68. Enantio- and Diastereoselective Aldol-Reaction of 2,6-Dimethylphenyl Propionate Using Titanium-Carbohydrate Complexes[1])

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Chloro(cyclopentadienyl)bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl)titanium (**1**) is used for the transmetallation of Li-enolates obtained from propionyl derivatives. While such Ti-enolates of ketones and hydrazones appear to be unreactive, the (*E*)-enolate **13** of 2,6-dimethylphenyl propionate (**11**) adds to the *re*-side of aldehydes, affording various *syn*-aldols **14** with high dia- and enantioselectivity (92–97% ds, 91–97% ee, *cf. Scheme 2* and *Table 1*). Racemic *syn*-aldols (±)-**14** are obtained analogously from the achiral bis(2-propyloxy)-Ti-enolate **15** (*Scheme 2* and *Table 2*). In contrast to the unstable Li-enolate **10**, the Ti-enolates **13** and **15** isomerize at −30°, presumably to the thermodynamically more stable (*Z*)-enolates (*Scheme 4*). While the diastereoselectivity of the achiral enolate **15** is lost upon this equilibration, the chiral (*Z*)-enolate **27** quite unexpectedly affords *anti*-aldols **12** of high optical purity (94–98% ee) and, in most cases, with acceptable-to-good diastereoselectivity (82–90% ds). Notable exceptions are branched unsaturated and aromatic aldehydes which form a greater proportion of *syn*-epimers of moderate optical purity (*Scheme 5* and *Table 3*). Consistent with these findings, *re*-facial- and *anti*-selective aldol-addition is also exhibited by the (*Z*)-configurated Ti-enolate **22** of *N*-propionyl-oxazolidinone **19** (*Scheme 3*).

1. Introduction. – In previous communications [1], we have described the synthesis of chloro(cyclopentadienyl)bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl)-titanate (**1**) from [TiCpCl$_3$] (**2**) and diacetoneglucose (DAGOH) **3**. The novel complex **1**, whose structure was studied by X-ray diffraction analysis, ^{1}H-, and ^{13}C-NMR [1d], proved to be a potent chiral template for enantioselective reactions. Exchange of the Cl-atom in **1** for allyl (→ **4**) or ester-enolates (→ **5** or **6**) and reaction with aldehydes gives homoallyl alcohols **7** [1a], β-hydroxy-esters **8** [1b], and *threo*-β-hydroxy-α-amino acids **9** [1c], respectively, with high enantio- and diastereoselectivity (*Scheme 1*). This accomplishment led to the experiments with propionyl-enolates described below.

The stereocontrolled aldol addition of propionyl-enolates is one of the most important reactions for the construction of complex acyclic or macrocyclic natural products of propionate/acetate biogenesis [2]. While excellent methods are known for the enantioselective synthesis of *syn*-aldols (*cf.* [2]), optically pure *anti*-diastereoisomers are less readily available: the Li-enolates of bulky aryl propionates give access to racemic *anti*-aldols [3], asymmetric induction and *anti*-selectivity is achieved with enantioselective variants [4] of the *Mukaiyama* reaction [5], chiral borinyl-enolates [6], and miscellaneous other methods [7].

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[1]) Part 5 of 'Enantioselective Syntheses with Titanium-Carbohydrate Complexes'. Part 4: [1d].

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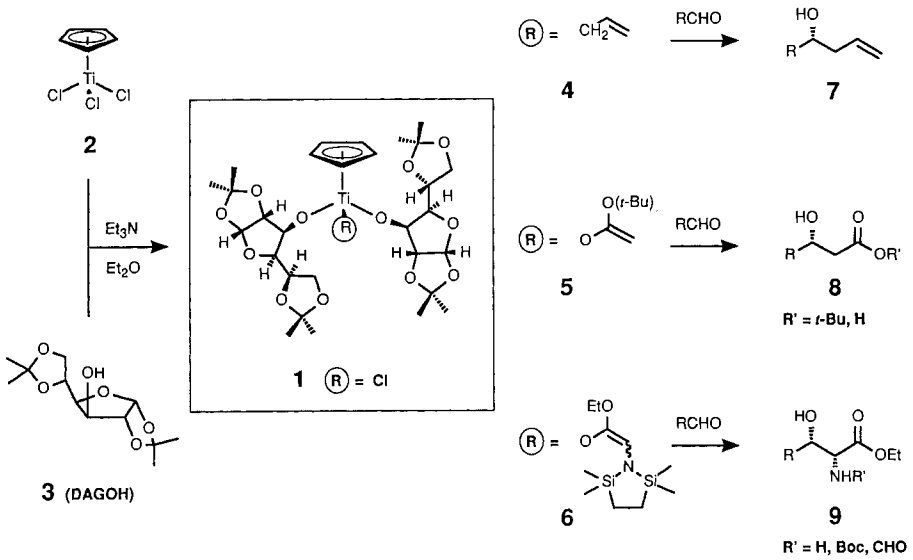
Scheme 1

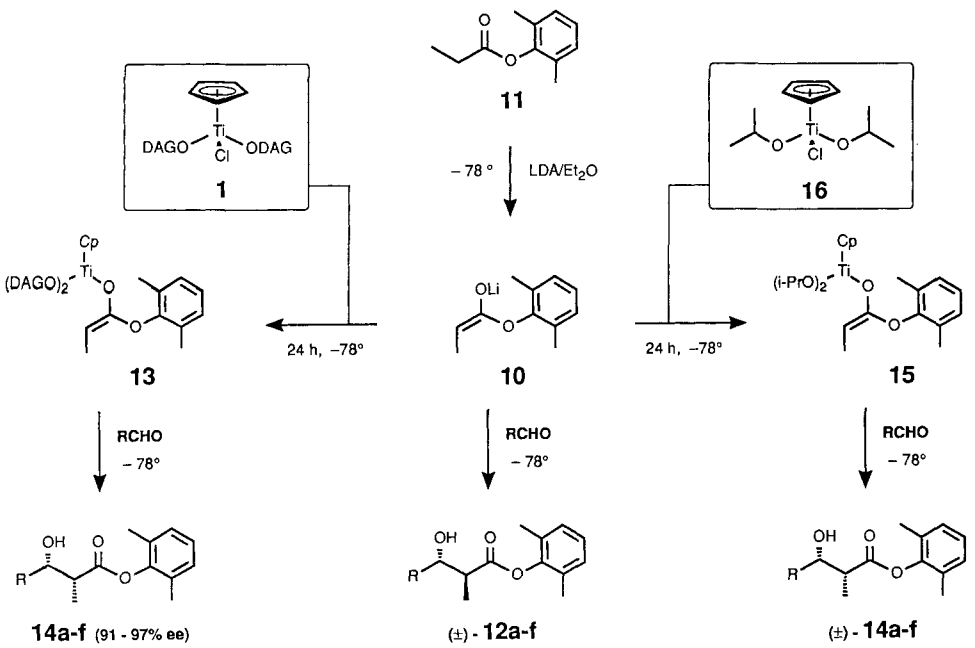


Since the pioneering work of *Reetz* and *Peter* [8a], aldol reactions of Ti(IV)-enolates have been described by several authors [8]. In general, better diastereoselectivity in aldol reactions is observed upon transmetallation of Li-enolates with achiral chlorotitanates. It appears that, in analogy to Zr and other transition-metal enolates [9] as well as enol-borates [10], titanium-enolates without cyclopentadienyl ligands lead to *syn*-aldols irrespective of the enolate geometry. It has been found, however, that chlorobis(cyclopentadienyl)Ti-enolates react *anti*-selectively [8j, m]. While moderate-to-excellent diastereofacial differentiation has been achieved in aldol-additions of Ti-enolates with a covalently attached chiral auxiliary [8f–i], to our knowledge, no propionyl-enolates with chiral Ti-complexes have been described so far. The concept of an external auxiliary, affording enantiomers directly upon hydrolytic workup, has proved to be very successful in the case of borinyl-[6a–d] [7b] [11] and tin-enolates [12], to a lesser extent even for Li-enolates [7a] [13], and enol-borates [10g].

2. Results. – a) syn-*Aldols from (*E*)-Enolates.* The starting point for this work was the well studied Li-enolate **10** of 2,6-dimethylphenyl propionate (**11**). The isomeric homogeneity of **10** is reflected in its diastereoselective addition to a variety of aldehydes, affording racemic *anti*-*β*-hydroxy-*α*-methylcarboxylates (±)-**12** in good yield [3] (*Scheme 2* and *Table 2*). When **10** is treated at −78° with [TiCp(ODAG)$_2$Cl] **1**, the formation of a Ti-enolate, presumably of structure **13**, is evidenced by the reaction with aldehydes to *syn*-aldols **14** of high optical purity (*Scheme 2*)[4]). This metal exchange is rather slow, and

[4]) The structure assignment of the known *anti*-diastereoisomers **12** and the new *syn*-diastereoisomers **14** is based on the ^{1}H-coupling constants between H–C(2) and H–C(3). With the exception of the *t*-Bu-substituted aldols **12c** [3b] and **14c** (J(2,3) = 3 Hz and 2.6 Hz, respectively), the characteristic J values [4b] [14], 6.5–8.5 Hz for the *anti*-isomers and 3.5–5 Hz for the *syn*-epimers, were observed (*cf. Exper. Part*).

Scheme 2



after 4 h at −78° still *ca.* 30% of racemic *anti*-aldol (±)-**12** are formed. Maximal diastereoselectivity (92–97%) is ensured by a transmetallation-time of 24 h, whereupon even the minor *anti*-diastereoisomer has moderate-to-high optical purity, indicating a complete conversion of the more reactive Li-enolate **10** to the titanate **13**. This is in sharp contrast to observations with [TiCl(2-propyloxy)$_3$], where complete transmetallation requires 2–4 equiv. of chlorotitanate [8g–i]. The results of the aldol reaction of **13** with representative aldehydes are summarized in *Table 1*.

When enolate **10** is generated with LDA, the diastereoselectivity (ds) of **13** ranges from 92 to 97%, the optical purity from 93 to 97%. An exception is the reaction of pivaldehyde (→ **14c**). In this case, the lower stereoselectivity (89% ds, 91% ee) is partially due to the higher reaction temperature (−50°) required for efficient conversion, and partially to isomerisation of the Ti-enolate **13** at this temperature (see below). Higher stereoselectivity is obtained by using more hindered Li-amides (Lithium-cyclohexylisopropylamide, dicyclohexylamide, and 2,2,6,6-tetramethylpiperidide). The reactions become, however, sluggish, and much lower yields result *(Table 1)*.

Needing racemic *syn*-aldols (±)-**14** as reference compounds for the determination of optical purities, we instigated the synthesis of the achiral (cyclopentadienyl)bis(*O*-2-propyloxy)Ti-enolate **15**. Reaction of [TiCpCl$_3$] **2** with 2 equiv. of i-PrOH gives an ethereal solution of complex **16**, which was used directly for the transmetallation of Li-enolate **10**. As expected, reaction of **15** with aldehydes gives racemic *syn*-aldols (±)-**14**

Table 1. *Optically Active* syn-*Aldols* **14** *from* (E)-*Enolate* **13**

	R	Yield [%][a]	*syn*-Diastereoisomer **14**		*anti*-Diastereoisomer **12**
			Configuration[b]	Enantiomeric excess ee [%][c]	Amount [%][d]
a	Pr	87	(2*R*,3*S*)	95	8.0
b	i-Pr	76	(2*R*,3*S*)	97	5.7
		43[e]		97	4.4
		24[f]		98	3.2
		27[g]		98	3.6
c	*t*-Bu	71[h]	(2*R*,3*R*)	91	11.0
d	Vinyl	79	(2*R*,3*S*)	96	3.0
e	1-Methylvinyl	61	(2*R*,3*R*)	93[i]	3.8
f	Ph	82	(2*R*,3*R*)	94	3.7

[a]) Total yield of aldol products.
[b]) Ester **14b** was converted [3] to the known (2*R*,3*S*)-3-hydroxy-2,4-dimethylpentanoic acid [15], the other configurations are assigned by analogy (addition to the *re*-side of RCHO), an assumption which is corroborated by the same order of elution from the chiral GLC column [16b] *(cf. Table 4, Exper. Part)*. Melting points and optical rotations are compiled in *Table 5 (Exper. Part)*.
[c]) Determined by cap. GLC (*Chirasil-Val*[R], [16]; *cf. Table 4, Exper. Part*).
[d]) Percentage of aldol products.
[e]) Deprotonation with Li-cyclohexylisopropylamide.
[f]) Deprotonation with Li-dicyclohexylamide.
[g]) Deprotonation with Li-2,2,6,6-tetramethylpiperidide.
[h]) Reaction at $-50°$.
[i]) Determined by ^{1}H-NMR of the 3,3,3-trifluoro-2-methoxy-2-phenylpropionate [17].

with good-to-excellent diastereoselectivity (*Scheme 2* and *Table 2*). As exemplified by the addition to isobutyraldehyde (→ (±)-**14b**), the *syn*-selectivity of the CpTi-enolate **15** is higher than observed with the corresponding [$ZrCp_2Cl$]-enolate [9a, b], or with the enolate species obtained upon transmetallation with 1.3 equiv. of [$TiCl(NEt_2)_3$] [8a, b] and [$TiCl$(2-propyloxy)$_3$] [8a, g–i] *(Table 2)*. For the latter two cases, better results might, however, be obtained with several equiv. of chlorotitanium reagent [8g, i].

b) anti-*Aldols from (Z)-Configurated Ti-Enolates.* The high stereoselectivity in aldol reactions of the (*E*)-configurated Ti-enolate **13** led to the question, whether a similar cyclopentadienyl-bis(alkoxy)Ti-enolate of (*Z*)-geometry would afford *syn*- or *anti*-products. First experiments were performed with the Li-enolate of the α-(trimethylsiloxy)-ketone **17**, a versatile propionate equivalent, which reacts cleanly to *syn*-aldols [18]. However, the transmetallation with [$TiCpCl_3$] **2** is extremely slow, even at 0°, and the resulting Ti species gives almost no aldol products, when reacted with isobutyraldehyde at −78°. The rather sluggish reactivity of (cyclopentadienyl)bis(alkoxy)Ti-enolates of ketones was later confirmed with diethyl ketone and the ene-hydrazide derived from hydrazone **18** *(Scheme 3)*. In contrast to this finding, the corresponding trichloro-, trialkoxy-, and tris(dialkylamido)Ti-enolates of ketones and hydrazones are more reactive [8a, b, d, g, i]. Surprisingly, successful aldol reactions have also been reported with [$TiCp_2Cl$]- and [$ZrCp_2Cl$]-enolates [8l] [9] of ketones.

N-Acyl-oxazolidin-2-ones are especially versatile derivatives for stereoselective alkylations [19], aldol reactions [2b] [14b], and cycloadditions [11c] [20]. For this reason, we

Table 2. *Racemic Aldols from Enolates* **15** *and* **10** (for m.p., *cf. Table 5, Exper. Part*)

	R	Yield [%][a])	*syn*-Aldol **14** from **15** ds [%]	*anti*-Aldol **12** from **10**[b]) ds [%]
a	Pr	62	95.0	–[c])
b	i-Pr	59	92.7	93
		55[d])	86.0	
		70[e]	70.0	
		81[f])	66.0	
c	*t*-Bu	53[g])	78.0	89
d	Vinyl	65	98.0	81
e	1-Methylvinyl	63	98.0	96
f	Ph	68	98.8	89

[a]) Total yield of aldol products.
[b]) Prepared according to [3].
[c]) Not determined ($\geq 97\%$).
[d]) Transmetallation with $[ZrCp_2Cl_2]$ (1.3 equiv. [9a, b]).
[e]) Transmetallation with $[TiCl(NEt_2)_3]$ (1.3 equiv. [8a, b]).
[f]) Transmetallation with [TiCl(2-propyloxy)$_3$] (1.3 equiv. [8a, b, g–i].
[g]) Reaction at $-30°$.

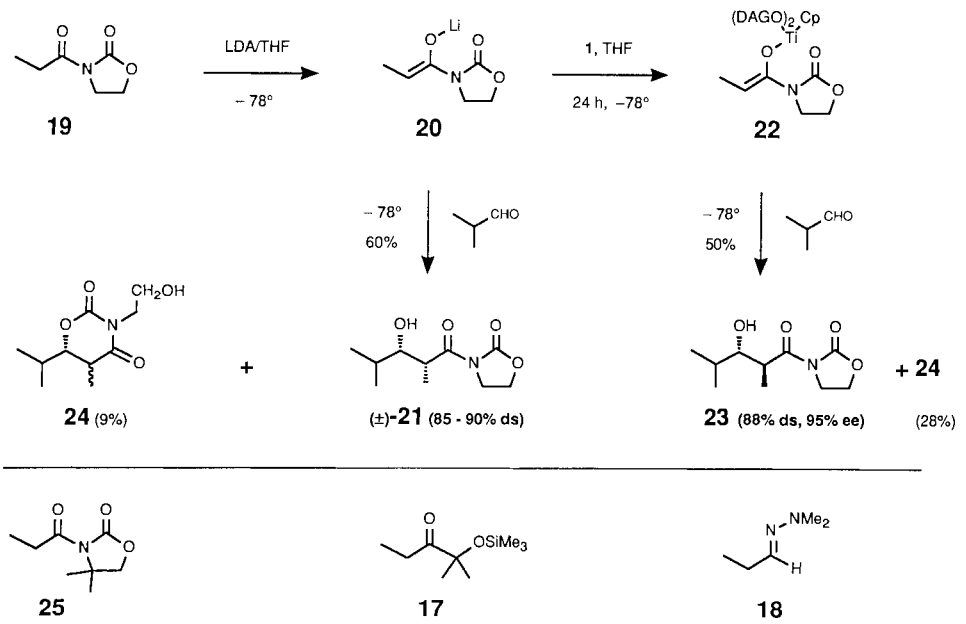
chose the achiral propionyl-oxazolidinone **19** [21] as a further substrate for the preparation of a (*Z*)-enolate. Deprotonation with LDA in THF or Et_2O gives the Li-enolate **20**, which adds at $-78°$ to isobutyraldehyde giving the racemic *syn*-aldol (±)-**21** with good diastereoselectivity. When **20** is treated for 24 h at $-78°$ with $[TiCp(ODAG)_2Cl]$ **1** in THF[5]), a Ti-enolate **22** is obtained. Quite unexpectedly, the ensuing aldol reaction proceeds with complete reversal of diastereoselectivity affording the *anti*-isomer **23** of high optical purity (95% ee)[6]). Unfortunately, this most interesting result is attenuated by the low solubility of **19** and by an ill-controllable side-reaction to the heterocycle **24** (10–30% of products) from both enolates **20** and **22** *(Scheme 3)*. Since such rearrangements have not been reported for aldol reactions of acyl-oxazolidinones, monosubstituted at C(4) [2b] [14b], the 4,4-dimethyl derivative **25** was chosen as a substitute for **19**. Although the expectation for better solubility of **25** was fulfilled, the transmetallation of its Li-enolate with $[TiCp(ODAG)_2Cl]$ **1** is slow, and the ensuing aldol-reaction turned out to be sluggish and unselective (29% yield, *ca.* 5% ds, 50% ee).

An unexpected solution for the problem of the enantioselective *anti*-aldol formation was finally discovered during the search for optimal conditions for the transmetallation of the Li-enolate **10** with **1** (→ **13**, *Scheme 2*). The long transmetallation time at $-78°$ (24 h) can be shortened to *ca.* 3 h, when the reaction temperature is increased to 30° for 30–45 min. In this case, however, more of the *anti*-aldol **12b** (15–30%) of high optical

[5]) A solution of **1** in THF can be obtained by evaporation of the solvent from an ethereal stock solution of **1** and redissolving of the residue in dry THF under inert conditions.

[6]) The absolute and relative configuration of **23** was determined by cleavage of the imide (LiOH, H_2O_2, THF [22]), esterification of the resulting acid (CH_2N_2), and comparison with the methyl ester obtained from the optically active aryl ester (–)-**12b** (see below; *Scheme 5* and *Table 3*) by saponification [3] and re-esterification (CH_2N_2). The transformation of **23** to the corresponding methyl ester (68% yield) is accompanied by an increase of the amount of the *syn*-isomer from 12 to 27%. Since the optical purity of both epimers is high ($\geq 95\%$), a partial *retro*-aldolisation seems improbable. Either epimerisation at C(2) or different yields for the cleavage of the two isomers of **23** could explain this change in ratio.

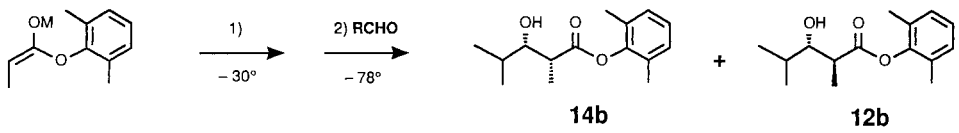
Scheme 3



purity (95% ee) is obtained upon reaction with isobutyraldehyde. As the Li-enolate **10** decomposes in a few hours at −30°, the effect of warming a solution of the Ti-enolate **13** was studied by transmetallation at −78°, raising the temperature to −30°, and probing this change by analyzing the course of the aldol reaction with isobutyraldehyde at −78°. As shown in *Scheme 4*, the original *syn*-selectivity (92% ds) of **13** is entirely reversed to a high *anti*-preference (92% ds) after 5 h at −30°. The optical purity (95% ee) of both aldols **12** and **14** is thereby maintained. Interestingly, the (cyclopentadienyl)bis(2-propyloxy)Ti-enolate **15** behaves differently: the rates of whatever process occurs at −30° appear to be slower than for **13**, and the *anti*-selectivity reaches only 64% at equilibrium. Not unexpectedly, warming a solution of the corresponding [$ZrCp_2Cl$]-enolate **26** to −30° has no effect on the steric course of its aldol reaction [9a,b] *(Scheme 4)*.

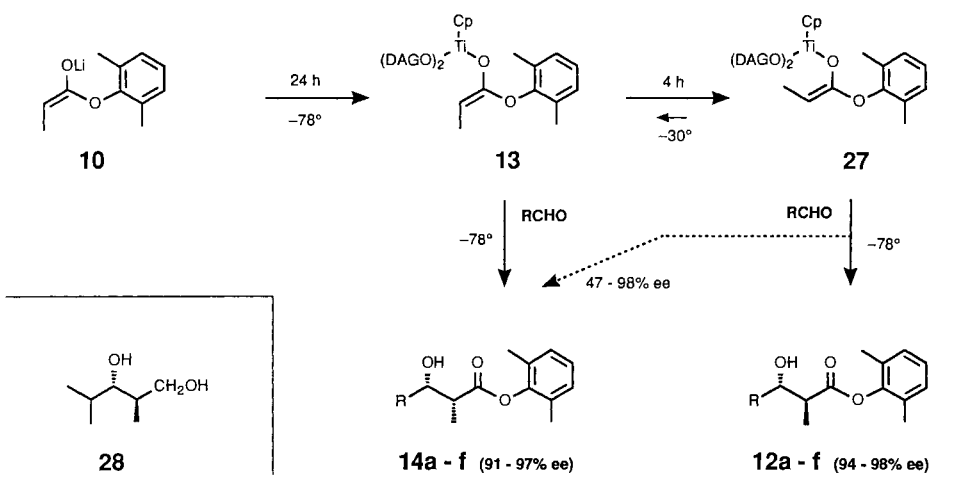
The described behaviour is best explained by assuming, that the (*E*)-enolate **13** isomerises to the more stable (*Z*)-isomer **27** at −30° *(Scheme 5)*. The observed reversal of diastereoselectivity would then imply that *anti*-aldols **12** are formed from (*Z*)-enolate **27**. Such a rationalisation is in accordance with the *anti*-selectivity observed for the imid-enolate **22**, which, most probably, has the (*Z*)-geometry as well. The mechanism of such an (*E*/*Z*)-isomerisation is not clear. In the case of a silylated enolate, catalysis by a trialkylammonium salt was invoked for a similar isomerisation with thermodynamic preference of the (*Z*)-isomer [23]. To estimate the scope of this novel enantioselective access to *anti*-aldols, the enolate **27** was allowed to react with the same aldehydes as the (*E*)-enolate **13** (*Scheme 5* and *Table 3*). The optical purity of the *anti*-aldols formed is high (94–98% ee) in all cases. The diastereoselectivity, however, turned out to be dependent of the structure of the aldehyde. Moderate-to-good diastereoselectivity (82–90% ds)

Scheme 4



10	M = Li	5 h - 30°	Decomposition	
13	M = [TiCp(ODAG)$_2$]	0 h - 30°	**12 : 1**	(92% ds, 95% ee)
		2 h - 30°	1 : 7.7	(88% ds, 95% ee)
		5 h - 30°	**1 : 12.3**	(92% ds, 95% ee)
15	M = [TiCp(i-PrO)$_2$]	0 h - 30°	**53 : 1**	(98% ds, rac.)
		5 h - 30°	1.3 : 1	(56% ds, rac.)
		24 h - 30°	1 : 1.6	(61% ds, rac.)
		45 h - 30°	**1 : 1.8**	(64% ds, rac.)
26	M = [ZrCp$_2$Cl]	0 h - 30°	**6.1 : 1**	(86% ds, rac.)
		5 h - 30°	**5.9 : 1**	(85% ds, rac.)

Scheme 5



is exhibited by saturated as well as unbranched unsaturated aldehydes[7]). Almost no diastereoselectivity is, on the contrary, observed with methacrolein (→ **12e**), and with benzaldehyde the *syn*-isomer **14** is the major product (77%). In the reactions with low *anti*-selectivity or *syn*-preference, the enantiomeric excess of the *syn*-isomers **14** is consistently low (47–72% ee), although high optical purity is observed for the accompanying *anti*-isomers **12**, or for the *syn*-aldols **14**, when the same aldehydes are brought to

[7]) The lower diastereoselectivity observed for pivalaldehyde (→ **12c**) could again be partially due to the higher reaction temperature (–30°).

Table 3. *Optically Active* anti-*Aldols* **12** *from (Z)-Enolate* **27**

	R	Yield [%][a]	*anti*-Diastereoisomer **12**		*syn*-Diastereoisomer **14**	
			Configuration[b]	Enantiomeric excess ee [%][c]	Amount [%][d]	ee [%]
a	Pr	74	(2*S*,3*S*)	95	11.0	98
b	i-Pr	76	(2*S*,3*S*)	96	10.3	–[e]
c	*t*-Bu	59[f]	(2*S*,3*R*)	98	17.0	72
d	Vinyl	61	(2*S*,3*S*)	98	18.6	66
e	1-Methylvinyl	50	(2*S*,3*R*)	94	46.3	55
f	Ph	73	(2*S*,3*R*)	94	77.0	47

[a]) Total yield of aldol products.

[b]) Ester **12b** was reduced to the known [6a,b] (2*R*,3*S*)-2,4-dimethylpentane-1,3-diol (**28**, *Scheme 5*); the other configurations are assigned by analogy (addition to the *re*-side of RCHO), an assumption which is corroborated by the same order of elution from the chiral GLC column [16b] *(cf. Table 4, Exper. Part)*. Melting points and optical rotations are compiled in *Table 5 (Exper. Part)*.

[c]) Determined by cap. GLC (*Chirasil-Val*^{R}, [16]; *cf. Table 4, Exper. Part*).

[d]) Percentage of aldol products.

[e]) Not determined (usually $\geq 95\%$).

[f]) Reaction at $-30°$.

reaction with the isomeric Ti-enolate **13**. This observation was corroborated by preparing a solution of the Ti-enolate **27** and treating samples of this solution with different aldehydes at $-78°$.

3. Discussion. – From the results presented, it is evident, that (*E*)-configurated (cyclopentadienyl)bis(alkoxy)Ti-enolates of propionyl derivatives afford *syn*-aldols with high stereoselectivity. Products of high optical purity can, thus, be obtained using commercially available DAGOH **3** as chiral ligand. According to a number of theoretical studies on the mechanism of aldol additions, this is best explained by assuming a six-membered cyclic transition state with a boat or twist-boat conformation [10b] [19a] [24]. The same steric course has been observed for Zr- and Sn-enolates [9] [12c], Ti-enolates [8], as well as for enol-borates [10] with (*E*)-(*O*)-geometry. In these cases, however, the corresponding (*Z*)-(*O*)-enolates react in a chair-like transition state, thereby affording *syn*-aldols as well. In contrast to this stereoconvergent behaviour, it seems now very likely, that certain (*Z*)-configurated Ti-enolates (**22** and **27**, *cf.* [8j, m]) lead to *anti*-products probably *via* a boat transition state. The common feature of these reagents is one or two Ti-bound cyclopentadienyl ligands. This hypothesis needs to be further substantiated by an unambiguous structure determination of the Ti-enolates **13**, **15**, **22**, and **27**. So far, *anti*-aldols have been obtained exclusively from (*E*)-(*O*)-configurated enolates, when cyclic transition states are involved [3] [6] [7], or when noncyclic open transition states are invoked [4] [5] [25]. This novel *anti*-selective aldol process is sensitive to the aldehyde structure. The high proportion of *syn*-products formed with certain unsaturated and aromatic aldehydes indicates the availability of an alternative chair-like transition state which is close in energy. The addition of the related *trans*-but-2-enyl group prefers a chair transition state as well, since *anti*-products are formed exclusively using the [TiCp(ODAG)$_2$] template [1a] [26]. Without knowing the structures of the Ti-enolates **13**, **15**, and **27**, it is not possible to explain the remarkable difference in behaviour observed upon warming of solutions of **13** and **15** *(cf. Scheme 4)*. The equilibration rates become slower

by replacing the diacetoneglucose ligand with i-PrO groups, and the different ratio of *syn*- and *anti*-products is either due to a shift in the equilibrium or to a different degree of diastereoselectivity in the aldol reactions of the corresponding (*Z*)-enolates.

With the aid of (cyclopentadienyl)bis(alkoxy)Ti complexes, the 2,6-dimethylphenyl propionate (**11**), developed by *Heathcock* and coworkers [3] for the stereoselective preparation of racemic *anti*-aldols, can now be transformed in addition to racemic *syn*-aldols and to either *syn*- or *anti*-adducts of high optical purity. With some exceptions for the asymmetric *anti*-aldol reaction, the diastereoselectivity of these reactions is in general high. With 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose as chiral alkoxy ligand, the enolate is added to the *re*-side of the aldehydes. The same preference has already been observed before in other reactions using the [TiCp(ODAG)$_2$] system (*cf. Scheme 1*, [1a–c]). Since L-glucose is not readily available, at present only one enantiomer can be prepared by this method. Part of our effort in this field is, therefore, directed at finding a similar complex, which favours the transition states leading to the enantiomeric products[8]).

Experimental Part

General. Reaction temp. of −78° stands for external cooling with a dry-ice/acetone bath, without controlling the actual internal temp. Prolonged cooling to temp. between −78° and 0° (ice-bath) has been done with the aid of a *HAAKE EK 100-Cryostat* equipped with a flexible immersion-cooler and a temp.-control unit. In this case, the reaction temp. has been monitored as well. Cap.-GLC analyses were done on a *Carlo-Erba Strumentatione HRGC 5300* instrument using a *DBWAX-30N* column (30 m, 0.25 mm diameter, 0.25 μm film) and *Chirasil-Val-III*^{R} columns [16] (50 m, 0.32 mm diameter, *Altech Applied Science Labs*, Deerfield, Ill. 60015, serial *No. 986 L*; considerable variation in t_R and separation has been observed with different columns). M.p. are not corrected and have been determined in open capillaries on a *Büchi 535* apparatus. $[\alpha]_D$ Values were measured in a 1-ml micro-cuvette (10 cm) on a *Perkin-Elmer Polarimeter 241* at ambient temp. (20–25°).

*Chloro(cyclopentadienyl)bis(1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranos-3-*O*-yl)titanium* (**1**) [1a]. To a soln./suspension of *trichloro(cyclopentadienyl)titanium* (**2**) [28] (11.0 g, 50 mmol, freshly sublimed) in 400 ml of dry Et_2O *1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose* (**3**, 26.0 g, 100 mmol; crystallised from cyclohexane) was added (Ar, exclusion of moisture). After stirring for 2 min at r.t., a soln. of Et_3N (15.2 ml, 110 mmol) in 125 ml of Et_2O was added within 1 h. Stirring was continued for *ca.* 15 h, and the precipitated $Et_3N \cdot HCl$ (14.2 g) was then separated by filtration under Ar and washed three times with *ca.* 50 ml of Et_2O. The pale yellow (sometimes brownish) filtrate is used without further manipulations as stock solution of **1**; its concentration (*ca.* 0.09 M) is calculated from the volume of the filtrate by assuming a quant. conversion (the amount of dried $Et_3N \cdot HCl$ precipitated should not exceed 15 g). If moisture is excluded, this soln. can be stored for serveral months in a refrigerator (8°) without deterioration.

Chloro(cyclopentadienyl)bis(2-propyloxy)titanium (**16**). To a soln./suspension of **2** [28] (11.0 g, 50.1 mmol; freshly sublimed) in 400 ml of dry Et_2O, i-PrOH (6.0 g, 100 mmol; dried over 4-Å molecular sieves) and, after 5 min, Et_3N (15.2 ml, 110 mmol) in 125 ml of Et_2O were added dropwise within 1 h (Ar). After stirring over night at r.t., $Et_3N \cdot HCl$ (13.5 g after drying) was removed by filtration under Ar and washed with Et_2O (3 × 50 ml). The yellow filtrate (0.085M assuming a quant. conversion) was used without further manipulations as a stock solution of **16**.

Method A: General Procedure for the Preparation of Optically Active syn-*Aldols* **14** via *(cyclopentadienyl)-bis(1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranos-3-*O*-yl)titanium-(*E*)-enolate* **13** *of 2,6-Dimethylphenyl Propionate* (**11**). BuLi (4 ml of a 1.55M soln. in hexane, 6.2 mmol) is added, at −20°, to a soln. of $(i\text{-}Pr)_2NH$ (1 ml, 7.07 mmol) in 30 ml of Et_2O (Ar). After 15 min, the temp. is lowered to −78°, and a soln. of **11** (1.0 g, 5.61 mmol [3]) in 10 ml of Et_2O is added dropwise. Stirring at −78° is continued for 1.5 h, and then 80 ml of an 0.088M ethereal solution of **1** (7.04 mmol, 1.25 equiv. based on **11**, precooled to −78°) is added carefully *via* canula under Ar pressure. After stirring for 24 h at −78°, and aldehyde (7.29 mmol, *ca.* 1.3 equiv.) is added, and the course of the

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[8]) *Note added in proof:* A recent report of *Heathcock* and coworkers [27] describes the formation of optically active *anti*-aldols from 3-(arylthio)propenals and the (*Z*)-boron-enolate of *N*-propionyl-oxazolidinones in the presence of a *Lewis* acid and excess of $(i\text{-}Pr)_2NEt$.

reaction (−78°) is monitored by TLC (hexane/AcOEt 4:1). Quenching is achieved by the addition of NH_4Cl (2 g) and 10 ml of THF/H_2O 1:1 (*v/v*). After stirring for 2 h at 0°, the precipitated Ti salts are separated by filtration and washed with Et_2O. The filtrate is extracted with 1N HCl (25 ml), sat. $NaHCO_3$ soln. (10 ml), and sat. brine. The aq. washings are re-extracted with AcOEt (2 × 50 ml). The residue of the dried ($MgSO_4$) org. phase containing products and **3** is either separated directly by chromatography (silica gel, hexane/AcOEt 5:1) or first stirred for 1 h with 0.1N HCl (200 ml), extracted with Et_2O (3 × 100 ml), and washed with sat. $NaHCO_3$ soln. and brine, thereby removing the glucose as the H_2O soluble 1,2-acetonide.

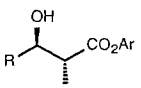
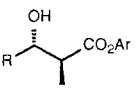
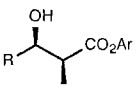
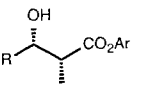
Method B: General Procedure for the Preparation of Optically Active anti-*Aldols* **12** via *(cyclopentadienyl)-bis(1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranos-3-*O*-yl)titanium-(Z)-enolate* (**27**) *of* **11**. BuLi (4 ml of a 1.55M soln. in hexane, 6.2 mmol) is added at −20° to a soln. of $(i\text{-}Pr)_2NH$ (1 ml, 7.07 mmol) in 30 ml of Et_2O (Ar). After 15 min, the temp. is lowered to −78°, and a soln. of **11** (1.0 g, 5.61 mmol [3]) in 10 ml of Et_2O is added dropwise. Stirring at −78° is continued for 1.5 h, and then 80 ml of an 0.088M ethereal soln. of **1** (7.04 mmol, 1.25 equiv. based on **11**; precooled to −78°) is added carefully *via* canula under Ar pressure. The mixture is first stirred for 20–24 h at −78° and then for 4 h at −25 to −30°. Before the addition of an aldehyde (7.29 mmol, *ca.* 1.3 equiv.), the solution, which may contain some precipitated material, is recooled to −78°. Afterwards, one proceeds as described under *Method A*.

Method C: General Procedure for the Preparation of Racemic syn-*Aldols (±)*-**14** via *(Cyclopentadienyl)bis(2-propyloxy)titanium-(E)-enolate* (**15**) *of* **11**. BuLi (4 ml of a 1.58M soln. in hexane, *ca.* 6.3 mmol) is added at −20° to a soln. of $(i\text{-}Pr)_2NH$ (1 ml, 7.07 mmol) in 28 ml of dry Et_2O (Ar). After 15 min, the temp. is lowered to −78°, and a soln. of **11** (1.0 g, 5.61 mmol [3]) in 5–10 ml of Et_2O is added dropwise. Stirring at −78° is continued for 1.5 h, and then 82 ml of a 0.085M ethereal solution of **16** (*ca.* 7 mmol; precooled to −78°) is added carefully *via* canula under Ar pressure. After stirring for 24 h at −78°, an aldehyde (*ca.* 7.3 mmol) is added, and the course of the reaction at −78° is followed by TLC. One then proceeds as described under *Method A*.

*2,6-Dimethylphenyl (2*RS,*3*SR*)-3-Hydroxy-2-methylhexanoate* ((±)-**14a**). Butyraldehyde (700 µl, *ca.* 7.8 mmol) was added at −78° to an ethereal soln. of **15** prepared from **11** (1.007 g, 5.66 mmol) according to *Method C*. After stirring for 4 h at −78°, the mixture was worked up *(Method A)*: 876 mg (62%) of aldols, 95% of (±)-**14a** and 5% of (±)-**12a** (GLC, *DBWAX*, 180°, 0.6 kbar, t_R (**12a**) 23.6 min; t_R (**14a**) 24.3 min). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.98 (*t*, *J* = 7, 3 H–C(6)); 1.40 (*d*, *J* = 7, CH_3–C(2)); 1.3–1.7 (*m*, 2 H–C(4), 2 H–C(5)); 2.16 (*s*, CH_3–C(2′), CH_3–C(6′)); 2.43 (*d*, *J* = 5, OH); 2.85 (*dq*, *J* = 3.5, 7, H–C(2)); 4.11 (*dddd*, *J* = 7.5, 5, 4, 3.5, H–C(3)); 7.06 (*m*, $w_{1/2} \approx 3$, H–C(3′), H–C(4′), H–C(5′)).

*2,6-Dimethylphenyl (2*R,*3*S*)-3-Hydroxy-2-methylhexanoate* (**14a**). Butyraldehyde (630 µl, *ca.* 7.0 mmol) was added at −78° to an ethereal soln. of **13** prepared from **11** (982 mg, 5.52 mmol) according to *Method A*. After stirring for 2 h −78°, the mixture was worked up (*Method A*): 1.201 g (87%) of aldols, 92% of **14a** and 8% of **12a** (GLC, see above). Re-chromatography (silica gel, hexane/AcOEt 6:1) gave 820 mg of **14a**/**12a** and 304 mg of pure **14a** (95% ee, *Table 4*), waxy solid. $[\alpha]_D = -0.25$, $[\alpha]_{365} = +0.99$ (*c* = 1.2, $CHCl_3$).

Table 4. *GLC Retention Times* (t_R) *on* Chirasil-Val^R [16]

	anti-Aldols **12**		*syn*-Aldols **14**		Carrier[a])	Temp. [°C]
						
R	t_R [min]	t_R [min]	t_R [min]	t_R [min]		
Pr	43.9	45.9	45.2	45.9	130	130
i-Pr	12.1	12.4	12.9	12.97	70	170
t-Bu	22.9	23.6	26.9	26.9	70	160
			47.1[b])	48.7[b])	90	180
Vinyl	47.9	50.6	44.6	45.3	100	130
1-Methylvinyl	29.9	31.2	29.5	29.9	70	150
Ph	42.1	43.7	39.3	40.2	100	180

[a]) Pressure of the carrier gas (H_2) in kilo-Pascal (1 atm = 1.01325 × 10^5 Pascal).
[b]) Derivatized with *N*-Isopropyl isocyanate [16].

Table 5. *Melting Points and Optical Rotations of Aldols* **12** *and* **14**

	R	*syn*-Diastereoisomer **14**					*anti*-Diastereoisomer **12**				
		M.p. [°C]		$[\alpha]_D$	$[\alpha]_{365}$	ee	M.p. [°C]		$[\alpha]_D$	$[\alpha]_{365}$	ee
		(±)	(2*R*)	($c \approx 1$, $CHCl_3$)		[%]	(±)	(2*S*)	($c \approx 1$, $CHCl_3$)		[%]
a	Pr	oil	waxy	−0.3	+1.0	95	oil	oil	−8.3	−28.1	95
b	i-Pr	51–53	62–63[a])	+16.3	+50.9	98	78–80	99–100[a])	−1.4	−9.0	99
c	*t*-Bu	oil	oil	+13.2	+36.8	91	77–79[b])	97–99	−9.6	−44.0	99
d	Vinyl	oil	oil	+3.3	+9.5	96[c])	oil	oil	−10.8	−39.7	98[d])
e	1-Methylvinyl	73–74	93–95[a])	+42.9	+149.2	95	oil	–[e])	–[e])	–[e])	
f	Ph	105–106	130–131[a])	+2.3	−12.9	97	oil	57–60	+55.1	+189.4	94

[a]) The racemate crystallises as a conglomerate of enantiomorphic crystals, as judged by a higher melting point and identical IR (KBr), of the enantiomerically pure compound [29].

[b]) The IR (KBr) is different from the IR of the enantiomerically pure compound.

[c]) Contains 3% of *anti*-isomer.

[d]) Contains 19% of *syn*-isomer (66% ee).

[e]) Not determined, because the *syn*-isomer (46%) could not be separated.

2,6-Dimethylphenyl (2S,3S)-3-Hydroxy-2-methylhexanoate (**12a**). Butyraldehyde (630 µl, ca. 7.0 mmol) was added at −78° to an ethereal soln. of **27** prepared from **11** (1.0 g, 5.62 mmol) according to *Method B*. After stirring for 15 h at −78°, the mixture was worked up (*Method A*). 1.044 g (74%) of aldols, 89% of **12a** and 11% of **14a** (GLC, see above). Re-chromatography (silica gel, hexane/AcOEt 5:1) afforded 218 mg of **12a** (95% ee, *Table 4*), 700 mg of **12a/14a**, and 43 mg of **14a** (98% ee, *Table 4*). $[\alpha]_D = -8.26$, $[\alpha]_{365} = -28.05$ ($c = 1.5$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.96 (*m*, 3 main peaks, 3 H–C(6)); 1.35–1.7 (*m*, 2 H–C(4), 2 H–C(5)); 1.44 (*d*, $J = 7.5$, CH_3–C(2)); 2.16 (*s*, CH_3–C(2′), CH_3–C(6′)); 2.3–2.6 (br., OH); 2.84 (*quint.*, $J = 7.5$, H–C(2)); 3.82 (*m*, H–C(3)); 7.06 (*m*, $w_{½} \approx 3$, H–C(3′), H–C(4′), H–C(5′)).

2,6-Dimethylphenyl (2RS,3SR)-3-Hydroxy-2,4-dimethylpentanoate (±)-**14b**. 2-Methylpropanal (700 µl, *ca.* 7.6 mmol) was added at −78° to an ethereal soln. of **15** prepared from **11** (1.04 g, 5.84 mmol) according to *Method C*. After stirring for 2.5 h at −78°, the mixture was worked up and the product was isolated as described in *Method A*: 0.865 g (59%) of aldols, 92.7% (±)-**14b** and 7.3% of (±)-**12b** (GLC, *Table 4*). Crystallisation from hexane afforded 569 mg of (±)-**14b** (97.4% ds), recrystallisation (hexane) 554 mg (38%) of pure (±)-**14b**. M.p. 51–53°. IR (KBr): 3045*w*, 3025*w*, 2990*w*, 2960*m*, 2930*m*, 2900*w*, 2875*m*, 1750*s*, 1730*s*, 1480*m*, 1470*m*, 1455*m*, 1380*w*, 1367*m*, 1340*m*, 1270*m*, 1175*s*, 1155*s*, 1145*s*, 1105*s*, 1060*m*, 995*s*, 970*m*, 920*w*, 885*m*, 830*w*, 800*w*, 770*s*, 700*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.95, 1.08, 1.40 (3*d*, $J = 6.5$, CH_3–C(2), CH_3–C(4), 3 H–C(5)); 1.65–1.9 (*m*, H–C(4)); 2.15 (*s*, CH_3–C(2′), CH_3–C(6′)); 2.2–2.6 (br., OH); 3.0 (*dq*, $J = 4, 6.5$, H–C(2)); 3.65 (*dd*, $J = 7.5, 4$, H–C(3)); 7.06 (*m*, $w_{½} \approx 5$, H–C(3′), H–C(4′), H–C(5′)).

2,6-Dimethylphenyl (2R,3S)-3-Hydroxy-2,4-dimethylpentanoate (**14b**). 2-Methylpropanal (700 µl, *ca.* 7.6 mmol) was added at −78° to an ethereal soln. of **13** prepared from **11** (1.0 g, 5.61 mmol) according to *Method A*. After stirring for 3 h at −78°, the mixture was worked up and the product was isolated as described in *Method A*: 1.081 g (76%) of aldols, 94.3% of **14b** (97% ee) and 5.7% of **12b** (GLC, *Table 4*). Crystallisation (hexane) afforded 836 mg (60%) of optically pure **14b** containing 1.2% of **12b**. M.p. 62–63°. $[\alpha]_D = +16.3$, $[\alpha]_{365} = +50.9$ ($c = 1$, $CHCl_3$). IR (KBr): identical to spectrum of (±)-**14b**.

A sample of **14b** (100 mg, 92% ee) was saponified according to [3] to *(2R,3S)-3-hydroxy-2,4-dimethylpentanoic acid*. $[\alpha]_D = +10.6$ ($c = 0.16$, $CHCl_3$; [15a]: $[\alpha]_D = +10.54$ ($c = 1.4$, $CHCl_3$)).

2,6-Dimethylphenyl (2S,3S)-3-Hydroxy-2,4-dimethylpentanoate (**12b**). 2-Methylpropanal (700 µl, *ca.* 7.6 mmol) was added at −78° to an ethereal soln. of **27** prepared from **11** (980 mg, 5.5 mmol) according to *Method B*. After stirring for 15 h at −78°, the mixture was worked up, and the product was isolated as described in *Method A*: 1.05 g (76%) of aldols, 89.7% of **12b** (96% ee) and 10.3% of **14b** (GLC, *Table 4*). Crystallisation (hexane) afforded 783 mg (57%) of **12b** (≥ 99% ee). M.p. 99–100°. $[\alpha]_D = -1.35$, $[\alpha]_{365} = -9.04$ ($c = 1$, $CHCl_3$). IR (KBr, identical to the spectrum of (±)-**12b**): 3010*w*, 2980*m*, 2965*m*, 2950*m*, 2940*m*, 2930*m*, 2910*m*, 2890*m*, 2875*m*, 1743*s*, 1700*w*, 1685*w*, 1470*m*, 1465*w*, 1380*m*, 1365*m*, 1333*m*, 1305*w*, 1290*w*, 1270*w*, 1252*m*, 1157*s*, 1135*s*, 1120*m*, 1090*w*, 1073*w*, 1033*m*, 1000*m*, 970*m*, 920*w*, 905*w*, 880*w*, 830*w*, 820*w*, 787*s*, 750*w*, 735*w*, 695*w*, 615*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.99, 1.06, 1.44 (3*d*, $J = 6.5$, CH_3–C(2), CH_3–C(4), 3 H–C(5)); 1.8–1.95 (*m*, H–C(4)); 2.16 (*s*, CH_3–C(2′),

CH_3–C(6′)); 2.3–2.6 (br., OH); 2.98 (*quint.*, J = 6.5, H–C(2)); 3.56 (*dd*, J = 6.5, 6, H–C(3)); 7.06 (*m*, $w_{1/2} \approx 3$, H–C(3′), H–C(4′), H–C(5′)).

A sample of **12b** (104 mg, 99% ee) was saponified according to [3] to *(2S,3S)-3-hydroxy-2,4-dimethylpentanoic acid*: $[\alpha]_D = +1.9$, $[\alpha]_{365} = +5.7$ (c = 0.63, $CHCl_3$). CD (EtOH, $7.155 \cdot 10^{-3}$M): 217 (min., $\Delta\varepsilon = -0.159$); 212 (max., $\Delta\varepsilon = -0.14$); 210 (min., $\Delta\varepsilon = -0.156$); 205 (max., $\Delta\varepsilon = -0.102$); 202 (min., $\Delta\varepsilon = -0.125$).

(2R,3S)-2,4-Dimethylpentane-1,3-diol (**28**). Propionate **12b** (117 mg, 0.47 mmol, 94% ee), dissolved in 1 ml of dry Et_2O, was added at 0° to 35 mg (0.93 mmol) of $LiAlH_4$ in 5 ml of dry Et_2O. After stirring for 1 h at 0° (Ar), the reaction was quenched by the addition of 1N NaOH (140 µl). Filtration, drying ($MgSO_4$), evaporation of solvent, and chromatography (silica gel, hexane/AcOEt 1:2) afforded 45 mg (72%) of **28**. $[\alpha]_D = -18.2$, $[\alpha]_{365} = -53.3$ (c = 0.6, $CHCl_3$; [6a] (suppl. material): $[\alpha]_D = -20.2$, $[\alpha]_{365} = -60.1$ (c = 1.04, $CHCl_3$)). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.87, 1.92, 1.98 (3*d*, J = 7, CH_3–C(2), CH_3–C(4), 3 H–C(5)); 1.75–1.95 (*m*, H–C(2), H–C(4)); 2.36 (br., $w_{1/2} \approx 5$, 2 OH); 3.36 (*dd*, J = 8.5, 4, H–C(3)); 3.65 (*dd*, J = 11, 7), 3.77 (*dd*, J = 11, 4) (2 H–C(1)). Anal. calc. for $C_7H_{16}O_2$ (132.2): C 63.60, H 12.20, O 24.21; found: C 63.09, H 12.94, O 24.39.

2,6-Dimethylphenyl (2RS,3RS)-3-Hydroxy-2,4,4-trimethylpentanoate ((±)-**14c**). Pivalaldehyde (800 µl, *ca.* 7.28 mmol) was added at −78° to an ethereal soln. of **15** prepared from **11** (1.0 g, 5.61 mmol) according to *Method C*. The mixture was stirred for 18 h at −50 to −55° and for 24 h at −27 to −30°. Workup *(Method A)* yielded 796 mg (53%) of aldols: 78% of (±)-**14c** and 22% of (±)-**12c** (GLC, *Table 4*). Re-chromatography (silica gel, toluene/AcOEt 20:1) afforded 316 mg of (±)-**14c**/**12c** and 480 mg of pure (±)-**14c**. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.05 (*s*, 2 CH_3–C(4), 3 H–C(5)); 1.45 (*d*, J = 7.5, CH_3–C(2)); 2.16 (*s*, CH_3–C(2′), CH_3–C(6′)); 2.32 (*d*, J = 5, OH); 3.20 (*dq*, J = 2.5, 7.5, H–C(2)); 3.88 (*dd*, J = 5, 2.5, H–C(3)); 7.08 (*m*, $w_{1/2} \approx 5$, H–C(3′), H–C(4′), H–C(5′)).

2,6-Dimethylphenyl (2R,3R)-3-Hydroxy-2,4,4-trimethylpentanoate (**14c**). Pivalaldehyde (850 µl, *ca.* 7.7 mmol) was added at −78° to an ethereal soln. of **13** prepared from **11** (1.03 g, 5.78 mmol) according to *Method A*. After 15 min at −78°, the mixture was stirred for 15 h at −50 to −55°. Workup *(Method A)* afforded 1.09 g (71%) of aldols: 89% of **14c** and 11% of **12c** (89% ee, GLC, *Table 4*). Re-chromatography (silica gel, toluene/AcOEt 20:1) afforded 395 mg of **14c**/**12c** and 629 mg of **14c** (90.6% ee, GLC, *Table 4*). $[\alpha]_D = +13.2$, $[\alpha]_{365} = +36.8$ (c = 1.02, $CHCl_3$).

2,6-Dimethylphenyl (2S,3R)-3-Hydroxy-2,4,4-trimethylpentanoate (**12c**). Pivalaldehyde (800 µl, *ca.* 7.28 mmol) was added at −30° to an ethereal soln. of **27** prepared from **11** (1.0 g, 5.61 mmol) according to *Method B*. The mixture was stirred for 16 h at −26 to −30°. Workup *(Method A)* and re-chromatography (silica gel, toluene/AcOEt 20:1) afforded 735 mg (49%) of **12c** (98% ee) and 156 mg (10%) of **14c** (72% ee, GLC, *Table 4*). M.p. 97–99° (hexane). $[\alpha]_D = -9.6$, $[\alpha]_{365} = -44.0$ (c = 1.0, $CHCl_3$). IR (KBr): 3020*w*, 2980*w*, 2960*m*, 2870*w*, 1750*s*, 1475*m*, 1455*m*, 1395*w*, 1375*w*, 1360*m*, 1340*w*, 1280*m*, 1260*w*, 1250*w*, 1215*w*, 1175*m*, 1140*s*, 1110*s*, 1055*m*, 1025*w*, 1015*m*, 985*m*, 970*w*, 895*w*, 850*w*, 830*w*, 790*w*, 780*s*, 770*w*, 730*w*, 685*w*, 595*m*, 530*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.01 (*s*, 2 CH_3–C(4), 3 H–C(5)); 1.61 (*d*, J = 7.5, CH_3–C(2)); 2.18 (*s*, CH_3–C(2′), CH_3–C(6′)); 3.07 (*dq*, J = 3, 7.5, H–C(2)); 3.32 (*dd*, J = 9, 3, H–C(3)); 3.61 (*d*, J = 9, OH); 7.06 (*m*, $w_{1/2} \approx 2$, H–C(3′), H–C(4′), H–C(5′)).

2,6-Dimethylphenyl (2SR,3RS)-3-Hydroxy-2,4,4-trimethylpentanoate ((±)-**12c**). Racemic (±)-**12c** was prepared from **11** *via* Li-enolate **10** according to [3]. Yield: 84% of aldols, 89% (±)-**12c** and 11% (±)-**14c** (GLC, *Table 4*). Crystallisation from hexane afforded pure (±)-**12c**. M.p. 77–79°. IR (KBr): 3070*w*, 3040*w*, 3010*w*, 2960*m*, 2910*w*, 2890*w*, 2870*w*, 1740*s*, 1480*m*, 1385*w*, 1375*w*, 1360*m*, 1350*m*, 1335*m*, 1295*w*, 1265*m*, 1170*s*, 1150*s*, 1085*m*, 1065*m*, 1040*w*, 1015*m*, 950*m*, 930*w*, 900*w*, 870*m*, 825*w*, 790*w*, 765*s*, 730*w*, 695*m*, 670*w*, 570*w*, 550*w*, 530*w*.

2,6-Dimethylphenyl (2RS,3SR)-3-Hydroxy-2-methylpent-4-enoate ((±)-**14d**). Acrolein (480 µl, *ca.* 7.2 mmol) was added at −78° to an ethereal soln. of **15** prepared from **11** (1.0 g, 5.61 mmol) according to *Method C*. After stirring for 1 h at −78°, the mixture was worked up as usual *(Method A)*: 862 mg (65%) of aldols, 98% (±)-**14d** and 2% of (±)-**12d** (GLC, *Table 4*). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.39 (*d*, J = 7, CH_3–C(2)); 2.15 (*s*, CH_3–C(2′), CH_3–C(6′)); 2.56 (*d*, J = 5, OH); 2.97 (*dq*, J = 4, 7, H–C(2)); 4.62 (*m*, H–C(3)); 5.28 (*dt*, J = 10.5, 1.5), 5.41 (*dt*, J = 17, 1.5) (2 H–C(5)); 5.97 (*ddd*, J = 17, 10.5, 5.5, H–C(4)); 7.06 (*m*, $w_{1/2} \approx 3$, H–C(3), H–C(4′), H–C(5′)).

2,6-Dimethylphenyl (2R,3S)-3-Hydroxy-2-methylpent-4-enoate (**14d**). Acrolein (490 µl, *ca.* 7.3 mmol) was added at −78° to an ethereal soln. of **13** prepared from **11** (1.0 g, 5.61 mmol) according to *Method A*. After stirring for 2 h at −78°, the mixture was worked up as usual *(Method A)*. Bulb-to-bulb distillation (220°/0.04 mm) afforded 1.04 g (79%) of aldols, 97.2% of **14d** (96% ee) and 2.8% of **12d** (GLC, *Table 4*). $[\alpha]_D = +3.3$, $[\alpha]_{365} = +9.5$ (c = 1.03, $CHCl_3$).

2,6-Dimethylphenyl (2S,3S)-3-Hydroxy-2-methylpent-4-enoate (**12d**). Acrolein (500 µl, *ca.* 7.5 mmol) was added at −78° to an ethereal soln. of **27** prepared from **11** (1.0 g, 5.61 mmol) according to *Method B*. After stirring for 15 h at −78°, the mixture was worked up as usual (*Method A*; 810 mg, 61% of aldols). Bulb-to-bulb distillation (220°/0.01 mm) afforded 752 mg of aldols, 81.4% **12d** (98% ee) and 18.6% of **14d** (66% ee; GLC *Table 4*).

$[\alpha]_D = -10.8$ (pure **12d** calc. $-13.8°$), $[\alpha]_{365} = -39.7$ ($c = 1.05$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.41 (*d*, $J = 7$, CH_3–C(2)); 2.16 (*s*, CH_3–C(2'), CH_3–C(6')); 2.64 (*d*, $J = 6$, OH); 2.89 (*quint.*, $J = 7$, H–C(2)); 4.34 (*m*, H–C(3)); 5.28 (*dt*, $J = 10.5, 1.5$), 5.39 (*dt*, $J = 17, 1.5$) (2 H–C(5)); 5.94 (*ddd*, $J = 17, 10.5, 6.5$, H–C(4)); 7.05 (*m*, $w_{1/2} \approx 4$, H–C(3'), H–C(4'), H–C(5')).

*2,6-Dimethylphenyl (2*RS,*3*RS*)-3-Hydroxy-2,4-dimethylpent-4-enoate* ((±)-**14e**). Methacrolein (600 µl, *ca.* 7.0 mmol) was added at −78° to an ethereal soln. of **15** prepared from **11** (1.0 g, 5.61 mmol) according to *Method C*. After stirring for 2 h at −78°, the mixture was worked up as usual *(Method A)*: 880 mg (63%) of aldols, 98% of (±)-**14e** and 2% of (±)-**12e** (^{1}H-NMR). Crystallisation (hexane) afforded 570 mg (41%) of pure (±)-**14e**. M.p. 73–74°. IR (KBr): 3080*w*, 3050*w*, 3030*w*, 2990*w*, 2970*m*, 2950*m*, 2930*m*, 2880*w*, 1730*s*, 1690*w*, 1650*w*, 1590*w*, 1480*m*, 1455*s*, 1410*w*, 1375*m*, 1360*m*, 1330*w*, 1295*w*, 1270*w*, 1250*m*, 1170*s*, 1155*s*, 1090*w*, 1080*m*, 1065*w*, 1040*s*, 1010*w*, 990*w*, 975*w*, 910*s*, 895*m*, 835*w*, 780*s*, 750*m*, 725*w*, 700*m*, 570*m*, 550*w*, 530*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.33 (*d*, $J = 7$, CH_3–C(2)); 1.81 (*m*, $w_{1/2} \approx 3$, CH_3–C(4)); 2.16 (*s*, CH_3–C(2'), CH_3–C(6')); 2.43 (*d*, $J = 3.5$, OH); 3.02 (*dq*, $J = 4, 7$, H–C(2)); 4.61 (*dd*, $J = 4, 3.5$, H–C(3)); 5.02, 5.17 (2*m*, 2 H–C(5)); 7.06 (*m*, $w_{1/2} \approx 1.5$, H–C(3'), H–C(4'), H–C(5')).

*2,6-Dimethylphenyl (2*R,*3*R*)-3-Hydroxy-2,4-dimethylpent-4-enoate* (**14e**). Methacrolein (600 µl, *ca.* 7.0 mmol) was added at −78° to an ethereal soln. of **13** prepared from **11** (1.0 g, 5.61 mmol) according to *Method A*. After stirring for 15 h at −78°, the mixture was worked up as usual *(Method A)*: 853 mg (61%) of aldols, 94% of **14e** (93% ee) and 6% of **12e** (70% ee, ^{1}H-NMR, integration of (+)-MTP-ester [18], see below). Crystallisation (hexane) afforded 512 mg of **14e**. M.p. 93–95°. $[\alpha]_D = +42.9$, $[\alpha]_{365} = +149.2$ ($c = 1.01$, $CHCl_3$). IR (KBr): identical spectrum of the crystals of (±)-**14e**. A sample (56 mg) of the crude material was treated with (+)-(*S*)-2-methoxy-3,3,3-trifluoro-2-phenylpropionyl chloride (50 µl) in pyridine (0.5 ml) for 16 h at r.t. [18]. Extractive workup and filtration (silica gel, hexane/AcOEt 8:1) afforded 100 mg of (+)-MTP-ester. ^{1}H-NMR (300 MHz, $CDCl_3$, integration of the signals corresponding to CH_3–C(4)): 1.64 ((2*R*,3*S*)-**12e**, 0.6%); 1.77 ((2*S*,3*S*)-**14e**, 3.3%); 1.81 ((2*S*,3*R*)-**12e**, 3.2%); 1.87 ((2*R*,3*R*)-**14e**, 92.9%).

Reaction of **27** *with Methacrolein.* Methacrolein (645 µl, *ca.* 7.8 mmol) was added at −78° to *ca.* 1/3 of an ethereal soln. of **27** prepared from **11** (2.6 g, 14.61 mmol) according to *Method B*. After stirring for 15 h at −78°, the mixture was worked up as usual *(Method A)*: 590 mg (*ca.* 50%) of aldols, 54% of **12e** (94% ee) and 46% of **14e** (55% ee) (^{1}H-NMR, integration of (+)-MTP-ester [18], see above). The separation of **12e** and **14e** by column chromatography (silica gel) is difficult.

*2,6-Dimethylphenyl (2*RS,*3*RS*)-3-Hydroxy-2-methyl-3-phenylpropanoate* ((±)-**14f**). Benzaldehyde (750 µl, *ca.* 7.4 mmol) was added at −78°, to an ethereal soln. of **15** prepared from **11** (1.0 g, 5.61 mmol) according to *Method C*. After stirring for 3.5 h at −78°, the mixture was worked up as usual *(Method A)*: 1.09 g (68%) of aldols, 98.8% of (±)-**14f** and 1.2% of (±)-**12f** (GLC, *Table 4*). Crystallisation from hexane afforded 853 mg (53%) of (±)-**14f**. M.p. 105–106°. IR (KBr): 3080*w*, 3060*w*, 3030*w*, 2980*w*, 2950*w*, 2940*w*, 2910*w*, 2880*w*, 2860*w*, 1730*s*, 1480*m*, 1455*m*, 1380*m*, 1365*m*, 1310*m*, 1270*w*, 1245*m*, 1200*w*, 1170*s*, 1160*s*, 1090*w*, 1070*m*, 1040*s*, 1020*m*, 970*w*, 915*w*, 890*m*, 850*w*, 830*m*, 775*m*, 765*s*, 745*w*, 700*s*, 670*w*, 630*w*, 550*w*, 530*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.38 (*d*, $J = 7$, CH_3–C(2)); 2.0 (*m*, $w_{1/2} \approx 9$, CH_3–C(2'), CH_3–C(6')); 2.3–2.9 (br., OH); 3.15 (*dq*, $J = 5, 7$, H–C(2)); 5.23 (*d*, $J = 5$, H–C(3)); 7.03 (*m*, $w_{1/2} \approx 3$, H–C(3'), H–C(4'), H–C(5')); 7.25–7.5 (*m*, C_6H_5–C(3)).

*2,6-Dimethylphenyl (2*R,*3*R*)-3-Hydroxy-2-methyl-3-phenylpropanoate* (**14f**). Benzaldehyde (740 µl, *ca.* 7.3 mmol) was added at −78° to an ethereal soln. of **13** prepared from **11** (1.007g, 5.65 mmol) according to *Method A*. After stirring for 2 h at −78°, the mixture was worked up as usual *(Method A)*: 1.33 g (82%) of aldols, 96.3% of **14f** (94% ee) and 3.7% of **12f** (GLC, *Table 4*). M.p. (hexane, 97% ee) 130–131°. $[\alpha]_D = +2.3$, $[\alpha]_{365} = -12.9$ ($c = 1.19$, $CHCl_3$). IR (KBr): identical to the spectrum of (±)-**14f**.

*2,6-Dimethylphenyl (2*S,*3*R*)-3-Hydroxy-2-methyl-3-phenylpropanoate* (**12f**). Benzaldehyde (740 µl, *ca.* 7.3 mmol) was added at −78° to an ethereal solution of **27** prepared from **11** (997 mg, 5.6 mmol) according to *Method B*. After stirring for 15 h at −78°, the mixture was worked up as usual *(Method A)*: 1.174 g (73%) of aldols, 77% of **14f** (47% ee) and 23% of **12f** (94% ee) (GLC, *Table 4*). Chromatography (silica gel, hexane/AcOEt 6:1) afforded 51 mg of **12f**, 449 mg of **12f**/**14f**, and 432 mg of **14f**. M.p. (hexane) 56.5–59.5°. $[\alpha]_D = +55.1$, $[\alpha]_{365} = +189.4$ ($c = 0.63$, $CHCl_3$, 94% ee). IR (KBr): 3060*w*, 3030*m*, 2980*m*, 2950*w*, 2920*m*, 2880*w*, 2860*w*, 1723*s*, 1605*w*, 1480*m*, 1450*s*, 1410*w*, 1375*s*, 1365*m*, 1330*w*, 1310*w*, 1265*m*, 1245*m*, 1195*m*, 1175*s*, 1155*s*, 1085*m*, 1050*s*, 995*m*, 940*m*, 915*w*, 870*m*, 850*w*, 830*m*, 780*s*, 760*m*, 745*m*, 715*m*, 700*s*, 685*m*, 630*w*, 580*m*, 530*m*, 510*m*, 500*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.28 (*d*, $J = 7$, CH_3–C(2)); 2.12 (*m*, $w_{1/2} \approx 5$, CH_3–C(2'), CH_3–C(6')); 2.5–3.2 (br., OH); 3.16 (*dq*, $J = 8.5, 7$, H–C(2)); 4.87 (*d*, $J = 8.5$, H–C(3)); 7.07 (*m*, $w_{1/2} \approx 3$, H–C(3'), H–C(4'), H–C(5')); 7.2–7.5 (*m*, C_6H_5–C(3)).

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