CHEMISTRY LETTERS, pp. 1009-1010, 1990.

Resolution of Diels-Alder Adducts Using a Chiral Carbodiimide

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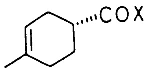
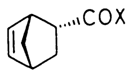
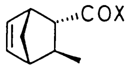
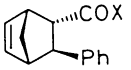
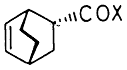
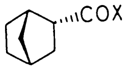
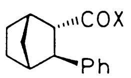
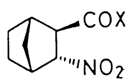
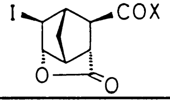
The relation between the separability and the stereochemistry of the acylurea derivatives prepared from chiral mono-, bi- and tricyclic acids and N,N'-bis((S)-1-phenylethyl)carbodiimide were investigated. Conventionally separated diastereomers by silica gel column chromatography were converted to optically pure methyl esters of the corresponding acids upon methanolysis.

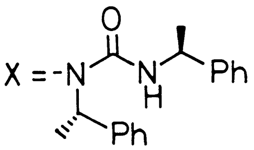
To obtain an optically pure product (100% ee) is often problematic even in these days. Resolution of products obtained is only one solution to this problem. In our previous works we established the method to afford optically pure enantiomers by easy indirect resolution using a chiral carbodiimide (N,N'-bis((S)-1-phenylethyl)carbodiimide).[1,2] In this paper we describe the relationship between the separability and the stereochemistry of mono-, bi- and tricyclic acylureas and the preparation of both optically pure methyl esters of the corresponding acids by the removal of the chiral auxiliary under mild conditions.

In the presence of triethylamine the chiral carbodiimide and cyclic acids prepared by Diels-Alder reactions were reacted in acetonitrile at room temperature to give the corresponding acylureas. The α values of the acylureas were measured by HPLC and shown in Table 1. All α values are large enough to separate each diastereomer by conventional column chromatography (except monocyclic acylurea 1).[3] The results indicate the following features; (a) a bicyclic ring gives larger α value than a monocyclic ring (entries 1 and 2), (b) an introduction of β-substituent group decreases the value (entries 2-4 and entries 6 and 7), (c) bicyclo[2. 2. 1]heptene system gives larger α value than that of bicyclo[2. 2. 2]octene system (entries 2 and 5), (d) in the case of bicyclo-[2. 2. 1]heptene system, hydrogenation of the double bond increases the value (entries 2 and 6, and entries 4 and 7), (e) the absolute configuration can be estimated from the order of the eluants,[4] and (f) the tricyclic iodolactone gives an extremely large α value (α = 2.24).

Table 1. α values of cyclic acylureas[a]

Entry	Acylurea (faster eluant)		α[b]
1		1a	1.08[c]
2		2a	1.56[c]
3		3a	1.51[c]
4		4a	1.29
5		5a	1.42[c]
6		6a	1.81
7		7a	1.46
8		8a	1.23
9		9a	2.24

a) Merck Lichrosorb Si 60; ϕ10 × 250; hexane-ethyl acetate (4:1). b) Separability factor (Ref. 3). c) Ref. 1.



Diastereomeric separation of acylureas **4a** and **4b**, **9a** and **9b** were perfectly accomplished by conventional column chromatography on silica gel (hexane-ethyl acetate (9:1)) with over 99% de. Efficient removal of the chiral auxiliary by methanolysis with sodium methoxide (3 equiv., at 0° C) gave optically active methyl esters, **4c** (X = OMe in entry 4, $[\alpha]_D^{25}$ +136° (c 0.71, $CHCl_3$)) and **9c** (X = OMe in entry 9, $[\alpha]_D^{25}$ +50.8° (c 0.92, CHCl)) from the faster eluants **4a** and **9a** respectively with no epimerization.

Accordingly this developed method using a chiral carbodiimide is efficient for the resolution of bi- and tricyclic carboxylic acids, and also for the estimation of the α value.

We thank the fund of Mitsui Petrochemical Industries, Ltd., for a fellowship (K. K.).

References

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2) K. Kishikawa, M. Yamamoto, S. Kohmoto, and K. Yamada, *Chem. Lett.*, **1989**, 787.

3) W. H. Pirkle and J. Finn, "Separation of Enantiomers by Liquid Chromatographic Methods," in "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, New York (1983), Vol. 1, Chap. 6.

4) From polarimetric analysis of **2c**, **4c**, and **9c** these configuration were confirmed and the other configurations were estimated from the sequence of ^1H NMR data. J. A. Berson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, **81**, 4083 (1989); G. Helmchen, R. Karge, and J. Weetman, "Asymmetric Diels-Alder Reactions with Chiral Enolates as Dienophiles," in "Modern Synthetic Methods 1986," ed by R. Scheffold, Springer-Verlag, Berlin, Vol. 4, p. 294.

(Received April 4, 1990)