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First stereoselective total synthesis of (6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2*H*-pyran-2-one☆

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Abstract—A stereoselective total synthesis of (6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2*H*-pyran-2-one is reported. The strategy utilizes an iterative Jacobsen hydrolytic kinetic resolution, ring opening with a chiral propargylic synthon and a preferential (*Z*)-Wittig olefination reaction and lactonization as the key steps.

The α-pyrone moiety is one of the most commonly encountered structural motifs among natural product skeletons, many of which exhibit varied pharmacological properties.[1] The α-pyrone (6-substituted 5,6-dihydro-2*H*-pyran-2-one or α,β-unsaturated-δ-lactone) containing natural products are most often connected through a polyoxygenated chain to a lactone moiety. The various biological activities shown by these compounds include antimicrobial, antifungal and cytotoxicity against human tumour cells.[2] (6*R*)-6-[(4*R*,6*R*)-4,6-Dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2*H*-pyran-2-one **1**[3] is one such natural product which was isolated from *Ravensara crassifolia* along with a structurally similar compound the synthesis of which was reported earlier.[4] As a part of our interest in the synthesis of lactone skeleton-containing bioactive natural products,[5] herein we report the first stereoselective total synthesis of **1** through a ring-opening reaction of chiral epoxide **4**, obtained by an iterative Jacobsen's kinetic resolution protocol with the known[6] chiral propargyl alcohol **5** and elaboration of the ensuing triol **3** to the target compound.

The retrosynthetic analysis, envisions that **1** could be obtained from **2** by functional group transformations, elaboration and lactonization while **2** in turn could be visualized from **3** itself formed by the ring-opening reaction of chiral epoxide **4** with chiral propargylic alcohol **5**. Compound **4**, in turn, could be conveniently derived from **6** by an iterative Jacobsen's hydrolytic kinetic resolution (HKR)-epoxide ring-opening reaction protocol of its olefin derivative obtained from **6** to garner the requisite 1,3-*anti*-polyol system.

The synthesis of **1** (Scheme 1), began from commercially available 5-phenylpentan-1-ol **6** which on oxidation under Swern reaction conditions gave the corresponding aldehyde (92% yield), which on Wittig olefination ($CH_3P^+Ph_3Br^-$/*n*-BuLi/THF/0 °C) afforded the terminal olefinic compound (55%). This olefin on exposure to *m*-CPBA gave racemic epoxide **7** (95%). Compound **7** was subjected to Jacobsen's hydrolytic kinetic resolution[7] with 0.55 equiv of water using (*R*,*R*)-(salen)Co^{III}(OAc) **A** as the catalyst to provide enantiomerically pure **8** and diol **8a** each in 42% yield. Diol **8a** was recycled to **8** by a three-step sequence. Thus, **8a** was mono-benzoylated ($BzCl/Et_3N/CH_2Cl_2$/rt) followed by tosylation of the secondary hydroxyl (TsCl/Et_3N/CH_2Cl_2/DMAP/rt) to give the diprotected compound. Base induced deprotection of the benzoate generated an alkoxide, which prompted simultaneous elimination of the tosylate and ring closure by an S_N2 mode to afford the desired epoxide **8**,[8] $[\alpha]_D^{25}$ +11.17

Keywords: α-Pyrone; Jacobsen hydrolytic kinetic resolution; 1,3-*anti*-Polyol; (*Z*)-Wittig olefination reaction; Lactonization.
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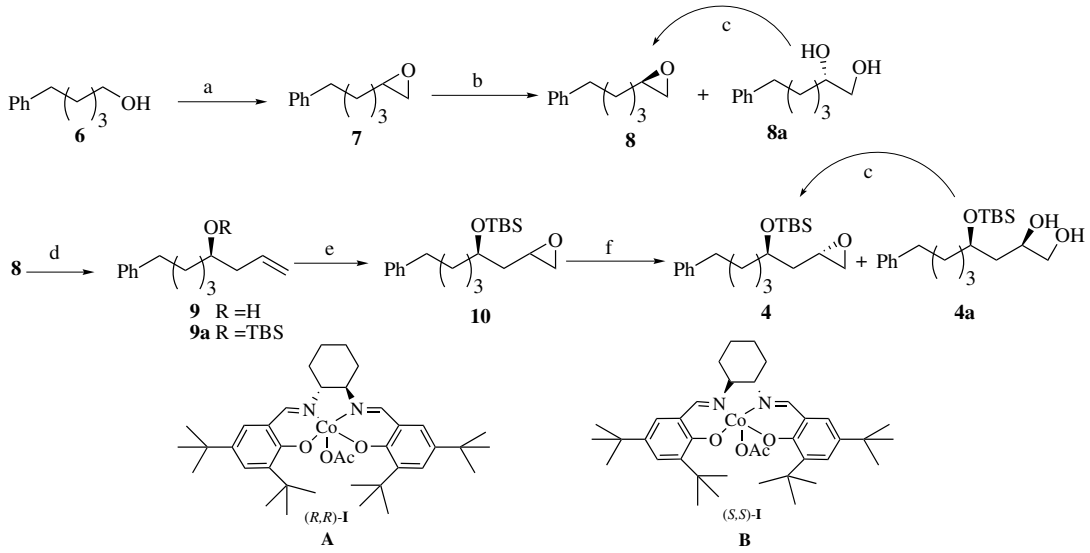
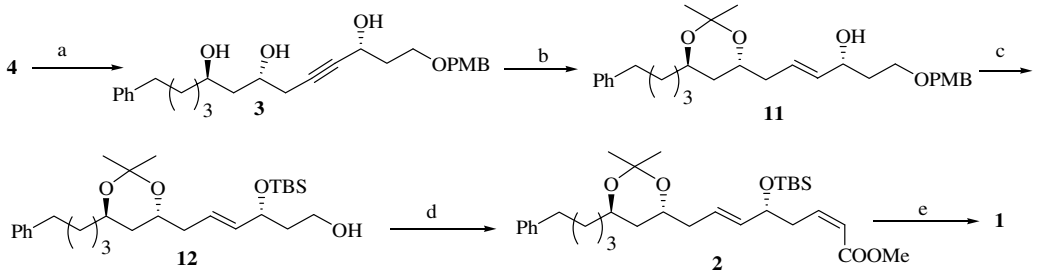


Scheme 1. Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, Et_3N, −78 °C, 92%, (ii) $CH_3{}^+PPh_3Br^-$, *n*-BuLi, 0 °C, 55%, (iii) *m*-CPBA, CH_2Cl_2, rt, 95%; (b) (*R*,*R*)-(salen)Co^{III}(OAc) **A**, 0.55 equiv H_2O, 42%; (c) (i) PhCOCl, Et_3N, CH_2Cl_2, rt, (ii) TsCl, Et_3N, DMAP (cat), CH_2Cl_2, rt, (iii) K_2CO_3, MeOH, rt; (d) vinylmagnesium bromide, CuI, THF, rt, 71%; (e) (i) TBSCl, imidazole, CH_2Cl_2, rt, 92%, (ii) *m*-CPBA, CH_2Cl_2, rt, 96%; (f) (*S*,*S*)-(salen)Co^{III}(OAc) **B**, 0.55 equiv H_2O, 41%.

(*c* 1.00, $CHCl_3$) in 63% yield over the three steps (ee 88%). Ring-opening of epoxide **8** with vinylmagnesium bromide gave homoallylic alcohol **9** (71%) which was then protected as TBS ether **9a** (92%) with TBSCl in CH_2Cl_2 at room temperature. The stereochemical assignment and the chiral homogeneity of **9a** were ascertained by comparing the spectral data of the independently accessed compound through the Sharpless strategy.[9] Subsequently, epoxidation of **9a** with *m*-CPBA in CH_2Cl_2 furnished diastereomeric epoxide **10** (96%). Epoxide **10** on Jacobsen's hydrolytic kinetic resolution (HKR) with 0.55 equiv of water using (*S*,*S*)-(salen)-Co^{III}(OAc) **B** as the catalyst provided enantiomerically pure **4** and diol **4a** each in 41% yield. Diol **4a** was recycled to **4** under similar conditions to those previously described. The optical purity (de 97%) of the obtained epoxide was evaluated by comparing the spectral data of an earlier sample.

Next, nucleophilic ring-opening of epoxide **4** (Scheme 2) with the acetylenic anion generated from the known[6] chiral propargylic alcohol **5** gave the corresponding diol (72%) which on desilylation with TBAF in THF at room temperature gave triol **3** (87%). Triol **3** was converted to its acetonide derivative (95%) using 2,2′-DMP in CH_2Cl_2 catalyzed by PTSA and selective reduction of the propargylic alcohol with LAH in THF generated allylic alcohol **11** (85%). The stereochemical assignment of the newly created stereogenic hydroxyl groups was made based on Rychnovsky's analogy[10] wherein the ^{13}C NMR spectra of **11** exhibited both the acetonide methyl carbons at δ 24.8 and 24.7 and the quaternary carbon at δ 100.3, characteristic of the acetonide of an *anti*-1,3-diol moiety. Later, the allylic hydroxyl group was protected as its TBS ether (98%) with TBSCl in CH_2Cl_2 at room temperature. Removal of the PMB group (DDQ/CH_2Cl_2–H_2O/rt) followed by oxidation of the hydroxyl group using IBX in DMSO at room temperature gave the aldehyde, which was then chain-elongated via a Wittig reaction to afford the corresponding α,β-unsaturated ester **2** {$(F_3CCH_2O)_2POCH_2$-COOMe, KHMDS, 18-crown-6, THF, −78 °C, 76% over two steps} predominantly as the (*Z*)-isomer,[11] as characterized by ^1H and ^{13}C NMR spectroscopy. For



Scheme 2. Reagents and conditions: (a) (i) **5**, *n*-BuLi, BF_3OEt_2, THF, −78 °C, 72%, (ii) TBAF, THF, rt, 87%; (b) (i) 2,2′-DMP, CH_2Cl_2, PTSA (cat), rt, 95%, (ii) LAH, THF, rt, 85%; (c) (i) TBSCl, imidazole, CH_2Cl_2, rt, 98%, (ii) DDQ, CH_2Cl_2:H_2O, rt, 79%; (d) (i) IBX, DMSO, rt, (ii) $(F_3CCH_2O)_2POCH_2COOMe$, KHMDS, 18-crown-6, THF, 76% (over two steps); (e) PTSA, C_6H_6, rt, 65%.

example, the coupling constant ($J = 11.3$ Hz) of the olefinic protons confirmed the (*Z*)-geometry of the olefin. Finally, acid-catalyzed (PTSA) desilylation followed by concomitant lactone cyclization yielded target compound **1** (65%). Mp 66–68 °C; $[\alpha]_D^{25}$ +51.70 (*c* 0.25, $CHCl_3$); {lit.[3] mp 74 °C; $[\alpha]_D^{25}$ +59.00 (*c* 2.00, $CHCl_3$)}. The physical and spectroscopic data of **1** were identical to the reported values of the natural product.

In conclusion, the first stereoselective synthesis of **1** has been accomplished by a convergent strategy wherein one of the advanced intermediates was accessed by iterative Jacobsen's hydrolytic kinetic resolutions with two enantiomeric salens for installing the 1,3-*anti*-polyol system.[12] The synthesis reported herein establishes the absolute stereochemistry of the isolated natural product.

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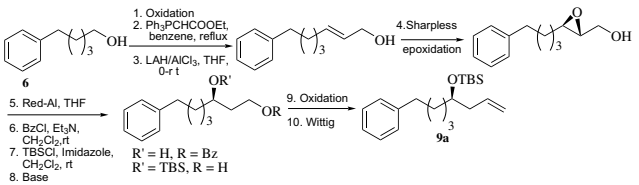
8. *Compound* **8** *spectral data*: $[\alpha]_D^{25}$ +12.70 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.10 (m, 5H, Ar-H), 2.86–2.80 (m, 1H, H-2), 2.68 (dd, $J = 5.28$, 9.06 Hz, 1H, H-1), 2.61 (t, $J = 6.79$ Hz, 2H, Ar-CH_2), 2.39 (dd, $J = 2.26$, 5.28 Hz, 1H, H-1), 1.73–1.63 (m, 2H, CH_2), 1.59–1.45 (m, 4H, $2 \times CH_2$).
9. Compound **9a** was independently synthesized as follows:



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12. *Spectral data of selected compounds*. Compound **9a**: light yellow liquid; $[\alpha]_D^{25}$ +53.80 (*c* 0.35, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26–7.10 (m, 5H, Ar-H), 5.89–5.68 (m, 1H, –*CH*=CH_2), 5.14–5.04 (m, 2H, *CH*$_2$=CH–), 3.65–3.54 (m, 1H, –*CH*–OH), 2.61 (dd, $J = 6.9$, 14.7 Hz, 2H, Ph–*CH*$_2$–), 2.32–2.02 (m, 2H, –*CH*$_2$–CH=CH_2), 1.72–1.57 (m, 2H, –CH_2), 1.53–1.40 (m, 4H, $2 \times$–CH_2–); ^{13}C NMR (100 MHz, $CDCl_3$): 142.4, 134.7, 128.2, 125.5, 117.9, 70.4, 41.8, 36.5, 35.8, 31.3, 25.2; IR (neat): 3449, 2912, 2857, 1223 cm^{-1}; LCMS; 227 $(M+Na)^+$. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.32; H, 9.83. Compound **11**: Colorless liquid; $[\alpha]_D^{25}$ −62.25 (*c* 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25–7.19 (m, 5H, Ar-H), 7.14–7.09 (m, 2H, Ar-H), 6.79 (d, $J = 8.8$ Hz, 2H, Ar-H), 5.67–5.42 (m, 2H, –*CH*=*CH*–), 4.41 (s, 2H, Ar-*CH*$_2$–O–), 4.22 (q, $J = 6.43$, 12.07 Hz, 1H, –*CH*–OH), 3.78 (s, 3H, –O*CH*$_3$), 3.76–3.51 (m, 4H, $2 \times$–*CH*–OH, –*CH*$_2$–OPMB), 2.58 (t, $J = 7.24$, 15.29 Hz, 2H, Ph–*CH*$_2$–), 2.30 (m, 2H, –*CH*$_2$–CH=CH–), 1.74 (m, 2H, –CH_2–), 1.64–1.33 (m, 8H, $4 \times$–CH_2–), 1.28 (2s, 6H, $2 \times$–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 159.1, 142.9, 134.8, 130.1, 129.2, 128.2, 128.1, 126.6, 125.5, 113.7, 100.0, 72.8, 71.4, 67.9, 66.4, 66.2, 55.1, 38.4, 38.0, 36.6, 35.7, 35.6, 31.3, 24.9, 24.8, 24.7; IR (neat): 3447, 2933, 2858, 1611, 1246 cm^{-1}; LCMS; 505 $(M + Na)^+$. Anal. Calcd for $C_{30}H_{42}O_5$: C, 74.65; H, 8.77. Found: C, 74.61; H, 8.72. Compound **2**: Thick syrup; $[\alpha]_D^{25}$ −29.20 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.09 (m, 5H, Ar-H), 6.32–6.24 (m, 1H, –*CH*=CH–COOMe), 5.81 (d, $J = 11.3$ Hz, 1H, –CH=*CH*–COOMe), 5.61–5.41 (m, 2H, CH=CH), 4.20 (q, $J = 5.28$ Hz, 1H, –*CH*–OTBS), 3.80–3.6 (m, 2H, $2 \times$ –*CH*–OH), 3.68 (s, 3H, –OCH_3), 2.82 (t, $J = 6.40$, 12.84 Hz, 2H, –HOCH$_2$–*CH*$_2$–CH=CH),2.59 (t, $J = 7.55$, 15.86 Hz, 2H, Ph–*CH*$_2$), 2.24–2.09 (m, 2H, –CH_2–), 1.66–1.36 (m, 6H, $3 \times$–CH_2–), 1.28 (s, 6H, $2 \times$ –CH_3), 0.87 (s, 9H, tBu), 0.02 (s, 6H, $2 \times CH_3$–Si); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 146.5, 135.3, 128.2, 128.1, 126.4, 125.7, 120.2, 100.3, 72.3, 68.8, 66.4, 66.3, 50.9, 38,5, 38.1, 37.5, 35.8, 35.6, 31.3, 25.8, 25.0, 24.7, 18.1, −4.3, −4.8; IR (neat): 2929, 2856, 1724, 1643, 1220 cm^{-1}; LCMS; 553 $(M + Na)^+$. Anal. Calcd for $C_{31}H_{50}O_5Si$: C, 70.14; H, 9.49. Found: C, 70.10; H, 9.51. Compound **1**: White solid, mp: 66–68 °C; $[\alpha]_D^{25}$ +51.70 (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.10 (m, 5H, Ar-H), 6.88–6.80 (m, 1H, –*CH*=CH–CO), 6.01 (d, $J = 9.8$ Hz, 1H, –CH=*CH*–CO), 5.85 (ddd, $J = 7.5$, 7.5, 14.4 Hz, 1H, –*CH*=CH–), 5.64 (dd, $J = 6.5$, 15.1 Hz, 1H, –CH=*CH*–), 4.86 (q, $J = 7.5$, 14.4 Hz, 1H, –*CH*–O–), 4.05–3.95 (m, 1H, –*CH*–OH), 3.94–3.85 (m, 1H, –*CH*–OH), 2.59 (t, $J = 7.5$, 15.1 Hz, 2H, –*CH*$_2$–Ph), 2.45–2.38 (m, 2H, –CH_2–), 2.29–2.27 (m, 2H, –CH_2–), 1.68–1.58 (m, 2H, –CH_2–), 1.54–1.39 (m, 6H, $3 \times CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1, 144.7, 142.4, 131.4, 129.7, 128.3, 128.2, 125.6, 121.4, 77.8, 69.2, 68.2, 42.0, 40.3, 37.3, 35.8, 31.3, 29.7, 25.4; IR (neat): 3414, 2924, 2854, 1708, 1248 cm^{-1}; LCMS; 367 $(M+Na)^+$. Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.30; H, 8.17.