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Development of Methods for the Synthesis of Chiral, Highly Functionalized 2-Amino-4-Aryl-4*H*-Pyrans

José L. Marco,[*a] Nazario Martín,[*b] Angeles Martínez-Grau,[b] Carlos Seoane,[*b] Armando Albert[c] and Félix H. Cano[†c]

[a] Instituto de Química Orgánica General (CSIC), Juan de la Cierva 3, 28006-Madrid, Spain.
[b] Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain.
[c] U.E.I. Cristalografía, Instituto de Química Física "Rocasolano" (CSIC), Serrano 119, 28006-Madrid, Spain.

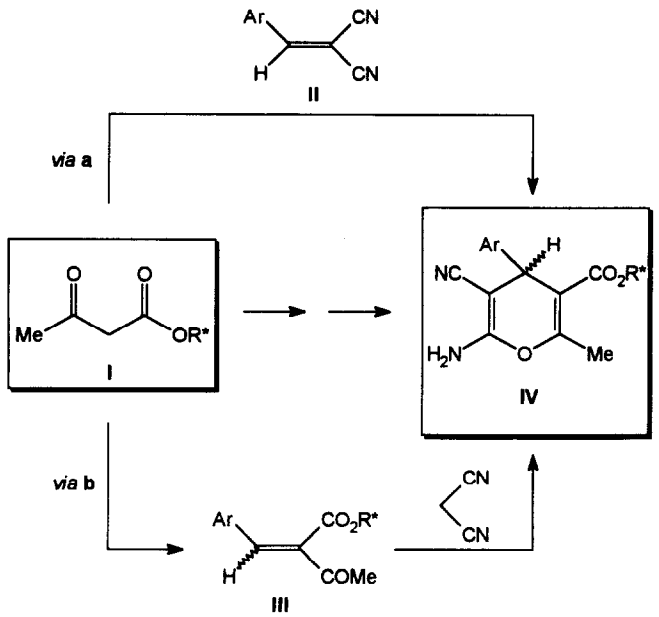
Abstract: The development of new methods for the asymmetric synthesis of highly functionalized 2-amino-4-aryl-4*H*-pyrans is described. Two alternative synthetic routes: the 1,4-conjugate addition of chiral ß-ketoesters **3** or the *N*-acetoacetyl sultam **11** to arylidenemalononitriles **6**, and the Michael addition of malononitrile to enantiomerically pure α-acetylcinnamates **5**, have been designed. Depending upon the chiral auxiliary, the resulting 4*H*-pyrans were obtained in low [(-)-menthol, (-)-borneol, (-)-ethyl lactate] to good (Oppolzer's sultam) diastereomeric excesses. The absolute configuration at the new stereocenter in the minor isomer of compound **12a** was determined as *S* by X-ray diffraction analysis. Reductive cleavage of 4*H*-pyrans **12** with lithium aluminiun hydride yielded the enantiomerically pure or enriched alcohols **14**.

INTRODUCTION

The chemistry of 2-amino-4*H*-pyrans has been a permanent area of interest in our laboratory; during the last years some of us have developed new and efficient strategies for the synthesis of polyfunctionalized 2-amino-4-substituted-4*H*-pyrans.[1] An obvious issue in this subject is the obtention of enantiomerically pure compounds of this type. To this end, very recently we have reported the asymmetric Michael addition[2] of malononitrile to chiral α-acyl,ß-alkylacrylates; the intermediate δ-oxonitriles cleanly cyclized leading to the homochiral 2-amino-4-alkyl-4*H*-pyrans.[3] Continuing our studies in this area we have now focussed our attention into the preparation of the analogous chiral 2-amino-4-aryl-4*H*-pyrans.[4] These compounds are isosteres of 1,4-dihydropyridines[5] with potential pharmacological interest.

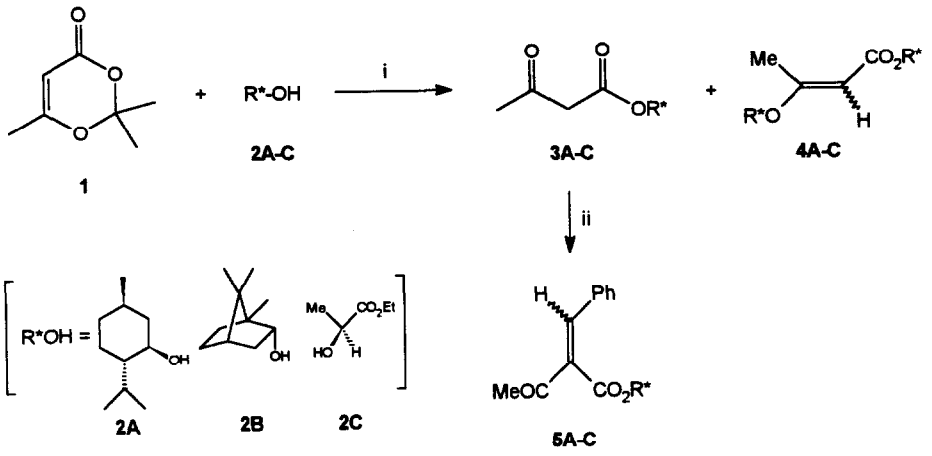
RESULTS AND DISCUSSION

In the present approach, our usual methodology for 2-amino-4*H*-pyran synthesis has been followed.[1] The critical ß-ketoesters **I** (Scheme 1) have been prepared in enantiomerically pure form using standard manipulation and easily available chiral auxiliaries (see below). The key Michael addition has been performed following two alternative routes. In the first *via* **a**, the chiral ß-ketoesters (Michael donors) **I** have been reacted with the corresponding arylidenemalononitriles **II** (Scheme 1). In the *via* **b** malononitrile was added to the chirally modified α-acetylcinnamates **III** (Michael acceptors). By using this type of complementary donor-acceptor (chiral-achiral) combinations the desired target molecules **IV** have been prepared in good yield and from low to good diastereomeric excesses. To our knowledge the asymmetric Michael addition of chiral ß-dicarbonyl compounds to highly deactivated acceptors, as shown in Scheme 1, has not been previously reported.[6]



Scheme 1

Reaction of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **1** with (1*R*,2*S*,5*R*)-(-)-menthol (**2A**), [(1*S*)-endo]-(-)-borneol (**2B**) and ethyl (*S*)-(-)-lactate (**2C**) following the standard method,[7] gave minor products **4A-C** and the expected, known ß-ketoesters **3A**[8], **3B**[9] and **3C**[10] (Scheme 2). Compounds **4A-C** are the normal esterification plus *O*-alkylation reaction products and have been detected in low yield; they have been obtained as single isomers whose stereochemistry at the double bond has not been established.



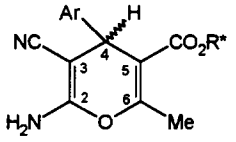
Reagents. i: xylene, 150°C; ii: PhCHO, toluene, piperidine, reflux.

Scheme 2

The Knoevenagel type reaction of compounds **3A-C** with benzaldehyde in mild basic conditions gave the new and expected products **5A-C** (Scheme 2) in good yield. Substrates **5A-C** have been obtained as a mixture of *Z*/*E* isomers in 85:15, 67:33 and 70:30 ratios, respectively. These values have been determined by ^{1}H NMR analysis of the crude reaction mixtures integrating the signals of the vinylic protons. After flash chromatography,[11] pure (*Z*)-**5A**, (*Z*)-**5B**, (*E*)-**5B** and **5C**, as a mixture of isomers (*Z*/*E* : 75/25), were obtained and submitted to further reaction (see below). The assignment as *Z* to the major isomer in this reaction follows from the analysis of the chemical shifts of the vinylic protons in the ^{1}H NMR spectra of compounds **5** and comparison with those reported in literature[12a] for related compounds. In accordance with this, in the ^{1}H NMR spectra of compounds (*Z*)-**5** the signals of the vinylic proton [*HC*=C (δ): **5A** (s, 7.54), **5B** (s, 7.57), **5C** (s, 7.67)] appear more shielded than in the case of the (*E*)-isomers [*HC*=C (δ): **5A** (s, 7.65), **5B** (s, 7.66), **5C** (s, 7.73)]. In order to confirm the assignment we analyzed the coupling constants in the ^{13}C NMR spectra of major **5A** and **5B**. As expected,[12b] they showed a large ^{3}J value (**5A**: 12.5 Hz, **5B**: 12.4 Hz) between the ester carbonyl [δ (ppm): 167.41 (**5A**), 168.11 (**5B**)] and the vinylic proton and a small ^{3}J value (**5A**: 6.4 Hz, **5B**: 6.1 Hz) between the keto carbonyl [δ (ppm): 194.59 (**5A**), 194.33 (**5B**)] and the vinylic proton.

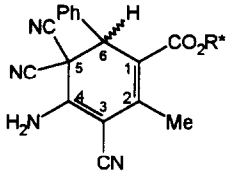
With compounds **3**/**5** on hand, the asymmetric Michael reaction was studied. Using *via* **a** (see Scheme 1) as methodological path, compounds **3A-C** were treated with benzylidenemalononitrile (**6a**) in the usual,[1] mild basic conditions. After flash chromatography[11] compounds **7A-C** (Figure 1) were obtained in an excellent yield (Table 1), but low and constant diastereomeric excesses [10%; determined in the crude

reaction mixtures by ^{1}H NMR analysis integrating the signals for C(6)H_3]. Unfortunately, after chromatography and recrystallization we could not isolate these isomers in pure or improved diastereomeric ratios. The spectroscopic and analytical data were as expected for these structures. In the ^{1}H NMR spectra, C(6)H_3 appeared at 2.43 ppm (d, J = 1.2 Hz) and at 2.34 ppm (d, J = 1.2 Hz), in the major and minor isomers **7A**, respectively. On the contrary, in the ^{1}H NMR spectra of the isomers **7B,C**, C(6)H_3 signals appeared more shielded for the major isomers than for the minor ones. The absolute configuration at C-4 in the major isomer could not be inequivocally determined in any case. We have tentatively assigned it as *R* in **7B** and **7C** by comparison of the chemical shifts for C(6)H_3 and H-4 with the corresponding for **12a** (see below).



7A-C (Ar = C_6H_5)

9A-C (Ar = *m*-$NO_2C_6H_4$)



8A-B

Figure 1

Table 1. Synthesis of compounds **7**, **8**, and **9**.

via	R*OH	**7**		**8**		**9**	
		Yield[1] (%)	d.e.[2]	Yield[1] (%)	d.e.[2]	Yield[1] (%)	d.e.[2]
a	A	93	10	-	-	91	10
	B	94	10	-	-	94	10
	C	93	10	-	-	73	10
b	A	52	10	19	10	-	-
	B	59	10	11	10	-	-
	C	85	10	-	-	-	-

[1] After chromatography. [2] Determined by ^{1}H NMR (300 MHz) in the crude reaction mixtures.

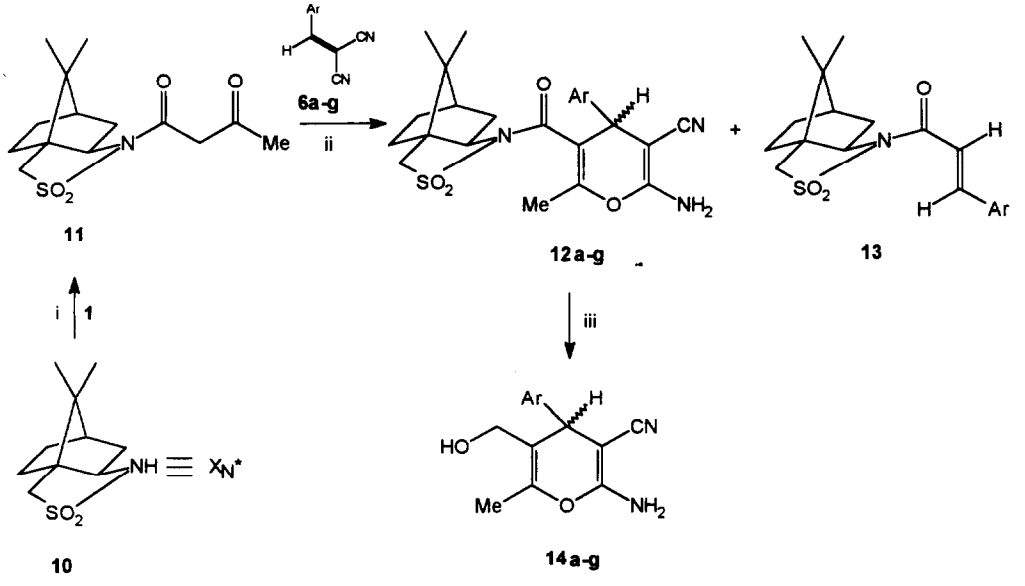
In the alternative *via* **b** (Scheme 1) and starting from compounds (*Z*)-**5A**, (*Z*)-**5B** and **5C** (*Z*/*E*, 75:25) the same, inseparable mixture of isomers **7A-C** (Figure 1) was obtained (Table 1), the major isomer being always the same previously obtained following the *via* **a**. In this process products **8A,B** (Figure 1) have been isolated and fully characterized. These compounds appear as a mixture of isomers at C-6 in low diastereomeric excess (10%) and chemical yield (see **Experimental Part**); these isomers could not be

separated and the absolute configuration at the new stereocenter in the major isomer could not be determined. Compounds **8A-B** showed obvious similar ^{1}H NMR data to those of **7A,B** [(**8A**): H-6: 4.70, d, J=1.2 Hz; (**8B**) H-6: 4.71, d, J=0.9 Hz], but the mass spectrum along with the analytical data strongly support these structures. The formation of this type of products, in similar experimental conditions, has also been detected, analyzed and commented in a previous communication,[1b] and will not be discussed here. It is worth noting that no by-product of type **8** was detected in the addition of malononitrile to **5C**.

When compound (*E*)-**5B** was used as starting material, the mixture of isomers **7B** was obtained in the same diastereomeric excess (see Table 1), but in an inverted ratio compared with (*Z*)-**5B**.

It is interesting to point out that independently of the stereochemistry of the double bond in compounds **5** or the chiral auxiliary used and the chosen *via* (**a** or **b**), the same and low diastereomeric excesses have been observed.

In an effort in order to expand this strategy to other substrates, the reaction of compounds **3A-C** with *m*-nitrobenzylidenemalononitrile (**6b**) was studied. This process gave the corresponding products **9A-C** (Figure 1) in high yield and low, identical diastereomeric excess (10%; Table 1). As for products **7A-C**, we were unable to separate the major isomers. Thus, the absolute configuration at the new stereocenter has not been directly determined. After inspection of the spectroscopic data, the major isomers in compounds **9A-C** show the same absolute configuration at C-4. We have established it as *R* by comparison with major isomers of compounds **12a,b** (see below).



Reagents. i: toluene, 130°C; ii: dry toluene, piperidine, r.t.; iii: $LiAlH_4$, THF/ether, 0° C.

Scheme 3

Table 2. Synthesis of the 2-Amino-4-aryl-4*H*-pyrans **12** and **14**.

entry	Ar	12		14	
		Yield[1] (%)	d.e.[2] (d.e.)[3]	Yield[1] (%)	e.e.
a	C_6H_5	65	60 (>99)	73	>99
b	*m*-NO_2-C_6H_4	85	70	40	70
c	*o*-CH_3-C_6H_4	62	60	72	60
d	*p*-CH_3-C_6H_4	42	70	59	70
e	*p*-Br-C_6H_4	91	60	41	60
f	*p*-Cl-C_6H_4	64	70 (>99)	42	>99
g	*p*-CN-C_6H_4	77	20	60	20

[1] After chromatography. [2] Determined by ^{1}H NMR (300 MHz) on the crude reaction mixtures. [3] After recrystallization.

The low asymmetric induction observed in the manipulation of compounds **3A-C** (*via* **a** or **b**) coupled to the unexpected resistence of products **7A-C** to be reduced to yield the corresponding alcohol and the recovered chiral auxiliary, moved us to explore a new, essentially different chiral reagent.

In fact, Oppolzer's sultam **10**[13] has (Scheme 3) perfectly fullfilled our expectations. Following the same procedure,[7] the desired key intermediate **11** was prepared in multigram quantities and good yield. At this point, *via* **b** as shown above, could not be developed as we were unable to prepare the Knoevenagel product by condensation of compound **11** with benzaldehyde. Then, alternatively we have submitted product **11** to reaction with a series of arylidenemalononitriles (**6a-g**). After extensive experimentation,[4] the usual (see **Experimental Part**) conditions were successfully employed. After flash chromatography[11] cinnamates **13** (traces) and the pyrans **12a-g** were isolated and separated. From the results shown in Table 2 we conclude that we have obtained consistent and good values for the d.e.,s (60-70 %) in the asymmetric addition of our N-acetoacetyl sultam **11** to the Michael acceptors **6a-f**; in entry **g** (Table 2), surprinsingly the d.e. drops to 20%. These values are also independent of the nature and position of the substituent attached to the phenyl ring in compound **6**. In the ^{1}H NMR spectra of these diastereomeric mixtures, major and minor isomers **12** showed clearly resolved signals for H-4 at 4.7-4.6 ppm and 4.3-4.2 ppm, respectively. Unfortunately, we were unable to separate these isomers by flash chromatography;[11] only in cases **12a** and **12f** (see Table 2) we could obtain pure major and minor isomers by recrystallization. After careful analysis of the ^{1}H NMR spectra (see above) of diastereomers **12**, it is clear that in all these cases the major isomer has the same absolute configuration at the new stereocenter (C-4). This stereochemistry has been established as *R* by X-Ray diffraction analysis of minor **12a**-(*S*) (Figure 2) (see **Experimental Part**).

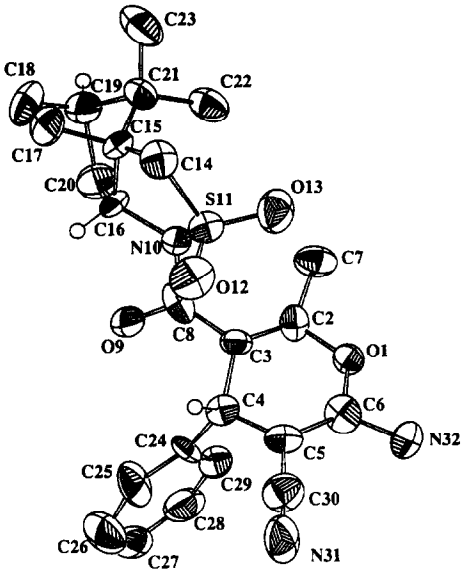


Figure 2. Molecular structure of minor **12a** (C-4 *S*) showing the atomic numbering.

Basic hydrolysis conditions or titanium catalyzed transesterification[14] gave complex reaction mixtures, which were not further investigated. Finally, the pure major isomers **12a,f** and the diastereomeric mixtures **12b-e**, when treated with lithium aluminium hydride,[14] gave the recovered sultam **10** [75-95% yield; $[\alpha]_D^{25}$= -31.18° (*c* 1.08, $CHCl_3$); $[\alpha]_D^{25}$ (lit[13b]) = -31.3° (*c* 0.69, $CHCl_3$)] and the enantiomerically pure or enriched alcohols (**14a,f** or **14b-e** respectively). Careful analysis of these compounds with Eu(hfc)$_3$ showed coherent e.e. values (see Table 2), showing that no racemization had ocurred in the last step.

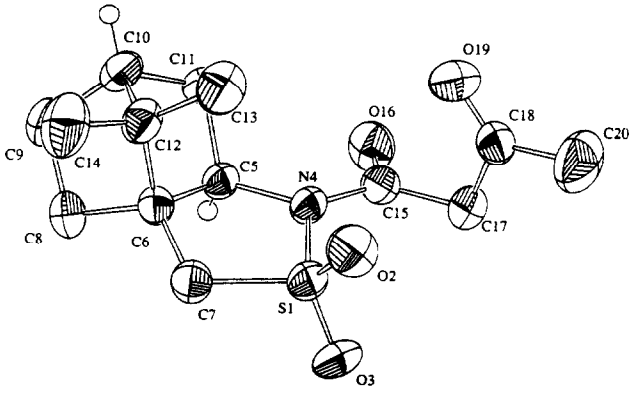


Figure 3. Molecular structure of compound **11**.

The formation of major **12** (C-4*R*) isomers during the present Michael addition has been reported in the preliminary communication.[4] We had assumed that the *N*-acylsultam reacts in a conformation where the carbonyl is *anti* to the SO_2 group[15] [also confirmed by X-Ray analysis of compound **11** (Figure 3, see **Experimental Part**)] and *s-cis* to the Cα,Cß bond due to a presumed internal chelate between the piperidinium cation and the 1,3-dicarbonyl group. The face differentiation is then dictated by the Michael addition to the arylidenemalononitrile from the less hindered bottom face. This particular behaviour has also been observed during the 1,4-hydride addition to enoylsultams.[16] However, very recently Kim and coworkers[17] have concluded that the nitrile oxide cycloadditions with Oppolzer's chiral sultam cannot be explained in terms of conventional face shielding by sterically bulky groups. They remark that in this type of cycloaddition the face discrimination originates from Coulombic interactions (repulsion) between the dipolar oxygen and the sultam oxygens. In our present case, similar Coulombic interactions could also be operating. Then, in view of this, we propose that the incoming nucleophile would be forced to attack from the top face as shown in Figure 4.

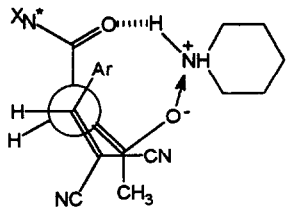


Figure 4

The results reported here add to the large panoply of asymmetric syntheses with camphor sultam derivatives and give a clear picture of the power of this chiral auxiliary in order to induce good selectivity in Michael additions. Compound **11** is thus an efficient acetoacetyl chiral equivalent[18] of potential interest in asymmetric synthesis. In addition, with these results, we have improved, in yields and diastereoselectivity, our former experiments[3] in the asymmetric synthesis of multiply functionalized 2-amino-4*H*-pyrans.

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EXPERIMENTAL

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 acid spray, with a solution of ammonium molybdate (VI) tetrahydrate (12.5 g) and cerium sulfate hydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL) or with 1% aqueous potassium permanganate solution. Anhydrous $MgSO_4$ was used to dry the organic solutions during workups, and the removal of the solvents was done under vacuum with a rotavapor. Flash column chromatography[11] was performed using Kiesselgel 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 internal standard and $CDCl_3$ or CD_3COCD_3 as solvents.

General Procedure for Acetoacetylation[7]: A solution of alcohol **2A-C** (1 equiv.) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **1** (1 equiv.) in xylene (3 mL xylene/5 mmol dioxinone) was inmersed in an oil bath previously heated to 150°C, and the solution was vigorously stirred. The evolution of acetone became apparent in several minutes. After 90 min the reaction was complete. The solvent was evaporated and the residue submitted to flash chromatography[11] (hexane/ethyl acetate 19:1, 9:1 and 4:1) to give in order of elution the compounds **4A-B** (the corresponding compound **4C** was detected by TLC, but not isolated) and **3A-C**. **3B**: Yield 82%; liquid; $[\alpha]_D^{25}$= - 37.06 ° (*c* 1.3, $CHCl_3$); IR (KBr) ν : 2960, 2880, 1745, 1720, 1650, 1470, 1450, 1410, 1360, 1320, 1240, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 4.94 (ddd, 1H, *J*=9.9, 3.6 and 2.1 Hz, H-2'), 3.46 (s, 2H, $COCH_2COO$), 2.36 (m, 1H, H-4'), 2.27 (s, 3H, CH_3CO), 1.94-1.65 (m, 3H), 1.34-1.16 (m, 2H), 0.99 (dd, 1H, *J*= 13.8 and 3.6 Hz), 0.89 (s, 3H, CH_3), 0.86 (s, 3H, CH_3), 0.83 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.54 (CO), 167.27 (COO), 81.03 (C-2'), 50.27 ($COOCH_2CO$), 48.68, 47.71 (C-1'and C-7'), 44.63 (C-4'), 36.43 (CH_2), 30.00 (CH_3CO), 27.81 (CH_2), 26.86 (CH_2), 19.51 (CH_3), 18.65 (CH_3), 13.31 (CH_3); MS (70 eV) *m/z*: 238 (M^+, 2), 154 (7), 137 (72), 121 (45), 108 (23), 95 (100), 93 (42), 85 (31), 69 (18), 55 (16), 43 (65); Anal. Calcd. for $C_{14}H_{22}O_5$: C, 70.65; H, 9.32. Found: C, 70.35; H, 9.03. **3C**: Yield 80%; liquid; $[\alpha]_D^{25}$= -29.2° (*c* 1.0, $CHCl_3$); IR (film) ν : 2990, 2940, 1750, 1720, 1660, 1630, 1450, 1410, 1370, 1210, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 5.07 (q, 1H, *J*=7.2 Hz, $CHCH_3$), 4.16 (q, 2H, *J*=7.2 Hz, $COOCH_2CH_3$), 3.48 (s, 2H, $COCH_2COO$), 2.27 (s, 3H, CH_3CO), 1.46 (d, 3H, *J*=7.2 Hz, CH_3CH), 1.24 (t, 3H, *J*=7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) ν: 199.89 (CO), 170.07 ($COOCH_2CH_3$), 166.26 (COO), 69.26 ($CHCH_3$), 61.31 (CH_2CH_3), 49.55 ($COCH_2COO$), 29.75 (CH_3CO), 16.62 (CH_3CH), 13.84 (CH_2CH_3); MS (70 eV) *m/z*: 202 (M^+, 12), 160 (24), 157 (10), 129 (20), 85 (100), 73 (6), 43 (50); Anal. Calcd. for $C_9H_{14}O_5$: C, 53.45; H, 6.97. Found: C, 52.98; H, 6.96. **4A**: Yield 4%; oil; $[\alpha]_D^{25}$= -129.7° (*c* 0.7, $CHCl_3$); IR (KBr) ν : 3020, 2970, 2920, 2840, 1695, 1610, 1450, 1370, 1280, 1140, 1040, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 4.98 (s, 1H, HC=C), 4.70 (dt, 1H, *J*=4.5 and 10.8 Hz, H-1), 3.91 (dt, 1H, *J*=4.2 and 10.5 Hz, H-1'), 2.27 (s, 3H, CH_3C=C), 2.2-0.8 (several m, 18H, H-2, H-2', 2H-3, 2H-3', 2H-4, 2H-4', H-5, H-5', 2H-6, 2H-6', H-7, H-7'), 0.93-0.88 (several d, 12H, *J*=6.9 Hz, 4 CH_3), 0.77 (d, 3H, *J*=6.9 Hz, CH_3), 0.74 (d, 3H, *J*=6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.21, 167.92 (COO and CH_3-*C*=C), 90.67 (C=*C*H), 76.92 (C-1'), 72.52 (C-1), 47.47, 47.07 (C-2, C-2'), 41.28, 38.95 (C-6, C-6'), 34.26, 34.22 (C-4, C-4'), 31.33, 31.09 (C-5, C-5'), 26.09, 26.01 (C-7, C-7'), 23.51, 23.37 (C-3, C-3'), 21.96, 21.90 (C-10, C-10'), 20.73, 20.53 (C-9, C-9'), 19.49 (CH_3-C=C), 16.57, 16.26 (C-8, C-8'); MS (70 eV) *m/z*: 319 (2), 239 (1), 223 (2), 183 (4), 168 (5), 139 (23), 138 (31), 97 (16), 95 (31), 83 (100), 69 (33), 55 (49); Anal. Calcd. for $C_{24}H_{42}O_3$: C, 76.14; H, 11.18. Found: C, 76.12; H, 11.31. **4B:** Yield 7%; solid; m.p. 90-93 °C; $[\alpha]_D^{25}$= -109.2° (*c* 1.2, $CHCl_3$); IR (KBr) ν : 2960, 2880, 1715, 1640, 1620, 1480, 1450, 1390, 1280, 1140, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 4.90 (ddd, 1H, *J*=9.9, 3.3 and 2.1 Hz, H-2), 4.85 (s, 1H, HC=C), 4.14 (ddd, 1H, *J*=9.3, 3.0 and 1.8 Hz, H-2'), 2.35 (m, 2H), 2.29 (s, 3H, CH_3C=C), 2.12-1.92 (m, 2H), 1.80-1.64 (m, 4H), 1.36 (m, 4H), 1.05 (m, 2H), 0.92 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.87 (s, 6H, 2 CH_3), 0.85 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.61, 168.65 (COO and CH_3-*C*=C), 92.15 (C=*C*H), 82.91, 78.57 (C-2, C-2'), 49.13, 48.54, 47.62, 47.35 (C-1, C-1', C-7, C-7'), 44.83, 44.78 (C-4, C-4'), 36.81, 36.41, 27.97, 27.66, 27.14, 26.72 (C-3, C-3', C-5, C-5',

C-6, C-6'), 19.65, 19.52 (2 CH_3), 19.32 (CH_3-C=C), 18.87, 18.74 (2 CH_3), 13.49 (2 CH_3); MS (70 eV) *m/z*: 374 (M^+, 24), 343 (24), 278 (40), 265 (17), 221 (14), 137 (100), 95 (32), 81 (85), 69 (19), 67 (19), 55 (19), 43 (21); Anal. Calcd. for $C_{24}H_{38}O_3$: C, 76.96; H, 10.22. Found: C, 76.81; H, 10.53.

General Procedure for Knoevenagel Reaction: Compound **3A-C** (1 equiv.) and benzaldehyde (1 equiv.) were dissolved in toluene (15 mL) and five drops of piperidine were added. The reaction mixture was heated at reflux in a Dean-Stark apparatus for 45-90 min and then, the solvent was evaporated.

(-)-(1*R*,2*S*,5*R*)-Menthyl 3-oxo-2-phenylmethylene butanoate (5A): Compound **3A** (0.97 g, 4.04 mmol) and benzaldehyde (0.428 g, 4.04 mmol, 1 equiv.) were submitted to reaction for 60 min following the general procedure. Toluene was evaporated obtaining a solid that was purified washing with cold hexane. In order to separate both isomers, the solid obtained (1.168 g, 88 % yield) was dissolved in CH_2Cl_2 and submitted to flash chromatography[11] (hexane, hexane/ethyl acetate 9:1) isolating a mixture 60:40 of *Z*/*E* isomers (0.375 g, 28 % yield) and pure major (*Z*)-**5A** isomer (0.760 g, 58 % yield): Solid; m.p. 123-124°C; $[\alpha]_D^{25}$= -32.8° (*c* 1.0, $CHCl_3$); IR (KBr) ν : 3060, 2960, 2920, 2860, 1715, 1660, 1620, 1600, 1575, 1450, 1400, 1230, 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 7.54 (s, 1H, HC=C), 7.52-7.36 (m, 5H, aromatic), 4.89 (dt, 1H, $J_{ax,ax}$=10.8 Hz, $J_{ax,eq}$=4.5 Hz, H-1'), 2.42 (s, 3H, CH_3CO), 2.25-0.70 (several m, 9H, H-2', 2H-3', 2H-4', H-5', 2H-6', H-7'), 0.92 (d, 3H, *J*=6.9 Hz, CH_3), 0.79 (d, 3H, *J*=6.9 Hz, CH_3), 0.76 (d, 3H, *J*=6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.59 (CO), 167.41 (COO), 140.36 (PhCH=C), 135.19 (PhCH=*C*), 132.80, 130.39, 129.38, 128.58 (aromatic), 75.93 (C-1'), 46.63 (C-2'), 39.97 (C-6'), 33.92 (C-4'), 31.36 (C-5'), 26.32 (C-7'), 25.24 (CH_3CO), 22.76 (C-3'), 21.86 (CH_3), 20.61 (CH_3), 15.65 (CH_3); Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.42; H, 8.63. (*E*)-**5A**: ^1H NMR (300 MHz, $CDCl_3$), δ: 7.65 (s, 1H, HC=C), 7.52-7.36 (m, 5H, aromatic), 4.85 (dt, 1H, $J_{ax,ax}$=10.8 Hz, $J_{ax,eq}$=4.5 Hz, H-1'), 2.35 (s, 3H, CH_3CO), 2.25-0.70 (several m, 9H, H-2', 2H-3', 2H-4', H-5', 2H-6', H-7'), 0.90 (d, 3H, *J*=6.9 Hz, CH_3), 0.79 (d, 3H, *J*=6.9 Hz, CH_3), 0.76 (d, 3H, *J*=6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 202.97 (CO), 163.91 (COO), 140.06 (PhCH=C), 134.57 (PhCH=*C*), 130.98, 130.16, 129.56, 128.76 (aromatic), 75.63 (C-1'), 47.04 (C-2'), 40.73 (C-6'), 34.13 (C-4'), 31.36 (C-5'), 31.08 (CH_3CO), 26.30 (C-7'), 23.37 (C-3'), 21.88 (C-10'), 20.69 (C-9'), 16.23 (C-8').

(-)-(1*S*,2*R*,4*S*)-Bornyl 3-oxo-2-phenylmethylene butanoate (5B): Compound **3B** (1.0 g, 4.2 mmol) and benzaldehyde (0.445 g, 4.2 mmol, 1 equiv.) were submitted to reaction for 90 min following the general procedure. Toluene was evaporated and the residue was dissolved in CH_2Cl_2 and washed with brine. After drying and evaporation, the residue was purified by flash chromatography[11] (hexane/ethyl acetate 19:1, 9:1) isolating minor isomer (*E*)-**5B** (158 mg, 34% yield) and major isomer (*Z*)-**5B** (303 mg, 66% yield). Total yield: 82%. (*Z*)-**5B**: Solid; m.p. 60-64 °C; $[\alpha]_D^{25}$= -9.8° (*c* 0.8, $CHCl_3$); IR (film) ν : 3060, 2970, 2890, 1720, 1670, 1625, 1600, 1575, 1450, 1390, 1360, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 7.57 (s, 1H, HC=C), 7.48-7.36 (m, 5H, aromatic), 5.06 (ddd, 1H, *J*=9.9, 3.6 and 2.1 Hz, H-2'), 2.42 (s, 3H, CH_3CO), 2.41 (m, 1H, H-4'), 1.77-1.61 (m, 3H), 1.25-1.11 (m, 2H), 1.07 (dd, 1H, *J*=13.8 and 3.6 Hz), 0.92 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 0.78 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.33 (CO), 168.11 (COO), 140.69 (PhCH=C), 135.05 (PhCH=*C*), 133.10, 130.37, 129.35, 128.68 (aromatic), 81.79 (C-2'), 48.74, 47.77 (C-1' and C-7'), 44.75 (C-4'), 35.91 (CH_2), 27.75 (CH_2), 26.90 (CH_2), 26.63 (CH_3CO), 19.51 (CH_3), 18.75 (CH_3), 13.26 (CH_3); Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.26; H, 8.03. Found: C, 76.88; H, 7.99. (*E*)-**5B**: Solid; m.p. 74-77 °C; $[\alpha]_D^{25}$= - 55° (*c* 0.2, $CHCl_3$); IR (film) ν : 3060, 2960, 2880, 1720, 1690, 1620, 1575, 1450, 1390, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 7.66 (s, 1H, HC=C), 7.48-7.36 (m, 5H, aromatic), 5.02 (ddd, 1H, *J*=9.9, 3.6 and 2.1 Hz, H-2'), 2.43 (m, 1H, H-4'), 2.38 (s, 3H, CH_3CO), 1.92-1.63 (m, 3H), 1.41-1.20 (m, 2H), 1.07 (dd, 1H, *J*=13.8 and 3.6 Hz), 0.93 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.87 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 202.94 (CO), 164.57 (COO), 140.05 (PhCH=C), 134.42 (PhCH=*C*), 132.91, 130.22, 129.56, 128.79 (aromatic), 81.40 (C-2'), 48.96, 47.77 (C-1' and C-7'), 44.83 (C-4'), 36.73 (CH_2), 31.09 (CH_3CO), 27.91 (CH_2), 27.12 (CH_2), 19.57 (CH_3), 18.77 (CH_3), 13.47 (CH_3); Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.26; H, 8.03. Found: C, 77.01; H, 8.00.

3-Oxo-2-phenylmethylene butanoate of (*S*)-ethyl lactate (5C): Compound **3C** (1.0 g, 4.95 mmol)

and benzaldehyde (0.525 g, 4.95 mmol, 1 equiv.) were submitted to reaction for 45 min following the general procedure. Toluene was evaporated in vacuum. The residue was dissolved in CH_2Cl_2 and washed with brine. After drying and evaporation, the residue was submitted to flash chromatography[11] (hexane/ethyl acetate 9:1) separating 0.106 g of mixture 80:20 (*E*/*Z*) and 1.1 g of mixture 25:75 (*E*/*Z*). Total yield: 84%. (*Z*)-**5C**: Oil; $[\alpha]_D^{25}$= -56.7° (*c* 1.02, $CHCl_3$); IR (film) ν : 3020, 2960, 2910, 1735, 1700, 1670, 1620, 1600, 1575, 1450, 1370, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 7.67 (s, 1H, HC=C), 7.57-7.38 (m, 5H, aromatic), 5.28 (q, 1H, *J*=7.2 Hz, C*H*CH_3), 4.24 (q, 2H, *J*=7.2 Hz, $COOCH_2CH_3$), 2.47 (s, 3H, CH_3CO), 1.46 (d, 3H, *J*=7.2 Hz, CH_3CH), 1.29 (t, 3H, *J*=7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) ν: 194.02 (CO), 170.01 ($COOCH_2CH_3$), 166.99 (COO), 142.32 (PhCH=C), 133.08, 132.64 (PhCH=*C* and C aromatic), 130.69, 129.74, 128.64 (aromatic), 69.64 ($CHCH_3$), 61.42 (CH_2CH_3), 26.98 (CH_3CO), 16.64 (CH_3CH), 13.96 (CH_2CH_3); MS (70 eV) *m/z*: 290 (M^+, 43), 289 (32), 203 (7), 173 (47), 144 (10), 131 (63), 102 (32), 85 (15), 77 (13), 43 (100); Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.24. Found: C, 65.83; H, 6.22. (*E*)-**5C**: ^1H NMR (300 MHz, $CDCl_3$), δ: 7.73 (s, 1H, HC=C), 7.63-7.35 (m, 5H, aromatic), 5.24 (q, 1H, *J*=7.2 Hz, C*H*CH_3), 4.24 (q, 2H, *J*=7.2 Hz, $COOCH_2CH_3$), 2.42 (s, 3H, CH_3CO), 1.56 (d, 3H, *J*=7.2 Hz, CH_3CH), 1.30 (t, 3H, *J*=7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) ν: 202.65 (CO), 170.23 ($COOCH_2CH_3$), 163.68 (COO), 141.57 (PhCH=C), 133.08, 132.64 (HC=*C*-COO and C aromatic), 130.51, 129.71, 128.79 (aromatic), 69.39 ($CHCH_3$), 61.42 (CH_2CH_3), 31.07 (CH_3CO), 16.74 (CH_3CH), 13.96 (CH_2CH_3).

2-Amino-3-cyano-5-[(-)-(1*R'*,2*S'*,5*R'*)-menthyloxycarbonyl]-6-methyl-4-phenyl-4*H*-pyran (7A):
Method A: To a solution of acetoacetate **3A** (500 mg, 2.1 mmol) in dry ether (15 mL), benzylidene-malononitrile (321 mg, 2.1 mmol, 1 equiv.) and three drops of piperidine were added. The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue submitted to flash chromatography[11] (hexane/ethyl acetate 9:1, 4:1 and 7:3) to give **7A** (762 mg, 93% yield) as a mixture of isomers (d.e. 10%) that we could not separate: Solid; m.p. 149-152 °C; IR (KBr) ν : 3480, 3320, 3210, 3180, 3060, 3020, 2950, 2920, 2860, 2210, 1715, 1680, 1650, 1600, 1450, 1410, 1380, 1260, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major and minor diastereomers) δ: 7.33-7.14 (m, 5H, aromatic), 4.59 (m, 1H, H-1'), 4.48 (s, 2H, NH_2 minor), 4.44 (s, 2H, NH_2 major), 4.42 (d, 1H, *J*=1.2 Hz, H-4), 2.43 (d, *J*=1.2 Hz, CH_3 major), 2.34 (d, *J*=1.2 Hz, CH_3 minor), 1.94-0.90 (several m, 9H, H-2', 2H-3', 2H-4', H-5', 2H-6', H-7'), 0.87, 0.83, 0.76, 0.62, 0.51, 0.36 (6 d, 9H, 3 CH_3 minor and major); ^{13}C NMR (75 MHz, $CDCl_3$) (major and minor diastereomers) δ: 165.41, 165.27 (COO), 157.54, 157.28, 157.14, 155.37 (C-2 and C-6), 143.76, 143.52, 128.47, 128.29, 127.47, 126.94, 126.87 (aromatic), 118.99, 118.94 (CN), 108.03, 107.29 (C-5), 74.53, 74.25 (C-1'), 62.22, 61.61 (C-3), 46.79, 46.59 (C-2'), 40.87, 39.92 (C-6'), 38.79, 38.35 (C-4), 33.90 (C-4'), 31.25, 31.04 (C-5'), 26.06, 24.58 (C-7'), 23.17, 22.33 (C-3'), 21.82, 21.72 (CH_3), 20.90, 20.56 (CH_3), 18.33, 18.08 (CH_3-C=C), 16.11, 15.00 (CH_3); MS (70 eV) *m/z*: 317 (M^+-77, 9), 256 (24), 255 (97), 211 (23), 179 (80), 139 (33), 138 (41), 97 (17), 95 (42), 83 (92), 77 (19), 69 (51), 55 (77), 43 (100); Anal. Calcd. for $C_{24}H_{30}N_2O_3$: C, 73.06; H, 7.66; N, 7.10. Found: C, 72.87; H, 7.51; N, 6.89.
Method B: To a solution of α-acetylcinnamate [(*Z*)-**5A**] (328 mg, 1.0 mmol) in dry ether (20 mL), malononitrile (79 mg, 1.2 mmol, 1.2 equiv.) and three drops of piperidine were added. The reaction mixture was stirred at room temperature for 10 hours. The solvent was evaporated and the residue dissolved in CH_2Cl_2. The solution was washed with brine, dried, concentrated and submitted to flash chromatography[11] (hexane/ethyl acetate, 9:1) to give in order of elution **8A** (85 mg, 19% yield) and **7A** (204 mg, 52% yield). **8A:** Solid; m.p. 93-97 °C; IR (KBr) ν : 3340, 3230, 2970, 2940, 2880, 2220, 1710, 1650, 1620, 1565, 1460, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major and minor diastereomers, δ: 7.50-7.18 (m, 5H, aromatic), 5.87 (br s, 2H, NH_2), 4.70 (d, 1H, *J*=1.2 Hz, C*H*Ph), 4.62 (m, 1H, H-1'), 2.63 (s, 3H, CH_3 minor), 2.54 (s, 3H, CH_3 major), 2.40-1.00 (several m, 9H, H-2', 2H-3', 2H-4', H-5', 2H-6', H-7'), 0.90, 0.85, 0.80, 0.65, 0.53, 0.37 (6 d, 9H, 3 CH_3 minor and major); ^{13}C NMR (75 MHz, CD_3COCD_3) major and minor diastereomers, δ: 165.09, 164.78 (COO), 148.57, 148.37, 131.28, 131.17 [$(CH_3)C$=C and $(NH_2)C$=C], 134.32, 133.98, 130.32, 130.12, 130.04, 129.63, 129.58 (aromatic), 116.02 [(CO)*C*=C], 115.66, 114.92 (CN), 113.67, 113.56 (CN), 111.69 (CN), 83.77, 83.53 [(CN)*C*=C], 75.08, 74.60 (C-1'), 48.91, 48.48 (*C*HPh), 47.98, 47.75 (C-2'), 42.94, 42.81 [*C*$(CN)_2$], 41.77, 41.39 (C-6'), 34.95, 34.91 (C-4'), 32.15, 32.03 (C-5'), 27.17, 25.84 (C-7'), 24.15, 23.45 (C-3'), 22.34, 22.22 (CH_3),

21.23, 21.02 (CH_3), 19.08, 18.93 (CH_3-C=C), 16.70, 15.73 (CH_3); MS (70 eV) *m/z*: 442 (M^+, 2), 306 (16), 304 (7), 259 (71), 183 (7), 139 (20), 138 (42), 123 (20), 95 (56), 91 (14), 83 (100), 77 (20), 69 (68), 55 (74), 43 (42); Anal. Calcd. for $C_{27}H_{30}N_4O_2$: C, 73.28; H, 6.83; N, 12.66. Found: C, 73.21; H, 7.11; N, 12.40.

2-Amino-5-[(-)-(1*S'*,2*R'*,4*S'*)-bornyloxycarbonyl]-3-cyano-6-methyl-4-phenyl-4*H*-pyran (7B): **Method A:** To a solution of acetoacetate **3B** (300 mg, 1.26 mmol) in dry ether (15 mL), benzylidenemalononitrile (194 mg, 1.26 mmol, 1 equiv.) and two drops of piperidine were added. The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue submitted to flash chromatography[11] (hexane/ethyl acetate 9:1, 4:1) to give **7B** (464 mg, 94% yield) as a mixture of isomers at C-4 (d.e. 10%) that we could not separate: Solid; m.p. 165-168 °C; IR (KBr) ν : 3480, 3320, 3210, 3180, 3040, 2950, 2880, 2200, 1710, 1690, 1640, 1600, 1450, 1410, 1380, 1310, 1220, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major and minor diastereomers, δ: 7.37-7.18 (m, 5H, aromatic), 4.81, 4.71 (ddd, 1H, J=9.9, 3.6 and 2.1 Hz, H-2'), 4.49 (d, 1H, J=0.9 Hz, H-4 major), 4.48 (d, 1H, J=0.9 Hz, H-4 minor), 4.42 (br s, 2H, NH_2), 2.43 (d, J=0.9 Hz, CH_3 minor), 2.41 (d, J=0.9 Hz, CH_3 major), 2.29, 2.06 (m, 1H, H-4'), 1.78-1.48 (m, 3H), 1.30-1.17 (m, 2H), 0.90-0.80 (m, 1H), 0.82, 0.81, 0.80, 0.79, 0.77 (5 s, 9H, 3 CH_3 minor and major); ^{13}C NMR (75 MHz, $CDCl_3$) major and minor diastereomers, δ: 166.13, 166.10 (COO), 157.26, 157.18, 157.08, 156.90 (C-2 and C-6), 143.49, 143.41, 128.56, 128.54, 126.99, 126.93 (aromatic), 118.93 (CN), 107.39, 107.28 (C-5), 80.66, 80.38 (C-2'), 62.22, 62.04 (C-3), 48.40, 48.37, 47.62, 47.56 (C-1' and C-7'), 44.50, 44.42 (C-4'), 38.48 (C-4), 36.74, 35.82 (CH_2), 27.81, 27.43 (CH_2), 27.28, 26.94 (CH_2), 19.46, 19.42 (CH_3), 18.60, 18.55 (CH_3), 18.35, 18.19 (CH_3), 13.31, 12.69 (CH_3); MS (70 eV) *m/z*: 255 (51), 239 (16), 179 (64), 161 (9), 137 (10), 131 (37), 95 (63), 93 (46), 81 (61), 77 (52), 67 (100); Anal. Calcd. for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.44; H, 6.81; N, 7.20.

Method B: To a solution of α-acetylcinnamate [(*Z*)-**5B**] (480 mg, 1.47 mmol) in dry ether (20 mL), malononitrile (116 mg, 1.76 mmol, 1.2 equiv.) and three drops of piperidine were added. The reaction mixture was stirred at room temperature for 10 hours. The solvent was evaporated and the residue dissolved in CH_2Cl_2. The solution was washed with brine, dried, concentrated and submitted to flash chromatography[11] (hexane/ethyl acetate, 9:1) to give **8B** (73 mg, 11% yield) and **7B** (340 mg, 59% yield). **8B:** Solid; m.p. 194-197 °C; IR (KBr) ν : 3360, 3320, 3200, 2950, 2870, 2210, 1700, 1660, 1620, 1560, 1450, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major and minor diastereomers, δ: 7.50-7.20 (m, 5H, aromatic), 5.79 (br s, 2H, NH_2), 4.86, 4.81 (ddd, 1H, J=9.9, 3.6 and 2.1 Hz, H-2'), 4.71 (d, 1H, J=0.9 Hz, C*H*Ph), 2.62 (d, J=0.9 Hz, CH_3 minor), 2.61 (d, J=0.9 Hz, CH_3 major), 2.40-2.17 (m, 1H, H-4), 1.80-1.50 (m, 3H), 1.36-1.14 (m, 2H), 1.00-0.90 (m, 1H), 0.85, 0.84, 0.83, 0.80 (4 s, 9H, 3 CH_3 minor and major); ^{13}C NMR (75 MHz, $CDCl_3$) major and minor diastereomers, δ: 164.72, 164.68 (COO), 145.29, 145.25, 131.13, 131.01 [$(CH_3)C$=C and $(NH_2)C$=C], 142.28, 141.88, 129.73, 129.09, 129.04, 128.93, 129.84 (aromatic), 115.56, 115.37, 115.05 [(CO)*C*=C and CN], 111.67 (CN), 110.54 (CN), 84.77, 84.72 [(CN)*C*=C], 81.07 (C-2'), 48.67, 48.59, 48.46, 48.36, 47.66, 47.64 (CH, C-1', and C-7'), 44.63, 44.51 (C-4'), 42.11 [$C(CN)_2$], 36.73, 36.55 (CH_2), 27.90, 27.67 (CH_2), 27.47, 27.21 (CH_2), 19.51, 19.48 (CH_3), 19.00, 18.97 (CH_3-C=C), 18.65, 18.62 (CH_3), 13.47, 12.93 (CH_3); MS (70 eV) *m/z*: 440 (M^+,10), 304 (4), 287 (96), 259 (31), 153 (21), 137 (63), 136 (22), 109 (40), 95 (44), 81 (100), 77 (22), 69 (36), 55 (27), 43 (26); Anal. Calcd. for $C_{27}H_{28}N_4O_2$: C, 73.61; H, 6.41; N, 12.72. Found: C, 73.57; H, 6.52; N, 12.43.

2-Amino-3-cyano-6-methyl-5-[oxycarbonyl of (*S*)-ethyl lactate]-4-phenyl-4*H*-pyran (7C): **Method A:** To a solution of acetoacetate **3C** (300 mg, 1.48 mmol) in dry ether (15 mL), benzylidenemalononitrile (229 mg, 1.48 mmol, 1 equiv.) and two drops of piperidine were added. The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue submitted to flash chromatography[11] (hexane/ethyl acetate, 7:3) to give **7C** (447 mg, 93% yield) as a mixture of isomers at C-4 that we could not separate: Solid; m.p. 104-109 °C; IR (KBr) ν : 3410, 3330, 3270, 3220, 3070, 3030, 2990, 2940, 2200, 1740, 1700, 1675, 1645, 1605, 1450, 1410, 1360, 1260, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major and minor diastereomers, δ: 7.33-7.15 (m, 5H, aromatic), 4.97, 4.83 (q, 1H, J=7.2 Hz, C*H*CH_3), 4.60 (br s, 2H, NH_2), 4.49 (s, 1H, H-4 major), 4.47 (s, 1H, H-4 minor), 4.15, 4.04 (q, 2H,

$COOCH_2CH_3$), 2.40 (s, CH_3 minor), 2.38 (s, CH_3 mayor), 1.40, 1.26 (d, 3H, J=7.2 Hz, CH_3CH), 1.22, 1.13 (t, 3H, J=7.2 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) major and minor diastereomers, δ: 170.41, 170.20 ($COOCH_2CH_3$), 165.18, 164.94 (COO), 158.08, 157.41, 157.22, 155.15 (C-2 and C-6), 143.67, 143.30, 128.37, 127.35, 127.02 (aromatic), 118.72, 118.65 (CN), 107.31, 106.87 (C-5), 69.05, 68.67 ($CHCH_3$), 62.13, 61.93 (C-3), 61.21, 61.09 (CH_2), 38.54, 38.48 (C-4), 18.57, 18.32 (CH_3C=C), 16.65, 16.36 (CH_3CH), 13.86, 13.78 (CH_2CH_3); MS (70 eV) *m/z*: 356 (M^+, 2), 279 (40), 255 (65), 239 (25), 238 (23), 211 (17), 179 (8), 161 (63), 131 (25), 77 (25), 43 (100); Anal. Calcd. for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.65; N, 7.86. Found: C, 64.26; H, 5.60; N, 7.38.

Method B: To a solution of α-acetylcinnamate **5C** (*Z*/*E*, 75:25) (350 mg, 1.21 mmol) in dry ether (20 mL) malononitrile (96 mg, 1.45 mmol, 1.2 equiv.) and three drops of piperidine were added. The reaction mixture was stirred at room temperature 6 hours. The solvent was evaporated and the residue dissolved in CH_2Cl_2. The solution was washed with brine, dried, concentrated and submitted to flash chromatography[11] (hexane/EtOAc 4:1, 7:3) to give **7C** (334 mg, 85% yield).

2-Amino-3-cyano-5-[(-)-(1*R'*,2*S'*,5*R'*)-menthyloxycarbonyl]-6-methyl-4-(*m*-nitrophenyl)-4*H*-pyran (9A): To a solution of acetoacetate **3A** (600 mg, 2.5 mmol) in dry toluene (15 mL), *m*-nitrobenzylidene-malononitrile **6b** (497 mg, 2.5 mmol, 1 equiv.) and three drops of piperidine were added. The reaction mixture was stirred at room temperature for 1.5 h. The solvent was evaporated and the residue submitted to flash chromatography[11] (hexane/ethyl acetate 7:3) to give **9A** (1.004 g, 91% yield): Solid; m.p. 80-84 °C; IR (KBr) ν : 3450, 3340, 3200, 2950, 2920, 2860, 2200, 1710, 1675, 1640, 1600, 1530, 1450, 1350, 1260, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major and minor diastereomers, δ: 8.11 (m, 1H, aromatic), 8.05 (m, 1H, aromatic), 7.58 (m, 1H, aromatic), 7.50 (dt, 1H, J_o=7.8 Hz, J_p=1.8 Hz, H-5 aromatic), 4.73 (s, 2H, NH_2 major), 4.69 (s, 2H, NH_2 minor), 4.62 (m, 1H, H-1'), 4.57 (d, 1H, J=0.9 Hz, H-4 major), 4.54 (d, 1H, J=0.9 Hz, H-4 minor), 2.47 (d, J=0.9 Hz, CH_3 minor), 2.37 (d, J=0.9 Hz, CH_3 major), 1.94-0.90 (several m, 9H, H-2', 2H-3', 2H-4', H-5', 2H-6', H-7'), 0.88, 0.83, 0.77, 0.60, 0.50, 0.40 (6 d, J=6.9 Hz, 9H, 3 CH_3 minor and major); ^{13}C NMR (75 MHz, $CDCl_3$) major and minor diastereomers, δ: 164.78, 164.63 (COO), 158.67, 157.64, 157.44, 156.57 (C-2 and C-6), 148.34, 148.20 (C-1 aromatic), 146.30, 145.86 (C-3 aromatic), 134.03, 133.81 (C-6 aromatic), 129.47, 129.31 (C-5 aromatic), 122.61, 122.17, 122.04, 121.96 (C-2 and C-4 aromatic), 118.42, 118.31 (CN), 107.04, 106.32 (C-5), 74.89, 74.61 (C-1'), 60.97, 60.30 (C-3), 46.88, 46.63 (C-2'), 40.89, 40.30 (C-6'), 38.76, 38.47 (C-4), 33.81, 33.76 (C-4'), 31.22, 31.05 (C-5'), 26.19, 25.08 (C-7'), 23.09, 22.30 (C-3'), 21.78, 21.69 (C-10'), 20.70, 20.50 (C-9'), 18.61, 18.35 (CH_3-C=C), 16.01, 15.06 (C-8'). MS (70 eV) *m/z*: 439 (M^+, 4), 317 (9), 301 (21), 300 (90), 284 (37), 179 (76), 161 (11), 139 (18), 138 (54), 95 (73), 83 (74), 69 (36), 43 (100); Anal. Calcd. for $C_{24}H_{29}N_3O_5$: C, 65.59; H, 6.65; N, 9.56. Found: C, 65.78; H, 6.81; N, 9.42.

2-Amino-5-[(-)-(1*S'*,2*R'*,4*S'*)-bornyloxycarbonyl]-3-cyano-6-methyl-4-(*m*-nitrophenyl)-4*H*-pyran (9B): To a solution of acetoacetate **3B** (600 mg, 2.52 mmol) in dry toluene (15 mL), *m*-nitrobenzylidene-malononitrile **6b** (500 mg, 2.52 mmol, 1 equiv.) and three drops of piperidine were added. The reaction mixture was stirred at room temperature for 1.5 h. The solvent was evaporated and the residue submitted to flash chromatography[11] (hexane/ethyl acetate 7:3) to give **9B** (1.033 g, 94% yield): Solid; m.p. 92-96°C; IR (KBr) ν : 3450, 3330, 3180, 2950, 2870, 2200, 1710, 1670, 1630, 1600, 1530, 1470, 1450, 1350, 1260, 1060 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major and minor diastereomers, δ: 8.11 (m, 1H, aromatic), 8.05 (m, 1H, aromatic), 7.60 (m, 1H, aromatic), 7.50 (dt, 1H, J_o=7.8 Hz, J_p=3.0 Hz, H-5 aromatic), 4.84, 4.71 (ddd, 1H, J=9.9, 3.6 and 2.1 Hz, H-2'), 4.65 (br s, 2H, NH_2), 4.59 (d, 1H, J=0.9 Hz, H-4), 2.46 (d, J=0.9 Hz, CH_3 minor), 2.44 (d, J=0.9 Hz, CH_3 major), 2.29, 2.10 (m, 1H, H-4'), 1.80-1.50 (m, 3H), 1.33-1.08 (m, 2H), 0.85-0.75 (m, 1H), 0.81, 0.80, 0.79, 0.78, 0.75, 0.38 (6 s, 9H, 3 CH_3 minor and major); ^{13}C NMR (75 MHz, $CDCl_3$) major and minor diastereomers, δ: 165.53, (COO), 158.38, 158.01, 157.39, 157.37 (C-2 and C-6), 148.35 (C-1 aromatic), 145.86, 145.78 (C-3 aromatic), 133.53 (C-6 aromatic), 129.58 (C-5 aromatic), 122.26 (C-2 aromatic), 121.89 (C-4 aromatic), 118.35 (CN), 106.41, 106.34 (C-5), 81.21, 80.76 (C-2'), 60.99, 60.81 (C-3), 48.48, 48.35, 47.64, 47.61 (C-1' and C-7'), 44.38, 44.33 (C-4'), 38.51 (C-4), 36.77, 36.15 (CH_2), 27.81, 27.60 (CH_2), 27.28, 26.99 (CH_2), 19.44, 19.40 (CH_3), 18.67, 18.57 (CH_3), 18.51 (CH_3-C=C and CH_3), 13.31, 12.88 (CH_3); MS (70 eV) *m/z*: 437 (M^+,4), 315 (9), 301 (11), 300 (55), 284 (13), 179 (41), 153 (48), 137 (61), 136 (43), 95 (100), 81 (69), 67 (54),

43 (95). Anal. Calcd. for $C_{24}H_{27}N_3O_5$: C, 65.89; H, 6.22; N, 9.60. Found: C, 65.69; H, 6.19; N, 9.36.

2-Amino-3-cyano-6-methyl-4-(*m*-nitrophenyl)-5-[oxycarbonyl of (*S*)-ethyl lactate]-4*H*-pyran (9C): To a solution of acetoacetate **3C** (600 mg, 2.97 mmol) in dry toluene (15 mL), *m*-nitrobenzylidenemalononitrile **6b** (591 mg, 2.97 mmol, 1 equiv.) and three drops of piperidine were added. The reaction mixture was stirred at room temperature for 1.5 h. The solvent was evaporated and the residue submitted to flash chromatography[11] (hexane/ethyl acetate 7:3) to give **9C** (868 mg, 73% yield): Oil; IR (KBr) ν : 3470, 3400, 2980, 2930, 2200, 1740, 1710, 1680, 1630, 1600, 1530, 1440, 1350, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major and minor diastereomers, δ: 8.10 (m, 1H, aromatic), 8.06 (m, 1H, aromatic), 7.60 (m, 1H, aromatic), 7.49 (t, 1H, J_o=7.8 Hz, H-5 aromatic), 4.96 (q, 1H, J=7.2 Hz, C*H*CH_3 minor), 4.93 (q, 1H, J=7.2 Hz, C*H*CH_3 major), 4.71 (br s, 2H, NH_2), 4.63 (d, 1H, J=0.9 Hz, H-4 major), 4.61 (d, 1H, J=0.9 Hz, H-4 minor), 4.15, 4.04 (q, 2H, $COOCH_2CH_3$), 2.43 (d, J=0.9 Hz, CH_3 minor), 2.42 (d, J=0.9 Hz, CH_3 major), 1.41, 1.28 (d, 3H, J=7.2 Hz, CH_3CH), 1.22, 1.13 (t, 3H, J=7.2 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) major and minor diastereomers, δ: 170.19, 169.95 ($COOCH_2CH_3$), 164.66, 164.40 (COO), 159.21, 158.64, 157.74, 157.66 (C-2 and C-6), 148.18 (C-1 aromatic), 146.03, 145.62 (C-3 aromatic), 134.05, 133.92 (C-6 aromatic), 129.38, 129.33 (C-5 aromatic), 122.57, 122.45, 122.22 (C-2 and C-4 aromatic), 118.33, 118.27 (CN), 106.14, 105.92 (C-5), 69.22, 68.86 ($CHCH_3$), 61.38, 61.21 (CH_2), 60.42, 60.22 (C-3), 38.48, 38.44 (C-4), 18.79, 18.59 (CH_3C=C), 16.64, 16.42 (CH_3CH), 13.84, 13.76 (CH_2CH_3); MS (70 eV) *m/z*: 401 (M^+, 5), 384 (42), 374 (2), 373 (2), 356 (2), 300 (8), 284 (12), 279 (15), 256 (15), 255 (18), 179 (8), 161 (47), 101 (14), 73 (12), 43 (100). Anal. Calcd. for $C_{19}H_{19}N_3O_7$: C, 56.85; H, 4.77; N, 10.47. Found: C, 56.64; H, 4.53; N, 10.48.

***N*-(3-oxobutanoil)bornane-10,2-sultam (11):** To a solution of sultam **10** (4 g, 18.6 mmol) in toluene (18 mL; 3 mL toluene/5 mmol dioxinone), 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **1** (3.96 g, 27.9 mmol, 1.5 equiv.) was added. This mixture was inmersed in an oil bath preheated to 130°C, and the solution was vigorously stirred for 1 h. The solvent was evaporated and the residue submitted to flash chromatography[11] (hexane/ethyl acetate 9:1 and 4:1) to obtain **11** (4.56 g, 82% yield): Solid; m.p. 78-81 °C; $[\alpha]_D^{25}$= -77.5° (*c* 1.06, $CHCl_3$); IR (KBr) ν: 2960, 2890, 1730, 1690, 1630, 1455, 1420, 1335, 1135 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 4.00 (d, 1H, J_{gem}=16.8 Hz, CH_2CO), 3.87 (dd, 1H, J=7.8 and 4.8 Hz, $CHNSO_2$), 3.66 (d, 1H, J_{gem}=16.8 Hz, CH_2CO), 3.49 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.42 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 2.30-2.03 (m, 2H), 2.23 (s, 3H, CH_3CO), 1.95-1.85 (m, 3H), 1.45-1.32 (m, 2H), 1.13 (s, 3H, CH_3), 0.95 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.80 ($COCH_3$), 178.42 (CON), 64.83 ($CHNSO_2$), 52.53 (CH_2SO_2), 50.55 (CH_2CO), 48.42, 47.63 (C-7' and C-1'), 44.36 (CH), 37.84 (CH_2), 32.54 (CH_2), 30.09 (CH_3CO), 26.26 (CH_2), 20.32 (CH_3), 19.72 (CH_3); MS (70 eV) *m/z*: 299 (M^+,2), 284 (1), 214 (11), 192 (14), 151 (24), 136 (48), 119 (55), 108 (57), 93 (55), 43 (100); Anal. Calcd. for $C_{14}H_{21}NO_4S$: C, 56.16; H, 7.07; N, 4.68; S, 10.71. Found: C, 56.29; H, 7.28; N, 4.81; S, 10.42.

X-Ray Crystal Analysis Structure of 11[19]: Crystal data: $C_{14}H_{21}NO_4S$, molecular mass = 299.384, orthorombic, $P2_12_12_1$, a = 23.000(2) Å, b = 9.3675(3) Å, c = 6.9047(2) Å, V = 1487.6(1) $Å^3$, Z = 4, Dc = 1.34 gr/cm^3, F(000) = 640, μ = 20.05 cm^{-1}. Refined cell parameters were obtained from setting angles of 86 reflections. Prismatic white (0.35x0.30x0.15 mm) sample was used for the analysis. Data collection: Automatic four circle diffractometer Philips PW 1100 with graphite orientated monochromated Cu-Kα radiation. The intensity data were collected using the $\kappa/2\Theta$ scan mode between $2 < \Theta < 65°$; two standard reflections were measured every 90 minutes with no intensity variation. A total of 1496 reflections were measured and 1422 were considered observed [$I > 3\sigma(I)$ criterium]. The data were corrected for Lorentz and Polarization effects. Structure solution and refinement: The structure was solved by direct methods using SIR88[20] and DIRDIF92[21]. Hydrogen atoms were located from Fourier difference except those involved in methyl groups that were calculated and fixed in the final mixed refinement; isotropic thermal parameters of these atoms were considered as fixed contributions. A convenient weighting scheme was applied to eliminate the dependence in $<w\Delta^2F>$ vs. $<F_o>$ and $<\sin\Theta/\lambda>$[22]. Final R (Rw) value was 4.2 (5.1). Atomic scattering factors for the compound were taken from International Tables for X-Ray Crystallography[23] and calculations were performed using XRAY80,[24] XTAL,[25] HSEARCH[26] and PARST.[27]

General Procedure for the Synthesis of Pyrans 12a-g: Compound **11** (1.0 equiv.) was dissolved

in dry toluene and piperidine (four drops) plus the appropiate arylidenemalononitrile **6a-g** (1.5 equiv.) were added. The solution was stirred at r.t. for 24-48 h. The solvent was removed under vacuum and the residue submitted to flash chromatography[11] giving compounds **13** (traces) and **12a-g**.

2-Amino-3-cyano-6-methyl-5-(*N*-oxobornane-10,2-sultam)-4-phenyl-4*H*-pyran (12a): Compound **12a** was synthesized following the general procedure. After flash chromatography[11] (hexane/ethyl acetate 9:1 and 17:3), both isomers (ratio 80:20) were isolated. Total yield: 65%. By recrystallization from mixture hexane/ethyl acetate both isomers could be separated. **Major isomer:** Solid; m.p. 185-187 °C; $[\alpha]_D^{25}$ = -165.6° (*c* 0.9, $CHCl_3$); IR (KBr) ν : 3450, 3350, 3200, 3030, 2960, 2880, 2200, 1700, 1645, 1610, 1460, 1415, 1395, 1365, 1335, 1280, 1230, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.33-7.18 (5H, aromatic), 4.64 (d, 1H, J=1.2 Hz, H-4), 4.50 (br s, 2H, NH_2), 3.82 (dd, 1H, J=7.8 and 4.8 Hz, $CHNSO_2$), 3.48 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.38 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 1.99 (d, 3H, J=1.2 Hz, CH_3-C=C), 1.93-1.22 (several m, 7H, 3 CH_2, CH), 1.09 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.45 (CO), 157.45 (C-2), 149.75 (C-6), 141.13, 128.49, 127.95, 127.54 (aromatic), 118.91 (CN), 110.35 (C-5), 64.29 ($CHNSO_2$), 61.31 (C-3), 52.87 (CH_2SO_2), 48.14, 47.60 (C-7' and C-1'), 44.11 (C-4'), 40.34 (C-4), 37.35, 32.45, 26.39 (3 CH_2), 20.44 [$C(CH_3)_2$], 19.68 [$C(CH_3)_2$], 17.25 (CH_3-C=C); MS (70 eV) *m/z*: 453 (M^+,3), 376 (6), 372 (7), 345 (4), 263 (5), 239 (11), 238 (9), 211 (15), 173 (72), 152 (16), 131 (64), 119 (72), 117 (58), 43 (100); Anal. Calcd. for $C_{24}H_{27}N_3O_4S$: C, 63.56; H, 5.99; N, 9.26; S, 7.07. Found: C, 63.58; H, 5.67; N, 9.56; S, 6.94. **Minor isomer:** Solid; m.p. 222-225°C; $[\alpha]_D^{25}$= +72.4° (*c* 0.9, $CHCl_3$); IR (KBr) ν : 3450, 3350, 3200, 3040, 2960, 2880, 2200, 1690, 1640, 1610, 1455, 1410, 1390, 1330, 1275, 1225, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.38-7.19 (5H, aromatic), 4.51 (s, 2H, NH_2), 4.25 (s, 1H, H-4), 3.85 (t, 1H, $CHNSO_2$), 3.52 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.45 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 2.00 (s, 3H, CH_3-C=C), 2.00-1.30 (varios m, 7H, 3CH_2, CH), 1.15 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.35 (CO), 157.91, 149.63 (C-2 and C-6), 142.76, 128.44, 127.69, 127.27 (aromatic), 118.87 (CN), 109.31 (C-5), 65.07 ($CHNSO_2$), 61.83 (C-3), 53.08 (CH_2SO_2), 48.00, 47.00 (C-7' and C-1'), 44.65 (CH), 39.79 (C-4), 38.12, 33.03, 26.18 (3 CH_2), 20.74 [$C(CH_3)_2$], 19.72 [$C(CH_3)_2$], 18.03 (CH_3); Anal. Calcd. for $C_{24}H_{27}N_3O_4S$: C, 63.56; H, 5.99; N, 9.26; S, 7.07. Found: C, 63.57; H, 6.15; N, 9.46; S, 6.88.

X-Ray Crystal Analysis Structure of Minor 12a[19] isomer: Crystal data: $C_{24}H_{27}N_3O_4S.CHCl_3$, molecular mass= 572.933, orthorombic, $P2_12_12_1$, a = 19.907(1) Å, b = 13.066(1) Å, c = 10.534(1) Å, V = 2739.9(4) $Å^3$, Z = 4, Dc = 1.39 gr/cm^3, F(000) = 1192, μ = 40.89 cm^{-1}. Refined cell parameters were obtained from setting angles of 69 reflections. Prismatic colorless crystals (0.33x0.27x0.20 mm) was used for the analysis. Data collection: Automatic four circle diffractometer Seifert XRD300-S running with the CRYSOM program system with graphite orientated monochromated Cu-Kα radiation. The intensity data were collected using the $\kappa/2\Theta$ scan mode between $2 < \Theta < 65°$; two standard reflections were measured every 100 minutes with no intensity variation. A total of 1878 reflections were measured and 1094 were considered observed [$I > 2\sigma(I)$ criterium], showing the poor quality of the crystall. The data were corrected for Lorentz and Polarization effects. Structure solution and refinement: The structure was solved by direct methods using SIR88[20] and sucesive Fourier syntheses finding a chloroform molecule in these syntheses. An empirical absortion correction was applied. Hydrogen atoms were located geometrically and were considered as fixed contributions. A convenient weighting scheme was applied to obtain flat dependence in $<w\Delta^2F>$ vs. $<F_0>$ and $<\sin\Theta/\lambda>$[22]. Final R (Rw) value was 8.1 (8.2). Thermal parameters for the chloroform molecule suggest a disorder model for this molecule. Atomic scattering factors for the compound were taken from International Tables for X-Ray Crystallography[23] and calculations were performed using XRAY80,[24] XTAL,[25] DIFABS,[28] HSEARCH[26] and PARST.[27]

2-Amino-3-cyano-6-methyl-4-(*m*-nitrophenyl)-5-(*N*-oxobornane-10,2-sultam)-4*H*-pyran (12b): Compound **12b** was synthesized following the general procedure. After flash chromatography[11] (hexane/ethyl acetate 9:1, 4:1, 7:3 and 3:2), both isomers (ratio 85:15) could be isolated. Total yield: 85%. Solid; m.p. 115-120 °C; IR (KBr) ν : 3450, 3350, 3200, 2970, 2890, 2205, 1700, 1650, 1610, 1540, 1420, 1360, 1290, 1240, 1160, 1065, 780 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): **Major isomer**, δ: 8.13 (m, 1H, aromatic), 8.06 (m, 1H, aromatic), 7.61-7.52 (m, 2H, aromatic), 4.79 (d, 1H, J=1.2 Hz, H-4), 4.76 (s, 2H, NH_2), 3.82 (dd, 1H, J=7.8 and 4.8 Hz, $CHNSO_2$), 3.52 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.41 (d,

1H, J_{gem}=13.8 Hz, CH_2SO_2), 1.99 (d, 3H, J=1.2 Hz, CH_3-C=C), 1.98-1.22 (several m, 7H, $3CH_2$, CH), 1.14 (s, 3H, CH_3), 0.96 (s, 3H, CH_3). **Minor isomer**, δ: 8.13 (m, 1H, aromatic), 8.06 (m, 1H, aromatic), 7.57-7.48 (m, 2H, aromatic), 4.76 (s, 2H, NH_2), 4.41 (s, 1H, J=0.9 Hz, H-4), 3.86 (m, 1H, $CHNSO_2$), 3.55 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.48 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 2.03 (d, 3H, J=0.9 Hz, CH_3-C=C), 1.98-1.22 (several m, 7H, $3CH_2$, CH), 1.16 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): **Major isomer**, δ: 166.78 (CO), 158.02, 150.37 (C-2 and C-6), 148.12, 143.47, 134.29, 129.68, 122.97, 122.78 (aromatic), 118.43 (CN), 109.42 (C-5), 64.41 ($CHNSO_2$), 60.23 (C-3), 52.86 (CH_2SO_2), 48.24, 47.63 (C-7' and C-1'), 44.11 (CH), 40.33 (C-4), 37.55, 32.49, 26.32 (3 CH_2), 20.32 [$C(CH_3)_2$], 19.60 [$C(CH_3)_2$], 17.44 (CH_3). **Minor isomer**, δ: 165.16 (CO), 158.27, 150.21 (C-2 and C-6), 148.26, 145.04, 134.14, 129.31, 122.89, 122.42 (aromatic), 118.43 (CN), 108.26 (C-5), 65.07 ($CHNSO_2$), 59.59 (C-3), 53.07 (CH_2SO_2), 48.12, 47.49 (C-7' and C-1'), 44.66 (CH), 39.59 (C-4), 38.02, 33.00, 26.16 (3 CH_2), 20.69 [$C(CH_3)_2$], 19.67 [$C(CH_3)_2$], 18.05 (CH_3); MS (70 eV) *m/z*: 498 (M^+,4), 481 (62), 417 (3), 376 (4), 325 (6), 256 (1), 218 (36), 214 (32), 176 (44), 134 (17), 93 (22), 67 (33), 43 (100); Anal. Calcd. for $C_{24}H_{26}N_4O_6S$: C, 57.82; H, 5.25; N, 11.24. Found: C, 57.66; H, 5.59; N, 11.07.

2-Amino-3-cyano-6-methyl-4-(*o*-methylphenyl)-5-(*N*-oxobornane-10,2-sultam)-4*H*-pyran (12c): Compound **12c** was synthesized following the general procedure. After flash chromatography[11] (hexane/ethyl acetate 9:1, 4:1 and 7:3), both isomers (ratio 80:20) could be isolated. Total yield: 62%. Solid; m.p. 227-230 °C; IR (KBr) ν: 3450, 3350, 3200, 2960, 2880, 2200, 1690, 1640, 1600, 1490, 1460, 1385, 1335, 1280, 1230, 1150, 1055, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): **Major isomer**, δ: 7.23-7.07 (m, 4H, aromatic), 5.06 (d, 1H, J=1.2 Hz, H-4), 4.43 (s, 2H, NH_2), 3.80 (dd, 1H, J=7.8 and 4.8 Hz, $CHNSO_2$), 3.47 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.38 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 2.38 (s, 3H, CH_3Ph), 2.00 (d, 3H, J=1.2 Hz, CH_3-C=C), 1.92-1.20 (several m, 7H, 3 CH_2, CH), 0.97 (s, 3H, CH_3), 0.91 (s, 3H, CH_3). **Minor isomer**, δ: 7.23-7.07 (m, 4H, aromatic), 4.67 (s, 1H, H-4), 4.46 (s, 2H, NH_2), 3.80 (m, 1H, $CHNSO_2$), 3.52 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.46 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 2.33 (s, 3H, CH_3Ph), 1.97 (d, 3H, J=1.2 Hz, CH_3-C=C), 1.92-1.20 (several m, 7H, $3CH_2$, CH), 1.15 (s, 3H, CH_3), 0.97 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): **Major isomer**, δ: 166.52 (CO), 157.46, 150.52 (C-2 and C-6), 138.32, 136.21, 130.82, 129.51, 127.36, 126.04 (aromatic), 118.95 (CN), 109.94 (C-5), 64.57 ($CHNSO_2$), 60.81 (C-3), 52.93 (CH_2SO_2), 47.98, 47.51 (C-7' and C-1'), 44.04 (CH), 36.66 (C-4), 37.36, 32.55, 26.38 (3 CH_2), 20.47 [$C(CH_3)_2$], 19.61 [$C(CH_3)_2$], 19.01 (CH_3Ph), 17.40 (CH_3); MS (70 eV) *m/z*: 467 (M^+,15), 452 (42), 403 (50), 386 (62), 376 (100), 359 (34), 277 (59), 253 (60), 237 (61), 225 (83), 161 (39), 152 (73), 115 (49), 91 (50), 67 (57); Anal. Calcd. for $C_{25}H_{29}N_3O_4S$: C, 64.22; H, 6.25; N, 8.99; S, 6.86. Found: C, 64.31; H, 6.09; N, 8.87; S, 6.85.

2-Amino-3-cyano-6-methyl-4-(*p*-methylphenyl)-5-(*N*-oxobornane-10,2-sultam)-4*H*-pyran (12d): Compound **12d** was synthesized following the general procedure. After flash chromatography[11] (hexane/ethyl acetate 4:1, 3:1 and 7:3), both isomers (ratio 85:15) could be isolated. Total Yield: 42%. Solid; m.p. 185-188°C; IR (KBr) ν: 3450, 3350, 2960, 2880, 2200, 1700, 1650, 1600, 1520, 1390, 1340, 1285, 1230, 1170, 1150, 1060, 770 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): **Major isomer**, δ: 7.08 (m, 4H, aromatic), 4.58 (d, 1H, J=1.2 Hz, H-4), 4.49 (s, 2H, NH_2), 3.82 (dd, 1H, J=7.8 and 4.5 Hz, $CHNSO_2$), 3.48 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.38 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 2.29 (s, 3H, CH_3Ph), 1.97 (d, 3H, J=1.2 Hz, CH_3-C=C), 1.92-1.22 (several m, 7H, $3CH_2$, CH), 1.11 (s, 3H, CH_3), 0.94 (s, 3H, CH_3). **Minor isomer**, δ: 7.08 (m, 4H, aromatic), 4.52 (s, 2H, NH_2), 4.21 (s, 1H, H-4), 3.84 (m, 1H, $CHNSO_2$), 3.51 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.44 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 2.31 (s, 3H, CH_3Ph), 1.99 (d, 3H, J=1.2 Hz, CH_3-C=C), 1.92-1.22 (several m, 7H, $3CH_2$, CH), 1.15 (s, 3H, CH_3), 0.97 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): **Major isomer**, δ: 166.48 (CO), 157.40, 149.39 (C-2 and C-6), 138.27, 137.06, 129.21, 127.71 (aromatic), 118.98 (CN), 110.51 (C-5), 64.27 ($CHNSO_2$), 61.49 (C-3), 52.85 (CH_2SO_2), 48.15, 47.60 (C-7' and C-1'), 44.12 (CH), 39.98 (C-4), 37.41, 32.43, 26.40 (3 CH_2), 20.99 (CH_3Ph), 20.44 [$C(CH_3)_2$], 19.67 [$C(CH_3)_2$], 17.22 (CH_3). **Minor isomer**, δ: 165.34 (CO), 157.86, 149.39 (C-2 and C-6), 139.84, 136.75, 129.21, 127.55 (aromatic), 118.98 (CN), 109.45 (C-5), 67.07 ($CHNSO_2$), 61.81 (C-3), 53.05 (CH_2SO_2), 47.97, 47.46 (C-7' and C-1'), 44.65 (CH), 39.39 (C-4), 38.11, 33.01, 26.16 (3 CH_2), 20.99 (CH_3Ph), 20.72 [$C(CH_3)_2$], 19.67 [$C(CH_3)_2$], 18.00 (CH_3); MS (70 eV) *m/z*: 467 (M^+,20), 452 (16), 403 (19), 386 (57), 376 (27), 359 (22), 277 (32), 253 (31), 237 (34), 225 (46), 187 (100), 145

(80), 115 (35), 91 (37), 67 (60), 43 (78); Anal. Calcd. for $C_{25}H_{29}N_3O_4S$: C, 64.22; H, 6.25; N, 8.99; S, 6.86. Found: C, 64.24; H, 6.21; N, 8.99; S, 6.85.

2-Amino-4-(*p*-bromophenyl)-3-cyano-6-methyl-5-(*N*-oxobornane-10,2-sultam)-4*H*-pyran (12e): Compound **12e** was synthesized following the general procedure. After flash chromatography[11] (hexane/ethyl acetate 9:1, 4:1 and 7:3), both isomers (ratio 80:20) could be isolated. Total Yield: 91%. Solid; m.p. 119-124 °C; IR (KBr) ν : 3450, 3350, 2970, 2880, 2200, 1700, 1645, 1600, 1490, 1410, 1385, 1340, 1285, 1230, 1150, 1060, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): **Major isomer**, δ: 7.42 (d, 2H, J=8.4 Hz, aromatic), 7.07 (d, 2H, J=8.4 Hz, aromatic), 4.60 (d, 1H, J=1.2 Hz, H-4), 4.57 (s, 2H, NH_2), 3.81 (dd, 1H, J=7.8 and 4.5 Hz, $CHNSO_2$), 3.47 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.38 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 1.97 (d, 3H, J=1.2 Hz, CH_3-C=C), 1.92-1.20 (several m, 7H, $3CH_2$, CH), 1.06 (s, 3H, CH_3), 0.93 (s, 3H, CH_3). **Minor isomer**, δ: 7.42 (m, 2H, aromatic), 7.07 (m, 2H, aromatic), 4.59 (s, 2H, NH_2), 4.22 (s, 1H, H-4), 3.83 (m, 1H, $CHNSO_2$), 3.51 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.43 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 1.98 (d, 3H, J=1.2 Hz, CH_3-C=C), 1.92-1.20 (several m, 7H, $3CH_2$, CH), 1.14 (s, 3H, CH_3), 0.96 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): **Major isomer**, δ: 166.16 (CO), 157.53, 150.02 (C-2 and C-6), 140.26, 131.67, 129.66, 121.55 (aromatic), 118.70 (CN), 109.78 (C-5), 64.31 ($CHNSO_2$), 60.73 (C-3), 52.86 (CH_2SO_2), 48.21, 47.61 (C-7' and C-1'), 44.09 (CH), 39.90 (C-4), 37.49, 32.44, 26.37 (3 CH_2), 20.42 [$C(CH_3)_2$], 19.65 [$C(CH_3)_2$], 17.30 (CH_3). **Minor isomer**, δ: 165.26 (CO), 157.99, 149.87 (C-2 and C-6), 141.84, 131.54, 129.46, 121.22 (aromatic), 118.68 (CN), 108.81 (C-5), 65.08 ($CHNSO_2$), 61.07 (C-3), 53.06 (CH_2SO_2), 48.04, 47.48 (C-7' and C-1'), 44.65 (CH), 39.31 (C-4), 38.07, 33.01, 26.16 (3 CH_2), 20.71 [$C(CH_3)_2$], 19.69 [$C(CH_3)_2$], 18.00 (CH_3); Anal. Calcd. for $C_{24}H_{26}BrN_3O_4S$: C, 54.14; H, 4.92; N, 7.89. Found: C, 53.95; H, 5.33; N, 7.51.

2-Amino-4-(*p*-chlorophenyl)-3-cyano-6-methyl-5-(*N*-oxobornane-10,2-sultam)-4*H*-pyran (12f): Compound **12f** was synthesized following the general procedure. After flash chromatography[11] (hexane/ethyl acetate 9:1, 4:1 and 7:3), both isomers (ratio 85:15) could be isolated. Yield: 64%. By recrystallization major isomer could be separated. **Major isomer**: Solid; m.p. 200-203 °C; $[\alpha]_D^{25}$= -161.5° (*c* 1.3, $CHCl_3$); IR (KBr) ν : 3460, 3350, 3200, 2960, 2880, 2200, 1695, 1645, 1600, 1490, 1410, 1385, 1335, 1280, 1230, 1145, 1055, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 7.27 (d, 2H, J=8.7 Hz, aromatic), 7.13 (d, 2H, J=8.7 Hz, aromatic), 4.62 (d, 1H, J=1.2 Hz, H-4), 4.57 (s, 2H, NH_2), 3.81 (dd, 1H, J=7.8 and 4.5 Hz, $CHNSO_2$), 3.47 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.38 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 1.97 (d, 3H, J=1.2 Hz, CH_3-C=C), 1.92-1.22 (several m, 7H, $3CH_2$, CH), 1.07 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 166.24 (CO), 157.53, 150.15 (C-2 and C-6), 139.81, 133.40, 129.39, 128.74 (aromatic), 118.57 (CN), 110.05 (C-5), 64.44 ($CHNSO_2$), 61.18 (C-3), 52.92 (CH_2SO_2), 48.26, 47.66 (C-7' and C-1'), 44.25 (CH), 39.92 (C-4), 37.53, 32.55, 26.42 (3 CH_2), 20.48 [$C(CH_3)_2$], 19.68 [$C(CH_3)_2$], 17.29 (CH_3); MS (70 eV) *m/z*: 488 (M^+,3), 487 (7), 376 (7), 273 (10), 245 (15), 209 (16), 207 (30), 165 (30), 136 (20), 93 (24), 67 (42), 43 (100); Anal. Calcd. for $C_{24}H_{26}ClN_3O_4S$: C, 59.07; H, 5.37; N, 8.61; S, 6.57; Cl, 7.26. Found: C, 59.31; H, 5.58; N, 8.33; S, 6.43; Cl, 7.29. **Minor isomer**: ^1H NMR (300 MHz, $CDCl_3$), δ: 7.27 (m, 2H, aromatic), 7.13 (m, 2H, aromatic), 4.59 (s, 2H, NH_2), 4.24 (s, 1H, H-4), 3.83 (m, 1H, $CHNSO_2$), 3.51 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.43 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 1.98 (d, 3H, J=0.9 Hz, CH_3-C=C), 1.92-1.22 (several m, 7H, $3CH_2$, CH), 1.14 (s, 3H, CH_3), 0.96 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 165.26 (CO), 158.03, 149.84 (C-2 and C-6), 141.31, 133.07, 129.17, 128.63 (aromatic), 118.57 (CN), 109.09 (C-5), 65.18 ($CHNSO_2$), 61.85 (C-3), 53.12 (CH_2SO_2), 48.12, 47.54 (C-7' and C-1'), 44.77 (CH), 39.37 (C-4), 38.14, 33.09, 26.22 (3 CH_2), 20.73 [$C(CH_3)_2$], 19.68 [$C(CH_3)_2$], 17.94 (CH_3).

2-Amino-3-cyano-4-(*p*-cyanophenyl)-6-methyl-5-(*N*-oxobornane-10,2-sultam)-4*H*-pyran (12g): Compound **12g** was synthesized following the general procedure. After flash chromatography[11] (hexane/ethyl acetate 9:1, 4:1, 7:3 and 3:2), both isomers (ratio 60:40) could be isolated. Total yield: 77%. Solid; m.p. 109-113 °C; IR (KBr) ν : 3450, 3350, 3200, 2970, 2890, 2220, 2205, 1700, 1650, 1610, 1510, 1420, 1350, 1290, 1240, 1160, 1065, 780 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): **Major isomer**, δ: 7.62 (d, 2H, J=8.4 Hz, aromatic), 7.33 (d, 2H, J=8.4 Hz, aromatic), 4.74 (s, 2H, NH_2) 4.72 (d, 1H, J=0.9 Hz, H-4), 3.82 (dd, 1H, $CHNSO_2$), 3.49 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.40 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 2.00

(d, 3H, J=0.9 Hz, CH_3-C=C), 2.00-1.26 (several m, 7H, $3CH_2$, CH), 1.06 (s, 3H, CH_3), 0.96 (s, 3H, CH_3). **Minor isomer**, δ: 7.63 (d, 2H, J=8.4 Hz, aromatic), 7.32 (d, 2H, J=8.4 Hz, aromatic), 4.76 (s, 2H, NH_2) 4.32 (s, 1H, H-4), 3.84 (m, 1H, $CHNSO_2$), 3.54 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 3.46 (d, 1H, J_{gem}=13.8 Hz, CH_2SO_2), 2.02 (s, 3H, CH_3-C=C), 2.00-1.26 (several m, 7H, $3CH_2$, CH), 1.15 (s, 3H, CH_3), 0.98 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): **Major isomer**, δ: 165.93 (CO), 157.72 (C-2), 150.75 (C-6), 146.36, 132.47, 128.89, 111.58 (aromatic), 118.49, 118.31 (2 CN), 109.24 (C-5), 64.44 ($CHNSO_2$), 60.24 (C-3), 52.92 (CH_2SO_2), 48.29, 47.67 (C-7' and C-1'), 44.16 (CH), 40.51 (C-4), 37.54, 32.53, 26.38 (3 CH_2), 20.46 [$C(CH_3)_2$], 19.67 [$C(CH_3)_2$], 17.41 (CH_3). **Minor isomer**, δ: 165.24 (CO), 158.16 (C-2), 150.52 (C-6), 148.01, 132.35, 128.64, 111.16 (aromatic), 118.69, 118.31 (2 CN), 108.32 (C-5), 65.15 ($CHNSO_2$), 60.68 (C-3), 53.14 (CH_2SO_2), 48.16, 47.55 (C-7' and C-1'), 44.72 (CH), 39.93 (C-4), 38.09, 33.09, 26.22 (3 CH_2), 20.73 [$C(CH_3)_2$], 19.73 [$C(CH_3)_2$], 18.03 (CH_3); Anal. Calcd. for $C_{25}H_{26}N_4O_4S$: C, 62.74; H, 5.47; N, 11.71. Found: C, 62.71; H, 5.87; N, 11.40.

General Procedure for Reductive Cleavage: To a stirred suspension of $LiAlH_4$ (2.5 equiv.) in dry ether (4 mL/mmol) at 0°C a solution of compound **12a-g** (1.0 equiv.) in THF/ether (1:5, 18 mL/0.5 mmol) was added. The reaction mixture was stirred at 0°C for 2-3 h. Addition of saturated aqueous NH_4Cl, extraction with ether, drying, concentration and flash chromatography[11] gave the recovered sultam **10** and the respective alcohol **14a-g**.

2-Amino-3-cyano-5-hydroxymethylene-6-methyl-4-phenyl-4*H*-pyran(14a): Following the general reduction procedure, from **12a** (400 mg, 0.88 mmol), after flash chromatography[11] (hexane/ethyl acetate 3:2 and 1:1), sultam **10** (180 mg, 95% yield) and alcohol **14a** (157 mg, 73% yield, e.e. >99) were obtained. Solid; m.p. 95-98°C; $[\alpha]_D^{25}$= +25.0° (c 1.3, CH_3COCH_3); IR (KBr) ν : 3450, 3310, 3200, 2180, 1710, 1640, 1600, 1455, 1410, 1390, 1225, 1150, 1050, 1000 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 7.36-7.20 (m, 5H, aromatic), 5.86 (s, 2H, NH_2), 4.21 (d, 1H, J=1.2 Hz, H-4), 4.11 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 3.82 (s, 1H, OH), 3.60 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 1.97 (s, 3H, J=1.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.51 (C-2), 145.30, 129.26, 128.77, 127.67 (aromatic), 144.23 (C-6), 120.46 (CN), 113.36 (C-5), 59.63 (C-3), 59.03 (CH_2OH), 40.53 (C-4), 15.44 (CH_3); Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.15; H, 5.87; N, 11.38.

2-Amino-3-cyano-5-hydroxymethylene-6-methyl-4-(*m*-nitrophenyl)-4*H*-pyran (14b): Following the general reduction procedure, from **12b** (300 mg, 0.60 mmol), after flash chromatography[11] (hexane/ethyl acetate 3:2, 1:1 and 2:3), sultam **10** (100 mg, 77% yield) and alcohol **14b** (69 mg, 40% yield, e.e. =70) were obtained. Solid; m.p. 164-167 °C; $[\alpha]_D^{25}$ = +6.0° (c 0.4, CH_3COCH_3); IR (KBr) ν : 3400, 3300, 3200, 2180, 1710, 1645, 1600, 1530, 1420, 1385, 1350, 1220, 1170, 1150, 1060, 990 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 8.17-8.10 (m, 2H, aromatic), 7.72 (td, 1H, J=8.1 Hz, aromatic), 7.65 (t, 1H, J=8.1 Hz, aromatic), 6.06 (br s, 2H, NH_2), 4.43 (s, 1H, H-4), 4.16 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 3.67 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 2.09 (s, 1H, OH), 2.00 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.79 (C-2), 144.96 (C-6), 149.47, 147.82, 135.37, 130.68, 123.34, 122.75 (aromatic), 119.99 (CN), 112.46 (C-5), 59.12 (CH_2OH), 58.77 (C-3), 40.56 (C-4), 15.56 (CH_3); Anal. Calcd. for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.60; H, 4.96; N, 14.37.

2-Amino-3-cyano-5-hydroxymethylene-6-methyl-4-(*o*-methylphenyl)-4*H*-pyran (14c): Following the general reduction procedure, from **12c** (200 mg, 0.43 mmol), after flash chromatography[11] (hexane/ethyl acetate 3:2 and 1:1), sultam **10** (88 mg, 95% yield) and alcohol **14c** (79 mg, 72% yield, e.e. =60) were obtained. Solid; m.p. 114-116 °C; $[\alpha]_D^{25}$ = +12.37° (c 1.0, CH_3COCH_3); IR (KBr) ν : 3460, 3250, 3060, 2975, 2940, 2200, 1710, 1670, 1610, 1490, 1470, 1370, 1270, 1170 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 7.13 (m, 4H, aromatic), 5.82 (s, 2H, NH_2), 4.60 (d, 1H, J=0.9 Hz, H-4), 4.11 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 3.74 (s, 1H, OH), 3.47 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 2.43 (s, 3H, CH_3Ph), 1.96 (s, 3H, J=0.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.38 (C-2), 144.23 (C-6), 143.57, 136.64, 131.01, 129.60, 127.34, 127.29 (aromatic), 120.58 (CN), 113.45 (C-5), 59.40 (C-3), 59.23 (CH_2OH), 36.04 (C-4), 19.52 (CH_3Ph), 15.39 (CH_3); Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.48; H, 6.40; N, 10.63.

2-Amino-3-cyano-5-hydroxymethylene-6-methyl-4-(*p*-methylphenyl)-4*H*-pyran (14d): Following the general reduction procedure, from **12d** (200 mg, 0.43 mmol), after flash chromatography[11] (hexane/ethyl acetate 3:2 and 1:1), sultam **10** (74 mg, 80% yield) and alcohol **14d** (64 mg, 59% yield, e.e.=70) were obtained. Solid; m.p. 151-154 °C; $[\alpha]_D^{25}$ = +6.5° (*c* 0.43, CH_3COCH_3); IR (KBr) ν : 3460, 3320, 3200, 2190, 1710, 1645, 1605, 1510, 1410, 1390, 1230, 1175, 1155, 1000 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ: 7.12 (m, 4H, aromatic), 5.82 (s, 2H, NH_2), 4.16 (s, 1H, *J*=1.2 Hz, H-4), 4.09 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 3.65 (s, 1H, OH), 3.60 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 2.29 (s, 3H, CH_3Ph), 1.96 (s, 3H, *J*=1.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.43 (C-2), 144.13 (C-6), 142.33, 137.06, 129.84, 128.70 (aromatic), 120.48 (CN), 113.49 (C-5), 59.86 (C-3), 59.04 (CH_2OH), 40.16 (C-4), 21.04 (*C*H_3Ph), 15.44 (CH_3); Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.32; H, 5.81; N, 11.05.

2-Amino-4-(*p*-bromophenyl)-3-cyano-5-hydroxymethylene-6-methyl-4*H*-pyran (14e): Following the general reduction procedure, from **12e** (200 mg, 0.37 mmol), after flash chromatography[11] (hexane/ethyl acetate 3:2 and 1:1), sultam **10** (61 mg, 75% yield) and alcohol **14e** (50 mg, 41% yield, e.e.=60) were obtained. Solid; m.p. 155-159 °C; $[\alpha]_D^{25}$ = +6.7° (*c* 0.26, CH_3COCH_3); IR (KBr) ν : 3500, 3455, 3300, 3250, 3200, 2180, 1710, 1650, 1600, 1490, 1425, 1385, 1220, 1155, 1060, 995 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ: 7.50 (m, 2H, *J*=8.4 Hz, aromatic), 7.46 (m, 2H, *J*=8.4 Hz, aromatic), 5.91 (s, 2H, NH_2), 4.21 (s, 1H, *J*=0.9 Hz, H-4), 4.13 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 3.74 (s, 1H, OH), 3.62 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 1.96 (s, 3H, *J*=0.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.59 (C-2), 144.79, 132.31, 130.93, 121.02 (aromatic), 144.55 (C-6), 120.16 (CN), 112.95 (C-5), 59.33 (C-3), 59.09 (CH_2OH), 40.23 (C-4), 15.49 (CH_3); Anal. Calcd. for $C_{14}H_{13}BrN_2O_2$: C, 52.35; H, 4.08; N, 8.72. Found: C, 52.42; H, 4.20; N, 8.54.

2-Amino-4-(*p*-chlorophenyl)-3-cyano-5-hydroxymethylene-6-methyl-4*H*-pyran (14f): Following the general reduction procedure, from **12f** (250 mg, 0.51 mmol), after flash chromatography[11] (hexane/ethyl acetate 3:2 and 1:1), sultam **10** (100 mg, 91% yield) and alcohol **14f** (60 mg, 42% yield, e.e.>99) were obtained. Solid; m.p. 111-113 °C; $[\alpha]_D^{25}$ = +37.6° (*c* 1.23, CH_3OH); IR (KBr) ν : 3480, 3300, 3250, 3200, 2180, 1710, 1650, 1600, 1490, 1430, 1220, 1155, 1060, 990 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.30 (td, 2H, *J*=8.7 Hz, aromatic), 7.18 (td, 2H, *J*=8.7 Hz, aromatic), 4.56 (br s, 2H, NH_2), 4.18 (d, 1H, *J*=0.9 Hz, H-4), 4.07 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 3.74 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 1.98 (d, 3H, *J*=0.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ : 158.71 (C-2), 144.61 (C-6), 141.58, 133.14, 129.22, 128.90 (aromatic), 119.44 (CN), 111.28 (C-5), 60.46 (C-3), 59.71 (CH_2OH), 39.34 (C-4), 15.34 (CH_3); Anal. Calcd. for $C_{14}H_{13}ClN_2O_2$: C, 60.77; H, 4.74; N, 10.12. Found: C, 60.90; H, 4.82; N, 10.03.

2-Amino-3-cyano-4-(*p*-cyanophenyl)-5-hydroxymethylene-6-methyl-4*H*-pyran (14g): Following the general reduction procedure, from **12g** (200 mg, 0.42 mmol), after flash chromatography[11] (hexane/ethyl acetate 3:2 and 1:1), sultam **10** (68 mg, 75% yield) and alcohol **14g** (67 mg, 60% yield, e.e.=20) were obtained. Solid; m.p. 165-168 °C; $[\alpha]_D^{25}$ = +2.81° (*c* 0.64, CH_3COCH_3); IR (KBr) ν : 3480, 3420, 3300, 3250, 3200, 2240, 2180, 1710, 1650, 1600, 1500, 1430, 1225, 1155, 1060, 1000 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ: 7.75 (m, 2H, *J*=8.4 Hz, aromatic), 7.46 (m, 2H, *J*=8.4 Hz, aromatic), 6.05 (s, 2H, NH_2), 4.33 (s, 1H, H-4), 4.15 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 3.87 (s, 1H, OH), 3.62 (d, 1H, J_{gem}=12.3 Hz, CH_2OH), 1.98 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.76 (C-2), 144.88 (C-6), 150.83, 133.21, 129.82 (aromatic), 120.12, 119.35 (2 CN), 112.34, 111.39 (aromatic and C-5), 59.13 (CH_2OH), 58.50 (C-3), 40.71 (C-4), 15.51 (CH_3); Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.10; H, 5.12; N, 15.78.

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† To whom correspondence about X-ray crystallographic analysis should be addresed.

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