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Stereocontrolled Routes to Derivatives of 3-Alkoxycarbonyl-2-amino-4-aryl-5-cyano-6-phenyl-4*H*-pyrans

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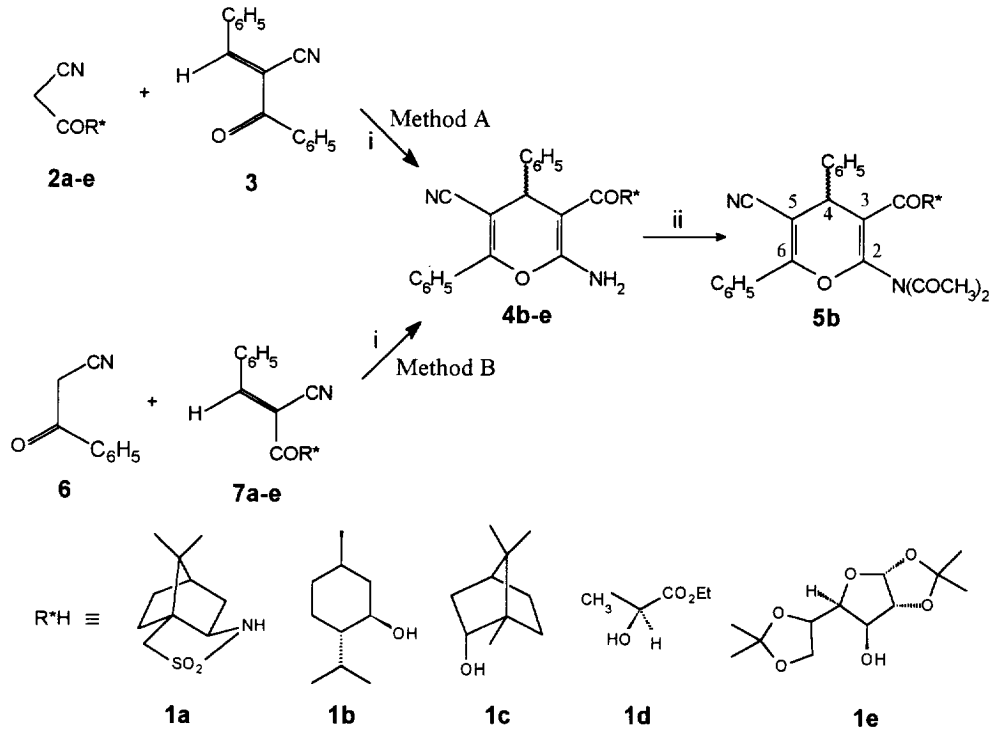
Abstract: The asymmetric Michael addition of cyanoacetates **2b-e** and benzoylacetonitrile **6** to α-benzoylcinnamonitrile **3** and α-cyanocinnamates **7b-e**, respectively, has been studied. The resulting 3-alkoxycarbonyl-2-amino-4-aryl-5-cyano-6-phenyl-4*H*-pyrans **4b-e** have been obtained in moderate diastereomeric excess and good chemical yield.

INTRODUCTION

The asymmetric synthesis of the elusive 2-amino-4*H*-pyran ring systems[1] has attracted our interest in the last years. As a result we have reported different strategies for the preparation of enantiomerically pure, multiply functionalized 2-amino-4*H*-pyrans.[2] Our efforts have been now directed to the synthesis of some 3-alkoxycarbonyl-2-amino-4-aryl-5-cyano-6-phenyl-4*H*-pyrans **4b-e**. Two stereocontrolled routes have been designed. In Method **A**, an enantiomerically pure cyanoacetate **2**, acting as a Michael donor, has been reacted with α-benzoylcinnamonitrile[3] **3** and in the alternative Method **B**, benzoylacetonitrile **6** has been treated with homochiral α-cyanocinnamate **7** (Scheme 1).

RESULTS AND DISCUSSION

Due to the excellent results obtained with Oppolzer´s sultam[4] **1a** in our previous work in this area,[2c,d] we used this chiral auxiliary in our preliminary experiments. Thus, we prepared the key intermediates **2a** and **7a**[5]. Unfortunately, following Methods **A** and **B**, under a variety of basic conditions [piperidine or triethylamine (cat.), toluene, room temperature; NaH, THF, 0°C; *N,N*-diisobutyl-2,4-dimethyl-3-pentylamine (cat.), toluene, room temperature] no 2-amino-4*H*-pyran was detected, with (2*R*)-bornane-10,2-sultam (**1a**) being the only product isolated in all cases. These unexpected and disappointing results led us to use the readily available chiral auxiliaries **1b-e** [(1*R*,2*S*,5*R*)-(-)-menthol (**1b**), (1*S*)-endo-(-)-borneol (**1c**), ethyl (*S*)-(-)-lactate (**1d**) and 1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose (**1e**)]. Cyanoacetates **2b-e**[6] were synthesized from cyanoacetic acid following known methodologies.[6b,7] The Knoevenagel type reaction of compounds **2b-e** with benzaldehyde, under mild basic conditions gave exclusively the expected *E* isomers (**7b-e**)[6a,8] in good yield.



Scheme 1. *Reagents.* i: toluene, piperidine (cat.), r.t.; ii: Ac_2O/pyridine (1:1), reflux.

Under standard conditions[9] [piperidine (cat.), toluene, room temperature] substrates **2b-e** and **7b-e** were treated with the corresponding Michael acceptor or donor, respectively (Scheme 1). For the sake of experimental simplicity and in view of the discouraging results previously obtained in our laboratory[2b] using other counterions (lithium, sodium or magnesium), other different bases were not tested. As shown in the Table, independently of the Method **A** or **B**, the same 2-amino-4*H*-pyrans **4b-e** were obtained in good yield (60-80%) and moderate diastereomeric excess (20-60%). All the new compounds **4b-e** showed spectroscopic and analytical data in excellent agreement with the proposed structures. We could not separate diastereoisomers in compounds **4b-e** by flash chromatography. Fortunately, after the recrystallization, major isomers **4c** (entry 3) and **4d** (entry 5) (see Table) were isolated diastereomerically pure. The diastereomeric excesses have been determined from the ^{1}H NMR spectra ($CDCl_3$ as solvent) of the purified compounds, by integrating the observed signals for H-4 [δ: 4.51 (**4b**), 4.59 (**4c**) and 4.64 (**4d**) for the major isomer; δ: 4.50 (**4b**), 4.58 (**4c**) and 4.59 (**4d**) for the minor one)]. In the case of compound **4e**, H-4 (in both isomers) and H-2' (in the major isomer) appear at the same δ value. When the ^{1}H NMR spectrum of **4e** was recorded in CD_3COCD_3 the signals for H-2' and H-4 were clearly separated. Then, we were able to observe that H-4

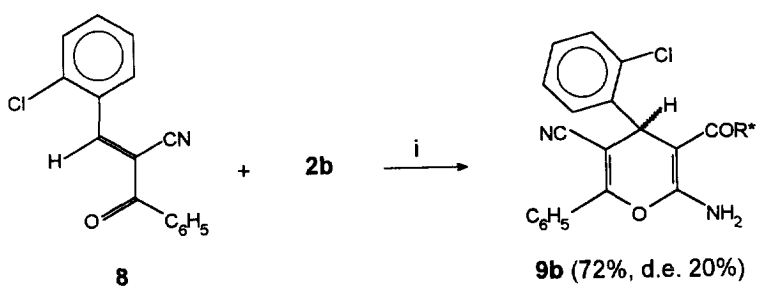
in the minor isomer was more deshielded (4.56 ppm) than in the major one (4.54 ppm). In the ^{1}H NMR spectra of compounds **4b-d**, using CD_3COCD_3 as solvent, we could detect that, also in these cases, the relative δ values for H-4 were reversed. Thus, we can conclude, by comparison of the chemical shifts for H-4, that in compounds **4**, independent of the Method used (**A** or **B**) and the chiral auxiliary analyzed, the major isomer had always the same absolute configuration at C-4.

Table. 2-Amino-4*H*-pyrans **4b-e**.

Entry	Compound	*Via*	Temp (°C)	Yield[1] (%)	Ratio[1] S:R (d.e.)[2]
1	**4b**	A	25	81	60:40
2		B	25	72	60:40
3	**4c**	A	25	80	80:20 (>99)
4		B	25	71	60:40
5	**4d**	A	25	70	70:30 (>99)
6		B	25	68	60:40
7	**4e**	A	25	60	75:25
8		B	25	58	70:30

[1] After flash chromatography. [2] After flash chromatography and recrystallization.

In view of these results, several parameters were modified. It was observed that running the reaction at 0°C did not improve the stereoisomeric ratios, but slowed down the rate of the process and diminished the chemical yield. Changing the substitution on the phenyl ring in the α-benzoylcinnamonitrile **8**, as shown in Scheme 2, did not affect the stereochemical course of the reaction. The major isomer **9b** had also the same configuration at C-4, showing H-4 in the major isomer (5.20 ppm) more deshielded than the minor one (5.16 ppm) in the ^{1}H NMR spectrum in $CDCl_3$.



Scheme 2. *Reagents.* i: toluene, piperidine (cat.), r.t.

Finally, after X-ray diffraction analysis[3] of a suitable crystal of pure major isomer of **4c**, the absolute

configuration at C-4 could be established as *S*. Then, by comparison of the chemical shifts for H-4 (see above), we could assign as *S* the absolute configuration at C-4 in the major isomers of all members of this series. From this analysis it was observed that the conformation of the pyran ring can be considered as a 1,4-boat, but the displacement of C-4 from the plane defined by C-2, C-3, C-5 and C-6 is larger than that of O-1. This situation is similar to what we have found in other 4*H*-pyrans[2] and could be due to the steric hindrance of the phenyl ring.

Several attempts to remove the chiral auxiliary in compound **4b** were carried out. After extensive experimentation {basic hydrolysis [NH_3, EtOH, r.t.], reduction [$LiAlH_4$, THF or ether, r.t.[2d]; DIBALH, toluene] and transesterification under neutral conditions [$Ti(OEt)_4$, EtOH, reflux[10]; Ph_3P, DEAD, MeOH[11]]} we were unable to recover the chiral auxiliary. In these reactions the starting material was obtained unchanged or decomposed. Initially we assumed that this anomalous behavior was due to the hydrogen bond between the amino group at C-2 and the carbonyl at C-3.

For this reason compound **4b**, after reaction with acetic anhydride/pyridine at reflux, was transformed into imide **5b** (Scheme 1). Very surprisingly, again, this compound proved to be very resistant to all the conditions tested {basic hydrolysis[12] [KOH, EtOH], reduction [$LiAlH_4$, THF, r.t.[2d]; DIBALH, toluene], transesterification [$Ti(OEt)_4$, EtOH, reflux[10]] and non-hydrolytic cleavage[13] conditions [$MgI_2 \cdot Et_2O$, toluene, reflux]} to try to liberate the chiral auxiliary. In this case, and contrary to our previous observations in related compounds,[2c,d] it is obvious that the sum of electronic and steric factors make nucleophilic attack onto the carbonyl at C-3 difficult.

In summary, the results obtained in this study show that the Michael addition of chiral (or achiral) donors to racemic (or chiral) acceptors proceeds in moderate diastereomeric excess and good chemical yield. These observations should open the path for a new insight in this relatively unexplored area. The implications of this result are under further investigation.

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EXPERIMENTAL PART

All the reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was by UV (254 nm), followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous $MgSO_4$ was used to dry the organic solutions during workups, and the removal of solvents was carried out under vacuum with a rotavapor. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh, Merck) and hexane-ethyl acetate mixtures as the eluent. Melting points were determined in capillary tubes and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 Polarimeter with a 1 dm cell. IR spectra were recorded with Perkin-Elmer 257 and 781 instruments. ^1H and ^{13}C NMR spectra were recorded with a Varian VXR-300S spectrometer, using tetramethylsilane as the internal standard.

***N*-Cyanoacetylbornane-10,2-sultam (2a):** To a solution of 10,2-bornane-sultam **1a** (3.0 g, 13.95 mmol, 1.0 equiv) in dry toluene (30 mL), Me_3Al [8.4 mL (solution 2.0 M in hexane), 16.74 mmol, 1.2 equiv] was added dropwise at room temperature under argon. The solution was stirred for 30 min and methyl cyanoacetate (1.933 g, 19.53 mmol, 1.4 equiv) was added dropwise. The reaction was refluxed for 1.5 h. After cooled, 5% aqueous hydrochloric acid solution was added. The precipitate formed was filtered over Celite 521 and washed with ethyl acetate. The aqueous phase was extracted twice with ethyl acetate; the organic phase was washed with 10% aqueous sodium bicarbonate solution and dried over $MgSO_4$. The solvent was evaporated giving an oil that was submitted to flash chromatography (hexane/ethyl acetate 4:1, 7:3) giving compound **2a** (3.37 g, 86% yield) as a solid. M.p. 148-149°C; $[\alpha]_D^{25}$ + 141.7 (*c* 0.9, $CHCl_3$); IR (KBr) ν: 2980, 2860, 2260, 1700, 1480, 1450, 1410, 1390, 1350, 1335 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.96 (d, 1H, J = 21 Hz, CH_2CN), 3.89 (d, 1H, J = 21 Hz, CH_2CN), 3.90 (dd, 1H, J = 7.8 and 5.1 Hz, $CHNSO_2$), 3.55 (d, 1H, J = 13.8 Hz, CH_2SO_2), 3.48 (d, 1H, J = 13.8 Hz, CH_2SO_2), 2.24-2.06 (m, 2H), 2.02-1.85 (m, 3H), 1.48-1.33 (m, 2H), 1.13 (s, 3H, CH_3), 0.98 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.05 (CO), 112.14 (CN), 65.48 ($CHNSO_2$), 52.59 (CH_2SO_2), 48.98, 47.86 [$C(CH_3)_2$ and C-1'], 44.55 (CH), 37.83 (CH_2), 32.71 (CH_2), 26.34, 26.29 (CH_2 and CH_2CN), 20.62 (CH_3), 19.74 (CH_3); Anal. Calcd. for $C_{13}H_{18}N_2O_3S$: C, 55.30; H, 6.42; N, 9.92; Found: C, 55.18; H, 5.92; N, 9.91.

1'(*S*)-Ethoxycarbonylethyl cyanoacetate (2d): To a stirred solution of cyanoacetic acid (3.0 g, 35.26 mmol, 1.0 equiv) in dry CH_2Cl_2 (100 mL) 4-dimethylaminopyridine (3.446 g, 28.21 mmol, 0.8 equiv) and ethyl (*S*)-(-)-lactate **1d** (4.165 g, 35.26 mmol, 1.0 equiv) were added. Dicyclohexylcarbodiimide was added to the reaction mixture at 0°C, and then stirred for 12 h at room temperature. Precipitated dicyclohexylurea was then filtered over Celite 521 and the filtrate evaporated. The residue was dissolved in CH_2Cl_2 and more dicyclohexylurea was filtered off again. The organic solution was washed twice with 5% aqueous hydrochloric acid solution, saturated aqueous sodium bicarbonate solution, brine and dried over $MgSO_4$. The solvent was removed and the residue submitted to flash chromatography (hexane/ethyl acetate 7:3) to give **2d** (4.47 g, 68% yield): liquid; $[\alpha]_D^{25}$ -39.8 (*c* 1.0, $CHCl_3$); IR (KBr) ν: 2990, 2940, 2880, 2270, 1745, 1450, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.16 (q, 1H, J=7.2 Hz, $CHCH_3$), 4.22 (q, 2H, OCH_2), 3.59 (s, 2H, CH_2CN), 1.55 (d, 3H, J=7.2 Hz, CH_3CH), 1.29 (t, 3H, J=7.2 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.30 (CO_2Et), 162.37 (COO), 112.46 (CN), 70.52 ($CHCH_3$), 61.62 (OCH_2), 24.33 (CH_2), 16.44 (CH_3CH), 13.83 (CH_3CH_2); MS (70 eV) *m/z*: 186 (M^++1,45), 140(24), 112 (18), 68(100). Anal. Calcd. for $C_8H_{11}NO_4$: C, 51.88; H, 5.98; N, 7.56. Found: C, 51.55; H, 5.62; N, 7.21

***N*-α-Cyanocinnamoylbornane-10,2-sultam (7a):** To a solution of compound **2a** (100 mg, 0.35 mmol, 1.0 equiv) in ethanol (20 mL), freshly distilled benzaldehyde (38 mg, 0.35 mmol, 1.0 equiv) and piperidine (one drop) were added. The solution was stirred at room temperature for 4 h. The solvent was evaporated giving compound **7a** (124 mg, 95% yield) as a solid that was washed with cold methanol. M.p. 181-182 °C; $[\alpha]_D^{25}$ + 146.5 (*c* 1.0, $CHCl_3$); IR (KBr) ν: 3050, 2980, 2950, 2880, 2220, 1685, 1610, 1570, 1490, 1450, 1410, 1390, 1360, 1340, 1290, 1250, 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.95-7.46 (5H, aromatic), 7.87 (s, 1H, HC=C), 4.13 (dd, 1H, J = 7.5 and 4.5 Hz, $CHNSO_2$), 3.56 (d, 1H, J = 13.8 Hz, CH_2SO_2), 3.48 (d, 1H, J = 13.8 Hz, CH_2SO_2), 2.15-1.90 (m, 5H), 1.53-1.35 (m, 2H), 1.27 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.67 (CO), 154.27 (Ph*C*=C), 132.92, 131.21, 130.63, 129.04 (aromatic), 114.52 (CN), 105.58 (PhC=*C*), 65.49 ($CHNSO_2$), 53.16 (CH_2SO_2), 48.38, 47.76 [$C(CH_3)_2$ and C-1'], 44.86 (CH), 37.84 (CH_2), 32.85 (CH_2), 26.30 (CH_2), 21.01 (CH_3), 19.72 (CH_3); Anal. Calcd. for $C_{20}H_{22}N_2O_3S$: C, 64.84; H, 5.98; N, 7.56. Found: C, 64.54; H, 5.68; N, 7.54.

General Procedure for the Synthesis of Pyrans 4:

Method A: To a solution of compound **2** (1.1 equiv) in dry toluene, α-benzoylcinnamonitrile **3** (1.0 equiv) and several drops of piperidine were added. The reaction mixture was stirred at room temperature for 10 h. After the solvent was evaporated, the residue was dissolved in CH_2Cl_2 and washed with brine. The organic phase was dried ($MgSO_4$) and the oil obtained was submitted to flash chromatography to give compound **4**.

Method B: To a solution of compound **7** (1.0 equiv) in dry toluene, benzoylacetonitrile **6** (1.2 equiv) and several drops of piperidine were added. The reaction mixture was stirred at room temperature for 48

h. After the solvent was evaporated, the residue was dissolved in CH_2Cl_2 and washed with brine. The organic phase was dried ($MgSO_4$) and the oil obtained was submitted to flash chromatography to give compound **4**.

2-Amino-5-cyano-3-[(-)-(1′*R*,2′*S*,5′*R*)-menthyloxycarbonyl]-4,6-diphenyl-4*H*-pyran (4b): Following Method **A**, a solution of compound **2b** (459 mg, 2.05 mmol, 1.1 equiv) and α-benzoylcinnamonitrile **3** (435 mg, 1.87 mmol, 1.0 equiv) in dry toluene (10 mL) with four drops of piperidine was stirred at room temperature for 10 h. The crude reaction mixture was submitted to flash chromatography (hexane/ethyl acetate 19:1, 9:1) to give compound **4b** (690 mg, 81% yield) as a mixture of diastereomers (60:40) that could not be separated by recrystallization. Following Method **B**, a solution of compound **7b** (265 mg, 0.85 mmol, 1.0 equiv) and benzoylacetonitrile **6** (148 mg, 0.85 mmol, 1.2 equiv) in dry toluene (5 mL) with one drop of piperidine was stirred at room temperature for 48 h. The crude reaction mixture was submitted to flash chromatography (hexane/ethyl acetate 19:1) to give compound **4b** (272 mg, 70% yield) as a mixture of diastereomers (60:40) that could not be separated by recrystallization. **4b:** Solid; m.p. 148-151°C; IR (KBr) ν : 3480, 3320, 2960, 2930, 2870, 2220, 1680, 1645, 1615, 1510, 1450, 1400, 1340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) [major (C-4 *S*) and minor (C-4 *R*) diastereomers] δ: 7.75 (m, 2H, aromatic), 7.45 (m, 3H, aromatic), 7.28 (m, 5H, aromatic), 6.35 (br s, 2H, NH_2), 4.59 (dt, 1H, $J_{ax,ax}$=10.8 Hz, $J_{ax,eq}$=4.2 Hz, H-1'), 4.51 (s, 1H, H-4 major), 4.50 (s, 1H, H-4 minor), 2.02-0.80 (several m, 9H, H-2', 2H-3', 2H-4', H-5', 2H-6', H-7'), 0.94, 0.90, 0.78, 0.73, 0.46, 0.36 (d, J = 6.9 Hz, 3 CH_3 major and minor); ^{13}C NMR (75 MHz, $CDCl_3$) [major (C-4 *S*) diastereomer] δ: 167.93 (COO), 158.36 (C-2), 156.54 (C-6), 143.69-127.11 (aromatic), 117.87 (CN), 92.99 (C-5), 77.62 (C-3), 73.27 (C-1'), 46.69 (C-2'), 41.29 (C-6′), 39.92 (C-4), 34.01 (C-4'), 31.29 (C-5'), 24.29 (C-7'), 22.34 (C-3'), 21.92 (CH_3), 20.98 (CH_3), 15.04 (CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) [minor (C-4 *R*) diastereomer] δ: 167.93 (COO), 157.92 (C-2), 156.81 (C-6), 143.79-127.06 (aromatic), 117.94 (CN), 92.77 (C-5), 77.62 (C-3), 73.54 (C-1'), 46.98 (C-2'), 40.17 (C-4), 40.11 (C-6'), 33.99 (C-4'), 31.02 (C-5'), 26.29 (C-7'), 23.32 (C-3'), 21.73 (CH_3), 20.74 (CH_3), 16.40 (CH_3); MS (70 eV) *m/z*: 456(M^+,19), 379(9), 318(20), 273(100), 241(78), 139(16), 138(32), 105(66), 83 (33), 77(24); Anal. Calcd. for $C_{29}H_{32}N_2O_3$: C, 76.28; H, 7.06; N, 6.13. Found: C, 75.91; H, 7.17; N, 5.78

2-Amino-3-[(-)-(1′*S*,2′*R*,4′*S*)-bornyloxycarbonyl]-5-cyano-4,6-diphenyl-4*H*-pyran (4c): Following Method **A**, a solution of compound **2c** (457 mg, 2.07 mmol, 1.1 equiv) and α-benzoylcinnamonitrile **3** (439 mg, 1.88 mmol, 1.0 equiv) in dry toluene (10 mL) with four drops of piperidine was stirred at room temperature for 10 h. The crude reaction mixture was submitted to flash chromatography (hexane/ethyl acetate 19:1, 9:1) to give compound **4c** (680 mg, 80% yield) as a mixture of diastereomers (80:20). Major diastereomer was separated by recrystallization. Following Method **B**, a solution of compound **7c** (250 mg, 0.81 mmol, 1.0 equiv) and benzoylacetonitrile **6** (141 mg, 0.97 mmol, 1.2 equiv) in dry toluene (5 mL) with one drop of piperidine was stirred at room temperature for 48 h. The crude reaction mixture was submitted to flash chromatography (hexane/ethyl acetate 19:1, 9:1, 4:1) to give compound **4c** (257 mg, 70% yield) as a mixture of diastereomers (60:40) that could not be separated by recrystallization. **Major 4c (C-4 *S*) diastereomer:** Solid; m.p. 190-192 °C; $[\alpha]_D^{25}$ + 107.8 (*c* 1.02, CH_2Cl_2); IR (KBr) ν : 3400, 3300, 3060, 3020, 2960, 2880, 2220, 1700, 1650, 1620, 1540, 1450, 1400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.73 (m, 2H, aromatic), 7.45 (m, 3H, aromatic), 7.36-7.22 (m, 5H, aromatic), 6.38 (br s, 2H, NH_2), 4.70 (ddd, 1H, J=9.9, 3.6 and 2.1 Hz, H-2'), 4.59 (s, 1H, H-4), 2.33 (m, 1H, H-4'), 1.66 (m, 3H), 1.16 (m, 2H), 0.97 (dd, 1H, J=13.8 and 3.6 Hz), 0.82 (s, 3H, CH_3), 0.79 (s, 3H, CH_3), 0.31 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.70 (COO), 158.56 (C-2), 156.64 (C-6), 143.46, 131.19, 130.31, 128.58, 128.46, 127.63, 127.48, 127.26 (aromatic), 117.89 (CN), 93.20 (C-5), 79.80 (C-2'), 77.16 (C-3), 48.49, 47.54 (C-1' and C-7'), 44.72 (C-4'), 40.07 (C-4), 37.05 (CH_2), 27.95 (CH_2), 26.89 (CH_2), 19.47 (CH_3), 18.61 (CH_3), 12.55 (CH_3); MS (70 eV) *m/z*: 454(M^+,22), 377(15), 318(15), 301(19), 273(100), 241(41), 137(30), 105(53), 95(25), 81(33), 77(23); Anal. Calcd. for $C_{29}H_{30}N_2O_3$: C, 76.63; H, 6.65; N, 6.16. Found: C, 76.35; H, 6.74; N, 5.98. **Minor 4c (C-4 *R*) diastereomer:** ^1H NMR (300 MHz, $CDCl_3$) δ: 7.73 (m, 2H, aromatic), 7.45 (m, 3H, aromatic), 7.36-7.22 (m, 5H, aromatic), 6.38 (br s, 2H, NH_2), 4.92 (ddd, 1H, J=9.9, 3.6 and 2.1 Hz, H-2'), 4.58 (s, 1H, H-4), 2.06 (m, 1H, H-4'), 1.61-1.46 (m, 3H), 0.90-0.62 (m, 2H), 0.85 (s, 3H, CH_3), 0.82 (s, 6H, 2 CH_3), 0.34 (dd, 1H, J=13.8 and 3.6 Hz).

2-Amino-5-cyano-3-[1´(*S*)-ethoxycarbonylethoxycarbonyl]-4,6-diphenyl-4*H*-pyran (4d): Following Method **A**, a solution of compound **2d** (549 mg, 2.97 mmol, 1.1 equiv) and α-benzoylcinnamonitrile **3** (630 mg, 2.70 mmol, 1.0 equiv) in dry toluene (12 mL) with four drops of piperidine was stirred at room temperature for 10 h. The crude reaction mixture was submitted to flash chromatography (hexane/ethyl acetate 19:1, 9:1) to give compound **4d** (790 mg, 70% yield) as a mixture of diastereomers (70:30). Major diastereomer was separated by recrystallization. Following Method **B**, a solution of compound **7d** (900 mg, 3.29 mmol, 1.0 equiv) and benzoylacetonitrile **6** (572 mg, 3.94 mmol, 1.2 equiv) in dry toluene (15 mL) with four drops of piperidine was stirred at room temperature for 48 h. The crude reaction mixture was submitted to flash chromatography (hexane/ethyl acetate 9:1, 4:1) to give compound **4d** (939 mg, 68% yield) as a mixture of diastereomers (60:40) that could not be separated by recrystallization. **Major 4d (C-4 *S*) diastereomer:** Solid; m.p. 127-129°C; $[\alpha]_D^{25}$ + 96.1 (*c* 0.93, CH_2Cl_2); IR (KBr) *ν*: 3420, 3320, 3060, 3020, 2980, 2940, 2220, 1740, 1690, 1650, 1615, 1530, 1450, 1400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 7.77-7.22 (m, 10H, aromatic), 6.38 (br s, 2H, NH_2), 4.89 (q, 1H, *J*=7.2 Hz, $CHCH_3$), 4.64 (s, 1H, H-4), 4.21 (q, 2H, CH_2), 1.28 (t, 3H, *J*=7.2 Hz, CH_3CH_2), 1.26 (d, 3H, *J*=7.2 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 171.19 (CO_2Et), 167.33 (COO), 158.73 (C-2), 156.76 (C-6), 143.58, 131.27, 130.12, 128.50, 128.42, 127.75, 127.60, 127.23 (aromatic), 117.59 (CN), 93.13 (C-5), 76.90 (C-3), 68.13 ($CHCH_3$), 61.18 (CH_2), 39.90 (C-4), 16.58 (CH_3CH), 13.99 (CH_3CH_2); MS(70 eV) *m/z*: 418(M^+,9), 389 (7), 341(79), 318(10), 317(46), 301(18), 300(19), 273(100), 105(44), 77(19). Anal. Calcd. for $C_{24}H_{22}N_2O_5$: C, 68.89; H, 5.30; N, 6.69. Found: C, 68.68; H, 5.73; N, 6.68. **Minor 4d (C-4 *R*) diastereomer:** ^1H NMR (300 MHz, $CDCl_3$) *δ*: 7.80-7.20 (m, 10H, aromatic), 6.38 (br s, 2H, NH_2), 5.02 (q, 1H, *J*=7.2 Hz, $CHCH_3$), 4.59 (s, 1H, H-4), 3.98 (m, 2H, CH_2), 1.41 (d, 3H, *J*=7.2 Hz, CH_3CH), 1.06 (t, 3H, *J*=7.2 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 170.63 (CO_2Et), 167.16 (COO), 158.67 (C-2), 156.96 (C-6), 143.22, 131.31, 130.09, 128.50, 128.38, 127.64, 127.60, 127.17 (aromatic), 117.75 (CN), 93.04 (C-5), 76.75 (C-3), 68.41 ($CHCH_3$), 60.86 (CH_2), 39.87 (C-4), 16.93 (CH_3CH), 13.77 (CH_3CH_2).

2-Amino-5-cyano-3-[3´-(1´2´:5´6´-diisopropylidene)-α-*D*-glucofuranoxycarbonyl]-4,6-diphenyl-4*H*-pyran (4e): Following Method **A**, a solution of compound **2e** (457 mg, 1.39 mmol, 1.1 equiv) and α-benzoylcinnamonitrile **3** (297 mg, 1.27 mmol, 1.0 equiv) in dry toluene (10 mL) with four drops of piperidine was stirred at room temperature for 10 h. The crude reaction mixture was submitted to flash chromatography (hexane/ethyl acetate 9:1) to give compound **4e** (426 mg, 60 % yield) as a mixture of diastereomers (75:25) that could not be separated by recrystallization. Following Method **B**, a solution of compound **7e** (1.0 g, 2.41 mmol, 1.0 equiv) and benzoylacetonitrile **6** (419 mg, 2.89 mmol, 1.2 equiv) in dry toluene (20 mL) with four drops of piperidine was stirred at room temperature for 48 h. The crude reaction mixture was submitted to flash chromatography (hexane/ethyl acetate 19:1) to give compound **4e** (783 mg, 58% yield) as a mixture of diastereomers (70:30) that could not be separated by recrystallization. **4e:** Solid; m.p. 120-122 °C; IR (KBr) *ν*: 3400, 3300, 2990, 2940, 2880, 2220, 1700, 1660, 1620, 1530, 1450, 1375 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) [major (C-4 *S*) diastereomer] *δ*: 7.78-7.24 (m, 10H, aromatic), 6.60 (br s, 2H, NH_2), 5.89 (d, 1H, *J*=3.6 Hz, H-1'), 4.47 (d, 1H, *J*=3.6 Hz, H-2'), 4.47 (s, 1H, H-4), 4.26 (d, 1H, H-3'), 4.10 (d, 1H, H-4'), 3.73 (dd, 1H, H-6'), 3.58 (dd, 1H, H-6'), 2.91 (m, 1H, H-5'), 1.49, 1.43, 1.31, 1.27 (s, 12H, 4 CH_3); MS (70 eV) *m/z*: 545(M^+-15,27), 502(25), 483(15), 400 (40), 318(24), 317(76), 301(42), 300(67), 289(66), 273(100), 241(18), 233(29), 156(19), 105(35), 101(47), 77(10). Anal. Calcd. for $C_{31}H_{32}N_2O_8$: C, 66.42; H, 5.75; N, 4.99. Found: C, 66.15; H, 5.97; N, 4.57.

2-(*N*,*N*-Diacetylamino)-5-cyano-3-[(-)-(1´*R*,2´*S*,5´*R*)-menthyloxycarbonyl]-4,6-diphenyl-4*H*-pyran (5b): Compound **4b** (500 mg, 1.09 mmol) was dissolved in acetic anhydride/pyridine (1:1, 20 mL) and the mixture was heated at reflux. After 2 h, the solvents were removed to reduced pressure and the residue was dissolved in CH_2Cl_2 and washed with 10% aqueous sodium bicarbonate solution and brine. Organic phase was dried, filtered and the black oil submitted to flash chromatography (hexane/ethyl acetate 9:1) giving compound **5b** (510 mg, 86% yield) as a mixture of diastereomers (60:40). **5b:** Solid; m.p. 147-151 °C; IR (KBr) *ν*: 2980, 2950, 2880, 2230, 1740, 1725, 1680, 1640, 1460, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) [major (C-4 *S*) and minor (C-4 *R*) diastereomers] *δ*: 7.80-7.30 (m, 10H, aromatic), 4.84 (s, 1H, H-4 major), 4.79 (s, 1H, H-4 minor), 4.69 (m, 1H, H-1' major and minor), 2.48, 2.47 [s, 6H, $(CH_3CO)_2N$ minor], 2.40, 2.38 [s, 6H, $(CH_3CO)_2N$ major], 2.33-0.70 (several m, 9H, H-2', 2H-3', 2H-4', H-5', 2H-6',

H-7'), 0.87, 0.82, 0.81, 0.65, 0.56, 0.48 (d, J=6.9 Hz, 3 CH_3 major and minor); ^{13}C NMR (75 MHz, $CDCl_3$) [major (C-4 *S*) and minor (C-4 *R*) diastereomers] δ: 170.91, 170.82, 170.61, 170.48, [$(CH_3CO)_2N$], 162.63, 162.44 (COO), 158.68, 158.50 (C-6), 148.83, 146.97 (C-2), 140.79-127.70 (aromatic), 117.09 (CN), 109.01, 108.19 (C-3), 91.07, 90.30 (C-5), 75.73, 75.59 (C-1'), 46.90, 46.79 (C-2'), 42.19, 42.09 (C-4), 40.64, 40.13 (C-6'), 33.79 (C-4'), 31.28, 31.17 (C-5'), 26.77, 26.00, 25.60, 25.48, 25.32, 25.00 [C-7', $(CH_3CO)_2N$], 22.93, 22.34 (C-3'), 21.76, 21.72 (CH_3), 20.87, 20.58 (CH_3), 15.76, 15.05 (CH_3); Anal. Calcd. for $C_{33}H_{36}N_2O_5$: C, 73.31; H, 6.71; N, 5.18. Found: C, 73.07; H, 6.81; N, 4.88.

2-Amino-4-(*o*-chlorophenyl)-5-cyano-3-[(-)-(1'*R*,2'*S*,5'*R*)-menthyloxycarbonyl]-6-phenyl-4*H*-pyran (9b): Following Method **A**, a solution of compound **2b** (600 mg, 2.69 mmol, 1.0 equiv) and α-benzoyl-ß-(*o*-chlorophenyl)acrylonitrile **8** (863 mg, 3.23 mmol, 1.2 equiv.) in dry toluene (10 mL) with four drops of piperidine was stirred at room temperature for 10 h. The crude reaction mixture was submitted to flash chromatography (hexane/ethyl acetate 19:1, 9:1, 4:1) to give compound **9b** (950 mg, 72% yield) as a mixture of diastereomers (60:40) that could not be separated by recrystallization. **9b**: Solid; m.p. 128-130 °C; IR (KBr) ν: 3400, 3300, 3050, 2940, 2920, 2880, 2210, 1690, 1640, 1610, 1520, 1460, 1440, 1390, 1340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) [major (C-4 *S*) and minor (C-4 *R*) diastereomers] δ: 7.77-7.15 (m, 9H, aromatic), 6.41 (br s, 2H, NH_2), 5.20 (s, 1H, H-4 major), 5.16 (s, 1H, H-4 minor), 4.62 (dt, 1H, $J_{ax,ax}$=10.8 Hz, $J_{ax,eq}$=4.5 Hz, H-1'), 4.56 (dt, 1H, $J_{ax,ax}$=10.8 Hz, $J_{ax,eq}$=4.5 Hz, H-1'), 2.02-0.80 (several m, 9H, H-2', 2H-3', 2H-4', H-5', 2H-6', H-7'), 0.93, 0.90, 0.77, 0.70 (d, J=6.9 Hz, 3 CH_3 major and minor); ^{13}C NMR (75 MHz, $CDCl_3$) [major (C-4 *S*) diastereomer] δ: 167.82 (COO), 158.55 (C-2), 157.26 (C-6), 141.35-127.20 (aromatic), 117.09 (CN), 91.81 (C-5), 76.81 (C-3), 73.35 (C-1'), 46.79 (C-2'), 41.28 (C-6'), 36.47 (C-4), 34.12 (C-4'), 31.44 (C-5'), 24.69 (C-7'), 22.50 (C-3'), 21.91 (CH_3), 21.08 (CH_3), 15.11 (CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) [minor (C-4 *R*) diastereomer] δ: 167.82 (COO), 158.25 (C-2), 157.30 (C-6), 141.41-127.07 (aromatic), 117.16 (CN), 91.55 (C-5), 76.81 (C-3), 73.65 (C-1'), 46.66 (C-2'), 40.13 (C-6'), 36.85 (C-4), 34.12 (C-4'), 31.09 (C-5'), 26.25 (C-7'), 23.36 (C-3'), 21.73 (CH_3), 20.70 (CH_3), 16.29 (CH_3); MS (70 eV) *m/z*: 490(M^+,14), 379(9), 352(16), 309(23), 307(59), 241 (73), 232(34), 139(15), 138(45), 105(100), 95(51), 83(56), 77(87); Anal. Calcd. for $C_{29}H_{31}ClN_2O_3$: C, 70.93; H, 6.36; N, 5.70; Cl, 7.23. Found: C, 70.78; H, 6.52; N, 5.54; Cl, 7.59.

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