Inter- and Intramolecular Hetero Diels-Alder Reactions, 36[1]

Synthesis of Dihydropyrans by Hetero Diels-Alder Reaction of Enaminones An Efficient Route to 3-Amino Sugar Derivatives

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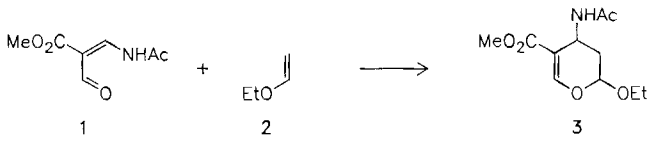
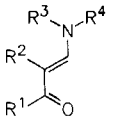
The hetero Diels-Alder reaction of the *N*-monoacyl- and *N,N*-diacyl-enamino ketones **4a–g** containing an electron-withdrawing group at C-2 of the oxadiene moiety with the electron-rich dienophiles **5a–d** affords the diastereomeric adducts **6a–i** and **7a–i** in 78–98% yield with the *cis* adducts **7a–i** as the main products. The highest selectivity is obtained with the *N,N*-phthalimido-protected enamino ketones **4d–g**.

The hetero Diels-Alder reaction of α,β-unsaturated carbonyl compounds[2] is an excellent method for the synthesis of the pyran moiety, which is a characteristic of carbohydrates. The rate of the cycloaddition can be greatly increased by introducing an electron-withdrawing group in position 2 or 3 of the oxadiene due to a lowering of the LUMO of the diene, since the overlap of the LUMO of the heterodiene with the HOMO of the dienophile is most important in this hetero Diels-Alder reaction, which belongs to the inverse type[2a]. Recently, we have shown that enamine carbaldehydes[3] can be used as heterodienes if an electron-withdrawing group such as an ester moiety is present in the position 3 of the oxadiene and the nitrogen is acylated as in **1** to give a dihydropyran **3** with a vinyl ether **2**[4]. This reaction allows an easy access to branched 3-amino sugars of the garosamine type, a component of the widely used antibiotic gentamicine C[5].



1 2 3

Moreover, many unbranched 3-amino sugars[6] show also a pronounced biological activity. Thus, one of the most efficient anticancer agents today is the anthracyclinone derivative doxorubicin, which contains the 3-amino sugar daunosamine. Doxorubicin displays a high cardiotoxicity which can be reduced by replacement of daunosamine by other amino sugars[7]. Therefore, the development of new synthetic methods leading to natural and unnatural 3-amino sugars and their derivatives is of interest[8]. In this paper we describe a new entry to 3-amino sugar derivatives by a hetero Diels-Alder reaction of enamino ketones **4a–g** with an electron-withdrawing group in the position 2 of the oxabutadiene. A main advantage of this approach is the direct formation of glycosides in the cycloaddition step; thus, the often tedious glycosidation is avoided. As electron-withdrawing groups the trichloromethyl, dichlorofluoromethyl and the trifluoromethyl as well as the methoxycarbonyl group have been used. A part of this work has already been published as a communication[9].



4

4	R^1	R^2	R^3	R^4
a	CO_2Me	H	PhCO	H
b	CO_2Me	H	MeO_2CCO	H
c	CO_2Et	Br	PhCO	H
d	CO_2Me	H	Phthaloyl	
e	CCl_3	H	Phthaloyl	
f	$CClF_2$	H	Phthaloyl	
g	CF_3	H	Phthaloyl	

Interestingly, enamino ketones with an *S*-phenyl group in the position 3 of the oxabutadiene moiety also show a strong reactivity in hetero Diels-Alder reactions[9,10]. These transformations lead to natural 3-amino sugars and will be described later.

The synthesis of the enamino ketones **4a–e** and **4g** has recently been described[3a,c]. The synthesis of **4f** has been accomplished in analogy to **4g** starting with chlorodifluoroacetic anhydride to afford **4f** in 43% overall yield.

The hetero Diels-Alder reaction is performed by heating a solution of the dienes **4a–g** and 5–50 equivalents of the dienophiles **5a–c** in toluene/dichloromethane at 110 to 140°C for 12–170 h. The reaction conditions, the yields, and the selectivity of the cycloadditions are given in Table 1.

Reaction of the enamino ketones **4a–c** carrying an NHCOR group and a methoxycarbonyl group as an electron-accepting group in the position 2 of the oxabutadiene with ethyl vinyl ether (**5a**) gives the adducts **6a–c** and **7a–c** with a low *exo/endo* selectivity (1:1.5–1:1.8). The selectivity is, however, greatly enhanced by using the enamino ketone

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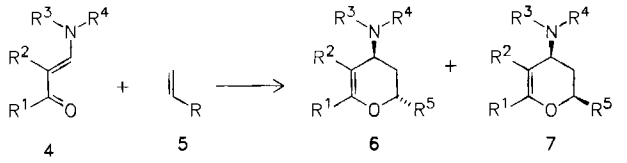
4d–g with a phthalimido group. Thus, the reaction of **4d** and **5a** affords the dihydropyrans **6d** and **7d** in a ratio of 1:6.3 in 95% yield. The highest selectivity is obtained by use of phenyl vinyl sulfide (**5c**) giving the adducts **6f** and **7f** in a ratio of 1:66.



4 5 6 7

5	R
a	OEt
b	$OCMe_3$
c	SPh
d	OMe

6, 7	R^1	R^2	R^3	R^4	R^5
a	CO_2Me	H	PhCO	H	OEt
b	CO_2Me	H	MeO_2CCO	H	OEt
c	CO_2Et	Br	PhCO	H	OEt
d	CO_2Me	H	Phthaloyl		OEt
e	CO_2Me	H	Phthaloyl		$OCMe_3$
f	CO_2Me	H	Phthaloyl		SPh
g	CCl_3	H	Phthaloyl		OEt
h	$CClF_2$	H	Phthaloyl		OEt
i	CF_3	H	Phthaloyl		OEt

Table 1. Synthesis of dihydropyrans **6a–i** and **7a–i** from **4** and **5**

6 + 7	a	b	c	d	e
Ratio [6:7]	1:1.6[a]	1:1.8[a]	1:1.5[a]	1:6.3[b]	1:2.3[b]
Yield [%]	98	78	84	95	94
Reaction conditions [h/°C]	12/135	16/140	110/110	12/120	60/110

6 + 7	f	g	h	i
Ratio [6:7]	1:66[c]	1:1.5[a]	1:1.9[c]	1:2.8[d]
Yield [%]	86	94	97	89
Reaction conditions [h/°C]	72/110	12/125	36/110	24/110

[a] ^1H NMR of crude products. – [b] After isolation. – [c] HPLC. – [d] ^{13}C NMR of crude products.

The results can best be explained by assuming that the enamino ketones **4a–c** may react in both the (*E*) and (*Z*) configuration; the normally preferred *endo* addition to (*E*)-**4a–c** would afford the dihydropyrans **7a–c** and to (*Z*)-**4a–c** the dihydropyrans **6a–c**. Vice versa, these considerations can also be applied to the *exo* addition. Thus, two counteracting effects must be operative in these reactions: (i) Stabilization of the (*Z*)-like transition structure by a hydrogen bond and (ii) destabilization of the transition structure with the (*Z*)-dienes by steric effects. It is, of course, well-known that (*Z*)-dienes react much slower than (*E*)-dienes[11]. The higher selectivity of the *N,N*-phthalimido-protected enamino ketones **4d–g** can now be explained by assuming that these compounds react exclusively from the (*E*) configuration to give predominantely the *cis*-substituted dihydropyrans **7d–i** by *endo* addition. In agreement with these assumptions, the enol ether **5b** with the bulky *tert*-butyl group shows a lower selectivity due to a disfavoring of the *endo* transition structure because of steric interaction (**6e**:**7e** = 1:2.3); in contrast, the cycloaddition with phenyl vinyl sulfide (**5c**), which is usually *endo*-selective, gives **6f** and **7f** in a ratio of 1:66.

The cycloadditions of **4a–g** and **5a–c** are kinetically controlled reactions leading to the thermodynamically less stable *cis* cycloadducts **7a–i** preferentially. However, in some cases a Lewis acid catalyzed isomerization allows a complete transformation into the thermodynamically more stable *trans* cycloadducts **6**. Thus, treatment of the crude mixture of **6d**/**7d** with Et_2O-BF_3 gives predominantely **6d**, which can be obtained in 86% yield (based on **4d**) by crystallization and repeated treatment of the mother liquors with Et_2O-BF_3. In a similar way, the cycloaddition of **4e** and **5a** yields 78% of **6g** after isomerization. The lower ground-state energy of **6d** and **6g** compared to **7d** and **7a** can be explained by the favored axial orientation of the ethoxy group at C-2 and the equatorial orientation of the *N*-phthaloyl group at C-4.

Transformation of the Dihydropyrans 6 and 7

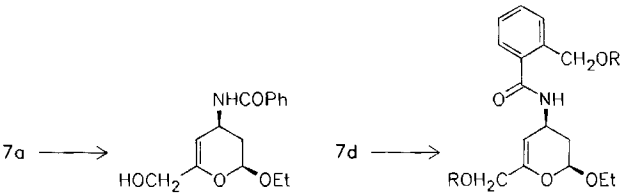
The dihydropyrans **6a–i** and **7a–i** obtained by the hetero Diels-Alder reaction of **4** and **5** may be transformed in several ways:

i) Reduction and transformation of the electron-withdrawing group at C-6.

ii) Hydrogenation of the double bond to give the corresponding tetrahydropyrans.

iii) Removal of the *N*-protecting group.

Reduction of the methoxycarbonyl group in **7a** to the labile **8** in 48% yield is achieved with $LiAlH_4$ in dimethoxyethane. In a similar way, **7d** is reduced to the diol **9a** which, however, has not been isolated but transformed into the diacetate **9b** by treatment with acetyl chloride in pyridine. It should be noted that the allylic alcohols of type **8** or **9a** are highly sensitive, especially in the presence of acid.

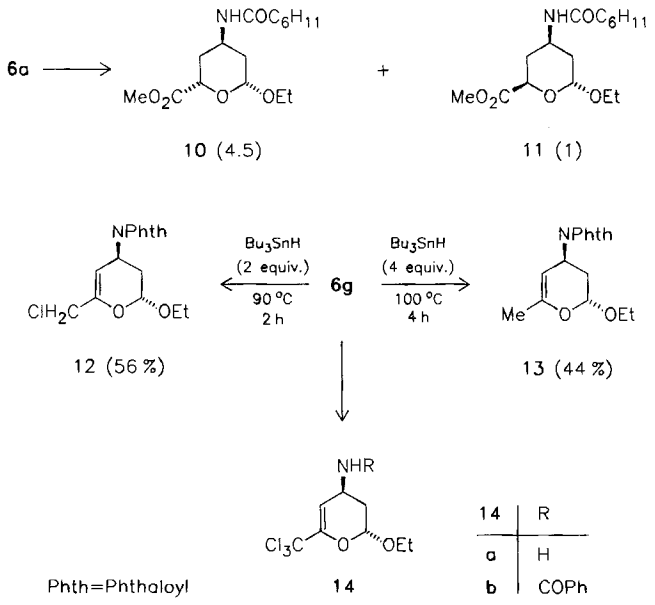


8

9	R
a	H
b	Ac

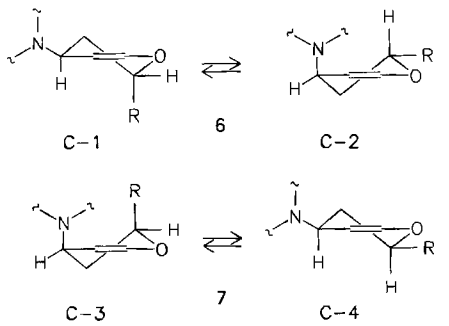
The hydrogenation of the double bond in compounds of type **6**/**7** requires harsh conditions. Thus, even with platinum as catalyst and increased hydrogen pressure (50 bar) a hydrogenation of the double bond in **6a** can only be achieved in ethanol in the presence of acetic acid. By the application of these conditions the aromatic ring is also reduced to give a 4.5:1 mixture of **10** and **11** from **6a** in 70% yield. In addition, a small amount of C-2 isomers is formed due to

the acidic reaction conditions. Many 3-amino sugars have a methyl group at C-5. Therefore, it has been of interest to transform the trichloromethyl group at C-6 (sugar nomenclature: C-5) in the dihydropyrans **6g/7g** into a methyl group. Treatment of **6g** with two equivalents of tri-*n*-butyltin hydride affords the chloromethyl-substituted dihydropyran **12** in 56% yield, whereas with four equivalents 44% of **13** is obtained. The phthaloyl group can be removed by hydrazinolysis; thus, treatment of **6g** with hydrazine in ethanol gives **14a** with a free amino group at C-4 which is benzoylated to yield the (benzoylamino)dihydropyran **14b** in 86% overall yield.



Structure Determination of the Cycloadducts

The configuration and conformation of the cycloadducts **6a–i** and **7a–i** has mainly been determined by ^{1}H-NMR spectroscopy. The conformation of the cycloadducts with an NHCOR group at C-4 in **6a–c** and **7a–c** is governed by the anomeric effects despite the orientation of the amido group giving preference to the conformations **C-1** and **C-3**.



In contrast, for the cycloadducts **6d–i** and **7d–i** with the *N*-phthalimido group at C-4, conformations **C-1** and **C-4**, respectively, with the bulky *N*-phthalimido group in a pseudoequatorial orientation are preferred. The conformation and configuration of the cycloadducts can be deduced from the resonances and coupling constants for 2-H and 4-H in the ^{1}H-NMR spectra. 2-H in **6a–c** resonates at δ = 5.20–5.28 with J = 2.3–4.5 Hz and **7a–c** at δ = 5.44–5.48 with J = 2.0–2.2 Hz. This clearly indicates that for both **6a–c** and **7a–c** the conformation with an axial ethoxy group is preferred, since otherwise a larger coupling constant should be observed. For 4-H in **6a–c** signals at δ = 4.92–5.14 with $J_{3,4}$ = 8.5–10.4 Hz and for 4-H in **7a–c** at δ = 4.72–5.17 with $J_{3,4}$ = 4.5–5.0 Hz are found. These signals can only be explained, if the substituents at C-2 and C-4 display a *trans* relationship in **6** and a *cis* relationship in **7**. The resonances for 2-H and 4-H in **6d,e,g–i** are found at δ = 5.40–5.70 with $J_{3,4}$ = 2.5–3.0 Hz and δ = 5.27–5.34 with $J_{3,4}$ = 11.0–11.4 Hz, respectively. In these compounds the ethoxy group occupies an axial and the phthalimido group a pseudoequatorial orientation indicating a 2,4-*trans* relationship of the substituents. In contrast, the ethoxy group of **7d,e,g–i** must hold an equatorial position since 2-H resonates at δ = 5.12–5.23 with J = 8.6–11.0 Hz, whereas the signals for 4-H appear with similar chemical shift values and coupling constants compared to those observed for 4-H of **6d,e,g–i**. Thus, the phthalimido group in **7d,e,g–i** should also display a pseudoequatorial orientation, which means that there is a 2,4-*cis* relationship of the substituents.

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Experimental

^{1}H and ^{13}C NMR: Varian XL-200, VXR-200, and FT-80 A; multiplicities were determined with the APT pulse sequence. – UV: Varian Cary 219. – Melting points: Kofler melting point apparatus (corrected values). – Elemental analyses were carried out in the analytical laboratory of the university. – All solvents were distilled prior to use. All reactions were carried out under nitrogen and monitored by TLC (Macherey-Nagel, Alugram Sil G/UV$_{254}$). Products were isolated by flash chromatography on SiO_2 (Baker, 30–60, active). – All chiral compounds were obtained as racemic mixtures.

Synthesis of 1-Chloro-1,1-difluoro-4-phthalimido-3-buten-2-one (**4f**). – A) *1-Chloro-4-ethoxy-1,1-difluoro-3-buten-2-one:* To a solution of 4-(dimethylamino)pyridine (2.20 g, 18.0 mmol) in chlorodifluoroacetic anhydride (24.0 g, 99.0 mmol) was added dropwise with stirring at –15 °C ethyl vinyl ether (10.0 ml, 104 mmol). Stirring was continued at 0 °C for 12 h and the solvent removed in vacuo. Repeated distillation afforded 11.6 g (58%) of 1-chloro-4-ethoxy-1,1-difluoro-3-buten-2-one as a colorless oil; b.p. 74 °C/12 Torr. – IR (film): $\tilde{\nu}$ = 2992 cm^{-1} (CH), 1710 (C=O), 1600 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 273 nm (3.966). – ^{1}H NMR ($CDCl_3$): δ = 1.35 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 4.08 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 5.53 (d, J = 13.0 Hz, 1H, 3-H), 7.78 (d, J = 13.0 Hz, 1H, 4-H).

$C_6H_7ClF_2O_2$ (184.6)
Calcd. C 39.05 H 3.82 Cl 19.21 F 20.6
Found C 39.17 H 3.84 Cl 19.14 F 20.7

B) *4-Amino-1-chloro-1,1-difluoro-3-buten-2-one:* An excess of ammonia was passed through a stirred solution of 1-chloro-4-ethoxy-1,1-difluoro-3-buten-2-one in anhydrous tetrahydrofuran (120 ml) at 0 °C for about 1 h. The mixture was concentrated in vacuo and

the residue distilled (60–61°C, 0.4 Torr) to give 4-amino-1-chloro-1,1-difluoro-3-buten-2-one (9.48 g, 97%). – IR (film): $\tilde{\nu}$ = 3300 cm^{-1} (NH), 1652 (C=O), 1600 (C=C). – UV (CH_3CN): λ_{max} (lgε) = 308 nm (4.198). – ^1H NMR ($CDCl_3$): δ = 5.40 (m, 0.95H, 3-H, *Z*), 5.65 (m, 0.05H, 3-H, *E*), 6.25 (br., 1H, NH), 7.25 (dt, *J* = 15.0, 8.0 Hz, 0.95H, 4-H, *Z*), 7.85 (q, *J* = 12.0 Hz, 0.05H, 4-H, *E*), 8.75 (br., 1H, NH chelat.).

$C_4H_4ClF_2NO$ (155.5)
Calcd. C 30.89 H 2.59 Cl 22.80 F 24.4 N 9.01
Found C 31.09 H 2.74 Cl 22.76 F 24.4 N 9.01

C) *1-Chloro-1,1-difluoro-4-phthalimido-3-buten-2-one* (**4f**): To a stirred solution of 4-amino-1-chloro-1,1-difluoro-3-buten-2-one, 4-(dimethylamino)pyridine (400 mg, 3.28 mmol) and pyridine (16.8 ml, 187 mmol) in anhydrous tetrahydrofuran (40 ml) was added phthaloyl chloride (14.6 g, 72.3 mmol) at 0°C. The mixture was allowed to warm up to room temp. and stirred for 14 h. After addition of 80 ml of *tert*-butyl methyl ether, the solution was washed with brine (20 ml) and dried with Na_2SO_4. After evaporation of the solvent in vacuo, the residue was purified by chromatography (diethyl ether/petroleum ether, 1:2) to give **4f** (12.6 g, 77%). – M.p. 80°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 3118 cm^{-1} (CH), 1736 (C=O), 1610 (C=C). – UV (CH_3CN): λ_{max} (lgε) = 285 nm (4.437), 222 (4.342). – ^1H NMR ($CDCl_3$): δ = 7.62 (dt, *J* = 15.0, 1.0 Hz, 1H, 3-H), 7.95 (m_c, 4H, Ph-H), 8.24 (d, *J* = 15.0 Hz, 1H, 4-H).

$C_{12}H_6ClF_2NO_3$ (285.7)
Calcd. C 50.46 H 2.12 Cl 12.41 F 13.3 N 4.90
Found C 50.53 H 2.20 Cl 12.49 F 13.1 N 4.87

Synthesis of the Dihydropyrans **6a–i** *and* **7a–i** *by Diels-Alder Reaction. – General Procedure I: Reaction of 1-Oxabutadienes* **4a–g** *with the Dienophiles* **5a–d**: To a solution of the dienes **4a–g** (3.00 mmol) in toluene, dichloromethane, or toluene/dichloromethane mixtures (2–20 ml) were added the dienophiles **5a–d** (5–50 equivalents) and hydroquinone (0.1 mmol). The mixtures were heated at 110–140°C for 12–110 h in a pressure flask or an autoclave. After removal of the solvent in vacuo, the crude products were purified by flash chromatography and/or crystallization.

Reaction of **4a** *and* **5a**: A mixture of **4a** (700 mg, 3.00 mmol) and **5a** (2.16 g, 30.0 mmol) in toluene (10 ml) was heated in a pressure flask (12 h, 135°C) according to procedure I to yield after chromatography (ethyl acetate/diethyl ether/petroleum ether, 1:3:2) **7a** (559 mg, 61%) and **6a** (339 mg, 37%).

Fraction 1: Methyl (2R,4R)-(±)-4-Benzoylamino-2-ethoxy-3,4-dihydro-2H-pyran-6-carboxylate (**7a**): R_f = 0.34. – M.p. 109°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 3270 cm^{-1} (NH), 2990 (CH), 1740, 1635 (C=O). – UV (CH_3CN): λ_{max} (lg ε) = 241 nm (4.122). – ^1H NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.18 (m_c, 2H, 3-H), 3.65 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 3.83 (s, 3H, OCH_3), 3.93 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 4.95 (dddd, *J* = 9.0, 5.0, 4.5, 2.2 Hz, 1H, 4-H), 5.48 (t, *J* = 2.2 Hz, 1H, 2-H), 6.34 (d, *J* = 5.0 Hz, 1H, 5-H), 7.35 (br., d, *J* = 9.0 Hz, 1H, NH), 7.4–7.8 (m, 5H, Ph-H). – ^{13}C NMR ($CDCl_3$): δ = 15.21 (OCH_2CH_3), 31.82 (C-3), 37.50 (C-4), 52.37 (OCH_3), 64.52 (OCH_2CH_3), 96.93 (C-2), 111.4 (C-5), 126.8 (*m*-Ph), 128.5 (*o*-Ph), 131.5 (*p*-Ph), 134.2 (*i*-Ph), 141.1 (C-6), 163.0 (CO_2CH_3), 165.8 (C=O).

$C_{16}H_{19}NO_5$ (305.3)
Calcd. C 62.94 H 6.27 N 4.59
Found C 63.08 H 6.38 N 4.64

Fraction 2: Methyl (2S,4R)-(±)-4-Benzoylamino-2-ethoxy-3,4-dihydro-2H-pyran-6-carboxylate (**6a**): R_f = 0.29. – M.p. 150°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 3330 cm^{-1} (NH), 2980 (CH), 1735, 1635 (C=O). – UV (CH_3CN): λ_{max} (lgε) = 239 nm (4.218). – ^1H NMR ($CDCl_3$): δ = 1.22 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.82 (ddd, *J* = 13.0, 10.2, 2.5 Hz, 1H, 3-H_{ax}), 2.37 (dddd, *J* = 13.0, 6.5, 3.2, 1.2 Hz, 1H, 3-H_{eq}), 3.63 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 3.82 (s, 3H, OCH_3), 3.90 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 5.12 (dddd, *J* = 10.2, 8.2, 6.5, 2.8 Hz, 1H, 4-H), 5.28 (dd, *J* = 3.2, 2.5 Hz, 1H, 2-H), 6.12 (dd, *J* = 2.8, 1.0 Hz, 1H, 5-H), 6.22 (br., d, *J* = 8.2 Hz, 1H, NH), 7.4–7.9 (m, 5H, Ph-H). – ^{13}C NMR ($CDCl_3$): δ = 15.03 (OCH_2CH_3), 32.44 (C-3), 40.14 (C-4), 52.38 (OCH_3), 64.58 (OCH_2CH_3), 98.00 (C-2), 112.5 (C-5), 127.0 (*m*-Ph), 128.4 (*o*-Ph), 131.7 (*p*-Ph), 134.0 (*i*-Ph), 141.1 (C-6), 163.0 (CO_2CH_3), 167.0 (C=O).

$C_{16}H_{19}NO_5$ (305.3)
Calcd. C 62.94 H 6.27 N 4.59
Found C 62.96 H 6.26 N 4.58

Reaction of **4b** *and* **5a**: A mixture of **4b** (645 mg, 3.00 mmol) and **5a** (1.08 g, 15.0 mmol) in toluene (10 ml) was heated at 140°C for 16 h according to procedure I to yield after chromatography (chloroform/*tert*-butyl methyl ether, 1:1) **7b** (440 mg, 51%) and **6b** (237 mg, 27%).

Fraction 1: Methyl (2R,4R)-(±)-2-Ethoxy-4-(2-methoxy-1,2-dioxo-1,2-ethanediylamino)-3,4-dihydro-2H-pyran-6-carboxylate (**7b**): R_f = 0.60. – M.p. 101°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 3420 cm^{-1} (NH), 2980 (CH), 1730, 1700, 1635 (C=O). – UV (CH_3CN): λ_{max} (lgε) = 241 nm (4.086). – ^1H NMR ($CDCl_3$): δ = 1.28 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.13 (m_c, 2H, 3-H), 3.67 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 3.84 (s, 3H, OCH_3), 3.88 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 3.92 (s, 3H, OCH_3), 4.72 (m_c, 1H, 4-H), 5.46 (t, *J* = 2.0 Hz, 1H, 2-H), 6.22 (d, *J* = 5.2 Hz, 1H, 5-H), 8.18 (br., d, *J* = 9.2 Hz, 1H, NH).

$C_{12}H_{17}NO_7$ (287.3)
Calcd. C 50.17 H 5.97 N 4.88
Found C 50.30 H 5.83 N 4.80

Fraction 2: Methyl (2S,4R)-(±)-2-Ethoxy-4-(2-methoxy-1,2-dioxo-1,2-ethanediylamino)-3,4-dihydro-2H-pyran-6-carboxylate (**6b**): R_f = 0.37. – M.p. 93°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 3230 cm^{-1} (NH), 2960 (CH), 1735, 1680 (C=O). – UV (CH_3CN): λ_{max} (lgε) = 240 nm (4.073). – ^1H NMR ($CDCl_3$): δ = 1.20 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.77 (ddd, *J* = 13.0, 10.4, 2.5 Hz, 1H, 3-H_{ax}), 2.31 (dddd, *J* = 13.0, 6.2, 3.2, 1.2 Hz, 1H, 3-H_{eq}), 3.66 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 3.82 (s, 3H, OCH_3), 3.86 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 3.92 (s, 3H, OCH_3), 4.92 (dddd, *J* = 10.4, 8.8, 6.2, 2.8 Hz, 1H, 4-H), 5.28 (dd, *J* = 3.2, 2.5 Hz, 1H, 2-H), 6.00 (dd, *J* = 2.8, 1.2 Hz, 1H, 5-H), 7.10 (br., d, *J* = 8.8 Hz, 1H, NH).

$C_{12}H_{17}NO_7$ (287.3)
Calcd. C 50.17 H 5.97 N 4.88
Found C 50.39 H 6.05 N 4.83

Reaction of **4c** *and* **5a**: A mixture of **4c** (978 mg, 3.00 mmol) and **5a** (10.8 g, 150 mmol) in toluene (15 ml) was heated in a pressure flask (110 h, 110°C) according to procedure I to yield after chromatography (ethyl acetate/petroleum ether, 1:3) **6c** (406 mg, 34%) and **7c** (597 mg, 50%).

Fraction 1: Ethyl (2S,4R)-(±)-4-Benzoylamino-5-bromo-2-ethoxy-3,4-dihydro-2H-pyran-6-carboxylate (**6c**): R_f = 0.30. – M.p. 143°C (ethyl acetate/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3320 cm^{-1} (NH), 2990 (CH), 1740, 1645 (C=O). – UV (CH_3CN): λ_{max} (lgε) = 227 nm (4.168). – ^1H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.37 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.11 (ddd, *J* = 13.5, 8.5, 2.3 Hz, 1H, 3-H_{ax}), 2.47 (ddd, *J* = 13.5, 6.2, 4.5 Hz, 1H, 3-H_{eq}), 3.64 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 3.94 (dq, *J* =

9.5, 7.0 Hz, 1H, OCH_2CH_3), 4.33 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 5.14 (ddd, J = 8.5, 8.2, 6.2 Hz, 1H, 4-H), 5.20 (dd, J = 4.5, 2.3 Hz, 1H, 2-H), 6.22 (br., d, J = 8.2 Hz, 1H, NH), 7.4–8.0 (m, 5H, Ph-H).

$C_{17}H_{20}BrNO_5$ (398.3)
Calcd. C 51.27 H 5.06 Br 20.06 N 3.52
Found C 51.32 H 5.08 Br 20.16 N 3.54

Fraction 2: Ethyl (2R,4R)-(±)-4-Benzoylamino-5-bromo-2-ethoxy-3,4-dihydro-2H-pyran-6-carboxylate (**7c**): R_f = 0.24. – M.p. 89°C (diethyl ether/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3450 cm^{-1} (NH), 1745, 1670 (C=O). – UV (CH_3CN): λ_{max} (lgε) = 227 nm (4.175). – ^1H NMR ($CDCl_3$): δ = 1.32 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.36 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.31 (m, 2H, 3-H), 3.65 (dq, J = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 3.96 (dq, J = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 4.34 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 5.17 (ddd, J = 10.0, 5.0, 2.6 Hz, 1H, 4-H), 5.44 (t, J = 2.2 Hz, 1H, 2-H), 7.23 (br., d, J = 10.0 Hz, 1H, NH), 7.4–7.8 (m, 5H, Ph-H).

$C_{17}H_{20}BrNO_5$ (398.3)
Calcd. C 51.27 H 5.06 Br 20.06 N 3.52
Found C 51.20 H 4.99 Br 20.21 N 3.51

Reaction of **4d** *and* **5a**: A mixture of **4d** (778 mg, 3.00 mmol) and **5a** (4.32 g, 60.0 mmol) in toluene/dichloromethane (5:1, 10 ml) was heated in an autoclave (12 h, 120°C) according to procedure I to yield after chromatography (ethyl acetate/petroleum ether, 1:1) **6d** (129 mg, 13%) and **7d** (815 mg, 82%).

Fraction 1: Methyl (2S,4R)-(±)-2-Ethoxy-4-phthalimido-3,4-dihydro-2H-pyran-6-carboxylate (**6d**): R_f = 0.37. – M.p. 139°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 2970 cm^{-1} (CH), 1715 (C=O), 1660 (C=C). – UV (CH_3CN): λ_{max} (lgε) = 219 nm (4.543). – ^1H NMR ($CDCl_3$): δ = 1.24 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.07 (ddt, J = 12.5, 6.5, 2.5 Hz, 1H, 3-H_{eq}), 2.58 (ddd, J = 12.5, 11.4, 2.5 Hz, 1H, 3-H_{ax}), 3.69 (dq, J = 9.8, 7.0 Hz, 1H, OCH_2CH_3), 3.84 (s, 3H, OCH_3), 3.92 (dq, J = 9.8, 7.0 Hz, 1H, OCH_2CH_3), 5.33 (ddd, J = 11.4, 6.5, 2.5 Hz, 1H, 4-H), 5.46 (t, J = 2.5 Hz, 1H, 2-H), 6.08 (t, J = 2.5 Hz, 1H, 5-H), 7.83 (m_c, 4H, Ph-H). – ^{13}C NMR ($CDCl_3$): δ = 14.64 (OCH_2CH_3), 28.83 (C-3), 39.83 (C-4), 51.77 (OCH_3), 63.92 (OCH_2CH_3), 97.31 (C-2), 111.1 (122.9) (*o*-Ph), 131.4 (*i*-Ph), 133.8 (*m*-Ph), 141.3 (C-6), 162.2 (CO_2CH_3), 167.1 (C=O).

$C_{17}H_{17}NO_6$ (331.3)
Calcd. C 61.63 H 5.17 N 4.23
Found C 61.44 H 5.00 N 4.22

Fraction 2: Methyl (2R,4R)-(±)-2-Ethoxy-4-phthalimido-3,4-dihydro-2H-pyran-6-carboxylate (**7d**): R_f = 0.28. – M.p. 121°C (ethyl acetate/*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 2990 cm^{-1} (CH), 1715 (C=O), 1650 (C=C). – UV (CH_3CN): λ_{max} (lgε) = 219 nm (4.578). – ^1H NMR ($CDCl_3$): δ = 1.24 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.15 (dddd, J = 13.0, 6.5, 2.2, 1.2 Hz, 1H, 3-H_{eq}), 2.40 (ddd, J = 13.0, 9.5, 8.6 Hz, 1H, 3-H_{ax}), 3.66 (dq, J = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 3.80 (s, 3H, OCH_3), 4.08 (dq, J = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 5.18 (ddd, J = 8.6, 6.5, 3.0 Hz, 1H, 4-H), 5.20 (dd, J = 9.5, 2.2 Hz, 1H, 2-H), 7.03 (dd, J = 3.0, 1.2 Hz, 1H, 5-H), 7.90 (m_c, 4H, Ph-H). – ^{13}C NMR ($CDCl_3$): δ = 15.03 (OCH_2CH_3), 31.03 (C-3), 42.98 (C-4), 52.22 (OCH_3), 64.89 (OCH_2CH_3), 100.0 (C-2), 109.8 (C-5), 123.3 (*o*-Ph), 131.8 (*i*-Ph), 134.2 (*m*-Ph), 143.5 (C-6), 162.4 (CO_2CH_3), 167.3 (C=O).

$C_{17}H_{17}NO_6$ (331.3)
Calcd. C 61.63 H 5.17 N 4.23
Found C 61.52 H 5.24 N 4.25

Reaction of **4a** *and* **5b**: A mixture of **4a** (778 mg, 3.00 mmol) and **5b** (3.00 g, 30.0 mmol) in dichloromethane (2 ml) was heated in a pressure flask (60 h, 110°C) according to procedure I to yield after chromatography (chloroform/*tert*-butyl methyl ether/petroleum ether, 10:1:5) **6e** (313 mg, 29%) and **7e** (701 mg, 65%).

Fraction 1: Methyl (2S,4R)-(±)-2-tert-Butoxy-4-phthalimido-3,4-dihydro-2H-pyran-6-carboxylate (**6e**): R_f = 0.32. – M.p. 141°C (*tert*-butyl methyl ether/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 2980 cm^{-1} (CH), 1720 (C=O), 1660 (C=C). – UV (CH_3CN): λ_{max} (lgε) = 219 nm (4.569). – ^1H NMR ($CDCl_3$): δ = 1.30 [s, 9H, $C(CH_3)_3$], 1.94 (dddd, J = 13.0, 6.6, 3.0, 1.6 Hz, 1H, 3-H_{eq}), 2.34 (ddd, J = 13.0, 11.2, 3.0 Hz, 1H, 3-H_{ax}), 3.79 (s, 3H, OCH_3), 5.34 (ddd, J = 11.2, 6.6, 2.8 Hz, 1H, 4-H), 5.70 (t, J = 3.0 Hz, 1H, 2-H), 6.05 (dd, J = 2.8, 1.6 Hz, 1H, 5-H), 7.84 (m_c, 4H, Ph-H).

$C_{19}H_{21}NO_6$ (359.4)
Calcd. C 63.50 H 5.89 N 3.90
Found C 63.66 H 5.91 N 3.94

Fraction 2: Methyl (2R,4R)-(±)-2-tert-Butoxy-4-phthalimido-3,4-dihydro-2H-pyran-6-carboxylate (**7e**): R_f = 0.25. – M.p. 188°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 2980 cm^{-1} (CH), 1740, 1710 (C=O), 1655 (C=C). – UV (CH_3CN): λ_{max} (lgε) = 239 nm (4.563). – ^1H NMR ($CDCl_3$): δ = 1.32 [s, 9H, $C(CH_3)_3$], 2.01 (dddd, J = 13.0, 6.6, 2.1, 1.4 Hz, 1H, 3-H_{eq}), 2.62 (ddd, J = 13.0, 10.0, 9.0 Hz, 1H, 3-H_{ax}), 3.80 (s, 3H, OCH_3), 5.12 (ddd, J = 10.0, 6.6, 3.0 Hz, 1H, 4-H), 5.40 (t, J = 9.0, 2.1 Hz, 1H, 2-H), 5.98 (dd, J = 3.0, 1.4 Hz, 1H, 5-H), 7.80 (m_c, 4H, Ph-H).

$C_{19}H_{21}NO_6$ (359.4)
Calcd. C 63.50 H 5.89 N 3.90
Found C 63.67 H 5.96 N 3.84

Methyl (2R,4S)-2-Phenylthio-4-phthalimido-3,4-dihydro-2H-pyran-6-carboxylate (**7f**): A mixture of **4a** (778 mg, 3.00 mmol) and **5c** (2.04 g, 15.0 mmol) in dichloromethane (10 ml) was heated in a pressure flask (72 h, 110°C) according to procedure I to yield after chromatography (chloroform/*tert*-butyl methyl ether/petroleum ether, 10:1:10) **7f** (1.02 g, 86%). – M.p. 158°C (ethyl acetate/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 2960 cm^{-1} (CH), 1720 (C=O), 1655 (C=C). – UV (CH_3CN): λ_{max} (lgε) = 218 nm (4.051). – ^1H NMR ($CDCl_3$): δ = 2.34 (ddd, J = 13.0, 6.5, 2.0 Hz, 1H, 3-H_{eq}), 2.66 (ddd, J = 13.0, 11.6, 11.0 Hz, 1H, 3-H_{ax}), 3.28 (s, 3H, OCH_3), 5.23 (ddd, J = 11.0, 6.5, 2.5 Hz, 1H, 4-H), 5.41 (dd, J = 11.6, 2.0 Hz, 1H, 2-H), 5.99 (t, J = 2.1 hz, 1H, 5-H), 7.3–7.9 (m, 9H, Ph-H).

$C_{21}H_{17}NO_5S$ (395.4)
Calcd. C 63.79 H 4.33 N 3.54 S 8.11
Found C 63.67 H 4.38 N 3.52 S 8.10

Reaction of **4e** *and* **5a**: A mixture of **4e** (956 mg, 3.00 mmol) and **5a** (4.32 g, 60.0 mmol) in toluene (20 ml) was heated in an autoclave (12 h, 125°C) according to procedure I to yield after chromatography (chloroform/petroleum ether, 10:1) **6g** (440 mg, 38%) and **7g** (661 mg, 56%).

Fraction 1: (2S,4R)-(±)-2-Ethoxy-4-phthalimido-6-trichloromethyl-3,4-dihydro-2H-pyran (**6g**): R_f = 0.35. – M.p. 148°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 2990 cm^{-1} (CH), 1710 (C=O). – UV (CH_3CN): λ_{max} (lgε) = 222 nm (4.670). – ^1H NMR ($CDCl_3$): δ = 1.26 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.10 (dddd, J = 13.0, 6.6, 2.6, 1.4 Hz, 1H, 3-H_{eq}), 2.30 (ddd, J = 13.0, 11.0, 2.7 Hz, 1H, 3-H_{ax}), 3.74 (dq, J = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 4.10 (dq, J = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 5.34 (ddd, J = 11.0, 6.6, 2.5 Hz, 1H, 4-H), 5.52 (t, J = 2.7 Hz, 1H, 2-H), 5.74 (dd, J = 2.5, 1.4 Hz, 1H, 5-H), 7.80 (m_c, 4H, Ph-H). – ^{13}C NMR ($CDCl_3$): δ = 14.95 (OCH_2CH_3), 29.38 (C-3), 40.56 (C-4), 64.60 (OCH_2CH_3), 92.50 (CCl_3), 98.70 (C-

2), 101.3 (C-5), 123.2 (*o*-Ph), 131.8 (*i*-Ph), 134.2 (*m*-Ph), 149.0 (C-6), 167.5 (C=O).

$C_{16}H_{14}Cl_3NO_4$ (390.6)
Calcd. C 49.19 H 3.61 N 3.59
Found C 49.29 H 3.71 N 3.52

Fraction 2: (2R,4R)-(±)-2-Ethoxy-4-phthalimido-6-trichloromethyl-3,4-dihydro-2H-pyran (**7g**): R_f = 0.31. – M.p. 138°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 2990 cm^{-1} (CH), 1730 (C=O). – UV (CH_3CN): λ_{max} (lgε) = 221 nm (4.634). – ^1H NMR ($CDCl_3$): δ = 1.26 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.18 (dddd, *J* = 13.0, 7.0, 2.0, 1.0 Hz, 1H, $3H_{eq}$), 2.62 (ddd, *J* = 13.0, 9.5, 8.5 Hz, 1H, $3\text{-}H_{ax}$), 3.75 (dq, *J* = 9.6, 7.0 Hz, 1H, OCH_2CH_3), 4.10 (dq, *J* = 9.6, 7.0 Hz, 1H, OCH_2CH_3), 5.20 (ddd, *J* = 9.5, 7.0, 3.0 Hz, 1H, 4-H), 5.24 (dd, *J* = 8.5, 2.0 Hz, 1H, 2-H), 5.74 (dd, *J* = 3.0, 1.0 Hz, 1H, 5-H), 7.80 (m_c, 4H, Ph-H). – ^{13}C NMR (CD_3Cl): δ = 14.98 (OCH_2CH_3), 31.00 (C-3), 42.92 (C-4), 65.24 (OCH_2CH_3), 92.09 (CCl_3), 100.3 (C-2), 101.2 (C-5), 123.3 (*o*-Ph), 131.8 (*i*-Ph), 134.2 (*m*-Ph), 150.7 (C-6), 167.3 (C=O).

$C_{16}H_{14}Cl_3NO_4$ (390.6)
Calcd. C 49.19 H 3.61 N 3.59
Found C 49.29 H 3.71 N 3.52

Reaction of **4f** *and* **5a**: A mixture of **4f** (858 mg, 3.00 mmol) and **5a** (4.00 g, 55.5 mmol) in toluene (15 ml) was heated in a pressure flask (36 h, 110°C) according to procedure I to yield after chromatography (chloroform/petroleum ether, 6:1) **6h** (343 mg, 32%) and **7h** (698 mg, 65%).

Fraction 1: (2S,4R)-(±)-6-(Chlorodifluoromethyl)-2-ethoxy-4-phthalimido-3,4-dihydro-2H-pyran (**6h**): R_f = 0.26. – M.p. 119°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 2960 cm^{-1} (CH), 1704 (C=O), 1612 (C=C). – UV (CH_3CN): λ_{max} (lgε) = 221 nm (4.730), 240 (4.044), 293 (3.336). – ^1H NMR ($CDCl_3$): δ = 1.26 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.08 (dddd, *J* = 13.0, 6.2, 3.5, 1.5 Hz, 1H, $3\text{-}H_{eq}$), 2.63 (ddd, *J* = 13.0, 11.0, 2.5 Hz, 1H, $3\text{-}H_{ax}$), 3.70 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 4.00 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 5.29 (m_c, 1H, 4-H), 5.4–5.5 (m, 2H, 2-H, 5-H), 7.83 (m_c, 4H, Ph-H).

$C_{16}H_{14}ClF_2NO_4$ (357.7)
Calcd. C 53.72 H 3.94 Cl 9.91 F 10.6 N 3.92
Found C 53.70 H 3.94 Cl 10.08 F 10.7 N 3.89

Fraction 2: (2R,4R)-(±)-6-(Chlorodifluoromethyl)-2-ethoxy-4-phthalimido-3,4-dihydro-2H-pyran (**7h**): R_f = 0.17. – M.p. 122°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 2980 cm^{-1} (CH), 1708 (C=O), 1612 (C=C). – UV (CH_3CN): λ_{max} (lgε) = 221 nm (4.713), 239 (4.056), 293 (3.344). – ^1H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.18 (dddd, *J* = 13.0, 6.8, 2.2, 1.5 Hz, 1H, $3\text{-}H_{eq}$), 2.65 (ddd, *J* = 13.0, 10.0, 8.5 Hz, 1H, $3\text{-}H_{ax}$), 3.70 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 4.08 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 5.18 (m_c, 1H, 4-H), 5.26 (dd, *J* = 8.5, 2.0 Hz, 1H, 2-H), 5.47 (dd, *J* = 3.0, 1.5 Hz, 1H, 5-H), 7.84 (m_c, 4H, Ph-H).

$C_{16}H_{14}ClF_2NO_4$ (357.7)
Calcd. C 53.72 H 3.94 Cl 9.91 F 10.6 N 3.92
Found C 53.92 H 4.02 Cl 10.06 F 10.3 N 3.85

Reaction of **4g** *and* **5a**: A mixture of **4g** (808 mg, 3.00 mmol) and **5a** (4.32 g, 60.0 mmol) in toluene (5 ml) was heated in an autoclave (24 h, 110°C) according to procedure I to yield after chromatography (chloroform/petroleum ether, 5:1) **6i** (235 mg, 23%) and **7i** (676 mg, 66%).

Fraction 1: (2S,4R)-(±)-2-Ethoxy-4-phthalimido-6-trifluoromethyl-3,4-dihydro-2H-pyran (**6i**): R_f = 0.29. – M.p. 109°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 2988 cm^{-1} (CH), 1704 (C=O). – UV (CH_3CN): λ_{max} (lgε) = 220 nm (4.696). – ^1H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.08 (dddd, *J* = 13.0, 6.5, 3.0, 1.5 Hz, 1H, $3\text{-}H_{eq}$), 2.62 (ddd, *J* = 13.0, 11.0, 3.0 Hz, 1H, $3\text{-}H_{ax}$), 3.68 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 3.94 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 5.27 (m_c, 1H, 4-H), 5.40 (t, *J* = 3.0 Hz, 1H, 2-H), 5.48 (m_c, 1H, 5-H), 7.82 (m_c, 4H, Ph-H).

$C_{16}H_{14}F_3NO_4$ (341.3)
Calcd. C 56.31 H 4.13 N 4.10 F 16.7
Found C 56.42 H 4.17 N 4.06 F 16.5

Fraction 2: (2R,4R)-(±)-2-Ethoxy-4-phthalimido-6-trifluoromethyl-3,4-dihydro-2H-pyran (**7i**): R_f = 0.22. – M.p. 123°C (*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 2982 cm^{-1} (CH), 1708 (C=O). – UV (CH_3CN): λ_{max} (lgε) = 219 nm (4.715). – ^1H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.18 (dddd, *J* = 13.0, 6.5, 2.0, 1.5 Hz, 1H, $3\text{-}H_{eq}$), 2.65 (ddd, *J* = 13.0, 9.5, 8.5 Hz, 1H, $3\text{-}H_{ax}$), 3.68 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 4.03 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 5.18 (m_c, 1H, 4-H), 5.26 (dd, *J* = 9.5, 2.0 Hz, 1H, 2-H), 5.50 (m_c, 1H, 5-H), 7.84 (m_c, 4H, Ph-H).

$C_{16}H_{14}F_3NO_4$ (341.3)
Calcd. C 56.31 H 4.13 N 4.10 F 16.7
Found C 56.45 H 4.37 N 4.19 F 17.0

(2R,4R)-(±)-4-Benzoylamino-2-ethoxy-6-hydroxymethyl-3,4-dihydro-2H-pyran (**8**): To a solution of **7a** (57.0 mg, 0.16 mmol) in anhydrous dimethoxyethane (5 ml) was added lithium aluminum hydride (16.0 mg, 0.73 mmol) and the mixture was heated to 50°C for 30 min. The solvent was removed in vacuo and after addition of a satd. aqueous solution of ammonium chloride (3 ml) to the residue, the aqueous layer was extracted with dichloromethane (2 × 10 ml). The extracts were combined and the solvent was removed under reduced pressure; purification of the residue by chromatography (ethyl acetate) afforded **8** (24.0 mg, 48%), which decomposes at room temp. – M.p. 145–147°C (*tert*-butyl methyl ether). – ^1H NMR ($CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 2.00 (br., 1H, OH), 2.13–2.20 (m, 2H, 3-H), 3.58 (dq, *J* = 9.5, 7.2 Hz, 1H, OCH_2CH_3), 3.90 (dq, *J* = 9.5, 7.2 Hz, 1H, OCH_2CH_3), 4.05 (s, 2H, CH_2OH), 4.79 (m_c, 1H, 4-H), 5.19 (d, *J* = 5.3 Hz, 1H, 5-H), 5.34 (t, *J* = 2.5 Hz, 1H, 2-H), 7.36 (br., d, *J* = 9.0 Hz, 1H, NH), 7.4–7.8 (m, 5H, Ph-H).

(2R,4R)-(±)-6-Acetoxymethyl-4-[2-(acetoxymethyl)benzoylamino]-2-ethoxy-3,4-dihydro-2H-pyran (**9b**): A mixture of **7d** (350 mg, 1.06 mmol) and lithium aluminum hydride (100 mg, 4.60 mmol) in anhydrous dimethoxyethane (10 ml) was heated to 60°C for 2 h. After hydrolysis with a satd. aqueous solution of ammonium chloride (20 ml), the aqueous layer was extracted (dichloromethane, 2 × 50 ml), and the combined extracts were dried (Na_2SO_4). The solvent was evaporated, the residue dissolved in anhydrous dichloromethane (5 ml), and with vigorous stirring anhydrous pyridine (300 mg, 3.80 mmol) and acetyl chloride (250 mg, 3.18 mmol) were added. After stirring at room temp. for 2 h, the mixture was washed with water (2 ml) and the solvent evaporated in vacuo. Purification of the residue was accomplished by chromatography (ethyl acetate/petroleum ether, 1:2) to yield **9b** (160 mg, 43%) as colorless oil. – IR (film): $\tilde{\nu}$ = 3430 cm^{-1} (NH), 2990 (CH), 1750, 1660 (C=O). – ^1H NMR ($CDCl_3$): δ = 1.20 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.10 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 2.15 (m_c, 2H, 3-H), 3.64 (dq, *J* = 10.0, 7.0 Hz, 1H, OCH_2CH_3), 3.84 (dq, *J* = 10.0, 7.0 Hz, 1H, OCH_2CH_3), 4.44 (d, *J* = 13.0 Hz, 1H, CH_2OAc), 4.76 (m_c, 1H, 4-H), 5.20 (d, *J* = 5.3 Hz, 1H, 5-H), 5.30 (t, *J* = 2.2 Hz, 1H, 2-H), 5.37 (m_c, 2H, $PhCH_2OAc$), 6.94 (br., d, *J* = 9.0 Hz, 1H, NH), 7.2–7.5 (m, 4H, Ph-H).

$C_{20}H_{25}NO_7$ (391.4)
Calcd. C 61.37 H 6.44 N 3.58
Found C 61.09 H 6.37 N 3.48

β-Ethyl Glycoside of Racemic Methyl N-Cyclohexylcarbonyl-2-deoxy-3-epi-ezoaminuroate (**10**): A mixture of **6a** (81.0 mg, 0.26 mmol), PtO_2 (35 mg, 50 mol%), glacial acetic acid (2 ml), and ethanol (10 ml) was hydrogenated in an autoclave (12 h, 50 bar H_2). After filtration, the solvent was removed in vacuo and the residue purified by chromatography (ethyl acetate/petroleum ether, 1:3) to yield **10** (59 mg, 70%) as colorless crystals. – M.p. 144°C (diethyl ether/petroleum ether). – IR (KBr): $\tilde{\nu}$ = 3316 cm^{-1} (NH), 2976, 2932, 2856 (CH), 1730, 1644 (C=O). – ^1H NMR ($CDCl_3$): δ = 1.18 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.20–2.20 (m, 15H, 2-H, 4-H, cyclohexyl H), 3.48 (dq, *J* = 9.4, 7.0 Hz, 1H, OCH_2CH_3), 3.78 (s, 3H, OCH_3), 3.96 (dq, *J* = 9.4, 7.0 Hz, 1H, OCH_2CH_3), 4.30 (dd, *J* = 8.0, 4.2 Hz, 1H, 5-H), 4.43 (m_c, 1H, 3-H), 4.77 (dd, *J* = 6.5, 3.0 Hz, 1H, 1-H), 5.45 (br., d, *J* = 7.0 Hz, 1H, NH).

$C_{16}H_{27}NO_5$ (313.4) Calcd. C 61.32 H 8.68
Found C 61.23 H 8.57

(2R,4S)-(±)-6-Chloromethyl-2-ethoxy-4-phthalimido-3,4-dihydro-2H-pyran (**12**): A mixture of **6g** (500 mg, 1.28 mmol), tri-*n*-butyltin hydride (745 mg, 2.56 mmol), azoisobutyronitrile (2.10 mg, 1 mol-%), and toluene (2 ml) was heated at 90°C for 2 h. The solvent was removed in vacuo and the residue purified by chromatography (chloroform/*tert*-butyl methyl ether/petroleum ether, 10:1:1) to yield **12** (230 mg, 56%). – M.p. 141°C (diethyl ether). – IR (KBr): $\tilde{\nu}$ = 3070 cm^{-1} (C=CH), 2950 (CH), 1700 (C=O). – UV (CH_3CN): λ_{max} (lgε) = 220 nm (4.658). – ^1H NMR ($CDCl_3$): δ = 1.26 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.04 (dddd, *J* = 13.0, 6.5, 2.8, 1.5 Hz, 1H, 3-H_{eq}), 2.77 (ddd, *J* = 13.0, 10.8, 2.8 Hz, 1H, 3-H_{ax}), 3.69 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 3.94 (d, *J* = 12.0 Hz, 1H, CH_2Cl), 4.02, (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 4.06 (d, *J* = 12.0 Hz, 1H, CH_2Cl), 4.98 (m_c, 1H, 5-H), 5.26 (m_c, 1H, 4-H), 5.35 (t, *J* = 2.8 Hz, 1H, 2-H), 7.82 (m_c, 4h, Ph-H).

$C_{16}H_{16}ClNO_4$ (321.8)
Calcd. C 59.73 H 5.01 N 4.35
Found C 59.67 H 5.04 N 4.33

(2R,4S)-(±)-2-Ethoxy-6-methyl-4-phthalimido-3,4-dihydro-2H-pyran (**13**): To a magnetically stirred solution of **6g** (1.70 g, 4.35 mmol) in toluene (5 ml) were added at 100°C tri-*n*-butyltin hydride (5.40 g, 18.5 mmol) and azoisobutyronitrile (1.00 g, 6.10 mmol). After stirring at the same temperature for 4 h, the solvent was removed under reduced pressure, and the residue was purified twice by chromatography [ethyl acetate/petroleum ether, I) 1:5, II) 1:3] and by crystallization (*tert*-butyl methyl ether) to furnish **13** (552 mg, 44%). – M.p. 121°C (diethyl ether). – IR (KBr): $\tilde{\nu}$ = 2930 cm^{-1} (CH), 1715 (C=O). – UV (CH_3CN): λ_{max} (lgε) = 217 mm (4.631). – ^1H NMR ($CDCl_3$): δ = 1.26 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.82 (dd, *J* = 2.2, 1.0 Hz, 3H, CH_3), 2.02 (dddd, *J* = 13.0, 6.6, 2.8, 1.4 Hz, 1H, 3-H_{eq}), 2.52 (ddd, *J* = 13.0, 9.6, 2.8 Hz, 1H, 3-H_{ax}), 3.65 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 3.90 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 4.54 (m_c, 1H, 5-H), 5.13 (ddt, *J* = 9.6, 6.6, 2.2 Hz, 1H, 4-H), 5.30 8t, *J* = 2.8 Hz, 1H, 2-H), 7.82 (m_c, 4H, Ph-H).

$C_{16}H_{17}NO_4$ (287.3)
Calcd. C 66.89 H 5.96 N 4.88
Found C 65.86 H 5.94 N 4.79

(2S,4R)-(±)-Benzoylamino-2-ethoxy-6-trichloromethyl-3,4-dihydro-2H-pyran (**14b**): A solution of **6g** (100 mg, 0.25 mmol), hydrazine (383 mg, 7.65 mmol), and ethanol (3 ml) was stirred at room temp. for 12 h to furnish **14a**. The solvent was removed in vacuo and the residue dissolved in anhydrous dichloromethane (3 ml). After addition of triethylamine (253 mg, 2.50 mmol) and benzoyl chloride (176 mg, 1.25 mmol), the mixture was stirred at room temp. for 2 h. The precipitate was filtered off, the solvent removed in vacuo, and the residue purified by chromatography (ethyl acetate/petroleum ether, 1:3) to yield **14b** (77.5 mg, 85%). – M.p. 161–164°C (ethyl acetate/*tert*-butyl methyl ether). – IR (KBr): $\tilde{\nu}$ = 3330 cm^{-1} (NH), 2990, 2940 (CH), 1640 (C=O). – ^1H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.85 (ddd, *J* = 13.0, 10.0, 2.6 Hz, 1H, 3-H_{ax}), 2.39 (dddd, *J* = 13.0, 6.5, 3.2, 1.0 Hz, 1H, 3-H_{eq}), 3.68 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 4.07 (dq, *J* = 9.5, 7.0 Hz, 1H, OCH_2CH_3), 5.17 (dddd, *J* = 10.0, 8.0, 6.5, 2.6 Hz, 1H, 4-H), 5.36 (dd, *J* = 3.2, 2.6 Hz, 1H, 2-H), 5.84 (dd, *J* = 2.6, 1.0 Hz, 1H, 5-H), 6.12 (br., d, *J* = 8.0 Hz, 1H, NH), 7.2–7.9 (m, 5H, Ph-H).

$C_{15}H_{16}Cl_3NO_3$ (364.7) Calcd. C 49.41 H 4.42
Found C 49.56 H 4.51

CAS Registry Numbers

4a [(*E*)isomer]: 110914-23-3 / **4a** [(*Z*) isomer]: 116952-49-9 / **4b** [(*E*) isomer]: 110945-42-1 / **4b** [(*Z*) isomer]: 116952-50-2 / **4c** [(*E*) isomer]: 116952-56-8 / **4c** [(*Z*) isomer]: 131154-11-5 / **4d**: 120417-47-2 / **4e**: 110945-43-2 / **4f**: 131153-96-3 / **4g**: 120417-46-1 / **5a**: 109-92-2 / **5b**: 926-02-3 / **5c**: 1822-73-7 / **5d**: 107-25-5 / **6a**: 110914-36-8 / **6b**: 131153-97-4 / **6c**: 131153-99-6 / **6d**: 110945-44-3 / **6e**: 110914-39-1 / **6g**: 110914-40-4 / **6h**: 131154-02-4 / **6i**: 131154-04-6 / **7a**: 110914-28-8 / **7b**: 131153-98-5 / **7c**: 131154-00-2 / **7d**: 110914-32-4 / **7e**: 110914-31-3 / **7f**: 131154-01-3 / **7g**: 110914-33-5 / **7h**: 131154-03-5 / **7i**: 131154-05-7 / **8**: 110914-45-9 / **9b**: 131154-06-8 / **10**: 131154-07-9 / **11**: 131154-08-0 / **12**: 131178-03-5 / **13**: 131154-09-1 / **14b**: 131154-10-4 / chlorodifluoroacetic anhydride: 2834-23-3 / 1-chloro-4-ethoxy-1,1-difluoro-3-buten-2-one: 131153-94-1 / 4-amino-1-chloro-1,1-difluoro-3-buten-2-one: 131153-95-2

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