Diastereo- and Enantioselective Formal Synthesis of (+)-Conagenin via Asymmetric [2,3]-Wittig Rearrangement

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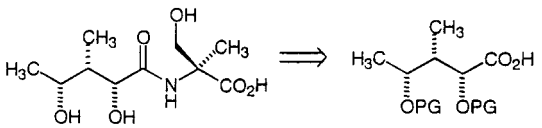
Abstract: The formal synthesis of the immunomodulator (+)-conagenin (**1**) is accomplished in a twelve-step sequence with good overall yield (19%), diastereoselectivity and enantiomeric excess (ds_{syn} = 88%, ee = 91%). Key steps of the synthesis are the asymmetric [2,3]-Wittig rearrangement of crotyloxyacetaldehyde-SAEP-hydrazone (*S*)-**5** and the diastereoselective reduction of methylketone (*R*,*S*)-**12**. The absolute configuration of the (4*R*)-stereogenic center was determined by ^{1}H NMR NOE-measurements with respect to the known absolute configuration of the (2*R*,3*S*)-stereogenic centers of lactone (*R*,*S*,*R*)-**14**.

Key words: conagenin, immunomodulator, [2,3]-Wittig rearrangement, chiral hydrazone, asymmetric synthesis

(+)-Conagenin (**1**) was isolated from fermentation broths of *Streptomyces roseosporus* MI696-AF3 in 1991[1] and its structure and absolute configuration were determined by X-ray analysis.[1] (+)-Conagenin is of significant biological interest due to its activity as immunomodulator.[2] Unlike most low molecular weight immunomodulators produced by microorganisms, e.g. cytogenin and cytoblastin, (+)-conagenin stimulates activated T-cells, and not macrophages.[3] These T-cells produce lymphokines and generate antitumor effector cells. In addition (+)-conagenin has been shown to improve the efficiency of antitumor agents given to tumor carrying mice, by acting as a chemoprotector against myelosuppression, a side effect caused by these drugs in cancer chemotherapy.[2,3]

The novel biological activity and the unique highly functionalized structure of (+)-conagenin, has fostered interest in the total synthesis of **1**. Until now an asymmetric synthesis[4] and an *ex-chiral-pool* synthesis of the (3*R*)-epimer[5] have been reported in the literature. Both syntheses utilized a protected 2,4-dihydroxy-3-methylpentanoic acid **2** as a central building block.



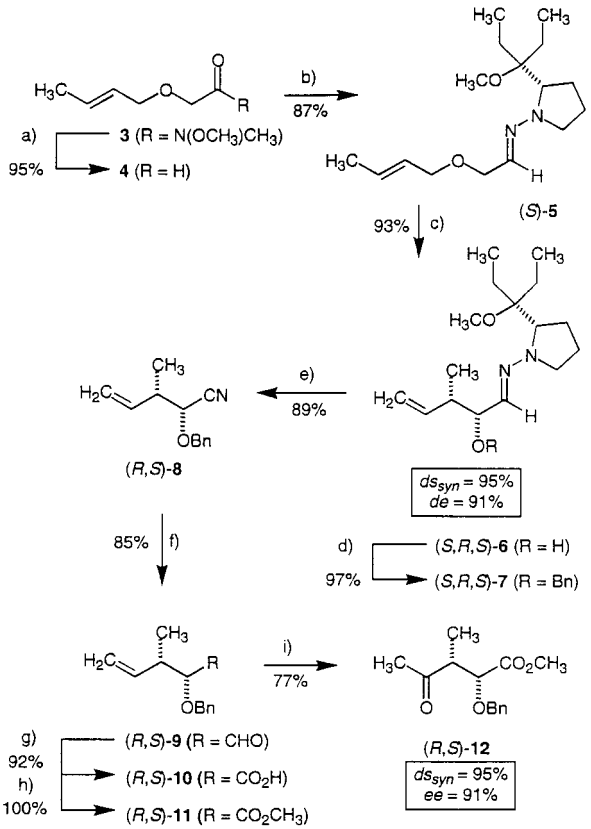
(+)-conagenin (**1**) (*R*,*S*,*R*)-**2**

Recently, we reported on the diastereo- and enantioselective synthesis of (–)-oudemansin A[6] as an application of our well established diastereo- and enantioselective synthesis of protected β-substituted γ,δ-unsaturated α-hydroxyaldehydes by asymmetric [2,3]-Wittig rearrangement of SAEP-hydrazones.[7] We now wish to disclose a further application of this methodology to the diastereo- and enantioselective formal synthesis of the title compound (+)-conagenin. This method has the advantage of opening a preparative route to analogs differing at all the stereogenic centers of the pentanoic acid moiety.

Starting from the readily accessible stable Weinreb amide[8] **3**, the (*E*,*S*)-crotyloxyacetaldehyde hydrazone (*S*)-**5** can be generated by $LiAlH_4$ reduction and, after subsequent workup, condensation with the commercially available chiral auxiliary (*S*)-1-amino-2-(1-ethyl-1-methoxypropyl)pyrrolidine (SAEP)[9] in good overall yield (83%, 2 steps). Deprotonation of the hydrazone (*S*)-**5** with lithium diisopropylamide (LDA) in THF/DMPU (5:1) at –78 °C and additional stirring for 22 hours affords the rearrangend product (*S*,*R*,*S*)-**6** in excellent yield (93%).[6,7] The observed *syn*/*anti*-selectivity is very good (95% *syn*) and the asymmetric induction is high (de = 91%) (Scheme 1).

At this stage it is possible to enrich the predominant isomer by column chromatography or HPLC, (de ≥98%), as previously reported.[6,7] In view of the further transformations the hydroxy group was protected as the benzyl ether. Complete conversion of the hydroxy function only took place by using a potassium hydride/18-crown-6/BnBr reaction system. Thus the benzylated hydrazone (*S*,*R*,*S*)-**7** could be isolated without epimerization in excellent yield (97%). Oxidative removal of the auxiliary with magnesium monoperoxyphthalate (MMPP)[10] and reductive conversion of the resulting nitrile (*R*,*S*)-**8** with diisobutylaluminium hydride (DIBAL-H)[11] affords the aldehyde (*R*,*S*)-**9** in very good yield (76%, 2 steps). In order to avoid epimerization, it was necessary to perform the reduction in pentane, since in dichloromethane,[6] even less than one equivalent of DIBAL-H lead to epimerization at the α-center (20%). Attempts to hydrolyze the nitrile (*R*,*S*)-**8** directly to the desired acid (*R*,*S*)-**10** or the methyl ester (*R*,*S*)-**11** failed (decomposition or recovery of starting material) under various conditions (acidic or basic).

Oxidation of the aldehyde with pyridinium dichromate (PDC)[12] in DMF generates the acid (*R*,*S*)-**10**, which reacts with diazomethane to afford the methyl ester (*R*,*S*)-**11** in excellent yield (92%, 2 steps). In order to prove that this reaction sequence took place without epimerization or racemization, the enantiomeric excess of the acid (*R*,*S*)-**10** was determined by ^{1}H NMR spectroscopy using the chiral cosolvent (–)-(*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol and compared with the corresponding racemate.[13]

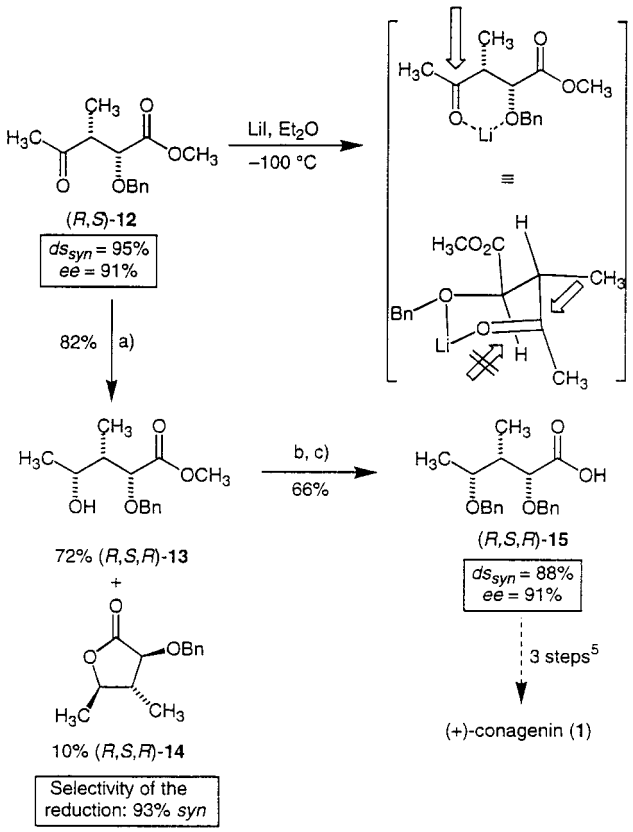


Reagents and conditions: a) 1. $LiAlH_4$ (10 equiv)/THF, 0 °C, 2. 3 N HCl, 0 °C; b) SAEP, 0 °C to r.t. (16 h); c) LDA (2.5 equiv)/THF/DMPU, –78 °C (22 h), 2. NH_4Cl; d) 1. BnBr (2 equiv)/18-crown-6 (1 equiv)/KH (2 equiv)/THF, 0 °C, 2. NH_4Cl; e) 1. MMPP (2.5 equiv)/MeOH, 0 °C (1 h), 2. $NaHCO_3$; f) DIBAL-H (1 equiv)/pentane, –78 °C (2 h), 2. MeOH, –78 to 0 °C (2 h), 3. 1 N H_2SO_4, 0 °C (1 h); g) 1. PDC (6 equiv)/DMF, r.t. (12 h), 2. 6 N HCl; h) CH_2N_2 (2 equiv)/Et_2O, r.t.; i) $PdCl_2$ (0.1 equiv)/CuCl (1 equiv)/O_2 (5 bar)/H_2O/acetone, 70 °C (4 h)

Scheme 1

There are two main possibilities to introduce in a Markownikow sense a hydroxy group on the terminal double bond of ester (*R*,*S*)-**11**, these being the oxymercuration and Wacker reaction. Since the oxymercuration failed,[14] we turned our attention to the Wacker reaction. The original protocol of Tsuji et al.[15] affords the methylketone (*R*,*S*)-**12** in good yield (73%). Unfortunately, epimerization up to 20% was observed in the ^{1}H NMR spectrum, possibly due to the formation of p-allylpalladium(II)-comlexes in DMF/H_2O. Fortunately, a change in the solvent was found to repress this effect. In acetone/H_2O no epimerization was observed in the ^{1}H NMR spectrum and the resulting methylketone (*R*,*S*)-**12** could be isolated in good yield (77%).

An initial test reaction according to the literature showed,[16] that a simple reduction of ketone (*R*,*S*)-**12** with $LiBH_4$ at –100 °C proceeded with a *syn*-selectivity of 75%. In order to improve the asymmetric induction, an excess of lithium iodide was added to the ketone in diethyl ether, based on a method of Suzuki et al.[17] The lithium cation probably chelates with the ketone and ether oxygens at low temperature. The conformation of the resulting intermediate complex is therefore locked and the hydride anion attacks from the least hindered face of the complex to form the *syn*-product (*R*,*S*,*R*)-**13** (93% *syn*) in good yield (72%), in addition to 10% of the corresponding lactone (*R*,*S*,*R*)-**14** (93% *syn*) (Scheme 2).



Reagents and conditions: a) 1. LiI (10 equiv)/$LiBH_4$ (10 equiv)/Et_2O, –100 °C (2 h), 2. H_2O, r.t. (0.5 h), 3. 25% AcOH; b) *O*-benzyltrichloroacetimidate (2 equiv)/BF_3•OEt_2 (cat)/cyclohexane, r.t. (0.5 h); c) 1.1 M K_2CO_3/MeOH, r.t. (12 h), 2. 1 N HCl

Scheme 2

The lactone (*R*,*S*,*R*)-**14**, which is produced from (*R*,*S*,*R*)-**13** due to basic reaction and workup conditions and separated from (*R*,*S*,*R*)-**13** by column chromatography, was formed with the same diastereoselectivity as alcohol (*R*,*S*,*R*)-**13** (^{1}H NMR). The absolute configuration of the newly generated stereogenic centre of lactone (*R*,*S*,*R*)-**14** was determined by ^{1}H NMR NOE-measurements and shown to be 4*R* relative to the known absolute configuration of the stereocentres 2*R*,3*S* (Figure). The absolute con-

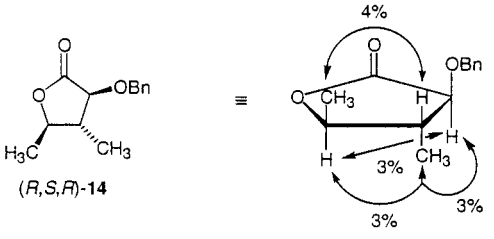


Figure NOE-effects of lactone (*R,S,R*)-**14**

figuration of the newly generated stereogenic centre of the corresponding alcohol (*R*,*S*,*R*)-**13** is assigned based on the assumption of a uniform reaction pathway in generating lactone (*R*,*S*,*R*)-**14**.

Finally, the hydroxy group of (*R*,*S*,*R*)-**13** is protected as benzyl ether with *O*-benzyltrichloracetimidate under Lewis acid catalysis (BF_3•OEt_2).[18] Direct saponification of the resulting ester intermediate produced acid (*R*,*S*,*R*)-**15** in good yield (66%, 2 steps) and high selectivity (ds_{syn} = 88%, ee = 91%). This material was found to be consistent with an intermediate in the *epi*-conagenin synthesis of Herzegh and Sztaricskai et al.[5] Thus, the synthesis of (+)-conagenin can be completed in 3 steps according to these authors, affording the natural product via coupling of acid (*R*,*S*,*R*)-**15** with the protected amino acid α-methyl serine[19] and final deprotection (Scheme 2).

In conclusion, the asymmetric [2,3]-Wittig-rearrangement of crotyloxyacetaldehyde-SAEP-hydrazone opens an efficient, diastereo- and enantioselective entry to conagenin and its analogues. With respect to potential drug design, our synthesis offers several synthetic opportunities for producing related compounds with potentially higher biological activity than the natural product itself.

Solvents were dried and purified prior to use. THF was freshly distilled from K under Ar. CH_2Cl_2 was distilled from CaH_2 and stored under Ar. Et_2O and pentane were distilled prior to use. Analytical glass TLC plates (silica gel 60 F_{254}) and silica gel (230–400 mesh) were purchased from Merck, Darmstadt. Reagents and solvents of commercial quality were used from freshly opened containers unless otherwise stated. Optical rotations were measured at 22 °C using a Perkin-Elmer P241 polarimeter using solvents of Merck Uvasol quality. Microanalyses were obtained with a CHN-O-Rapid, Elementar Vario EL elemental analyser. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300, Gemini 300 (300 and 75 MHz), Unity 500 (500 and 125 MHz) using TMS as internal standard. IR spectra were recorded on a Perkin-Elmer FT/IR 1750 spectrophotometer. Mass spectra were obtained on a Varian MAT 212, EI 70 eV. High resolution mass spectra were recorded on a Finnigan MAT, MAT 95 spectrometer.

Compounds **3** and (*S*,*R*,*S*)-**6** were prepared according to literature procedures.[6]

_N_-[(2*R*,3*S*)-2-(Benzyloxy)-3-methylpent-4-enylidene]-_N_-[(2'*S*)-2-(1-ethyl-1-methoxypropyl)tetrahydro-1*H*-1-pyrrolyl]amine [(*S*,*R*,*S*)-7]

To a stirred solution of hydrazone (*S*,*R*,*S*)-**6** (282 mg, 1 mmol) in anhyd THF (30 mL) at 0 °C under an atmosphere of Ar were added KH (80 mg, 2 equiv). After 10 min 18-crown-6 (265 mg, 2 equiv) was added, and stirred for additional 10 min. Benzyl bromide (206 mg, 2 equiv) was then added and the ice bath was removed. After stirring for 2 h at 25 °C, the dark brown mixture was poured into aq NH_4Cl solution (5 mL) and extracted with Et_2O (4 × 20 mL). The Et_2O extracts were combined, washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel: Et_2O/pentane, 1:9) afforded 357 mg of a slightly yellow liquid of (*S*,*R*,*S*)-**7** (97%); ds_{syn} = 95%, de = 91%); $[\alpha]_D$+52.59 (*c* = 0.72, $CHCl_3$). It was possible to scale up the reaction to 20 mmol of hydrazone (*S*,*R*,*S*)-**6** without loss of selectivity and yield.

IR (neat): ν = 3065 (CH=CH_2), 3029, 2967, 2938, 2879, 2826, 1640 (CH=CH_2), 1589 (C=N), 1496, 1455, 1376, 1344, 1303, 1282, 1207, 1132, 1117, 1086 (COC), 1068, 1029, 992, 953 (CH=CH_2), 914, 734 (Ar), 697 (Ar) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 6 H, *J* = 7.4 Hz, CH_2CH_3), 1.10 (d, 3 H, *J* = 6.9 Hz, $CHCH_3$), 1.55 (m, 2 H, CH_2CH_3), 1.68 (m, 1 H, $CHCH_3$), 1.70 (m, 2 H, CH_2CH_3), 1.85 (m, 2 H, $NCH_2CH_2CH_2$), 1.97 (m, 2 H, $NCH_2CH_2CH_2$), 2.56 (m, 1 H, CHNHCH), 2.72 (m, 1 H, CHNHCH), 3.23 (s, 3 H, OCH_3), 3.60 (m, 1 H, OCH), 3.72 (t, 1 H, *J* = 6.9 Hz, $CHNCH_2$), 4.45 (d, 1 H, *J* = 12.1 Hz, OHCH), 4.60 (d, 1 H, *J* = 12.1 Hz, OHCH), 5.10 (m, 2 H, =CH_2), 5.86 (ddd, 1 H, *J* = 17.0/10.7/7.4 Hz, CH=), 6.28 (d, 1 H, *J* = 12.1 Hz, CNH), 7.32 (m, 5 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.8, 8.5 (CH_2CH_3), 15.9, 23.7 (CH_2CH_3), 23.6 (CH_3), 24.5, 26.2 (5-ring CH_2), 41.9 ($CHCH_3$), 50.3 (OCH_3), 50.6 (NCH_2), 68.4 (NCH), 70.2 (CH_2Ph), 80.4 (OC), 83.5 (OCH), 114.4 (CH_2=), 127.2, 127.7, 128.1 (CH_{arom}), 133.0 (=CH), 139.1 (C_{arom}), 140.4 (C=N).

MS (EI, 70 °C, 80 eV): *m*/*z* (%) = 271 ($M^{+\bullet}$ + 1, – $C_6H_{13}O$, 4), 264 ($M^{+\bullet}$ – C_7H_7O, 16), 163 ($M^{+\bullet}$ – C_7H_7O, – $C_6H_{13}O$, 100), 94 (64), 70 ($C_4H_8N^+$, 57).

MS (CI, isobutane): *m*/*z* (%) = 373 ($M^{+\bullet}$ + 1, 75), 341 ($M^{+\bullet}$ – OCH_3, 15), 271 ($M^{+\bullet}$ + 1, – $C_6H_{13}O$, 21), 265 ($M^{+\bullet}$, – C_7H_7O, 100).

Anal. calcd for $C_{23}H_{36}N_2O_2$ (372.5): C 74.15, H 9.74, N 7.52; found C 74.01, H 9.82, N 8.01.

(2*R*,3*S*)-2-(Benzyloxy)-3-methylpent-4-enonitrile [(*R*,*S*)-8]

MMPP (1.45 g, 2.25 equiv) was added to a solution of hydrazone (*S*,*R*,*S*)-**7** (373 mg,1 mmol) in MeOH (20 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and for 1 h at 25 °C, then poured into aq $NaHCO_3$ solution (20 mL) and extracted with Et_2O (4 × 50 mL). The Et_2O extracts were combined, washed with brine (3 × 50 mL), dried ($MgSO_4$) and concentrated in vacuo (25 °C). Purification by flash chromatography (silica gel: Et_2O/pentane, 1:9) afforded 179 mg of a slightly yellow liquid of (*R*,*S*)-**8** (89%); ds_{syn} = 95%, ee = 91%; $[\alpha]_D$ + 82.19 (*c* = 1.40, $CHCl_3$). It was possible to scale up the reaction to 15 mmol of hydrazone (*S*,*R*,*S*)-**7** without loss of selectivity and yield.

IR (neat): ν = 3087 (=CH_2), 3066, 3032, 2973, 2935, 2873, 2833, 2237 (CN), 1726, 1643 (C=C), 1497, 1455, 1421, 1397, 1377, 1340, 1208, 1183, 1090 (COC), 1027, 995 (COC), 962, 926, 881, 741 (Ar), 699 (Ar) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (d, 3 H, *J* = 6.9 Hz, $CHCH_3$), 2.65 (m, 1 H, $CHCH_3$), 3.99 (d, 1 H, *J* = 6.1 Hz, OCH), 4.54 (d, 1 H, *J* = 11.5 Hz, OHCH), 4.87 (d, 1 H, *J* = 11.6 Hz, OHCH), 5.20 (m, 2 H, =CH_2), 5.84 (ddd, 1 H, *J* = 17.3, 10.4, 7.4 Hz, CH=), 7.36 (m, 5 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9 (CH_3), 41.5 ($CHCH_3$), 72.6 (CHO), 72.9 (CH_2O), 117.8 (CN), 118.2 (CH_2=), 128.7, 129.0, 129.2 1 (CH_{arom}), 136.5 (C_{arom}), 137.5 (=CH).

MS (EI, 80 °C, 70 eV): *m*/*z* (%) = 201 ($M^{+\bullet}$, 1), 172 (10), 91 ($C_7H_7^+$, 100), 65 (13), 55 ($C_4H_7^+$, 31).

MS (CI, isobutane): *m*/*z* (%) = 259 ($M^{+\bullet}$ + C_4H_{10}, 18), 258 ($M^{+\bullet}$ + C_4H_9, 100), 240 (4), 201 ($M^{+\bullet}$, 2), 175 ($M^{+\bullet}$ – CN, 13).

Anal. calcd for $C_{13}H_{15}NO$ (201.3): C 77.50, H 7.51, N 6.59; found C 77.58, H 7.63, N 6.69.

(2*R*,3*S*)-2-(Benzyloxy)-3-methylpent-4-enal [(*R*,*S*)-9]

To a solution of the nitrile (*R*,*S*)-**8** (100 mg, 0.5 mmol) in pentane (30 mL) at –78 °C was added DIBAL-H (1 M in hexane, 1 equiv) under an Ar atmosphere. After stirring for 1 h MeOH (2 mL) was added via a syringe and the mixture was allowed to warm to 0 °C. After stirring additionally for 2 h, 1 N H_2SO_4 (2 mL) was added and

the resulting mixture was stirred for a further 1 h. The mixture was diluted with H_2O (30 mL), extracted with Et_2O (4 × 30 mL), and the combined Et_2O extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo (25 °C). Purification by flash column chromatography (silica gel: Et_2O/pentane, 1:9) afforded 87 mg of a colourless liquid of (*R*,*S*)-**9** (85%); ds_{syn} = 95%, ee = 91%; $[\alpha]_D$ +23.17 (*c* = 0.77, $CHCl_3$). It was possible to scale up the reaction to 10 mmol of nitrile (*R*,*S*)-**8** without loss of selectivity and yield.

IR (neat): ν = 3066 (=CH_2), 3032, 2970, 2931, 2871, 1732 (C=O), 1640 (C=C), 1497, 1455, 1421, 1376, 1343, 1208, 1092 (COC), 1028, 998 (COC), 919, 737 (Ar), 699 (Ar) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, 3 H, *J* = 6.9 Hz, CHCH_3), 2.69 (m, 1 H, C*H*CH_3), 3.62 (dd, 1 H, *J* = 5.5, 2.5 Hz, OCH), 4.53 (d, 1 H, *J* = 11.8 Hz, OHC*H*), 4.67 (d, 1 H, *J* = 11.8 Hz, O*H*CH), 5.07 (m, 2 H, =CH_2), 5.84 (ddd, 1 H, *J* = 17.6, 10.4, 7.7 Hz, CH=), 7.35 (m, 5 H, C_6H_5), 9.62 (d, 1 H, *J* = 2.7 Hz, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.5 (CH_3), 40.0 (*C*HCH_3), 73.4 (OCH_2), 87.0 (CHO), 116.5 (CH_2=), 128.5, 128.6, 129.0 (CH_{arom}), 137.9 (C_{arom}), 139.3 (=CH), 204.1 (C=O).

MS (EI, 80 °C, 70 eV): *m*/*z* (%) = 175 ($M^{+\bullet}$ – CHO, 5), 147 (4), 91 ($C_7H_7^+$, 100), 65 (12), 55 ($C_4H_7^+$, 4).

MS (CI, isobutane): *m*/*z* (%) = 205 ($M^{+\bullet}$ + 1, 18), 187 ($M^{+\bullet}$ + 1, –H_2O, 84), 175 ($M^{+\bullet}$ – CHO, 51), 159 (24), 147 (53), 129 (16), 117 (24), 101 (12), 91 (22).

Anal. calcd for $C_{13}H_{16}O_2$ (204.3): C 76.45, H 7.90; found C 76.42, H 7.93.

(2*R*,3*S*)-2-(Benzyloxy)-3-methylpent-4-enoic acid [(*R*,*S*)-10]

To a vigorously stirred solution of the aldehyde (*R*,*S*)-**9** (204 mg, 1 mmol) in DMF at 25 °C (25 mL) were added PDC (2.26 g, 6 equiv). The orange-brown solution was stirred overnight and diluted with H_2O (50 mL). The mixture was acidified with 6 N HCl to pH 1 and extracted with Et_2O (4 × 30 mL). The Et_2O extracts were combined, washed with brine (2 × 50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel, Et_2O) afforded 202 mg of a brown-yellow oil of (*R*,*S*)-**10** (92%); ds_{syn} = 95%, ee = 91%; $[\alpha]_D$ + 37.60 (*c* = 0.67, $CHCl_3$). It is possible to scale up the reaction to 8 mmol of aldehyde (*R*,*S*)-**9** without loss of selectivity and yield.

IR (neat): ν = 3400 (OH), 3066 (=CH_2), 3032, 2977, 2933, 2875, 1719 (C=O), 1642 (C=C), 1497, 1455, 1421, 1384, 1338, 1209, 1128, 1097 (COC), 1060, 1029, 996 (COC), 919, 737 (Ar), 698 (Ar) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.11 (d, 3 H, *J* = 6.9 Hz, CHCH_3), 2.74 (m, 1 H, C*H*CH_3), 3.90 (d, 1 H, *J* = 5.0 Hz, OCH), 4.47 (d, 1 H, *J* = 11.5 Hz, OHC*H*), 4.74 (d, 1 H, *J* = 11.5 Hz, O*H*CH), 5.10 (m, 2 H, =CH_2), 5.84 (ddd, 1 H, *J* = 17.6, 10.4, 7.7 Hz, CH=), 7.35 (m, 5 H, C_6H_5), 9.76 (br s, 1 H, CO_2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (CH_3), 41.5 (*C*HCH_3), 73.5 (OCH_2), 82.1 (CHO), 116.3 (CH_2=), 128.6, 128.7, 129.0 (CH_{arom}), 137.6 (C_{arom}), 139.7 (=CH), 177.5 (CO_2H).

MS (EI, 80 °C, 70 eV): *m*/*z* (%) = 114 (4), 107 (11), 91 ($C_7H_7^+$, 100), 65 (14), 55 ($C_4H_7^+$, 7).

MS (CI, isobutane): *m*/*z* (%) = 221 ($M^{+\bullet}$ + 1, 100), 203 ($M^{+\bullet}$ + 1, –H_2O, 22), 175 ($M^{+\bullet}$, – CO_2H, 62), 107 ($C_7H_7O^+$, 60).

Anal. calcd for $C_{13}H_{16}O_3$ (220.3): C 70.89, H 7.32; found C 70.33, H 7.60.

Methyl-(2*R*,3*S*)-2-(Benzyloxy)-3-methylpent-4-enoate [(*R*,*S*)-11]

To a colorless stirred solution of the acid (*R*,*S*)-**10** (660 mg, 3 mmol) in Et_2O (100 mL) at 25 °C was added a solution of diazomethane in Et_2O until TLC indicated complete conversion of the starting material. The solution was dried ($MgSO_4$) and concentrated in vacuo which afforded 702 mg of a slightly yellow oil of (*R*,*S*)-**11** (quant); ds_{syn} = 95%, ee = 91%; $[\alpha]_D$ + 51.27 (*c* = 0.55, $CHCl_3$).

IR (neat): ν = 3067 (=CH_2), 3031, 2978, 2978, 2952, 2934, 2873, 1751 (C=O), 1641 (C=C), 1497, 1455, 1435, 1398, 1351, 1313, 1268, 1203, 1164, 1136, 1098 (COC), 1061, 1028, 997 (COC), 919, 739 (Ar), 699 (m, Ar) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (d, 3 H, *J* = 6.9 Hz, CHCH_3), 2.66 (m, 1 H, C*H*CH_3), 3.38 (s, 3 H, OCH_3), 3.82 (d, 1 H, *J* = 6.0 Hz, OCH), 4.41 (d, 1 H, *J* = 11.8 Hz, OHC*H*), 4.68 (d, 1 H, *J* = 11.8 Hz, O*H*CH), 5.05 (m, 2 H, =CH_2), 5.76 (ddd, 1 H, *J* = 17.3, 10.4, 8.0 Hz, CH=), 7.35 (m, 5 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 (CH_3), 41.3 (*C*HCH_3), 51.6 (OCH_3), 72.5 (OCH_2), 82.2 (CHO), 115.4 (CH_2=), 127.8, 127.9, 128.3 (CH_{arom}), 137.4 (C_{arom}), 139.2 (=CH), 172.4 (*C*O_2CH_3).

MS (EI, 60 °C, 70 eV): *m*/*z* (%) = 128 (13), 112 (9), 91 ($C_7H_7^+$, 100), 65 (11), 55 ($C_4H_7^+$, 5).

MS (CI, isobutane): *m*/*z* (%) = 235 ($M^{+\bullet}$ + 1, 100), 217 ($M^{+\bullet}$ + 1, –H_2O, 30), 175 ($M^{+\bullet}$, –CO_2CH_3, 42), 157 (5), 128 (6).

Anal. calcd for $C_{14}H_{18}O_3$ (234.3): C 71.77, H 7.74; found C 71.82, H 8.08.

Methyl (2*R*,3*S*)-2-(Benzyloxy)-3-methyl-4-oxopentanoate [(*R*,*S*)-12]

A suspension of 10 mol% $PdCl_2$ (23 mg) and CuCl (190 mg, 1 equiv) in (5 mL) water and acetone (30 mL) containing the ester (*R*,*S*)-**11** (702 mg, 3 mmol) was stirred under an atmosphere of oxygen at 5 bar at 70 °C for 4 h. The mixture was allowed to cool to r.t., Et_2O/H_2O (200 mL, 1:1) were added and extracted with Et_2O (3 × 100 mL). The Et_2O extracts were combined, washed with brine (2 × 50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel: Et_2O/pentane, 1:2) afforded 578 mg of a brown liquid of (*R*,*S*)-**12** (77%); ds_{syn} = 95%, ee = 91%; $[\alpha]_D$ + 67.01 (*c* = 0.59, $CHCl_3$).

IR (neat): ν = 3064, 3031, 2975, 2952, 2879, 1750 (C=O), 1719 (C=O), 1497, 1455, 1436, 1399, 1381, 1357, 1270, 1207, 1171, 1143, 1109 (COC), 1075, 1028, 1016 (COC), 741 (Ar), 700 (Ar) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (d, 3 H, *J* = 7.4 Hz, CHCH_3), 2.13 (s, 3 H, CCH_3), 2.99 (m, 1 H, C*H*CH_3), 3.76 (s, 3 H, OCH_3), 4.33 (d, 1 H, *J* = 5.4 Hz, OCH), 4.46 (d, 1 H, *J* = 11.4 Hz, OHC*H*), 4.77 (d, 1 H, *J* = 11.4 Hz, O*H*CH), 7.35 (m, 5 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.7 (CH_3), 28.5 (*C*H_3C), 49.5 (*C*HCH_3), 52.1 (OCH_3), 73.1 (OCH_2), 78.4 (CHO), 128.0, 128.2, 128.4 (CH_{arom}), 137.1 (C_{arom}), 172.0 (*C*O_2CH_3), 208.9 (CH_3*C*).

MS (EI, 60 °C, 70 eV): *m*/*z* (%) = 144 ($M^{+\bullet}$ + 1, – C_7H_7O, 13), 101 (34), 91 ($C_7H_7^+$, 100), 65 (12).

MS (CI, isobutane): *m*/*z* (%) = 251 ($M^{+\bullet}$ + 1, 100), 143 ($M^{+\bullet}$, –C_7H_7O, 21).

Anal. calcd for $C_{14}H_{18}O_4$ (250.3): C 67.19, H 7.25; found C 67.63, H 7.62.

Methyl (2*R*,3*S*,4*R*)-2-(Benzyloxy)-4-hydroxy-3-methylpentanoate [(*R*,*S*,*R*)-13]

To a solution of the ketone (*R*,*S*)-**12** (375 mg, 1.5 mmol) in Et_2O (30 mL) at 25 °C under an atmosphere of Ar, were added LiI (1.99 g, 10 equiv). After stirring for 5 min at –40 °C the mixture was cooled to –100 °C and $LiBH_4$ (217 mg, 10 equiv) was added. The mixture was stirred for an additional 2 h at –100 °C and then hydrolysed by addition of H_2O (10 mL) and AcOH (10 mL, 25%). After stirring for 30 min, Et_2O (100 mL) was added and the aqueous phase

extracted with Et_2O (3 × 30 mL). The Et_2O extracts were combined, washed with aq $NaHCO_3$ soln (2 × 50 mL) and pH 7 buffer (2 × 50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel, Et_2O/pentane, 1:2) afforded 272 mg of (*R*,*S*,*R*)-**13** (72%) and 25 mg of (*R*,*S*,*R*)-**14** (10%) as colorless liquids (induction = 93 % *syn*); ds_{syn} = 88%, ee = 91%; $[\alpha]_D$ + 66.38 (*c* = 0.47, $CHCl_3$).

IR ($CHCl_3$): ν = 3427 (OH), 3088, 3064, 3031, 2973, 2951, 2936, 2880, 1748 (C=O), 1497, 1454, 1436, 1400, 1385, 1330, 1271, 1208, 1135 (COC), 1066, 1026 (COC), 911, 739 (Ar), 699 (Ar) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, 3 H, *J* = 7.1 Hz, CHC*H*$_3$), 1.14 (d, 3 H, *J* = 6.4 Hz, OCHC*H*$_3$), 1.93 (m, 1 H, C*H*CH$_3$), 2.74 (br s, 1 H, OH), 3.77 (s, 3 H, OCH_3), 3.97 (m, 1 H, OC*H*CH$_3$), 4.14 (d, 1 H, *J* = 3.7 Hz, OCHCO), 4.36 (d, 1 H, *J* = 11.1 Hz, OHC*H*), 4.77 (d, 1 H, *J* = 11.1 Hz, O*H*CH), 7.34 (m, 5 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.4 (*C*H$_3$CHCHOC=O), 20.7 (*C*H$_3$CHOH), 41.9 (*C*HCHOC=O), 51.8 (OCH_3), 69.7 (CHOH), 72.7 (OCH_2), 81.6 (*C*HOCH$_2$), 128.2, 128.5, 128.5 (CH_{arom}), 136.9 (C_{arom}), 172.2 (*C*O$_2$CH$_3$).

MS (EI, 80 °C, 70 eV): *m*/*z* (%) = 146 ($M^{+\bullet}$+1, – C_7H_7O, 7), 114 (21), 91 ($C_7H_7^+$, 100), 65 (12).

MS (CI, isobutane): *m*/*z* (%) = 253 ($M^{+\bullet}$ + 1, 100), 221 ($M^{+\bullet}$, –CH_3O, 48).

Anal. calcd for $C_{14}H_{20}O_4$ (252.3): C 66.65, H 7.99; found C 66.22, H 7.95.

(2*R*,3*S*,4*R*)-2,4-Dibenzyloxy-3-methylpentanoic acid [(*R*,*S*,*R*)-15]

a) Lewis Acid Catalyzed Benzylation:

To a stirred solution of the ester (*R*,*S*,*R*)-**13** (100 mg, 0.4 mmol) and *O*-benzyltrichloroacetimidate (2 equiv) in cyclohexane (15 mL) at 25 °C, was added a catalytical amount of $BF_3{\cdot}OEt_2$. After stirring for 30 min pentane (10 mL) was added and the separated trichloroacetamide was removed by filtration. The aqueous phase was extracted with pentane (100 mL), the combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product, containing *O*-benzyltrichloroacetimidate, was used directly in the next step.

b) Saponification:

The crude ester was dissolved in MeOH (12 mL) and aq 1 M K_2CO_3 soln (4 mL). The mixture was stirred 12 h at 25 °C and diluted with H_2O (20 mL). The aqueous phase was washed with pentane (30 mL) and then carefully acidified with 1 N HCl to pH 1. The precipitated acid (*R*,*S*,*R*)-**15** was extracted with Et_2O (3 × 50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel, Et_2O) afforded 83 mg of (*R*,*S*,*R*)-**15** (66%, 2 steps) as a colourless liquid; ds_{syn} = 88%, ee = 91%; $[\alpha]_D$ +13.17 (*c* = 0.30, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.07 (d, 3 H, *J* = 7.1 Hz, CHC*H*$_3$), 1.16 (d, 3 H, *J* = 6.1 Hz, OCHC*H*$_3$), 2.17 (m, 1 H, C*H*CH$_3$), 3.65 (m, 1 H, OC*H*CH$_3$), 4.10 (d, 1 H, *J* = 4.0 Hz, OCHCO), 4.41 (d, 1 H, *J* = 11.4 Hz, COOHCHOHC*H*), 4.46 (d, 1 H, *J* = 11.4 Hz, OHC*H*), 4.56 (d, 1 H, *J* = 11.4 Hz, O*H*CH), 4.70 (d, 1 H, *J* = 11.4 Hz, COOHCHO*H*CH), 7.33 (m, 10 H, ArH), 9.80 (br s, 1 H, CO_2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2 (*C*H$_3$CHCHOC=O), 17.1 (*C*H$_3$CHOBn), 42.2 *C*HCHOC=O), 71.3, 73.2 (OCH_2), 76.3 (CH$_3$*C*HOBn), 79.3 (*C*HOC=O), 128.1, 128.2, 128.0, 128.4, 128.9, 129.0 (CH_{arom}), 137.9, 139.2 (C_{arom}), 178.2 (*C*O$_2$CH$_3$).

MS (CI, isobutane): *m*/*z* (%) = 329 ($M^{+\bullet}$ + 1, 100), 239 ($M^{+\bullet}$ + 1, –C_7H_7, 5). The other analytical data are consistent with the literature.[5]

(3*R*,4*S*,5*R*)-3-Benzyloxy-4,5-dimethyltetrahydrofuran-2-one [(*R*,*S*,*R*)-14]

The lactone (*R*,*S*,*R*)-**14** derived from (*R*,*S*,*R*)-**13** by basic reaction and workup conditions was separated from (*R*,*S*,*R*)-**13** by column chromatography (*vide supra*); (induction = 93% *syn*); ds_{syn} = 88%, ee = 91%; $[\alpha]_D$ + 111.36 (*c* = 0.40, $CHCl_3$).

IR ($CHCl_3$): ν = 3064, 3031, 2975, 2933, 2878, 1781 (C=O), 1497, 1455, 1387, 1354, 1327, 1240, 1191, 1162, 1135 (COC), 1050, 1030, 1002, 986, 957, 917, 742 (Ar), 698 (Ar) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.10 (d, 3 H, *J* = 6.7 Hz, CHC*H*$_3$), 1.39 (d, 3 H, *J* = 6.4 Hz, OCHC*H*$_3$), 2.12 (m, 1 H, C*H*CH$_3$), 3.82 (d, 1 H, *J* = 10.0 Hz, C*H*OPh), 4.00 (m, 1 H, OCOCH), 4.77 (d, 1 H, *J* = 12.1 Hz, OHC*H*), 4.89 (d, 1 H, *J* = 12.1 Hz, O*H*CH), 7.36 (m, 5 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (*C*H$_3$CHCHOBn), 18.1 (*C*H$_3$CHO), 44.7 (CH$_3$*C*HCHOBn), 72.1 (OCH_2), 78.7 (CH$_3$*C*HO), 79.6 (CH*C*HOBn), 128.0, 128.2, 128.4 (CH_{arom}), 137.2 (C_{arom}), 175.0 (C=O).

MS (EI, 40 °C, 70 eV): *m*/*z* (%) = 221 ($M^{+\bullet}$ + 1, 0.7), 99 (50), 91 ($C_7H_7^+$, 100), 65 (25).

MS (CI, isobutane): *m*/*z* (%) = 221 ($M^{+\bullet}$ + 1, 100), 131 ($M^{+\bullet}$ + 1, –C_7H_7, 4), 114 ($M^{+\bullet}$ –C_7H_7O, 2).

Anal. calcd for $C_{13}H_{16}O_3$ (220.25): C 70.89, H 7.32; found C 70.78, H 7.33.

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References

(1) Yamashita, T.; Iijima, M.; Nakamura, H.; Issiki, K.; Naganawa, H.; Hattori, S.; Hamada, M.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1991**, *44*, 557.
(2) Kawatsu, M.; Yamashita, T.; Osono, M.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1993**, *46*, 1687.
Kawatsu, M.; Yamashita, T.; Osono, M.; Masuda, T.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1993**, *46*, 1692.
Kawatsu, M.; Yamashita, T.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 1123.
Kawatsu, M.; Yamashita, T.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1995**, *48*, 222.
(3) Kawatsu, M.; Yamashita, T.; Ishizuka, M.; Takeuchi, T.; Ueno M. *Int. J. Immunopharmac.* **1995**, *17*, 133.
(4) Hatakayama, S.; Fukuyama, H.; Mukugi, Y.; Irie, H. *Tetrahedron Lett.* **1996**, *37*, 4047.
(5) Kovacs-Kulyassa, A.; Herczegh, P.; Sztaricskai, F.J. *Tetrahedron Lett.* **1996**, *37*, 2499.
Kovacs-Kulyassa, A.; Herczegh, P.; Sztaricskai, F.J. *Tetrahedron* **1997**, *53*, 13883.
(6) Enders, D.; Bartsch, M.; Backhaus, D. *Synlett* **1995**, 869.
(7) Enders, D.; Backhaus, D.; Runsink, J. *Angew. Chem.* **1994**, *106*, 2167; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2098.
Enders, D.; Backhaus, D. *Tetrahedron* **1996**, *52*, 1503.
(8) Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(9) Enders, D.; Backhaus, D.; Reinhold, U. *Acros Organics Acta* **1995**, *1*, 35.
(10) Enders, D.; Plant, A. *Synlett* **1994**, 1054.
(11) Hayashi, M.; Toshiga, T.; Nakatani, K.; Ono, K.; Oguni, N. *Tetrahedron* **1994**, *50*, 2821 and references cited therein.

(12) Corey, E.J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.
(13) Prepared in analogy to the described procedure but using *N*,*N*-dimethylhydrazine.
(14) Brown, H.C.; Geoghegan Jr., P.J. *J. Org. Chem.* **1970**, *35*, 1844.
Cormick, R.; Löfstedt, J.; Perlmutter, P.; Westman, G. *Tetrahedron Lett.* **1997**, *38*, 2737.
Kang, S.H.; Lee, J.H.; Lee, S.B. *Tetrahedron Lett.* **1998**, *39*, 59.
(15) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, *34*, 2975.
(16) Bonini, C.; Bianco, A.; Di Fabio, R.; Mecozzi, S.; Proposito, A.; Righi, G. *Gazz. Chim. Ital.* **1991**, *121*, 75.
(17) Mori, Y.; Kuara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419.
(18) Smith III, A.B.; Condon, S.M.; McCauley, J.A.; Leazer, J.L.; Leahy, J.W.; Maleczka, R.E. *J. Am. Chem. Soc.* **1997**, *119*, 947.
Iversen, T.; Bundle, D.R. *J.C.S. Chem. Comm.* **1981**, 1240.
(19) Groth, U.; Chiang, Y.-C.; Schöllkopf, U. *Liebigs Ann. Chem.* **1982**, 1756.
Seebach, D.; Aebi, J. D.; Naef, R., Weber, T. *Helv. Chim. Acta* **1985**, *68*, 144.