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Michael Addition of Malononitrile to Chiral α-Acylacrylates

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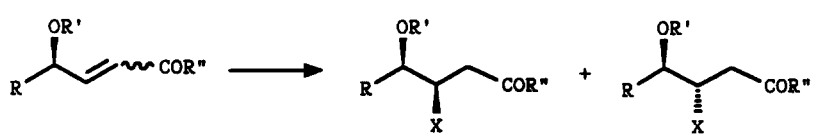
Abstract: *Starting from 2,3-O-isopropylidene-D-glyceraldehyde (1), 3-O-methyl and 3-O-benzyl-1,2-O-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose (4a, 4b), we describe the synthesis of the α-acyl-β-alkyl substituted acrylates 2 and 5. The Michael addition of malononitrile to these substrates gives the polyfunctionalized 2-amino-4H-pyrans 3 and 6 with moderate diastereoselectivity and reasonable overall yield from diols 7 and 8a,b. A detailed analysis is performed scanning different type of bases in the Michael reaction. We find that, while for acceptor 2 no changes are observed, for compound 5 the stereochemical outcome of the 1,4-addition is reversed in going from piperidine, sodium hydride or potassium t-butoxide to lithium diisopropylamide or lithium diisopropylamide/magnesium iodide reagent. Several models for rationalising the results are proposed.*

INTRODUCTION

The Michael reaction is one of the most useful processes in organic synthesis.[1] In particular, in recent years a great deal of attention has been devoted to the conjugate additions to γ-oxygenated α,β-unsaturated carbonyl compounds **A**[2] (Scheme 1). In this case the stereochemical outcome of the reaction depends on the nature of the incoming nucleophile. A Felkin-like transition state model[3] can be used to rationalize alkoxide,[2a] amine[2b] and organolithium[2c] additions (*syn* selectivity), but does not explain the results with the cuprate[2d] and alkylcopper[2e] nucleophiles (*anti* selectivity). It is possible that in these cases a chelation control by the γ-oxygen[4] operates.



A *syn* *anti*

Scheme 1

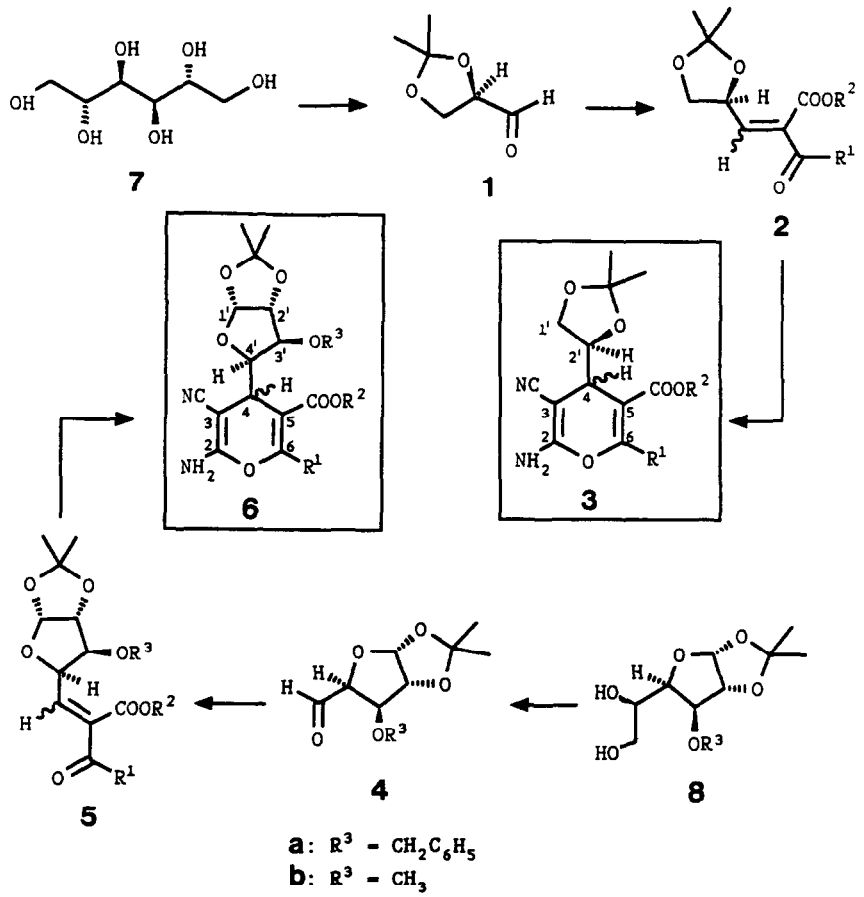
In this rather complex context, we have recently embarked in a project directed to the analysis of the asymmetric Michael addition[5] of 1,3-dicarbonyl carbanions, stabilized by π-conjugation, to enantiomerically pure α-substituted alkenoates. As a result, we have reported the synthesis of multiply polyfunctionalized 2-amino-4*H*-pyrans[6] *via* tandem one-pot Michael addition of malononitrile to α-acyl-ß-alkylacrylates and sequential *O*-ring closure.[7] To our knowledge, intramolecular 1,4-nucleophilic additions to such a type of Michael acceptors, are not documented in the literature.[2h,8] These compounds are ideal new substrates in order to study several effects (solvent, counterions and the presence of an α-acyl substituent) in the stereochemical outcome of the process.

RESULTS AND DISCUSSION

Starting from readily available aldehydes **1**[9], **4a**[10], **4b**[11] (Scheme 2) and following protocols well known in our laboratory,[12] compounds **2** and **5** were obtained after treatment with the appropiate ß-ketoester in mild, non racemizing conditions.[7,13] Without isolation, these compounds were transformed, after reaction with malononitrile in toluene/piperidine (-78°C → r.t.) (see **Experimental**), into the pyrans **3** and **6** in reasonable overall yield from diols **7** and **8a,b** and moderate diastereoselectivity (Table).

Except for compound **6c** (entry 13, Table) we have been unable to separate by chromatography the diastereomers at the new stereocenter C-4 (compounds **3** and **6a, b, d**). Fortunately, in some cases, after flash chromatography[14] and recrystallization, *major* (in **3b** and **3c**) or *minor* (**6d**) diastereomers were obtained pure (*in suitable crystalls for X-ray diffraction analysis; see below*) or in a largely improved diastereomeric excess (**3a**, d.e.: 80%).

All new compounds showed good analytical and spectroscopic data. In major diastereomers **3**, in the ^{1}H NMR spectra, we could observe H-4 at 3.60-3.80 ppm as doublets ($J_{4,4'}$=3.0-3.6 Hz). In the ^{1}H NMR spectra of major compounds **6**, after selective ^{1}H-^{1}H decoupling experiments, we have localized H-4 (4.00 ppm, d, $J_{4,4'}$=9.7 Hz) and H-4' (3.90 ppm, dd, $J_{4,4'}$=9.7 Hz, $J_{4',3'}$=3.0 Hz). These values are consistent with other ones described in literature for similar compounds.[15] Minor isomers in **6c** and **6d** showed H-4 at 4.32 and 3.92 ppm ($J_{4,4'}$=6.0 Hz), respectively. The data obtained from the ^{13}C NMR spectra are in good agreement with the expected values for these compounds.[16] In major **6** isomers C-3 and C-4 appear at ≈55.00 and 32.00 ppm, respectively; these values are shifted ($\Delta\delta$ + 1 ppm) in minor **6a** (C-3: 56.74 ppm; C-4: 32.38 ppm), minor **6b** (C-3: 55.90 ppm; C-4: 33.50 ppm) and minor **6d** (C-3: 57.65 ppm; in major **6d**, C-3: 55.54) isomers.



Scheme 2

The absolute stereochemistry at the new stereocenter (C-4) in major compounds [**3**(C-4 *R*) and **6** (C-4 *R*)] has been established by X-ray diffraction analysis. Comparison of the ^{1}H and ^{13}C NMR experiments in the pure recrystallized samples with the spectra of the diastereomeric mixtures obtained after chromatography, showed clearly that the X-ray analysis have been performed on major **3b**, major **3c**, and minor **6d** (*C*-4 *S*)[17] isomers. The crystall structures were solved by direct methods. A view of the solid-state conformation of compound minor **6d** isomer is presented in Figure 1. The absolute stereochemistry shown follows from that of the starting diol **8b**. From a structural standpoint, the conformation of the pyran ring corresponds to a 1,4-boat; C-4 is farther above the plane formed by C-2, C-3, C-5 and C-6, than O-1; this shift is more important here than in pyrans **3b** or **3c**; this is probably due to the greater steric hindrance produced by the *transoid* furanose ring at C-4.

Table. New 2-Amino-4*H*-pyrans (**3**, **6**).

Entry	Compound	R^1	R^2	R^3	Base/Solvent	R:S[a]	Yield[b] (%)
1	**3a**	Me	Et	-	piperidine/toluene	70:30	36
2	**3b**	Me	Me	-	piperidine/toluene	80:20	45
3	**3b**	Me	Me	-	LDA/toluene	75:25	40
4	**3b**	Me	Me	-	LDA/MgI_2-Et_2O/toluene	71:19	41
5	**3c**	Ph	Et	-	piperidine/toluene	55:45	51
6	**6a**	Me	Me	Bn	piperidine/toluene	82:18	58
7	**6a**	Me	Me	Bn	LDA/THF	35:65	30
8	**6a**	Me	Me	Bn	LDA/toluene	24:76	49
9	**6a**	Me	Me	Bn	NaH/THF[c]	75:25	32
10	**6a**	Me	Me	Bn	*t*-BuOK/THF	60:40	20
11	**6a**	Me	Me	Bn	LDA/MgI_2-Et_2O/toluene	19:81	53
12	**6b**	Ph	Et	Bn	piperidine/toluene	74:26	33
13	**6c**	Me	Me	Me	piperidine/toluene	70:30	53
14	**6d**	Ph	Et	Me	piperidine/toluene	76:24	59

[a] Ratio determined by ^1H NNR in crude reaction mixtures.
[b] Overall yield from diols **7**, **8a** or **8b** after flash chromatography.
[c] 0°C → r.t.

At this point and in view of the results obtained with the piperidine/toluene system, we tried several different conditions in order to promote the Michael addition and if possible, improve yields and diastereomeric excesses.

Using acceptor **2b** as the substrate and lithium diisopropylamide (Table, entry 3) (toluene, -78°C → r.t.) as the base, pyran **3b** was obtained in moderate yield (≈40%) and similar *R*:*S* ratios (50-60%), the major isomer at C-4 (*R*) being the same as obtained in the initial experiment (Table, entry 2). A similar result (Table, entry 4) was obtained when magnesium idodide etherate was added to the Li^+,NCCH⁻CN reagent.

Regarding the furanose **5**, we have selected acceptor **5a** as a representative example, and different conditions were also tested (Table, entries 7-11). Using lithium (in THF or toluene) or magnesium as counterions (see **Experimental Part**), compound **6a** was also obtained in modest yield, with inversion of the stereochemical outcome: the major isomer is now **6a** (C4 *S*) with diastereomeric excesses ranging from 30% (entry 7), 52% (entry 8) to 62% (Table, entry 11). Conversely, when sodium hydride or potassium *t*-butoxide were used as base the same major isomer **6a** (C4 *R*) was obtained, but in a lower *R*:*S* ratio (75:25, Table, entry 9; 60:40, entry 10) compared with the initial conditions (Table, entry 6).

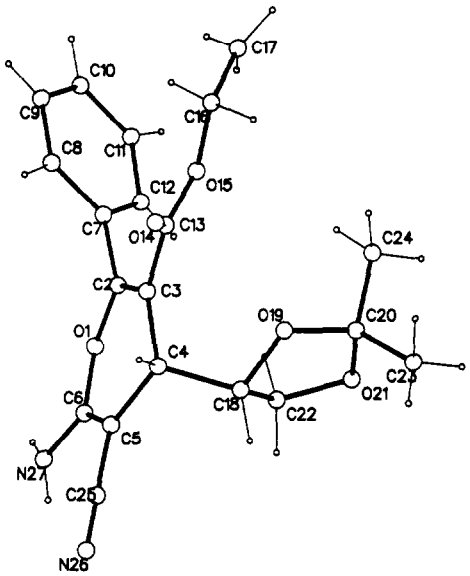


Figure 1. ORTEP diagram showing the atomic numbering scheme and solid state conformation of **6d** (C-4 *S*).

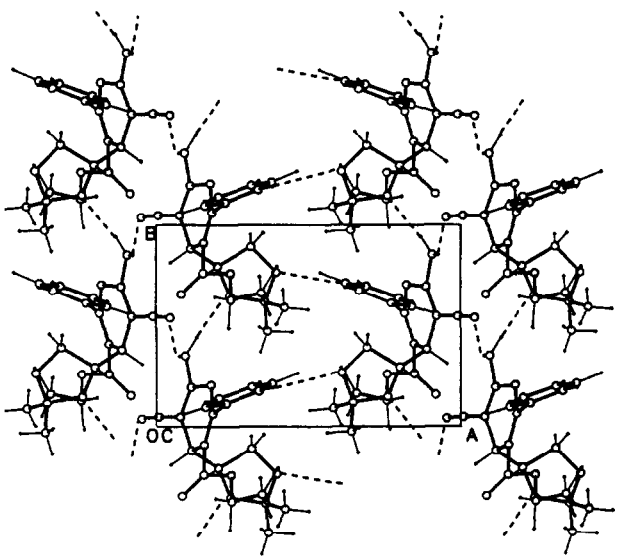


Figure 2. Packing diagram of compound **6d** (C-4 *S*).

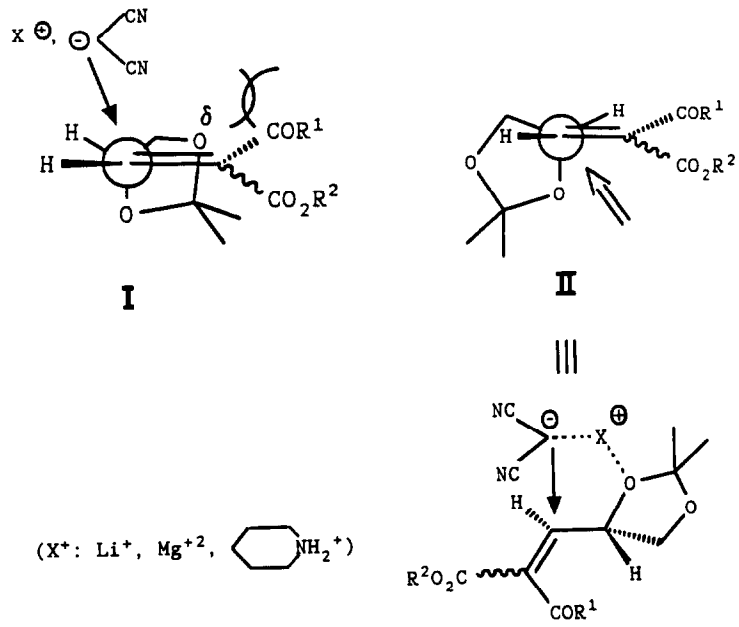


Figure 3

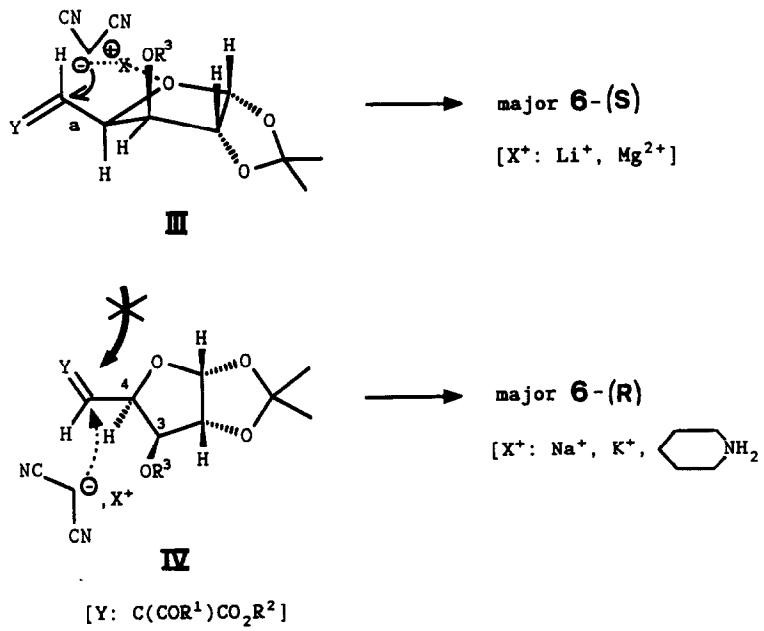


Figure 4

These observations point out that the effect of the counterion is playing an important role. In the formation of major **3** (C4 *R*) isomers in the base catalyzed addition of malononitrile to compounds **2** we can assume: the demonstrated similarity of the $C=C(COR^1)CO_2R^2$ group to C=O in many reactions[18] and that the electron-withdrawing γ-alkoxy group is perpendicular to the carbonyl plane (Felkin-Ahn model).[19] In the present case we could rationalize the observed results as shown in model I (Figure 3). We propose a non-chelated transition state, where the attacking nucleophile approaches from the face of the α-acylacrylate opposite to the electronegative oxygen. This is in good agreement with the results reported by Mulzer[2a] in the treatment of the γ-alkoxyalkenoate derived from D-glyceraldehyde acetonide with sodium methoxide. However, in this case it appears that the existence of a strong interaction between the carbonyl function and the $-CH_2O(\delta)$ destabilizes conformer I in favour of conformer II.[2h] Thus the major **3** (C4 *R*) isomer could be formed by chelation assisted reaction of the reagent from the same face as the oxygen atom[2g] (Figure 3).

In the preparation of major **6** isomers and, as qualitative model, we propose that for precursor **5**, the eclipsed conformation III (Figure 4) is strongly favoured due to the avoidance of 1,3-allylic strain.[20] However, partial rotation (30°) about bond **a** allows the system to adopt conformation IV (Figure 4) in which the electronegative oxygen atom is coplanar with the π-system. This conformation meets the stereoelectronic requirements for antiperiplanar addition of malononitrile,[21] but new destabilizing steric effects appear between the carbonyl group and C4-O, and a delicate balance in the equilibrium (III ⇌ IV) should result. For a low counterion´s affinity for oxygen (Na^+, K^+, $C_5H_{12}N^+$) a non chelated transition state where malononitrile attacks from the less hindered bottom face in IV (Figure 4) should operate. This stereocontrol may be reversed by introducing a chelating metal ion (Li^+, Mg^{+2}). Chelation from the ß face with the C4-O in conformer IV is prevented due to evident steric repulsion with the substituent at C-3. However, double chelation of the ion with C4-O/C3-O and delivering the nucleophile from the ß face, or perhaps better, a chelate as shown in conformer III, free of other destabilizing effects, leads to the opposite major isomer.

In summary, we have deeply explored for the first time the intermolecular Michael addition of malononitrile to some chiral α-acyl-ß-alkylacrylates and, althought diastereomeric excesses in the key nucleophilic addition and chemical yields are moderate, these studies show new insights in the Michael addition to γ-oxygenated alkenoates.

EXPERIMENTAL

All the reactions were performed under argon atmosphere and monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (5539, Merck). 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 was performed using Kiesselgel 60 and mixtures of ethyl acetate-hexane as eluent. Melting points were determined in capillary tubes and are uncorrected. Optical rotations

were determined in Perkin-Elmer 241 Polarimeter. ^1H and ^{13}C NMR spectra were recorded with a Varian XL-300 spectrometer, using tetramethylsilane as internal standard and $CDCl_3$ as the solvent.

Standard Procedure for the Synthesis of the Pyrans 3 and 6 using piperidine as base. To a solution of the diols **7**[6], **8a**[7] or **8b**[8] in methanol, cooled in an ice bath, an aqueous solution of sodium metaperiodate (1.2 equiv) was added. The mixture was warmed at room temperature (30 min), filtered over Celite 545 and the cake crushed washed with methanol; the filtrate was evaporated and the residue diluted with methylene chloride, washed with brine, dried and concentrated. The crude aldehyde was dissolved in toluene, cooled at -78°C, and piperidine (three drops) plus the appropiate ß-ketoester were added; after 3h, compounds **2** or **5** were obtained. Malononitrile (1.0 equiv) was added at -78°C and the mixture was warmed at room temperature for 24 h. The solvent was removed and the residue submitted to flash chromatography.[11]

Standard Procedure for the Synthesis of the Pyrans 3 and 6 using LDA as base. A stirred solution of dry diisopropylamine (1.0 equiv) in dry toluene or THF (1 mL / 0.2 mmol) was cooled at -78°C and treated with *n*-BuLi (1.0 equiv, 1.6 M in hexane) under argon. After the mixture was stirred for 20 min, a solution of malononitrile (1.0 equiv) in toluene or THF (1 mL / 0.2 mmol) was added dropwise at -78°C. After 30 min, a solution of the appropriate compound **2** or **5** (1.0 equiv) in toluene or THF (1 mL/ 0.2 mmol) was added at this temperature and the mixture was warmed at room temperature. After 45 min, saturated aqueous NH_4Cl was added. Extraction with ether, drying, concentration and flash chromatography (hexane/EtOAc, 7:3) gave the pyrans **3** or **6**.

Standard Procedure for the Synthesis of the Pyrans 3 and 6 using LDA/MgI_2-Et_2O as base. A stirred solution of dry diisopropylamine (1.0 equiv) in dry toluene (1 mL / 0.2 mmol) was cooled at -78°C and treated with *n*-BuLi (1.0 equiv, 1.6 M in hexane) under argon. After the mixture was stirred for 20 min, a solution of malononitrile (1.0 equiv) in toluene (1 mL / 0.2 mmol) was added dropwise at -78°C, and 30 min later, MgI_2Et_2O (1.2 equiv) was added. The solution was warmed to room temperature and stirred 10 min. The cloudy solution was cooled at -78°C and a solution of the appropriate compound **2** or **5** (1.0 equiv) in toluene (1 mL / 0.2 mmol) was added. The mixture was warmed at room temperature. After 60 min, saturated aqueous NH_4Cl was added. Extraction with ethyl acetate, drying, concentration and flash chromatography (hexane/EtOAc, 7:3) gave the pyrans **3** or **6**.

Standard Procedure for the Synthesis of the Pyran 6 using NaH as base. To a suspension of NaH (1.0 equiv) in dry THF (1 mL / 0.1 mmol) a solution of malononitrile (1.0 equiv) in THF (1 mL / 0.2 mmol) was added dropwise, at 0°C, under argon. After the mixture was stirred for 20 min, a solution of compound **5** (1.0 equiv) in THF (1 mL / 0.2 mmol) was added at 0°C and the mixture was warmed to room temperature. After 90 min, saturated aqueous NH_4Cl was added. Extraction with ether, drying, concentration and flash chromatography (hexane/EtOAc, 7:3) gave the pyran **6**.

Standard Procedure for the Synthesis of the Pyran 6 using *t*-BuOK as base. To a solution of *t*-BuOK (1.0 equiv) in dry THF (1 mL / 0.1 mmol) a solution of malononitrile (1.0 equiv) in THF (1 mL/ 0.2 mmol) was added dropwise, at -78°C, under argon. After the mixture was stirred for 20 min, a solution of compound **5** (1.0 equiv) in THF (1 mL / 0.2 mmol) was added and the mixture was warmed at room temperature. After 60 min, saturated aqueous NH_4Cl was added. Extraction with ether, drying, concentration and flash chromatography (hexane/EtOAc, 7:3) gave the pyran **6**.

Pyran 3a. Diol **7** (800 mg, 3.0 mmol) was transformed following the general procedure. Flash chromatography (hexane/EtOAc, 4:1) gave compound **3a** (308 mg, 36%) as a mixture of diastereomers that we could not separate in the flash chromatography. An aliquot was recrystallized from *n*-butanol giving **3a** in an improved diastereomeric excess (d.e.: 80%): m.p. 157-160°C; IR (KBr) ν: 3320, 2190, 1700 cm^{-1}; ^1H NMR (major isomer C-4 *R*) δ: 1.31 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.32 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 2.31 (d, J=0.7 Hz, 3H, =C-CH_3), 3.60 (dd, J=3.4 and 0.7 Hz, 1H, H-4), 3.87-4.20 (m, 3H, 2 H-1', H-2'), 4.23 (q, J=7.1 Hz, 2H, OCH_2CH_3), 4.64 (s, 2H, NH_2); ^{13}C NMR (major isomer C-4 *R*) δ: 14.01 (OCH_2CH_3), 18.37 (=C-CH_3), 24.96 and 25.85 (2 CH_3), 35.34 (C-4), 54.84 (C-3), 60.70 (OCH_2CH_3), 65.84 (C-1'), 79.21 (C-2'), 105.76 (C-5), 109.45 [$C(CH_3)_2$], 119.68 (CN), 158.74 (C-6), 160.76 (C-2), 166.04 ($CO_2CH_2CH_3$); MS *m/e* 308 (M^+, 14). Anal. Calcd. for $C_{15}H_{20}N_2O_5$: C, 58.44; H, 6.49; N, 9.09. Found: C, 58.29; H, 6.63; N, 8.76.

Pyran 3b. Diol **7** (800 mg, 3.0 mmol) was transformed according to the general procedure. Flash chromatography (hexane/EtOAc, 4:1) gave pyran **3b** (382 mg, 45% yield) as a mixture of diastereomers that we could not separate in the chromatography. An aliquot was recrystallized from *n*-butanol giving pure major **3b** (C-4 *R*) isomer: m.p. 180-182°C; $[\alpha]_D^{25}$ +40° (*c* 0.9, $CHCl_3$); IR (KBr) ν: 3320, 2180, 1715 cm^{-1}; ^1H NMR δ: 1.30 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.30 (s, 3H, =C-CH_3), 3.60 (d, J=3.0 Hz, 1H, H-4), 3.76 (s, 3H, OCH_3), 3.86-4.20 (m, 3H, 2 H-1', H-2'), 4.77 (s, 2H, NH_2); ^{13}C NMR δ: 18.47 (CH_3), 24.97 and 25.90 (2 CH_3), 35.44 (C-4), 51.76 (CO_2CH_3), 54.90 (C-3), 65.88 (C-1'), 78.23 (C-2'), 105.59 (C-5), 109.57 [$C(CH_3)_2$], 119.68 (CN), 159.02 (C-6), 160.81 (C-2), 166.64 (CO_2CH_3); MS *m/e* 294 (M^+, 2). Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.12; N, 9.52. Found: C, 57.21; H, 6.24; N, 9.38.

Pyran 3c. Diol **7** (800 mg, 3.0 mmol) was transformed into the pyran **3c** (555 mg, 51%), obtained as a mixture of diastereomers that we could not separate in the flash chromatography (hexane/EtOAc, 4:1). An aliquot was recrystallized from *n*-butanol giving pure major **3c** (C-4 *R*) isomer: m.p. 187-189°C; $[\alpha]_D^{25}$ +19° (*c* 1.1, $CHCl_3$); IR (KBr) ν: 3320, 2180, 1715 cm^{-1}; ^1H NMR δ: 0.93 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.32 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 3.75 (d, J=3.6 Hz, 1H, H-4), 3.94-4.08 (m, 4H, $CO_2CH_2CH_3$, 2 H-1'), 4.29-4.33 (m, 1H, H-2'), 4.73 (s, 2H, NH_2), 7.37-7.44 (m, 5H, C_6H_5); ^{13}C NMR δ: 13.41 ($CO_2CH_2CH_3$), 25.06 and 25.91 (2 CH_3), 36.43 (C-4), 54.85 (C-3), 60.81 ($CO_2CH_2CH_3$), 65.98 (C-1'), 78.30 (C-2'), 107.15 (C-5), 109.65 [$C(CH_3)_2$], 119.58 (CN), 127.89-129.95 (C_6H_5), 156.96 (C-6), 161.14 (C-2), 166.35 ($CO_2CH_2CH_3$); MS *m/e* 355 (M^+-15, 2). Anal. Calcd. for $C_{20}H_{22}N_2O_5$: C, 64.86; H,

5.94; N, 7.57. Found: C, 65.10; H, 5.98; N, 7.70.

Pyran 6a. Diol **8a** (777 mg, 2.5 mmol) was transformed into pyran **6a** following the standard procedure. Flash chromatography (hexane/EtOAc, 3:1) gave compound **6a** obtained as a mixture of diastereomers that we could not separate in the flash chromatography (640 mg, 58%; amorphous solid that we could not crystallize; d.e.: 64%): m p. 52-61°C; IR (KBr) ν: 3420, 2200, 1715 cm^{-1}; ^1H NMR (major isomer C-4 *R*) δ: 1.25 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.25 (s, 3H, =C-CH_3), 3.71 (s, 3H, CO_2CH_3), 3.90 (dd, $J_{3'4'}$=2.9 Hz, $J_{4,4'}$=9.7 Hz, 1H, H-4'), 4.04 (d, $J_{3'4'}$=2.9 Hz, 1H, H-3'), 4.06 (d, $J_{4,4'}$=9.7 Hz, 1H, H-4), 4.58 (d, $J_{1'2'}$=3.9 Hz, 1H, H-2'), 4.59 (d, J=10.7 Hz, 1H, $OCH_2C_6H_5$), 4.79 (d, J=10.7 Hz, 1H, $OCH_2C_6H_5$), 4.82 (s, 2H, NH_2), 5.82 (d, $J_{1'2'}$=3.9 Hz, 1H, H-1'), 7.27 (m, 5H, C_6H_5); ^{13}C NMR (major isomer C-4 *R*) δ: 18.10 (=C-CH_3), 26.21 and 26.78 (2 CH_3), 31.20 (C-4), 51.61 (CO_2CH_3), 55.70 (C-3), 71.18 ($OCH_2C_6H_5$), 81.44, 83.06, 84.50 (C-2',3',4'), 104.88 (C-1'), 108.08 [$C(CH_3)_2$], 111.59 (C-5), 119.43 (CN), 127.67-137.39 (C_6H_5), 156.30 (C-2), 160.66 (C-6), 167.00 (CO_2CH_3); MS *m/e* 334 (2), 91 (100). Anal. Calcd. for $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.13; H, 5.61; N, 6.07.

Pyran 6b. Diol **8a** (904 mg, 2.91 mmol) was converted into pyran **6b** (505 mg, 33%) obtained as a mixture of diastereomers that we could not separate in the flash chromatography (hexane/EtOAc, 7:3): m.p. 70-77°C (amorphous solid that we could not recrystallize; d.e.: 48%); IR (KBr) ν: 3400, 2200, 1720 cm^{-1}; ^1H NMR (major isomer C-4 *R*) δ: 0.92 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.29 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.97 (q, J=7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.00-4.15 (m, 3H, H-3',4,4'), 4.60 (d, $J_{1'2'}$=3.8 Hz, 1H, H-2'), 4.60 (s, 2H, NH_2), 4.62 (d, J=10.9 Hz, 1H, $OCH_2C_6H_5$), 4.80 (d, J=10.9 Hz, 1H, $OCH_2C_6H_5$), 5.84 (d, $J_{1'2'}$=3.8 Hz, 1H, H-1'), 7.28 (m, 10H, C_6H_5); ^{13}C NMR (major isomer C-4 *R*) δ: 13.29 ($CO_2CH_2CH_3$), 25.93 and 26.56 (2 CH_3), 32.57 (C-4), 54.92 (C-3), 60.59 ($OCH_2C_6H_5$), 71.17 ($CO_2CH_2CH_3$), 81.20, 81.38, 84.45 (C-2',3',4'), 104.67 (C-1'), 111.16 [$C(CH_3)_2$], 111.29 (C-5), 119.50 (CN), 127.42-137.62 (2 C_6H_5), 153.92 (C-2), 161.64 (C-6), 166.65 ($CO_2CH_2CH_3$); MS *m/e* 269 (20), 91(100). Anal. Calcd. for $C_{29}H_{30}N_2O_7$: C, 67.17; H, 5.83; N, 5.40. Found: C, 67.21; H, 5.65; N, 5.31.

Pyran 6c. Diol **8b** (950 mg, 4.0 mmol) was transformed into pyran **6c** following the standard procedure; after flash chromatography (hexane/EtOAc, 4:1) we have obtained **6c** (C-4 *S*) (248 mg, 17%) and **6c** (C-4 *R*) (570 mg, 39%).

6c (C-4 *S*): m.p. 115-117°C; $[\alpha]_D^{25}$ +76° (*c* 0.55, $CHCl_3$); IR (KBr) ν: 3390, 2200, 1720 cm^{-1}; ^1H NMR δ: 1.30 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.46 (s, 3H, =C-CH_3), 3.33 (s, 3H, OCH_3), 3.68 (d, $J_{3'4'}$=3.3 Hz, 1H, H-3'), 3.79 (s, 3H, CO_2CH_3), 4.27 (dd, $J_{4,4'}$=5.7 Hz, $J_{3',4'}$=3.3 Hz, 1H, H-4'), 4.32 (d, $J_{4,4'}$=5.7 Hz, 1H, H-4), 4.54 (d, $J_{1'2'}$=3.8 Hz, 1H, H-2'), 5.80 (s, 2H, NH_2), 5.84 (d, $J_{1'2'}$=3.8 Hz, 1H, H-1'); ^{13}C NMR δ: 19.45 (=C-CH_3), 26.12 and 26.69 (2 CH_3), 38.49 (C-3), 40.60 (C-4), 52.98 (OCH_3), 56.26 (CO_2CH_3), 77.67, 80.66, 82.99 (C-2',3',4'), 104.05 (C-1'), 111.23 [$C(CH_3)_2$], 112.21 (C-5), 115.63 (CN), 142.54 (C-6), 147.94 (C-2), 169.42 (CO_2CH_3); MS *m/e* 325 (5), 87 (100). Anal. Calcd. for $C_{17}H_{22}N_2O_7$: C, 55.73; H, 6.05; N, 7.65. Found: C, 55.95; H, 6.06; N, 7.90.

6c (C-4 *R*): m.p. 204-207°C; $[\alpha]_D^{25}$ -2° (*c* 0.22, $CHCl_3$); IR (KBr) ν: 3400, 2200, 1715 cm^{-1}; ^1H NMR δ: 1.29 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 2.26 (s, 3H, =C-CH_3), 3.46 (s, 3H OCH_3), 3.74 (s, 3H, CO_2CH_3), 3.75 (d, $J_{3',4'}$=3.1 Hz, 1H, H-3'), 3.84 (dd, $J_{3',4'}$=3.1 Hz, $J_{4,4'}$=9.8 Hz, 1H, H-4'), 3.95 (d, $J_{4,4'}$=9.8 Hz, 1H, H-4), 4.56 (d, $J_{1',2'}$=3.9 Hz, 1H, H-2'), 4.74 (s, 2H, NH_2), 5.82 (d, $J_{1',2'}$=3.9 Hz, 1H, H-1'); ^{13}C NMR δ: 18.09 (=C-*C*H_3), 25.91 and 26.52 (2 CH_3), 31.50 (C-4), 51.79 (OCH_3), 55.72 (C-3), 56.89 (CO_2CH_3), 80.63, 82.74, 84.46 (C-2',3',4'), 104.81 (C-1'), 108.26 [*C*$(CH_3)_2$], 111.23 (C-5), 119.27 (CN), 156.42 (C-6), 161.20 (C-2), 167.11 (*C*O_2CH_3); MS *m/e* 366 (M^+, 1). Anal. Calcd. for $C_{17}H_{22}N_2O_7$: C, 55.73; H, 6.05; N, 7.65. Found: C, 55.57; H, 6.17; N, 7.36.

Pyran 6d. Diol **8b** (750 mg, 3.0 mmol) was transformed into pyran **6d** (789 mg, 59%; flash chromatography, hexane/EtOAc, 4:1), obtained as a mixture of diastereomers that we could not separate in the chromatography (d.e.:52%). An aliquot was recrystallized from hexane/EtOAc giving pure minor **6d** (C-4 *S*) isomer [major **6d** (C-4 *R*) isomer remained in the mother liquors, impurified with **6d** (C-4 *S*) and could not be isolated pure)]: m.p. 193-195°C; $[\alpha]_D^{25}$ -47° (*c* 0.6, $CHCl_3$); IR (KBr) ν: 3390, 2200, 1710 cm^{-1}; ^1H NMR δ: 1.01 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.31 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.38 (s, 3H, OCH_3), 3.77 (d, $J_{3',4'}$=3.7 Hz, 1H, H-3'), 3.92 (d, $J_{4,4'}$=6.2 Hz, 1H, H-4), 4.00 (q, *J*=7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.22 (dd, $J_{4,4'}$=6.2 Hz, $J_{4',3'}$=3.7 Hz, 1H, H-4'), 4.58 (d, $J_{1',2'}$=3.9 Hz, 1H, H-2'), 4.61 (s, 2H, NH_2), 5.89 (d, $J_{1',2'}$=3.9 Hz, 1H, H-1'), 7.26 (m, 5H, C_6H_5); ^{13}C NMR δ: 13.55 ($CO_2CH_2CH_3$), 26.17 and 26.77 (2 CH_3), 33.80 (C-4), 56.97 (OCH_3), 57.65 (C-3), 60.82 ($CO_2CH_2CH_3$), 81.28, 83.09, 84.39 (C-2',3',4'), 104.85 (C-1'), 108.94 [*C*$(CH_3)_2$], 111.51 (C-5), 119.33 (CN), 127.79-133.00 (*C*$_6H_5$), 154.81 (C-2), 160.84 (C-6), 166.54 (*C*$O_2CH_2CH_3$); MS *m/e* 442 (M^+, 1). Anal. Calcd. for $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.55; H, 5.89; N, 6.56. **X-ray Crystall Structure Analysis of 6d** (C-4 *S*) $C_{23}H_{26}N_2O_7$, M_r 442.468, monoclinic, $P2_1$, a=14.08(1) Å, b=8.402(3) Å, c=10.3741(4) Å, b=102.506(3)°, V=11477(1) $Å^3$, Z=2, Dc=1.282 g/cm^3, F(000)=468, m=756 cm^{-1}. Refined cell parameters were obtained from setting angles of 86 reflections. A prismatic colorless crystall (0.31x0.10x0.07 mm) was used for the analysis. *Data collection*: Automatic four circle diffractometer Philips PW 1100 with graphite oriented monochromated Cu-Kα radiation. The intensity data were collected using the w/2q scan mode between $2<\theta<65°$; two standard reflections were measured every 90 minutes with no intensity variation. A total of 2111 reflections were measured and 1936 were considered as 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 and succesive Fourier synthesis. H Atoms were located from Fourier difference; except five of them, H atoms were included in a mixed refinement together with their isotropic thermal parameters. A convenient weighting scheme was applied to obtain flat dependence in $<w\Delta^2F>$ vs. $<F_o>$ and $<\sin\theta/l>$. Final R (Rw) values were 3.9 (4.5). Atomic scattering factors were taken from International Tables for X-Ray Crystallography.[22] Figure 1 shows the structures with their atom labelling. Figure 2 shows a packing diagram of the title compound.

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