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Role of Pseudoephedrine as Chiral Auxiliary in the "Acetate-Type" Aldol Reaction with Chiral Aldehydes; Asymmetric Synthesis of Highly Functionalized Chiral Building Blocks

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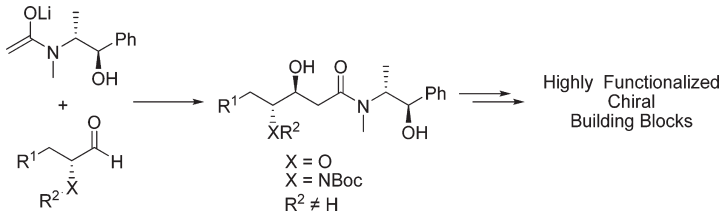

We have studied in depth the aldol reaction between acetamide enolates and chiral α-heterosubstituted aldehydes using pseudoephedrine as chiral auxiliary under double stereodifferentiation conditions, showing that high diastereoselectivities can only be achieved under the *matched* combination of reagents and provided that the α-heteroatom-containing substituent of the chiral aldehyde is conveniently protected. Moreover, the obtained highly functionalized aldols have been employed as very useful starting materials for the stereocontrolled preparation of other interesting compounds and chiral building blocks such as pyrrolidines, indolizidines, and densely functionalized β-hydroxy and β-amino ketones using simple and high-yielding methodologies.

Introduction

The asymmetric aldol reaction is one of the fundamental transformations in organic chemistry not only as an extremely powerful C−C bond-forming reaction but also as a direct and very effective procedure for the generation of 1,3-dioxygenated structures in a stereocontrolled manner.[1] As a matter of fact, the literature shows a considerable number of reports dealing with the total synthesis of natural products or therapeutics that have been accomplished using this reaction as key step.[2] Consequently, a plethora of different strategies and methods have been developed by many research groups worldwide in order to carry out this important reaction in a stereocontrolled fashion.[1] In this context, one of the most widely used methodological approaches for carrying out asymmetric aldol reactions relies on the use of chiral auxiliaries, and therefore many different chiral reagents have been developed to be used in this reaction, including the so-called "privileged auxiliaries", which have demonstrated an outstanding performance in many total syntheses.[3] Our group has also contributed to this field, and a few years ago we developed a protocol for performing highly stereocontrolled aldol reactions using the amino

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(2) See, for example: Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506.

(3) For selected recent reviews, see: (a) Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899. (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619. See also ref 1.

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alcohol (*S*,*S*)-(+)-pseudoephedrine as chiral auxiliary.[4] The main advantages of the use of this auxiliary rely upon the fact that it is a cheap reagent commercially available in both enantiomeric forms and also that it is very easy to attach to the starting carbonyl compound and to remove from the final aldol adduct and can also be recovered in a very efficient way after its removal, which allows recycling for further uses.[5] In addition, the pseudoephedrine amide moiety has shown an outstanding synthetic versatility in the sense that the aldol adducts could be easily transformed into many other interesting chiral building blocks.

However, while many fundamental studies have been performed for carrying out diastereoselective aldol reactions with chiral reagents in which there is a single chirality source devoted to the stereochemical control incorporated either at the nucleophile (a chiral enolate or related derivative) or at the electrophile (a chiral aldehyde or ketone), the same reaction in which both reagents are chiral (double stereodifferentiation conditions)[6] incorporates true elements of complexity that makes it very often a difficult problem to be solved, especially when large structural fragments have to be coupled together in the synthesis of a complex compound, as is the case, for example, in the synthesis of polyketides.[2] In addition, there is also still a long-standing problem associated with the asymmetric aldol reaction in general and the chiral auxiliary-mediated methodologies in particular related to the fact that although most of the auxiliaries developed behave well with reactions in which the enolate reagent bears an α-substituent (typically a methyl group, the so-called "propionate-type" aldol reactions), most of them perform poorly when the enolate lacks of this substituent (the "acetate-type" aldol reaction).[7] This situation, which is apparently simpler in the sense that only one stereogenic center is formed and therefore the *syn*/*anti* isomerism (simple selectivity) problem is no longer present, turns out to be an unexpectedly problematic reaction that deserves special attention. Related to this topic, some research groups worldwide have worked on the design of new chiral auxiliaries that specifically apply to the acetate aldol reaction.[8] We have also carried out investigations directed to survey the applicability of pseudoephedrine as chiral auxiliary in asymmetric acetate-type aldol reactions but with little success, observing that the aldol reaction between either aromatic or aliphatic aldehydes and metal enolates derived from (*S*,*S*)-(+)-pseudoephedrine acetamide always takes place with very low diastereoselectivities under all conditions tried.[9] Alternatively, we explored the use of this chiral auxiliary in the acetate-type aldol reaction using a chiral α-aminoaldehyde (***R***)-**2a** (Garner's aldehyde),[10] in a process proceeding under double stereodifferentiation conditions, observing that, in this case, the chiral auxiliary was an effective stereocontrolling element that allowed the preparation of the corresponding aldol in higher diastereoselectivity than that observed in the simple reaction between an achiral acetamide enolate and the same chiral aldehyde (Scheme 1).

With all of these precedents in mind, we decided to further investigate the scope and limitations of this methodology with regard to the use of other different chiral α-heterosubstituted aldehydes.[11] In this article, we wish to report in detail our findings when working on the expansion of our original procedure, together with an exploration of the synthetic applicability of the obtained aldol adducts directed toward the stereoselective preparation of interesting

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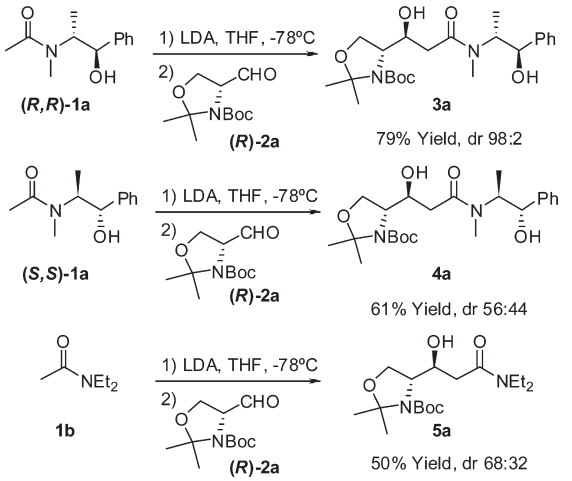
(10) Vicario, J. L.; Rodríguez, M.; Badía, D.; Carrillo, L.; Reyes, E. *Org. Lett.* **2004**, *6*, 3171.

(11) For some reviews, see: (a) Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514. (b) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (c) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121. (d) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (e) Golebiowski, A.; Jurczak, J. *Synlett* **1993**, 241.

SCHEME 1



highly functionalized chiral building blocks and heterocyclic compounds. These later transformations have focused on exploiting the particular reactivity pattern displayed by the pseudoephedrine amide moiety.

Results and Discussion

In our aforementioned preliminary report[10] we had set up the best conditions for carrying out the aldol reaction between pseudoephedrine acetamide enolates and (*R*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (***R*)-2a** (also known as Garner's aldehyde,[12] see Scheme 1) and had also identified *matched* and *mismatched* combinations of reagents, concluding that (*R*,*R*)-pseudoephedrine acetamide (***R*,*R*)-1a** and (***R*)-2a** furnished the corresponding aldol with excellent diastereoselectivity and therefore that both reagents configured the *matched* couple (Scheme 1). With these conditions in hand we proceeded next to carry out the aldol reaction between pseudoephedrine acetamides (***R*,*R*)-1a** and (***S*,*S*)-1a** and other different cyclic chiral α-heterosubstituted aldehydes (***R*)-2b** and (***R*)-2c**,[13] which are structurally related to Garner's aldehyde (***R*)-2a**

SCHEME 2

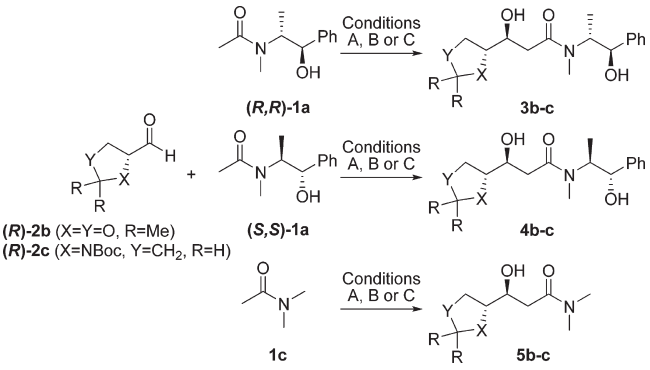


TABLE 1. Diastereoselective Aldol Reaction between Pseudoephedrine Acetamides and α-Heterosubstituted Chiral Aldehydes (*R*)-2b and (*R*)-2c[a]

entry	aldehyde	amide **1**	product	conditions[a]	yield (%)[b]	dr[c]
1	(*R*)-**2b**	(*R*,*R*)-**1a**	**3b**	A	81	94:6
2	(*R*)-**2b**	(*S*,*S*)-**1a**	**4b**	A	72	84:16
3	(*R*)-**2b**	**1c**	**5b**	A	58	86:14
4	(*R*)-**2c**	(*R*,*R*)-**1a**	**3c**	A	89	73:27
5	(*R*)-**2c**	(*S*,*S*)-**1a**	**4c**	A	53	50:50
6	(*R*)-**2c**	**1c**	**5c**	A	91	64:36
7	(*R*)-**2c**	(*R*,*R*)-**1a**	**3c**	B	90	85:15
8	(*R*)-**2c**	**1c**	**5c**	B	68	75:25
9	(*R*)-**2c**	(*R*,*R*)-**1a**	**3c**	C	67	80:20
10	(*R*)-**2b**	(*R*,*R*)-**1a**	**3b**	C	81	99:1
11	(*R*)-**2b**	**1c**	**5b**	C	58	89:11

[a]Conditions. Method A: (i) LDA, THF, −78 °C; (ii) **2b**−**c**, THF, −105 °C. Method B: (i) LDA, LiCl (4 equiv), THF, −78 °C; (ii) **2b**−**c**, THF, −100 °C. Method C: (i) LDA, THF, −78 °C; (ii) Cp_2ZrCl_2, THF, −78 °C; (iii) **2b**−**c**, THF, −100 °C. [b]Yield of combined diastereoisomeric aldol products after flash column chromatography. [c]Determined by HPLC analysis of crude reaction mixture (see Supporting Information).

(Scheme 2). The obtained results have been summarized in Table 1.

As it can be seen in this table, whereas the aldol reaction between (***R*,*R*)-1a** and (***R*)-2a** proceeded with excellent diastereoselectivity under our optimized conditions (see Scheme 1), when these conditions were applied to chiral aldehyde (***R*)-2b** derived from glyceraldehyde,[14] we observed the formation of both diastereoisomers in a 94:6 ratio (entry 1). We also checked that in this case (***R*,*R*)-1a** and (***R*)-2b** still formed the *matched* combination of reagents by carrying out the aldol reaction with (***S*,*S*)-1a**, obtaining as expected a lower degree of diastereoselection (entry 2). The *matched*/*mismatched* experiment was also completed with the corresponding reaction using the enolate derived from achiral *N*,*N*-dimethylacetamide **1c**, yielding the corresponding aldol in a 86:14 ratio (entry 3).[15] The same protocol was followed with *N*-Boc-(*R*)-prolinal (***R*)-2c**, observing a very similar behavior, with (***R*,*R*)-1a** and (***R*)-2c** arising as the *matched* combination of reagents

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(13) Aldehydes (***R*)-2a**, (***R*)-2b**, and (***R*)-2e** are commercially available compounds. The other α-amino aldehydes **2** were prepared from the corresponding *N*-protected β-amino alcohols according to a procedure developed by us: Ocejo, M.; Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E. *Synlett* **2005**, 2110.

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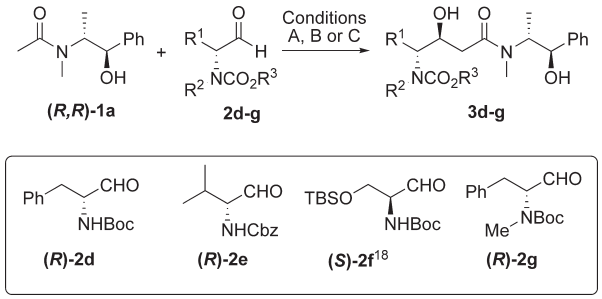
SCHEME 3



that furnished the highest diastereoselectivity (entry 4), whereas the reaction with (***S,S***)**-1a** (entry 5) and with achiral **1c** (entry 6) proceeded with lower stereocontrol.[16,17] We next decided to survey some other modified conditions in order to improve the diastereoselectivity of the reaction, starting with the incorporation of LiCl as an additive to the reaction scheme (reaction conditions B), which in some cases has been reported to have a beneficial effect on the diastereoselectivity of processes in which pseudoephedrine amide enolates are involved.[18] In our case, the diastereoselectivity of the aldol reaction using *N*-Boc-(*R*)-prolinal (***R***)**-2c** in the presence of 4 equiv of LiCl led to a better 85:15 dr (entry 7) under the *matched* conditions. The beneficial effect associated to the presence of the chiral auxiliary was confirmed by comparing this result with the lower diastereoselectivity obtained using the enolate derived form achiral **1c** under the same reaction conditions (entry 8 vs 7). We also surveyed changing the nature of the enolate counterion by carrying out a transmetalation reaction with Cp_2ZrCl_2 prior to the aldol addition step (reaction conditions C), which we had already observed had a positive effect in the diastereoselectivity of the closely related "propionate-type" aldol reaction using pseudoephedrine as chiral auxiliary.[19] However, in this case we could not demonstrate any important improvement, observing that the final aldol product had been formed as a 80:20 mixture of diastereoisomers (entry 9). On the other hand, when these conditions were applied to the reaction with glyceraldehyde derivative (***R***)**-2b**, the reaction proceeded with complete diastereocontrol, furnishing the corresponding aldol as a single diastereoisomer (entry 10). Once again, the positive contribution of the chiral auxiliary was confirmed by carrying out the reaction using **1c** as the enolate source under these conditions (entry 11 vs 10). It has also to be pointed out that the absolute configuration of the newly generated stereocentre in the major diastereoisomer was the same in all of the reactions, which indicates that in all cases the influence exerted by the chiral aldehyde in the stereochemical outcome of the reaction was more important than the contribution made by the chiral auxiliary.

TABLE 2. Diastereoselective Aldol Reaction between Pseudoephedrine Acetamide (*R,R*)-1a and α-Aminoaldehydes 2d−g

entry	aldehyde	compound	conditions[a]	yield (%)[b]	dr[c]
1	(***R***)**-2d**	**3d**	B	75	69:31
2	(***R***)**-2d**	**3d**	B[d]	70	52:48
3	(***R***)**-2d**	**3d**	A	80	64:36
4	(***R***)**-2d**	**3d**	C	65	59:41
5	(***R***)**-2e**	**3e**	B	50	50:50
6[d]	(***S***)**-2f**	***ent*-3f**	B	45	56:44
7	(***R***)**-2g**	**3g**	B	90	98:2
8[e]	(***R***)**-2g**	**3g**	B	72	80:20
9	(***R***)**-2g**	**3g**	A	60	98:2

[a]Conditions. Method A: (i) LDA, THF, −78 °C; (ii) **2d**−**g**, THF, −100 °C. Method B: (i) LDA, LiCl (4 equiv), THF, −78 °C; (ii) **2d**−**g**, THF, −100 °C. Method C: (i) LDA, THF, −78 °C; (ii) Cp_2ZrCl_2, THF, −78 °C; (iii) **2d**−**g**, THF, −100 °C. [b]Yield of combined diastereoisomeric aldol products after flash column chromatography. [c]Determined by HPLC analysis of crude reaction mixture (see Supporting Information). [d](***S,S***)**-1a** was employed as the enolate source. [e]**1c** was employed as the enolate source.

We next evaluated the use of other different open-chain α-amino aldehydes **2d**−**g**[13] employing the *matched* combination of reagents (Scheme 3), with the results shown in Table 2. First, we checked that with reaction conditions B (***R,R***)**-1a** and (*R*)-*N*-Boc-phenylalaninal (***R***)**-2d** formed the *matched* combination of reagents by carrying out the aldol reaction with (***S,S***)**-1a**, obtaining as expected a lower diastereoselectivity in the later case compared with the former (entries 1 vs 2). Nevertheless, when either the standard conditions (Method A) or the modified ones (Methods B and C) were applied to (***R***)**-2d**, we observed in all cases that the reaction proceeded with very poor levels of diastereoselection (entries 1, 3, and 4). We also tested α-aminoaldehydes (***R***)**-2e**[20] and (***S***)**-2f**,[21] but also in these cases the reaction furnished mixtures of the two isomeric aldols in similar ratios as those observed with (***R***)**-2d** (entries 5 and 6 vs 1), which indicated that neither the nature of the alkyl side chain of the α-aminoaldehyde reagent nor the carbamate protecting group had an striking influence in the diastereoselectivity of the process. We therefore hypothesized that the lower diastereoselectivity observed in these reactions compared to that observed for **2d**−**f** could be possibly attributable to the presence of an acidic N−H group in the aldehyde, and in fact, when we carried out the reaction using *N*-methyl substituted derivative (***R***)**-2g** in the reaction with (***R,R***)**-1a** in the presence of LiCl as an additive (Method B), a fully diastereoselective reaction occurred, isolating the corresponding aldol **3g** in excellent yield and as a highly diastereopure material (entry 7). The positive influence of the presence of the chiral auxiliary in the diastereoselectivity of the reaction was also confirmed with the corresponding experiment using the lithium enolate derived from achiral **1c** under the same reaction conditions, obtaining in this case a 80:20 mixture of diastereoisomers (entry 8). In this case,

(16) It has been previously reported that the addition of the lithium enolate of ethyl acetate to aldehyde (***R***)**-2c** in THF at −78°C furnished a 4:1 mixture of diastereoisomers: Hanson, G. J.; Baran, J. S.; Lindberg, T. *Tetrahedron Lett*. **1986**, *27*, 3577. On the other hand, the addition of the corresponding zinc enolate to the same aldehyde furnished a 2:1 mixture of diastereoisomers (see ref 12n). In all cases, the *anti* isomer was preferentially formed.

(17) The addition of the lithium enolate of heptan-2-one to *N*-Cbz-(*R*)-prolinal in THF at −78°C has been reported to proceed with excellent diastereoselectivity, forming the corresponding *anti* aldol: Snider, B. B.; Gao, X. *Org. Lett*. **2005**, *7*, 4419.

(18) For the influence of LiCl in the reactivity of pseudoephedrine enolates, see: (a) Rück, K. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 433. (b) Henderson, K. W.; Dorigo, A. E.; Liu, Q.-Y.; Williard, P. G.; Schleyer, P. v. R.; Bernstein, P. R. *J. Am. Chem. Soc*. **1996**, *118*, 1339 and references therein. See also refs 5a, 5k, and 5l.

(19) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem*. **2000**, *65*, 3754.

(20) Aldehyde (***R***)**-2g** was prepared from D-mannitol according to a literature procedure: Leyes, A. E.; Poulter, C. D. *Org. Lett*. **1999**, *1*, 1067.

(21) (***S***)**-2f** had to be used because the corresponding β-amino alcohol needed for its preparation was commercially available only as the (*S*) enantiomer. Consequently, the aldol reaction under *matched* conditions was carried out using (***S,S***)**-1a** as nucleophile.

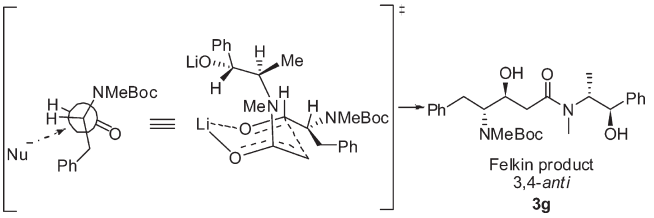


FIGURE 1. Proposed model for the diastereoselective aldol reaction of (***R*,*R*)-1a** and chiral aldehyde (***R*)-2g.**

when the reaction was carried out under standard conditions (Method A, without the presence of LiCl), only the yield of the reaction became affected, obtaining the same high diastereoselectivity in the reaction between (***R*,*R*)-1a** and (***R*)-2g** as that obtained in the presence of LiCl (entry 9 vs 7).

These results can be rationalized by making use of the polar Felkin−Ahn model[22] and also assuming a Zimmermann−Traxler-like six-membered transition state[23] with no chelation issues involved, as is normally accepted for the aldol reactions of metal enolates with α-heterosubstituted aldehydes. In our case, we have observed that the chirality at the aldehyde plays the main role in regard to stereochemical control, producing the 3,4-*anti* configured products in all cases regardless of the configuration of the chiral auxiliary. This indicates that pseudoephedrine is playing a secondary role with regard to stereocontrol, although its incorporation enables small but relevant increases on diastereoselectivity when compared with the parent reaction when an achiral enolate was employed (see for example entries 7 vs 8 and 10 vs 11 in Table 1 and entries 7 vs 8 in Table 2). As is shown in Figure 1 using the reaction between (***R*,*R*)-1a** and α-aminoaldehyde (***R*)-2g** as a model, a Felkin−Ahn model accounts for the formation of the final adducts by assuming that chiral aldehydes **2** would interact with the enolate derived from (***R*,*R*)-1a** through a reactive conformation in which the C=O and C−N (or C−O) bonds should remain in an antiperiplanar position because of repulsion between the electronegative O- and N-atoms. As a result, the aldehyde *si* face is sterically more accessible for the attack of the enolate nucleophile. As is shown in Figure 1, a chairlike transition state is proposed, although the possibility of the reaction to proceed through a boat-like transition state should not be discarded, as it is also proposed in the literature for many cases of acetate-type aldol reactions.[24] However, the fundamental role played by the chirality of the aldehyde in this reaction makes this feature a minor fact to be considered here. Other possible explanations for this selectivity involving alternative models reported in the literature, such as a Cornforth-type transition state or *syn*-pentane interactions operating in the transition state, have not been considered

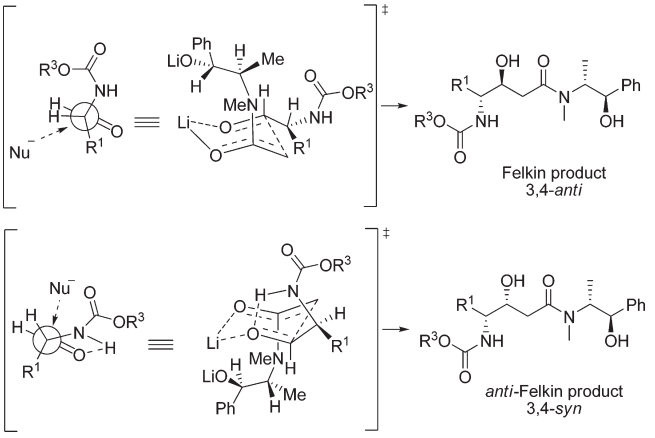


FIGURE 2. Proposed model for the diastereoselective aldol reaction of (***R*,*R*)-1a** and (***R*)-2d−f**.

for this case because of the absence of any substituent at the α-carbon of the enolate reagent.[22] Regarding the stereochemical influence of the chiral auxiliary, this proposal takes also into account the previously proposed models[5b,k] for other reactions between (*S*,*S*)-(+)-pseudoephedrine amide enolates and different electrophiles in which the final product arises from the attack to the less hindered face of an intermediate in an opened staggered conformation, which remains rigid with the help of bridging solvent or $i\mathrm{Pr}_2\mathrm{NH}$ (from LDA) molecules.[25] For this reason, we can assume that in this case one of the diastereotopic faces of the enolate reagent is effectively blocked, although this is not a relevant question operating in this case because of the nature of the enolate reagent which, due to the lack of the α-substituent does not lead to the formation of an stereocenter at this position and therefore the facial discrimination of the diastereotopic faces of the enolate does not have any consequences on the stereochemical outcome of this reaction. Nevertheless, the presence of the chiral auxiliary can also be consider to contribute to the stabilization of the chairlike transition state vs the competitive formation of other possible boat-type structures with similar energies for the two transition states leading to each of the two possible diastereoisomers.[26] The exact role played by LiCl in this reaction when used as additive which slightly increases the diastereoselectivity of the reaction still remains unknown to us, although a plausible proposal might involve its participation as bridging species similar to those mentioned before which communicates both lithium atoms of the pseudoephedrine acetamide lithium enolate therefore contributing to a more rigid transition state, although it might be simply operating by modifying the aggregation state of the enolate species as it has been pointed out earlier.[18]

A possible explanation for the poor stereoselectivity obtained when N−H containing chiral α-aminoaldehydes **2d−f** were employed in this reaction can be found on the hypothetical formation of an intramolecular hydrogen bond that would stabilize an alternative conformation for the chiral electrophile, which would turn the *re* face more accessible

(22) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (c) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145. (d) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353. See also: (e) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

(23) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(24) See for example: (a) Crimmins, M. T.; Shamszad, M. *Org. Lett.* **2007**, *9*, 149. (b) Saito, S.; Hatanaka, K.; Kano, T.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3378. (c) Pridgen, L. N.; Abdel-Magid, A. F.; Lantos, I.; Shilcrat, S.; Eggleston, D. S. *J. Org. Chem.* **1993**, *58*, 5107 and references therein. See also: (d) Goodman, J. M.; Kahn, S. D.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3295. See also ref 7.

(25) Vicario, J. L.; Badia, D.; Dominguez, E.; Carrillo, L. *J. Org. Chem.* **1999**, *64*, 4610.

(26) For several discussions, see: (a) Diaz-Oltra, S.; Carda, M.; Murga, J.; Falomir, E.; Marco, J. A. *Chem.—Eur. J.* **2008**, *14*, 9240. (b) Diaz-Oltra, S.; Murga, J.; Falomir, E.; Carda, M.; Peris, G.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 8130. (c) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1761.

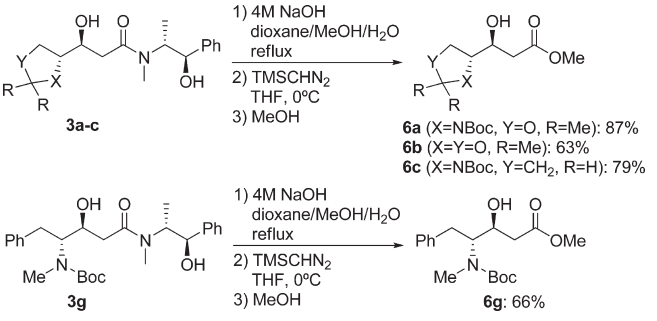
for the nucleophilic attack, therefore accounting for the formation of the *anti*-Felkin 3,4-*syn* diastereoisomer (Figure 2). We assume that, under the reaction conditions, both possible transition states could eventually compete and therefore mixtures of the two possible diastereoisomers can be formed in variable amounts. The formation of such an intramolecular hydrogen bond in asymmetric aldol reactions with chiral α-aminoaldehydes has also been proposed in previous reports in order to explain *anti*-Felkin selectivity in aldol reactions involving α-substituted enolates.[27] It should also be pointed out that all of the reactions carried out with these NH-containing α-amino aldehydes proceeded with complete conversion of the starting material, which also indicates that the addition of the enolate to the aldehyde has to occur faster than the possible competitive quenching of the enolate reagent by the acidic NH hydrogen, which would lead to the recovery of starting unreacted acetamide (***R*,*R*)-1a**. This behavior is also in agreement with other literature examples.[12m,n,28]

After studying the aldol reaction and once the required conditions for obtaining the corresponding aldols were fully understood, we next faced the task of exploring the reactivity of these highly functionalized compounds with a focus on the preparation of polyfunctionalized chiral building blocks. In this context, effective protocols have to be developed for the removal of the chiral auxiliary in a clean way, using simple and high-yielding procedures and, if possible, allowing the recycling of the auxiliary. It is in this particular situation where pseudoephedrine amides have found a wide field of application because of the particular reactivity displayed by this moiety. For this purpose, we limited our study to the reactivity of aldols **3a**−**c** and **3g**, which were obtained as highly stereoenriched compounds.

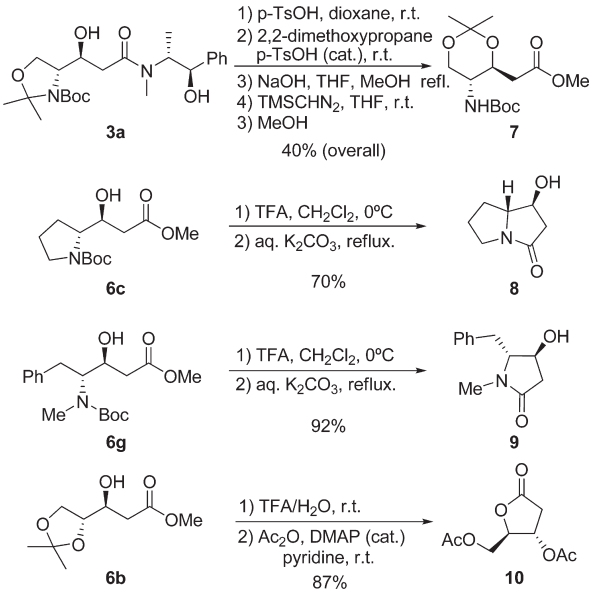
We started with the removal of the chiral auxiliary by hydrolysis, which would allow the preparation of γ-amino-β-hydroxy carboxylic acid derivatives. When we carried the hydrolysis under acidic conditions, which has been the methodology of choice in many other examples,[5] we obtained only complicated mixtures of unidentified products. Alternatively, base-promoted hydrolysis proceeded smoothly, providing cleanly the corresponding carboxylic acids, and these were subsequently subjected to esterification with trimethylsilyldiazomethane[29] for better purification (Scheme 4). Remarkably, the chiral auxiliary (*R*,*R*)-(−)-pseudoephedrine could be easily recovered after the hydrolysis step by standard acid−base workup, which allowed its recycling for further uses.

At this point, we also faced the determination of the configuration of the new stereogenic center generated in

SCHEME 4



SCHEME 5



the diastereoselective aldol reaction. For this purpose, we decided to prepare conformationally locked cyclic derivatives of the esters **6**, which would be appropriate molecules for the determination of the relative configuration by NOE experiments, given the known configuration of the stereocenter that was introduced at the starting aldehyde. We had already described in our preceding communication, the determination of the absolute configuration of aldol **3a** (see Scheme 5),[10] which could not be carried out directly from ester **6a** and was needed for a four-step sequence starting from **3a**. The case of esters **6b**, **6c**, and **6g** turned to be much easier; for example, for **6c** and **6g** we were able to prepare pyrrolizidine derivative **8** and γ-lactam **9**, respectively, by TFA-mediated deprotection followed by base-promoted intramolecular amide formation. Cyclic lactone **10** was also prepared in a very simple way from ester **6b** by first carrying out the acid hydrolysis of the acetonide moiety, which proceeded concomitantly with a lactonization process, and next peracetylation was carried out for better characterization purposes. Analyses of NOE experiments carried out on these cyclic derivatives confirmed the *anti* relationship between both contiguous stereogenic centers and therefore allowed us to establish a (3*S*) absolute configuration for the stereocenter created in the aldol reactions. It has to be emphasized that this configuration of the major aldols **3** was the same in all cases, confirming that the stereochemical outcome of the diastereoselective aldol reaction of chiral α-heterosubstituted aldehydes with pseudoephedrine acetamides did not change when α-amino aldehydes (***R*)-2c** and (***R*)-2g** or α-alkoxyaldehyde (***R*)-2b** were employed as electrophiles.

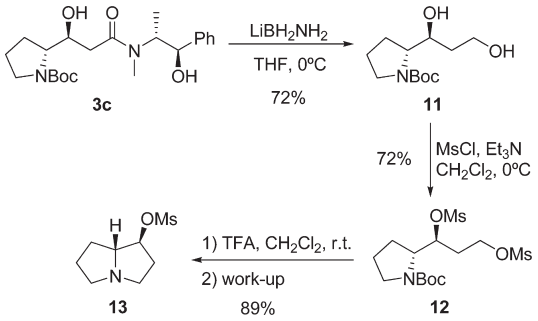
We also evaluated the possibility of removing the chiral auxiliary by reduction, in order to obtain highly

(27) Vicario, J. L.; Badia, D.; Dominguez, E.; Carrillo, L. *J. Org. Chem.* **1999**, *64*, 4610.

(28) (a) Jung, C.-K.; Kirsche, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 17051. See also: (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439. (c) Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074.

(29) (a) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475. (b) Hodnett, N. S. *Synlett* **2003**, 2095.

SCHEME 6



functionalized primary alcohols. We tried the use of lithium amidotrihydroborate (LAB), which is known as a very effective reagent for the conversion of pseudoephedrine amides into the corresponding alcohols, [30] and in our case, we observed that aldol **3c** underwent fast and clean reduction, under the typical conditions, furnishing diol **11** good yield (Scheme 6). This compound was subsequently employed as starting material for an alternative synthesis of pyrrolizidines, which is the main structural basis of many important natural products and therapeutics,[31] following a set of transformations as shown in Scheme 6. First, **11** was reacted with excess MsCl, yielding cleanly dimesylated compound **12**, and next, removal of the *N*-Boc protecting group occurred with a subsequent intramolecular cyclization that happened during the workup procedure, which involved basic conditions. In this way, pyrrolizidine **13** was isolated in excellent yield and as a single diastereoisomer, indicating that all of the reactions proceeded with no epimerization in any of the stereogenic centers present at the corresponding precursors.

Finally, we also decided to evaluate the removal of the chiral auxiliary by exploiting the known ability of the pseudoephedrine amide moiety to undergo fast and clean 1,2-addition of organolithium reagents, affording the corresponding ketones after aqueous workup (Scheme 7). This moiety has shown a behavior comparable in this context to that of Weinreb amides.[32] We had already demonstrated in our preceding paper that aldol **3a** was an excellent substrate for this transformation, and a wide range of γ-amino-β,δ-dihydroxyketones were prepared using different organolithium reagents[10] (Table 3, entries 1−6). We therefore proceeded to check whether aldol **3b**, which does not contain any amino moiety on its structure, was also a suitable substrate for this transformation, and indeed, the reaction of **3b** with organolithium reagents proved to be equally efficient, yielding a set of different ketones in excellent yields and as single diastereoisomers (entries 7−12 in Table 3). As can be observed in Table 3, a wide range of organolithium

SCHEME 7

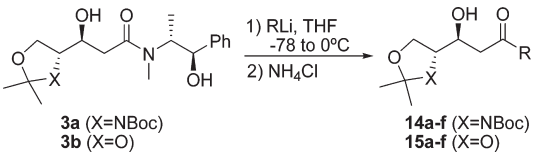


TABLE 3. Selective 1,2-Addition of Organolithium Reagents to Aldols 3a and 3b

entry	substrate	X	R	product	yield (%)[a]
1	**3a**	NBoc	Me	**14a**	94
2	**3a**	NBoc	Et	**14b**	88
3	**3a**	NBoc	*i*-Pr	**14c**	87
4	**3a**	NBoc	*n*-Bu	**14d**	89
5	**3a**	NBoc	*t*-Bu	**14e**	71
6	**3a**	NBoc	Ph	**14f**	68
7	**3b**	O	Me	**15a**	93
8	**3b**	O	Et	**15b**	75
9	**3b**	O	*i*-Pr	**15c**	77
10	**3b**	O	*n*-Bu	**15d**	85
11	**3b**	O	*t*-Bu	**15e**	71
12	**3b**	O	Ph	**15f**	72

[a]Yield of pure product after flash column chromatography purification.

reagents are acceptable regardless of their structure, and therefore primary, secondary, and even tertiary alkyllithium reagents, as well as phenyllithium, underwent clean 1,2-addition, with no evidence of competitive aldolization at the two highly acidic α-protons of the substrate under these extremely basic conditions. It has also to be pointed out that also in this case, the chiral auxiliary (*R*,*R*)-(−)-pseudoephedrine could be easily recovered after standard acid−base work up and could be recycled for further uses.

Conclusions

In conclusion, we have shown that acetate-type aldol reactions using chiral α-heterosubstituted aldehydes as electrophiles can be carried out with high yields and stereoselectivities using pseudoephedrine as chiral auxiliary provided that the correct *matched* combination of reagents is employed and also that the chiral aldehyde electrophile does not contain any acidic H-atom at the α-heteroatom containing substituent. Although the diastereoselectivity of the reaction is dominated by the chiral electrophile, the matched combination is crucial to ensure a useful and high stereoselectivity. From a mechanistic point of view, the obtained results can be explained by making use of the polar Felkin−Ahn model with no contribution of any chelating element in the transition state, and the poorer level of stereoselection observed when α-aminoaldehydes containing an acidic NH group were employed should be attributed to the presence of a competitive reaction pathway involving a chelation-controlled transition state. On the other hand, it has also been shown that the highly stereoenriched aldol adducts obtained could be easily transformed into a variety of different valuable chiral building blocks by exploiting the rich reactivity profile of the pseudoephedrine amide moiety.

Experimental Section

General Procedures for the Diastereoselective Aldol Reaction of Pseudoephedrine Acetamide and Chiral α-Heterosubstituted Aldehydes. Method A. A solution of the acetamide (***R***,***R***)**-1a** or

(30) (a) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623. (b) Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett* **1997**, 457. See also: (c) Whitlock, G. A.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 2007 and ref 5.

(31) (a) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, 2670. (b) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773.

(32) For a detailed study see ref 5b. For other related examples, see: (a) Zhou, X.-T.; Lu, L.; Furkert, D. P.; Wells, C. E.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7622. (b) Robertson, J.; Dallimore, J. W. P.; Meo, P. *Org. Lett.* **2004**, *6*, 3857. (c) White, J. D.; Xu, Q.; Lee, C.-S.; Valeriote, F. A. *Org. Biomol. Chem.* **2004**, *2*, 2092. (d) Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2003**, *14*, 489. (e) Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2002**, *13*, 745. (f) Smith, A. B., III.; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925.

(*S*,*S*)-**1a** (1.0 mmol) in dry THF (10 mL) was slowly added to a cooled (−78 °C) solution of LDA (2.0 mmol) in dry THF (20 mL). The mixture was stirred at this temperature for 1 h and allowed to reach room temperature. After stirring for 30 min, the mixture was cooled again to −100 °C at which temperature a solution of the starting chiral aldehyde **2** (1.5 mmol) in dry THF (5 mL) was dropwise added within 20 min. The mixture was stirred at −100 °C for 7 h and quenched with a saturated NH_4Cl solution (50 mL). The mixture was extracted with CH_2Cl_2, the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to yield a yellowish oil, which was flash column chromatographed affording the corresponding aldols **3**.

Method B. A solution of the acetamide (*R*,*R*)-**1a** (1.0 mmol) or (*S*,*S*)-**1a** (1.0 mmol) in dry THF (10 mL) was slowly added to a cooled (−78 °C) solution of LDA (2.0 mmol) in dry THF (20 mL) and LiCl (5.0 mmol). The mixture was stirred at this temperature for 1 h and allowed to reach room temperature. After stirring for 30 min, the mixture was cooled again to −100 °C at which temperature a solution of the starting chiral aldehyde **2** (1.5 mmol) in dry THF (5 mL) was dropwise added within 20 min. The mixture was stirred at −100 °C for 7 h and quenched with a saturated NH_4Cl solution (50 mL). The mixture was extracted with CH_2Cl_2, the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to yield a yellowish oil, which was flash column chromatographed affording the corresponding aldols **3**.

Method C. A solution of the acetamide (*R*,*R*)-**1a** (1.0 mmol) or (*S*,*S*)-**1a** (1.0 mmol) in dry THF (10 mL) was slowly added to a cooled (−78 °C) solution of LDA (2.0 mmol) in dry THF (20 mL). The mixture was stirred at this temperature for 1 h and allowed to reach room temperature. After stirring for 30 min, the mixture was cooled again to −78 °C, and next a solution of Cp_2ZrCl_2 (2.0 mmol) in dry THF (5 mL) was added at once. After stirring for 1 h at this temperature, the reaction was cooled to −100 °C at which temperature a solution of chiral aldehyde **2** (1.5 mmol) in dry THF (3 mL) was dropwise added within 20 min. The mixture was stirred at −100 °C for 7 h and quenched with a saturated NH_4Cl solution (50 mL). The mixture was extracted with CH_2Cl_2, the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to yield a yellowish oil, which was flash column chromatographed affording the corresponding aldols **3**.

(−)-(1″*R*,2″*R*,3*S*,4′*R*)-3-(2′,2′-Dimethyl[1,3]dioxolan-4′-yl)-3-hydroxy-*N*-(1″-hydroxy-1″-phenylpropan-2″-yl)-*N*-methylpropanamide (3b). Amide **3b** was prepared according to procedure C (see Table 1, entry 10) starting from amide (*R*,*R*)-**1a** (2.00 g, 9.66 mmol) and using LDA (21.25 mmol), Cp_2ZrCl_2 (5.65 g, 19.32 mmol), and aldehyde (*R*)-**2b** (1.88 g, 14.49 mmol). Yield: 81% (2.64 g, 7.82 mmol). HPLC analysis of the crude reaction mixture (Chiralcel OD column, hexanes/2-propanol 97:3, flow rate 0.85 mL/min) indicated a 99:1 diastereomeric ratio. t_R for the minor (1″*R*,2″*R*,3*R*,4′*R*) isomer: 52.0 min. t_R for the major (1″*R*,2″*R*,3*S*,4′*R*) isomer: 61.3 min. $[\alpha]^{20}_D$ −84.4 (*c* 0.7 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) (3:1 rotamer ratio; *indicates minor rotamer resonances): 0.99 (d, 3H, *J* = 6.7 Hz); 1.31 (s, 3H); 1.37 (s, 3H); 2.44 (dd, 1H, *J* = 16.2, 7.1 Hz); 2.64 (d, 1H, *J* = 16.2 Hz); 2.84 (s, 3H); 2.89* (s, 3H); 3.89−4.07 (m, 5H); 4.51 (m, 2H); 4.64−4.70 (m, 1H); 7.29 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm) (*indicates minor rotamer resonances): 14.3; 15.2*; 25.2; 26.7; 31.2; 35.7*; 37.1; 56.1*; 58.1; 67.5; 70.1; 75.3; 75.8; 109.3; 126.6; 126.7*; 127.8*; 128.4; 128.6; 141.3*; 141.7; 173.5*; 173.9. IR (film): 3412 (OH); 1613 (C═O). MS (EI) *m*/*z* (relative intensity): 301 ($M^+ - 2H_2O$, 11), 202 (14), 147 (19), 118 (20), 100 (16); 91 (21), 71 (20), 58 (100). Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.12; H, 8.15; N, 4.08.

(−)-(1′*S*,1″*R*,2*R*,2″*R*)-*N*-*tert*-Butoxycarbonyl-2-{1′-hydroxy-2′-[*N*-(2″-hydroxy-1″-methylethyl-2″-phenyl)-*N*-methylcarbamoyl]ethyl}pyrrolidine (3c). Amide **3c** was prepared according to procedure B (see Table 1, entry 7) starting from amide (*R*,*R*)-**1a** (0.35 g, 1.67 mmol) and using LDA (3.34 mmol), aldehyde (*R*)-**2c** (0.50 g, 2.51 mmol), and LiCl (0.36 g, 8.36 mmol) and isolated as a yellowish oil after flash column chromatography purification (hexanes/AcOEt 2:8). Yield: 90% (0.61 g, 1.51 mmol). HPLC analysis of the crude reaction mixture (Chiralcel OJH column, hexanes/2-propanol 97:3, flow rate 1.00 mL/min) indicated a 85:15 diastereomeric ratio. t_R for the minor (1′*R*,1″*R*,2*R*,2″*R*) isomer: 15.29 min. t_R for the major (1′*S*,1″*R*,2*R*,2″*R*) isomer: 26.04 min. $[\alpha]^{20}_D$ −30.7 (*c* 1.0 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) (4:1 rotamer ratio; *indicates minor rotamer resonances): 0.86 (d, 3H, *J* = 6.8 Hz), 1.45 (s, 9H), 1.75−1.93 (m, 3H), 2.14−2.27 (m, 1H), 2.46 (dd, 1H, *J* = 16.0, 3.8 Hz), 2.68 (dd, 1H, *J* = 16.0, 3.4 Hz), 2.89 (s, 3H), 2.93* (s, 3H), 3.23−3.41 (m, 2H), 3.54−3.66 (m, 1H), 4.08−4.18 (m, 1H), 4.45−4.65 (m, 2H), 4.84−4.97 (m, 1H), 5.50 (d, 1H, *J* = 9.0 Hz), 7.25−7.43 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm) (*indicates minor rotamer resonances): 14.5 15.2*, 23.3, 26.9*, 27.2, 28.4, 28.5*, 29.5, 35.0, 47.4, 54.9, 58.0*, 60.4, 61.4*, 70.4, 75.5, 75.7*, 79.4, 79.7*, 126.8*, 127.2, 127.8, 128.3, 128.6*, 141.2*, 141.3, 155.8, 173.8*, 174.8. IR ($CHCl_3$): 3396 (OH), 1687, 1618 (C═O). MS (CI) *m*/*z* (relative intensity): 407 (M^++H, 5), 389 (5), 333 (5), 308 (19), 307 (100), 305 (3), 243 (14), 236 (16), 166 (12), 148 (7), 142 (3). HRMS (*m*/*z*): $[M + H]^+$ calcd for $[C_{22}H_{35}N_2O_5]^+$ 407.2540. Found: 407.2535.

(−)-(1′*R*,2′*R*,3*S*,4*R*)-4-*tert*-Butoxycarbonylmethylamino-3-hydroxy-*N*-methyl-*N*-(2′-hydroxy-1′-methylethyl-2′-phenyl)-5-phenylpentanamide (3g). Amide **3g** was prepared according to procedure B (see Table 2, entry 7) starting from amide (*R*,*R*)-**1a** (0.26 g, 1.26 mmol)and using LDA (2.52 mmol), aldehyde (*R*)-**2g** (0.50 g, 1.90 mmol), and LiCl (0.27 g, 6.33 mmol) and isolated as a yellowish oil after flash column chromatography purification (hexanes/AcOEt 2:8). Yield: 90% (0.53 g, 1.13 mmol). $[\alpha]^{20}_D$ −38.3 (*c* 1.0 in CH_2Cl_2). Determination of the diastereoselectivity of the reaction was carried out by HPLC analysis of the corresponding methyl ester **6g** obtained by hydrolysis/esterification of the crude reaction mixture following the general procedure (see Supporting Information for details). This analysis showed that aldol **3g** had been obtained as a 98:2 mixture of diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) (1:1 rotamer ratio; *indicates rotamer resonances): 0.90 (d, 3H, *J* = 6.9 Hz), 0.96* (d, 3H, *J* = 6.8 Hz), 1.03* (d, 3H, *J* = 6.7 Hz), 1.19* (s, 9H), 1.29 (s, 9H), 1.33* (s, 9H), 2.32−2.96 (m, 3H), 2.55 (s, 3H), 2.80* (s, 3H), 2.84 (s, 3H), 2.93* (s, 3H), 3.24−3.42 (m, 1H), 3.80−4.74 (m, 4H), 4.76−4.94 (m, 1H), 5.43 (d, 1H, *J* = 5.6 Hz), 7.16−7.42 (m, 10H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm) (*indicates minor rotamer resonances): 14.3*, 14.6, 15.2,* 15.3*, 26.7*, 28.1*, 28.2, 28.3*, 30.3, 31.6, 33.6*, 34.0, 35.6, 37.0*, 55.6, 57.9, 68.9*, 70.2, 75.4, 76.0*, 79.3*, 79.8, 125.9, 126.0, 126.5, 126.6, 126.7, 127.0, 127.8, 128.1, 128.2, 128.3, 128.4, 128.7, 128.8, 129.0, 138.6, 139.1*, 141.3, 141.4, 141.8, 155.6*, 156.2*, 156.3, 173.6*, 173.7*, 174.0, 174.4*. IR ($CHCl_3$): 3406 (OH), 1687, 1617 (C═O). MS (CI) *m*/*z* (relative intensity): 471 (M^++H, 18), 453 (8), 415 (15), 399 (14), 379 (16), 372 (26), 371 (100), 307 (9), 236 (27), 208 (8), 164 (8), 148 (12). HRMS (*m*/*z*): $[M + H]^+$ calcd for $[C_{27}H_{39}N_2O_5]^+$ 471.2853, found 471.2872.

General Procedure for the Hydrolysis/Esterification of Aldols 3. To a solution of the amide **3a**−**c** or **3g** (1.00 mmol) in dioxane (3 mL), MeOH, (3 mL) and H_2O (6 mL) was added NaOH (5 mmol). The mixture was then refluxed for 2 h and allowed to reach room temperature. More water (10 mL) was added, and the mixture was washed with Et_2O (3 × 15 mL). After drying (Na_2SO_4), filtering, and removing the solvents, the chiral auxiliary (*R*,*R*)-(−)-pseudoephedrine was recovered in 71% yield as

a white solid after crystallization in hexane/AcOEt. The basic aqueous layer was then carefully basified with 1 M HCl until pH = 3, and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to yield the corresponding carboxylic acid, which was directly subjected to esterification. This was carried out by the addition of $TMSCHN_2$ (4.00 mmol) over a cooled (0 °C) solution of the crude acid in dry THF (10 mL). After stirring for 2 h, MeOH (1 mL) was added at once, and the mixture was stirred for further 45 min, after which it was quenched with water (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to yield ester **6a**−**c**, **6g** as colorless oils after flash column chromatography purification.

(−)-(3*S*,4′*R*)-3-(2′,2′-Dimethyl[1,3]dioxolan-4′-yl)-3-hydroxypropanoic Acid Methyl Ester (6b). Ester **6b** was prepared according to the general procedure starting from aldol **3b** (0.46 g, 1.36 mmol), NaOH (0.14 g, 3.6 mmol), and $TMSCHN_2$ (3.04 mL of a 2 M solution in Et_2O, 6.08 mmol) and isolated as a colorless oil after flash column chromatography purification (hexanes/AcOEt 1:1). NMR analysis of crude reaction mixture indicated that ester **6b** had been obtained as a >95:5 dr. Yield: 63% (0.17 g, 0.86 mmol). $[\alpha]^{20}_D$ −11.8 (*c* 0.4 in $CHCl_3$). (lit.[33] −10.6, *c* 1.0 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 1.30 (s, 3H); 1.36 (s, 3H); 2.43 (dd, 1H, *J* = 16.7, 8.5 Hz); 2.68 (dd, 1H, *J* = 16.7, 2.4 Hz); 3.28 (bs, 1H); 3.67 (s, 3H); 3.95 (m, 2H); 4.03 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C, δ, ppm): 25.0; 26.5; 37.5; 51.8; 66.5; 69.1; 77.5; 109.4; 173.0. IR (film): 3472 (OH); 1737 (C=O). MS (EI) *m*/*z* (relative intensity): 190 (6), 189 (66), 147 (7), 131 (3), 129 (38), 115 (21), 103 (15); 101 (100), 97 (52), 87 (7), 83 (9); 73 (34), 72 (18); 71(12); 61 (13); 59 (43); 55 (20).

(+)-(3*S*,4*R*)-3-(*N*-*tert*-Butoxycarbonyl-pyrrolidin-2′-yl)-3-hydroxy-2-methylpropanoic Acid Methyl Ester (6c). Ester **6c** was prepared according to the general procedure starting from aldol **3c** (0.15 g, 0.37 mmol), NaOH (0.07 g, 1.85 mmol), and $TMSCHN_2$ (0.74 mL of a 2 M solution in Et_2O, 1.48 mmol) and isolated as a yellowish oil after flash column chromatography purification (hexanes/AcOEt 6:4). Yield: 79% (0.08 g, 0.29 mmol). HPLC analysis (Chiralcel OJH column, hexanes/2-propanol 97:3, flow rate 1.00 mL/min) indicated a 90:10 diastereomeric ratio. t_R for the major (1′*S*,2*R*) isomer: 10.09 min. t_R for the minor (1′*R*,2*R*) isomer: 10.94 min. $[\alpha]^{20}_D$ +40.5 (*c* 1.67 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 1.42 (s, 9H), 1.63−2.05 (m, 4H), 2.28−2.51 (m, 2H), 3.16−3.24 (m, 1H), 3.37−3.50 (m, 1H), 3.65 (s, 3H), 3.83−3.94 (m, 1H), 4.09−4.16 (m, 1H), 4.45 (bs, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm) (*indicates minor rotamer resonances): 23.3*, 23.9, 26.4*, 27.5, 28.2*, 28.3, 37.7, 38.5*, 46.8*, 47.7, 51.6, 61.2*, 62.1, 69.0*, 70.2, 79.9, 80.3*, 154.7*, 156.2, 172.7. IR ($CHCl_3$): 3448 (OH), 1740, 1693 (C=O). MS (CI) *m*/*z* (relative intensity): 274 (M^++H, 3), 228 (3), 218 (17), 200 (14), 174 (100), 170 (19), 156 (11), 142 (9), 124(6), 114 (27). HRMS (*m*/*z*): $[M + H]^+$ calcd for$[C_{13}H_{24}NO_5]^+$ 274.11649, found 274.1662.

(+)-(3*S*,4*R*)-4-(*tert*-Butoxycarbonyl(methyl)amino)-3-hydroxy-5-phenylpentanoic Acid Methyl Ester (6g). Ester **6g** was prepared according to the general procedure starting from aldol **3g** (0.23 g, 0.49 mmol), NaOH (0.10 g, 2.44 mmol), and $TMSCHN_2$ (0.97 mL of a 2 M solution in Et_2O, 1.96 mmol) and isolated as a yellowish oil after flash column chromatography purification (hexanes/AcOEt 6:4). Yield: 66% (0.08 g, 0.29 mmol). HPLC analysis (Chiralcel OJH column, hexanes/2-propanol 96:4, flow rate 1.00 mL/min) indicated a 99:1 diastereomeric ratio. t_R for the major (3*S*,4*R*) isomer: 13.76 min. t_R for the minor (3*R*,4*R*) isomer: 17.37 min. $[\alpha]^{20}_D$ +30.5 (*c* 0.18 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) (*indicates minor rotamer resonances): 1.22* (s, 9H), 1.35 (s, 9H), 2.39−2.66 (m, 3H), 2.51 (s, 3H), 2.91−3.00 (m, 1H), 3.15 (dd, 1H, *J* = 14.1, 3.8 Hz), 3.28* (dd, 1H, *J* = 14.0, 2.3 Hz), 3.40−3.51* (m, 1H), 3.70* (s, 3H), 3.71 (s, 3H), 3.90−4.28 (m, 2H), 7.14−7.27 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm) (*indicates minor rotamer resonances): 28.1*, 28.2, 33.2, 34.3*, 37.9, 38.7*, 51.7*, 51.8, 60.9*, 62.9, 69.1*, 70.2, 79.7, 126.1*, 126.2, 128.2*, 128.3, 128.9, 138.8, 155.5*, 156.2, 173.1*, 173.4. IR ($CHCl_3$): 3433 (OH), 1664 (C=O). MS (CI) *m*/*z* (relative intensity): 338 (M^+ + H, 1), 280 (1), 264 (13), 246 (14), 238 (100), 234 (14), 206 (6), 178 (22), 146 (17), 134(11), 114 (5). HRMS (*m*/*z*): $[M + H]^+$ calcd for$[C_{18}H_{28}NO_5]^+$ 338.1962, found 338.1983.

(+)-(1*S*,8*R*)-1-Hydroxypyrrolizidin-3-one (8). To a solution of the ester **6c** (0.05 g, 0.18 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C was added TFA (0.28 mL, 3.66 mmol). The mixture was stirred for 1 h, and then the solvent was removed *in vacuo*, after which an aqueous solution of K_2CO_3 4.0 M (10 mL) was added. The mixture was then refluxed for 30 min and allowed to reach room temperature. Then was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to yield lactam **8** as colorless oils.Yield: 70% (0.02 g, 0.13 mmol). $[\alpha]^{20}_D$ +93.1 (*c* 0.14 in $CHCl_3$). (lit.[16] −91.5, *c* 1.0 in $CHCl_3$ for the 1*R*,8*S* isomer). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 1.39−1.52 (m, 1H), 1.95−2.20 (m, 3H), 2.75 (d, 2H, *J* = 8.3 Hz), 3.00−3.08 (m, 1H), 3.52−3.61 (m, 1H), 3.72−3.79 (m, 1H), 4.21−4.28 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm): 26.6, 29.8, 41.6, 44.4, 69.3, 73.2, 172.5. IR ($CHCl_3$): 3386 (OH), 1664 (C=O). MS (CI) *m*/*z* (relative intensity): 142 (M^+ + H, 100), 141 (23), 124 (23), 123 (4), 112 (10). HRMS (*m*/*z*): [M + H]$^+$ calcd for$[C_7H_{12}NO_2]^+$ 142.0863, found 142.0866.

(−)-(4*S*,5*R*)-5-Benzyl-4-hydroxy-1-methylpyrrolidin-2-one (9). To a solution of the ester **6g** (0.08 g, 0.24 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C was added TFA (0.36 mL, 4.75 mmol). The mixture was stirred for 1 h, and then the solvent was removed *in vacuo*, after which an aqueous solution of K_2CO_3 4.0 M (10 mL) was added. The mixture was then refluxed for 30 min and allowed to reach room temperature. Then it was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to yield lactam **9** as colorless oil.Yield: 92% (0.04 g, 0.24 mmol). $[\alpha]^{20}_D$ −64.0 (*c* 0.38 in $CHCl_3$). (lit.[34] $[\alpha]^{20}_D$ −64.4, *c* 0.4 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 2.02 (s, 1H), 2.10 (d, 1H, *J* = 17.6 Hz), 2.24 (dd, 1H, *J* = 17.6, 5.9 Hz), 2.69 (dd, 1H, *J* = 14.0, 7.4 Hz), 2.81 (s, 3H), 2.91 (dd, 1H, *J* = 14.0, 5.1 Hz), 3.64−3.68 (m, 1H), 4.06−4.14 (m, 1H), 7.11−7.32 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm): 28.3, 36.8, 39.5, 68.4, 70.3, 126.9, 128.7, 129.1 136.3, 173.2. IR ($CHCl_3$): 3315 (OH), 1668 (C=O). MS (CI) *m*/*z* (relative intensity): 205 (M^+, 5), 168 (3), 116 (54), 114 (52), 96 (16), 70 (100), 57 (46). HRMS (*m*/*z*): $[M]^+$ calcd for$[C_{12}H_{15}NO_2]^+$ 205.1103, found 205.1107.

(−)-(4*S*,5*R*)-4-Acetoxy-5-acetoxymethyl-4,5-dihydrofuran-2(3*H*)-one (10). A solution of the ester **6b** (180 mg, 0.88 mmol) in TFA/H_2O/THF (5 mL/1 mL/3 mL) was stirred at room temperature during 4 h. Then, the solvent was removed *in vacuo*, after which the mixture was dissolved in pyridine (2 mL) and acetic anhydride (0.40 mL, 3.53 mmol) was added. The mixture was stirred at rt for 24 h after which HCl 4 M (4 mL) was added. Then the reaction crude was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to yield after flash column chromatography purification

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(hexanes/AcOEt 1:1) lactone **10** as colorless oil. Yield: 87% (166 mg, 0.77 mmol). $[\alpha]^{20}_D$ −10.9 (*c* 0.6 in CH_2Cl_2). (lit.[35] −11.5, *c* 0.7 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 2.05 (s, 3H); 2.07 (s, 3H); 2.57 (dd, 1H, *J* = 18.9, 2.0, Hz); 2.97 (dd, 1H, *J* = 18.7, 7.5 Hz); 4.23 (dd, 1H, *J* = 12.3, 3.6, Hz); 4.34 (dd, 1H, *J* = 12.3, 3.6 Hz); 4.64 (m, 1H); 5.22 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm) 20.5, 20.6, 34.7, 63.2, 71.0, 82.0, 170.0, 170.2, 173.7. IR ($CHCl_3$): 3472 (OH), 1737 (C=O). MS (EI) *m*/*z* (relative intensity): 217 (M^+ + 1, 1), 145 (5), 143 (44), 128 (26), 126 (6), 114 (7), 103 (10), 96 (6), 86 (15), 84 (29), 83 (100), 73 (4), 71 (14), 68 (4), 55 (14).

LAB-Mediated Reduction of Aldol 3c. Synthesis of (+)-(1′*S*,2*R*)-*N*-*tert*-Butoxycarbonyl-2-(1′,3′-dihydroxypropyl)-pyrrolidine (11). *n*-BuLi (4.27 mL of a 1.3 M solution in hexane, 5.55 mmol) was added over a solution of diisopropylamine (0.76 mL, 5.38 mmol) in dry THF (10 mL) at −78 °C, and the mixture was stirred for 15 min. The reaction was warmed to 0 °C, and $NH_3 \cdot BH_3$ (0.17 g, 5.47 mmol) was added at once. The mixture was stirred 15 min at 0 °C and another 15 min at room temperature, after which a solution of 3c (0.37 g, 0.91 mmol) in THF (5 mL) was added via canula at 0 °C, and the reaction was stirred for 2 h. Then the reaction was quenched with HCl 1 N (15 mL) and extracted with AcOEt (3 × 15 mL). The organic fractions were collected, washed with satd $NaHCO_3$, dried over Na_2SO_4, and filtered, and the solvent removed *in vacuo* affording the wanted alcohol **11** after flash column chromatography purification (hexanes/AcOEt 1:9). Yield: 72% (0.16 g, 0.65 mmol). $[\alpha]^{20}_D$ +48.3 (*c* 1.0 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 1.46 (s, 9H), 1.51−2.06 (m, 7H), 3.19−3.28 (m, 2H), 3.48−3.57 (m, 1H), 3.82−4.00 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm) (*indicates minor rotamer resonances): 24.1, 28.1, 28.3*, 28.4, 32.9, 47.4*, 48.1, 61.4*, 61.8, 63.1, 74.5, 80.4, 80.7*, 156.8. IR ($CHCl_3$): 3396, 2972 (OH), 1670 (C=O). MS (EI) *m*/*z* (relative intensity): 172 (M^+ − 73, 7), 170 (24), 114 (100), 108 (25), 98 (26), 96 (45), 70 (72), 57 (43). HRMS (*m*/*z*): $[M]^+$ calcd for$[C_{12}H_{23}NO_4]^+$: 245.1627, found 245.1626.

(+)-(1′*S*,2*R*)-*N*-*tert*-Butoxycarbonyl-2-(1′,3′-bis(dimethanesulfonyloxy)propyl)pyrrolidine (12). To a solution of alcohol **10** (0.16 g, 0.65 mmol) in CH_2Cl_2 (20 mL) at 0 °C, was added triethylamine (0.18 mL, 1.31 mmol) and methanesulfonyl chloride (0.10 mL, 1.31 mmol). The mixture was stirred for 1 h at room temperature, after which the reaction was quenched with 2 M KOH (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic fractions were collected, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to yield **12** as a yellowish oil after flash column after flash column chromatography purification (hexanes:AcOEt 1:9). Yield: 74% (0.19 g, 0.48 mmol). $[\alpha]^{20}_D$ +45.1 (*c* 1.0 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) (*indicates rotamer resonances): 1.45*, 1.46 (s, 9H), 1.75−2.10 (m, 6H), 2.97 (s, 3H), 3.04 (s, 3H), 3.20−3.30 (m, 1H), 3.37−3.65 (m, 1H), 3.71−3.92 (m, 1H), 4.28−4.42 (m, 2H), 5.24−5.40 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm) (*indicates rotamer resonances): 23.8*, 24.0, 25.1, 25.7*, 28.3, 32.2, 37.3, 37.9, 38.3*, 47.1, 59.9, 65.9, 78.8, 79.4*, 80.1, 80.8*, 156.8. IR ($CHCl_3$): 1686 (C=O), 1356 (SO_2), 1174 (SO_2). MS (EI) *m*/*z* (relative intensity): 401 (M^+, 3), 335 (15), 242 (44), 238 (31), 148 (34), 147 (100), 118 (27), 117 (33), 115 (27), 91 (21), 73 (71). HRMS (*m*/*z*): $[M]^+$ calcd for$[C_{14}H_{27}NO_8S_2]^+$ 401.1178, found 401.1176.

(+)-(1*S*,8*R*)-1-Methanesulfonyloxypyrrolizidine (13). To a solution of **12** (0.15 g, 0.37 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C was added TFA (0.57 mL, 7.48 mmol). The mixture was stirred for 1 h, and then an aqueous solution of KOH 2.0 M (5 mL) was added. The mixture was stirred for 2 h. Then was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to yield pyrrolizidine **13** as colorless oil. Yield: 89% (0.07 g, 0.34 mmol). $[\alpha]^{20}_D$ +31.6 (*c* 1.0 in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 1.39−1.52 (m, 1H), 1.70−1.81 (m, 2H), 1.99−2.20 (m, 3H), 2.44−2.53 (m, 1H), 2.69−2.76 (m, 1H), 3.01 (s, 3H), 3.01−3.08 (m, 1H), 3.15−3.23 (m, 1H), 3.54−3.60 (m, 1H), 4.82−4.84 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm): 25.8, 30.2, 31.3, 38.6, 52.1, 55.2, 70.1, 86.0. IR ($CHCl_3$): 1351 (SO_2), 1173 (SO_2). MS (CI) *m*/*z* (relative intensity): 206 (M^+ + H, 33), 204 (10), 126 (32), 110 (100), 108 (3). HRMS (*m*/*z*): $[M + H]^+$ calcd for$[C_8H_{16}NO_3S]^+$ 206.0845, found 206.0846.

General Procedure for the Selective 1,2-Addition of Organolithium Reagents to Aldols 3a and 3b. The organolithium (3.5 mmol) was added over a solution of amide **3a** or **3b** (1.00 mmol) in dry THF (20 mL) at −78 °C. The reaction mixture was stirred 15 min at this temperature and then it was warmed to 0 °C and stirred for further 45 min, after which a saturated NH_4Cl solution (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic fractions were collected, dried over Na_2SO_4, and filtered, and the solvent removed *in vacuo* affording the wanted ketone **14a**−**f** or **15a**−**f** after flash column chromatography purification (AcOEt/hexanes 1:1).

(−)-(4*S*,4′*R*)-4-(2′,2′-Dimethyl[1,3]dioxolan-4′-yl)-4-hydroxybutan-2-one (15a). The ketone **15a** was prepared according to the general procedure starting from amide **3b** (120 mg, 0.36 mmol) and MeLi (1.26 mL of a 1.0 M solution in Et_2O, 1.26 mmol) as a white solid. Yield: 87% (63 mg, 0.33 mmol). Mp 132−134 °C (hexanes/AcOEt). $[\alpha]^{23}_D$ −30.6 (*c* 0.2 in $CHCl_3$). (lit.[36] −28.0, *c* 1.2 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 1.32 (s, 3H); 1.38 (s, 3H); 2.20 (s, 3H); 2.59 (dd, 1H, *J* = 17.8, 8.3 Hz); 2.80 (dd, 1H, *J* = 18.0, 2.0 Hz); 3.73 (m, 1H); 3.93 (m, 2H); 4.06 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm): 25.1; 26.6; 30.7; 46.2; 66.8; 68.9; 76.5; 109.4; 209.7. IR (film): 3436 (OH); 1707 (C=O). MS (EI) *m*/*z* (relative intensity): 173 (M^+ − 15, 8), 113 (8), 101 (100); 95 (56), 87 (20), 83 (13), 73 (27), 61 (12), 59 (32), 55 (14).

(−)-(1*S*,4′*R*)-4-(2′,2′-Dimethyl[1,3]dioxolan-4′-yl)-1-hydroxypentan-3-one (15b). The ketone **15b** was prepared according to the general procedure starting from amide **3b** (126 mg, 0.37 mmol) and EtLi (2.88 mL of a 0.45 M solution in benzene/cyclohexane, 1.29 mmol) as a yellowish oil. Yield: 75% (56 mg, 0.28 mmol). $[\alpha]^{23}_D$ −25.4 (*c* 0.3 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 1.05 (t, 3H, *J* = 7.5 Hz), 1.33 (s, 3H), 1.38 (s, 3H), 2.48 (q, 2H, *J* = 7.5 Hz), 2.58 (m, 1H), 2.77 (dd, 1H, *J* = 17.0, 2.0 Hz), 3.27 (bs, 1H), 3.95 (m, 3H), 4.06 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm): 7.5, 25.1, 26.6, 36.7, 44.8, 66.9, 69.1, 77.5, 107.6, 212.5. IR (film): 3443 (OH); 1703 (C=O). MS (EI) *m*/*z* (relative intensity): 187 (M^+ − 15, 6), 127 (9), 109 (53); 101 (100); 97 (13), 83 (11), 73 (28), 59 (36), 57 (72); 55 (13). Anal. Calcd for$C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.28; H, 9.03.

(−)-(1*S*,4′*R*)-4-(2′,2′-Dimethyl[1,3]dioxolan-4′-yl)-1-hydroxy-4-methylpentan-3-one (15c). The ketone **15c** was prepared according to the general procedure starting from amide **3b** (123 mg, 0.36 mmol) and *i*-PrLi (2.00 mL of a 0.62 M solution in pentane, 1.26 mmol) as a yellowish oil. Yield: 77% (60 mg, 0.28 mmol). $[\alpha]^{23}_D$ −40.3 (*c* 0.1 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 1.10 (d, 6H, *J* = 7.1 Hz), 1.33 (s, 3H), 1.39 (s, 3H); 2.58 (m, 2H), 2.85 (d, 1H, *J* = 17.4 Hz), 3.34 (bs, 1H, OH), 3.94 (m, 3H); 4.05 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm): 17.9, 25.1, 26.6, 41.5, 42.9, 67.0, 69.3, 77.5, 109.4, 216.1. IR (film): 3448 (OH); 1707 (C=O). MS (EI) *m*/*z* (relative

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intensity): 201 ($M^+ - 15$, 4), 141 (4); 127 (11), 123 (35); 115 (37); 101 (100); 97 (25), 84 (9), 73 (28), 71 (58); 59 (37), 55 (9). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.13; H, 9.38.

(−)-(1*S*,4′*R*)-4-(2′,2′-Dimethyl[1,3]dioxolan-4′-yl)-1-hydroxyheptan-3-one (15d). The ketone **15d** was prepared according to the general procedure starting from amide **3b** (107 mg, 0.32 mmol) and *n*-BuLi (0.80 mL of a 1.45 M solution in hexane, 1.12 mmol) as a yellowish oil. Yield: 85% (65 mg, 0.27 mmol). $[\alpha]^{23}_D$ −36.1 (*c* 0.3 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 0.88 (t, 3H, J = 7.1 Hz), 1.27 (m, 2H), 1.32 (s, 3H), 1.38 (s, 3H), 1.55 (m, 2H), 2.44 (t, 2H, J = 7.1 Hz), 2.51 (dd, 1H, J = 17.4, 9.5 Hz), 2.80 (d, 1H, J = 17.4 Hz), 3.30 (bs, 1H), 3.91 (m, 3H), 4.05 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm): 13.8, 22.2, 25.1, 25.6, 26.6, 43.4, 45.2, 66.9, 69.1, 77.5, 109.4, 212.3. MS (EI) m/z (relative intensity): 215 ($M^+ - 15$, 3), 137 (38), 129 (24), 127 (9); 101 (100); 97 (10), 85 (44), 73 (24), 59 (27), 57 (29). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 61.49; H, 9.60.

(−)-(1*S*,4′*R*)-4-(2′,2′-Dimethyl[1,3]dioxolan-4′-yl)-1-hydroxy-4,4-dimethylpentan-3-one (15e). The ketone **15e** was prepared according to the general procedure starting from amide **3b** (120 mg, 0.36 mmol) and *t*-BuLi (1.26 mL of a 1.45 M solution in hexane, 1.26 mmol) as a yellowish oil. Yield: 71% (58 mg, 0.25 mmol). $[\alpha]^{23}_D$ −45.2 (*c* 0.2 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 1.16 (s, 9H), 1.34 (s, 3H), 1.39 (s, 3H), 2.62 (dd, 1H, J = 18.2, 8.3 Hz), 2.95 (dd, 1H, J = 18.1, 2.0 Hz), 3.40 (bs, 1H), 3.95 (m, 3H), 4.08 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm): 25.2, 26.1, 26.7, 29.7, 39.5, 67.1, 69.5, 77.5, 107.6, 217.8. MS (EI) m/z (relative intensity): 215 ($M^+ - 15$, 4), 137 (27); 129 (28), 127 (23); 115 (18); 101 (92); 97 (60), 85 (42), 73 (36), 69 (20); 61 (10); 59 (57), 57 (100); 55 (12). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.53; H, 9.71.

(−)-(3*S*,4′*R*)-4-(2′,2′-Dimethyl[1,3]dioxolan-4′-yl)-1-phenyl-3-hydroxypropan-3-one (15f). The ketone **15f** was prepared according to the general procedure starting from amide **3b** (112 mg, 0.33 mmol) and PhLi (0.58 mL of a 2.00 M solution in Et_2O, 1.16 mmol) as a yellowish oil. Yield: 72% (60 mg, 0.23 mmol). $[\alpha]^{23}_D$ −48.9 (*c* 0.3 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 1.36 (s, 3H), 1.41 (s, 3H), 3.10 (dd, 1H, J = 17.8, 8.7 Hz), 3.51 (dd, 1H, J = 17.8, 2.3 Hz), 3.51 (bs, 1H, OH); 3.98−4.15 (m, 4H), 7.45 (t, 2H, J = 7.1 Hz), 7.55 (t, 1H, J = 1.7 Hz), 7.95 (d, 2H, J = 1.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) (δ, ppm): 25.1, 26.7, 41.6, 65.5, 67.1, 69.4, 109.5, 128.1, 128.6, 128.9. 133.5, 200.7. MS (EI) m/z (relative intensity): 235 ($M^+ - 15$, 4), 175 (5); 157 (31); 149 (32); 131 (5); 105 (100); 101 (87); 83 (8), 77 (51), 73 (28); 59 (27), 55 (10); 51 (15). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.25; H, 7.31.

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Supporting Information Available: Detailed descriptions of determination of diastereomeric ratios and copies of HPLC traces and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.