ORGANIC LETTERS

2010
Vol. 12, No. 10
2222−2225

Synthesis of (−)-(*S*,*S*)-clemastine by Invertive N → C Aryl Migration in a Lithiated Carbamate

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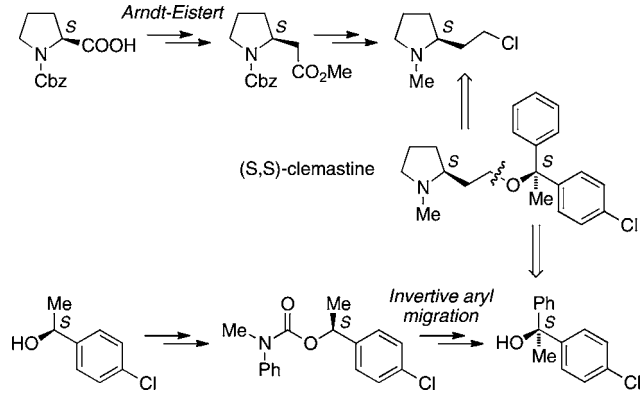
Received March 17, 2010

ABSTRACT



The first enantioselective synthesis of the antihistamine agent clemastine, as its (*S*,*S*)-stereoisomer, has been achieved by ether formation between a proline-derived chloroethylpyrrolidine and an enantiomerically enriched tertiary alcohol. The tertiary alcohol was formed from the carbamate derivative of α-methyl-*p*-chlorobenzyl alcohol by invertive aryl migration on lithiation. The (*S*,*S*)-stereochemistry of the product confirms the invertive nature of the rearrangement.

Clemastine **1** is a selective histamine H1 antagonist with anticholinergic and sedative effects.[1] The synthesis of all four possible stereoisomers of clemastine was reported by Ebnöther and Weber in 1976.[2] Coupling of two racemic components (±)-**2a** and (±)-**3a** in a low-yielding alkylation, followed by a series of purification and resolution steps, allowed each of the stereoisomers to be characterized as its fumarate salt.[2,3] The most active isomer was identified as the (+)-(*R*,*R*)-isomer, with the stereochemistry of the quaternary center α to oxygen determining activity to a greater extent than the center in the pyrrolidine ring.[2] Published routes to clemastine all employ resolution,[2,4] and no asymmetric synthesis of clemastine has been described, although a synthesis of (−)-hydroxyclemastine was reported in 2007.[5]

We now report the enantioselective synthesis of the active diastereoisomer of clemastine (as its (*S*,*S*)-enantiomer) from two enantiomerically pure or enriched components: the chloroethylpyrrolidine (*S*)-**2a** derived from (*S*)-proline and the tertiary alcohol (*S*)-**3a**. This alcohol was made using our recently reported[6] stereospecific aryl migration of lithiated carbamates (Scheme 1). Comparison

(1) Nelson, W. L. Antihistamines and related antiallergic and antiulcer agents. In *Foye's Principles of Medicinal Chemistry*; Williams, D. A., Thomas, L. L., Eds.; Lippincott Williams & Wilkins: Philadelphia, 2002; pp 794−818.

(2) Ebnöther, A.; Weber, H.-P. *Helv. Chim. Acta* **1976**, *59*, 2462.

(3) Parvez, M.; Wendling, M. A. *Acta Crystallogr.* **1991**, *C47*, 613.

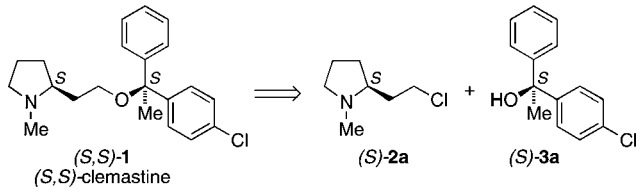
(4) Nikiforov, T.; Stanchev, S.; Milenkov, B.; Dimitrov, V. *Synth. Commun.* **1990**, 1977. Takaoka, M. Optical resolution of clemastine. Japanese patent JP53012857, 1978.

(5) Jung, J. W.; Kim, H.-D. *Arch. Pharm. Res.* **2007**, *30*, 1521.

(6) Clayden, J.; Farnaby, W.; Grainger, D. M.; Hennecke, U.; Mancinelli, M.; Tetlow, D. J.; Hillier, I. H.; Vincent, M. A. *J. Am. Chem. Soc.* **2009**, *131*, 3410.

10.1021/ol100627c
Published on Web 04/20/2010

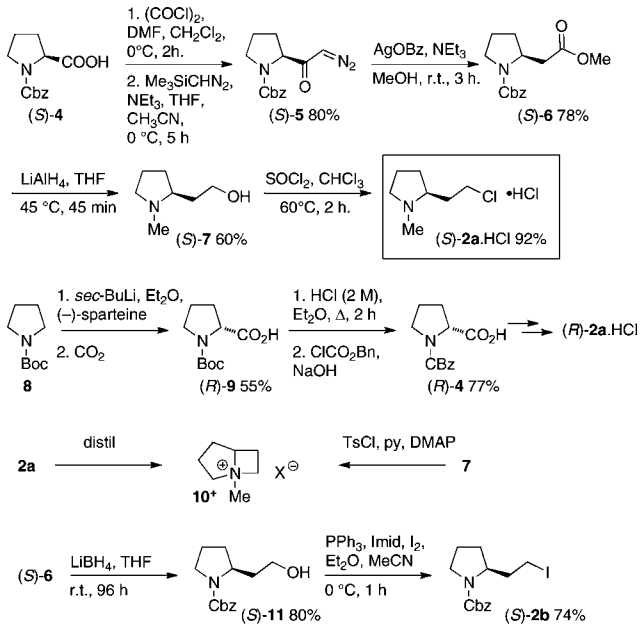
Scheme 1. Retrosynthesis of Clemastine



of our synthetic (*S*,*S*)-clemastine and its fumarate salt with literature data furthermore confirms the invertive nature of the aryl migration.

Both enantiomers of the pyrrolidine fragment **2a** were made by homologation of *N*-Cbz-proline **4** using an Arndt−Eistert reaction (Scheme 2).[7] For the (*S*) enantiomer, Cbz-L-proline (*S*)-**4** was converted to its acid chloride with oxalyl chloride and then treated with trimethylsilyldiazomethane to generate, after 5 h at 0 °C, the diazoketone (*S*)-**5**[7] in 80% yield. Decomposition of the diazoketone with silver benzoate in the presence of methanol and base[8] returned the chain-extended methyl ester (*S*)-**6**[9] in 78% yield. Lithium aluminum hydride in THF at 45 °C reduced both the ester and the carbamate protecting group,[10] giving the hydroxyethylpyrrolidine derivative (*S*)-**7**[11] in 60% yield. The alcohol was converted to the chloroethylpyrrolidine coupling partner with thionyl chloride in chloroform at 60 °C,[12] which returned the amine hydrochloride (*S*)-**2a**·HCl[13] in 92% yield.

Scheme 2. Pyrrolidine Fragment (*S*)-**2**



(*R*)-**2a**·HCl was made by a parallel route starting with *N*-Boc pyrrolidine **8**, which was lithiated with *s*-BuLi in the presence of (−)-sparteine, and the resulting complex was quenched with dry CO_2[14] to yield *N*-Boc-(*R*)-proline (*R*)-**9** in 55% yield and >99:1 er after crystallization.[15] As a result of the incompatibility of the Boc group with the conditions used for diazoketone formation, a protecting group swap[16] was necessary, which was achieved using 2 M HCl followed by benzyl chloroformate. The product (*R*)-**4** was taken through the same series of transformations to yield (*R*)-**2a**·HCl.

A small amount of **2a**·HCl was converted to its free base **2a** by purification on an SCX cartridge,[17] but we found that prolonged storage of **2a** either neat or in solution led to the formation of significant quantities of the bicyclic ammonium salt $\mathbf{10}^{+}Cl^{-}$. The same cyclization was observed in good yield on attempted purification of **2a** by distillation.[12] Cyclization to $\mathbf{10}^{+}\cdot TsO^{-}$ was likewise observed on attempted formation of the tosylate derivative of **7**. In general therefore we chose to store and use **2a** as its stable hydrochloride salt.

In view of this instability, an alternative coupling partner lacking a basic nitrogen atom, the CBz-protected iodide **2b**, was also made. Selective reduction of **6** with lithium borohydride in THF[18] gave the alcohol **11**, which was converted to the iodide **2b** with triphenylphosphine and iodine. At 0 °C, **2b** was formed in good yield and was stable to prolonged heating at 100 °C.

The tertiary alcohol (*S*)-**3a** was made from *p*-chloroacetophenone **12**, which was reduced by the method of Noyori[19] using formic acid in the presence of the ruthenium complex (*S*,*S*)-**13** to provide the alcohol (*S*)-**14a**[20] in 91% yield and >99:1 er. This alcohol was converted to its carbamate derivative **15a** by reaction with phenyl isocyanate and methylation with sodium hydride and methyl iodide (Scheme 3).[6] For the purpose of stereochemical confirmation

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(10) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.
(11) Nikiforov, T.; Stanchev, S.; Milenkov, B.; Dimitrov, V. *Heterocycles* **1986**, *24*, 1825.
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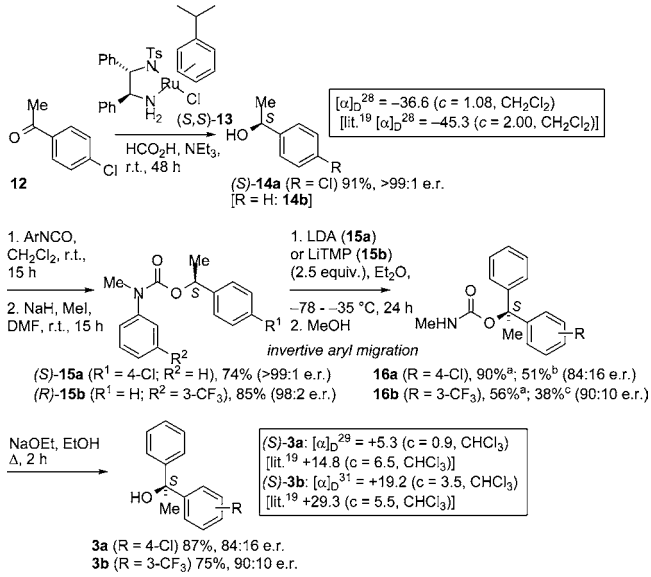
(13) Japanese patent JP53046967, 1993.
(14) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.
(15) The er was determined by conversion to the 3-5-dimethylanilides (Pirkle, W. H.; McCune, J. E. *J. Chromatogr.* **1989**, *479*, 419) and HPLC β-GEM/Regis, 250 mm × 4.6 mm, with a flow rate of 1 mL/min and a detection wavelength of 254 nm. t_R: (*R*) 23.9 min, (*S*) 21.2 minThe method of Mani et al. (Deng, X.; Mani, N. S *Tetrahedron Asymmetry* **2005**, *16*, 661), quenching the lithiopyrrolidine with ethylene oxide, was unsuccessful in our hands.
(16) Rispens, M. T.; Gelling, O. J.; de Vries, A. H. M.; Meetsma, A.; van Bolhuis, F.; Feringa, B. L. *Tetrahedron* **1996**, *52*, 3521.
(17) SCX (Strong Cation Exchange) cartridges are manufactured by Biotage and contain an immobilized benzenesulfonic acid.
(18) Campbell, J. A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6313.
(19) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521.
(20) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature (London)* **2008**, *456*, 778.

Scheme 3. Tertiary Alcohols (*S*)-**3**



[a] In the presence of DMPU (25% v/v). [b] LDA, conditions as indicated. [c] LiTMP, conditions as indicated.

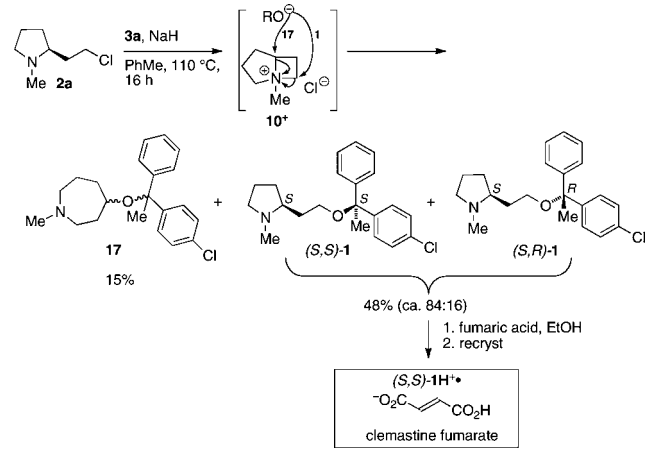
(see below), a second rearrangement substrate (*R*)-**15b** was made from (*R*)-α-methylbenzyl alcohol **14b** and *m*-trifluoromethylphenyl isocyanate in a similar way.

Previous studies[6] of aryl migration in lithiated carbamates had shown that stereospecificity is maximal if the reaction is carried out with a lithium amide base at a temperature no greater than −30 °C. Accordingly, both carbamates were treated with lithium amides (optimally **15a** with LDA and **15b** with LiTMP) at −78 °C, and the reactions were allowed to warm slowly to −35 °C and quenched with MeOH after 24 h. Rearranged products were formed in moderate yield in both cases: the chlorophenyl-substituted carbamate **16a** with 84:16 er and the trifluoromethyl-substituted carbamate **16b** with 90:10 er (Scheme 3). Addition of DMPU to the reactions gave considerably higher yields but returned racemic products.

Alcoholysis of the carbamate products to give 1,1-diarylethanols was achieved by heating to reflux with sodium ethoxide in ethanol, which gave alcohol (*S*)-**3a** in 87% yield and alcohol (*S*)-**3b** in 75% yield. The stereochemistry of both products was confirmed as (*S*) by comparison with literature data,[20] as shown in Scheme 3. Both rearrangements evidently proceed with mechanistic inversion of configuration.

(*S*)-**2a**·HCl and (*S*)-**3a** were prepared for the challenging formation of the hindered ether by free-basing (*S*)-**2a** with KOH and deprotonating (*S*)-**3a** with sodium hydride. Heating (*S*)-**2a** and the resulting sodium alkoxide of (*S*)-**3a** together at reflux in toluene for a period of 16 h returned a mixture of isomers: 15% of the azepanes **17**, and 48% of the diastereoisomers of **1** (Scheme 4).

Scheme 4. Formation of Ether Linkage and Isolation of Clemastine Fumarate



The formation of **17**[2] presumably arises through participation of the amine N in the substitution to form **10**$^+$, followed by expansion of the resulting bicyclic cation. However, when N participation was discouraged by use of the carbamate **2b**, we observed no coupling of any sort, suggesting that participation of the amine N is involved in the pathways to *both* products and that anchimeric assistance to departure of Cl^- is essential to the method.

This mixture of diastereoisomers of **1** displayed a single set of peaks by ^{1}H and ^{13}C NMR in both $CDCl_3$ and CD_3OD, and no separation into diastereoisomers was observed by HPLC on a variety of chiral and achiral stationary phases. However, on addition of 1 equiv of fumaric acid, an 87:13 mixture of diastereoisomeric fumarate salts was evident by ^{1}H NMR in $CDCl_3$. This mixture was recrystallized to constant melting point and $[\alpha]_D$, resulting in crystals that contained, by NMR, none of the minor diastereoisomer. The filtrate, by contrast, was a ca. 1:1 mixture of the two diastereoisomers by ^{1}H NMR.

Table 1. Physical Data for Clemastine and Clemastine Fumarate[2]

compound	mp (°C)	mp (lit.[2]) (°C)	$[\alpha]^{25}_D$[a]	$[\alpha]^{25}_D$ (lit.[2])[a]
(*S*,*S*) + (*S*,*R*)-**1**[b]			−37.4	−33.7 (*S*,*S*); −58.8 (*S*,*R*)
(*S*,*S*) + (*S*,*R*)-**1**H$^+$·fum^{-c}	170−172	177−178 (*S*,*S*); 159−160 (*S*,*R*)	−17.3	−16.9 (*S*,*S*); −32.8 (*S*,*R*)
(*S*,*S*)-**1**H$^+$·fum^{-d}	**176−177**	**177−178**	**−17.1**	**−16.9**

[a] c = 2.0 (EtOH for **1**; MeOH for **1**H$^+$·fum$^-$. [b] Presumed ca. 84:16 mixture of diastereoisomers resulting from coupling enantiopure **2a** with **3a** of 84:16 er. [c] Fumarate salt of this mixture, which ^{1}H NMR indicates contains an 87:13 diastereoisomeric ratio. [d] Recrystallized fumarate salt with <10% minor diastereoisomer by ^{1}H NMR.

The polarimetric and melting point data for the fumarate salts and corresponding literature values[2] are shown in Table 1. These are fully consistent with the hypothesis that the initial coupling produces principally (*S*,*S*)-clemastine contaminated with ca. 15% (*S*,*R*)-clemastine but that recrystallization removes the minor diastereoisomer and returns a pure sample of (*S*,*S*)-clemastine.

The correspondence of the major product with the data for (*S*,*S*)-clemastine further confirms that the rearrangement of the lithiated carbamate proceeds with inversion of stereochemistry at the migration terminus,[6] in contrast with related ureas.[21] Further modeling and experimental work to establish the origin of this stereodivergent behavior is ongoing.

Acknowledgment. We are grateful to GlaxoSmithKline and the EPSRC for a studentship (to A.M.F) and to Dr Christopher Nichols for helpful discussions.

Supporting Information Available: Characterization data and experimental details for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100627C

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