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A FACILE ASYMMETRIC SYNTHESIS OF β-SUBSTITUTED ALKANOIC ACID THE HIGHLY STEREOSELECTIVE MICHAEL ADDITION OF GRIGNARD REAGENTS TO α,β-UNSATURATED CARBOXYLIC AMIDES DERIVED FROM L-EPHEDRINE

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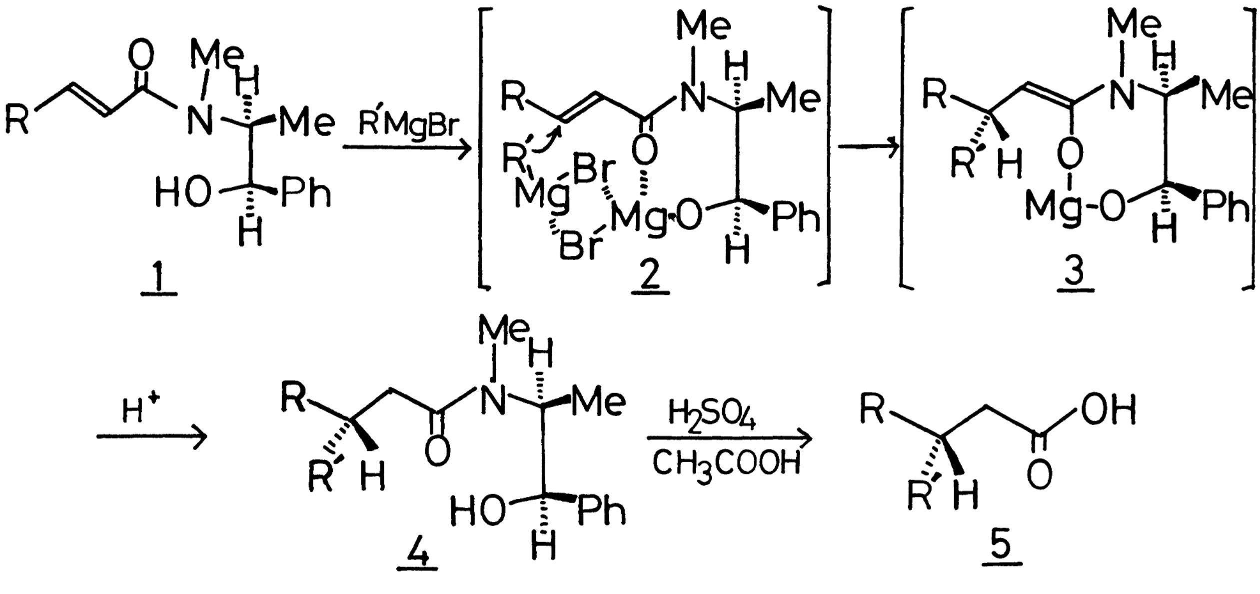
The Michael addition of Grignard reagents to chiral α,β-unsaturated carboxylic amides derived from l-ephedrine affords highly optically active β-substituted alkanoic acids after acid hydrolysis. This high stereoselectivity is explained by considering the formation of rigid internal chelate complexes.

Nucleophilic 1,4-addition of organometallic reagents to chiral α,β-unsaturated carbonyl equivalents is the most common method for the synthesis of optically active β-substituted carbonyl compounds. Recently, several efficient procedures were reported to give highly optically active β-substituted carbonyl compounds using oxazoline derivatives,1) tert-leucine derivatives2) and oxazepine derivatives.3) However, these methods require tedious works in the preparation of the starting Michael acceptors or have some difficulties in obtaining the chiral sources.

We now wish to report a facile and efficient method for the preparation of highly optically active β-substituted alkanoic acids by treating α,β-unsaturated carboxylic amides 1 with excess Grignard reagents.4)



It is supposed that the initial formation of the internal chelate complexes 2 would fix the conformation of the molecule very rigidly owing to the planarity of the amide group, and excess Grignard reagents would approach the molecules from the less sterically hindered side (that is, the opposite side of the phenyl and methyl groups on the asymmetric carbons) by means of strong interaction with the magnesium salts as depicted in 2. Further, the formation of the stable enolate 3 would prevent the side reactions often observed in the 1,4-addition of Grignard reagents to the α,β-unsaturated carboxylic amides.[5]

The starting α,β-unsaturated carboxylic amides 1 were prepared quite easily in high yields from the corresponding acyl halides and l-ephedrine in the presence of N,N,N',N'-tetramethyl-1,8-diaminonaphthalene (proton sponge) as a base.

In the first place, we examined the effects of the solvent and the kind of the organometallic reagents on the optical purity of the corresponding alkanoic acid by employing crotonic acid derivative 1 (R=Me) and various n-butyl metallic reagents (R'=n-Bu). The results are summarized in the Table I and II.

Table I. The Effect of the Solvent

Solvent	Yield(%) 4	Yield(%) 5	Optical Yield (%ee)	Absolute Configuration
Me_2O	83 (99)[b]	80	19	S
Et_2O	63 (99)[b]	84	85	S
THF	83 (91)[b]	62	22	S
toluene	71 (85)[b]	80	48	S

a) The reaction was carried out at -40°C for 48 hours using six equivalents of n-BuMgBr.

b) The yield in parenthesis is based on the consumed starting material.

Table II. The Effect of the Kind of the Organometallic Reagents

n-BuM	Reaction condition	Yield(%) 4	Yield(%) 5	Optical Yield(%ee)	Absolute Configuration
n-BuLi[b]	-40°C, 2h	71 (78)[a]	82	28	S
n-BuMgCl	-40°C, 48h	81 (89)[a]	90	72	S
n-BuMgBr	-40°C, 48h	63 (99)[a]	84	85	S
n-BuMgI[c]	0°C, 24h	84 (93)[a]	84	34	S
n-BuMgBr	0°C, 3h	77 (84)[a]	74	70	S

a) The yield in parenthesis is based on the consumed starting material.

b) Two equivalents of n-BuLi was used.

c) The reaction did not proceed at -40°C.

When dimethyl ether or tetrahydrofuran, having a strong coordinating property, was used as a solvent, it would coordinate to the metal salts and prevent the formation of the rigid chelate complexes, and it was made clear that diethyl ether was the choice of the solvents.

Among various n-butyl metallic reagents screened, differences of the optical purity could also be explained by the strength of the coordination of the metal salts to the carbonyl oxygen. When n-BuLi or n-BuMgI was used as a nucleophile, the conformation of the molecule could not be sufficiently fixed to bring forth high asymmetric induction. Thus, the best result was obtained when the reaction was carried out in diethyl ether at -40°C using n-BuMrBr as a nucleophile.

In the same manner, various highly optically active β-substituted alkanoic acids were obtained as shown in Table III.

Table III. Chiral β-Substituted Alkanoic Acids

Entry	R(of 1)	R'MgBr	Yield(%)		$[\alpha]_D^{b)}$ (of 5)	Lit$[\alpha]_D^{d)}$	Optical Purity(%ee)	Absolute Configuration
			4	5				
1	Me	n-Bu	63 (99)$^{c)}$	84	-3.59 (neat)	-4.2 (neat)	85	S
2	Me	Ph	63 (92)$^{c)}$	87	-54.56 (c10,PhH)	+57.23 (c9,PhH)	95	R
3	Me	Et	79 (99)$^{c)}$	73	+7.98 (neat)	-8.15 (neat)	98	S
4	Me	n-hexyl	73 (99)$^{c)}$	86	-4.62 (neat)	+5.10 (neat)	91	S
5	Ph	Et	48 (76)$^{c)}$	97	+48.54 (c7,PhH)	-49.96 (c7,PhH)	98	S
6	Ph	n-Bu	71 (96)$^{c)}$	89	+37.05 (c8,PhH)	-34.4 (c8,PhH)	99	S
7	Et	Ph	76 (91)$^{c)}$	82	-46.34 (c7,PhH)	-49.96 (c7,PhH)	93	R
8	Et	n-Bu	59 (96)$^{c)}$	75	-2.31 (neat)	+2.94 (neat)	79	S
9	n-Bu	Ph	64 (92)$^{c)}$	85	-35.25 (c8,PhH)	-34.4 (c8,PhH)	99	R
10	n-Bu	Et	69 (99)$^{c)}$	88	+3.01 (neat)	+2.94 (neat)	99	R

a) All reactions were carried out in diethyl ether at -40°C for 48 hours using six equivalents of R'MgBr reagents.

b) All rotations were taken at 23±2°C at 589 nm except for entry 6 and 9, which were recorded at 577 nm.

c) The yield in parenthesis is based on the consumed starting materials.

d) The values of specific rotation were cited from references 1) and 3).

e) All the products gave satisfactory NMR and IR spectra.

A typical procedure is described for the preparation of (S)-3-methylheptanoic acid.

To an ether solution (35 ml) of 1 (R=Me) (537 mg, 2.3 mmol) was added an ether solution (15.7 ml) of n-butylmagnesium bromide (0.88 mmol/ml, 13.8 mmol) at -78°C under an argon atmosphere. After being stirred for 48 hours at -40°C, a phosphate buffer solution (pH 7, 20 ml) was added to the reaction mixture. The resulting insoluble materials were filtered off through Celite and washed with ethyl acetate. The organic layer was extracted with ethyl acetate and the extract was dried over anhydrous $MgSO_4$ and then evaporated in vacuo. The residue was purified by silica gel column chromatography to give the Michael adduct 4 (R=Me, R'=n-Bu) (426 mg, 1.5 mmol, 63% yield). This adduct was dissolved in acetic acid (5 ml) and 6N sulfuric acid (10 ml), and then refluxed for 3 hours. The organic layer was extracted with ether and the extract was washed with brine, dried over anhydrous $MgSO_4$ and then evaporated in vacuo. The residue was distilled according to the Kugel-Rohr method (bath temperature 150°C/4 mmHg) to give (S)-3-methylheptanoic acid (177 mg, 84% yield).

A general method for the preparation of highly optically pure β-substituted carboxylic acids was established by employing α,β-unsaturated carboxylic amides derived from l-ephedrine and various Grignard reagents. We are currently under investigation for various modifications and applications of the present synthetic method.

References and Note

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4) As to the 1,4-addition of RLi and RMgX reagents to α,β-unsaturated amides, see the following paper and references are cited therein.
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