Michael Addition of Benzoylacetonitrile to Chiral α-Cyanoacrylates Derived from Enantiomerically Pure α-Hydroxyaldehydes: Synthesis of 3-Alkoxycarbonyl-4-alkyl-2-amino-5-cyano-6-phenyl-4*H*-pyrans

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We describe the Michael addition of benzoylacetonitrile to α-cyanoacrylates **4a-c** and **5a** obtained from readily available chiral α-hydroxyaldehydes **1a-c**. The resulting polyfunctionalized 4-alkyl-2-amino-4*H*-pyrans **6a-c**, **7a** have been obtained in good yield and moderate diastereoselectivity.

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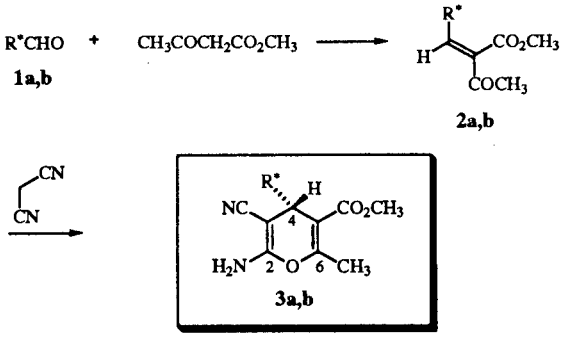
In a previous communication [1] from these laboratories we have reported the Michael reaction between malononitrile and some chiral α-acylacrylates **2a,b** derived from readily available, enantiomerically pure α-hydroxyaldehydes **1a,b** (see Scheme 1). The resulting, densely functionalized 2-amino-4*H*-pyrans [2] **3a,b** have been obtained in good yield and moderate diastereoselectivity.

Scheme 1



In order to gain a new insight into the stereochemical outcome of this unprecedented asymmetric Michael addition [3], we have now designed a different, alternative approach, based on the 1,4-conjugate addition of benzoylacetonitrile to chiral α-cyanoacrylates derived from enantiomerically pure α-hydroxyaldehydes. In addition, the expected chiral 3-alkoxycarbonyl-4-alkyl-2-amino-4*H*-pyrans **6** (Scheme 2) are isomers of those previously synthesized [1] and will be of interest in order to test comparative biological or pharmacological activity.

As shown in Scheme 2, starting from 2,3-*O*-isopropylidene-D-glyceraldehyde [4] (**1a**), 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylopentodialdofuranose [5] (**1b**) and (*S*)-2-*O*-benzyl-2-hydroxypropionaldehyde [6] (**1c**), the Knoevenagel condensation with methyl or ethyl cyanoacetate, in mild and non-racemizing conditions [7,8], gave the desired (*E*)-α-cyanoacrylates **4** and **5** in good yield, and as the only detected and isolated isomer. Cyanoacrylate **4c** could not be isolated by chromatography due to its instability in silica-gel and was used without further purification. The assignment as *E* of the stereochemistry of the double bond in compounds **4** and **5** is based on the results of the analogous reported reactions already described in the literature and by comparison of the ^1H and ^{13}C nmr data with the reference compounds [9].

Subsequent treatment of compounds **4** and **5** with benzoylacetonitrile, in toluene as solvent and piperidine as catalyst, afforded the 2-amino-4*H*-pyrans **6** and **7** in good yield and moderate diastereomeric excess (Table 1). Lowering the reaction temperature at -78° slightly increased the d.e. (50%), but slowed down the reaction time (8 hours) and the chemical yield (64%).

Unfortunately, we were unable to separate the stereo-

Scheme 2

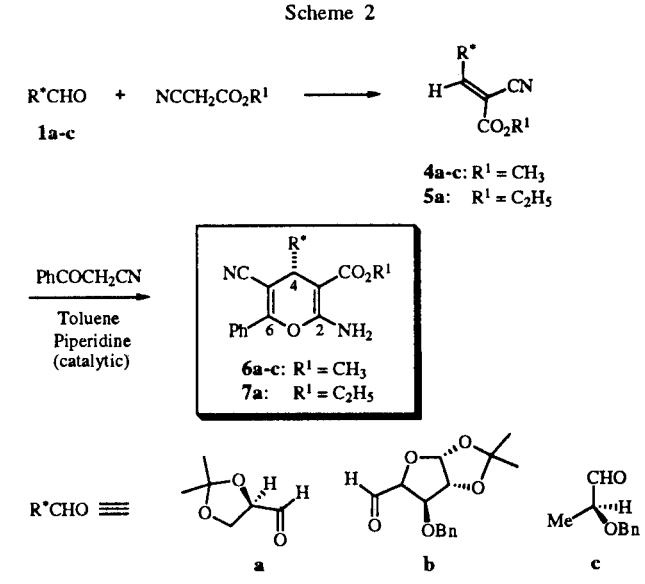


Table 1

2-Amino-4*H*-pyrans **6a-c** and **7a**

	d.e. (%)	Yield (%)
6a	40	74
6b	52	71
6c	20	61
7a	40	70

isomers at C-4 by chromatography or recrystallization. All these compounds showed coherent spectroscopic values and satisfactory analytical data. In the ir spectra typical and expected signals were observed: 3420-3400 and 3320-3300 cm^{-1} (NH), 2200 cm^{-1} (CN), 1690 cm^{-1} (α,β-unsaturated carbonyl group). In the ^1H nmr spectra we could observe significant differences for the major and minor isomers at C-4 (see Table 2). From these data it was evident that in these substrates the major isomer has the same absolute configuration at C-4 in the new stereocenter.

Table 2

Selected ^1H NMR Data of Compounds **6a-c**, **7a**

		H-4
6a	major.	3.88 (d), J = 3.6 Hz
	minor.	3.63 (d), J = 4.5 Hz
6b	major.	4.19 (d), J = 7.5 Hz
	minor.	4.07 (s)
6c	major.	3.95 (d), J = 3.3 Hz
	minor.	4.07 (s)
7a	major.	3.91 (d), J = 3.6 Hz
	minor.	3.65 (d), J = 4.5 Hz

By analogy with the chemical shift (H-4) and vicinal coupling constants ($J_{4,4'}$) of the new substrates **6a** and **7a** with the same data for the major isomer **3a**[1] (major isomer: $J_{4,4'}$ = 3.3 Hz; minor isomer $J_{4,4'}$ = 5.2 Hz), we can conclude that the absolute configuration at C-4 in the major isomer of compounds **6a** and **7a** is also **R**.

In summary, we have described for the first time the Michael addition of benzoylacetonitrile to chiral α-cyanoacrylates, readily available from chiral α-hydroxyaldehydes, leading to polyfunctionalized 2-amino-4*H*-pyrans in good yield and moderate diastereoselectivity.

EXPERIMENTAL

All the reactions were monitored by tlc using precoated silica gel aluminum plates containing a fluorescent indicador (Merck, 5539). Detection was by uv (250 nm). Flash column chromatography [10] was performed using Kieselgel 60 (230-400 mesh, Merck) and hexane-ethyl acetate mixtures as the eluent. Melting points were recorded with a Perkin-Elmer 681 spectrometer as potassium bromide pellets. The ^1H nmr spectra were recorded on a Varian XL-300 spectrometer. The ^{13}C nmr spectra were recorded on a Bruker AM-200 (50 MHz). Elemental analyses were obtained by the Microanalysis Service of IQOG (CSIC).

General Procedure for the Synthesis of Compounds **4a** and **5a**.

To a solution of 1,2;5,6-di-*O*-isopropylidene-D-mannitol (1.0 equivalent) in dry tetrahydrofuran, lead tetraacetate (1.1 equivalents) was added at 0°. After 5 minutes, the appropriate cyanoacetate (2.3 equivalents) and acetic anhydride (4.3 equivalents) were added and the reaction was refluxed for 18 hours. The mixture was filtered over Celite 541. The solvent was evaporated and the residue submitted to flash chromatography. Compounds **4a** and **5a** were obtained and isolated as the only pure *E* isomers.

Methyl α-Cyano-β-[2',2'-dimethyl-1',3'-dioxolan-4'(*S*)-yl]acrylate (**4a**).

1,2;5,6-Di-*O*-isopropylidene-D-mannitol (0.6 g, 2.3 mmoles, 1.0 equivalent) was transformed following the general procedure using methyl cyanoacetate (0.53 g, 53.5 mmoles, 2.3 equivalents). Flash chromatography (hexane/ethyl acetate, 17:3) gave compound **4a** (0.372 g, yield 77%) as an oil; ir (film): ν 3000, 2960, 2880, 2240, 1745, 1635, 1440, 1385, 1375, 1260, 1220, 1070 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.58 (d, 1H, J = 7.8 Hz, HC=C), 5.06 (q, 1H, J = 6.6 Hz, CHO), 4.34 (dd, 1H, J = 6.6 and 8.7 Hz, HC*H*), 3.89 (s, 3H, OCH_3), 3.79 (dd, 1H, J = 6.3 and 8.7 Hz, HC*H*), 1.49 (s, 3H, CH_3), 1.43 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 160.8 (CO_2CH_3), 159.4 (HC=C), 112.5 (CN), 111.2 (C=CH), 109.7 [$C(CH_3)_2$], 73.5 (CHO), 68.0 (CH_2O), 53.3 (CO_2CH_3), 26.2 (CH_3), 25.2 (CH_3).

Anal. Calcd. for $C_{10}H_{13}NO_4$ (211.22): C, 56.86; H, 6.20; N, 6.63. Found: C, 56.68; H, 6.35; N, 6.98.

Ethyl α-Cyano-β-[2',2'-dimethyl-1',3'-dioxolan-4'(*S*)-yl]acrylate (**5a**).

1,2;5,6-Di-*O*-isopropylidene-D-mannitol (3.0 g, 11.4 mmoles, 1.0 equivalent) was transformed following the general procedure using ethyl cyanoacetate (2.966 g, 26.22 mmole, 2.3 equivalents). Flash chromatography (hexane/ethyl acetate, 17:3) gave compound **5a** (2.032 g, yield 79%) as an oil; ir (film): ν 2980, 2930, 2240, 1740, 1640, 1430, 1385, 1375, 1230, 1070 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.56 (d, 1H, J = 8.1 Hz, HC=C), 5.06 (m, 1H, CHO), 4.35 (q, 2H, $CO_2CH_2CH_3$), 4.34 (dd, 1H, J = 6.6 and 8.7 Hz, HC*H*), 3.80 (dd, 1H, J = 6.3 and 8.7 Hz, HC*H*), 1.49 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.37 (t, 3H, $CO_2CH_2CH_3$); ^{13}C nmr (deuteriochloroform): δ 160.3 ($CO_2CH_2CH_3$), 159.0 (HC=C), 112.6 (CN), 111.3 (C=CH), 110.3 [$C(CH_3)_2$], 73.6 (CHO), 68.2 (CH_2O), 62.8 ($CO_2CH_2CH_3$), 26.3 (CH_3), 25.3 (CH_3), 13.9 ($CO_2CH_2CH_3$).

Anal. Calcd. for $C_{11}H_{15}NO_4$ (225.24): C, 58.66; H, 6.71; N, 6.22. Found: C, 58.84; H, 6.93; N, 5.90.

General Procedure for the Synthesis of Compounds **4b-c**.

To a solution of the aldehyde **1b-c** (1.0 equivalent) in dry toluene, methyl cyanoacetate (1.0 equivalent) and piperidine (drops) were added. The mixture was stirred for 3 hours at room temperature. The solvent was evaporated and the residue submitted to flash chromatography.

Methyl α-Cyano-β-[4'(*R*),5'(*R*)-isopropyliden-3'(*S*)-benzyloxy-tetrahydrofur-2'(*R*)-yl]acrylate (**4b**).

A solution of aldehyde **1b** (1.0 g, 3.6 mmoles, 1.0 equivalent) was allowed to react following the general procedure. Flash

chromatography (hexane/ethyl acetate, 9:1 and 4:1) gave compound **4b** (1.0 g, yield 78%) as an oil; ir (film): ν 3060, 3025, 2990, 2970, 2240, 1750, 1640, 1500, 1460, 1440, 1380, 1260, 1170 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.66 (d, 1H, J = 7.2 Hz, HC=C), 7.38-7.22 (m, 5H, aromatic), 6.05 (d, 1H, J = 3.9 Hz, H-5'), 5.11 (dd, 1H, J = 3.6 and 7.2 Hz, H-4'), 4.67 (d, 1H, J = 3.9 Hz, H-2'), 4.64 (d, 1H, J = 12.0 Hz, OCH_2Ph), 4.45 (d, 1H, J = 12.0 Hz, OCH_2Ph), 4.24 (d, 1H, J = 3.6 Hz, H-3'), 3.90 (s, 3H, OCH_3), 1.51 (s, 3H, CH_3), 1.33 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{21}NO_6$ (359.38): C, 63.50; H, 5.89; N, 3.89. Found: C, 63.79; H, 6.03; N, 3.51.

General Procedure for the Synthesis of Pyrans **6** and **7**.

To a solution of compounds **4a-d** or **5a** (1.0 equivalent) in dry toluene, benzoylacetonitrile (1.2 equivalents) and piperidine (several drops) were added. The mixture was stirred at room temperature for 1.5-20 hours. The solvent was removed and the residue submitted to flash chromatography.

2-Amino-5-cyano-4-[2',2'-dimethyl-1',3'-dioxolan-4'(*S*)-yl]-3-methoxycarbonyl-6-phenyl-4*H*-pyran (**6a**).

Compound **4a** (0.602 g, 2.85 mmoles) was transformed by following the general procedure (1.5 hours at room temperature). Flash chromatography (hexane/ethyl acetate, 9:1 and 17:3) gave compound **6a** (0.750 g, yield 74%) as a mixture of diastereomers (70:30) that we could not separate by chromatography. The compound obtained was an amorphous solid that we could not recrystallize, mp 52-54°; ir (potassium bromide): ν 3420, 3320, 2990, 2940, 2220, 1690, 1645, 1620, 1530, 1440, 1380, 1300, 1250 cm^{-1}; ^1H nmr (deuteriochloroform): major diastereomer, δ 7.80 (m, 2H, aromatic), 7.48 (m, 3H, aromatic), 6.39 (br s, 2H, NH_2), 4.37 (ddd, 1H, J = 3.6 and 6.6 Hz, CHO), 3.99 (dd, 1H, J = 6.6 and 8.7 Hz, HC*H*), 3.88 (d, 1H, J = 3.6 Hz, H-4), 3.76 (s, 3H, OCH_3), 3.69 (dd, 1H, J = 6.6 and 8.7 Hz, HC*H*), 1.52 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): major diastereomer, δ 168.4 (CO_2CH_3), 160.5, 160.2 (C-2 and C-6), 131.4, 130.2, 128.6, 127.9 (aromatic), 118.2 (CN), 109.7 [$C(CH_3)_2$], 89.3 (C-5), 78.2 (CHO), 73.4 (C-3), 65.5 (CH_2O), 51.1 (CO_2CH_3), 36.6 (C-4), 25.9 (CH_3), 24.9 (CH_3); ^{13}C nmr (deuteriochloroform): minor diastereomer, δ 168.2 (CO_2CH_3), 160.7, 160.5 (C-2 and C-6), 131.4, 130.3, 128.6, 127.9 (aromatic), 118.8 (CN), 109.5 [$C(CH_3)_2$], 89.0 (C-5), 79.7 (CHO), 75.0 (C-3), 66.3 (CH_2O), 51.1 (CO_2CH_3), 37.4 (C-4), 26.4 (CH_3), 25.1 (CH_3); ms: (70 eV) m/z 341 (M^+-15, 2), 299 (3), 255 (64), 223 (18), 156 (14), 140 (14), 105 (90), 101 (34), 77 (64), 43 (100).

Anal. Calcd. for $C_{19}H_{20}N_2O_5$ (356.38): C, 64.03; H, 5.65; N, 7.86. Found: C, 64.03; H, 6.00; N, 7.71.

2-Amino-5-cyano-3-ethoxycarbonyl-4-[2',2'-dimethyl-1',3'-dioxolan-4'(*S*)-yl]-6-phenyl-4*H*-pyran (**7a**).

Compound **5a** (5.1 g, 22.6 mmoles) was transformed following the general procedure (1.5 hours at room temperature). Flash chromatography (hexane/ethyl acetate, 9:1 and 17:3) gave compound **7a** (5.867 g, yield 70%) as a mixture of diastereomers (70:30) that we could not separate by chromatography. The compound was obtained as an amorphous solid that we could not recrystallize, mp 117-122°; ir (potassium bromide): ν 3400, 3300, 2990, 2930, 2870, 2220, 1690, 1645, 1620, 1540, 1450, 1410, 1385, 1375, 1255 cm^{-1}; ^1H nmr (deuteriochloroform): major diastereomer, δ 7.80 (m, 2H, aromatic), 7.46 (m, 3H, aromatic), 6.34 (br s, 2H, NH_2), 4.38 (ddd, 1H, J = 3.6 and 6.6 Hz, CHO), 4.23 (q, 2H, $COOCH_2CH_3$), 3.99 (dd, 1H, J = 6.6 and 8.7 Hz, HC*H*), 3.91 (d, 1H, J = 3.6 Hz, H-4), 3.70 (dd, 1H, J = 6.6 and 8.7 Hz, HC*H*), 1.52 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.32 (t, 3H, $COOCH_2CH_3$); ^{13}C nmr (deuteriochloroform): major diastereomer, δ 168.0 (CO_2CH_3), 160.5, 160.1 (C-2 and C-6), 131.4, 130.1, 129.0, 128.3 (aromatic), 118.4 (CN), 109.6 [$C(CH_3)_2$], 89.0 (C-5), 78.1 (CHO), 73.2 (C-3), 65.4 (CH_2O), 59.9 ($CO_2CH_2CH_3$), 36.3 (C-4), 25.9 (CH_3), 24.9 (CH_3), 14.4 ($CO_2CH_2CH_3$); ^{13}C nmr (deuteriochloroform): minor diastereomer, δ 168.0 (CO_2CH_3), 160.7, 160.5 (C-2 and C-6), 131.3, 130.2, 128.5, 127.9 (aromatic), 118.9 (CN), 109.4 [$C(CH_3)_2$], 88.9 (C-5), 79.8 (CHO), 74.9 (C-3), 66.3 (CH_2O), 59.9 ($CO_2CH_2CH_3$), 37.3 (C-4), 26.3 (CH_3), 25.1 (CH_3), 14.4 ($CO_2CH_2CH_3$); ms: (70 eV) m/z 355 (M^+-15, 1), 313 (1), 269 (43), 241 (4), 223 (14), 169 (5), 156 (6), 140 (7), 105 (100), 101 (11), 77 (68), 43 (35).

Anal. Calcd. for $C_{20}H_{22}N_2O_5$ (370.41): C, 64.85; H, 5.98; N, 7.56. Found: C, 65.04; H, 6.05; N, 7.50.

2-Amino-5-cyano-4-[4'(*R*),5'(*R*)-isopropyliden-3'(*S*)-benzyloxytetrahydrofur-2'(*R*)-yl]-3-methoxycarbonyl-6-phenyl-4*H*-pyran (**6b**).

Compound **4b** (1.040 g, 2.89 mmoles) was transformed following the general procedure (18 hours at room temperature). Flash chromatography (hexane/ethyl acetate, 9:1, 4:1, 7:3 and 3:2) gave compound **6b** (0.824 g, yield 71%) as a mixture of diastereomers (76:24) that we could not separate by chromatography. The compound was obtained as an amorphous solid that we could not recrystallize, mp 76-78°; ir (film): ν 3420, 3300, 2980, 2940, 2880, 2220, 1690, 1640, 1610, 1530, 1440, 1380, 1300, 1260, 1230, 1170 cm^{-1}; ^1H nmr (deuteriochloroform): major diastereomer, δ 7.57-7.18 (m, 10H, aromatic), 6.23 (br s, 2H, NH_2), 5.99 (d, 1H, J = 3.9 Hz, H-1'), 4.57 (d, 1H, J = 3.9 Hz, H-2'), 4.56 (s, 2H, OCH_2Ph), 4.29 (dd, 1H, J = 7.5 and 3.3 Hz, H-4'), 4.19 (d, 1H, J = 7.5 Hz, H-4), 4.00 (d, 1H, J = 3.3 Hz, H-3'), 3.73 (s, 3H, OCH_3), 1.48 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ms: m/z 504 (M^+, 10), 489 (23), 471 (20), 359 (43), 277 (6), 255 (67), 105 (42), 91 (100).

Anal. Calcd. for $C_{28}H_{28}N_2O_7$ (504.54): C, 66.65; H, 5.59; N, 5.55. Found: C, 66.37; H, 5.28; N, 5.38.

2-Amino-4-[1'(*S*)-benzyloxyethyl]-5-cyano-3-methoxycarbonyl-6-phenyl-4*H*-pyran (**6c**).

Compound **4c** (1.136 g, 4.63 mmoles) was transformed following the general procedure (6 hours at room temperature). Flash chromatography (hexane/ethyl acetate, 9:1 and 4:1) gave compound **6c** (1.209 g, yield 67%) as a mixture of diastereomers (60:40) that we could not separate by chromatography. The compound was obtained as an oil; ir (potassium bromide): ν 3500, 3410, 3320, 3065, 3030, 2980, 2950, 2870, 2220, 1700, 1650, 1620, 1530, 1450, 1400, 1380, 1365, 1310, 1260, 1230 cm^{-1}; ^1H nmr (deuteriochloroform): major diastereomer, δ 7.82-7.22 (m, 10H, aromatic), 6.27 (br s, 2H, NH_2), 4.60 (d, 1H, J = 12.0 Hz, OCH_2Ph), 4.24 (d, 1H, J = 12.0 Hz, OCH_2Ph), 3.95 (d, 1H, J = 3.3 Hz, H-4), 3.71 (m, 1H, CH), 3.70 (s, 3H, $COOCH_3$), 1.13 (d, 3H, J = 6.6 Hz, CH_3); ^{13}C nmr (deuteriochloroform): major and minor diastereomers, δ 168.6, 168.5 (CO_2CH_3), 160.7, 160.2, 160.2, 160.0 (C-2 and C-6), 138.5-127.2 (aromatics), 119.1, 118.3 (CN), 88.9, 88.8 (C-5), 77.8, 77.0 (CH), 75.5, 74.2 (C-3), 70.9, 70.5 (CH_2Ph), 51.1, 51.0 (CO_2CH_3), 39.5, 37.6 (C-4), 16.7, 14.9 (CH_3).

Anal. Calcd. for $C_{23}H_{22}N_2O_4$ (390.44): C, 70.75; H, 5.68; N, 7.17. Found: C, 70.68; H, 5.87; N, 7.31.

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