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Diastereoselective addition of methylmetal reagents to 2-methylaldehydes

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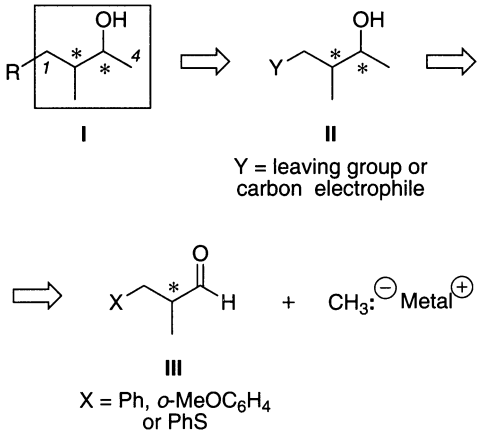
Abstract—The preparation of compounds incorporating the 3-hydroxy-2-methyl-1-butyl moiety of high diastereomeric purity is described. These compounds can serve as potential building blocks for the preparation of several kinds of natural products. The diastereoselective addition of a number of methylmetal derivatives to three 3-substituted 2-methylaldehydes in various solvents was studied. An excellent diastereomeric ratio (95:5 anti-Cram/Cram) was obtained with 2-methyl-3-(phenylsulfanyl)propanal (**5**) and Me_2Zn in the presence of $TiCl_4$.

1. Introduction

A number of natural products, such as some pheromones[1] and antibiotics[2] contain the stereoisomerically pure 3-hydroxy-2-methyl-1-butyl moiety shown in **I** and **II** (Scheme 1) and various approaches are available for the synthesis of such compounds.[1–3] Our interest in the development of new methods for the preparation of compounds of type **II** is related to the synthesis of pine sawfly sex pheromones, which are esters of pure stereoisomers of type **I** (R=methyl branched alkyl group). If an efficient and highly diastereoselective addition of a methyl moiety to chiral aldehydes of type **III** could be accomplished, we would have easy access to synthons of type **II** for further transformation to targets of type **I**.



Scheme 1. Retrosynthetic analysis for target **I** derived from the isomerically pure 3-hydroxy-2-methyl synthon **II**. *=stereogenic center of defined configuration (relative or absolute).

The nucleophilic addition of an organometallic reagent to a carbonyl group is one of the most powerful and reliable methods of carbon–carbon bond formation known in organic synthesis. When the carbonyl compound has diastereotopic faces, diastereoselective reactions are possible and they usually proceed according to Cram's rule.[4] Since its introduction in 1952, the models for open chain systems have been further developed by, among others, Cornforth, Karabatsos, Felkin and Ahn.[5] In simple systems, all models predict the formation of the same major diastereomer, the so-called Cram-product. For carbonyl compounds incorporating a suitably placed heteroatom (for example O, N or S in the α-, β-, or γ-position) chelation can occur. In such cases, the addition usually proceeds according to Cram's cyclic model, which leads to the so-called anti-Cram-product.[4,6] Since the introduction of that latter model, many new chelation-controlled diastereoselective carbonyl additions have been developed.[7]

A frequently used non-chelating substrate for the study of the diastereoselectivity in 1,2-additions of organometals is 2-phenylpropanal. It has been shown that such reactions proceed according to Cram's rule.[8] Aliphatic 2-methylaldehydes have also been investigated. The diastereoselectivity obtained in methyl-Grignard reactions of e.g. 2,6,10-trimethyldodecanal and 2-methylbutanal is 70:30 and 55:45 (Cram/anti-Cram), respectively.[1e,9]

2. Results and discussion

The objective of this investigation was to find a suitable

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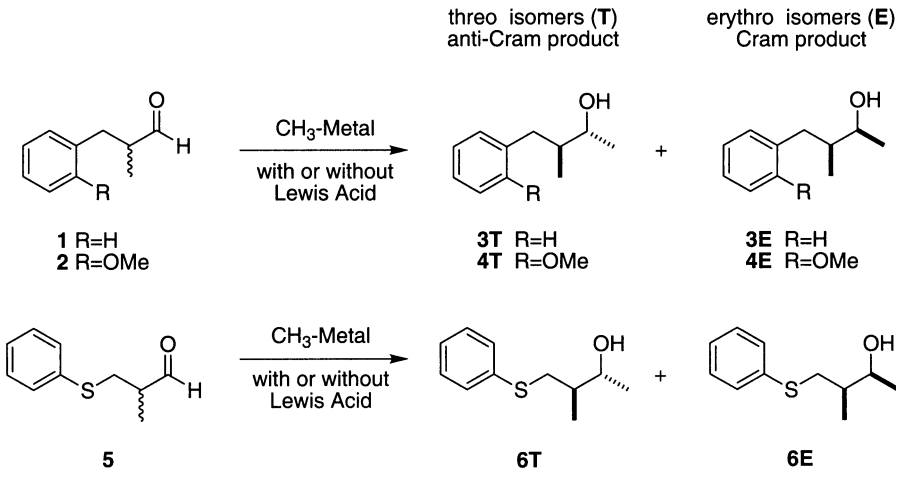


Scheme 2. Preparation of mixtures of the *threo* and *erythro* isomers (**T** and **E**, respectively) of compounds **3**, **4** and **6**.

substituent X in compounds of type **III** and appropriate reaction conditions for transforming them into diastereomerically highly enriched products of type **II**, which could then be converted into either of the following three alternatives where X is transformed into (a) an electrophilic carbon e.g. a carbonyl carbon, (b) a good leaving group or (c) a group which renders the adjacent carbon nucleophilic.

Many types of aryl groups (X=Ar) can be transformed into carboxylic acids through oxidation with $RuCl_3$–$NaIO_4$, which converts the substituent (X=Ar) into an electrophilic carbonyl group (e.g. X=COOR). In the 1,2-additions studied here, aryl groups are, in general, not able to form chelated intermediates. However, provided the aryl group is properly substituted (for example X=*o*-$MeOC_6H_4$), chelation could potentially occur. On the other hand, if X itself is a donor group (e.g. X=PhS), chelation might also be expected to take place. In the latter case, the resulting addition product would contain a PhS-group, which after further transformation, could serve as a leaving group, making the adjacent methylene carbon electrophilic. Alternatively, after oxidation to X=$PhSO_2$, the same carbon would become nucleophilic after deprotonation.

We have studied the reactions of various methylmetals with aldehydes **1**, **2** and **5** (Scheme 2) in various solvents with or without added chelating agents (Table 1). In this study, 2-methyl-3-phenylpropanal (**1**) served as the reference for a non-chelating substrate. The identification of the diastereomeric products was made by transformation of these into mixtures of the known[1a] 3,4-dimethyl-γ-butyrolactone diastereomers.

In accordance with earlier results[9,10] the reactions of aldehyde **1** (Table 1: entries 2, 6 and 8) demonstrated that the steric effects were very small in this case. Karabatsos[11] has pointed out that the differences in conformational energies between the three main conformations are small

Table 1. Diastereomeric ratios (dr) obtained when reacting methylmetal reagents with aldehydes **1**, **2** and **5** either with or without added Lewis acids

Entry[a]	Reagent	Equiv. MeMetal (Lewis acid)	Substrate	Temperature (°C)	Dr[b] **T/E** (anti-Cram/Cram)	Solvent
1	MeLi	1.5	2	−70	60:40	Et_2O
2	MeLi	1.5	1	−70	50:50	Et_2O
3	MeLi	1.5	2	−70	65:35	THF/Cumene[c]
4	MeLi	1.5	2	−100	60:40	Et_2O
5	MeMgBr	1.5	2	−50	55:45	Et_2O
6	MeMgBr	1.5	1	−50	47:53	Et_2O
7	MeTi(O-*i*-Pr)$_3$	1.5	2	−40	46:54	Et_2O
8	MeTi(O-*i*-Pr)$_3$	1.5	1	−40	54:46	Et_2O
9	(1)$TiCl_4$, (2)Me_2Zn	(1.0)1.6	2	−70	45:55	CH_2Cl_2[d]
10	Me_2TiCl_2	1.5	2	−70	39:61	CH_2Cl_2[d]
11	MeLi	1.5	5	−70	65:35	Et_2O
12	(1)$TiCl_4$, (2)MeLi	(1.0)1.6	5	−70	58:42	Et_2O
13	MeLi	1.5	5	−70	56:44	CH_2Cl_2[d]
14	(1)$TiCl_4$, (2)MeLi	(1.0)1.6	5	−70	69:31	CH_2Cl_2[d]
15	Me_2TiCl_2	1.5	5	−70	79:21	CH_2Cl_2[d]
16	(1)$TiCl_4$, (2)Me_2Zn	(1.01.6)	5	−70	95:05	CH_2Cl_2[d]
17	(1)$TiCl_4$, (2)Me_2Zn	(2.0)1.6	5	−70	95:05	CH_2Cl_2[d]
18	(1)$TiCl_4$, (2)Me_2Zn	(0.5)1.6	5	−70	86:14	CH_2Cl_2[d]
19	Me_2Zn	1.5	5	−70	–[e]	CH_2Cl_2[d]

[a] Yields were in range of 40–95%, according to GC and in entry 16 the isolated yield was 85%.
[b] Diastereomeric ratio was determined by GC analysis on the alcohol products **3** and **4**, or on the butyrate of alcohol product **6**.
[c] Proportions: 10/90.
[d] Mixed with a small amount (3–6 vol%) of the solvent from the methylmetal reagent.
[e] Only starting material was isolated.

in cases like this, thereby leading to transition-states of similar energy. This could explain the poor selectivity observed.

These results indicated that a chelating substrate would probably lead to an improved selectivity. Screening experiments with 3-(2-methoxyphenyl)-2-methylpropanal (**2**) were performed. The diastereoselectivity obtained with aldehyde **2** was in the range from 39:61 to 65:35 (anti-Cram/Cram, see Table 1). When attacking an aldehyde, $MeTi(O\text{-}i\text{-}Pr)_3$ is a known non-chelating reagent.[12] In our hands, this reacted with **2** to give a low preference for the Cram-product (entry 7). In comparison with the phenyl substituted aldehyde **1**, the substrate **2** should be more sterically demanding. This could explain the product distributions observed. On the other hand, a good chelating reagent such as MeMgBr,[13] furnished a slightly increased anti-Cram diastereoselectivity from 47:53 for compound **1** to 55:45 for compound **2** (entry 6 and 5, respectively). When using some other complex methylmetal reagents or Lewis acids [e.g. $MeYb(OTf)_2$, $MeCeCl_2$, $CeCl_3$, Me_2CuLi, $MeZrCl_3$, $ZrCl_4$],[14] the diastereoselectivity was not improved. The highest anti-Cram/Cram ratio (65:35) was observed with MeLi in THF/Cumene (entry 3).

Although chelates might be involved in the transition-state in some of the reactions with 2-methoxyphenyl substituted aldehyde **2**, the resulting eight-membered ring system would be relatively flexible leading to several possible transition states of similar energy. This probably explains the modest improvements in selectivity observed, when switching from substrate **1** to **2**. The product distribution could also be due to solvent effects[15] or the nature of the Lewis acid used. When for example $TiCl_4$ in CH_2Cl_2 was used, a certain extent of complex formation could occur with binding to the carbonyl oxygen only. This would lead to a higher population of the Felkin–Ahn conformation[16] in the transition state, which would favor the formation of the Cram-product.

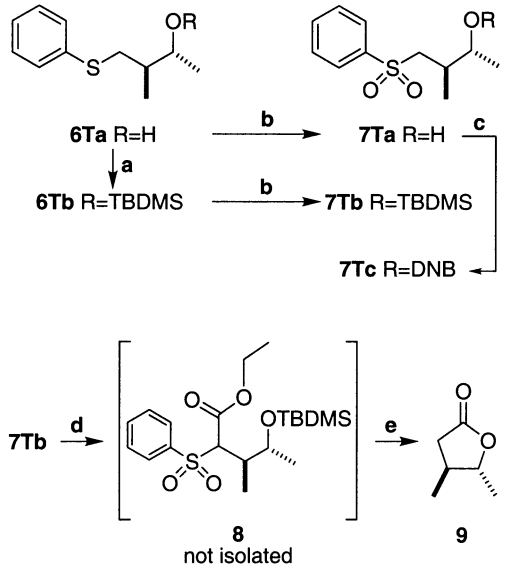
Because poor diastereofacial control was obtained from the additions of methylmetal reagents to both substrates **1** and **2**, we turned our attention to another substrate with the potential for better chelation control. In accordance with earlier observations made with some substrates containing sulfur,[7j] a suitably placed sulfur atom in an aldehyde substrate would be expected to promote chelation with a Lewis acid. The readily available 2-methyl-3-(phenylsulfanyl)propanal (**5**)[17] could serve as such a substrate which, in the presence of a Lewis acid would form a chelate between the carbonyl oxygen and the sulfur atom. After addition of a methylmetal reagent, a six-membered ring transition state would form. This would react to give a building block of type **II** (Scheme 1), namely compound **6** favoring one diastereomer, either **6T** or **6E**. The preparation of various stereoisomers of compound **6** have been described earlier.[18–20]

This hypothesis was confirmed experimentally, because in the reactions of various methylmetal reagents with aldehyde **5**, the anti-Cram-product **6T** was in excess in all cases (entries 11–18, Table 1). This indicated that chelation occurred even in the absence of an added chelating agent. When adding such an agent, the diastereomeric ratios were improved in some cases (compare e.g. entries 13 and 14) and not in others (entries 11 and 12).

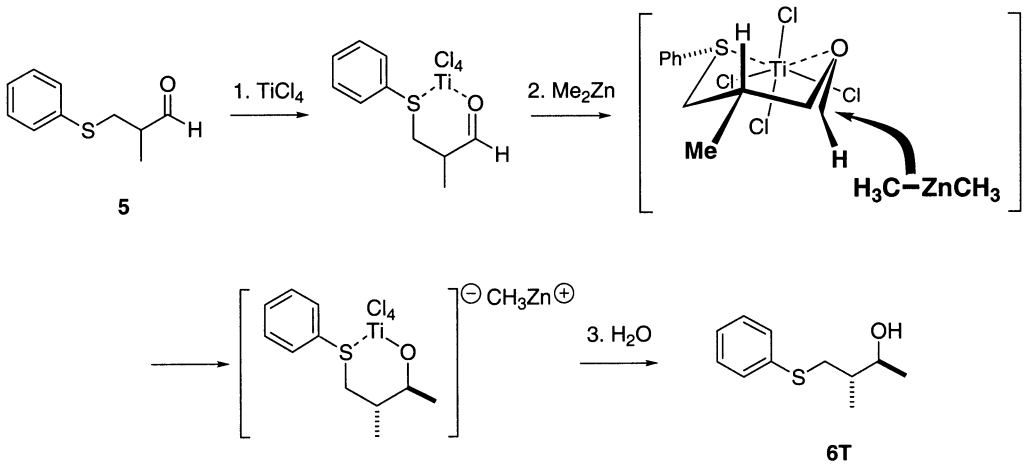
It is known that dimethylzinc is unable to add to aldehydes without activation (confirmed in entry 19).[21] However, in the presence of 1 equiv. of $TiCl_4$ in CH_2Cl_2 at a low temperature aldehyde **5** reacted readily with dimethylzinc. The product **6** was obtained in an excellent diastereomeric ratio (95:5 **6T/6E**, entry 16). Using 0.5 equiv. of $TiCl_4$ relative to the substrate (entry 18) gave a lower diastereoselectivity, whereas increasing it from 1.0 to 2.0 equiv. (entry 17) did not influence the selectivity (cf Ref. 16).

When using Me_2TiCl_2 as the reagent (entry 15), the diastereomeric ratio was somewhat lower, probably caused by competition between the intermolecular addition pathway (as is the case for entry 16) and an 1,3-intramolecular migration.[22] When using $TiCl_4$ followed by MeLi, we obtained a low diastereoselectivity. In this case, the potential cyclic chelate was probably decomposed, leading to an open chain intermediate and hence a poor selectivity. When screening other Lewis acids[7b–f,14,23] with Me_2Zn and compound **5**, either the diastereoselectivity was low or no product was obtained.

In order to confirm the relative configurations of the stereogenic centres in the major secondary alcohol product **6T**, its ^1H NMR spectrum was compared with those of the previously known diastereomers, **6E** and **6T**. The spectra of these were previously known to display different coupling constants for some protons.[18,19] Our major product showed shifts and coupling constants identical with those of **6T**. Similarly, the ^1H NMR spectrum of the known acetate[20] of **6E** was also used for stereoisomer assignment. From these comparisons we concluded that the major diastereomer obtained from the dimethylzinc–$TiCl_4$-reaction with compound **5** was the anti-Cram-product, **6T**.



Scheme 3. Isomers **6–9E** are epimeric at C2 and are not shown. Reactions: (a) TBDMSCl, CH_2Cl_2, Et_3N. (b) *m*-CPBA, CH_2Cl_2. (c) 3,5-Dinitrobenzoyl chloride, pyridine, C_6H_6. (d) 1. *n*-BuLi, THF, −78°C. 2. Ethyl chloroformate. (e) 1. Li, NH_3, −78°C. 2. $PhCO_2Na$. 3. MeOH, HCl, Δx.



Scheme 4. Proposed mechanism for the formation of compound **6T** in the $TiCl_4$ catalyzed reaction of aldehyde **5** with dimethylzinc.

In order to obtain a diastereomerically pure derivative of **6T**, a crystalline compound was desirable. After oxidation to the sulfone **7Ta** (Scheme 3), the 3,5-dinitrobenzoate was prepared and recrystallized to give the diastereomerically pure compound **7Tc** (mp 128–130°C). The epimeric dinitrobenzoate, the *erythro*-diastereomer **7Ec**, is a known compound (mp 156.5–158°C).[20] The ^{1}H NMR spectra of the two compounds were very similar except for the peak at 5.2 ppm, where our compound, **7Tc**, displayed an apparent quintet with a coupling constant of 6.3 Hz whereas **7Ec** had been reported[20] to display a doublet of quartets (J=3.8 and 6.6 Hz) at 5.3 ppm.

In order to establish unambiguously the relative configuration of *threo*-**6T** and *erythro*-**6E**, 3,4-dimethyl-γ-butyrolactone (**9**) was synthesized from a mixture of both (Scheme 3). The alcohol **6** (**T/E** ratio 61:39) was protected as its *tert*-butyldimethylsilylether **6b**. After oxidation with *meta*-chloroperbenzoic acid, the sulfone **7b** was obtained. Acylation with ethyl chloroformate of the α-sulfonyl carbanion generated from **7b** furnished **8**. Removal of the phenylsulfonyl group was accomplished with lithium in liquid ammonia. Subsequent hydrolysis gave the target lactone **9** (*trans*/*cis*-ratio: 65:35 by GC, when compared with authentic samples of both the *cis*- and *trans*-lactone **9**[1a]).

We demonstrated above that the diastereoselective addition of Me_2Zn to 2-methyl-3-(phenylsulfanyl)propanal (**5**) with $TiCl_4$ as a Lewis acid catalyst, furnished the addition product **6T** in an excellent diastereomeric ratio (95:5 anti-Cram/Cram). Because experiments made it clear that an equimolar amount of $TiCl_4$ relative to the substrate was needed, this indicated that the reaction took place via a 1:1 substrate/Lewis acid complex. Because the effect of a lower amount of Lewis acid was lower selectivity, it appeared as if the catalyst was still bound as a 1:1 alkoxy-complex in the product. This complex could in turn function as a Lewis acid catalyst, but with lower selectivity explaining the results obtained when using less than an equimolar amount of the catalyst. We tentatively suggest that the reaction between compound **5**, $TiCl_4$ and dimethylzinc in CH_2Cl_2 proceeds via the path described in Scheme 4.

Thus, we have established an efficient method for acquiring a possible building block [the *threo*-isomer of the 3-hydroxy-2-methyl-1-butyl moiety **II** (Scheme 1)], which should be useful for the preparation of various natural products. Because the building block we prepared is racemic, an efficient resolution strategy for this is needed. Lipase catalysis has proved very efficient for compounds of this type. Alternatively, methods for preparing the starting aldehyde **5** enantiomerically pure should be developed. At present, we are studying these routes.

3. Experimental

3.1. General experimental procedure

Commercially available chemicals were used without further purification unless otherwise stated. Me_2Zn was purchased as a 2.0 M solution in toluene, MeLi as a 1.6 M solution in Et_2O or as a 1.0 M solution in THF/Cumene (10:90) and MeMgBr as a 3.0 M solution in Et_2O. All dried materials were stored under argon. Commercially available anhydrous $CeCl_3$ was heated at 1 mbar at 140°C for 3 h before use. Et_2O ($LiAlH_4$), THF (K, benzophenone), CH_2Cl_2 (CaH_2) and toluene (CaH_2) were distilled from the indicated drying agents. Preparative liquid chromatography (LC) was performed on straight phase silica gel (Merck 60, 230–400 mesh, 0.040–0.063 mm) employing a gradient technique using an increasing concentration (0–100%) of distilled Et_2O in distilled pentane or of distilled ethyl acetate in distilled cyclohexane, as eluent. The progress was followed by thin layer chromatography or GC. NMR spectra were recorded on a Bruker DMX 250 (250 MHz ^{1}H and 62.9 MHz ^{13}C) spectrometer using $CDCl_3$ as solvent and TMS as internal reference. The diastereoisomeric ratio of the alcohols **3** and **4** were determined using a Varian 3700 gas chromatograph equipped with a CP-Wax 52CB, 30 m, 0.25 mm i.d. d_f=0.25 μm, carrier gas He, 15 psi, split 1:30. (GC programme: 130°C/1 min, 3°C/min, 175°C). The *cis*/*trans* ratio of the diastereomeric mixture of 3,4-dimethyl-γ-butyrolactone was determined using a 30 m, 0.25 mm i.d. capillary column coated with CP-Sil 19CB, d_f=0.25 μm; carrier gas N_2~100 kPa, split 30:1. The diastereoisomeric ratio of the butyrates of alcohol **6** was determined using a

Varian 3700 gas chromatograph equipped with a CP-Sil 88, 50 m, 0.25 mm i.d. d_f=0.20 μm, carrier gas He, 15 psi, split 1:30. (GC programme: 100°C/3 min, 1°C/min, 200°C). Retention time (min): 90.0 (*threo* isomer, butyrate of **6T**) and 90.6 (*erythro* isomer, butyrate of **6E**). Mass spectra were recorded on a Saturn 2000 instrument, operating in the EI or CI (CH_3CN as chemical ionization gas) mode, coupled to a Varian 3800 GC instrument. Boiling points are uncorrected, and those marked with BTB are given as air-bath temperatures (bath temperature/mbar) in a bulb-to-bulb (BTB, Büchi-GKR-51) apparatus. Elemental analysis was performed by Mikrokemi AB, SE-752 28 Uppsala, Sweden.

3.2. Preparation of starting materials

3.2.1. 3-(2-Methoxyphenyl)-2-methylpropanal (2). *o*-Anisaldehyde (50 g, 368 mmol) was added to a solution of KOH (21 g, 370 mmol) in EtOH (300 mL, 95%) and cooled to 0°C. Propanal (35 g, 606 mmol) was added at a speed so that the temperature did not exceed 10°C and then stirred for 3 h. After addition of HCl (50 mL, 6 M, aq.) and extraction with Et_2O (3×75 mL) the organic layer was dried ($MgSO_4$) and concentrated to give an oil. After distillation, (bp 125–130°C/3.0 mbar), (2*E*)-3-(2-methoxyphenyl)-2-methylprop-2-enal (44.0 g, 68%) was obtained. This (30.0 g, 170 mmol) in MeOH (500 mL) was stirred with a suspension of Raney nickel in water (~20 g) under H_2 at room temperature during 15 h. The suspension was filtered and the solid collected was washed thoroughly with MeOH (5×50 mL). The solvent was evaporated off and the resulting mixture, containing the product and remaining starting material, was dissolved in Et_2O (250 mL) and shaken with $Na_2S_2O_5$ (11×35 mL, sat. aq.). The pH of the combined aqueous phase was adjusted to ~9 using NaOH (5 M, aq., ~50 mL). Extraction with ether (3×100 mL) followed by drying ($MgSO_4$) and concentration furnished a colorless oil (14.0 g, 46%), 98% pure by GC. Bp 80–85°C/2.0 mbar (lit.[24] 113–114°C/6.7 mbar), $n^{21}{}_D$ 1.5195. The ^1H NMR spectral data was similar to that reported in the literature.[25]

3.3. General procedures for the methylmetal addition reactions

3.3.1. 3-Methyl-4-phenylbutan-2-ol (3), 4-(2-methoxyphenyl)-3-methylbutan-2-ol (4) and 3-methyl-4-(phenylsulfanyl)butan-2-ol (6). *(a) Entries 1–6, 11, 13 and 19, Table 1.* The appropriate aldehyde (1.0 mmol) in freshly distilled dry solvent (2.0 mL) was added dropwise to the methylmetal reagent (1.5 mmol) in the same solvent (5.0 mL) at a given temperature (see Table 1). The reaction was stirred at that temperature for 10 min and at room temperature for 1.5 h. NH_4Cl (5 mL, sat. aq.) was added followed by HCl (3 mL, 3 M, aq.). Extractive work-up with Et_2O (3×10 mL), $NaHCO_3$ (20 mL, sat. aq.), H_2O (20 mL) and brine (20 mL), followed by drying ($MgSO_4$) and solvent removal in vacuo furnished the product.

(b) Entries 7–8, 10 and 15, Table 1. $TiCl_4$[26] or $TiCl(O\text{-}i\text{-}Pr)_3$[27] (1.5 mmol) was dissolved in freshly distilled solvent (10 mL) and cooled to −70°C. Dropwise addition of a MeLi or Me_2Zn[28] (entries 10 and 15) solution (see Section 3.1) (1.5 mmol), followed by dropwise addition of the appropriate aldehyde (1.0 mmol) in the specified solvent (2.0 mL) at the specified temperature (see Table 1). The reaction was stirred at that temperature for 4 h and worked up as above.

(c) Entries 9, 12, 14 and 16–18, Table 1. $TiCl_4$ (1.0 mmol, except for entries 17 and 18 there the equivalents of Lewis acid were 2.0 and 0.5 mmol, respectively) was added to the appropriate aldehyde (1.0 mmol) in the specified solvent (15 mL) at −70°C. After the mixture was stirred at that temperature for 20 min, a solution (see above) of the appropriate methylmetal reagent (1.6 mmol) was added dropwise at −78°C and stirred for 4 h and worked up as above.

3.4. Description of specific compounds

3.4.1. 3-Methyl-4-phenylbutan-2-ol (3). (Entry 6, *erythro*/*threo*, **3E/3T**, 53:47). $n^{21}{}_D$ 1.5164 (lit.[29] 1.519), bp 85°C/0.5 mbar (BTB) (lit.[29] 124°C/14.7 mbar). ^1H NMR: δ 7.32–7.16 (5H, m), 3.79–3.67 (1H, m), 2.92–2.78 (1H, m), 2.44–2.30 (1H, m), 1.88–1.73 (1H, m), 1.36 (1H, br s, OH), 1.21 (1.41H, d, *J*=6.3 Hz), 1.20 (1.59H, d, *J*=6.3 Hz), 0.86 (1.59H, d, *J*=6.9 Hz), 0.83 (1.41H, d, *J*=6.8 Hz) ppm. ^1H NMR was similar to that reported in the literature.[30] ^{13}C NMR: 141.3, 129.2, 128.3, 125.8, 71.4, 70.3, 42.3, 41.8, 39.3, 39.1, 20.6, 19.8, 14.6, 13.5 ppm. MS (EI): *m*/*z* 146 (100) $(M-H_2O)^+$, 131 (68), 91 (13). Retention time (min.): 14.6 and 15.2 for *erythro* (**3E**) and *threo* (**3T**), respectively.

3.4.2. 4-(2-Methoxyphenyl)-3-methylbutan-2-ol (4). (Entry 5, *threo*/*erythro*, **4T/4E**, 55:45). $n^{21}{}_D$ 1.5210. Bp 130°C/0.7 mbar (BTB). ^1H NMR: δ 7.23–7.11 (2H, m,), 6.94–6.85 (2H, m), 3.84 (3H, d, *J*=1.6 Hz), 3.67–3.54 (1H, m), 2.90–2.74 (1H, m), 2.55 (0.45H, dd, *J*=7.7 and 13.4 Hz), 2.39 (0.55H, dd, *J*=7.0 and 13.3 Hz), 2.20 (1H, br s, OH), 1.86–1.68 (1H, m), 1.17 (1.35H, d, *J*=6.3 Hz), 1.12 (1.65H, d, *J*=6.4 Hz), 0.93 (1.65H, d, *J*=6.8 Hz), 0.85 (1.35H, d, *J*=6.9 Hz) ppm. ^{13}C NMR: 157.3, 131.3, 131.0, 129.3, 127.2 (2C), 120.8, 120.4, 110.3 (2C), 71.2, 68.6, 55.4, 41.1, 40.9, 33.5, 33.1, 19.9, 19.7, 15.3, 13.5 ppm. MS (EI): *m*/*z* 194 (100) (M^+), 177 (27), 121 (44). Anal. Calcd for $C_{12}H_{18}O_2$: C 74.2; H 9.3. Found: C 74.5; H 9.4.

The racemic *threo*-isomer **4T** of the alcohol can be separated from the *erythro*-one (**4E**) through LC. The diastereomers were identified by comparison of ^1H NMR of the mixture to that of the pure *threo* isomer. GC-retention time (min): 22.6 and 24.4 for **4T** and **4E**, respectively. Identification of the *erythro*-/*threo*-isomers of **4** (and also of **3**) was performed through a preparation of 3,4-dimethyl-γ-butyrolactone from the alcohol**4** (and **3**) via acylation, followed by $RuCl_3/NaIO_4$ oxidation and acid catalysed lactone formation following a reaction sequence described for a different 3-aryl-2-methylalcohol.[31] The retention times of the lactone stereoisomers so obtained were compared with those of authentical lactone samples.

3.4.3. (2*R,3*S**)-4-(2-Methoxyphenyl)-3-methylbutan-2-ol (4T).** (*threo*/*erythro*, **4T/4E**, >200:1). $n^{21}{}_D$ 1.5212. Bp 110°C/0.9 mbar (BTB). ^1H NMR: δ 7.23–7.12 (2H, m), 6.94–6.85 (2H, m), 3.84 (3H, s), 3.67–3.60 (1H, m), 2.85 (1H, dd, *J*=8.4 and 13.3 Hz), 2.39 (1H, dd, *J*=6.9 and

13.3 Hz), 2.19 (1H, d, OH, J=4.1 Hz), 1.78–1.68 (1H, m), 1.13 (3H, d, J=6.5 Hz), 0.93 (3H, d, J=6.9 Hz) ppm. ^{13}C NMR: 157.4, 131.0, 129.3, 127.2, 120.8, 110.3, 68.6, 55.4, 40.9, 33.6, 19.9, 13.5 ppm. MS (EI): m/z 194 (100) (M^+), 177 (27), 121 (46).

3.4.4. (2*R,3*R**)-3-Methyl-4-(phenylsulfanyl)butan-2-ol (6T).** Entry 16. 2-Methyl-3-(phenylsulfanyl)propanal[17] (**5**, 12.0 g, 66.7 mmol), was dissolved in CH_2Cl_2 (500 mL) and stirred and cooled to −70°C and then $TiCl_4$ (8.1 mL, 74 mmol) was added dropwise via a syringe. An orange viscous solution was obtained and this was kept at −70°C. After stirring for 1 h, Me_2Zn [49.5 mL (2 M in toluene), 99 mmol] was added dropwise followed by stirring at −70°C. After stirring over night, at which point the temperature had reached 10°C, water (200 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (3×100 mL) and the combined ether extract was washed with $NaHCO_3$ (2×100 mL, sat. aq.), dried (Na_2SO_4). filtered and the solvent was evaporated off, furnishing a yellowish oil (11.0 g, 85%) after LC (EtOAc gradient in cyclohexane), 99% pure by GC. (*threo*/*erythro*; 95:05). ^{1}H NMR: δ 7.37–7.13 (5H, m), 4.04–3.94 (0.05H, m), 3.77 (0.95H, app. quintet, J=6.3 Hz), 3.21 (1H, dd, J=4.6 and 12.8 Hz), 2.79 (1H, dd, J=8.2 and 12.8 Hz), 1.87–1.74 (1H, m), 1.59 (1H, br s, OH), 1.20 (3H, d, J=6.4 Hz), 1.04 (3H, d, J=6.8 Hz) ppm. ^{13}C NMR: 136.9, 128.9 (4C), 125.8, 71.1, 40.2, 37.3, 20.4, 15.4 ppm. MS (EI): m/z 196 (100) (M^+), 179 (10), 123 (2), 109 (4). The ^{1}H NMR and ^{13}C NMR spectral data were similar to those reported in the literature for the *threo*-isomer.[19]

3.4.5. Acetate of (2*R,3*R**)-3-methyl-4-(phenylsulfanyl)-butan-2-ol (acetate of 6T).** Into a solution of **6T** (50 mg, 0.26 mmol) in CH_2Cl_2 (2 mL) acetyl chloride (0.09 mL, 1.3 mmol) was added and the mixture was stirred for 6 h at room temperature. The crude product was concentrated and subjected to LC which gave the product (57 mg, 92%), >99% pure by GC (*threo*/*erythro*; 95:5). ^{1}H NMR: δ 7.36–7.14 (5H, m), 5.07–4.98 (0.05H, m), 4.90 (0.95H, app. quintet, J=6.4 Hz), 3.11 (0.95H, dd, J=4.3 and 12.9 Hz), 3.07 (0.05H, dd, J=5.2 and 12.9 Hz), 2.66 (1H, dd, J=9.0 and 12.9 Hz), 2.03 (3H, s), 1.99–1.89 (1H, m), 1.20 (3H, d, J=6.4 Hz), 1.07 (0.15H, d, J=6.9 Hz), 1.05 (2.85H, d, J=6.8 Hz) ppm. The ^{1}H NMR spectral data was identical to that reported in the literature for the *erythro*-isomer[20] except for the peak at 4.9 ppm, where our ester displayed an apparent quintet with a coupling constant of 6.4 Hz, whereas a doublet of quartets (J=4.0 and 6.6 Hz) at 5.0 ppm was reported for the acetate of **6E**.

3.4.6. (1*R,2*R**)-1,2-Dimethyl-3-(phenylsulfonyl)propyl-3,5-dinitrobenzoate (7Tc).** The oxidation protocol of Nicolau et al.[32] was applied to **6Ta** (1.0 g, 5.10 mmol; **6T**/**6E**-ratio: 93:7), which was dissolved in CH_2Cl_2 (15 mL) and mixed with *m*-CPBA (2.1 g, 12.8 mmol) in CH_2Cl_2 (6 mL) and stirred for 6 h at reflux temperature. Extractive work-up with $NaHCO_3$ (20 mL, sat. aq.), Et_2O (3×15 mL), brine (20 mL), followed by drying (Na_2SO_4) and solvent removal in vacuo furnished crude 3-methyl-4-(phenylsulfonyl)-butan-2-ol (**7Ta**). Without purification and using the protocol of Liu et al.[20] this compound (0.1 g, 0.44 mmol) in pyridine (64 μL, 0.79 mmol) and benzene (2 mL) was mixed with 3,5-dinitrobenzoyl chloride (152 mg, 0.66 mmol) at 0°C. Stirring over night at room temperature followed by extractive work-up with HCl (10 mL, 6 M), Na_2CO_3 (10 mL, sat. aq.), brine (10 mL), drying (Na_2SO_4) and solvent removal in vacuo gave a solid, which after recrystallization from ethanol and toluene furnished the title compound (50 mg, 27%) as colorless crystals; mp 128–130°C (Lit.[20] 156.5–158°C for the *erythro*-isomer) The ^{1}H NMR spectrum was similar with that reported in the literature for the *erythro*-isomer,[20] except for the peak at 5.2 ppm, where our compound displayed an apparent quintet with a coupling constant of 6.3 Hz. ^{13}C NMR: 161.8, 148.7 (2C), 139.5, 134.0, 133.8, 129.5 (2C), 129.4, 127.9 (2C), 122.5 (2C), 76.1, 58.8, 33.4, 16.7, 16.3 ppm. MS (CI, CH_3CN): m/z 423 (5) $(M+H)^+$, 211 (30), 143 (100), 125 (63).

3.4.7. *tert*-Butyl-(1,2-dimethyl-3-(phenylsulfonyl)propoxy)-dimethylsilane (7b). Compound **6a** (0.5 g, 2.55 mmol; **6T**/**6E**-ratio: 69:31) in 5 mL of CH_2Cl_2 was mixed with triethylamine (0.7 mL, 5.1 mmol) and *tert*-butylchlorodimethylsilane (0.77 g, 5.1 mmol) at room temperature, followed by reflux over night. Extractive work-up with Et_2O (3×15 mL), NH_4Cl (20 mL, sat. aq.), brine (20 mL) followed by drying (Na_2SO_4) and solvent removal in vacuo gave a colorless oil (**6b**) (0.50 g, 63%) after distillation, 98% pure by GC. Bp 125°C/0.7 mbar (BTB). This (0.35 g, 1.13 mmol) was oxidized as described above[32] (Section 3.4.6) to give the title compound (0.36 g, 93%), 98% pure by GC. ^{1}H NMR: δ 8.10–7.89 (2H, m), 7.69–7.40 (3H, m), 3.83 (0.31H, dq, J=3.6 and 6.3 Hz), 3.65 (0.69H, dq, J=4.2 and 6.2 Hz), 3.34 (1H, dd, J=2.7 and 14.5 Hz), 2.89–2.78 (0.31H, m), 2.83 (0.69H, dd, J=9.3 and 14.4 Hz), 2.18–1.93 (1H, m), 1.21–0.92 (1.86H, m), 1.10 (2.07H, d, J=6.9 Hz), 1.02 (2.07H, d, J=6.2 Hz), 0.80 (5.49H, s), 0.79 (3.51H, s), 0.01 (3H, s), −0.01 (3H, s) ppm. MS (CI, CH_3CN): m/z 343 (30) $(M+H)^+$, 211 (100), 143 (30), 125 (20). The ^{1}H NMR spectrum was similar to that reported in the literature for the enantiomerically pure *threo* isomer.[33]

3.4.8. 3,4-Dimethyl-γ-butyrolactone (9). We applied the acylation protocol of Gannet et al.[34] to compound **7b** (0.18 g, 0.54 mmol) (**7Tb/7Eb**-ratio: 69:31) dissolved in dry THF (2.5 mL) and stirred at −78°C. *n*-Butyllithium in hexane (0.82 mL, 1.19 mmol, 1.45 M) was added and the resulting solution was stirred at −20°C for 0.5 h and then cooled to −78°C. Ethyl chloroformate (0.15 mL, 1.62 mmol) in THF (2 mL) was added. The resulting mixture was stirred at 0°C for 2 h and then at room temperature over night. Addition of NH_4Cl (5 mL, sat. aq.) followed by extractive work-up with Et_2O (3×15 mL), brine (20 mL) and then drying ($MgSO_4$) and solvent removal in vacuo followed by LC gave 3-methyl-2-phenylsulfonyl-4-tert-butyldimethylsilanyloxy-pentanoic acid ethyl ester (**8**) (0.080 g, 0.19 mmol; 70% pure by GC), MS (CI, CH_3CN): m/z 413 (5) $(M-H)^+$, 283 (75), 223 (32), 141 (100). Without further purification the crude product was subjected to phenylsulfonyl group removal performed according to a slightly modified protocol compared with that described in Trost et al.[35] Thus compound **8** (0.054 g, 0.13 mmol) in Et_2O (1 mL) was added to a slurry of Li (0.1 g,

14.5 mmol) in freshly distilled NH_3 (10 mL) at −78°C. After stirring for 10 min at −78°C, 10 min at −30°C and recooling to −78°C, solid sodium benzoate was added until the blue color discharged. NH_4Cl (5 mL, sat. aq.) and Et_2O (5 mL) were added and the ammonia was allowed to evaporate over night. Extractive work-up with Et_2O (3×15 mL), brine (20 mL), drying ($MgSO_4$) and solvent removal in vacuo furnished the crude product, the TBDMS protected ethyl ester, 3-methyl-4-tertbutyldimethylsilanyloxy-pentanoic acid ethyl ester (0.019 g, 0.07 mmol). To this, which was used without further purification, MeOH (2 mL) and HCl (0.5 mL, 6 M) were added and the reaction was kept under reflux for 12 h, followed by extractive work-up with Et_2O (5×5 mL).After washing with brine (10 mL) and drying ($MgSO_4$), the solvent was distilled off through a column. After careful evaporation of the residual solvent a small amount of the lactone **9** in a diastereomeric ratio of 65:35 (*trans*/*cis* by GC) was obtained. The lactone **9** is very water soluble and therefore difficult to extract from water. Hence, the isolated yield was low. The isomer ratio in our material was established by using GC and GC-MS performed with our material and with authentic samples of *cis*- and *trans*-3,4-dimethyl-γ-butyrolactone (**9**).[1a] Retention time [GC see Section 3.1: isothermal 100°C]: 7.58 and 9.00 min for *trans*-**9** and *cis*-**9**, respectively. The mass spectra obtained from the isomers present in our sample were identical with those obtained from the the authentical samples of lactone **9**.

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