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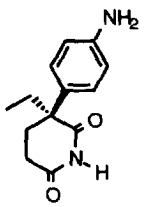
Asymmetric Construction of Benzylic Quaternary Carbons from Chiral Malonates : Formal Synthesis of both (-)- and (+)-Aminoglutethimides AG and Analogues

Antoine FADEL* and Sebastien GARCIA-ARGOTE

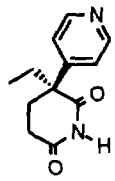
Laboratoire des Carbocycles (Associe au CNRS), Institut de Chimie Moleculaire d'Orsay
Bât. 420, Universite de Paris-Sud, 91405 ORSAY (France)

Abstract : From a single chiron (R)-(+)-5, available with high enantiomeric excess (97%) by enzymatic hydrolysis (PLE acetonic powder) of a malonate, were prepared convenient precursors of aminoglutethimides (-)-AG-1 and (+)-AG-1. This versatile method also allows preparation of the b-hydroxy ester (R)-9 and its enantiomer (S)-9 as well as the glutethimides (S)-4 and (R)-4 and other analogues.

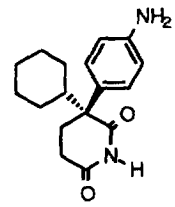
Asymmetric quaternary carbon centres are found in numerous natural products and pharmacueticals.[1] In particular, benzylic centres are present in various members of the aminoglutethimide family [2] such as (*R*)-aminoglutethimide AG-**1**, rogletimide **2** and cyclohexylpiperidinedione **3**. Convenient methods for their enantioselective construction have been investigated.[3]



AG-(-)-1



Rogletimide-2

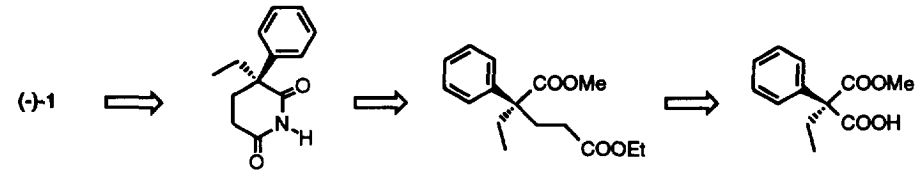


Cyclohexylpiperidinedione-3

These aminoglutethimide AG-**1** and analogues **2** and **3** are known to be efficient aromatase inhibitors and effective drugs against breast cancer for postmenopausal patients.[3b,4] These kinds of breast carcinomas which are oestrogen-dependent[5] occur in postmenopausal women, and in fact their growth is stimulated by oestrogen in physiological concentrations. The last step of oestrogen biosynthesis is catalysed by the cytochrome P_{450}-dependent enzyme aromatase. [6]

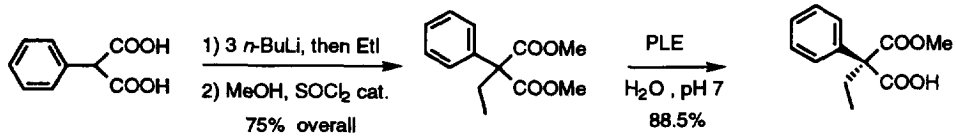
In previous papers, we have described the asymmetric construction of quaternary carbons from chiral malonates and their subsequent transformation into both enantiomers of cuparenones and laurene[7] and into the natural analgesic (-)-aphanorphine.[8] Herein we report that this strategy can be applied to the synthesis of glutethimide derivatives **4**. This approach provides a general pathway for the preparation of a wide variety of

aminoglutethimides analogues. It is illustrated by the synthesis, from acid ester **5** via the corresponding diester **6**, of the glutethimide **4**, an efficient precursor of the aminoglutethimide AG-1.



(-)-4 **6** (*R*)-(+)-5

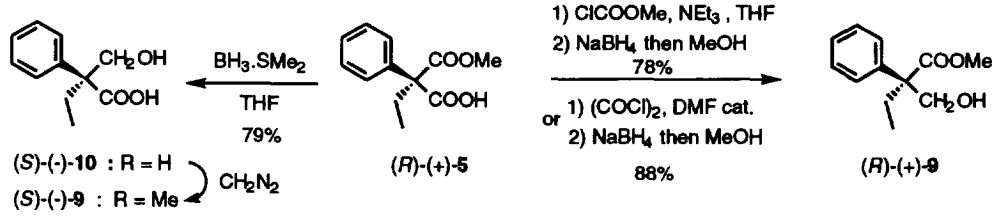
Thus the prochiral dimethyl malonate **7** and derivatives are obtained in good yield from phenylmalonic acid **8** by alkylation with ethyl iodide,[9] followed by acidic esterification.



8 **7** ee = 83% (*R*)-(+)-5
recryst. ee = 97%

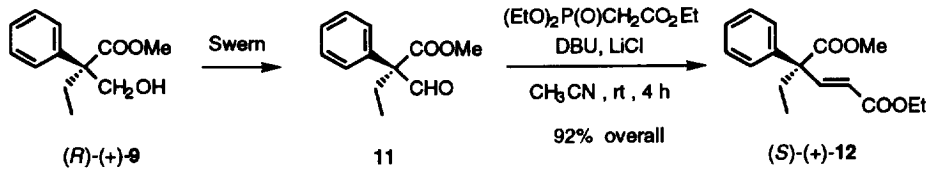
The enantioselective enzymatic hydrolysis of **7** by pig liver esterase (acetonic powder PLE) provided in 88.5% yield the acid ester (*R*)-(+)-**5**.[10,11] The enantiomeric excess of **5**, determined from the 250 MHz ^{1}H NMR spectra of its salt with (*R*)-(+)-1-naphthylethylamine, was 83% and can be raised to 97% ee after recrystallisation (see experimental part) $[\alpha]_D^{20}$ + 36 (c = 1, $CHCl_3$), ee = 97%].

We have previously reported, the chemoselective reduction of the acid ester such as **5**.[7b] Thus reaction of (*R*)-(+)-**5** with 1 equiv. of methyl chloroformate in the presence of triethylamine gave a mixed anhydride which, upon reduction with 3 equiv. of sodium borohydride in THF then addition of MeOH [12] gave the β-hydroxy ester (*R*)-(+)-**9** in 78% overall yield accompanied with 4.5% of the methyl 2-phenylbutanoate (retro-aldol product). This retro-aldol product is suppressed by reduction ($NaBH_4$, THF then MeOH)[12] of the corresponding acyl chloride (**5**, $(COCl)_2$, DMF cat., CH_2Cl_2). [13] Thus the β-hydroxy ester (+)-**9** was obtained in 88% overall yield, $[\alpha]_D^{20}$ +31 (c = 1, $CHCl_3$).



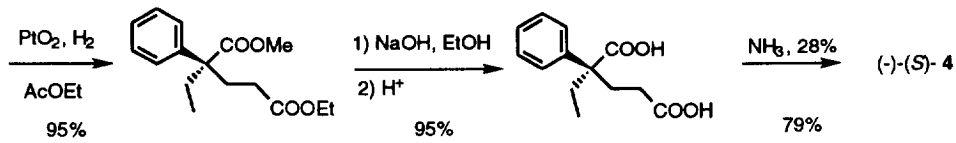
(*R*)-(+)-5 (*R*)-(+)-9

On the other hand, reduction of (*R*)-(+)-**5** with borane (BH_3-Me_2S) in THF afforded the β-hydroxy acid (*S*)-(-)-**10** (79% yield). Diazomethane esterification gave the other enantiomer (*S*)-(-)-**9** quantitatively, $[\alpha]_D^{20}$ -31.5 (c = 1, $CHCl_3$).



(*R*)-(+)-**9** **11** (*S*)-(+)-**12**

The Swern oxidation [14] of hydroxy ester (*R*)-(+)-**9** gave the aldehyde (*R*)-**11** quantitatively. Due to its instability, this aldehyde was used in the next step without further purification. At this stage, the introduction of the two remaining carbons was carried out by Wittig-Horner reaction. Reaction of crude aldehyde (*R*)-**11** with triethylphosphonoacetate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the presence of LiCl (Masamune's conditions),[15] led exclusively to the *trans* ester (*S*)-(+)-**12** (92% overall yield ;$[\alpha]_D^{20}$ + 11 (c = 1, $CHCl_3$). The one pot reaction (oxidation then Wittig-Horner reaction) afforded only 50% yield of the expected ester **12** and 40% of aldehyde intermediate **11**.



(*S*)-(+)-**6** (*S*)-(+)-**13**

This ester **12**, upon treatment with Pd/C 10% or with PtO_2 (w/w : 1/5), under hydrogen, gave the diester **6** in 95% yield, ($[\alpha]_D^{20}$ +15 (c = 1, $CHCl_3$).

The diester (*S*)-(+)-**6** containing the complete carbon framework of (-)-**1**, was converted into the diacid (*S*)-(+)-**13** by 2N aq NaOH in EtOH at reflux followed by acidification (quantitative yield) $[\alpha]_D^{20}$ +11.5 (c = 1, MeOH)[16]; lit.[17] (*R*)-antipode : $[\alpha]_D^{20}$ -13.7 (c = 1, $CHCl_3$). The treatment of the diacid **13** with ammonia and subsequent ring closure of the ammonium salt led to the expected glutethimide (*S*)-(-)-**4** in 79% yield. These specific rotations, $[\alpha]_D^{20}$ -181.5 (c = 1, MeOH), and $[\alpha]_D^{20}$ -190 (c = 1, $CHCl_3$) , were also in agreement with the value reported in the literature [17,18] for its enantiomer (*R*) : $[\alpha]_D^{20}$ +181 (c = 1, MeOH). In the same way diester (*S*)-(+)-**13**, upon treatment with ammonia at reflux, underwent also cyclisation into the glutethimide (S)-(-)-4 (82% yield). The (*S*)-absolute configuration of the glutethimide (-)-**4**, in agreement with the literature,[17] prove the (*R*)-absolute configuration of the malonic acid ester **5** and confirm our assignment upon enzymatic hydrolysis of prochiral malonate **7**.

Since the transformation of glutethimide (-)-**4** into aminoglutethimide (-)-**1** was reported [17] in 80% overall yield. The formal preparation of (-)-aminoglutethimide AG-1 can be considered to be achieved. Furthermore, it must be also stressed that asymmetric synthesis of its antipode (*R*)-(+)-aminoglutethimide **1** is conceivable from the enantiomeric β-hydroxy ester (*S*)-**9**, available in two steps from the acid ester (*R*)-**5**, through the same sequence proposed herein for (*S*)-(-)-**1**.

In conclusion, from a readily available chiron (ee = 97%), we developed, via a Wittig-Horner homologation and cyclisation, a rapid and competitive approach to the glutethimide (*S*)-**4** (4 steps, 56% overall yield). The enantiomer (*R*)-(+)-**4**, was obtained as shown *vide supra* from the same intermediate (*R*)-**5**.

Moreover the synthesis of a wide variety of aminoglutethimide analogues such as rogletimide **2** and cyclohexylpiperidinedione **3** following the same pathway should be accessible. Further synthetic applications of this approach to other analogues are currently under investigation.

EXPERIMENTAL SECTION

The general experimental procedures and the analytical instruments employed have been described in detail in a previous paper.[7b]

Dimethyl 2-ethyl-2-phenylmalonate 7.

2-Ethyl-2-phenyl malonic acid was prepared from the commercially available 2-phenylmalonic acid **8** (0.1 mol) and *n*BuLi (0.3 mol) then EtI (0.25 mol), following the procedure described in reference.[9] The crude solid was used in the next step without further purification; ^{1}H NMR (DMSO-d_6) δ : 6.25-5.90 (m, 5H), 0.94 (q, J = 7.5 Hz, 2H), -0.45 (t, J = 7.5 Hz, 3H).

The crude malonic acid (0.1 mol) in dry MeOH (300 mL) and $MgSO_4$ (5 g) was treated dropwise at 20°C with $SOCl_2$ (10 mL). The mixture was stirred at 50°C for 10 h. Then the solvent was eliminated under reduced pressure. The residue, basified with sat. aqueous $NaHCO_3$ to pH ~ 8, was extracted with CH_2Cl_2 (3x200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give 17.7 g of diester **7**, as a colourless oil, with 75% overall yield from phenylmalonic acid **8**. The basic aqueous layer was acidified to pH ~ 3 and extracted with ethyl acetate (3x100 mL). The organic extracts were dried ($MgSO_4$) and concentrated to furnish 1.2 g of crude monomethyl ethylphenylmalonate (±)-**5** (5.4% yield). Recrystallised from ether-hexane gave 1 g (in 2 crops) of pure crystals (±)-**5**: mp. 89.7°C, (Lit.[19], mp : 90°C).

Diester **7** : R_f : 0.5 (TLC, acetone); IR (neat) : 1740, 1605, 1585, 1240, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ : 7.50-7.20 (m, 5H), 3.76 (s, 6H), 2.37 (q, J = 7.5 Hz, 2H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ : 171.0 (2s), [6 arom. C : 136.7 (s), 128.0 (2d), 127.8 (2d), 127.3 (d)], 63.0 (s), 52.3 (2q), 28.8 (t), 9.2 (q) ; MS (EI) : 237 (M^++1, 2.6), 236 (M^+, 12), 177 (16), *121* (100), 118 (12), 117 (68), 116 (11.5), 115 (48), 105 (40), 103 (23), 91 (59), 89 (16), 77 (34), 59 (73), 51 (13).

(*R*)-(+)-2-(Methoxycarbonyl)-2-phenylbutyric acid 5.

To a stirred solution of malonate **7** (14.76 g, 60 mmol) in water (70 mL) was added at 25°C, pig liver esterase (3 g, acetonic powder purchased from Sigma L 8251). The pH of the reaction was kept at 7.2 by regular addition of 2N aqueous NaOH via a syringe pump interfaced with a pH controller. After a stirring period of 3 h another portion of PLE (3 g) was added. When 30.1 mL of aqueous 2N NaOH (40 h) was added, the enzyme was eliminated by filtration (addition of Celite to the mixture facilitates the filtration). The precipitate was washed with water (50 mL) and with chloroform (100 mL). After separation, the aqueous layer was acidified (3N aqueous HCl) until pH 2 and the malonate monoester (+)-**5** was extracted with $CHCl_3$ (4x300 mL). The combined organic extracts, were washed with brine, dried and evaporated, to give 12.4 g. Product purification was achieved by chromatography on silica gel (elution with 2:8 → 4:6, ether: hexane). There was isolated 11.8 g (88.6%) of acid ester (+)-**5** ; ee = 83%[10] from ^{1}H NMR spectra in the presence of (*R*)-(+)-1-naphthylethylamine (> 99% ee). Crystallisation of (+)-**5** from ether/hexane allowed to remove 1.8 g of a white

solid with (45:55, (*S*):(*R*)) ratio as shown from the ^{1}H NMR spectra in the presence of the same chiral amine. And the mother liquid was concentrated, to furnish 10 g (75%) of a colourless oil : $[\alpha]_D^{20}$ +36 (c = 1, $CHCl_3$) ; with ee = 97%; IR (neat) : 3250, 1740, 1715, 1600, 1585, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ : 11.75 (br, s, H), 7.37 (sharp m, 5H), 3.84 (s, 3H), 2.70-2.48 (m, 1H), 2.48-2.30 (m, 1H), 1.00 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ : 175.5 (s), 171.9 (s), [6 arom. C : 136.2 (s), 128.2 (2d), 127.7 (2d), 127.5 (d)], 62.8 (s), 52.7 (q), 28.2 (t), 9.2 (q) . Anal. calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found : C, 64.63; H, 6.32.

(*R*)-(+)-Methyl 2-hydroxymethyl-2-phenylbutyrate 9.

A-From mixed anhydride: To a cold (-15°C) stirred solution of malonate monoester (+)-**5** (4.44 g, 20 mmol) in dry THF (50 mL) was added Et_3N (3.4 mL, 22 mmol, 1.1 equiv.). After 15 min, MeOCOCl (1.65 mL, 21 mmol, 1.05 equiv.) was added dropwise and stirred for 15 min at -15°C. The mixture was then filtered under argon, and the resulting white precipitate was washed with THF (2x25 mL). To the filtrate cooled at -10°C, was added $NaBH_4$ (2.28 g, 60 mmol, 3 equiv.) in one portion and then MeOH (12.5 mL)[12] was added dropwise over 1 h 30 min. After stirring at 0°C for a supplementary 2 h, the reaction mixture was hydrolysed with 6N aqueous HCl (dropwise to pH 2). The hydroxy ester was extracted with CH_2Cl_2 (4x100 mL). The combined organic extracts were washed with brine, dried and concentrated. Product separation was achieved by chromatography on silica gel (elution with 15/85 ethyl acetate/hexane). There were isolated 3.25 g (78%) of the hydroxy ester (+)-**9** as a colourless oil, and 170 mg (4.6%) of retro-aldol product the methyl 2-phenylbutyrate.

B-From acyl chloride: To a stirred solution of acid ester (+)-**5** (4.44 g, 20 mmol, 97% ee) and 2 drops of DMF[13] in dry CH_2Cl_2 (100 mL) was added dropwise $(COCl)_2$ (5.24 mL, 60 mmol, 3 equiv.). The mixture was stirred at room temperature for 2 h (complete reaction as evidenced by TLC). The solvent evaporated to dryness, gave quantitatively the corresponding acyl chloride. Which was used in the next step without further purification.

To a cold (-30°C) stirred solution of crude acyl chloride (20 mmol) in dry THF was added in one portion $NaBH_4$ (2.28 g, 60 mmol, 3 equiv.) and then MeOH (12.5 mL)[12] was added dropwise over 1 h 30 min. After stirring at -30°C for 1 h, then at rt. for 2 h. The reaction mixture was hydrolysed with 6N aq. HCl (to pH 2). Usual work up, as noted above, and flash chromatography afforded exclusively 3.66 g (88%) of β-hydroxy ester (R)-(+)-**9**; R_f = 0.33 (TLC, AcOEt/hexane : 3/7). $[\alpha]_D^{20}$ +31.2 (c = 1, $CHCl_3$); IR (neat): 3460, 1730, 1605, 1585, 1235, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ : 7.40-7.20 (m, 5H), 4.00 (m, 2H, CH_2-OH), 3.75 (s, 3H), 2.27-2.00 (m, 2H), 2.13 (br s, OH), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ : 175.8 (s, C(1)), [6 arom. C : 139.9 (s), 128.5 (2d), 127.1 (d), 126.8 (2d)], 66.0 (t), 56.4 (q), 52.0 (s), 26.3 (t), 9.0 (q); MS (EI) : 209 (M^++1, 0.5), 178 (M^+-HCHO, 63), 146 (38), 131 (16), 117 (32), 115 (22), 105 (14), 103 (49), *91* (100), 77 (33), 59 (17). Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found : C, 69.02; H, 7.51.

(*S*)-(-)-2-Hydroxymethyl-2-phenylbutyric acid 10.

To a stirred solution of malonate monoester (+)-**5** (2.22g, 10 mmol) in dry THF (30 mL) was added dropwise at 10°C $Me_2S.BH_3$ (6 mL of a 2M solution in toluene, 12 mmol, 1.2 equiv.) during the addition, the temperature must not exceed 15°C. The mixture was stirred for 5 h at 20°C then cooled at 0°C and quenched with 2N HCl to pH 2. The hydroxy acid (-)-**10** was extracted with ethyl acetate (3x100 mL). The combined organic extracts were dried, and concentrated. The resulting product was purified by chromatography on silica

gel column (elution with 1:9 → 4:6 ; AcOEt-CH_2Cl_2). There was isolated 1.53 g (79%) of hydroxy acid (-)-**10** as a colourless solid (recrystallised from ether-hexane): mp 75.3°C: $[\alpha]_D^{20}$ -16.5 (c = 1, $CHCl_3$); (lit.[20] mp 94-96° for the racemic); IR (neat): 3580, 3420-3100, 1710, 1605, 1585, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ : 7.50-7.20 (m, 5H), 6.50-4.50 (br, s, 2H), 4.07 (AB system, $\Delta\nu_{AB}$ = 25 Hz, J_{AB} = 12 Hz, 2H), 2.17 (q, J = 7.5 Hz, 2H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ : 180.4 (s), [6 arom. C : 138.9 (d), 128.5 (2d), 127.3 (d), 126.9 (2d)], 65.3 (t), 56.1 (s), 26.3 (t), 8.8 (q). Anal. calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found : C, 68.29; H, 7.05.

(*S*)-(-)-Methyl 2-hydroxymethyl-2-phenylbutyrate 9.

To a stirred solution of hydroxy acid (*S*)-(-)-**10** (1.17 g, 6 mmol) was added dropwise an excess of CH_2N_2 (3 equiv. ethereal solution). After being stirred at rt. for further 30 min, the solvent was evaporated and the residue obtained with quantitative yield, gave the pure hydroxy ester (*S*)-(-)-**9** as shown in the ^1H NMR spectra, $[\alpha]_D^{20}$ -31.5 (c = 1, $CHCl_3$). Spectral data were identical with those reported for the (*R*)-(+)-material **9**.

(*S*)-(+)-1-Ethyl 5-methyl 4-ethyl-4-phenylglutaconate 12.

The aldehyde (*R*)-methyl 2-ethyl-2-phenyl-3-oxopropionate **11** was prepared, following Swern procedure [14] and as described in ref.,[7b] from alcohol (+)-**9** (2.5 g, 12 mmol), $(COCl)_2$ (1.125 mL, 13.2 mmol, 1.1 equiv.) and DMSO (1.86 mL, 26.4 mmol, 2.2 equiv.) in CH_2Cl_2 (70 mL) at -60°C then Et_3N (6.67 mL, 48 mmol, 4 equiv.). Usual work up gave quantitatively 2.6 g of crude aldehyde. This aldehyde, not very stable, was used without further purification in the next step. ^1H NMR ($CDCl_3$) δ : 9.92 (s, CHO), 7.50-7.10 (m, 5H), 3.83 (s, 3H), 2.54-2.27 (m, 1H), 2.27-2.02 (m, 1H), 0.92 (t, J = 7.5 Hz, 3H).

To a stirred solution of triethylphosphonoacetate (5.9 g, 26.4 mmol, 2.2 equiv.) and LiCl (1.12 g, 26.4 mmol) in dry CH_3CN (45 mL) was added dropwise DBU (3.58 mL, 24 mmol, 2 equiv.).[15] After stirring at rt. for 1 h a solution of crude aldehyde **11** (2.6 g, 12 mmol) in CH_3CN (30 mL) was added over 20 min. The solution was stirred at rt. for 4 h (complete reaction as shown by TLC). The solvent was removed, and the residue was filtered over Celite (Et_2O elution). The filtrates concentrated gave a pale orange oil. Which was purified by chromatography on silica gel (elution with 1:9:90, AcOEt-hexane-CH_2Cl_2). There was isolated 3.05 g (92%) as a colourless oil of the *trans* (+)-**12** : $[\alpha]_D^{20}$ +11 (c = 1, $CHCl_3$); IR (neat) 1740, 1655, 1605, 1585, 1315, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ : 7.48 (d, J = 16 Hz, H_{olefin}), 7.41-7.10 (m, 5H), 5.74 (d, J = 16 Hz, H_{olefin}), 4.22 (q, J = 7.2 Hz, $2H_{ester}$), 3.75 (s, 3H, Me_{ester}), 2.45-2.25 (m, 1H), 2.25-2.03 (m, 1H), 1.31 (t, J = 7.2 Hz, $3H_{ester}$), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ : 173.4 (s, C(1)), 166.2 (s, COOEt), 149.0 (d, C_{olefin}), [6 arom. C : 140.3 (s), 128.4 (2d), 127.2 (d), 126.9 (2d), 122.3 (d)], 60.4 (t), 57.4 (s), 52.3 (q), 29.5 (t), 14.1 (q), 9.2 (q); MS (EI) : 276 (M^+, 15), 217 (14), 216 (12), 202 (16), 144 (13), *143* (100), 128 (22), 115 (21), 91 (12), 77 (12).Anal. calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found : C, 69.39; H, 7.03.

(*S*)-(+)-5-Ethyl 1-methyl 2-ethyl-2-phenylglutarate 6.

A solution of conjugated ester (+)-**12** (1.655 g, 6 mmol) in AcOEt (20 mL) was hydrogenated in the presence of PtO_2 as catalyst (200 mg, w/w : 12%) at room temperature under hydrogen (1 atm) for 20 h. After purging in the argon the resulting mixture was filtered and concentrated. The crude residue, purified by

chromatography on silica gel column (elution with 1:19, hexane-CH_2Cl_2) furnished 1.585 g (95%) of diester (+)-**6** as a colourless oil : $[\alpha]_D^{20}$ +15.1 (c = 1, $CHCl_3$); IR (neat) : 1735, 1605, 1585, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ : 7.40-7.15 (m, 5H), 4.09 (q, J = 7.2 Hz, $2H_{ester}$), 3.68 (s, 3H, Me_{ester}), 2.52-2.55 (m, 2H), 2.25-1.85 (m, 4H), 1.25 (t, J = 7.2 Hz, $3H_{ester}$), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ : 175.7 (s), 173.2 (s), [6 arom. C : 141.6 (s), 128.3 (2d), 126.8 (d), 126.4 (2d)], 60.3 (t), 53.8 (s), 52.0 (q), 29.5 (t), 29.4 (t), 27.7 (t), 14.1 (q), 8.6 (q); MS (EI) : 276 (M^++1, 2), 278 (M^+, 10), 219 (22), 218 (16), 173 (62), 145 (60), 132 (22), *131* (100), 129 (16), 121 (23), 117 (68), 116 (15), 115 (62), 105 (21), 103 (21), 91 (52), 77 (15). Anal. calcd for $C_{16}H_{22}O_4$: C, 69.03; H, 7.97. Found : C, 69.04; H, 7.93.

(*S*)-(+)-2-Ethyl-2-phenylglutaric acid 13.

A mixture of glutarate (+)-**6** (1.11 g, 4 mmol), EtOH (6 mL), NaOH (360 mg, 9 mmol), and H_2O (11 mL) was boiled to reflux for 10 h. The reaction mixture was concentrated in vacuum, acidified with 6N HCl, and extracted with ethyl acetate (3x200 mL) to give a crude solid. Which, recrystallised from $CHCl_3$ gave 940 mg (quantitative) of glutaric acid (+)-**13** : mp 114°C, \s\DO1([α]\O(\D\BA9() $_D^{20}$)) +11.5 (c = 1, MeOH), [lit.[17] mp 108-110°C, $[\alpha]_D^{20}$ -13.7 (c = 1, $CHCl_3$) for the enantiomer (*R*)]. ^1H NMR (DMSO-d_6) δ : 11.40 (br, s, 2H), 7.42-7.13 (m, 5H), 2.27-2.04 (m, 2H), 2.04-1.74 (m, 4H), 0.73 (t, J = 7.5 Hz, 3H).

(*S*)-(-)-2-Ethyl-2-phenylglutarimide 4.

Glutaric acid (+)-**13** (1.18 g, 5 mmol) was treated with 30% NH_3 (5 mL) with vigorous stirring. The resulting solution was heated to 180-200°C for 4 h. The residue was partitioned between a saturated $NaHCO_3$ solution and ethyl acetate. The organic layer concentrated and the resulting solid was crystallised from ether-hexane to afford the glutarimide (-)-**4** (856 mg, 79%): mp 100.6°C; $[\alpha]_D^{20}$ -181.5 (c = 1, MeOH), $[\alpha]_D^{20}$ -190 (c = 1, $CHCl_3$); [lit.[17] mp 95-96°C, $[\alpha]_D^{20}$ +181 (c = 1, MeOH) for the (*R*)-enantiomer)]. ^1H NMR ($CDCl_3$) δ : 7.9 (br s, 1H), 7.45-7.15 (m, 5H), 2.70-2.10 (m, 4H), 2.20-1.80 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H).

From the diester **6** : A mixture of glutarate (+)-**6** (0.78 g, 3 mmol) and 30% NH_3 (5 mL), was vigorously stirred. The solution was heated to 170-180°C for 4h. Usual work up as above gave 540 mg (83% yield) of glutarimide (-)-**4**.

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