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# Syntheses of Highly Constrained β–Aryl Isohexanoic Acid Derivatives Via Asymmetric Michael Addition

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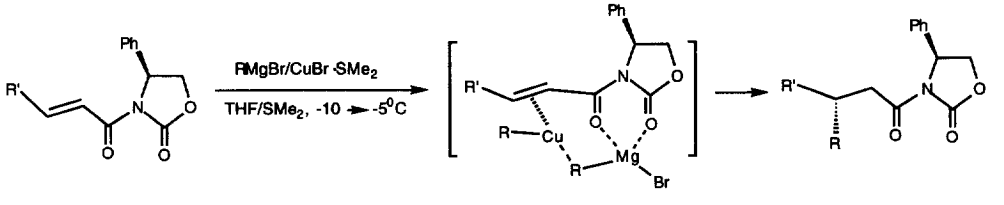
**Abstracts**: A series of enantiomerically pure highly sterically hindered β-branched isohexanoic acid derivatives have been synthesized with high diastereoselectivity via asymmetric Michael addition. The X-ray crystal structure of (4S,3'S)-3-[3'-(2,6-dimethylphenyl)isohexanyl]-4-phenyl-2-oxazolidinone demonstrated that the β–configuration was induced from the Si-face, and that the torsional angle $\chi_2$ was restricted by the bulky β-isopropyl group to the range expected from molecular modeling.


The stereoselective Michael addition of organometallic reagents to α,β–unsaturated acyl derivatives which contain a chiral auxiliary is one of the most reliable methods to synthesize optically pure β-branched carbonyl derivatives.[1-4] Although various products have been prepared with high diastereoselectivity via asymmetric Michael additions to chiral oxazoline,[2] ester,[3] amide,[4] or imide derivatives,[5] to our knowledge there still have not been any examples of the syntheses of highly sterically hindered β-branched carboxylic acids derivatives by this method. As part of our efforts to design and synthesize conformationally constrained novel β-branched amino acids,[6] we have developed an efficient procedure to prepare these important intermediates (*i.e.* enantiomerically pure β-methyl carboxylic acid derivatives) via asymmetric Michael addition by using optically pure 4-phenyloxazolidinone as an auxilliary.[7] Using this methodology, the asymmetric Michael addition of




various non-hindered Grignard reagents in the presence of $CuBr{\cdot}SMe_2$ and the co-solvent dimethylsulfide could be carried out with high stereoselectivity and in reasonable yields.[7] However, in our initial attempts to

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synthesize much more sterically-hindered β–isopropyl aromatic amino acids, the Michael addition of isopropyl magnesium chloride to the Michael acceptor, (4R,2E)-3-[3′-(4-methoxyphenyl)propenoyl]-4-phenyl-2-oxazolidinone, did not work well using the previously developed reaction conditions. Instead, we applied a chiral resolution method to synthesize the desired optically pure intermediates of β-phenylisohexanoic acid derivatives.[8]

Recently, we have re-examined the asymmetric Michael reaction in order to develop a general approach for the asymmetric syntheses of hindered unusual β–isopropyl aromatic amino acids. A new Michael reaction acceptor, (4S,2E)-3-(1-oxo-2-isohexenyl)-4-phenyl-2-oxazolidinone, was tested, and it was found that it could react with a variety of aromatic Grignard reagents, including the highly sterically hindered 2′,6′-dimethylphenyl magnesium bromide under mild conditions.

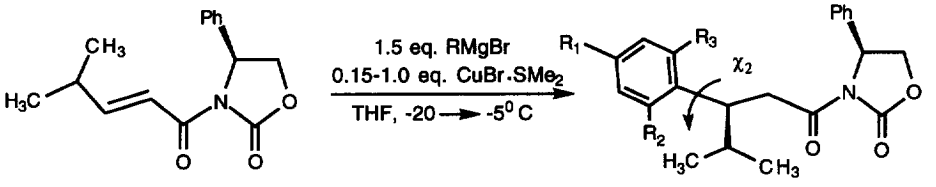


Table 1. Diastereoselective Syntheses of β-Aryl Isohexanoic Acid Derivatives

| Entry | $R_1$ | $R_2$ | $R_3$ | Yield[a] | de[b] | $[\alpha]_D^{20°}$ [c] | $\Delta\upsilon$(Hz)[d] |
|---|---|---|---|---|---|---|---|
| **1** | H | H | H | 82% | >90% | +9.7° | 57.2 |
| **2** | $OCH_3$ | H | H | 97% | >90% | +6.0° | 56.8 |
| **3** | $OCH_3$ | $CH_3$ | H | 94% | >90% | +7.3° | 69.9 |
| **4** | H | $CH_3$ | $CH_3$ | 68% | >90% | +7.6° | 98.9 |
| **5** | $OCH_3$ | $CH_3$ | $CH_3$ | 86% | >90% | +6.6° | 98.6 |

a. The yield was calculated from the weight of product after column chromatography purification; b. The de was determined from $^1$H NMR of crude product,[11] de>90% means that no diasteroisomer was observed from $^1$H NMR; c. [c] = 1mg/mL in $CDCl_3$. d. $\Delta\upsilon$ is the chemical shift difference between the two methyl groups of the β–isopropyl group.

As compared to the previously reported reaction conditions,[7] we have found the reactions of the phenyl or substituted phenyl Grignard reagents only require catalytic amounts of $CuBr{\cdot}SMe_2$ and no dimethylsulfide as co-solvent. However, the para-methoxylated phenyl Grignard reagents needed one equivalent of $CuBr{\cdot}SMe_2$ to secure the complete conjugation addition reaction. Otherwise, 1,2-addition reactions could be observed, and even became the major reaction pathway.[9] The reason why phenyl and para-methoxyphenyl Grignard reagents require different amounts of Cu(I) catalyst for 1,4-conjugation addition is still not clear, and is under investigation. In any case, all products were obtained in good to excellent yields with high optical purity (Table 1). These β-branched isohexanoic acid derivatives could be easily converted into their corresponding unusual β-isopropyl aromatic amino acids using chemistry previously elaborated in our laboratory.[7]

An X-ray crystal structure of the compound (4S,3'S)-3-[3'-(2,6-dimethylphenyl)isohexanyl]-4-phenyl-2-oxazolidinone **4** has been determined and the results are shown in Figure 1. These results suggested that in the asymmetric synthesis, the β-carbon configuration was induced from the Si-face presumably because the Re-face was shielded by the phenyl ring of the oxazolidinone in the Michael reaction transition state,[9] and the rotation of aromatic ring is found to be $\chi_2$=+112.6° which is in the angle range expected from computer modeling.[10] The chemical shift differences (Δυ) of the two isopropyl methyl groups could be used to assess the degree of constraint in these β-aryl isohexanoic acid derivatives. As seen from the Table 1, Δυ increases with the number of methyl substituents on the aromatic ring. Compounds **4** and **5** have the largest Δυ values, compounds **1** and **2** the smallest Δυ value. The para-methoxy substituent on the aromatic ring has no effects on Δυ values. Thus, the presence of the 2' and 6'-dimethyl groups and of the β-isopropyl group produce torsional constraints which reduce greatly the flexibility of β-aryl isohexanoic acid derivatives, which are important precursors for preparation of β-isopropyl aromatic amino acids.

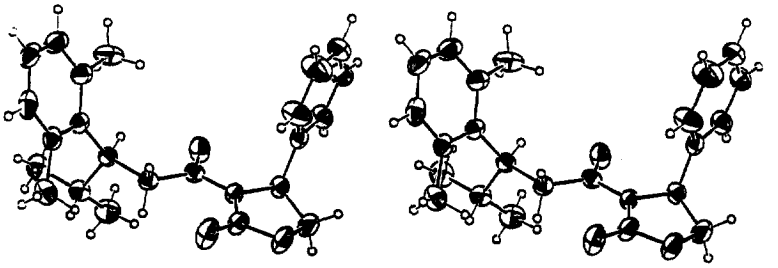

Figure 1. The Stereo view of the crystal structure of (4S, 3'S)-3-[3'-(2,6-dimethyl-phenyl)isohexanyl]-4-phenyl-2-oxazolidinone **4**

Experimental Procedures: To a mixture of RMgBr (1.7 mmol, 1.5 equivalents) and CuBr·$SMe_2$ (36 mg, 0.15 equivalents except for para-methoxyphenyl magnesium bromide which needs 1.0 equivalent) in 5 mL THF at -20°C was added dropwise a solution of (4S,2E)-3-(1-oxo-2-isohexenyl)-4-phenyl-2-oxazolidinone (1.16 mmol, 1.0 equivalent) in 3 mL of freshly distilled THF. A yellow color was observed during the addition process. The resulting mixture was kept stirring at -15°C for two hours, then slowly warmed to room temperature during one hour. The reaction was then quenched with 20 mL of saturated ammonium chloride, and the product was extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (2 x 20 mL), water (20 mL), and dried over anhydrous magnesium sulfate. After evaporation of dried organic phases, the crude product was purified by silica gel chromatography.

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11. $^1$H NMR: δ ppm **2.** 7.20-6.74(m, 9H, aromatic protons), 5.31(dd, J=8.7, 4.Hz, 1H, oxazolidinone, -CHAr-), 4.58(t, J=8.7Hz, 1H, oxazolidinone, -$CH_2$-/proR), 4.08(dd, J=7.1, 4.8Hz, 1H, oxazolidinone, -$CH_2$-/proS), 3.80(s, 3H, -$ArOCH_3$), 3.74(dd, J=15.5, 5.2Hz, 1H, -$C_\alpha$H-/proS), 3.07(dd, J=15.5, 5.1Hz, 1H, -$C_\alpha$H-/proR), 2.87(m, 1H, -$C_\beta$H-), 1.83[m, 1H, -$CH(CH_3)_2$], 0.95(d, J=6.7Hz, 3H, -$CH_3$), 0.72(d, J=6.7Hz, 3H, -$CH_3$); **3.** 7.20-6.52(m, 8H, aromatic protons), 5.28(dd, J=8.7, 4.1Hz, 1H, oxazolidinone, -CHAr-), 4.53(t, J=8.8Hz, 1H, oxazolidinone, -$CH_2$-/proR), 4.04(dd, J=8.7, 4.1Hz, 1H, oxazolidinone, -$CH_2$/proS), 3.80(dd, J= 15.0, 10.0Hz, 1H, -$C_\alpha$H-/proS ), 3.79(s, 3H, -$ArOCH_3$), 3.13(m, 1H, -$C_\beta$H-), 2.97(dd, J=15.0, 4.7Hz, 1H, -$C_\alpha$H/proR), 2.07(s, 3H, -$ArCH_3$), 1.81[m, 1H, -$CH(CH_3)_2$], 1.00(d, J=6.6Hz, 3H, -$CH_3$), 0.72(d, J=6.7Hz, 3H, -$CH_3$); **4.** 7.25-6.83(m, 8H, aromatic protons), 5.31(dd, J=8.74, 4.0Hz, 1H, oxazolidinone -CHAr-), 4.60(t, J=8.7Hz, 1H, oxazolidinone, -$CH_2$-/proR), 4.13(dd, J=8.7, 4.1Hz, 1H, oxazolidinone, -$CH_2$-/proS), 3.64-3.35(m, 3H, -$C_\alpha H_2 C_\beta$H-), 2.45(s, 3H, -$CH_3$), 2.25-2.18[m, 1H, -$CH(CH_3)_2$], 2.17(s, 3H, -$CH_3$), 1.06(d, J=6.4Hz, 3H, -$CH_3$), 0.66(d, J=6.7Hz, 3H, -$CH_3$); **5.** 7.26-6.39(m, 7H, aromatic protons), 5.31(dd, J=8.7, 4.0Hz, 1H, oxazolidinone, -CHAr-), 4.59(t, J=8.7Hz, 1H, oxazolidinone, -$CH_2$/proR), 4.13(dd, J=8.8, 4.0Hz, H, oxazolidinone, -$CH_2$-/proS), 3.74(s, 3H, -$ArOCH_3$), 3.65(dd, J=15.0, 7.8Hz, 1H, -$C_\alpha$H-/proS), 3.50-3.27(m, 2H, -$C_\alpha$H-/proR and -$C_\beta$H--), 2.43(s, 3H, -$ArCH_3$), 2.14[m, 1H, -$CH(CH_3)_2$], 2.13(s, 3H, -ArCH3), 1.05(d, J=6.5Hz, 3H, -$CH_3$), 0.66(d, J=6.7Hz, 3H, -$CH_3$).


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