A Chiral, Oxidatively Cleavable Auxiliary in β-Lactam Synthesis – Double Diastereocontrol with *p*-Methoxyphenethyl-Substituted Imines

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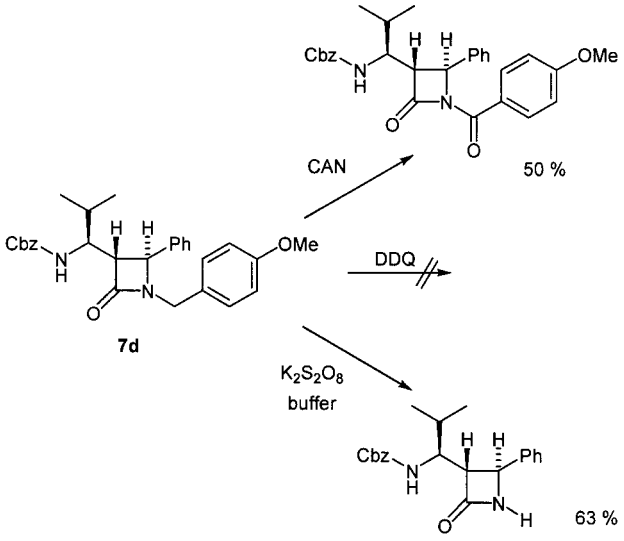
Received 19 August 1998; revised 16 October 1998

Abstract: A new chiral, oxidatively removable auxiliary for the Staudinger reaction is presented. When diazo ketones **1–3** prepared from suitably protected amino acids reacted with *p*-methoxyphenethyl (PMPE)-substituted imines, the corresponding *trans*-substituted β-lactams **7** and **8a–h** were formed. With the (*S*)-configured imine **5**, an improvement of the selectivities is observed in comparison with achiral *p*-methoxybenzyl (PMB)-substituted imines by double stereoselection; consequently, the ratio of isomers decreased with the (*R*)-imine **4**. The auxiliary could be removed with cerium ammonium nitrate (CAN).

Key words: protecting groups, double stereoinduction, β-lactam synthesis, diazo ketones, imines

β-Lactams (2-azetidinones) are essential substructures of natural products with antibiotic properties.[1] The most frequently used synthesis of β-lactams is the Staudinger reaction, in which in situ generated ketenes, preferentially prepared from acid chlorides, are reacted with imines.[2] β-Lactams bearing no protection or substitution at the nitrogen are not accessible via this reaction; they can be obtained through cleavage of the substituent introduced with the imine. Recently, we presented a new variation of the Staudinger reaction, in which ketenes **A** were prepared in situ via a photochemical rearrangement of diazo ketones prepared from amino acids, which react diastereoselectively with imines to yield *trans*-substituted β-lactams.[3] The diastereoselectivities can be additionally improved when chiral, *N*-phenethyl-substituted imines are used.[4] Nevertheless, this auxiliary which also acts as a protecting group is, as well as the benzyl group, difficult to remove.[5] We utilized the *p*-methoxybenzyl (PMB)-group[6,7] in this reaction,[3b] and we found that this auxiliary in the β-lactams we used, cannot be removed with CAN.[6] With these conditions an over-oxidation to the corresponding *p*-methoxybenzoyl-substituted β-lactam was observed. While no cleavage of the PMB-group was observed with 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ),[8] a reaction to the deprotected β-lactams can be realized with potassium peroxodisulfate in buffered media (Scheme 1).[9]

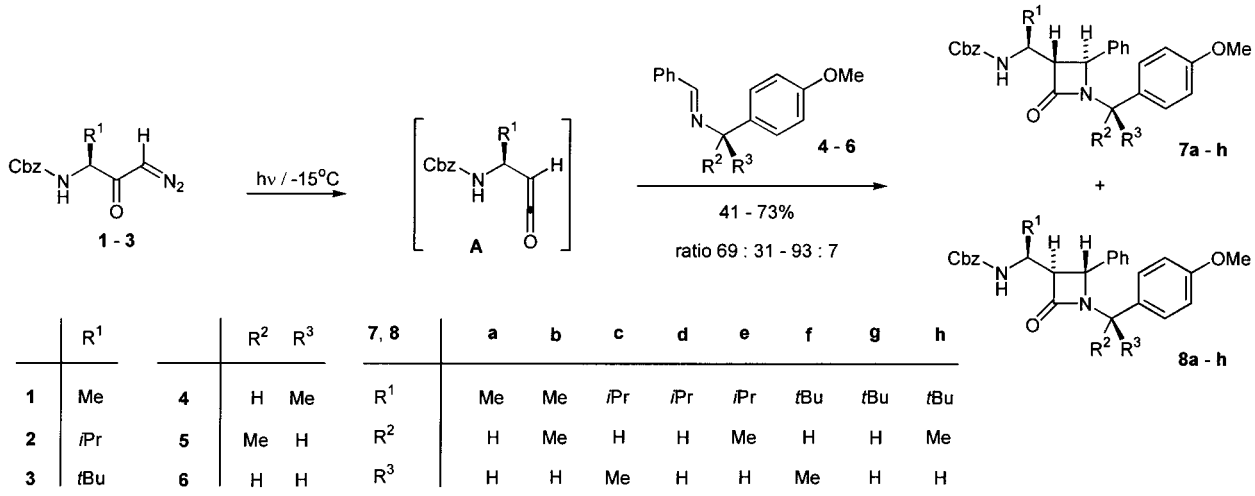
In this paper we describe a chiral, oxidatively removable auxiliary as an alternative to the phenethyl group. We combined the positive influence of the phenethyl group on the diastereoselectivity with the facile removability of the PMB group. We used the resulting *p*-methoxyphenethyl (PMPE) group as an *N*-substituent in imines for the Staudinger reaction.



Scheme 1

The starting materials used herein, diazo ketones **1–3** were prepared from suitably protected amino acids (alanine, valine and *tert*-leucine) in accordance with published procedures.[10] The imines **4–6** can be synthesized without racemization and, above all, without tautomerization using a method by Texier–Boullet starting from benzaldehyde and the respective *p*-methoxybenzylamine.[11] The chiral, enantiomerically pure amines can be obtained by enzymatic resolution using lipases, e.g. *candida antarctica*.[12] In addition, (*R*)- and (*S*)-*p*-methoxyphenethylamine, are commercially available.

Photochemically induced rearrangement of diazo ketones in the presence of PMPE-substituted imines led to the formation of the corresponding β-lactams. Similar to prior investigations, exclusively *trans*-substituted β-lactams were observed (Scheme 2 and Table). As with phenethyl-substituted imines, the selectivity decreased with the (*R*)-configured imine **4**; with the (*S*)-imine **5** an improvement of the product ratio was observed. Rearrangement of the diazo ketones with the achiral imine **6** led, as expected, to diastereoselectivities in between. In all cases, the major isomers **7a–h** were first eluted in chromatography. The relative configuration of all isomers could be assigned by comparison with similar compounds.[3] In the Staudinger reaction of chiral ketenes with chiral imines, the latter has generally no great influence on the asymmetric induction.[13] Nevertheless, the effects we found significantly



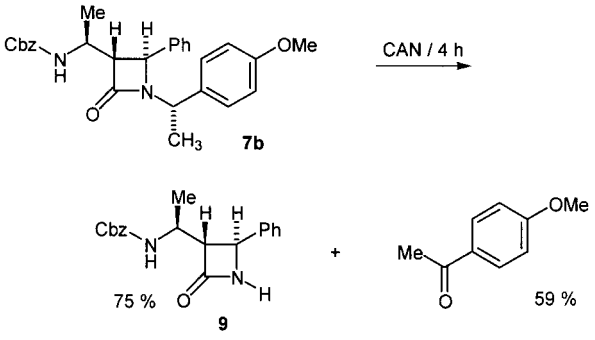
	R^1		R^2	R^3	7, 8	a	b	c	d	e	f	g	h
1	Me	4	H	Me	R^1	Me	Me	*i*Pr	*i*Pr	*i*Pr	*t*Bu	*t*Bu	*t*Bu
2	*i*Pr	5	Me	H	R^2	H	Me	H	H	Me	H	H	Me
3	*t*Bu	6	H	H	R^3	H	H	Me	H	H	Me	H	H

Scheme 2

show a match-mismatch relationship. Besides the better diastereoselectivities, which can be obtained when the (*S*)-configured imine **5** was used in our reaction, a much easier separation of the products can be achieved. The two isomers, e.g. **7** and **8a**, bearing a PMB-group with no centre of chirality, could not be separated, either by HPLC, or by MPLC. The isomers **7** and **8b** with a PMPE-group, with an additional stereogenic centre, can be easily separated by chromatography (α-value indicating the separation: 1.4).

Several methods for the cleavage of the PMPE-group in **7b** were tested: While oxidation with *N*-bromosuccinimide[14] led to decomposition of the substrate, no reaction was observed with triphenylcarbenium tetrafluoroborate,[15] *m*-chloroperbenzoic acid (mCPBA),[16] or dimethyldioxirane (prepared in situ from oxone/acetone)[17] or under electrolytical conditions.[18] Oxidation with ammonium peroxodisulfate/silver nitrate (catalytic amount)[19] gave the deprotected β-lactam product, but due to the formation of a side product, whose identity could not be solved, the yields were unsatisfactory (46%). Since no over-oxidation (vide supra) is possible with the PMPE group, even stronger oxidising agents can be used. Consequently, we tested CAN as oxidant, which gave best results. Nevertheless, in comparison with published procedures,[6,14,20] longer reaction times have to be accepted. The unprotected β-lactam **9** could be isolated after 4 h in 75% yield (Scheme 3). The auxiliary was liberated as 4-methoxyacetophenone (59%).

In the present paper, we have demonstrated the versatility of a new chiral, oxidatively removable auxiliary in the preparation of β-lactams. Of course, this auxiliary is not restricted to usage in β-lactam chemistry. It may also find useful applications in all fields of diastereoselective synthesis. Work in this direction is currently ongoing in our laboratories.



Scheme 3

Solvents for chromatography and for workup, e.g. EtOAc and light petroleum (PE) were distilled prior to use, Et_2O was distilled over KOH/$FeSO_4$. Et_2O used for the reactions was distilled over Na/benzophenone. The diazo ketones **1–3**[10a,21] and the imines **4–6**[11] were prepared according to literature procedures, the parent chiral amines can be purchased from Lancaster. Photochemically induced rearrangements were performed in a UV reactor system (Heraeus) with a quartz filter. An immersion UV lamp TQ 150 (Philips) was used. Flash column chromatography: Merck silica gel 60 (230 – 400 mesh). TLC: precoated sheets, Alugram SIL G/UV_{254} Macherey-Nagel; detection by UV extinction, by cerium molybdate soln [phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concd H_2SO_4 (60 mL), H_2O (940 mL)]. MPLC: detection with a UV detector. HPLC: Analyses of diastereoisomer distribution were carried out with a Pharmacia LKB, RSD 2140 apparatus with a Pharmacia LKB, RSD 2249 mixer and diode-array detection (Pharmacia RSD 2140) on a LiChrosorb Si 60, Merck (hexane/ EtOAc, flow: 2.0 mL/min) chromatographic column. ^1H and ^{13}C NMR spectra: δ in ppm relative to internal TMS (0 ppm) or to resonances of the solvent (^1H: $CHCl_3$, 7.25 ppm; ^{13}C: $CDCl_3$, 77.0 ppm); in spectra of higher order, δ and *J* values are not corrected. Assignment of the ^{13}C signals was made with DEPT spectra. Mass spectra were recorded using FAB or CI (CH_4 or NH_3) techniques. IR spectra were recorded with a FTIR instrument. Elemental analyses were performed by the service of the Institut für Organische Chemie, University of Stuttgart. Mps are uncorrected.

Table β-Lactam Synthesis with PMPE- and PMB-Substituted Imines.

Starting Diazo Ketone	Starting Imine	Product[a]	Yield (ratio[b])	$[\alpha]^{20}_D$ [c]	mp (°C) (Et_2O/PE)	IR (KBr/film) ν (cm^{-1})	^{1}H NMR[d] (500 MHz, $CDCl_3$) δ (ppm), *J* (Hz)	^{13}C NMR[d] (126 MHz, $CDCl_3$) δ (ppm)
1	**6**	**7a**[e,f]	63% 7 : 3	–6	128–129	3270, 3020, 1721, 1705	1.32 (d, 3 H, *J* = 6.9, H-2'), 3.11 (dd, 1 H, *J* = 2.4, 2.4, H-3), 3.67 (d, 1 H, NCH_aH_b, partly covered), 3.68 (s, 3 H, OCH_3), 4.19 (m, 1 H, H-1'), 4.23 (br s, 1 H, H-4), 4.78 (d, 1 H, *J* = 14.9, NCH_aH_b), 4.95 (d, 1 H, *J* = 8.9, NH)	19.8 (q, C-2'), 43.8 (t, NCH_2Ph), 45.1 (d, C-1'), 55.1, 56.6 (q, d, C-4, OCH_3), 65.0 (d, C-3), 167.5 (s, C-2)
1	**5** (*S*)	**7b**	53% 4 : 1	–3	139–140	3263, 2960, 2918, 1703	1.31 (d, 3 H, *J* = 6.9, H-2'), 1.70 (d, 3 H, *J* = 7.1, H-2"), 3.03 (dd, 1 H, *J* = 2.9, 2.9, H-3), 3.68 (s, 3 H, OCH_3), 4.19 (br s, 2 H, H-4, H-1'), 4.24 (q, 1 H, *J* = 7.3, H-1"), 4.97 – 4.99 (m, 1 H, NH, covered)	19.7, 19.9 (2 q, 2 $CHCH_3$), 45.1 (d, C-1'), 53.8, 55.1, 56.6 (q, 2 d, C-4, C-1", OCH_3), 64.2 (d, C-3), 167.6 (s, C-2)
		8b		–20	oil	3320, 2974, 1736	1.19 (d, 3 H, *J* = 6.7, H-2'), 1.28 (d, 3 H, *J* = 7.1, H-2"), 2.99 (dd, 1 H, *J* = 7.9, 2.2, H-3), 3.79 (s, 3 H, OCH_3), 4.07 (sextet, 1 H, *J* = 7.3, H-1'), 4.18 (br s, 1 H, H-4), 4.84 (d, 1 H, *J* = 8.8, NH), 4.93 (q, 1 H, *J* = 7.0, H-1")	18.4, 19.9 (2 q, C-2', C-2"), 45.9 (d, C-1'), 51.5, 55.0, 57.7 (q, 2 d, C-4, C-1", OCH_3), 64.5 (d, C-3), 167.6 (s, C-2)
2	**4** (*R*)	**7c**	73% 7 : 3	+28	oil	3317, 2962, 1736	0.89 [d, 3 H, *J* = 6.8, $CH(CH_3)_2$], 0.91 [d, 3 H, *J* = 6.8, $CH(CH_3)_2$], 1.25 (d, 3 H, *J* = 7.2, H-2"), 1.89 [m, 1 H, H-2'], 3.20 (dd, 1 H, *J* = 2.7, 2.7, H-3), 3.71 (s, 3 H, OCH_3), 3.78 (m, 1 H, H-1'), 4.10 (d, 1 H, *J* = 2.2, H-4), 4.80 (d, 1 H, *J* = 10.2, NH), 4.91 (q, 1 H, *J* = 7.2, H-1")	18.9, 19.7 [2 q, $CH(CH_3)_2$, C-2", partly covered], 31.8 (d, C-2'), 51.5, 54.9, 55.1, 57.4 (q, 3 d, C-4, C-1', C-1", OCH_3), 61.5 (d, C-3), 167.7 (s, C-2)
		8c		–11	oil	3425, 2962, 1741	0.82 [d, 3 H, *J* = 6.9, $CH(CH_3)_2$], 0.90 [d, 3 H, *J* = 6.8, $CH(CH_3)_2$], 1.71 (d, 3 H, *J* = 7.1, H-2"), 2.21 (m, 1 H, H-2'), 2.99 (dd, 1 H, *J* = 9.7, 2.2, H-3), 3.74 (s, 3 H, OCH_3), 4.08 (ddd, 1 H, *J* = 10.0, 10.0, 3.9, H-1'), 4.27 (d, 1 H, *J* = 2.1, H-4), 4.31 (q, 1 H, *J* = 7.2, H-1"), 4.55 (d, 1 H, *J* = 10.2, NH)	16.1, 19.8 [2 q, $CH(CH_3)_2$, C-2", partly covered], 29.9 (d, C-2'), 53.6, 55.2, 55.7, 58.2 (q, 3 d, C-4, C-1', C-1", OCH_3), 62.4 (d, C-3), 167.2 (s, C-2)
2	**6**	**7d**[e]	50% 5 : 1	+14	oil	3315, 2961, 1739	0.93 [d, 3 H, *J* = 6.8, $CH(CH_3)_2$], 0.94 [d, 3 H, *J* = 6.7, $CH(CH_3)_2$], 1.93 [m, 1 H, H-2'], 3.25 (dd, 1 H, *J* = 2.6, 2.6, H-3), 3.67 (d, 1 H, *J* = 15.3, NCH_aH_b), 3.68 (s, 3 H, OCH_3), 3.85 (ddd, 1 H, *J* = 10.5, 7.6, 3.0, H-1'), 4.19 (d, 1 H, *J* = 2.2, H-4), 4.77 (d, 1 H, *J* = 14.8, NCH_aH_b), 4.88, (d, 1 H, *J* = 10.3, NH)[g]	18.8, 19.7 [2 q, $CH(CH_3)_2$], 31.7 (d, C-2'), 43.7 (t, NCH_2), 54.9, 54.9, 57.1 (q, 2 d, C-4, C-1, OCH_3), 62.3 (d, C-3), 167.3 (s, C-2)[g]
2	**5** (*S*)	**7e**	61% 9 : 1	+19	oil	3318, 2961, 1738	0.93 [d, 6 H, *J* = 6.8, $CH(CH_3)_2$], 1.68 (d, 3 H, *J* = 7.1, H-2"), 1.93 (m, 1 H, H-2'), 3.18 (dd, 1 H, *J* = 2.7, 2.7, H-3), 3.68 (s, 3 H, OCH_3), 3.84 (ddd, 1 H, *J* = 10.3, 7.4, 3.0, H-1'), 4.14 (d, 1 H, *J* = 2.4, H-4), 4.25 (q, 1 H, *J* = 7.2, H-1"), 4.94 (d, 1 H, *J* = 10.2, NH)	18.9, 19.7, 19.9 [3 q, $CH(CH_3)_2$, C-2"], 31.9 (d, C-2'), 53.9, 55.0, 55.2, 57.3 (q, 3 d, C-4, C-1', C-1", OCH_3), 61.6 (C-3), 167.5 (s, C-2)

Table (continued)

Starting Diazo Ketone	Starting Imine	Product[a]	Yield (ratio[b])	$[\alpha]^{20}_D$ [c]	mp (°C) (Et_2O/PE)	IR (KBr/film) ν (cm^{-1})	^{1}H NMR[d] (500 MHz, $CDCl_3$) δ (ppm), *J* (Hz)	^{13}C NMR[d] (126 MHz, $CDCl_3$) δ (ppm)
		8e		–25	79–80	3340, 2940, 1736, 1712	0.80 [d, 3 H, *J* = 6.9, $CH(CH_3)_2$], 0.86 [d, 3 H, *J* = 6.8, $CH(CH_3)_2$], 1.31 (d, 3 H, *J* = 7.1, H-2"), 2.13 (m, 1 H, H-2'), 3.04 (dd, 1 H, *J* = 9.5, 2.3, H-3), 3.76 (s, 3 H, OCH_3), 4.02 (ddd, 1 H, *J* = 9.8, 9.8, 4.0, H-1'), 4.19 (d, 1 H, *J* = 1.9, H-4), 4.49 (d, 1 H, *J* = 10.1, NH), 4.87 (q, 1 H, *J* = 7.1, H-1")	16.3, 19.2, 19.8 (3 q, 3 $CHCH_3$), 30.0 (d, C-2'), 51.9, 55.2, 55.5, 58.4 (q, 3 d, C-4, C-1', C-1", OCH_3), 62.4 (d, C-3), 167.4 (s, C-2)
3	**4** (*R*)	**7f**	41% 7 : 1	+49	oil	3322, 2963, 1740	0.90 [s, 9 H, $C(CH_3)_3$], 1.24 (d, 3 H, *J* = 7.2, H-2"), 3.26 (dd, 1 H, *J* = 2.3, 2.3, H-3), 3.72 (s, 3 H, OCH_3), 3.83 (dd, 1 H, *J* = 10.7, 2.1, H-1'), 4.08 (d, 1 H, *J* = 2.5, H-4), 4.86 (q, 1 H, *J* = 7.2, H-1"), 4.98 (d, 1 H, *J* = 10.8, NH)	18.8 (q, C-2"), 26.7 [q, $C(CH_3)_3$], 34.6 (s, C-2'), 51.7, 55.1, 57.9, 58.2 (q, 3 d, C-4, C-1', C-1", OCH_3), 60.4 (d, C-3), 167.3 (s, C-2)
		8f		–84	142–145	3250, 2942, 1744, 1722	0.85 [s, 9 H, $C(CH_3)_3$], 1.71 (d, 3 H, *J* = 7.1, H-2"), 3.27 (dd, 1 H, *J* = 4.6, 1.8, H-3), 3.68 (s, 3 H, OCH_3), 3.95 (d, 1 H, *J* = 1.6, H-4), 4.10 (q, 1 H, *J* = 7.1, H-1"), 4.13 (dd, 1 H, *J* = 10.7, 5.2, H-1'), 4.65 (d, 1 H, *J* = 10.6, NH)	20.4 (q, C-2"), 26.8 [q, $C(CH_3)_3$], 34.7 (s, C-2'), 54.2, 55.2, 56.7, 57.7 (q, 3 d, C-4, C-1', C-1", OCH_3), 60.7 (d, C-3), 167.6 (s, C-2)
3	**6**	**7g**[e]	72% 11 : 1	+37	oil	3317, 2960, 1746	0.93 [s, 9 H, $C(CH_3)_3$], 3.27 (dd, 1 H, *J* = 1.9, 1.9, H-3), 3.65 (d, 1 H, *J* = 15.3, NCH_aH_b), 3.69 (s, 3 H, OCH_3), 3.90 (dd, 1 H, *J* = 10.7, 2.3, H-1'), 4.17 (d, 1 H, *J* = 2.3, H-4), 4.75 (d, 1 H, *J* = 14.9, NCH_aH_b), 5.07 (d, 1 H, *J* = 10.7, NH)[g]	26.7 [q, $C(CH_3)_3$], 34.6 (s, C-2'), 43.8 (t, NCH_2), 55.1 (d, C-1'), 58.0, 58.1 (q, d, C-4, OCH_3), 61.2 (d, C-3), 167.0 (s, C-2)[g]
3	**5** (*S*)	**7h**[e]	69% 13 : 1	+35	oil	2326, 2963, 1740	0.92 [s, 9 H, $C(CH_3)_3$], 1.67 (d, 3 H, *J* = 7.1, H-2"), 3.25 (dd, 1 H, *J* = 2.0, 2.0, H-3), 3.68 (s, 3 H, OCH_3), 3.88 (dd, 1 H, *J* = 10.7, 1.9, H-1'), 4.12 (d, 1 H, *J* = 2.3, H-4), 4.23 (q, 1 H, *J* = 7.1, H-1"), 5.10 (d, 1 H, *J* = 10.7, NH)	19.9 (q, C-2"), 26.7 [q, $C(CH_3)_3$], 34.6 (s, C-2'), 53.8, 55.1, 57.9, 58.1 (q, 3 d, C-4, C-1', C-1", OCH_3), 60.4 (d, C-3), 167.2 (s, C-2)

[a] Satisfactory elemental analyses obtained (C ±0.33, H ±0.13, N ±0.14), except for **7f** (C –0.44) and **7h** (C –0.68). Mass spectra are in accordance with the proposed structures.
[b] Determined by HPLC and ^{1}H NMR spectrsocopy.
[c] *c* = 0.5 – 1.6 ($CHCl_3$).
[d] NMR data of the Cbz group and the aromatic rings are omitted.
[e] The minor isomer was not isolated. The diastereoselectivity was determined by evaluation of the proton signals at C-3 which are not covered by other signals: **8a**: δ 3.34; **8d**: δ 3.17; **8g**: δ 3.24; **8h**: δ 3.18.
[f] The diastereoisomers could not be separated by MPLC. Pure **7a** was obtained by recrystallization (Et_2O / PE).
[g] ^{1}H NMR: 250 MHz, ^{13}C NMR: 63 MHz.

β-Lactams 7 and 8; General Procedure

In a quartz photo reactor diazo ketone (2 mmol) and imine (4 mmol) were dissolved in Et_2O (300 mL), the mixture was cooled to –15 °C and irradiated for 90 min. The mixture was stirred for further 30 min at this temperature and then warmed to r.t. The solvent was removed and the isomer ratio was determined by HPLC and ^{1}H NMR spectroscopy. The diastereoisomers were separated by flash chromatography or MPLC.

(3*R*,4*S*,1'*S*)-3-[1-(Benzyloxycarbonylamino)ethyl]-4-phenylazetidin-2-one (9)

CAN (540 mg, 985 μmol) was added at 0 °C to a solution of β-lactam **7b** (150 mg, 327 μmol) in a mixture of H_2O (4.6 mL) and MeCN (3.5 mL) and the mixture was allowed to warm to r.t. After 4 h, the solution was extracted with EtOAc (3 × 20 mL) and re-extracted with sat. $NaHCO_3$ (20 mL) and brine (20 mL). The resulting $NaHCO_3$ and brine solutions were additionally extracted with EtOAc (20 mL) and the combined organic phases were dried ($MgSO_4$) and the solvents were removed. Chromatography (PE/EtOAc 9: 1 → 2: 1) yielded β-lactam **9** (80 mg, 75%) and 4-methoxyacetophenone (29 mg, 59%).

Compound 9

Colourless solid, mp 177 – 178 °C (Et_2O/PE); R_f = 0.29 (TLC, PE / EA 1: 1); $[\alpha]^{20}_D$ +22 (*c* = 0.5, $CHCl_3$).

IR (film): ν = 3250 (NH), 3050 (CH), 1740, 1690 (C=O) cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (d, 3 H, *J* = 7.0 Hz, H-2'), 3.14 (m_c, 1 H, H-3), 4.28 (br s, 1 H, H-1'), 4.54 (br s, 1 H, H-4), 5.03 (d, 1 H, *J* = 9.0 Hz, OCH_aH_b), 5.11–5.17 (m, 2 H, carbamate-NH, OCH_aH_b), 6.11 (br s, 1 H, lactam-NH), 7.32 – 7.37 (m, 10 H, 2 Ph).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.6 (q, C-2'), 45.1 (d, C-1'), 54.1 (d, C-4), 67.0 (d, C-3), 66.4 (t, OCH_2), 125.6, 128.1, 128.3, 128.3, 128.6, 128.9 (6 d, 2 Ph), 136.3, 139.4 (2 s, 2 Ph), 156.3 (s, OC=O), 168.4 (s, C-2).

MS (EI): *m/z* = 324 (M^+, 6), 296 (26), 146 (59), 91 ($C_7H_7^+$, 100).

Anal. calcd for $C_{19}H_{20}N_2O_3$ (324.4): C, 70.35%; H, 6.21%; N, 8.64%. Found: C, 70.14%; H, 6.16%; N, 8.53%.

Acknowledgement

The help of all members of the Institut für Organische Chemie, especially of Prof. Dr. V. Jäger and Prof. Dr. Dr. h. c. F. Effenberger is gratefully acknowledged. We also thank Dr. A. Klein for his help with the electrolytical experiments and M. Schütz for his work as part of the advanced practical course. This work was further supported by the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, the Stiftungsfonds Mitsubishi Electric Europe, the Landesgraduiertenförderung Baden-Württemberg, the BASF AG (donation of enantiopure amines), and the Degussa AG (amino acids).

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