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A Synthetic Approach to 3-Hydroxy 4-Substituted Carboxylic Acids based on the Stereoselective Reduction of 1-Trimethylsilyl-1-alkyn-3-ones

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Abstract—The oxazaborolidine-mediated reduction of chiral, 4-substituted 1-trimethylsilyl-1-alkyn-3-ones followed by hydroboration affords *syn* or *anti* 3-hydroxy 4-substituted carboxylic acids, common substructures of a number of biologically active macrolides, peptides and depsipeptides, with high control on the new C(3) stereocenter. This strategy has been applied to the synthesis of (3*S*,4*S*)-3-hydroxy-4-methylheptanoic acid and of *N*-Boc-statine, constituents of permentin A and pepstatin, respectively.

Introduction

Achieving stereocontrol in the construction of acyclic systems is a challenging goal in organic synthesis. In this connection, the incorporation of a chiral 3-hydroxy-4-methylbutanoic acid moiety, as well as its 4-methoxy analogue, to a growing framework is of great interest since they are common structural elements of a number of biologically active natural and synthetic macrolides of interest in pharmacy and veterinary (e.g. tylosin and leucomycins).[1] In the same way, structurally related 3-hydroxy 4-amino acids are also deserving interest since relatively simple compounds as statine (**1**) or cyclohexylstatine (**2**) became key components of peptidomimetic protease inhibitors.[2] Interestingly, the *syn* (*threo*) relative configuration of the amino and hydroxy groups, which mimics the tetrahedral transition state for peptide bond hydrolysis, has been revealed essential for their bioactivity. However, several members of the corresponding diastereomeric *anti* (*erythro*) series are also of natural occurrence.[3] Representative examples of these substructures are isostatine (**3**) and (3*R*,4*S*)-3-hydroxy-4-methylamino-5-phenylpentanoic acid (**4**), constituents of the bioactive depsipeptides didemnins A–C[4,5] and of hapalosin,[6] respectively (Fig. 1).

Obvious routes to 3-hydroxy 4-substituted carboxylic acid substructures of **1** and **2** (see **5**) and of **4** (see **6**) include the addition of the appropiate reagents (e.g. allyl boron reagents[7] or enolates[8]) to chiral α-substituted aldehydes **7**, as well as the reduction of the corresponding 3-keto esters **8**. In particular, when X are protected amino groups, the intensive search for diastereoselective synthetic approaches to such compounds carried out over the last decade, both in academic and industrial laboratories,[9] has led to a number of useful preparations of some of these compounds in reasonable yields and stereoselectivities.[10] However, the stereochemical control at the emergent stereocenter on C(3) is

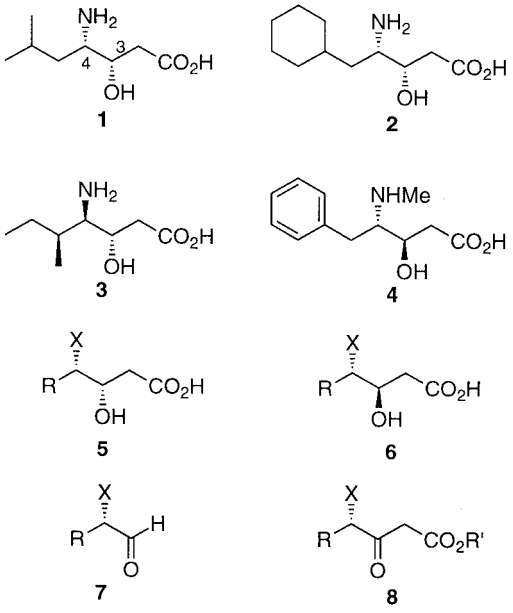

Figure 1.

Keywords: oxazaborolidines; amino acids and derivatives; hydroxy acids and derivatives; reduction.

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not always satisfactory, specially in the mismatched cases, and a general and unified route to both, *syn* and *anti* stereoisomers (**5** and **6**, respectively), is still a challenge.

By adoption of the strategy based on double-asymmetric synthesis,[11] this goal could be attained in a predictible and controlled manner from a common precursor with the use of a chiral reagent (or catalyst) capable of displaying such high asymmetric induction that could override the normally small diastereofacial selectivity of a chiral substrate (e.g. **7** or **8**). In this connection, oxazaborolidine-mediated reduction of ketones could obviously accomplish that requirement due to the high level of enantioselectivity observed in many cases.[12]

Studies in our laboratory[13] and others[14] have demonstrated that prochiral 1-trialkylsilyl-1-alkyn-3-ones are especially adequate substrates for such reductions. In addition, the highly enantioenriched propargylic alcohols obtained are versatile building blocks for asymmetric synthesis. Based on these studies, we report herein an alternative, stereodivergent route to compounds **5** and **6**, which is summarized in Scheme 1.[15]

Preparation of α,β-acetylenic ketones

A set of representative chiral α-substituted acetylenic ketones **10a–c** were easily prepared by reaction of freshly generated solution of lithium trimethylsilylacetylide (1–2 equiv.) with the Weinreb amides **9a–c** (86–90% yield) which, in turn, were obtained by standard methods from the corresponding chiral acids or methyl esters.[16] Besides ketones **10**, a small amount (5–8%) of desilylated ketones were also isolated by flash chromatography.[17] On the other hand, α-Boc-amino ketones **10d** and **10e** were also available in a similar way following Rappoport's protocol.[18]

Reduction of α,β-acetylenic ketones

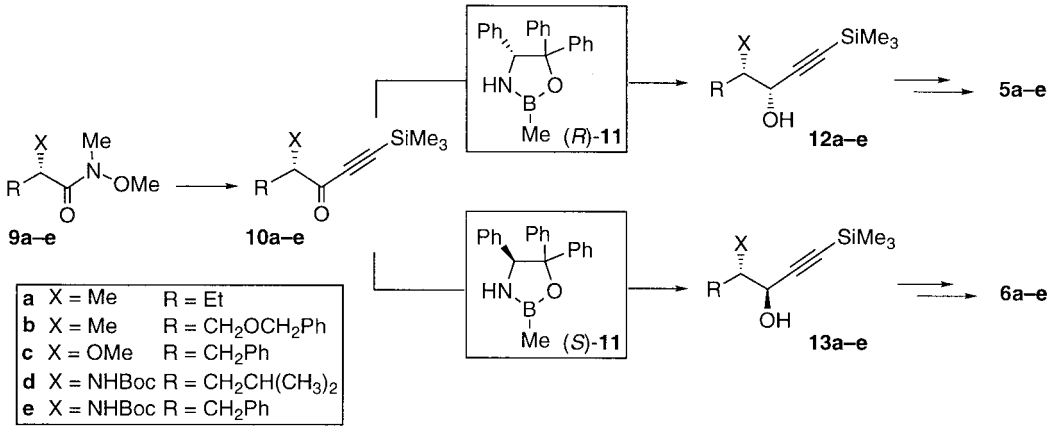
Reductions of **10** were performed by slow addition of the ketone to a solution of BH_3:SMe_2 and (*R*)- or (*S*)-**11** in THF. To our satisfaction, the oxazaborolidine–borane system largely overcame the intrinsic facial bias of the carbonyl group of **10** resulting in good to excellent diastereoselectivities even in the mismatched cases, as shown in Table 1. In sharp contrast, reductions of **10** with $NaBH_4$ in MeOH led to a mixture of diastereomeric alcohols **12/13** (from 1:1.2 to 1:3.5 *syn*/*anti* ratio) in all the cases.

Table 1. Reduction of ketones **10** with BH_3:SMe_2 in the presence of oxazaborolidines **11**

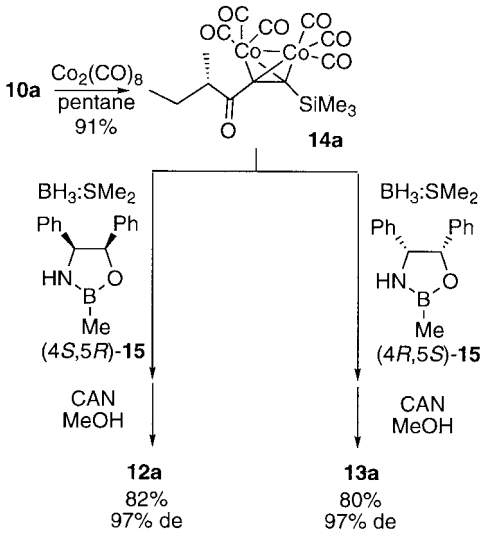
Entry	Ketones	Catalyst	Yield[a] (%)	**12/13** Ratio[a,b]
1	**10a**	(*R*)-11	97 (90)	24:1 (19:1)
2		(*S*)-11	90 (91)	1:24 (1:19)
3	**10b**	(*R*)-11	75 (70)	49:1 (24:1)
4		(*S*)-11	80 (71)	1:49 (1:24)
5	**10c**	(*R*)-11	74 (70)	32:1 (7.3:1)
6		(*S*)-11	80 (79)	1:10 (1:8)
7	**10d**	(*R*)-11	85 (60)	9:1 (9:1)
8		(*S*)-11	85 (76)	1:33.5 (1:32)
9	**10e**	(*R*)-11	55 (60)	>50:1 (25:1)
10		(*S*)-11	52	16.8

[a] Reactions were carried out by slow addition of **10** (1.0 mmol) to a mixture of BH_3:SMe_2 (1.2 mmol) and catalyst (1.0 mmol) in THF at 0°C. Within parentheses values using 0.2 mmol of catalyst.
[b] Determined by ^{19}F NMR analysis of the corresponding Mosher esters. Configuration at C(3) was determined by the Kakisawa method.[19] In addition, stereochemistry of **12a**, **12d**, **12e**, **13a**, **13d** and **13e** were confirmed by chemical correlation with the known acids (**5** or **6**) or their methyl esters (see text).

Reduction of the hexacarbonyldicobalt complexes derived from **10** were also investigated. Ketones **10a** and **10b** were easily transformed into their cobalt complexes **14a** and **14b**, respectively, with octacarbonyldicobalt in pentane. Since our previous experience indicated that oxazaborolidines **11** were inefficient for the reduction of very crowded ketones such as **14**,[13a,b] we treated **14a** with BH_3:SMe_2 in the presence of less steric demanding oxazaborolidines **15**[20] in THF under Ar at 0°C. As expected, the temporary transformation of the acetylenic moiety in a much bulkier group enhanced the selectivity in the reduction step leading to propargylic alcohols **12a** or **13a**, in good yields and selectivities after regeneration of the triple bond with the aid of a mild oxidant like Ce(IV). Unfortunately, when we attempted to extent this strategy to the only slightly more crowded ketone **14b**, it was sluggishly reduced under similar conditions. In conclusion, the reduction of the Co complexes of acetylenic ketones could give excellent



Scheme 1.



Scheme 2.

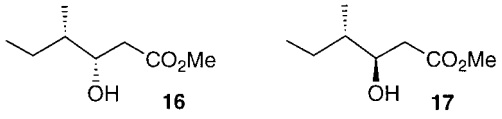
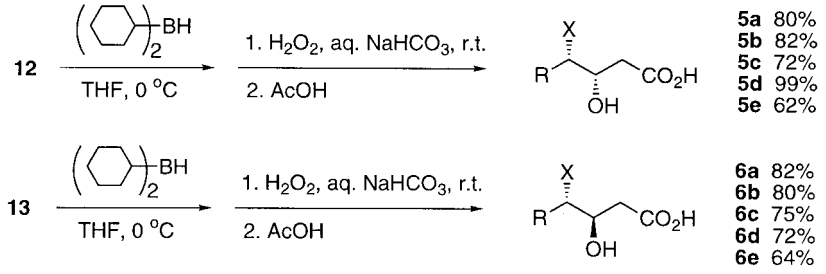


Figure 2.



Scheme 3.

stereoselectivities but it seems to be only suitable for substrates with low steric requeriments (Scheme 2).[14c]

Transformation of alcohols 12 and 13 into β-hydroxy acids

Having in hand stereochemically enriched propargylic alcohols, we undertook their transformation into β-hydroxy acids. Accordingly, hydroboration[21] of **12a** with dicyclohexylborane followed by oxidative workup in a basic medium[22] afforded **5a**, a constituent of antibiotic depsipeptide permetin A,[23] which was further transformed[24] into its known methyl ester derivative **16**.[25] In a similar way, **13a** was transformed to **6a** and then into the diastereomeric *anti* β-hydroxy methyl ester **17** (Fig. 2).[26,27]

Eventually, the remaining alcohols **12** and **13** showed a similar trend and were stereoselectively converted into the desired β-hydroxy acids **5** and **6**, respectively, in good yields (Scheme 3).

Conclusions

In summary, we have demonstrated that the tandem stereoselective reduction/hydroboration applied to α-substituted, chiral trimethylsilyl acetylenic ketones constitutes an efficient, alternative approach to *syn* or *anti* 3-hydroxy 4-substituted carboxylic acids with high control on the C(3) configuration. Similar reduction of the corresponding Co complexes, although highly stereoselective, has proved to be only suitable for the less crowded ketone **10a**. This strategy has been applied to the synthesis of different chiral β-hydroxy acids, including (3*S*,4*S*)-3-hydroxy-4-methylheptanoic acid (**5a**), present in permentin A, and *N*-Boc-statine (**5d**).

Experimental

General methods

All the solvents were distilled from an appropriate drying agent and stored under nitrogen atmosphere. The crude products were purified by column chromatography on silica gel of 230–400 mesh (flash chromatography). Thin-layer chromatograms were performed on HF 254 silica gel plates (using CH_2Cl_2, CH_2Cl_2/MeOH, hexane/AcOEt or CH_2Cl_2/hexane as the eluents, as indicated after the R_f values). Melting points are uncorrected. ^1H, ^{13}C, and ^{19}F NMR spectra were obtained in $CDCl_3$ at 200, 50.3 and 282.2 MHz, respectively; and chemical shifts are given in ppm with respect to internal TMS. Infrared spectra were measured on a Perkin–Elmer 681 on NaCl plates (neat) or in KBr; only the most significant absorptions, in cm^{-1}, are indicated. Microanalyses were performed by the Serveis Científico-Tècnics (Universitat de Barcelona). Optical rotations were measured at 20±2°C. Chemical ionization mass spectra (NH_3) are given in *m/z*. HRMS (EI and FAB) were obtained at the Centro de Apoio Cientifico-Tecnoloxico a Investigación (CACTI, Universidad de Vigo). Weinreb amides **9b**,[28] **9c**,[29] **9d**,[30] and **9e**[31] as well as oxazaborolidines **11**[13a] and **15**,[20] were prepared according to published procedures.

(*S*)-*N*-Methoxy-2,*N*-dimethylbutanamide (9). Prepared according to a described protocol.[32] To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (1.91 g, 19.6 mmol) in anh. CH_2Cl_2 (40 mL), triethylamine (4.0 mL, 29.3 mmol), (*S*)-2-methylbutanoic acid (0.53 mL, 4.89 mmol), a solution of 4-dimethylaminopyridine (4-DMAP, 1.20 g, 9.8 mmol) in CH_2Cl_2 (5 mL), and

diisopropylcarbodiimide (1.53 mL, 9.8 mmol) were added successively. After 48 h at rt, the suspension was diluted with CH_2Cl_2 (60 mL). After washing with water (4×20 mL), the organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to yield 702 mg (99%) of **9a**: oil; R_f 0.38 (CH_2Cl_2/MeOH, 95:5); ^{1}H NMR δ 0.89 (t, J=7.4 Hz, 3H), 1.11 (d, J=6.4 Hz, 3H), 1.41 (m, 1H), 1.66 (m, 1H), 2.80 (m, 1H), 3.19 (s, 3H), 3.70 (s, 3H); ^{13}C NMR δ 11.8, 16.9, 26.6, 32.0, 36.5, 61.2, 178.3; IR (neat) 2980, 2940,1660; $[\alpha]_D^{20}$=+34.9 (c 1.0, $CHCl_3$); MS (NH_3/CI) m/z (rel. int.) 163 (100, $[M+NH_4^+]$); Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41. Found: C, 58.02; H, 10.20.

General procedure for preparation of acetylenic ketones

Ketone 10a. To a stirred solution of trimethylsilylacetylene (0.31 mL, 2.2 mmol) in anh. THF (8 mL) at −78°C, a solution of BuLi in hexanes (1.40 mL, 2.1 mmol) were added dropwise. The solution was stirred for 30 min. Then, a solution of 290 mg (2.0 mmol) of **9a** in 5 mL of anh. THF was dropwise added and the mixture was allowed to warm to rt The progress of the reaction was monitored by TLC. After 3 h, the reaction mixture was slowly added via cannula into pH 7 phosphate buffer (15 mL) and the mixture was partitioned with diethyl ether (40 mL). The organic layer was dried over $MgSO_4$, filtered and carefully concentrated in vacuo. The crude which was purified by a short flash chromatography (CH_2Cl_2) to yield 317 mg (87%) of (*S*)-4-methyl-1-trimethylsilylhex-1-yn-3-one, **10a**,[33] as a volatile yellowish oil: R_f 0.48 (hexane/CH_2Cl_2 1:1); ^{1}H NMR δ 0.25 (s, 9H), 0.93 (t, 3H, J=7.4 Hz), 1.17 (d, 3H, J=6.8 Hz), 1.51 (m, 1H), 1.80 (m, 1H), 2.50 (m, 1H); ^{13}C NMR δ −0.8, 11.4, 15.3, 25.7, 49.7, 98.4, 101.2, 191.9; IR (film) 2980, 2940, 2150, 1680, 1615, 850; $[\alpha]_D^{20}$=+14.4 (c 1.1, $CHCl_3$) [lit.[33] +10.37 for 61% o.p.]; HRMS calcd for $C_{10}H_{18}SiO$ (M^+) 182.1127, found 182.1127.

(*S*)-5-Benzyloxy-4-methyl-1-trimethylsilylpent-1-yn-3-one (10b). 90% Yield of a yellowish oil. R_f 0.56 (CH_2Cl_2); ^{1}H NMR δ 0.28 (s, 9H), 1.25 (d, 3H, J=7.0 Hz), 2.94 (m, 1H), 3.64 (dd, 1H, J=5.4, 9.2 Hz), 3.81 (dd, 1H, J=7.0, 9.2 Hz), 4.57 (s, 2H), 7.15–7.40 (m, 5H); ^{13}C NMR δ −0.8, 13.1, 48.9, 71.3, 73.3, 98.9, 101.1, 127.5, 127.6, 128.3, 138.1, 189.3; IR (film) 2980, 2170, 1690. $[\alpha]_D^{20}$=−1.5 (c 1.1, $CHCl_3$); MS (NH_3/CI) m/z (rel. int.) 292 (100, $[M+NH_4^+]$); HRMS calcd for $C_{16}H_{23}SiO_2$ (M^++1) 275.1461, found 275.1456.

(*S*)-4-Methoxy-5-phenyl-1-trimethylsilylpent-1-yn-3-one (10c). 86% Yield of a yellowish oil. R_f 0.54 (CH_2Cl_2/hexane 7:3); ^{1}H NMR δ 0.27 (s, 9H), 2.95 (dd, 1H, J=8.4, 14.4 Hz), 3.12 (dd, 1H, J=4.5, 14.4 Hz), 3.36 (s, 3H), 3.95 (dd, 1H, J=4.5, 8.4 Hz), 7.20–7.40 (m, 5H); ^{13}C NMR δ −0.8, 38.3, 58.6, 88.2, 100.3, 102.2, 126.7, 128.4, 129.3, 136.1, 188.2; IR (film) 2980, 2161, 1680. $[\alpha]_D^{20}$=−12.1 (c 1.1, $CHCl_3$); MS (NH_3/CI) m/z (rel. int.) 278 (37, $[M+NH_4^+]$); HRMS calcd for $C_{15}H_{21}SiO_2$ (M^+) 261.1311, found 261.1318.

(*S*)-4-(*tert*-Butoxycarbonylamino)-6-methyl-1-trimethylsilylhept-1-yn-3-one (10d). To a stirred solution of trimethylsilylacetylene (1.0 mL, 7.1 mmol) in anh. THF (5 mL) at −78°C, a solution of BuLi in hexanes (4.2 mL, 6.7 mmol) were added dropwise. The solution was stirred for 30 min and then allowed to warm to 0°C. Then, a solution of amide **9d** (800 mg, 2.92 mmol) in anh. THF (3 mL) was dropwise added and the mixture was stirred at 0°C. The progress of the reaction was monitored by TLC. After 40 min, the reaction mixture was slowly added via cannula into *p*H 7 phosphate buffer (50 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by a short flash chromatography (CH_2Cl_2) to yield 672 mg (74%) of ketone **10d** as a yellowish oil: R_f 0.54 (CH_2Cl_2); ^{1}H NMR δ 0.23 (s, 9H), 0.94 (d, 3H, J=6.2 Hz), 0.95 (d, 3H, J=2.1 Hz), 1.40 (m, 2H), 1.42 (s, 9H), 1.73 (m, 1H), 4.36 (m, 1H), 5.02 (d, 1H, J=8.0 Hz); ^{13}C NMR δ 1.1, 21.5, 23.0, 24.7, 28.1, 40.5, 59.6, 79.9, 100.1, 101.6, 155.3, 187.4; IR (film) 3360, 2149, 1718, 1684; $[\alpha]_D^{20}$=+25.5 (c 1.4, $CHCl_3$); HRMS calcd for $C_{16}H_{29}NSiO_3$ (M^+) 311.1917, found 311.1921.

Further elution with CH_2Cl_2/MeOH (95:5) led to recover 120 mg (15%) of starting amide **9d**.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-phenyl-1-trimethylsilylpent-1-yn-3-one (10e). The procedure described above was applied to prepare **10e** as a yellowish oil in 50%. R_f 0.73 (CH_2Cl_2); ^{1}H NMR δ 0.25 (s, 9H), 1.41 (s, 9H), 3.17 (dd, 1H, J=6.3, 14.1 Hz), 3.21 (dd, 1H, J=5.7, 14.1 Hz), 4.67 (m, 1H), 5.02 (broad d, N*H*, J=4.8 Hz), 7.15–7.31 (m, 5H); ^{13}C NMR δ −0.9, 28.3, 37.3, 61.9, 79.9, 100.2, 102.6, 126.5, 127.0, 129.5, 135.5, 155.0, 186.7; IR (film) 3850, 2150, 1717, 1685. $[\alpha]_D^{20}$=+5.4 (c 0.36, $CHCl_3$); MS (NH_3/CI) m/z (rel. int.) 346 (100, $[M+H^+]$); HRMS calcd for $C_{19}H_{27}SiNO_3Si$ (M^+) 345.1760, found 345.1764.

General procedure for oxazaborolidine-mediated reduction of acetylenic ketones

Alcohol 12a. A solution of **10a** (292 mg, 1.6 mmol) in THF (6 mL) was slowly (ca. 45 min) added to a solution of (*R*)-**11** (1.6 mmol) and BH_3:SMe_2 (190 μL, 1.9 mmol) in THF (4 mL) at 0°C under Ar. Upon completion of the addition, TLC revealed the disappearance of the starting ketone. Reaction was cautiously quenched by addition of MeOH (3 mL) at 0°C. The solution was stirred for 2 h at rt and then concentrated under vacuum. The residue was partitioned with CH_2Cl_2 and aq. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2 and then CH_2Cl_2/MeOH 95:5 to recover the amino alcohol derived from **11**) to yield 286 mg (97%) of (3*R*,4*S*)-4-methyl-1-trimethylsilylhex-1-yn-3-ol, **12a**: oil; R_f 0.40 (CH_2Cl_2); ^{1}H NMR δ 0.21 (s, 9H), 0.97 (t, 3H, J=7.2 Hz), 1.03 (d, 3H, J=6.9 Hz), 1.30 (m, 1H), 1.65 (m, 2H), 2.0 (broad s, 1H), 4.29 (d, 1H, J=4.8 Hz); ^{13}C NMR δ 0.2, 11.6, 14.4, 24.7, 41.0, 66.9, 89.9, 106.0; IR (neat) 3450, 2940, 2130, 1245, 825; $[\alpha]_D^{20}$=+5.4 (c 1.9, $CHCl_3$); MS (NH_3/CI) m/z (rel. int.) 202 (92, $[M+NH_4^+]$). HRMS calcd for $C_{10}H_{19}Si$ (M^+-H_2O+1) 167.1256, found 167.1255.

An analytical sample was transformed into the corresponding Mosher ester derived from Mosher's (*R*)-acid. ^{1}H and

^{19}F NMR analysis of the sample revealed as composition **12a/13a**=24:1.

In a similar way, the reduction of 1 mmol of **10a** using 0.2 mmol (*R*)-**11** and 1.1 mmol of BH_3:SMe_2 afforded 90 % of alcohols (**12a/13a** 19:1).

(3*R*,4*S*)-5-Benzyloxy-4-methyl-1-trimethylsilylpent-1-yn-3-ol (12b). Oil; R_f 0.39 (CH_2Cl_2); ^1H NMR δ 0.18 (s, 9H), 0.92 (d, 3H, *J*=7.2 Hz), 2.26 (m, 1H), 3.52 (m, 1H), 3.71 (m, 1H), 4.41 (dd, 1H, *J*=3.3, 8.4 Hz), 4.50 (d, 1H, *J*=11.8 Hz), 4.55 (d, 1H, *J*=11.8 Hz), 7.15–7.31 (m, 5H); ^{13}C NMR δ −0.1, 12.7, 38.5, 67.0, 73.5, 73.6, 90.2, 104.9, 127.6, 127.7, 128.4, 137.7; IR (neat) 3450, 2180; $[\alpha]_D^{20}$=+42.3 (*c* 1.1, $CHCl_3$); MS (NH_3/CI) *m/z* (rel. int.) 294 (100, $[M+NH_4^+]$). HRMS calcd for $C_{16}H_{25}O_2Si$ (M^++1) 277.1624, found 277.1623.

(3*S*,4*S*)-4-Methoxy-5-phenyl-1-trimethylsilylpent-1-yn-3-ol (12c). Oil; R_f 0.36 (CH_2Cl_2); ^1H NMR δ 0.19 (s, 9H), 2.61 (d, O*H*, *J*=5.6 Hz), 2.85 (dd, 1H, *J*=7.0, 14.0 Hz), 3.00 (dd, 1H, *J*=5.6, 14.0 Hz), 3.42 (s, 3H), 3.50 (m, 1H), 4.19 (dd, 1H, *J*=5.8, 5.8 Hz), 7.20–7.40 (m, 5H); ^{13}C NMR δ −0.2, 37.0, 59.5, 64.2, 85.2, 90.9, 104.3, 126.3, 128.3, 129.5, 137.8; IR (neat) 3450, 2180; $[\alpha]_D^{20}$=−18.3 (*c* 1.0, $CHCl_3$); MS (NH_3/CI) *m/z* (rel. int.) 280 (100, $[M+NH_4^+]$). HRMS calcd for $C_{15}H_{21}OSi$ (M^+-H_2O+1) 245.1362, found 245.1367.

(3*S*,4*S*)-4-(*tert*-Butoxycarbonylamino)-6-methyl-1-trimethylsilylhept-1-yn-3-ol (12d). Yellowish oil; R_f 0.54 (CH_2Cl_2/AcOEt 9:1); ^1H NMR δ 0.18 (s, 9H), 0.93 (d, 3H, *J*=4.2 Hz), 0.95 (d, 3H, *J*=4.2 Hz), 1.45 (s, 9H), 1.46 (m, 2H), 1.68 (m, 1H), 3.21 (broad s, O*H*), 3.87 (broad d, 1H, *J*=7.2 Hz), 4.41 (m, 1H), 4.65 (d, 1H, N*H*, *J*=8.4 Hz); ^{13}C NMR δ 0.2, 21.8, 23.4, 24.8, 28.3, 39.7, 53.4, 66.0, 79.6, 90.6, 104.4, 156.3; IR (film) 3400, 2174, 1696; $[\alpha]_D^{20}$=−41.0 (*c* 1.2, $CHCl_3$). HRMS calcd for $C_{16}H_{32}NSiO_3$ (M^++1) 314.2151, found 314.2162.

(3*S*,4*S*)-4-(*tert*-Butoxycarbonylamino)-5-phenyl-1-trimethylsilylpent-1-yn-3-ol (12e). Mp=73–5°C; R_f 0.17 (CH_2Cl_2); ^1H NMR δ 0.17 (s, 9H), 1.33 (s, 9H), 2.81 (m, 1H), 2.95 (dd, 1H, *J*=3.4, 12.0 Hz), 3.85 (m, 1H), 4.33 (d, 1H, *J*=3.4 Hz), 4.78 (d, 1H, N*H*, *J*=6.0 Hz), 7.20–7.31 (m, 5H); ^{13}C NMR δ −0.8, 28.1, 37.0, 56.4, 68.2, 76.4, 79.9, 126.3, 128.3, 129.3, 135.5, 158.0; IR (KBr) 3250, 1700, 2185; $[\alpha]_D^{20}$=+6.8 (*c* 5.1, $CHCl_3$) for a mixture **12e/13e** 6.8:1; HRMS calcd for $C_{19}H_{30}NSiO_3$ (M^++1) 348.1995, found 348.2002.

(3*S*,4*S*)-4-Methyl-1-trimethylsilylhex-1-yn-3-ol (13a). Oil; R_f 0.40 (CH_2Cl_2); ^1H NMR δ 0.21 (s, 9H), 0.95 (t, 3H, *J*=7.4 Hz), 1.01 (d, 3H, *J*=6.6 Hz), 1.30 (m, 1H), 1.65 (m, 2H), 2.1 (broad s, 1H), 4.28 (d, 1H, *J*=4.8 Hz); ^{13}C NMR δ 0.2, 11.5, 14.1, 25.3, 40.8, 67.0, 90.2, 105.4; IR (neat) 3460, 2930, 2140, 1245, 830; $[\alpha]_D^{20}$=−1.41 (*c* 1.0, $CHCl_3$); MS (NH_3/CI) *m/z* (rel. int.) 202 (90, $[M+NH_4^+]$). HRMS calcd for $C_{10}H_{19}Si$ (M^+-H_2O+1) 167.1256, found 167.1254.

(3*S*,4*S*)-5-Benzyloxy-4-methyl-1-trimethylsilylpent-1-yn-3-ol (13b). Oil; R_f 0.22 (CH_2Cl_2); ^1H NMR δ 0.22 (s, 9H), 1.10 (d, 3H, *J*=7.0 Hz), 2.13 (m, 1H), 3.52 (dd, 1H, *J*=6.8, 9.4 Hz), 3.75 (dd, 1H, *J*=4.6, 9.4 Hz), 4.47 (d, 1H, *J*=6.2 Hz), 4.57 (s, 2H), 7.15–7.31 (m, 5H); ^{13}C NMR δ −0.1, 13.1, 39.4, 66.6, 73.4, 73.5, 90.0, 105.5, 127.6, 127.7, 128.4, 137.9; IR (neat) 3400, 2180; $[\alpha]_D^{20}$=+3.6 (*c* 1.0, $CHCl_3$); MS (NH_3/CI) *m/z* (rel. int.) 294 (100, $[M+NH_4^+]$). HRMS calcd for $C_{16}H_{25}O_2Si$ (M^++1) 277.1624, found 277.1622.

(3*R*,4*S*)-4-Methoxy-5-phenyl-1-trimethylsilylpent-1-yn-3-ol (13c). Oil; R_f 0.34 (CH_2Cl_2); ^1H NMR δ 0.21 (s, 9H), 2.57 (d, O*H*, *J*=6.2 Hz), 2.96 (d, 2H, *J*=6.6 Hz), 3.36 (s, 3H), 3.50 (m, 1H), 4.41 (dd, 1H, *J*=3.6, 6.2 Hz), 7.20–7.40 (m, 5H); ^{13}C NMR δ −0.1, 36.3, 58.5, 63.8, 84.8, 91.6, 103.3, 126.3, 128.3, 129.2, 138.1; IR (neat) 3400, 2170; $[\alpha]_D^{20}$=+70.9 (*c* 1.0, $CHCl_3$); MS (NH_3/CI) *m/z* (rel. int.) 280 (100, $[M+NH_4^+]$). HRMS calcd for $C_{15}H_{21}OSi$ (M^+-H_2O+1) 245.1362, found 245.1364.

(3*R*,4*S*)-4-(*tert*-Butoxycarbonylamino)-6-methyl-1-trimethylsilylpent-1-yn-3-ol (13d). Yellowish oil; R_f 0.54 (CH_2Cl_2/AcOEt 9:1); ^1H NMR δ 0.17 (s, 9H), 0.92 (d, 3H, *J*=2.7 Hz), 0.95 (d, 3H, *J*=3.0 Hz), 1.45 (s, 9H), 1.46 (m, 2H), 1.70 (m, 1H), 3.20 (broad s, O*H*), 3.76 (broad s, 1H), 4.30 (m, 1H), 4.65 (d, 1H, N*H*, *J*=8.7 Hz); ^{13}C NMR δ 0.2, 22.0, 23.2, 24.7, 28.3, 40.0, 53.6, 66.8, 79.9, 91.0, 103.5, 156.7; IR (film) 3400, 2174, 1696; $[\alpha]_D^{20}$=−57.0 (*c* 1.17, $CHCl_3$). HRMS calcd for $C_{16}H_{32}NSiO_3$ (M^++1) 314.2151, found 314.2150.

(3*R*,4*S*)-4-(*tert*-Butoxycarbonylamino)-5-phenyl-1-trimethylsilylhept-1-yn-3-ol (13e). Viscous oil; R_f 0.17 (CH_2Cl_2); ^1H NMR δ 0.21 (s, 9H), 1.39 (s, 9H), 2.88 (m, 2H), 4.12 (m, 1H), 4.40 (d, 1H, *J*=3.4 Hz), 4.75 (d, 1H, N*H*, *J*=4.7 Hz), 7.15–7.31 (m, 5H); ^{13}C NMR δ 0.7, 28.1, 37.6, 56.8, 64.1, 76.4, 79.9, 126.4, 128.5, 129.0, 135.5, 158.0; IR (KBr) 3250, 2185, 1700; $[\alpha]_D^{20}$=−13.7 (*c* 3.5, $CHCl_3$); HRMS calcd for $C_{19}H_{30}NSiO_3$ (M^++1) 348.1995, found 348.2003.

General procedure for conversion of propargylic alcohols into β-hydroxy acids

Preparation of 16 and 17. To a solution of cyclohexene (0.18 mL, 1.78 mmol) in anh. THF (2 mL), BH_3:SMe_2 (80 μL, 0.80 mmol) were added at 0°C under Ar. When the stirred solution was allowed to warm to rt a white suspension of dicyclohexylborane was observed. After 3 h, the mixture was cooled again to 0°C and a solution of **12a** (184 mg, 0.30 mmol) in anh. THF (2 mL) were added via cannula. After 1.5 h of stirring at rt, TLC (98:2 CH_2Cl_2/MeOH) revealed the disappearance of the starting alcohol. The reaction flask was then quenched by addition of saturated aq. $NaHCO_3$ (2 mL) and H_2O_2 (aq. 30%, 0.5 mL) under vigorous stirring and allowed overnight at rt Afterwards, most of solvent were removed under vacuo and aq. 2 M NaOH was added to *p*H=9. The mixture was washed with diethyl ether and the aqueous layer was acidified with HCl until *p*H=2. It was then carefully extracted with CH_2Cl_2, dried ($MgSO_4$) and the volatiles were eliminated in vacuo. The residue was filtered through a pad of silica gel (CH_2Cl_2/MeOH 95:5) to yield 36 mg (82%) of crude acid **5a** [R_f 0.10 (CH_2Cl_2/MeOH 95:5)] which was then dissolved in anh. DMF (1 mL). To the solution, $NaHCO_3$ (50 mg,

0.5 mmol) and methyl iodide (50 μL, 0.8 mmol) were added and the mixture was stirred at rt for 4 h. The reaction was quenched by addition of water (1 mL) and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and carefully concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 95:5) to yield methyl (3*S*,4*S*)-3-hydroxy-4-methylhexanoate, **16**, (20 mg, 62%) as a very volatile liquid. R_f 0.50 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR δ 0.91 (t, 3H, *J*=6.8 Hz), 0.92 (d, 3H, *J*=7.1 Hz), 1.15 (m, 1H), 1.40 (m, 2H), 2.46 (dd, 1H, *J*=10.0, 16.3 Hz), 2.47 (dd, 1H, *J*=2.2, 16.3 Hz), 3.01 (broad s, O*H*), 3.71 (s, 3H), 3.95 (m, 1H); ^{13}C NMR δ 11.7, 13.8, 25.9, 37.7, 39.8, 51.8, 71.6, 174.0; IR (neat) 3400–3000, 2980, 2920, 1740; $[\alpha]_D^{20}=-32.8$ (*c* 1.0, $CHCl_3$) [lit.[26] −33.0]; MS (NH_3/CI) *m*/*z* (rel. int.) 178 (100, $[M+NH_4^+]$).

In a similar way, hydroboration of alcohol **13a** with dicyclohexylborane followed by treatment with saturated aq. $NaHCO_3$ and 30% H_2O_2 gave 82% yield of crude (3*R*,4*S*)-3-hydroxy-4-methylhexanoic acid which was then transformed without purification into its methyl ester ($NaHCO_3$/MeI/DMF, 50%), methyl (3*R*,4*S*)-3-hydroxy-4-methylhexanoate, **17**:[26] oil; R_f 0.50 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR δ 0.89 (t, 3H, *J*=7.1 Hz), 0.92 (d, 3H, *J*=7.1 Hz), 1.20 (m, 1H), 1.50 (m, 2H), 2.41 (dd, 1H, *J*=10.0, 16.3 Hz), 2.49 (dd, 1H, *J*=2.2, 16.3 Hz), 3.01 (broad s, O*H*), 3.71 (s, 3H), 3.87 (m, 1H); ^{13}C NMR δ 11.4, 14.4, 24.9, 37.7, 39.8, 51.8, 71.6, 174.0; IR (neat) 3400–3000, 2980, 2920, 1740; $[\alpha]_D^{20}=+34.8$ (*c* 0.5, $CHCl_3$) [lit.[25] +32.37]; MS (NH_3/CI) *m*/*z* (rel. int.) 178 (100, $[M+NH_4^+]$).

(3*S*,4*S*)-5-Benzyloxy-3-hydroxy-4-methylpentanoic acid (5b). Oil; R_f 0.13 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR δ 0.97 (d, 3H, *J*=6.9 Hz), 1.99 (m, 1H), 2.46 (dd, 1H, *J*=3.6, 16.2 Hz), 2.56 (dd, 1H, *J*=9.6, 16.2 Hz), 3.50 (dd, 1H, *J*=6.9, 9.3 Hz), 3.56 (dd, 1H, *J*=4.5, 9.3 Hz), 4.22 (m, 1H), 4.50 (d, 1H, *J*=12.0 Hz), 4.54 (d, 1H, *J*=12.0 Hz), 7.20–7.40 (m, 5H); ^{13}C NMR δ 11.2, 37.6, 38.3, 70.3, 73.5, 73.7, 127.6, 127.8, 128.5, 137.6, 175.4; IR (neat) 3400–3000, 1715, 1455, 1180; $[\alpha]_D^{20}=-8.8$ (*c* 1.8, $CHCl_3$); MS (NH_3/CI) *m*/*z* (rel. int.) 256 (100, $[M+NH_4^+]$). HRMS calcd for $C_{13}H_{19}O_4$ (M^++1) 239.1283, found 239.1278.

(3*S*,4*S*)-4-Methoxy-5-phenylpentanoic acid (5c). Oil; R_f 0.10 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR δ 2.53 (dd, 1H, *J*=4.2, 16.0 Hz), 2.65 (dd, 1H, *J*=8.2, 16.0 Hz), 2.89 (m, 2H), 3.32 (s, 3H), 3.33 (m, 1H), 3.98 (m, 1H), 7.15–7.35 (m, 5H); ^{13}C NMR δ 36.1, 38.2, 58.6, 68.2, 84.3, 126.3, 128.4, 129.4, 137.9, 176.8; IR (neat) 3400–3300, 1730; $[\alpha]_D^{20}=+3.2$ (*c* 1.7, $CHCl_3$); MS (NH_3/CI) *m*/*z* (rel. int.) 242 (100, $[M+NH_4^+]$). HRMS calcd for $C_{12}H_{17}O_4$ (M^++1) 225.1127, found 225.1120.

(3*S*,4*S*)-4-(*tert*-Butoxycarbonylamino)-3-hydroxy-6-methylheptanoic acid (5d). Mp 115–116°C [lit.[34] 117–118°C]; R_f 0.13 (CH_2Cl_2/AcOEt 9:1); ^{1}H NMR δ 0.92 (d, 6H, *J*=6.2 Hz), 1.25 (m, 2H), 1.46 (s, 9H), 1.72 (m, 1H), 2.53 (m, 2H), 3.65 (m, 1H), 4.01 (broad s, 1H), 4.83 (d, 1H, *J*=8.7 Hz, N*H*); ^{13}C NMR δ 22.1, 23.0, 24.7, 28.3, 39.7, 41.4, 52.1, 69.8, 79.6, 156.4, 177.8; IR (KBr) 3340, 1716, 1686; $[\alpha]_D^{20}=-38.4$ (*c* 1.0, MeOH) [lit.[34] −39.6].

(3*S*,4*S*)-4-(*tert*-Butoxycarbonylamino)-3-hydroxy-5-phenylpentanoic acid (5e). Mp 149–150°C [lit.[35] 148–148.5°C]; R_f 0.40 (CH_2Cl_2/MeOH/AcOH 95:5:1); ^{1}H NMR (CD_3OD, 200 MHz) δ 1.34 (s, 9H), 2.43 (m, 2H), 2.69 (dd, 1H, *J*=9.0, 13.5 Hz), 2.86 (dd, 1H, *J*=5.8, 14.0 Hz), 3.77 (m, 1H), 4.05 (m, 1H), 6.25 (broad d, *J*=8.7 Hz, N*H*), 7.20–7.35 (m, 5H); ^{13}C NMR (CD_3OD, 50.3 MHz) δ 28.7, 38.8, 40.1, 57.3, 69.9, 79.5, 127.2, 128.5, 129.3, 140.1, 158.2, 182.4; IR (KBr) 3360, 2927, 1711, 1690. $[\alpha]_D^{20}=-39.0$ (*c* 1.4, MeOH) [lit.[35] −37.0, lit.[36] −39.0].

(3*R*,4*S*)-5-Benzyloxy-3-hydroxy-4-methylpentanoic acid (6b).[37] Oil; R_f 0.13 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR δ 0.93 (d, 3H, *J*=6.9 Hz), 1.95 (m, 1H), 2.47 (dd, 1H, *J*=8.7, 15.9 Hz), 2.58 (dd, 1H, *J*=3.3, 15.9 Hz), 3.51 (dd, 1H, *J*=6.9, 9.3 Hz), 3.57 (dd, 1H, *J*=5.1, 9.3 Hz), 4.00 (m, 1H), 4.52 (s, 2H), 6.40 (broad s, 2H, O*H*), 7.20–7.40 (m, 5H); ^{13}C NMR δ 13.6, 38.1, 39.2, 71.8, 73.4, 73.9, 127.6, 127.7, 128.4, 137.6, 175.4; IR (neat) 3400–3000, 1725, 1452; $[\alpha]_D^{20}=+17.8$ (*c* 1.1, $CHCl_3$); MS (NH_3/CI) *m*/*z* (rel. int.) 256 (100, $[M+NH_4^+]$). HRMS calcd for $C_{13}H_{19}O_4$ (M^++1) 239.1283, found 239.1288.

(3*R*,4*S*)-4-Methoxy-5-phenylpentanoic acid (6c). Oil; R_f 0.10 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR δ 2.59 (dd, 1H, *J*=8.7, 16.5 Hz), 2.69 (dd, 1H, *J*=3.3, 16.5 Hz), 2.85 (d, 2H, *J*=6.3 Hz), 3.31 (s, 3H), 3.44 (m, 1H), 4.00 (m, 1H), 7.15–7.30 (m, 5H); ^{13}C NMR δ 36.2, 36.7, 58.6, 69.0, 84.5, 126.4, 128.4, 129.4, 138.0, 178.0; IR (neat) 3400–3300, 1730; $[\alpha]_D^{20}=+9.1$ (*c* 0.9, $CHCl_3$); MS (NH_3/CI) *m*/*z* (rel. int.) 242 (100, $[M+NH_4^+]$). HRMS calcd for $C_{12}H_{17}O_4$ (M^++1) 225.1127, found 225.1122.

(3*R*,4*S*)-4-(*tert*-Butoxycarbonylamino)-3-hydroxy-6-methylheptanoic acid (6d). Mp 132–134°C [lit.[34] 135–136°C]; R_f 0.07 (CH_2Cl_2/MeOH 95:5); ^{1}H NMR δ 0.91 (d, 3H, *J*=6.6 Hz), 0.94 (d, 3H, *J*=6.6 Hz), 1.32 (m, 2H), 1.45 (s, 9H), 1.66 (m, 1H), 2.59 (m, 2H), 3.70 (m, 1H), 4.01 (broad s, 1H), 4.72 (d, 1H, *J*=8.1 Hz, N*H*), 5.90 (broad s, 1H, O*H*); ^{13}C NMR δ 21.5, 23.5, 24.7, 28.3, 37.2, 38.8, 53.0, 71.4, 80.1, 156.6, 175.8; IR (KBr) 3340, 1716, 1686; $[\alpha]_D^{20}=-25.3$ (*c* 0.2, MeOH) [lit.[34] −27.6].

(3*R*,4*S*)-4-(*tert*-Butoxycarbonylamino)-3-hydroxy-5-phenylpentanoic acid (6e). Mp 183–185°C [lit.[35] 187.5°C]; R_f 0.33 (CH_2Cl_2/MeOH/AcOH 95:5:1); ^{1}H NMR (CD_3OD, 200 MHz) δ 1.18 (s, 9H), 2.36 (dd, 1H, *J*=9.3, 15.6 Hz), 2.54 (m, 2H), 3.07 (dd, 1H, *J*=3.3, 13.9 Hz), 3.61 (m, 1H), 3.90 (m, 1H), 6.40 (broad d, *J*=10.9 Hz, N*H*), 7.10–7.25 (m, 5H); ^{13}C NMR (CD_3OD, 50.3 MHz) δ 28.7, 37.7, 40.2, 58.0, 72.0, 79.9, 127.1, 129.2, 130.4, 140.2, 153.9, 175.7; IR (KBr) 3355, 3000, 1700, 1680; $[\alpha]_D^{20}=-17.2$ (*c* 1.4, MeOH) [lit.[35] −16.1]; HRMS calcd for $C_{16}H_{24}NO_5$ (M^++1) 310.1654, found 310.1647.

Representative procedure for reduction of cobalt complexes

Reduction of 14a with BH_3:SMe_2 catalysed by 15. To a solution of of $Co_2(CO)_8$ (250 mg, 0.66 mmol) in anh. pentane (2 mL) under Ar at rt, a solution of ketone **10a** (115 mg, 0.63 mmol) in anh. pentane (1 mL) was added via cannula. The dark red solution was stirred at rt After 2 h, TLC

revealed the disappearance of the starting ketone. Concentration and column chromatography (hexane/CH_2Cl_2 4:6) afforded of **14a** (268 mg, 91%) as a red oil which was stored under Ar until the reduction step: R_f 0.52 (CH_2Cl_2/hexane 1:1); ^{1}H NMR δ 0.36 (s, 9H), 0.93 (t, 3H, J=7.4 Hz), 1.23 (d, 3H, J=7.0 Hz), 1.56 (m, 1H), 1.80 (m, 1H), 2.77 (m, 1H); ^{13}C NMR δ 0.7, 12.0, 17.9, 25.7, 49.5, 111.3, 112.3, 199.6, 205.9; IR (film) 2980, 2940, 2040, 1680, 1260, 840. A solution of ketone **14a** (240 mg, 0.51 mmol) in THF (2 mL) was added dropwise over ~50 min to a solution of BH_3:SMe_2 (61 μL, 0.61 mmol) and (4*R*,5*S*)-**15** (0.56 mmol, from a toluene solution after removing the solvent under vacuum) in THF (1 mL), at 0°C under Ar. After 90 min, TLC revealed the disappearance of the starting ketone. The reaction was then cautiously quenched by adding 1 mL of MeOH, allowed to warm to rt, and stirred for additional 30 min. The mixture was carried to dryness under vacuum and the residue was filtered through a pad of silica gel (hexane/CH_2Cl_2, 3:7) to afford after removing the solvent under vacuo, besides recovered ketone **14a** (19 mg, 8%), the hexacarbonyldicobalt complex of the propargylic alcohol **13a** (204 mg, 85%): R_f 0.42 (CH_2Cl_2/hexane 1:1); ^{1}H NMR δ 0.34 (s, 9H), 0.96 (t, 3H, J=7.2 Hz), 1.05 (d, 3H, J=7.0 Hz), 1.56 (m, 2H), 1.80 (m, 1H), 4.51 (broad m, 1H); ^{13}C NMR δ 1.1, 11.0, 16.4, 24.4, 42.6, 77.4, 114.9, 115.2, 199.0, 205.9; IR (film) 3450, 2980, 2000, 1580, 1250, 840. To a solution of the crude complex (168 mg, 0.36 mmol) in MeOH (4 mL), CAN (987 mg, 1.8 mmol) were added at rt A vigorous gas release was observed. After 1 h (TLC monitoring), the volatiles were eliminated under vacuo and the residue was partitioned with CH_2Cl_2 and saturated aqueous NaCl. The organic phase was dried over $MgSO_4$. Evaporation of the solvent and purification by column chromatography (CH_2Cl_2) yielded 62 mg (0.34 mmol, 94%) of **13a**. An analytical sample of **13a** was transformed into the corresponding Mosher ester derived from Mosher's (*R*)-acid. ^{1}H and ^{19}F NMR analysis of the sample revealed 97% d.e.

A similar reduction of **14a** was performed with BH_3:SMe_2 (1.2 equiv.) and (4*S*,5*R*)-**15** (1.1 equiv.) to afford **12a** in 82% yield and 97% d.e.

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