Pergamon

Tetrahedron Letters, Vol. 37, No. 28, pp. 4837-4840, 1996
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0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00964-1

Catalytic Enantioselective Synthesis of the Second Generation Histamine Antagonist Cetirizine Hydrochloride

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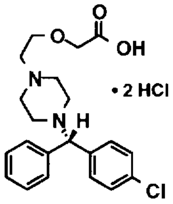
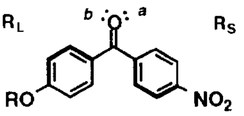
Summary: *The first enantioselective synthesis of cetirizine hydrochloride (1) has been developed using the highly stereospecific chiral oxazaborolidine (CBS) reduction of 4-[η^6-chromium tricarbonylbenzoyl]chlorobenzene to establish the benzhydryl stereocenter. The chromium tricarbonyl unit also served as stereocontroller to allow the stereospecific displacement of hydroxyl by amino at the benzylic stereocenter, as outlined in Scheme 1.* Copyright © 1996 Elsevier Science Ltd

We report herein the first enantioselective synthesis of the commercially important, second-generation histamine H_1 antagonist *cetirizine hydrochloride*, **1**, an effective treatment for a range of allergic diseases.[1,2] Cetirizine hydrochloride is currently marketed as the racemate. The only reported synthesis of the enantiomeric cetirizines employed resolution of a (±)-4-chlorobenzhydrylamine as the salt with tartaric acid.[3] The key step in our synthesis is the chiral oxazaborolidine-catalyzed (CBS) reduction, using catecholborane as the stoichiometric reductant, of an unsymmetrical benzophenone.

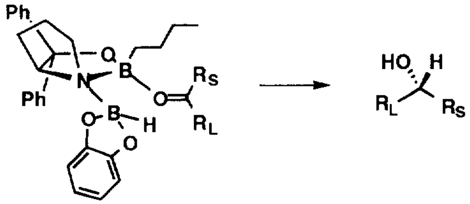
We have recently demonstrated that the electronic effect of remote substituents in π-conjugated ketones can bias the absolute stereochemical course of carbonyl reduction through a type of second order steric effect.[4] Thus, 4-nitro-4'-trialkylsilyloxy benzophenones **2** undergo CBS reduction in the sense expected for coordination of the catalyst to lone pair *a* in **2**, with the 4'-trialkylsilyloxy phenyl group acting effectively as a bulkier carbonyl substituent (R_L) than the 4-nitrophenyl group (R_S), as shown below. In this way 4-nitro-4'-triisopropylsilyloxybenzhydrol could be synthesized in 95% ee.[4] π-Complexation of one of the aromatic rings in the benzophenone system with the η^6-π-$Cr(CO)_3$ group also produces an electronic dissymmetry which translates into efficient enantioselection in the CBS reduction with the π-complexed aromatic ring behaving as the larger



1



2 R = *i*-Pr$_3$Si

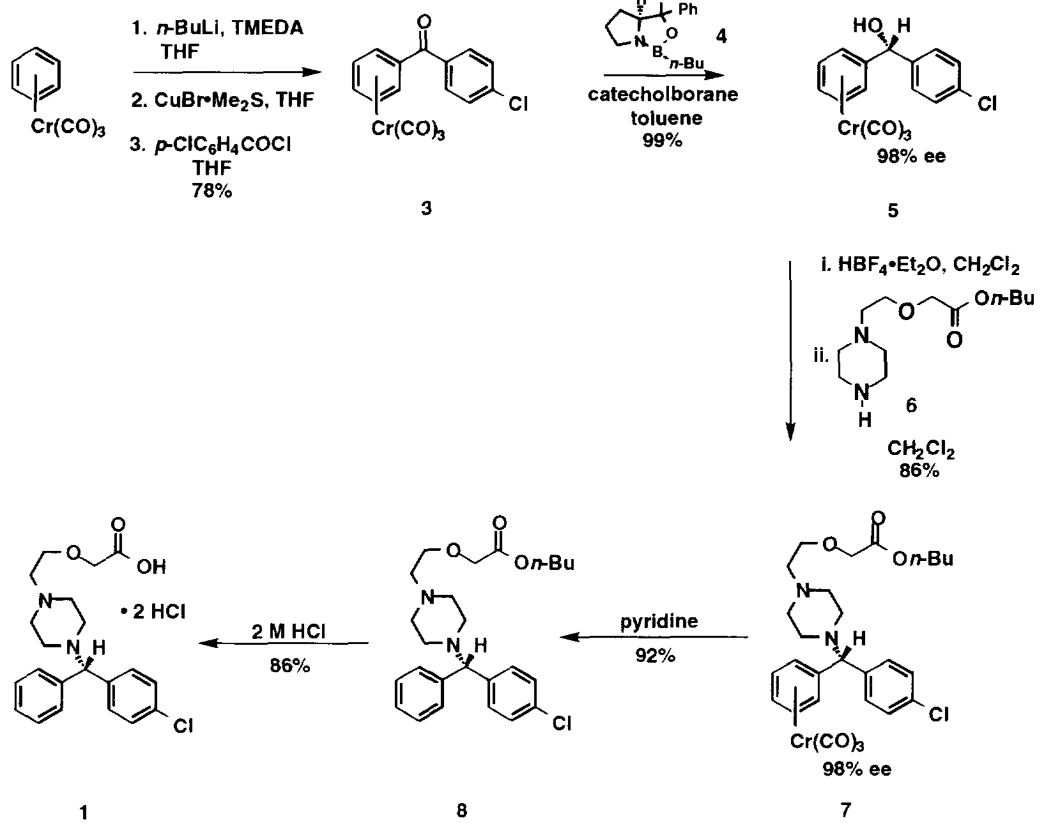


carbonyl substituent.[4] This enantioselective reduction is eminently suited to the synthesis of chiral **1** since the π-chromium tricarbonyl group can serve as an effective stereocontroller in displacement reactions at the benzylic carbon.

The process developed for the enantioselective synthesis of cetirizine is outlined in Scheme 1. Lithiation of benzene chromium tricarbonyl[5] with 1 equiv of *n*-BuLi in the presence of 1 equiv of TMEDA in THF at -78 °C for 45 min, addition to 1 equiv of CuBr-Me$_2$S in THF at -78 °C and stirring for 30 min, followed by treatment with 1.2 equiv of freshly distilled 4-chlorobenzoyl chloride in THF at -78 °C then warming to r.t. and stirring for 18 h gave the desired ketone **3** as an orange solid (78% yield, m.p. 105-107 °C).[6] Addition of **3** as a solution in toluene to 0.15 equiv of **4**[7] and 2 equiv of catecholborane in toluene at -78 °C over 5 min, stirring for 2 min at -78 °C, then warming to -40 °C for 2.5 h afforded **5** in 99% yield and 98% ee as a viscous yellow oil (crystallization from CHCl$_3$-pentane bilayer gave a yellow solid, m.p. 90-91 °C, $[\alpha]^{22}_{D}$ +29.4° (c 0.034, CHCl$_3$)).[8] Dropwise addition of 2 equiv of 85% tetrafluoroboric acid-diethyl ether complex over 1 min to **5** in CH$_2$Cl$_2$ at -60 °C, stirring for 20 seconds, then rapid transfer via a dry ice-cooled cannula to 5 equiv of **6**[9] in CH$_2$Cl$_2$ at -60 °C resulted in an instantaneous reaction which yielded **7**, $[\alpha]^{23}_{D}$ +83.3° (c 0.030, CHCl$_3$), as a viscous yellow oil in 86% yield and 98% ee, corresponding to a complete maintenance of optical purity.[10] Conversion of alcohol **5** to the optically active benzhydryl piperazine **7** takes advantage of the configurational stability of Cr(CO)$_3$ stabilized carbocations. It has been shown[11] that the ionization of optically active chromium tricarbonyl-benzylic alcohol complexes in the presence of nucleophiles can provide substitution products with complete *retention* of configuration at the benzylic center. A solution of **7** in pyridine was heated to reflux for 4 h, cooled to room temperature, diluted with dry Et$_2$O, filtered to remove (pyr)$_3$Cr(CO)$_3$[12] (70% recovery, brown solid), and concentrated to give after silica gel chromatography **8** in 92% yield, $[\alpha]^{23}_{D}$ +7.33° (c 0.75, CHCl$_3$). Hydrolysis of **8** in 2 M HCl at 50 °C for 4 h, followed by neutralization with NaOH to pH 7 and purification via ion exchange chromatography[13] provided (–)-cetirizine hydrochloride in 86% yield, m.p. 157-161 °C; [α](365 nm) -10.6° (c 1.0, H$_2$O); lit.[14] [α](365 nm) -11.1° (c 1.0, H$_2$O).

The above described synthesis of cetirizine hydrochloride in 5 steps and 53% overall yield from readily available benzene chromium tricarbonyl is convergent and permits recovery and recycling of the chromium carbonyl. This approach can be applied to the efficient enantioselective synthesis of a variety of benzhydrylamines as well as other benzhydrilic compounds, and demonstrates a practical application of remote electronic effects in the CBS oxazaborolidine-catalyzed reduction.[15]

Scheme 1



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7. Formation of **4**: Toluene (15 mL) was added to (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol (126.5 mg, 0.500 mmol) and *n*-BuB(OH)$_2$ (82 mg, 0.80 mmol) in a round-bottom flask fitted with a Dean-Stark apparatus (side-arm filled with mol. sieve 4A) and a reflux condenser. The mixture was vigorously refluxed for 12 h. The toluene was removed by distillation via the Dean-Stark side-arm until ca. 2 mL was left. After cooling to room temperature, the Dean-Stark apparatus was replaced by a rubber septum and the

remaining toluene was removed *in vacuo* at 40 °C. Toluene (2.5 mL) was then added to provide a 0.2 M solution of catalyst. Complete formation of the catalyst was ascertained by ^{1}H NMR (300 MHz, $CDCl_3$).

8. Addition of **3** (azeotropically dried with toluene) in toluene (1.75 mL) to **4** (0.2 M in toluene, 200 μL, 0.04 mmol) and catecholborane (60 μL, 0.57 mmol) as a solution in toluene (100 μL) at -78 °C was carried out over 5 min The solution was stirred for 2 min at -78 °C, then warmed to -40 °C for 2.5 h. The reaction was cooled to -78 °C, MeOH (200 μL) was added, and the solution was warmed to room temperature. The reaction was diluted with Et_2O (50 mL), washed with pH 13 buffer until the aqueous washings were clear, then washed with brine (2 x 10 mL). Concentration of the organic layer to ca. 10 mL and treatment with HCl (0.5 M in MeOH, 0.04 mmol) resulted in the precipitation of the amino alcohol-HCl salt which was recovered by filtration. The organic layer was concentrated *in vacuo* and the residue was purified by silica gel chromatography (3 : 1 hexanes–EtOAc with 5% triethylamine) to give 99 mg (99%) of a viscous yellow oil. Analysis by HPLC (Chiralcel OD, 20% *i*-PrOH in hexanes, λ=254 nm, 1 mL/min) showed the product to be of 98% ee (R_t: 15.7 min, major; 25.4 min, minor). $[\alpha]^{22}_{D}$ +29.4° (c 0.034, $CHCl_3$); crystallization from a $CHCl_3$-pentane bilayer gave a solid, m.p. 90-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 4H), 5.65 (d, J=6.3 Hz, 1H), 5.44 (s, 1H), 5.40 (m, 1H), 5.30 (m, 2H), 5.21 (d, J=6.0 Hz, 1H), 2.60 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.08, 140.2, 134.41, 129.04, 127.80, 114.64, 92.52, 92.40, 92.17, 91.70, 90.08, 73.63 ppm; FT-IR (neat, cm^{-1}) 1964.8, 1879.4, 1488.7, 1089.6, 1013.5; MS (EI): M+ (7.5%), 270 (28%), 183 (70%), 165 (77%), 105 (100%); HRMS (EI): calcd. for $[C_{16}H_{11}ClCrO_4]$: 353.9751; found: 353.9763.
9. Preparation of **6**: commercially available 2-(2-chloroethoxy)-ethanol (0.1 M solution in acetone) was oxidized to the acid by dropwise addition over 6 h to Jones Reagent (3.8 equiv CrO_3, 9 equiv H_2SO_4 (1.5 M), 0 °C, 77%), esterified (1.1 equiv DCC, 1.2 equiv *n*-BuOH, 0.1 equiv 4-*N*,*N*-dimethylaminopyridine, CH_2Cl_2, r.t., 91%) coupled with *N*-CBz-piperazine (1.1 equiv *n*-butyl ester, 1 equiv NaI, 1.5 equiv Na_2CO_3, propionitrile, reflux, 95%), and deprotected (10% Pd on carbon, 1 atm H_2, EtOAc, 98%).
10. Analysis by HPLC (Chiralcel AD, 10% *i*-PrOH in hexanes with 0.1% diethylamine, 1 mL/min, λ=254 nm) showed the product to be of 98% ee (R_t: 30.35 min, major; 44.17 min, minor).
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13. The final product was purified by BIO-RAD Analytical Grade Cation Exchange Resin, Bio-Rex 70, 200-400 mesh, H+ form. Application of a pH 7 solution of the reaction solution to the resin was followed by elution with H_2O, 0.5 M HCl, 1.0 M HCl, and 2.0 M HCl. TLC analysis was used to ascertain the presence of the substrate in the fractions collected. ^{1}H NMR (400 MHz, D_2O) δ 7.46 (m, 4H), 7.33 (m, 5H), 5.10 (s, 1H), 4.06 (s, 2H), 3.77 (t, J=4.4 Hz, 2H), 3.51 (br s, 4H), 3.37 (t, J=4.5 Hz, 2H), 3.23 (br s, 4H) ppm.
14. We are indebted to Dr. C. J. Opalka at Albany Molecular Research, Inc., for an authentic sample of (–)-cetirizine hydrochloride.
15. This research was assisted financially by a grant from the National Science Foundation and a fellowship to C.J.H.(NSF).

(*Received in USA* 8 *May* 1996; *accepted* 15 *May* 1996)