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Asymmetric Transfer Hydrogenation of Functionalized Acetylenic Ketones

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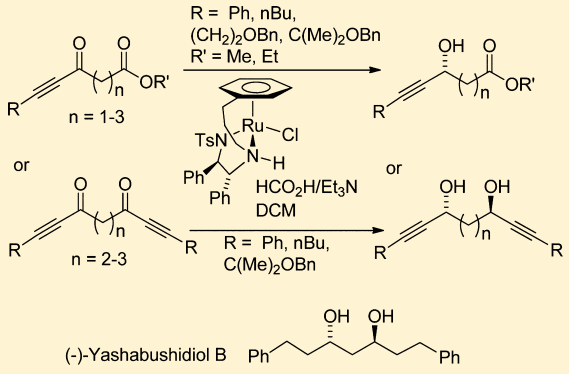
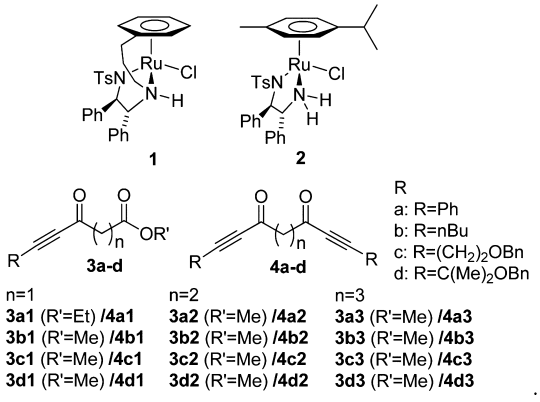
Supporting Information

ABSTRACT: A systematic study of the asymmetric transfer hydrogenations of functionalized acetylenic ketones and diketones has been completed, together with a total synthesis of (*S*,*S*)-(−)-yashabushidiol B. In several cases, excellent enantioselectivities and yields were achieved.



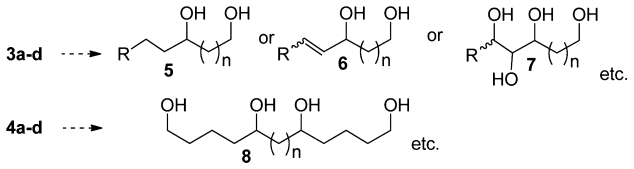
INTRODUCTION

In previous reports, we have described the preparation of novel Ru(II)-based complex **1**[1] and its application as a catalyst in the asymmetric transfer hydrogenation (ATH) of ketones.[2] As part of an ongoing series of investigations into the substrate scope of complex **1**,[3] we undertook a systematic investigation into its applicability to ATH of functionalized acetylenic ketones and diketones. Substrates of this class may be reduced in high enantioselectivity by a number of reagents[4,5] including diisopinylcampheryl borane[4a−d] and oxazaborolidines.[4e−k] They are also been reported to be highly compatible with reduction by ATH[5] using the well-established catalyst **2**, which were first reported by Noyori and co-workers,[6] and several applications involving acetylenic ketones have been described.[5] Specifically, we focused on two classes of substrate: **3**, containing an ester function, and **4**, a diketone derivative. The effect of variations of the separation between these functional groups and of the functional group on the alkyne were examined.



The reduction products may act as precursors for numerous derivatives, including saturated chain products **5**, *Z*- or *E*-alkenes **6**, and other products, for example, polyols **7**. The diol products from **4** could likewise be converted to stereochemically pure polyol products such as **8** (Scheme 1).

Scheme 1. Products That May Be Derived from Reduction Products 3 and 4



RESULTS AND DISCUSSION

The synthesis of ester **3a1** was achieved through addition of diethyl malonate **10** to precursor PhCCCOBt **9**, followed by monodeesterification with aqueous TsOH.[7a] An alternative route, the BF_3-catalyzed reaction of a terminal acetylene with an acid chloride **11**,[7b] was also efficient and provided access to substrates **3b1**−**3d1** and the α-methylated derivatives **12**−**15** in good yields. Thioesters **16** and **17** were also prepared from **9** by use of ethyl and phenyl thioacetate, respectively.[8]

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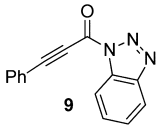

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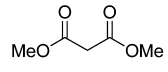

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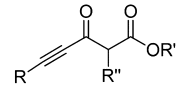
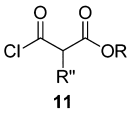


12 R=Ph,R'=Et, R''=Me
13 R=nBu, R'=Et, R''=Me
14 R=R=$(CH_2)_2OBn$, R'=Et, R''=Me
15 R=$C(Me)_2OBn$, R'=Et, R''=Me



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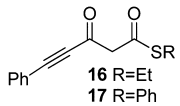
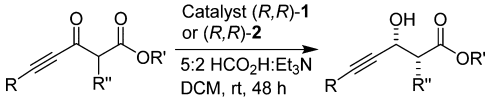


16 R=Et
17 R=Ph

The subsequent ATH of β-keto esters has precedence[9] and worked well on our substrates with both **1** and **2** as catalyst, consistently furnishing products in high yield and enantiomeric excess (ee) (Table 1). The absolute configuration of the products

Table 1. Asymmetric Transfer Hydrogenation of Acetylenic β-Keto Esters



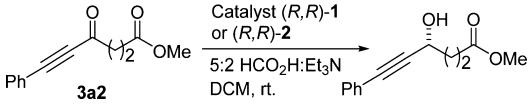
substrate	catalyst	S/C	yield,[a] %	syn/anti[a]	ee,[b] %
3a1	(*R*,*R*)-**1**	200	95	n/a	92
3b1	(*R*,*R*)-**1**	200	92	n/a	97
3c1	(*R*,*R*)-**1**	200	92	n/a	97
3d1	(*R*,*R*)-**1**	200	99	n/a	99
12	(*S*,*S*)-**1**	200	98	13/1	99 (syn)[c]
12	(*R*,*R*)-**1**	100	94	13/1	99 (syn)
12	(*R*,*R*)-**2**	30	99	24/1	98 (syn)
12	(TsEN)Ru[d]	30	88	11/1	n/a
13	(*R*,*R*)-**1**	200	92	14/1	>99 (syn)
13	(*R*,*R*)-**2**	30	87	27/1	99 (syn)
14	(*R*,*R*)-**1**	200	92	14/1	>99 (syn)
14	(*R*,*R*)-**2**	30	76	31/1	>98 (syn)
15	(*R*,*R*)-**1**	200	97	12/1	>99 (syn)
15	(*R*,*R*)-**2**	30	90	27/1	99 (syn)

[a]Syn/anti ratios were determined by ^{1}H NMR; isolated yields are given. [b]Enantiomeric excess values were determined by chiral HPLC. [c](*S*,*S*)-**1** used, *ent*-product formed. [d]Ligand $TsNHCH_2CH_2NH_2$ (TsEN) was used.

[*R* when (*R*,*R*)-catalyst was employed] was based upon total synthesis of a natural product of known configuration described below, from the product of ATH of **3a1** by use of (*R*,*R*)-**1**. The observed configuration also matches that which would be expected from the reported precedents[5,9] for this class of substrate. In addition, an efficient dynamic kinetic resolution (DKR) was observed with the α-methylated substrates.[10] In our tests, catalyst **1** was more active than **2**, and could therefore be employed at higher substrate to catalyst (S/C) ratios. In the DKR studies, this was also the case; however, catalyst **2** furnished products with a higher diastereomeric ratio (dr). In all cases, the syn product was favored, and this was assigned by comparison of the ^{1}H NMR data for the reduction product of **13** with that of the analogous reported decynoate (see Supporting Information).[11] The use of a nonchiral catalyst based on TsEN[1a] provided a convenient method for the preparation of racemic products of similar dr. Thioesters **16** and **17** could not be reduced under these conditions, however, even at a catalyst loading as high as 10 mol %.

Our studies were next extended to the γ-keto esters **3a2**−**3d2** and δ-keto esters **3a3**−**3d3**, which were prepared by the reaction of acid chlorides with the lithium anion of the appropriate acetylene, in the presence of either $BF_3{\cdot}Et_2O$ or $ZnCl_2$.[5ex,7b,12,13] A series of reductions of **3a2** were then investigated (Table 2). Both **1** and **2** were effective catalysts,

Table 2. Asymmetric Transfer Hydrogenation of Acetylenic γ-Keto Ester 3a2[a]



3a2

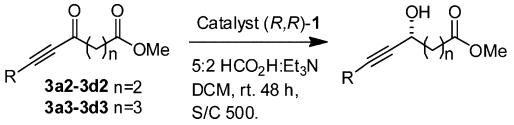
catalyst	solvent	S/C	*T*, °C	*t*, h	conv,[b] %	ee,[c] %	yield,[b] %
(*R*,*R*)-**2**	DCM	50	rt	15	100	94 (*R*)	67
(*R*,*R*)-**2**	CH_3CN	50	rt	15	100	90 (*R*)	78
(*R*,*R*)-**1**	DCM	500	rt	30	100	94 (*R*)	89
(*R*,*R*)-**1**	DCM	1000	rt	144	73	95 (*R*)	69
(*R*,*R*)-**1**	DCM	1000	30	144	78	95 (*R*)	73
(*R*,*R*)-**1**	DCM	2000	40	144	53	94 (*R*)	30

[a]DCM, dichloromethane; rt, room temperature. [b]Conversions and yields were determined by separation of starting materials and products. [c]Enantiomeric excess values were determined by chiral HPLC.

although **1** was more active and could be employed at S/C up to 500 before a drop in conversion (but not enantioselectivity) was observed.

The γ-keto esters **3b2**−**3d2** and δ-keto esters **3a3**−**3d3** were more reactive than β-keto esters (Table 3) and gave products in

Table 3. Asymmetric Transfer Hydrogenation of Acetylenic γ- and δ-Keto Esters



3a2-3d2 n=2
3a3-3d3 n=3

substrate	yield,[a] %	ee,[a] %
3a2	89	94 (*R*)
3b2	89	93 (*R*)
3c2	95	98 (*R*)
3d2	77	99 (*R*)
3a3	89	96 (*R*)
3b3	81	99 (*R*)
3c3	99	99 (*R*)
3d3	84	98 (*R*)

[a]Enantiomeric excess values were determined by chiral HPLC; isolated yields are given.

consistently high enantiomeric excesses and yield.[14] In all cases the absolute configurations were assigned by analogy with the reductions of **3a1**−**3d1** described above, and on the basis of the known directing effect of the triple bond in ATH reductions.[5]

Next we turned to diketones.[15] The acetylenic 1,3-diketone **18** was successfully prepared in the reaction between the enolate of acetophenone and PhCCCOBt **9**.[16] 1,3-Diketone **18** is relatively inactive to reduction, in contrast to nonacetylenic substrates.[17] This may be due to the high enol/ketone ratio it exhibits (ca. 35/1 in $CDCl_3$) in solution. Unfortunately all

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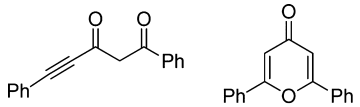
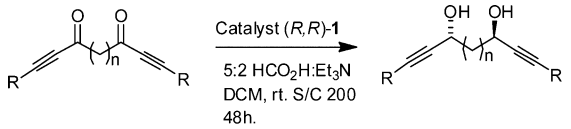
attempts at ATH of **18** resulted in exclusive formation of the cyclized product **19**.[18]



18 **19**

More success was recorded with the longer-chain substrates **4a2**, **4b2**, **4d2**, **4a3**, and **4d3**, which were prepared by reported methods.[19] Reduction of the 1,4- and 1,5-diketones was highly enantioselective, with products formed in high dr and ee (higher than 99% in all cases), with a predictable preference for the anti isomers (Table 4). The high ees in this case arise in part from the double enantioselection, which results in formation of meso product rather than a minor enantiomer.[20] In all cases the absolute configurations were assigned by analogy with the reductions of **3a1**−**3d1** described above and on the basis of the known directing effect of the triple bond in ATH reductions.[5] These results indicate that 1,4- and 1,5-acetylenic diketones are excellent substrates for ATH with Ru(II)/*N*-tosyl 1,2-diphenylethylenediamine (TsDPEN) type catalysts.

Table 4. Asymmetric Transfer Hydrogenation of 1,4- and 1,5-Diketones

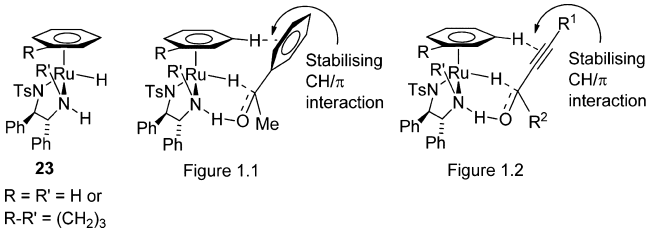


substrate	catalyst	yield,[a] %	dr[a]	ee,[a,b] %
4a2	(*R*,*R*)-**1**	81	26/1	>99
4a2	(*S*,*S*)-**1**	78	49/1	>99
4a3	(*R*,*R*)-**1**	96	35/1	>99
4a3	(*S*,*S*)-**1**	81	76/1	>99
4b2	(*R*,*R*)-**1**	87	33/1	>99
4b2	(*S*,*S*)-**1**	82	28/1	>99
4d2	(*R*,*R*)-**1**	83	44/1	>99
4d2	(*S*,*S*)-**1**	70	124/1	>99
4d3	(*R*,*R*)-**1**	86	76/1	>99
4d3	(*S*,*S*)-**1**	97	110/1	>99

[a]Diastereomeric ratio and enantiomeric excess values were determined by chiral HPLC; isolated yields are given. [b]The (*R*,*R*) catalyst enantiomer gives rise to the (*R*,*R*) diol, and vice versa.

An application of the reductive methodology directed by a triple bond adjacent to the ketone was found in the synthesis of (−)-yashabushidiol B **20** (Scheme 2).[21] It was possible to form the required target by sequential control of the reduction of each acetylenic ketone in turn.[5b,f] The absolute configuration of the product **20**, as well as its precursors **21** and **22**, was confirmed by comparison of the sign of the optical rotations of these compounds with those reported (see Supporting Information).[21] This also served to confirm the absolute configuration of the reduction product of **3a1** and hence the *β*-keto ester reductions in Table 1. The ee and dr of **20** were determined by comparison of the chiral HPLC spectrum with that of a racemic/meso product mixture.

With regard to control of the enantioselectivity, it has been established that Ru(II)/TsDPEN catalysts form a reactive hydride **23** as a single diastereoisomer, and that it is the concerted transfer of two hydrogen atoms from this complex to the ketone which controls the product enantioselectivity. In the case of aryl/alkyl ketones such as acetophenone derivatives, a strong CH/*π* interaction favors positioning of the aromatic ring of the substrate in the "upper" position (as illustrated in Figure 1),[5,22] thereby controlling the face to which hydride is transferred. Our results, in common with those of others, indicate that the alkyne group has a similar dominating stereocontrolling effect (Figure 1).[5] Hence reductions of acetylenic ketones are highly enantioselective in a predictable sense and tolerant to a wide range of substituents at other positions.

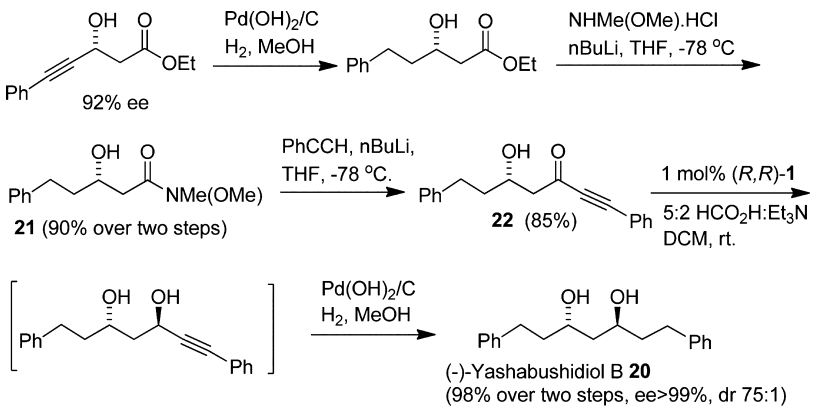


23
R = R' = H or
R-R' = $(CH_2)_3$

Figure 1.1 Figure 1.2

Figure 1. Contrasted stabilizing interactions in transition states of reduction of acetophenone derivatives and acetylenic ketones with **1** [R−R′ = $(CH_2)_3$] and (*R*,*R*)-**2** (R = R′ = H).

Scheme 2. Synthesis of (−)-*S*,*S*-Yashabushidiol B 20



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CONCLUSIONS

In summary, a series of functionalized acetylenic ketones have been reduced to enantiomerically enriched alcohols via ATH with a tethered Ru(II)/TsDPEN-derived catalyst. In the majority of cases, the reductions proceed in excellent ee and yield. The reductions provide a basis for the total asymmetric synthesis of dihydroxylated natural products in high enantiopurity.

EXPERIMENTAL SECTION

General Procedures. Air-sensitive reactions were carried out under a nitrogen or argon atmosphere. NMR spectra were recorded on a 300 or 400 MHz instrument. Chemical shifts are reported in parts per million (ppm) downfield from TMS (Me_4Si). Coupling constants (J) are reported in hertz. Multiplicity in ^1H NMR is reported as singlet (s), doublet (d), broad singlet (br s), broad doublet (br d), triplet (t), quartet (q), and multiplet (m). Mass spectra were recorded on an electrospray instrument. High-resolution mass spectra were recorded on Micro ToF. Infrared spectra were recorded on a Fourier transform infrared (FTIR) spectrometer. Optical rotations were measured on a polarimeter. Chiral HPLC measurements were carried out under the conditions described on HPLC with a chiral column (250 mm × 4.6 mm). Melting points were determined on a melting point apparatus and are uncorrected. Purification of compounds was done by flash column chromatography on silica gel A40−63 μm. Known compounds were identified by comparison of their spectroscopic data to that reported in the references cited.

3-Oxo-5-phenyl-4-pentynoic Acid, Ethyl Ester ***3a1***.[23] Diethyl malonate **10** (96 mg, 0.6 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole (123 mg, 0.50 mmol), and anhydrous $MgBr_2{\cdot}OEt_2$ powder (258 mg, 1.0 mmol) were combined in a flask, and CH_2Cl_2 (2.5 cm^3) was added. The suspension was stirred at room temperature (rt) for 2 h, and then i-Pr_2NEt (194 mg, 1.5 mmol) was added dropwise. A clear orange solution was formed immediately, and the solution was allowed to stir at rt for 1 h. Saturated NH_4Cl (1.5 cm^3) was added, followed by aqueous HCl (10%, 1.0 cm^3), and stirring was continued for 5 min. After a clear solution was formed, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 cm^3) and the combined organic extract was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was semipurified on a short silica gel column (eluent hexane/EtOAc = 15/1) to afford a mixture of Claisen adduct and diethyl malonate. $TsOH{\cdot}H_2O$ (20 mg) and water (6.0 cm^3) were added to the aforementioned mixture, and the resulting solution was refluxed for 6 h. The aqueous phase was extracted with Et_2O (3 × 10 cm^3) and the combined organic phase was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by a silica gel column (eluent hexane/EtOAc = 15/1, R_f = 0.71 hexane/EtOAc 4/1) to afford the product **3a1** as a colorless oil (71 mg, 0.33 mmol, 66% for two steps, enol/β-keto = 1/2). IR (neat) 2983, 2203, 1739, 1671, 1613, 1207, 1029, 756, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.58−7.32 (m, 5H), 4.27−4.20 (m, 2H), 3.69 (s, 2H), 1.30 (t, J = 7.1 Hz, 3H) for ketone, 11.98 (s), 5.45 (s), 1.32 (t, J = 7.1 Hz) for enol; ^{13}C NMR (100 MHz, $CDCl_3$) 178.8, 172.2, 166.1, 155.3, 133.3, 133.1, 132.2, 130.2, 130.8, 129.9, 128.7, 128.6, 128.5, 120.8, 119.5, 97.2, 93.4, 87.3, 83.4, 61.7, 60.7, 51.4, 50.6, 14.2, 14.1 enol and ketone mixture; m/z (EIMS) 239.1 $(M + Na)^+$.

Procedure for Synthesis of Thioesters 16 and 17.[16] Thioester (2.0 mmol), 1-(3-phenyl-1-oxo-2-propynyl)benzotriazole (2.0 mmol), and anhydrous $MgBr_2{\cdot}OEt_2$ powder (1.54 g, 6.0 mmol) were combined in a flask and CH_2Cl_2 (8.0 cm^3) was added. The suspension was stirred at rt for 2 h and then i-Pr_2NEt (257 g, 2.0 mmol) was added dropwise. The solution was allowed to stir at rt for 0.5 h. Saturated NH_4Cl (4 cm^3) was added, followed by aqueous HCl (10%, 4 cm^3), and stirring was continued for 5 min. After a clear solution was formed, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 cm^3) and the combined organic extract was dried over $MgSO_4$. Solvent was evaporated under reduced pressure and the crude product was purified on a silica gel column (eluent hexane/EtOAc = 20/1−15/1) to afford the pure product.

3-Oxo-5-phenyl-4-pentynethioic Acid, S-Ethyl Ester ***16***. This compound was prepared by the general procedure above with ethyl thioacetate (52 mg, 0.5 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole (124 mg, 0.5 mmol), anhydrous $MgBr_2{\cdot}OEt_2$ powder (387 mg, 1.5 mmol), and i-Pr_2NEt (257 mg, 2.0 mmol). The product was isolated as a colorless oil (90 mg, 0.39 mmol, 78%, enol/β-keto = 1.9/1). R_f = 0.63 hexane/EtOAc 8/1; [found (ESI) M^+ + Na, 255.0450; $C_{13}H_{12}O_2S$ requires M, 255.0455]; IR (neat) 2931, 2972, 2003, 1706, 1666, 1602, 1587, 1366, 1284, 1076, 865, 754, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 12.53 (s, 1H), 7.59−7.35 (m, 5H), 5.84 (s, 1H), 2.97 (q, J = 7.4 Hz, 2H), 1.33−1.27 (m, 3H) for enol; ^{13}C NMR (100 MHz, $CDCl_3$) 195.1, 178.2, 152.6, 133.3, 130.0, 132.3, 131.3, 130.6, 130.1, 128.7, 128.6, 120.7, 119.4, 106.3, 94.1, 83.3, 62.1, 59.4, 24.2, 23.1, 14.7, 14.1 enol and ketone mixture; m/z (EIMS) 250.0 $(M + Na)^+$.

3-Oxo-5-phenyl-4-pentynethioic Acid, S-Phenyl Ester ***17***. This compound was prepared by the general procedure above with phenyl thioacetate (304 mg, 2.0 mmol), 1-(3-phenyl-1-oxo-2-propynyl)-benzotriazole (500 mg, 2.0 mmol), anhydrous $MgBr_2{\cdot}OEt_2$ powder (1.54 g, 6.0 mmol), and i-Pr_2NEt (1.04 g, 8.0 mmol). The product was isolated as a white solid (500 mg, 1.79 mmol, 88%, enol/β-keto = 2.0/1). R_f = 0.83 hexane/EtOAc 6/1; mp 52 °C; [found (ESI) M^+ + Na, 303.0449; $C_{17}H_{12}O_2S$ requires M, 303.0455]; IR (neat) 1632, 1580, 1546, 1368, 1079, 1022, 745, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 12.29 (s, 1H), 7.48−7.24 (m, 10H), 5.80 (s, 1H) for enol; ^{13}C NMR (100 MHz, $CDCl_3$) 193.8, 177.9, 153.9, 135.0, 134.5, 133.4, 132.5, 131.4, 130.3, 130.0, 129.5, 129.4, 128.8, 128.7, 126.6, 120.5, 105.0, 94.9, 83.3, 58.9 enol and ketone mixture; m/z (EIMS) 303.0 $(M + Na)^+$.

General Procedure for Synthesis of Propargylic β-Keto Esters from Acyl Chlorides.[7b] To a solution of alkyne (8.6 mmol) in anhydrous tetrahydrofuran (THF, 12 cm^3) at −78 °C was added n-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol) via a syringe over 3 min. The mixture was stirred at the same temperature for 60 min and then $BF_3{\cdot}Et_2O$ (1.1 cm^3, 8.5 mmol) was injected. After 10 min, malonic acid chloride monomethyl ester (495 mg, 3.63 mmol) in THF (1 cm^3) was added. The mixture was stirred for 2 h , and then the reaction was quenched by saturated NH_4Cl (5 cm^3) and water (5 cm^3). The aqueous phase was extracted with Et_2O (3 × 20 cm^3) and the extracts were dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the crude product was purified by silica gel column chromatography (eluent hexane/EtOAc = 20/1−15/1) to afford pure products.

3-Oxo-4-nonynoic Acid, Methyl Ester ***3b1***. This compound was prepared by the general procedure above with 1-hexyne (705 mg, 8.6 mmol), n-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), $BF_3{\cdot}Et_2O$ (1.1 cm^3, 8.5 mmol), and malonic acid chloride monomethyl ester (495 mg, 3.63 mmol). The product was isolated as a colorless oil (320 mg, 1.75 mmol, 48%). R_f = 0.66 hexane/EtOAc 4/1; [found (ESI) M^+ + Na, 205.0837; $C_{10}H_{14}O_3$ requires M, 205.0840]; IR (neat) 2958, 2935, 2213, 1746, 1676, 1611, 1441, 1245, 1169, 1142, 805 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 3.76 (s, 3H), 3.58 (s, 2H), 2.41−2.35 (m, 2H), 1.61−1.54 (m, 2H), 1.48−1.39 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H) for ketone, 11.81 (s), 5.29 (s), 3.75 (s) for enol; ^{13}C NMR (100 MHz, $CDCl_3$) 178.7, 172.6, 166.6, 165.9, 97.1, 96.4, 95.8, 80.3, 52.5, 51.5, 51.1, 29.9, 29.5, 21.9, 18.9, 18.7, 13.4 enol and ketone mixture; m/z (EIMS) 205.1 $(M + Na)^+$.

3-Oxo-7-benzyloxy-4-heptynoic Acid, Methyl Ester ***3c1***. This compound was prepared by the general procedure above with alkyne (963 mg, 6.0 mmol), n-BuLi (1.6 M in hexane, 3.5 cm^3, 5.6 mmol), $BF_3{\cdot}Et_2O$ (0.77 cm^3, 6.0 mmol), and malonic acid chloride monomethyl ester (300 mg, 2.2 mmol). The product was isolated as a colorless oil (230 mg, 0.88 mmol, 45%). R_f = 0.42 hexane/EtOAc 4/1; [found (ESI) M^+ + Na, 283.0941; $C_{15}H_{16}O_4$ requires M, 283.0946]; IR (neat) 2869, 2217, 1743, 1676, 1250, 1099, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.37−7.26 (m, 5H), 4.53 (s, 2H), 3.72 (s, 3H), 3.62 (t, J = 6.7 Hz, 2H), 3.57 (s, 2H), 2.67 (t, J = 6.7 Hz, 2H) for ketone, 11.80 (s), 5.27 (s), 4.54 (s), 3.73 (s) for enol; ^{13}C NMR (100

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MHz, $CDCl_3$) 178.6, 172.6, 166.6, 155.5, 137.7, 128.5, 127.9, 127.7, 96.3, 93.5, 92.9, 80.9, 76.3, 73.1, 73.0, 67.3, 67.0, 52.5, 51.6, 51.0, 20.8, 20.6 enol and ketone mixture; *m*/*z* (EIMS) 283.1 $(M + Na)^+$.

3-Oxo-6-benzyloxy-6 methyl-4-heptynoic Acid, Methyl Ester ***3d1***. This compound was prepared by the general procedure above with alkyne (1.36 g, 7.9 mmol), *n*-BuLi (1.6 M in hexane, 4.6 cm^3, 7.4 mmol), $BF_3{\cdot}Et_2O$ (1.01 cm^3, 7.8 mmol), and malonic acid chloride monomethyl ester (390 mg, 2.8 mmol). The product was isolated as a colorless oil (313 mg, 1.14 mmol, 40%). R_f = 0.69 hexane/EtOAc 4/1; [found (ESI) M^+ + Na, 297.1097; $C_{16}H_{18}O_4$ requires M, 297.1102]; IR (neat) 2989, 2954, 2220, 1748, 1610, 1443, 1382, 1214, 1156, 805, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.39−7.26 (m, 5H), 4.63 (s, 2H), 3.73 (s, 3H), 3.58 (s, 3H), 1.60 (s, 6H) for ketone, 11.79 (s), 5.35 (s), 4.62 (s), 3.76 (s) for enol; ^{13}C NMR (100 MHz, $CDCl_3$) 178.4, 154.9, 138.5, 138.2, 128.44, 128.39, 127.74, 127.67, 127.57, 97.0, 96.1, 82.7, 78.8, 70.8, 70.6, 67.1, 67.0, 52.6, 51.7, 51.1, 28.4, 28.1 enol and ketone mixture; *m*/*z* (EIMS) 297.1 $(M + Na)^+$.

General Procedure for Asymmetric Transfer Hydrogenation of Propargylic β-Keto Esters. (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0×10^{-3} mmol) and HCO_2H/Et_3N 5/2 azeotropic mixture (168 mg) was added into a flask, and freshly prepared β-keto ester (0.2 mmol) in degassed dichloromethane (1 cm^3) was injected under a nitrogen atmosphere. The mixture was stirred at rt until the starting material was completely consumed (1−2 days) and then concentrated and directly purified by silica gel column chromatography (eluent hexane/EtOAc = 10/1−5/1) to give the chiral alcohols.

(3R)-Hydroxy-5-phenyl-4-pentynoic Acid, Ethyl Ester, Reduction Product of ***3a1***.[24] This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0×10^{-3} mmol), ketone **3a1** (43.2 mg, 0.20 mmol), HCO_2H/Et_3N 5/2 (168 mg), and CH_2Cl_2 (1.0 cm^3), and the product was isolated as a colorless oil (41.4 mg, 0.19 mmol, 95%, 92% ee). R_f = 0.46 hexane/EtOAc 4/1; $[\alpha]_D^{26}$ +18.9 (*c* 0.6 in $CHCl_3$) 92% ee (*R*); [found (ESI) M^+ + Na, 241.0835; $C_{13}H_{14}O_3$ requires M, 241.0840]; IR (neat) 3429, 2982, 1717, 1159, 1025, 756, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.44−7.40 (m, 2H), 7.35−7.27 (m, 3H), 5.00 (t, *J* = 6.0 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.24 (br s, 1H), 2.84 (d, *J* = 6.0 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.3, 131.8, 128.6, 128.3, 122.3, 88.3, 85.0, 61.1, 59.2, 42.2, 14.2; *m*/*z* (EIMS) 241.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 95/5, 0.6 cm^3/min, *T* = 30 °C. Retention times: (major, *R*) 17.0 min, (minor, *S*) 20.6 min. The absolute configuration assignment of this compound is based on comparisons to reported data for (−)-yashabushidiol B and two intermediates to this described below.

(3R)-Hydroxy-4-nonynoic Acid, Methyl Ester, Reduction Product of ***3b1***. This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0×10^{-3} mmol), ketone **3b1** (41.0 mg, 0.22 mmol), HCOOH/Et_3N 5/2 (168 mg), and CH_2Cl_2 (1.0 cm^3), and the product was isolated as a colorless oil (38.0 mg, 20.6 mmol, 92%, 97% ee). R_f = 0.31 hexane/EtOAc 4/1; $[\alpha]_D^{26}$ +27.1 (*c* 0.9 in $CHCl_3$) 97% ee (*R*); [found (ESI) M^+ + Na, 207.0992; $C_{10}H_{16}O_3$ requires M, 207.0997]; IR (neat) 3475, 2958, 1738, 1438, 1276, 1162, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.71−4.65 (m, 1H), 3.66 (s, 3H), 3.00 (d, *J* = 5.7 Hz, 1H), 2.66 (d, *J* = 1.6 Hz, 1H), 2.65 (s, 1H), 2.13 (td, *J* = 7.1, 2.0 Hz, 2H), 1.45−1.26 (m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.8, 86.0, 79.3, 58.9, 51.9, 42.3, 30.5, 21.8, 18.3, 13.5; *m*/*z* (EIMS) 207.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 96/4, 0.5 cm^3/min, *T* = 30 °C. Retention times: (major, *R*) 17.8 min, (minor, *S*) 17.0 min.

(3R)-Hydroxy-7-benzyloxy-4-heptynoic Acid, Methyl Ester, Reduction Product of ***3c1***. This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0×10^{-3} mmol), ketone **3c1** (52.0 mg, 0.20 mmol), HCOOH/Et_3N 5/2 (168 mg), and CH_2Cl_2 (1.0 cm^3), and the product was isolated as a colorless oil (48.3 mg, 0.18 mmol, 92%, 97% ee). R_f = 0.26 hexane/EtOAc 4/1; $[\alpha]_D^{28}$ +17.6 (*c* 1.0 in $CHCl_3$) 97% ee (*R*); [found (ESI) M^+ + Na, 285.1097; $C_{15}H_{18}O_4$ requires M, 285.1102]; IR (neat) 3427, 2865, 1735, 1163, 1096, 1062, 1027, 737, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38−7.26 (m, 5H), 4.78−4.72 (m, 1H), 4.54 (s, 2H), 3.72 (s, 3H), 3.57 (t, *J* = 7.0 Hz, 2H), 2.94 (d, *J* = 5.9 Hz, 1H), 2.72 (d, *J* = 6.0 Hz, 2H), 2.52 (td, *J* = 7.0, 1.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.7, 138.0, 128.4, 127.8, 127.7, 82.5, 80.5, 72.9, 68.2, 58.8, 51.9, 42.2, 20.1; *m*/*z* (EIMS) 285.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 96/4, 0.5 cm^3/min, *T* = 30 °C. Retention times: (major, *R*) 55.3 min, (minor, *S*) 53.0 min.

(3R)-Hydroxy-6-benzyloxy-6-methyl-4-heptynoic Acid, Methyl Ester, Reduction Product of ***3d1***. This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0×10^{-3} mmol), ketone **3d1** (53.2 mg, 0.20 mmol), HCOOH/Et_3N 5/2 (168 mg), and CH_2Cl_2 (1.0 cm^3), and the product was isolated as a colorless oil (53.1 mg, 1.92 mmol, 99%, 99% ee). R_f = 0.40 hexane/EtOAc 2/1; $[\alpha]_D^{28}$ +21.4 (*c* 0.8 in $CHCl_3$) 99% ee (*R*); [found (ESI) M^+ + Na, 299.1254; $C_{16}H_{20}O_4$ requires M, 299.1259]; IR (neat) 3420, 2983, 1736, 1154, 1049, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.35−7.15 (m, 5H), 4.67−4.80 (m, 1H), 4.52 (s, 2H), 3.61 (s, 3H), 3.08 (br s, 1H), 2.65 (d, *J* = 6.4 Hz, 2H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.6, 139.0, 128.3, 127.7, 127.4, 87.4, 83.5, 70.5, 66.5, 58.8, 52.0, 42.0, 28.8; *m*/*z* (EIMS) 299.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 96/4, 0.5 cm^3/min, *T* = 30 °C. Retention times: (major, *R*) 18.7 min, (minor, *S*) 18.1 min.

General Procedure for Synthesis of Propargylic α-Methyl-β-keto Esters.[7b] To a solution of alkyne (8.6 mmol) in anhydrous THF (12 cm^3) at −78 °C was added *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol) via a syringe over 3 min. The mixture was stirred at the same temperature for 10 min and then $BF_3{\cdot}EtO_2$ (1.1 cm^3, 8.5 mmol) was injected. After 10 min, 3-chloro-2-methyl-3-oxopropanoic acid ethyl ester (510 mg, 3.10 mmol) in THF (1 cm^3) was added in one portion. The mixture was stirred for 1.5 h and then the reaction was quenched by saturated NH_4Cl (5 cm^3) and water (5 cm^3). The aqueous phase was extracted with Et_2O (2 × 20 cm^3), and the organic phase was dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the crude product was purified by silica gel column chromatography (eluent hexane/DCM = 10/1−10/3) to afford the pure product.

2-Methyl-3-oxo-5-phenyl-4-pentynethioic Acid, Ethyl Ester ***12***.[25] This compound was prepared by the general procedure above with phenylacetylene (877 mg, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), $BF_3{\cdot}EtO_2$ (1.1 cm^3, 8.5 mmol), and freshly prepared 3-chloro-2-methyl-3-oxopropanoic acid ethyl ester (510 mg, 3.10 mmol). The product was isolated as light yellow crystals (551 mg, 2.40 mmol, 77%). R_f = 0.72 hexane/EtOAc 4/1; mp 59 °C; [found (ESI) M^+ + Na, 253.0835; $C_{14}H_{14}O_3$ requires M, 253.0840]; IR (neat) 2994, 2931, 2905, 2211, 1631, 1604, 1379, 1276, 1188, 1061, 789, 753, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 12.21 (s, 1H), 7.60−7.51 (m, 2H), 7.46−7.33 (m, 3H), 4.28−4.21 (m, 2H), 2.00 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H) for enol, 3.68 (q, *J* 7.2), 1.50 (d, *J* 7.2), 1.28 (t, *J* = 7.1 Hz) for ketone; ^{13}C NMR (100 MHz, $CDCl_3$) 128.9, 173.0, 152.0, 133.2, 132.0, 131.1, 129.7, 128.7, 128.5, 121.3, 119.6, 104.2, 97.7, 96.3, 86.4, 83.0, 61.6, 61.0, 55.0, 14.2, 14.1, 13.2, 12.9 enol and ketone mixture; *m*/*z* (EIMS) 253.1 $(M + Na)^+$.

2-Methyl-3-oxo-4-nonynoic Acid, Ethyl Ester ***13***. This compound was prepared by the general procedure above with 1-hexyne (706 mg, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), $BF_3{\cdot}EtO_2$ (1.1 cm^3, 8.5 mmol), and freshly prepared 3-chloro-2-methyl-3-oxopropanoic acid ethyl ester (510 mg, 3.10 mmol). The product was isolated as a light yellow oil (538 mg, 2.56 mmol, 82%). R_f = 0.54 hexane/EtOAc 8/1; [found (ESI) M^+ + Na, 233.1148; $C_{12}H_{18}O_3$ requires M, 233.1153]; IR (neat) 2961, 2935, 2211, 1741, 1678, 1644, 1600, 1334, 1243, 1121 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 12.15 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.44 (t, *J* = 7.1 Hz, 2H), 1.89 (s, 3H), 1.62−1.53 (m, 2H), 1.50−1.41 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.934 (t, *J* = 7.3 Hz, 3H) for enol; ^{13}C NMR (100 MHz, $CDCl_3$) 173.1, 169.7, 152.4, 103.0, 100.3, 97.1, 79.4, 74.9, 61.4, 60.8, 54.9, 30.1, 29.6, 21.94, 21.89, 19.1, 18.7, 14.2 14.0, 13.5 13.4, 12.9, 12.8 enol and ketone mixture; *m*/*z* (EIMS) 233.1 $(M + Na)^+$.

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2-Methyl-3-oxo-7-benzyloxy-4-heptynoic Acid, Ethyl Ester ***14***. This compound was prepared by the general procedure above with acetylene (640 mg, mmol), *n*-BuLi (1.6 M in hexane, 2.32 cm^3, 3.71 mmol), $BF_3{\cdot}EtO_2$ (0.50 cm^3, 3.9 mmol), and freshly prepared 3-chloro-2-methyl-3-oxopropanoic acid ethyl ester (237 mg, 1.44 mmol). The product was isolated as a colorless oil (298 mg, 1.03 mmol, 72%). R_f = 0.33 hexane/EtOAc 8/1; [found (ESI) M^+ + Na, 311.1254; $C_{17}H_{20}O_4$ requires M, 311.1259]; IR (neat) 2865, 2225, 1738, 1643, 1600, 1374, 1334, 1243, 1119, 1096, 1025, 804, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 12.05 (s, 1H), 7.35−7.18 (m, 5H), 4.49 (s, 2H), 4.19−4.06 (m, 2H), 3.61−3.40 (m, 3H), 2.67 (t, *J* = 6.9 Hz, 2H), 1.81 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H) for enol; ^{13}C NMR (100 MHz, $CDCl_3$) 173.1, 152.0, 137.9, 128.6, 128.5, 128.3, 128.1, 127.8, 127.7, 103.5, 96.7, 75.8, 73.1, 67.7, 67.1, 67.0, 61.5, 61.4, 60.9, 54.8, 46.2, 21.0, 20.6, 14.2, 14.0, 13.6, 13.0 enol and ketone mixture; *m*/*z* (EIMS) 311.1 $(M + Na)^+$.

2-Methyl-3-oxo-6-benzyloxy-6 methyl-4-heptynoic Acid, Ethyl Ester ***15***. This compound was prepared by the general procedure above with acetylene (1.50 g, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), $BF_3{\cdot}EtO_2$ (1.1 cm^3, 8.5 mmol), and freshly prepared 3-chloro-2-methyl-3-oxopropanoic acid ethyl ester (510 mg, 3.10 mmol). The product was isolated as a colorless oil (864 mg, 2.86 mmol, 92%). R_f = 0.43 hexane/EtOAc 8/1; [found (ESI) M^+ + Na, 325.1410; $C_{18}H_{22}O_4$ requires M, 325.1415]; IR (neat) 2986, 2218, 1735, 1643, 1600, 1374, 1333, 1207, 1155, 1086, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 12.06 (s, 1H), 7.12−7.39 (m, 5H, m), 4.58 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 1.83 (s, 3H), 1.54 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H) for enol; ^{13}C NMR (100 MHz, $CDCl_3$) 172.9, 151.5, 138.6, 128.4, 128.3, 127.8, 127.7, 127.6, 104.2, 100.3, 96.1, 86.9, 78.3, 71.0, 67.0, 61.6, 61.4, 61.0, 55.0, 46.2, 40.9, 30.5, 28.6, 28.2, 19.0, 14.2, 14.1, 13.1, 12.8 enol and ketone mixture; *m*/*z* (EIMS) 325.1 $(M + Na)^+$.

General Procedure for Asymmetric Transfer Hydrogenation/Dynamic Kinetic Resolution of α-Methyl-β-keto Esters. *(2R)-Methyl-(3R)-hydroxy-5-phenyl-4-pentynoic Acid, Ethyl Ester, Reduction Product of* ***12***. This compound was prepared by the general procedure above with (*R*,*R*)-**2** (1.7 mg, 2.7 × 10^{-3} mmol), ketone (20.0 mg, 0.087 mmol), HCOOH/Et_3N 5/2 (84 mg), and CH_2Cl_2 (0.5 cm^3), and the product was isolated as a colorless oil (20.0 mg, 0.086 mmol, 99%, 98% ee, dr 24/1). R_f = 0.46 hexane/EtOAc 4/1; $[\alpha]_D^{23}$ +2.1 (*c* 0.3 in $CHCl_3$) 98% ee (*R*), dr 24/1; [found (ESI) M^+ + Na, 255.0992; $C_{14}H_{16}O_3$ requires M, 255.0997]; IR (neat) 3450, 2982, 1717, 1188, 1027, 755, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.45−7.40 (m, 2H), 7.34−7.27 (m, 5H), 4.83 (dd, *J* = 6.9, 4.1 Hz, 1H), 4.22 (q, *J* = 6.7 Hz, 2H), 3.15 (d, *J* = 6.9 Hz, 1H), 2.88−2.81 (m, 1H), 1.37 (d, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.2, 131.8, 128.6, 128.3, 122.4, 87.3, 85.7, 64.3 61.0, 45.5, 14.2, 12.0; *m*/*z* (EIMS) 255.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 96/4, 0.5 cm^3/min, *T* = 30 °C. Retention times: (major, 2*R*,3*R*) 17.7 min, (minor, 2*S*,3*S*) 25.2 min. (*R*,*R*)-Teth-TsDPEN-RuCl **1** (S/C = 200/1) 94% yield, 13/1 dr, >99% ee.

(2R)-Methyl-(3R)-hydroxy-4-nonynoic Acid, Ethyl Ester, Reduction Product of ***13***. This compound was prepared by the general procedure above with (*R*,*R*)-**2** (4.2 mg, 6.7 × 10^{-3} mmol), ketone (41.0 mg, 0.20 mmol), HCOOH/Et_3N 5/2 (168 mg), and CH_2Cl_2 (1.0 cm^3), and the product was isolated as a colorless oil (35.9 mg, 0.17 mmol, 87%, 99% ee, dr 27/1). R_f = 0.43 hexane/EtOAc 4/1; $[\alpha]_D^{28}$ +4.7 (*c* 1.0 in $CHCl_3$) 99% ee (2*R*,3*R*), dr 27/1; [found (ESI) M^+ + Na, 235.1305; $C_{12}H_{20}O_3$ requires M, 235.1310]; IR (neat) 3442, 2958, 2934, 2874, 1732, 1251, 1184, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.61−4.57 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.04 (d, *J* = 7.1 Hz, 1H), 2.71 (td, *J* = 7.2, 4.2 Hz, 1H), 2.20 (td, *J* = 6.9, 2.0 Hz, 2H), 1.52−1.35 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.28 (d, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7. Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.3, 86.4, 78.5, 62.9, 60.8, 45.7, 30.6, 21.8, 18.3, 14.2, 13.5, 11.9; *m*/*z* (EIMS) 235.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IC column (250 mm × 4.6 mm), hexane/*i*-PrOH 96/4, 0.5 cm^3/min, *T* = 30 °C. Retention times: (major, 2*R*,3*R*) 23.8 min, (minor, 2*S*,3*S*) 21.4 min. (*R*,*R*)-Teth-TsDPEN-RuCl **1** (S/C = 200/1) 92% yield, 14/1 dr, >99% ee. Comparison of the ^1H NMR data with that for the reported *syn*-decynoate analogue[11] permitted assignment of the relative configuration of the product.

(2R)-Methyl-(3R)-hydroxy-7-benzyloxy-4-heptynoic Acid, Ethyl Ester, Reduction Product of ***14***. This compound was prepared by the general procedure above with (*R*,*R*)-**2** (4.2 mg, 6.7 × 10^{-3} mmol), ketone (61.2 mg, 0.21 mmol), HCOOH/Et_3N 5/2 (168 mg), and CH_2Cl_2 (1.0 cm^3), and the product was isolated as a colorless oil (46.5 mg, 0.16 mmol, 76%, >98% ee, dr 31/1). R_f = 0.23 hexane/EtOAc 4/1; $[\alpha]_D^{28}$ +4.0 (*c* 0.7 in $CHCl_3$) 98% ee, dr 31/1; [found (ESI) M^+ + Na, 313.1410; $C_{17}H_{22}O_4$ requires M, 313.1415]; IR (neat) 3446, 2981, 2939, 1729, 1187, 1094, 1027, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.37−7.26 (m, 5H), 4.62−4.58 (m, 1H), 4.53 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.57 (t, *J* = 7.1 Hz, 2H), 3.02 (d, *J* = 6.9 Hz, 1H), 2.70 (qd, *J* = 7.2, 4.2 Hz, 1H), 2.52 (td, *J* = 7.2, 2.0 Hz, 2H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.3, 138.0, 128.4, 127.71, 127.70, 83.1, 79.6, 73.0, 68.3, 63.9, 60.9, 45.4, 20.1, 14.2, 11.8; *m*/*z* (EIMS) 313.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IC column (250 mm × 4.6 mm), hexane/*i*-PrOH 96/4, 0.8 cm^3/min, *T* = 30 °C. Retention times: (major, 2*R*,3*R*) 39.9 min, (minor, 2*S*,3*S*) 57.0 min. (*R*,*R*)-Teth-TsDPEN-RuCl **1** (S/C = 200/1) 92% yield, 14/1 dr, >99% ee.

(2R)-Methyl-(3R)-hydroxy-6-benzyloxy-6-methyl-4-heptynoic Acid, Ethyl Ester, Reduction Product of ***15***. This compound was prepared by the general procedure above with (*R*,*R*)-**2** (4.2 mg, 6.7 × 10^{-3} mmol), ketone (60.4 mg, 0.20 mmol), HCOOH/Et_3N 5/2 (168 mg), and CH_2Cl_2 (1.0 cm^3), and the product was isolated as a colorless oil (54.9 mg, 0.18 mmol, 90%, 99% ee, dr 27/1). R_f = 0.30 hexane/EtOAc 4/1; $[\alpha]_D^{28}$ +5.4 (*c* 0.6 in $CHCl_3$) 99% ee, dr 27/1; [found (ESI) M^+ + Na, 327.1567; $C_{18}H_{24}O_4$ requires M, 327.1572]; IR (neat) 3441, 2983, 1732, 1244, 1186, 1156, 1041, 1028, 735, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.37−7.22 (m, 5H), 4.62 (dd, *J* = 7.1, 4.3 Hz, 1H), 4.60 (s, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.12 (d, *J* = 7.1 Hz, 1H), 2.78−2.71 (m, 1H), 1.53 (s, 6H), 1.30−1.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.0, 139.0, 128.3, 127.7, 127.4, 87.9, 82.8, 70.6, 66.6, 63.8, 61.0, 45.5, 28.9, 14.2, 12.1; *m*/*z* (EIMS) 327.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IC column (250 mm × 4.6 mm), hexane/*i*-PrOH 96/4, 0.5 cm^3/min, *T* = 30 °C. Retention times: (major, 2*R*,3*R*) 16.6 min, (minor, 2*S*,3*S*) 18.5 min. (*R*,*R*)-Teth-TsDPEN-RuCl **1** (S/C = 200/1) 97% yield, 12/1 dr, >99% ee.

General Procedure for Synthesis of Propargylic γ-Keto Esters.[7b] To a solution of acetylene (7.5 mmol) in anhydrous THF (6 cm^3) at −78 °C was added *n*-BuLi (1.6 M in hexane, 4.7 cm^3, 7.5 mmol) over 3 min. The mixture was stirred at 0 °C for 1 h and then recooled to −78 °C, at which point $BF_3{\cdot}Et_2O$ (1.46 g in 8 cm^3 of THF, 10.0 mmol) was added dropwise after 10 min. The mixture was cooled to −90 °C, and 4-chloro-4-oxobutanoic acid methyl ester (1.46 g in 2 cm^3 of THF, 10.0 mmol) was added in one portion. The reaction was quenched by saturated NH_4Cl (8 cm^3) and water (8 cm^3) after 2 h, extracted with Et_2O (2 × 30 cm^3), and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the crude product was purified by silica gel column chromatography (eluent hexane/EtOAc = 15/1−8/1).

4-Oxo-6-phenyl-5-hexynoic Acid, Methyl Ester ***3a2***.[26] This compound was prepared by the general procedure above with phenylactylene (1.63 g, 16 mmol), *n*-BuLi (1.6 M in hexane, 9.5 cm^3, 15.0 mmol), $BF_3{\cdot}EtO_2$ (2.0 cm^3, 16.0 mmol), and 4-chloro-4-oxobutanoic acid methyl ester (2.62 g, 17.4 mmol). The product was isolated as a colorless oil (1.61 g, 7.4 mmol, 49%). R_f = 0.33 hexane/EtOAc 8/1; [found (ESI) M^+ + Na, 239.0682;$C_{13}H_{12}O_3$ requires M, 239.0684]; IR (neat) 2953, 2200, 1734, 1667, 1205, 1168, 1093, 758, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.60−7.56 (m, 2H), 7.49−7.44 (m, 1H), 7.41−7.36 (m, 2H), 3.71 (s, 3H), 3.03 (t, *J* = 6.7 Hz, 2H), 2.72 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 185.4, 172.5, 133.0, 130.8, 128.7, 119.8, 91.4, 87.4, 51.9, 40.0, 27.8; *m*/*z* (EIMS) 239.1 $(M + Na)^+$.

4-Oxo-5-decynoic Acid, Methyl Ester ***3b2***.[27] This compound was prepared by the general procedure above with 1-hexyne (705 mg, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), $BF_3{\cdot}EtO_2$ (1.1 cm^3, 8.5 mmol), and 4-chloro-4-oxobutanoic acid methyl ester

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(1.57 g, 10.4 mmol). The product was isolated as a colorless oil (417 mg, 2.1 mmol, 27%). R_f = 0.58 hexane/EtOAc 4/1; [found (ESI) M^+ + Na, 219.0992; $C_{11}H_{16}O_3$ requires M, 219.0997]; IR (neat) 2958, 2210, 1737, 1675, 1208, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 3.69 (s, 3H), 2.88 (t, J = 6.7 Hz, 2H), 2.64 (t, J = 6.7 Hz, 2H), 2.38 (t, J = 7.1 Hz, 2H), 1.63−1.51 (m, 2H), 1.51−1.35 (m, 2H), 0.93 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 185.5, 172.6, 95.1, 80.4, 51.8, 40.0, 29.6, 27.8, 21.9, 18.6, 13.4; m/z (EIMS) 219.1 $(M + Na)^+$.

4-Oxo-8-benzyloxy-5-octynoic Acid, Methyl Ester ***3c2***. This compound was prepared by the general procedure above with alkyne (674 mg, 4.3 mmol), *n*-BuLi (1.6 M in hexane, 2.5 cm^3, 4.0 mmol), anhydrous $ZnCl_2$ (950 mg, 7.0 mmol), and 4-chloro-4-oxobutanoic acid methyl ester (451 mg, 3.0 mmol). The product was isolated as a colorless oil (204.9 mg, 0.75 mmol, 25%). R_f = 0.26 hexane/EtOAc 4/1; [found (ESI) M^+ + Na, 297.1097; $C_{16}H_{18}O_4$ requires M, 297.1102]; IR (neat) 2952, 2864, 2213, 1734, 1674, 1208, 1155, 1100, 738, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.39−7.27 (m, 5H), 4.56 (s, 2H), 3.68 (s, 3H), 3.64 (t, J = 6.8 Hz, 2H), 2.89 (t, J = 6.8 Hz, 2H), 2.69 (t, J = 6.8 Hz, 2H), 2.64 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 185.4, 172.6, 137.7, 128.5, 127.9, 127.7, 91.5, 81.0, 73.1, 67.1, 51.9, 40.0, 27.8, 20.5; m/z (EIMS) 275.1 $(M + H)^+$.

4-Oxo-7-benzyloxy-7-methyl-5-octynoic Acid, Methyl Ester ***3d2***. This compound was prepared by the general procedure above with alkyne (1.50 g, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), $BF_3{\cdot}EtO_2$ (1.1 cm^3, 8.5 mmol), and 4-chloro-4-oxobutanoic acid methyl ester (1.57 g, 10.4 mmol). The product was isolated as a colorless oil (541 mg, 1.9 mmol, 22%). R_f = 0.67 hexane/EtOAc 4/1; [found (ESI) M^+ + Na, 311.1254; $C_{17}H_{20}O_4$ requires M, 311.1259]; IR (neat) 3032, 2210, 1737, 1679, 1122, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38−7.24 (m, 5H), 4.62 (s, 2H), 3.68 (s, 3H), 2.89 (t, J = 7.6 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.59 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 185.1, 172.4, 138.4, 128.4, 127.7, 127.6, 94.2, 82.9, 70.6, 67.0, 51.9, 40.1, 28.2, 27.6; m/z (EIMS) 311.1 $(M + Na)^+$.

Synthesis of 5-oxo-7-phenyl-6-heptynoic Acid, Methyl Ester 3a3.[26,28] To a solution of phenylacetylene (326 mg, 3.2 mmol) in anhydrous THF (6 cm^3) at −78 °C was added *n*-BuLi (1.6 M in hexane, 1.9 cm^3, 3.0 mmol) in 3 min. The mixture was stirred at −78 °C for 1 h and then $BF_3{\cdot}Et_2O$ (454 mg, 0.4 cm^3, 3.2 mmol) was added dropwise. After 10 min, the mixture was cooled to −90 °C and glutaric acid monomethyl ester chloride (526 mg in 1 cm^3 of THF, 3.2 mmol) was added in one portion. After 2 h at −78 °C, the reaction was quenched by saturated NH_4Cl (6 cm^3) and water (6 cm^3), extracted with Et_2O (2 × 15 cm^3), and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the crude product was purified by silica gel column chromatography (eluent hexane/EtOAc = 15/1−8/1) to afford the product as a colorless oil (300 mg, 1.3 mmol, 43%). R_f = 0.54 hexane/EtOAc 4/1; [found (ESI) M^+ + Na, 253.0833; $C_{14}H_{14}O_3$ requires M, 253.0840]; IR (neat) 2952, 2199, 1733, 1667, 1197, 1168, 758, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.60−7.55 (m, 2H), 7.49−7.43 (m, 1H), 7.41−7.35 (m, 2H), 3.69−3.66 (m, 3H), 2.82−2.73 (m, 2H), 2.44−2.35 (m, 2H), 2.10−2.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 186.8, 173.3, 133.0, 130.8, 128.6, 119.8, 90.9, 87.7, 51.6, 43.3, 32.8, 19.1. m/z (EIMS) 253.1 $(M + Na)^+$.

General Procedure for Synthesis of Other Propargylic δ-Keto Esters.[13] To a solution of acetylene (8.6 mmol) in anhydrous THF (20 cm^3) at −78 °C was added *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol) in 3 min. The mixture was stirred at −78 °C for 1 h, anhydrous $ZnCl_2$ (1.90 g in 8 cm^3 of THF, 14.0 mmol) was added, and the mixture was warmed to 0 °C for 30 min, then glutaric acid monomethyl ester chloride (987 mg, 6.0 mmol) was added in one portion. The reaction was stirred overnight and quenched by saturated NH_4Cl (10 cm^3) and water (10 cm^3), extracted with Et_2O (2 × 30 cm^3), and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the crude product was purified by silica gel column chromatography (eluent hexane/EtOAc = 15/1−8/1).

5-Oxo-6-undecynoic Acid, Methyl Ester ***3b3***.[29] This compound was prepared by the general procedure above with 1-hexyne (1.42 g, 17.2 mmol), *n*-BuLi (1.6 M in hexane, 10.0 cm^3, 16.0 mmol), anhydrous $ZnCl_2$ (3.77 g, 28 mmol), and 4-chloro-4-oxobutanoic acid methyl ester (1.97 g, 12.0 mmol). The product was isolated as a colorless oil (1.33 g, 6.3 mmol, 53%). R_f = 0.20 hexane/EtOAc 8/1; [found (ESI) M^+ + Na, 233.1148; $C_{12}H_{18}O_3$ requires M, 233.1153]; IR (neat) 2958, 2210, 1736, 1671, 1196, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 3.60 (s, 3H), 2.54 (t, J = 7.2 Hz, 2H), 2.30 (t, J = 7.0 Hz, 2H), 2.29 (t, J = 7.2 Hz, 2H), 1.94−1.86 (m, 2H), 1.56−1.50 (m, 2H), 1.48−1.43 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 187.0, 173.3, 94.6, 80.7, 51.5, 44.3, 32.8, 29.6, 21.9, 19.1, 18.5, 13.4. m/z (EIMS) 233.1 $(M + Na)^+$.

5-Oxo-9-benzyloxy-6-nonynoic Acid, Methyl Ester ***3c3***. This compound was prepared by the general procedure above with acetylene (1.50 g, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), anhydrous $ZnCl_2$ (1.90 g, 14.0 mmol), and 4-chloro-4-oxobutanoic acid methyl ester (987 mg, 6.0 mmol). The product was isolated as a colorless oil (1.274 g, 4.4 mmol, 73%). R_f = 0.35 hexane/EtOAc 4/1; [found (ESI) M^+ + Na, 311.1254; $C_{17}H_{20}O_4$ requires M, 311.1259]; IR (neat) 2952, 2866, 2214, 1733, 1671, 1199, 1162, 1099, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38−7.26 (m, 5H), 4.62 (s, 2H), 3.66 (s, 3H), 3.63 (t, J = 6.7 Hz, 2H), 2.66 (t, J = 6.7 Hz, 2H), 2.61 (t, J = 7.2 Hz, 2H), 2.35 (t, J = 7.2 Hz, 2H), 2.00−1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 186.9, 173.3, 137.8, 128.5, 127.8, 127.7, 91.1, 81.3, 73.1, 67.2, 51.6, 44.3, 32.8, 20.5, 19.0. m/z (EIMS) 311.1 $(M + Na)^+$.

5-Oxo-8-benzyloxy-8-methyl-6-nonynoic Acid, Methyl Ester ***3d3***. This compound was prepared by the general procedure above with acetylene (1.50 g, 8.6 mmol), *n*-BuLi (1.6 M in hexane, 5.0 cm^3, 8.0 mmol), anhydrous $ZnCl_2$ (1.90 g, 14.0 mmol), and 4-chloro-4-oxobutanoic acid methyl ester (987 mg, 6.0 mmol). The product was isolated as a colorless oil (884 mg, 2.90 mmol, 48%). R_f = 0.53 hexane/EtOAc 4/1; [found (ESI) M^+ + Na, 325.1410; $C_{18}H_{22}O_4$ requires M, 325.1415]; IR (neat) 2987, 2952, 2213, 1734, 1676, 1156, 1049, 737, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38−7.24 (m, 5H), 4.62 (s, 2H), 3.66 (s, 3H), 2.63 (t, J = 7.2 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H), 2.00−1.93 (m, 2H), 1.60 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 186.5, 173.2, 138.4, 128.4, 127.63, 127.60, 93.8, 83.2, 70.6, 67.0, 51.7, 44.4, 32.7, 28.3, 19.0. m/z (EIMS) 325.1 $(M + Na)^+$.

Asymmetric Transfer Hydrogenation of γ- and δ-Keto Esters. (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0 × 10^{-3} mmol) was dissolved in $HCOOH/Et_3N$ 5/2 azeotropic mixture, and γ-keto ester in degassed dichloromethane was injected under a nitrogen atmosphere. The mixture was stirred at rt until starting material was completely consumed (2−3 days). After the reaction was complete, the reaction mixture was concentrated and directly purified by silica gel column chromatography (eluent hexane/EtOAc = 10/1−5/1) to give the products.

(4R)-Hydroxy-6-phenyl-5-hexynoic Acid, Methyl Ester, Reduction Product of ***3a2***.[30] This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0 × 10^{-3}mmol), 4-oxo-6-phenyl-5-hexynoic acid methyl ester (118.0 mg, 5.5 mmol), $HCOOH/Et_3N$ 5/2 (105 mg), and CH_2Cl_2 (2.5 cm^3), and the product was isolated as a colorless oil (106.5 mg, 4.9 mmol, 89%, 94% ee). R_f = 0.22 hexane/EtOAc 4/1; $[\alpha]_D^{24}$ +13.3 (*c* 0.7 in $CHCl_3$) 94% ee (*R*); [found (ESI) M^+ + Na, 241.0835; $C_{13}H_{14}O_3$ requires M, 241.0841]; IR (neat) 3414, 2952, 1733, 1490, 1440, 1254, 1200, 1166, 1067, 756, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.50−7.27 (m, 5H), 4.71 (t, J = 6.0 Hz, 1H), 3.69 (m, 3H), 2.70−2.54 (m, 3H), 2.19−2.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.1, 131.7, 128.5, 128.3, 122.4, 89.1, 85.4, 62.0, 51.8, 32.5, 29.8; m/z (EIMS) 241.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 95/5, 0.8 cm^3/min, T = 30 °C. Retention times: (major, *R*) 18.6 min, (minor, *S*) 49.1 min.

(4R)-Hydroxy-5-decynoic Acid, Methyl Ester, Reduction Product of ***3b2***. This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0 × 10^{-3} mmol), ketone (101 mg, 0.52 mmol), $HCOOH/Et_3N$ 5/2 (210 mg), and CH_2Cl_2 (2.5 cm^3), and the product was isolated as a colorless oil (90.8 mg, 0.46 mmol, 89%, 93% ee). R_f = 0.22 hexane/EtOAc 4/1; [found (ESI) M^+ + Na, 221.1148; $C_{11}H_{18}O_3Na$ requires M, 221.1153]; IR (neat) 3435, 2957, 2934, 1737, 1437, 1167, 1061 cm^{-1}; ^1H NMR (400 MHz,

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$CDCl_3$) 7.50−7.27 (m, 5H), 4.38 (br s, 1H), 3.61 (s, 3H), 2.64 (br s, 1H), 2.53−2.39 (m, 2H), 2.13 (t, J = 6.9 Hz, 2H), 1.98−1.90 (m, 2H), 1.44−1.28 (m, 4H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.2, 85.9, 80.3, 61.5, 51.7, 32.8, 30.6, 29.8, 21.9, 18.3, 13.5; m/z (EIMS) 221.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IC column (250 mm × 4.6 mm), hexane/*i*-PrOH 94/6, 0.8 cm^3/min, T = 30 °C. Retention times: (major, *R*) 28.5 min, (minor, *S*) 50.8 min.

(4R)-Hydroxy-8-benzyloxy-5-octynoic Acid, Methyl Ester, Reduction Product of ***3c2****.* This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.4 mg, 6.7 × 10^{-4} mmol), ketone (92.2 mg, 0.335 mmol), HCOOH/Et_3N 5/2 (278 mg), and CH_2Cl_2 (1.5 cm^3), and the product was isolated as a colorless oil (87.9 mg, 0.318 mmol, 95%, 98% ee). R_f = 0.15 hexane/EtOAc 4/1; $[\alpha]_D^{34}$ +8.3 (*c* 0.7 in $CHCl_3$) 98% ee (*R*); [found (ESI) M^+ + Na, 299.1254; $C_{16}H_{20}O_4$ requires M, 299.1259]; IR (neat) 3415, 2951, 2864, 1733, 1096, 1063, 737, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.35−7.26 (m, 5H), 4.54 (s, 2H), 4.43 (tt, J = 6.1, 2.0 Hz, 1H), 3.67 (m, 3H), 3.57 (t, J = 7.0 Hz, 2H), 2.59−2.45 (m, 5H), 1.99 (td, J = 7.2, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.1, 138.0, 128.4, 127.8, 127.7, 82.7, 81.5, 73.0, 68.3, 61.6, 51.8, 32.7, 29.8, 20.1; m/z (EIMS) 299.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 95/5, 0.7 cm^3/min, T = 30 °C. Retention times: (major, *R*) 26.4 min, (minor, *S*) 27.9 min.

(4R)-Hydroxy-7-benzyloxy-7-methyl-5-octynoic Acid, Methyl Ester, Reduction Product of ***3d2****.* This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.4 mg, 6.7 × 10^{-4} mmol), ketone (104 mg, 0.36 mmol), HCOOH/Et_3N 5/2 (277 mg), and CH_2Cl_2 (1.6 cm^3), and the product was isolated as a colorless oil (80.2 mg, 0.28 mmol, 77%, 99% ee). R_f = 0.38 hexane/EtOAc 4/1; $[\alpha]_D^{28}$ +5.4 (*c* 1.2 in $CHCl_3$) 99% ee (*R*); [found (ESI) M^+ + Na, 313.1410; $C_{17}H_{22}O_4$ requires M, 313.1415]; IR (neat) 3424, 2987, 2935, 1736, 1244, 1154, 1052, 1027, 736, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 4.37−4.23 (m, 5H), 4.60 (s, 2H), 4.51 (t, J = 6.1 Hz, 1H), 3.68 (m, 3H), 2.66−2.46 (m, 2H), 2.14 (br s, 1H), 2.05−1.98 (m, 2H), 1.53 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.0, 139.0, 128.3, 127.6, 127.4, 87.6, 84.3, 70.6, 66.5, 61.4, 51.8, 32.5, 29.8, 29.0; m/z (EIMS) 313.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IC column (250 mm × 4.6 mm), hexane/*i*-PrOH 94/6, 0.8 cm^3/min, T = 30 °C. Retention times: (major, *R*) 20.4 min, (minor, *S*) 19.2 min.

(5R)-Hydroxy-7-phenyl-6-heptynoic Acid, Methyl Ester, Reduction Product of ***3a3****.* This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0 × 10^{-3} mmol), 5-oxo-7-phenyl-6-heptynoic acid methyl ester (115 mg, 5.0 mmol), HCOOH/Et_3N 5/2 (105 mg), and CH_2Cl_2 (2.5 cm^3), and the product was isolated as a colorless oil (104 mg, 0.45 mmol, 89%, 96% ee). R_f = 0.24 hexane/EtOAc 4/1; $[\alpha]_D^{24}$ +0.5 (*c* 0.7 in $CHCl_3$) 96% ee (*R*); [found (ESI) M^+ + Na, 255.0992; $C_{14}H_{16}O_3$ requires M, 255.0997]; IR (neat) 3407, 2952, 1733, 1097, 1053, 756, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.36−7.34 (m, 2H), 7.26−7.19 (m, 3H), 4.54 (t, J = 6.0 Hz, 1H), 3.60 (m, 3H), 2.35−2.32 (m, 2H), 2.26 (br s, 1H), 1.85−1.73 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.0, 131.7, 128.4, 128.3, 122.5, 89.8, 85.1, 62.4, 51.6, 37.1, 33.6, 20.6. m/z (EIMS) 255.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 95/5, 0.8 cm^3/min, T = 30 °C. Retention times: (major, *R*) 16.4 min, (minor, *S*) 68.5 min.

(5R)-Hydroxy-6-undecynoic Acid, Methyl Ester, Reduction Product of ***3b3****.* This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0 × 10^{-3} mmol), ketone (105 mg, 1.0 × 10^{-3} mmol), HCOOH/Et_3N 5/2 (415 mg), and CH_2Cl_2 (2.0 cm^3), and the product was isolated as a colorless oil (85.6 mg, 4.0 mmol, 81%, 99% ee). R_f = 0.26 hexane/EtOAc 4/1; $[\alpha]_D^{34}$ +4.1 (*c* 1.1 in $CHCl_3$) 99% ee (*R*); [found (ESI) M^+ + Na, 235.1305; $C_{12}H_{20}O_3$ requires M, 235.1310]; IR (neat) 3441, 2955, 2933, 1732, 1236, 1196, 1161, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 4.37 (tt, J = 6.4, 1.9 Hz, 1H), 3.68 (s, 3H), 2.37 (t, J = 7.5 Hz, 2H), 2.20 (td, J = 6.9, 1.9 Hz, 2H), 2.16 (br s, 1H), 1.84−1.75 (m, 2H), 1.75−1.67 (m, 2H), 1.53−1.44 (m, 2H), 1.44−1.35 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.0, 85.7, 80.8, 62.1, 52.5, 37.4, 33.6, 30.7, 21.9, 20.6, 18.3, 13.6. m/z (EIMS) 235.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IA column (250 mm × 4.6 mm), hexane/*i*-PrOH 100/0, 0.8 cm^3/min, T = 30 °C. Retention times: (major, *R*) 13.35 min, (minor, *S*) 13.02 min. Chiral and racemic standards were analyzed by HPLC after being converted to *tert*-butyldiphenylsilyl (TBDPS) ethers.

(5R)-Hydroxy-9-benzyloxy-6-nonynoic Acid, Methyl Ester, Reduction Product of ***3c3****.* This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.4 mg, 6.7 × 10^{-4} mmol), ketone (101.2 mg, 3.51 mmol), HCOOH/Et_3N 5/2 (277 mg), and CH_2Cl_2 (1.6 cm^3), and the product was isolated as a colorless oil (101.1 mg, 3.48 mmol, 99%, 99% ee). R_f = 0.33 hexane/EtOAc 2/1; $[\alpha]_D^{30}$ +5.5 (*c* 1.4 in $CHCl_3$) 99% ee (*R*); [found (ESI) M^+ + Na, 313.1410; $C_{17}H_{22}O_4$ requires M, 313.1415]; IR (neat) 3431, 2950, 2866, 1733, 1096, 1078, 1027, 737, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.37−7.25 (m, 5H), 4.54 (s, 2H), 4.37−4.31 (m, 1H), 3.66 (m, 3H), 3.57 (t, J = 7.0 Hz, 2H), 2.55 (br s, 1H), 2.51 (td, J = 7.0, 2.0 Hz, 2H), 2.35 (t, J = 7.1 Hz, 2H), 1.83−1.73 (m, 2H), 1.73−1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.0, 138.0, 128.4, 127.8, 127.7, 82.2, 82.1, 72.9, 68.3, 62.0, 51.6, 37.2, 33.6, 20.6, 20.1. m/z (EIMS) 313.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IC column (250 mm × 4.6 mm), hexane/*i*-PrOH 94/6, 1.0 cm^3/min, T = 30 °C. Retention times: (major, *R*) 67.7 min, (minor, *S*) 66.2 min.

(5R)-Hydroxy-8-benzyloxy-8-methyl-6-nonynoic Acid, Methyl Ester, Reduction Product of ***3d3****.* This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.4 mg, 6.7 × 10^{-4} mmol), ketone (101.0 mg, 0.334 mmol), HCOOH/Et_3N 5/2 (280 mg), and CH_2Cl_2 (1.6 cm^3), and the product was isolated as a colorless oil (85.7 mg, 0.28 mmol, 84%, 98% ee). R_f = 0.28 hexane/EtOAc 4/1; $[\alpha]_D^{28}$ +10.1 (*c* 1.2 in $CHCl_3$) 98% ee (*R*); [found (ESI) M^+ + Na, 327.1567; $C_{18}H_{24}O_4$ requires M, 327.1572]; IR (neat) 3432, 2984, 1736, 1153, 1051, 1028, 736, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.38−7.22 (m, 5H), 4.61 (s, 2H), 4.39 (t, J = 6.2 Hz, 1H), 3.65 (m, 3H), 2.35 (t, J = 7.2 Hz, 2H), 2.24 (br s, 1H), 1.83−1.74 (m, 2H), 1.74−1.65 (m, 2H), 1.53 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.9, 139.1, 128.3, 127.6, 127.4, 87.2, 85.1, 70.6, 66.5, 61.9, 51.6, 37.1, 33.5, 29.0, 20.6. m/z (EIMS) 327.1 $(M + Na)^+$. HPLC separation conditions: Chiralpak IC column (250 mm × 4.6 mm), hexane/*i*-PrOH 94/6, 1.0 cm^3/min, T = 30 °C. Retention times: (major, *R*) 15.8 min, (minor, *S*) 19.1 min.

Synthesis of 1,5-Diphenyl-4-pentyne-1,3-dione 18.[16] Acetophenone (873 mg, 7.4 mmol), 1-(3-phenyl-1-oxo-2-propynyl)benzotriazole (1.84 g, 7.6 mmol), and anhydrous $MgBr_2{\cdot}OEt_2$ powder (3.92 g, 15.2 mmol) were added to a flask, and laboratory-grade CH_2Cl_2 (1.5 cm^3) was added via syringe. The suspension was stirred at rt for 3 h and then *i*-Pr_2NEt (2.51 g, 20.0 mmol) was added dropwise. A clean yellow solution was formed immediately, and the solution was allowed to stir at rt for 5 h. Saturated NH_4Cl (3 cm^3) was added, followed by aqueous HCl (10%, 1 cm^3), and stirring was continued for 5 min. After a clear solution had formed, the aqueous layer was extracted with CH_2Cl_2 (2 × 5 cm^3) and the combined organic extract was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the yellow solid product was dissolved in the minimum amount of CH_2Cl_2 and purified by silica gel column chromatography [eluent hexane/CH_2Cl_2/EtOAc = 10/1/0−10/1/(0.2−0.4)]. The product was isolated as light yellow crystals (1.49 g, 6.0 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.71−7.68 (m, 2H), 7.38−7.31 (m, 3H), 7.27−7.13 (m, 5H), 6.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 184.7, 169.7, 133.9, 132.3, 132.1, 129.8, 128.3, 128.2, 128.0, 126.7, 119.8, 100.7, 93.3, 85.5.

Synthesis of 19 via Attempted Asymmetric Transfer Hydrogenation of 18.[18c,d] Complex (*R*,*R*)-**2** (1.2 mg, 2 × 10^{-3} mmol) was dissolved in HCO_2H/Et_3N 5/2 azeotropic mixture (42 mg) under a nitrogen atmosphere, and ketone **18** (24 mg, 0.96 mmol) in degassed dichloromethane (0.5 cm^3) was injected. The mixture was stirred at rt until starting material was completely consumed (12 h), and then the reaction was quenched by saturated $NaHCO_3$ (0.5 cm^3). The resulting mixture was extracted with EtOAc (3 × 5 cm^3) and the combined organic phase was dried over anhydrous $MgSO_4$.

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After concentration, the crude product was purified by silica gel column chromatography (eluent hexane/EtOAc = 6/1−3/1) to give **19** as an oil (20 mg, 0.081 mmol, 84%). R_f = 0.18 hexane/EtOAc 8/1. ^{1}H NMR (400 MHz, $CDCl_3$) 7.89−7.86 (m, 4H), 7.55−7.53 (m, 6H), 6.83 (s, 2H). Data for the cyclization product **19**, which was formed in all attempts at ATH, matched those reported.[18c,d]

Synthesis of 1,4- and 1,5-Diketones. To a solution of acetylene (7.5 mmol) in anhydrous THF (6 cm^3) at −78 °C was added *n*-BuLi (1.6 M in hexane, 4.7 cm^3, 7.5 mmol) in 3 min. The mixture was stirred at −78 °C for 1 h and was added dropwise to a diester (2.5 mmol in 8 cm^3 of THF) and BF_3·OEt_2 (6.5 mmol) mixture at −78 °C. After 1 h, saturated NH_4Cl (10 cm^3) was added and the mixture was extracted with diethyl ether (3 × 30 cm^3). The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc = 15/1).

1,8-Diphenyl-1,7-octadiyne-3,6-dione ***4a2***.[19b,c] This compound was prepared by the general procedure above with phenylacetylene (1.76 g, 17.2 mmol), *n*-BuLi (10.0 cm^3, 16.0 mmol), dimethyl succinate (778 mg, 5.3 mmol), and BF_3·OEt_2 (1.73 cm^3, 13.8 mmol). The product was isolated as a white solid (394 mg, 1.38 mmol, 26%). R_f = 0.77 hexane/EtOAc 4/1; mp 102−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.60−7.57 (m, 4H), 7.49−7.44 (m, 2H), 7.41−7.37 (m, 4H), 3.12 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 185.1, 133.1, 130.9, 128.7, 119.8, 91.7, 87.5, 34.0.

1,9-Diphenyl-1,8-nonadiyne-3,7-dione ***4a3***.[19a] This compound was prepared by the general procedure above with phenylacetylene (0.88 g, 8.6 mmol), *n*-BuLi (5.0 cm^3, 8.0 mmol), dimethyl glutarate (457 mg, 2.86 mmol), and BF_3·OEt_2 (1.1 cm^3, 8.5 mmol). The product was isolated as a white solid (148 mg, 0.49 mmol, 17%). R_f = 0.62 hexane/EtOAc 4/1; mp 51−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.60−7.23 (m, 10H), 2.71 (t, J = 7.2 Hz, 4H), 2.12−2.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 186.9, 133.1, 130.8, 128.7, 119.8, 91.2, 87.7, 44.2, 18.3.

General Procedure for Synthesis of 1,4- and 1,5-Diketones from Weinreb Amides.[19a] To a solution of acetylene (2.4 mmol) in anhydrous THF (10 cm^3) at −78 °C was added *n*-BuLi (1.6 M in hexane, 1.5 cm^3, 2.4 mmol) in 3 min. The mixture was stirred at −78 °C for 1 h, and a Weinreb diamide (204 mg in 3 cm^3 THF, 1.0 mmol) solution was added dropwise. After 1 h at −78 °C, the temperature was raised to −10 °C during 2 h, and saturated NH_4Cl (20 cm^3) and 2 M HCl solution (5 cm^3) were added at −10 °C. The mixture was extracted with diethyl ether (3 × 20 cm^3), and the combined organic phase was dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc = 12/1−8/1).

1,8-Dibutyl-1,7-octadiyne-3,6-dione ***4b2***.[31] This compound was prepared by the general procedure above with Weinreb diamide (326 mg, 1.6 mmol), *n*-BuLi (3.0 cm^3, 4.8 mmol), and 1-hexyne (417 mg, 2.4 mmol), and the product was isolated as described above as a colorless oil (361 mg, 1.47 mmol, 92%). R_f = 0.48 hexane/EtOAc 8/1; [found (ESI) M$^+$ + Na, 269.1512; $C_{16}H_{22}O_2$ requires M, 269.1517]; IR (neat) 2959, 2934, 2872, 2219, 1670, 1192, 1150 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 2.89 (s, 4H), 2.37 (t, J = 7.3 Hz, 4H), 1.61−1.53 (m, 4H), 1.48−1.39 (m, 4H), 0.93 (t, J = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 185.4, 95.2, 80.5, 38.9, 29.6, 21.9, 18.6, 13.5; m/z (EIMS) 268.9 (M + Na)$^+$.

1,10-Dibenzyloxy-1,10-tetramethyl-2,8-octadiyne-4,7-dione ***4d2***. This compound was prepared by the general procedure above with Weinreb diamide (204 mg, 1.0 mmol), *n*-BuLi (1.5 cm^3, 2.4 mmol), and alkyne (417 mg, 2.4 mmol), and the product was isolated as described above as a yellow oil (186 mg, 0.43 mmol, 43%). R_f = 0.25 hexane/EtOAc 8/1; [found (ESI) M$^+$ + Na, 453.2036; $C_{28}H_{30}O_4$ requires M, 453.2041]; IR (neat) 2987, 2210, 1675, 1235, 1157, 1113, 1047, 735, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.38−7.24 (m, 10H), 4.62 (s, 4H), 2.91 (m, 4H), 1.59 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 184.6, 183.3, 128.4, 127.67, 127.64, 94.4, 82.9, 70.6, 67.1, 38.8, 28.2; m/z (EIMS) 453.1 (M + Na)$^+$.

1,11-Dibenzyloxy-1,11-tetramethyl-2,9-nonadiyne-4,8-dione ***4d3***. This compound was prepared by the general procedure above with Weinreb diamide (327 mg, 1.5 mmol), *n*-BuLi (3.0 cm^3, 4.8 mmol), and alkyne (870 mg, 5.0 mmol), and the product was isolated as described above as a yellow oil (527 mg, 1.19 mmol, 79%). R_f = 0.33 hexane/EtOAc 8/1; [found (ESI) M$^+$ + Na, 467.2193; $C_{29}H_{32}O_4$ requires M, 467.2198); IR (neat) 2982, 2937, 2211, 1674, 1236, 1156, 1047, 735, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.32−7.18 (m, 10H), 4.54 (s, 4H), 2.54 (t, J = 7.1 Hz, 4H), 1.90 (q, J = 7.1 Hz, 2H), 1.52 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 186.4, 138.4, 128.4, 127.6, 93.9, 83.2, 70.6, 67.0, 44.1, 28.3, 17.7; m/z (EIMS) 467.1 (M + Na)$^+$.

General Procedure for Asymmetric Transfer Hydrogenation of 1,4- and 1,5-Diketones. (*R*,*R*)-Teth-TsDPEN-RuCl or (*S*,*S*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0 × 10^{-3} mmol) was dissolved in HCO_2H/Et_3N 5/2 azeotropic mixture (372 mg), and 1,4-diketone (0.2 mmol) in degassed dichloromethane (1.0 cm^3) was injected under nitrogen atmosphere. The mixture was stirred at rt until starting material was completely consumed. After the reaction was complete, saturated $NaHCO_3$ (4 cm^3) and water (4 cm^3) were added and the reaction mixture was extracted with CH_2Cl_2 (3 × 15 cm^3), concentrated, dried over anhydrous $MgSO_4$, and purified by silica gel column chromatography (eluent hexane/EtOAc = 6/1−3/1) to give the title products. The position of the meso compound in the chiral HPLC was established in each case by reducing a sample of ketone with a racemic sample of catalyst **2** under the general conditions above.

1,8-Diphenyl-1,7-octadiyne-(3R, 6R)-diol, Reduction Product of ***4a2***.[19b,c] This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl or (*S*,*S*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0 × 10^{-3} mmol), HCO_2H/Et_3N 5/2 azeotropic mixture (84 mg), diketone (57.2 mg, 0.2 mmol), and degassed dichloromethane (1 cm^3). The product was isolated as described above as white crystals [47.1 mg, 0.16 mmol, 81%, >99% ee, dr 26/1 for (*R*,*R*) diol; 45.0 mg, 0.15 mmol, 78%, >99% ee, dr 49/1 for (*S*,*S*) diol]. R_f = 0.11 hexane/EtOAc 4/1; $[\alpha]_D^{28}$ +9.2 [*c* 0.9 in $CHCl_3$ for (*R*,*R*) diol]; $[\alpha]_D^{28}$ −8.5 [*c* 0.7 in $CHCl_3$ for (*S*,*S*) diol]; mp 79−80 °C; [found (ESI) M$^+$ + Na, 313.1199; $C_{20}H_{18}O_2$ requires M, 313.1204]; IR (neat) 3191, 1488, 1004, 750, 687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.44−7.42 (m, 4H), 7.37−7.26 (m, 6H), 4.74 (t, J = 5.7 Hz, 2H), 2.81 (s, 2H), 2.16−2.01 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 131.8, 128.5, 128.3, 122.5, 89.6, 85.3, 62.5, 33.4; m/z (EIMS) 313.1 (M + Na)$^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 80/20, 0.8 cm^3/min, T = 30 °C. Retention times: (*R*) 9.3 min, (meso) 24.8 min, (*S*) 51.2 min.

1,8-Dibutyl-1,7-octadiyne-(3R, 6R)-diol, Reduction Product of ***4b2***. This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl or (*S*,*S*)-Teth-TsDPEN-RuCl **1** (0.6 mg, 1.0 × 10^{-3} mmol), HCO_2H/Et_3N 5/2 azeotropic mixture (372 mg), diketone (54.5 mg, 0.2 mmol), and degassed dichloromethane (2.0 cm^3). The product was isolated as described above as a colorless oil [48.1 mg, 0.19 mmol, 87%, >99% ee, dr 33/1 for (*R*,*R*) diol; 45 mg, 0.18 mmol, 82%, >99% ee, dr 28/1 for (*S*,*S*) diol]. R_f = 0.26 hexane/EtOAc 2/1; $[\alpha]_D^{30}$ +14.9 [*c* 0.8 in $CHCl_3$ for (*R*,*R*) diol], $[\alpha]_D^{30}$ −14.6 [*c* 0.7 in $CHCl_3$ for (*S*,*S*) diol]; [found (ESI) M$^+$ + Na, 273.1825; $C_{16}H_{26}O_2$ requires M, 273.1830); IR (neat) 3329, 2957, 2931, 2862, 1456, 1328, 1022 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 4.45 (br s, 2H), 2.38−2.32 (br s, 2H), 2.20 (td, J = 6.8, 1.8 Hz, 4H), 1.94−1.82 (m, 4H), 1.52−1.45 (m, 4H), 1.45−1.36 (m, 4H), 0.91 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 85.9, 80.8, 62.3, 33.7, 30.7, 21.9, 18.4, 13.6; m/z (EIMS) 272.9 (M + Na)$^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 90/10,0.6 cm^3/min, T = 30 °C. Retention times: (*R*) 10.7 min, (meso) 12.5 min, (*S*) 11.1 min.

1,10-Dibenzyloxy-1,10-tetramethyl-2,8-octadiyne-(4R,7R)-diol, Reduction Product of ***4d2***. This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl or (*S*,*S*)-Teth-TsDPEN-RuCl **1** (0.3 mg, 5.0 × 10^{-4} mmol), HCO_2H/Et_3N 5/2 azeotropic mixture (186 mg), diketone (41 mg, 0.1 mmol), and degassed dichloromethane (1.0 cm^3). The product was isolated as described above as a colorless oil [34.5 mg, 0.079 mmol, 83%, >99% ee, dr 44/1 for (*R*,*R*) diol; 29.1 mg, 0.067 mmol, 70%, >99% ee, dr

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124/1 for (*S*,*S*) diol]. R_f = 0.31 hexane/EtOAc 2/1; $[\alpha]_D^{26}$ +13.5 [*c* 1.3 in $CHCl_3$ for (*R*,*R*) diol]; $[\alpha]_D^{30}$ −13.0 [*c* 1.5 in $CHCl_3$ for (*S*,*S*) diol]; [found (ESI) M^+ + Na, 457.2349; $C_{28}H_{34}O_4$ requires M, 457.2354]; IR (neat) 3395, 2983, 1244, 1152, 1048, 1027, 734, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.39−7.22 (m, 10H), 4.60 (s, 4H), 4.45 (br s, 2H), 2.62 (s, 2H), 1.96−1.77 (m, 4H), 1.52 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.0, 128.4, 127.7, 127.4, 87.4, 84.9, 70.7, 66.5, 61.8, 33.3, 29.0; *m*/*z* (EIMS) 457.1 (M + Na)$^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 95/5, 0.6 cm^3/min, *T* = 30 °C. Retention times: (*R*) 17.7 min, (meso) 21.0 min, (*S*) 19.6 min.

1,8-Nonadiyne-1,9-diphenyl-(3R,7R)-diol, Reduction Product of ***4a3****.*[19a,32] This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl or (*S*,*S*)-Teth-TsDPEN-RuCl **1** (0.2 mg, 3.3 × 10^{-4} mmol), HCOOH/Et_3N 5/2 azeotropic mixture (56 mg), diketone (19.9 mg, 0.067 mmol), and degassed dichloromethane (0.5 cm^3). The product was isolated as described above as white crystals [19.4 mg, 0.064 mmol, 96%, >99% ee, dr 35/1 for (*R*,*R*) diol; 16.3 mg, 0.054 mmol, 81%, >99% ee, dr 78/1 for (*S*,*S*) diol]. R_f = 0.16 hexane/EtOAc 2/1; $[\alpha]_D^{23}$ −26.2 (*c* 0.4 in $CHCl_3$) >99% ee (*S*,*S*), 97% de; $[\alpha]_D^{23}$ +30.9 (*c* 0.2 in $CHCl_3$) >99% ee (*R*,*R*), 97% de; mp 102 °C; [found (ESI) M^+ + Na, 327.1356; $C_{21}H_{20}O_2$ requires M, 327.1361]; IR (neat) 3348, 2949, 2915, 1489, 1416, 1107, 1068, 914, 758, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.43−7.37 (m, 4H), 7.32−7.23 (m, 6H), 4.64 (t, *J* = 6.4 Hz, 2H), 2.24 (s, 2H), 1.93−1.84 (m, 4H), 1.83−1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 131.7, 128.4, 128.3, 122.6, 89.9, 85.1, 62.8, 37.4, 21.1; *m*/*z* (EIMS) 327.1 (M + Na)$^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 80/20, 0.8 cm^3/min, *T* = 30 °C. Retention times: (*R*) 9.0 min, (meso) 24.5 min, (*S*) 51.2 min.

1,11-Dibenzyloxy-1,11-tetramethyl-2,9-octadiyne-(4R,8R)-diol, Reduction Product of ***4d3****.* This compound was prepared by the general procedure above with (*R*,*R*)-Teth-TsDPEN-RuCl or (*S*,*S*)-Teth-TsDPEN-RuCl **1** (0.3 mg, 5.0 × 10^{-4} mmol), HCO_2H/Et_3N 5/2 azeotropic mixture (186 mg), diketone (45.0 mg, 0.1 mmol), and degassed dichloromethane (1.0 cm^3). The product was isolated as described above as a colorless oil [38.9 mg, 0.8 mmol, 86%, >99% ee, dr 76/1 for (*R*,*R*) diol; 43.6 mg, 0.1 mmol, 97%, >99% ee, dr 110/1 for (*S*,*S*) diol]. R_f = 0.29 hexane/EtOAc 2/1; $[\alpha]_D^{28}$ +0.29 [*c* 0.9 in $CHCl_3$ for (*R*,*R*) diol]; $[\alpha]_D^{28}$ −0.23 [*c* 0.6 in $CHCl_3$ for (*S*,*S*) diol]; [found (ESI) M^+ + Na, 471.2506; $C_{29}H_{36}O_4$ requires M, 471.2511]; IR (neat) 3380, 2984, 2934, 1243, 1152, 1049, 1027, 734, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.38−7.22 (m, 10H), 4.60 (s, 4H), 4.37 (t, *J* = 6.1 Hz, 2H), 1.86 (s, 2H), 1.78−1.66 (m, 4H), 1.66−1.58 (m, 2H), 1.53 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 139.1, 128.3, 127.6, 127.4, 87.2, 85.3, 70.6, 66.5, 62.2, 37.4, 29.0, 21.0; *m*/*z* (EIMS) 471.1 (M + Na)$^+$. HPLC separation conditions: Chiralpak IB column (250 mm × 4.6 mm), hexane/*i*-PrOH 95/5, 0.5 cm^3/min, *T* = 30 °C. Retention times: (*R*) 28.6 min, (meso) 31.8 min, (*S*) 33.2 min.

Synthesis of (−)-Yashabushidiol B. *Ethyl (3S)-Hydroxy-5-phenylpentanoate.*[33,34] Alcohol (*R* configuration reduction product of **3a1**, 92% ee) (306 mg, 1.40 mmol) was stirred vigorously with $Pd(OH)_2/C$ (129 mg, 20% $Pd(OH)_2$) at 1 atm H_2 atmosphere at rt in degassed MeOH (10 cm^3). After 1 h the catalyst was removed by filtration and washed with MeOH. The eluent was concentrated and used in the next step without purification. ^1H NMR (400 MHz, $CDCl_3$) 7.31−7.24 (m, 2H), 7.22−7.15 (m, 3H), 4.16 (s, *J* = 7.2 Hz, 2H), 4.06−3.98 (m, 1H), 2.86−2.78 (d, *J* = 2.8 Hz, 1H), 2.74−2.66 (s, 1H), 2.51 (dd, *J* = 12.4, 3.4 Hz, 1H), 2.44 (dd, *J* = 12.4, 8.6 Hz, 1H), 1.90−1.69 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.0, 141.7, 128.5, 128.4, 125.9, 76.2, 60.8, 41.3, 38.1, 31.8, 14.2. The configurational assignment is based on conversion to amide in the next step and to yashabushidiol B.

(3S)-Hydroxy-N-methoxy-N-methylbenzene Pentanamide ***21****.*[34,35] To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (549 mg, 5.6 mmol) in THF (8 cm^3) was added *n*-BuLi (1.6 M in hexane, 6.9 cm^3, 11.0 mmol) dropwise at −78 °C. After being stirred at room temperature for 10 min, the mixture was cooled to −78 °C and a solution of the crude ester from the previous step (1.40 mmol) in THF (2.0 cm^3) was added. The reaction mixture was stirred at −78 °C for 4 h, then quenched with saturated NH_4Cl (6 cm^3) and extracted with EtOAc (3 × 20 cm^3); the combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc = 4/1−1/1) to afford the Weinreb amide (288.1 mg, 1.28 mmol, 90% for two steps from alkyne, R_f = 0.09 hexane/EtOAc 2/1;). $[\alpha]_D^{22}$ +34.5 (*c* 0.5 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.30−7.16 (m, 5H), 4.08−4.01 (m, 1H), 3.88 (d, *J* = 2.9 Hz, 1H), 3.67 (s, 3H), 3.19 (s, 3H), 2.86 (ddd, *J* = 13.8, 10.0, 5.4 Hz, 1H), 2.76−2.64 (m, 2H), 2.48 (dd, *J* = 16.8, 9.5 Hz, 1H), 1.94−1.84 (m, 1H), 1.78−1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.8, 142.0, 128.5, 128.4, 125.8, 67.2, 61.3, 38.2 (2C), 31.9 (2C); *m*/*z* (ESI-MS) 238.1 (M + H)$^+$. Lit.[34] (*S*)-Weinreb amide $[\alpha]_D^{25}$ +28.6 (*c* 1.08, $CHCl_3$, >99% ee).

(5S)-Hydroxy-1,7-diphenylhept-1-yn-3-one ***22****.*[35,36] To a solution of phenylacetylene (146 mg, 1.45 mmol) in anhydrous THF (6 cm^3) at −78 °C was added *n*-BuLi (1.6 M in hexane, 0.79 cm^3, 1.26 mmol) in 3 min. The mixture was stirred at −78 °C for 1 h and a Weinreb amide (81.1 mg in 0.5 cm^3 of THF, 0.36 mmol) solution was added dropwise. After 30 min at −78 °C, the temperature was raised to −10 °C for 2 h and saturated NH_4Cl (5 cm^3) was added at −10 °C. The mixture was extracted with EtOAc (3 × 20 cm^3) and the combined organic phase was dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (eluent hexane/EtOAc = 8/1−5/1, R_f = 0.31 hexane/EtOAc 4/1) to afford the ketone as a light yellow solid (86.0 mg, 0.30 mmol, 85%); mp 43−44 °C; $[\alpha]_D^{26}$ +27.6 (*c* 0.5 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.60−1.54 (m, 2H), 7.50−7.45 (m, 1H), 7.42−7.37 (m, 2H), 7.32−7.27 (m, 2H), 7.24−7.17 (m, 3H), 4.24−4.17 (m, 1H), 2.91−2.80 (m, 3H), 2.77−2.69 (m, 2H), 1.93−1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 186.3, 140.6, 132.1, 130.0, 127.6, 127.4(2C), 124.9, 118.6, 90.9, 86.8, 65.9, 51.3, 37.0, 30.7; *m*/*z* (ESI-MS) 279.1 (M + H)$^+$. Lit.[35] mp 45−50 °C; *S* enantiomer $[\alpha]_D$ +17.7 (*c* 1.0 in $CHCl_3$, 96% ee).

(−)-Yashabushidiol B ***20****.*[21] (*R*,*R*)-Teth-TsDPEN-RuCl **1** (0.3 mg, 5 × 10^{-4} mmol) was dissolved in HCO_2H/Et_3N 5/2 azeotropic mixture (60 mg), and ketone **22** (13.2 mg, 0.047 mmol) in degassed dichloromethane (0.5 cm^3) was injected under a nitrogen atmosphere. The mixture was stirred at rt until starting material was completely consumed, and then the reaction was quenched by aqueous $NaHCO_3$ (0.5 cm^3), extracted with EtOAc (3 × 5 cm^3), and the combined organic phase was dried over anhydrous $MgSO_4$. After concentration, $Pd(OH)_2/C$ [5 mg, 20% $Pd(OH)_2$] and MeOH (2.0 cm^3) were added. The solution was degassed once and stirred vigorously at 1 atm H_2 atmosphere for 1 h. The catalyst was removed by filtration, washed by MeOH, concentrated, and purified by silica gel column chromatography (eluent hexane/EtOAc = 6/1−2/1) to afford (−)-yashabushidiol B as white needles (13.2 mg, 0.047 mmol, 98%, >99 ee, dr >20/1 (determined by ^1H NMR), dr = 75/1 (determined by HPLC), R_f = 0.43 hexane/EtOAc 2/1); mp 87 °C; $[\alpha]_D^{22}$ −5.0 (*c* 0.5 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 7.31−7.24 (m, 4H), 7.22−7.16 (m, 6H), 4.03−3.94 (m, 2H), 2.78 (ddd, *J* = 13.7, 8.9, 5.8 Hz, 2H), 2.66 (ddd, *J* = 13.7, 8.4, 6.5 Hz, 2H), 2.34 (br s, 2H), 1.91−1.82 (m, 2H), 1.82−1.71 (m, 2H), 1.67 (t, *J* = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 141.9, 128.5, 128.4, 125.9, 68.9, 42.6, 39.1, 32.2. *m*/*z* (ESI-MS) 285.1 (M + H)$^+$. HPLC separation conditions: Chiralpak IC column (250 mm × 4.6 mm), hexane/*i*-PrOH 92/8, 0.8 cm^3/min, *T* = 30 °C. Retention times: (*R*,*R*) 16.0 min, (*S*,*S*) 17.9 min, (meso) 21.6 min. Lit.[21a] mp 91−92 °C; (*S*,*S*)-(−) $[\alpha]_D$ −7.3 (*c* 1, $CHCl_3$). The synthetic approach to a racemic/meso mixture of yashabushidiol B for HPLC comparison is given in a following section.

Racemic Ethyl-3-hydroxy-5-phenylpentanoate. To a solution of diisopropylamine (3.23 g, 32 mmol) in THF (40 cm^3) at −78 °C was added *n*-BuLi (1.6 M in hexane, 20.0 cm^3, 32 mmol) dropwise over 20 min. A solution of ethyl acetate (2.45 g, 27.8 mmol) in THF (10 cm^3) was then added dropwise over 20 min. After the mixture was stirred for 1.5 h, 3-phenylpropionaldehyde [3.16 g, 23.5 mmol in THF (10 cm^3)] was added in one portion. The resulting mixture was stirred at −78 °C for 2 h, after which time saturated NH_4Cl (50 cm^3) was added. The mixture was extracted with ethyl acetate (3 × 50 cm^3) and the combined organic phase was washed with brine (15 cm^3) and dried over anhydrous $MgSO_4$. The crude product was purified by silica

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gel column chromatography (eluent hexane/EtOAc = 8/1) to afford the racemic compound as a colorless oil (4.5 g, 20.2 mmol, 86%). The data matched those for the enantiomerically enriched product described above.

Racemic/meso Mixture of Yashabushidiol B ***20***. The substrate for this reaction was prepared from racemic ethyl-3-hydroxy-5-phenylpentanoate by the procedure for the enantiomerically enriched compound. Racemic reduction catalyst **2** was prepared by combining equal masses of each enantiomerically pure catalyst. Due to weighing errors on the small scale required, the product exhibits a small residual enantiomeric excess (see HPLC in Supporting Information). Racemic catalyst **2** (6 mg, 0.01 mmol) was dissolved in HCO_2H/Et_3N 5/2 azeotropic mixture (84 mg), and racemic ketone **22** (60 mg, 0.21 mmol) in degassed CH_2Cl_2 (1.5 cm^3) was injected under a nitrogen atmosphere. The mixture was stirred at rt until starting material **22** was completely consumed, and the reaction was quenched by saturated $NaHCO_3$ (1 cm^3). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 cm^3), and the combined organic phase was dried over anhydrous $MgSO_4$. After concentration, $Pd(OH)_2/C$ [30 mg, 20% $Pd(OH)_2$] and MeOH (10 cm^3) were added. The solution was degassed once and stirred vigorously under a H_2 atmosphere (1 atm) for 1.5 h. The catalyst was removed by filtration and washed by MeOH (20 cm^3), concentrated, and purified by silica gel column chromatography (eluent hexane/EtOAc = 4/1−2/1) to afford the diol as white solid (racemic/meso 5/1). The ^1H NMR features of the major diastereoisomer (yashabushidiol) match those previously reported. The only distinct peaks for the meso diastereoisomer can be observed at ^1H NMR (400 MHz, $CDCl_3$) 3.90−3.70 (m, 2H), which permits a d.e. to be assigned. All other ^1H NMR peaks overlap with the racemic compound. HPLC separation conditions: Chiralpak IC column (250 mm × 4.6 mm), hexane/*i*-PrOH 92/8, 0.8 cm^3/min, T = 30 °C. Retention times: (*R*,*R*) 16.0 min, (*S*,*S*) 17.9 min, (meso) 21.6 min.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of all intermediates and products and chiral HPLC spectra of reduction products (ee determination data). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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