23. Diastereoselective Spirocyclization of Imines of 2-Substituted 1*H*-Indole-3-ethylamines (= Tryptamines): Variation of the Electrophile and the Substituent at C(2) and Its Influence on the Steric Outcome

6th Communication on Indoles, Indolenines, and Indolines[1])

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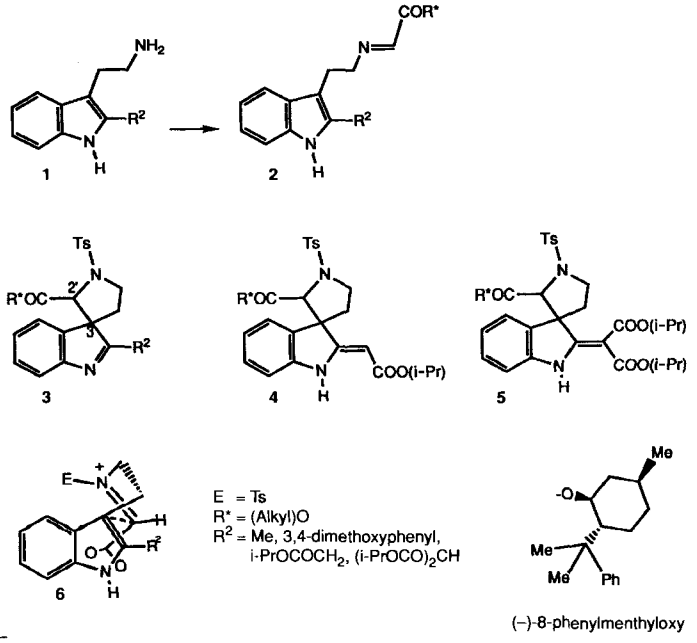
Tryptimines of type **7** form with various acyl halogenides EX preferentially tricycles of type **8** (*cf. Scheme 2*). The homochiral imines **9** and **17** are transformed into (2′*R*,3*S*)-configurated products. The synthetic and mechanistic importance of these results is discussed.

1. Introduction. – Recently, we reported on the spirocyclization of *C*-(alkoxycarbonyl)formimines **2** of 2-substituted tryptamines **1** by TsCl as electrophile in the presence

Scheme 1



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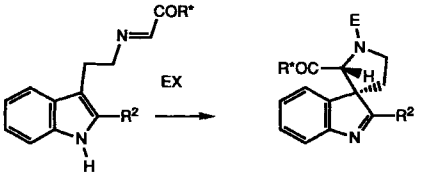
of 2,4,6-trimethylpyridine, affording tricycles of the types **3**–**5** [1]. High diastereoselectivity in favor of (2′*R**,3*S**)-configurated products was observed, if R^2 was Me or 3,4-dimethoxyphenyl, and this could be explained assuming that the reaction takes place *via* a transition state of type **6** (*Scheme 1*). With R* = (−)-8-phenylmenthyloxy and R^2 = Me, (2′*R*,3*S*)-configurated compounds were obtained.

In view of possible applications of this reaction in the synthesis of indole alkaloids, we undertook supplementary studies with respect to its scope. Variation of the electrophile EX and of the substituent R^2 in the reaction **7** → **8** (*Scheme 2*) seemed of particular interest in this connection. It could, in addition, corroborate the mechanistic hypothesis. We describe in the following pertinent investigations.

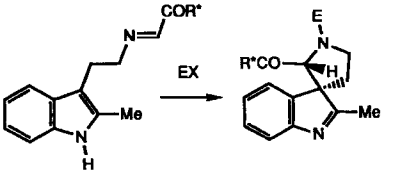
Scheme 2



7 R^2 = Alkyl **8**

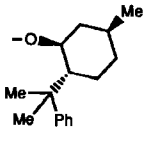
2. Variation of the Electrophile EX. – To ensure comparability with former results, again the imine **9** [1] was used as substrate for the spirocyclization (*Scheme 3*). Two aspects were essential for the choice of the electrophiles EX: *a*) ease of detaching E from the products **10**; *b*) broad variation with respect to size, shape, and electronic character.

Scheme 3



9 **10**

R* =



a E = Ts
b E = (4-methoxy-2,3,6-trimethylphenyl)sulfonyl
c E = MeCO
d E = CN
e E = 4-NO_2–C_6H_4–CH_2OCO

In the *Table*, the results, obtained under equal (and nonoptimized) conditions with five different acyl halogenides, are compiled. The 'voluminous' 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride (MTB-Cl) [2] provided with 94% d.e. even better diastereoselectivity than TsCl. Remarkably, the outcome with the 'small' and linear BrCN (97% de) was quite comparable. This was also the case with AcCl and [(4-nitroben-

Table. *Spirocyclization* **9** → **10** *with Five Different Acyl Halogenides EX* (in CH_2Cl_2/2,4,6-Trimethylpyridine, 48 h, −78°)

EX	Product	Chemical Yield [%]	% d.e.[a])
TsCl[b])	**10a**	57.9	86
MTB-Cl	**10b**	29.0	94
MeCOCl	**10c**	35.1	96
BrCN	**10d**	44.0	97
4-NO_2–$C_6H_4CH_2OCOCl$	**10e**	39.8	95

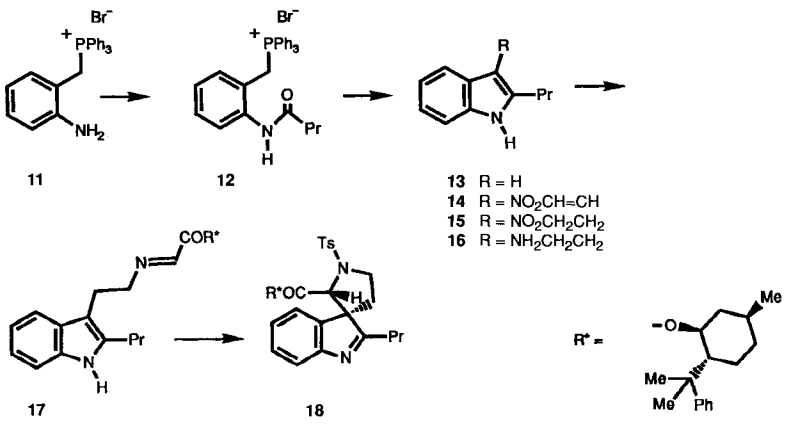
[a]) Limit of error *ca.* 2%.
[b]) 72 h, −90°, *cf.* [1].

zyl)oxy]carbonyl chloride. All products possess (2′*R*,3*S*)-configuration, as shown by CD comparison (minima at *ca.* 260 and 210 nm, maxima at *ca.* 230 nm) and by NOE experiments (irradiation at Me–C(2) signal→increase of H–C(2′) signal). Considering the steric orientation of the substituent E in the transition state **6**, a severe influence of EX on the diastereoselectivity was indeed not to be expected.

From compounds of types **10b** and **10e**, the substituents E are easily removable by treatment with CF_3COOH/thioanisol [2] and catalytic hydrogenation, respectively. To preserve the tricyclic skeleton, the N=C bond has to be reduced in advance [3].

3. Variation of the Substituent at C(2). – The four substituents at C(2) (Me, 3,4-dimethoxyphenyl, i-PrOCOCH$_2$, and (i-PrOCO)$_2$CH) of the tryptamine derivatives studied in [1] differ strongly with respect to their electronic character. Therefore, the influence of size and shape of these groups on the steric outcome of the spirocyclization cannot be judged. We were particularly interested in the effect brought about by a medium aliphatic chain and, for this reason, synthesized 2-propyltryptamine (**16**), as shown in *Scheme 4*[3]), transformed it into the imine **17**, and cyclized the latter with TsCl under the conditions

Scheme 4



[3]) *Cf. Capuano et al.* [4].

used for **9a**. Again, a (2′*R*,3*S*)-configurated tricycle **18** resulted. The diastereoselectivity was with *ca.* 92% d.e. better than in the case of the corresponding 2-methyl analogue (86% d.e.). The absolute and relative configuration of **18** followed from CD comparisons and an NOE experiment (irradiation at CH_2–C(2) signal→increase of H–C(2′) signal).

4. Discussion and Conclusions. – Of particular interest from a synthetic point of view are the following findings.

a) Besides TsCl, various acyl halogenides EX can effect the transformation of imines of type **9** into (2′*R**,3*S**)-configurated tricycles of type **10** with good-to-excellent diastereoselectivity. Comparably good results obtained with MTB-Cl and with BrCN show that size and shape of E have only little or no influence on the steric outcome. The generalization seems to be allowed that (apart from BrCN) various compounds of the general formulae $ArSO_2Cl$, RCOCl (R = alkyl or aryl), and ROCOCl (R = alkyl or aryl) may serve as EX, including those, the E of which is easily removable from the products.

b) Pr as substituent at C(2) instead of Me or aryl does not impair the diastereoselectivity of the spirocyclization. A certain generalization (at least to higher alkyl) also of this finding may be permissible.

The discussed results are in agreement with the mechanistic hypothesis (transition state **6**) and even corroborate it.

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Experimental Part

General. See [5]. If not stated otherwise, the molecular sieves used for imine formation were from *Merck* (0.4 nm). Solns. in aprotic solvents were dried with $MgSO_4$ or Na_2SO_4 before evaporation. Diastereoselectivities (% de) were estimated by ^{1}H-NMR (400 MHz; *s* of H–C(2′) of combined chromatographic fractions).

1. *(1S,2R,5S)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (E)-{[2-(2-Methyl-1H-indol-3-yl)ethyl]imino}acetate* (**9**; soln. in CH_2Cl_2). To a slowly stirred mixture of *2-methyl-1H-indole-3-ethylamine* (**1**; R^2 = Me) [1] (2 mmol), molecular sieves, and CH_2Cl_2 (5 ml), a soln. of (1*S*,2*R*,5*S*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl glyoxylate [6] (577 mg, 2 mmol) in CH_2Cl_2 (5 ml) was added dropwise. After 24 h at 25°, the mixture was stored at 4° in an ice-box.

2. *Spirocyclization of* **9** *by Various Acyl Halogenides (EX).* A soln. of EX (0.58 mmol) in CH_2Cl_2 (3 ml) was added dropwise at −78° to a stirred soln. of **9** (0.25 mmol) and 2,4,6-trimethylpyridine (0.1 ml) in CH_2Cl_2 (2.5 ml). After 48 h, 0.5N citric acid (5 ml) was added and the stirred mixture warmed to r.t. The aq. phase was extracted twice with CH_2Cl_2, the combined org. phase dried with molecular sieves and evaporated. The crude product was purified by chromatography on silica gel, as indicated for the individual compounds.

3. *(1S,2R,5S)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2′R,3S)-1′-[(4-Methoxy-2,3,6-trimethylphenyl)sulfonyl]-2-methylspiro[3H-indole-3,3′-pyrrolidine]-2′-carboxylate* (**10b**). The crude product obtained with 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride was chromatographed twice on silica gel (20 g and 25 g, respectively) with hexane/$CHCl_3$/AcOEt 6:2:1, affording pure **10b** (88.3 mg) and a 2.2:1 mixture of **10b** and a diastereoisomer of **10b** (10.1 mg). Chemical yield for **10b** 29.0%; de 93.7%. UV (EtOH): 249.3 (4.24). CD (MeOH): 263 (−4.61), 229 (5.65). IR (KBr): 1754, 1560, 1520, 1458, 1378, 1272, 1233, 1181, 1142, 1119, 1017, 802, 770, 702, 662. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.50–1.70 (*m*, *ca.* 8 H); 0.50 (*d*, *J* = 6.4, 3 H); 0.93 (*s*, 3 H); 1.13 (*s*, 3 H); 2.15 (*s*, 3 H); 2.20 (*s*, 3 H); 2.38–2.50 (*m*, 1 H); 2.81 (*s*, 3 H); 2.83 (*s*, 3 H); 3.53–3.66 (*m*, 1 H); 3.86 (*s*, 3 H); 3.90–4.00 (*m*, 1 H); 4.22–4.33 (*m*, 1 H); 4.53 (*s*, 1 H); 6.60 (*s*, 1 H); 7.09–7.50 (*m*, 9 arom. H).

4. *(1S,2R,5S)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2'R,3S)-1'-Acetyl-2-methylspiro[3H-indole-3,3'-pyrrolidine]-2'-carboxylate* (**10c**). The crude product obtained with AcCl was chromatographed on silica gel (17.5 g) with hexane/$CHCl_3$/AcOEt 2:2:1, affording pure **10c** (84 mg). Combined impure fractions (12 mg) were chromatographed with the same solvent system on a 0.5-mm silica-gel layer and gave a 1:1 mixture of **10c** and a diastereoisomer of **10c** (3.1 mg). Chemical yield for **10c** 35.1%, de 96.4%. UV (EtOH): 259.3 (3.65). CD (MeOH): 261 (−3.25), 230 (3.86), 212 (−7.92). IR (KBr): 1748, 1662, 1581, 1454, 1407, 1212, 1180, 769, 702. ^{1}H-NMR (400 MHz, (D_6)DMSO, mixture of rotamers *ca.* 4:1): 0.50–1.70 (*m*, *ca.* 8 H); 0.52 (*d*, J = 6.4, 3 H); 1.04 (*s*, *ca.* 0.6 H); 1.06 (*s*, *ca.* 2.4 H); 1.15 (*s*, *ca.* 0.6 H); 1.17 (*s*, *ca.* 2.4 H); 1.91 (*s*, *ca.* 0.6 H); 1.99 (*s*, *ca.* 2.4 H); 2.12 (*s*, *ca.* 0.6 H); 2.15 (*s*, *ca.* 2.4 H); 2.33–2.47 (*m*, 1 H); 3.88–4.25 (*m*, 3 H); 4.14 (*s*, *ca.* 0.8 H); 4.29 (*s*, *ca.* 0.2 H); 7.07–7.42 (*m*, 9 arom. H). On warming the soln. to 90°, doubling of the signals disappears. MS: 486 (6, $M^{+\cdot}$), 273 (54), 272 (28), 227 (100), 213 (36), 185 (86).

5. *(1S,2R,5S)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2'R,3S)-1'-Cyano-2-methylspiro[3H-indole-3,3'-pyrrolidine]-2'-carboxylate* (**10d**). The crude product obtained with BrCN was chromatographed on silica gel (35 mg) with hexane/$CHCl_3$/AcOEt 4:2:1, affording pure **10d** (95.7 mg) and a 10:1:1 mixture of **10d** with two diastereoisomers of **10d** (9.1 mg). Chemical yield for **10d** 44%, de 97.1%. UV (EtOH): 261.2 (3.65). CD (MeOH): 262 (−4.77), 232 (1.96), 207 (−9.07). IR (KBr): 2200, 1746, 1582, 1493, 1455, 1368, 1347, 1316, 1287, 1255, 1214, 1148, 770, 703. ^{1}H-NMR (400 MHz, $CDCl_3$): −0.02–0.10 (*m*, 1 H); 0.60 (*d*, J = 6.5, 3 H); 0.64–0.68 (*m*, 1 H); 0.94–*ca.* 1.1 (*m*, 2 H); 1.05 (*s*, 3 H); 1.19 (*s*, 3 H); 1.50–1.62 (*m*, *ca.* 2 H); 1.71–1.90 (*m*, 2 H); 2.06 (*s*, 3 H); 2.20–2.31 (*m*, 1 H); 3.09 (*s*, 1 H); 3.72–3.81 (*m*, 1 H); 3.89–3.98 (*m*, 1 H); 4.47–4.57 (*m*, 1 H); 7.10–7.47 (*m*, 9 arom. H). MS: 470 (100, $[M + 1]^+$), 391 (19).

6. *(1S,2R,5S)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2'R,3S)-2-Methyl-1'-{[(4-nitrobenzyl)-oxy]carbonyl}spiro[3H-indole-3,3'-pyrrolidine]-2'-carboxylate* (**10e**). The crude product obtained with [(4-nitrobenzyl)oxy]carbonyl chloride was chromatographed on silica gel (100 g) with hexane/$CHCl_3$/AcOEt 4:2:1, affording a 5.2:1 mixture of **10e** and (4-nitrophenyl)methanol (148.0 mg). Chemical yield of **10e** 124.1 mg, 39.8% de 95%. CD (MeOH)[4]: 263 (−3.87), 232 (7.71), 213 (7.24). ^{1}H-NMR (400 MHz, (D_6)DMSO, 363° K, only signals of **10e**): −0.25–−0.12 (*m*, 1 H); 0.11–0.21 (*m*, 1 H); 0.45–0.62 (*m*, 1 H); 0.55 (*d*, J = 7, 3 H); 0.67–1.17 (*m*, *ca.* 8 H); 1.30–1.42 (*m*, 2 H); 1.53–1.64 (*m*, 2 H); 2.11 (*s*, 3 H); 2.40–2.50 (*m*, 1 H); 3.77–3.88 (*m*, 1 H); 3.93–4.06 (*m*, 1 H); 4.20 (*s*, 1 H); 4.21–4.30 (*m*, 1 H); 5.27–5.39 (*m*, 2 H); 7.09–8.24 (*m*, 13 arom. H).

7. *[2-(Butanamido)benzyl]triphenylphosphonium Bromide* (**12**). Butanoyl chloride (2.1 ml, 20 mmol) was added dropwise to a stirred mixture of *(2-aminobenzyl)triphenylphosphonium bromide* (**11**) [4] (8.97 g, 20 mmol) and CH_2Cl_2 (50 ml). After 4 h, the solvent was evaporated and the residue recrystallized from H_2O/MeOH 1:2 (100 ml), affording **12** (5.05 g, 48.7%). Evaporation of the mother liquor and recrystallization of the residue gave an additional crop of **12** (2.44 g, 23.5%). ^{1}H-NMR (250 MHz, (D_6)DMSO): 0.80 (*t*, J = 7.4, 3 H); 1.38–1.44 (*m*, 2 H); 1.94 (*t*, J = 7.6, 2 H); 5.21 (*d*, J = 15, 2 H); 6.90–7.94 (*m*, 19 arom. H); 9.30 (*s*, 1 H).

8. *2-Propyl-1H-indole* (**13**)[5]. A soln. of sodium *tert*-pentylate (5 mmol) in toluene (7.5 ml) was added dropwise to an intensively stirred suspension of **12** (2.71 g, 5.2 mmol) in toluene (15 ml). The mixture was refluxed for 3 h, then cooled to r.t. and filtered. The filtrate was washed with H_2O and evaporated, the residue chromatographed on silica gel (110 g) with hexane/CH_2Cl_2/AcOEt 4:2:1, affording **13** (0.67 g, 80.9%) as a colorless oil. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.01 (*t*, J = 7.4, 3 H); 1.70–1.80 (*m*, 2 H); 2.73 (*t*, J = 7.3, 2 H); 6.24 (*s*, 1 H); 7.00–7.57 (*m*, 4 arom. H); 7.84 (br. *s*, 1 H).

9. *3-(2-Nitroethenyl)-2-propyl-1H-indole* (**14**). A soln. of **13** (670 mg, 4.2 mmol) in CH_2Cl_2 (5 ml) was added dropwise at 0° to a stirred soln. of *N,N*-dimethyl-2-nitroethyleneamine (490 mg, 4.2 mmol) and CF_3COOH (1 ml) in CH_2Cl_2 (5 ml). Stirring was continued for 2½ h at 0° and 15 h at r.t. The mixture was then evaporated. The soln. of the residue in CH_2Cl_2 was washed with 2N Na_2CO_3 and H_2O, filtered through silica gel (50 g), and evaporated. The residue was crystallized from AcOEt/CH_2Cl_2 affording **14** (380 mg, 39.3%). M.p. 166–168°. ^{1}H-NMR (250 MHz, (D_6)DMSO): 0.95 (*t*, J = 7.4, 3 H); 1.65–1.80 (*m*, 2 H); 2.96 (*t*, J = 7.6, 2 H); 7.16–7.90 (*m*, 4 arom. H); 7.94 (*d*, J = 13.2, 1 H); 8.32 (*d*, J = 13.2, 1 H); 12.22 (*s*, 1 H). Anal. calc. for $C_{13}H_{14}N_2O_2$ (230.27): C 67.81, H 6.13, N 12.17; found: C 67.39, H 6.15, N 12.09.

10. *3-(2-Nitroethyl)-2-propyl-1H-indole* (**15**). A mixture of **14** (1.0 g, 4.34 mmol), benzene (20 ml), and tris(triphenylphosphine)rhodium(I) chloride (*Fluka*; 100 mg) was stirred under H_2 (10 bar) at 55° for 18 h and then

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[4]) Calculated for pure **10e**.

[5]) This compound has been prepared before by various methods.

filtered and evaporated. The residue was chromatographed on silica gel (40 g) with hexane/$CHCl_3$/AcOEt 6:2:1, affording **15** (990 mg, 98.2%) as a yellowish viscous oil. A sample was crystallized from Et_2O/pentane. M.p. 65–66°. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.99 (*t*, *J* = 7.4, 3 H); 1.61–1.77 (*m*, 2 H); 2.72 (*t*, *J* = 7.5, 2 H); 3.45 (*t*, *J* = 7.5, 2 H); 4.49 (*t*, *J* = 7.5, 2 H); 7.07–7.52 (*m*, 4 arom. H); 7.79 (br. *s*, 1 H). Anal. calc. for $C_{13}H_{16}N_2O_2$ (232.28): C 67.22, H 6.94, N 12.0; found: C 67.29, H 7.02, N 12.10.

11. *2-Propyl-1*H*-indole-3-ethylamine* (**16**). A soln. of **15** (464.2 mg, 2 mmol) in MeOH (20 ml) was hydrogenated over Pd/C at 25° for 1½ h (150 ml of H_2, calc. 146.7 ml). The catalyst was removed by filtration under N_2, the filtrate evaporated, and the residue treated with benzene and again evaporated: crude **16** (*ca.* 100%), suitable for imine formation.

12. *(1*S*,2*R*,5*S*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2'*R*,3*S*)-2-Propyl-1'-(4-toluenesulfonyl)-spiro[3*H*-indole-3,3'-pyrrolidine]-2'-carboxylate* (**18**). A mixture of **16** (2 mmol), (1*S*,2*R*,5*S*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl glyoxylate [6] (588.2 mg, 2.04 mmol), CH_2Cl_2 (10 ml), and molecular sieves, was stirred for 26½ h at r.t. and then filtered. The residue was washed with CH_2Cl_2 (2 ml). To the combined solns., containing the imine **17**, first 2,4,6-trimethylpyridine (0.4 ml) was added and then, under stirring at –82 to –85°, dropwise a soln. of TsCl (380.9 mg, 2.0 mmol) in CH_2Cl_2 (2 ml). After 120 h, the mixture was treated with 0.5N citric acid (5 ml) and warmed up to r.t. The org. phase was washed with H_2O and evaporated. The residue was chromatographed on silica gel (140 g) with hexane/$CHCl_3$/AcOEt 6:2:1, affording a 89:3 mixture of **18** and a diastereoisomer of **18** (476.5 mg, 38.0%, de 93.5%). UV (EtOH): 268.5 (3.60). CD (MeOH): 268 (–2.10), 229 (2.72), 203 (7.3). IR (KBr): 1750, 1598, 1524, 1495, 1455, 1360, 1330, 1192, 1092, 1030. ^{1}H-NMR (400 MHz, $CDCl_3$): signals of **18** between 2.4 and 8.1 ppm at 2.48 (*s*, 3 H); 3.57–3.67 (*m*, 1 H); 3.92–3.99 (*m*, 1 H); 4.33 (*s*, NCHCO); 4.39–4.47 (*m*, 1 H); 7.08–8.03 (*m*, *ca.* 13 arom. H); *s* of NCHCO of the diastereoisomer at 4.12.

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