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A New Stereocontrolled Synthesis of Dihydroxerulin, a Potent Noncytotoxic Inhibitor of the Biosynthesis of Cholesterol

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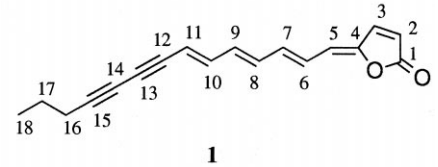
Abstract—Dihydroxerulin, **1**, has been stereoselectively synthesized by a convergent approach in which a key step was the Wittig reaction between (*Z*)-5-[(*E*)-3-formyl-2-propenylidene]-5*H*-furan-2-one, **15**, and the phosphonium ylid which derived from [(*E*)-2-decen-4,6-diyn-1-yl]triphenylphosphonium bromide, **19**. Compound **19** was conveniently prepared by a short reaction sequence involving a Stille reaction between 1-trimethylstannyl-1,3-heptadiyne, **17**, and (*E*)-3-iodo-2-propen-1-ol, **18**. On the other hand, compound **15** was prepared in eight steps by a reaction sequence in which an immediate precursor to this butenolide, i.e. (*Z*)-5-[(2*E*)-4-hydroxy-2-butenylidene]-5*H*-furan-2-one, **34**, was regio- and stereoselectively synthesized by Ag(I)-catalysed lactonization of the corresponding (*Z*)-2-en-4-ynoic acid. The structure and stereochemistry of **1** were established on the basis of its ^{1}H and ^{13}C NMR spectra at 600 and 150 MHz, respectively, and by a combination of 2D NMR techniques.

Dihydroxerulin, **1**, is a noncytotoxic inhibitor of the biosynthesis of cholesterol which was isolated in 90:10–65:35 mixtures with xerulin, **2**, from cultures of *Xerula melanotricha*.[1] The structures of compounds **1** and **2** and their stereochemistry were elucidated by spectroscopic methods,[1] but the configuration of their $\Delta^{8,9}$ double bond remained unknown. Nevertheless, this carbon–carbon double bond was assumed to be *E* because compounds **1** and **2** co-occurred with a structurally related (*Z*)-5-ylidene-5*H*-furan-2-one, i.e. xerulinic acid, **3**, in which the H-8 and H-9 protons exhibited a coupling constant ($J_{8,9}$=14.9 Hz) which is typical for an *E* carbon–carbon double bond.[1]



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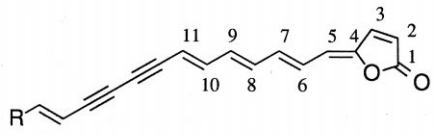

2 : R = CH_3
3 : R = COOH

Very recently, Siegel and Brückner[2] reported the first total synthesis of dihydroxerulin, **1**, and confirmed the stereochemistry previously assigned to this compound.[3] In this convergent synthesis (Scheme 1) the carbon skeleton of **1** was assembled by a Wittig reaction between the highly unsaturated ylid **10** and the 95–98% stereoisomerically pure aldehyde (*Z*)-**13**, which was prepared from a chiral nonracemic building block, i.e. L-gulono-1,4-lactone, **11**. The ylid **10** was synthesized in a convergent way from 1,4-dichloro-2-butyne, **6**, and 90% stereoisomerically pure (*E*)-2-penten-4-yn-1-ol, **7**, which in turn was synthesized from sodium acetylide, **4**, and epichlorohydrin, **5**.[2] On the other hand, the (*Z*)-5-ylidene-5*H*-furan-2-one derivative (*Z*)-**13** was prepared by a reaction sequence in which the key step was the stereocontrolled conversion of the 6-*tert*-butyldimethylsilyl derivative of **11** into (*Z*)-5-[2-(*tert*-butyldimethylsilyloxy)ethylidene]-3-(trifluoro-methanesulfonyloxy)-5*H*-furan-2-one, (*Z*)-**12**.[2]

It must be noted that dihydroxerulin, **1**, which was prepared by this route, was initially obtained in a mixture with at least two isomers and that only careful purification by repetitive passages through silica gel-filled flash chromatography columns led to pure **1**.[2]

More recently, as part of our ongoing projects relating to the development of efficient and selective procedures for the synthesis of natural and synthetic unsaturated five-membered lactones,[4] we became interested in the development of a new method for the efficient and stereocontrolled synthesis of **1**. The synthetic route we were looking for had to fulfil the following requirements: (i) to allow the

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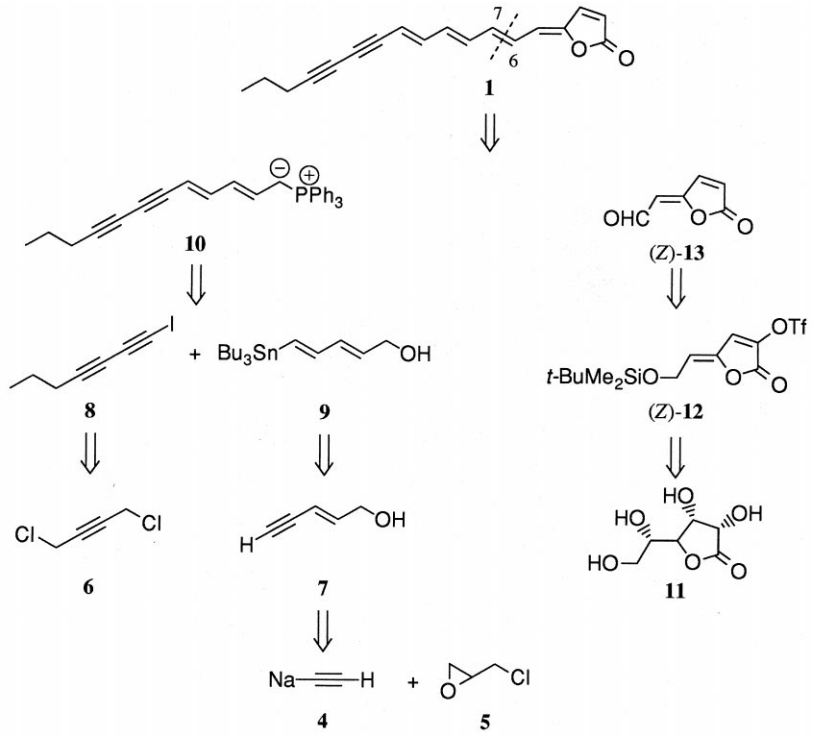
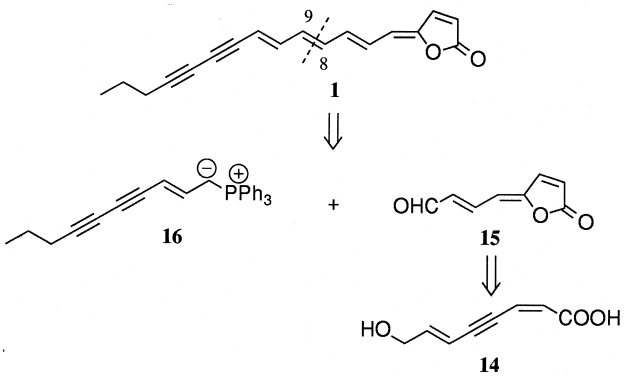


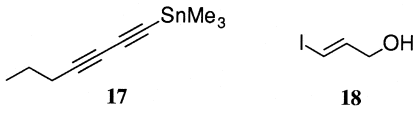
Scheme 1.

preparation of compound **1** having high chemical and stereoisomeric purity starting from commercially available, inexpensive and achiral starting materials without the use of careful and repetitive chromatographic purifications; and (ii) to be amenable to provide compound **1** on a scale larger than that used in the first total synthesis of this natural product.[2] In fact, we needed some hundreds of milligrams of this compound in order to test its fungicidal, insecticidal and herbicidal properties. Thus, we envisioned preparation of **1** by a convergent approach (Scheme 2) which involved: (i) the formation of the $\Delta^{8,9}$ double bond of this compound by a stereoselective Wittig reaction between the unsaturated ylid **16** and (*Z*)-5-[(*E*)-3-formyl-2-propenylidene]-5*H*-furan-2-one, **15**; and (ii) the synthesis of an immediate precursor of **15** by transition metal-catalysed lactonization of a suitable (*Z*)-2-en-4-ynoic acid, i.e. compound **14**. In fact, palladium- or silver-catalysed lactonization reactions have been recently employed successfully as a key step in the stereoselective and efficient synthesis of several natural and synthetic (*Z*)-5-ylidene-5*H*-furan-2-ones.[4b,d,5]



Scheme 2.

Moreover, in a preliminary investigation we had found that the phosphonium salt, which is the precursor to **16**, could be conveniently prepared by a short reaction sequence in which a Stille reaction between easily available 1-trimethylstannyl-1,3-heptadiyne, **17**, and (*E*)-3-iodo-2-propen-1-ol, **18**,[6] was used as a key step.

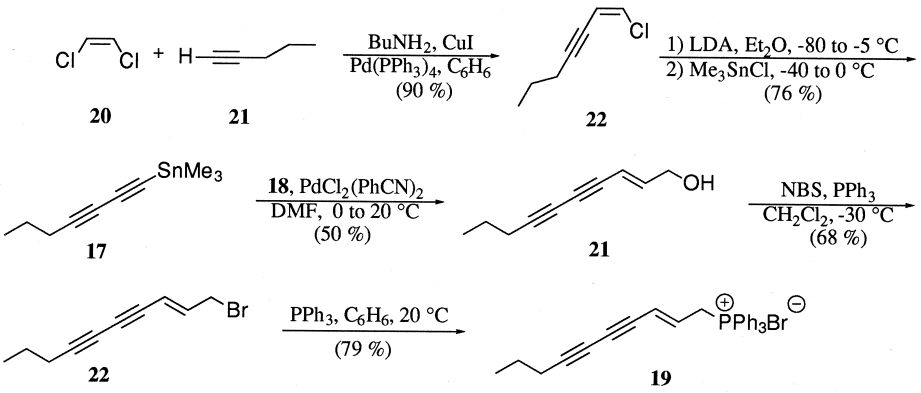


We now wish to report and comment on the results obtained in the study of this new stereocontrolled synthesis of dihydroxerulin, **1**.

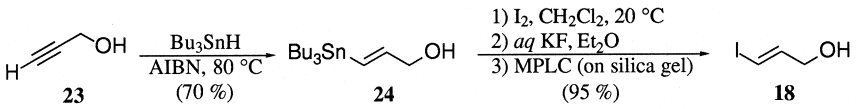
Results and Discussion

According to our synthetic strategy (Scheme 2), ylid **16** was a key intermediate of the synthesis of dihydroxerulin, **1**. We prepared the precursor to this ylid, i.e. [(*E*)-2-decen-4,6-diyn-1-yl]triphenylphosphonium bromide, **19**, by the reaction sequence illustrated in Scheme 3.

In particular, using the general procedure described by Ratovelomanana and Linstrumelle[7] for the synthesis of (*Z*)-1-chloro-1-en-3-ynes, a benzene solution of 1-pentyne, **21**, was reacted with 2.5 equiv. of (*Z*)-1,2-dichloroethene, **20**, in the presence of 5 equiv. of butylamine and catalytic amounts of $Pd(PPh_3)_4$ and CuI at room temperature for 22 h



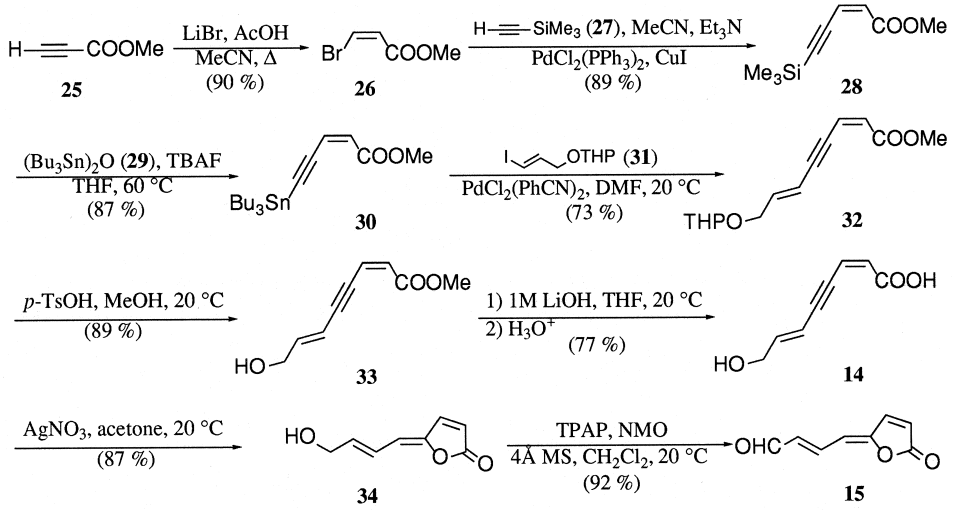
Scheme 3.



Scheme 4.

to give (*Z*)-1-chloro-1-hepten-3-yne, **22**, in 90% yield. Dehydrohalogenation of this compound by treatment with 2.5 equiv. of lithium diisopropylamide (LDA) in Et_2O at −80°C and subsequent reaction of the intermediary lithioacetylide with 3.0 equiv. of chlorotrimethylstannane afforded 1-trimethylstannyl-1,3-heptadiene, **17**, in 76% yield.[8] The cross-coupling reaction between **17** and 0.83 equiv. of (*E*)-3-iodo-2-propen-1-ol, **18**, which was carried out in DMF at room temperature in the presence of a catalytic amount of $PdCl_2(PhCN)_2$, i.e. using experimental conditions very similar to those employed by Stille and Simpson[9] for the Pd-catalysed reaction of vinyl iodides with acetylenic tin reagents, furnished a mixture of (*E*)-2-decen-4,6-diyn-1-ol, **21**, and 4,6,8,10-tetradecatetrayne, which was derived from homocoupling of **17**, in ca. 84:16 molar ratio, respectively. Purification of this mixture by MPLC on silica gel allowed us to obtain stereoisomerically pure **21** in 50% yield. It must be noted that stereoisomerically pure compound **18**, which we used as electrophilic partner in this cross-coupling reaction, was synthesized either by treatment of ethyl (*E*)-3-iodo-2-propenoate with $LiAlH_4$ in Et_2O at 0°C,[4d,6] or on a larger scale by reaction of propargyl alcohol, **23**, with tributyltin hydride and a catalytic amount of azobis(isobutyronitrile) (AIBN) at 80°C for 2 h[10] followed by treatment of the so-obtained (*E*)-3-tributylstannyl-2-propen-1-ol, **24**, with iodine in CH_2Cl_2 at room temperature (Scheme 4). The allylic alcohol **21** was then regioselectively and stereospecifically converted in 54% yield into the phosphonium salt **19** by reaction with 1.2 equiv. of PPh_3 and 1.1 equiv. of *N*-bromosuccinimide (NBS) in CH_2Cl_2 solution at −30°C followed by treatment of the resulting stereoisomerically pure bromide **22**, which had chemical purity higher than 97%, with PPh_3 in benzene at room temperature.[11]

The second key intermediate of our synthetic strategy, i.e. (*Z*)-5-[(*E*)-3-formyl-2-propenylidene]-5*H*-furan-2-one, **15**, was prepared as shown in Scheme 5. Thus, methyl

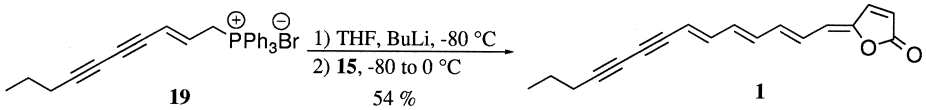


Scheme 5.

(*Z*)-3-bromo-2-propenoate, **26**, which was synthesized in 90% yield by reaction of methyl propiolate, **25**, with lithium bromide and acetic acid in acetonitrile under reflux,[12] was reacted with 1.5 equiv. of trimethylsilylacetylene, **27**, in a mixture of Et_3N and acetonitrile at room temperature in the presence of 2 mol% $Pd(PPh_3)_4$ and 4 mol% CuI. Stereoisomerically pure methyl (*Z*)-5-trimethylsilyl-2-penten-4-ynoate, **28**, which was so obtained in 89% yield,[13] was then directly converted into the corresponding 5-tributylstannyl derivative, **29**, according to the general procedure reported in the literature for the conversion of alkynyl-, allyl- and benzyltrimethylsilanes into the corresponding tributylstannanes in one step.[14,15] In particular, a mixture of 0.5 equiv. of bis(tributyltin)oxide, **29**, and 1.07 equiv. of compound **28** in dry THF was treated with 0.02 equiv. of tetrabutylammonium fluoride (TBAF) and the resulting mixture was heated to 65°C for 4.5 h. The volatiles, i.e. THF, the molar excess of **28** and bis(trimethylsilyl)oxide, which was formed in the reaction, were then removed in vacuo and the residue, which was diluted with hexane, was filtered over Celite. The filtrate was concentrated in vacuo to give in 87% yield the required organotin 92% chemically pure derivative **30** which had stereoisomeric purity higher than 97%.

The cross-coupling reaction between this crude compound and 0.87 equiv. of (*E*)-3-iodo-1-tetra-hydropyranyloxy-2-propene, **31**, in DMF at room temperature in the presence of a catalytic amount of $PdCl_2(PhCN)_2$ furnished **32** in 73% yield. Removal of the tetrahydropyranyloxy group from this compound by treatment with a catalytic amount of *p*-toluenesulfonic acid in methanol provided in 89% yield hydroxy ester **33** which was reacted with a molar excess of a 1 M solution of LiOH at room temperature followed by acidification. Lactonization of the so-obtained crude carboxylic acid **14** by reaction with 20 mol% $AgNO_3$ in acetone at 20°C afforded crude **34**, which was purified by MPLC on silica gel. Chemically and stereoisomerically pure (*Z*)-5-[(*E*)-4-hydroxy-2-butenylidene]-5*H*-furan-2-one, **34**, was so obtained in 66% yield based on **33**. This hydroxy derivative was then oxidized by reaction with tetrapropylammonium perruthenate (TPAP), 4-morpholine *N*-oxide (NMO) and powdered 4 Å molecular sieves in CH_2Cl_2 for 45 min at room temperature under argon.[16] On completion the reaction mixture was filtered through a short pad of silica gel, eluting with AcOEt and the filtrate was concentrated in vacuo to afford 95% chemically pure **15**.

Finally, our total synthesis of **1** was completed by a Wittig reaction between **15** and the phosphonium ylid **16**, which was obtained by treatment of **19** with butyllithium at −80°C (Eq. (1))



(1)

The crude product of this reaction was purified by MPLC on silica gel to give in 54% yield compound **1** for which the melting point (133–135°C) proved to be identical to that reported in the literature for synthetic dihydroxerulin.[2] Nevertheless, it must be noted that our sample of **1**, which was recrystallized from a mixture of benzene and hexane, had mp 139–142°C. The ^1H- and ^{13}C NMR spectra of this compound at 600 and 150 MHz, respectively, showed that it had stereoisomeric purity higher than 90%. Moreover, these NMR spectra, HPLC-MS measurements and a combination of NMR techniques, which included a homonuclear shift correlated spectroscopy experiment ($^1H-^1H$ COSY), a $^1H-^{13}C$ heteronuclear multi-quantum coherence (HMQC) experiment, a $^1H-^{13}C$ long-range heteronuclear shift correlated experiment and a total homonuclear correlation spectroscopy (TOCSY) experiment, allowed us to confirm the structure assigned to **1**. Interestingly, these structural assignments proved to be in good agreement with those reported in the literature for synthetic dihydroxerulin.[2]

Finally, it is worth mentioning that a Nuclear Overhauser experiment (NOESY) allowed us to assign the configuration of the carbon double bonds of **1**. In fact, the NOESY 2D map showed cross-peaks between the resonances of the following protons: H-2 and H-3; H-3 and H-5; H-5 and H-7; H-6 and H-8; H-7 and H-9; H-9 and H-11. Therefore, it was possible to infer that: (i) the H-5 and H-3 protons are near in space and, thus, the $\Delta^{4,5}$ double bond of **1** has the *Z* configuration; (ii) the H-7 and H-9 protons are also near in space and, thus, the $\Delta^{8,9}$ double bond of **1** has the *E* configuration. It must also be noted that this last configurational assignment was confirmed by the magnitude (14.5 Hz) of the vicinal coupling constant $J_{8,9}$ which, on the contrary to what was previously reported,[1,2] we succeeded in measuring.

In conclusion, we accomplished a new stereocontrolled synthesis of dihydroxerulin, **1**, by a strategy distinct from that employed by Siegel and Brückner.[2] In fact, whereas the approach of these authors involved the formation of the $\Delta^{6,7}$ carbon–carbon double bond of this butenolide derivative,[2] a key step of our convergent synthesis was the formation of the $\Delta^{8,9}$ double bond of **1** by a Wittig reaction between (*Z*)-5-[(*E*)-3-formyl-2-propenylidene]-5*H*-furan-2-one, **15**, and the phosphonium ylid derived from [(*E*)-2-decen-4,6-diyn-1-yl]triphenylphosphonium bromide, **19**. This last stereoisomerically pure compound was conveniently synthesized by a short reaction sequence involving a Stille reaction between readily available 1-trimethylstannyl-1,3-heptadiyne, **17**, and (*E*)-3-iodo-2-propen-1-ol, **18**. Moreover, whereas in the previous synthesis of **1**[2] the (*Z*)-ylidene-5H-furan-2-one sub-unit of this compound was prepared starting from L-gulono-1,4-lactone, in our approach the functionalized (*Z*)-5-ylidene-5*H*-furan-2-one derivative, which was employed as carbonyl partner of the Wittig reaction, i.e. compound **15**, was prepared by a reaction sequence in which an immediate precursor to **15**, i.e. compound **34**, was regio- and stereoselectively synthesized by silver(I)-catalysed lactonization of the corresponding (*Z*)-2-en-4-ynoic acid. Finally, it must be mentioned that our convergent approach, which did not involve repetitive chromatographic purifications of the reaction

products, allowed us to prepare some hundreds of milligrams of compound **1** having stereoisomeric purity higher than 90%.

Experimental

All boiling and melting points are uncorrected. Precoated plastic silica gel sheets Merck 60 F_{254} were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani data station 86.01. Two types of capillary columns were used: an Alltech AT-1 bonded FSOT column (30 m×0.25 mm i.d.) and an Alltech AT-35 bonded FSOT column (30 m×0.25 mm i.d.). Purifications by MPLC were performed on a Büchi instrument, using a Bischoff 8100 differential refractometer as detector. GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin–Elmer 8500 gas-chromatograph. The HPLC-MS measurements involving dihydroxerulin, **1**, were performed using a Perkin–Elmer 200 liquid chromatograph interfaced with a Perkin–Elmer Sciex API III plus triple quadrupole mass spectrometer. In these measurements the HPLC analyses was performed using a Supelco Discovery C 18 column (15 cm× 4.6 mm×4 μm) and two solvents, A and B, respectively, as mobile phase. Solvent A was constituted of a 5 mM aqueous solution of ammonium acetate and solvent B was constituted of acetonitrile saturated with ammonium acetate. The operative conditions were: 100% A for 5 min; a linear gradient for 30 min until 100% B; 100% B for 5 min. The APCI-mass spectrum was recorded using the following operative parameters: discharge current: 3 μA; temperature of the nebulizer: 500°C; orifice voltage: 60 V; scan range: 100–400 amu; step 0.2 amu; Dwell time: 1 ms; scan time: 1.58 s; interscan delay: 0.052 ms; resolution >1 amu. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer or a Bruker AMX 600 spectrometer using TMS and $CDCl_3$ as an internal standard, respectively. IR spectra were recorded on a Perkin–Elmer 1725-X FT-IR spectrophotometer. All reactions of air- and water-sensitive materials were performed in flame dried glassware under an atmosphere of argon or nitrogen. Air- and water-sensitive solutions were transferred with hypodermic syringes or double-ended needles. Solvents were dried and distilled before use. The following compounds were prepared according to the literature: $PdCl_2(PhCN)_2$,[17] $PdCl_2(PPh_3)_2$[18] and $Pd(PPh_3)_4$.[19] (*E*)-3-Tributylstannyl-2-propen-1-ol, **24**, was prepared in 70% yield by treatment of propargyl alcohol, **23**, with tributyltin hydride and a catalytic amount of AIBN at 80°C for 2 h.[10]

(*E*)-3-Iodo-2-propen-1-ol 18. A solution of iodine (4.83 g, 19.01 mmol) in CH_2Cl_2 (300 ml) was added to a solution of (*E*)-3-tributylstannyl-2-propen-1-ol, **24** (6.0 g, 17.29 mmol) in CH_2Cl_2 (50 ml) and the resulting mixture was stirred for 3.5 h at room temperature. It was then washed with a 10% aqueous $Na_2S_2O_3$ solution and water. The organic phase was stirred for 40 min with a 6 M aqueous KF solution (150 ml) and the resulting mixture was filtered over Celite. The filtrate was extracted with CH_2Cl_2 and the organic extract was washed with water, dried and concentrated. The residue was fractionally distilled to give chemically and stereoisomerically pure (*E*)-3-iodo-2-propen-1-ol, **18** (3.01 g, 95% yield) as a pale yellow liquid: bp 90–91°C/18 Torr [lit.[6]: bp 72–74°C/12 Torr]. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.56 (1H, dt, J=14.5 and 5.3 Hz, H-2), 6.40 (1H, d, J=14.5 Hz, H-3), 4.09 (2H, d, J=5.3 Hz, H-1), 2.04 ppm (1H, br s, OH). The spectral properties of this compound were in satisfactory agreement with those previously reported.[6] Alternatively, compound **18** was prepared in 50% yield by treatment of ethyl (*E*)-3-iodo-2-propenoate with $LiAlH_4$ in Et_2O at 0°C.[6]

(*Z*)-1-Chloro-1-hepten-3-yne 22. To a solution of 1-pentyne, **21** (5.62 g, 82.52 mmol) in dry benzene (500 ml), which was stirred under argon, was added butylamine (30.18 g, 412.6 mmol) followed by (*Z*)-1,2-dichloroethene, **20** (20.0 g, 206.3 mmol). To this solution was added CuI (2.36 g, 12.38 mmol) followed by $Pd(PPh_3)_4$ (4.77 g, 4.13 mmol) and the mixture was stirred for 22 h at room temperature. It was then washed repeatedly with brine (6×100 ml) and water (3×200 ml), dried and concentrated at 350 Torr. The residue was diluted with hexane (250 ml) and filtered over Celite. The filtrate was concentrated under reduced pressure and the residue was fractionally distilled to give stereoisomerically pure **22** (9.55 g, 90% yield) as a colourless liquid: bp 65–66°C/51 Torr. MS, *m*/*z* (%): 128 (28), 101 (12), 99 (40), 91 (84), 86 (24), 77 (100), 73 (51), 65 (37), 63 (52). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.29 (1H, d, J=7.3 Hz, H-1), 5.85 (1H, dt, J=7.3 and 2.1 Hz, H-2), 2.37 (2H, dt, J=7.0 and 2.0 Hz, H-5), 1.60 (2H, *pseudo*-sext; J=7.0 Hz, H-6), 1.03 ppm (3H, t, J=7.0 Hz, H-7). Anal. Calcd for C_7H_9Cl: C, 65.38; H, 7.05. Found: C, 64.95; H, 7.12.

1-Trimethylstannyl-1,3-heptadiyne 17. To a 1.79 M hexane solution of butyllithium (46.6 ml, 83.60 mmol), which was maintained at 0°C, was added Et_2O (200 ml). Subsequently diisopropylamine (8.46 g, 83.60 mmol) was added dropwise over a few minutes and the mixture was stirred for 45 min. It was then cooled to −80°C and a solution of compound **22** (4.30 g, 33.44 mmol) in Et_2O (15 ml) was added over 30 min. The resulting reaction mixture was stirred for 30 min at −80°C, allowed to warm up to −5°C and stirred at this temperature for 3 h. After this period a GLC analysis of a sample of the reaction mixture, which was hydrolysed with an aqueous NH_4Cl solution, showed that compound **22** had completely reacted. The reaction mixture was then cooled to −40°C and a solution of trimethyltin chloride (19.99 g, 100.32 mmol) in Et_2O (30 ml) was added dropwise over 30 min. The resulting mixture was stirred for 30 min at −40°C, allowed to warm up to 0°C and stirred at this temperature for 1.5 h. It was then poured into a large excess of a saturated aqueous NH_4Cl solution and extracted repeatedly with Et_2O (4×100 ml). The collected organic extracts were washed with water (6×100 ml) dried and concentrated under reduced pressure. The residue was fractionally distilled to give compound **17** (6.48 g, 76% yield) as a colourless liquid: bp 83–85°C/ 5 Torr. MS, *m*/*z* (%): 256 (4), 254 (4), 241 (100), 239 (76), 211 (37), 209 (25), 182 (13), 120 (36), 118 (25). IR (film): ν 2966, 2934, 2874, 2223, 2089, 1462, 1168, 777, 733, 538, 517 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.24 (2H, t, J=7.0 Hz, H-5), 1.55 (2H, *pseudo*-sext, J=7.0 Hz, H-6), 0.98 (3H, t, J=7.0 Hz, H-7), 0.31 ppm (9H, s, $SnMe_3$).

Anal. Calcd for $C_{10}H_{16}Sn$: C, 47.11; H, 6.32. Found: C, 46.91; H, 6.50.

(*E*)-2-Decen-4,6-diyn-1-ol 21. A degassed solution of (*E*)-3-iodo-2-propen-1-ol, **18** (2.48 g, 13.48 mmol) in DMF (25 ml) was added to a degassed solution of $PdCl_2(PhCN)_2$ (0.155 g, 0.404 mmol) in DMF (100 ml), which was stirred under argon at 0°C. A degassed solution of compound **17** (4.12 g, 16.17 mmol) in DMF (25 ml) was added and the resulting mixture was stirred for 2.5 h at 0°C. After this period a GLC analysis of a sample of the reaction mixture, which was poured into water and extracted with Et_2O, showed that compound **18** had completely reacted. Moreover, a GLC/MS analysis of this sample of the reaction mixture showed the presence of two compounds, in ca. 84:16 molar ratio, which had MS spectra corresponding to the desired cross-coupled compound **21** and to 4,6,8,10-tetradacatetrayne, respectively. This last compound had MS, *m*/*z* (%): 182 (83), 165 (63), 152 (100), 151 31), 139 (49), 115 (30), 110 (39), 98 (25), 87 (14). The reaction mixture was then poured into a large excess of water (500 ml) and extracted repeatedly with Et_2O (4×100 ml). The collected organic extracts were washed with brine (2×150 ml) and water (4×100 ml), dried and concentrated in vacuo. The residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (60:40) as eluent, to give compound **21** (0.99 g, 50% yield) as a pale yellow solid: mp 32–35°C. MS, *m*/*z* (%): 148 (4), 133 (4), 119 12), 105 (21), 103 (13), 91 (100), 89 (22), 79 (19), 77 (32). IR (KBr): ν 3371, 2235, 1459, 1425, 1381, 1340, 1266, 1093, 1021, 978, 951 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.37 (1H, dt, J=16.5 and 5.0 Hz, H-2), 5.78 (1H, d, J=16.0 Hz, H-3), 4.23 (2H, dd, J=5.0 and 1.7 Hz, H-1), 2.31 (2H, t, J=7.0 Hz, H-8), 1.72 (1H, br s, OH), 1.58 (2H, *pseudo*-sext; J=7.0 Hz, H-9), 1.00 ppm (3H, t, J=7.3 Hz, H-10). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.76; H, 7.71. GLC analysis showed that stereoisomerically pure compound **21** had chemical purity higher than 96%.

(*E*)-1-Bromo-2-decen-4,6-diyne 22. To a stirred solution of compound **21** (1.80 g, 12.15 mmol) in CH_2Cl_2 (50 ml), which was cooled to −30°C under argon, were sequentially added recrystallized PPh_3 (3.82 g, 14.58 mmol) and recrystallized NBS (2.38 g, 13.37 mmol). The course of the reaction was followed by TLC. After stirring for 3 h at −30°C the reaction was complete. The mixture was then poured into a large excess of a saturated aqueous $NaHCO_3$ solution (200 ml) and extracted repeatedly with pentane (4×100 ml). The collected organic extracts were washed with brine (2×100 ml), dried, and concentrated under reduced pressure. The red oily residue was diluted with pentane (130 ml) and filtered over Celite. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel, using hexane as eluant, to give **22** (1.75 g, 68% yield) as a pale yellow liquid. MS, *m*/*z* (%): 212 (5), 210 (5), 131 (100), 115 (41), 102 (40), 91 (81), 89 (44), 75 (42), 63 (46). ^1H NMR (200 MHz, $CDCl_3$): δ 6.36 (1H, dt, J=15.5 and 7.9 Hz, H-2), 5.76 (1H, d, J=15.5 Hz, H-3), 3.98 (2H, d, J=7.9 Hz, H-1), 2.32 (2H, t, J=7.0 Hz, H-8), 1.58 (2H, *pseudo*-sext, J=7.3 Hz, H-9), 1.00 ppm (3H, t, J=7.3 Hz, H-10). Anal. Calcd for $C_{10}H_{11}Br$: C, 56.90; H, 5.25. Found: C, 57.34; H, 4.95. GLC analysis showed that stereoisomerically pure compound **22** had chemical purity higher than 97%.

[(*E*)-2-Decen-4,6-diyn-1-yl]triphenylphophonium bromide 19. Allyl bromide **22** (1.75 g, 8.29 mmol) was dissolved in anhydrous benzene (19 ml) and recrystallized PPh_3 (2.61 g, 9.95 mmol) was added under argon at room temperature. The mixture was stirred at 20°C for 23 h, then it was diluted with anhydrous Et_2O (50 ml) and filtered. The collected solid was washed with anhydrous Et_2O (2×25 ml) and dried in vacuo to give compound **19** (2.57 g) as a pale grey solid which had: mp 176–178°C. ^1H NMR (200 MHz, $CDCl_3$): δ 7.95–7.55 (15H, m, C_6H_5), 6.24 (1H, dd, J_{H3-P}=5.1 Hz, J_{H2-H3}=7.3 Hz, H-1), 6.12–5.88 (1H, m, H-2), 5.11 (2H, dd, J_{H1-P}=16.0 Hz, J_{H1-H2}=7.3 Hz, H-1), 2.27 (2H, t, J=7.0 Hz, H-8), 1.54 (2H, *pseudo*-sext, J=7.0 Hz, H-9), 0.97 ppm (3H, t, J=7.3 Hz, H-10). Anal. Calcd for $C_{28}H_{26}BrP$: C, 71.04; H, 5.53. Found: C, 70.85; H, 5.99. A further amount of compound **19** (0.51 g), which had mp 174–176°C, was obtained from the collected filtrates, which were concentrated under reduced pressure, diluted with cold Et_2O (20 ml) and filtered. Compound **19** was so obtained in 79% yield based on **22**.

Methyl (*Z*)-3-bromo-2-propenoate 26. This compound was synthesized in 90% yield by reaction of methyl propiolate, **25**, with lithium bromide and acetic acid in acetonitrile under reflux according to the same procedure reported in the literature for the synthesis of ethyl (*Z*)-3-bromo-2-propenoate.[11] Compound **26** had: bp 71–72°C/35 Torr [lit.[20]: bp 61.5–63°C/10 Torr]. ^1H NMR (200 MHz, $CDCl_3$): δ 7.02 (1H, d, J=8.4 Hz, H-2 or H-3), 6.64 (1H, d, J=8.4 Hz, H-3 or H-2), 3.79 ppm (3H, s, CH_3). GLC and NMR analyses showed that compound **26** was stereoisomerically pure.

Methyl (*Z*)-5-trimethylsilyl-2-penten-4-ynoate 28. $PdCl_2(PPh_3)_2$ (1.40 g, 2.0 mmol), CuI (0.76 g, 4.0 mmol) and trimethylsilylacetylene, **27** (14.73 g, 150 mmol) were sequentially added to a degassed solution of **26** (16.5 g, 100 mmol) in acetonitrile (50 ml) and Et_3N (250 ml), which was stirred at room temperature. After stirring for 4 h the mixture was poured into a large excess of a saturated aqueous NH_4Cl solution and the resulting mixture, which was stirred for 0.5 h in the air, was extracted repeatedly with Et_2O (5×100 ml). The collected organic extracts were washed with water (2×150 ml), a 5% aqueous solution of HCl (1×200 ml) and water (5×50 ml), dried and concentrated under reduced pressure. The residue was diluted with hexane (100 ml) and filtered over Celite. The filtrate was concentrated under reduced pressure and the residue was fractionally distilled to give compound **28** (16.15 g, 89% yield) as a colourless liquid: bp 51–54°C/0.1 Torr. MS, *m*/*z* (%): 182 (12), 167 (100), 151 (11), 113 (27), 107 (22), 97 (17), 93 (10), 89 (15), 83 (26). ^1H NMR (200 MHz, $CDCl_3$): δ 6.17 (1H, d, J=11.6 Hz, H-2 or H-3), 6.10 (1H, d, J=11.6 Hz, H-3 or H-2), 3.77 (3H, s, CH_3), 0.24 ppm (9H, s, $SiMe_3$). GLC analyses showed that stereoisomerically pure compound **28** had chemical purity higher than 98%. The spectral properties of this compound were in good agreement with those previously reported.[12]

Methyl (*Z*)-5-tributylstannyl-2-penten-4-ynoate 30. A flame-dried reaction vessel, which was maintained under an argon atmosphere, was charged with a degassed solution of **28** (15.85 g, 87.18 mmol) in THF (200 ml) and bis(tributyltin)oxide, **29** (24.24 g, 40.70 mmol). A 1 M THF solution of TBAF (1.74 ml, 1.74 mmol) was added and a mild exothermic effect was observed. The mixture was then stirred at 65°C for 4.5 h at which time the volatiles were removed in vacuo (0.01 Torr). The residue was diluted with hexane (250 ml) and filtered over Celite. The filtrate was concentrated in vacuo to give compound **30** (30.41 g, 87% yield) as a red oil. MS, *m*/*z* (%): 343 (100), 341 (71), 339 (42), 229 (27), 199 (20), 171 (20), 151 (62). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.18 (1H, d, J=11.6 Hz, H-2 or H-3), 6.01 (1H, d, J=11.6 Hz, H-3 or H-2), 3.75 3H, s, $COOCH_3$), 1.70–1.48 (3×2H, m, CH_2), 1.45–1.15 (3×2H, m, CH_2), 1.06 (3×2H, t, J=7.6 Hz, CH_2-Sn), 0.91 ppm (3×3H, t, J=7.2 Hz, CH_3). GLC/MS analysis showed that compound **30** was 92% chemically pure and had stereoisomeric purity higher than 97%. This crude compound was used in the next step without any further purification and characterization.

(*E*)-3-Iodo-1-tetrahydropyranyloxy-2-propene 31. *p*-Toluenesulfonic acid monohydrate (1.37 g, 7.23 mmol) was added to a solution of (*E*)-3-iodo-2-propen-1-ol, **18** (16.33 g, 88.80 mmol) and 3,4-dihydro-2*H*-pyran (14.90 g, 177.57 mmol) in dry CH_2Cl_2 (145 ml) which was stirred at 0°C. After stirring the reaction mixture for 4 h at room temperature, solid $NaHCO_3$ (5.0 g) was added and the mixture was stirred for 15 min. It was then poured into a large excess of a saturated aqueous $NaHCO_3$ solution (300 ml) and extracted with Et_2O (4×100 ml). The organic extract was dried and concentrated in vacuo and the residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (95:5) as eluent, to give compound **31** (20.59 g, 86% yield) as a pale yellow liquid. MS, *m*/*z* (%): 167 (39), 85 (100), 67 (14), 57 (10), 55 (24), 43 (18), 41 (28). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.65 (1H, dt, J=14.4 and 5.6 Hz, H-2), 6.39 (1H, d, J=14.4 Hz, H-1), 4.65 (1H, d, J=3.3 Hz, H-2′), 4.15 (1H, ddd, J=13.5, 5.1 and 1.4 Hz, H-3), 3.96 (1H, dd, J=5.1 and 1.4 Hz, H-3), 3.90–3.73 (1H, m, H-6′), 3.56–3.48 (1H, m, H-6′), 2.00–1.35 ppm (6H, m, H-3′, H-4′ and H-5′). Anal. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89. Found: C, 36.01; H, 5.02.

Methyl (2*Z*,6*E*)-8-tetrahydropyranyloxy-2,6-octadien-4-ynoate 32. A degassed solution of **31** (4.01 g, 14.93 mmol) in anhydrous DMF (20 ml) and a degassed solution of compound **30** (6.84 g, 17.17 mmol) in anhydrous DMF (20 ml) were sequentially added to a degassed solution of $PdCl_2(PhCN)_2$ (0.286 g, 0.746 mmol) in anhydrous DMF (110 ml) which was stirred under argon. The resulting mixture was stirred at room temperature for 5 h at which time the reaction was complete. It was then poured into a large excess of water (300 ml) and extracted repeatedly with Et_2O (5×100 ml). The collected organic extracts were washed with water (4×80 ml) and concentrated under reduced pressure. The residue was diluted with Et_2O (100 ml), treated with a 6 M aqueous KF solution (300 ml) and the resulting mixture was stirred for 1 h at room temperature. It was the filtered over Celite and the filtrate was extracted repeatedly with Et_2O (5×100 ml). The collected organic extracts were washed with water (3×100 ml), dried, concentrated in vacuo and the residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (70:30) as eluent, to give compound **32** (2.71 g, 73% yield) as a yellow liquid. MS, *m*/*z* (%): 165 (58), 149 (19), 106 (17), 91 (14), 89 (20), 85 (100), 67 (18), 63 (17), 57 (11). IR (film): ν 2188, 1728, 1439, 1200, 1179, 1156, 1131, 1037, 1027, 984, 954 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.38 (1H, dt, J=11.5 Hz, H-2), 6.02 (1H, dq, J=15.5 and 2.0 Hz, H-6), 4.66 (1H, t, J=3.0 Hz, H-2′), 4.34 (1H, ddd, J=15.1, 4.8 and 1.6 Hz, H-6′), 4.09 (1H, ddd, J=15.1, 4.8 and 1.6 Hz, H-6′), 4.00–3.70 (1H, m, H-8), 3.60–3.45 (1H, m, H-8), 3.77 (3H, s, $COOCH_3$), 1.95–1.45 ppm (6H, m, H-3′, H-4′ and H-5′). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.44; H, 6.95. GLC analysis showed that compound **32** had purity higher than 97.5%. It must also be noted that in a second preparation according to the above reported procedure compound **32** was synthesized in 70% yield.

Methyl (2*Z*,6*E*)-8-hydroxy-2,6-octadien-4-ynoate 33. *p*-Toluenesulfonic acid monohydrate (0.40 g, 2.10 mmol) was added to a solution of compound **32** (5.46 g, 21.84 mmol) in methanol (60 ml) and the mixture was stirred for 8 h at room temperature. It was then diluted with Et_2O (400 ml) and washed repeatedly with a saturated aqueous $NaHCO_3$ solution (5×50 ml) and brine (4×100 ml). The organic extract was dried and concentrated in vacuo and the residue was purified by MPLC on silica gel, using a mixture of Et_2O and petroleum ether (70:30) as eluent, to give compound **33** (3.23 g, 89% yield) as a colourless oil. MS, *m*/*z* (%): 151 (6), 137 (13), 106 (72), 95 (17), 79 (51), 77 (100), 63 (37), 53 (15), 51 (24). IR (film): ν 2187, 1712, 1603, 1441, 1238, 1205, 1182, 953, 911 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.43 (1H, dt, J=15.8 and 4.8 Hz, H-7), 6.29 (1H, dd, J=11.4 and 2.3 Hz, H-3), 6.09 (1H, d, J=11.4 Hz, H-2), 6.01 (1H, dq, J=15.8 and 2.0 Hz, H-6), 4.26 (2H, br s, H-8), 3.77 (3H, s, $COOCH_3$), 2.78 ppm (1H, br s, OH). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.06. Found: C, 64.96; H, 6.19.

(2*Z*,6*E*)-8-Hydroxy-2,6-octadien-4-ynoic acid 14. A 1 M aqueous LiOH solution (60 ml, 60.0 mmol) was added to a solution of compound **33** (3.12 g, 18.80 mmol) in THF (90 ml) which was cooled to 0°C. The resulting mixture was stirred at room temperature for 22 h and then concentrated in vacuo. The residue was diluted with water (300 ml) and extracted repeatedly with Et_2O (4×50 ml). The resulting aqueous solution was cooled to 0°C, acidified with 10% H_2SO_4 and extracted repeatedly with Et_2O (5×100 ml). The collected organic extracts were washed with water, dried and concentrated in vacuo to give compound **14** (2.20 g, 77% yield) as a pale yellow solid. Mp 140–144°C. MS, *m*/*z* (%): 152 (62), 123 (100), 121 (27), 96 (38), 95 (45), 82 (66), 77 (39), 67 (29), 65 (25). ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.70 (1H, br s, COOH), 6.50–6.30 (2H, m, H-3 and H-7), 6.14 (1H, d, J=11.5 Hz, H-2), 6.00 (1H, dq, J=15.8 and 2.0 Hz, H-6), 4.22 ppm (3H, br s, H-8 and OH). This crude compound was used in the next step without any further purification and characterization.

(*Z*)-5-[(*E*)-4-Hydroxy-2-butenylidene]-5*H*-furan-2-one 34. To a degassed solution of **14** (2.10 g, 13.80 mmol) in acetone (140 ml) was added $AgNO_3$ (0.47 g, 2.76 mmol) and the resulting mixture was stirred under argon in the dark at room temperature for 96 h. It was then concentrated in vacuo and the residue was diluted with a mixture of CH_2Cl_2 and THF (95:5) and filtered over Celite. The filtrate was concentrated in vacuo and the residue was purified by MPLC on silica gel, using a mixture of CH_2Cl_2 and THF (95:5) as eluent, to give compound **34** (1.80 g, 86% yield) as a pale yellow solid. Mp 45–47°C. The MS spectrum of this compound proved to be identical to that of **14**. IR (KBr): ν 1776, 1747, 1647, 1334, 1119, 1086, 965, 940, 885 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.74 (1H, d, J=5.3 Hz, H-4), 6.78 (1H, ddt, J=15.0, 11.5 and 2.0 Hz, H-7), 6.38–6.18 (2H, m, H-3 and H-8), 6.09 (1H, d, J=11.5 Hz, H-6), 4.26 (2H, d, J=2.0 Hz, H-9), 4.11 ppm (1H, br s, OH). Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.50; H, 5.43.

(*Z*)-5-[(*E*)-3-Formyl-2-propenylidene]-5*H*-furan-2-one 15. Solid tetrapropylammonium perruthenate (TPAP) (0.207 g, 0.59 mmol) was added in one portion to a degassed mixture of **34** (1.78 g, 11.70 mmol), 4-methylmorpholine *N*-oxide (NMO) (2.06 g, 17.55 mmol) and powdered 4 Å molecular sieves (5.85 g) in dry CH_2Cl_2 (160 ml) which was stirred under argon. After stirring the mixture for 45 min at room temperature, a TLC analysis of a sample of the reaction mixture, which was diluted with AcOEt and filtered over silica gel, showed that the reaction was complete. The reaction mixture was then filtered through a short pad of silica gel eluting with AcOEt and the filtrate was evaporated to give compound **15** (1.61 g, 92% yield) as a green solid. Mp 168–173°C. MS, *m*/*z* (%): 150 (18), 95 (7), 82 (100), 68 (12), 66 (13), 65 (25), 54 (24). IR (KBr): 1785, 1750, 1665, 1628, 1260, 990, 880, 803 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 9.61 (1H, d, J=7.9 Hz, H-9), 7.55 (1H, dd, J=15.8 and 11.6 Hz, H-7), 7.43 (1H, d, J=5.6 Hz, H-4), 6.35 (1H, d, J=5.6 Hz, H-3), 6.28 (1H, dd, J=15.8 and 7.9 Hz, H-8), 5.98 ppm (1H, d, J=11.6 Hz, H-3). This crude product, which on the basis of a GLC analysis had chemical purity higher than 95%, was used in the next step without any further purification and characterization.

Dihydroxerulin 1. A 2.01 M hexane solution of butyllithium (3.0 ml, 6.05 mmol) was added dropwise to a solution of the phosphonium bromide **19** (3.0 g, 6.34 mmol) in THF (120 ml) which was stirred at −80°C under argon. The dark red reaction mixture was stirred for 15 min at −80°C, allowed to warm up to 0°C and then cooled to −80°C. A solution of the aldehyde **15** (0.86 g, 5.76 mmol) in THF (30 ml), which was maintained at −80°C, was added and the resulting reaction mixture was stirred for 4 h at −80°C and then allowed to warm up to 0°C over 1.5 h. After this period a TLC analysis, using a mixture of hexane and CH_2Cl_2 (40:60) as eluent, showed that the reaction was complete. Thus, the brown reaction mixture was poured into water (300 ml) and extracted repeatedly with Et_2O (4×80 ml) and subsequently with CH_2Cl_2 (2×100 ml). The collected organic extracts were washed with brine (4×100 ml), dried and concentrated in vacuo. The green solid residue was treated with a mixture of hexane and CH_2Cl_2 (150 ml, 50:50) and filtered over Celite. The filtrate was concentrated in vacuo and the residue was purified by MPLC on silica gel, using a mixture of hexane and CH_2Cl_2 (50:50) as eluent, to give compound **1** (0.82 g, 54% yield) as an orange solid. Mp 133–135°C. Lit.[2] mp 132–135°C. Compound **1**, which was recrystallized from a mixture of benzene and hexane, had: mp 139–142°C. APCI-MS, *m*/*z* 265. IR (KBr): 1769, 1742, 1531, 1180, 1093, 987, 935, 878, 844, 821, 766, 670 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.36 (1H, d, J=5.3 Hz, H-3), 6.81 (1H, dd, J=14.8 and 11.7 Hz, H-6), 6.75 (1H, dd, J=15.3 and 10.4 Hz, H-10), 6.52 (1H, dd, J=14.8 and 10.0 Hz, H-7), 6.45 (1H, dd, J=14.5 and 10.0 Hz, H-8), 6.41 (1H, dd, J=14.5 and 10.4 Hz, H-9), 6.17 (1H, d, J=5.3 Hz, H-2), 5.89 (1H, d, J=11.7 Hz, H-5), 5.70 (1H, dd, J=15.3 and 1.0 Hz, H-4), 2.33 (2H, td, J=7.3 and 1.0 Hz, H-16), 1.58 (2H, sext, J=7.3 Hz, H-17), 1.00 ppm (3H, t, J=7.3 Hz, H-18). A NOESY experiment (mixing time: 400 ms) showed the presence of cross-peaks between the resonances of the following protons: H-2 and H-3; H-3 and H-5; H-5 and H-7; H-6 and H-8; H-7 and H-9; H-9 and H-11. ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.33 (C-1), 149.45 (C-4), 143.66 (C-10), 142.55 (C-3), 137.87 (C-7), 135.27 (C-8), 135.14 (C-9), 127.60 (C-6), 118.87 (C-2), 114.71 (C-5), 112.36 (C-11), 87.38 (C-15), 79.75 (C-13), 74.84 (C-12), 65.55 (C-14), 21.76 (C-16), 21.76 (C-17), 13.48 ppm (C-18). Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.66; H, 6.24. The ^1H- and ^{13}C NMR spectra showed that compound **1** had stereoisomeric purity higher than 90%.

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