols, and acetonides, spectral data of Mosher esters, results of X-ray structure analyses, and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rainer.mahrwald@rz.hu-berlin.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Deutsche Forschungsgemeinschaft (Priority Program Organocatalysis), Bayer-Schering Pharma AG, Chemtura Organometallics GmbH Bergkamen, Bayer Services GmbH, BASF AG, and Sasol GmbH for financial support.

■ REFERENCES

(1) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.

(2) (a) Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, *17*, 7585–7591. (b) Chowdari, N. S.; Ramachary, D. B.; Cordova, A.; Barbas, C. F. III. *Tetrahedron Lett.* **2002**, *43*, 9591–9595. (c) Pihko, P. M.; Erkkila, A. *Tetrahedron Lett.* **2003**, *44*, 7607–7609. (d) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152–2154. (e) Kofoed, J.; Machuqueiro, M.; Reymond, J.-L.; Darbre, T. *Chem. Commun.* **2004**, 1540–1541. (f) Thayumanavan, R.; Tanaka, F.; Barbas, C. F. III. *Org. Lett.* **2004**, *6*, 3541–3544. (g) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752–1755. (h) Storer, R. I.; MacMillan, D. W. C. *Tetrahedron* **2004**, *60*, 7705–7714. (i) Cordova, A. *Tetrahedron Lett.* **2004**, *45*, 3949–3952. (j) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696–3697. (k) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Cordova, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1343–1345. (l) Reyes, E.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 6605–6609. (m) Cordova, A.; Engqvist, M.; Ibrahem, I.; Casas, J.; Sunden, H. *Chem. Commun.* **2005**, 2047–2049. (n) Cordova, A.; Ibrahem, I.; Casas, J.; Sunden, H.; Engqvist, M.; Reyes, E. *Chem.—Eur. J.* **2005**, *11*, 4772–4784. (o) Kofoed, J.; Reymond, J.-L.; Darbre, T. *Org. Biomol. Chem.* **2005**, *3*, 1850–1855. (p) Zhao, G.-L.; Liao, W.-W.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 4929–4932. (q) Smith, A. B. III; Tomioka, T.; Risatti, C. A.; Sperry, J. B.; Sfouggatakis, C. *Org. Lett.* **2008**, *10*, 4359–4362.

(3) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527–3529.

(4) Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6722–6724.

(5) Li, J.; Fu, N.; Li, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2010**, *75*, 4501–4507.

(6) Kano, T.; Sugimoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 18130–18133.

(7) (a) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. *J. Org. Chem.* **2011**, *76*, 3005–3015. (b) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. *J. Am. Chem. Soc.* **2011**, *133*, 7065–7074. (c) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. *Chem. Science* **2011**, *2*, 1793–1803. (d) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293.

(8) (a) Markert, M.; Scheffler, U.; Mahrwald, R. *J. Am. Chem. Soc.* **2009**, *131*, 16642–16643. (b) Scheffler, U.; Mahrwald, R. *Synlett* **2011**, 1660–1667.

(9) (a) Y.-h. Lam, Houk, K. N.; Scheffler, U.; Mahrwald, R. Manuscript in preparation (b) Lam, Y.-h.; Houk, K. N. Abstracts 241st ACS Natl. Meeting, Anaheim, CA, 2011, 27–31.

(10) For a similar discussion in threonine-catalysis, see: Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Tanaka, F.; Barbas, C. F. III. *Angew. Chem. Int. Ed.* **2007**, *46*, 5572−5575.
(11) Hricoviniova, Z.; Lamba, D.; Hricovini, M. *Carb. Res.* **2005**, *340*, 455−458.
(12) Searle, P. A.; Molinski, T. F. *J. Org. Chem.* **1995**, *60*, 4296−4298.
(13) For a synthesis of *epi*-trachycladine A and B, see: Enders, D.; Breuer, I.; Drosdow, E. *Synthesis* **2005**, 3239−3244.
(14) For an overview of classical approaches to chiral pantolactones, see: Camps, P.; Munoz-Torrero, D. *Curr. Org. Chem.* **2004**, *8*, 1339−1380.
(15) Shinkre, B. A.; Deshmukh, A. R. A. S. *Tetrahedron: Asymmetry* **2004**, *15*, 1081−1084.
(16) Tadano, K.; Kanazawa, S.; Ogawa, S. *J. Org. Chem.* **1988**, *53*, 3868−3870.
(17) Zhdanko, A. G.; Gulevich, A. V.; Nenajdenko, V. G. *Tetrahedron* **2009**, *65*, 4692−4702.
(18) Falck, J. R.; He, A.; Fuki, H.; Tsutsui, H.; Radha, A. *Angew. Chem., Int. Ed.* **2007**, *24*, 4527−4529.
(19) Carley, S.; Brimble, M. A. *Org. Lett.* **2009**, *11*, 563−566.
(20) Fernandes, R. A.; Chavan, V. P. *Eur. J. Org. Chem.* **2010**, 4306−4311.
(21) Hoppe, D.; Tarara, G.; Wilckens, M. *Synthesis* **1989**, 83−88.
(22) Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Philips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056−4058.
(23) Bianchi, P.; Roda, G.; Riva, S.; Danieli, B.; Zabelinskaja-Mackova, A.; Griengl, H. *Tetrahedron* **2001**, *57*, 2213−2220.
(24) Palik, M.; Karlubikova, O.; Lasikova, A.; Kozisek, J.; Gracza, T. *Eur. J. Org. Chem.* **2009**, 709−715.
(25) Huang, H.-L.; Liu, R.-S. *J. Org. Chem.* **2003**, *68*, 805−810.
(26) (a) Wiggins, L. F. *J. Chem. Soc* **1946**, 13−14. (b) Bourne, E. J.; McSweeney, G. P.; Wiggins, L. F. *J. Chem. Soc.* **1952**, 3113−3114.
(27) Woods, R. J.; Neish, A. C. *Can. J. Chem.* **1954**, *32*, 404−414.
(28) Hricoviniova-Bilikova, Z.; Hricovini, M.; Petrusova, M.; Serianni, A. S.; Petrus, L. *Carb. Res.* **1999**, *319*, 38−46.
(29) Akita, H.; Matsukura, H.; Oishi, T. *Chem. Pharm. Bull.* **1986**, *34*, 2656−2659.
(30) Upadhya, T. T.; Gurunath, S.; Sudalai, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2899−2904.
(31) Evans, D. A.; Jimmy, W.; Masse, C. E.; MacMillan, D. W. C. *Org. Lett.* **2002**, *4*, 3379−3382.
(32) Pansare, S. V.; Bhattacharyya, A. *Tetrahedron* **2003**, *59*, 3275−3282.
(33) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. (b) Seco, J. M.; Qinoa, E.; Giguera, R. *Chem. Rev.* **2004**, *104*, 17−118. (c) Freire, F.; Seco, J. M.; Quinoa, E.; Riguera, R. *J. Org. Chem.* **2005**, *70*, 3778−3790.