178. Alkylation of Imidazolidinone Dipeptide Derivatives: Preparation of Enantiomerically Pure Di- and Tripeptides by 'Chirality Transfer' *via* a Pivalaldehyde N,N-Acetal Center

Preliminary Communication

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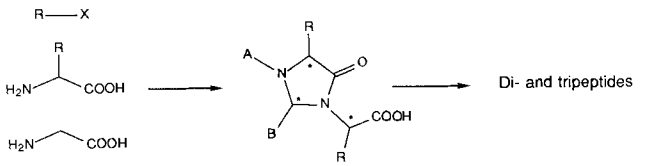
Glycylglycine, glycyl-(*S*)-alanine, and (*S*)-alanylglycine esters are cyclized through pivalaldehyde imines to give dipeptide-derived 3-(benzyloxycarbonyl)-2-(*tert*-butyl)-5-oxoimidazolidine-1-acetates **1–3**. These are alkylated diastereoselectively by Li-enolate formation and addition of alkyl bromides or iodides (products **4–6**). Starting from (*S*)-alanine and glycine, (*S*)-alanyl-(*S*)-alanine or (*R*)-alanyl-(*R*)-alanine, and (*R*)-alanyl-(*R*)-alanyl-(*S*)-alanine have thus been prepared, with the (*tert*-butyl)-substituted N,N-acetal center playing the role of a pivot or lever for diastereoselective formation of new stereogenic centers under kinetic or thermodynamic control.

1. Introduction. – For some time now we have been active in demonstrating the utility of acetals [1] for the self reproduction of stereogenic centers in the synthesis of amino acids and other α- and β-substituted carboxylic acids [2–9] (reviews: [7][9]). Known imidazolidinone peptide derivatives (see *Formula* in *Scheme 1*), which were used as

Scheme 1



R–X = alkylating agent, A = protecting group, B = *t*-Bu group

'inactivators' of biologically active peptides [10–13] and isolated as by-products [14] observed during the hydrogenolysis of Z-protected peptides, suggested to us that *'chirality transfer'* from one amino-acid residue in a peptide chain to an adjacent residue might be possible *via* an intervening acetal center (diastereoselectivity by 1,3 and/or 1,4 induction). Similar more substituted dipeptide derivatives had been synthesized [15–17] but were not exploited for any synthetic purposes. In the course of our studies we have discovered a new, exocyclic 1,3 induction using pivalaldehyde N,N-acetals (see *Scheme 1*).

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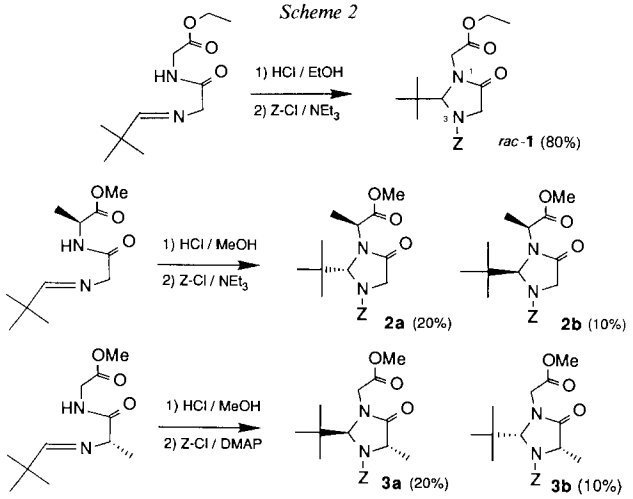
11. Preparation of Imidazolidinones from Dipeptides. – Our hope was that a dipeptide imine could be selectively cyclized and protected to yield diastereoisomeric imidazolidinones **1, 2,** and **3** (see *Scheme 2*). In practice there proved to be two problems with this approach: with the exception of the glycylglycine derivative the yields were not high and the selectivities rather poor [13]. While the unsubstituted glycylglycine-derived imidazolidinone **1** was formed in more than 80% yield from the corresponding imine, the epimeric imidazolidinones **2a** and **2b** resulted in *ca.* 20 and 10% yield, respectively, from glycylalanine using the standard methodology [1] [2] [4]. Simple flash chromatography served to separate the two diastereoisomers. Thus, it seems that the additional CH_3 group retards the cyclization process more than it directs the stereochemical outcome of the acetal formation[2][3]). By placing the CH_3 group adjacent to the imine moiety diastereoisomeric imidazolidinones **3a** and **3b** were obtained in a similar fashion. The utility of these derivatives will become apparent in the following section.

Scheme 2



Z = BnOCO; DMAP = 4-(dimethylamino)pyridine (*Steglich* base)

The benzyloxycarbonyl group (Z) was chosen to protect the N(3)-atom for its ease of removal. It has been shown previously for imidazolidinones from glycine that Z derivatives exhibit high diastereoselectivities in alkylations [2]. In one case we used the *tert*-butoxycarbonyl (Boc) group as protecting moiety with results[4]) comparable to those obtained with the Z protecting group.

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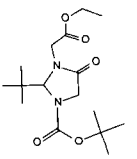
[2]) Although no definitive studies have been done, it seems likely that there is an equilibrium between the open iminium and the cyclized oxoimidazolidinium species. A study of *primary* amino amides cyclized with formaldehyde has been done [18], but the mechanism for these reactions is quite different from cases with *secondary* amino amides (see also [19]).

[3]) Similar cyclization experiments with N^1-benzylglycine amide and N^1-phenethylglycine amide showed a decrease in yield from over 60° to 5% on addition of a CH_3 group. In this case, however, the diastereoselectivity of the reaction is quite high, the minor isomer being below the limit of detection.

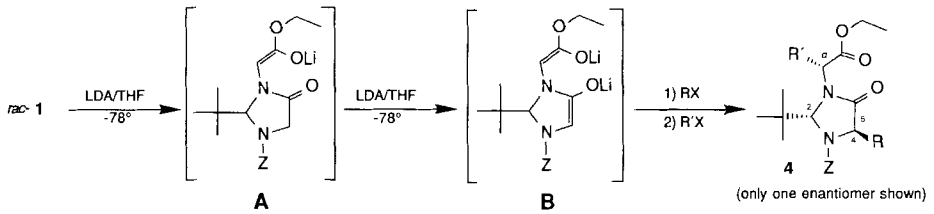
[4]) Compound **i** was prepared analogously to **1** and alkylated using the same procedure to give a 6:1 ratio of diastereoisomers.



i

III. Alkylation of the Imidazolidinones. – Substrate **1** was treated with *slightly less than 2 equiv.* of lithium diisopropylamide (LDA) and then with MeI. To our surprise a dimethylated derivative was formed in high yield and with very high diastereoselectivity. Treatment of **1** with *slightly less than 1 equiv.* of LDA and then with MeI yielded the same dimethylated product and an equivalent amount of starting material. Apparently, the formation of the bis-enolate **B** *(Scheme 3)* is favored over the mono-enolate **A** under normal conditions using LDA. Several alkylations were performed in order to test the general applicability of the bis-enolate alkylation. Mono-alkylation of the endocyclic position was effected by using 1 equiv. of alkylating agent, and the intermediate mono-enolate could be either quenched with a proton source or alkylated with a second alkylating agent *(Scheme 3)*. Only products epimeric at the exocyclic α-position could be observed by high-field NMR spectroscopy in the crude alkylation mixtures; any products epimeric at the endocyclic position were below the limit of detection. From these results it was clear that the most reactive enolate position, and presumably the site of the second deprotonation ('Hauser's rule' [20–23]), was the endocyclic imidazolidinone methylene group.

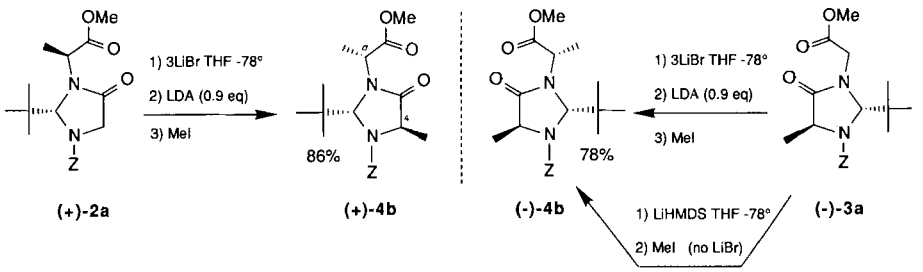
Scheme 3



Product	RX	R'X	Yield [%]	d.r. (by ^{1}H-NMR)
4a	MeI	HOH	77	50:1 (*l/u*)
4b	MeI	MeI	81	7:1 (*l,l/lu*)
4c	EtI	HOH	61	50:1 (*l/u*)
4d	EtI	EtI	47	11:1 (*l,l/l,u*)
4e	BnBr	MeI	75	8:1 (*l,l/l,u*)
4f	BnBr	BnBr	87	25:1 (*l,l/l,u*)

To diastereoselectively alkylate a glycine residue with induction by an adjacent chiral aminoacyl moiety ('transfer of chirality' from an amino-acid residue to an adjacent glycine moiety!) a *mono*-enolate species was required. Simple treatment of **2a** or **2b** with 1 equiv. of LDA and then with MeI in the usual fashion [2] ('kinetic conditions' [24–27]) resulted in a complex mixture of mono- and dialkylated products, including starting material. Similar results were obtained with **3a** and **3b**. Thus, enolization at C(α) of the exocyclic ester or even bis-enolization might have occurred. Literature reports indicated that the generation of an ester enolate in the presence of an ester is a troublesome problem [28]. Proton-exchange processes are very fast even under carefully controlled conditions [29]. Indeed, *Garratt* and coworkers, and others [28] [29] have noted that certain bis-enolates are remarkably stable species, whereas the corresponding mono-enolates give product mixtures. In spite of these facts we found that the bis-enolate generated from **1** could be alkylated twice in high yield, even when the second alkylation was quite slow. The second alkylation must have proceeded *via* a mono-enolate of the required type.

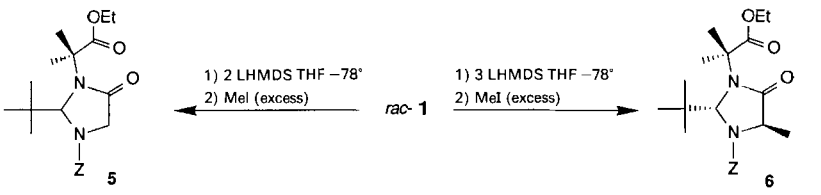
Scheme 4



We wondered if the crucial difference between the mono-enolate generated *via* mono-alkylation of the glycylglycine bis-enolate and the enolate derived from deprotonation of the alanylglycine derivative **3a** was the presence of 1 equiv. of lithium halide formed in the first alkylation of the bis-enolate. Addition of 3 equiv. of LiBr to (–)-**3a** followed by dropwise addition of less than 1 equiv. of LDA at −78° ('thermodynamic conditions' [24–27]) gave an enolate which was alkylated to yield the imidazolidinone (–)-**4b** and the α-epimer in a 7:1 ratio *(Scheme 4)* with no epimerization occurring at the endocyclic 4-position. Using the same conditions for enolization the glycylalanine derivative (+)-**2a** was alkylated at the endocyclic 4-position to yield the enantiomer (+)-**4b**, again with a 7:1 ratio of the α-epimers, with inversion of the original stereogenic center C(α) in the exocyclic position! Thus, by merely inverting the sequence of the amino acids in the original dipeptide, *either enantiomer* may be obtained using the LDA/LiBr conditions. Judging from the identical diastereoselectivities in both cases as well as from the results of additional control experiments, it would appear that the ratio of α-epimers is a result of thermodynamic control. In none of the cases examined could epimerization at the endocyclic position be detected by ^{1}H-NMR or TLC. Nuclear *Overhauser* experiments (NOE) were fully consistent with this interpretation of the alkylation results. Proof of the configuration was provided by deprotection and hydrolysis of the methylated product (+)-**4b** (see *Sect. V*) which yielded (*R*)-alanyl-(*R*)-alanine identical with authentic material.

Contrary to previous reports [27], lithium hexamethyldisilazide (LHMDS) proved to be an effective base for enolization at C(α) of the ester moiety [30]. In practice this base was more selective than LDA/LiBr. By adding slightly less than 1 equiv. of LHMDS to **3a** in the absence of LiBr at −78° followed by MeI at −78° (–)-**4b** was obtained with a 20:1 preference over the α-epimer (see *Scheme 4*). It was not possible to alkylate **2a** using the same conditions. Treatment of **2a** with LHMDS and MeI as before yielded a mixture

Scheme 5

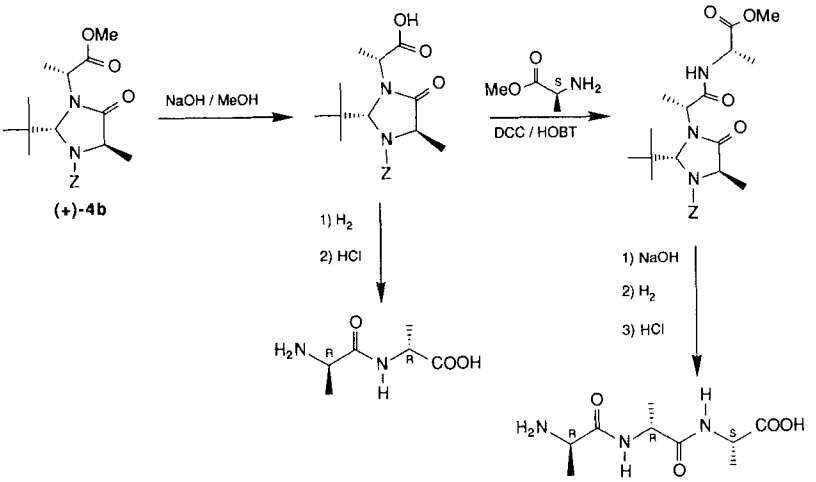


consisting mostly of starting material, epimerized starting material, and a compound which was alkylated at C(α). Additional experiments with the glycylglycine derivative *rac*-**1** (see *Scheme 5*) showed that LHMDS exhibited a completely different behavior towards this substrate than did LDA or LDA/LiBr. Apparently the weaker base, LHMDS, reacts first with the exocyclic ester, and only after that position is completely blocked by alkylation (see **5**), the reagent attacks at C(4) of the endocyclic amide moiety (see **6**).

IV. The Role of LiBr. – We think that the LiBr in this system can play an essential role in de-aggregation, thereby slowing intra-aggregate proton transfer, which has been shown to be extremely fast [31]. LiBr is well known to significantly affect the reactivity of many organometallic species [32–34], and its structural role is slowly beginning to emerge [35–40]. While it is conceivable that the LiBr complexes with the enolate once formed [41] [42], slowing down the proton transfer between enolates, the alkylation results using LHMDS clearly show that *the LiBr is not necessary* for the overall process. Lithium amides are known to exist in a variety of aggregation states [43] [44] and X-ray data [45–48] show aggregation numbers ranging between 1 (no aggregation) and 4, with lithium coordination numbers from 2 to 5. Thus, it is far more likely that the LiBr de-aggregates the LDA, thereby preventing intra-aggregate attack of a second LDA molecule [31] on the enolate to form a bis-enolate. The aggregation state of the LHMDS may not be important due to its lower basicity[5]).

V. Hydrolysis and Further Transformations of (+)-4b. – Deprotection of (+)-**4b** was accomplished in the following manner (*Scheme 6*): *1*) The methyl ester was saponified with NaOH/MeOH. *2*) The Z group was removed with H_2/Pd. *3*) The imidazolidinone was hydrolysed in dilute HCl solution. The resulting dipeptide was recrystallized in good yield and shown to be identical with authentic (*R*)-alanyl-(*R*)-alanine [49] [50] in all

Scheme 6



[5]) It is doubtful that this base is capable of forming bis-enolates in this system. Further experiments are in progress to test the possible uses of LDA/LiBr in other troublesome systems.

respects (TLC, HPLC co-injection, and $[\alpha]_D$). Either the ester group or the Z group may be removed first. Attempts to isolate the dipeptide ester by first removing the Z group and hydrolysing the resulting oxoimidazolidinester resulted in diketopiperazine formation[6]).

As shown in *Scheme 6*, we have used the Z-protected acid intermediate for peptide formation applying a traditional peptide coupling method. Deprotection of these tripeptide derivatives is straightforward.

VI. Conclusions. – The results described here demonstrate the diastereoselective preparation of racemic dipeptides *via* bis-alkylation of glycylglycine derivatives and of enantiomerically pure dipeptides *via* mono-alkylation of alanyl-glycine and glycyl-alanine derivatives. In addition we have demonstrated that the resulting alkylated derivatives may be coupled with other amino-acid residues and deprotected to yield higher peptides. The imidazolidinone dipeptide and tripeptide derivatives are lipophilic enough to be chromatographed on normal silica gel and are, in many cases, crystalline. Conceptually, this represents a new strategy *(Scheme 1)* for peptide synthesis: starting with an intact peptide bond and subsequently adding the amino-acid side chain. This is the first step toward the introduction of novel side chains on intact peptides.

At present we are experimenting with other acetal moieties for stereoselective alkylation of imidazolidinone peptide derivatives, as well as attempting to optimize the yield and selectivity of the imidazolidinone formation. We hope that control experiments will show us more about the precise mechanism and sequence of events in the deprotonation-epimerization-alkylation step. We will report full experimental details of this work in due course.

Typical Alkylation Procedure Using LDA/LiBr. – *Synthesis of (αS,2S,4S)-Methyl 3-(Benzyloxycarbonyl)-2-(tert-butyl)-4,α-dimethyl-5-oximidazolidine-1-acetate* (+)-**4b**. LiBr (500 mg, 5.76 mmol) was weighed into a flame-dried flask and flame-dried once again under Ar. Imidazolidinone **2a** (673 mg, 1.86 mmol) was added and dissolved in 13 ml of dry, O_2-free THF under a positive pressure of Ar. After cooling to −78° a soln. of LDA · $2Et_2O$ in hexane (1.1M, *ca.* 1.76 mmol) was added dropwise (→ colorless soln.). After 45 min MeI (0.35 ml, 5.6 mmol) was added and the mixture stirred at −78° for 16 h. Citric acid (10%, 5 ml) was added at −78° and the mixture was worked up with AcOEt and sat. $NaHCO_3$ soln. in the usual fashion. After evaporation the material was chromatographed [55] on SiO_2 (115 × 30 mm) using AcOEt/hexane (30%) to yield a solid material after solvent removal. Recrystallization from EtOH yielded 604 mg (86%) of crystalline (+)-**4b**.

(+)-**4b**: M.p. 110–111°. $[\alpha]_D = 24.6°$ (*c* = 2.05, AcOEt). ^{1}H-NMR: 3.77 (*s*, $COOCH_3$); 1.49 (*d*, *J* = 6.7, CH_3–C(4)); 1.45 (*d*, *J* = 6.9, CH_3–C(α)); 1.01 (*s*, $(CH_3)_3C$).

rac-**1**: M.p. 69–70. ^{1}H-NMR: 4.17 (*q*, *J* = 7.1, CH_3CH_2O); 1.23 (*t*, *J* = 7.1, CH_3CH_2O); 0.97 (*s*, $(CH_3)_3C$).

2a: M.p. 123–124°. $[\alpha]_D = 14.0°$ (*c* = 2.37, AcOEt). ^{1}H-NMR: 3.77 (*s*, $COOCH_3$); 1.49 (*d*, *J* = 7.0, CH_3–C(α)); 1.04 (*s*, $(CH_3)_3C$).

3a: M.p. 62–70°. $[\alpha]_D = -22.6°$ (*c* = 2.44, AcOEt). ^{1}H-NMR: 3.84 (*s*, $COOCH_3$); 1.59 (br. *d*, *J* = 5.5, CH_3–C(4)); 0.93 (*s*, $(CH_3)_3C$).

(−)-**4b**: M.p. 110–111°. $[\alpha]_D = -23.6°$ (*c* = 1.82, AcOEt). ^{1}H-NMR: identical with that of (+)-**4b**.

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[6]) Diketopiperazines are the starting materials in *Schöllkopf*'s bis-lactim-ether method of preparing amino acids in an overall enantioselective process, with an amino-acid moiety as stoichiometric chiral auxiliary. For recent reviews, see [51–53]; newest application, see [54].

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