Addition Reactions of Aldehydes to Lithium Enolates of 1,3-Dioxolan-4-ones: A Configurational Reassessment

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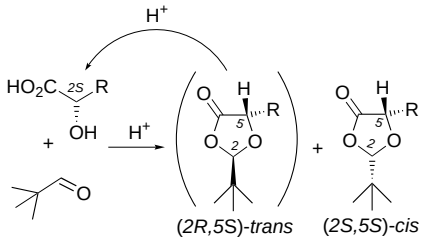
Abstract: The results for the addition reactions of chiral lithium (2*S*)-enolates of 1,3-dioxolan-4-ones to aldehydes and to acetophenone, yielding the corresponding dioxolanone alcohols have been revised. The results reported herein differ from those reported in the literature, both in product distribution and in the stereochemical assignment of the products. In fact, in several cases no stereocontrol was observed at the C5 carbon atom of the lithium enolate. The (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*) stereochemistry was also reassessed for several dioxolanone alcohols. The major conformers are considered to have an intramolecular hydrogen-bonded five-membered ring structure instead of the six-membered ring structure previously suggested for cyclic dioxolanone alcohols.

Keywords: aldehydes · aldol reactions · dioxolanones · α-hydroxy acids · stereoselective synthesis

Introduction

Chiral 2,3-dihydroxy acids and their derivatives are versatile tools in the synthesis of biologically active compounds such as the aminosugar L-daunosamine,[1] leukotriene B_4,[2] tocopherol,[3] bicyclomycin,[4] citreoviral,[5] macrolide antibiotics,[6a–f] and antitumor pyrrolizidine alkaloids.[7a,b] The 2,3-dihydroxy acids can be prepared easily, without the use of chiral auxiliaries, by starting from inexpensive, naturally occurring chiral compounds such as α-hydroxy acids, and by following the synthetic principle of self-regeneration of stereocenters (SRS).[8a,b] According to this principle, chiral α-hydroxy acids are transformed into *cis*/*trans* mixtures of cyclic 1,3-dioxolan-4-ones by acetalization with an aldehyde or a ketone; for this pivalaldehyde has usually been employed (Scheme 1). The *cis*-1,3-dioxolan-4-ones are usually obtained as the major isomers and they can be isolated enantiomerically pure.[8b, 9]



Scheme 1. Synthesis of diastereoisomeric mixtures of (2*S*,5*S*)- and (2*R*,5*S*)-1,3-dioxolan-4-ones obtained from the acetalization of an (*S*)-α-hydroxy acid with pivalaldehyde.

The dioxolanone is transformed into a nonracemic enolate by annihilation of the original stereogenic center at C5 with a base such as lithium diisopropylamide (LDA) at low temperatures. Subsequent reaction of the enolate with an aldehyde or a ketone proceeds under the influence of the temporary stereogenic acetal C2 center, yielding a dioxolanone alcohol. Removal of the auxiliary center affords the 2,3-dihydroxycarbonyl derivative. As an example, the stereochemical outcome of the reaction of an aldehyde to a (2*S*)-enolate of the dioxolanone derived from the acetalization of (*S*)-α-lactic acid with pivaladehyde is shown in Scheme 2. Two of the four possible stereoisomers are formed via the transition states TS **I** and TS **II**, (2*S*,5*R*,1′*S*, and 2*S*,5*R*,1′*R* respectively). The other two stereoisomers are formed via the transition states TS **III** and TS **IV** (2*S*,5*S*,1′*R* and 2*S*,5*S*,1′*S*). Transition states TS **I** and TS **II** are kinetically favored over TS **III** and TS **IV** because the aldehyde approaches the enolate from the less hindered enantiotopic face which bears the hydrogen atom.

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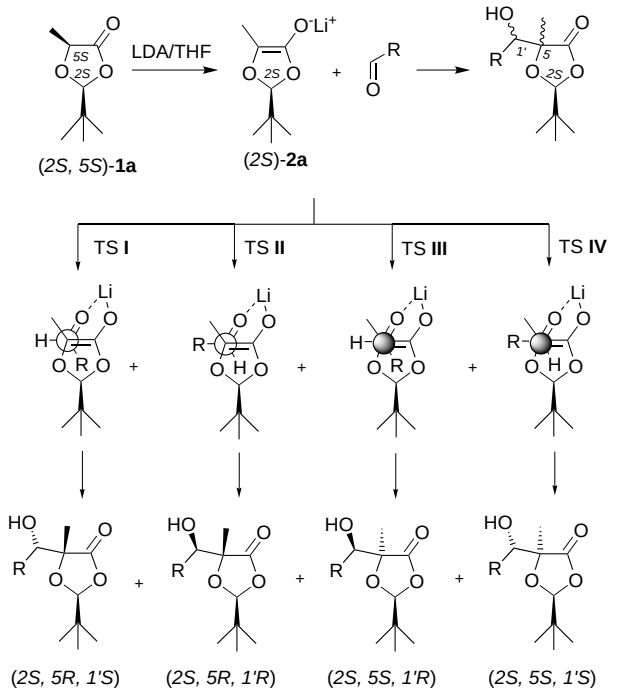
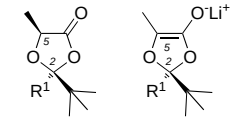
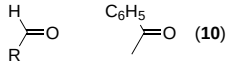


Scheme 2. Stereochemical outcome of the addition reactions of (2*S*)-**2a** to aldehydes affording diastereoisomeric mixtures of dioxolanone alcohols.

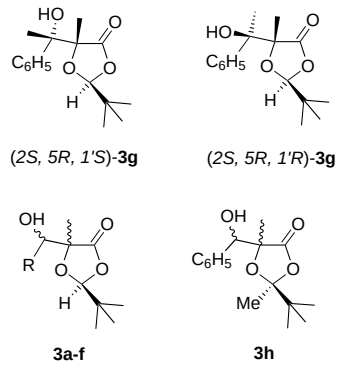


R^1 = H (**1a**, **2a**)
R^1 = Me (**1b**, **2b**)



R: Me (**4**), C_2H_5 (**5**), Me_3C (**6**), C_6H_5 (**7**), C_9H_{19} (**8**), Me_2CH (**9**)

Seebach's diastereoselective studies[8b] of the addition reactions of the (2*S*)-enolate **2a** of the 2-*tert*-butyl-5-methyl-1,3-dioxolan-4-one (**1a**) to aldehydes **4**–**7** and acetophenone **10** showed that the aldehydes and the ketone react with enantioface selectivity according to the kinetically favored transition states TS **I** and TS **II.** For dioxolanone alcohols **3a**–**d** and **3g**, only the diastereomeric pairs (2*S*,5*R*,1′*S*) (or *u* isomers)[10] and (2*S*,5*R*,1′*R*) (or *l* isomers) were obtained. The (2*S*,5*R*,1′*S*) isomers were formed with strong preference (% ds 82 (**3a**), 85 (**3b**), 53 (**3c**), 84 (**3d**), and 93 (**3g**)). The configuration of compounds **3a**–**d** and **3g** was assigned on the basis of ^{1}H NMR spectral data,[8b] on the assumption that the main conformers exist in an intramolecular hydrogen-bonded form of a six-membered ring structure (Figure 1, structures **A** and **B**). On the other hand, alternative five-membered hydrogen-bonded ring structures have been suggested to explain the ^{1}H and ^{13}C NMR spectral data of alicyclic 2,3-dihydroxy-α-methylcarbonyl compounds.[11a] If these structures are valid for the cyclic dioxolanone alcohols (**A′** and **B′**, Figure 1), the shielding effects of the C-1′ substituents on the acetal hydrogen, shown by the C2-H resonances, are expected to be opposite to those observed for **A** and **B**. Because of this, assignment of configuration by ^{1}H NMR spectroscopy might be misleading, because an exchange of the (2*S*,5*R*,1′*S*) and (2*S*,5*R*,1′*R*) structures is expected in the two models, so that (2*S*,5*R*,1′*S*)-**A** might correspond to (2*S*,5*R*,1′*R*)-**B′** and (2*S*,5*R*,1′*R*)-**B** to (2*S*,5*R*,1′*S*)-**A′**.[12] Compound (2*S*,5*R*,1′*S*)-**3b** was the only exception, as its stereochemistry was also assigned by chemical correlation with the 2,3-dihydroxy acid (2*R*,3*S*)-**13** (Scheme 3).



R = Me (**3a**), C_2H_5 (**3b**), Me_3C (**3c**), C_6H_5 (**3d**), C_9H_{19} (**3e**), Me_2CH (**3f**)

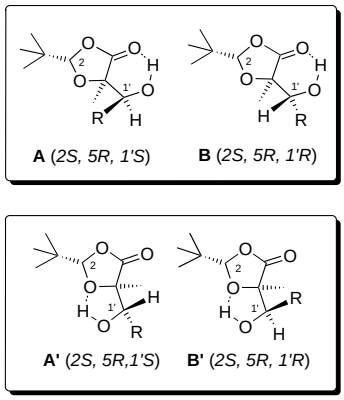


Figure 1. Six- (**A**, **B**) and five-membered (**A′**, **B′**) hydrogen-bonded ring structures of the main conformers of dioxolanone alcohols.

The aim of the present study was to re-examine the addition reactions of enolate **2a** (2*S*/2*R* = 98:2) to aldehydes **4**–**7** and to ketone **10**, to provide reliable methods, such as X-ray and chemical correlation, for the assessment of the relative configuration of the substituents at the C5–C1′ carbon atoms. The absolute configuration was also determined in some

Abstract in Italian: *Il controllo delle reazioni di addizione di litio (2S)-enolati di 1,3-diossolan-4-oni ad aldeidi e all'acetofenone, che danno luogo ai corrispondenti diossolanoni-alcoli, ha portato a risultati diversi da quelli descritti in letteratura sia per quanto riguarda la distribuzione dei prodotti che il loro assegnamento configurazionale. Infatti, in molti casi non è stato osservato alcun controllo stereochimico al carbonio C5 dei litio enolati. Per molti diossolanoni-alcoli è stata anche effettuata una revisione della stereochimica. Tale revisone è in linea con l'ipotesi di una struttura ad anello a cinque atomi intramolecolarmente chelata con un atomo di idrogeno dei maggiori conformeri, invece di una struttura ciclica a sei atomi suggerita precedentemente nel caso dei diossolanoni-alcoli.*

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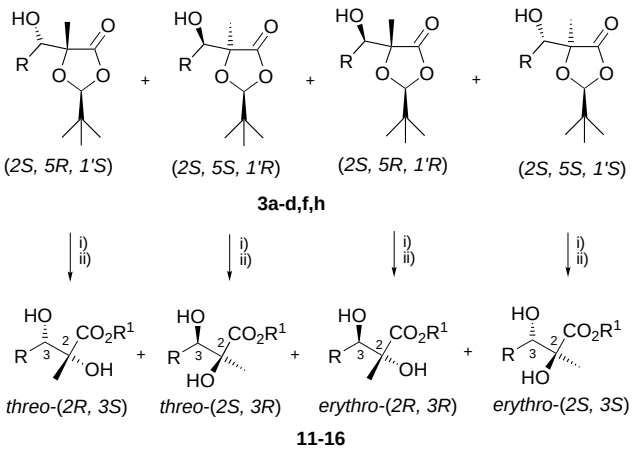


Scheme 3. Formation of 2,3-dihydroxycarbonyl derivatives **11**–**16** from the solvolysis of dioxolanone alcohols **3a–d**, **f**, **h**. **11**: R = Me, R^1 = Me; **12**: R = Me, $R^1 = C_2H_5$; **13**: R = C_2H_5, R^1 = H; **14**: R = Me_3C, R^1 = Me; **15**: R = C_6H_5, R^1 = Me; **16**: R = Me_2CH, R^1 = Me. i) – Me_3CCH=O. ii) +R^1OH.

cases. As we were interested in employing this protocol for synthesis of other trisubstituted chiral 2,3-dihydroxy-3-methyl acid derivatives, we thought it would be helpful to ascertain whether the six- or the five-membered ring structure may be used as a possible model for the assessment of configuration by ^{1}H NMR spectroscopy. In the course of this study, we have extended this procedure to the addition reactions of **2a** to aldehydes **8** and **9**, and of enolate **2b** (2*S*/2*R* = 87:13) to **7**.

Results and Discussion

Contrary to the reported result,[8b] the addition reactions of **2a** to linear aliphatic aldehydes **4** and **5** and benzaldehyde **7** lacked stereochemical control at the C-5 carbon atom, since (2*S*,5*S*,1′*S*), (2*S*,5*R*,1′*R*), and (2*S*,5*R*,1′*S*) mixtures of **3a**, **3b**, and **3d** were obtained. Similar distributions were also observed for **3e** and **3h** obtained by addition of **2a** to decanal **8** and **2b** to **7**. Instead, only (2*S*,5*R*,1′*R*) and (2*S*,5*R*,1′*S*) mixtures of **3c**, **3f**, and **3g** were isolated from the addition of **2a** to branched aldehydes **6** and **9** and ketone **10**.[13] The formation of the third (2*S*,5*S*,1′*S*) isomer is a serious limitation to the application of the "SRS" synthetic principle to our targets, that is, the trisubstituted 2,3-dihydroxycarbonyl compounds, because the removal of the auxiliary center of the diastereomeric pair of dioxolanone alcohols (2*S*,5*R*,1′*S*) and (2*S*,5*S*,1′*R*) affords enantiomeric *erythro*-(2*S*,3*S*)/(2*R*,3*R*) mixtures of products (Scheme 3).

The stereochemistry of (2*S*,5*R*,1′*R*)-**3d**, (2*S*,5*R*,1′*R*)-**3g** and (2*S*,5*R*,1′*S*)-**3h** was established by X-ray structural analysis.[14] Compounds (2*S*,5*S*,1′*S*)-**3a**, **b**, **d**, (2*S*,5*R*,1′*R*)-**3b, c, d, f, g**, **h**, and (2*S*,5*R*,1′*S*)-**3b**, **c**, **h** were isolated as pure diastereomers. Water- or alcohol-induced removal of the auxiliary center allowed the chemical correlation with the corresponding (2*R*,3*R*), (2*S*,3*S*), and (2*R*,3*S*)-2,3-dihydroxy acids or esters **11**–**16** (Scheme 3). Quite important is that we have isolated the dihydroxy acid *threo*-(2*R*,3*S*)-**13** in 89 % yield by hydrolysis of pure (2*S*,5*R*,1′*S*)-**3b**. The same compound was, instead, reported[8b] to be isolated after recrystallization of the crude reaction mixture obtained from the acid-induced hydrolysis of the (2*S*,5*S*,1′*S*)/(2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 23:44:32 mixture of dioxolanone alcohols **3b** (entry 2, Table 1), which was

Table 1. Relative product distribution of dioxolanone alcohols **2a**–**h**.[a]

Entry	Reagents	Product	2*S*,5*S*,1′*S*	2*S*,5*R*,1′*R*[b]	2*S*,5*R*,1′*S*[b]	Yield [%]
1	**1a** + **4**	**3a**	22	45 (18)	33 (82)	72
2	**1a** + **5**	**3b**	23	44 (15)	32 (85)	69
3	**1a** + **6**	**3c**	–	46 (47)	54 (53)	83
4	**1a** + **7**	**3d**	15	59 (16)	26 (84)	81
5	**1a** + **8**	**3e**	33	41	28	67
6	**1a** + **9**	**3f**	–	44	56	74
7	**1a** + **10**	**3g**	–	90 (7)	10 (93)	67
8	**1b** + **7**	**3h**	19	63	18	89

[a] In THF at −78 °C. [b] See ref. [8b].

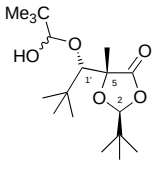
believed to be a (2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 15:85 mixture. Compounds (2*S*,5*S*,1′*S*)-**3e, h**, (2*S*,5*R*,1′*S*)-**3a, e, d, f, g**, and (2*S*,5*R*,1′*R*)-**3a, e** were obtained as major products of diastereomeric mixtures. Their alcoholysis gave mixtures of 2,3-dihydroxy esters with the same diastereomeric ratios of the parent dioxolanone alcohols (see Experimental Section). A comparison of the ^{1}H and ^{13}C NMR data of the major ester derivatives with the data reported in the literature allowed the configuration at C5–C1′ of the dioxolanone alcohols to be determined. The absolute configuration could also be assigned when the [α] values of diastereomerically pure 2,3-dihydroxy acids or esters were available for comparison with literature data.

Consistent trends of the C2-H and C5-Me resonances were observed. The C2-H resonances of the (2*S*,5*R*,1′*S*) isomers of **3a, b, c, e**, **f**, obtained from aliphatic aldehydes **4**–**6**, **8**, and **9**, absorbed in the narrow range of δ = 5.36–5.38, downfield from (2*S*,5*R*,1′*R*) (δ = 5.27–5.38) and (2*S*,5*S*,1′*S*) (δ = 5.20–5.21). Instead, the C2-H signal of (2*S*,5*R*, 1′*R*)-**3d** and **3g**, obtained from benzaldehyde **7** and acetophenone **10**, absorbed upfield (δ = 4.84 and 4.67) to the corresponding (2*S*,5*R*,1′*S*) (δ = 5.48 and 5.04). The ^{1}H and ^{13}C NMR C5-Me signals of the (2*S*,5*R*,1′*S*) isomers absorbed at higher field than the corresponding (2*S*,5*S*,1′*S*) and (2*S*,5*R*,1′*R*). This upfield shift is explained[11b] by the shielding effect of the *cis*-alkyl substituents in the five-membered ring chelate. Accordingly, the substituents at C′1 were found to be trans to the Me group at C5 in the (2*S*,5*S*,1′*S*) and (2*S*,5*R*,1′*R*) isomers in structures **A′** and **B′** and *cis* in (2*S*,5*R*,1′*S*). These typical trends allow the configuration of the **3f** diastereomers to be assigned. That is, the C2-H peak at δ = 5.18 is typical of (2*S*,5*S*,1′*S*) because it is upfield from the C2-H signals of (2*S*,5*R*,1′*R*) and (2*S*,5*R*,1′*S*) at δ = 5.33 and 5.35, respectively, while the C5-Me resonance at δ = 1.35 allows the assessment of (2*S*,5*R*,1′*S*), because it is upfield from the C5-Me signals of (2*S*,5*S*,1′*S*) and (2*S*,5*R*,1′*R*) at δ = 1.44 and 1.46.

From a comparison of the C2-H and C5-Me ^{1}H NMR resonances of our three diastereomers with that of the two (2*S*,5*R*,1′*R*) and (2*S*,5*S*,1′*S*) diastereomers of compounds **3a**, **3b**,[15] and **3d** reported in the literature,[8b] it appears that the literature minor (2*S*,5*R*,1′*R*) isomer corresponds to our (2*S*,5*S*,1′*S*), while the literature major (2*S*,5*R*,1′*S*) corresponds

to the sum of our (2*S*,5*R*,1′*R*) and (2*S*,5*R*,1′*S*). The relevant ^{1}H NMR data of our dioxolanone alcohols **3c** correspond to those reported in literature,[8b] even if a doublet centered at δ 1.51 ($J = 5.0$ Hz, 3H) was wrongly described. Finally, X-ray structural analysis of our (2*S*,5*R*,1′*R*)-**3g** confirmed that the stereochemistry of the isomers (2*S*,5*R*,1′*R*) and (2*S*, 5*R*, 1′*S*) is the opposite to that reported in the literature.

The product distributions of the reactions of aldehydes **4**–**9** and ketone **10** with **2a** (2*S*/2*R* = 98:2) and of **7** with **2b** (2*S*/2*R* = 87:13) at −78 °C in THF with LDA as base are listed in Table 1; the literature data are reported in parentheses.[8b] The distributions were determined by ^{1}H NMR spectroscopy after the crude reaction mixture was allowed to warm to −15 °C, being continuously stirred for 3 h, according to the protocol described in the literature.[8b] No appreciable variation in yields and product distribution was observed, on ^{1}H NMR scale, when the protocol was modified. For example, the reactions of entries 1, 2, and 4 (Table 1) were conducted at −105 °C and quenched in the usual manner, and the reactions of entries 2, 3, and 4 (Table 1) were conducted at −80 °C and quenched at this temperature, after 1 min, with acetic acid. The reactions of entries 4 and 8 (Table 1) were performed with 1.0 equivalent of aldehyde and a slight excess of LDA and dioxolanone (1.2 equiv) or in an excess of LDA and dioxolanone (2.0 equiv). Best overall yields were obtained with 1.0 equivalents of aldehyde and 1.3–1.5 equivalents of LDA and dioxolanone. Finally, no epimerization was noticed when THF solutions of pure isomers of **3b**, (2*S*,5*R*,1′*R*)-**3d**, (2*S*,5*S*,1′*S*)-**3d**, and (2*S*,5*R*,1′*S*)-**3h** were warmed from −80 °C to −15 °C in the presence of 0.5 equivalents of LDA. Unlike what is reported,[8b] the major isomer of compounds **3a, b, d, e, g, h**, obtained from linear aliphatic and aromatic aldehydes **4**, **5**, **7**, and **8** and ketone **10** was (2*S*,5*R*,1′*R*) instead of (2*S*,5*R*,1′*S*). It is worth noting that the sterically demanding $CH_3(CH_2)_8$ substituent of linear aldehyde **8** did not favor the formation of the (2*S*,5*R*,1′*S*) isomer. An inversion of the relative (2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) ratio was noticed only when branched aldehydes **6** and **9** were treated with the enolate **2a**.



(2*S*,5*R*,1′*S*)-**17**

However, the product distribution of compounds **3c** was difficult to assess, because variable amounts of the 2:1 adduct **17** were isolated when the product mixture was warmed to −30/−15 °C before being quenched. Compound **17** derived from selective addition of the lithium alkoxide of diastereomer (2*S*,5*R*,1′*S*)-**3c** to pivalaldehyde. The selectivity of this addition was confirmed by MeO^--induced methanolysis of **17**, which gave (2*R*,3*S*)-**14**, exclusively. The relative (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*) product distribution of **3c** was determined after the reaction mixture was quenched at −78 °C, because no formation of the 2:1 adduct **17** was observed at this temperature.

Conclusion

The following pertinent points emerged from this study: 1) The five-membered hydrogen-bond ring chelate[11a] is a reliable model to account for the ^{1}H and ^{13}C NMR spectral data of our dioxolanone alcohols, whose structures, in most cases, were independently assigned by X-ray and chemical correlation. By contrast, the wrong stereochemical assignment at C-5 is arrived at when the six-membered ring structure is used. 2) Contrary to the previous report,[8b] the "SRS" synthetic principle fails to provide good diastereoselectivity at the 1′-position of the products, regardless of the steric demand of the aldehyde partner. The (2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) trends are a typical consequence of the Zimmermann–Traxler right-angle transition-state geometry.[16] That is, the aromatic or linear aliphatic aldehydes approach the enolate with the hydrogen atom preferably oriented towards the acetal center. However, the (2*S*,5*R*,1′*R*) selectivity is rather weak and competitive amounts of (2*S*,5*R*,1′*S*) and (2*S*,5*R*,1′*R*) isomers are formed because the substituent of the aldehyde, regardless of its size, does not interact significantly with the acetal hydrogen of the enolate. It is significant that our (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*) ratios are similar to those observed in the aldol additions to achiral enolates of 5-methyl-[1,3]-dioxolan-4-one and trimethyl-[1,3]-dioxolan-4-one.[11b] The methyl substituent of the **2b** enolate provides only slight steric discrimination: an increase of (2*S*,5*S*,1′*S*) and a decrease of (2*S*,5*R*,1′*S*) was noticed when the product distribution of **3h** is compared with that of **3d**. 3) The "SRS" synthetic principle also fails to provide good diastereoselectivity at the C-5 position of the products when aromatic or linear aliphatic aldehyde partners, regardless of size, are used (see, e.g., decanal **8**). Instead, diastereoselectivity increases when branched substituents are present in the aldehyde. It turns out that the interaction of the hydrogen atom of the aldehyde and the *tert*-butyl substituent is not as efficient as reported,[8b] and therefore does not prevent the formation of significant amounts of (2*S*,5*S*,1′*S*) isomers; the interaction of sterically demanding substituents of the aldehyde, such as Me_2CH and Me_3C of **6** and **9**, with the methyl group at C5 of the enolates **2a** and **2b** is more important for this type of selectivity. The formation of the (2*S*,5*S*,1′*S*) isomers, associated with a poor (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*) selectivity, is a serious limitation to the application of the "SRS" synthetic principle to the synthesis of macrolides and alkaloids as documented in the literature. It is, in fact, quite surprising that random diastereomeric mixtures of dioxolanone alcohols were isolated in the addition reactions of aldehydes to (2S)-enolates of dioxolanones derived from the acetalization of 2-(*S*)-hydroxybutyric[6c] and 2-(*S*)-hydroxy-3-methyl-butyric[7a] acids to pivalaldehyde. The information we have gained from this research will be a starting point for stimulating the design of new strategies to improve the diastereoselectivity of reactions involving chiral dioxolanones.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer with Me_4Si or $CHCl_3$ ($CDCl_3$) as internal standards. Mass spectra were recorded on an ion-trap spectrometer with an ionization potential of 70 eV. Gas–liquid chromatography (GC) was carried out on a GC-mass spectrometer (ion trap, 70 eV). Infrared spectra were recorded on a Fourier-transform IR spectrometer. The dioxolanones were prepared

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according to literature methods and were purified by distillation under vacuum. For preparative HPLC chromatography, a Hypersil column (10 μm CN CPS, 250 × 10.0 mm, *n*-hexane/MeOH, 88.5:1.5) was used.

General procedure for the synthesis of dioxolanone alcohols: A solution of the dioxolanone (1.0 equiv) in THF was added to a cooled (−78 °C), stirred solution of LDA (1.5 equiv). After the mixture was stirred for 15 min at −78 °C, the aldehyde (1.5–2.0 equiv) was added. Unless otherwise stated, the reaction mixture was allowed to warm to −15 °C with continuous stirring over 3 h. The reaction solution was quenched by the addition of saturated NH_4Cl solution (10 mL). The reaction mixture was extracted with ethyl acetate. The extracts were combined, dried, and concentrated under reduced pressure. The crude reaction mixture was directly used for establishing the diastereomeric composition of the dioxolanone alcohols by ^{1}H NMR spectroscopy. The mixture of dioxolanone alcohols was subjected to the first purification by flash chromatography on silica; on this material the determination of overall yields and the diastereomeric composition by ^{1}H NMR, capillary GC, and HPLC was based. No variation of the product distribution was observed after this chromatography. A second or third flash chromatography, or preparative HPLC allowed diastereomerically pure samples or enriched fractions of dioxolanone alcohols to be isolated.

General procedure for the synthesis of methyl (ethyl) 2,3-dihydroxy esters: MeO^- (or EtO^-) in MeOH (or EtOH) (0.2 equiv, 1.0 M) was added to a stirred solution (MeOH or EtOH, 1.5 mL) of dioxolanone alcohol (1.0 equiv). The reaction was left at 60 °C for 30 min. The crude reaction mixture was treated with saturated NH_4Cl solution (5 mL) and extracted with ethyl acetate. The extract was dried and concentrated under reduced pressure to yield the 2,3-dihydroxy esters (2*S*,3*S*) [from (2*S*,5*S*,1′*S*)], (2*R*,3*R*) [from (2*S*,5*R*,1′*R*)], and (2*R*,3*S*) [from (2*S*,5*R*,1′*S*)] in 85–95% yields.

General procedure for the synthesis of 2,3-dihydroxy acids: A solution of the dioxolanone alcohol in MeOH (5 mL) containing HCl (1 mL of 36%) was heated at 60 °C for 60 min. The solvent was removed under reduced pressure, the residue was dissolved in water and extracted with diethyl ether. The aqueous solution was concentrated under reduced pressure to give the known diastereomerically pure 2,3-dihydroxy acid.

Synthesis of (2*S*,5*S*,1′*S*), (2*S*,5*R*,1′*R*), and (2*S*,5*R*,1′*S*)-2-(*tert*-butyl)-5-(1′-hydroxyethyl)-5-methyl-1,3-dioxolan-4-ones (3a): Compounds **3a** were prepared from dioxolanone **1a** ((2*S*,5*S*)/(2*R*,5*S*) = 98:2) (0.50 g, 3.2 mmol) and aldehyde **4** (0.28 g, 6.3 mmol). The residue was purified by chromatography (SiO_2, *n*-pentane/EtOAc, 13:1) to give a (2*S*,5*S*,1′*S*)/(2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 22:45:33 mixture (0.46 g, 2.3 mmol, 72%). A second purification by chromatography gave (2*S*,5*S*,1′*S*) and the following mixtures: (2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 3:1 and (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*) = 3:1. IR ($CDCl_3$): $\tilde{\nu}$ = 3600–3500, 1780, 1731 cm^{-1}; MS: *m*/*z*: 202 [M^+], 187, 157; elemental analysis calcd (%) for $C_{10}H_{18}O_4$: C 59.39, H 8.97; found: C 59.64, H 8.86. (2*S*,5*S*,1′*S*)-**3a**: $[\alpha]_D^{20}$ = +16.0 (*c* = 0.6 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.00 (s, 9H; 3Me), 1.30 (d, *J* = 6.4 Hz, 3H; Me), 1.43 (s, 3H; Me), 2.58 (b, 1H; OH), 3.95 (m, 1H; C1′-H), 5.21 (s, 1H; C2-H); ^{1}H NMR (relevant resonances) (DMSO): δ = 1.33 (s, 3H; Me), 5.32 (s, 1H; C2-H); ^{13}C NMR ($CDCl_3$): δ = 14.7, 16.4, 23.7, 34.5, 70.4 (C1′), 81.0 (C5), 107.6 (C2), 174.8. (2*S*,5*R*,1′*R*)-**3a**: ^{1}H NMR ($CDCl_3$): δ = 0.96 (s, 9H; 3Me), 1.34 (d, *J* = 6.4 Hz, 3H; Me), 1.43 (s, 3H; Me), 2.10 (b, 1H; OH), 3.96 (m, 1H; C1′-H), 5.38 (s, 1H; C2-H); ^{1}H NMR (relevant resonances) (DMSO): δ = 1.27 (s, 3H; Me), 5.43 (s, 1H; C2-H); ^{13}C NMR ($CDCl_3$): δ = 18.1, 20.0, 23.4, 34.9, 72.7(C1′), 82.6 (C5), 110.3 (C2), 174.0. (2*S*,5*R*,1′*S*)-**3a**: ^{1}H NMR ($CDCl_3$): δ = 0.97 (s, 9H; 3Me), 1.31 (d, *J* = 6.4 Hz, 3H; Me), 1.36 (s, 3H; Me), 2.07 (b, 1H; OH), 4.06 (m, 1H; C1′-H), 5.38 (s, 1H; C2-H); ^{1}H NMR (relevant resonances) (DMSO): δ = 1.20 (s, 3H; Me), 5.38 (s, 1H; C2-H); ^{13}C NMR ($CDCl_3$): δ = 16.7, 19.7, 23.4, 34.8, 71.1 (C1′), 83.1 (C5), 110.2 (C2), 175.3.

Methyl 2-methyl-2,3-dihydroxybutanoates (11): Compound (2*S*,3*S*)-**11** was obtained from (2*S*,5*S*,1′*S*)-**3a**. $[\alpha]_D^{20}$ = +8.7 (*c* = 0.6 in $CDCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.16 (d, *J* = 6.4 Hz, 3H; Me), 1.45 (s, 3H; Me), 2.40 (b, 1H; OH), 3.48 (b, 1H; OH), 3.82 (q, 1H; C*H*Me), 3.82 (s, 3H; OMe); ^{13}C NMR ($CDCl_3$): δ = 17.9, 22.4, 53.0, 72.2, 77.2, 175.7. (2*R*,3*R*)-**11** was obtained as the major isomer of a (2*R*,3*R*)/(2*R*,3*S*) = 3:1 mixture from a (2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 3:1 mixture of **3a**. The ^{1}H and ^{13}C NMR spectral data of (2*R*,3*R*) matched the data of its enantiomer (2*S*,3*S*). Compound (2*R*,3*S*)-**11** was obtained as the major isomer of a (2*R*,3*S*)/(2*R*,3*R*) = 3:1 mixture from a (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*) = 3:1 mixture of **3a**. ^{1}H NMR ($CDCl_3$): δ = 1.23 (d, *J* = 6.8 Hz, 3H; Me), 1.33 (s, 3H; Me), 2.20 (b, 1H; OH), 3.42 (b, 1H; OH), 3.82 (s, 3H; OMe), 3.95 (q, 1H; C*H*Me); Literature[17] ^{1}H NMR ($CDCl_3$): δ = 1.23, 1.33, 2.94, 3.82, 3.96; ^{13}C NMR ($CDCl_3$): δ = 16.6, 21.6, 53.0, 71.7, 77.5, 176.5. Literature[17] ^{13}C NMR ($CDCl_3$): δ = 16.2, 21.3, 52.6, 71.5, 77.4, 176.5.

Ethyl 2-methyl-2,3-dihydroxybutanoates (12): (2*S*,3*S*)-**12** was prepared from (2*S*,5*S*,1′*S*)-**3a**. $[\alpha]_D^{20}$ = +6.9 (*c* = 1.1 in $CHCl_3$). The literature[9d, 18] $[\alpha]_D^{23}$ value of the enantiomer (2*R*,3*R*) is −8.2 (*c* = 1.2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.14 (d, *J* = 6.4 Hz, 3H; Me), 1.29 (t, 3H; Me), 1.42 (s, 3H; Me), 2.50 (b, 1H; OH), 3.57 (b, 1H; OH), 3.78 (m, 1H; C*H*Me), 4.24 (m, 2H; CH_2). Literature[9d] ^{1}H NMR ($CDCl_3$): δ = 1.15, 1.30, 1.43, 2.45, 3.54, 3.80, 4.25; ^{13}C NMR ($CDCl_3$): δ = 14.2, 17.7, 22.4, 62.3, 72.1, 77.0, 175.2. Literature[9d] ^{13}C NMR ($CDCl_3$): δ = 14.0, 17.5, 22.2, 62.0, 72.1, 76.9, 175.4.

Synthesis of (2*S*,5*S*,1′*S*), (2*S*,5*R*,1′*R*), and (2*S*,5*R*,1′*S*)-2-(*tert*-butyl)-5-(1′-hydroxypropyl)-5-methyl-1,3-dioxolan-4-ones (3b): Compounds **3b** were prepared from aldehyde **5** (0.34 g, 5.9 mmol) and dioxolanone **1a** [(2*S*,5*S*)/(2*R*,5*S*) = 98:2] (0.50 g, 3.2 mmol). The residue was purified by chromatography (SiO_2, *n*-pentane/EtOAc, 13:1) to give a mixture (2*S*,5*S*,1′*S*)/(2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 23:44:32 (0.47 g, 2.2 mmol, 69%) Preparative HPLC chromatography gave diastereomerically pure samples. IR ($CDCl_3$): $\tilde{\nu}$ = 3600–3500 (br), 1784 cm^{-1}; MS: *m*/*z*: 217 [M^++1], 187, 170, 157; elemental analysis calcd (%) for $C_{11}H_{20}O_4$: C 61.09, H 9.32; found: C 61.36, H 9.16. (2*S*,5*S*,1′*S*)-**3b**: $[\alpha]_D^{20}$ = +5.83 (*c* = 1.16 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 0.98 (s, 9H; 3Me), 1.05 (t, *J* = 7.6 Hz, 3H; Me), 1.43 (s, 3H; Me), 1.55–1.61 (m, 2H), 2.51 (b, 1H; OH), 3.61 (m, J_1 = 3.0 Hz, J_2 = 9.5 Hz, 1H; C1′-H), 5.20 (s, 1H; C2-H); ^{13}C NMR ($CDCl_3$): δ = 11.0, 15.0, 23.7, 27.5, 34.6, 76.1 (C1′), 81.3 (C5), 108.0 (C2), 175.6.

(2*S*,5*R*,1′*R*)-**3b**: $[\alpha]_D^{20}$ = +3.05 (*c* = 1.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 0.95 (s, 9H; 3Me), 1.03 (t, *J* = 7.6 Hz, 3H; Me), 1.43 (s, 3H; Me), 1.55–1.65 (m, 2H), 2.02 (b, 1H; OH), 3.65 (m J_1 = 4.7 Hz, J_2 = 9.0 Hz, 1H; C1′-H), 5.34 (s, 1H; C2-H); ^{13}C NMR ($CDCl_3$): δ = 10.8, 20.1, 23.5, 24.7, 35.1, 78.0 (C1′), 82.7 (C5), 110.5 (C2), 174.7. (2*S*,5*R*,1′*S*)-**3b**: $[\alpha]_D^{20}$ = +2.59 (*c* = 1.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 0.97 (s, 9H; 3Me), 1.05 (t, *J* = 7.6 Hz, 3H; Me), 1.38 (s, 3H; Me), 1.50–1.75 (m, 2H), 1.80–2.20 (b, 1H; OH), 3.74 (m, J_1 = 2.8 Hz, J_2 = 10.4 Hz, 1H; C1′-H), 5.36 (s, 1H; C2-H); ^{13}C NMR ($CDCl_3$): δ = 10.4, 19.7, 23.3, 23.6, 34.8, 76.6 (C1′), 83.3 (C5), 110.4 (C2), 175.7.

2-Methyl-2,3-dihydroxypentanoic acids (13): Compound (2*S*,3*S*)-**13** was obtained from (2*S*,5*S*,1′*S*)-**3b**. $[\alpha]_D^{20}$ = -13.7 (*c* = 0.98 in D_2O). Literature[19] $[\alpha]_D^{20}$ = −13.3; ^{1}H NMR (relevant resonances) (D_2O): δ = 0.87 (t, *J* = 7.2 Hz, 3H; Me), 1.33 (s, 3H; Me), 1.25–1.45 (m, 2H; CH_2), 3.52 (m, 1H; CH). (2*R*,3*R*)-**13** was obtained from (2*S*,5*R*,1′*R*)-**3b**. $[\alpha]_D^{20}$ = +13.3 (*c* = 2.1 in D_2O). Literature[19] $[\alpha]_D^{20}$ = +13.8; ^{13}C NMR (D_2O): δ = 10.3, 21.1, 23.9, 77.2, 78.2, 177.0. (2*R*,3*S*)-**13** was obtained from (2*S*,5*R*,1′*S*)-**3b**. $[\alpha]_D^{20}$ = −27.3 (*c* = 0.97 in D_2O). Literature[19] $[\alpha]_D^{20}$ = −27.1; ^{1}H NMR (relevant resonances) (D_2O): δ = 0.77 (t, *J* = 7.4 Hz, 3H; Me), 1.05–1.20 (m, 1H; CH_2), 1.15 (s, 3H; Me), 1.40–1.52 (m, 1H; CH_2), 3.46 (d, *J* = 10.6 Hz, 1H; CH).

Synthesis of (2*S*,5*R*,1′*R*), and (2*S*,5*R*,1′*S*)-2-(*tert*-butyl)-5-(1′-hydroxy-2′-dimethylpropyl)-5-methyl-1,3-dioxolan-4-ones (3c): Compounds **3c** were prepared from dioxolanone **1a** ((2*S*,5*S*)/(2*R*,5*S*) = 98:2) (0.5 g, 3.8 mmol) and aldehyde **6** (0.52 g, 7.0 mmol). The mixture was stirred for 30 min at −78 °C and quenched at this temperature by sequential addition of acetic acid (1.0 mL) and saturated NH_4Cl solution (10 mL). The residue was purified by chromatography (SiO_2, *n*-pentane/EtOAc, 9.6:0.4) to give (2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 46:54 (0.77 g, 3.2 mmol, 83%). A second chromatographic separation gave diastereomerically pure (2*S*,5*R*,1′*R*) and (2*S*,5*R*,1′*S*)-**3c**. IR ($CDCl_3$): $\tilde{\nu}$ = 3600–3500 (br), 1781 cm^{-1}; MS: *m*/*z*: 244 [M^+], 187, 158, 87, 70, 57; elemental analysis calcd (%) for $C_{13}H_{24}O_4$: C 63.91, H 9.90; found: C 63.59, H 9.83. (2*S*,5*R*,1′*R*)-**3c**: $[\alpha]_D^{20}$ = +15.5 (*c* = 0.97 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 0.98 (s, 9H; 3 Me), 1.08 (s, 9H; 3Me), 1.56 (s, 3H; Me), 2.33 (d, *J* = 5.2 Hz, 1H; OH), 3.52 (d, 1H; C1′-H), 5.27 (s, 1H; C2-H); ^{13}C NMR ($CDCl_3$): δ = 21.3, 23.5, 27.5, 34.8, 36.4, 78.4 (C1′), 82.0 (C5), 108.8 (C2), 175.6. (2*S*,5*R*,1′*S*)-**3c**: $[\alpha]_D^{20}$ = +19.5 (*c* = 0.75 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 0.96 (s, 9H; 3Me), 1.09 (s, 9H; 3Me), 1.51 (s, 3H; Me), 2.20–2.50 (b, 1H; OH), 3.61 (m, 1H; C1′-H), 5.36 (s, 1H; C2-H); ^{13}C NMR ($CDCl_3$): δ = 23.1, 23.5, 27.5, 34.5, 36.4, 81.4 (C1′), 84.9 (C5), 110.1 (C2), 176.3.

(2*S*,5*R*,1′*S*)-2-*t*-Butyl-5-[1-(1-hydroxy-2,2-dimethyl-propoxy)-2,2-dimethyl-propyl]-5-methyl-1,3-dioxolan-4-one (17): In an identical experiment the

reaction mixture was warmed to $-30\,^{\circ}C$ in 3.0 hrs before quenching. The residue was purified by chromatography (SiO_2, *n*-pentane/EtOAc, 9.6:0.4) to give a (2*S*,5*R*,1′*R*)-**3c**/(2*S*,5*R*,1′*S*)-**3d**/(2*S*,5*R*,1′*S*)-**17** = 46:31:23 mixture (0.81 g, 3.4 mmol, 88%). A second chromatography gave diastereomerically pure (2*S*,5*R*,1′*S*)-**17:** MS: *m*/*z*: 330 [M^+], 274, 243, 158, 87; ^{1}H NMR ($CDCl_3$): $\delta = 0.91$ (s, 9H; 3Me), 0.97 (s, 9H; 3Me), 1.11 (s, 9H; 3Me), 1.58 (s, 3H; Me), 3.10 (d, $J = 12.1$ Hz, 1H; OH,), 3.91 (s, 1H; CH), 4.36 (d, 1H; HC-OH), 5.28 (s, 1H; CH); ^{13}C NMR ($CDCl_3$): $\delta = 23.5$, 24.3, 24.7, 28.2, 34.4, 36.6, 37.7, 82.4, 86.7, 104.2, 108.9, 177.6; elemental analysis calcd (%) for $C_{18}H_{34}O_5$: C 65.42, H 10.37; found: C 65.17, H 10.50.

Methyl 2,4,4-trimethyl-2,3-dihydroxy-pentanoates (14): Compound (2*R*, 3*R*)-**14** was prepared from (2*S*,5*R*,1′*R*)-**3c**. IR ($CDCl_3$): $\tilde{\nu} = 3650-3500$ (br), 1728 cm^{-1}; elemental analysis calcd (%) for $C_9H_{18}O_4$: C 56.82, H 9.54; found: C 56.48, H 9.63; $[\alpha]_D^{20} = -40.8$ ($c = 1.23$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.95$ (s, 9H; 3Me), 1.52 (s, 3H; Me), 2.27 (d, $J = 11.2$, 1H; OH), 3.15 (s, 1H; OH), 3.42 (d, 1H; CH), 3.79 (s, 3H; OMe). Literature[11b] ^{1}H NMR ($CDCl_3$): $\delta = 1.00$, 1.53, 3.20, 3.50, 3.73; ^{13}C NMR ($CDCl_3$): $\delta =$ 26.6, 27.1, 36.5, 52.7, 76.8, 81.5, 177.0. Literature[11b] ^{13}C NMR (relevant resonances) ($CDCl_3$): $\delta = 26.3$, 27.0, 52.3, 81.6, 177.2. Compound (2*R*,3*S*)-**14** was prepared from (2*S*,5*R*,1′*S*)-**3c** and from compound **17**; $[\alpha]_D^{20} = +22.9$ ($c = 1.23$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.02$ (s, 9H; 3 Me), 1.48 (s, 3H; Me), 2.53 (d, $J = 11.0$, 1H; OH), 3.48 (b, 1H; OH), 3.50 (d, 1H; CH), 3.80 (s, 3H; OMe). Literature[11b] ^{1}H NMR: $\delta = 1.08$, 1.51, 3.20, 3.50, 3.75; ^{13}C NMR ($CDCl_3$): $\delta = 24.8$, 27.7, 36.2, 53.1, 78.5, 81.4, 177.2. Literature[11a,b] ^{13}C NMR (relevant resonances) ($CDCl_3$): $\delta = 24.6$, 27.6, 52.8, 77.0,[20] 177.2.

Synthesis of (2*S*,5*S*,1′*S*), (2*S*,5*R*,1′*R*), and (2*S*,5*R*,1′*S*)-2-(*tert*-butyl)-5-(1′-hydroxy-1′-phenylmethyl)-2-methyl-1,3-dioxolan-4-ones (3d): Compounds **3d** were prepared from dioxolanone **1a** [(2*S*,5*S*)/(2*R*,5*S*) = 98:2] (0.3 g, 1.9 mmol) and aldehyde **7** (0.30 g, 2.8 mmol). Chromatography (SiO_2, CH_2Cl_2/*n*-pentane, 1:1) gave a (2*S*,5*S*,1′*S*)/(2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 15:59:26 mixture (0.41 g, 1.5 mmol, 81%). A second chromatographic separation gave (2*S*,5*S*,1′*S*), (2*S*,5*R*,1′*R*) and a 5:1 (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*) mixture. IR ($CDCl_3$): $\tilde{\nu} = 3600-3500$ (br), 1780 cm^{-1}; MS: *m*/*z*: 264 [M^+], 245, 219, 207, 179, 158, 133, 105; elemental analysis calcd (%) for $C_{15}H_{20}O_4$: C 68.16, H 7.63; found: C 68.55, H 7.54. (2*S*,5*S*,1′*S*)-**3d**: $[\alpha]_D^{20} = +4.6$ ($c = 0.3$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.96$ (s, 9H; 3Me), 1.37 (s, 3H; Me), 3.45 (d, $J = 2.2$ Hz, 1H; OH), 4.94 (d, 1H; C1′-H), 5.21 (s, 1H; C2-H), 7.3–7.45 (m, 5H; arom); ^{13}C NMR ($CDCl_3$): $\delta = 14.5$, 23.6, 34.4, 75.4 (C1′), 80.5 (C5), 108.2 (C2), 127.5, 127.9, 128.2, 137.1, 175.7. (2*S*,5*R*,1′*R*)-**3d**: $[\alpha]_D^{20} =$ $+23.3$ ($c = 1.2$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.91$ (s, 9H; 3Me), 1.43 (s, 3H; Me), 2.71 (d, J = 4.3 Hz, 1H; OH), 4.84 (s, 1H; C2-H), 4.87 (d, J = 4.3 Hz, 1H; C1′-H), 7.3–7.4 (m, 5H; arom); ^{13}C NMR ($CDCl_3$): $\delta = 20.6$, 23.2, 34.6, 77.5 (C1′), 82.8 (C5), 109.8 (C2), 127.3, 128.3, 128.7, 138.4, 173.9. (2*S*,5*R*,1′*S*)-**3d**: ^{1}H NMR ($CDCl_3$): $\delta = 0.96$ (s, 9H; 3Me), 1.20 (s, 3H; Me), 2.54 (b, 1H; OH), 4.85 (b, 1H; C1′H), 5.48 (s, 1H; C2-H), 7.3–7.4 (m, 5H; arom); ^{13}C NMR ($CDCl_3$): $\delta = 20.7$, 23.3, 34.6, 78.5 (C1′), 82.5 (C5), 110.9 (C2), 128.1, 128.3, 128.7, 138.4, 176.0.

Synthesis of (2*S*,5*S*,1′*S*), (2*S*,5*R*,1′*R*), and (2*S*,5*R*,1′*S*)-2-(*tert*-butyl)-5-(1′-hydroxy-1′-phenylmethyl)-2,5-methyl-1,3-dioxolan-4-ones (3h): Compounds **3h** were prepared from dioxolanone **1b** [(2*S*,5*S*)/(2*R*,5*S*) = 87:13] (1.00 g, 5.8 mmol) and aldehyde **7** (0.91 g, 8.6 mmol). Chromatography (SiO_2, EtOAc/*n*-pentane, 3:17) gave a (2*S*,5*S*,1′*S*)/(2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 19:63:18 mixture (1.44 g, 5.2 mmol, 89%). A second chromatographic separation gave (2*S*,5*R*,1′*R*), (2*S*,5*R*,1′*S*), and a (2*S*,5*S*,1′*S*)/(2*S*,5*R*,1′*R*) = 4:1 mixture. IR ($CDCl_3$): $\tilde{\nu} = 3600-3500$, 1775 cm^{-1}; MS: *m*/*z*: 278 [M^+], 261, 221, 172, 133, 115; elemental analysis calcd (%) for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 68.90, H 7.92. (2*S*,5*S*,1′*S*)-**3h**: ^{1}H NMR ($CDCl_3$): $\delta = 1.13$ (s, 9H; 3Me), 1.41 (s, 3H; Me), 1.57 (s, 3H; Me), 3.80 (b, 1H; OH), 5.05 (s, 1H; C1′H), 7.3–7.45 (m, 5H; arom); ^{13}C NMR ($CDCl_3$): $\delta = 18.2$, 22.7, 25.0, 39.1, 75.3 (C1′), 79.3 (C5), 116.0(C2), 127.2, 127.7, 128.0, 136.8, 176.6. (2*S*,5*R*,1′*R*)-**3h**: $[\alpha]_D^{20} = +43.2$ ($c = 1.0$ in $CDCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.02$ (s, 9H; 3 Me), 1.36 (s, 3H; Me), 1.59 (s, 3H; Me), 3.09 (b, 1H; OH), 5.00 (s, 1H; C1′-H), 7.30–7.45 (m, 5H; arom); ^{13}C NMR ($CDCl_3$): $\delta = 18.5$, 23.2, 25.0, 38.9, 76.4 (C1′), 81.3 (C5), 116.0 (C2), 127.5, 127.9, 128.1, 137.5, 175.3. (2*S*,5*R*,1′*S*)-**3h**: $[\alpha]_D^{20} = +84.5$ ($c = 0.4$ in $CDCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.00$ (s, 9H; 3Me), 1.25 (s, 3H; Me), 1.80 (s, 3H; Me), 2.47 (b, 1H; OH), 4.81 (s, 1H; C1′-H), 7.30–7.45 (m, 5H; arom); ^{13}C NMR ($CDCl_3$): $\delta = 21.5$, 21.7, 25.2, 39.1, 77.1 (C1′), 83.1 (C5), 116.0 (C2), 128.1, 128.3, 128.5, 138.3, 174.7.

Methyl 2,3-dihydroxy-2-methyl-3-phenylpropanoates (15): Compound (2*R*,3*R*)-**15** was prepared from (2*S*,5*R*,1′*R*)-**3d**. $[\alpha]_D^{20} = -26.7^{\circ}$ ($c = 0.72$ in $CHCl_3$). Compound (2*R*,3*R*)-**15** was also prepared from dioxolanone alcohol (2*S*,5*R*,1′*R*)-**3h**. The ^{1}H and and ^{13}C NMR spectral data of (2*R*,3*R*) matched the data of its enantiomer (2*S*,3*S*). Compound (2*S*,3*S*)-**15** was prepared from (2*S*,5*S*,1′*S*)-**3d**. $[\alpha]_D^{20} = +26.9^{\circ}$ ($c = 0.40$ in $CHCl_3$). Literature[21]: $[\alpha]_D^{29} = +27.2$ ($c = 0.43$ in $CHCl_3$). Compound (2*S*,3*S*)-**15** was also prepared as the major component of a (2*S*,3*S*)/(2*R*,3*R*) = 4:1 mixture from the methanolysis of a (2*S*,5*S*,1′*S*)/(2*S*,5*R*,1′*R*) = 4:1 mixture of **3h**. ^{1}H NMR ($CDCl_3$): $\delta = 1.56$ (s, 3H; Me), 3.0–3.2 (br, 2H; OH), 3.64 (s, 3H; OMe), 4.74 (s, 1H); 7.2–7,4 (m, 5H; arom); Literature[21, 22] ^{1}H NMR ($CDCl_3$): $\delta =$ 1.56, 3.0, 3.64, 4.74, 7.2–7.4; ^{13}C NMR ($CDCl_3$): $\delta = 22.4$, 52.5, 77.3, 78.0, 126.8, 128.1, 128.3, 139.1, 175.0; Literature[21, 22] ^{13}C NMR ($CDCl_3$): $\delta = 22.4$, 52.6, (C2 obscured by solvent), 78.0, 126.8, 128.1, 128.3, 139.1, 175.0. Compound (2*R*,3*S*)-**15** was prepared from (2*S*,5*R*,1′*S*)-**3h** and as a (2*R*,3*S*)/(2*R*,3*R*) = 5:1 mixture from the methanolysis of a (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*) = 5:1 mixture of **3d**. ^{1}H NMR ($CDCl_3$: $\delta = 1.20$ (s, 3H; Me), 2.60–3.0 (br, 2H; 2 OH), 3.86 (s, 3H; OMe), 4.85 (s, 1H); 7.2–7,4 (m, 5H; arom);[11b, 22] ^{13}C NMR ($CDCl_3$): $\delta = 22.4$, 53.0, 77.4, 78.0, 127.8, 128.0, 128.3, 138.5, 176.1; Literature[11b, 22] ^{13}C NMR ($CDCl_3$): $\delta = 21.9$, 52.7, 77.6, 127.8, 176.2.

Synthesis of (2*S*,5*S*,1′*S*), (2*S*,5*R*,1′*R*), and (2*S*,5*R*,1′*S*)-2-(*tert*-butyl)-5-(1′-hydroxydecyl)-5-methyl-1,3-dioxolan-4-ones (3e): Compounds **3e** were prepared from dioxolanone **1a** ((2*S*,5*S*)/(2*R*,5*S*) = 98:2) (0.41 g, 2.6 mmol) and aldehyde **8** (0.61 g, 3.9 mmol). The residue was purified by chromatography (SiO_2, *n*-pentane/EtOAc, 13:1) to give a (2*S*,5*S*,1′*S*)/(2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 23:41:36 mixture (0.55 g, 1.74 mmol, 67%). A second chromatographic separation gave the following mixtures: (2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 2.5:1, (2*S*,5*S*,1′*S*)/(2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 7:2:1, and (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*) = 1.5:1. IR ($CDCl_3$): $\tilde{\nu} = 3600-3500$, 1785 cm^{-1}; MS: *m*/*z*: 314 [M^+], 257, 187, 174; elemental analysis calcd (%) for $C_{18}H_{34}O_4$: C 68.75, H 10.90; found: C 68.55, H 10.77. (2*S*,5*S*,1′*S*)-**3e**: ^{1}H NMR ($CDCl_3$): $\delta = 0.87$ (t, $J = 7.4$ Hz, 3H; Me), 0.97 (s, 9H; 3Me), 1.20–1.40 (b, 16H), 1.43 (s, 3H; Me), 2.57 (b, 1H; OH), 3.68 (d, $J = 10.8$ Hz, 1H; C1′-H), 5.18 (s, 1H; C2-H); ^{13}C NMR relevant resonances ($CDCl_3$): $\delta = 15.1$, 23.0, 24.0, 26.5, 27.7, 29.7, 29.8, 30.7, 32.2, 34.7, 74.5 (C′1), 81.3 (C5), 107.9 (C2), 175.6. (2*S*,5*R*,1′*R*)-**3e**: ^{1}H NMR ($CDCl_3$): $\delta = 0.87$ (t, $J = 7.5$ Hz, 3H; Me), 0.95 (s, 9H; 3Me), 1.20–1.40 (b, 16H), 1.43 (s, 3H; Me), 1.55 (b, 1H; OH), 3.72 (d, $J = 10.4$ Hz, 1H; C1′-H), 5.33 (s, 1H; C2-H); ^{13}C NMR relevant resonances ($CDCl_3$): $\delta = 20.2$, 22.9, 23.5, 26.3, 29.5, 29.8, 30.2, 31.6, 35.1, 76.5 (C1′), 82.7 (C5), 110.5 (C2), 174.7. (2*S*,5*R*,1′*S*)-**3e**: ^{1}H NMR ($CDCl_3$): $\delta = 0.87$ (t, $J = 7.5$ Hz, 3H; Me), 0.95 (s, 9H; 3Me), 1.20–1.40 (b, 16H), 1.35 (s, 3H; Me), 1.55 (b, 1H; OH), 3.80 (d, $J = 10.4$ Hz, 1H; C1′-H), 5.35 (s, 1H; C2-H); ^{13}C NMR relevant resonances ($CDCl_3$): $\delta = 19.7$, 22.9, 23.5, 29.6, 29.7, 29.9, 32.1, 34.9, 75.1 (C1′), 83.4 (C5), 110.4 (C2), 174.7.

Synthesis of (2*S*,5*R*,1′*R*) and (2*S*,5*R*,1′*S*)-2-(*tert*-butyl)-5-(1′-hydroxy-2′-methylpropyl)-5-methyl-1,3-dioxolan-4-ones (3f): Compounds **3f** were prepared from dioxolanone **1a** ((2*S*,5*S*)/(2*R*,5*S*) = 98:2) (0.5 g, 3.2 mmol) and aldehyde **9** (0.43 g, 6.0 mmol). The residue was purified by chromatography (SiO_2, *n*-pentane/EtOAc, 7:1) to give a mixture of (2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 44:56 (0.54 g, 2.3 mmol, 74%). A second chromatographic separation gave (2*S*,5*R*,1′*R*) and a 1:2 mixture of (2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*)-**3f**. IR ($CDCl_3$): $\tilde{\nu} = 3600-3500$, 1780 cm^{-1}; MS: *m*/*z*: 230 [M^+], 157, 86, 69, 55; elemental analysis calcd (%) for $C_{12}H_{22}O_4$: C 62.58, H 9.63; found: C 62.29, H 9.77. (2*S*,5*R*,1′*R*)-**3f**: $[\alpha]_D^{20} = +24.5$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.97$ (s, 9H; 3Me), 1.01 (d, $J = 6.6$ Hz, 3H; Me), 1.03 (d, $J =$ 5.5 Hz, 3H; Me), 1.47 (s, 3H; Me), 1.96 (m, 1H; C*H*Me$_2$), 1.90–2.00 (b, 1H; OH), 3.55 (m, 1H; C1′-H), 5.28 (s, 1H; C2-H); ^{13}C NMR ($CDCl_3$): $\delta = 17.8$, 19.4, 21.4, 23.4, 30.0, 34.8, 78.7 (C1′-H), 82.4 (C5), 109.3 (C2), 174.8. (2*S*,5*R*,1′*S*)-**3f**: ^{1}H NMR ($CDCl_3$): $\delta = 0.96$ (s, 9H; 3Me), 1.01 (d, $J =$ 6.4 Hz, 3H; Me), 1.04 (d, $J = 6.4$ Hz, 3H; Me), 1.36 (s, 3H; Me), 2.07 (m, 2H; 1H of OH and 1H of C*H*Me$_2$), 3.75 (m, 1H; C1′-H), 5.38 (s, 1H; C2-H); ^{13}C NMR ($CDCl_3$): $\delta = 15.5$, 20.6, 21.4, 23.4, 28.6, 34.7, 78.8 (C1′), 83.5 (C5), 110.4 (C2), 176.1.

Methyl 2,4-dimethyl-2,3-dihydroxypentanoates (16): Compound (2*R*,3*R*)-**16** was prepared from (2*S*,5*R*,1′*R*)-**3f**. ^{1}H NMR ($CDCl_3$): $\delta = 0.93$ (d, $J =$ 7.2 Hz, 3H; Me), 0.96 (d, $J = 7.2$ Hz, 3H; Me), 1.48 (s, 3H; Me), 1.64 (m, 1H; C*H*Me$_2$), 2.25 (b, 1H; OH), 3.26 (b, 1H; OH), 3.46 (m, 1H; C3-H), 3.80 (s, 3H; OMe); Literature[11b] ^{1}H NMR (relevant resonances) ($CDCl_3$): $\delta = 0.94$, 1.50, 3.43, 3.77; ^{13}C NMR ($CDCl_3$): $\delta = 16.9$, 21.5, 24.4, 30.7, 52.8, 77.2, 79.2, 176.3. Literature[11b] ^{13}C NMR relevant resonances ($CDCl_3$): $\delta =$ 16.8, 21.0, 24.0, 30.3, 52.2, 79.2, 176.3. Compound (2*R*,3*S*)-**16** was obtained as the major isomer of a (2*R*,3*S*)/(2*R*,3*R*) = 2:1 mixture from a

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(2*S*,5*R*,1′*S*)(2*S*,5*R*,1′*R*) = 2:1 mixture of **3f**: ^{1}H NMR ($CDCl_3$): $\delta = 0.95$ (d, $J = 6.8$ Hz, 3H; Me), 1.04 (d, $J = 6.8$ Hz, 3H; Me), 1.38 (s, 3H; Me), 2.04 (m, 1H; C*H*Me$_2$), 2.25 (b, 1H; OH), 3.50 (b, 1H; OH), 3.66 (m, 1H; C3-H), 3.81 (s, 3H; OMe). Literature[11b] ^{1}H NMR (relevant resonances) ($CDCl_3$): $\delta = 0.98$, 1.40, 3.43, 3.72; ^{13}C NMR ($CDCl_3$): $\delta = 15.8$, 21.8, 22.7, 28.5, 53.2, 77.7 (C), 78.2 (CH), 177.1. Literature[11b] ^{13}C NMR (relevant resonances) ($CDCl_3$): $\delta = 15.7$, 21.4, 22.0, 28.2, 52.5, 78.3 176.9.

Synthesis of (2*S*,5*R*,1′*R*), and (2*S*,5*R*,1′*S*)-2-(*tert*-butyl)-5-(1′-hydroxy-1′-phenylethyl)-2,5-methyl-1,3-dioxolan-4-ones (3g): Compounds **3g** were prepared from dioxolanone **1a** ((2*S*,5*S*)/(2*R*,5*S*) = 98:2) (0.50 g, 3.2 mmol) and acetophenone **10** (0.53 g, 4.4 mmol). Chromatography (SiO_2, *n*-pentane/EtOAc, 13:1) gave a mixture of (2*S*,5*R*,1′*R*)/(2*S*,5*R*,1′*S*) = 90:10 (0.59 g, 2.1 mmol, 67%). A second chromatographic separation gave (2*S*,5*R*,1′*R*)-**3g** and a mixture of (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*) = 4.5:1.0; elemental analysis calcd (%) for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 68.88, H 7.89. (2*S*,5*R*,1′*R*)-**3g**: $[\alpha]_D^{20} = +45.2$ ($c = 1.2$ in $CHCl_3$); IR ($CDCl_3$): $\tilde{\nu} = 3600$–3500, 1770 cm^{-1}; MS: *m*/*z*: 278 [M^+], 187, 157; (2*S*,5*R*,1′*R*)-**3g**: ^{1}H NMR ($CDCl_3$): $\delta = 0.90$ (s, 9H; 3Me), 1.43 (s, 3H; Me), 1.73 (s, 3H; Me), 2.80–2.90 (b, 1H; OH), 4.67 (s, 1H), 7.25–7.45 (m, 5H; arom); ^{13}C NMR ($CDCl_3$): $\delta = 20.3$, 23.4, 25.3, 34.8, 77.3 (C1′), 84.6 (C5), 109.9 (C2), 126.1, 127.8, 127.9, 142.3, 174.5. (2*S*,5*R*,1′*S*)-**3g**: ^{1}H NMR ($CDCl_3$): $\delta = 0.90$ (s, 9H; 3Me), 1.42 (s, 3H; Me), 1.80 (s, 3H; Me), 2.65–2.75 (m, 1H; OH), 5.04 (s, 1H), 7.25–7.45 (m, 5H; arom). ^{13}C NMR ($CDCl_3$): $\delta = 20.4$, 23.4, 24.0, 34.7, 78.3 (C1′), 83.8 (C5), 110.2 (C2), 126.9, 127.6, 127.8, 142.3, 174.7.

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[10] The conventional terms *u* and *l* isomers were used[8b] as descriptors for the dioxolanone alcohols (2*S*,5*R*,1′*S*) and (2*S*,5*R*,1′*R*), respectively.
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[12] It is worth noting that the addition reactions of aldehydes **5** and **7** to the lithium enolate of the achiral 5-methyl-1,3-dioxolan-4-one afforded *l*-dioxolanone alcohols (5*RS*,1′*RS*) as the major isomers.[11b] In our opinion, it is rather difficult to rationalize the opposite stereochemical trends observed in references [8b] and [11b]. In fact, the reactive faces of the transition states TS **I** and TS **II** of enolate (2*S*)-**2a** and of the enolate of the achiral dioxolanone bear a hydrogen atom at C2 and display identical steric requirements, so that a closely similar product distribution would be expected.
[13] By capillary GC and HPLC analysis, we detected two minor peaks (1:1 ratio) in the crude reaction mixture of dioxolanone alcohols **3f**. Their mass spectra showed fragmentation patterns consistent with a structure of a dioxolanone alcohol, thus suggesting the presence of minor amounts of the diastereomers (2*S*,5*S*,1′*S*) and (2*S*,5*S*,1′*R*). The ^{1}H NMR spectrum of the reaction mixture showed two minor peaks at $\delta = 5.33$ and 5.19, which may be attributed to the C2-H resonances of these isomers. Our attempts at finding further evidence failed. Total integration of these two minor peaks was 9% of the total amount of the major diastereomers (2*S*,5*R*,1′*R*) and (2*S*,5*R*,1′*S*).
[14] Crystallographic data (excluding structure factors) for the structures (2*S*,5*R*,1′*R*)-**3d**, (2*S*,5*R*,1′*R*)-**3g**, and (2*S*,5*S*,1′*S*)-**3h** reported in this paper were deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-138252, CCDC-138253, and CCDC-138254. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ (UK) (fax: (+44) 1223-336-033, e-mail: deposit@ccdc.cam.ac.uk., WWW: http://www.ccdc.com.ac.uk.)
[15] Two values[8b] were erroneously given for the C2-H resonance of (2*S*,5*R*,1′*S*)-**3b** (or *u* isomer): δ appears as 5.23 in the figure and as 5.32 in the Experimental Section.
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[17] W. Ladner, *Chem. Ber*. **1983**, *116*, 3413–3426.
[18] The [α] value of (2*R*,2*R*)-**13**, that is, the enantiomer of (2*S*,3*S*) was obtained as a private communication.
[19] L. D. Bergel′son, E. V. Dyatlovitskaya, M. Tichy, V. V. Voronkova, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* **1962**, 1612 [*Chem. Abstr*. **1963**, *58*, 4416e].
[20] An erroneus ^{13}C NMR resonance value, 77.0[11a] appeared for the C3 carbon atom of racemic (2*RS*,3*SR*)-**15**. We observed δ at 81.4 for the enantiomer (2*R*,3*S*)-**15**.
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[22] We noticed that the literature[11a] ^{1}H NMR spectral data of the *erythro*-(2*RS*,3*RS*) mixture of compounds **15** and the *threo*-(2*RS*,3*SR*) compound were swopped around. In fact, the ^{1}H NMR data of our *erythro* isomers (2*R*,3*R*)-**15** and (2*S*,3*S*)-**15** were consistent with the data of the (2*S*,3*S*) isomer of reference [17], but fitted with the data of the *threo*-(2*RS*,3*SR*) mixture of reference [11b], while the data of our *threo*-(2*R*,3*S*)-**15** were consistent with the data of *erythro*-(2*RS*,3*RS*). The ^{1}H NMR spectral data ($CDCl_3$) of the (2*RS*,3*SR*) and (2*RS*,3*RS*) mixtures of reference [11a] were the following: (2*RS*,3*RS*): $\delta = 1.17$ (s, 3), 3.83 (s, 3), 4.83 (s, 2), 4.85 (s, 1), 7.33 (s, 5); (2*RS*,3*SR*): $\delta = 1.47$ (s, 3), 3.53 (s, 3), 4.00 (s, 2), 4.70 (s, 1), 7.17 (s, 5). Instead, the ^{13}C NMR data of the *erythro*/*threo* mixtures of reference [11] and the ^{13}C NMR data of the (2*S*,3*S*) isomer of reference [17] were consistent with our data.

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