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Synthesis of Enantiomerically Pure ω-Amino Acids by Asymmetric α-Alkylation of Chiral ω-Aminoalkyloxazolines

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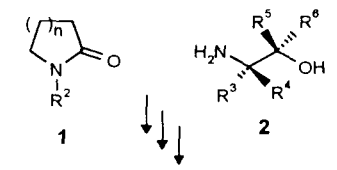
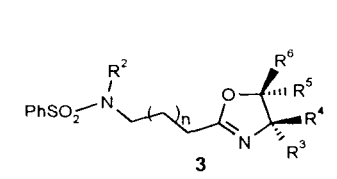
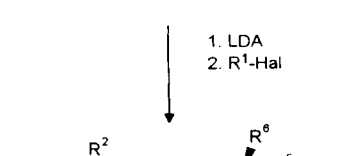
Abstract: Enantiomerically pure α-alkyl-ω-aminocarboxylic acids **5**, **6** and the corresponding α-alkyllactams **7** are synthesized starting from lactams **1** by ring transformation with a chiral aminoalcohol **2**, asymmetric α-alkylation of the resulting 2-(ω-aminoalkyl)-oxazolines **3** and final hydrolysis.

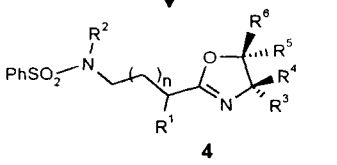
(*R*)-4-Amino-2-methyl-butyric acid was used as building block in the synthesis of calyculine A. [1,2] It was synthesized by amination/decarboxylation of (*R*)-2-methylglutaric acid derivatives. Other routes used for the synthesis of a few optically active α-alkyl-ω-aminocarboxylic acids are based on the reduction of corresponding ω-azidocarboxylic acids derived from ω-halocarboxylic acids [3] and by resolution of racemates. [4] We report now a general synthesis of enantiomerically pure α-alkyl-ω-aminocarboxylic acids **5** and **6** and of corresponding lactams **7** via side chain alkylation of chiral 2-(ω-aminoalkyl)-oxazolines **3**. [5] The precursors **3** can be obtained [6] in enantiomerically pure form starting from lactams **1** via corresponding lactam acetals or lactim ethers that are ring transformed with chiral amino alcohols **2** adopting a known procedure reported for non-optically active 2-(ω-aminoalkyl)oxazolines. [7] The 2-(ω-aminoalkyl)-oxazolines **3** were further submitted to the well-known α-alkylation of 2-alkyl-1,3-oxazolines developed by Meyers based on α-lithiation and treatment of the resulting azaenolate with an alkyl halide. [8] Since Meyers asymmetric side chain alkylation is only highly stereoselective in cases of 4-MOM-substituted oxazolines we used corresponding 2-(ω-aminoalkyl)-4-methoxymethyl-5-phenyl-oxazolines **3** (R^3=MOM, R^4=R^5=H, R^6=Ph). Amazingly, after the lithiation with LDA and further reaction with methyl iodide a stereoselectivity was observed that was unacceptably low (see Table 1 entry 3) as compared with stereoselectivities attained with corresponding 2-alkyloxazolines lacking the ω-amino group (65 - 82% d.e.). Furthermore exchanging the MOM group by a non-chelating group such as Me (R^3=Me, R^4=R^6=H, R^5=Ph) gave rise to the formation of a major stereoisomer **4a** of the same configuration in α-position (see entry 1) , i. e. the MOM group (R^3=MOM) acted as a non-chelating substituent. This gives clear evidence that Meyers model can not be applied to the α-alkylation of ω-aminoalkyloxazolines **3**. Obviously the MOM group fails to chelate in the azaenolate formed after deprotonation with LDA because another chelation is more favoured. We therefore propose the formation of a lithium azaenolate such as **8** (for a 4-(*S*)-configured oxazoline) with the lithium being chelated by the terminal sulfonamino group. [9] Consequently the *E*-azaenolate is formed rather than the *Z*-isomer commonly observed with 2-alkyloxazolines lacking the ω-amino group. [8,10] Since the substituent R^3 is generally passive (i. e. non-chelating) the lithium is directed to the opposite side of the oxazoline ring. Finally the alkyl halide attacks from the Li-substituted face (*re* in case of **8**) directed by a Hal-Li-interaction.

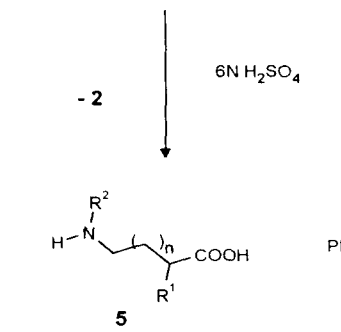


3	4	5	6	7	R^1/(conf.)	R^2	n	R^3	R^4	R^5	R^6
a	a		a		Me(*R*)	Me	1	Me	H	Ph	H
b	b		a		Me(*R*)	Me	1	MOM	H	H	Ph
c	c		c		Me(*S*)	Me	1	H	Et	H	H
d	d		d		Me(*S*)	Me	3	H	Et	H	H
e	e		e	e	Et(*R*)	H	1	MOM	H	H	Ph
f	f	f			*i*-Pr(*R*)	Me	1	MOM	H	H	Ph
g	g		g	g	*n*-Bu(*S*)	H	9	H	Et	H	H









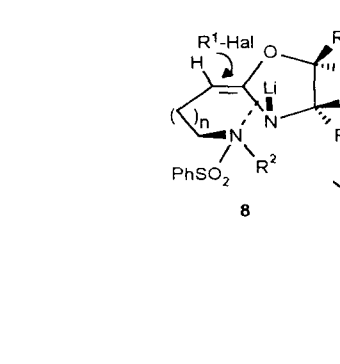


Table 1: Synthesis of 2-(ω-Aminoalkyl)-oxazolines **4**, α-Alkyl-ω-aminocarboxylic Acids **5**, **6** and α-Alkyllactams **7**

entry	reactant	addition of BEt_3	product	% yield/ (% d.e.)
1	**3a**	-	**4a**	52 (24)
2	**3a**	+	**4a**[11]	58 (>90)
3	**3b**	-	**4b**	69 (50)
4	**3b**	+	**4b**	65 (72)
5	**3c**	+	**4c**	58 (>90)
6	**3d**	+	**4d**	54 (>90)
7	**3e**	-	**4e**	49 (28)
8	**3e**	+	**4e**	52 (>90)
9	**3f**	+	**4f**	52 (>90)
10	**3g**	+	**4g**	68 (>90)
11	**4a**	3N HCl [a]	**6a**[12]	95 (>90[b])
12	**4c**	3N HCl [a]	**6c**[13]	95 (>90[b])
13	**4d**	6N H_2SO_4 [a]	**6d**	93 (>90[b])
14	**4e**	1.6N H_2SO_4 [a] 2. DCCI	**7e**[14]	90 (>90[b])
15	**4f**	6N H_2SO_4 [a]	**5f**[15]	50 (>90[b])
16	**4g**	3N HCl [a]	**7g**	66 (>90[b])

[a] conditions for hydrolysis [b] % ee

The stereoselectivity of the α-alkylation of 2-(ω-benzolsulfonylaminoalkyl)-oxazolines **3** can dramatically be improved by the addition of triethylborane to the lithiumazaenolate primarily formed. Only one stereoisomer could be detected by ^{13}C NMR spectroscopy also if other alkyl halides were used (see entries 2,5,6,8,9,10). By changing the configuration of the chiral auxiliary **2** from $R^3 \neq H$, $R^4 = H$ to R3=H, $R^4 \neq H$ the opposite (*si*-attack) α-alkylation can be achieved (see entry 5 versus entry 2). Based on results in the borenolate chemistry [16, 17] as well as in BEt_3-assisted reactions of azaenolate derived from 2-methyloxadiazoles[18] the favourable effect of triethylborane can be explained by a transmetallation of the azaenolate (e. g. **8** → **9**) occurring from the face opposite to the lithium followed by elimination of ethene. In the resulting borazaenolate the borate-like moiety[19] shields the corresponding face very efficiently thus directing the attack of the alkyl halide totally to the opposite side (e. g. *re*-attack in case of **9**).

The oxazoline ring of the α-alkylated 2-(ω-sulfonylaminoalkyl)-oxazolines **4** can easily be cleaved by acid hydrolysis (see Table 1, entries 11 - 16). If the benzolsulfonylamino group is substituted ($R^2 \neq H$) hydrolysis results in 2-alkyl-ω-benzolsulfonylaminocarboxylic acids **6** or 2-alkyl-ω-aminocarboxylic acids **5**. [20] N-Unsubstituted ω-benzolsulfonyl-aminoalkyloxazolines **4** ($R^2 = H$) are hydrolyzed either to analogous ω-sulfonylaminoacids **6** or to mixtures of **6** and corresponding lactams **7**. These mixtures can be converted to pure lactams **7** by additional treatment with DCCI (see entry 14).

The aforementioned reaction sequence demonstrates an efficient asymmetric synthesis of enantiomerically pure ω-amino carboxylic acids **5**, **6** and corresponding lactams **7** of any desired configuration starting from lactams **1**.

Acknowledgement

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9. R^2 = Li in **8** if R^2 = H in corresponding **3**.
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11. **4a**: A solution of 0.187 g (0.5 mmol) of **3a** in 5 ml of dry THF was added to a solution of 1.5 mmol of LDA (from 0.26 ml of diisopropylamine and 1.39 ml of 1.6 M n-buthyllithium in hexane) at -78° C under argon. The resulting dark yellow solution was stirred at -78° C for 5 min, 1.5 mmol of triethylborane (1M solution in THF) were added. After stirring at -78°C for 20 min 2 mmol (0.23 ml) of methyl iodide were added dropwise over 10 min. The resulting, almost pale yellow solution was stirred for 2 h and was then allowed to reach room temperature overnight. The reaction mixture was poured into 30 ml of saturated NH_4Cl solution and extracted (4 x 10 ml) with dichloromethane, dried (Na_2SO_4) and concentrated. Column chromatography on silica gel (R_f = 0.5; ethyl acetate: hexane /9:1) gave 0.112 g (2.9 mmol, 58%) of an oil: $[\alpha]_D^{20}$ = -77.8 (c 0.9, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ / ppm; J / Hz: 0.65-0.68 (d, J = 7.0, 3H, CH_3); 1.22-1.25 (d, J = 7.1, 3H, CH_3); 1.61-1.70 (m, 1H, CH_2); 1.89-2.00 (m, 1H, CH_2); 2.24-2.28 (m, 1H, CH); 2.67 (s, 3H, N-CH_3); 3.03-3.07 (t, J = 7.2, 2H, N-CH_2); 3.99-4.07 (m, 1H, N-CH); 5.46-5.50 (d, J = 9.8, 1H, O-CH); 7.24-7.33 (m, 5H, Ph); 7.41-7.52 (m, 3H, Ph); 7.62-7.72 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ / ppm: 17.8 CH_3; 17.9 CH_3; 30.8 CH-CH_2; 31.7 CH_2; 34.8 N-CH_3; 48.1 N-CH_2; 64.7 N-CH; 83.8 O-CH; 126.1 2xCH_{Ph}; 127.4 2xCH_{Ph}; 127.8 CH_{Ph}; 128.3 2xCH_{Ph}; 129.1 2xCH_{Ph}; 132.6 CH_{Ph}; 136.9 C_{Ph}; 137.3 C_{Ph}; 169.5 C=N.
12. **6a**: 0.077g (0.2 mmol) of **4a** in 10 ml of 3 N HCl were refluxed for 3.5 h. After cooling to room temperature 10 ml of water were added and the reaction mixture was extracted (5 x 10 ml) with dichloromethane, dried (Na_2SO_4) and concentrated to give 0.052 g (1.9 mmol) of pure **6a**: $[\alpha]_D^{20}$ = -14.4 (c 0.14, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ / ppm; J / Hz: 1.20-1.23 (d, J = 7.1, 3H, CH_3); 1.54-1.65 (m, 1H, CH_2); 1.82-2.02 (m, 1H, CH_2); 2.55-2.62 (q, J = 6.9, 1H, CH); 2.70 (s, 3H, N-CH_3); 3.00-3.11 (m, 2H, N-CH_2); 7.23-7.56 (m, 3H, Ph); 7.74-7.76 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ / ppm: 16.8 CH_3; 30.9 CH_2; 34.8 N-CH_3; 36.3 CH-CH_2; 47.9 N-CH_2; 127.3 2xCH_{Ph}; 129.1 2xCH_{Ph}; 132.6 CH_{Ph}; 137.3 C_{Ph}; 181.7 C=O.
13. **6c**: $[\alpha]_D^{20}$ = +13.3 (c 0.1, $CDCl_3$).
14. **7e**: 0.080g (0.2 mmol) of **4e** in 10 ml of 6 N H_2SO_4 was refluxed for 7 h. After cooling to room temperature 30 ml of water were added and the reaction mixture was extracted (5 x 10 ml) with dichloromethane, dried (Na_2SO_4) and concentrated to give 0.060 g of a crude mixture of (*R*)-2-ethyl-4-benzolsulfonylamino-butanoic acid **6e** and (*R*)-3-ethyl-γ-N-benzolsulfonyl-butyrolactam **7e**. The mixture was dissolved in 5 ml of dry acetonitrile. A solution of 0.041g (0.2 mmol) dicyclohexylcarbodiimide (DCCI) in 5 ml of acetonitrile was added with stirring over a period of 10 min. The mixture was stirred at room temperature for 6 h. The dicyclohexylurea is filtered off. Concentration and purification by column chromatography on silicagel (R_f = 0.7; ethyl acetate: hexane /9:1) gave 0.045g (0.18 mmol) of pure lactam **7e**: $[\alpha]_D^{20}$ = -19.5 (c 0.32, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ / ppm; J / Hz: 0.79-0.84 (t, J = 7.5, 3H, CH_3); 1.18-1.36 (m, 1H, CH_2); 1.59-1.74 (m, 2H, CH_2); 2.12-2.17 (m, 1H, CH_2); 2.18-2.32 (m, 1H, CH); 3.59-3.67 (m, 1H, N-CH_2); 3.85-3.91 (m, 1H, N-CH_2); 7.19-7.60 (m, 3H, Ph); 7.95-7.98 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ / ppm: 11.1 CH_3; 23.2 CH_2; 24.4 CH_2; 44.5 CH-CH_2; 45.4 N-CH_2; 127.9 2xCH_{Ph}; 129.0 2xCH_{Ph}; 133.9 CH_{Ph}; 138.1 C_{Ph}; 175.2 C=O.
15. **5f**: $[\alpha]_D^{20}$ = -17.5 (c 0.4, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ / ppm; J / Hz: 0.78-0.80 (d, J = 6.8, 3H, CH_3); 0.92-0.95 (d, J =6.9, 3H, CH_3); 1.69-1.81 (m, 1H, CH_2); 1.90-1.99 (m, 1H, CH); 2.15-2.21 (m, 1H, CH_2); 2.33-2.38 (m, 1H, CH); 2.79 (s, 3H, N-CH_3); 3.21-3.26 (t, J = 6.2, 2H, N-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ / ppm: 17.4 CH_3; 19.3 CH_2; 20.5 CH_3; 28.3 CH-CH_3; 29.3 N-CH_3; 47.4 CH-CH_2; 47.9 N-CH_2; 176.4 C=O.
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19. ^{11}B NMR chemical shifts of intermediates **9** were measured in the range of -7 to +7 ppm with $BF_3 \cdot OEt_2$ as standard giving evidence for borate-like species.
20. e.e. was determined by HPLC on a chiral phase. The absolute configuration of **6a** was determined by independent synthesis starting from known (*R*)- 4-amino-2-methyl-butanoic acid[4].

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