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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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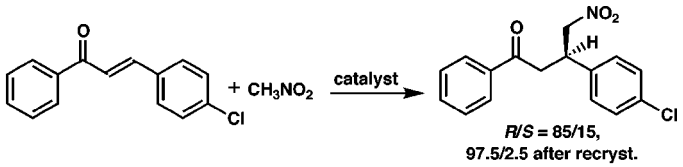
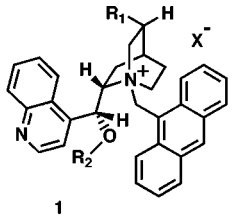
ABSTRACT



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 tetroxide[1] 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-



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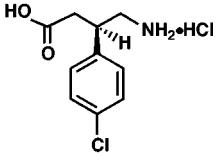
2 $R_1 = C_2H_5$
$R_2 = CH_2Ph$



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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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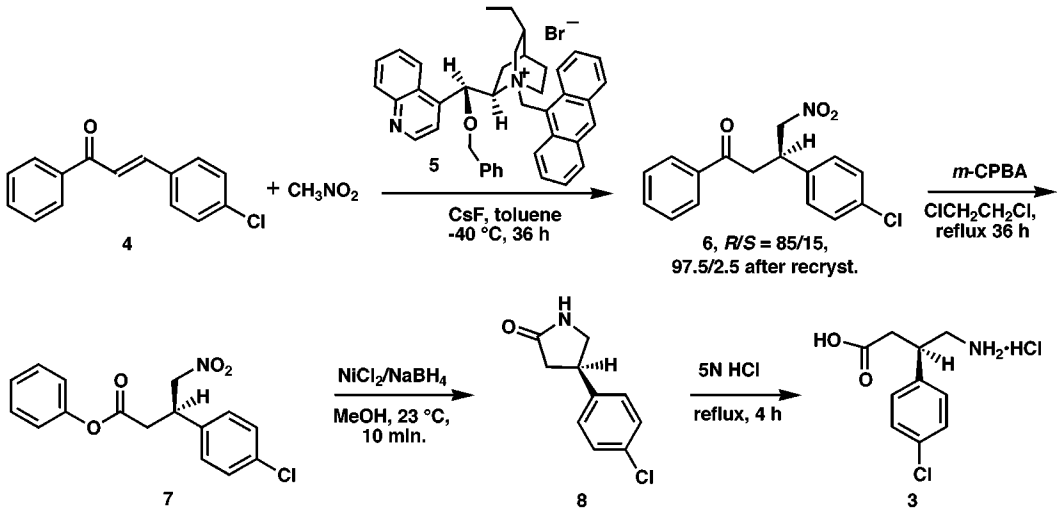
Scheme 1



enantiomer is essentially inactive. As a consequence there have been many studies on the synthesis of (*R*)-baclofen, including syntheses from (*S*)-glutamic acid[11] 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-chlorobenzylidineacetophenone, the cinchoninium salt **5** (10 mol %), and powdered cesium fluoride (10 equiv) in toluene at −40 °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 99−100 °C, $[\alpha]^{23}_D$ −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 °C for 30 min gave the (*R*)-γ-lactam **8**, mp 116−117 °C, $[\alpha]^{23}_D$ −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**), $[\alpha]^{23}_D$ −1.5 (c = 1, H_2O), mp 200 °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 cinchonidium salt **2** as catalyst and CsF as base in toluene at −40 °C for 36 h to afford the

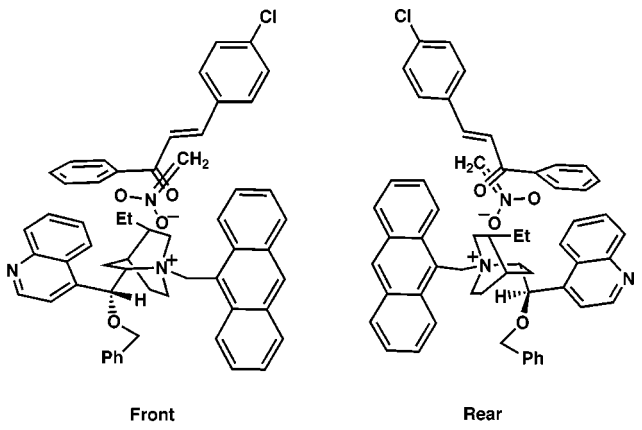


Figure 1.

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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 cinchonidium catalyst **2** and the *R* adduct predominating with the diastereomeric cinchoninium catalyst **5**.
(19) A mixture of powdered, flame-dried CsF (1.52 g, 10.0 mmol), the chiral cinchoninium salt **5** (66 mg, 0.1 mmol), and chlorochalcone **4** (243 mg, 1.0 mmol) in toluene (2.5 mL) was cooled to −40 °C and treated with nitromethane (0.54 mL, 10 mmol). The mixture was stirred at −40 °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 110−112 °C; $[\alpha]^{23}_D$ = +17.9 (c = 1, CH_2Cl_2); FTIR (film) 1682.9 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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}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 (CI^+) calcd $[C_{16}H_{14}ClNO_3 + NH_4]^+$ 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, λ = 254 nm, retention times minor 18.1 min, major 25.9 min. One recrystallization from ethyl acetate−hexane gave colorless crystals: mp 121−122 °C; $[\alpha]^{23}_D$ +24.3 (c = 1, CH_2Cl_2); ee 95%.

(*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 $CH_2NO_2^-$ and **2** to **4** forming *ent*-**6**.

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