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INFLUENCE OF *N*-PROTECTING GROUPS ON THE STEREOCHEMICAL COURSE OF [4+2] CYCLOADDITION OF ACTIVATED DIENES TO α-AMINO ALDEHYDES

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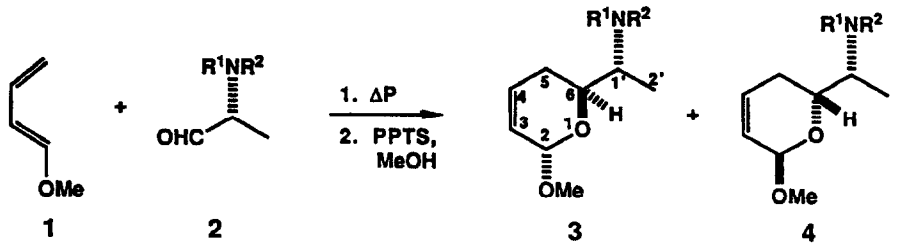
Abstract. Stereochemical aspects of high-pressure [4+2] cycloaddition between 1-methoxybuta-1,3-diene and *N*-protected α-amino aldehydes are discussed. In addition, the zinc bromide catalyzed cyclocondensation of 1-ethoxy-3-silyloxybuta-1,3-diene and *N*-protected α-amino aldehydes is studied, at ambient pressure.

The hetero-Diels-Alder reaction between 1-oxygenated or 1,3-dioxygenated buta-1,3-diene derivatives and *N*-protected α-amino aldehydes is a convenient method for the preparation of chiral synthons for syntheses of some important components of aminoglycoside antibiotics,[1,2] which are difficult to obtain by other routes. There are only a few reports in the literature concerning the stereochemical control of the [4+2] cycloaddition to the carbonyl group of α-amino aldehydes.[3-6] In the basic studies of the cyclocondensation reaction of activated 1,3-dienes with various aldehydes, Danishefsky and coworkers[7] have tested BOC-L-leucinal as a dienophile. The reaction of diene **5** with this aldehyde, catalyzed by zinc chloride, resulted in a 9:1 *syn-anti* diastereomeric mixture of pyrones. The high selectivity could be explained by a strong chelating interaction forming the quasi-cyclic structure of *N*-protected α-amino aldehyde as well as by the high steric demand of the approaching planar diene conformer. Similar diastereoselectivity has also been observed for the reaction of the same diene **5** with aldehydes derived from L-serine.[5] Since this is an area of great importance, which requires deeper understanding, we decided to study the influence of the nature of the amine-protecting groups on the stereochemical course of this Diels-Alder reaction with α-amino aldehydes.[8-10]

We have chosen to study various *N*-protected D-alaninals **2** since they represent the simplest example of a chiral α-amino aldehyde. Initially we investigated the high-pressure reaction between 1-methoxybuta-1,3-diene (**1**) and D-alaninals **2**. The reactions were performed without catalyst, or in the presence of very mild Lewis acids e.g. $Eu(fod)_3$[11] (Scheme 1).



Scheme 1

We found a large difference in the asymmetric induction when substituting either one or two amino protons with a protecting group (Table I). The direction of asymmetric induction was reversed when *N,N*-diprotected α-amino aldehydes were used instead of the *N*-monoprotected ones.

Table I. Results of High-Pressure [4+2] Cycloaddition of 1-Methoxybuta-1,3-diene (1) to *N*-Protected D-Alaninals (2)

Entry	Aldehyde	R^1	R^2	Catalyst	Yield[a] [%]	Diastereoizomer ratio[b] 3:4
1	**2a**	H	Cbz	2% $Eu(fod)_3$	50	33:67
2[c]	**2a**	H	Cbz	------	35	33:67
3	**2b**	H	BOC	2% $Eu(fod)_3$	55	25:75
4[c]	**2b**	H	BOC	------	12	25:75
5	**2c**	Bn	Bn	2% $Eu(fod)_3$	58	92:8
6	**2d**	Bn	Tos	2% $Eu(fod)_3$	79	94:6
7	**2e**	Bn	BOC	2% $Eu(fod)_3$	80	94:6
8	**2f**	Pht		2% $Eu(fod)_3$	75	83:17

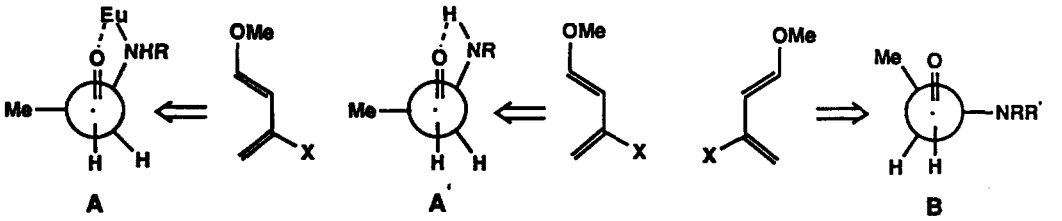
[a] Yield calculated for the isolated pure compounds.

[b] Ratio determined by ^1H NMR (400 MHz).

[c] Very high pressure (25 kbar) was used.

The stereochemical results obtained for *N*-monoprotected α-amino aldehydes in the presence of a catalyst were consistent with chelation-controlled cycloaddition of the diene to conformer A (Scheme 2). Further, reaction of *N*-monoprotected α-amino aldehydes without the presence of a catalyst gave, unexpectedly, similar results. This can be explained by the presence of a hydrogen-bonding interaction between the carbonyl group and the NH proton as shown for conformer A' (Scheme 2). This assumption, has been confirmed by our recent studies on the conformations of α-amino aldehydes in solution. Thus, double protection of the amino group, which "consumes" both NH_2 protons, ought to reverse the direction of asymmetric induction. Indeed, the 6,1' *anti* diastereoisomers **3** were obtained as

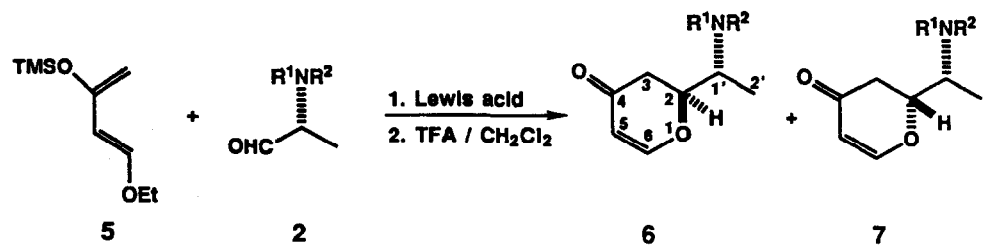
the major products when the *N,N*-diprotected D-alaninals **2c**, **2d**, **2e**, and **2f** were employed. The latter results may be explained by the predominance of conformer B (Scheme 2).



Scheme 2

The low availability of the high-pressure equipment in chemical laboratories prompted us to extend our studies of this Diels-Alder reaction to ambient-pressure conditions.

Also in this case, various protected D-alaninals **2** were chosen as model dienophiles. These aldehydes were reacted with Danishefsky's diene (**5**)[12] (Scheme 3) to afford adducts, which could be easily correlated with known compounds (see below). The results of these reactions are listed in Table II.



Scheme 3

Table II. Results of [4+2] Cycloaddition of Danishefsky's Diene (**5**) to *N*-Protected D-Alaninals (**2**)

Entry	Aldehyde 2	R^1	R^2	Yield[a] [%]	Diastereoisomer ratio[b] 6:7
1	**2a**	H	Cbz	78	33:67
2	**2b**	H	BOC	75	25:75
3	**2c**	Bn	Bn	80	90:10
4	**2d**	Bn	Tos	91	91: 9
5	**2e**	Bn	BOC	85	93: 7
6	**2f**	Pht		82	75:25
7	**2g**	H	Tos	74	50:50

[a] Yield calculated for isolated pure compounds.

[b] Ratio determined by ^{1}H NMR (400 MHz).

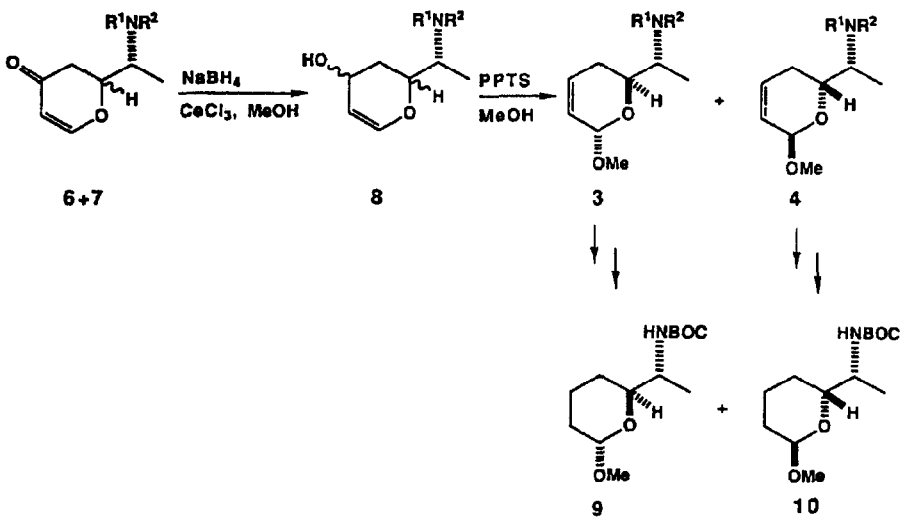
The obtained results seem to be of general validity, when considering all experiments performed under different reaction conditions. The collected data show that the stereoselectivity is reversed for the *N,N*-diprotected D-alaninals (**2c**, **2d**, **2e**, and **2f**) when compared to the *N*-monoprotected analogs (**2a**, and **2b**). Evidently, *N*HBOC- and *N*HCbz-protected alaninals (**2a** and **2b**) react *via* α-chelated conformer A (Scheme 2). It is not clear why the stereochemistry of the cycloaddition of these aldehydes is almost independent of the presence or absence of Lewis acid. This fact can be rationalized on the basis of the dominance of hydrogen-bonding forces over chelate-forming interactions.

In *N*HTos-protected alaninal **2g**, the nature of the blocking group is intermediate between the chelating and the steric type. The sulfonyl function strongly deactivates the nitrogen center, and the remaining amino proton affects much weaker α-chelation.

N,N-Diprotected alaninals exhibit strong *anti*-selectivity. Clearly, in the case of these compounds, conformation B (Scheme 2) is dominant. Thus, there is also evident correlation between the diastereoselectivity of the reaction and the steric hindrance of the blocking groups.

A similar *anti*-selectivity has been observed by Reetz *et al.*[13-16] for nucleophilic additions to *N,N*-dibenzyl α-amino aldehydes. The same stereochemical interpretation, based on the Felkin model, has also been proposed by these authors.

Spectroscopic methods were used to establish the relative 6,1'-stereochemistry of 6-substituted-2-methoxy-5,6-dihydro-2*H*-pyrans (**3** and **4**) and 2,1'-stereochemistry of 2-substituted-2,3-dihydropyran-4-ones (**6** and **7**).[17] Further, all obtained adducts were chemically correlated with compounds **9** and **10** (Scheme 4). Thus, **6** and **7** were reduced by Luche's method[18] to afford the corresponding mixture of alcohols **8** (Scheme 4).



Scheme 4

The Ferrier rearrangement[19] in conjunction with *cis-trans* isomerisation[20] afforded a

mixture of adducts **3** and **4**. The cycloadducts **3** and **4** from the high-pressure reaction were hydrogenated. After amino group deprotection, they were correlated with adducts **3b** and **4b** *via* compounds **9** and **10**. The absolute configurations of adducts **3b** and **4b** were established earlier, *via* their transformation into purpurosamine B and enantiomer of 6-*epi* purpurosamine B, respectively.[3,21]

Experimental Section

^{1}H NMR spectra were recorded at 400 MHz with a Bruker AM-400 spectrometer. ^{13}C NMR spectra were measured at 100 MHz with a Bruker AM-400 spectrometer. Infrared spectra were recorded on a Beckman IR-4240 spectrophotometer. Optical rotations were determined with a Perkin-Elmer 141 polarimeter.

Column chromatography was carried out with Merck Kieselgel 60 (230-400 mesh), according to Still's procedure.[22] All chromatographic separations were monitored by TLC analyses, performed on Merck DC Alufolien Kieselgel 60F-254. Yields are reported for chromatographically pure compounds.

High-pressure reactions were carried out in a piston-cylinder type apparatus with a working volume of about 90 mL. Construction details have been reported previously.[23] The pressure was measured with a manganine coil calibrated to ±0.1 kbar. The temperature was measured with a thermocouple calibrated to ±1°C.

trans-1-Methoxybuta-1,3-diene (**1**)[24], *trans*-1-ethoxy-3-[(trimethylsilyl)oxy]-buta-1,3-diene (**5**)[25], and *N*-protected α-amino aldehydes **2a**,[26] **2b**,[3] **2c**,[13] **2d**,[27] **2e**,[28] **2f**,[29] and **2g**[30] were prepared according to literature procedures.

Adducts 3 and 4. Procedure I.

A teflon ampoule containing a solution of diene **1** (0.67 g, 8 mmol), aldehyde **2** 4 mmol), and Eu(fod)$_3$ (83.2 mg, 0.08 mmol) in Et$_2$O (5 mL) was placed in a high-pressure vessel filled with pentane. The pressure was slowly (10 min) raised to 15 kbar at 50 °C. After 24 h (for *N*-monoprotected alaninals) or 48 h (for *N,N*-diprotected alaninals), the reaction mixture was cooled, decompressed, and the solvent was evaporated. The residue was filtered through a short silica gel pad using hexane-ethyl acetate (85:15). The solvents were evaporated and the residue was dissolved in methanol (10 mL) at room temperature. Catalytic amount of pyridinium *p*-toluenesulfonate (25.1 mg, 0.1 mmol) was added and the reaction mixture was maintained at room temperature overnight.[31] Then Et$_2$O was added (40 mL) and the mixture was washed with saturated NaHCO$_3$. Inorganic layer was extracted with diethyl ether (3x20 mL). Organic layers were combined, dried over MgSO$_4$, concentrated *in vacuo* and purified by flash chromatography.

(2S,6S,1'R) - and (2R,6R,1'R)-6-[(1'-*N*-benzyloxycarbonylamino)-ethyl]-5,6-dihydro-2-methoxy-2*H*-pyran (3a and 4a). (29:71 - 6,1'*anti-syn* mixture): oil; IR (film) 3350, 2940, 1730, 1535, 1520, 1460, 1410, 1350, 1060 cm^{-1}; Anal.Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.97; H, 7.09; N, 4.79.

3a: ^{1}H NMR (CDCl$_3$) δ 7.34 (m, 5 H), 5.98 (m, 1 H), 5.70 (m, 1 H), 5.10 (m, 3 H), 4.83 (br s, 1 H), 3.82 (m, 2 H), 3.38 (s, 3 H),2.10-1.90 (m, 2 H), 1.20 (d, *J* = 6.4 Hz, 3 H); ^{13}C

NMR ($CDCl_3$) δ 155.9, 136.7, 129.7, 128.9, 128.6, 128.1, 126.8, 125.3, 96.0, 69.1, 55.3, 49.7, 26.2, 15.9.

4a: ^{1}HNMR ($CDCl_3$) δ 7.34 (m, 5 H), 5.98 (m, 1 H), 5.70 (m, 1 H), 5.10 (m, 3 H), 4.83 (br s, 1 H), 3.82 (m, 2 H), 3.39 (s, 3 H), 2.24-1.72 (m, 2 H), 1.27 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.3, 136.6, 129.7, 128.9, 128.6, 128.1, 126.8, 125.1, 95.9, 68.9, 66.7, 55.2, 49.5, 27.3, 18.7.

(2S,1'R,6S)- and (2R,6R,1'R)-6-[(1'-*N*-*tert*-butoxycarbonylamino)-ethyl]-5,6-dihydro-2-methoxy-2*H*-pyran (3b and 4b).

3b: oil; $[\alpha]_D^{20}$ 46.2° (*c* 1.5, $CHCl_3$); IR (film) 3350, 1710, 1170,1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.01 (m, 1 H), 5.72 (m, 1 H), 4.86 (s, 1 H), 4.85 (m, 1 H), 3.82 (m, 1 H), 3.73 (m, 1 H), 3.41 (s, 3H), 2.10-1.95 (m, 2 H), 1.45 (s, 9 H), 1.17 (d, *J* = 6.5 Hz, 3 H), ^{13}C NMR δ ($CDCl_3$) 128.3, 124.3, 95.4, 68.6, 54.8, 48.6, 28.3, 27.6, 18.6; Anal.Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.68; H, 9.16; N, 5.39.

4b: oil; $[\alpha]_D^{20}$ -28.5° (*c* 3.0, $CHCl_3$); IR (film) 3340, 1710, 1190, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.00 (m, 1 H), 5.70 (m, 1 H), 4.85 (m, 1 H), 4.85 (d, *J* = 1.5 Hz, 1 H), 3.82 (m 1H), 3.77 (m, 1 H), 3.41 (s, 3 H), 2.25-1.80 (m, 2 H), 1.45 (s, 9 H), 1.24 (d, *J* = 6.8 Hz 3H); ^{13}C NMR ($CDCl_3$) δ 128.0, 124.6, 95.4, 68.9, 54.0, 49.0, 28.3, 26.9, 15.9; Anal.Calcd for $C_{13}H_{23}NO_4$: C, 60,68; H, 9.01; N, 5.44. Found: C, 60.93; H, 9.06; N, 5.68.

(2S,6S,1'R) - and (2R,6R,1'R)-6-[(1'-*N*,*N*-dibenzylamino)ethyl]-5,6-dihydro-2-methoxy-2*H*-pyran (3c and 4c). (92:8 - 6,1' *anti-syn* mixture): oil; IR (film) 3400, 1270, 1050, 740 cm^{-1}; Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.07; N, 4.15. Found: C, 78.45; H, 8.11; N, 4.01.

3c: ^{1}H NMR ($CDCl_3$) δ 7.41-7.20 (m, 10 H), 6.06-6.00 (m, 1 H), 5.72-5.67 (m, 1 H), 4.80 (d, *J* = 1.1 Hz, 1 H), 3.94 (m, 1 H), 3.77 (d_{AB}, *J* = 13.7 Hz, 2 H), 3.44 (d_{AB}, *J* = 13.7 Hz ,2 H), 3.41 (s, 3 H), 2.72 (dq, *J* = 6.8 Hz,3 H), 2.35 (m, 1 H), 1.82 (m, 1 H), 1.19 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.0, 129.7, 128.7, 126.8, 125.0, 96.1, 68.9, 56.4, 55.3, 54.2, 29.2, 8.5.

4c: ^{1}HNMR ($CDCl_3$) δ 7.41-7.20 (m, 10 H), 6.03 (m, 1 H), 5.69 (m, 1 H), 4.92 (br s, 1 H), 4.04 (d_{AB}, *J* = 13.5 Hz,2 H), 3.93 (m, 1 H), 3.48 (d_{AB}, *J* = 13.5 Hz, 2 H), 3.42 (s, 3 H), 2.84 (m, 1 H), 2.50 (m, 1 H), 1.65 (m, 1 H), 1.18 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 140.0, 129.7, 128.2, 128.1, 126.6, 125.0, 96.0, 68.9, 56.4, 55.0, 27.5, 8.8.

(2S,6S,1'R,)- and (2R,6R,1'R)-6-[(1'-*N*-benzyl-*N*-tosylamino)-ethyl]-5,6-dihydro-2-methoxy-2*H*-pyran (3d and 4d).

3d: mp. 114.0-115.0 °C; $[\alpha]_D^{16}$ -2.6° (*c* 1.5, $CHCl_3$); IR (film) 2940, 1660, 1605, 1350, 1160, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68 (d_{AB}, *J* = 8.3 Hz, 2 H), 7.38-7.23 (m, 7 H), 5.84 (m, 1 H), 5.58 (dd, *J* = 10.2 and 2.4 Hz, 1 H), 4.75 (d, *J* = 2.4 Hz, 1 H), 4.58 (d_{AB}, *J* = 15.4 Hz, 1 H), 4.19 (d_{AB}, *J* = 15.4 Hz, 1 H), 3.89 (dq, *J* = 6.9 and 1.5 Hz, 1 H), 3.48 (m, 1 H), 3.29 (s, 3 H), 2.43 (s, 3 H), 1.91 (m, 2 H), 1.09 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.2, 137.9, 137.3, 129.7, 129.0, 128.7, 128.4, 128.2, 127.7, 127.1, 124.5, 96.0, 68.8, 57.5, 55.2, 48.1, 28.1, 21.5, 14.5; Anal. Calcd for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78; N, 3.49; S, 7.98. Found: C, 65.87; H, 6.75; N, 3.37; S, 7.96.

4d: oil; $[\alpha]_D^{16}$ 16.3° (*c* 0.5, $CHCl_3$); IR (film) 2940, 1680, 1600, 1500, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (d_{AB}, *J* = 8.3 Hz, 2 H), 7.41 (d_{AB}, *J* = 8.3 Hz, 2 H), 7.29-7.22 (m, 5 H), 5.95 (m, 1 H), 5.64 (m, 1 H), 4.67 (d_{AB}, *J* = 15.8 Hz, 1 H), 4.51 (br s, 1H), 4.18 (d_{AB}, *J* = 15.8 Hz, 1 H), 4.13 (dq, *J* = 7.2, 7.2 Hz, 1 H), 3.89 (ddd, *J* = 14.7, 7.6 and 3.4 Hz, 1 H), 3.13 (s, 3 H), 2.41 (s, 3 H), 2.05-1.97 (m, 1 H), 1.87-1.79 (m, 1 H), 0.95 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.6, 138.5, 129.1, 128.7, 128.4, 128.2, 127.8, 127.3, 125.1, 95.8, 67.6, 57.4, 55.7, 47.8, 28.0, 21.2, 17.5; Anal. Calcd for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78; N, 3.49; S,7.98. Found: C, 65.91; H, 6.74; N, 3.39; S, 7.88.

(2S,6S,1'R) - and (2R,6R,1'R) -6-[(1'-*N*-benzyl-*N*-*tert*-butoxycarbonylamino)ethyl]-5,6-dihydro-2-methoxy-2*H*-pyran (3e and 4e). (94:6 - 6,1' *anti-syn* mixture): oil; IR (film) 2980, 1700, 1455, 1370, 1170, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 60°C) δ 7.30-7.20 (m, 5 H), 5.93 (m, 1 H), 5.68 (m, 1 H), 4.83 (d, *J* = 1.4 Hz, 1 H), 4.48 (d_{AB}, *J* = 15.8 Hz, 1 H), 4.37 (d *J* = 15.8 Hz, 1 H), 4.03 (q, *J* = 6.8 Hz, 1 H), 3.85 (m, 1 H), 3.38 (s, 3 H), 1.93-1.85 (m, 2 H), 1.43 (br s, 9 H), 1.24 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 60°C) δ 128.9, 128.2, 127.7, 127.0, 126.6, 125.2, 98.8, 96.0, 69.0, 55.2, 28.5, 28.3, 27.7, 15.9, 14.7; Anal. Calcd for $C_{20}H_{29}NO_4$: C,69.16; H, 8.41; N, 4.03. Found: C, 69.30; H, 8.50; N, 4.19.

(2S,6S,1'R)- and (2R,6R,1'R)-6-[(1'-*N*-phtaloylamino)ethyl]-5,6-dihydro-2-methoxy-2*H*-pyran (3f and 4f). **3f**: mp. 148-151 °C; $[\alpha]_D^{20}$ 73.9° (*c* 2.3, $CHCl_3$); IR (film) 3450, 1770, 1710, 1460, 1370, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82 (m, 2H), 7.72 (m, 2 H), 5.90 (m, 1 H), 5.73 (m, 1 H), 4.90 (br s, 1 H), 4.41 (dt, *J* = 3.4 and 9.5 Hz, 1 H), 4.34 (dq, *J* = 9.3 and 6.8 Hz, 1 H), 3.47 (s, 3 H), 2.01-1.82 (m, 2 H), 1.59 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 134.0, 131.8, 128.0, 125.4, 123.3, 95.9, 67.0, 55.3, 50.5, 27.6, 15.4; Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.59; H, 5.74; N, 4.68.

4f: mp. 92-95 °C; $[\alpha]_D^{20}$ -35.1° (*c* 1.1, $CHCl_3$); IR (film) 3450, 1780, 1700, 1460, 1370, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82 (m, 2 H), 7.68 (m, 2 H), 5.98 (m, 2 H), 5.68 (m, 1 H), 4.72 (br s, 1 H), 4.44 (td, *J* = 10.3 and 3.2 Hz, 1 H), 4.34 (qd, *J* = 6.9 and 6.8 Hz, 1 H) 2.99 (s, 3 H), 2.18-1.96 (m, 2 H), 1.48 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 134.1, 132.0, 128.9, 125.6, 123.1, 95.6, 66.3, 54.8, 50.7, 28.4, 14.5; Anal.Calcd for $C_{16}H_{17}NO_4$: C, 66.89 ; H, 5.96; N, 4.87. Found: C, 66.80; H, 6.01; N, 5.05.

Adducts 6 and 7. Procedure II.

To a solution of aldehyde 2 (1 mmol) in dry THF (10 mL), at room temperature, diene 5 (285.6 μL, 1.5 mmol) was added, followed by a catalytic amount of anhydrous $ZnBr_2$ (22.5 0.1 mmol). The reaction mixture was maintained at room temperature and was monitored by TLC until the disappearance of the starting aldehyde. Then a saturated $NaHCO_3$ solution (10 mL) was added and reaction mixture was transferred to a separatory funnel. The water layer was extracted with Et_2O (3 x 20 mL) and the organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The oily residue was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. After addition of trifluoroacetic acid (85 μL, 1.1 mmol), the reaction mixture was stirred at 0°C for 1 h, and then was allowed to warm to room temperature, whereupon a saturated $NaHCO_3$ solution (20 mL) was added. The reaction mixture was transferred to a separatory funnel, and the organic layer was washed with brine and dried over

$MgSO_4$. After evaporation of solvents, the residue was purified by column chromatography to give a mixture of adducts **6** and **7**.

(2S,1'R)- and (2R,1'R)-2-[(1'-*N*-Benzyloxycarbonylamino)ethyl]-2,3-dihydropyran-4-one (6a and 7a). (25:75- 2,1' *anti-syn* mixture): oil; IR (film) 3330, 2940, 1730, 1680, 1600, 1540, 1280, 1230 cm^{-1}; Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.65; H, 6.34; N, 4.80.

6a: ^1H NMR ($CDCl_3$) δ 7.36-7.30 (m, 6 H), 5.42 (dd, *J* = 5.7 and 1.3 Hz, 1 H), 5.11 (m, 3 H), 4.40 (br d, *J* = 14.6 Hz, 1 H), 4.0 (br s, 1 H), 2.57 (m, 1 H), 2.40 (m, 1 H), 1.24 (d *J* = 6.9 Hz, 3H), ^{13}C NMR ($CDCl_3$) δ 155.7, 136.4, 128.6, 128.2, 128.1, 98.0, 70.7, 66.9, 63.0, 49.6, 46.6, 44.0, 29.6, 18.5.

7a: ^1H NMR ($CDCl_3$) δ 7.36-7.30 (m, 6 H), 5.41 (dd, *J* = 5.9 and 1.3 Hz, 1 H), 5.11 (brs, 2 H), 4.89 (br d, *J* = 8.6 Hz, 1 H), 4.37 (br d, *J* = 14.7 Hz, 1 H), 4.01 (m, 1 H), 2.68 (m, 1 H), 2.39 (m, 1 H), 1.30 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.2, 136.4, 128.6, 128.5, 128.1, 98.0, 70.8, 67.0, 63.0, 49.6, 46.4, 46.4, 44.4, 29.7, 28.4, 14.8.

(2S,1'R)- and (2R,1'R)-2-[(1'-*N*-*tert*-butoxycarbonylamino)ethyl]-2,3-dihydropyran-4-one (6b and 7b). (33:67- 2,1'*anti-syn* mixture): oil; IR (film) 3350, 1730, 1720, 1700, 1610, 1540, 1280, 1180 cm^{-1}; Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N,5.80. Found: C, 59.71; H, 8.01; N, 5.94.

6b. ^1H NMR ($CDCl_3$) δ 7.37 (d, *J* = 5.8 Hz, 1 H), 5.43 (d, *J* = 5.8 Hz, 1 H), 4.76 (m, 1 H), 4.37 (m, 1 H), 3.95 (m, 1 H), 2.40 (m, 1 H), 2.36 (m, 1 H), 1.45 (s, 9 H), 1.23 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 191.8, 162.7, 155.0, 107.3, 90.7, 81.6, 79.9, 48.5, 38.9, 28.3, 15.3.

7b. ^1H NMR ($CDCl_3$) δ 7.35 (d, *J* = 5.8 Hz, 1 H), 5.42 (dd, *J* = 6.0 and 1.3 Hz, 1 H), 4.62 (m, 1 H), 4.37 (m, 1 H), 3.95 (m, 1 H), 2.44 (m, 1 H), 2.34 (m, 1 H), 1.45 (s, 9 H), 1.28 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 192.3, 162.5, 155.3, 107.3, 90.7, 81.5, 48.1, 38.7, 28.3, 17.6.

(2S,1'R)- and (2R,1'R)-2-[(1'-*N*,*N*-dibenzylamino)ethyl]-2,3-dihydropyran-4-one (6c and 7c) (90:10 - 2,1' *anti-syn* mixture): oil; IR (film) 3350, 1730, 1700, 1610, 1300 cm^{-1}; Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.44; H, 7.21; N, 4.36. Found: C, 78.51; H, 6.99; N, 4.52.

6c: ^1H NMR ($CDCl_3$) δ 7.37-7.20 (m, 11 H), 5.37 (dd, *J* = 5.9 and 1.2 Hz, 1 H), 4.39 (ddd, *J* = 14.2, 8.0 and 3.3 Hz, 1 H), 3.74 (d_{AB}, *J* = 13.7 Hz, 2 H), 3.47 (d_{AB}, *J* = 13.7 Hz, 2 H), 2.94 (dq, *J* = 7.8 and 6.8 Hz, 1 H), 2.81 (dd, *J* = 16.8, 2.5 Hz, 1 H), 2.31 (dd, *J* = 17.0 and 14.3 Hz, 1 H), 1.23 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.0, 139.2, 128.7, 128.3, 127.1, 107.2, 81.2, 55.7, 54.3, 40.3, 8.4.

7c: ^1H NMR ($CDCl_3$) δ 7.37-7.20 (m, 11 H), 5.38 (dd, *J* =6.0 and 1.2 Hz,1 H), 4.32 (ddd, *J* = 16.0, 3.5 and 3.3 Hz, 1 H), 3.98 (d_{AB}, *J* = 13.5 Hz, 2 H), 3.43 (d_{AB}, *J* = 13.5 Hz, 2 H), 3.08 (m, 1 H), 2.95 (m, 1 H), 2.10 (m, 1 H), 1.24 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.0, 140.0, 128.6, 128.3, 127.0, 107.0, 83.2, 54.8, 54.1, 39.9, 9.0.

(2S,1'R)- and (2R,1'R)-2-[(1'-*N*-benzyl-*N*-tosylamino)ethyl]-2,3-dihydropyran-4-one (6d and 7d). 6d: mp. 126-127 °C, $[\alpha]_D^{18}$ -0.8° (*c* 1.2, CH_2Cl_2); IR (KBr) 3460, 3000, 2360, 1670, 1600, 1410, 1340, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d_{AB}, *J* = 8.2 Hz, 2 H), 7.34-7.20 (m,

7 H), 7.07 (d, J = 5.9 Hz, 1 H), 5.23 (d, J = 5.9 Hz, 1 H), 4.65 (d_{AB}, J = 15.3 Hz, 1 H) 4.09-4.05 (m, 1 H), 4.07 (d_{AB}, J = 15.3 Hz, 1 H), 3.89-3.82 (m, 1 H), 2.52-2.34 (m, 2 H), 2.43 (s, 3 H), 1.11 (d, J = 6.9, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.8, 162.1, 143.8, 130.0, 128.7, 128.5, 128.1, 127.1, 107.5, 81.0, 56.1, 48.3, 39.6, 21.6, 13.3; Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.02; N, 3.63; S, 8.32. Found: C, 65.30; H, 5.88; N, 3.57; S, 8.16.

7d: oil; $[\alpha]_D^{16}$ -22.9° (c 1.0, $CHCl_3$); IR (KBr) 3420, 3000, 2340, 1680, 1600, 1400, 1320, 1300 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (d_{AB}, J = 8.4 Hz, 2 H), 7.36-7.23 (m, 7 H), 6.96 (d, J = 6.0 Hz, 1 H), 5.23 (dd, J = 6.0 and 1.0 Hz, 1 H), 4.61 (d_{AB}, J = 15.8 Hz, 1 H), 4.24-4.10 (m, 2 H), 4.16 (d_{AB}, J = 15.8 Hz, 1 H), 2.48 (dd, J = 13.6 and 16.8 Hz, 1 H), 2.44 (s, 3 H), 2.30 (dd, J = 3.6 and 16.8 Hz, 1 H), 1.05 (d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.5, 162.2, 143.5, 129.7, 128.5, 127.8, 127.3, 107.1, 79.6, 56.0, 48.5, 39.3, 29.7, 21.6, 14.8; Anal. Calcd for $C_{21}H_{23}NO_4$: C, 65.43; H, 6.02; N, 3.63; S, 8.32. Found: C, 65.58; H, 5.96; N, 3.49; S, 8.32.

(2S,1'R)- and (2R,1'R)-2-[(1'-*N*-Benzyl-*N*-*tert*-butoxycarbonylamino)ethyl]-2,3-dihydropyran-4-one (6e and 7e). (93:7 mixture): oil; IR (film) 1750, 1710, 1540, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 60°C) δ 7.25 (m, 5 H), 6.31 (dd, J = 6.1 and 1.2 Hz, 1 H), 4.73 (br d, J = 6.1 Hz 1 H), 4.42 (m, 2 H), 4.30 (m, 1 H), 4.01 (m, 1 H), 2.17-2.10 (m, 2 H), 1.42 (br s, 9 H), 1.20 (d, J = 6.8 Hz, 3 H); Anal Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H,7.60; N,4.22. Found: C, 69.01; H, 7.58; N, 4.35.

(2S,1'R)- and (2R,1'R)-2-[(1'-*N*-Phtaloylamino)ethyl]-2,3-dihydropyran-4-one (6f and 7f).

6f: mp. 87-90 °C; $[\alpha]_D^{20}$ 130.5° (c 4.5, CH_2Cl_2); IR (film) 3450, 1780, 1730, 1690, 1400, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (m, 2 H), 7.74 (m, 2 H), 7.38 (d, J = 5.9 Hz, 1 H), 5.43 (d, J = 5.9 Hz, 1 H), 4.91 (ddd, J = 13.0, 9.0 and 3.8 Hz, 1 H), 4.60 (dq, J = 8.8 and 7.0 Hz, 1 H), 2.52-2.34 (m, 2 H), 1.61 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.3, 167.9, 162.7, 134.4, 131.6, 123.6, 107.6, 79.0, 49.2, 39.0, 14.9. Anal Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.32; H, 4.82; N, 5.20.

7f: mp. 117.0-117.5 °C; $[\alpha]_D^{20}$ 9.3°(c 1.0, $CHCl_3$); IR (film) 3450, 1790, 1740, 1690, 1400, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (m, 2 H), 7.73 (m, 2 H), 7.20 (d, J = 6.0 Hz, 1 H), 5.40 (dd, J = 6.0 and 1.2 Hz, 1 H); 5.02 (ddd, J = 13.4, 9.6 and 3.8 Hz, 1 H), 4.61 (dq, J = 9.6 and 7.1 Hz, 1 H), 2.69-2.50 (m, 2 H), 1.50, (d, J = 7.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 190.9, 168.2, 162.5, 134.2, 131.8, 123.4, 107.4, 78.1, 49.2, 39.5, 14.5; Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.53; H, 4.87; N, 5.21.

(2S,1'R) - and (2R,1'R)-2-[(1'-*N*-Tosylamino)ethyl]-2,3-dihydropyran-4-one (6g and 7g) (50:50- 6,7 *anti-syn* mixture): oil; IR (film) 3270, 2930, 1730, 1600, 1100 cm^{-1}; Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 57.02; H, 5.83; N, 4.90.

6g: ^1H NMR ($CDCl_3$) δ 7.76 (d_{AB}, J = 8.3 Hz, 2 H), 7.32 (d_{AB}, J = 8.3 Hz, 2 H), 7.28 (d, J = 6.0 Hz, 1 H), 5.38 (d, J = 6.0 Hz, 1 H), 5.02 (m, 1 H), 4.33 (dd, J = 3.8 and 3.8 Hz, 1 H), 3.55 (m, 1 H), 2.53-2.35 (m, 2 H), 2.44 (s, 3 H), 1.13 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.3, 162.4, 143.7, 137.7, 129.8, 126.9, 107.4, 81.2, 51.6, 38.6, 21.5, 17.9.

7g: ^1H NMR ($CDCl_3$) δ 7.76 (d_{AB}, J = 8.3 Hz, 2 H), 7.32 (d_{AB}, J = 8.3 Hz, 2 H), 7.27 (d, J

= 6.0 Hz, 1 H), 5.37 (d, J = 6.0 Hz, 1 H), 4.82 (m, 1 H), 4.28 (dd, J = 3.6 and 3.6 Hz, 1 H), 3.60 (m, 1H), 2.78-2.21 (m, 2 H), 2.43 (s, 3 H), 1.11 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.9, 162.1, 143.7, 137.7, 129.8, 126.9, 107.3, 81.1, 51.4, 38.1, 21.5, 15.7.

Chemical correlation of obtained products.

Transformation of adducts 6 and 7 into 3 and 4, respectively.

Luche reduction. Synthesis of 2-substituted-2,3-dihydro-4*H*-pyran-4-ols (8). Procedure III

To a solution of a mixture of adducts **6** and **7** (1 mmol) and cerium (III) chloride heptahydrate (558.8 mg, 1.5 mmol) in methanol (10 mL), at -78°C, under argon, sodium borohydride (56.7 mg, 1.5 eq) in absolute ethanol (2 mL) was added. The reaction mixture was allowed to warm to 0°C, whereupon it was diluted with Et_2O (40 mL) and quenched with a pH 7 buffer (20 mL). The reaction mixture was transferred to a separatory funnel, and the water layer was extracted with Et_2O (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo* and used in the next step without further purification.

Ferrier rearrangement. Procedure IV:

Crude alcohols **8** (1 mmol) are dissolved in methanol (10 mL) at room temperature. Catalytic amount of pyridinium *p*-toluenosulfonate (25.1 mg, 0.1 mmol) is added, and the reaction mixture is maintained at room temperature. The reaction is monitored by TLC. After disappearance of the starting alcohol, Et_2O is added (40 mL) and the mixture is washed with saturated $NaHCO_3$ solution. The inorganic layer is extracted with Et_2O (3 x 20 mL). Organic layers are combined, dried over $MgSO_4$, concentrated *in vacuo*, and the obtained mixture of compounds **3** and **4** is purified by flash chromatography.

Hydrogenation of adducts 3b and 4b. Procedure V.

(2S,6S,1'R)-6-[(1'-*N*-*tert*-butoxycarbonylamino)ethyl]-2-methoxy-tetrahydropyran (9).

Adduct **3b** (257 mg, 1 mmol) was dissolved in methanol (5 mL), and 30 mg of 10% Pd/C was added in one portion under argon atmosphere. After flushing of the flask (25 mL) with hydrogen, magnetic stirrer is switched on and the reaction is monitored by TLC (hexane-ethyl acetate, 8:2). After hydrogenation for 1h, the reaction mixture is filtered through Celite , and the filtrate is evaporated *in vacuo* to give 255 mg (98% yield) of pure product **9**.

9: oil; $[\alpha]_D^{20}$ -90.5° (*c* 1.4, $CHCl_3$); IR (film) 3400, 1700, 1530, 1370, 1180, 1030, 880, cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.75 (m, 1 H), 4.71 (s, 1 H), 3.65 (m, 2 H), 3.32 (s, 3 H), 1.85-1.75 (m, 2 H), 1.71-1.40 (m, 5 H), 1.43 (s, 9 H), 1.11 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.4, 103.6, 98.5, 70.9, 54.3, 49.5, 31.0, 29.7, 28.4, 27.4, 21.9, 18.0, 15.2; Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.20; H, 9.72; N, 5.40. Found: C, 60.29; H, 10.04; N, 5.41

(2R,6R,1'R)-6-[(1'-*N*-*tert*-butoxycarbonylamino)ethyl]-2-methoxytetrahydropyran (10).

Using procedure V adduct **4b** (257 mg, 1 mmol) was hydrogenated to give 253 mg (97% yield) of product **10**.

10: oil; $[\alpha]_D^{20}$ 64.7° (*c* 1.5, $CHCl_3$); IR (film) 3400, 1700, 1540, 1380, 1160, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.77 (m, 1 H), 4.72 (s, 1H), 3.64 (m, 2 H), 3.34 (s, 3 H), 1.84-1.72 (m, 2 H), 1.70-1.40 (m, 5 H), 1.45 (s, 9 H), 1.19 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.9, 103.4, 98.6, 71.1, 54.4, 49.7, 31.9, 29.6, 28.5, 26.9, 22.7, 18.6, 14.1; Anal.

Calcd for $C_{13}H_{25}NO_4$: C, 60.20; H, 9.72; N, 5.40. Found: C, 59.87; H, 9.49; N, 5.25.

Transformation of adducts 3 and 4 into compounds 9 and 10, respectively.

3a and **4a** into **9** and **10**. Procedure VI.

Using procedure V adducts **3a** and **4a** (a 1:2.5 mixture, 291 mg, 1 mmol) were hydrogenated to give crude amine which was dissolved in ethyl acetate (5 mL). Di-*tert*-butyl dicarbonate (218 mg, 1 mmol) was added and the reaction was stirred for 16 h at room temperature. After evaporation of the solvent, a crude mixture of compounds **9** and **10** was analyzed using ^{1}H NMR technique.

3c and **4c** into **9** and **10**. Procedure VII.

Using procedure V adducts **3c** and **4c** (a 12:1 mixture, 337 mg, 1 mmol) were hydrogenated. The crude product was dissolved in THF (5 mL) and added to a solution of sodium (115 mg, 5 mmol) in liquid ammonia (ca. 50 mL). After 10 min, the reaction was quenched by addition of ammonium chloride and few drops of water (ca. 0.5 mL); then ammonia was evaporated off under ambient pressure, while the rest of the liquids under reduced one. The oily residue was dissolved in ethyl acetate (2 mL), di-*tert*-butyl dicarbonate (218 mg, 1 mmol) was added, and the reaction was stirred for 16 h at room temperature. After evaporation of the solvent the crude product was roughly chromatographed on a short silica gel pad (hexane-ethyl acetate, 85:15). The reaction products were analyzed using ^{1}H NMR.

3d and **4d** into **9** and **10**.

Using procedure VII adducts **3d** and **4d** (a 15:1 mixture, 401 mg, 1 mmol) were transformed into mixture of compounds **9** and **10**, which was analyzed using ^{1}H NMR technique.

3e and **4e** into **9** and **10**. Procedure VIII.

Using procedure V adducts **3e** and **4e** (a 16:1 mixture, 347 mg, 1 mmol) were hydrogenated. The crude product was dissolved in THF (5 mL) and added to a solution of sodium (115 mg, 5 mmol) in liquid ammonia (ca. 50 mL). After 10 min, the reaction was quenched by addition of ammonium chloride and few drops of water (ca. 0.5 mL), ammonia was evaporated off under ambient pressure, while the rest of the liquids were removed under reduced one. The crude oil was dissolved in Et_2O (10 mL) and washed with water (2 x 10 ml), brine (10 mL), dried ($MgSO_4$) and evaporated. The obtained products were analyzed using ^{1}H NMR.

3f and **4f** into **9** and **10**. Procedure IX.

Using procedure V adducts **3f** and **4f** (a 5:1 mixture, 287 mg,1 mmol) were hydrogenated. The crude product was dissolved in ethanol (2 mL); then hydrazine hydrate (85%, 120 μL, 2 mmol) was added and the reaction mixture was refluxed for 30 min. A few drops of acetic acid were added and the reaction mixture was cooled to room temperature, filtered through Celite and evaporated. The oily residue was dissolved in ethyl acetate, di-*tert*-butyl dicarbonate (218 mg,1 mmol) was added, and the reaction mixture was stirred for 16 h at room temperature. After evaporation of the solvent, the crude mixture of compounds **9** and **10** was analyzed using ^{1}H NMR technique.

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