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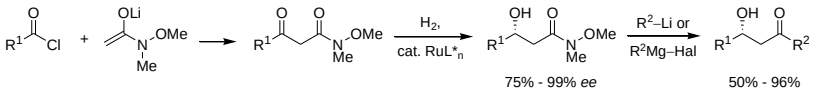
((For Table of Contents:)) Julian Diehl, Reinhard Brückner

Synthesis of Enantiomerically Pure β-Hydroxyketones via β-Keto Weinreb Amides by a Condensation / Asymmetric Hydrogenation / Acylation Sequence

((Short Title)) Preparation and Asymmetric Hydrogenation of β-Keto Weinreb Amides



A condensation route to β-keto Weinreb amides was developed (10 examples). They were hydrogenated in the presence of 0.5 mol-% $[Me_2NH_2]^{\oplus}$ $\{[RuCl(S)\text{-BINAP}]_2(\mu\text{-}Cl)_3\}^{\ominus}$ at 5 bar with up to 99% *ee*. The resulting β-hydroxy Weinreb amides and organolithium or Grignard compounds reacted to give enantiopure β-hydroxyketones in good yields (28 examples). The latter provided *syn*-1,3-diols by Narasaka-Prasad reductions (6 examples) and *anti*-1,3-diols by further hydrogenation (10 examples).

Key Topic for Table of Contents: Asymmetric Hydrogenation

Synthesis of Enantiomerically Pure β-Hydroxyketones via β-Keto Weinreb Amides by a Condensation / Asymmetric Hydrogenation / Acylation Sequence

Dedicated to Professor Gerhard Bringmann at the occasion of his 65th birthday

Julian Diehl[a] and Reinhard Brückner*[a]

Abstract: An established route to enantiomerically pure β-hydroxyketones proceeds via the asymmetric hydrogenation of β-ketoesters, an ester/amide exchange, and employing the resulting β-hydroxyamide for the acylation of an organometallic compound. We shortened this route by establishing that β-keto Weinreb amides are hydrogenated with up to 99% *ee* in the presence of 0.5 mol-% $[Me_2NH_2]^{\oplus}$ $\{[RuCl(S)\text{-BINAP}]_2(\mu\text{-}Cl)_3\}^{\ominus}$ at room temp. / 5 bar. These Weinreb amides were prepared by seemingly obvious yet unprecedented condensations of lithiated *N*-methoxy-*N*-methylacetamide with carboxylic chlorides (51-87% yield). The resulting β-hydroxy Weinreb amides acylated organolithium and Grignard compounds. They provided enantiomerically pure β-hydroxyketones thereby (28 examples). A selection thereof gave an *anti*-1,3-diol after another C=O-bond hydrogenation or a *syn*-1,3-diol by a Narasaka-Prasad reduction.

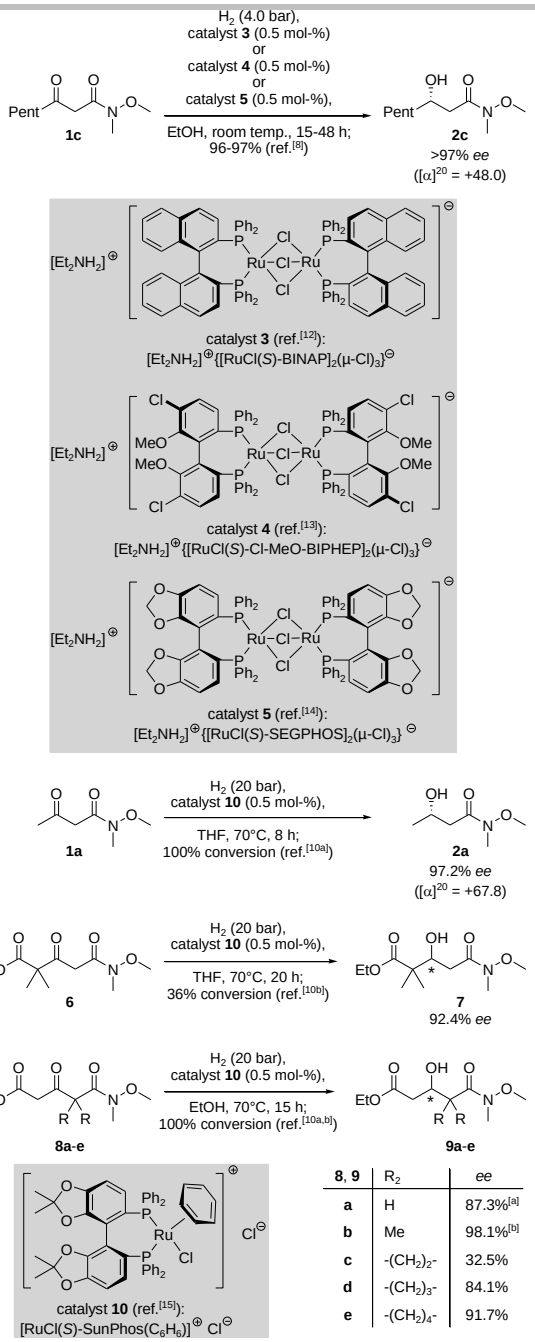
Introduction

Three pivotal contributions of Ryōji Noyori to the field of asymmetric catalysis appeared in the 1980s. One of them disclosed the invention of (*R*)- and (*S*)-BINAP and the aptitude of these ligands to exert entiofacial control in Rh-catalyzed hydrogenations of α-(acylamido)acrylic acids.[1] The second publication described the Ru-catalyzed asymmetric hydrogenation of β-ketoesters in the presence of the same ligands.[2] The third contribution extended such Ru-catalyzed asymmetric C=O-hydrogenations to a variety of other types of ketones with a Lewis-basic coordination site α or β to their carbonyl group.[3] The BINAP ligands and the mentioned hydrogenations were attributed an outstanding importance and immense value.[4] It came with little surprise that they earned their originator his share of the 2001 Nobel Prize in Chemistry.[5]

Noyori´s asymmetric hydrogenations of functionalized ketones[3] affected, besides representatives of other compound classes, a single β-ketoamide, i. e., the *N,N*-dimethylamide of acetoacetic acid. It was hydrogenated in the presence of 0.14 mol-% of (*S*)-BINAP-complexed Ru(II) under 86 bar H_2 pressure at 20-32°C in ethanol solution for 86 h. This provided 100% of the (*S*)-enantiomer of the corresponding β-hydroxyamide with 96% ee.[3] This pioneering reaction did not attract many followers[6] until we reported that 5 bar H_2 pressure suffice for Ru-catalyzed asymmetric hydrogenations of ß-ketoamides at room temp. to go to completion within less than a day.[7] These conditions are generalizable:[8,9] 0.5 Mol-% of the dinuclear Ru(II) complex $[Et_2NH_2]^{\oplus}$ $\{[RuCl(S)\text{-BINAP}]_2(\mu\text{-}Cl)_3\}^{\ominus}$, ethanol as the solvent, 4 bar of H_2 pressure, and reaction times of 14-36 h let β-hydroxyamides become available with over 91% *ee*.[9] Additional β-ketoamides were hydrogenated asymmetrically by Zhang *et al*. using the SunPhos-based Ru(II) catalyst **10** (Scheme 1).[10] Their conditions (20 bar H_2 pressure at 70°C) were harsher than ours. Milder conditions than in the Zhang group but more stringent conditions than in ours – 5-6 bar H_2 pressure at 65°C – allowed the $Ru(OAc)_2[(S)\text{-tol-BINAP}]$-catalyzed enantioselective hydrogenation of a β-keto-γ-lactam.[11]

At the time, our asymmetric β-ketoamide hydrogenations included one β-keto *Weinreb* amide **1c** (Scheme 1, top half).[8] Whether the Ru(II) catalyst contained BINAP (cf. **3**[12a,b]), BIPHEP (cf. **4**[13a,b]) or SEGPHOS (cf. **5**[14]) was inconsequential for the yield (96%) and the enantiomeric purity (>97% *ee*) of the resulting β-hydroxy Weinreb amide (**2c**).[8] Zhang *et al.* hydrogenated β-keto *Weinreb* amides asymmetrically, too (Scheme 1, bottom half).[10] Like us, they studied one "simple" Weinreb amide (**1a**).[10a] Controlled by their Ru(II) catalyst **10**[15] it provided the hydroxy Weinreb amide **2a** with 97% *ee*.[16] Then they proceeded to more complex substrates, i. e., to the ester-containing β-keto Weinreb amides **6**[10b] and **8a-e**.[10a,b] **10**-Catalyzed hydrogenations thereof gave the ester-containing β-hydroxy Weinreb amides **7** and **9a-e**, respectively, with up to 98% *ee*.

Enantiomerically pure β-hydroxy Weinreb amides **2** were recognized as synthetically worthwhile before they became accessible as described above.[17] This is because they acylate organolithium compounds or Grignard compounds yielding enantiomerically pure β-hydroxyketones **18** (Scheme 2).[18a,b] The latter are valuable precursors of enantiomerically pure 1,3-diols **19**, be they *anti*- or *syn*-configured. The β-hydroxy Weinreb amides **2**, which provided the 1,3-diols of the mentioned study,[17] were obtained from enantiomerically pure β-hydroxyesters **17**.[18] This required performing an ester / Weinreb amide exchange **17**→**2** as a preparatory step.

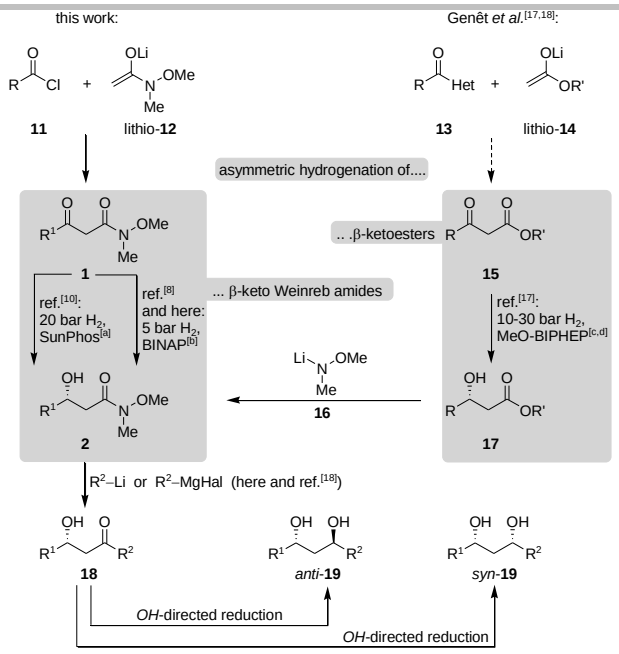


8, 9	R_2	*ee*
a	H	87.3%[a]
b	Me	98.1%[b]
c	-$(CH_2)_2$-	32.5%
d	-$(CH_2)_3$-	84.1%
e	-$(CH_2)_4$-	91.7%

Scheme 1: Literature precedence for the asymmetric hydrogenation of the "simple" β-keto Weinreb amides **1c**[8] und **1a**[10a] and the functionalized β-keto Weinreb amides **6**[10b] und **8a-e**[10a,b].

[a] In THF; [b] H_2 (30 bar), 75°C.

From now on, such an exchange can be obviated. This is because, firstly, β-hydroxy Weinreb amides **2** are broadly accessible by hydrogenating β-keto Weinreb amides **1** asymmetrically. Secondly, β-keto Weinreb amides **1** can be prepared in a hitherto unexploited manner, namely by a C_2 extension of a carboxylic acid chloride with the lithium enolate of *N*-methoxy-*N*-methylacetamide. Both reactions are described in the following. They shorten Genêt´s route to enantiomerically pure β-hydroxyketones **18**, 1,3-diols *anti*-**19**, and 1,3-diols *syn*-**19** by one step (Scheme 2). Making this possible was our objective.



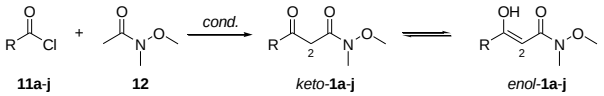
Scheme 2: Synthetic context and objective of this study.

[a] This ligand is a constituent of the catalyst **10** (formula: Scheme 1); [b]this ligand is a constituent of the catalyst **3** (formula: Scheme 1) and was used in ref.[8]. Being commercially available $[Me_2NH_2]^{\oplus}$ {[RuCl(*S*)-BINAP]$_2$(μ-Cl)$_3$}$^{\ominus}$ was employed as a catalyst in the present study, though. It contains the same anion as **3** but a modified cation; [c]this ligand is a constituent of the catalyst **4** (formula: Scheme 1); [d]in reality,[17] this hydrogenation was performed with [Ru(*R*)-MeO-BIPHEP)]Br_2. It incorporates the mirror image of the ligand depicted in Scheme 1. By consequence the β-hydroxyesters **17** and their follow-up products are depicted here with the opposite configurations as published.[17,18]

Results and Discussion

Ten variations **a**-**j** of β-keto Weinreb amides **1** were prepared from one equivalent each of a carboxylic acid chloride **11**, the lithium enolate of *N*-methoxy-*N*-methylacetamide (**12**), and LDA (Table 1). The latter was added such that once the β-keto Weinreb amide – a C,H acid – forms it would not protonate unconsumed lithio-**12** but the stronger base LDA. Enolate lithio-**12** was generated over the course of 90 min from Weinreb amide **12** and LDA at −78°C. The acid chlorides, by which it was acylated, gave the highest yields when they could not – or should not – β-eliminate HCl and form a ketene. Cyclopropylformyl chloride gave 78% yield (→**1f**), pivaloyl chloride 87% (→**1i**), and benzoyl chloride 85% (→**1j**). The lowest yields resulted from acetyl chloride (→ 51% **1a**), hexanoyl chloride (→ 56% **1c**), and *tert*-butylacetyl chloride (→ 57% **1e**)

Table 1: β-Keto Weinreb Amide Syntheses

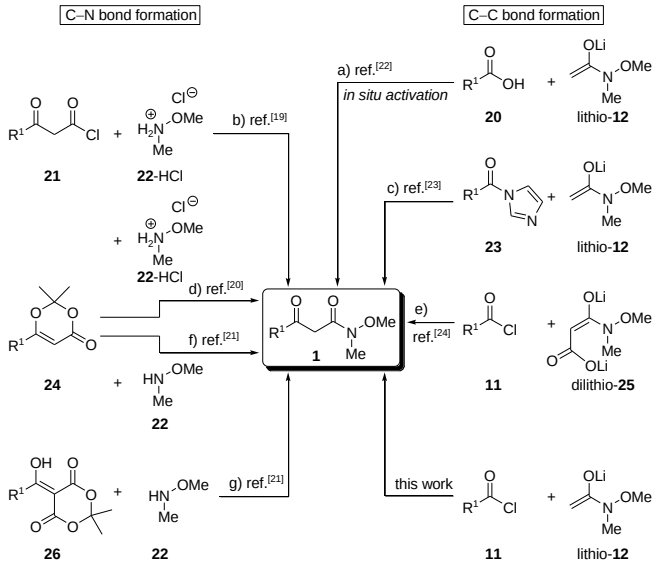


11, **1**	R	*keto*-**1** : *enol*-**1**	$\delta_{2\text{-}H_2}$/ppm in *keto*-**1**	$\delta_{2\text{-}H}$/ppm in *enol*-**1**	δ_{OH}/ppm in *enol*-**1**	Yield/%
a	Me	85 : 15	3.54	5.36	13.69	51

b	Et	88 : 12	3.56	5.39	13.72	65
c	Pent	85 : 15	3.55	5.38	13.71	56
d	*i*PrCH$_2$	77 : 23	3.54	5.36	13.67	69
e	*t*BuCH$_2$	64 : 36	3.55	5.33	13.65	57
f	*c*Pr	96 : 4	3.70	5.51	13.95	78
g	*i*Pr	82 : 18	3.63	5.39	13.77	69
h	*c*Hex	82 : 18	3.61	5.36	13.75	72
i	*t*Bu	77 : 23	3.69	5.44	13.98	87
j	Ph	66 : 34	4.14	6.09	14.24	85

Conditions: *iPr$_2$NH (2.2 equiv.), nBuLi (2.0 equiv., solution in hexane), THF, −78°C, 1 h; addition of* ***12****, −78°C, 1.5 h (→ lithio-****12****); addition of* ***11a-j*** *(1.0 equiv.), −78°C, 3 h.*

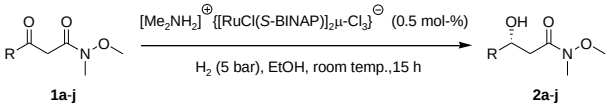
The ^{1}H-NMR data of the resulting β-keto Weinreb amides **1** showed that they were 2:1 – 24:1 mixtures of the keto- and *one* enol-tautomer. It is plausible that the latter possesses a *Z*-configured C=C bond as depicted in formula *enol*-**1** of Table 1.



Scheme 3: Established strategies for making β-keto Weinreb amides (a-g) vs. our own synthesis (bottom right).

A survey of literature syntheses of β-keto Weinreb amides **1** revealed two preferred strategies (Scheme 3): forming a C−N bond between a β-ketocarboxylic acid derivative and either *N*-methoxy-*N*-methylamine (**22**) or its hydrochloride (**22-HCl**; reactions b,[19] d,[20] f,[21] and g[21]) or forming a C−C bond between an acylating agent and a Weinreb amide enolate derived from acetic acid (→ lithio-**12**) or monolithium malonate (→ dilithio-**25**; reactions a,[22] c,[23] and e[24]). Such C−N bond forming routes to β-keto Weinreb amides engaged three β-ketocarboxylic acid derivatives: a β-keto acid chloride (R^1 = Me) **21**,[19] dioxinones (**24**)[20,21] or a *C*-acylated Meldrum's acid (R^1 = Ph) (**26**; the extra carbon is lost as CO_2 during the workup).[21] C−C bond forming routes to β-keto Weinreb amides employed an in-situ activated carboxylic acid **20**,[22] imidazolides **23**[23] or carboxylic acid chlorides **11**[24] as acylating agents. The latter were used exclusively in conjunction with dilithio-**25** as an enolate.[24] The carbon in excess was expelled as CO_2 during the workup. Staying with carboxylic acid chlorides as the most common acylating agent *our* procedure simplifies the nucleophile, too, by employing lithio-**12** (reaction e, Scheme 3) instead of dilithio-**25**.[24,25]

Table 2: Asymmetric β-Keto Weinreb Amide Hydrogenations (*ee* determined by HPLC analysis; the full details of the particular methods are given in the Supporting Information).



1, **2**	R	Yield/%	Sign of specific rotation[a]	Configuration of **2**	*ee*/%
a	Me	98	+	*S*[b]	99.0
b	Et	96	+	*S*[c]	98.8
c	Pent	99	+	*S*[b]	98.9
d	*i*PrCH$_2$	99	+	*S*[c]	98.9
e	*t*BuCH$_2$	96	+	—[d]	85.7
f	*c*Pr	99	+	—[d]	98.9
g	*i*Pr	96	+	*R*[b]	98.7
h	*c*Hex	97	+	*R*[b]	96.3
i	*t*Bu	99	+	*R*[c]	92.8
j	Ph	92	+	*R*[b]	76.8

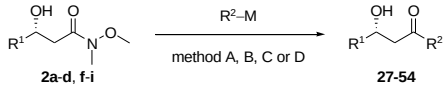
[a] At 589 nm (D-line of Na vapor).– [b] The sign (and magnitude) of our specific rotation allowed to assign this configuration in conjunction with respective references value from the following sources: ref.[10] for **2a**[26], ref. for **2c**, ref.[18b] for **2g**, ref.[27] for **2h**, and ref.[18b] for **2j**.– [c] *This* configurational assignment was made after conversion into a β-hydroxyketone (Table 3) whose the 3D structure could be inferred from comparing *its* specific rotation to a reference value, which the literature gave for specimens of the same β-hydroxyketones *there* obtained: ref.[28] for **32** (which we prepared from **2b**), ref.[29] for **40** (which we prepared from **2d**), and ref.[30] for **52** (which we prepared from **2i**).– [d] No specific rotation value available in the literature.

The β-keto Weinreb amides **1a-j** were hydrogenated at ambient temperature under an H_2 atmosphere of 5 bar in ethanol solution in the presence of 0.5 mol-% of $Me_2NH_2^{\oplus}$ {[RuCl(*S*)-BINAP]$_2$(μ-Cl)$_3$}$^{\ominus}$ (Table 2). After routinely admitted durations of 15 h the β-hydroxy Weinreb amides **2a-j** were the only recognizable compounds. With yields of 96-99%, the enantiomeric purity of the 6 top products amounted to 99% *ee*. This outcome resembles that of asymmetric hydrogenations of analogously substituted β-ketoesters.[2] Our other β-hydroxy Weinreb amides resulted with 96, 93, 86, and 77% *ee*. The last value is low and therefore remindful of the dissatisfactory *ee*-values of equally BINAP-controlled asymmetric hydrogenations of the analogously phenylated ethyl (85% *ee*[2]) or methyl ester (90% *ee*[31]).

We assigned the absolute configuration of eight of the ten β-hydroxy Weinreb amides of Table 2 by comparing their specific rotation – or the specific rotation of a β-hydroxyketone subsequently prepared therefrom (Table 3) – with a reference value from the literature. The geometry was always the same

even if the CIP stereodescriptor varied. This justifies assuming that the two remaining Weinreb amides of Table 2 posses the analogous 3D structures. This would mean that the rule "hydrogenations catalyzed by Ru complexes of *S*-BINAP establish *hashed* C–OH bonds – provided the product is oriented as **2** – " applies not only to such hydrogenations of β-ketoesters[2] and β-keto amides[7b] but to β-keto Weinreb amides as well.

Table 3: β-Hydroxyketone Syntheses



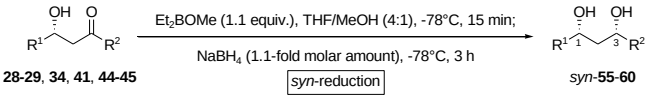
2a-d, **f-i** **27-54**

Entry	Substrate	R^2–M	Method[a]	Sign of specific rotation[b]	Product	Yield/%
1		MeMgI	A	+	**27**	62
2		PhMgBr		+	**28**	70
3	Me **2a**	*n*BuLi	B	+	**29**	68
4		*i*PrLi	C	+	**30**	73
5		*t*BuLi	D	+	**31**	50
6		MeMgI	A	+	**32**	58
7	Et **2b**	PhMgBr		+	**33**	82
8		*n*BuLi	B	+	**34**	77
9		MeMgI	A	+	**35**	96
10	Pent **2c**	PhMgBr		+	**36**	79
11		*n*BuLi	B	+	**37**	73
12		MeMgI	A	+	**38**	84
13	**2d**	PhMgBr		+	**39**	73
14		*n*BuLi	B	+	**40**	74
15		MeMgI	A	+	**41**	81
16	*c*Pr **2f**	PhMgBr		+	**42**	84
17		*n*BuLi	B	+	**43**	74
18		MeMgI	A	+	**44**	92
19	*i*Pr **2g**	PhMgBr		+	**45**	78
20		*n*BuLi	B	+	**46**	81
21		*i*PrLi	C	+	**47**	66
22		MeMgI	A	+	**48**	90
23	cC_6H_{11} **2h**	PhMgBr		+	**49**	91
24		*n*BuLi	B	+	**50**	65
25		cHEXLi	C	+	**51**	74
26		MeMgI	A	+	**52**	88
27	*t*Bu **2i**	PhMgBr		+	**53**	90
28		*n*BuLi	B	+	**54**	88

[a] Method A: RMgX (2.5 equiv., in Et_2O), Et_2O, 0°C, 1 h; room temp.; 1 - 15 h.– Method B: *n*Buli (3.0 equiv., in hexane), THF, −78°C, 3 h; room temp., 0 – 3 h.– Method C: Di-*tert*-butylbiphenyl (0.35 mol-% of R^2Cl), lithium (6.4 equiv.), THF, 0°C, 4 h; R^2Cl (3.2 equiv.), −78°C, 15 h; addition of **2**, −78°C, 1.5 h.– Method D: *t*Buli (3.0 equiv., in pentane), THF, −78°C, 3 h; room temp., 3 h.– [b] at 589 nm (D-line of Na vapor).

Eight of the ten β-hydroxy Weinreb amides **2a-j** from the asymmetric hydrogenations of Table 2 exhibited *ee* values ≥92%. They were used to acylate representative Grignard reagents (MeMgI, PhMgBr) and organolithium compounds (*n*BuLi, *i*PrLi, *c*HexLi, *t*BuLi). This made available a total of 28 enantiomerically pure β-hydroxyketones **27**-**54** in 77% average yield (highest yield 96%, lowest yield 50%; Table 3). Attaining these compounds accomplished our goal of making such compounds available based on catalytic asymmetric hydrogenations of β-keto Weinreb amides **1** and more directly than via the β-ketoester (**15**) hydrogenation route of Genêt et al.[17,18] (Scheme 2).

Table 4: *Syn*-1,3-diol Syntheses.



28-29, **34**, **41**, **44-45** *syn*-**55-60**

Substrate	R^1	R^2	Diol	*Syn:anti* [a]	$\delta_{C\text{-}1}$/ppm $\delta_{C\text{-}3}$/ppm	Sign of specific rotation[b]	Yield/%
29	Me	*n*Bu	*syn*-**55**	100:0	69.3 73.3	+	91
28	Me	Ph	*syn*-**56**	100:0	69.0 75.5	+	93
34	Et	*n*Bu	*syn*-**57**	100:0	73.3 74.7	+	99
41	*c*Pr	Me	*syn*-**58**	100:0	78.0 68.8	+	96
44	*i*Pr	Me	*syn*-**59**	95:5	78.1 69.5	+	93
45	*i*Pr	Ph	*syn*-**60**	100:0	77.8 75.8	+	79

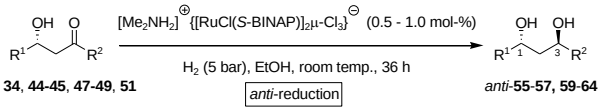
[a]The *syn:anti* ratios are the integral ratios over appropriate ^{1}H-NMR resonances of the *purified* materials; their compositions might vary relative to the composition of the respective crude product; [b] at 589 nm (D-line of Na vapor).

Enantiomerically pure β-hydroxyketones akin to our specimens of **27**-**54** (Table 3) can be processed to sterically homogenous 1,3-diols. This relies on reductants, which exhibit a high facial selectivity because intermittently they bind to the OH group of the substrate. Preparing *syn*-1,3-diols in such a manner the method of choice is the Narasaka-Prasad reduction.[32] We applied it to six β-hydroxyketones from our stock successfully

(Table 4). The 1,3-diols **55**-**58** and **60** resulted uniquely with a *syn*-configuration and the 1,3-diol **59** with a 95:5 preponderance.[33]

The conversion of β-hydroxyketones into *anti*-1,3-diols has been achieved mostly by the Evans(-Saksena) reduction.[34] However, diastereocontrol there is less efficient than in Narasaka-Prasad reductions. According to Genêt *et al.* OH-directed Ru-catalyzed C=O hydrogenations constitute an excellent alternative for such *anti*-reductions.[18a,b] They turn β-hydroxyketones into *anti*-1,3-diols with *ds* up to 99:1 even if the metal usually was complexed with an achiral phosphane, namely PPh_3.[35]

Table 5: *Anti*-1,3-diol Syntheses.



28-29, **34**, **44-45**, **47-49**, **51** — *anti*-**55-57**, **59-64**

Substrate	R^1	R^2	Diol	*Anti:syn* [a]	$\delta_{C\text{-}1}$/ppm $\delta_{C\text{-}3}$/ppm	Sign of specific rotation[b]	Yield /%
29	Me	*n*Bu	*anti*-**55**	100:0	65.7 69.6	+	82
28	Me	Ph	*anti*-**56**	94:6	65.6 72.0	+	99
34	Et	*n*Bu	*anti*-**57**	100:0	69.6 71.0	+	95
44	*i*Pr	Me	*anti*-**59**	100:0	74.1 65.8	+	88
45	*i*Pr	Ph	*anti*-**60**	85:15	74.0 72.0	+	99
47	*i*Pr	*i*Pr	*anti*-**61**	100:0	74.4 74.4	+	93
48	*c*Hex	Me	*anti*-**62**	100:0	73.5 65.8	+	95
49	*c*Hex	Ph	*anti*-**63**	86:14	73.5 72.0	+	88[c]
51	*c*Hex	*c*Hex	*anti*-**64**	100:0	73.8 73.8	+	93

[a] The *anti:syn* ratios are the integral ratios over appropriate ^{1}H-NMR resonances of the *purified* materials; their compositions might vary relative to the composition of the respective crude product; [b] at 589 nm (D-line of Na vapor); [c] 72 h.

We adopted the last-mentioned method for hydrogenating nine β-hydroxyketones from the stock of Table 3 *anti*-selectively (Table 5). For being on the safe side[35] we performed these reactions in the presence of (*S*)-configured BINAP. This ligand was administered as part of our ruthenium source, $Me_2NH_2^{\oplus}$ $\{[RuCl(S\text{-BINAP}]_2(\mu\text{-}Cl)_3\}^{\ominus}$. We assumed that this BINAP enantiomer and whatever enantiomerically pure hydroxyketone from Table 3 we combined led to a matched pair. In this regard our choice of (*S*)-BINAP was in line with the (scarce) literature precedence.[17] However, we did not corroborate our assertion experimentally. We simply found the following: The desired *anti*-1,3-diols *anti*-**55**, *anti*-**57**, *anti*-**59**, *anti*-**61**, *anti*-**62** and *anti*-**64** were isolable with perfect diastereomeric purities. If traces of the *syn*-diastereomer were accompanying initially they were readily removed by flash chromatography on silica gel.[36] If the β-hydroxyketone bore a phenyl group (R^2) like in **28**, **45** or **49** the amount of *syn*-diastereomer increased and, annyingly, could not be removed. This implies that phenyl-substituted ketones are awkward substrates for the Ru-BINAP-catalyzed hydrogenation.[37]

The result of Tables 4-5 makes our asymmetric hydrogenation route to enantiomerically pure β-hydroxyketones (Tables 1-3) part of efficient 4-step syntheses of enantiomerically pure 1,3-diols of any absolute or relative configuration. 1,3-Diol motifs abound natural products – particularly, if they are polyketide-based, but not only then.[38] Methods for synthesizing 1,3-diols stereoselectively are of great importance, accordingly.[39,40]

Experimental Section

General Working Technique and Analytic Techniques

Working technique: All reactions, which did not require the presence of water were carried out under an atmosphere of dry N_2. Reaction flasks were dried in an oven (65°C) and under reduced pressure with a heat gun prior to use. Liquids were added with syringe and via cannula through a rubber septum. Solids were added in a countercurrent of dry N_2. Reactions, which required or allowed the presence of water were carried out in laboratory atmosphere. **Solvents:** Prior to use, diethyl ether (Et_2O) was distilled over sodium/potassium alloy, tetrahydrofuran (THF) over potassium, dichloromethane (CH_2Cl_2), and triethyl amine (NEt_3) as well as diisopropyl amin (iPr_2NH) over CaH_2 under an atmosphere of dry N_2. Other solvents, which were obtained commercially as "dry" or "extra dry" solvents, were used without further purification. Cyclohexane ($c\text{-}C_6H_{12}$) and ethyl acetate (EtOAc), for workup and column chromatography were distilled prior to use using a rotary evaporator to remove high boiling fractions. Dichloromethane (CH_2Cl_2), and *tert*-butyl methyl ether (TBME) for workup were obtained as p. a. grade solvents and used without further purification. **Organolithium compounds** and **Grignard reagents** were stored in a freezer in Schlenk flasks with PTFE screw caps and PTFE valves. Prior to use, organolithium compounds and Grignard reagents were titrated using salicylaldehyde phenylhydrazone.[41] Chromatography: **Thin layer chromatography** (TLC) on Merck silica plates with glass as supporting material (TLC Silica gel 60 F_{254}) was used to monitor reactions and assess purification procedures. If possible, chromatograms were marked in UV light at 254 nm and subsequently stained using permanganate stain (2 g $KMnO_4$, 4 g $NaHCO_3$, 100 mL H_2O) or vanillin stain (4.5 g vanillin, 75 mL EtOH, 4 mL conc. H_2SO_4). Macherey-Nagel & Co silica gel 60® (230-400 mesh) was used for **flash column chromatography**.[36] Chromatography conditions are documented at the respective experiment in the following manner: (d × h cm, solv1:solv2, a:b - c:d), which means: a column with the inner diameter d cm was packed with h cm silica gel. The product was eluted with the solvents solv1 and solv2 in the ratio a:b. **HPLC:** Determinations of the enantiomeric excess (*ee*) were conducted by A. Schuschkowski using a Merck Hitachi LaChrom L 7100; further details: cf. individual experimental descriptions. **NMR spectroscopy:** NMR spectra were recorded by Dr. M. Keller, F. Reinbold, and M. Schonhard on a Bruker Avance 400 spectrometer [^{1}H (400 MHz), ^{13}C (100 MHz), DQF-COSY, and edHSQC ("C,H-COSY")], and a Bruker Avance III HD 500 spectrometer [^{1}H (500 MHz), ^{13}C (126 MHz), DQF-COSY, and edHSQC ("C,H-COSY")] or on an automated Varian Mercury VX 300 spectrometer [^{1}H (300 MHz)] or an automated Bruker Avance III HD 300 spectrometer [^{1}H (300 MHz)]. Spectra were referenced internally by the ^{1}H- and ^{13}C-NMR signals of the solvent [$CDCl_3$: 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C)]. ^{1}H-NMR data are reported as follows: chemical shift (δ in ppm), multiplicity (s for singlet; d for doublet; t for triplet; m for multiplet; m_c for symmetrical multiplet; br for

broad signal), coupling constant(s) (Hz; ^3J couplings unless otherwise noted), integral, and specific assignment. For AB signals the high-field part is named A and the low-field part B. ^{13}C-NMR data are reported in terms of chemical shift and assignment. The atom numbering used for NMR assignments follows the IUPAC nomenclature. **High resolution mass spectra** were recorded by Dr. J. Wörth and C. Warth on a Thermo Exactive mass spectrometer equipped with an orbitrap analyzer. Ionization methods: Electron spray ionization (ESI; spray voltage: 4-5 kV) or atmospheric pressure chemical ionization (APCI; spray current: 5 µA). **Elemental analyses** were obtained by A. Siegel on an Elementar Vario El CHNS analyzer. **IR spectra** were recorded on a Perkin Elmer Spectrum 65 FT-IR spectrometer for a film of the substance on a NaCl plate. **Optical rotations** were measured on a Perkin-Elmer polarimeter 341 at 589 nm (Na lamp). $[\alpha]_\lambda^{20}$ was calculated as follows: $[\alpha]_\lambda^{20} = (\alpha_{exp.} \times 100)/(c \times d)$, where λ [nm] is the wavelength, $\alpha_{exp.}$ [°] the experimental result, c [g/100 mL] the concentration, and d [dm] the length of the optical cell. $[\alpha]_\lambda^{20}$ is given as the arithmetic mean of five measurements.

***N*-Methoxy-*N*-methylacetamide** (**12**) was prepared following the description of KERR *et al.*[42] NEt_3 (23.1 mL, 16.8 g, 166 mmol, 2.0 equiv) was added to a stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (**22**-HCl, 8.05 g, 82.8 mmol, 1.0 equiv) in CH_2Cl_2 (200 ml) at 0°C. Acetyl chloride (**11a**, 5.91 mL, 6.50 g, 82.8 mmol) was added dropwise at 0°C. The resulting mixture was stirred for 17 h at ambient temp. The reaction was quenched with satd. aq. $NaHCO_3$ (130 mL). The aq. layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with aq. HCl (1M, 50 mL) and brine (50 mL) and dried over Na_2SO_4. Removing the solvent under reduced pressure and purifying the residue by distillation (bp. 65°C, 50 mbar) furnished the title compound **12** (7.09 g, 83%, ref.[42] 98%[43]) as a colorless liquid.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 2.12 (s, 3H, 2-H_3), 3.18 (s, 3H, NCH_3), 3.69 (s, 3H, OCH_3) ppm. These data are consistent with those reported in the literature.[42]

Preparation of *N*-Methoxy-*N*-methyl-3-oxobutanamide (1a), i. e., the Simplest β-Keto Weinreb Amide of this Study: At −78°C *n*-BuLi (16.5 mL, 2.34 M solution in *n*-hexane, 38.8 mmol, 2.0 equiv) was added to a solution of *i*Pr_2NH (6.00 mL, 4.32 g, 42.7 mmol, 2.2 equiv) in THF (60 mL). After stirring for 1 h *N*-Methoxy-*N*-methylacetamide **12** (2.00 g, 19.4 mmol) in THF (20 mL) was added slowly. The resulting mixture was stirred at −78°C for 1.5 h. Acetyl chloride (**11a**, 1.38 mL, 1.52 g, 19.4 mmol, 1.0 equiv) was added. After stirring at −78°C for 30 min the reaction was quenched with aq. HCl (1M, 80 mL), and the organic layer was separated. The aq. layer was extracted with EtOAc (3 × 80 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel[36] (4 × 15 cm, *c*-C_6H_{12}:EtOAc = 3:1). This furnished the title compound **1a** (1.43 g, 51%[44]) as an orange oil.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.94 [s, 3H, 4-H_3, (*enol*-**1a**)], 2.22 [s, 3H, 4-H_3, (**1a**)], 3.15 [s, 3H, NCH_3, (*enol*-**1a**)], 3.18 [s, 3H, NCH_3, (**1a**)], 3.54 [s, 2H, 2-H_2, (**1a**)], 3.646 [s, 3H, OCH_3, (**1a**)] superimposed by 3.650 [s, 3H, OCH_3, (*enol*-**1a**)], 5.36 [s, 1H, 2-H, (*enol*-**1a**)], 13.69 [s, 1H, 3-O*H*, (*enol*-**1a**)] ppm. These data are consistent with those reported in the literature.[10]

Preparation of *N*-Methoxy-*N*,4,4-trimethyl-3-oxopentanamide (1i), i. e., the Highest-Yielding β-Keto Weinreb Amide of this Study: At −78°C *n*-BuLi (16.6 mL, 2.34 M solution in *n*-hexane, 38.8 mmol, 2.0 equiv) was added to a solution of *i*Pr_2NH (6.00 mL, 4.32 g, 42.7 mmol, 2.2 equiv) in THF (60 mL). After stirring for 1 h *N*-Methoxy-*N*-methylacetamide (**12**) (2.01 g, 19.4 mmol) in THF (20 mL) was added slowly. The resulting mixture was stirred at −78°C for 1.5 h. Pivaloyl chloride (**11i**, 2.39 mL, 2.34 g, 19.4 mmol, 1.0 equiv) was added. After stirring at −78°C for 1 h the reaction was quenched with aq. HCl (1 M, 80 mL). The organic layer was separated. The aq. layer was extracted with EtOAc (3 × 80 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel[36] (4 × 14 cm, *c*-C_6H_{12}:EtOAc = 4:1). This furnished the title compound **1i** (3.16 g, 87%) as an orange oil.

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.17 [s, 9H, 4-(CH_3)$_3$, (*enol*-**1i**)], 1.18 [s, 9H, 4-(CH_3)$_3$, (**1i**)], 3.20 [s, 3H, NCH_3, (*enol*-**1i**)], 3.21 [s, 3H, NCH_3, (**1i**)], 3.65 [s, 3H, OCH_3, (**1i**)], 3.69 [s, 2H, 2-H_2, (**1i**)], 3.70 [s, 3H, OCH_3, (*enol*-**1i**)], 5.44 [s, 1H, 2-H, (*enol*-**1i**)], 13.98 [s, 1H, 3-O*H*, (*enol*-**1i**)] ppm.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.41 [4-(CH_3)$_3$, (**1i**)], 27.77 [4-(CH_3)$_3$, (*enol*-**1i**)], 32.09 [NCH_3, (*enol*-**1i**)], 32.23 [NCH_3, (**1i**)], 36.95 [C-4, (*enol*-**1i**)], 42.79 [C-2, (**1i**)], 44.75 [C-4, (**1i**)], 61.33 [OCH_3, (**1i**)], 61.36 [OCH_3, (*enol*-**1i**)], 82.32 [C-2, (*enol*-**1i**)], 186.09 [C-1, (**1i**)], 209.13 [C-3, (**1i**)] ppm.

IR (film): ν = 2970, 2940, 1710, 1665, 1620, 1480, 1465, 1445, 1385, 1370, 1220, 1065, 770 cm^{-1}.

Combustion analysis: found: C: 57.73%, H: 9.16%, N: 7.39%; calculated for $C_9H_{17}NO_3$: C: 57.73%, H: 9.15%, N: 7.48%.

HRMS (pos. APCI): M+H$^+$, found m/z = 188.12870, i.e., δ = +0.2 ppm versus what $C_9H_{18}NO_3$ requires (188.12867).

Representative Procedures[45] for Asymmetric Hydrogenations, Acylations, *syn*- and *anti*-Reductions [all exemplarily for the Follow-up Products of *N*-Methoxy-*N*-methyl-3-oxobutanamide (**1a**), the Simplest β-Keto Weinreb Amide of this Study]:

(*S*)-3-Hydroxy-*N*-methoxy-*N*-methylbutanamide (*S*-2a): $[Me_2NH_2]^\oplus$ $\{[RuCl(S)\text{-BINAP}]_2(\mu\text{-Cl})_3\}^\ominus$ (4.0 mg, 2.4 µmol, 0.5 mol-%) was weighed in an autoclave. The autoclave was evacuated and flushed with nitrogen. A solution of the Weinreb amid **1a** (78 mg, 0.54 mmol) in degassed EtOH (6 mL) was added. The resulting mixture was stirred under H_2 pressure (5.0 bar) at ambient temp. for 15 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel[36] (1 × 12 cm, *c*-C_6H_{12}:EtOAc = 1:2). This furnished the title compound *S*-**2a** (79 mg, 98%, 99.0% *ee*[46]) as a brown liquid.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.24 (d, $J_{4,3}$ = 6.3 Hz, 3H, 4-H_3), AB signal [δ_A = 2.44 and δ_B = 2.65 ($^2J_{AB}$ = 17.1 Hz, part A additionally split by $J_{2A,3}$ = 9.3 Hz, 2H, 2-H_2)], 3.19 (s, 3H, NCH_3), 3.69 (s, 3H, OCH_3), 3.82 (br. s, 1H, O*H*), 4.21 (m_c, 1H, 3-H) ppm. These data are consistent with those reported in the literature.[47]

$[\alpha]_D^{20}$ = +61.0 (c = 1.42, $CHCl_3$)

(*S*)-4-Hydroxypentan-2-one (*S*-27), i. e. Example for Method A (Table 3): A solution of the Weinreb amide *S*-**2a** (474 mg, 3.22 mmol) in Et_2O (13 mL) was treated with MeMgI (1.47 M solution in Et_2O, 5.48 mL, 8.05 mmol, 2.5 eq) at 0°C and stirred for 1 h at 0°C. The mixture was stirred for another 2 h at ambient temperature. Satd. aq. NH_4Cl (30 mL) was added, the layers were separated, and the aq. layer was extracted with *t*BuOMe (3 × 30 mL). The aq. layer was acidified with aq. HCl (1 M) and again extracted with *t*BuOMe (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel[36] (3 × 16 cm, C_6H_{12}:EtOAc = 1:1). This furnished the title compound *S*-**27** (204 mg, 62%) as a colorless liquid.

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.19 (d, $J_{5,4}$ = 6.3 Hz, 3H, 5-H_2), 2.17 (s, 3H, 1-H_3), AB signal [δ_A = 2.54 and δ_B = 2.63 ($^2J_{AB}$ = 17.8 Hz, part A additionally split by $J_{3A,4}$ = 3.4 Hz, part B additionally split by $J_{3B,4}$ = 8.7 Hz, 2H, 3-H_2)], 3.01 (br. s, 1H, 4-O*H*), 4.22 (m_c, 1H, 4-H) ppm. These data are consistent with those reported in the literature.[48]

$[\alpha]_D^{20}$ = +67.7(c = 1.06, $CHCl_3$)

(*S*)-3-Hydroxy-1-phenylbutan-1-one (*S*-28), i. e. Example for Method A (Table 3): A solution of the Weinreb amide *S*-**2a** (510 mg, 3.47 mmol) in Et_2O (15 mL) was treated with PhMgBr (1.54 M solution in Et_2O, 5.63 mL, 8.66 mmol, 2.5 eq) at 0°C and stirred for 1 h at 0°C. Thereafter the mixture was stirred for another 1 h at ambient temperature. Satd. aq. NH_4Cl (35 mL) was added, the layers were separated, and the aq. layer was extracted with *t*BuOMe (3 × 35 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel[36] (3 × 18 cm, C_6H_{12}:EtOAc = 10:1). This furnished the title compound *S*-**28** (399 mg, 70%) as a colorless liquid.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.31 (d, $J_{4,3}$ = 6.3 Hz, 3H, 4-H_3), AB signal [δ_A = 3.05 and δ_B = 3.17 ($^2J_{AB}$ = 17.7 Hz, part A additionally split by $J_{2A,3}$ = 3.0 Hz, part B additionally split by $J_{2B,3}$ = 8.8 Hz, 2H, 2-H_2)], 3.28 (br. s, 1H, 3-O*H*), 4.41 (m_c, 1H, 3-H), 7.45-7.62 (m, 3H, 3 × Ar-H), 7.94-7.97 (m, 2H, 2 × Ar-H) ppm. These data are consistent with those reported in the literature.[49]
$[\alpha]_D^{20}$ = +76.1 (c = 1.88, $CHCl_3$)

(*S*)-2-Hydroxyoctan-4-one (*S*-29), i. e. Example for Method B (Table 3): A solution of the Weinreb amide *S*-**2a** (323 mg, 2.20 mmol) in THF (10 mL) was treated with *n*BuLi (2.36 M solution in hexane, 2.79 mL, 6.59 mmol, 3.0 eq) at −78°C and stirred for 3 h at −78°C. Satd. aq. NH_4Cl (10 mL) was added, the layers were separated, and the aq. layer was extracted with EtOAC (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel[36] (3 × 16 cm, C_6H_{12}:EtOAc = 4:1). This furnished the title compound *S*-**29** (216 mg, 68%) as a colorless liquid.
^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.91 (t, $J_{8,7}$ = 7.3 Hz, 3H, 8-H_3), 1.19 (d, $J_{1,2}$ = 6.3 Hz, 3H, 1-H_3), 1.32 (m_c, 2H, 7-H_2), 1.56 (m_c, 2H, 6-H_2), 2.41 (t, $J_{5,6}$ = 7.5 Hz, 2H, 5-H_2), AB signal [δ_A = 2.50 and δ_B = 2.59 ($^2J_{AB}$ = 17.6 Hz, part A additionally split by $J_{3A,2}$ = 3.2 Hz, part B additionally split by $J_{3B,2}$ = 8.7 Hz, 2H, 3-H_2)], 3.09 (br. s, 1H, 2-O*H*), 4.21 (m_c, 1H, 2-H) ppm. These data are consistent with those reported in the literature.[50]
$[\alpha]_D^{20}$ = +53.5 (c = 1.17, $CHCl_3$)

(*S*)-5-Hydroxy-2-methylhexan-3-one (*S*-30), i. e. Example for Method C (Table 3): A solution of 4,4'-di-*tert*-butylbiphenyl (0.91 g, 3.4 mmol, contains 0.35 mol-% of 2-chloropropane) in THF (40 mL) was treated with small pieces of lithium (134 mg, 19.3 mmol, 6.3 equiv.) at 0°C. The mixture was stirred at 0°C for 4 h. The mixture was cooled to −78°C, 2-chloropropane (0.89 mL, 0.77 g, 9.8 mmol, 3.2 equiv) was added, and the mixture was stirred at −78 C for 15 h. A solution of the Weinreb amide *S*-**2a** (450 mg, 3.06 mmol) in THF (10 mL) was added by means of a syringe pump over a period of 90 min. The mixture was stirred for another 8 h and then treated with satd. aq. NH_4Cl (35 mL). The layers were separated and the aq. layer was extracted with EtOAC (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel[36] (3 × 18 cm, C_6H_{12}:EtOAc = 5:1). This furnished the title compound *S*-**30** (291 mg, 73%) as a colorless liquid.
^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.10 (d, $J_{2\text{-}Me,2}$ = 7.0 Hz, 3H, 2-CH_3), 1.11 (d, $J_{2\text{-}Me,2}$ = 7.0 Hz, 3H, 2-CH_3), 1.19 (d, $J_{6,5}$ = 6.4 Hz, 3H, 6-H_3), AB signal [δ_A = 2.54 and δ_B = 2.64 ($^2J_{AB}$ = 17.7 Hz, part A additionally split by $J_{4A,5}$ = 3.0 Hz, part B additionally split by $J_{4B,5}$ = 8.7 Hz, 2H, 4-H_2)] superimposed by 2.58 (qq, 2 × $J_{2,2\text{-}Me}$ = 6.9 Hz, 1H, 2-H), 3.21 (br. s, 1H, 5-O*H*), 4.20 (m_c, 1H, 5-H) ppm. These data are consistent with those reported in the literature.[51]
$[\alpha]_D^{20}$ = +64.8 (c = 1.51, $CHCl_3$)

(*S*)-5-Hydroxy-2,2-dimethylhexan-3-one (*S*-31), i. e. Example for Method D (Table 3): A solution of the Weinreb amide *S*-**2a** (267 mg, 1.81 mmol) in THF (10 mL) was treated with *t*BuLi (1.43 M solution in pentane, 3.79 mL, 5.41 mmol, 3.0 eq) at −78°C, stirred for 3 h at −78°C and for another 3 h at 0°C. Satd. aq. NH_4Cl (10 mL) was added, the layers were separated, and the aq. layer was extracted with *t*BuOMe (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel[36] (3 × 16 cm, C_6H_{12}:EtOAc = 4:1). This furnished the title compound *S*-**31** (131 mg, 50%) as a colorless liquid.
^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.14 (s, 9H, 2-(CH_3)$_3$), 1.20 (d, $J_{6,5}$ = 6.3 Hz, 3H, 6-H_3), AB signal [δ_A = 2.54 and δ_B = 2.69 ($^2J_{AB}$ = 17.9 Hz, part A additionally split by $J_{4A,5}$ = 2.8 Hz, part B additionally split by $J_{4B,5}$ = 8.9 Hz, 2H, 4-H_2)], 3.34 (br. s, 1H, 5-O*H*), 4.18 (dqd, $J_{5,4B}$ = 9.0 Hz, $J_{5,6}$ = 6.3 Hz, $J_{5,4A}$ = 2.7 Hz, 1H, 5-H) ppm. These data are consistent with those reported in the literature.[52]
$[\alpha]_D^{20}$ = +65.0 (c = 1.63, $CHCl_3$)

(2*S*,4*R*)-Octane-2,4-diol (*syn*-55): A solution of the β-hydroxy ketone *S*-**29** (346 mg, 2.40 mmol) in THF/MeOH (4:1, 20 mL) was treated with Et_2BOMe (1 M solution in THF, 2.64 mL, 2.64 mmol, 1.10 equiv.) at −78°C and stirred for 20 min at this temperature. $NaBH_4$ (100 mg, 2.64 mmol, 1.10 equiv.) was added. The resulting mixture was stirred for 3 h at 0°C. MeOH (10 mL), aq. NaOH (1 M, 5.9 mL), and aq. H_2O_2 (30%, 2.9 mL) were added. The resulting mixture was stirred for 15 h at ambient temperature. The reaction mixture was concentrated. The residue was dissolved in a mixture of CH_2Cl_2 (15 mL) and brine (15 mL). The layers were separated. The aq. layer was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic extracts were washed with satd. aq. Na_2SO_3 (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel[36] (3 × 15 cm, C_6H_{12}:EtOAc = 9:1). This furnished the title compound *syn*-**55** (321 mg, 91%) as a colorless liquid.
^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.91 (t, $J_{8,7}$ = 7.1 Hz, 3H, 8-H_3), 1.21 (d, $J_{1,2}$ = 6.3 Hz, 3H, 1-H_3), 1.25-1.61 (m, 8H, 3-H_2, 5-H_2, 6-H_2, 7-H_2), 3.01 (br. s, 2H, 2-O*H*, 4-O*H*), 3.82-3.88 (m, 1H, 4-H), 4.01-4.09 (m, 1H, 2-H) ppm.
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.16 (C-8), 22.83 (C-7), 24.39 (C-1), 27.65 (C-6), 38.14 (C-5), 44.91 (C-3), 69.33 (C-2), 73.27 (C-4) ppm. These data are consistent with those reported in the literature.[53]
$[\alpha]_D^{20}$ = +6.5(c = 1.08, $CHCl_3$)

(1*S*,3*S*)-1-Phenylbutane-1,3-diol (*syn*-56): A solution of the β-hydroxy ketone *S*-**28** (316 mg, 1.92 mmol) in THF/MeOH (4:1, 18 mL) was treated with Et_2BOMe (1 M solution in THF, 2.12 mL, 2.12 mmol, 1.10 equiv.) at −78°C and stirred for 20 min at this temperature. $NaBH_4$ (80.0 mg, 2.64 mmol, 1.10 equiv.) was added. The resulting mixture was stirred for 3 h at 0°C. MeOH (8 mL), aq. NaOH (1 M, 4.8 mL), and aq. H_2O_2 (30%, 2.4 mL) were added. The resulting mixture was stirred for 15 h at ambient temperature. The mixture was concentrated. The residue was dissolved in a mixture of CH_2Cl_2 (15 mL) and brine (15 mL). The layers were separated and the aq. layer was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic extracts were washed with satd. aq. Na_2SO_3 (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel[36] (3 × 18 cm, C_6H_{12}:EtOAc = 2:1). This furnished the title compound *syn*-**56** (297 mg, 93%) as a colorless liquid.
^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.23 (d, $J_{4,3}$ = 6.2 Hz, 3H, 4-H_3), AB signal [δ_A = 1.76 and δ_B = 1.86 ($^2J_{AB}$ = 14.6 Hz, part A additionally split by $J_{2A,1}$ = 9.8 Hz, $J_{2A,3}$ = 9.8 Hz, part B additionally split by $J_{2B,1}$ = 3.1 Hz, $J_{2B,3}$ = 2.5 Hz, 2H, 2-H_2)], 3.04 (br. s, 1H, 3-O*H*)*, 3.22 (br. s, 1H, 1-O*H*)*, 4.10-4.18 (m, 1H, 3-H), 4.93 (dd, $J_{1,2A}$ = 10.1 Hz, $J_{1,2B}$ = 3.2 Hz, 1H, 1-H), 7.25-7.38 (m, 5H, 5 × Ar-H) ppm; *assignments interchangeable
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.29 (C-4), 47.30 (C-2), 68.99 (C-3), 75.50 (C-1), 125.80 (2 × C_o), 127.79 (C_p), 128.68 (2 × C_m), 144.62 (C_{ipso}) ppm. These data are consistent with those reported in the literature.[54]
$[\alpha]_D^{20}$ = +56.8 (c = 1.46, $CHCl_3$)

(2*S*,4*S*)-Octane-2,4-diol (*anti*-55): $[Me_2NH_2]^{\oplus}$ {[RuCl(*S*)-BINAP]$_2$(μ-Cl)$_3$}$^{\ominus}$ (27 mg, 16 μmol, 0.5 mol-%) was weighed in an autoclave. The autoclave was evacuated and flushed with nitrogen. A solution of the β-hydroxy ketone *S*-**29** (465 mg, 3.22 mmol) in degassed EtOH (32 mL) was added. The resulting mixture was stirred under H_2 pressure (5.0 bar) at ambient temp. for 36 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel[36] (3 × 16 cm, C_6H_{12}:EtOAc = 5:1). This furnished the title compound *anti*-**55** (385 mg, 82%) as a brown liquid.
^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.91 (t, $J_{8,7}$ = 7.1 Hz, 3H, 8-H_3), 1.24 (d, $J_{1,2}$ = 6.3 Hz, 3H, 1-H_3), 1.25-1.57 (m, 6H, 5-H_2, 6-H_2, 7-H_2), 1.60 (m_c, 2H, 3-H_2), 2.60 (br. s, 2H, 2-O*H*, 4-O*H*), 3.91-3.97 (m, 1H, 4-H), 4.71-4.20 (m, 1H, 2-H) ppm.
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.17 (C-8), 22.84 (C-7), 23.71 (C-1), 28.10 (C-6), 37.30 (C-5), 44.21 (C-3), 65.70 (C-2), 69.58 (C-4) ppm. These data are consistent with those reported in the literature.[29]
$[\alpha]_D^{20}$ = +17.0 (c = 1.52, $CHCl_3$)

(1*R*,3*S*)-1-Phenylbutane-1,3-diol (*anti*-56): $[Me_2NH_2]^{\oplus}$ {[RuCl(*S*)-BINAP]$_2$(μ-Cl)$_3$}$^{\ominus}$ (18 mg, 11 μmol, 0.5 mol-%) was weighed in an autoclave. The autoclave was evacuated and flushed with nitrogen. A solution of the β-hydroxy ketone *S*-**28** (346 mg, 2.11 mmol) in degassed EtOH (20 mL) was added. The resulting mixture was stirred under H_2-pressure (5.0 bar) at ambient temp. for 36 h. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel[36] (3 × 18 cm, C_6H_{12}:EtOAc = 3:1). This furnished the title compound *anti*-**56** (347 mg, 99%, *anti*:*syn* 94:6) as a brown liquid.

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.24 (d, $J_{4,3}$ = 6.3 Hz, 3H, 4-H$_3$), AB signal [δ_A = 1.86 and δ_B = 1.92 ($^2J_{AB}$ = 14.5 Hz, part A additionally split by $J_{2A,1}$ = 7.7 Hz, $J_{2A,3}$ = 3.3 Hz, part B additionally split by $J_{2B,3}$ = 8.1 Hz, $J_{2B,1}$ = 3.8 Hz, 2H, 2-H$_2$)], 2.36 (br. s, 1H, 3-O*H*)*, 2.99 (br. s, 1H, 1-O*H*)*, 4.07 (m$_c$, 1H, 3-H), 5.05 (dd, $J_{1,2A}$ = 7.7 Hz, $J_{1,2B}$ = 3.8 Hz, 1H, 1-H), 7.25-7.39 (m, 5H, 5 × Ar-H) ppm; *assignments interchangeable

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.78 (C-4), 46.30 (C-2), 65.60 (C-3), 71.99 (C-1), 125.72 (2 × C$_o$), 127.51 (C$_p$), 128.61 (2 × C$_m$), 144.61 (C$_{ipso}$) ppm. These NMR data are consistent with those reported in the literature.[55]

$[\alpha]_D^{20}$ = +17.9 (c = 1.48, $CHCl_3$)

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