207. Enantioselective Syntheses of α-Amino Acids from 10-(Aminosulfonyl)-2-bornyl Esters and Di(*tert*-butyl) Azodicarboxylate

Preliminary Communication[1])

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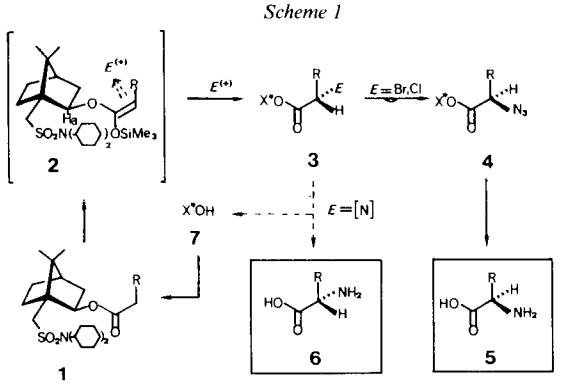
Succesive treatment of chiral esters **1** with $LiN(i\text{-}Pr)_2/Me_3SiCl$ and di(*tert*-butyl) azodicarboxylate/$TiCl_4$/$Ti(i\text{-}PrO)_4$ gave *N,N'*-di[(*tert*-butoxy)carbonyl]hydrazino esters **9** which on deacylation, hydrogenolysis, transesterification, and acidic hydrolysis furnished (2*S*)-α-amino acids **6** in high enantiomeric purity with efficient recovery of the auxiliary alcohol **7**.

The synthesis of enantiomerically pure α-amino acids is an exciting issue which has been adressed increasingly during the last years [1]. Recently, we have met this challenge *via* a simple π-face selective ester halogenation (**1**→**2**→**3**; E^+ = *N*-bromo- or *N*-chlorosuccinimide) [2] and subsequent S_N2-type halide substitution by azide (**3**→**4**) which provided free amino acids **5** in 94 to 98% e.e. and in 42 to 57% overall yield [3] *(Scheme 1)*.

In extension of this work, we present here a topologically reversed approach to amino acids **6** featuring a direct asymmetric formation of the C(2)–N bond, *i.e.* **1**→**2**→**3** with E^+ = di(*tert*-butyl) azodicarboxylate (**8**). As a nitrogen electrophile ([N]), we chose **8** in view of early work showing smooth 1,4-addition of enols and enolates to diethyl azodi-

Scheme 1



[1]) Presented (*W.O.*) in part at the IASOC II Meeting, Ischia, May 1986. At the same occasion, *C. Gennari* presented an independent approach to amino acids *via* asymmetric addition of ephedrine-derived ketene silyl acetals to di(*tert*-butyl) azodicarboxylate.

carboxylate [4] as well as of our own experience which revealed the need of removing the *N*-acyl groups prior to N,N-hydrogenolysis. Exploratory trapping of the (*E*)- and (*Z*)-lithium enolates derived from esters **1** with azoesters proceeded with moderate stereodifferentiation from the predicted face. Thus 'kinetic' (1.1 mol-equiv. of $LiN(i\text{-}Pr)_2$, THF, −78°) or 'thermodynamic' (1.1 mol-equiv. of $LiN(i\text{-}Pr)_2$, THF/hexamethylphosphoric triamide 4:1, −78°) deprotonation [5] of **1f** (R = Bu) followed by addition of di(*tert*-butyl) azodicarboxylate (1.25 mol-equiv., −78°, 1 h furnished adducts **9f** (R = Bu) and 2-epi-**9f** (R = Bu) in ratios of 81:19 and 27:73, respectively.

Scheme 2

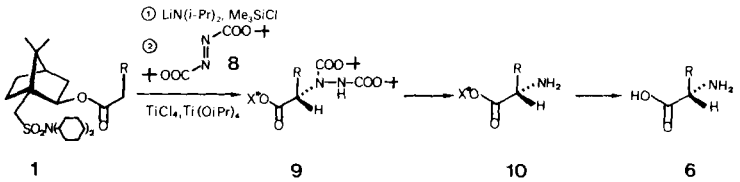


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Table. *Enantioselective Preparation of α-Amino Acids* **6** *from Esters* **1**

Series	R	Azo-ester addition **1 + 8→9**		Deacylation/ hydrogenolysis **9→10**	Ester cleavage **10→6 + 7**	
		Yield of **9**[a]) [%]	d.e. of **9**[b]) [%]	Yield of **10** (cryst.) [%]	Yield of **6**·HCl [%]	e.e of **6** [%]
a	CH_3	81	> 99 (93.7)	80	83	94.9
b	C_2H_5	84	> 99 (96)	77	91	99.7
c	C_3H_7	72(88)	> 99 (96.4)	81	86	99.1
d	i-C_3H_7	73(95)	99 (95)	71	90	99.1
e	i-C_4H_9	71(87)	> 99 (93)	70	86	97.6
f	C_4H_9	85	> 99 (92.5)	80	95	97.5
g	Hexyl	69(93)	> 99 (91)	55	89	97.0
h	$PhCH_2$	76(82)	> 99 (96.3)	64[c])	88[c])	98.5[c])
i	1-Adamantyl-CH_2	65(81)	> 99 (64)	78	65	97.2

[a]) After chromatography; in parentheses, yield based on recovered starting ester **1**.
[b]) After chromatography; in parentheses d.e. of crude adducts **9**.
[c]) R = Cyclohexyl-CH_2.

Significantly higher selectivities were observed in the *Lewis* acid promoted reactions **1→2→9** as depicted in *Scheme 2* and in the *Table*[2]). The crystalline starting esters **1**[3]) were usually obtained in 82 to 96% yield by reaction of auxiliary alcohol **7** with acyl chlorides in the presence of AgCN [2] [9]. Kinetically controlled deprotonation/silylation of esters **1** [10] followed by treatment of the resulting crude ketene silyl acetals **2** with $TiCl_4$/Ti(i-

[2]) For $TiCl_4$/$Ti(i\text{-}PrO)_4$-mediated 1,4-additions of ketene silyl acetals to enoates and enones, see [6]; for highly π-face-selective acetoxylations, halogenations, and aldolisations of **2** see [7], [2], and [8], respectively.
[3]) All new compounds were characterized by IR, ^{1}H-NMR, and MS.

$PrO)_4$ 2:1 and azo ester **8** at −78° gave adducts **9**[3]) in good yields[4]). Direct HPLC and ^{1}H-NMR (360 MHz, 100°) analyses of crude *N,N*-diacylhydrazoesters **9** revealed initial diastereoisomeric purities (d.e.) of 91 to 96.4% (**9a–h**) and 64% d.e. (**9i**) which were routinely increased to virtually 100% d.e. by flash chromatography. Adduct **9a** was also purified by crystallization. The lower π-face differentiation observed on formation of **9i** may be attributed to the exceptional steric bulk of the adamantyl group in **2i**.

To achieve the required *N,N*-hydrogenolysis the *tert*-butoxy carbonyl groups were first removed by stirring **9** in CF_3COOH/CH_2Cl_2 1:1 (0°→r.t., 3 h). Evaporation of the solution and shaking of the residue with PtO_2 (catalytic amount, *Fluka* or *Ventron*) in EtOH under H_2 (75 psi, r.t., 12–24 h) afforded smoothly crystalline amino esters **10**[3]) (55 to 80%)[5]). The N,N-cleavage of **9h** showed that hydrogenation of the phenyl ring occurred concomitantly to give cleanly the hexahydrophenylalanin ester **10h**[3]). Although acidic hydrolysis of esters **10** gave straightaway amino acids **6**, the auxiliary **7** was destroyed. More advantageously, we regenerated the chiral alcohol **7** in > 95% yield by non-destructive transesterification of **10** in the presence of Ti $(EtO)_4$ (1 mol-equiv., EtOH, 70°, 3 h for **10a**, 20°, 60 h). Heating of the resulting crude amino acid ethyl esters in 6N aq. HCl under reflux and evaporation of the solution afforded the amino-acid hydrochlorides **6**·HCl (65 to 95% yield from **10**). The indicated absolute configurations and enantiomeric purities (94.9 to 99.7% e.e.) of the crude amino acids **6** were readily determined by GC (chiral capillary column) comparison [3] [12] of their *N*-(trifluoroacetyl)propyl esters with those of racemic and enantiomerically pure authentic samples and were further supported by chiroptic measurements [13].

In summary, we have described here a new and predictable enantioselective entry to (2*S*)-α-amino acids **6**, readily applicable to the syntheses of (2*R*)-α-amino acids **5** given the commercial availability of both antipodal auxiliaries.

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Note Added in Proof. – After submission of this manuscript the approach of *Gennari et al.* and further aminations of chiral enolates have been published [14].

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[4]) The following experimental procedure is representative for the conversion **1**→**9**: Addition of ester **1** to a mixture of freshly prepared $LiN(i\text{-}Pr)_2$ (1.1 mol-equiv.) and $ClSiMe_3$ (1.75 mol-equiv., −78°) stirring the mixture at −78° for 1 h and, after removal of the cooling bath, stirring for 0.5 h, evaporation, extraction with pentane (for **2i**, CH_2Cl_2), and filtration and evaporation of the pentane solution furnished crude ketene silyl acetal **2**. Crude **2** (in CH_2Cl_2) was added over 10 min to a mixture of $TiCl_4$ (1 mol-equiv.), Ti-(i-PrO)$_4$ (0.5 mol-equiv.), and freshly recrystallized azo ester **8** (1.25 mol-equiv.) in CH_2Cl_2 at −78°. Stirring of the mixture at −78° for 1 h, quenching with aq. $NaHCO_3$ soln., and workup gave crude *N,N'*-diacylhydrazino ester **9**.

[5]) For an example of N,N-hydrogenolysis, see [11]. Reductive N,N-cleavage of **9** or the corresponding diethylazodicarboxylate adducts could not be accomplished. Attemps to hydrogenolyse the *isolated* hydrazino esters obtained by CF_3COOH-mediated deacylation of **9** and alkaline workup gave erratic results.

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