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A catalytic asymmetric protocol for the enantioselective synthesis of 3(2*H*)-furanones

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General Information

Modified AD-mix-α containing a total of 1 mol% of potassium osmate was prepared according to a literature procedure.[1] Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use and dichloromethane was distilled from calcium hydride. Petroleum ether (40-60 °C fraction) and ethyl acetate were distilled prior to use. For moisture-sensitive reactions, glassware was oven-dried (120 °C, > 4 h), assembled hot and cooled under a stream of nitrogen gas before use. Reactions involving air-sensitive materials were carried out by standard syringe techniques. Temperatures of –78 °C were obtained by the addition of dry ice to acetone. Unless otherwise stated, mixtures were stirred using a Teflon-covered stirring bar. Evaporation refers to the removal of solvent under reduced pressure using a Büchi rotary evaporator.

Melting points are uncorrected. Thin-layer chromatography (TLC) analyses were performed on Merck 0.2 mm aluminum-backed silica gel 60 F_{254} plates and components were visualized by illumination with UV light or by staining with aqueous potassium permanganate. Flash column chromatography was performed using Merck 0.040 to 0.063 mm, 230 to 400 mesh silica gel. ^{1}H NMR spectra were recorded on a 300 MHz Bruker AC300 spectrometer. Chemical shifts are reported in ppm downfield from internal tetramethylsilane (TMS), using residual chloroform (δ 7.27 ppm) as an integral standard. The following abbreviations are used to describe NMR signals: δ, chemical shift; s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; b, broad. Coupling constants *J* are quoted in Hertz (Hz). ^{13}C NMR were recorded on a 300 (75 MHz) Bruker AC300 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using the middle resonance of $CDCl_3$ (77.2 ppm) as an integral standard. Infrared (IR) spectra were recorded on a Perkin-Elmer PE-983 spectrophotometer: absorption frequencies were recorded in wavenumbers (ν_{max} in cm^{-1}). Mass spectra were obtained by using a VG7070H mass spectrometer with Finigan Incos II operating in chemical ionization (CI) or electron impact (EI) modes. Optical rotations were measured on an AA-10 Optical Activity digital polarimeter at sodium D line (589 nm) and are quoted in concentration (c = g/100 mL) at 20 °C.

Enantiomeric purities were determined by HPLC analysis using either a Chiralcel OD or Chiralcel OJ column, or in the case of the desilylated alcohol corresponding to **3a**, by derivatisation of the 3(2*H*)-furanone as its Mosher ester. Assignment of absolute configurations followed from those of the diol precursors whose configurations were based upon the well-established rule for olefin facial selectivity for Sharpless catalytic asymmetric dihydroxylations.

Experimental Procedures

Representative preparation an allylic alcohol: (*E*)-4-Methyl-1-phenylhept-4-en-1-yn-3-ol. A solution of phenylacetylene (3.73 g, 36.5 mmol) in dry tetrahydrofuran (50 mL) was treated dropwise at 25 °C with a solution of *n*-butyllithium (15.3 mL, 38.3 mmol, 2.5 M). The mixture was stirred at 25 °C for 30 min, then treated dropwise with a solution of (*E*)-2-methylpent-2-enal (3.0 g, 30.6 mmol) in dry tetrahydrofuran (20 mL). The mixture was stirred for 3 h, then poured into saturated aqueous ammonium carbonate (20 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography on silica gel (5:95 ethyl acetate: petroleum ether) to give **(*E*)-4-methyl-1-phenylhept-4-en-1-yn-3-ol** (5.80 g, 94%) as a pale yellow oil; IR ν_{max} 3390, 2202, 1626 cm^{-1}; ^{1}H NMR δ_H 7.45 (2H, m), 7.30 (3H), 5.67 (1H, t, J = 7.2 Hz), 4.97 (1H, s), 2.09 (2H, pentet, J = 7.5 Hz), 1.60 (s, 3H), 0.90 (t, J = 7.5 Hz); ^{13}C NMR δ_C 133.3, 131.7, 130.2, 128.4, 128.6, 123.0, 88.6, 85.9, 68.6, 21.1, 13.8, 14.5. HRMS calcd for $C_{14}H_{16}O$ 200.1201; found 200.1216.

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[1]Bennani, Y. L.; Sharpless, K. B. Tetrahedron Lett. **1993**, 34, 2079.

Representative preparation of a series including an enynone, a diol and a furan-3(2*H*)-one

(*E*)-4-Methyl-1-phenylhept-4-en-1-yn-3-one (1c). A solution of (*E*)-4-methyl-1-phenylhept-4-en-1-yn-3-ol (4.0 g, 19.9 mmol) in dichloromethane (5 mL) was added in one portion to a stirred suspension of manganese dioxide (27.7 g, 0.32 mol) in dichloromethane (100 mL) under an atmosphere of nitrogen. Stirring was continued at 20 °C for 24 h, after which the mixture was filtered through celite, and the celite was washed thoroughly with dichloromethane (4 x 20 mL). The combined organic filtrates were evaporated and the residue was purified by flash column chromatography (silica gel, 10:90, ethyl acetate: hexanes) to give **1c** (3.35 g, 90%) as an orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.60 (2H, d, J = 6.8 Hz), 7.40 (3H, m), 7.24 (1H, t, J = 6.8 Hz), 2.36 (2H, pentet, J = 7.6 Hz), 1.86 (3H, s), 1.15 (3H, t, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 180.5, 151.8, 138.0, 132.7, 130.3, 128.8, 120.6, 91.0, 86.1, 22.8, 12.9, 10.5. HRMS calcd for $C_{14}H_{14}O$ (M+H) 199.1123; found 199.1118.

(4*R*,5*S*)-4,5-Dihydroxy-4-methyl-1-phenylhept-1-yn-3-one (2c). To a stirred solution of modified AD-mix-α (5.0 g, containing 1 mol% of potassium osmate) in 1:1 *tert*-butyl alcohol-water (50 mL) was added sodium hydrogen carbonate (1.28 g) and methanesulfonamide (0.50 g) at 0 ˚C. A solution of (*E*)-4-methyl-1-phenylhept-4-en-1-yn-3-one (1.0 g, 5.05 mmol) in toluene (3 mL) was added and the mixture was stirred until the reaction was complete as determined by TLC (~24 h). Ethyl acetate (20 mL) was added followed by sodium metabisulfite (6.5 g) and the solution was allowed to warm to 20 ˚C with stirring. The separated aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were washed with aqueous sodium hydroxide (2 x 35 mL, 1 M) then dried (Na_2SO_4), filtered and evaporated. Flash column chromatography (30:70 ethyl acetate: petroleum ether) gave **2c** (0.77 g, 66%); as an orange oil; $[\alpha]_D^{20}$ + 1.69 (*c* 0.59 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.61 (2H, dd, J = 8.5, 1.5 Hz), 7.50-7.30 (3H, m), 3.96 (1H, br s), 2.34 (1H, br s), 1.78(1H, m), 1.54 (1H, m), 1.43 (3H, s), 1.06 (3H, t, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 192.9, 133.1, 131.2, 129.4, 119.8, 97.3, 84.8, 82.6, 76.7, 24.1, 21.9, 10.8. HRMS calcd for $C_{14}H_{16}O_3$ 232.1099; found 232.1103.

4,5-Dihydroxy-4-methyl-1-phenylhept-1-yn-3-one (*rac*-2c). (*E*)-4-methyl-1-phenylhept-4-en-1-yn-3-one (**1c**) (1.0 g, 5.05 mmol) and citric acid (0.79 g, 3.77 mmol) were dissolved with stirring in a 1:1 mixture of *tert*-butyl alcohol-water (5 mL) in a 25 mL Erlenmeyer flask. Potassium osmate (18.5 mg, 0.0502 mmol) was then added followed by 4-methylmorpholine *N*-oxide (0.75 g, 5.53 mmol). The bright green mixture was stirred at 20 ˚C for 24 h, by which time it had become nearly colourless. The *tert*-butyl alcohol was evaporated, and the aqueous residue was then acidified with hydrochloric acid (1mL, 1M) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give racemic **2c** (0.59 g, 50%) as an orange oil. Spectroscopic data were identical to those given for enantiomeric **2c** as prepared above.

(2*R*)-2-((*S*)-1-Hydroxypropyl)-2-methyl-5-phenylfuran-3(2*H*)-one (3c). *Method A, using mercury^{II} catalysis*. To a stirred solution of 4,5-dihydroxy-4-methyl-1-phenylhept-1-yn-3-one (0.30 g, 1.14 mmol) in acetone (30 mL, HPLC grade) at 20 ˚C was added acidified mercury^{II} sulfate solution (0.45 mL, 0.1 M, obtained by dissolving mercury^{II} oxide in aqueous 2.5% sulfuric acid). The mixture was stirred for 30 min then neutralized by the addition of powdered sodium hydrogen carbonate. The mixture was stirred for a further 1.5 h, filtered and the filtrate evaporated. The residue was dissolved in diethyl ether (15 mL) and the solution was washed with water (25 mL). The aqueous layer was extracted with diethyl ether (2 x 15 mL) and the combined extracts were washed with saturated aqueous sodium hydrogen

carbonate (30 mL), then brine (30 mL), dried over Na_2SO_4 and filtered. Evaporation gave a residue which was purified by flash column chromatography on silica gel (30:70 ethyl acetate: petroleum ether) to give **3c** (0.285 g, 95%) as white needles, mp 114-116 °C; $[\alpha]_D^{20}$ + 120.4 (*c* 0.04 in $CHCl_3$); IR (KBr) ν_{max} 3400, 1674 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.85 (2H, d, *J*= 7.5 Hz), 7.56 (1H, t, *J*= 7.5 Hz), 7.50 (2H, t, *J*= 7.5 Hz), 6.17 (1H, s), 3.75 (1H, apparent d, *J* = 8.0 Hz), 1.74 (1H, m), 1.55 (3H, s), 1.39 (1H, m), 1.03 (3H, t, *J*= 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 210.3, 185.0, 132.9, 128.9, 128.8, 127.2, 100.6, 91.7, 77.0, 24.0, 19.3, 10.5. HRMS calcd for $C_{14}H_{16}O_3$ (M+H) 233.1172; found 233.1173.

Enantiomeric excess of **3c** was determined by HPLC analysis using a Chiralcel OJ column (50:50 ethanol: *n*-hexane, λ=210 nM), the major enantiomer eluting after 5.32 min and the minor enantiomer after 6.84 min. A racemic sample of **3c** was used to confirm the HPLC peaks as the pair of enantiomers.

X-Ray Crystallographic Data for (2*R*)-2-((*S*)-1-Hydroxypropyl)-2-methyl-5-phenylfuran-3(2*H*)-one (3c).

Crystal structure data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 260551.

Table 1. Crystal data and structure refinement for furan-3(2*H*)-one **3c**.

Identification code	**05src0001 (EE1/UCL)**	
Empirical formula	$C_{14}H_{16}O_3$	
Formula weight	232.27	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.2521(3) Å	α = 90°
	b = 9.3237(17) Å	β = 90°
	c = 20.809(4) Å	γ = 90°
Volume	1213.0(3) Å^3	
Z	4	
Density (calculated)	1.272 Mg / m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	496	
Crystal	Slab; colourless	
Crystal size	0.34 × 0.15 × 0.12 mm^3	
θ range for data collection	2.93 – 27.48°	
Index ranges	$-8 \le h \le 7$, $-11 \le k \le 12$, $-27 \le l \le 24$	
Reflections collected	27007	
Independent reflections	2773 [R_{int} = 0.0356]	
Completeness to θ = 27.48°	99.5 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9895 and 0.9705	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2773 / 0 / 158	
Goodness-of-fit on F^2	0.984	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0306, *wR2* = 0.1038	
R indices (all data)	*R1* = 0.0318, *wR2* = 0.1059	
Absolute structure parameter	0.7(8)	
Extinction coefficient	0.037(11)	
Largest diff. peak and hole	0.222 and –0.165 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). S**tructure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Structural representation of furan-3(2*H*)-one **3c**.