Asymmetric Steering of Oxa Diels–Alder Reactions with Silyloxydienes Employing Proline Esters as Chiral Auxiliary Groups

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Chiral aldehydes **4a**,**b**, obtained by the ozonolysis of the corresponding *N*,*N*′-fumaroylbis[(*S*)-proline esters] **3** react in the presence of lanthanoid chelate complexes $Eu(fod)_3$ or $Eu(hfc)_3$ with silyloxydienes **7** or **12** to give δ-lactones **10** or dihydro-γ-pyrones **13** with very high diastereomeric ratios (up to 99:1). The absolute configuration of the predominating diastereoisomer of compound **10b** was unequivocally determined by X-ray structural analysis.

Introduction

Hetero Diels−Alder reactions belong to the synthetically most useful methodologies for the synthesis of dihydropyranes and dihydropiperidines, which are important building blocks in the syntheses of carbohydrates[1] and alkaloids.[2] Whereas aliphatic and aromatic carbonyl compounds react with non-activated dienes only under forcing reaction conditions (at elevated temperatures and at high pressure[3]), compounds containing the glyoxylate or oxomalonate[4] functionalities react with electron-rich silyloxydienes already under very mild reaction conditions. In this manner several new routes to carbohydrates and their analogs, applicable in the total syntheses of higher monosaccharides, were developed.[5]

High diastereoselectivity was observed for oxa Diels−Alder reactions, when 8-phenylmenthol,[6] camphorsulfonic acid[7] or oxazolidinone derivatives[8] were applied as chiral auxiliaries. In several cases a high level of stereoselection was also attained in the presence of chiral catalysts.[9]

We have used the readily accessible amino acid esters as chiral auxiliaries in various asymmetric syntheses.[10] In the course of these investigations in particular proline esters turned out to be efficient mediators of chirality for cycloadditions like carbo Diels−Alder reactions[11] and 1,3-dipolar cycloadditions.[12] These auxiliaries are readily introduced, induce high diastereoisomer ratios and can readily be removed under a variety of different reaction conditions.

In order to extend the application of proline esters as chiral auxiliary groups we have now used them for the steric steering of the Eu^{III}-mediated[13] cycloadditions between electron-rich silyloxy dienes and oxa heterodienophiles.

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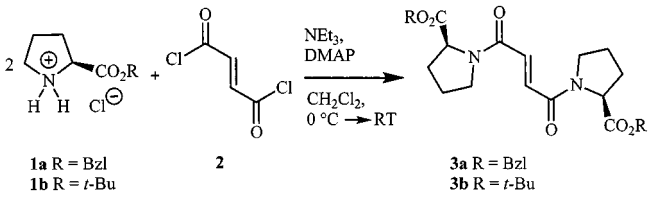
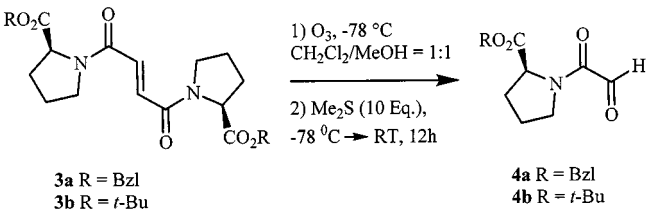
Results and Discussion

Proline ester derived heterodienophiles **4** were chosen to study the ability of the proline chiral auxiliary group to direct the sterochemical course of the planned oxa Diels−Alder reactions. Aldehydes **4** were prepared in a two-step reaction sequence from the corresponding proline esters **1**. To this end, first fumaric acid derivatives **3** were prepared by acylation of proline esters **1** with fumaroyl chloride **2** in the presence of 4-(dimethylamino)pyridine (DMAP, Scheme 1).



Scheme 1. Synthesis of fumaric acid prolyl amides **3**

The aldehydes **4** were then obtained with moderate yields (30−50%) after ozonolysis of the *N*,*N*′-fumaroyl[bis(*S*)-proline esters] **3** in a 1:1 mixture (v/v) of dichloromethane and methanol at −78°C followed by reductive cleavage of the primarily formed ozonides by 10 equivalents of dimethyl sulfide for 12 hours at room temperature (Scheme 2).



Scheme 2. Synthesis of proline ester derived heterodienophiles

In the ^{1}H-NMR spectra of the aldehydes **4** in addition to the typical aldehyde signals, singlets, typical for methoxy groups appear at δ = 3.4. In the ^{13}C-NMR spectra typical

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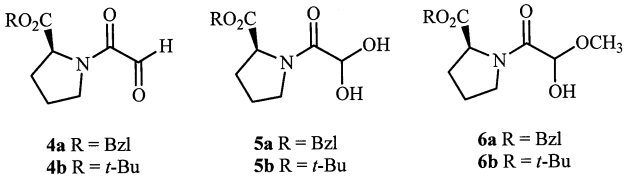
signals are present at around δ = 90, which are characteristic for hydrates. Also the IR spectra of the aldehydes **4** show broad absorption bands of the hydroxy groups. Thus, aldehydes **4**, obtained after ozonolysis, are formed partially as hydrates **5** or hemiacetals **6** of the *N*-glyoxyloyl-(*S*)-proline esters **4** (Figure 1).



4a R = Bzl
4b R = *t*-Bu

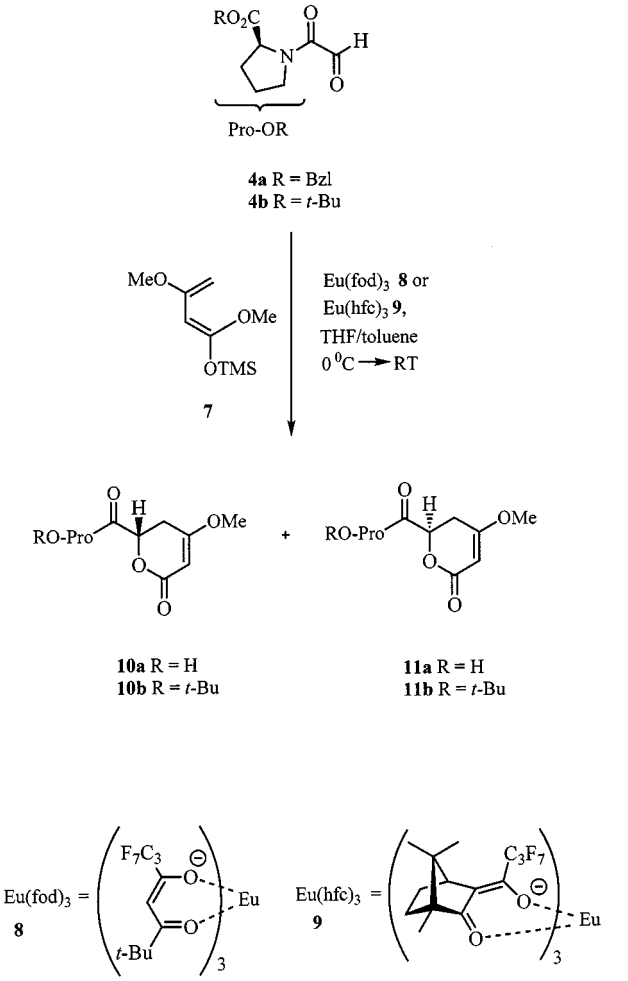
5a R = Bzl
5b R = *t*-Bu

6a R = Bzl
6b R = *t*-Bu

Figure 1

The oxa Diels–Alder reactions employing heterodienophiles **4** were best carried out in toluene or THF solutions in the presence of an Eu^{III} Lewis acid by slowly adding the diene component at room temperature. The controlled slow addition of the diene to the reaction mixture by syringe pump significantly improved the yields of the cycloadducts formed in comparison with addition of the reagents in one portion. After quenching the reaction mixtures with 0.1 N HCl, extraction with dichloromethane and purification by flash chromatography, the resulting cycloadducts were obtained partly as crystalline solids. The heterodienophiles **4** reacted with the electron-rich Brassard diene **7** to give the corresponding δ-lactones **10**/**11** with moderate yields (30–68%) and with high diastereoselectivity (Scheme 3, Table 1).

The results given in Table 1 demonstrate that the change of the solvent from toluene to THF and an increase of the molar ratio diene/heterodienophile from 1 to 2 improved the yields of the cycloadducts. Furthermore, significantly higher diastereoselectivities were observed when chiral Lewis acid **9** was used as an additional mediator of chirality instead of the achiral Eu^{III} salt **8** (exception: entry 4, Table 1). The size of the ester group in aldehydes **4** does not have a significant influence on the stereoselectivity of the reaction in the presence of 10 mol-% of $Eu(hfc)_3$ (Table 1, compare entries 3 and 5), but the diastereomeric ratios of the δ-lactones **10**/**11** formed from the aldehyde **4a** decreased from dr = 96:4 to dr = 90:10 after changing the chiral lanthanoid **9** from the D- to the L-camphor derivative (Table 1, entries 3 and 4). Clearly, double stereodifferentiation occurs in the reactions employing the chiral heterodienophiles and the chiral europium catalysts **9a**,**b**. In the transformations of aldehyde **4b** similarly high diastereoselectivities



Scheme 3. Asymmetric oxa Diels–Alder reaction employing diene **7**

were achieved with both enantiomers of the Lewis acids **9a**,**b**. (Table 1, entries 5 and 6).

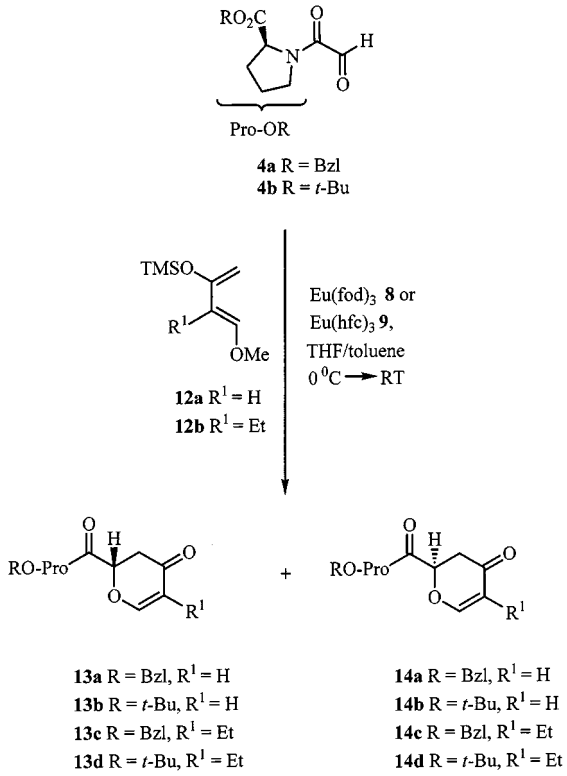
The absolute configuration of the predominant diastereomer of the lactone **10b** was unequivocally determined by X-ray structural analysis (see the Experimental Section).

In order to extend the scope of the Eu^{III}-mediated reactions of the proline-derived aldehydes **4**, reactions with other electron-rich dienes, like the Danishefsky diene **12a** and its ethyl derivative **12b** were studied (Scheme 4).

The highest diastereomeric ratio of the dihydropyrones **13**/**14** obtained (dr = 97:3 to 99:1) was achieved by oxa Diels–Alder reaction of aldehyde **4a** with the Danishefsky

Table 1. Results of the asymmetric oxa Diels–Alder reactions between *N*-glyoxyloyl-(*S*)-proline esters **4** with Brassard's diene **7** to give δ-lactones **10**/**11**

entry	**4** R	**7** (equiv.)	Lewis acid [mol-%]	solvent	*T* [°C]	reaction time [h]	yield [%]	**10**/**11**
1	Bzl	1	$Eu(fod)_3$ (**8**) [100]	toluene	0→r.t.	24	30	89:11
2	Bzl	2	$Eu(fod)_3$ (**8**) [10]	toluene	r.t.	14	47	90:10
3	Bzl	2	D-$Eu(hfc)_3$ (**9a**) [10]	THF	r.t.	12	68	96:4
4	Bzl	2	L-$Eu(hfc)_3$ (**9b**) [10]	THF	r.t.	12	55	90:10
5	*t*Bu	2	D-$Eu(hfc)_3$ (**9a**) [10]	THF	r.t.	20	67	96:4
6	*t*Bu	2	L-$Eu(hfc)_3$ (**9b**) [2]	THF	r.t.	6	53	97:3



Scheme 4. Asymmetric oxa Diels−Alder reactions employing dienes **12**

diene in the presence of catalytic amounts of the chiral Lewis acids **9a**/**b** (Table 2, entries 3 and 4). When the reactions were carried out with aldehyde **4b** in the presence of the chiral catalysts **9a** or **9b**, the diastereomeric ratio of the products decreased to dr = 88:12 and 94:6 (Table 2, entries 5 and 6). When the achiral catalyst **8** was employed, the stereoselectivity of the oxa Diels−Alder reaction studied could be enhanced by using higher molar ratios of the Lewis acid as well as by performing the reactions at lower temperatures (Table 2, entries 1 and 2).

In the oxa Diels−Alder reactions of heterodienophiles **4a**/**b** with the ethyl-substituted diene **12b** different diastereoselectivities were observed (Table 2, entries 7−9). In the reaction of the aldehyde **4a** with diene **12b** the diastereomeric ratio decreased from dr = 90:10 [in the presence of D-Eu(hfc)$_3$] to 80:20, when L-Eu(hfc)$_3$ was applied as a catalyst (Table 2, entries 7 and 8). On the contrary the reactions with the sterically more hindered heterodienophile **4b** gave in the presence of 5 mol-% of L-Eu(hfc)$_3$ **9b** a slightly higher diastereomeric ratio of the dihydropyrones **13** (dr = 92:8) compared with the use of the D-Eu(hfc)$_3$ **9a** (dr = 90:10, Table 2, entries 9 and 6). The absolute configurations of the dihydropyrones **13**/**14** were assigned by analogy to the absolute configuration determined for the compound **10b**.

In conclusion, the results described above demonstrate that the steric course of oxa Diels−Alder reactions employing electron-rich silyloxydienes can be steered efficiently by employing a combination of proline esters as chiral auxiliary group and a chiral camphor-derived europium catalyst.

Experimental Section

General: All melting points were recorded with a Büchi melting point apparatus and are uncorrected. − Infrared spectra were measured with a Bruker IFS 88 spectrometer. − ^{1}H and ^{13}C NMR spectra were measured with a Bruker AC-250 and a Bruker AM-400 spectrometer. − Specific optical rotation values were determined with a Perkin−Elmer polarimeter 241. − Elemental analyses were performed with an Elementary CHN-Rapid analyzer. − High-pressure liquid chromatography (HPLC) was performed with a Merck Hitachi instrument equipped with an L-3000 diode array detector, using a LiChrospher 100 RP18 250 × 4-mm column, a LiChrospher 60 RP-select B 125 × 4-mm column, various mixtures of methanol/water (v/v) and a solvent flow rate of 0.6 mL/min.

Materials: The preparation of *N*,*N*′-fumaroylbis(proline esters) **3** is described in an earlier paper.[11b] Eu(fod)$_3$ (**8**), D-**9a** and L-Eu(hfc)$_3$ (**9b**) are commercially available and were used without further purification. Tetrahydrofuran (THF) was distilled from potassium immediately prior to its use.

***N*,*N*′-Fumaroylbis[(*S*)-proline *tert*-Butyl Ester] (3b):** Compound **3b** was synthesized according to a procedure published for analogous compounds.[11b] − M.p. 69°C; $[\alpha]_D^{22} = -108.2$ (c = 1, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 [d, ^3J(H,H) = 14.60 Hz, 1 H, C*H*=CH], 7.08 [d, ^3J(H,H) = 14.60 Hz, 1 H, C*H*=CH], 4.45−4.42 (m, 2 H, 2 α-H), 3.71−3.58 (m, 4 H, 2 NCH_2), 2.22−2.15 (m, 2 H, 2 CH_2CH_2), 2.09−1.88 (m, 6 H, 2 CH_2CH_2). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.75 (C=O), 170.69 (C=O), 163.58 (C=O), 162.95 (C=O), 131.54 (*C*H=CH), 131.43 (CH=*C*H), 82.40 [*C*(CH_3)$_3$], 82.31 [*C*(CH_3)$_3$], 59.82 (N*C*HCH_2), 59.63 (NCH*C*H$_2$), 47.55 (NCH_2), 46.55 (NCH_2), 31.04 (*C*H_2CH$_2$), 29.48 (*C*H_2CH$_2$), 27.77 [C(*C*H_3)$_3$], 27.69 [C(*C*H_3)$_3$], 24.46 (CH_2*C*H_2), 22.35 (CH_2*C*H_2). − MS (70 eV); *m*/*z* (%): 422 (0.14) [M^+], 321 (69.59) [$M^+ - C_5H_9O_2$], 196 (100) [321 − $C_7H_9O_2$], 70 (65.67)

Table 2. Results of the asymmetric oxa Diels−Alder reactions between *N*-glyoxyloyl-(*S*)-proline esters **4** with silyloxydienes **12a** /**b** to give dihydro-γ-pyrones **13**/**14**

entry	**4** R	diene (2 equiv.)	Lewis acid [mol-%]	solvent	*T* [°C]	reaction time [h]	yield [%]	**13**/**14**
1	Bzl	**12a**	Eu(fod)$_3$ (**8**) [200]	toluene	−78→r.t.	18	59	97:3
2	Bzl	**12a**	Eu(fod)$_3$ (**8**) [10]	toluene	r.t.	14	57	91:9
3	Bzl	**12a**	D-Eu(hfc)$_3$ (**9a**) [10]	THF	r.t.	12	73	97:3
4	Bzl	**12a**	L-Eu(hfc)$_3$ (**9b**) [2]	THF	r.t.	9	70	99:1
5	*t*Bu	**12a**	D-Eu(hfc)$_3$ (**9a**) [10]	THF	r.t.	17	63	88:12
6	*t*Bu	**12a**	L-Eu(hfc)$_3$ (**9b**) [2]	THF	r.t.	8	68	94:6
7	Bzl	**12b**	D-Eu(hfc)$_3$ (**9a**) [10]	THF	r.t.	72	58	90:10
8	Bzl	**12b**	L-Eu(hfc)$_3$ (**9b**) [10]	THF	r.t.	14	69	80:20
9	*t*Bu	**12b**	L-Eu(hfc)$_3$ (**9b**) [5]	THF	r.t.	5	71	92:8

$[C_4H_8N^+]$. – $C_{22}H_{34}N_2O_6$ (422.5): calcd. C 62.54, H 8.11, N 6.63; found C 62.45, H 8.03, N 6.48. – HRMS: $C_{22}H_{34}N_2O_6$ (422.5): calcd. 422.2396; found 422.2417.

General Procedure for the Preparation of *N*-Glyoxyloyl-(*S*)-proline Esters 4: Ozone was bubbled through a cold (−78°C) solution of *N*,*N*′-fumaroylbis[(*S*)-proline ester] **3** (10 mmol) in a 1:1 mixture of CH_2Cl_2 and methanol (40 mL) until the solution turned blue. After the mixture was flushed with nitrogen, an excess of dimethyl sulfide (100 mmol, 10 equiv.) was added at −78°C. After stirring at room temperature over a period of 12 h, the solvents and dimethyl sulfide were evaporated in vacuo affording the crude *N*-glyoxyloyl-(*S*)-proline esters **4**, which were further purified by flash chromatography (*n*-hexane/acetone, 2:1). In this manner the following compounds were prepared.

***N*-Glyoxyloyl-(*S*)-proline Benzyl Ester (4a):** Oil; $[\alpha]_D^{22} = -80.0$ (c = 1, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3384 cm^{-1} (OH), 2886 (CHO), 1744 (C=O), 1656 (Ph). – ^1H NMR (400 MHz, $CDCl_3$): δ = 9.31 (s, 1 H, CHO), 7.39−7.30 (m, 5 H, Ph), 5.17 [d, ^2J(H,H) = 11.60 Hz, 2 H, CH_2Ph], 4.61 [dd, ^3J(H,H) = 3.95 Hz, ^3J(H,H) = 8.87 Hz, 1 H, NCH], 3.58−3.77 (m, 2 H, NCH_2), 2.24−2.16 (m, 1 H, CH_2CH_2), 2.05−1.89 (m, 3 H, CH_2CH_2). – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 188.26 (CHO), 171.63 (C=O), 167.41 (C=O), 135.44, 128.67, 128.61, 128.57, 128.24, 128.12 (Ph), 67.07 (CH_2Ph), 59.06 (NCH), 47.65 (NCH_2), 28.97 (NCHCH_2), 25.13 (NCH_2CH_2). – MS (70 eV); *m/z* (%): 262 (0.04) [M^+ + H], 232 (3.11) [M^+ − CHO], 91 (100) [$C_7H_7^+$], 70 (46.53) [$C_4H_8N^+$]. – $C_{14}H_{15}NO_4$ (261.4): calcd. C 64.36, H 5.79, N 5.36; found C 64.00, H 6.39, N 5.27. – HRMS: $C_{14}H_{16}NO_4$ (262.4): calcd. 262.1051; found 262.1079.

***N*-Glyoxyloyl-(*S*)-proline *tert*-Butyl Ester (4b):** M.p. 109°C; $[\alpha]_D^{22}$= −80.0 (c = 1, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3384 cm^{-1} (OH), 2886 (CHO), 1744 (C=O), 1656 (Ph). – ^1H NMR (400 MHz, $CDCl_3$,): δ = 9.27 (s, 1 H, CHO), 4.38−4.24 (m, 1 H, NCH), 3.80−3.44 (m, 2 H, NCH_2), 2.19−2.07 (m, 1 H, CH_2CH_2), 2.00−1.83 (m, 3 H, CH_2CH_2), 1.39 [s, 9 H, $C(CH_3)_3$]. – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 188.00 (CHO), 170.68 (C=O), 166.74 (C=O), 81.54 [$C(CH_3)_3$], 59.88 (NCH), 46.22 (NCH_2), 28.78 (NCHCH_2), 27.77 [$C(CH_3)_3$], 24.41 (NCH_2CH_2). – MS (70 eV); *m/z* (%): 228 (0.10) [M + H^+], 199 (1.06) [M^+ − CHO], 126 (100) [199 − C_4H_9O], 70 (88.61) [$C_4H_8N^+$], 57 (60.69) [$C_3H_7N^+$]. – $C_{11}H_{17}NO_4$ (227.4): calcd. C 58.14, H 7.54, N 6.16; found C 57.81, H 7.62, N 6.20. – HRMS: $C_{11}H_{18}NO_4$ (228.4): calcd. 228.1209; found 228.1236.

General Procedure for the Synthesis of δ-Lactones 10/11 and Dihydro-γ-pyrones 13/14: To a solution of heterodienophile **4** (1 mmol) and appropriate amounts of lanthanoid(III) salt (Tables 1 and 2) in dry THF or toluene (15 mL) was slowly added 1−2 equiv. of silyloxydiene **7** (or **12a**/**b**) over the period and at the temperature given in Tables 1 and 2. Then the mixture was washed with 0.1 N HCl (10 mL), extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried with magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel by using mixtures of acetone/*n*-hexane as eluents to give the pure diastereomers **10** (or **13**). The diastereomeric ratios of the products were determined by HPLC using samples which were directly taken from the crude product mixtures. The reaction conditions as well as the results are listed in Table 1. In this manner the following cycloadducts were prepared.

***N*-[(6*S*)-5,6-Dihydro-4-methoxy-2-oxo-2*H*-pyran-6-oyl]-(*S*)-proline Benzyl Ester (10a):** Oil; $[\alpha]_D^{22} = -21.6$ (c = 1, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 1716 cm^{-1} (C=O), 1661 (Ph), 1623 (C=C). – ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.32 (m, 5 H, Ph), 5.21 [d, ^2J(H,H) = 12.38 Hz, 1 H, CH_2Ph], 5.13 (s, 1 H, OCOCH), 5.11 [d, ^2J(H,H) = 12.38 Hz, 1 H, CH_2Ph], 5.08 [dd, ^3J(H,H) = 4.97 Hz, ^3J(H,H) = 8.65 Hz, 1 H, OCHCO], 4.54 [dd, ^3J(H,H) = 3.16 Hz, ^3J(H,H) = 8.88 Hz, 1 H, NCH], 3.95−3.90 (m, 1 H, NCH_2), 3.76 (s, 3 H, OCH_3), 3.74−3.71 (m, 1 H, NCH_2), 3.09 [dd, 1 H, ^2J(H,H) = 17.47 Hz, ^3J(H,H) = 8.65 Hz, 1 H, OCHCH_2], 2.60 [dd, ^2J(H,H) = 17.47 Hz, ^3J(H,H) = 4.97 Hz, 1 H, OCHCH_2], 2.22−2.17 (m, 1 H, CH_2CH_2), 2.09−1.93 (m, 3 H, CH_2CH_2). – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.13 (C=O), 171.63, (C=O), 165.37 (C=O), 165.26 (OCH_3C=CH), 135.52, 128.55, 128.51, 128.29, 128.05, 128.13 (Ph), 89.64 (OCH_3C=*C*H), 73.49 (O*C*HCO), 66.91 (CH_2Ph), 59.62 (NCH), 56.20 (OCH_3) 47.32 (NCH_2), 28.71 (OCHCH_2), 28.61 (NCHCH_2), 24.70 (NCH_2CH_2). – MS (70 eV); *m/z* (%): 359 (0.02) [M^+], 224 (97.30) [M^+ − $C_8H_7O_2$], 127 (100) [224 − C_5H_7NO], 91 (35.38) [$C_7H_7^+$], 70 (33.93) [$C_4H_8N^+$]. – $C_{19}H_{21}NO_6$ (359.6): calcd. C 63.49, H 5.89, N 3.90; found C 62.99, H 5.93, N 3.75. – HRMS: $C_{19}H_{21}NO_6$ (359.6): calcd. 359.1369; found 359.1393.

***N*-[(6*S*)-5,6-Dihydro-4-methoxy-2-oxo-2*H*-pyran-6-oyl]-(*S*)-proline *tert*-Butyl Ester (10b):** M.p. 86°C; $[\alpha]_D^{22} = -71.3$ (c = 1, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 1716 cm^{-1} (C=O), 1656 (Ph), 1627 (C=C). – ^1H NMR (400 MHz, $CDCl_3$): δ = 5.11 (s, 1 H, OCOCH), 5.05 [dd, ^3J(H,H) = 4.97 Hz, ^3J(H,H) = 8.57 Hz, 1 H, OCHCO], 4.35 [dd, ^3J(H,H) = 3.05 Hz, ^3J(H,H) = 8.70 Hz, 1 H, NCH], 3.92−3.86 (m, 1 H, NCH_2), 3.74 (s, 3 H, OCH_3), 3.71−3.65 (m, 1 H, NCH_2), 3.08 [dd, ^2J(H,H) = 17.50 Hz, ^3J(H,H) = 8.58 Hz, 1 H, OCHCH_2], 2.60 [dd, ^2J(H,H) = 17.50 Hz, ^3J(H,H) = 4.99 Hz, 1 H, OCHCH_2], 2.18−2.10 (m, 1 H, CH_2CH_2), 2.03−1.95 (m, 3 H, CH_2CH_2), 1.43 [s, 9 H, $C(CH_3)_3$]. – ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.22 (C=O), 171.03, (C=O), 165.38 (C=O), 165.13 (OCH_3C=CH), 89.64 (OCH_3C=*C*H), 81.47 [*C*$(CH_3)_3$], 73.61 (O*C*HCO), 60.29 (NCH), 56.18 (OCH_3) 47.33 (NCH_2), 28.79 (OCHCH_2), 28.66 (NCHCH_2), 27.95 [C(*C*$H_3)_3$], 24.57 (NCH_2CH_2). – MS (70 eV); *m/z* (%): 325 (0.05) [M^+], 224 (100) [M^+ − $C_5H_9O_2$], 127 (72.00) [224 − C_5H_7NO], 70 (51.00) [$C_4H_8N^+$]. – $C_{16}H_{23}NO_6$ (325.4): calcd. C 59.07, H 7.13, N 4.30; found C 58.82, H 7.13, N 4.54. – HRMS: $C_{16}H_{23}NO_6$ (325.4): calcd. 325.1525; found 325.1508. – Crystal data: $C_{16}H_{23}NO_6$, monoclinic crystals, space group *P*2 (1), with a = 6.086(1) Å, b = 11.925(2) Å, c = 11.564(2) Å, Z = 2, β = 97.10(3). 4277 reflections were measured (diffractometer STOE STADI IV, Mo-K_α radiation: λ = 0.7107 Å, graphite monochromator), of which 3637 were independent with $I > 2\ \sigma(I)$. The structure determination was carried out with direct methods (SHELX-76 and SHELX-93). $R1$ = 0.0362, $wR2$ = 0.0961, $w = 1/\sigma^2F + 0.0001\ F^2$. All C, N, and O atoms were anisotropically refined. The hydrogen atoms were found in the calculated sites with the appropriate isotropic temperature factors for CH, CH_2 and CH_3. Further details of the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen (FRG) on quoting the depository number CSD-58112 and the journal citation.

***N*-[(2*S*)-2,3-Dihydro-4-oxo-4*H*-pyran-2-oyl]-(S)-proline Benzyl Ester (13a):** Oil; $[\alpha]_D^{22} = +46.5$ (c = 1, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 1743 cm^{-1} (C=O), 1688 (C=O), 1646 (Ph). – ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39−7.30 (m, 5 H, Ph), 7.33 [d, ^3J(H,H) = 5.92 Hz, 1 H, OC*H*=CH], 5.47 [d, ^3J(H,H) = 5.92 Hz, 1 H, OCH=C*H*], 5.21 [d, ^2J(H,H) = 12.26 Hz, 1 H, CH_2Ph], 5.13 [dd, ^3J(H,H) = 12.77 Hz, ^3J(H,H) = 4.17 Hz, 1 H, OCHCO], 5.12 [d, ^2J(H,H) = 12.26 Hz, 1 H, CH_2Ph], 4.61 [dd, ^3J(H,H) = 3.48 Hz, ^3J(H,H) = 8.90 Hz, 1 H, NCH], 3.76−3.61 (m, 2 H, NCH_2), 2.99 [dd, ^2J(H,H) = 17.20 Hz, ^3J(H,H) = 12.77 Hz, 1 H, OCHCH_2], 2.61 [dd, ^2J(H,H) = 17.20 Hz, ^3J(H,H) = 4.17 Hz, 1 H, OCHCH_2], 2.28−2.17 (m, 1 H, CH_2CH_2), 2.11−1.92 (m, 3 H, CH_2CH_2). –

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 190.55 (C=O), 171.33, (C=O), 165.20 (C=O), 161.15 (O*C*H=CH), 135.44, 128.84, 128.76, 128.61, 128.40, 128.17 (Ph), 107.90 (OCH=*C*H), 76.40 (O*C*HCO), 67.07 (CH_2Ph), 59.43 (NCH), 46.99 (NCH_2), 37.60 (OCH*C*H_2), 28.76 (NCH*C*H_2), 24.84 (NCH_2*C*H_2). − $C_{18}H_{19}NO_5$ (329.4): calcd. C 65.64, H 5.82, N 4.25; found C 65.22, H 6.12, N 4.44.

***N*-[(2*S*)-2,3-Dihydro-4-oxo-4*H*-pyran-2-oyl]-(*S*)-proline *tert*-Butyl Ester (13b):** M.p. 119°C; $[\alpha]_D^{22}$ = +48.2 (*c* = 1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1739 cm^{-1} (C=O), 1640 (Ph), 1604 (C=C). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34 [d, ^3J(H,H) = 5.87 Hz, 1 H, OC*H*=CH], 5.46 [d, ^3J(H,H) = 5.87 Hz, 1 H, OCH=C*H*], 5.15 [dd, J^3(H,H) = 4.40 Hz, ^3J(H,H) = 12.32 Hz, 1 H, OCHCO], 4.45 [dd, ^3J(H,H) = 3.52 Hz, ^3J(H,H) = 8.61 Hz, 1 H, NCH], 3.75−3.69 (m, 1 H, NCH_2), 3.67−3.61 (m, 1 H, NCH_2), 3.04 [dd, ^2J(H,H) = 17.50 Hz, ^3J(H,H) = 12.32 Hz, 1 H, OCHC*H*$_2$], 2.66 [dd, ^2J(H,H) = 17.50 Hz, ^3J(H,H) = 4.40 Hz, 1 H, OCHC*H*$_2$], 2.23−2.15 (m, 1 H, CH_2CH_2), 2.11−1.92 (m, 3 H, C*H*$_2$C*H*$_2$), 1.47 [s, 9 H, C(CH_3)$_3$].− ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 190.54 (C=O), 170.64, (C=O), 165.00 (C=O), 161.27 (O*C*H=C), 107.79 (OCH=*C*), 81.63 [*C*(CH_3)$_3$], 76.47 (O*C*HCO), 60.13 (NCH), 46.94 (NCH_2), 37.69 (OCH*C*H_2), 28.79 (NCH*C*H_2), 27.93 [C(*C*H_3)$_3$], 24.75 (NCH_2*C*H_2). − MS (70 eV); *m/z* (%): 295 (0.05) [M^+], 194 (91.42) [$M^+ - C_5H_9O_2$], 70 (100) [$C_4H_8N^+$]. − $C_{15}H_{21}NO_5$ (295.4): calcd. C 60.99, H 7.17, N 4.74; found C 60.70, H 7.23, N 4.97. − HRMS: $C_{15}H_{21}NO_5$ (295.4): calcd. 295.1420; found 295.1400.

***N*-[(2*S*)-2,3-Dihydro-5-ethyl-4-oxo-4*H*-pyran-2-oyl]-(S)-proline Benzyl Ester (13c):** Oil; $[\alpha]_D^{22}$ = +23.5 (*c* = 1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1744 cm^{-1} (C=O), 1667 (Ph), 1618 (C=C). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.32 (m, 5 H, Ph), 7.17 (s, 1 H, OCH=C), 5.20 [d, ^2J(H,H) = 12.27 Hz, 1 H, CH_2Ph], 5.11 [d, ^2J(H,H) = 12.27 Hz, 1 H, CH_2Ph], 5.06 [dd, ^3J(H,H) = 3.96 Hz, ^3J(H,H) = 13.11 Hz, OCHCO], 4.59 [dd, ^3J(H,H) = 5.43 Hz, ^3J(H,H) = 8.49 Hz, 1 H, NCH], 3.75−3.64 (m, 2 H, NCH_2), 2.96 [dd, ^2J(H,H) = 17.15 Hz, ^3J(H,H) = 13.11 Hz, 1 H, OCHC*H*$_2$], 2.59 [dd, ^2J(H,H) = 17.15 Hz, ^3J(H,H) = 13.11 Hz, 1 H, OCHC*H*$_2$], 2.26−2.11 (m, 1 H, C*H*$_2$CH$_2$, 2 H, C*H*$_2$CH$_3$), 2.09−1.93 (m, 3 H, C*H*$_2$C*H*$_2$), 1.02 [t, ^3J(H,H) = 7.46 Hz, 3 H, CH_2C*H*$_3$]. − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 190.76 (C=O), 171.39, (C=O), 165.55 (C=O), 157.13 (O*C*H=C), 135.47, 128.89, 128.71, 128.58, 128.35, 128.13 (Ph), 120.50 (OCH=*C*), 76.35 (O*C*HCO), 66.99 (CH_2Ph), 59.38 (NCH), 46.95 (NCH_2), 37.55 (OCH*C*H_2), 28.74 (NCH*C*H_2), 24.82 (NCH_2*C*H_2) 18.56 (*C*H_2CH$_3$), 13.51 (CH_2*C*H_3). − MS (70 eV); *m/z* (%): 357 (0.04) [M^+], 98 (86.45) [$C_5H_8NO^+$], 70 (100) [$C_4H_8N^+$], 57 [$C_3H_7N^+$]. − $C_{20}H_{23}NO_5$ (357.4): calcd C 67.21, H 6.49, N 3.92; found C 66.71, H 6.76, N 4.30. − HRMS: $C_{20}H_{23}NO_5$ (357.4): calcd. 357.1576; found 357.1559.

***N*-[(2*S*)-2,3-Dihydro-5-ethyl-4-oxo-4*H*-pyran-2-oyl]-(*S*)-proline *tert*-Butyl Ester (13d):** M.p. 79°C. $[\alpha]_D^{22}$ = +28.0 (*c* = 1, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1738 cm^{-1} (C=O), 1665 (Ph), 1623 (C=C). − ^{1}H NMR (400 MHz, $CDCl_3$,): δ = 7.11 (s, 1 H, OCH=C), 5.00 [dd, ^3J(H,H) = 3.71 Hz, ^3J(H,H) = 13.20 Hz, 1 H, OCHCO], 4.34 [dd, 1 H, ^3J(H,H) = 3.74 Hz, ^3J(H,H) = 8.55 Hz, 1 H, NCH], 3.66−3.53 (m, 2 H, NCH_2), 2.90 [dd, ^2J(H,H) = 17.00 Hz, ^3J(H,H) = 13.20 Hz, 1 H, OCHC*H*$_2$], 2.55 [dd, ^2J(H,H) = 17.00 Hz, ^3J(H,H) = 13.20 Hz, 1 H, OCHC*H*$_2$], 2.15−1.87 (m, 4 H, CH_2CH_2, 2 H, C*H*$_2$CH$_3$), 1.37 [s, 9 H, C(CH_3)$_3$], 0.94 [t, ^3J(H,H) = 7.32 Hz, 3 H, CH_2C*H*$_3$]. − ^{13}C NMR (100.6 MHz, $CDCl_3$,): δ = 190.73 (C=O), 170.67, (C=O), 165.33 (C=O), 157.31 (O*C*H=C), 120.31 (OCH=*C*), 81.47 [*C*(CH_3)$_3$], 76.34 (O*C*HCO), 60.05 (NCH), 46.88 (NCH_2), 37.57 (OCH*C*H_2), 28.74 (NCH*C*H_2), 27.87 [C(*C*H_3)$_3$], 24.71 (NCH_2*C*H_2) 18.49 (*C*H_2CH$_3$), 13.47 (CH_2*C*H_3). − MS (70 eV); *m/z* (%): 323 (24.48) [M^+], 222 (95.30) [$M^+ - C_5H_9O_2$], 98 (30.26) [$C_5H_8NO^+$], 70 (100) [$C_4H_8N^+$]. − $C_{17}H_{25}NO_5$ (323.4): calcd. C 63.14, H 7.79, N 4.33; found C 62.84, H 7.93, N 4.71. − HRMS: $C_{17}H_{25}NO_5$ (323.4): calcd. 323.1733; found 323.1718.

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