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DEVELOPMENT OF CHIRAL β-DICARBONYL EQUIVALENTS. ENANTIODIVERGENT ALKYLATION OF ASPARTIC ACID.

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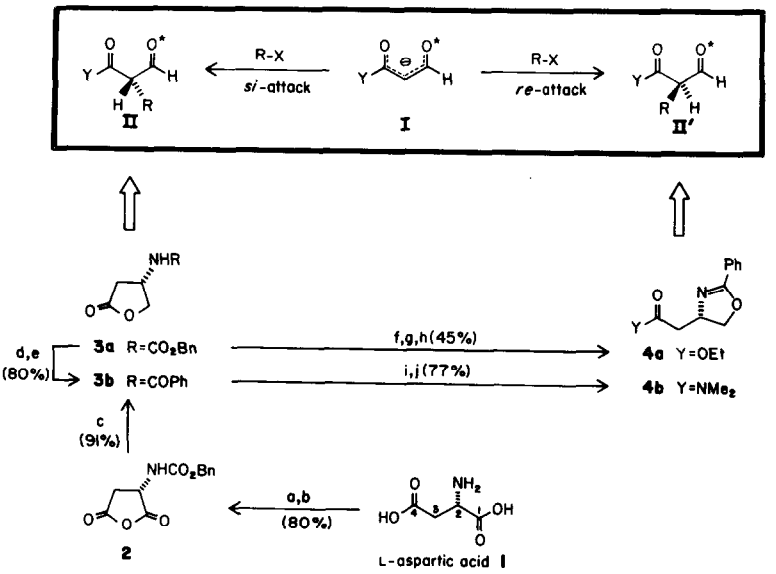
ABSTRACT: L-Aspartic acid has been converted to derivatives which undergo alkylation reactions with stereoselectivities that are enantiomerically complimentary.

We have considered the utility of intermediates that are functionally equivalent to enantiomeric β-dicarbonyl fragments of types II and II' in an effort to develop a practical synthetic strategy applicable to a range of polyfunctionalized natural products. These fragments feature valuable 1,3-oxygen substitution in chemically differentiable form for subsequent elaboration. Furthermore, both stereochemical series are formally derivable from a common precursor I through adjustment of the diastereofacial bias imparted by chirality residing in suitable pro-carbonyl functionality (-CHO*).[1]

Scheme.[5]



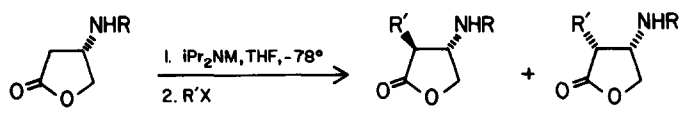
(a) $ClCO_2Bn, K_2CO_3, H_2O$; (b) Ac_2O, AcOH; (c) $NaBH_4$, THF; (d) HBr, AcOH; (e) ClCOPh, pyr.; (f) HCl(g), EtOH, Δ; (g) ClCOPh, Et_3N, $CHCl_3$; (h) Et_3N, DME, Δ; (i) Me_2NH, THF; (j) MsCl, Et_3N

Among the candidates that may serve as reasonable precursors to I, malic acid and related β-hydroxy esters have already received some attention along these lines.[2] For our purposes, however, readily available L-aspartic acid **1** seemed an attractive alternative.[3] Our plan was to take advantage of the facile oxidative cleavage of vicinal aminoalcohols as the means by which the latent aldehyde functionality (-CHO*) is unmasked.[4] This strategy requires the development of efficient methods for the appropriate modification of aspartic acid, as well as demonstration of the stereodirecting influence of the amino group (C-2 in **1**) in subsequent alkylation reactions. This communication reports our preliminary efforts in these directions.

Preparation of the desired derivatives of aspartic acid requires selective reduction of the C-1 carboxyl group. This key transformation was realized through regiospecific reduction of anhydride **2** to protected γ-butyrolactone **3a** (Scheme).[5] Lactones **3a** and readily derived **3b** were expected to allow entry to the stereochemical manifold of fragment II. The alternate series (fragment II') was approached by opening the lactone ring and protecting the aminoalcohol as an oxazoline to afford **4a** and **4b**.

With access to multigram quantities of these compounds in hand, attention was turned to the stereoselective alkylations of their derived enolates. The lactones **3a/3b** were smoothly transformed to their corresponding dianions which subsequently suffered alkylation favoring the expected trans product **5a** (Table I).[7] These product ratios are comparable to those recently reported for the

Table I.[5]



3 **5a** **5b**

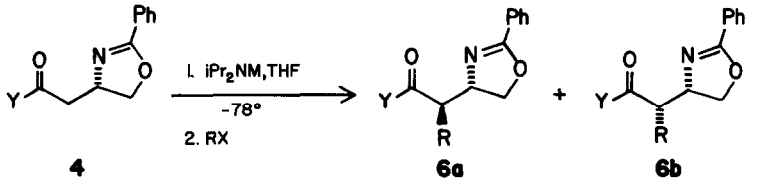
R	M	R'X	5a:5b[a]	Yield[b]
CO_2Bn	Li	MeI	88:12	97%
CO_2Bn	$MgCl^c$	MeI	88:12	88%
CO_2Bn	Li	$CH_2{=}CHCH_2Br$	88:12	80%
COPh	Li	MeI	91:9	77%

[a] Determined by NMR integration. [b] Following purification by column chromatography. [c] iPr_2NMgCl was prepared by refluxing nBuMgCl with iPr_2NH in THF for 15 min.

alkylation of analogous dianions of β-hydroxy-γ-butyrolactones[2a] and, as indicated in the Table, are quite insensitive to the nature of the metal and electrophile. Alternatively, it was expected that chelation with the β-nitrogen in the

enolates resulting from **4a/4b** would impose a diastereofacial bias opposite to that found in the lactones. Deprotonation of **4a/4b** afforded enolates that were stable to at least 0°C. which were sufficiently reactive to undergo alkylation reactions at low temperatures without activating agents such as HMPA.[8] As illustrated in Table II, our expectations were realized as the anti-isomer **6a** predominated. The highest stereoselection was exhibited by the lithium enolate of amide **4b**, which was at levels comparable to recently reported asymmetric alkylations.[9] Enhancing the utility of the amide enolates is the ease with which the diastereomeric product mixtures may often be resolved through simple column chromatography, thus allowing the convenient isolation of isomerically pure compounds.[10]

Table II.[5]



4 **6a** **6b**

Y	M	RX	6a:6b[a]	Yield[b]
OEt	$MgCl^c$	MeI	66:34	84%
OEt	Li	MeI	67:33	81 %
NMe_2	$MgCl^c$	MeI	76:24	——[d]
NMe_2	Li	MeI	83:17	78%
NMe_2	Li	$PhCH_2Br$	92:8	87 %
NMe_2	Li	$CH_2=CHCH_2Br$	94:6	69 %

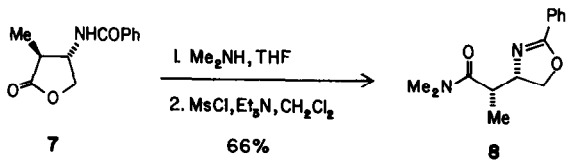
[a] Determined by NMR integration. [b] Following purification by column chromatography.

[c] iPr_2NMgCl was prepared by refluxing nBuMgCl with iPr_2NH in THF for 15 min.

[d] Crude yield of 100%, products were not further purified.

The complimentary nature of these enolates is demonstrated by conversion of the major isomer derived from **3b** to the minor isomer resulting from **4b** (**7→8**). Unfortunately, this transformation was accompanied by about 12% epimerization. However, this interconversion further serves to reinforce the stereochemical assignments that had been based upon spectral evidence and mechanistic reasoning.

While the present results afford synthetically useful entry to functional equivalents of the enantiomeric fragments II and II', work is continuing to improve both the stereoselectivity and flexibility of chiral fragments such as **4**. Application of this strategy to natural products will be reported in due course.



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References and Notes

1. A similar strategy has been recently disclosed.[2a]
2. For representative examples: (a) Chamberlin, A.R.; Dezube, M. Tetrahedron Lett. (1982), 3055; (b) Shieh, H.-M.; Prestwich, G.D. J. Org. Chem. (1981), **46**, 4319; (c) Miller, M.J.; Bajwa, J.S.; Mattingly, P.G.; Peterson, K. J. Org. Chem. (1982), **47**, 4928; (d) Seebach, D.; Wasmuth, D. Helv. Chim. Acta (1980), **63**, 197; (e) Fráter, G. Helv. Chim. Acta (1979), **62**, 2825.
3. For related studies: Seebach, D.; Wasmuth, D. Angew. Chem. Int. Ed. Engl. (1981), **20**, 971.
4. Stork, G.; Leong, A.Y.W.; Touzin, A.M. J. Org. Chem. (1976), **41**, 3491.
5. All compounds give satisfactory spectral and analytical data.
6. (a) Krishnamurthy, S.; Vreeland, W.B. Heterocycl. (1982), **18**, 265; and references cited therein; (b) Barton, D.H.R.; Bénéchie, M.; Khuong-Huu, F.; Potier, P.; Reyma-Pinedo, V. Tetrahedron Lett. (1982), 651.
7. The lactone dianions were formed by treating **3a** or **3b** with about 2.1 eq of base in THF at -78°C for 15 min. Subsequent alkylation took place within 2h at -78°C. We observed highest stereoselectivity when the enolate was rapidly introduced (cannula) to a chilled solution of the electrophile in THF.
8. However, alkylation was very slow and incomplete when only 1 eq of base was employed. Deprotonating with 2.1 eq of base (15 min at -78°C) resulted in a species that condensed at a reasonable rate (1 to 4 h at -78°C). No deleterious effect upon stereoselectivity has been observed by the presence of excess base.
9. Compare with Evans, D.A.; Ennis, M.D.; Mathre, D.J. J. Am. Chem. Soc. (1982), **104**, 1137, as well as references 2c-e.
10. For example, in the case R=Me, the mixture of **6a/6b** is resolved by simple flash chromatography: Still, W.C.; Kahn, M.; Mitra, A. J. Org. Chem. (1978), **43**, 2923.

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