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Hetero-*Diels-Alder* reaction of propenenitriles with enol ethers: a convenient approach to functionalized 3,4-dihydro-2*H*-pyrans

Aleksandra Pałasz, Krystyna Bogdanowicz-Szwed

Department of Organic Chemistry, Jagiellonian University, Kraków, Poland

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Abstract The hetero-*Diels-Alder* reaction of 3-(*N*-acetyl-*N*-benzylamino)-2-formylprop-2-enenitrile with enol ethers yielded *cis*/*trans* diastereoisomers of 2-alkoxy-4-amino-3,4-dihydro-2*H*-pyran-5-carbonitriles in moderate yields. Acidic hydrolysis of *cis*-diastereoisomer in concentrated sulfuric acid gave 2-oxo-1,2-dihydropyrydine-3-carbaldehyde. The reaction of 2-benzoyl-3-heteroaromaticprop-2-enenitriles with enol ethers afforded diastereoisomeric *cis*/*trans* cycloadducts in good yields. The structure of the products is discussed in terms of configuration and preferred conformation.

Keywords *Diels-Alder* reaction; Pyrans; α,β-Unsaturated carbonyl compounds; Enol ethers.

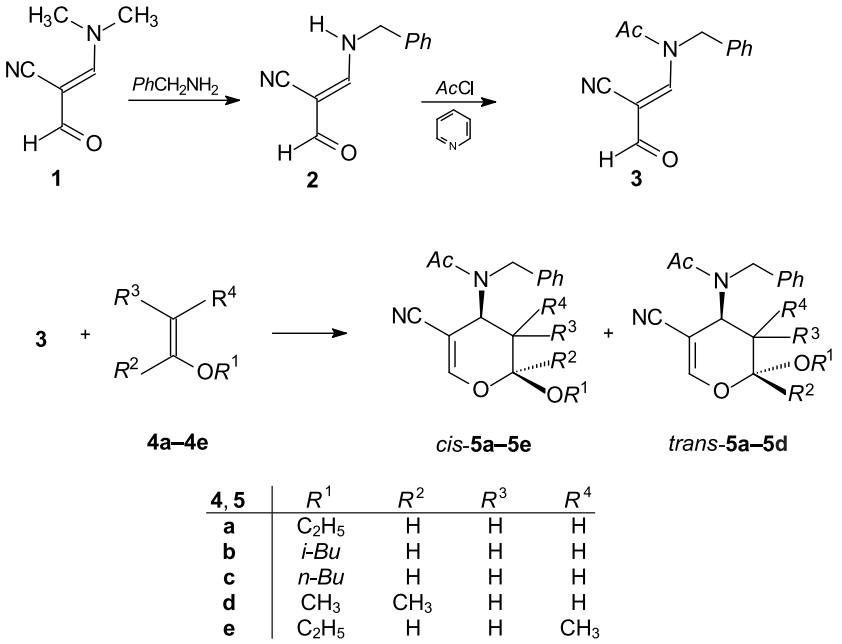
Introduction

Pyran derivatives are common structural subunits in a variety of important natural products, including carbohydrates, alkaloids, polyether antibiotics, pheromones, and iridoids. Especially 3-amino sugars are of great interest as parts of biological active compounds or because of their own potential biological activity. They are present in various antibiotics such as gentamycin C or adriamycin [1, 2]. Amino derivatives of 3,4-dihydro-2*H*-pyrans can be efficiently synthesized by an inverse-electron-demand hetero-*Diels-Alder* (H*DA*) reactions of α,β-unsaturated carbonyl compounds representing an 1-oxa-1,3-butadiene system with enol ethers [1–6]. It was stated that introducing an electron withdrawing group in the 1-oxa-1,3-diene system can enhance their reactivity [7–12]. Among the electron withdrawing substituents, the cyano group was found to have the most pronounced influence on facilitating the reaction of 1-oxadienes with enol ethers. *Wyler et al.* have reported that α,β-unsaturated acyl cyanides exhibit an extraordinary reactivity towards enol ethers, yielding 3,4-dihydro-2*H*-pyran-6-carbonitriles at room temperature [7, 8]. Recently, we have reported that H*DA* reactions of 3-cyano-1-oxa-1,3-butadienes with enol ethers [13, 14], styrenes [15], or *N*-vinyl-2-oxazolidinone [16] lead efficiently to 3,4-dihydro-2*H*-pyran-5-carbonitriles. Also, the influence of cyano, carbonyl, ethoxycarbonyl groups, or sulfur containing substituents at C-3 in 1-oxa-1,3-butadienes on the intramolecular H*DA* reaction was examined [17, 18].

Correspondence: Aleksandra Pałasz, Department of Organic Chemistry, Jagiellonian University, Kraków, Poland. E-mail: palasz@chemia.uj.edu.pl

Results and discussion

In this paper, the hetero-*Diels-Alder* reactions (H*DA*) of different 1-oxa-1,3-butadienes with cyano function at C-3 are described. The first aim of this work was to investigate reactions of enaminocarbaldehyde -3-(*N*-acetyl-*N*-benzylamino)-2-formylprop-2-enenitrile **3**, that acted as heterodiene in H*DA* reaction, with different enol ethers **4**. The object was to show



4, 5	R^1	R^2	R^3	R^4
a	C_2H_5	H	H	H
b	*i-Bu*	H	H	H
c	*n-Bu*	H	H	H
d	CH_3	CH_3	H	H
e	C_2H_5	H	H	CH_3

Scheme 1

that this enaminecarbaldehyde is a valuable precursor in the synthesis of 4-amino-3,4-dihydro-2*H*-pyrans with the skeleton of branched amino sugars of the garosamine-type [19]. The second aim was to study the H*DA* reactions 2-benzoyl-3-heteroaromaticprop-2-enenitrile **7** with enol ethers **4**.

The synthesis of enaminecarbaldehyde **3** was accomplished in a three-step reaction. Starting 3-*N*,*N*-dimethylamino-2-formylprop-2-enenitrile **1** (Scheme 1) was obtained in a *Vilsmayer-Haack* formylation reaction described by *Reichardt* and *Kermer* [20]. Compound **1** did not give any cycloadducts with enol ethers. This is due to the electron donating amino-function at C-3, which raises the LUMO energy of the heterodiene. Only *N*-acyl derivatives of enaminecarbaldehydes are capable to undergo H*DA* reactions [21]. In the next steps the appropriate modification of **1** was made. Reaction of **1** with benzylamine in methylene chloride afforded **2** in 52% yield. Compound **2** was transformed into the *N*-acetyl derivative **3** (65%) in reaction with acetyl chloride in dichloromethane:diethyl ether (2:1) in the presence of pyridine. The reactions of heterodiene **3** with enol ethers **4a**–**4e** were performed in toluene solution at 110°C for 30–96 h (Table 1). The progress of the reactions was monitored by TLC. They afforded two diastereoisomers of 4-(*N*-acetyl-*N*-benzylamino)-2-alkoxy-3,4-dihydro-2*H*-pyran-5-carbonitriles **5a**–**5e** in 48–77% yield (Scheme 1). The *cis* diastereoisomers were always the main products. The ratios of diastereoisomers *cis*/*trans* were determined on the basis of ^{1}H NMR spectra of crude products. The highest ratio of *cis*/*trans* diastereoselectivity was observed in the reaction of **3** with **4d**, leading to a product ratio of *cis*-**5d**:*trans*-**5d** = 3.2:1. In the case of the reaction of **3** with *cis*-ethyl-propenyl ether **4e** only one diastereoisomer **5e** was isolated. Compounds **5a**–**5e** were separated by column chromatography and purified further by crys-

Table 1 Synthesis of dihydropyrans **5a**–**5e** and **8a**–**8e**

Diene	Dienophile	Products	Reaction time/h	Yield/ %[a]	Ratio of *cis*: *trans*[b]
3	**4a**	**5a**	36	70	2.6:1
3	**4b**	**5b**	30	48	1.7:1
3	**4c**	**5c**	44	74	1.5:1
3	**4d**	**5d**	60	77	3.2:1
3	**4e**	**5e**	96	48	–
7a	**4a**	**8a**	48	79	10:1
7a	**4b**	**8b**	48	81	9:1
7a	**4d**	**8c**	48	76	4.5:1
7b	**4a**	**8d**	48	77	10:1
7c	**4a**	**8e**	24	88	12:1

[a] Isolated yields after column chromatography
[b] Ratio based on ^{1}H NMR spectra of crude products

Table 2 Signals of proton 2-H and 4-H in ^{1}H NMR spectra of dihydropyrans **5a**–**5e** and **8a**–**8e**

Compound	dd 2-H δ/ppm, $J_{3ax,2}/J_{3eq,2}$/Hz	dd 4-H δ/ppm, $J_{3ax,4}/J_{3eq,4}$/Hz	Compound	dd 2-H δ/ppm, $J_{3ax,2}/J_{3eq,2}$/Hz	dd 4-H δ/ppm, $J_{3ax,4}/J_{3eq,4}$/Hz
cis-**5a**	5.09, 8.3/2.1	5.72, 9.0/6.3	*trans*-**5a**	t 5.04, 2.7	4.87, 10.4/5.6 5.52, 10.2/6.3
cis-**5b**	5.09, 9.0/2.0	5.78, 8.8/6.5	*trans*-**5b**	t 5.05, 3.0	4.89 br, 5.51, 9.9/6.9
cis-**5c**	5.08, 8.5/2.5	5.76, 9.0/6.5	*trans*-**5c**	t 5.04, 2.5	4.82 br, 5.49, 9.9/6.6
cis-**5d**	–	ddd 5.59, 8.1/6.6/$J_{6,4}$1.5	*trans*-**5d**	–	4.90, 11.5/6.5, 5.95 br
5e	d 4.95, 3.5	d 5.68, 6.0	–	–	–
cis-**8a**	5.31, 8.1/2.1	4.21, 9.6/6.9	*trans*-**8a**	5.35, 4.5/2.4	4.24, 9.3/6.0
cis-**8b**	5.29, 7.8/2.1	4.20, 9.3/6.9	*trans*-**8b**	5.34, 4.2/2.4	4.24, 9.6/6.0
cis-**8c**	–	t 4.13, 7.2	*trans*-**8c**	–	4.27, 12.3/6.0
cis-**8d**	t 5.31, 5.0	t 3.99, 7.3	*trans*-**8d**	5.35, 4.8/2.7	4.03, 8.9/6.7
cis-**8e**	5.35, 6.9/2.4	t 3.94, 7.5	*trans*-**8e**	5.39, br t 2.7	4.02, 11.1/6.3

tallization. Compounds **5a**–**5e** were characterized by ^{1}H, ^{13}C NMR, IR, mass spectra, and elemental analysis. ^{1}H and ^{13}C signal assignments were confirmed by two-dimensional NMR COSY and HETCOR spectra. The relative *cis* and *trans* configurations at C-2, C-4 of substituents were assigned on the basis of ^{1}H NMR spectra. They were deducted from the chemical shift values and coupling constants of protons attached to C-2 and C-4 of the dihydropyran ring that exists in a half-chair conformation [22] (Table 2). In the ^{1}H NMR spectra of *cis*-**5a**–**5c** the signal of 2-H appeared as a doublet of doublets at $\delta = 5.08$–5.09 ppm with small and large coupling constants ($^3J = 2.0$–2.5, 8.3–9.0 Hz) due to coupling with two protons at C-3 (Table 2). Thus, 2-H occupies an *axial* position, and the alkoxy group adopts an *equatorial* orientation (Fig. 1).

The ^{1}H NMR spectra of *cis*-**5a**–**5d** reveal the signals of proton 4-H as a doublet of doublets at $\delta = 5.59$–5.78 ppm with two large coupling constants ($^3J = 6.3$–6.6, 8.1–9.0 Hz). In the spectrum of *cis*-**5d** the signal of 4-H is a doublet of doublets due to the coupling of 4-H with two protons 3-H and with proton 6-H ($^4J = 1.5$ Hz). Thus, 4-H is in the *pseudo-axial* position and *N*-acetyl-*N*-benzylamino moiety occupies the *pseudo-equatorial* position (Fig. 1). For *trans* diastereoisomers *trans*-**5a**–**5c**, the protons attached to C-2 give rise to triplets with small coupling constants ($^3J = 2.5$–3.0 Hz) at $\delta = 5.04$–5.05 ppm. This suggests that for *trans*-**5a**–**5c** the conformation with an *axial* alkoxy group is preferred due to stabilization by the anomeric effect. The proton 4-H of *trans*-**5a**–**5d** resonates at $\delta = 4.82$–5.95 ppm as broad signals and at $\delta = 5.49$–5.52 ppm as dd with two large coupling constants ($^3J = 6.3$–6.9 and 9.9–11.5 Hz). Thus, 4-H is *pseudo-axial* and large *N*-acetyl-*N*-benzylamino moiety occupies the *pseudo-equatorial* position (Fig. 1). The ^{1}H NMR spectrum of *trans*-**5a** was also recorded at 333 K. It is worth to note that in the spectrum measured at higher temperature two signals of proton 4-H ($\delta = 4.87$, 5.52 ppm) are observed as one broad signal $\delta = 5.31$ ppm. In the spectrum of **5e** the signal of 2-H is a doublet at $\delta = 4.97$ ppm due to the coupling with one proton 3-H ($^3J = 3.5$ Hz) and proton 4-H is also observed as doublet at $\delta = 5.70$ ppm with the coupling constants $^3J = 6.0$ Hz. This suggests that the substituents attached to C-2, C-3 and C-4 are in *cis* configuration, the same as in *cis*-ethyl-propenyl ether **4e**.

The preferred formation of *cis*-diastereoisomers (Table 1) results from the *endo* transition state interaction which is energetically more favorable than *exo* transition state one. Thus, *cis*-products arise from a kinetically controlled process [23].

It was found that *cis* diastereoisomers of 3,4-dihydro-2*H*-pyran derivatives undergo transformation to *trans* isomers in the presence of *Lewis* acid [3, 4,

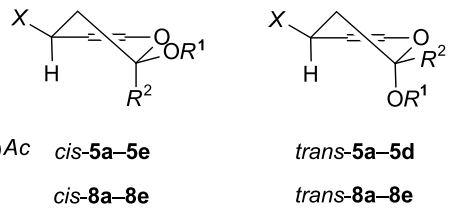
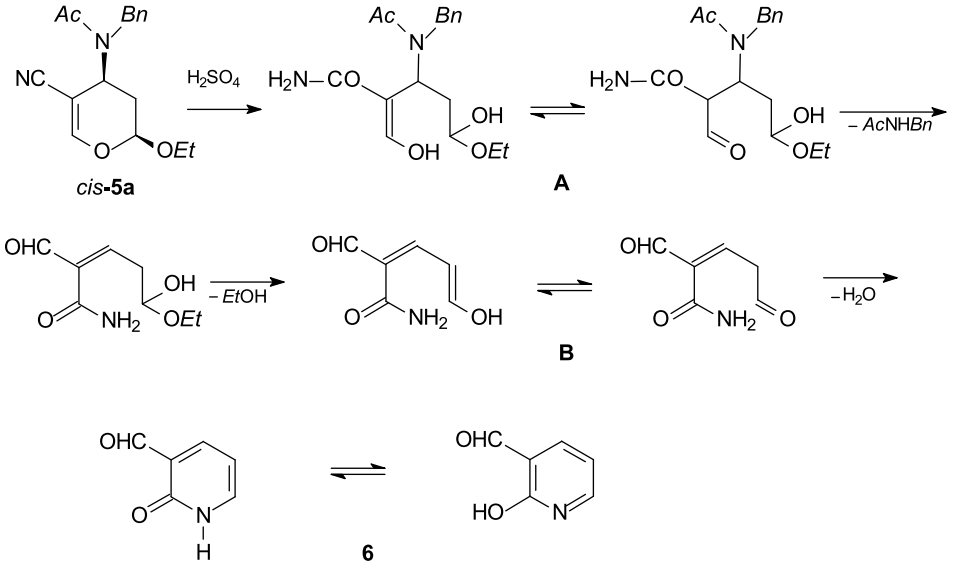


Fig. 1 Preferred *cis*:*trans* configurations and conformations of cycloadducts **5a**–**5e** and **8a**–**8e** based on ^{1}H NMR analysis



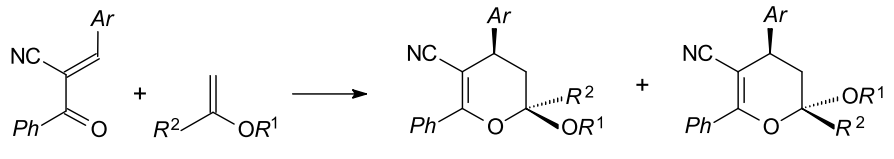
Scheme 2

21]. When *cis*-**5a** was submitted to the action of boron fluoride etherate, a mixture of *cis*-**5a**:*trans*-**5a** = 1:3.4 was obtained after 24 h at room temperature (^{1}H NMR analysis).

Acidic hydrolysis of *cis*-**5a** in concentrated sulfuric acid (60%) gave 2-oxo-1,2-dihydropyrydine-3-carbaldehyde **6** with 63% yield. Compound **6** has been already described [24, 25]. Formation of **6** can be rationalized as depicted in Scheme 2. In the first step, the acidic medium causes the opening of the pyran ring and the hydrolysis of the cyano group to the amide leading to the intermediate **A**. Elimination of acetylbenzylamine and ethanol from **A** furnishes the intermediate **B**, which undergoes intramolecular condensation yielding compound **6**.

In the next series of experiments the reactions of 2-benzoyl-3-heteroaromaticprop-2-enenitriles **7a**–**7c** with enol ethers **4a**, **4b**, and **4d** were investigated. The reactions were performed with methylene chloride as the solvent at room temperature for 1–2 days and the cycloadducts **8a**–**8e** were obtained with 76–88% yields (Scheme 3, Table 1). The highest ratio of *cis*/*trans* diastereosletivity was observed in the reaction of **7c** with **4a**, leading to a product ratio of *cis*-**8e**:*trans*-**8e** = 12:1. The reactions of **7a** or **7b** with ether **4a** gave products also with high diastereoselectivity *cis*:*trans* = 10:1.

The structure of dihydropyrans **8a**–**8e** was established on the basis of analytical and spectroscopic data. ^{1}H and ^{13}C signal assignments were confirmed



4	7	8	Ar	R^1	R^2
a	a	a	2-thienyl	C_2H_5	H
b	a	b	2-thienyl	*i*-Bu	H
d	a	c	2-thienyl	CH_3	CH_3
a	b	d	2-furyl	C_2H_5	H
a	c	e	*p*-NC-C_6H_4	C_2H_5	H

Scheme 3

by two-dimensional NMR COSY and HETCOR spectra. In the ^{1}H NMR spectra of *cis*-**8a**–**8e** the signal of 2-H appeared as a doublet of doublets at $\delta = 5.29$–5.35 ppm with small and large coupling constants ($^3J = 2.1$–2.4, 6.9–8.1 Hz) (Table 2). Thus, 2-H occupies an *axial* position, and the alkoxy group adopts an *equatorial* orientation (Fig. 1). The ^{1}H NMR spectra of *cis*-**8a**–**8e** reveal the signals proton 4-H at $\delta = 3.94$–4.21 ppm as a doublet of doublets with two large coupling constants ($^3J =$ 6.9, 9.3–9.6 Hz) or as triplets with $^3J = 7.2$–7.5 Hz. Thus, 4-H is the *pseudo-axial* and heteroaromatic moiety occupies the *pseudo-equatorial* position (Fig. 1). For *trans* diastereoisomers *trans*-**8a**–**8e**, the protons attached to C-2 give rise to doublet of doublets with two small coupling constants ($^3J =$ 2.4–2.7 and 4.2–4.8 Hz) at $\delta = 5.34$–5.39 ppm. This suggests that for *trans*-**8a**–**8e** the conformation with an *axial* alkoxy group is preferred due to stabilization by the anomeric effect. The proton 4-H of *trans*-**8a**–**8e** resonates at $\delta = 4.02$–4.27 ppm as doublet of doublets with two large coupling constants ($^3J =$ 6.0–6.7 and 8.9–12.3 Hz). Thus, 4-H is *pseudo-axial* and heteroaromatic ring occupies the *pseudo-equatorial* position (Fig. 1).

In conclusion, the present results indicate that 3-(*N*-acetyl-*N*-benzylamino)-2-formylprop-2-enenitrile **3** and 2-benzoyl-3-heteroaromaticprop-2-enenitriles **7a**–**7c** can act as valuable heterodienes in inverse electron demand H*DA* reaction with enol ethers. Enaminocarbaldehyde **3** was found to be less reactive than propenenitriles **7a**–**7c** because reactions **7a**–**7c** with enol ethers occurred at room temperature whereas reactions with **3** required heating in boiling toluene.

Experimental

Melting points were determined on a *Boetius* hot stage apparatus. IR spectra: Bruker IFS 48 in HCB/nujol, KBr pellets. ^{1}H NMR, ^{13}C NMR, COSY and HETCOR spectra: Bruker Avance II 300 (^{1}H: 300.18 MHz, ^{13}C: 75.48 MHz), in CDCl3 with *TMS* as an internal standard. Mass spectra: Finningan Mat 95 (70 eV). Microanalyses were performed with Euro EA 3000 Elemental Analyzer, their results agreed satisfactorily with the calculated values. 3-*N*,*N*-Dimethylamino-2-formylpropenenitrile (**1**) was obtained according to the procedure reported in Ref. [20]. Enol ethers **4a**–**4e** were commercially available. 2-Benzoyl-3-(2-thienyl)prop-2-enenitrile (**7a**), 2-benzoyl-3-(2-furyl)prop-2-enenitrile (**7b**), and 2-benzoyl-3-(4-cyanophenyl)prop-2-enenitrile (**7c**) were prepared by procedures described in Refs. [13, 26].

3-N-Benzylamino-2-formylprop-2-enenitrile (**2**, $C_{11}H_{10}N_2O$)
To a stirred solution of 1.9 g 3-*N*,*N*-dimethylamino-2-formylprop-2-enenitrile **1** (15 mmol) in 20 cm^3 anhydrous dichloromethane, a solution of 1.6 g benzylamine (15 mmol) in 10 cm^3 CH_2Cl_2 was added. The mixture was allowed to stir at room temperature for 1 h, then the solvent was evaporated. The crude mixture was triturated with 15 cm^3 toluene. The resulting precipitate was filtered off and purified by column chromatography on silica gel using chloroform/methanol (20/1) as eluent. Crystallization from toluene gave (1.45 g) colorless crystals; mp 117°C; yield 52%; IR (HCB/nujol): $\bar{\nu} = 3173$ (NH), 2930 (CH), 2200 (CN), 1633 (C=O), 1570 (C=C) cm^{-1}; ^{1}H NMR (300.18 MHz, $CDCl_3$): $\delta = 4.52$ (s, 0.85 CH_2*Ph*), 4.53 (s, 0.85 CH_2*Ph*), 4.56 (s, 0.15 CH_2*Ph*), 4.57 (s, 0.15 CH_2*Ph*), 7.23–7.43 (m, 6 3-H, *Ph*H), 9.12 (s, 0.15 CHO-*E*), 9.30 (d, $J = 3.4$ Hz, 0.85 CHO-*Z*), 10.77 (br, 1 NH) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 53.6$, 53.8 (NCH_2), 83.6 (C-2), 119.3 (CN), 127.7, 127.8, 128.9, 129.0, 129.3, 134.43, 134.8 (*Ph*C), 158.5, 158.8 (C-3), 187.9 (CHO) ppm; MS (EI, 70 eV): m/z (%) = 186 (8) $[M]^{+\bullet}$, 159 (25), 130 (14), 105 (12), 91 (100), 77 (43).

3-(N-Acetyl-N-benzylamino)-2-formylprop-2-enenitrile
(**3**, $C_{13}H_{12}N_2O_2$)
A three-necked round-bottomed flask (250 cm^3) was equipped with a stirrer, fitted with a thermometer, sealed with a septum, and placed under an argon atmosphere. The flask was charged with 1.9 g **2** (10 mmol), 30 cm^3 anh. CH_2Cl_2, 15 cm^3 anh. diethyl ether, and 1.2 cm^3 pyridine (15 mmol). Freshly distilled acetyl chloride (1.4 cm^3, 15 mmol) was added by syringe at 0°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 h. The precipitated ammonium salt of pyridine was filtered off, washed with diethyl ether (10 cm^3), and the combined organic layers were evaporated on vacuum. The residue was purified by column chromatography on silica gel using chloroform/methanol (20/1) as eluent. Crystallization from cyclohexane/ethyl acetate 3/1 gave (1.48 g) colorless crystals; mp 95°C; yield 65%; IR (HCB/nujol): $\bar{\nu} = 3020$, 2933, 2844 (CH), 2213 (CN), 1720, 1690 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR (300.18 MHz, $CDCl_3$): $\delta = 2.45$ (s, 3 $COCH_3$), 5.41 (s, 2 CH_2*Ph*), 7.13–7.50 (m, 5 *Ph*H), 8.55 (s, 1 3-H), 9.38 (s, 1 CHO) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 22.0$ ($COCH_3$), 48.9 (NCH_2), 94.7 (C-2), 113.5 (CN), 126.0, 127.6, 128.3, 129.3, 134.1 (*Ph*C), 158.8 (C-3), 170.7 (*C*OCH_3), 186.1 (CHO) ppm; MS (EI, 70 eV): m/z (%) = 228 (4) $[M]^{+\bullet}$, 186 (56), 158 (26), 149 (5), 106 (7), 91 (100), 43 (76).

*Procedures for the synthesis of 3,4-dihydro-2H-pyran-5-carbonitriles **5a**–**5e** and **8a**–**8e***
A solution of 2 mmol **3** in 10 cm^3 anh. toluene, 20 mmol appropriate vinyl ethers **4a**–**4e** (10 equivalents), and some crystals of hydroquinone was heated at 110°C in a pressure flask for the time given in Table 1. A solution of 2 mmol **7a**–**7c** in 10 cm^3 anh. CH_2Cl_2 and 20 mmol vinyl ether **4a**, **4b**, and **4d** (10 equiv.) was kept at room temp. for the time given in Table 1. The progress of the reactions was monitored by TLC. The solvent and excess of ethers were evaporated and

the mixture was separated and purified by column chromatography on silica gel using ethyl acetate/petrol ether: 1/1 (**5a–5c**), *t*-butyl methyl ether (**5d** and **5e**), *t*-butyl methyl ether/petrol ether: 1/3 (**8a** and **8c**), 1/1 (**8b** and **8e**), 1/2 (**8d**) as an eluent. Recrystallization from cyclohexane/ethyl acetate: 5/2 (**5a–5e**) or petrol ether/*t*-butyl methyl ether: 3/1 (**8a–8d**), petrol ether/*t*-butyl methyl ether: 2/1 (**8e**) gave **5a–5e** and **8a–8e** with yields listed in Table 1.

(2RS,4RS)-4-(N-Acetyl-N-benzylamino)-2-ethoxy-3,4-dihydro-2H-pyran-5-carbonitrile (*cis*-**5a**, $C_{17}H_{20}N_2O_3$)
Colorless crystals; mp 102°C; yield 50.5%; IR (HCB/nujol): $\bar{\nu}$ = 2973, 2920, 2880 (CH), 2200 (CN), 1640 (C=O), 1610 (C=C) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.1 Hz, 3 OCH_2CH_3), 1.84 (m, 1 3-H), 1.99 (s, 2.7 $COCH_3$), 2.09 (ddd, J = 2.1, 6.3, 13.5 Hz, 1 3-H), 2.27 (s, 0.3 $COCH_3$), 3.55 (dq, J = 7.1, 9.5 Hz, 1 OCH_2CH_3), 3.84 (dq, J = 7.1, 9.5 Hz, 1 OCH_2CH_3), 4.36 (d, J = 18.0 Hz, 1 CH_2Ph), 4.68 (d, J = 18.0 Hz, 1 CH_2Ph), 5.09 (dd, J = 2.1, 8.3 Hz, 1 2-H), 5.72 (dd, J = 6.3, 9.0 Hz, 1 4-H), 7.08–7.36 (m, 6 6-H, *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 14.8 (OCH_2CH_3), 22.3 ($COCH_3$), 31.7 (C-3), 46.2 (C-4), 47.9 (NCH_2), 65.6 (OCH_2CH_3), 90.4 (C-5), 100.7 (C-2), 116.6 (CN), 125.5, 127.7, 128.9, 137.4 (*Ph*C), 157.5 (C-6), 172.7 ($COCH_3$) ppm; MS (EI, 70 eV): m/z (%) = 300 (10) $[M]^{+\bullet}$, 209 (40), 167 (87), 148 (33), 139 (13), 106 (44), 91 (100), 72 (11), 43 (61).

(2RS,4SR)-4-(N-Acetyl-N-benzylamino)-2-ethoxy-3,4-dihydro-2H-pyran-5-carbonitrile (*trans*-**5a**, $C_{17}H_{20}N_2O_3$)
Colorless crystals; mp 154°C; yield 19.5%; IR (HCB/nujol): $\bar{\nu}$ = 2973, 2920, 2880 (CH), 2200 (CN), 1626 (C=O), 1613 (C=C) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.1 Hz, 3 OCH_2CH_3), 1.86 (ddd, J = 2.7, 10.2, 13.0 Hz, 1 3-H), 1.97 (ddd, J = 2.6, 6.1, 13.0 Hz, 1 3-H), 2.13 (s, 2.4 $COCH_3$), 2.35 (s, 0.6 $COCH_3$), 3.53 (dq, J = 7.1, 9.6 Hz, 1 OCH_2CH_3), 3.78 (dq, J = 7.1, 9.6 Hz, 1 OCH_2CH_3), 3.90 (br, 0.2 CH_2Ph), 4.41 (d, J = 18.0 Hz, 0.8 CH_2Ph), 4.74 (d, J = 18.0 Hz, 0.8 CH_2Ph), 4.87 (dd, J = 5.6, 10.4 Hz, 0.2 4-H), 5.04 (t, J = 2.7 Hz, 1 2-H), 5.31 (br, 0.2 CH_2Ph), 5.52 (dd, J = 6.3, 10.2 Hz, 0.8 4-H), 7.10-7.39 (m, 6 6-H, *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 14.8 (OCH_2CH_3), 22.2, 22.3 ($COCH_3$), 30.1, 31.6 (C-3), 44.4 (C-4), 47.7, 49.1 (NCH_2), 65.0, 65.2 (OCH_2CH_3), 91.5, 91.7 (C-5), 98.4, 98.7 (C-2), 116.1, 116.8 (CN), 125.7, 126.6, 126.9, 127.6, 128.5, 128.9, 137.3, 138.6 (*Ph*C), 155.9, 156.4 (C-6), 171.1, 172.2 ($COCH_3$) ppm; MS (EI, 70 eV): m/z (%) = 300 (20) $[M]^{+\bullet}$, 209 (32), 167 (59), 148 (31), 139 (8), 106 (54), 91 (100), 72 (11), 43 (66).

(2RS,4RS)-4-(N-Acetyl-N-benzylamino)-3,4-dihydro-2-isobutoxy-2H-pyran-5-carbonitrile (*cis*-**5b**, $C_{19}H_{24}N_2O_3$)
Colorless oil; yield 30%; IR (film): $\bar{\nu}$ = 2950, 2920, 2870 (CH), 2200 (CN), 1650 (C=O), 1615 (C=C) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): δ = 0.87 (d, J = 6.5 Hz, 6 $OCH_2CH(CH_3)_2$), 1.81 (m, 1 $OCH_2CH(CH_3)_2$), 1.89 (ddd, J = 8.8, 9.0, 13.5 Hz, 1 3-H), 2.06 (s, 2.8 $COCH_3$), 2.16 (ddd, J = 2.0, 6.5, 13.5 Hz, 1 3-H), 2.32 (s, 0.2 $COCH_3$), 3.23 (dd, J = 6.5, 9.5 Hz, 1 $OCH_2CH(CH_3)_2$), 3.63 (dd, J = 6.5, 9.5 Hz, 1 $OCH_2CH(CH_3)_2$), 4.39 (d, J = 18.0 Hz, 1 CH_2Ph), 4.73 (d, J = 18.0 Hz, 1 CH_2Ph), 5.09 (dd, J = 2.0, 9.0 Hz, 1 2-H), 5.78 (dd, J = 6.5, 8.8 Hz, 1 4-H), 7.15–7.40 (m, 6 6-H, *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 19.1, 19.2 ($OCH_2CH(CH_3)_2$), 22.3 ($COCH_3$), 28.3 ($OCH_2CH(CH_3)_2$), 31.6 (C-3), 46.4 (C-4), 48.0 (NCH_2), 77.6 ($OCH_2CH(CH_3)_2$), 90.3 (C-5), 101.3 (C-2), 116.7 (CN), 125.6, 125.5, 129.0, 137.4 (*Ph*C), 157.6 (C-6), 172.7 ($COCH_3$) ppm; MS (EI, 70 eV): m/z (%) = 328 (12) $[M]^{+\bullet}$, 237 (38), 211 (10), 195 (76), 163 (15), 148 (35), 139 (14), 106 (42), 91 (100).

(2RS,4SR)-4-(N-Acetyl-N-benzylamino)-3,4-dihydro-2-isobutoxy-2H-pyran-5-carbonitrile (*trans*-**5b**, $C_{19}H_{24}N_2O_3$)
Colorless oil; yield 18%; IR (film): $\bar{\nu}$ = 2960, 2920, 2882 (CH), 2200 (CN), 1659 (C=O), 1620 (C=C) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): δ = 0.86 (d, J = 6.5 Hz, 6 $OCH_2CH(CH_3)_2$), 1.83 (m, 1 $OCH_2CH(CH_3)_2$), 1.88 (m, 1 3-H), 2.15 (s, 2.4 $COCH_3$), 1.97 (ddd, J = 3.0, 6.0, 13.5 Hz, 1 3-H), 2.35 (s, 0.6 $COCH_3$), 3.22 (dd, J = 6.5, 9.5 Hz, 1 $OCH_2CH(CH_3)_2$), 3.49 (dd, J = 6.6, 9.5 Hz, 1 $OCH_2CH(CH_3)_2$), 3.92 (br, 0.2 CH_2Ph), 4.43 (d, J = 18.0 Hz, 0.8 CH_2Ph), 4.74 (d, J = 18.0 Hz, 0.8 CH_2Ph), 4.89 (br, 0.2 4-H), 5.05 (t, J = 3.0 Hz, 1 2-H), 5.30 (br, 0.2 CH_2Ph), 5.51 (dd, J = 6.9, 9.9 Hz, 0.8 4-H), 7.10–7.40 (m, 6 6-H, *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 19.0, 19.1 ($OCH_2CH(CH_3)_2$), 22.4 ($COCH_3$), 28.3 ($OCH_2CH(CH_3)_2$), 30.9 (C-3), 44.5 (C-4), 49.3 (NCH_2), 76.1 ($OCH_2CH(CH_3)_2$), 91.8 (C-5), 99.1 (C-2), 116.8 (CN), 125.9, 127.5, 127.6 (*Ph*C), 157.7 (C-6), 172.3 ($COCH_3$) ppm; MS (EI, 70 eV): m/z (%) = 328 (15) $[M]^{+\bullet}$, 237 (39), 211 (13), 195 (67), 163 (18), 148 (41), 139 (12), 106 (46), 91 (100).

(2RS,4RS)-4-(N-Acetyl-N-benzylamino)-3,4-dihydro-2-n-butoxy-2H-pyran-5-carbonitrile (*cis*-**5c**, $C_{19}H_{24}N_2O_3$)
Colorless crystals; mp 92°C; yield 44%; IR (film): $\bar{\nu}$ = 2963, 2938, 2874 (CH), 2211 (CN), 1653 (C=O), 1628 (C=C) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.5 Hz, 3 $O(CH_2)_3CH_3$), 1.28 (sext, 2 $O(CH_2)_2CH_2CH_3$), 1.48 (quit, 2 $OCH_2CH_2CH_2CH_3$), 1.87 (ddd, J = 8.5, 9.0, 13.5 Hz, 1 3-H), 2.00 (s, 2.8 $COCH_3$), 2.13 (ddd, J = 2.5, 6.5, 13.5 Hz, 1 3-H), 2.31 (s, 0.2 $COCH_3$), 3.48 (dt, J = 7.5, 9.5 Hz, 1 $OCH_2(CH_2)_2CH_3$), 3.79 (dt, J = 7.5, 9.5 Hz, 1 $OCH_2(CH_2)_2CH_3$), 4.36 (d, J = 18.0 Hz, 1 CH_2Ph), 4.68 (d, J = 18.0 Hz, 1 CH_2Ph), 5.08 (dd, J = 2.5, 8.5 Hz, 1 2-H), 5.76 (ddd, J = 1.3, 6.5, 9.0 Hz, 1 4-H), 7.06–7.40 (m, 6 6-H, *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): δ = 13.7 ($OCH_2(CH_2)_2CH_3$), 19.1 ($OCH_2CH_2CH_2CH_3$), 22.3 ($COCH_3$), 30.9 ($OCH_2CH_2CH_2CH_3$), 31.3 (C-3), 46.3 (C-4), 48.0 (NCH_2), 70.1 ($OCH_2(CH_2)_2CH_3$), 90.4 (C-5), 101.0 (C-2), 116.7 (CN), 125.6, 127.5, 129.0, 137.5 (*Ph*C), 157.6 (C-6), 172.7 ($COCH_3$) ppm; MS (EI, 70 eV): m/z (%) = 328 (14) $[M]^{+\bullet}$, 237 (35), 211 (8), 195 (71), 163 (13), 148 (35), 106 (44), 91 (100).

(2RS,4SR)-4-(N-Acetyl-N-benzylamino)-3,4-dihydro-2-n-butoxy-2H-pyran-5-carbonitrile (*trans*-**5c**, $C_{19}H_{24}N_2O_3$)
Colorless crystals; mp 82°C; yield 30%; IR (film): $\bar{\nu}$ = 2961, 2948, 2873 (CH), 2215 (CN), 1647 (C=O), 1626 (C=C)

cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.5$ Hz, $3O(CH_2)_3CH_3$), 1.28 (sext, 2 $O(CH_2)_2CH_2CH_3$), 1.49 (quit, 2 $OCH_2CH_2CH_2CH_3$), 1.80 (m, 1 3-H), 1.93 (ddd, $J = 2.5$, 6.5, 13.5 Hz, 1 3-H), 2.09 (s, 2.45 $COCH_3$), 2.30 (s, 0.55 $COCH_3$), 3.44 (dt, $J = 7.5$, 9.5 Hz, 1 $OCH_2(CH_2)_2CH_3$), 3.68 (dt, $J = 7.5$, 9.5 Hz, 1 $OCH_2(CH_2)_2CH_3$), 3.85 (br, 0.2 CH_2Ph), 4.38 (d, $J = 18.0$ Hz, 0.8 CH_2Ph), 4.70 (d, $J = 18.0$ Hz, 0.8 CH_2Ph), 4.82 (br, 0.2 4-H), 5.04 (t, $J = 2.5$ Hz, 1 2-H), 5.26 (br, 0.2 CH_2Ph), 5.49 (dd, $J = 6.6$, 9.9 Hz, 0.8 4-H), 7.00–7.40 (m, 6 6-H, *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta =$ 13.7 ($OCH_2(CH_2)_2CH_3$), 19.1 ($OCH_2CH_2CH_2CH_3$), 22.4 ($COCH_3$), 30.2 ($OCH_2CH_2CH_2CH_3$), 31.7 (C-3), 44.5 (C-4), 49.2 (NCH_2), 69.4 ($OCH_2(CH_2)_2CH_3$), 91.7 (C-5), 99.0 (C-2), 116.8 (CN), 125.8, 127.6, 128.5, 137.4 (*Ph*C), 155.9 (C-6), 172.3 ($COCH_3$) ppm; MS (EI, 70 eV): m/z (%) = 328 (15) $[M]^{+\bullet}$, 237 (38), 211 (11), 195 (74), 163 (13), 148 (31), 106 (47), 91 (100).

(2RS,4RS)-4-(N-Acetyl-N-benzylamino)-3,4-dihydro-2-methoxy-2-methyl-2H-pyran-5-carbonitrile
(*cis*-**5d**, $C_{17}H_{20}N_2O_3$)
Colorless crystals; mp 111°C; yield 58.5%; IR (KBr): $\bar{\nu} =$ 2992, 2960, 2848 (CH), 2224 (CN), 1664 (C=O), 1638 (C=C) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta =$ 1.48 (s, 2.4 2-CH_3), 1.80 (s, 0.6 2-CH_3), 1.90 (dd, $J = 6.5$, 14.0 Hz, 1 3-H), 2.05 (s, 2.4 $COCH_3$), 2.07 (dd, $J = 8.3$, 14.0 Hz, 1 3-H), 2.32 (s, 0.6 $COCH_3$), 3.20 (s, 3 OCH_3), 4.43 (d, $J = 18.0$ Hz, 1 CH_2Ph), 4.72 (d, $J = 18.0$ Hz, 1 CH_2Ph), 5.59 (ddd, $J = 1.5$, 6.6, 8.1 Hz, 1 4-H), 7.19–7.38 (m, 6 6-H, *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 21.6$ (2-CH_3), 22.5 ($COCH_3$), 35.4 (C-3), 46.6 (C-4), 48.6 (NCH_2), 49.6 (2-OCH_3), 89.1 (C-5), 103.4 (C-2), 116.9 (CN), 125.7, 127.4, 128.9, 137.7 (*Ph*C), 157.6 (C-6), 172.7 ($COCH_3$) ppm; MS (EI, 70 eV): m/z (%) = 300 (19) $[M]^{+\bullet}$, 209 (15), 177 (85), 167 (53), 150 (55), 148 (37), 136 (14), 135 (21), 120 (23), 106 (35), 91 (100), 72 (98), 43 (68).

(2RS,4SR)-4-(N-Acetyl-N-benzylamino)-2-methoxy-2-methyl-3,4-dihydro-2H-pyran-5-carbonitrile
(*trans*-**5d**, $C_{17}H_{20}N_2O_3$)
Colorless crystals; mp 110°C; yield 18.5%; IR (KBr): $\bar{\nu} =$ 3008, 2960, 2848 (CH), 2224 (CN), 1664 (C=O), 1630 (C=C) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 1.40$ (s, 2.9 2-CH_3), 1.65 (dd, $J = 11.5$, 13.5 Hz, 1 3-H), 1.70 (s, 0.1 2-CH_3), 1.92 (dd, $J = 6.5$, 13.5 Hz, 1 3-H), 2.10 (s, 2.25 $COCH_3$), 2.32 (s, 0.75 $COCH_3$), 3.30 (s, 3 OCH_3), 3.85 (d, $J = 18.0$ Hz, 0.25 CH_2Ph), 4.42 (d, $J = 18.0$ Hz, 0.75 CH_2Ph), 4.73 (d, $J = 18.0$ Hz, 0.75 CH_2Ph), 4.90 (dd, $J = 6.5$, 11.5 Hz, 0.25 4-H), 5.25 (d, $J = 18.0$ Hz, 0.25 CH_2Ph), 5.95 (br, 0.75 4-H), 6.90-7.45 (m, 6 6-H, *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 21.7$ (2-CH_3), 22.2 ($COCH_3$), 35.5 (C-3), 46.7 (C-4), 48.6 (NCH_2), 49.7 (2-OCH_3), 92.2 (C-5), 102.5 (C-2), 117.0 (CN), 125.7, 127.4, 129.0, 137.7 (*Ph*C), 157.7 (C-6), 172.7 ($COCH_3$) ppm; MS (EI, 70 eV): m/z (%) = 300 (15) $[M]^{+\bullet}$, 209 (8), 177 (62), 167 (23), 150 (42), 148 (23), 135 (18), 135 (18), 120 (53), 106 (32), 91 (100), 72 (68), 43 (67).

(2RS,3SR,4RS)-4-(N-Acetyl-N-benzylamino)-2-ethoxy-3,4-dihydro-3-methyl-2H-pyran-5-carbonitrile (**5e**, $C_{18}H_{22}N_2O_3$)
Colorless crystals; mp 117°C; yield 48%; IR (KBr): $\bar{\nu} =$ 3056, 2976, 2912 (CH), 2224 (CN), 1648 (C=O), 1622 (C=C) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 1.01$ (d, $J = 7.5$ Hz, 3 3-CH_3), 1.12 (t, $J = 7.0$ Hz, 3 OCH_2CH_3), 2.00 (s, 2.8 $COCH_3$), 2.31 (m, 1 3-H), 2.32 (s, 0.2 $COCH_3$), 3.55 (dq, $J = 7.0$, 9.5 Hz, 1 OCH_2CH_3), 3.82 (dq, $J = 7.0$, 9.5 Hz, 1 OCH_2CH_3), 4.49 (d, $J = 18.0$ Hz, 1 CH_2Ph), 4.81 (d, $J = 18.0$ Hz, 1 CH_2Ph), 4.95 (d, $J =$ 3.5 Hz, 1 2-H), 5.68 (d, $J = 6.0$ Hz, 1 4-H), 7.15–7.39 (m, 6 6-H, *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 11.5$ (3-CH_3), 14.7 (OCH_2CH_3), 23.0 ($COCH_3$), 36.4 (C-3), 47.1 (C-4), 49.5 (NCH_2), 65.7 (OCH_2CH_3), 89.2 (C-5), 100.0 (C-2), 117.9 (CN), 126.0, 126.9, 128.6, 138.3 (*Ph*C), 157.7 (C-6), 174.4 ($COCH_3$) ppm; MS (EI, 70 eV): m/z (%) = 314 (17) $[M]^{+\bullet}$, 223 (49), 181 (100), 153 (19), 148 (39), 135 (40), 106 (26), 91 (65), 86 (30), 43 (36).

(2RS,4SR)-2-Ethoxy-3,4-dihydro-6-phenyl-4-(2-thienyl)-2H-pyran-5-carbonitrile (*cis*-**8a**, $C_{18}H_{17}NO_2S$)
Colorless crystals; mp 70°C; yield 72%; IR (KBr): $\bar{\nu} =$ 3087, 2975, 2935, 2890 (CH), 2200 (CN), 1601 (C=C), 1146 (C–O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta =$ 1.29 (t, $J = 7.05$ Hz, 3 OCH_2CH_3), 2.24 (ddd, $J = 8.1$, 9.9, 13.8 Hz, 1 3-H), 2.51 (ddd, $J = 2.1$, 6.9, 13.8 Hz, 1 3-H), 3.73 (dq, $J = 7.05$, 9.5 Hz, 1 OCH_2CH_3), 4.07 (dq, $J = 7.05$, 9.5 Hz, 1 OCH_2CH_3), 4.21 (dd, $J = 6.9$, 9.6 Hz, 1 4-H), 5.31 (dd, $J = 2.1$, 8.1 Hz, 1 2-H), 6.97 (dd, $J = 3.6$, 5.1 Hz, 1 4′-H), 7.05 (dd, $J = 1.2$, 3.6 Hz, 1 3′-H), 7.23 (dd, $J = 1.2$, 5.1 Hz, 1 5′-H), 7.44 (m, 3 *Ph*H), 7.77 (m, 2 *Ph*H); ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 15.1$ (OCH_2CH_3), 35.5 (C-3), 36.5 (C-4), 65.4 (OCH_2CH_3), 88.6 (C-5), 100.8 (C-2), 119.1 (CN), 124.7 (C-5′), 126.0 (C-3′), 126.8 (C-4′), 128.2, 128.3, 128.4, 131.0, 132.9 (*Ph*C), 144.0 (C-2′), 163.2 (C-6) ppm; MS (EI, 70 eV): m/z (%) = 311 (16) $[M]^{+\bullet}$, 265 (56), 239 (67), 212 (52), 105 (100), 77 (47), 72 (13).

(2RS,4RS)-2-Ethoxy-3,4-dihydro-6-phenyl-4-(2-thienyl)-2H-pyran-5-carbonitrile (*trans*-**8a**, $C_{18}H_{17}NO_2S$)
Colorless oil; yield 7%; IR (KBr): $\bar{\nu} = 3087$, 2975, 2935, 2890 (CH), 2200 (CN), 1601 (C=C), 1146 (C–O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 1.30$ (t, $J = 7.05$ Hz, 3 OCH_2CH_3), 2.16 (ddd, $J = 2.4$, 9.3, 13.5 Hz, 1 3-H), 2.35 (ddd, $J = 4.2$, 6.0, 13.5 Hz, 1 3-H), 3.74 (dq, $J = 7.05$, 9.5 Hz, 1 OCH_2CH_3), 4.03 (dq, $J = 7.05$, 9.5 Hz, 1 OCH_2CH_3), 4.24 (dd, $J = 6.0$, 9.3 Hz, 1 4-H), 5.35 (dd, $J = 2.4$, 4.5 Hz, 1 2-H), 7.00 (dd, $J = 3.6$, 5.1 Hz, 1 4′-H), 7.04 (dd, $J = 1.2$, 3.6 Hz, 1 3′-H), 7.26 (dd, $J = 1.2$, 5.1 Hz, 1 5′-H), 7.44 (m, 3 *Ph*H), 7.77 (m, 2 *Ph*H); ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 15.1$ (OCH_2CH_3), 32.6 (C-3), 35.5 (C-4), 65.1 (OCH_2CH_3), 88.5 (C-5), 98.1 (C-2), 119.2 (CN), 124.8 (C-5′), 126.0 (C-3′), 127.1 (C-4′), 128.2, 128.3, 128.4, 130.2 (*Ph*C), 144.6 (C-2′), 162.5 (C-6) ppm; MS (EI, 70 eV): m/z (%) = 311 (14) $[M]^{+\bullet}$, 265 (48), 239 (68), 212 (40), 105 (100), 77 (42), 72 (12).

(2RS,4SR)-3,4-Dihydro-2-isobutoxy-6-phenyl-4-(2-thienyl)-2H-pyran-5-carbonitrile (*cis*-**8b**, $C_{20}H_{21}NO_2S$)
Colorless crystals; mp 70°C; yield 73%; IR (KBr): $\bar{\nu} = 3087$, 2975, 2935, 2890 (CH), 2200 (CN), 1601 (C=C), 1146 (C–O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 0.91$ (d, $J =$ 6.9 Hz, 6 $OCH_2CH(CH_3)_2$), 1.89 (m, $J = 6.6$ Hz, 1 OCH_2-$CH(CH_3)_2$), 2.28 (ddd, $J = 7.8$, 9.0, 13.8 Hz, 1 3-H), 2.50 (ddd, $J = 2.1$, 6.9, 13.8 Hz, 1 3-H), 3.39 (dd, $J = 6.6$, 9.0 Hz, 1 $OCH_2CH(CH_3)_2$), 3.78 (dd, $J = 6.3$, 9.0 Hz, 1 OCH_2-$CH(CH_3)_2$), 4.20 (dd, $J = 6.9$, 9.3 Hz, 1 4-H), 5.29 (dd, $J = 2.1$, 7.8 Hz, 1 2-H), 6.97 (dd, $J = 3.6$, 5.1 Hz, 1 4′-H), 7.05 (dd, $J = 1.2$, 3.6 Hz, 1 3′-H), 7.23 (dd, $J = 1.0$, 5.1 Hz, 1 5′-H), 7.44 (m, 3 *Ph*H), 7.77 (m, 2 *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 19.1$, 19.2 ($OCH_2CH(CH_3)_2$), 28.5 ($OCH_2CH(CH_3)_2$), 35.3 (C-3), 36.3 (C-4), 77.0 (OCH_2-$CH(CH_3)_2$), 88.3 (C-5), 101.2 (C-2), 119.2 (CN), 124.6 (C-5′), 125.9 (C-3′), 126.8 (C-4′), 128.2, 128.4, 131.0, 132.9 (*Ph*C), 144.2 (C-2′), 163.3 (C-6) ppm; MS (EI, 70 eV): m/z (%) = 339 (13) $[M]^{+\bullet}$, 265 (76), 239 (99), 212 (33), 105 (100), 100 (5), 77 (38), 73 (54).

(2RS,4RS)-3,4-Dihydro-2-isobutoxy-6-phenyl-4-(2-thienyl)-2H-pyran-5-carbonitrile (*trans*-**8b**, $C_{20}H_{21}NO_2S$)
Colorless crystals; mp 76°C; yield 8%; IR (KBr): $\bar{\nu} = 3087$, 2975, 2935, 2890 (CH), 2200 (CN), 1601 (C=C), 1146 (C–O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 0.95$ (d, $J =$ 6.9 Hz, 6 $OCH_2CH(CH_3)_2$), 1.85 (m, $J = 6.6$ Hz, 1 OCH_2-$CH(CH_3)_2$), 2.15 (ddd, $J = 2.4$, 9.6, 13.8 Hz, 1 3-H), 2.36 (ddd, $J = 4.2$, 6.0, 13.8 Hz, 1 3-H), 3.46 (dd, $J = 6.6$, 9.0 Hz, 1 $OCH_2CH(CH_3)_2$), 3.72 (dd, $J = 6.9$, 9.0 Hz, 1 OCH_2-$CH(CH_3)_2$), 4.24 (dd, $J = 6.0$, 9.6 Hz, 1 4-H), 5.34 (dd, $J = 2.4$, 4.2 Hz, 1 2-H), 7.00 (dd, $J = 3.6$, 5.1 Hz, 1 4′-H), 7.05 (dd, $J = 1.2$, 3.0 Hz, 1 3′-H), 7.24 (dd, $J = 0.9$, 5.1 Hz, 1 5′-H), 7.44 (m, 3 *Ph*H), 7.77 (m, 2 *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 19.3$, 19.5 ($OCH_2CH(CH_3)_2$), 29.7 ($OCH_2CH(CH_3)_2$), 32.5 (C-3), 35.5 (C-4), 77.0 (OCH_2CH-$(CH_3)_2$), 88.3 (C-5), 98.4 (C-2), 119.2 (CN), 124.6 (C-5′), 124.7 (C-3′), 125.9 (C-4′), 127.1, 128.2, 130.8, 133.0 (*Ph*C), 144.2 (C-2′), 163.3 (C-6) ppm; MS (EI, 70 eV): m/z (%) = 339 (13) $[M]^{+\bullet}$, 265 (76), 239 (94), 212 (36), 105 (100), 100 (7), 77 (38), 73 (2).

(2RS,4SR)-3,4-Dihydro-2-methoxy-2-methyl-6-phenyl-4-(4-thienyl)-2H-pyran-5-carbonitrile (*cis*-**8c**, $C_{18}H_{17}NO_2S$)
Colorless crystals; mp 85°C; yield 62%; IR (KBr): $\bar{\nu} = 3108$, 3085, 2990, 2971, 2942, 2836 (CH), 2202 (CN), 1613 (C=C), 1163, 1054 (C–O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 1.61$ (s, 3 2-CH_3), 2.26 (dd, $J = 7.2$, 13.8 Hz, 1 3-H), 2.37 (dd, $J = 7.5$, 13.8 Hz, 1 3-H), 3.41 (s, 3 OCH_3), 4.13 (t, $J = 7.2$ Hz, 1 4-H), 6.97 (dd, $J = 3.3$, 5.1 Hz, 1 4′-H), 7.05 (dd, $J = 1.2$, 3.6 Hz, 1 3′-H), 7.23 (dd, $J = 1.2$, 5.1 Hz, 1 5′-H), 7.44 (m, 3 *Ph*H), 7.78 (m, 2 *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 21.8$ (2-CH_3), 35.2 (C-3), 39.3 (C-4), 49.6 (2-OCH_3), 87.8 (C-5), 102.5 (C-2), 119.4 (CN), 124.8 (C-5′), 126.0 (C-3′), 126.7 (C-4′), 128.2, 128.4, 130.9, 133.1 (*Ph*C), 144.5 (C-2′), 163.2 (C-6) ppm; MS (EI, 70 eV): m/z (%) = 311 (35) $[M]^{+\bullet}$, 279 (35), 239 (33), 212 (18), 105 (52), 77 (34), 72 (100).

(2RS,4SR)-3,4-Dihydro-2-methoxy-2-methyl-6-phenyl-4-(4-thienyl)-2H-pyran-5-carbonitrile (*trans*-**8c**, $C_{18}H_{17}NO_2S$)
Colorless oil; yield 14%; IR (KBr): $\bar{\nu} = 3105$, 3083, 2987, 2972, 2939, 2836 (CH), 2205 (CN), 1615 (C=C), 1169, 1049 (C–O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta =$ 1.62 (s, 3 2-CH_3), 2.00 (dd, $J = 12.3$, 13.8 Hz, 1 3-H), 2.42 (dd, $J = 6.0$, 13.8 Hz, 1 3-H), 3.46 (s, 3 OCH_3), 4.27 (dd, $J =$ 6.0, 12.3 Hz, 1 4-H), 7.00 (dd, $J = 3.3$, 5.1 Hz, 1 4′-H), 7.05 (dd, $J = 1.2$, 3.6 Hz, 1 3′-H), 7.25 (dd, $J = 1.2$, 5.1 Hz, 1 5′-H), 7.44 (m, 3 *Ph*H), 7.78 (m, 2 *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 22.4$ (2-CH_3), 33.0 (C-3), 41.6 (C-4), 49.9 (2-OCH_3), 90.0 (C-5), 101.8 (C-2), 119.2 (CN), 124.6 (C-5′), 126.0 (C-3′), 127.0 (C-4′), 128.7, 128.8, 130.8, 133.3 (*Ph*C), 144.0 (C-2′), 162.0 (C-6) ppm; MS (EI, 70 eV): m/z (%) = 311 (16) $[M]^{+\bullet}$, 279 (24), 239 (57), 212 (23), 105 (100), 77 (62), 72 (71).

(2RS,4SR)-2-Ethoxy-4-(2-furyl)-3,4-dihydro-6-phenyl-2H-pyran-5-carbonitrile (*cis*-**8d**, $C_{18}H_{17}NO_3$)
Colorless crystals; mp 66°C; yield 70%; IR (KBr): $\bar{\nu} = 3143$, 3115, 2981, 2917, 2883 (CH), 2206 (CN), 1618 (C=C), 1141 (C–O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 1.24$ (t, $J = 7.05$ Hz, 3 OCH_2CH_3), 2.35 (m, 2 3-H), 3.69 (dq, $J = 7.05$, 9.5 Hz, 1 OCH_2CH_3), 4.02 (dq, $J = 7.05$, 9.5 Hz, 1 OCH_2CH_3), 3.99 (t, $J = 7.3$ Hz, 1 4-H), 5.31 (t, $J = 5.0$ Hz, 1 2-H), 6.29 (d, $J = 3.3$ Hz, 1 3′-H), 6.35 (dd, $J = 3.3$, 1.8 Hz, 1 4′-H), 7.42 (m, 4 5′-H, *Ph*H), 7.77 (m, 2 *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 15.0$ (OCH_2CH_3), 32.1 (C-3), 33.4 (C-4), 65.2 (OCH_2CH_3), 85.7 (C-5), 100.5 (C-2), 107.0 (C-3′), 110.5 (C-4′), 119.2 (CN), 128.2, 128.4, 130.9, 132.9, 141.9 (*Ph*C), 153.0 (C-5′), 163.8 (C-6) ppm; MS (EI, 70 eV): m/z (%) = 295 (9) $[M]^{+\bullet}$, 249 (67), 223 (100), 195 (10), 169 (7), 105 (98), 77 (38), 72 (14).

(2RS,4RS)-2-Ethoxy-4-(2-furyl)-3,4-dihydro-6-phenyl-2H-pyran-5-carbonitrile (*trans*-**8d**, $C_{18}H_{17}NO_3$)
Colorless oil; yield 7%; IR (KBr): $\bar{\nu} = 3143$, 3115, 2981, 2917, 2883 (CH), 2206 (CN), 1618 (C=C), 1141 (C–O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J =$ 7.05 Hz, 3 OCH_2CH_3), 2.27 (m, 2 3-H), 3.73 (dq, $J_= 7.05$, 9.5 Hz, 1 OCH_2CH_3), 4.00 (dq, $J = 7.05$, 9.5 Hz, 1 OCH_2-CH_3), 4.03 (dd, $J = 6.7$, 8.9 Hz, 1 4-H), 5.35 (dd, $J = 2.7$, 4.8 Hz, 1 2-H), 6.29 (d, $J = 3.3$ Hz, 1 3′-H), 6.35 (dd, $J = 3.3$, 1.8 Hz, 1 4′-H), 7.42 (m, 4 5′-H, *Ph*H), 7.77 (m, 2 *Ph*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 15.1$ (OCH_2CH_3), 29.7 (C-3), 31.4 (C-4), 65.1 (OCH_2CH_3), 85.8 (C-5), 98.4 (C-2), 107.6 (C-3′), 110.5 (C-4′), 119.1 (CN), 128.1, 128.3, 130.8, 133.2, 142.4 (*Ph*C), 153.3 (C-5′), 163.1 (C-6) ppm; MS (EI, 70 eV): m/z (%) = 295 (7) $[M]^{+\bullet}$, 249 (59), 223 (100), 195 (8), 169 (6), 105 (92), 77 (35), 72 (13).

(2RS,4SR)-4-(Cyanophenyl)-2-ethoxy-3,4-dihydro-6-phenyl-2H-pyran-5-carbonitrile (*cis*-**8e**, $C_{21}H_{18}N_2O_2$)
Colorless crystals; mp 140°C; yield 81%; IR (KBr): $\bar{\nu} = 3064$, 2979, 2940, 2903 (CH), 2228, 2201 (CN), 1606 (C=C), 1144 (C–O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 1.21$ (t, $J = 7.05$ Hz, 3 OCH_2CH_3), 2.13 (ddd, $J = 6.9$, 7.8, 13.8 Hz, 1 3-H), 2.42 (ddd, $J = 2.4$, 7.2, 13.8 Hz, 1 3-H), 3.68 (dq,

$J = 7.05$, 9.5 Hz, 1 OCH_2CH_3), 3.94 (t, $J = 7.5$ Hz, 1 4-H), 4.02 (dq, $J = 7.05$, 9.5 Hz, 1 OCH_2CH_3), 5.35 (dd, $J = 2.4$, 6.9 Hz, 1 2-H), 7.46 (m, 5 *Ar*H), 7.66 (m, 2 *Ar*H), 7.80 (m, 2 *Ar*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 15.0$ (OCH_2CH_3), 35.2 (C-3), 39.7 (C-4), 65.3 (OCH_2CH_3), 86.2 (C-5), 100.2 (C-2), 111.4 (*Ar*C), 118.7 (CN), 119.2 (CN), 128.1, 128.5, 128.8, 131.2, 132.6, 132.7, 146.7 (*Ar*C), 164.6 (C-6) ppm; MS (EI, 70 eV): m/z (%) = 330 (30) $[M]^{+\bullet}$, 284 (15), 105 (35), 77 (26), 72 (100).

(2RS,4RS)-4-(Cyanophenyl)-2-ethoxy-3,4-dihydro-6-phenyl-2H-pyran-5-carbonitrile (*trans*-**8e**, $C_{21}H_{18}N_2O_2$)
Colorless crystals; mp 186°C; yield 7%; IR (KBr): $\bar{\nu} = 3087$, 2975, 2935, 2890 (CH), 2200 (CN), 1601 (C=C), 1146 (C–O) cm^{-1}; ^{1}H NMR (300.18 MHz, $CDCl_3$): $\delta = 1.31$ (t, $J =$ 7.05 Hz, 3 OCH_2CH_3), 1.97 (ddd, $J = 2.7$, 11.1, 13.8 Hz, 1 3-H), 2.29 (ddd, $J = 3.0$, 6.3, 13.8 Hz, 1 3-H), 3.77 (dq, $J = 7.05$, 9.5 Hz, 1 OCH_2CH_3), 4.02 (dd, $J = 6.3$, 11.1 Hz, 1 4-H), 4.03 (dq, $J = 7.05$, 9.5 Hz, 1 OCH_2CH_3), 5.39 (br t, $J = 2.7$ Hz, 1 2-H), 7.46 (m, 5 *Ar*H), 7.69 (m, 2 *Ar*H), 7.78 (m, 2 *Ar*H) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 15.1$ (OCH_2CH_3), 34.9 (C-3), 36.9 (C-4), 65.1 (OCH_2CH_3), 87.2 (C-5), 97.6 (C-2), 111.7 (*Ar*C), 118.6 (CN), 119.0 (CN), 128.1, 128.5, 128.6, 131.1, 132.9, 133.0, 146.9 (*Ar*C), 163.6 (C-6) ppm; MS (EI, 70 eV): m/z (%) = 330 (24) $[M]^{+\bullet}$, 284 (11), 105 (34), 77 (26), 72 (100).

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