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SYNTHESIS OF 2,3-DIHYDRO-4(1*H*)-QUINAZOLINONES

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Abstract – An improved procedure for the synthesis of 2-substituted 2,3-dihydro-4(1*H*)-quinazolinones through diastereomer separation of the corresponding quinazolinones derivatives is presented. The determination of their absolute configurations was obtained by X-Ray diffraction.

INTRODUCTION

Preparation of quinazolinones are in demand because of their potential biological and pharmaceutical activities.[1] Unfortunately, synthetic methods for the elaboration of this bicyclic system are not general in scope, and often low-yielding. Here we wish to describe the preparation of eight new 2-substituted 2,3-dihydro-4(1*H*)-quinazolinones according to the literature procedures.[2]

RESULTS AND DISCUSSION

In continuation of our studies of asymmetric synthesis of β-amino acids,[3] we synthesized a series of 2-substituted 2,3-dihydro-4(1*H*)-quinazolinones derivatives. There are numerous methods available for the synthesis of quinazolinones and their derivatives.[2] We adapted the reaction of isatoic anhydride with different amines to prepare our starting materials,[4] aminobenzamides (**3**, **4**, **11** and **15**), and finally the procedure of direct cyclocondensation dehydrogenation with different aldehydes.[5] We then used X-Ray crystal-structure determinations to elucidate the stereochemical outcome of the reactions studied.

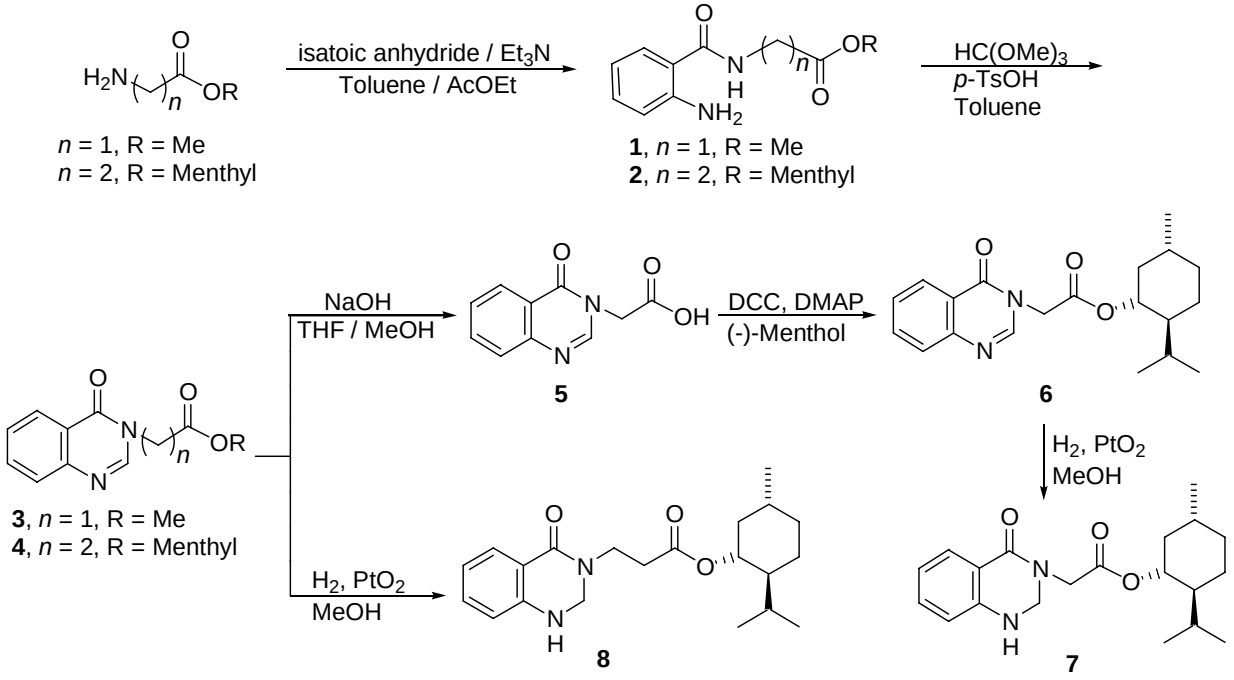
I. Synthesis of 2,3-dihydro-4(1*H*)-quinazolinones.

A. Synthesis of 2,3-dihydro-3-[(*1R,2S,5R*)-menthoxycarbonylmethyl]-4(1*H*)-quinazolinone (7) and 2,3-dihydro-3-[(*1R,2S,5R*)-menthoxycarbonylethyl]-4(1*H*)-quinazolinone (8).

The benzamides (**1**) and (**2**) were obtained through treatment of isatoic anhydride with glycine methyl ester hydrochloride and β-alanine menthyl ester respectively in presence of Et_3N (Scheme 1).[7] Cyclocondensation with trimethyl orthoformate and *p*-TsOH in toluene yielded the cyclized compounds

(**3**) and (**4**) in good yields. Hydrolysis of **3** with aqueous NaOH in THF-MeOH gave product (**5**). The 4(3*H*)-quinazolinone (**6**) was obtained with DCC and (-)-menthol in 52 % overall yield conversion. Finally, the 2,3-dihydro-4-(1*H*)-quinazolinone (**7**) and (**8**) were formed by hydrogenation.

Scheme 1



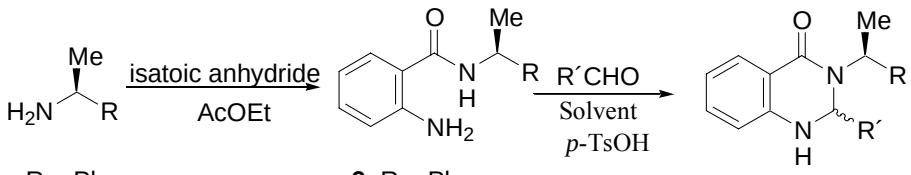
B. Synthesis of 2-substituted 2,3-dihydro-4(1*H*)-quinazolinone derivatives.

The benzamides (**9**) and (**10**) were prepared with isatoic anhydride and (*S*)-α–phenylethylamine and (*S*)-(+)-alanine methyl ester hydrochloride respectively. Subsequently, the cyclocondensation with different aldehydes in benzene or CH_2Cl_2, and *p*-TsOH yielded the diastereomers (*S*,*R*)- and (*S*,*S*)-(**11-16**). Assessment of diasteromeric product ratios (ds) was achieved by ^{1}H-NMR spectroscopic analysis of the crude products (Table 1). Final confirmation of the absolute configuration of the newly created stereogenic center at C(2) was carried out by analysis of solid-state structure for each.

II. X-Ray diffraction study of 2,3-dihydro-4(1*H*)-quinazolinone derivatives.

This study afforded relevant information on the conformation in the 4(1*H*)-quinazolinone derivatives. See Figures 1 and 2 for a view of the solid-state structures of **6** and **8**. It is interesting to note how the conformation of the amino acid segment changes. When the amino acid is β-alanine, this group is in the plane, meanwhile with glycine is above to the face to quinazolinone, and this contrasting behavior is explained by the approach of the menthol group.

Table 1. Diastereoselectivity of cyclocondensation of the benzamides (**9**) and (**10**) with different aldehydes**.**



R = Ph
R = CO_2Me

9, R = Ph
10, R = CO_2Me

11-(*S*,*R*) and **11-(*S*,*S*)**, R= R´= Ph
12-(*S*,*R*) and **12-(*S*,*S*)**, R = Ph, R´= Cy
13-(*S*,*R*) and **13-(*S*,*S*)**, R = Ph, R´= *o*-MeO-Ph
14-(*S*,*R*) and **14-(*S*,*S*)**, R = CO_2Me, R´ = Ph
15-(*S*,*R*) and **15-(*S*,*S*)**, R = CO_2Me, R´ = *t*-Bu
16-(*S*,*R*) and **16-(*S*,*S*)**, R = CO_2Me, R´ = *o*-NO_2-Ph

R	R´CHO	Solvent	Yield[a] (%)	ds: (*S*,*S*)/(*S*,*R*)
Ph	PhCHO	Benzene	88	90:10
Ph	CyCHO	CH_2Cl_2	71	53:47
Ph	*o*-MeOPhCHO	Benzene	51	75:25
CO_2Me	PhCHO	CH_2Cl_2	80	47:53
CO_2Me	*t*-BuCHO	CH_2Cl_2	58	85:15
CO_2Me	*o*-NO_2PhCHO	CH_2Cl_2	52	25:75

[a] Yield after flash chromatography.

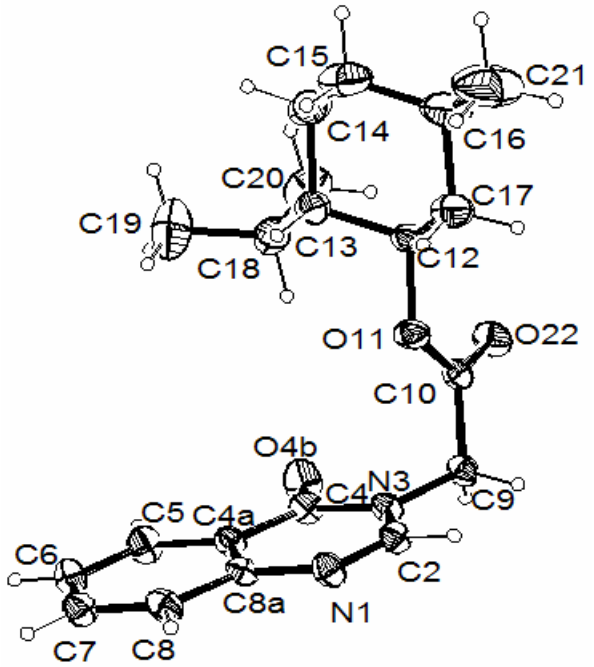


Figure 1. Structure and solid-state conformation of 3-[(*1R*,*2S*,*5R*)-menthoxycarbonylmethyl]-4(3*H*)-quinazolinone (**6**)**.**

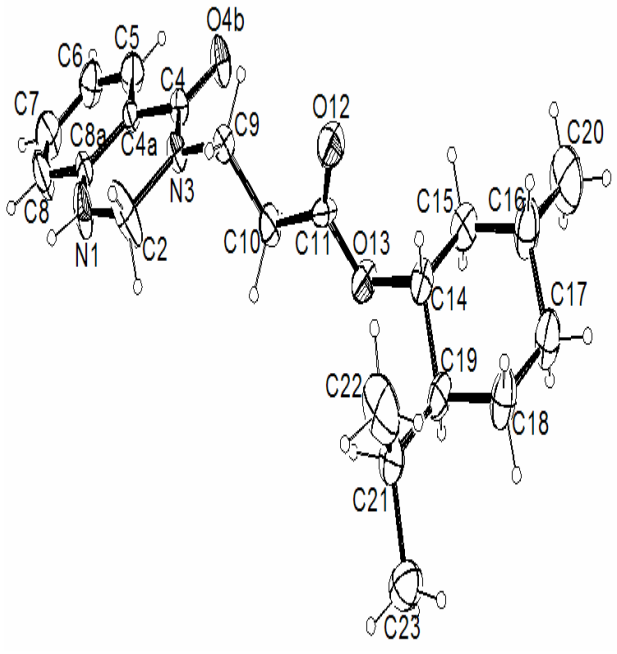


Figure 2. Structure and solid-state conformation of 2,3-dihydro-3-[(*1R*,*2S*,*5R*)-menthoxycarbonyl-ethyl]-4(1*H*)-quinazolinone (**8**)**.**

On the another hand, there is relevant information on the conformation at C(2) in the 2-substituted 2,3-dihydro-4(1*H*)-quinazolinones (*S*,*R*)-(**11**), (*S*,*R*)-(**12**), and (*S*,*S*)-(**13**). Here, we have the astonishing feature of the phenyl, cyclohexyl, and *o*-methoxyphenyl groups in quasi-axial or quasi-flagpole position! (Figures 3, 4, and 5). It is a clearly consequence of the powerful $A^{1,3}$-strain effect.[7] In addition to this effect, in the compound (**11**), is the stabilization between aromatic ring π- interaction crystal packing.[8] In particular, one wonders what role intramolecular hydrogen bonding/crystal packing might play in the conformation of these compounds. Analysis of these molecules precisely reveals the existence of an intramolecular hydrogen bonding between C(15)-H and the carbonyl adjacent (r = 2.16 Å), and anchor the phenylethyl segment in the quinazolinone.

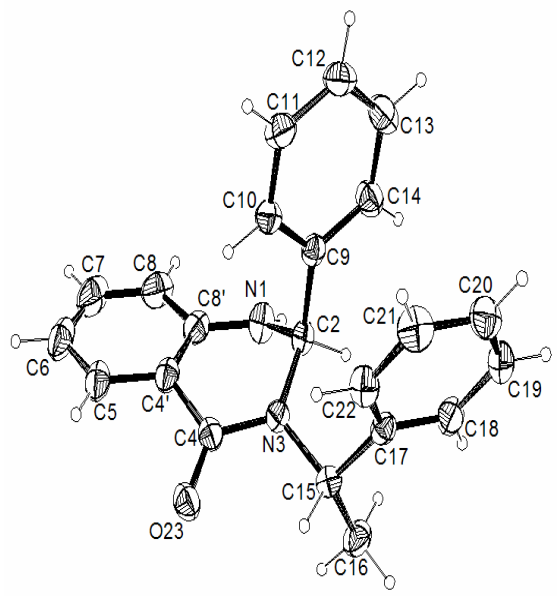


Figure 3. Structure and solid-state conformation of 2,3-dihydro-2(*R*)-phenyl-3-[(*S*)-α-phenylethyl]-4(1*H*)-quinazolinone (**11**).

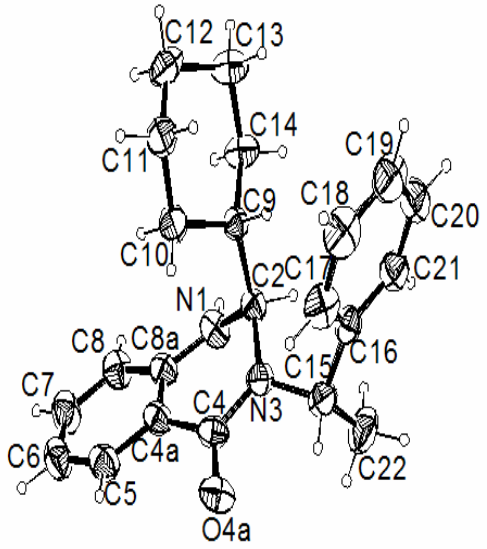


Figure 4. Structure and solid-state conformation of 2,3-dihydro-2(*R*)-cyclohexyl-3- [(*S*)-α-phenyl-ethyl]- 4(1*H*)-quinazolinone (**12**).

With the segment methyloxycarbonylethyl in quinazolinones [(*S*,*S*)-(**14**), (*S*,*S*)-(**15**), and (*S*,*R*)-(**16**)] the most interesting feature of the crystallographic structure of (*S*,*R*)-**16** is that the *o*-nitrophenyl group at C(2) adopts a pseudo equatorial conformaction**,** which can be explained by an intramolecular hydrogen bonging between oxygen(NO_2) and the protons in C(2)-H and N(1)-H (r = 2.20 Å), while with phenyl and *t*-butyl groups in (*S*,*S*)-**14** and (*S*,*S*)-**15** respectively, a pseudo axial oriented conformation at C(2) is expected (Figures 6, 7, and 8).

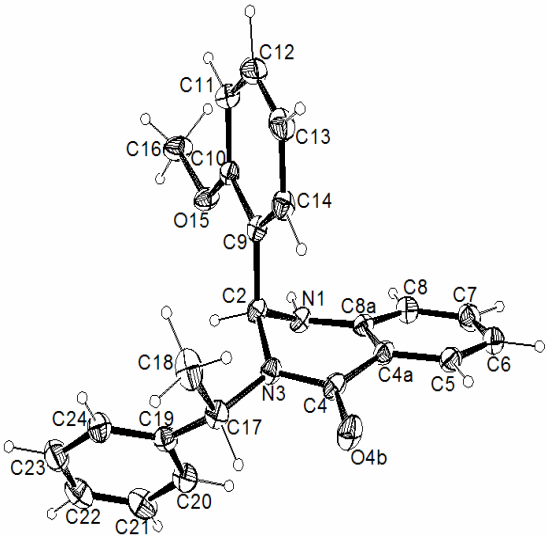


Figure 5. Structure and solid-state conformation of 2,3-dihydro-2(*S*)-(*o*-methoxyphenyl)-3-[(*S*)-α-phenylethyl]-4(1*H*)-quinazolinone (**13**).

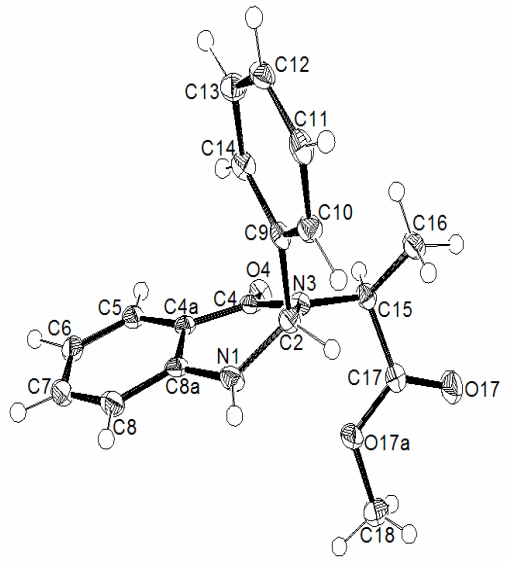


Figure 6. Structure and solid-state conformation of 2,3-dihydro-2(*S*)-phenyl-3-[(*S*)-methyloxy-carbonylethyl]-4(1*H*)- quinazolinone (**14**).

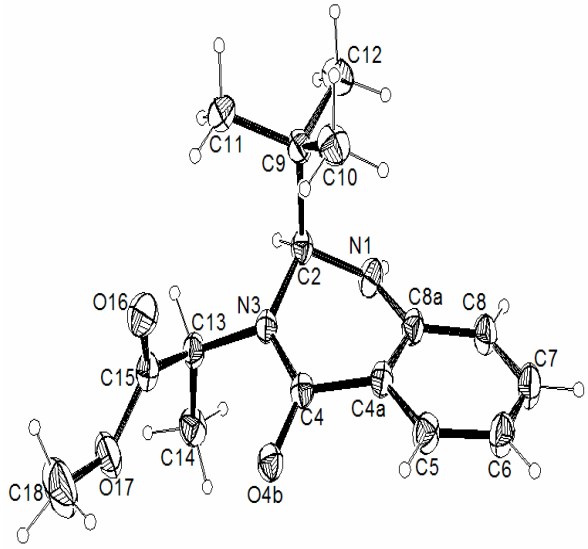


Figure 7. Structure and solid-state conformation of 2,3-dihydro-2(*S*)-*tert*-butyl-3-[(*S*)-methoxy-carbonylethyl]-4(1*H*)-quinazolinone (**15**).

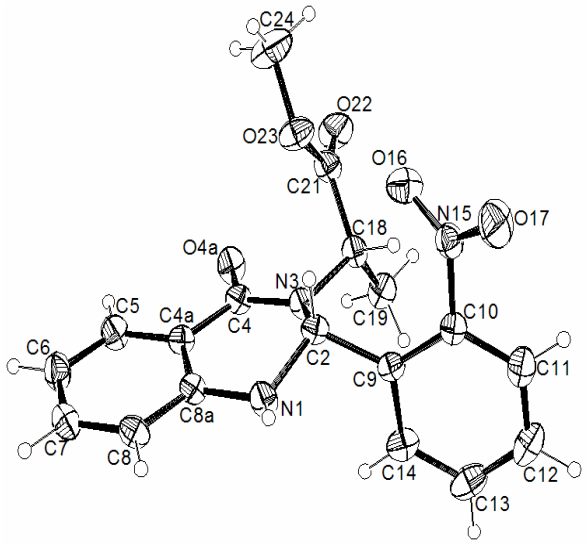


Figure 8. Structure and solid-state conformation of 2,3-dihydro-2(*R*)-(*o*-nitrophenyl)-3-[(*S*)-methoxycarbonylethyl]-4(1*H*)-quinazolinone (**16**).

EXPERIMENTAL

General. For a description of general experimental part for **1**, see ref.[9] Microanalyses were performed by Elementar Vario EL III.

The compound β-alanine methyl ester and glycine menthyl esters hydrochloride were prepared from β-alanine and glycine according to the literature.[10]

General Procedure for the Reaction of Isatoic Anhydride with Amines (*GP1*).

1.1 Equiv of the amine was added to a suspension of isatoic anhydride (1 equiv.) in a mixture of toluene/ethyl acetate (1:1, 0.62 M). The reaction mixture was warmed to 35-40 ^{o}C during 40 min. The solution was then concentrated under reduced pressure. The crude product was purified by FC.

General Procedure for the Preparation of Quinazolinones (*GP2*).

A solution of the aminobenzamide (1 equiv.) in benzene or CH_2Cl_2 (0.11 M) was treated with the aldehyde (1.1 equiv.) and *p*-toluenesulfonic acid monohydrate (0.1 equiv.), and the reaction mixture was heated to 40 ^{o}C for 2 h with azeotropic removal of water. The organic layer was then treated with 15 mL of saturated sodium bisulfide solution. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by FC.

2-Amine-*N*-(methoxycarbonylmethyl)benzamide (1).

A suspension of glycine methyl ester hydrochloride (4.0 g, 32 mmol) was treated with Et_3N (5.8 mL, 41 mmol), and isatoic anhydride (5.8 g, 35.2 mmol) according to *GP1*. The triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated on a rotary evaporator. Recrystallization (CH_2Cl_2/Hexane) of the benzamide (**1**) produced 5.9 g (88 %) as a yellow solid: mp 71-73 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (3H, s), 4.09 (2H, d, J = 6.0 Hz), 5.54 (2H, br s), 7.91 (1H, br s), 7.27-7.32 (2H, m), 7.78 (1H, td, J_{ortho} = 7.2 and J_{meta} = 1.2 Hz), 7.99 (1H, dd, J_{ortho} = 8.0 and J_{meta} = 1.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$): δ 41.8, 52.2, 116.2, 116.2, 117.8, 128.7, 133.1, 151.1, 170.4, 171.4. Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.35; H, 5.62; N, 13.52.

2-Amine-*N*-[(*1R,2S,5R*)-menthoxycarbonylethyl]benzamide (2).

β-Alanine menthyl ester (2.0 g, 8.8 mmol) was treated with isatoic anhydride (1.6 g, 9.7 mmol) according to *GP1*. Filtration of the mixture through charcoal and concentration on a rotary evaporator afforded 2.7 g (91 %) of the desired benzamide (**2**) as a yellow oil. For analytical purposes a sample was purified by FC [hexane-ethyl acetate (50:50)]: $[\alpha]_D^{24}$ -50.6 ^{o} (c = 0.50, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71-2.03 (18H, m), 2.60 (2H, m), 3.67 (2H, dd, J_1 = 6.0 and J_2 = 12.4 Hz), 4.70 (1H, dt, J_1 = 10.8 and J_2 = 4.4 Hz), 5.53 (2H, br s), 6.74 (1H, br s), 6.60-6.67 (2H, m), 7.18 (1H, td, J_{ortho} = 7.6 and J_{meta} = 1.2 Hz), 7.27 (1H, dd, J_{ortho} = 7.2 and J_{meta} = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 20.9, 22.7, 23.7, 26.8, 31.8, 34.5, 34.6, 35.4, 41.2, 47.3, 75.1, 116.0, 116.8, 117.5, 127.4, 132.5, 149.1, 169.4, 172.6. HRMS calcd for $C_{20}H_{30}N_2O_3$ 346.2256, found 346.2254.

3-Methoxycarbonylmethyl-3,4-dihydro-4(1*H*)-quinazolinone (3).

Compound (**1**) (3 g, 14.3 mmol) was treated with trimethyl orthoformate (3.6 mL, 21.5 mmol) according to *GP2*. Purification of the crude product by FC [hexane-ethyl acetate (50:50)] yielded (**3**) (2.47 g, 77 %) as a white solid. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): mp 158-160 ºC, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s), 4.74 (2H, s), 7.52 (1H, dt, J_{ortho} = 8.0 and J_{meta} = 1.6 Hz), 7.72 - 7.87 (2H, m), 8.00 (1H, s), 8.11 (1H, dd, J_{ortho} = 7.2 and J_{meta} = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.3, 53.0, 122.0, 127.0, 127.6, 127.8, 134.6, 146.2, 148.3, 161.0, 167.8. Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.38; H, 4.66; N, 12.71.

3,4-Dihydro-3-[(*1R,2S,5R*)-menthoxycarbonylethyl]-4(1*H*)-quinazolinone (4).

Compound (**2**) (2.0 g, 5.8 mmol) was treated with trimethyl orthoformate (0.97 mL, 6.3 mmol) according to *GP2*. Purification of the crude product by FC [hexane-ethyl acetate-methanol (60:38:2)] yielded (**5**) (1.98 g, 96 %) as a white solid. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): mp 98-99 ^{o}C, $[\alpha]_D^{24}$ -54.5 ^{o} (c = 0.50, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.61-1.96 (18H, m), 2.90 (2H, dt, J_1 = 6.2 and J_2 = 2.8 Hz), 4.27 (2H, t, J = 6.2 Hz), 4.69 (1H, dt, J_1 = 11.0 and J_2 = 4.4 Hz), 7.51 (1H, td, J_{ortho} = 7.9 and J_{meta} = 1.5 Hz), 7.79-7.82 (2H, m), 8.31 (1H, dd, J_{ortho} = 8.1 and J_{meta} = 1.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.5, 20.8, 22.3, 23.6, 26.6, 31.7, 33.5, 34.4, 41.1, 43.8, 47.1, 75.2, 121.9, 126.5, 127.2, 127.5, 134.3, 147.2, 148.1, 161.0, 170.6. Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.87; H, 7.94; N, 7.89.

3-Carboxymethyl-3,4-dihydro-4(1*H*)-quinazolinone (5).

1 g (4.4 mmol) of the quinazolinone (**3**), 20 mL of tetrahydrofuran and 20 mL of methanol was placed in a flask with a magnetic stirrer. This mixture was treated with 4 mL of a 2.5 N solution sodium hydroxide, and the mixture was stirred for 1 h. Then HCl (1N) was added to adjust pH = 2, and then extracted with ethyl acetate (x 3). The organic layer was dried ($MgSO_4$) and evaporated. FC [hexane-ethyl acetate-methanol (60:38:2)] yielded a solid of **5** (0.77g, 86%). For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): mp 215 ºC (decomp), ^{1}H NMR (400 MHz, CD_3OD): δ 4.83 (2H, s), 7.59 (1H, dt, J_{ortho} = 8.0 and J_{meta} = 1.2 Hz), 7.72 (1H, d, J_{ortho} = 8.4 Hz), 7.87 (1H, dt, J_{ortho} = 7.2 and J_{meta} = 1.6 Hz), 8.25 (1H, dd, J_{ortho} = 8.0 and J_{meta} = 1.6 Hz), 8.37 (1H, s); ^{13}C NMR (100 MHz, CD_3OD): δ 49.8, 122.9, 127.7, 127.8, 129.0, 136.2, 148.8, 149.6, 162.6, 170.9. HRMS calcd for $C_{10}H_8N_2O_3$ 204.0535, found 204.0537.

3,4-Dihydro-3-[(*1R,2S,5R*)-menthoxycarbonylmethyl]- 4(1*H*)-quinazolinone (6).

A stirred solution of **5** (1.0 g, 4.8 mmol) in 100 mL of CH_2Cl_2 was treated with 1.54 g (6.3 mmol) of DCC, 0.06 g (0.4 mmol) of DMAP, and 1.54 g (6.3 mmol) of (*1R,2S,5R*)-(-)-menthol. The mixture was

stirred overnight and then filtered and concentrated *in vacuo*. FC [hexane–ethyl acetate (70:30)] afforded the pure quinazolinone (**6**) as a solid white (1.5 g, 90 %). For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): mp 89-90º. $[\alpha]_D^{24}$ -26.8 º (c = 0.50, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.75-2.08 (18H, m), 4.69 (1H, s), 4.78 (1H, dt, J_1 = 11.0 and J_2 = 4.8 Hz), 7.52 (1H, td, J_{ortho} = 6.2 and J_{meta} = 1.8 Hz), 7.71-7.79 (2H, m,), 7.99 (1H, s), 8.31 (1H, d, J_{ortho} = 8.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.5, 20.87, 22.1, 23.6, 26.5, 31.6, 34.2, 40.7, 47.1, 47.7, 76.8, 122.1, 127.0, 127.6, 127.8, 134.7, 146.4, 148.3, 161.1, 167.0. Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.10; H, 7.71; N, 8.21. X-Ray crystallographic structure in Figure 2.[11]

2,3-Dihydro-3-[(*1R,2S,5R*)-menthoxycarbonylmethyl]- 4(1*H*)-quinazolinone (7).

A mixture of 0.1 g (0.29 mmol) of **6**, 20 mL of methanol and 0.01 g of PtO_2 catalyst was stirred and pressurized to 30 lb of hydrogen for 2.5 h. Filtration of the mixture through Celite and concentration on a rotary evaporator afforded 0.098 g (95 %) of the desired quinazolinone (**7**) as a white solid. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): mp 118-120 ºC, $[\alpha]_D^{24}$ - 56.3 º (c = 1.0, MeOH), ^{1}H NMR (400MHz, $CDCl_3$): δ 0.74-2.08 (18H, m), 4.26 (2H, s), 4.45 (1H, br s), 4.65-4.8 (3H, m), 6.67 (1H, d, J_{ortho} = 8.2 Hz), 6.87 (1H, td, J_{ortho} = 8.0 and J_{meta} = 1.2 Hz), 7.28 (1H, td, J_{ortho} = 8.0 and J_{meta} = 1.2 Hz), 7.92 (1H, dd, J_{ortho} = 7.6 and J_{meta} = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 21.1, 22.3, 23.7, 26.5, 31.7, 34.4, 41.1, 47.2, 47.6, 60.8, 75.8, 115.4, 117.2, 119.9, 128.9, 133.3, 147.6, 163.9, 168.6. Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.78; H, 8.19; N, 8.13. Found: C, 69.66; H, 8.12; N, 8.19.

2,3-Dihydro-3-[(*1R,2S,5R*)-menthoxycarbonylethyl]- 4(1*H*)-quinazolinone (8).

A mixture of 0.5 g (1.4 mmol) of **4**, 20 mL of methanol and 0.05 g of PtO_2 catalyst was stirred and pressurized to 30 lb of hydrogen for 2.5 h. Filtration of the mixture through Celite and concentration on a rotary evaporator produced 0.46 g (92 % yield) of the desired quinazolinone (**8**) as a white solid. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): mp 111-112 ºC, $[\alpha]_D^{24}$ -62.2 º (c = 0.50, $CHCl_3$), ^{1}H NMR (400MHz, $CDCl_3$): δ 0.62-1.98 (18H, m), 2.72 (2H, dt, J_1 = 6.4 and J_2 = 3.2 Hz), 3.75 (2H, t, J = 6.4 Hz), 4.69 (1H, dt, J_1 = 10.8 and J_2 = 4.4 Hz), 4.71 (2H, s), 6.69 (1H, d, J_{ortho} = 8.4 Hz), 6.89 (1H, td, J_{ortho} = 8.0 and J_{meta} = 1.2 Hz), 7.29 (1H, td, J_{ortho} = 8.0 and J_{meta} = 1.2 Hz), 7.92 (1H, dd, J_{ortho} = 7.6 and J_{meta} = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 20.9, 22.2, 23.5, 26.3, 31.6, 33.8, 34.3, 41.0, 42.4, 47.0, 61.0, 74.8, 115.2, 117.9, 120.0, 128.9, 133.3, 147.8, 164.0, 172.2. Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found: C, 70.16; H, 8.46; N, 7.78. X-Ray crystallographic structure in Figure 1.[11]

2-Amine-*N*-[(*S*)-α-phenylethyl]benzamide (9).

The isatoic anhydride (4.9 g, 30.0 mmol) was treated with (*S*)-phenylethylamine (4.2 g, 35.0 mmol) according to *GP1*. Filtration of the mixture through charcoal and concentration on a rotary evaporator produced 7.2 g (97 %) of the desired benzamide (**9**), as white solid. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): mp 136–138 °C, $[\alpha]_D^{24}$ +110.9 ° (c = 1.0, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (3H, d, J = 7.0 Hz), 5.28 (1H, dq, $J_1 = J_2$ = 7.0 Hz), 6.29 (1H, d, J = 6.2 Hz), 6.62 (1H, d, J_{ortho} = 7.3 Hz), 6.66 (1H, t, J_{ortho} = 8.4 Hz), 7.20 (1H, td, J_{ortho} = 7.7 and J_{meta} = 1.5 Hz), 7.26–7.40 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 48.9, 116.6, 116.6, 117.4, 126.1, 127.1, 127.4, 128.8, 132.2, 143.4, 148.8, 168.4. Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.22; H, 6.78; N, 11.32.

2-Amine-*N*-[(*S*)-methoxycarbonylethyl)]benzamide (10).

The isatoic anhydride (4.9 g, 30.0 mmol) was treated with (*S*)-alanine methyl ester hydrochloride (4.8 g, 35.0 mmol) according to *GP1*. Filtration of the mixture through charcoal and concentration on a rotary evaporator produced 5.6 g (82 %) of the desired benzamide (**10**) as white solid. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): mp 90-91 °C, $[\alpha]_D^{24}$ + 4.5 ° (c = 0.52, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.49 (3H, d, J = 7.0 Hz), 3.76 (3H, s), 4.72 (1H, dq, $J_1 = J_2$ = 7.1 Hz), 5.50 (1H, br s), 6.60 (1H, dd, J_{meta} = 1.2 and J_{ortho}= 7.6 Hz), 6.64 (1H, d, J_{ortho} = 7.6 Hz), 7.18 (1H, ddd, J_{meta} = 1.3 Hz, $J_{ortho} = J_{ortho}$ = 7.4 Hz), 7.37 (1H, dd, J_{meta} = 1.4 and J_{ortho} = 8.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.9, 48.5, 52.8, 115.2, 116.6, 117.3, 127.4, 132.5, 148.8, 168.5, 173.6. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.35; H, 6.28; N, 12.47.

2,3-Dihydro-2(*R*)- and 2,3-dihydro-2(*S*)-phenyl-3-[(*S*)-α-phenylethyl]-4(1*H*)-quinazolinone [(*S*,*R*)- and (*S*,*S*)-11].

Compound (**9**) (0.67 g, 2.8 mmol) was treated with *p*-toluenesulfonic acid (76 mg, 0.4 mmol) and benzaldehyde (0.31 g, 3 mmol) in benzene according to *GP2*. The crude products were purified by FC [hexane: ethyl acetate: CH_2Cl_2 (75:15:10)] to produce both diastereoisomers (0.80 g, 88 %).

(*S*,*S*)-**11**. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): white solid, mp 182–184 °C, $[\alpha]_D^{24}$ +301.0 ° (c = 0.52, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, d, J = 7.2 Hz), 4.54 (1H, s), 5.37 (1H, s), 6.24 (1H, q, J = 7.2), 6.39 (1H, d, J_{ortho} = 8.4 Hz), 6.82 (1H, td, J_{meta} = 1.2 Hz and J_{ortho} = 8.2 Hz), 7.15–7.41 (11H, m), 8.01 (1H, d, J_{ortho} = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5, 51.4, 68.0, 115.1, 117.1, 119.5, 125.7, 127.6, 127.7, 128.7, 128.8, 128.8, 129.0, 133.6, 140.8, 142.5, 144.5, 163.1. Anal. Calcd for $C_{22}H_{20}N_2O$: C, 80.48; H, 6.09; N, 8.54. Found: C, 80.41; H, 6.11; N, 8.57.

(*R*,*S*)-**11**. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): white solid, mp 156–158 °C, $[\alpha]_D^{24}$ -350.5 ° (c = 0.53, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.70 (3H, d, J = 7.4 Hz),

4.78 (1H, s), 5.60 (1H, d, J = 2.2), 5.87 (1H, q, J = 7.4 Hz), 6.44 (1H, d, J_{ortho} = 8.0 Hz), 6.78–7.05 (9H, m), 7.15–7.41 (3H, m), 7.96 (1H, dd, J_{meta} = 1.4 and J_{ortho} = 7.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.4, 53.0, 69.2, 114.8, 117.6, 119.4, 125.7, 127.5, 128.0, 128.1, 128.3, 128.4, 128.6, 133.5, 139.2, 141.1, 144.8, 163.0. Anal. Calcd for $C_{22}H_{20}N_2O$: C, 80.48; H, 6.09; N, 8.54. Found: C, 80.43; H, 6.13; N, 8.50. X-Ray crystallographic structure in Figure 3.[11]

2,3-Dihydro-2(*R*)- and 2,3-dihydro-2(*S*)-cyclohexyl-3-[(*S*)-α-phenylethyl]-4(1*H*)-quinazolinone [(*S*,*R*)- and (*S*,*S*)-12].

Compound (**9**) (0.67 g, 2.8 mmol) was treated with *p*-toluenesulfonic acid (76 mg, 0.4 mmol) and cyclohexanecarboxaldehyde (0.33 g, 3 mmol) in benzene according to *GP2*. The crude products were purified by FC [hexane: ethyl acetate: CH_2Cl_2 (80:10:10)] to produce both diastereoisomers (0.66 g, 71 %).

(*S*,*R*)-**12**. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): white solid, mp 144–145 °C, $[\alpha]_D^{24}$ -39.2 ^{o} (c = 0.49, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.58–0.61 (2H, m), 0.81-89 (5H, m), 1.23–1.27 (2H, m), 1.44–1.46 (2H, m), 1.72 (3H, d, J = 7.2 Hz), 4.49 (1H, d, J = 1.8 Hz), 5.29 (1H, s), 5.91 (1H, q, J = 7.2 Hz), 6.53 (1H, dd, J_{meta} = 0.8 and J_{ortho} = 8.0 Hz), 6.77 (1H, ddd, J_{meta} = 1.0 Hz, J_{ortho} = J_{ortho} = 7.2 Hz), 7.21 (1H, dd, J_{meta} = 1.6 Hz, J_{ortho} = J_{ortho} = 7.2 Hz), 7.25–7.48 (5H, m), 7.86 (1H, dd, J_{meta} = 1.2 and J_{ortho} = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 26.2, 26.3, 26.4, 27.4, 29.3, 45.4, 53.3, 70.8, 113.8, 117.8, 118.7, 127.8, 128.0, 128.6, 128.7, 133.3, 141.6, 146.4, 163.3. Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.04; H, 7.78; N, 8.38. Found: C, 78.69; H, 8.48; N, 7.44. X-Ray crystallographic structure in Figure 4.[11]

(*S*,*S*)-**12**. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): white solid, mp 147–149 °C, $[\alpha]_D^{24}$ -59.1 ^{o} (c = 0.51, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71–0.79 (1H, m), 0.83–0.88 (2H, m), 1.00–1.65 (8H, m), 1.67 (3H, d, J = 7.2 Hz), 4.17 (1H, dd, J_1 = 3.6 Hz, J_2 = 7.2 Hz), 4.34 (1H, d, J = 2.4 Hz), 6.06 (1H, q, J = 7.2 Hz), 6.51 (1H, dd, J_{meta} = 0.8 and J_{ortho} = 7.6 Hz), 6.77 (1H, ddd, J_{meta} = 1.0 Hz, J_{ortho} = J_{ortho} = 7.4 Hz), 7.22 (1H, ddd, J_{meta} = 1.6 Hz, J_{ortho} = J_{ortho} = 8.0 Hz), 7.25–7.40 (5H, m), 7.85 (1H, dd, J_{meta} = 1.6 Hz and J_{ortho} = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 26.3, 26.6, 27.8, 29.7, 47.1, 52.8, 69.9, 113.8, 117.5, 118.6, 127.7, 127.7, 128.7, 128.9, 133.4, 141.1, 146.3, 163.7. Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.00; H, 7.84; N, 8.38. Found: C,78.85; H,7.90; N,8.38.

2,3-Dihydro-2(*R*)- and 2,3-dihydro-2(*S*)-(*o*-methoxyphenyl)-3-[(*S*)-α-phenylethyl]-4(1*H*)-quinazolinone [(*S*,*R*)- and (*S*,*S*)-13].

Compound (**9**) (0.67 g, 2.8 mmol) was treated with *p*-toluenesulfonic acid (76 mg, 0.4 mmol) and *o*-methoxybenzaldehyde (0.40 g, 3 mmol) in benzene according to *GP2*. The crude products were purified

by FC [hexane: ethyl acetate: CH_2Cl_2 (75:15:10)] to produce both diastereoisomers (0.51g, 51 %).

(*S*,*S*)-**13**. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): white solid, mp 176–177 °C, $[\alpha]_D^{24}$ +418.0 ^{o} (c = 0.525, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (3H, d, *J* = 7.2 Hz), 3.84 (3H, s), 4.99 (1H, s), 5.83 (1H, d, *J* = 2.4 Hz); 6.29 (1H, q, *J* = 6.8 Hz), 6.39 (1H, dd, J_{meta} = 0.8 and J_{ortho} = 7.2 Hz), 6.75–6.86 (3H, m), 7.13 (1H, ddd, J_{meta} = 1.6 Hz, J_{ortho} = J_{ortho} = 8.0 Hz), 7.21 (1H, ddd, J_{meta} = 1.6 Hz, J_{ortho} = J_{ortho} = 7.6 Hz), 7.26-7.46 (6H, m), 7.98 (1H, dd, J_{meta} = 1.2 and J_{ortho} = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5, 51.3, 55.6, 62.7, 114.9, 110.6, 117.1, 119.2, 120.5, 127.3, 127.6, 127.8, 128.7, 128.9, 128.5, 129.2, 129.6, 133.4, 141.7, 145.8, 155.7, 164.1. Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.095; H, 6.145; N, 7.821. Found: C, 76.980; H, 6.246; N, 7.787. X-Ray crystallographic structure in Figure 5.[11]

(*R*,*S*)-**13**. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): white solid, mp 138–139 °C, $[\alpha]_D^{24}$ -100.8 ^{o} (c = 0.50, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (3H, d, *J* = 7.2 Hz), 3.85 (3H, s), 4.97 (1H, s), 5.98 (1H, q, *J* = 6.8 Hz), 6.03 (1H, s), 6.40 (1H, dd, J_{meta} = 0.4 and J_{ortho} = 8.0 Hz), 6.49 (1H, ddd, J_{meta} = 0.8 Hz, J_{ortho} = J_{ortho} = 7.6 Hz), 6.61 (1H, dd, J_{meta} = 0.8 and J_{ortho} = 8.0 Hz), 6.77 (1H, ddd, J_{meta} = 0.8 Hz, J_{ortho} = J_{ortho} = 7.8 Hz), 6.82 (1H, dd, J_{meta} = 1.4 and J_{ortho} = 7.4 Hz), 6.96–7.04 (4H, m), 7.12 (1H, ddd, J_{meta} = 1.3 and J_{ortho} = J_{ortho} = 7.6 Hz), 7.25–7.29 (2H, m), 7.95 (1H, dd, J_{meta} = 1.4 and J_{ortho} = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5, 51.3, 55.6, 62.7, 110.0, 114.9, 117.6, 119.3, 120.1, 127.6, 127.7, 127.9, 128.3, 128.6, 128.7, 129.0, 133.3, 139.1, 145.7, 151.4, 163.7. Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.095; H, 6.145; N, 7.821. Found: C, 76.237; H, 6.369; N, 7.297.

2,3-Dihydro-2(*R*)- and 2,3-dihydro-2(*S*)-phenyl-3-[(*S*)-methoxycarbonylethyl]-4(1*H*)-quinazolinone [(*S*,*R*)- and (*S*,*S*)-14].

Compound (**10**) (0.62 g, 2.8 mmol) was treated with *p*-toluenesulfonic acid (76 mg, 0.4 mmol) and benzaldehyde (0.31 g, 3 mmol) in CH_2Cl_2 according to *GP2*. The crude products were purified by FC [hexane: ethyl acetate (80:20 → 60:40)] to produce both diastereoisomers (0.69 g, 80 %).

(*S*,*R*)-**14**. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): white solid, mp 171–173 °C, $[\alpha]_D^{24}$ +118.1 ^{o} (c = 0.525, $CHCl_3$) ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (3H, d, *J* = 6.8 Hz), 3.56 (3H, s), 3.83 (1H, q, *J* = 7.0 Hz), 3.78 (1H, br s), 5.98 (1H, s), 6.56 (1H, dd, J_{meta} = 0.7 and J_{ortho} = 8.2 Hz), 6.83 (1H, ddd, J_{meta} = 1.2 Hz, J_{ortho} = J_{ortho} = 7.2 Hz), 7.26 (1H, ddd, J_{meta} = 1.4 Hz, J_{ortho} = J_{ortho} = 7.7 Hz), 7.37–7.53 (5H, m), 7.90 (1H, dd, J_{meta} = 1.4 and J_{ortho} = 7.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.8, 52.4, 54.0, 74.4, 114.1, 115.9, 119.4, 127.8, 128.8, 129.1, 130.0, 133.8, 138.6, 145.8, 163.8, 171.8. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.677; H, 5.806; N, 9.302. Found: C, 69.470; H, 5.900; N, 8.724.

(*S*,*S*)-**14**. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): white solid, mp

187–188 °C, $[\alpha]_D^{24}$ -292.7 ^{o} (c = 0.505, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (3H, d, *J* = 7.0 Hz), 3.69 (3H, s), 4.55 (1H, q, *J* = 7.2 Hz), 4.60 (1H, br s), 5.87 (1H, s), 6.52 (1H, dd, J_{meta} = 0.7 and J_{ortho} = 8.2 Hz), 6.82 (1H, ddd, J_{meta} = 1.2 Hz, J_{ortho} = J_{ortho} = 7.2 Hz), 7.22 (1H, ddd, J_{meta} = 1.4 Hz, J_{ortho} = J_{ortho} = 8.2 Hz), 7.31–7.46 (5H, m), 7.89 (1H, dd, J_{meta} = 1.6 and J_{ortho} = 7.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.9, 52.6, 52.8, 71.3, 114.9, 116.6, 119.6, 126.8, 128.6, 128.9, 129.4, 133.7, 139.9, 145.0, 162.9, 171.8. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.677; H, 5.806; N, 9.302. Found: C, 69.420; H, 5.851; N, 8.904. X-Ray crystallographic structure in Figure 6.[11]

2,3-Dihydro-2(*R*)- and 2,3-dihydro-2(*S*)-*tert*-butyl-3-[(*S*)-methyloxycarbonylethyl]-4(1*H*)-quinazolinone [(*S*,*R*)- and (*S*,*S*)-15].

Compound (**10**) (0.62 g, 0.62 g, 2.8 mmol) was treated with *p*-toluenesulfonic acid (76 mg, 0.4 mmol) and trimethylacetaldehyde (3 mmol) in CH_2Cl_2 according to *GP2*. The crude products were purified by FC [hexane: *n*-Butyl acetate: *i*-PrOH (75:15:10)] to produce both diastereoisomers (0.47 g, 58 %).

(*S*,*S*)-**15**. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): white solid, mp 162–164 °C, $[\alpha]_D^{24}$ -168.1 ^{o} (c = 0.565, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.01 (9H, s), 1.55 (3H, d, *J* = 7.0 Hz), 3.81 (3H, s), 4.38 (1H, d, *J* = 3.0 Hz), 4.71 (1H, br s), 6.57 (1H, dd, J_{meta} = 0.8 and J_{ortho} = 8.2 Hz), 6.71 (1H, ddd, J_{meta} = 1.2 Hz, J_{ortho} = J_{ortho} = 7.6 Hz), 7.22 (1H, ddd, J_{meta} = 1.4 Hz, J_{ortho} = J_{ortho} = 7.8 Hz), 7.73 (1H, dd, J_{meta} = 1.6 and J_{ortho} = 7.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.1, 26.0, 41.7, 52.4, 59.8, 78.2, 113.1, 116.6, 118.3, 128.2, 133.8, 146.7, 162.9, 171.3. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.21; H, 7.59; N, 9.65. Found: C, 66.92; H, 7.47; N, 9.13. X-Ray crystallographic structure in Figure 7.[11]

(*R*,*S*)-**15**. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): white solid, mp 133-134 °C, $[\alpha]_D^{24}$ +112.2 ^{o} (c = 0.51, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (9H, s), 1.90 (3H, d, *J* = 7.0 Hz), 3.71 (3H, s), 3.87 (1H, q, *J* = 7.0 Hz), 4.38 (1H, s), 4.55 (1H, br s), 6.57 (1H, dd, J_{meta} = 0.8 and J_{ortho} = 8.2 Hz), 6.73 (1H, ddd, J_{meta} = 0.8 Hz, J_{ortho} = J_{ortho} = 7.8 Hz), 7.20 (1H, ddd, J_{meta} = 1.5 Hz, J_{ortho} = J_{ortho} = 8.0 Hz), 7.71 (1H, dd, J_{meta} = 1.6 and J_{ortho} = 7.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.0, 26.3, 40.8, 52.7, 61.4, 80.2, 113.6, 117.5, 118.5, 128.1, 133.4, 146.2, 164.5, 171.7. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.21; H, 7.59; N, 9.65. Found: C, 65.99; H, 7.60; N, 9.59.

2,3-Dihydro-2(*R*)- and 2,3-dihydro-2(*S*)-(*o*-nitrophenyl)-3-[(*S*)-methoxycarbonylethyl]-4(1*H*)-quinazolinone [(*S*,*R*)- and (*S*,*S*)-16].

Compound (**10**) (0.62 g, 2.8 mmol) was treated with *p*-toluenesulfonic acid (76 mg, 0.4 mmol) and *o*-nitrobenzaldehyde (0.45 g, 3 mmol) in CH_2Cl_2 according to *GP2*. The crude products were purified by FC [hexane: CH_2Cl_2: ethyl acetate (74:20:6)] to produce both diastereoisomers (0.51 g, 52 %).

(*S*,*R*)-**16**. For analytical purposes a sample was recrystallized (CH_2Cl_2/Hexane): white solid, mp

156–158 °C, $[\alpha]_D^{24}$ +372.1 ^{o} (c = 0.51, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (3H, d, *J* = 7.4 Hz), 3.31 (3H, s), 5.09 (1H, q, *J* = 7.2 Hz), 5.37 (1H, d, *J* = 2.2 Hz), 6.44 (1H, d, *J* = 2.6 Hz), 6.50 (1H, d, J_{ortho} = 8.2 Hz), 6.84 (1H, ddd, J_{meta} = 1.2 Hz, J_{ortho} = J_{ortho} = 7.4Hz), 7.24 (1H, ddd, J_{meta} = 1.5 Hz, J_{ortho} = J_{ortho} = 7.4 Hz), 7.41–7.36 (3H, m), 7.95 (1H, dd, J_{meta} = 1.5 and J_{ortho} = 7.6 Hz), 8.03 (1H, dd, J_{meta} = 1.7 and J_{ortho} = 8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.6, 52.1, 52.7, 64.9, 115.1, 115.9, 119.8, 125.6, 128.7, 128.9, 129.8, 133.7, 134.4, 135.2, 144.2, 147.5, 163.4, 171.1. Anal. Calcd for $C_{18}H_{17}N_3O_5$: C, 59.17; H, 4.65; N, 11.50. Found: C, 60.07; H, 4.85; N, 11.73. X-Ray crystallographic structure in Figure 8.[11]

(*S*,*S*)-**16**: Spectroscopic analysis was not determined because we could not obtain a single diastereoisomer.

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