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A HIGHLY FLEXIBLE ROUTE TO 1,2,3,4,5,6-HEXAHYDRO-5-HYDROXYPYRIMIDIN-2-ONES AS POTENTIAL HIV PROTEASE INHIBITORS

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Abstract - The first asymmetric synthesis of potential HIV protease inhibitors of **type II**, **III** and **IV** is described. Key step of the synthesis is an auxiliary based stereoselective alkylation by means of the (*R*)-1-amino-2-methoxymethyl-pyrrolidine (RAMP)- / (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP)-hydrazone method starting from a readily available key building block, pyrimidin-2,5-dione (**6**). The synthesis is short and highly versatile in the choice of the substitution pattern as well as the absolute configuration of the alkylated 1,2,3,4,5,6-Hexahydro-5-hydroxypyrimidin-2-ones.

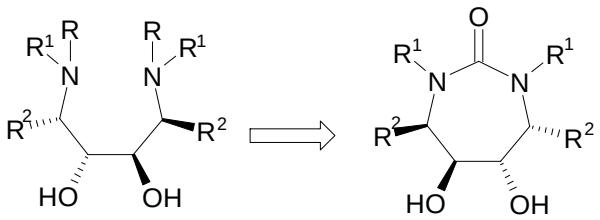
Introduction

HIV-1 infects millions of people worldwide to cause the lethal disease Accquired Immune Deficiency Syndrome (AIDS).[1, 2] An asymptomatic period precedes AIDS in which the immune system becomes progressively compromised and unable to fight opportunistic infections and certain cancers. To inhibit HIV-1 replication and slow down the destruction of the immune system, current therapies utilize a combination of protease and reverse transcriptase inhibitors.

The HIV protease belongs to the class of aspartate proteases, which cleaves the *gag*- and *gagpol* polyproteins (encoded by the *pol*- gene of the virus) into structural and functional proteins, which in turn are required for function of the mature virus.[3] Currently several FDA approved HIV protease inhibitors[4] are on the market, such as Saquinavir[5] (Hofmann-La Roche), Nelfinavir[6] (Agouron), Amprenavir[7] (Glaxo Wellcome), Indinavir[8] (Merck Research), Ritonavir[9] (Abbott) and Lopinavir[10] (Abbott). While suppression of viral replication through combination therapy delays progression to AIDS the HI virus

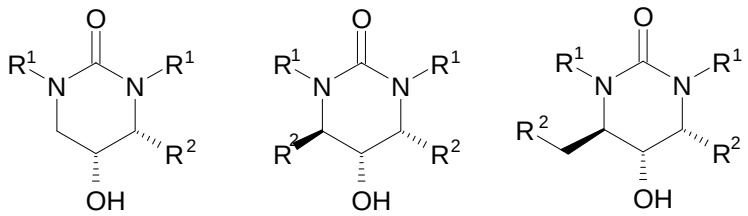
rapidly develops resistance against new drug molecules. Therefore there is an ongoing need for new chemical entities in this area.[11]

All HIV protease inhibitors of the first generation contained typical peptidomimetic structure elements. Coworkers of the *Merck Dupont* company could demonstrate that not only the acyclic molecules depicted in **Scheme 1** were excellent HIV protease inhibitors but also their corresponding cyclic analogues of **type I** if all stereogenic centers were inverted at the same time.[12, 13]



Scheme 1

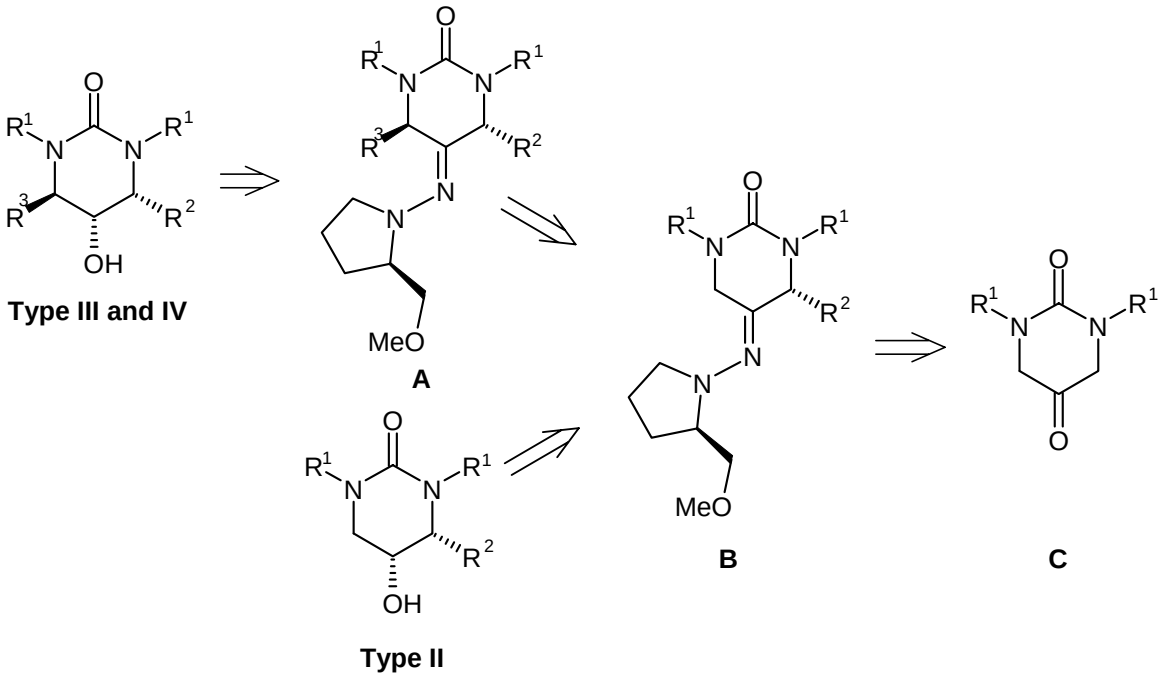
According to the C_2-symmetry of the HIV protease active site **type I** inhibitors retain the same symmetry. It was shown that the trans diaxial position of both substituents R^2 was not only the preferred conformation of the free molecule but also crucial for good enzyme inhibition.



Scheme 2

Investigation of the influence of different ring sizes resulted in HIV protease inhibitors of **type II**, **III** and **IV** (**Scheme 2**).[14] As expected in the six membered ring case the residues R^2 cannot be arranged in a *trans* diaxial manner and therefore are responsible for the low affinity to the HIV protease. However it was possible to nearly retain potency by simply introducing an additional methylene group on one of the two R^2 groups (**type IV** inhibitors). This additional CH_2 group functions as a joint to turn R^2 into a pseudoaxial position.

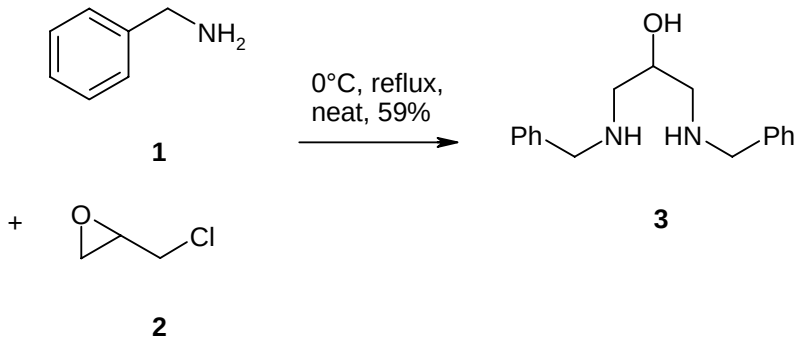
Retrosynthesis: Our retrosynthetic plan was to synthesize inhibitors of **type II**, **III** and **IV** using one mutual key building block as starting material (**Scheme 3**).



Scheme 3

It was desired that our synthesis should be short, efficient and allow a high flexibility in the choice of the residues R^1 and R^2 as well as free choice of the absolute configuration. Based on our investigations in the area of asymmetric alkylations of dioxanones[15, 16] we considered the RAMP-/SAMP-hydrazone method[17] to suit well for a stereoselective alkylation of ketone **C** leading after removal of the auxiliary and subsequent reduction of the ketone to compounds of **type II**, **III** or **IV**.

Results and Discussion

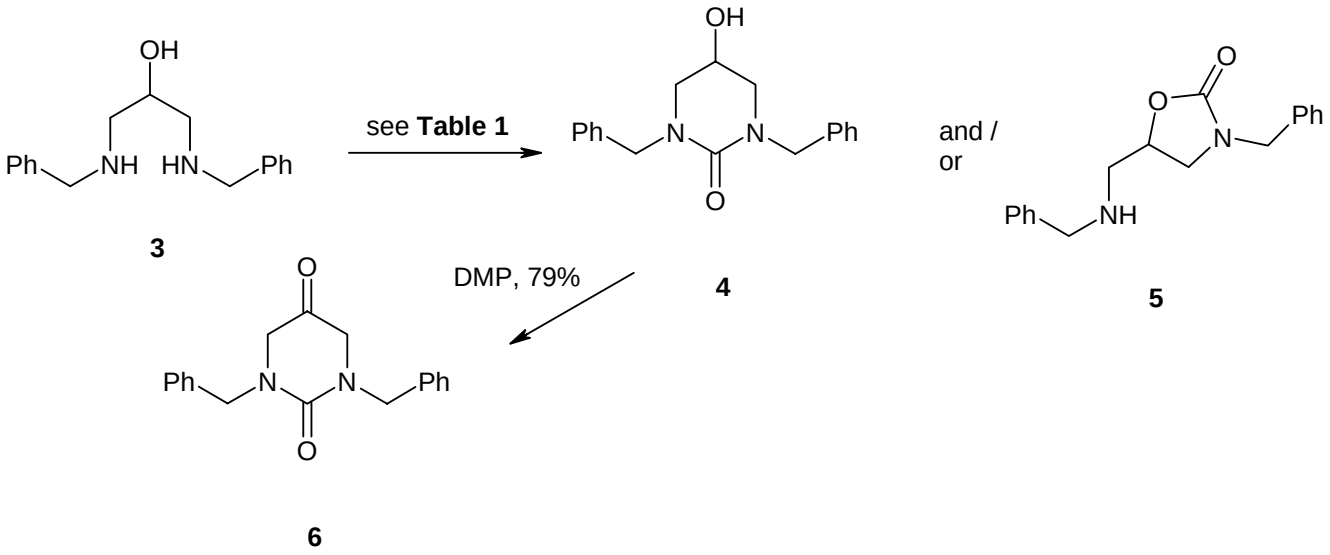


Scheme 4

The synthesis of the achiral key building block (**6**)[18] starts from readily available materials such as a primary amine and epichlorohydrine (**2**) (**Scheme 4**). With the choice of **1** as primary amine residue R^1

is determined. Diamino alcohol (**3**) could be easily synthesized in one step and purified by recrystallization of the corresponding hydrochloride salt.

The cyclization of **3** with a phosgene equivalent provided mixtures of the thermodynamically controlled product (**4**) and the kinetically controlled product (**5**) (**Scheme 5**) in favor of the latter.



Scheme 5

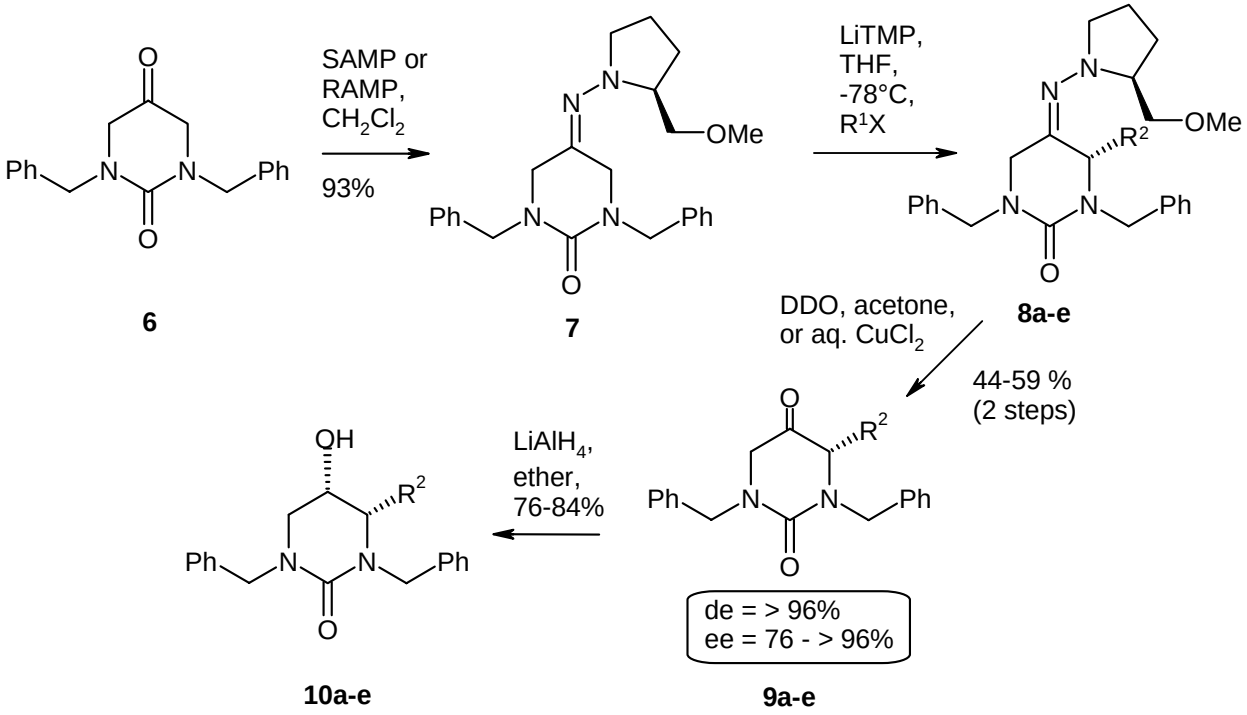
Several reaction conditions were applied in order to reverse the selectivity towards the desired six memberd urea (**4**), some of which are depicted in **Table 1**. According to the literature no solution of similar cyclization problems are described.[19] In our case only bis(4-nitrophenyl) carbonate as phosgene equivalent provided the desired urea (**4**) as single isomer in excellent yield. The purification of **4** is simple and does not require a chromatography. Basic extraction removes the 4-nitrophenol by-product and crystallization of the crude mixture gives rise to the alcohol (**4**) which is available in multigram quantities.

Table 1

Reaction Conditions	**Compounds detected**
Triphosgene, K_2CO_3, CH_2Cl_2, 0°C	**4** + **5**
Diphosgene, K_2CO_3, toluene, 0°C	**4** + **5**
CDI, CH_2Cl_2, 0°C	**4** + **5**
Diphenyl carbonate, CH_2Cl_2, reflux	No reaction
Bis(4-Nitrophenyl) carbonate, CH_2Cl_2, reflux	Only **4**

Subsequent oxidation of **4** with the *Dess-Martin* periodinane finishes the synthesis of our key building block (**6**) (**Scheme 5**).

By simply stirring dione (**6**) with RAMP or SAMP, the corresponding chiral hydrazones (**7**) could be obtained in excellent yield (**Scheme 6**). By choice of the alkyl halide as electrophile in the auxiliary directed aza-enolate alkylation, the residue R^2 is introduced.



Scheme 6

X-Ray structure analysis[20] of the allylated (*Z*)-configured SAMP-hydrazone (**8c**) confirmed the configuration at the newly formed stereogenic center, with the sense of asymmetric induction assenting to our SAMP/RAMP alkylation model (**Figure 1**).

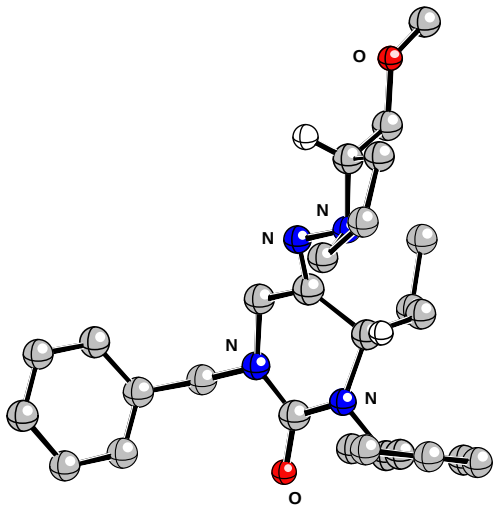


Figure 1

Without further purification the alkylated hydrazones (**8a-e**) were directly cleaved to the corresponding ketones (**9a-e**). The numerous reagents suitable for recovery of carbonyl compounds from dialkylhydrazones were reviewed recently.[21] The best overall yields were obtained when according to a hydrazone cleavage method published by *Curci* dimethyldioxirane (DDO) in acetone solution was used.[22] Slightly lower yield of ketones (**9a-e**) were obtained when an aqueous $CuCl_2$ was used. After column chromatography on silica gel, the alkylated ketones (**9a-e**) were reduced with $LiAlH_4$ to the desired *cis*-configured alcohols (**10a-e**) representing the desired potential HIV protease inhibitors of **type II**. The relative configuration was confirmed by an X-Ray structure analysis[23, 24] of alcohol (**10c**) (**Figure 2**).

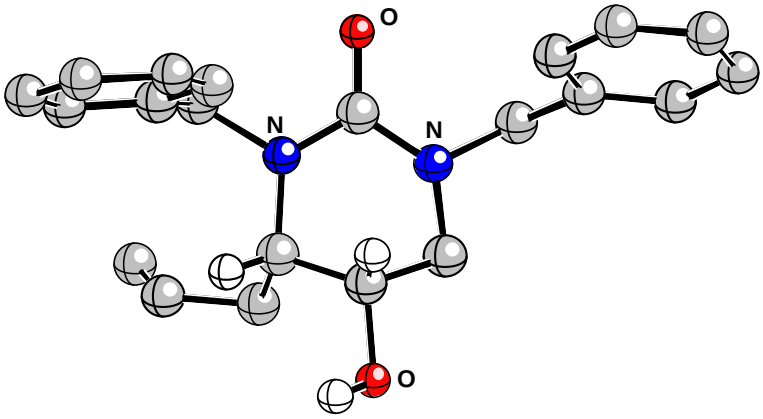


Figure 2

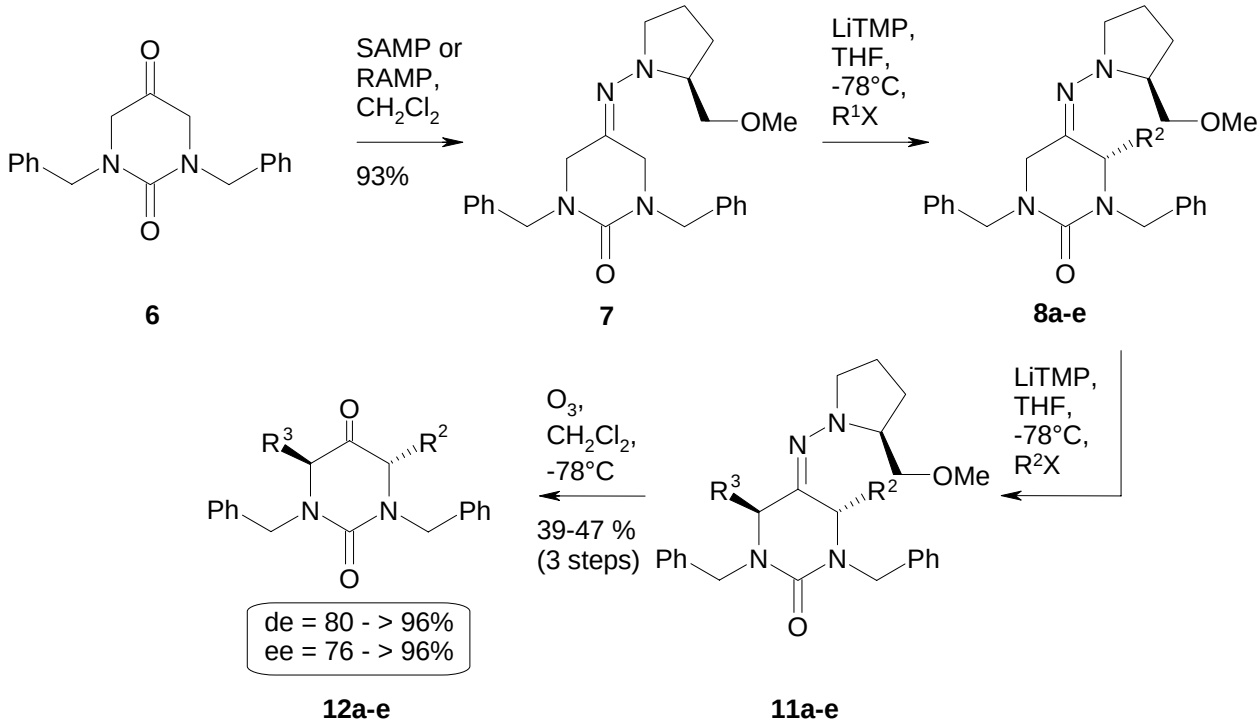
The diastereomeric excess of the $LiAlH_4$-reduction to the *cis*-alcohols (**10a-e**) was determined by ^{1}H-NMR spectroscopy (**Table 2)**. The enantiomeric excess of the alcohols (**10a-e**) was determined by ^{1}H-NMR spectrometry using Pirkle alcohol as shift reagent.

Table 2

10	**R^2**	**de [%]**	**ee [%]**
10a	Me	≥ 96	76
10b	n-Bu	≥ 96	≥ 96
10c	Allyl	≥ 96	80
10d	$PhCH_2$	≥ 96	76
10e	$PhCH_2CH_2$	≥ 96	86

The synthesis of inhibitors of **types III** and **IV** was carried out in a similar manner as the synthesis of **type II** inhibitors.[25] The monoalkylated hydrazones (**8a-e**) were subjected to a second alkylation to give rise to hydrazones (**11a-e**) (**Scheme 7**). The diastereomeric excess of the second alkylation could not be determined on this step as one abtains a mixture of the (*E*)- and the (*Z*)-configured hydrazone (**11a-e**). Attempts to alkylate **7** directly with two equivalents of base and electrophile failed and gave complex

mixtures of products. In case of the double alkylated hydrazones (**11a-e**) ozonolysis worked out as the best method to recover the ketones (**12a-e**)**.**



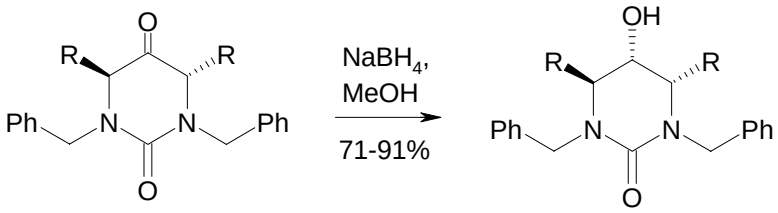
Scheme 7

Table 3

12	R^2	R^3	Electrophile	Yield over 3 steps [%]	de [%]	ee [%]
12a	i-Pr	i-Pr	i-PrI	43	>96	86
12b	n-Bu	n-Bu	n-BuI	39	>96	>96
12c	Bn	Bn	BnBr	40	>96	76
12d	$PhCH_2CH_2$	$PhCH_2CH_2$	$PhCH_2CH_2I$	47	>96	86
12e	Bn	$PhCH_2CH_2$	$BnBr/PhCH_2CH_2I$	34	80	76

The diastereomeric excess (de) of **12** was determined by ^{1}H-NMR spectrum and lies in the range of 80- > 96 % (**Table 3**). The enantiomeric excess (ee) was determined by ^{1}H-NMR-shift experiments with *(-)-Pirkle* alcohol.

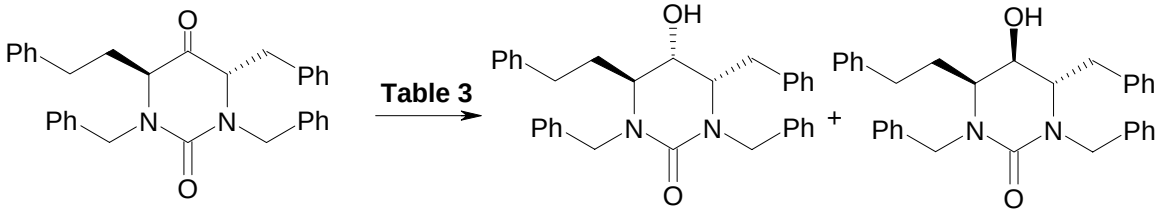
Because no new stereogenic center is formed the C_2-symmetrical ketones (**12a-d**) could be transformed into their corresponding alcohols (**13a-d**) using standard sodium borohydride reduction (**Scheme 8**) and thus completing the synthesis of potential **type III** HIV protease inhibitors.



12a-d **13a-d**

Scheme 8

The reduction of the unsymmetrical ketones such as **12e** (**Scheme 9**) leads to a new stereogenic center. As the benzyl and the phenylethyl residues in **12e** have similar bulk it was ambitious to find an appropriate reduction reagent leading to high diastereoselection.



12e **14** **15**

The reagents which were examined for the diastereoselective reduction of **12e** leading to the two diastereomeric alcohols (**14** and **15**) are listed in **Table 4**.

Table 4

Reaction conditions	**Diastereomeric Ratio 14 : 15**
$LiAlH_4$, Ether, 0 °C[26]	1 : 2
$NaBH_4$, MeOH, 0 °C[27]	1 : 2
(*L*)-Selectride, THF, -78 °C to rt[28]	only **15**
Superhydride, THF, Ether, -78 °C to rt[29]	1 : 8.7
Catecholborane, Ether, -78 °C to rt[30]	1.5 : 1
BH_3-SMe_2, THF, Ether, rt[31]	1.6 : 1

The best diastereomeric excess was observed with (*L*)-Selectride as reduction agent in favour of diasteomer (**15**). An inversion of selectivity was observed with borane reagents, however the diastereomeric ratio was not very high. The relative stereochemistry could be elaborated by comparison with literature data.[32] Thus, the asymmetric synthesis of inhibitors of **type IV** was completed.

Conclusion

The first asymmetric synthesis of potential HIV protease inhibitors of **types II**, **III** and **IV** is described. Key step of the synthesis is an auxiliary based stereoselective alkylation by means of the RAMP- /SAMP-

hydrazone method starting from a readily available key building block (**6**). The synthesis is short and highly versatile in the choice of the substitution pattern as well as the absolute configuration of products.

EXPERIMENTAL

Synthesis of Diamino alcohol (**3**):

Benzylamine (**1**) (120 mL, 1.1 mol) was cooled to 0 °C and epichlorohydrine **2** (20 mL, 0.31 mol) were added. The reaction was stirred for 5 h at 0 °C and then refluxed for 4 h. After cooling the reaction a colorless solid precipitated. Aqueous NaOH (1 M) was added until the precipitate disappeared. After extraction with CH_2Cl_2 the solvent and benzylamine were removed by destillation. The mixture was dissolved in EtOH, then crystallised as the hydrochloride salt by addition of conc. HCl (aq) and recrystallised from EtOH. The colorless solid was stirred with NaOH (2 M), extracted with ether, dried over $MgSO_4$ and evaporated. **3** was isolated in 59 % yield (175.2 g) as yellow oil wich solidified after standing (mp = 45 °C).^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 2.53 (3H, br s), 2.58 (2H, dd, ^2J = 12.1, ^3J = 8.0) 2.69 (2H, dd, ^2J = 12.1, ^3J = 3.7, 3.76 (4H, d, J = 3.0), 3.78 (1H, m), 7.30 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 53.1, 53.9 68.6, 127.2, 128.2, 128.5, 140.1; IR (KBr) (cm^{-1}) 3306, 3107, 3085, 3062, 3027, 2905, 2831, 1603, 1585, 1547, 1495, 1453, 1384, 1357, 1199, 1117, 1074, 1029, 1003, 972, 908, 868, 826, 738, 699, 601, 470; MS (EI, 70 eV, 80°C) *m/z* 150 (10.2 %), 146 (13.6 %), 145 (39.0 %), 134 (7.5 %), 121 (2.2 %), 120 (21.7 %), 119 (5.2 %), 107 (7.9 %), 106 (17.4 %), 92 (100 %), 65 (7.9%); MS (CI, 70 eV) *m/z* 273 (2.0 %), 272 (20.1 %), 271 (100 %), 270 (1.3 %), 269 (2.7 %), 145 (3.6 %). *Anal.* Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.19, H, 8.43; N, 10.28.

Synthesis of the Alcohol (**4**):

Bis(4-nitrophenyl) carbonate (10 g, 32.87 mmol) and diamino alcohol (**3**) (15 g, 55.56 mmol) were refluxed in CH_2Cl_2 (2.5 L) for 24 h. The reaction mixture was washed once with sat. citric acid and five times with NaOH (2M). After evaporation the product was recrystallised from ether and CH_2Cl_2. **4** was isolated in 85 % yield (8.3 g) as a colorless solid. mp=115°C. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 2.24 (1H, s), 3.15 (2H, dd, ^2J = 11.8, ^3J =4.0), 3.34 (2H, dd, ^2J = 11.8, ^3J = 3.4), 4.03 (1H, m), 4.53 (2H, d, J = 14.8), 4.67 (2H, d, J = 14.8), 7.30 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 51.7, 51.8, 62.0, 127.5, 128.1, 128.7, 138.1, 155.9; IR (KBr) (cm^{-1}) 3316, 3084, 3062, 3023, 2915, 2856, 1619, 1603, 1583, 1528, 1496, 1471, 1453, 1444, 1422, 1396, 1363, 1329, 1314, 1297, 1259, 1228, 1219, 1200, 1181, 1112, 1078, 1056, 1030, 981, 958, 840, 764, 748, 729, 698, 658, 621, 606, 554, 532, 476, 453; MS (EI, 70 eV, 100°C) *m/z* 297 (7.0 %), 295 (42.9 %), 294 (1.8 %), 204 (17.6 %), 144 (4.6 %), 132 (11.3 %), 120 (9.4 %), 118 (12.0 %), 106 (6.1 %), 105 (5.7 %), 104 (11.4 %), 92 (8.4 %), 91 (100 %), 90 (2.5 %), 89 (3.4 %), 77 (5.4

%)65 (9.9 %). MS (CI, 70 eV) *m/z* 299 (3.0 %), 298 (25.0 %), 297 (65 %), 296 (100 %). *Anal.* Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.64, H, 6.63; N, 9.36.

Synthesis of the Ketone (**6**):

Alcohol (**4)** (11.5 g, 38.85 mmol) and the freshly prepared *Dess-Martin* reagent (24.7 g, 58.28 mmol, 1.5 eq) were stirred overnight in CH_2Cl_2 (100 mL) saturated with water (TLC-control). The reaction was quenched by addition of saturated $NaHCO_3$ (aq.) and $Na_2S_2O_3$ (aq.) and stirred until the precipitate completely dissolved. After extraction with CH_2Cl_2, drying over $MgSO_4$ and evaporation the crude product was filtered through a short column of silica (ether : pentane 1 : 1). Ketone (**6**) was isolated as a yellow oil in 79% (9.0 g), which crystallized after some time. mp = 73 °C. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 3.69 (4H, s), 4.59 (4H, s), 7.30 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 51.8, 55.6, 128.4, 129.0, 129.4, 137.2, 158.7, 202.0; IR (KBr) (cm^{-1}) 3086, 3063, 3030, 3005, 2919, 2864, 1743, 1651, 1585, 1495, 1454, 1437, 1408, 1358, 1289, 1230, 1178, 1155, 1079, 1030, 961, 911, 883, 733, 702, 649, 608, 489, 456; MS (EI, 70 eV, 70°C) *m/z* 296 (1.7 %), 295 (13.2 %), 294 (80.1 %), 293 (3.1 %), 276 (2.4 %), 275 (7.2 %), 203 (13.6 %), 189 (4.1 %), 176 (3.7 %), 175 (38.6 %), 132 (18.2 %), 118 (12.8 %), 106 (12.9 %), 104 (7.5 %), 92 (8.1 %), 91 (100 %), 65 (15.4 %). MS (CI, 70 eV) *m/z* 296 (14.4 %), 295 (100 %), 294 (1.1 %). *Anal.* Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 72.64, H, 5.90; N, 9.39.

Synthesis of the Hydrazone (**7**):

Ketone (**6**) (9 g, 30.61 mmol) and SAMP or RAMP (4.48 mL, 33.67 mmol, 1.1 eq.) were dissolved in CH_2Cl_2 (150 mL) and stirred for 5 h at rt with molecular sieves (3 Å) (2 g). After filtration and evaporation of the solvent the crude product was filtered through a short column of silica (ether). **7** was isolated in 93% yield (11.6 g) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 1.59 (1H, m), 1.76 (2H, m), 1.93 (1H, m), 2.36 (1H, q, *J* = 7.97), 2.94 (1H, m), 3.18 (2H, m), 3.27 (3H, s), 3.30 (1H, m), 3.77 (1H, d, *J* = 17.85), 3.80 (2H, s), 4.06 (1H, d, *J* = 17.31), 4.43 (1H, d, *J* = 15.11), 4.57 (1H, d, *J* = 14.83), 4.67 (1H, d, *J* = 14.83), 4.78 (1H, d, *J* = 15.11), 7.33 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 23.2, 27.2, 48.0, 50.9, 51.9, 52.0, 55.3, 59.7, 67.3, 75.8, 128.0, 128.0, 128.7, 128.9, 129.1, 129.2, 138.0, 138.1, 154.8, 158.6; IR (neat) (cm^{-1}) 3086, 3063, 3029, 2973, 2923, 2875, 2243, 1645, 1586, 1497, 1454, 1428, 1384, 1358, 1304, 1239, 1202, 1179, 1107, 1078, 1030, 1002, 962, 911, 733, 703, 646, 610; MS (EI, 70 eV, 90°C) *m/z* 406 (11.8 %), 362 (5.3 %), 361 (28.3 %), 293 (6.3 %), 292 (13.2 %), 291 (6.1 %), 251 (6.1 %), 200 (9.3 %), 175 (9.9 %), 159 (9.4 %), 132 (8.6 %), 128 (6.4 %), 118 (4.4 %), 114 (5.1 %), 92 (7.3 %), 91 (100 %), 70 (11.2 %), 65 (4.9 %). High Resol. MS Calcd for $C_{24}H_{30}N_4O_2$: 406.236876. Found: 406.236794.

General procedure I for the synthesis of the alkylated hydrazones (**8a-e**) (1-3 mmol-scale):
TMP (1.3 eq.) was dissolved in dry THF (20 mL) in a pre-dried Schlenk-flask under argon and *n*BuLi-solution (1.2 eq. of a 1.6 M solution in hexane) was added. The pale yellow solution was stirred for 10 min at rt and then cooled to –78 °C. A solution of the hydrazone (**7**) (1eq., -78 °C) in THF (20 mL) was added slowly via a double ended needle. After stirring for 10 min at –78 °C a solution of the electrophile in THF (5 mL) was added with a syringe pump (5 mL / h), stirred for a further 2 more h at –78 °C and then quenched with sat. NH_4Cl. After extraction with ether and drying over $MgSO_4$ the solvent was removed. The crude hydrazones were used directly in the following hydrazone cleavage reactions.

General procedure II for the synthesis of the alkylated ketones (**9a-e**) (Method A):
The alkylated hydrazones (**8a-e**) were dissolved in acetone (20 mL) and water (5 mL). A 0.1 M solution of dimethyldioxirane (5 eq.) in acetone were added and stirred overnight (TLC-control). After addition of water, the reaction mixture was extracted with ether and dried over $MgSO_4$ and the solvent was removed. The product was purified by chromatography on silica (ether : pentane 1:3) to afford the ketones (**9a-e**) in 44-59% yield.

General procedure III for the synthesis of the alkylated ketones (**9a-e**) (Method B):
The alkylated hydrazones (**8a-e**) were dissolved in THF (5 mL) and water (1 mL). $CuCl_2$(5 eq.) was added and stirred overnight (TLC-control). After addition of water, the reaction mixture was extracted with ether, dried over $MgSO_4$ and the solvent removed. The product was purified by chromatography on silica (ether : pentane 1:3).

Ketone (**9a**) was prepared according to the general precedures I-III. Yields over two steps: Method A: 53 %; Method B: 50%. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 1.18 (3H, d, J = 7.05), 3.62 (3H, m), 4.08 (1H, d, J = 15.11), 4.38 (1H, d, J = 14.77), 4.67 (1H, d, J = 14.77), 5.02 (1H, d, J = 15.11), 7.24 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 15.6, 49.0, 51.1, 53.9, 60.0, 127.8, 127.9, 128.2, 128.5, 128.9, 128.9, 136.8, 137.4, 157.6, 203.8; IR (neat) (cm^{-1}) 3086, 3063, 3030, 2977, 2927, 2869, 1741, 1713, 1656, 1605, 1586, 1495, 1479, 1452, 1417, 1358, 1332, 1262, 1232, 1178, 1155, 1079, 1029, 1003, 974, 912, 734, 702, 649, 607, 457; MS (EI, 70 eV, 150°C) *m/z* 309 (10.9 %), 308 (50.11 %), 281 (5.3 %), 280 (30.5 %), 275 (8.1 %), 265 (20 %), 189 (32.5 %), 149 (6.1 %), 146 (4.5 %), 132 (15.4 %), 120 (10.9 %), 118 (12.0 %), 106 (15.9 %), 104 (8.3 %), 92 (10.2 %), 91 (100 %), 70 (4.9 %), 65 (10.1 %), 57 (6.1 %), 56 (5.7 %), 55 (5.1 %); MS (CI, 70 eV) *m/z* 310 (19.8 %), 309 (100 %), 308 (5.0 %), 283 (10.7 %), 282 (4.1 %), 281 (20.8 %), 269 (8.1 %). *Anal.* Calcd for $C_{19}H_{20}N_2O_2$: C, 74.03; H, 6.49; N, 9.09. Found: C, 73.81, H, 6.51; N, 9.33.

Ketone (**9b**) was prepared according to the general precedures I-III. Yields over two steps: Method A: 59 %; Method B: 52 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 0.84 (3H, m), 1.22 (4H, m), 1.68 (2H, m), 3.58 (1H, dd, ^{3}J = 6.38, ^{3}J = 3.70), 3.68 (2H, d, J = 8.39), 4.09 (1H, d, J = 15.11), 4.40 (1H, d, J = 14.77), 4.77 (1H, d, J = 5.19 (1H, d, J = 15.11), 7.30 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 14.4, 23.0, 27.6, 30.7, 50.2, 51.5, 54.6, 64.9, 128.3, 128.4, 128.7, 129.1, 129.4, 129.4, 137.4, 138.0, 158.1, 203.5; IR (solution in $CDCl_3$) (cm^{-1}) 3087, 3064, 3031, 3008, 2958, 2932, 2872, 1740, 1714, 1651, 1606, 1586, 1495, 1479, 1453, 1382, 1358, 1304, 1263, 1230, 1177, 1157, 1114, 1079, 1030, 1003, 968, 821, 754, 702, 666, 644, 613, 567, 492, 457; MS (EI, 70 eV, 120°C) *m/z* 351 (10.6 %), 350 (39.6 %), 294 (10.6 %), 293 (4.4 %), 266 (12.3 %), 265 (60.8 %), 231 (7.1 %), 203 (7.5 %), 132 (10.4 %), 106 (9.4 %), 92 (8.8 %), 91 (100 %), 65 (10.6 %); MS (CI, 70 eV) *m/z* 352 (24.4 %), 351 (100 %), 350 (7.5 %), 297 (7.4 %), 295 (18.5 %), 281 (9.7 %), 270 (8.1 %), 269 (44.8 %), 176 (9.2 %), 136 (19.3 %), 120 (6.4 %). *Anal.* Calcd for $C_{22}H_{26}N_2O_2$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.87, H, 7.35; N, 8.01.

Ketone (**9c**) was prepared according to the general precedures I-III. Yields over two steps: Method A: 44 %; Method B: 46 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 2.42 (2H, t, J = 6.72), 3.58 (1H, d, J = 18.80), 3.66 (1H, m), 3.68 (1H, d, J = 18.00), 4.13 (1H, d, J = 15.11), 4.38 (1H, d, J = 14.77), 4.67 (1H, d, J = 14.44), 4.98 (2H, m), 5.15 (1H, d, J = 15.11), 5.60 (1H, m), 7.28 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 35.5, 49.7, 51.1, 54.3, 64.3, 119.6, 127.8, 127.9, 128.2, 128.6, 128.8, 128.9, 131.8, 136.8, 137.5, 157.3, 202.1; IR (solution in $CDCl_3$) (cm^{-1}) 3310, 3064, 3031, 3006, 2978, 2925, 2858, 1739, 1713, 1651, 1606, 1586, 1495, 1479, 1453, 1419, 1385, 1358, 1335, 1287, 1231, 1178, 1156, 1113, 1078, 1030, 995, 923, 821, 751, 734, 702, 648, 620, 608, 488, 456; MS (EI, 70 eV, 70°C) *m/z* 334 (5.2 %), 294 (9.1 %), 293 (46.6 %), 92 (9.3 %), 91 (100 %), 65 (9.0 %); MS (CI, 70 eV) *m/z* 337 (5.1 %), 336 (22.7 %), 335 (100 %), 334 (3.2 %), 321 (7.8 %), 269 (9.7 %). High Resol. MS Calcd for $C_{21}H_{22}N_2O_2$: 334.168128. Found: 334.168271.

Ketone (**9d**) was prepared according to the general precedures I-III. Yields over two steps: Method A: 57 %; Method B: 51 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 2.87 (2H, d, J = 6.32), 3.34 (1H, d, J = 18.97), 3.52 (1H, dd, ^{2}J = 18.96, ^{3}J = 0.82), 3.64 (1H, d, J = 15.11), 3.74 (1H, t, J = 6.05), 4.21 (1H, d, J = 14.84), 4.25 (1H, d, J = 14.85), 5.08 (1H, d, J = 15.12), 6.95-7.22 (15H); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 37.0, 49.7, 51.0, 54.2, 65.6, 127.5, 127.9, 127.9, 128.3, 128.5, 128.7, 128.9, 129.0, 129.6, 135.7, 136.8, 137.2, 157.2, 202.5; IR (solution in $CDCl_3$) (cm^{-1}) 3311, 3108, 3087, 3063, 3030, 3006, 2929, 2870, 1740, 1712, 1651, 1606, 1586, 1495, 1479, 1454, 1384, 1359, 1257, 1230, 1181, 1157, 1079, 1030, 1004, 962, 911, 735, 701, 674, 648, 620, 607, 569, 508, 490; MS (EI, 70 eV, 130°C) *m/z* 384 (5.5 %), 293

(14.1 %), 92 (7.7 %), 91 (100 %), 74 (31.5 %), 65 (9.8 %), 59 (29.6 %), 45 (19.6 %); MS (CI, 70 eV) *m/z* 386 (17.5 %), 385 (63.4 %), 384 (5.4 %), 371 (6.5 %), 295 (4.9 %), 270 (4.4 %), 269 (25.3 %), 210 (14.9 %), 192 (11.4 %), 190 (10.4 %), 137 (13.3 %), 136 (100 %), 133 (4.1 %), 117 (43.3 %), 107 (6.1 %). *Anal.* Calcd for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.28. Found: C, 78.12, H, 6.51; N, 7.28.

Keton (**9e**) was prepared according to the general precedures I-III. Yields ober two steps: Method A: 56 %; Method B: 56 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 1.86 (2H, m), 2.35 (1H, m), 2.49 (1H, m), 3.47 (1H, m), 3.54 (2H, d, *J* = 7.05), 3.93 (1H, d, *J* = 15.11), 4.30 (1H, d, *J* = 14.77), 4.58 (1H, d, *J* = 14.77), 4.95 (1H, d, *J* = 14.77), 7.10 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 31.1, 31.9, 49.6, 51.1, 54.1, 63.4, 126.5, 127.8, 127.9, 128.2, 128.3, 128.6, 128.7, 128.9, 128.9, 136.8, 137.2, 140.2, 157.6, 202.7; IR (solution in $CDCl_3$) (cm^{-1}) 3086, 3062, 3029, 2928, 2864, 1737, 1713, 1651, 1586, 1495, 1480, 1453, 1384, 1358, 1231, 1180, 1156, 1077, 1030, 1003, 959, 909, 820, 751, 701, 667, 607, 566, 490, 457; MS (EI, 70 eV, 90°C) *m/z* 399 (3.2 %), 398 (10.3 %), 294 (15.4 %), 280 (6.9 %), 266 (5.8 %), 265 (27.9 %), 203 (10.3 %), 175 (4.7 %), 106 (5.9 %), 92 (8.9 %), 91 (100 %), 65 (9.1 %); MS (CI, 70 eV) *m/z* 401 (5.1 %), 400 (26.7 %), 399 (100 %), 398 (6.3 %), 397 (4.1 %), 385 (6.9 %), 301 (5.6 %). *Anal.* Calcd for $C_{26}H_{26}N_2O_2$: C, 78.39; H, 6.53; N, 7.04. Found: C, 77.85, H, 6.34; N, 7.10.

General procedure IV for the synthesis of the alkylated alcohols (**10a-e**):
A solution of ketone **9a-e** in THF (10 mL) was added to a suspension of $LiAlH_4$ (3 eq.) in dry ether (10 mL) at 0 °C. The reaction mixture was stirred for 1 h (TLC-control) at 0°C and then quenched with sat. NH_4Cl, filtered and washed with CH_2Cl_2, dried over $MgSO_4$ and the solvent removed. The pure alcohols (**10a-e**) were obtained after column chromatography on silica (ether:pentane 1:1) in 76-84% yield. The de of the reduction was in all cases ≥ 96 % (^{1}H-NMR spectrum). The enantioselectivities were determined with (-)-Pirkle-^{1}H-NMR-shift experiments (ee = 76 %).

Alcohol (**10a**) was prepared according to the general precedure IV. Yield: 76 %. The de of the reduction was ≥ 96 % (^{1}H-NMR spectrum). The enantioselectivities were determined with (-)-Pirkle-^{1}H-NMR-shift experiments: ee = 76 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 1.05 (3H, d, *J* = 6.6), 2.12 (s, 1H), 3.06 (1H, dd, ^2J = 11.55, ^3J = 8.52), 3.11 (1H, ddd, ^2J = 11.27, ^3J = 5.22, ^4J = 0.82), 3.29 (1H, m), 3.91 (1H, m), 3.94 (1H, d, *J* = 15.39),, 4.46 (1H, d, *J* = 14.85), 4.53 (1H, d, *J* = 14.85), 5.13 (1H, d, *J* = 15.40), 7.22 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 13.0, 48.2, 49.0, 51.7, 53.6, 64.9, 127.3, 127.4, 127.8, 128.0, 128.6, 128.7, 138.1, 138.8, 155.7; IR (neat) (cm^{-1}) 3314, 3108, 3086, 3065, 3030, 3005, 2956, 2930, 2873, 2859, 2245, 1949, 1604, 1505, 1468, 1453, 1381, 1354, 1305, 1254, 1215, 1160, 1126, 1093, 1077, 1050, 1030, 1002, 967, 910, 810, 734, 759, 701, 674, 648, 606, 565, 511, 487, 457; MS (CI, 70 eV)

m/z 311 (2.1 %), 310 (100 %), 309 (2.0 %). *Anal.* Calcd for $C_{19}H_{22}N_2O_2$: C, 73.55; H, 7.10; N, 9.03. Found: C, 73.60, H, 7.37 N, 9.05.

Alcohol (**10b**) was prepared according to the general precedure IV. Yield: 80 %. The de of the reduction was ≥ 96 % (^{1}H-NMR spectrum). The enantioselectivities were determined with (-)-Pirkle-^{1}H-NMR-shift experiments: ee ≥ 96 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 0.80 (3H, t, *J* = 7.14), 1.23 (2H, m), 1.39 (1H, m), 1.55 (1H, m), 2.16 (1H, d, *J* = 4.67), 3.02 (1H, dd, ^2J = 11.54, ^3J = 8.79), 3.10 (2H, m), 3.84 (1H, d, ^2J = 15.38), 3.86 (1H, m), 4.42 (1H, d, *J* = 14.83), 4.53 (1H, d, *J* = 14.84), 5.29 (1H, d, *J* = 15.38), 7.23 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 14.5, 23.6, 28.8, 29.6, 49.3, 50.8, 52.1, 58.5, 65.0, 127.8, 127.9, 128.3, 128.6, 129.2, 129.2, 138.5, 139.3, 156.3; IR (neat) (cm^{-1}) 3649, 3629, 3349, 3108, 3087, 3064, 3029, 3004, 2961, 2930, 2872, 2860, 2607, 2369, 2345, 1948, 1803, 1715, 1676, 1607, 1505, 1466, 1453, 1383, 1356, 1258, 1218, 1141, 1091, 1030, 968, 930, 873, 805, 759, 702, 667, 607, 563, 510, 492, 456; MS (EI, 70 eV, 80°C) *m/z* 353 (7.6 %), 352 (38.7 %), 295 (13.6 %), 261 (6.2 %), 205 (7.7 %), 132 (8.1 %), 120 (15.5 %), 92 (7.5 %), 91 (100 %), 74 (10.6 %), 65 (8.4 %), 59 (11.6 %); MS (CI, 70 eV) *m/z* 355 (2.9 %), 353 (100 %), 351 (2.9 %), 149 (25.7 %), 75 (29.3 %). *Anal.* Calcd for $C_{22}H_{28}N_2O_2$: C, 75.00; H, 7.95; N, 7.95. Found: C, 74.77, H, 8.13 N, 7.81.

Alcohol (**10c**) was prepared according to the general precedure IV. Yield: 79 %. The de of the reduction was ≥ 96 % (^{1}H-NMR spectrum). The enantioselectivities were determined with (-)-Pirkle-^{1}H-NMR-shift experiments: ee = 80 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 1.90 (1H, s), 2.29 (1H, m), 2.43 (1H, m), 3.13 (1H, dd, ^2J = 11.41, ^3J = 8.73), 3.23 (1H, dd, ^2J = 12.43, ^3J = 5.71), 3.32 (1H, m), 3.90 (1H, d, *J* = 15.44), 3.99 (1H, m), 4.52 (1H, d, 14.77), 4.66 (1H, d, *J* = 14.77), 5.09 (2H, m), 5.34 (2H, d, *J* = 15.44), 5.82 (1H, m), 7.30 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 33.2, 48.8, 49.9, 51.7, 57.8, 64.7, 118.2, 127.3, 127.5, 127.8, 128.2, 128.7, 128.7, 135.1, 138.0, 138.6, 155.7; IR (neat) (cm^{-1}) 3298, 3087, 3064, 3030, 2974, 2930, 1714, 1682, 1651, 1607, 1556, 1505, 1453, 1383, 1359, 1317, 1250, 1180, 1163, 1132, 1079, 1030, 1002, 959, 916, 879, 840, 819, 807, 751, 702, 667, 605, 565, 507, 457; MS (EI, 70 eV, 80°C) *m/z* 336 (6.2 %), 296 (7.5 %), 295 (24.5 %), 120 (21.8 %), 92 (13.8 %), 91 (100 %), 90 (21.4 %), 73 (5.4 %), 65 (9.7 %), 61 (5.6 %), 57 (5.0 %), 45 (9.8 %); MS (CI, 70 eV) *m/z* 339 (33.8 %), 337 (100 %). *Anal.* Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.45, H, 7.03 N, 8.21.

Alcohol (**10d**) was prepared according to the general precedure IV. Yield: 84 %. The de of the reduction was ≥ 96 % (^{1}H-NMR spectrum). The enantioselectivities were determined with (-)-Pirkle-^{1}H-NMR-shift experiments: ee = 76 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 2.34 (1H, s), 2.68 (1H, dd, ^2J = 13.19, ^3J = 8.52), 2.98 (1H, dd, ^2J = 13.19, ^3J = 5.50), 3.16 (2H, m), 3.21 (1H, d, *J* = 15.40), 3.42 (1H, m), 3.89

(1H, m), 4.48 (1H, d, *J* = 14.85), 4.69 (1H, d, *J* = 14.85), 5.19 (1H, d, *J* = 15.40), 7.20-7.35 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 34.5, 48.7, 49.9, 51.8, 59.9, 64.2, 115.4, 120.6, 126.7, 127.3, 127.6, 127.9, 128.1, 128.6, 129.5, 137.8, 138.2, 138.4, 155.7; IR (solution in $CHCl_3$) (cm^{-1}) 3294, 3064, 3028, 2926, 1707, 1607, 1510, 1469, 1453, 1389, 1358, 1296, 1250, 1217, 1179, 1140, 1093, 1076, 1053, 1029, 1001, 973, 913, 807, 754, 702, 668, 633, 607, 549, 507, 458 ; MS (EI, 70 eV, 80°C) *m/z* 296 (13.2 %), 295 (61.8 %), 120 (26.5 %), 92 (8.3 %), 91 (100 %), 65 (7.1 %); MS (CI, 70 eV) *m/z* 388 (28.5 %), 387 (100 %). *Anal.* Calcd for $C_{25}H_{26}N_2O_2$: C, 77.72; H, 6.74; N, 7.25. Found: C, 77.22; H, 6.67; N, 7.32.

Alcohol (**10e**) was prepared according to the general precedure IV. Yield: 83 %. The de of the reduction was ≥ 96 % (^{1}H-NMR spectrum). The enantioselectivities were determined with (-)-Pirkle-^{1}H-NMR-shift experiments: ee 86 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 1.78 (1H, m), 2.02 (1H, m), 2.34 (1H, s), 2.70 (2H, t), 3.09-3.28 (3H, m), 3.87 (1H, d, *J* = 15.44), 3.97 (1H, m), 4.49 (1H, d, *J* = 15.11), 4.59 (1H, d, *J* = 14.77), 5.33 (1H, d, *J* = 15.11), 7.25 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 30.3, 33.0, 48.6, 50.4, 51.7, 57.3, 64.5, 126.2, 127.3, 127.5, 128.0, 128.1, 128.4, 128.6, 128.7, 128.7, 138.0, 138.6, 141.5, 155.8; IR (solution in $CHCl_3$) (cm^{-1}) 3342, 3106, 3085, 3063, 3027, 3007, 2925, 2861, 1708, 1673, 1607, 1506, 1467, 1453, 1357, 1250, 1219, 1180, 1156, 1095, 1077, 1030, 1011, 958, 910, 809, 755, 701, 667, 608, 563, 510, 457; MS (EI, 70 eV, 80°C) *m/z* 401 (10.1 %), 400 (32.5 %), 296 (10.7 %), 295 (8.0 %), 279 (9.5 %), 265 (8.1 %), 206 (5.6 %), 205 (42.3 %), 132 (10.5 %), 92 (9.1 %), 91 (100 %), 65 (7.3 %); MS (CI, 70 eV) *m/z* 403 (5.4 %), 402 (28.6 %), 401 (100 %), 400 (6.4 %), 399 (5.8 %), 295 (6.6 %), 281 (11.1 %), 275 (5.1 %), 270 (5.2 %), 269 (17.7 %), 268 (52.4 %), 255 (15.9 %), 242 (6.9 %), 241 (33.8 %), 240 (47.1 %), 224 (9.0 %), 190 (7.4 %), 136 (10.4 %), 132 (6.1 %). *Anal.* Calcd for $C_{26}H_{28}N_2O_2$: C, 78.00; H, 7.00; N, 7.00. Found: C, 77.45; H, 7.11; N, 7.08.

General procedure V for the synthesis of the double alkylated hydrazones (**11a-e**) (1-3 mmol-scale):
The crude monoalkylated hydrazones (**8a-e**) (prepared according to general procedure I) were directly used for the second alkylation. TMP (1.3 eq.) was dissolved in dry THF (20 mL) in a pre-dried Schlenk-flask under argon and *n*BuLi-solution (1.2 eq. of a 1.6 M solution in hexane) was added. The pale yellow solution was stirred for 10 min at rt and then cooled to –78 °C. A solution of the hydrazones (**8a-e**) (1eq., -78 °C) in THF (20 mL) was added slowly *via* a double ended needle. After stirring for 10 min at -78 °C a solution of the electrophile in THF (5 mL) was added, stirred for a further 3 more h at -78 °C and then quenched with NH_4Cl (aq). After extraction with ether (3x) and drying over $MgSO_4$ the solvent was removed. The crude hydrazones were used directly in the following hydrazone cleavage reaction (general procedure VI).

General procedure VI for the synthesis of the double alkylated ketones (**12a-e**) **(**1-3 mmol scale):
Ozone was bubbled through a solution of hydrazone (**11a-e**) (1 eq.) in CH_2Cl_2 (250 mL) at –78°C with a flow of 75 L/h until a blue or green color is observed, then for 1 min air was bubbled through the reaction mixture until the color disappeared again. The solvent was removed under reduced pressure and the crude products were purified by column chromatography on silica gel (ether : pentane 1:1).

Ketone (**12a**) was prepared according to the general precedures V and VI. Yield over three steps: 43 %. The de of the second alkylation was ≥ 96 % (^{1}H-NMR spectrum). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 0.77 (3H, d, *J* = 7.05), 0.93 (3H, d, *J* = 6.72), 2.06 (1H, m), 3.30 (1H, d, *J* = 5.71), 3.90 (1H, d, *J* = 14.43), 5.28 (1H, d, *J* = 14.77), 7.30 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 18.7, 19.5, 31.6, 50.7, 68.9, 127.9, 128.7, 129.2, 136.9, 157.2, 204.7; IR (neat) (cm^{-1}) 3031, 2964, 2933, 2875, 2248, 1728, 1646, 1495, 1471, 1453, 1389, 1370, 1348, 1317, 1236, 1148, 1111, 1077, 1030, 910, 734, 702, 648; MS (EI, 70 eV, 80°C) *m/z* 380 (15.3 %), 338 (15.5 %), 337 (65.2 %), 181 (6.7 %), 162 (27.0 %), 120 (20.5 %), 92 (8.0 %), 91 (100 %). *Anal.* Calcd for $C_{24}H_{30}N_2O_2$: C, 76.19; H, 7.94; N, 7.41. Found: C, 75.80; H, 7.88; N, 7.58.

Ketone (**12b**) was prepared according to the general precedures V and VI. Yield over three steps: 39 %. The de of the second alkylation was ≥ 96 % (^{1}H-NMR spectrum). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 0.8-1.8 (9H, m), 3.54 (1H, m), 3.92 (1H, d, *J* = 14.77), 5.28 (1H, d, *J* = 14.78), 7.30 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 13.9, 22.6, 27.0, 30.4, 49.2, 63.1, 127.9, 128.8, 128.8, 137.2, 157.3, 205.1; IR (neat) (cm^{-1}) 3315, 3086, 3063, 3029, 3006, 2957, 2929, 2860, 1739, 1712, 1656, 1586, 1495, 1477, 1453, 1383, 1357, 1303, 1263, 1229, 1177, 1156, 1111, 1078, 1029, 968, 755, 702, 666; MS (EI, 70 eV, 80°C) *m/z* 407 (17.3 %), 406 (60.1 %), 350 (20.5 %), 349 (17.7 %), 322 (21.2 %), 321 (100 %), 315 (10.6 %), 259 (16.0 %), 244 (5.6 %), 176 (5.6 %), 106 (5.4 %), 92 (7.2 %), 91 (96.4 %); *Anal.* Calcd for $C_{26}H_{34}N_2O_2$: C, 76.85; H, 8.37; N, 6.90. Found: C, 76.51; H, 8.17; N, 7.21.

Ketone (**12c**) was prepared according to the general precedures V and VI. Yield over three steps: 40 %. The de of the second alkylation was ≥ 96 % (^{1}H-NMR spectrum). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 2.90 (2H, m), 3.68 (1H, d, *J* = 14.77), 3.72 (1H, m), 4.98 (1H, d, *J* = 14.77), 7.18 (4H, m), 7.28 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 37.1, 49.6, 63.9, 127.4, 128.0, 128.9, 129.0, 129.3, 129.8, 136.0, 137.0, 156.9, 203.3; IR (neat) (cm^{-1}) 3088, 3066, 3019, 2928, 2855, 1739, 1711, 1650, 1604, 1496, 1470, 1454, 1359, 1216, 1080, 1030, 757, 701, 669; MS (EI, 70 eV, 80°C) *m/z* 474 (3.8 %), 384 (18.3 %), 383 (64.7 %), 266 (21.1 %), 92 (7.1 %), 91 (100 %). *Anal.* Calcd for $C_{32}H_{30}N_2O_2$: C, 81.01; H, 6.33; N, 5.91. Found: C, 81.47; H, 6.23; N, 5.78.

Ketone (**12d**) was prepared according to the general precedures V and VI. Yield over three steps: 47 %. The de of the second alkylation was ≥ 96 % (^{1}H-NMR spectrum). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 1.97 (2H, m), 2.38 (1H, m), 2.56 (1H, m), 3.60 (1H, m), 3.87 (1H, d, *J* = 14.56), 5.20 (1H, d, *J* = 14.56), 7.10-7.33 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 31.1, 32.5, 49.5, 62.3, 126.6, 127.1, 128.1, 128.6, 128.8, 128.9, 137.1, 140.5, 157.0, 204.7; IR (neat) (cm^{-1}) 3084, 3061, 3027, 3003, 2926, 2861, 1734, 1658, 1602, 1584, 1495, 1453, 1384, 1356, 1303, 1278, 1236, 1170, 1119, 1078, 1030, 919, 751, 699, 619, 518, 499, 482; MS (EI, 70 eV, 80°C) *m/z* 503 (6.1 %), 502 (16.2 %), 399 (12.4 %), 398 (43.7 %), 397 (12.0 %), 370 (8.8 %), 369 (32.5 %), 307 (19.4 %), 295 (5.6 %), 294 (17.1 %), 293 (14.6 %), 203 (14.2 %), 149 (6.7 %), 132 (11.6 %), 105 (7.6 %), 92 (8.1 %), 91 (100 %), 57 (8.0 %). *Anal.* Calcd for $C_{34}H_{34}N_2O_2$: C, 81.27; H, 6.77; N, 5.58. Found: C, 81.66; H, 6.53; N, 5.31.

Ketone (**12e**) was prepared according to the general precedures V and VI. Yield over three steps: 34 %. The de of the second alkylation was ≥ 96 % (^{1}H-NMR spectrum). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 1.88 (2H, m), 2.30 (1H, m), 2.48 (1H, m), 2.98 (2H, m), 3.44 (1H, m), 3.63 (1H, d, *J* = 14.83), 3.84 (1H, m), 3.86 (1H, d, *J* = 14.56), 4.79 (1H, d, *J* = 14.83), 5.25 (1H, d, *J* = 14.56), 7.13-7.35 (20H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 31.1, 32.6, 37.5, 49.6, 49.8, 62.4, 64.6, 126.2, 126.5, 127.3, 127.5, 127.9, 128.7, 128.9, 129.0, 129.0, 129.1, 129.9, 129.9, 136.0, 137.0, 137.1, 140.5, 157.1, 204.2; IR (neat) (cm^{-1}) 3086, 3063, 3029, 2929, 2863, 2247, 1736, 1648, 1604, 1585, 1495, 1470, 1453, 1384, 1358, 1230, 1179, 1157, 1079, 1030, 910, 733, 701, 648; MS (EI, 70 eV, 80°C) *m/z* 309 (7.6 %), 118 (31.9 %), 92 (8.5 %), 91 (100 %). *Anal.* Calcd for $C_{33}H_{32}N_2O_2$: C, 81.15; H, 6.56; N, 5.74. Found: C, 80.41; H, 6.44, N, 5.82.

General procedure VII for the synthesis of the symmetrical double alkylated alcohols (**13a-d**) (1-3 mmol scale):

$NaBH_4$ (3 eq.) was added in small portions to a solution of the ketones (**12a-d**) (1 eq.) in MeOH (10 mL) and at 0°C. The reaction mixture was stirred for another 2 h at 0 °C, quenched with sat. aq. NH_4Cl and extracted with ether (3x). The combined organic layers were dried over $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (ether : pentane 1:1).

Alcohol (**13a**) was prepared according to the general precedure VII. Yield: 71 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 0.77 (3H, d, *J* = 6.59), 0.95 (3H, d, *J* = 7.14), 1.01 (3H, d, *J* = 6.87), 1.04 (3H, d, *J* = 6.87), 1.60 (1H, m), 1.88 (1H, s), 2.19 (1H, m), 2.79 (1H, dd, *J* = 9.06, *J* = 3.84) 2.86 (1H, dd, *J* = 5.77, *J*

= 4.39), 3.67 (1H, d, *J* = 14.56), 3.74 (1H, d, *J* = 15.11), 3.91 (1H, m), 5.55 (1H, d, *J* = 14.56), 5.60 (1H, d, *J* = 15.10), 7.30 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 18.5, 19.1, 20.4, 28.1, 31.4, 47.7, 52.2, 58.4, 66.4, 66.6, 127.6, 128.0, 128.5, 128.6, 128.8, 129.2, 137.9, 138.9, 157.0; IR (neat) (cm^{-1}) 3356, 3108, 3087, 3064, 3030, 2960, 2930, 2874, 1711, 1614, 1453, 1389, 1358, 1312, 1242, 1178, 1125, 1076, 1065, 1030, 1003, 966, 951, 911, 841, 820, 797, 734, 702, 633, 619, 606, 562, 542, 513, 455; MS (EI, 70 eV, 80°C) *m/z* 381 (5.0 %), 380 (17.8 %), 338 (16.6 %), 337 (69.7 %), 181 (7.4 %), 162 (29.3 %), 149 (5.3 %), 120 (22.4 %), 92 (8.3 %), 91 (100 %), 70 (8.3 %), 61 (6.5 %), 57 (6.3 %), 55 (5.8 %), 45 (6.1 %). *Anal.* Calcd for $C_{24}H_{32}N_2O_2$: C, 75.79; H, 8.42; N, 7.37. Found: C, 75.31; H, 8.23; N, 7.51.

Alcohol (**13b**) was prepared according to the general precedure VII. Yield: 85 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 0.86 (6H, m), 1.07-1.40 (8H, m), 1.56 (4H, m), 1.77 (1H, s), 3.13 (2H, m), 3.68 (1H, m), 3.87 (1H, d, *J* = 14.48), 4.01 (1H, d, *J* = 15.66), 5.34 (1H, d, *J* = 14.56), 5.40 (1H, d, *J* = 15.38), 7.30 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 14.3, 14.3, 23.1, 23.2, 27.4, 28.3, 28.4, 31.3, 48.1, 50.1, 55.2, 59.2, 65.8, 127.3, 127.8, 127.9, 128.6, 128.7, 129.0, 138.5, 138.9, 156.4; IR (neat) (cm^{-1}) 3348, 3108, 3087, 3064, 3029, 3003, 2957, 2931, 2871, 2861, 1605, 1494, 1453, 1382, 1356, 1304, 1247, 1218, 1169, 1120, 1103, 1076, 1030, 966, 808, 756, 701, 665, 647, 619, 605, 512; MS (EI, 70 eV, 80°C) *m/z* 409 (14.7 %), 408 (52.7 %), 352 (10.8 %), 351 (34.5 %), 318 (9.8 %), 317 (44.6 %), 181 (5.2 %), 177 (6.0 %), 176 (42.0 %), 132 (7.4 %), 120 (11.7 %), 106 (6.6 %), 92 (8.1 %), 91 (100 %). *Anal.* Calcd for $C_{26}H_{36}N_2O_2$: C, 76.47; H, 8.82; N, 6.68. Found: C, 76.01; H, 9.12; N, 6.88.

Alcohol (**13c**) was prepared according to the general precedure VII. Yield: 82 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 2.00 (1H, s), 3.43 (1H, dd, *J* = 13.74, *J* = 7.97), 2.73 (2H, m), 2.91 (1H, dd, *J* = 12.64, *J* = 5.50), 3.18 (1H, m), 3.25 (1H, m), 3.34 (1H, m), 3.70 (1H, d, *J* = 14.55), 3.86 (1H, d, *J* = 15.66), 5.27 (1H, d, *J* = 14.83), 5.42 (1H, d, *J* = 15.38), 6.74 (2H, m), 6.87 (2H, m), 7.05-7.30 (18 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 34.4, 38.2, 48.0, 50.1, 56.9, 60.7, 64.3, 126.7, 126.9, 127.0, 127.6, 128.0, 128.7, 128.8, 128.9, 129.1, 129.2, 129.3, 129.5, 136.8, 137.8, 138.3, 138.6, 156.2; IR (neat) (cm^{-1}) 3343, 3086, 3063, 3027, 3006, 2928, 2871, 1706, 1670, 1604, 1537, 1495, 1453, 1383, 1357, 1247, 1217, 1182, 1156, 1096, 1074, 1043, 1030, 1004, 974, 755, 702, 667, 609, 505; MS (EI, 70 eV, 80°C) *m/z* 386 (18.0 %), 385 (74.3 %), 210 (11.7 %), 182 (26.7 %), 155 (6.7 %), 120 (14.2 %), 92 (8.0 %), 91 (100 %), 65 (5.2 %), 57 (6.0 %), 55 (5.1 %); MS (CI, 70 eV) *m/z* 478 (30.4 %), 477 (90.0 %), 391 (12.3 %), 385 (9.2 %), 371 (10.1 %), 281 (5.2 %), 280 (9.0 %), 254 (5.1 %), 253 (6.5 %), 235 (7.5 %), 226 (30.0 %), 223 (6.8 %), 198 (40.5 %), 190 (24.0 %), 182 (12.8 %), 181 (93.9 %), 165 (22.7 %), 164 (18.8 %), 163 (100 %), 157 (8.1 %), 147 (14.4 %), 146 (5.8 %), 145 (10.6 %), 137 (6.1 %), 136 (10.8 %), 133 (12.7 %), 132 (9.0

%), 108 (56.0 %), 107 (34.1 %), 106 (14.6 %), 92 (8.2 %), 91 (25.4 %). *Anal.* Calcd for $C_{32}H_{32}N_2O_2$: C, 80.67; H, 6.72; N, 5.88. Found: C, 80.12, H, 6.81; N, 5.99.

Alcohol (**13d)** was prepared according to the general precedure VII. Yield: 91 %. ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 1.45-2.00 (4H, m), 2.43 (3H, m), 2.69 (1H, m), 3.12 (1H, m), 3.20 (1H, m), 3.78 (1H, m), 3.84 (1H, d, *J* = 14.56), 3.98 (1H, d, *J* = 15.38), 5.32 (1H, d, *J* = 14.84), 5.46 (1H, d, *J* = 15.39), 7.00 (4H, m), 7.25 (16H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 29.6, 31.6, 32.0, 33.1, 48.0, 50.1, 54.2, 58.6, 65.4, 126.3, 126.5, 127.5, 127.9, 128.1, 128.4, 128.5, 128.5, 128.7, 128.7, 128.8, 129.1, 138.1, 138.6, 141.0, 141.1, 156.8; IR (solution in $CHCl_3$) (cm^{-1}) 3345, 3085, 3063, 3026, 2927, 2860, 1603, 1495, 1453, 1384, 1357, 1245, 1217, 1179, 1156, 1077, 1030, 1002, 757, 700, 667; MS (EI, 70 eV, 80°C) *m/z* 505 (13.8 %), 504 (30.6 %), 503 (7.1 %), 414 (11.9 %), 413 (43.2 %), 400 (9.8 %), 399 (11.6 %), 296 (12.0 %), 295 (6.8 %), 279 (5.7 %), 224 (14.6 %), 205 (19.5 %), 120 (8.8 %), 92 (8.7 %), 91 (100 %). *Anal.* Calcd for $C_{34}H_{36}N_2O_2$: C, 80.95; H, 7.14; N, 5.56. Found: C, 80.61; H, 7.34; N, 5.28.

Synthesis of alcohol (**14**):

To a solution of ketone (**12e**) (100 mg, 0.2 mmol) in ether (10 mL) at –78 °C was added a solution of BH_3-SMe_2 in THF (1M, 0.61 mL). The reaction mixture was allowed to warm to ambient temperature overnight and quenched with saturated aqueous NH_4Cl solution. After extraction with ether (3 x) the collected organic phases were dried over $MgSO_4$. The solvent was removed and the crude product was analyzed by ^{1}H-NMR spectroscopy indicating an 1.6 : 1 mixture of the diastereomers (**14**) and (**15**). Both diasteomers could be seperated by flash chromatography on silica gel (ether : pentane 1:1). Yield of the diasteromeric mixture: 74 %. The enantioselectivity was determined with (-)-Pirkle-^{1}H-NMR-shift experiments: ee = 76 %. Analytical data for the major isomer (**14**): ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 1.61 (1H, m), 1.63 (1H, s), 1.87 (1H, m), 2.41 (2H, t, *J* = 8.24), 2.82 (1H, dd, *J* = 12.63, *J* = 9.34), 2.96 (1H, dd, *J* = 12.61, *J* = 5.46), 3.17 (1H, m), 3.33 (1H, m), 3.41 (1H, m), 3.84 (1H, d, *J* = 14.83), 3.90 (1H, d, *J* = 15.38), 5.40 (1H, d, *J* = 14.56), 5.47 (1H, d, *J* = 15.39), 7.00 (4H, m), 7.15-7.35 (16H, m); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm) 31.4, 33.8, 34.5, 48.3, 50.2, 57.3, 58.3, 65.0, 126.4, 126.8, 127.6, 127.9, 128.1, 128.4, 128.7, 128.8, 128.8, 128.9, 129.1, 129.4, 137.9, 138.2, 138.6, 140.9, 157.0; IR (solution in $CHCl_3$) (cm^{-1}) 3342, 3086, 3063, 3027, 2929, 2867, 1603, 1494, 1484, 1453, 1357, 1245, 1217, 1180, 1157, 1094, 1077, 1030, 756, 701, 668; MS (EI, 70 eV, 80°C) *m/z* 490 (23.1 %), 400 (23.1 %), 399 (77.6 %), 225 (5.2 %), 224 (30.1 %), 120 (18.4 %), 92 (8.2 %), 91 (100 %). *Anal.* Calcd for $C_{33}H_{34}N_2O_2$: C, 80.82; H, 6.94; N, 5.71. Found: C, 80.51; H, 7.33; N, 5.63.

Synthesis of alcohol (**15**):

To a solution of ketone (**12e**) (100 mg, 0.2 mmol) in ether (10 mL) at –78 °C was added a solution of (*L*)-Selectride in THF (1M, 0.61 mL). The reaction mixture was allowed to warm to ambient temperature overnight and quenched with saturated aqueous NH_4Cl solution. After an aqueous solution of H_2O_2 (30%) and NaOH (1 M) was added the reaction mixture was stirred for 5 more min. After extraction with ether (3 x) the collected organic phases were dried over $MgSO_4$. The solvent was removed and the crude product was analyzed by ^{1}H-NMR spectroscopy indicating **15** as the only diastereoisomer. The crude product was purified by flash chromatography on silica gel (ether : pentane 1:1). Yield: 89 %. The enantioselectivity was determined with (-)-Pirkle-^{1}H-NMR-shift experiments: ee = 76 %. Analytical data for **15**: ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm) 1.62 (1H, s), 1.95 (1H, m), 2.04 (1H, m), 2.38 (1H, m), 2.45 (1H, dd, *J* = 14.01, *J* = 8.27), 2.64 (1H, m), 2.79 (1H, dd, *J* = 13.73, *J* = 5.77), 3.22 (1H, m), 3.41 (1H, m), 3.62 (1H, m), 3.81 (1H, d, *J* = 14.56), 4.00 (1H, d, *J* = 15.39), 5.29 (1H, d, *J* = 11.54), 5.47 (1H, d, *J* = 15.38), 6.89 (2H, d), 6.98 (2H, d), 7.26 (16H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) (δ, ppm) 29.7, 31.9, 37.9, 47.9, 50.3, 54.1, 60.8, 65.2, 126.2, 127.1, 127.5, 128.0, 128.1, 128.4, 128.7, 128.8, 128.8, 129.0, 129.1, 129.2, 136.9, 138.1, 138.6, 141.0, 156.2; IR (neat) (cm^{-1}) 3338, 3085, 3062, 3027, 3003, 2928, 2861, 1604, 1495, 1453, 1384, 1358, 1246, 1030, 990, 969, 910, 733, 701, 647, 608; MS (EI, 70 eV, 80°C) *m/z* 490 (5.1 %), 400 (25.6 %), 399 (97.8 %), 295 (23.5 %), 224 (18.3 %), 181 (6.4 %), 120 (15.8 %), 92 (8.0 %), 91 (100 %). *Anal.* Calcd for $C_{33}H_{34}N_2O_2$: C, 80.82; H, 6.94; N, 5.71. Found: C, 80.41; H, 6.99; N, 5.51.

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