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Generation of Chiral Olefins Based on L-Aspartic Acid

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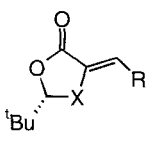
Abstract. A new chiral olefin **4** was synthesized starting from L-aspartic acid. The structures of the intermediate oxazolidinones **6** and **7** were proven by X-ray analysis to be diastereomers. It was shown that **4** is unreactive in Diels-Alder reactions with cyclopentadiene and 1,3-diphenylisobenzofuran because of its steric overloading (M.M. calculations) rather than by electronic effects (FMO by AM1 calculations).

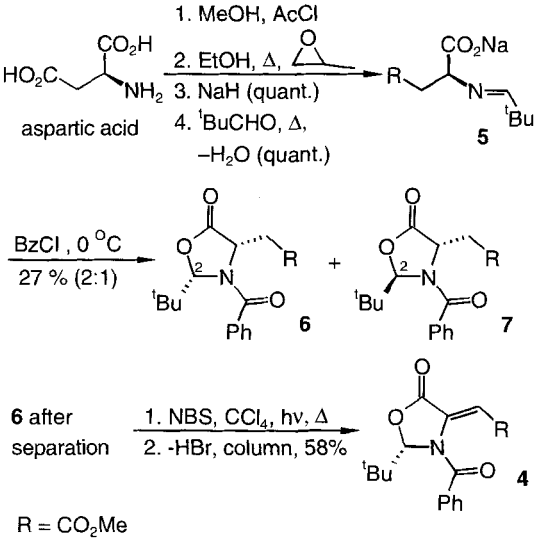
Although Alder's *endo* rule [2] predicts the stereoselectivity of the Diels-Alder reaction [3], we found unexpected high *exo* selectivities in the reactions of cyclopentadiene (**CP**) with **1** and **2**, respectively [4,5]. Other groups also showed that Alder's rule is not always obeyed [6]. Buono and co-workers established a correlation between the conformation of an α,β-unsaturated carbonyl compound and its *endo/exo* selectivity [7]. Whenever such a cyclic dienophile is fixed in a s-*cis* arrangement (**1–3**), the reaction with **CP** shows high *exo* selectivity.



	R	X
1	H	O
2	CO_2Et	O
3	H	NBz
4	CO_2Me	NBz

Chiral olefins derived from lactic acid (**1**) [4], malic acid (**2**) [5], alanine (**3**) [8] or methylcysteine [6b] form almost exclusively one diastereoisomer. Due to the substitution pattern these dienophiles behave like captodative (cd) olefins and therefore they are also suitable for Diels-Alder reactions with inverse electron-demand [4, 5a, 9]. The opposite stereoselectivity is observed for fixed s-*trans* olefins, i.e. an excess of *endo* adducts is obtained in the reaction with **CP**, as shown by Viehe [10], Feringa [11], and Font [12]. Only recently, Takeda combined these observations by successively expanding α,β-unsaturated lactones and by using them in Diels-Alder reactions [13]. From a particular ring size the s-*cis* conformation is adopted beside the s-*trans* conformation leading to nearly equal amounts of *endo* and *exo* adducts. In order to complete the series of heterocycles based on the chiral pool, we now describe the synthesis of olefin **4**. Experiments revealing its reactivity in Diels-Alder reactions are reported as well. The target molecule **4** was generated analogously to the synthesis of the chiral olefines **1–3** reported by Seebach [14] *et al.* In order to prevent **6** from decarboxylation during bromination with NBS [5], the corresponding β-methyl ester was synthesized first according to Rapoport (Scheme 1) [15].

Deprotonation of the remaining free acid was completed using sodium hydride without saponification of the ester, followed by reaction with pivalaldehyde to give the Schiff base **5**. After cyclization in the pres-



Scheme 1

ence of benzoyl chloride the oxazolidinones **6** and **7** were obtained as a 2:1 mixture. Based on X-ray analysis of both diastereoisomers, the substituents of the major isomer are arranged *cis/trans/cis* (Fig. 1) in agreement with Seebach's results [14]. Due to an angle sum of 351°, there is only a minor pyramidalization at nitrogen.

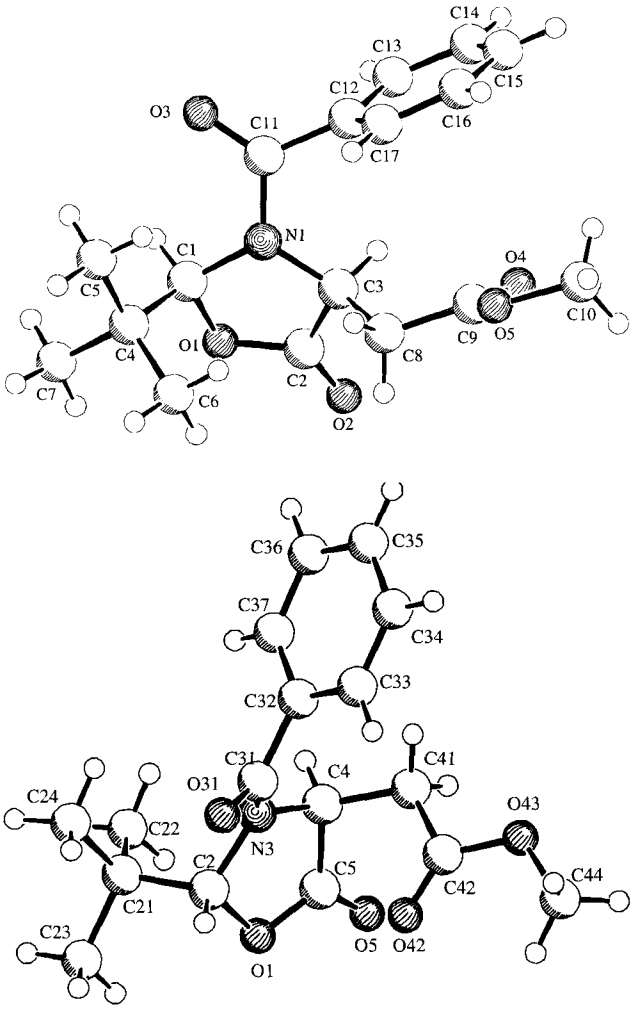
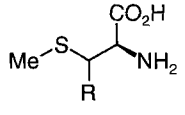


Fig. 1 Crystal structure of **6** and **7** (Schakal plots)

If acetyl chloride was used instead of benzoyl chloride, no product could be isolated. **6** was treated with NBS followed by spontaneous HBr elimination to give **4**. Alternatively, Pyne described the synthesis of **3** starting from **8a** [6b]. However, this procedure cannot be applied because 1-methyl-4-hydrogen-(2*RS*, 3*R*)-3-amino-2-methylsulfanyl butanedioate (**8b**) would be required as starting material.



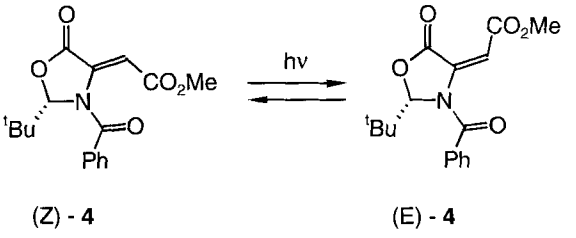
8a: R = H
8b: R = CO_2Me

In the following we tested **4** as dienophile in various Diels-Alder reactions. Reactions with **CP** showed no product neither at 20 °C and 50 °C, nor under high pressure conditions (10 kbar for 3 to7 days), nor by using of 5M $LiClO_4$ solution in diethyl ether [16], nor by Lewis acid catalysis ($TiCl_4$ in CH_2Cl_2). If 1,3-diphenyl isobenzofuran is used instead of **CP**, we also did not observe any product formation under various conditions (20 °C, 70 °C; $TiCl_4$ in CH_2Cl_2).

In order to get more information about the properties of olefin **4** we carried out molecular mechanic calculations [17] of the expected main products leading to the conclusion that this olefin is sterically overloaded. Obviously, the reactivity is not controlled by the energy differences of the frontier orbitals. Supposed that there is a Diels-Alder reaction with normal electron demand the HOMO of **CP** interacts with the LUMO of **4** (**CP**: HOMO: −8.72 eV, LUMO: 0.22 eV; calculations with AM1 [18] Mopac [19], cf. Table 1]). Although the smallest energy difference between the frontier orbitals should lead to a pronounced reactivity, olefins **1**, **2**, and **3** proved to be more reactive.

The capto–dative-concept [20] is confirmed referring to frontier orbital energies since the HOMO–LUMO difference decreases from **1**–**4** (entry 4 to table 1). Although **4** cannot be utilized in these cycloadditions, reactions with smaller partners will be subject of further investigation, e.g. radical additions.

4 was also photochemically isomerized to its *E*-isomer. The procedures were performed analytically and monitored by gas chromatography [21].



Scheme 2

By comparing the NMR spectra of **4** with **2** [7] it is assumed that the vinylic protons show resonances at $\delta = 5.81$ ppm (*Z*-isomer) and 5.51 ppm (*E*-isomer), respectively. The *Z*:*E* ratio using various photochemical procedures are the following [22]: in benzene, quartz filter (59:41); in acetone (56:44); in benzene with benzophenone (62:38) and in benzene with ethyl benzoate (59:41).

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Table 1 Time and yield of the reaction of various dienophiles with CP at room temperature, FMO energies [eV] based on AM1 calculations

entry	olefin	1	2	3	4
1	reaction time (d)/yield	3/86%	19/76%	14/70%	–
2	HOMO	−10.28	−10.50	−10.08	−10.06
3	LUMO	−0.25	−1.04	−0.51	−1.10
4	ΔE ($HOMO_{Olefin} - LUMO_{Olefin}$)	10.03	9.46	9.57	8.96
5	ΔE ($HOMO_{CP} - LUMO_{Olefin}$)	8.47	7.68	8.21	7.62

Experimental

Melting points (uncorrected): Büchi 510 apparatus – IR: Shimadzu IR-408 – ^{1}H NMR: Bruker WM 300 MHz; internal standard TMS or $CDCl_3$ (7.24 ppm) – ^{13}C NMR: Bruker AM 360 (90 MHz) internal standard $CDCl_3$ (77 ppm) or DMSO [d_6] (39.7 ppm). – MS: Varian MAT CH 7A (GLC-MS coupling) or Finnigan MAT 312 - HPLC: Kontron pump 420, RI detector Bischoff RI 8110, column 250 × 20 mm, LiChrosorb Si 60-5 (Merck) – Polarimetry: Perkin Elmer polarimeter 241; micrometer cuvette, length 9.998 cm; concentration given in g/100 ml – High pressure experiments: 12 kbar Hofer press – Elemental analysis: Heraeus CHN-O-Rapid or Perkin-Elmer 240 Elemental Analyser.

4-Methyl-1-sodium (2S)-2-(2,2-dimethylpropylidene- amino) butanedioate (**5**)

L-aspartic acid β-methyl ester [15] (1.00 g, 6.8 mmol) was suspended in 70 ml of dry THF. Sodium hydride (182 mg, 7.6 mmol) was added and the mixture was stirred over night. The remaining NaH was hydrolyzed with 4 ml of methanol and the solution was evaporated under reduced pressure until precipitation starts. The salt was used in the next step without further purification. Pentane (165 ml) and pivalaldehyde (1.25 ml, 10 mmol, 1.5 mol-equiv.) were added and the water was removed by azeotropic distillation for 6–8 h. Then the solvent was evaporated and the solid was dried under high vacuum for 6–8 h. The imine was obtained in quantitative yield and used without further purification. – ^{1}H NMR (MeOH-*D4*): δ 1.01 (s, 9 H, $(CH_3)_3$), 2.67 (dd, *J* = 9.1, 15.7 Hz, 1 H, CH_2), 2.86 (dd, *J* = 15.7, 4.8 Hz, 1 H, CH_2), 3.29 (s, 3 H, OCH_3), 3.91 (dd, *J* = 9.1, 4.8 Hz, 1 H, CH), 7.52 (s, 1H, imin-H). – ^{13}C NMR (MeOH-D4): δ 27.46 ($C(CH_3)_3$), 37.30 (CH_2), 40.07 ($C(CH_3)_3$), 50.11 (OCH_3), 52.16 (CH), 73.81 (Imine–C), 174.29 (C=O), 178.53 (C=O). – IR (KBr): ν = 2967 cm^{-1} (CH) (w), 1729 (C=O) (s), 1585 (carboxylate) (s), 1407 (m), 1302 (C–O) (w), 1209 (w), 1019 (w), 670 (w); *m.p.* 226–239 °C $[\alpha]_D^{20}$ = – 10.6° (c = 3.22 in H_2O).

Synthesis of the Oxazolidinones 6 and 7

Benzoyl chloride (0.78 g, 10.0 mmol) was dissolved in CH_2Cl_2 (20 ml) and added to a stirred suspension of freshly prepared **5** (1.74 g, 10.0 mmol) in CH_2Cl_2 (30 ml). The stirred suspension was allowed to warm up overnight, washed successively with 5% $NaHCO_3$ and water and dried over $MgSO_4$. Removal of the solvent yielded a brownish solid, from which the ratio of diastereomers was determined by ^{1}H NMR to be a 2:1 mixture of **6** and **7**. Column chromatography (silica gel; cyclohexane/ethyl acetate, 3:2) yielded 1.58 g **6** and **7** as colorless needles, 27%; *m.p.* 208–212 °C.

Pure **6** was isolated in two ways: a) Fractionated crystallization: The mixture was dissolved in a minimum of ethyl acetate. Then nine parts of cyclohexane were added and after 2 h crystals of **6** were isolated. This procedure was repeated until pure **6** was obtained (proof by GLC). **7** was obtained in 70% purity only. b) HPLC (cyclohexane/ethyl acetate 4:1) yields **7** in 80% purity.

(2S,4S)-3-Benzoyl-2-tert-butyl-4-methoxycarbonylmethyl-oxazolidine-5-one (**6**)

Single crystals of **6** suitable for X-ray analysis were obtained from ethyl acetate. – ^{1}H NMR ($CDCl_3$): δ 1.02 (s, 9 H, $(CH_3)_3$), 2.81 (dd, *J* = 17.0, 4.1 Hz, 1 H, CH_2), 2.90 (dd, *J* = 17.0 ,7.5 Hz, 1 H, CH_2), 3.56 (s, 3 H, OCH_3), 4.74 (dd, *J* = 4.1, 7.5 Hz, 1 H, H-C(4)), 6.13 (s, 1 H, H-C(2)), 7.25–7.40 (m, 5H, arom. H). – ^{13}C NMR (MeOH-D4): δ 25.12 ($C(\underline{C}H_3)_3$), 37.39 (CH_2), 39.46 ($\underline{C}(CH_3)_3$), 52.54 (OCH_3), 54.74 (C4), 95.71 (C2), 126.79 (d, arom. C), 129.17 (d, arom. C) 131.00 (d, arom. C), 135.58 (s, arom. C), 169.11 (C=O), 171.91 (C=O), 174.05 (C=O). – IR (KBr): ν = 3068 cm^{-1} (CH) (w), 2978 (CH) (m), 2875 (sh), 1787 (C=O, (C5)) (vs), 1750 (C=O, (ester)) (s), 1675 (C=O, (benzoyl)) (s), 1439 (w), 1368 (s), 1338 (m), 1296 (m), 1245 (m), 1203 (m), 1153 (m), 1044 (m), 996 (w), 906 (w), 710 (C-H) (m). – MS (70 eV): *m/z* (%) = no (M^+), 262 (6) (M^+ – ^{t}Bu), 234 (8) (– CO), 206 (4) (– CO), 105 (100), 77 (26), 57 (4), 51 (6); $[\alpha]_D^{20}$ = – 1.02° (c = 7.71 in $CHCl_3$), $[\alpha]_{Hg\,360}^{20}$ = – 16.86° (c = 7.71 in $CHCl_3$); Anal. Calcd for $C_{17}H_{21}NO_5$ (319.4): C 63.94 H 6.63 N 4.39; Found: C 63.89 H 6.77 N 4.40.

(2R,4S)-3-Benzoyl-2-tert-butyl-4-methoxycarbonylmethyl-oxazolidine-5-one (**7**)

Single crystals of **7** suitable for X-ray structure analysis were obtained from a mixture of **6** and **7** in ethyl acetate/cyclohexane (1:4). – ^{1}H NMR (C_6D_6): δ 0.92 (s, 9H, $(C(CH_3)_3$), 1.8–2.3 (s, broad signal, corresponds to 0.4 H, CH_2), 2.73 (d, 1 H, CH_2), 3.24 (s, 3 H, OCH_3), 4.04 [s, 1 H, H-C(4)], 6.44 [s, 1 H, H-C(2)], 7.11–7.23 (m, 3 H, arom. H), 7.53–7.56 (d, 2 H, arom. H). – ^{13}C NMR (C_6D_6): δ 24.65 ($\underline{C}(CH_3)_3$), 39.16 (weak signal, CH_2), 39.30 ($\underline{C}(CH_3)_3$), 51.51 (OCH_3), 55.01 (C4), 95.31 (C2), 127.50 (d, arom. C), 127.93 (d, arom. C), 128.24 (d, arom. C), 128.67 (d, arom. C), 128.84 (d, arom. C), 131.50 (s, arom. C), 169.01 (C=O), 169.75 (C=O), 171.71 (C=O). – MS (70 eV): *m/z* (%) = no M^+, 305 (4) (M^+ – Me), 262 (12) (M^+ – ^{t}Bu), 234 (14) (– CO), 206 (4) (– CO), 154 (4), 122 (4), 105 (100), 77 (26), 57 (7), 51 (9), 40 (16); Anal.

Calcd for $C_{17}H_{21}NO_5$ (319.4): C 63.94 H 6.63 N 4.39. Found: C 63.78 H 6.77 N 4.69 $[\alpha]_D^{20} = +94.3°$ (c = 13.63 in $CHCl_3$), $[\alpha]_{Hg\,360}^{20} = +366.7°$ (c = 13.63 in $CHCl_3$).

(2S)-3-Benzoyl-2-tert-butyl-4-methoxycarbonylmethyleneoxazolidine-5-one (**4**)

6 (560 mg) was dissolved in CCl_4 (20 ml) and NBS (332.5 mg, 1.84 mmol, 1.05 equiv.) was added. The round bottom flask was placed in a dish-shaped dewar flask and exposed to a 300 W bulb. After heating to reflux the brown solution was cooled to 0 °C, then filtered and evaporated. Column chromatography (silica gel, cyclohexane/ethyl acetate, 4:1) yielded 318 mg of a colorless solid, 58%; *m.p.* 103–113 °C. – ^{1}H NMR ($CDCl_3$): δ 0.99 (s, 9 H, $(CH_3)_3$, 3.26 (s, 3 H, OCH_3), 5.81 (s, 1 H, H-C(6)), 6.05 (s, 1 H, H-C(2)), 7.25–7.40 (m, 5 H, arom. H). – ^{13}C NMR ($CDCl_3$): δ 24.79 ($\underline{C}(CH_3)_3$), 39.65 ($C(CH_3)_3$), 51.71 (OCH_3), 97.14 (C2), 108.20 (C4), 128.14 (d, arom. C), 129.31 (d, arom. C) 131.50 (d, arom. C), 134.15 (s, arom. C), 164.28 (C=O), 169.26 (C=O), 175.10 (C=O). – MS (70 eV): *m/z* (%) = 317 (1) M^+, 260 (0.4) [$M^+ - {}^t$Bu], 258 (0.5) ($M^+ - C_2H_3O_2$), 207 (0.6), 144 (0.5), 105 (100), 77 (24), 51 (6). – IR (KBr): ν = 2981 cm^{-1} (arom. H) (w), 2967 (CH) (w), 1796 (C=O,5-On) (s), 1709 (C=O, ester) (s), 1696 (C=O, benzoyl) (s), 1670 (C=C) (m), 1444 (w), 1406 (w), 1296 (m), 1288 (m), 1263 (s), 1252 (s), 1023 (w), 763 (w), 702 (arom. H deform.) (m); Anal. Calcd for $C_{17}H_{19}NO_5$: C 64.34 H 6.03 N 4.41. Found: C 64.52 H 5.94 N 4.66 $[\alpha]_D^{20} = +62.4°$ (c = 6.81 in $CHCl_3$)

Crystal Data for compounds 6 and 7

6: $C_{17}H_{21}NO_5$, crystal size 0.63 × 0.50 × 0.44 mm^3, monoclinic, space group $P2_1/n$ (No. 14), a = 8.679(1), b = 19.552(2), c = 10.067(1) Å, β = 100.84(1)°, V = 1677.9(2) Å^3, Z = 4, $F(000)$ = 680, ρ_{calc} = 1.264 Mg/m^3, μ = 0.09 mm^{-1}, graphite monochromized Mo-Kα radiation, Enraf-Nonius CAD4 diffractometer, T = 293 K, $2\Theta_{max}$ = 52.3°, 3651 intensities measured, 3403 unique (R_{int} = 0.041), 1773 observed ($I \geq 2\sigma(I)$), structure solved with Direct Methods (SHELXS-86) and refined with Full-Matrix Least Squares on F^2 (SHELXL-93), hydrogen atoms placed in calculated positions and refined riding, all non-H atoms refined anisotropic, 212 parameters, R = 0.046, wR^2 = 0.099, final residual electron density 0.19 eÅ^3.

7: $C_{17}H_{21}NO_5$, crystal size 0.50× 0.30 × 0.3 mm^3, ortho- rhombic, space group $P2_12_12_1$ (No. 19), a = 9.041(2), b = 11.431(1), c = 15.768(2) Å, V = 1629.6(4) Å^3, Z = 4, $F(000)$ = 680, ρ_{calc} = 1.302 Mg/m^3, μ = 0.79 mm^{-1}, graphite monochromized Cu-Kα radiation, Enraf-Nonius CAD4 diffractometer, T = 223 K, $2\Theta_{max}$ = 148.0°, 2123 intensities measured, 1911 unique (R_{int} = 0.038), 1825 observed ($I \geq 2\sigma(I)$), structure solved with Direct Methods (SHELXS-86) and refined with Full-Matrix Least Squares on F^2 (SHELXL-93), hydrogen atoms placed in calculated positions and refined riding, all non-H atoms refined anisotropic, 213 parameters, R = 0.045, wR^2 = 0.125, final residual electron density 0.25 eÅ^3, Flack parameter 0.2(3).

Further details of crystal structures analyses can be obtained through Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen 2, Germany on quoting the depository numbers CSD 404882 and CSD 404883, the names of the authors and the journal citation.

Table 2 Comparision of selected bond lengths (Å) for **6** and **7**

N(1)-C(11)	1.372(3)	N(3)-C(31)	1.369(3)
N(1)-C(3)	1.458(3)	N(3)-C(4)	1.469(3)
N(1)-C(1)	1.476(3)	C(2)-N(3)	1.469(3)
O(1)-C(2)	1.338(3)	O(1)-C(5)	1.340(3)
O(1)-C(1)	1.441(3)	O(1)-C(2)	1.447(3)
O(2)-C(2)	1.192(3)	C(5)-O(5)	1.201(3)
O(3)-C(11)	1.218(3)	C(31)-O(31)	1.223(3)
O(4)-C(9)	1.194(3)	C(42)-O(42)	1.199(3)
O(5)-C(9)	1.329(3)	C(42)-O(43)	1.334(3)
O(5)-C(10)	1.448(3)	O(43)-C(44)	1.447(3)
C(1)-C(4)	1.531(3)	C(2)-C(21)	1.537(3)
C(2)-C(3)	1.504(3)	C(4)-C(5)	1.523(3)
C(3)-C(8)	1.531(3)	C(4)-C(41)	1.523(3)
C(8)-C(9)	1.500(3)	C(41)-C(42)	1.509(3)
C(11)-C(12)	1.496(3)	C(31)-C(32)	1.496(3)

References

[1] I. Schlachter, part of the Ph. D. thesis, Universität Münster, **1995**

[2] K. Alder, G. Stein, Angew. Chem. **50** (1937) 510

[3] a) J. Sauer, R. Sustmann, Angew. Chem. **92** (1980) 773; Angew. Chem., Int. Ed. Engl. **19** (1980) 779;
b) W. Carruthers, Cycloaddition Reactions in Organic Synthesis, Pergamon Press, Oxford **1990**

[4] a) J. Mattay, J. Mertes, G. Maas, Chem. Ber. **122** (1989) 327;
b) J. Mattay, G. Kneer, J. Mertes, Synlett **1990**, 145

[5] a) G. Kneer, J. Mattay, G. Raabe, C. Krüger, J. Lauterwein, Synthesis **1990**, 599;
b) G. Kneer, J. Mattay, Tetrahedron Lett. **33** (1992) 8051;
G. Kneer, J. Mattay, A. Heidbreder, G. Raabe, B. Krebs, M. Läge, J. Prakt. Chem. **337** (1995) 113

[6] a) W. R. Roush, B. B. Brown, J. Org. Chem. **57** (1992) 3380
b) S. G. Pyne, B. Dikic, P. A. Gordon, B. W. Skelton, A. H. White, Austr. J. Chem. **1993**, 73

[7] F. Fotiadu, F. Michel, G. Buono, Tetrahedron Lett. **31**(1990) 4863

[8] S. G. Pyne, B. Dikic, P. A. Gordon, B. W. Skelton, A. H. White, J. Chem. Soc., Chem. Comm. **1991**, 1505

[9] J. Mattay, J. Mertes, Helv. Chim. Acta **71** (1988) 742

[10] B. Bienfait, G. Coppe–Motte, R. Merényi, H. G. Viehe, W. Sicking, R. Sustmann, Tetrahedron **47** (1991) 8167

[11] B. L. Feringa, J. C. de Jong, J. Org. Chem. **53** (1988) 1125

[12] R. Battlori, J. Font, M. Monsalvatje, R. M. Ortuno, Tetrahedron **45** (1989) 1833

[13] K. Takeda, I. Imaoka, E. Yoshii, Tetrahedron **50** (1994) 10839

[14] D. Seebach, A. Fadel, Helv. Chim. Acta **68** (1985) 1243
[15] P. Gmeiner, P. L. Feldmann, M. Y. Chu-Moyer, H. Rapoport, J. Org. Chem. **55** (1990) 3068
[16] P. A. Grieco, S. T. Handy, J. P. Beck, Tetrahedron Lett. **35** (1994) 2663 and references cited therein
[17] MOBY 1.6, U. Höweler, Springer Verlag, Heidelberg 1995
[18] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, J. Am. Chem. Soc. **107** (1985) 3902
[19] MOPAC 6.0, Quantum Chemical Program Exchange (QCPE), No. 455, Indiana University, Bloomington, Indiana, USA **1995**
[20] R. Sustmann, H.-G. Korth in Adv. Phys. Org. Chem., Vol. **26**, (D. Bethell, Ed.), Academic Press, London 1990, p. 131
[21] 25 m SE 30 using a temperature program 60–10 °C/min–250 °C
[22] Light source: Philips HPK 125 W (high pressure mercury lamp)

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