

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

Preliminary Communication¹⁾

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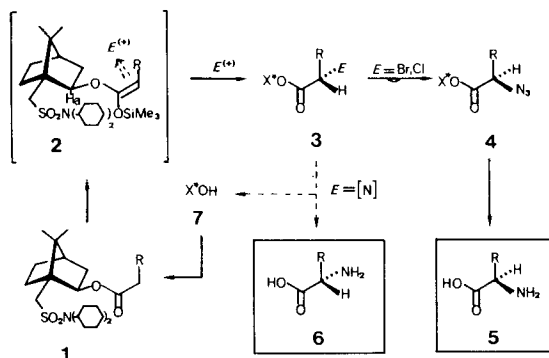
(3. X. 86)

Successive treatment of chiral esters **1** with $\text{LiN}(\text{i-Pr})_2/\text{Me}_3\text{SiCl}$ and di(*tert*-butyl) azodicarboxylate/ $\text{TiCl}_4/\text{Ti}(\text{i-PrO})_4$ gave *N,N'*-di[(*tert*-butoxy)carbonyl]hydrazino esters **9** which on deacylation, hydrogenolysis, transesterification, and acidic hydrolysis furnished (*2S*)- 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 addressed increasingly during the last years [1]. Recently, we have met this challenge *via* a simple π -face selective ester halogenation (**1**→**2**→**3**; $\text{E}^+ = \text{N}$ -bromo- or *N*-chloro-succinimide) [2] and subsequent $\text{S}_{\text{N}}2$ -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 $\text{E}^+ = \text{di}(\text{tert-butyl}) \text{ azodicarboxylate (8)}$. As a nitrogen electrophile ($[\text{N}]$), we chose **8** in view of early work showing smooth 1,4-addition of enols and enolates to diethyl azodi-

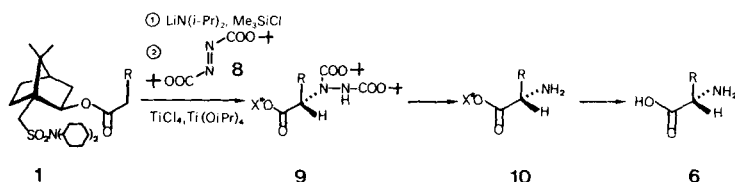
Scheme 1



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 stereo-differentiation from the predicted face. Thus 'kinetic' (1.1 mol-equiv. of $\text{LiN}(\text{i-Pr})_2$, THF, -78°) or 'thermodynamic' (1.1 mol-equiv. of $\text{LiN}(\text{i-Pr})_2$, THF/hexamethylphosphoric triamide 4:1, -78°) deprotonation [5] of **1f** ($\text{R} = \text{Bu}$) followed by addition of di(*tert*-butyl) azodicarboxylate (1.25 mol-equiv., -78° , 1 h) furnished adducts **9f** ($\text{R} = \text{Bu}$) and 2-epi-**9f** ($\text{R} = \text{Bu}$) in ratios of 81:19 and 27:73, respectively.

Scheme 2

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>i</i> - C_3H_7	73(95)	99 (95)	71	90	99.1
e	<i>i</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)} $\text{R} = \text{Cyclohexyl-CH}_2$.

Significantly higher selectivities were observed in the *Lewis* acid promoted reactions **1** → **2** → **9** as depicted in Scheme 2 and in the Table²⁾. 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 $\text{TiCl}_4/\text{Ti}(\text{i-PrO})_4$ -mediated 1,4-additions of ketene silyl acetals to enoates and enones, see [6]; for highly π -face-selective acetoxylation, halogenations, and aldolisations of **2** see [7], [2], and [8], respectively.

²⁾ For $\text{TiCl}_4/\text{Ti}(\text{i-PrO})_4$ -mediated 1,4-additions of ketene silyl acetals to enoates and enones, see [6]; for highly π -face-selective acetoxylation, halogenations, and aldolisations of **2** see [7], [2], and [8], respectively.

³⁾ All new compounds were characterized by IR, $^1\text{H-NMR}$, and MS.

PrO)₄ 2:1 and azo ester **8** at -78° gave adducts **9**³⁾ in good yields⁴⁾. Direct HPLC and ¹H-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 CF₃COOH/CH₂Cl₂ 1:1 (0° → r.t., 3 h). Evaporation of the solution and shaking of the residue with PtO₂ (catalytic amount, *Fluka* or *Ventron*) in EtOH under H₂ (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 6*N* 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.

Financial support of this work by the *Swiss National Science Foundation*, *Sandoz Ltd.*, Basel, and *Givaudan SA*, Vernier, is gratefully acknowledged. We thank Mr. *J. P. Saulnier*, Mr. *A. Pinto*, and Mrs. *C. Clément* for NMR and MS measurements and particularly Mr. *M. von Arx*, Mr. *T. Kobayashi*, and *A. J. M. Janssen* for their technical contribution.

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].

⁴⁾ The following experimental procedure is representative for the conversion **1** → **9**: Addition of ester **1** to a mixture of freshly prepared LiN(*i*-Pr)₂ (1.1 mol-equiv.) and ClSiMe₃ (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**, CH₂Cl₂), and filtration and evaporation of the pentane solution furnished crude ketene silyl acetal **2**. Crude **2** (in CH₂Cl₂) was added over 10 min to a mixture of TiCl₄ (1 mol-equiv.), Ti(*i*-PrO)₄ (0.5 mol-equiv.), and freshly recrystallized azo ester **8** (1.25 mol-equiv.) in CH₂Cl₂ at -78° . Stirring of the mixture at -78° for 1 h, quenching with aq. NaHCO₃ 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. Attempts to hydrogenolyse the *isolated* hydrazino esters obtained by CF₃COOH-mediated deacylation of **9** and alkaline workup gave erratic results.

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