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ENANTIOSELECTIVE SYNTHESIS OF OPTICALLY PURE NATURAL S(+) OR UNNATURAL R(-) DABA.

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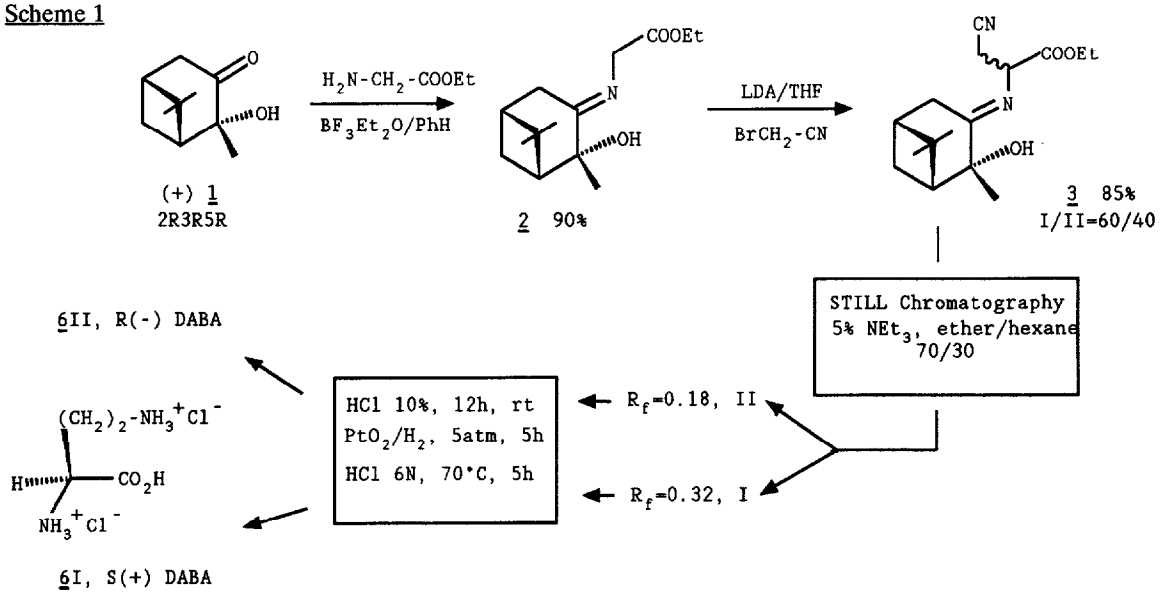
Abstract: After optimization of the reaction conditions, optically pure S(+) DABA is obtained in more than 80% overall yield. A model is proposed to explain the dependence of asymmetric induction on the nature of the counter ion (Li^+, Mg^{++}, Bu_4N^+).

Isolated from acid hydrolysates of antibiotic polypeptides of polymixins type (1,2), S(+) DABA **6** is the major neurotoxic principle of plants as *Lathyrus latifolius* (3). More recently, S(+) DABA was found to inhibit GABA transaminase, thus producing an elevation of GABA level (4), and to have an antitumor activity *in vitro* and *in vivo* against mouse fibrosarcoma cells (5).

S(+) DABA has been prepared by Curtius (6), Schmidt (7) or Hofmann (8) degradations from S-glutamic acid, but until now no asymmetric synthesis is available which would provide a desired enantiomer optically pure.

In the course of our study on asymmetric synthesis of both enantiomers of DABA, we have been interested in Stork's method (9) using as inducer of chirality 2-hydroxypinan-3-one, **1**, proposed by Yamada (10), and the inexpensive ethyl glycinate. However we have been immediately confronted with poor asymmetric induction (Table 1, entry 1), contrary to literature data (10, 11).

Scheme 1



We report here our successful attempt to increase the asymmetric induction to 100%.

The results are given on Table 1.

As shown on Scheme 1, Schiff base **2** is obtained in 90% yield using BF_3-etherate as catalyst, then alkylation of dianion **2a** with bromoacetonitrile affords imine **3**, as a 60/40 mixture of diastereomers (12), which are separated by column chromatography. After hydrolysis (HCl 10%), hydrogenation (PtO_2/EtOH/HCl, 5 atm) and again hydrolysis (HCl 6N), both antipodes of DABA hydrochloride are obtained (13). Full assignment of the 200MHz NMR spectrum of imines **2** has been done (14) ; therefore the yields of alkylation and the asymmetric induction can be easily determined on crude products **3**, thus avoiding false conclusions through accidental enrichment during purification and isolation.

TABLE 1: Addition of $BrCH_2CN$ on dianion **2a**

entry	Counter ion	Solvent	Base	Exchanging salt	Yield %(a)	Diastereomer ratio,%(b)	Configuration at C-α
1	Li^+	THF	LDA,2eq		100	60/40	S (c)
2	Li^+	hexane	LDA,2eq		55	55/45	-
3	Li^+	THF	tBuLi,2eq		100	66/33	S (d)
4	Zn^{+2}	THF	LDA,2eq	$ZnCl_2$,.5eq	100	80/20	S (d)
5	Mg^{+2}	THF	LDA,2eq	$MgBr_2$,2eq	35	100/0	S (d)
6	Mg^{+2}	THF	LDA,2eq	$MgBr_2$,1eq	65	100/0	S (d)
7	Mg^{+2}	THF	LDA,2eq	$MgBr_2$,.5eq	85	100/0	S (c)
8	Bu_4N^+	THF	LDA,2eq	TBAF,1eq	85	55/45	-

(a) The exchanging salt is added to the dianion at -78°C, the temperature is allowed to rise -40°C and is maintained at -40°C for 30min.; then the mixture is cooled to -78°C and the organo halide is added dropwise. Yields are determined from the amount of crude products and 200 MHz NMR of those crude products.
(b) The signal of the $\underline{CH}$-CH_2 (X part of an ABX) is deshielded by 0.05 ppm in the major diastereomer ($CDCl_3$/TMS).
(c) Based on isolated amino acid.
(d) Based on NMR see above (b).

The asymmetric induction obtained in the usual conditions (entries 1-3) is poor (10-30%), however the major diastereomer has the S configuration at C-α (based on the isolated amino-acid) in agreement with literature results (10).

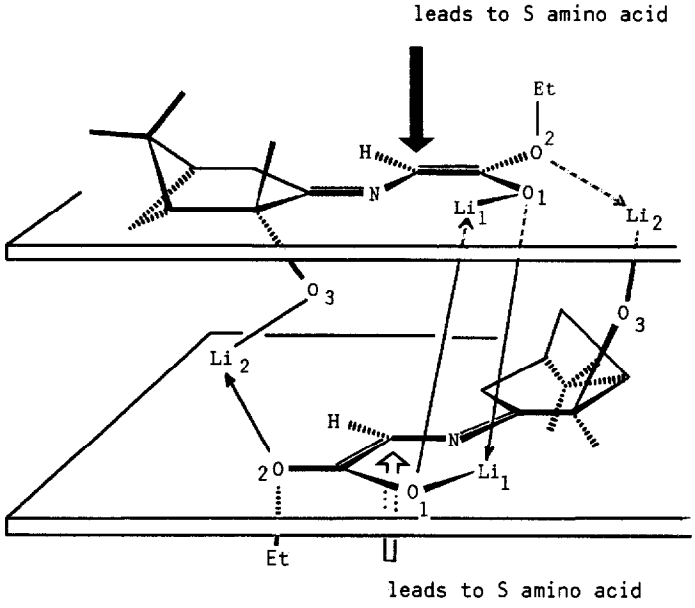
Addition of $MgBr_2$ (entries 5-7) increases the asymmetric induction to 100% and C-α retains the same S configuration. However, with 2 equivalents of $MgBr_2$ the reactivity drops down with chemical yields of 35%, the best conditions being obtained for 0.5 equivalent of $MgBr_2$ with 100% asymmetric induction and 85% chemical yield.

The high asymmetric induction (80%) obtained in the literature (10) was not straightforwardly explained through chelated-enforced chirality transfer as pointed out by Evans (15) neither was the nature

of the configuration obtained at C-α . As it is well accepted, since isolation by Seebach of crystalline enolates (16,17), that reactions can be discussed in terms of enolate aggregates (15,18,19) we have proposed (14) that a folded-dimer could be responsable for the observed diastereoselectivity (10).

The effects of Mg^{++} and Bu_4N^+ on the diastereoselectivity reported here appear to be consistent with this model (20).

Scheme 2



The poor asymmetric induction obtained in the usual conditions (entries 1-3) could be explained by the fact that the nitrogen lone pair of the bromoacetonitrile competes with oxygen O-2 for complexation with Li-2 thus allowing the "dimer" (scheme 2) to unfold with, as a consequence, a decrease in the face differentiation. It might also be that LiBr formed during the reaction disrupts the folding with the same consequence (19). Introduction of a stronger complexing metal (Mg^{++}) could then reinforce the folding through metal exchange or formation of extra-bridges, and would therefore prevent unfolding by bromoacetonitrile or LiBr and increase the asymmetric induction. One could also understand the decrease in yield obtained in the presence of 0.5 to 2 equivalents of $MgBr_2$ on the basis of known effect of cation on charge distribution and thus on the reactivity in enolates (21).

When TBAF is used, one can anticipate that "almost naked" F^- will also compete with the alkoxide O-3 for Li-2 (because of the high Li-F bond energy) and that the "folding-bridges" will be disrupted, the new cation being now unable to restore them by complexation. One can thus expect a decrease in asymmetric induction which is the case (10%, entry 8).

As it has been established that Zinc enolates might exist in a C-metal tautomeric form (22), the above model does not hold in this case (entry 4).

Works are in progress in this field and among which crystallization of the different enolates.

However at this stage of the work and apart from the fact that optically pure S(+) DABA has been obtained in more than 80% overall yield, it can be anticipate that the asymmetric induction is probably due, but indirectly, to the chiral auxiliary used. The main origin could be self clustering in bifunctionalized tridimensional dianions probably favored by the rigidity of the chiral fragment.

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12) 3.95mmol of imine **2** in 3.5ml of anhydrous THF are added dropwise to 7.9mmol of LDA in 4ml of THF at -78°C. Stirring is maintained 15min, then (at -78°C) 8mmol of $BrCH_2CN$ are added dropwise but rapidly and the mixture is stirred at -78°C for 2 hours. After pouring the solution into 50ml of saturated NH_4Cl , the aquous layer is extracted 7 times with 80ml ether .The etheral extracts are joined , dried over Na_2SO_4 and concentrated : yield = 80-85% .
13) DABA,2HCl 6I (obtained from 3I, R_f=0.32): $[\alpha]$=+14.3° (c 4.23, H_2O), lit. +15° (c 3.67, H_2O). Anal. calc. for $C_4H_{12}Cl_2N_2O_2$: C, 25.13; H, 6.28; Cl, 37.17; N, 14.66. Found: C, 25.08; H, 6.24; Cl, 36.18; N, 14.24. ^1H NMR (Bruker WP200 SY) in D_2O positioned at 4.8ppm: 2.25 (2H,m,CH_2), 3.20 (2H,m,CH_2), 4.15 (1H,d.d,CH). 6II (obtained from 3II, Rf=0.18): $[\alpha]$=-13.2° (c 3.75, H_2O)
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20) The folded-dimer has been built-up using FMN models (from Prentice-Hall, INC, Englewood Cliffs, N.J.). Bonds lengths come from X-Ray structure of enolates dimers (see above 17). To minimize steric constraints complexation of the Li-2 (bonded to the alkoxide oxygen O-3) has been envisaged with O-2 and not with O-1. Then one observes that the nitrogen lone pair is just in the right position to complex Li-1.
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