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Asymmetric Synthesis of Ibuprofen *via* Diastereoselective Alkylation of a Homochiral *N*-Acylbornanesultam

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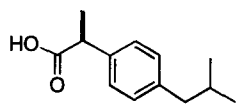
Abstract: A very short, 4 step synthesis of 2-(4-isobutylphenyl)propionic acid (ibuprofen) was achieved in 57% overall yield, using a highly diastereoselective alkylation of the chiral enolate derived from *N*-(4-isobutylphenyl)acetyl bornanesultam as a key step. © 1997 Elsevier Science Ltd. All rights reserved.

Everybody is now well aware of the importance for enantiopure compound synthesis in obtaining non-racemic chiral drugs.[1] The undesired enantiomer not only imposes an undesirable load on the metabolism but usually displays different physiological activities, with sometimes toxic side effects. Profens, an arylpropanoic acid class of compounds represented by 2-(4-isobutylphenyl)propionic acid (ibuprofen, **1**) and 2-(6-methoxy-2-naphtyl)propionic acid (naproxen, **2**), are clinically very important as non-steroidal antiinflammatory drugs.[2,3] Since their introduction almost two decades ago, more than a dozen of these compounds are currently used. The activity of these compounds, containing a stereogenic center (usually a methyl group) α to the aromatic ring, resides in the (*S*) isomers. Despite extensive investigations of methods for the production of optically pure profens, as witnessed by an explosive increase of publications and patents, they are all, with the exception of naproxen, administered as racemates.



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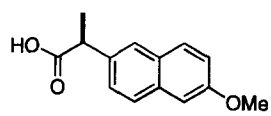

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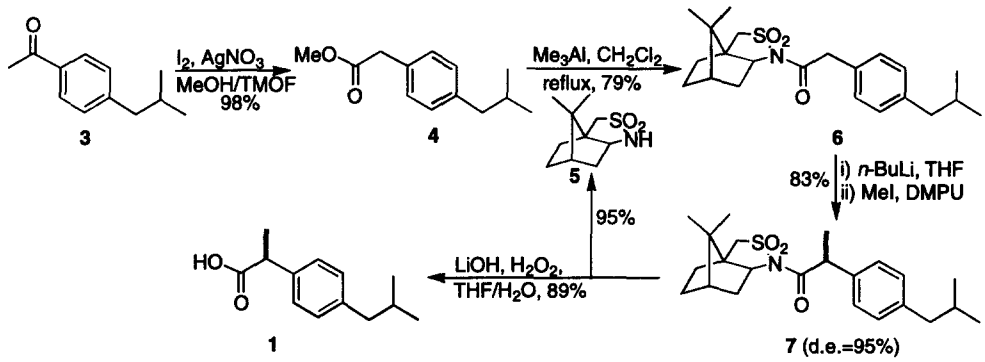
In addition to diastereomeric salt resolutions, chemical and enzymatic kinetic resolutions, asymmetric syntheses using chiral auxiliaries or chiral catalysts have been extensively used.[4] One of the obvious approaches involves the asymmetric alkylation of arylacetic acid derivatives.[5] An elegant application of the asymmetric alkylation of oxazolidinone-based chiral imide enolates has been reported, giving ibuprofen (**1**) in 8 steps with a diastereomeric excess of 92% for the alkylation step.[6] We developed a strategy for the diastereoselective alkylation of homochiral *N*-acylbornane- or toluenesultams with very high asymmetric induction.[7] Herein, we wish to present an application of this methodology towards a short asymmetric synthesis of 2-(4-isobutylphenyl)propionic acid (ibuprofen, **1**).

Thus, oxidative rearrangement of commercially available *p*-isobutylacetophenone (I_2, $AgNO_3$, trimethyl orthoformiate, MeOH)[8] yielded almost quantitatively methyl ester **4**. Acylation of commercially available (1*S*)-2,10-bornanesultam (**5**) with methyl ester **4** using Weinreb conditions[9] (Me_3Al, CH_2Cl_2, reflux) afforded bornanesultam derivative **6** in 79% yield.

† Deceased March 15, 1996.



Now the stage was set for the crucial alkylation step. Deprotonation of **6** with *n*-butyllithium at -78°C results in selective formation of the *Z*(O)-lithium enolate which was alkylated at -60°C with methyliodide in the presence of the non-carcinogenic *N,N'*-dimethylpropyleneurea (DMPU) as a cosolvent. The alkylated product **7** was obtained in 83% yield with a diastereomeric excess of 95%.[10] In the absence of cosolvent, the diastereomeric excess slighly decreased to 91% d.e. Finally, hydrogen peroxide assisted cleavage of the nitrogen-acyl bond, gave (*S*)-ibuprofen (**1**) {$[\alpha]_D$ = + 51 (c=1.0, $CHCl_3$)}[11] in 89% yield and 95% e.e. with recovery of the bornanesultam auxiliary (95%).

In summary, we have obtained (*S*)-2-(4-isobutylphenyl)propionic acid (ibuprofen, **1**), an important member of the non-steroidal antiinflammatory class of drugs, from *p*-isobutylacetophenone *via* a non-optimized 4 step sequence in 57% overall yield. This synthesis illustrates the potential of the asymmetric alkylation of *N*-acylsultams as a powerful method for the synthesis of α-substituted arylcarboxylic acid derivatives.

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10) All new compounds were characterized by IR, ^1H and ^{13}C NMR and mass spectra.
11) Compound **1** was identified by comparison of the spectroscopic data with a commercial sample (*Fluka AG, Switzerland).* The enantiomeric excess was determined by chiral HPLC (chiralcel OD column, hexane/*i*-PrOH 100:1), comparatively to a racemic sample.

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