

Enantioselective Michael Addition of Nitromethane to α,β -Enones Catalyzed by Chiral Quaternary Ammonium Salts. A Simple Synthesis of (*R*)-Baclofen

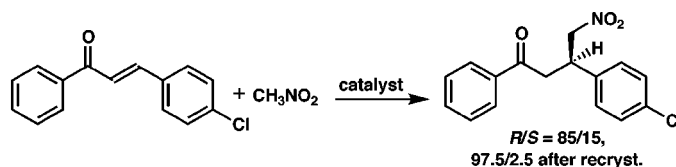
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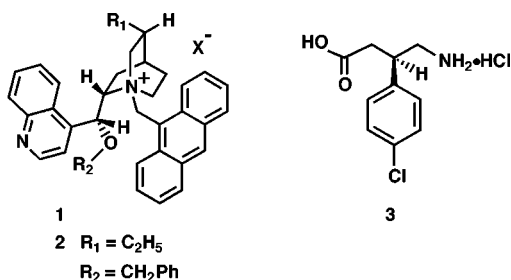
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ABSTRACT



Enantioselective Michael addition of nitromethane to an α,β -enone is a key step in the synthesis of (*R*)-baclofen.

Advances in understanding the three-dimensional pathways and transition states for the cinchona alkaloid catalyzed asymmetric dihydroxylation of olefins by osmium tetroxide¹ led to the development of rigid, structurally defined, chiral quaternary ammonium salts of type **1** for a variety of catalytic phase transfer reactions. With catalysts of type **1**, enantio-



selectivities of >20:1 were obtained in numerous alkylation,^{2–4} aldol,⁵ epoxidation,⁶ and Michael^{7,8} reactions. These chiral

catalysts can also be used to control diastereoselectivity, as demonstrated by highly effective and practical syntheses of HIV protease inhibitors by nitro aldol reactions of aldehydes with nitromethane.⁹ This Letter describes another new and useful reaction of nitromethane, the enantioselective Michael addition to α,β -enones to form chiral γ -nitro ketones. These versatile intermediates can serve as starting materials for a variety of further elaborated structures. Demonstrated herein is a route for the synthesis of the therapeutically useful GABA_B receptor agonist (*R*)-baclofen hydrochloride (**3**),¹⁰ a chiral γ -amino acid, via the corresponding γ -lactam. Racemic baclofen is used therapeutically to treat spasms caused by spinal cord injury or disease; however, the (*S*)-

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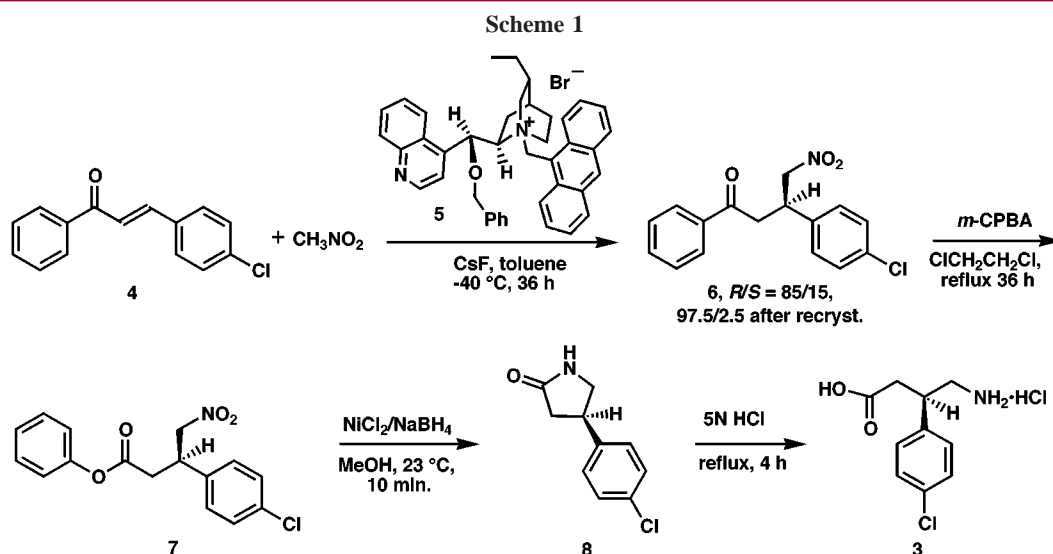
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enantiomer is essentially inactive. As a consequence there have been many studies on the synthesis of (*R*)-baclofen, including syntheses from (*S*)-glutamic acid¹¹ and (*S*)-*trans*-4-hydroxyproline,¹² syntheses involving resolution,^{13,14} and syntheses involving enzymatic reactions.^{15–17}

The pathway of the present catalytic enantioselective synthesis of (*R*)-baclofen is outlined in Scheme 1. Reaction of 10 equiv of nitromethane with 4-chlorobenzylideneacetophenone, the cinchonidinium salt **5** (10 mol %), and powdered cesium fluoride (10 equiv) in toluene at $-40\text{ }^{\circ}\text{C}$ with stirring for 36 h produced the crystalline Michael adduct

6 with *R/S* selectivity of 85/15 in 89% yield. Recrystallization of this product from EtOAc–hexane furnished **6** of 95% ee with good recovery. Baeyer–Villiger oxidation of this material afforded the γ -nitro ester **7** as a colorless solid, mp $99\text{--}100\text{ }^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{23} -19$ ($c = 1$, CH_2Cl_2), in 90% yield. Reduction of **7** in methanol with 10 equiv of sodium borohydride in the presence of nickel boride (prepared in situ from 1 equiv of NiCl_2 and 5 equiv of NaBH_4) at $23\text{ }^{\circ}\text{C}$ for 30 min gave the (*R*)- γ -lactam **8**, mp $116\text{--}117\text{ }^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{23} -37$ ($c = 1$, CH_3OH) (65%), the spectral and physical data for which matched those previously reported.¹³ Hydrolysis of γ -lactam **8** in 5 N aqueous HCl at reflux for 4 h afforded (*R*)-baclofen hydrochloride (**3**), $[\alpha]_{\text{D}}^{23} -1.5$ ($c = 1$, H_2O), mp $200\text{ }^{\circ}\text{C}$ (dec).

The enantiomer of **3** has also been synthesized enantioselectively by the approach outlined in Scheme 1 using as the initial step the Michael reaction of nitromethane to the α,β -enone **4** with the cinchonidinium salt **2** as catalyst and CsF as base in toluene at $-40\text{ }^{\circ}\text{C}$ for 36 h to afford the

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(18) The Michael reaction of nitromethane with benzalacetophenone is similar to the examples described above, the (*S*) adduct predominating with the cinchonidinium catalyst **2** and the *R* adduct predominating with the diastereomeric cinchonidinium catalyst **5**.

(19) A mixture of powdered, flame-dried CsF (1.52 g, 10.0 mmol), the chiral cinchonidinium salt **5** (66 mg, 0.1 mmol), and chloroacalzone **4** (243 mg, 1.0 mmol) in toluene (2.5 mL) was cooled to $-40\text{ }^{\circ}\text{C}$ and treated with nitromethane (0.54 mL, 10 mmol). The mixture was stirred at $-40\text{ }^{\circ}\text{C}$ for 36 h and then diluted with 10 mL of Et_2O and 10 mL of water. The organic phase was separated, concentrated, and purified by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) to afford (*R*)-**6** (270 mg, 89% yield, 70% ee) as a colorless solid: mp $110\text{--}112\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{23} = +17.9$ ($c = 1$, CH_2Cl_2); FTIR (film) 1682.9 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.91–7.21 (m, 9H), 4.83 (dd, $J = 12.4$ and 6.4 Hz, 1H), 4.65 (dd, $J = 12.4$ and 8.0 Hz, 1H), 4.21 (m, 1H), 3.45 (dd, $J = 17.6$ and 6.8 Hz, 1H), 3.39 (dd, $J = 17.6$ and 7.2 Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 196.3, 137.6, 136.2, 133.7, 129.2, 129.0, 128.9, 128.8, 128.0, 79.5, 41.5, 38.9 ppm; HRMS (Cl^+) calcd $[\text{C}_{16}\text{H}_{14}\text{ClNO}_3 + \text{NH}_4]^+$ 321.1006, found 321.1002. Enantioselectivity was determined by HPLC analysis with a Chiralcel AD column, 10% isopropyl alcohol in hexanes, 1.0 mL/min, $\lambda = 254$ nm, retention times minor 18.1 min, major 25.9 min. One recrystallization from ethyl acetate–hexane gave colorless crystals: mp $121\text{--}122\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{23} +24.3$ ($c = 1$, CH_2Cl_2); ee 95%.

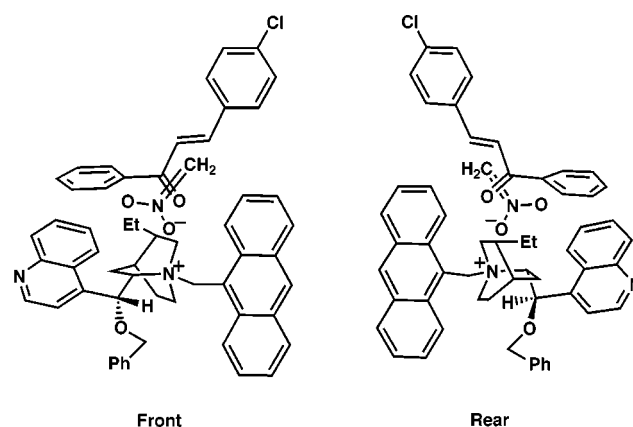


Figure 1.

(*S*)-enantiomer of **6** of 95% ee after a single recrystallization from EtOAc–hexane.¹⁸

The simplicity of the enantioselective methodology described herein is illustrated by the conversion of **4** to **6** using catalyst **5**.¹⁹

The absolute stereochemical course of the enantioselective Michael addition of nitromethane to **4** catalyzed by the chiral quaternary ammonium salts **2** and **5** can be explained by the

same type of pre-transition state assembly as previously discussed for other Michael reactions involving ClO⁻ or enolates as nucleophiles.^{6,7} Figure 1 shows two views (related by a 180° rotation about a vertical axis) of the transition state assembly for the addition of the contact ion pair of CH₂NO₂⁻ and **2** to **4** forming *ent*-**6**.

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