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ASYMMETRIC SYNTHESIS OF α-ALKYLATED α-AMINO ACIDS: AZEPANE-2-CARBOXYLIC ACIDS

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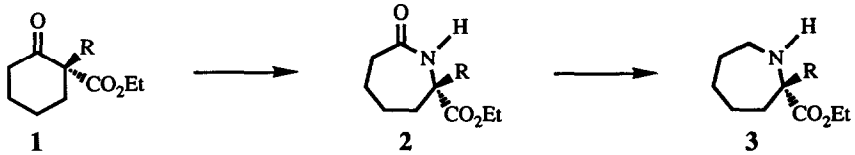
Abstract: The synthesis of optically active α-alkylated azepane-2-carboxylic acid esters **3** was achieved via Schmidt rearrangement of optically active ethyl 2-oxo-1-alkyl-cyclohexanecarboxylates **1** followed by selective reduction of the amide carbonyl group.

The asymmetric synthesis of unusual and non-proteinogenic α-amino acids is of continuing interest because of their demonstrated or potential biological activity. α-Substituted α-amino acids belong to this group of compounds. They possess enzyme inhibitory properties[2] and are also of interest in peptide chemistry[3] because the incorporation of α-alkylated α-amino acids into peptides restricts the available range of backbone conformations. Several elegant methods for the asymmetric synthesis of acyclic α-alkylated α-amino acids,[4] carbocyclic α-amino acids,[4,5] and α-substituted prolines[4,6] have been developed. The development of asymmetric methodology for the synthesis of higher ring homologues of proline, however, has not yet received much attention. A recent report by Schöllkopf[7] details the synthesis of α-alkylated pipecolic acids via the alkylation of mono-substituted bislactim ethers with dihalides, followed by an intramolecular ring closure.

We now wish to report on the first asymmetric synthesis of seven membered homologues of α-substituted prolines, the azepane-2-carboxylic acids. The methodology relies on ring expansion chemistry via the Schmidt rearrangement of optically active cyclic β-keto esters. We have previously reported[8] on related chemistry for the synthesis of acyclic α-alkylated amino acids and are now extending this methodology toward the asymmetric synthesis of α-substituted azepane-2-carboxylic acids **3** (eq 1).

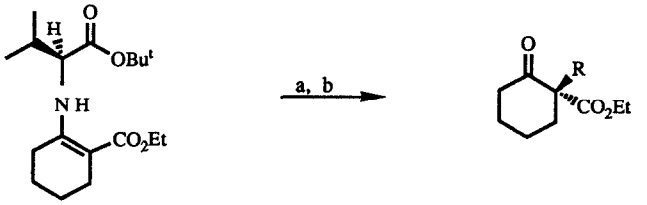


1 **2** **3** (eq 1)

The synthesis starts with optically active ethyl 2-oxo-1-alkyl-cyclohexanecarboxylates **1**, which were obtained through diastereoselective alkylation[9] of the lithio enamine of ethyl 2-oxo-cyclohexanecarboxylate utilizing the readily available *tert*-butyl ester of L-valine as

chiral auxiliary (**Scheme 1, Table 1**). The enantiomeric purity of the resulting β-keto esters was determined by ^{1}H-NMR experiments[10] and found to be >95% ee for benzylic derivatives (entries 1-4, **Table 1**). Alkylation with methyl bromoacetate (entry 5, **Table 1**), however, gave only an enantiomeric excess of 59%.[9]

Scheme 1



(a) Toluene, lithium isopropylcyclohexylamide, hexamethylphosphoramide, RBr, -78 to -50 °C, 18h; (b) Saturated citric acid.

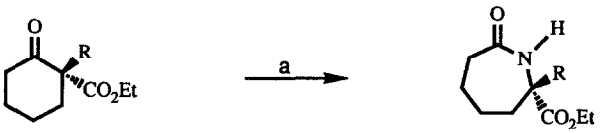
Table 1

entry	R	yield (%)	$[\alpha]_D^a$	e e %^{b}
1	$PhCH_2$-	83	-110°	>95
2	(2-naphthyl)CH_2-	83	-116°	>95
3	*p*-Br$PhCH_2$-	72	-94°	>95
4	*m*-Cl$PhCH_2$-	82	-60°	>95
5	$CH_3O_2CCH_2$-	68	-61°	59

^{a}The optical rotations were taken in chloroform, c ≅ 1. ^{b}Determined by ^{1}H-NMR after the addition of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium (III) derivative.

Schmidt rearrangement of ethyl 2-oxo-1-alkyl-cyclohexanecarboxylates **1** in chloroform with sodium azide (2-5 equiv) and methanesulfonic acid (9-11 equiv) afforded 7-ethoxycarbonyl-7-alkylazacycloheptan-2-ones **2** with retention of configuration[8] and in excellent yield (**Scheme 2, Table 2**).

Scheme 2



(a) NaN_3, CH_3SO_3H, $CHCl_3$, reflux, 0.5h.

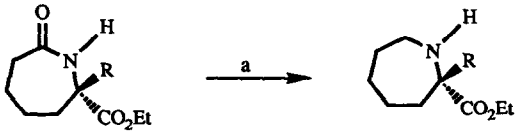
Table 2

entry	R	yield (%)	$[\alpha]_D^a$	e e %^{b}
1	$PhCH_2$-	91	+4.6°	>95
2	(2-naphthyl)CH_2-	71	+23.9°	>95
3	*p*-BrPhCH_2-	81	-2.3°	not determined
4	*m*-ClPhCH_2-	85	-19.1°	>95
5	$CH_3O_2CCH_2$-	95	-3.8°	62

[a]The optical rotations were taken in chloroform, c ≅ 1. [b]Determined by ^{1}H-NMR after the addition of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium (III) derivative.

Subsequent selective reduction[11] of the amide carbonyl group in the presence of an ester group with borane-methyl sulfide complex (3-3.5 equiv) in tetrahydrofuran completes the synthesis of the desired α-alkylated azepane-2-carboxylic acid ethyl esters[12] (**Scheme 3, Table 3**).

Scheme 3



(a) $BH_3 \cdot CH_3SCH_3$ (3-3.5 equiv), THF, -15 °C, 1 day.

Table 3

entry	R	yield (%)	$[\alpha]_D^a$	e e %^{b}
1	$PhCH_2$-	56	-7.6°	>95
2	(2-naphthyl)CH_2-	64	-10.2°^{c}	>95
3	*p*-BrPhCH_2-	67	-3.0°	>95
4	*m*-ClPhCH_2-	61	-10.5°	>95
5	$CH_3O_2CCH_2$-	62	-8.7°	59

[a]The optical rotations were taken in chloroform, c ≅ 1. [b]Determined by ^{1}H-NMR after the addition of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium (III) derivative. [c]365 nm.

The extension of this methodology toward the asymmetric synthesis of α-alkylated pipecolic acids and higher homologues of azepane-2-carboxylic acids is under investigation.

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