Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1605–1614

TETRAHEDRON: *ASYMMETRY*

Synthesis of versatile chiral intermediates by enantioselective conjugate addition of alkenyl Grignard reagents to enamides deriving from (*R*)-(−)- or (*S*)-(+)-2-aminobutan-1-ol

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Received 12 March 1998; accepted 31 March 1998

Abstract

Conjugate addition of but-3-enylmagnesium bromide to the chiral crotonamide (*R*)-(+)- and (*S*)-(−)-**3**, followed by hydrolysis and oxidation, afforded enantiopure (*R*)-(+)- and (*S*)-(−)-**3**-methyladipic acids **8**, respectively. Conjugate addition of vinylmagnesium chloride to the chiral crotonamide and cinnamamides (*R*)-(+)-**3–5**, followed by hydrolysis, gave the alkenoic acids (*S*)-**12–14**, respectively. Iodolactonization of the latter led to the 5-iodomethyllactones (+)-**15–17**, which were reduced by means of *n*-Bu_3SnH into the *trans*-disubstituted 5-methyllactones (+)-**19–21**, respectively. Treatment of the iodomethyllactone (+)-**16** with $LiMe_2Cu$ or *n*-Bu_2CuLi furnished the *trans*-5-alkyl-4-phenyllactones (−)-**22** or (+)-**23**.

1. Introduction

In both previous papers in this series,[1,2] we described the efficient diastereoselective conjugate addition of alkyl Grignard reagents to the tertiary crotonamide (*R*)-(+)-**3** and cinnamamide (*R*)-(+)-**4** derived from (*R*)-(−)-2-aminobutan-1-ol (*R*)-(−)-**1**, *via* the intermediate formation of the secondary amine (*R*)-(−)-**2** (Scheme 1). Next we contemplated the possibility of carrying out the same reaction by means of alkenyl Grignard reagents, since the resulting adducts could be potentially useful chiral intermediates.

2. Results and discussion

Reaction of *p*-chlorocinnamoyl chloride with the amine (*R*)-(−)-**2** in biphasic conditions (CH_2Cl_2/aqueous Na_2CO_3) gave high yields of the corresponding cinnamamide (*R*)-(+)-**5**. The

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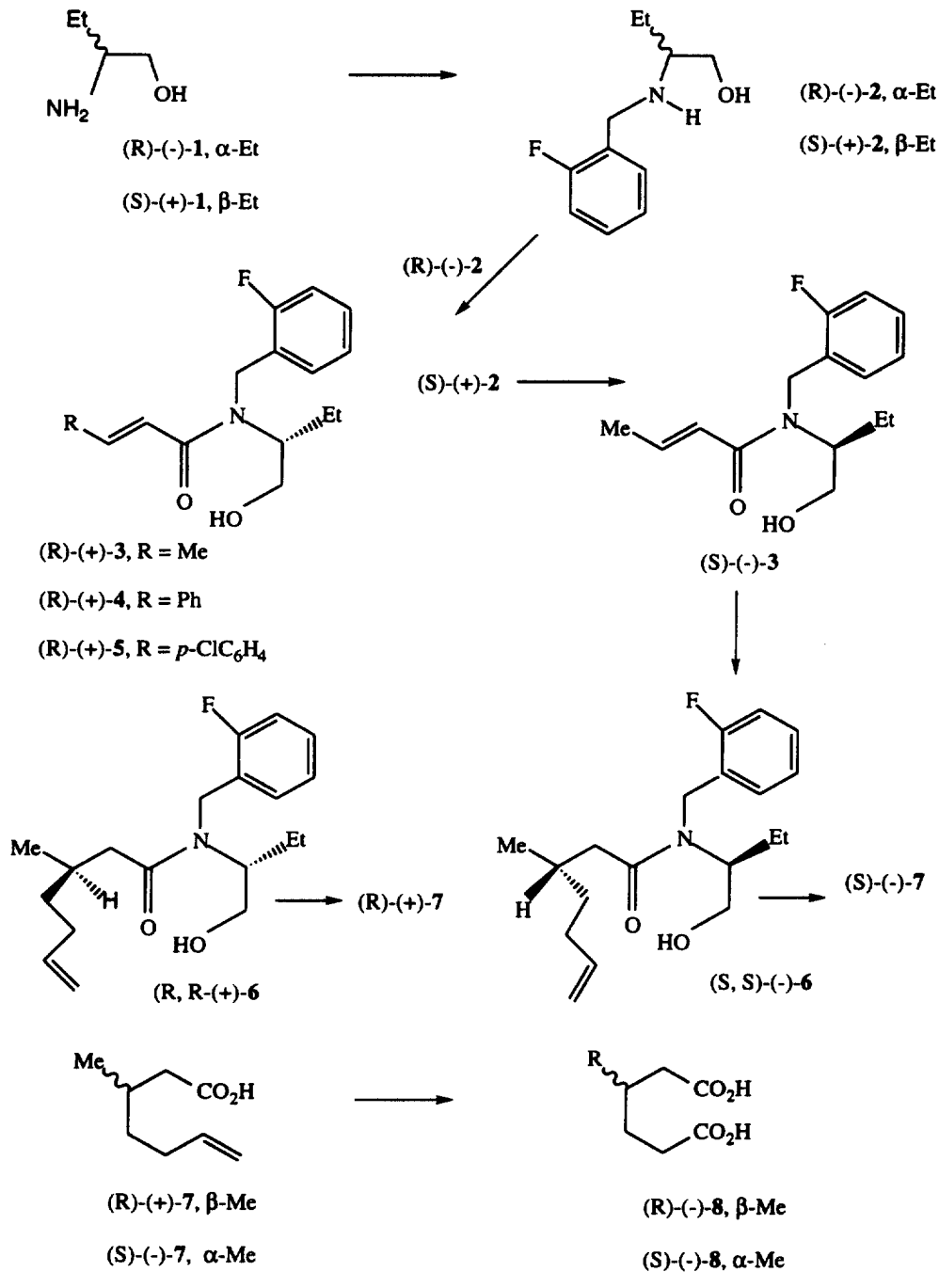
0957-4166/98/$19.00
PII: S0957-4166(98)00135-9



Scheme 1.

crotonamide (*S*)-(−)-**3** was similarly prepared from crotonoyl chloride and the secondary amine (*S*)-(+)-**2** derived from (*S*)-(+)-**1**. Conjugate addition of but-3-enylmagnesium bromide (sixfold molar excess) with the crotonamide (*R*)-(+)-**3** in ether at 0°C stereoselectively[1,2] afforded the corresponding adduct (*R*,*R*)-(+)-**6** in 82% yield, and having a d.e.=95.6% as shown from the ^{19}F NMR spectrum. The enantiomeric adduct (*S*,*S*)-(−)-**6** was similarly prepared from the crotonamide (*S*)-(−)-**3**. Saponification

of both adducts (*R*,*R*)- and (*S*,*S*)-**6** by means of KOH in aqueous ethanol yielded the corresponding free acids (*R*)-(+)-**7** and (*S*)-(−)-**7**, respectively. The e.e. of each acid **7** was assumed to be equal to the d.e. of the starting adduct **6**. The acid (*R*)-(+)-**7** was used by McWilliams and Clardy[3] in the synthesis of the natural antitumour compound octalactin A, whereas the acid (*S*)-(−)-**7** is an intermediate for various immunostimulants or immunoregulators.[4] Ozonolysis of the acids (*R*)-(+)- and (*S*)-(−)-**7** was next performed in acetone at −78°C followed by Jones' oxidation at 0°C, thus giving crystalline (*R*)-(+)- and (*S*)-(−)-3-methyladipic acids (*R*)-(+)- and (*S*)-(−)-**8**, respectively. The acid (*R*)-(+)-**8** was used in the synthesis of prostaglandins,[5] whereas the acid (*S*)-(−)-**8** is the precursor of an anticancer compound.[6]

Conjugate addition in ether/THF at 0°C of vinylmagnesium chloride (sixfold molar excess) with the crotonamide (*R*)-(+)-**3** and the cinnamamides (*R*)-(+)-**4** and (*R*)-(+)-**5** gave moderate yields of the corresponding (2′*R*,3*S*) adducts (+)-**9**, (−)-**10** and (+)-**11**, having d.e.'s=95.4, 93.2 and 94%, respectively (Scheme 2). Reaction of the crotonamide (*R*)-(+)-**3** with a threefold molar excess of vinylmagnesium chloride afforded diastereomerically pure adduct (2′*R*,3*S*)-(+)-**9** (d.e.=99%), albeit in poor yield (13%). Alkaline hydrolysis of the above adducts **9–11**, followed by mild acidification and evaporative distillation, furnished the corresponding (3*S*)-acids (+)-**12**, (−)-**13** and (−)-**14**, respectively. Here again, the e.e. of each acid was assumed to be equal to the d.e. of the starting adduct.

The enantiomerically enriched acids **12–14** were next used for the syntheses of various γ-butyrolactones. Thus, iodolactonization of these acids was carried out under thermodynamic control, as described by Bartlett et al.[7] ($3I_2$/acetonitrile/24 h/0°C) and gave the *trans*-disubstituted iodomethyl-γ-lactones **15–17**, respectively, contaminated by small amounts (2–8%) of the corresponding *cis*-isomer as shown by the ^{1}H NHR spectra: the proton at C5 gives a signal at *ca.* δ 4.1 ppm for the *trans*-isomer, and at *ca.* δ 4.9 ppm for the *cis*-isomer (see Experimental section). The *trans*-lactone (+)-**15** is an intermediate in the syntheses of the antibiotics aplidiasphingosin[8] and ambruticin.[9] Iodolactonization of the acid (−)-**13** under kinetic control[10] (I_2/aqueous $NaHCO_3$/6 h/0°C) gave a mixture of *cis*-lactone (−)-**18** and *trans*-lactone (+)-**16** (*cis:trans* ratio=78:22). Recrystallization afforded the pure *cis*-lactone (4*R*,5*R*)-(−)-**18** in 25% yield.

Reduction of the iodomethyllactones (+)-**15–17** with Bu_3SnH in the presence of AIBN in refluxing toluene for 24 h led to the corresponding 5-methylactones **19–21**, respectively, and in fair yields after purification. The diastereomerically pure lactones **20** and **21** were obtained by recrystallization. The *trans*-dimethylactone (+)-**19** is one of the components responsible for the aroma of whisky.[11]

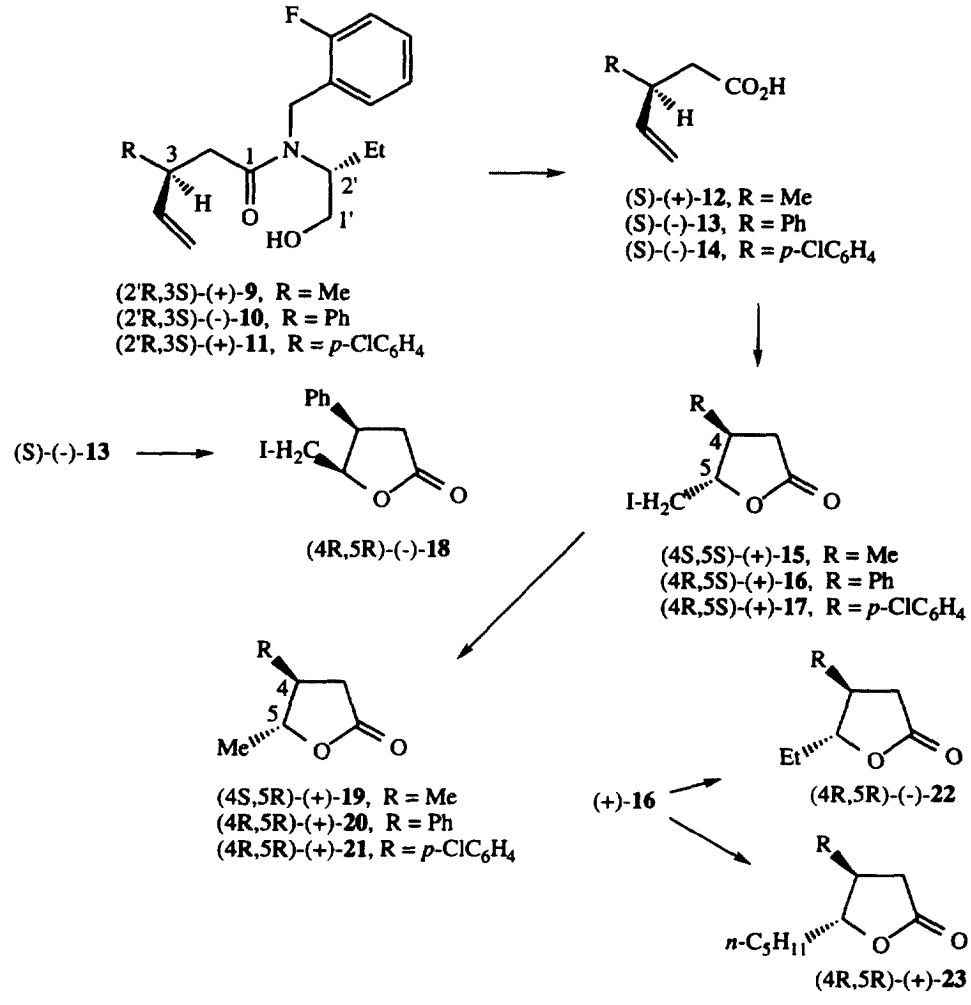
Reaction of the iodomethylactone (+)-**16** with 5 molar equivalents of Me_2CuLi in THF at 0°C gave the 5-ethyllactone (−)-**22** in 47% yield. Similarly, treatment of (+)-**16** with 5 molar equivalents of *n*-Bu_2CuLi in THF at low temperature furnished the 5-*n*-pentyllactone (+)-**23** in 25% yield. The enantiomer of the latter is an intermediate for the antitumour antibiotic methylenolactocin.[12]

Since both the chiral vectors (*R*)-(−)-**2** and (*S*)-(+)-**2** are readily available, all the chiral intermediates described above could be obtained in each enantiomeric form.

3. Experimental section

3.1. General

IR spectra were recorded with Nicolet 5DX and Genesis (Matteson) spectrophotometers. ^{1}H NMR (400 MHz) and ^{19}F NMR spectra were recorded with a Bruker AC 400 spectrometer, using Me_4Si (for ^{1}H) and $CFCl_3$ (for ^{19}F) as internal standards. Melting points were determined with a Reichert



Scheme 2.

microscope. Optical rotations were measured at 26°C with a Perkin–Elmer 241 micropolarimeter. Elemental analyses were carried out at the I.C.S.N. (C.N.R.S., Gif-sur-Yvette).

(*R*)-(−)- and (*S*)-(+)-2-Aminobutan-1-ol, $[\alpha]_D$ ±10.0 (neat), were kindly provided by SmithKline Beecham Laboratories (Mayenne).

3.2. (S)-(+)-N-(2-Fluorobenzyl)-2-aminobutan-1-ol (S)-(+)-2

This compound was prepared in the same way as its enantiomer (*R*)-(−)-**2**,[2] by alkylation of (*S*)-(+)-2-aminobutan-1-ol (*S*)-(+)-**1**, $[\alpha]_D$ +10 (neat), with 2-fluorobenzyl chloride. The secondary amine (*S*)-(+)-**2** was isolated in 95% yield, m.p. 48–54°C and $[\alpha]_D$ +21 (c 2.31, MeOH). ^{1}H NMR ($CDCl_3$) δ: 7.35 (1H, td); 7.25 (1H, td); 7.10 (1H, t); 7.01 (1H, t); 3.85 (1H, d); 3.80 (1H, d); 3.65 (1H, dd); 3.33 (1H, dd); 3.12 (1H); 2.60 (1H); 1.50 (2H); 0.92 (3H, t).

3.3. (S)-(−)-N-(1-Ethyl-2-hydroxy)ethyl-N-(2-fluorobenzyl)crotonamide (S)-(−)-3

This compound was prepared in the same way as its enantiomer (*R*)-(+)-**3**,[2] by *N*-acylation of the enantiomer of the secondary amine (*S*)-(+)-**2** with crotonoyl chloride. The crotonamide (*S*)-(−)-**3** was isolated in 83% yield, $[\alpha]_D$ −18.6 (c 1.56, MeOH). IR (film): 3390, 1656 and 1603 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.50–6.90 (5H); 6.40–6.10 (1H, d); 4.90 (d), 4.65 (d), 4.58 (d) and 4.38 (d) (total 2H); 4.0–3.40 (4H); 2.0–1.70 (3H); 1.70–1.50 (2H); 0.90 (3H, t). ^{19}F NMR ($CDCl_3$) δ: −118.6 (72%) and −119.8 (28%) (Z/E amide conformers).

3.4. (R)-(+)-N-(1-Ethyl-2-hydroxy)ethyl-N-(2-fluorobenzyl)-p-chlorocinnamamide (R)-(+)-5

A solution of *p*-chlorocinnamoyl chloride (4.0 g; 19.9 mmol) in dichloromethane (12 mL) was added at 0°C to the aminoalcohol (*R*)-(−)-**2** (3.92 g; 19.9 mmol) in dichloromethane (19 mL), and the mixture was treated with sodium carbonate (2.11 g; 19.9 mmol) in water (14 mL). The resulting biphasic medium was stirred at 20°C for 4 h. Work-up in the usual manner[2] gave an oil which was chromatographed over silica gel (eluent: cyclohexane:ether=6:4 and elution gradient), thus affording the amide (*R*)-(+)-**5** (6.47 g; 90%), $[\alpha]_D$ +12.3 (c 1.06, MeOH). Anal. calc. for $C_{20}H_{21}ClFNO_2$: C, 66.39; H, 5.85; N, 3.87. Found: C, 66.38; H, 5.83; N, 3.71. IR (film): 3390, 1650 and 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.65 (1H, d); 7.80–7.0 (8H); 6.75 (1H, d); 5.01 (d), 4.75 (d), 4.70 (d) and 4.45 (d) (total 2H); 4.25–3.50 (4H); 1.85 and 1.66 (2H); 0.95 (3H, t). ^{19}F NMR ($CDCl_3$) δ: −118.56 (68%) and −119.70 (32%) (Z/E amide conformers).

3.5. (R,R)-(+)-N-(1-Ethyl-2-hydroxy)ethyl-N-(2-fluorobenzyl)-3-methylhept-6-enamide (R,R)-(+)-6

The crotonamide (*R*)-(+)-**3**[2] (0.70 g; 2.6 mmol) in dry ether (20 mL) was added at 0°C to a solution of but-3-enylmagnesium bromide in dry ether (14 mL), prepared from 4-bromobut-1-ene (2.14 g; 15.9 mmol) and magnesium (0.433 g; 17.9 mmol). After stirring at 0°C for 19 h, the mixture was worked-up in the usual way.[2] The final residue was chromatographed over silica gel (eluent: cyclohexane:ether=5:5 and elution gradient), thus giving the adduct (*R,R*)-(+)-**6** (0.698 g; 82%), $[\alpha]_D$ +7.6 (c 1.12, MeOH). IR (film): 3399, 1623 and 1587 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.50–6.90 (4H); 5.80 (1H); 4.95 (2H); 4.86 (d), 4.61 (d), 4.49 (d) and 4.35 (d) (total 2H); 4.0–3.40 (4H); 2.55 (1H); 2.35 (1H); 2.25–1.90 (2H); 1.90–1.20 (5H); 1.0 and 0.94 (3H); 0.91 (3H, t). ^{19}F NMR ($CDCl_3$) δ: −118.46 (*R,R*) (97.8%); −118.48 (*S,R*) (2.2%); −119.80 [(*R,R*)+(*S,R*)] (100%) (amide conformers and diastereomers), d.e.=95.6%.

3.6. (S,S)-(−)-N-(1-Ethyl-2-hydroxy)ethyl-N-(2-fluorobenzyl)-3-methylhept-6-enamide (S,S)-(−)-6

The adduct (*S,S*)-(−)-**6**, $[\alpha]_D$ −7.5 (c 1.0, MeOH), was prepared in the same way as its enantiomer (*R,R*)-(+)-**6**, starting from the crotonamide (*S*)-(−)-**3**. Anal. calc. for $C_{19}H_{28}FNO_2$: C, 71.0; H, 8.78; N, 4.36. Found; C, 70.58; H, 8.78; N, 4.29. ^{19}F NMR ($CDCl_3$) δ: −118.47 (*S,S*) (96.8%); −118.5 (*R,S*) (3.2%); −119.81 [(*S,S*)+(*R,S*)] (100%) (amide conformers and diastereomers), d.e.=93.5%.

3.7. (R)-(+)-3-Methylhept-6-enoic acid (R)-(+)-7

The adduct (*R,R*)-(+)-**6** (0.589 g; 1.8 mmol), $[\alpha]_D$ +7.6 (c 1.12, MeOH) and d.e.=95.6%, in ethanol (4.5 mL) was treated with potassium hydroxide (0.421 g; 7.3 mmol) in water (1.5 mL). After stirring for 65 h at room temperature, the mixture was acidified with 10% aqueous hydrochloric acid, the ethanol was

removed under reduced pressure and the aqueous residue was extracted with ether. The organic extracts were dried ($MgSO_4$) and evaporated. Distillation of the residue under reduced pressure afforded the acid (*R*)-(+)-**7** (0.221 g; 85%), b.p.$_{20}$ 135–140°C and $[\alpha]_D$ +6.6 (c 0.98, $CHCl_3$). Lit.[3] (no characteristics given). IR (film): 3500–2500, 1710 and 1643 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 5.80 (1H); 5.0 (2H); 2.37 (dd) and 2.17 (dd) (total 2H); 2.15–1.90 (3H); 1.45 and 1.32 (2H); 1.0 (3H, d).

3.8. (S)-(−)-3-Methylhept-6-enoic acid (S)-(−)-7

The procedure is the same as for the enantiomeric acid (*R*)-(+)-**7**. The adduct (*S,S*)-(−)-**6** (0.617 g; 1.9 mmol), $[\alpha]_D$ −7.5 (c 1.0, MeOH) and d.e.=93.5%, in ethanol (4.7 mL) was treated with potassium hydroxide (0.431 g; 7.7 mmol) in water (1.6 mL). Work-up followed by distillation gave the acid (*S*)-(−)-**7** (0.195 g; 72%), b.p.$_{20}$ 135–140°C and $[\alpha]_D$ −6.7 (c 1.1, $CHCl_3$). Lit.[3] (no characteristics given).

3.9. (R)-(+)-3-Methyladipic acid (R)-(+)-8

A solution of the acid (*R*)-(+)-**7** (0.142 g; 1.0 mmol), $[\alpha]_D$ +6.6 (c 0.98, $CHCl_3$), in dry acetone (50 mL) was ozonolyzed at −78°C for 5 min. After spontaneous warming to 0°C, Jones' reagent was added dropwise until the orange colour persisted. The mixture was filtered and evaporated, followed by addition of ether (100 mL) and water (25 mL). The aqueous phase was extracted with ether (3×100 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. Evaporative distillation of the colourless oily residue gave the acid (*R*)-(+)-**8** as white crystals which were recrystallized from ether/pentane (0.100 g; 70%), m.p. 85–86°C, b.p.$_{0.1}$ 115–120°C and $[\alpha]_D$ +11.67 (c 1.2, $CHCl_3$). Lit.[13] $[\alpha]_D$ +11.5 (c 9.4, $CHCl_3$). IR ($CHCl_3$): 3500–2500 and 1700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.39 (2H); 2.33 (1H, dd); 2.21 (1H, dd); 2.01 (1H); 1.74 and 1.54 (2H); 0.98 (3H, d).

3.10. (S)-(−)-3-Methyladipic acid (S)-(−)-8

The acid (*S*)-(−)-**8**, m.p. 81–82°C and $[\alpha]_D$ −11.1 (c 1.1, $CHCl_3$) was prepared in the same way as its enantiomer (*R*)-(+)-**8**, but starting from the ethylenic acid (*S*)-(−)-**7**. Lit.[14] $[\alpha]_D$ −10.98 (c 3.2, $CHCl_3$).

3.11. (2′R,3S)-(+)-N-(1-Ethyl-2-hydroxy)ethyl-N-(2-fluorobenzyl)-3-methylpent-4-enamide (2′R,3S)-(+)-9

The adduct (+)-**9** was prepared in a similar manner as the adduct (+)-**6**. The crotonamide (*R*)-(+)-**3**[2] (0.700 g; 2.6 mmol) in dry ether (20 mL) was added at 0°C to vinylmagnesium chloride (1.370 g; 15.9 mmol; 15% solution in THF). After stirring at 0°C for 3 h, the mixture was worked-up in the usual way.[2] The final residue was chromatographed over silica gel (eluent: cyclohexane:ether=7:3 and elution gradient), thus affording the adduct (2′*R* 3*S*)-(+)-**9** (0.540 g; 70%), $[\alpha]_D$ +9.6 (c 1.1, MeOH). Anal. calc. for $C_{17}H_{24}FNO_2$: C, 69.60; H, 8.24; N, 4.77. Found: C, 69.61; H, 8.12; N, 4.76. IR (film): 3413, 1621 and 1587 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.50–6.95 (4H); 5.95–5.70 (1H); 5.06 (1H, dd); 4.98 (1H, dd); 4.88 (d), 4.59 (d), 4.52 (d) and 4.35 (d) (total 2H); 4.10–3.40 (4H); 3.00–2.50 (1H); 2.50–2.25 (2H); 1.90–1.50 (3H); 1.12 and 10.5 (3H); 0.90 (3H, t). ^{19}F NMR ($CDCl_3$) δ: −118.43 (*R,R*) (2.3%); −118.45 (*S,R*) (97.7%); −119.82 (*S,R*)+(*R,R*)] (100%) (amide conformers and diastereomers); d.e.=95.4%.

3.12. (2′R,3S)-(−)-N-(1-Ethyl-2-hydroxy)ethyl-N-(2-fluorobenzyl)-3-phenylpent-4-enamide (2′R,3S)-(−)-10

The adduct (−)-**10** was prepared in the usual manner. The cinnamamide (*R*)-(+)-**4**[1] (4.0 g; 12.2 mmol) in dry ether (110 mL) was added at 0°C to vinylmagnesium chloride (6.37 g; 73.4 mmol; 15% solution in THF). After stirring at 0°C for 3.5 h, the reaction mixture was worked-up[1,2] and the final residue was chromatographed over silica gel (eluent: cyclohexane:ether=7:3 and elution gradient), thus affording the adduct (2′*R*,3*S*)-(−)-**10** (2.26 g; 52%), $[\alpha]_D$ −3.47 (c 1.26, MeOH). Anal. calc. for $C_{22}H_{26}FNO_2$: C, 74.34; H, 7.37; N, 3.94. Found: C, 74.16; H, 7.33; N, 3.69. IR (film): 3409, 1623 and 1585 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.50–6.90 (9H); 6.20–5.9 (1H); 5.12 (2H); 4.75 (d), 4.52 (d), 4.39 (d) and 4.38 (d) (total 2H); 4.15 and 4.05 (1H); 3.80–3.40 (3H); 3.08 (dd), 2.93 (dd), 2.80 (dd) and 2.76 (dd) (total 2H); 1.70 (1H); 1.74 and 1.54 (2H); 0.86 and 0.81 (3H, 2t). ^{19}F NMR ($CDCl_3$) δ: −118.46 (*S*,*R*) (96.6%); −118.53 (*R*,*R*) (3.4%); −119.95 (*S*,*R*) (96.2%); −119.99 (*R*,*R*) (3.8%) (amide conformers and diastereomers); d.e.=93.2%.

3.13. (2′R,3S)-(+)-N-(1-Ethyl-2-hydroxy)ethyl-N-(2-fluorobenzyl)-3-(p-chlorophenyl)pent-4-enamide (2′R,3S)-(+)-11

The adduct (+)-**11** was prepared in the usual manner. The *p*-chlorocinnamamide (*R*)-(+)-**5** (3.55 g; 9.80 mmol) in dry ether (120 mL) was added at 0°C to vinylmagnesium chloride (5.11 g; 58.9 mmol; 15% solution in THF). After stirring at 0°C for 3.5 h, the reaction mixture was worked-up[1,2] and the final residue was chromatographed over silica gel (eluent: cyclohexane:ether=7:3 and elution gradient), thus affording the adduct (2′*R*,3*S*)-(+)-**11** (2.08 g; 54%), $[\alpha]_D$ +1.5 (c 1.2, MeOH). Anal. calc. for $C_{22}H_{25}ClFNO_2$: C, 67.77; H, 6.46; N, 3.59. Found: C, 67.72; H, 6.38; N, 3.37. IR (film): 3407, 1635 and 1587 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.40–6.90 (8H); 6.10–5.85 (1H); 5.10 (2H); 4.75 (d), 4.50 (d), 4.39 (d) and 4.31 (d) (total 2H); 4.15 and 4.05 (1H); 4.0–3.40 (3H); 3.05 (dd), 2.86 (dd), 2.70 (dd) and 2.63 (dd) (total 2H); 1.50 (1H); 1.75 and 1.49 (2H); 0.85 and 0.78 (3H, 2t). ^{19}F NMR ($CDCl_3$) δ: −118.42 (*S*,*R*) (97%); −118.54 (*R*,*R*) (3%); −119.93 (*S*,*R*) (94.2%); −120.00 (*R*,*R*) (5.8%) (amide conformers and diastereomers); d.e.=94%.

3.14. (S)-(+)-3-Methylpent-4-enoic acid (S)-(+)-12

The procedure is the same as for the preparation of the acid (*R*)-(+)-**7**. The adduct (2′*R*,3*S*)-(+)-**9** (2.88 g; 9.80 mmol), $[\alpha]_D$ +9.6 (c 1.1, MeOH) and d.e.=95.4%, in ethanol (21.6 mL) was treated with potassium hydroxide (2.20 g; 39.3 mmol) in water (7.2 mL). Work-up followed by distillation gave the acid (*S*)-(+)-**12** (0.885 g; 79%), b.p.$_{30}$ 110–120°C and $[\alpha]_D$ +15.14 (c 3.6, $CHCl_3$). Lit.[15] $[\alpha]_D$ +17.3 (c 2.07, $CHCl_3$). IR (film): 3400–2400, 1712 and 1643 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 5.80 (1H, ddd); 5.06 (d) and 4.99 (d) (total 2H); 2.70 (1H); 2.42 (dd) and 2.32 (dd) (total 2H); 1.09 (3H, d).

3.15. (S)-(−)-3-Phenylpent-4-enoic acid (S)-(−)-13

The procedure is the same as above. The adduct (2′*R*,3*S*)-(−)-**10** (2.42 g; 6.8 mmol), $[\alpha]_D$ −3.47 (c 1.3, MeOH) and d.e=93.2%, in ethanol (20 mL) was treated with potassium hydroxide (1.53 g; 27.3 mmol) in water (6.1 mL). Work-up followed by distillation gave the acid (*S*)-(−)-**13** (1.20 g; 100%), $[\alpha]_D$ −12.2 (c 1.0, PhH). Lit.[16] (described in racemic form). IR (film): 3500–2500, 1710, 1637 and 1602

cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.40–7.20 (5H); 5.96 (1H); 5.10 (2H); 3.85 (1H, qd); 2.80 (1H, dd); 2.75 (1H, dd).

*3.16. (S)-(−)-3-(p-Chlorophenyl)pent-4-enoic acid (S)-(−)-**14***

The procedure is the same as above. The adduct (2′*R*,3*S*)-(+)-**11** (2.04 g; 5.2 mmol), $[\alpha]_D$ +1.5 (c 1.2, MeOH) and d.e.=94%, in ethanol (16 mL) was treated with potassium hydroxide (1.17 g; 20.9 mmol) in water (8 mL). Work-up followed by distillation gave the acid (*S*)-(−)-**14** (0.757 g; 69%), m.p. 55–60°C and $[\alpha]_D$ −14.4 (c 1.39, PhH). Anal. calc. for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.95; H, 5.21. IR (film): 3400–2500, 1714, 1635 and 1616 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.35–7.00 (4H); 5.95 (1H, ddd); 5.08 (2H); 3.85 (1H); 2.80 (1H, dd); 2.70 (1H, dd).

*3.17. (4S,5S)-(+)-*trans*-4,5-Dihydro-5-iodomethyl-4-methyl-(3H)-furan-2-one (4S,5S)-(+)-**15***

The acid (*S*)-(+)-**12** (0.137 g; 1.20 mmol), $[\alpha]_D$ +15.14 (c 3.6, $CHCl_3$), in purified acetonitrile (4.4 mL) was treated at 0°C under nitrogen with iodine (0.91 g; 3.6 mmol). After stirring at 0°C in the dark and under nitrogen for 24 h, ether (5 mL) and saturated aqueous sodium hydrogen carbonate solution (5 mL) were added. The aqueous phase was extracted with ether and the combined organic solutions were washed with 10% aqueous sodium thiosulphate solution until colourless, and then washed with water. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The brown oily residue (0.247 g; 86%) was rapidly chromatographed over silica using ether as an eluent, thus affording the lactone (+)-**15** (0.227 g; 79%), $[\alpha]_D$ +16.3 (c 1.45, $CHCl_3$) with a *trans:cis* ratio=92:8 (from ^1H NMR). Lit.[8] $[\alpha]_D$ +18.14 ($CHCl_3$). IR (film): 1778 cm^{-1}. ^1H NMR ($CDCl_3$), major *trans*-isomer, δ: 4.05 (1H, q) (92%); 3.40 (1H, dd); 3.35 (1H, dd); 2.81 (1H, dd); 2.45 (1H); 2.25 (1H, dd); 1.25 (3H, d). Minor *cis*-isomer, δ: 4.67 (1H, q) (8%).

*3.18. (4R,5S)-(+)-*trans*-4,5-Dihydro-5-iodomethyl-4-phenyl-(3H)-furan-2-one (4R,5S)-(+)-**16***

The acid (*S*)-(−)-**13** (0.58 g; 3.30 mmol), $[\alpha]_D$ −12.2 (c 1.0, PhH), in purified acetonitrile (14 mL) was treated with iodine (2.49 g; 9.80 mmol) as above and was stirred at 0°C in the dark and under nitrogen for 24 h. Work-up as above gave a brown oil (0.860 g; 87%) which was rapidly chromatographed over silica using ether as an eluent, thus affording the lactone (+)-**16** (0.779 g; 79%), $[\alpha]_D$ +39.7 (c 1.0 acetone), with a *trans:cis* ratio=98:2 (from ^1H NMR), Lit.[7] (racemic form). IR (film): 1791 and 1602 cm^{-1}. ^1H NMR ($CDCl_3$), major *trans*-isomer, δ: 7.50–7.10 (5H); 4.32 (1H, dt) (98%); 3.60–3.50 (1H); 3.50 (1H, dd); 3.36 (1H, dd); 3.10 (1H, dd); 2.85 (1H, dd). Minor *cis*-isomer, δ 4.96 (1H, dt) (2%).

*3.19. (4R,5S)-(+)-*trans*-4-p-Chlorophenyl-4,5-dihydro-5-iodomethyl-(3H)-furan-2-one (4R,5S)-(+)-**17***

The acid (*S*)-(−)-**14** (0.50 g; 2.4 mmol), $[\alpha]_D$ −14.4 (c 1.39, PhH), in purified acetonitrile (9 mL) was treated with iodine (1.80 g; 70 mmol) as above and was stirred at 0°C in the dark and under nitrogen for 24 h. Work-up as above gave a brown oil (0.790 g; 99.6%) which was rapidly chromatographed over silica (ether as eluent), thus affording the lactone (+)-**17** (0.680 g; 86%), $[\alpha]_D$ +38.2 (c 1.02, acetone), with a *trans:cis* ratio=95:5 (^1H NMR). Anal. calc. for $C_{11}H_{10}ClIO_2$: C, 39.26; H, 2.99. Found: C, 39.44; H, 3.09. IR (film): 1789 and 1596 cm^{-1}. ^1H NMR ($CDCl_3$), major *trans*-isomer, δ: 7.50–7.10 (4H); 4.30 (1H, dt) (95%); 3.54 (1H); 3.47 (1H, dd); 3.34 (1H, dd); 3.10 (1H, dd); 2.80 (1H, dd). Minor *cis*-isomer, δ: 4.95 (1H, dt) (5%).

*3.20. (4R,5R)-(−)-cis-4,5-Dihydro-5-iodomethyl-4-phenyl-(3H)-furan-2-one (4R,5R)-(−)-**18***

Sodium hydrogen carbonate (0.141 g; 1.70 mmol) in water (3.2 mL) was added to the acid (*S*)-(−)-**13** (0.148 g; 0.84 mmol), $[\alpha]_D$ −12.2 (c 1.01, PhH), in purified dichloromethane (3.2 mL). The mixture was treated at 0°C with iodine (0.427 g; 1.70 mmol) and was stirred at 0°C in the dark and under nitrogen for 6 h. The organic phase was washed with 10% aqueous sodium thiosulphate solution until colourless, then washed with water, and was finally dried ($MgSO_4$) and evaporated. Rapid chromatography of the residue over silica (eluent: CH_2Cl_2/ether) afforded a partially crystalline mixture (0.170 g; 67%) of *cis*-lactone (−)-**18** and *trans*-lactone (+)-**16** (*cis:trans* ratio=78:22). Recrystallization from a mixture of diisopropylether and CH_2Cl_2 gave the pure *cis*-lactone (4*R*,5*R*)-(−)-**18** as white crystals (0.062 g; 25%), m.p. 110–112°C and $[\alpha]_D$ −119 (c 1.03, acetone). Lit.[7] (racemic form). IR (Nujol): 1791 and 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.50–7.15 (5H); 4.96 (1H); 4.10 (1H, ddd); 3.10 (2H); 2.85 (1H, dd); 2.72 (2H, dd).

*3.21. (4S,5R)-(+)-trans-4,5-Dihydro-4,5-dimethyl-(3H)-furan-2-one (4S,5R)-(+)-**19***

Tributyltin hydride (1.12 g; 3.9 mmol) and AIBN (0.014 g) were added to the iodomethyllactone (+)-**15** (0.500 g; 2.1 mmol), $[\alpha]_D$ +15.2 (c 1.2, $CHCl_3$) in dry toluene (43 mL). After refluxing for 24 h, the solvent was evaporated and the residue was distilled under reduced pressure, thus affording the dimethyllactone (+)-**19** (0.176 g; 74%), b.p.$_{30}$ 145–155°C and $[\alpha]_D$ +37.1 (c 1.2, $CHCl_3$) with a *trans:cis* ratio=91:9 (^1H NMR). Lit.[11a] +56.8 (c 1.6, $CHCl_3$). IR (film): 1779 cm^{-1}. ^1H NMR ($CDCl_3$), major *trans*-isomer, δ: 4.15 (1H, dq) (91%); 2.65 (1H); 2.22 (1H); 2.18 (1H); 1.40 (3H, d); 1.15 (3H, d). Minor *cis*-isomer, δ: 4.67 (1H, q) (9%).

*3.22. (4R,5R)-(+)-trans-4,5-Dihydro-5-methyl-4-phenyl-(3H)-furan-2-one (4R,5R)-(+)-**20***

Tributyltin hydride (0.534 g; 1.8 mmol) and AIBN (0.010 g) were added to the iodomethyllactone (+)-**16** (0.300 g; 1.0 mmol), $[\alpha]_D$ +38.8 (c 1.1, acetone), in dry toluene (20 mL). After refluxing for 24 h, the solvent was evaporated under reduced pressure and the residue was treated with ether (17 mL) and 10% aqueous potassium fluoride solution (17 mL). The aqueous phase was extracted with ether. The organic extracts were pooled, dried ($MgSO_4$) and evaporated, thus affording the *trans*-lactone (4*R*,5*R*)-(+)-**20** as white crystals (0.121 g; 70%), m.p. 56–59°C and $[\alpha]_D$ +20.2 (c 1.0, MeOH), with a *trans:cis* ratio=99:1 (^1H NMR). Lit.[17] (racemic form). IR (Nujol): 1785 and 1604 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.50–7.20 (5H); 4.60 (1H) (99%); 3.25 (1H, dt); 2.95 (1H, dd); 2.78 (1H, dd); 1.45 (3H, d). Minor *cis*-isomer, δ: 4.95 (1H) (1%).

*3.23. (4R,5R)-(+)-4-p-Chlorophenyl-4,5-dihydro-5-methyl-(3H)-furan-2-one (4R,5R)-(+)-**21***

Tributyltin hydride (0.800 g; 2.76 mmol) and AIBN (0.005 g) were added to the iodomethyllactone (+)-**17** (0.507 g; 1.5 mmol), $[\alpha]_D$ +38.2 (c 1.0, acetone), in dry toluene (31 mL). After refluxing for 25 h, the reaction mixture was worked-up as above, thus leading to the *trans*-lactone (4*R*,5*R*)-(+)-**21** as white crystals (0.201 g; 63.5%), m.p. 113–115°C and $[\alpha]_D$ +15.5 (c 1.1, MeOH), with a *trans:cis* ratio=99:1 (^1H NMR). Lit.[18] (racemic form). IR (Nujol): 1785 and 1576 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.35 (2H); 7.20 (2H); 4.52 (1H, dq) (99%); 3.25 (1H, dt); 2.95 (1H, dd); 2.75 (1H, dd); 1.42 (3H, d). Minor *cis*-isomer, δ: 4.92 (1H, dq) (1%).

3.24. (4R,5R)-(−)-4,5-Dihydro-5-ethyl-4-phenyl-(3H)-furan-2-one (4R,5R)-(−)-22

Lithium dimethylcuprate was generated at 0°C in dry THF (5 mL) from methyllithium (1.6 mol L^{-1} in ether; 6.5 mL; 10.4 mmol) and cuprous iodide (0.99 g; 5.2 mmol). The iodomethyllactone (4*R*,5*S*)-(+)-**16** (0.302 g; 1.0 mmol), $[\alpha]_D$ +39.7 (c 1.0, acetone), in dry THF (10 mL) was added and the mixture was stirred at 0°C for 5.5 h. Saturated aqueous ammonium chloride solution (20 mL) was added, the resulting biphasic medium was filtered through Celite, the latter was washed with ether and the aqueous phase was extracted with ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated. Column chromatography of the final residue over silica gel (eluent: petroleum ether:ether=9:1 and elution gradient) afforded the lactone (4*R*,5*R*)-(−)-**22** (0.090 g; 47%), $[\alpha]_D$ −11.7 (c 0.51, $CHCl_3$). Lit.[19] (no $[\alpha]_D$ reported). IR (film): 1778 and 1602 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 7.50–7.0 (5H); 4.40 (1H, dt); 3.32 (1H); 2.95 (1H, dd); 2.75 (1H, dd); 1.90–1.60 (2H); 1.00 (3H, t).

3.25. (4R,5R)-(+)-4,5-Dihydro-5-pentyl-4-phenyl-(3H)-furan-2-one (4R,5R)-(+)-23

Lithium dibutylcuprate was generated at *ca.* −40°C in dry THF (7 mL) from *n*-butyllithium (1.6 mol L^{-1} in hexane; 8.6 mL; 13.8 mmol) and cuprous iodide (1.31 g; 6.9 mmol). After cooling down to −78°C, the iodomethyllactone (4*R*,5*S*)-(+)-**16** (0.400 g; 1.3 mmol), $[\alpha]_D$ +39.7 (c 1.0, acetone), in dry THF (12 mL) was added. The mixture was stirred at −78°C for 3 h and at *ca.* −35°C for 2 h. Saturated aqueous ammonium chloride solution (30 mL) was added, and the resulting biphasic medium was worked-up as above. The final residue was chromatographed as above, thus affording the lactone (4*R*,5*R*)-(+)-**23** (0.076 g; 25%), $[\alpha]_D$ +26.7 (c 1.3, $CHCl_3$). Lit.[12b] $[\alpha]_D$ −25.6 (c 1.6, $CHCl_3$), for the enantiomer (4*S*,5*S*)-(−)-**23**. IR (film): 1778 and 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.50–7.00 (5H); 4.45 (1H, dt); 3.30 (1H, dt); 2.95 (1H, dd); 2.75 (1H, dd); 1.65 (2H); 1.50–1.20 (6H); 0.85 (3H, t).

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