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Efficient syntheses of optically active 2-arylalkanoic acids.

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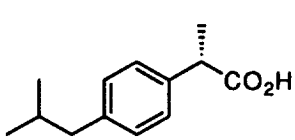
Abstract

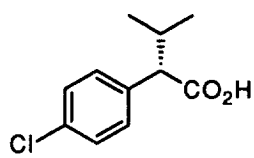
A highly enantioselective synthesis of 2-arylpropanoic acid was achieved, using a new developed methodology of cuprate addition to chiral carbonates derived from menthone.

Keywords: Asymmetric reactions, substitution, pesticides, antiinflammatory compounds.

A vast number of optically active 2-arylalkanoic acids, both natural and unnatural, perform useful functions as therapeutic, pest control, and other commercially important agents [1]. The profen family of non-steroidal antiinflammatory drugs [2,3] and the pyrethroid class of pesticides[1] are two examples of commercial compounds of massive importance. The asymmetric alkylation of arylacetic acid, the asymmetric hydrogenation of arylalkenoic acids and the hydroformylation of olefins have been used to construct these units [4]. We wish to report on a highly efficient and enantioselective synthesis of (S)-2-(4-isobutylphenyl)propionic acid ((+)-ibuprofen, **1**) and (S)-2-(4-chlorophenyl)-3-methylbutyric acid (**2**) (chiral fragment of fenvalerate, a synthetic pyrethroid insecticide in commercial use) and finally of unsubstituted (*S*)-3-methyl-2-phenyl butyric acid (**3**). All of these syntheses use our recently developed methodology of cuprate addition on chiral allylic carbonates derived from menthone [5].



1



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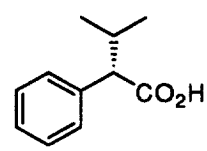


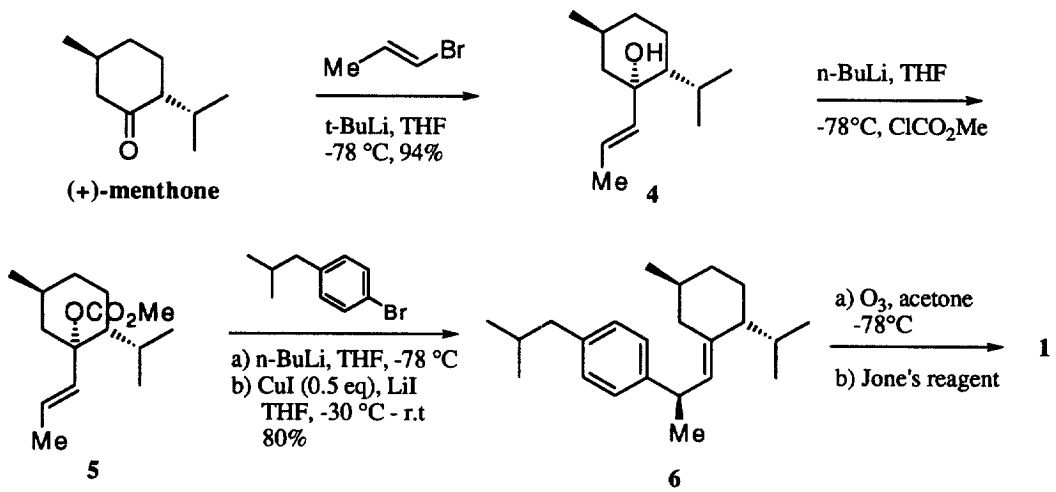
3

Scheme 1

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00055-6

1.Total synthesis of (+)-ibuprofen

The allylic alcohol **4** was obtained by the addition of (+)-menthone (98% ee) to a solution of propenyllithium in THF at -78°C to give in 94% yield the desired chiral alcohol with complete stereoselectivity as do most nucleophilic additions to menthone's carbonyl.[1] This alcohol was converted into carbonate **5** which was used crude in the following reaction with the cuprate reagent derived from 1-bromo-4-isobutylbenzene[2] (by metal halogen exchange using one equivalent of n-BuLi at -78 °C and subsequent reaction with copper iodide and lithium iodide at -30°C). The S_N2' addition product **6** was thus obtained in 80% yield (from **4**) with complete diastereoselectivity (> 99%) [5]. Ozonolysis furnished directly (+)-ibuprofen in 80% yield and an excellent ee of 98%[3] ($[\alpha]_D$ = + 47.4, abs EtOH, c = 1.01; lit. $[\alpha]_D$ = + 60, EtOH 95%, c = 2 [6]) after quenching the ozonide with Jone's reagent [7].



Scheme 2

2.Total synthesis of (S)-2-(4-chlorophenyl)-3-methyl butyric acid and (S)-2-phenyl-3-methyl butyric acid:

Propargylic alcohol **8** was prepared from commercially available isobutyraldehyde using the method of Corey-Fuchs [8]. Isobutyraldehyde was reacted with CBr_4 and PPh_3 in the presence of zinc to give the vinyl dibromide which was treated with 2 equivalents of n-butyllithium to generate the alkynyllithium **7** *in situ*. A mixture of (+)-menthone (98% ee) and $CeCl_3$ was added to **7** giving the chiral alcohol **8** in 87% yield in a diastereomeric ratio of 20:1. The minor

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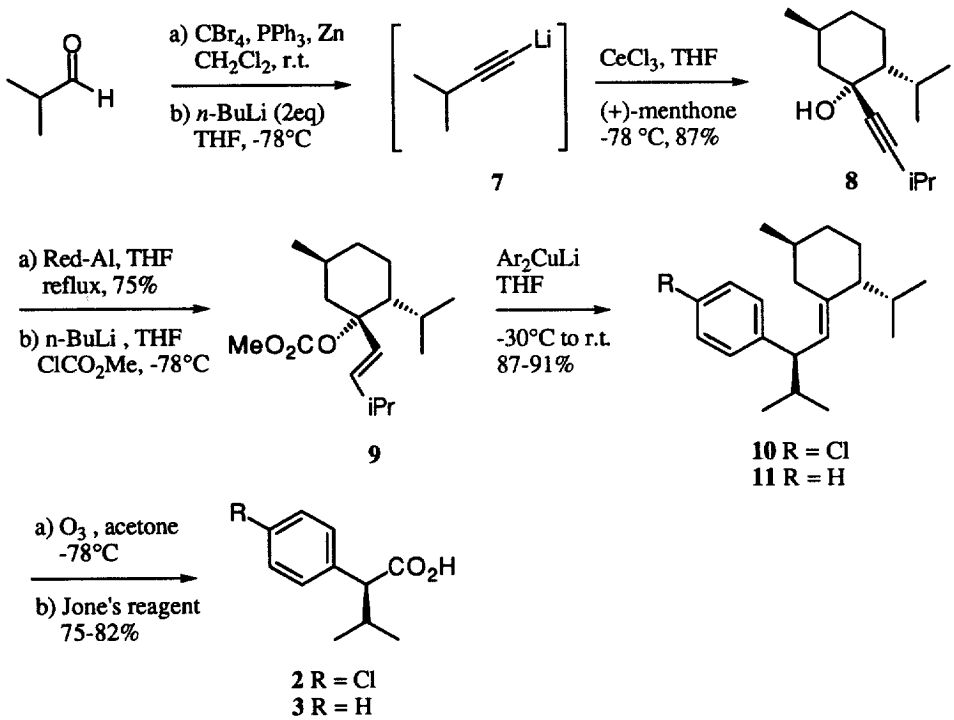
1. All new compounds gave satisfactory IR, NMR, Mass spectral data and exact masses.
2. 1-Bromo-4-isobutyl benzene was prepared by a Wittig reaction between 4-bromobenzaldehyde and isopropyltriphenylphosphonium iodide followed by hydrogenation on Pd/C.
3. Enantiomeric excesses were determined by reducing the acid to the alcohol, converting the latter to its Mosher ester, and integrating the fluorine and appropriate proton NMR signals.

undesired isomer was easily separated by flash chromatography. The allylic alcohol **9** was obtained by reduction of the resulting alkyne with Red-Al in 75% yield and then converted to the corresponding methyl carbonate. Then, diarylcuprate reagents were added to this carbonate. The latter were prepared by metal halogen exchange on 4-bromochlorobenzene (for **10**) with 1 equivalent of n-BuLi or from commercially available phenyllithium (for **11**) which were added to a suspension of copper iodide and lithium iodide. The S_N2' reactions led to exocyclic alkenes **10** and **11** in 91% and 87% yield respectively, again with complete diastereoselectivity. Ozonolysis gave acids **2** ($[\alpha]_D$ = + 57.2, $CHCl_3$, c = 1.37; lit. $[\alpha]_D$ = + 62.5, $CHCl_3$, c = 2) [9] or **3** ($[\alpha]_D$ = + 43.1, $CHCl_3$, c = 1.43) in 75% and 82% yield and ee's of 98%.

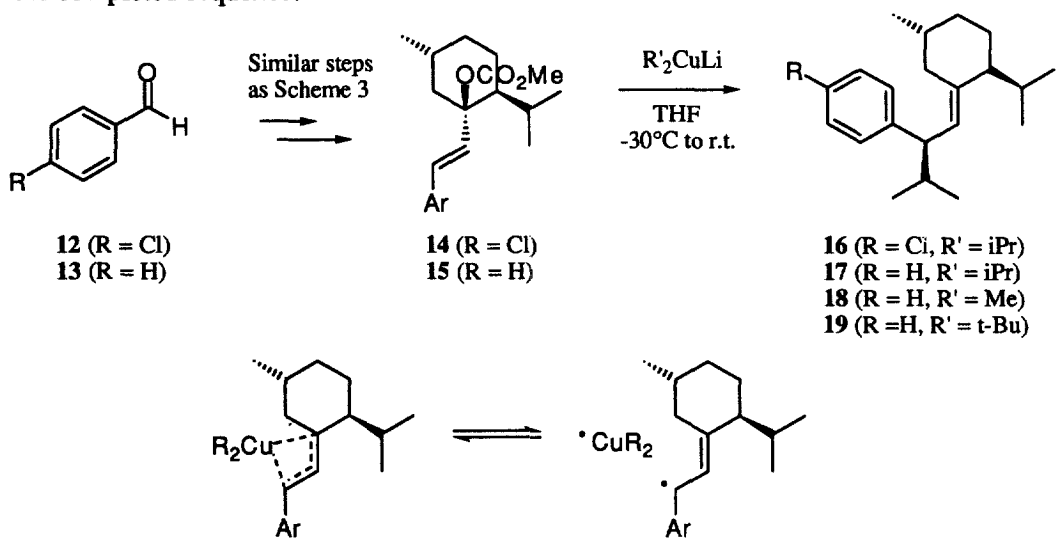


Scheme 3

Our original approaches for the synthesis of **2** and **3** were complementary to the one shown in Scheme 3. Starting with 4-chlorobenzaldehyde or benzaldehyde and (-)-menthone as starting material, we followed a similar sequence to that shown in Scheme 3 and performed the cuprate additions on the corresponding aromatic allylic carbonates **14** and **15** to obtain the S_N2' addition products **16** and **17** with a surprisingly low diastereoselectivity of 10:1 (Scheme 4). This was surprising because the addition of a methyl on carbonate **15** gave complete diastereoselectivity [5]. When we added *t*-Bu_2CuLi to **15** in the usual conditions, we obtained an even lower diastereoselectivity of 1.5:1. It seems that when an aryl vinyl group is attached to menthone, the selectivity of cuprate additions is dependent on the size of the nucleophile, possibly because

higher reaction temperatures and longer times are required for bulky nucleophiles. By contrast, we have never observed lower selectivities when arylcuprates are added to alkenyl carbonates derived from menthone, even when the alkenyl portion is large such as *t*-Bu or *i*-Pr. It seems, therefore, that aryl groups may promote the formation of stable radical intermediates which lead to a loss of selectivity (Scheme 4, bottom).

These three syntheses demonstrate the efficiency of our novel method and the quality of the end product it furnishes. Menthone is inexpensive and can be recycled in good yield (~60-70%) after the completed sequence.



12 (R = Cl)
13 (R = H)

14 (R = Cl)
15 (R = H)

16 (R = Cl, R' = iPr)
17 (R = H, R' = iPr)
18 (R = H, R' = Me)
19 (R =H, R' = t-Bu)

Scheme 4

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