Tetrahedron: Asymmetry Vol. 3, No. 3, pp. 343-346, 1992
Printed in Great Britain

0957-4166/92 $3.00+.00
Pergamon Press plc

Asymmetric Synthesis of Exo-norbornane-2-carboxylic Acids

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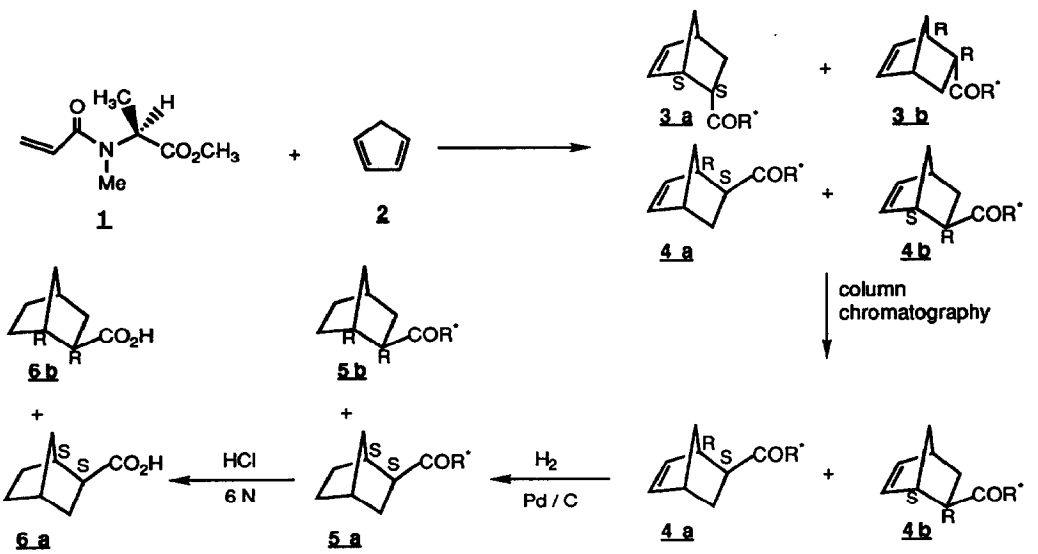
(*Received* 16 *January* 1992)

Abstract : The reaction between N-acryloyl-N-methyl-L-alanine methyl ester and cyclopentadiene is studied. The configuration of the cycloadducts preferably obtained depends on the reaction conditions and the Lewis acid used as a catalyst. In $TiCl_4$-catalyzed reactions, high exo:endo ratios and good diastereomeric excesses in exo cycloadducts are obtained under several conditions. So an interesting method for the asymmetric synthesis of derivatives of exo- norbornane-2-carboxylic acid is described.

Chiral derivatives of the acrylic acid have been extensively used as dienophiles in asymmetric Diels-Alder reactions where high endo:exo ratios and high levels of diasterofacial selectivity have been obtained[1]. So, the use of these dienophiles is an excellent method for the asymmetric synthesis of derivatives of endo-norbornane-2-carboxylic acids. However, there have been no procedures reported for obtaining the exo-compounds in an asymmetric manner. It has been recently described[2] that thermal cycloadditions of sililoxydienes with N,N-dimethylacrylamide proceed with unusual exo-selectivity. Furthermore, N-acryloyl-α-aminoesters are efficient dienophiles in asymmetric Diels-Alder reactions[3]. Consequently, we have studied the Diels-Alder reaction between cyclopentadiene and N-acryloyl-N-methyl-L-alanine methyl ester, in order to obtain the enantiomerically enriched exo-norbornane-2-carboxylic acid.

The chiral dienophile (1) was easily obtained by reaction of N-methyl-L-alanine with acryloyl chloride[4], followed by methylation with BF_3/MeOH complex. It was reacted with cyclopentadiene in CH_2Cl_2 under several conditions (Scheme1). The results of the reactions were determined by integration of the ^{1}H-NMR signals corresponding to $CO_2\underline{CH_3}$ and N-$\underline{CH_3}$ (Scheme1) and are shown in Table 1.



Compound	1	3a	3b	4a	4b
δ (NCH_3)	3.023	3.041	3.034	2.965	2.954
δ (CO_2CH_3)	3.721	3.677	3.696	3.714	3.705

Scheme 1

Table 1: Reaction of 1 with 6 eq. of 2. Percentage of cycloadducts in the overall amount of product.

Entry	Lewis acid (eq)	T ^{0}C	t (h)	Rto %	% 3a	%3b	% 4a	% 4b
1	$TiCl_4$ (0.75)	0	4	100	20.2	54.8	0.8	24.2
2	$TiCl_4$ (0.75)	0	16	100	25.5	49.5	2.5	22.5
3	$TiCl_4$ (0.5)	0	16	100	34.7	29.6	6.4	29.3
4	$TiCl_4$ (1.1)	-20	168	83	36.9	18.1	4.5	40.5
5	$TiCl_4$ (0.75)	25	69	100	29.6	10.4	21.6	38.4
6	$TiCl_4$ (0.5)	25	64	85	21.3	5.7	51.8	21.2
7	$TiCl_4$ (0.5)	-20	168	62	16.6	3.4	72	8.0
8	$AlCl_3$ (1.1)	-20	168	<5	___	___	___	___
9	$AlCl_3$ (1.1)[a]	20	15	100	63.1	19.9	11.4	5.6
10	$AlCl_3$ (1.1)[a]	20	168	83	42.6	22.9	19.6	14.8

[a]. 12 eq. of 2

The results obtained in $TiCl_4$-catalyzed reactions show inversions of the endo/exo, 3a:3b and 4a:4b ratios, depending on the reaction conditions. This fact can be explained by taking into account that the reaction is reversible, and this reversibility is favoured by long reaction times and small amounts of $TiCl_4$. Under kinetic conditions (entries 1 and 2) 3b is the major product and its proportion decreases such that under thermodynamic control it becomes the minor product. Conversely, 4a is the minor cycloadduct under kinetic conditions (entries 1 and 2) and the major one under thermodynamic conditions (entry 7). The percentage of 3a and 4b depends on the reaction conditions to a lesser degree, and these products are obtained in similar proportions in all cases. To sum up, 3b is obtained faster but 4a forms the more stable cycloadduct-$TiCl_4$ complex.

In $AlCl_3$ catalyzed reactions a great excess of diene is needed. If reactions carried out under kinetic conditions are considered (Table1, entries 1, 2 and 9, 10), an inversion of the configuration of the preferentially obtained cycloadducts, as a function of the Lewis acid used as a catalyst, is observed. This result can be explained by using the model chelate complex of dienophile-$TiCl_4$ proposed by Helmchen[5] and used by Waldmann[3b] to explain the results obtained in the reaction between N-acryloyl-L-proline benzyl ester and cyclopentadiene.

Absolute configurations of the major endo diastereomers were determined by transformation of the reaction mixtures into mixtures of the iodolactones derived from 3a and 3b, by treatment with I_2 in DME / H_2O [6], and comparison of the rotations with the values given in the literature[7].

Exo cycloadducts (4a + 4b)[8] were separated from a reaction carried out under thermodynamic conditions (column chromatography on silica gel with AcOEt:hexane = 3:7 as an eluent) and transformed into a mixture of exo-norbornane-2-carboxylic acids (6a + 6b) by hydrogenation and acid hydrolysis (Scheme 1). The rotation of this mixture was compared with the values given into the literature[9] showing that 6a, coming from 4a, is the major component.

To sum up, this reaction constitutes an interesting method for the preparation of derivatives of the exo-norbornane-2-carboxylic acid with good diastereofacial selectivity.

Acknowledgements: This work was made possible by the generous financial support of the Dirección General de Investigación Científica y Técnica (Project number PB88-0038). María P. Bueno would like to express her gratitude to the Diputación General de Aragón for a grant.

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8 A mixture of 4a + 4b was chromatographed several times (silica gel, AcOEt : Hexane = 7:3 as an eluent) to afford a small amount of pure 4a:
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.39 (d, J_1=7.2 Hz, 3H), 1.40-1.64 (m, 3H), 1.78-1.86 (m, 1H), 2.33-2.40 (m, 1H), 2.91 (bs, 1H), 2.97 (s, 3H), 3.01 (bs, 1H), 3.71 (s, 3H), 5.19 (q, J_1=7.2 Hz, 1H), 6.13-6.18 (m, 2H).
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 14.4, 30.8, 41.3, 41.5, 45.5, 46.3, 46.6, 52.0, 52.2, 135.9, 138.1, 172.5, 175.8.

This 4a was hydrogenated to afford a small amount of 5a:
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.39 (d, J_1=7.2 Hz, 3H), 1.41-1.59 (m, 7H), 1.68-1.75 (m, 1H), 2.28 (bs, 1H), 2.41-2.46 (m, 2H), 2.95 (s, 3H), 3.69 (s, 3H), 5.17 (q, J_1=7.2 Hz, 1H).
^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 14.3, 28.8, 29.5, 34.6, 35.9, 36.4, 40.2, 44.4, 46.3, 51.9, 52.1, 172.6, 175.6.

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