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An Efficient One-Pot Process for 10-Bromo-8-chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one, an Intermediate to SCH 66336

Xiaoyong Fu,* Timothy L. McAllister, Xiongwei Shi, T. K. Thiruvengadam, Chou-Hong Tann, and Junning Lee

Synthetic Chemistry Department, Schering-Plough Research Institute, 1011 Morris Avenue, Union, New Jersey 07083, U.S.A.

Abstract:

An efficient process for the preparation of 10-bromo-8-chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (7), an intermediate to an antitumor agent SCH 66336, is described. This one-pot method consists of a selective reduction of 8-chloro-7(9)-nitro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (4) with Sn(II) bromide (generated in situ from Sn(II) sulfate and HBr), followed by bromination at the 10 position, and deamination. The desired product (7) is isolated in 75% overall yield.

Introduction

Farnesyl protein transferase (FPT) is an enzyme that facilitates the signal transduction during cell proliferation. Inhibition of FPT, therefore, represents an attractive target for antitumor drugs. The farnesyl transferase inhibitors (FTIs) have shown[1] antitumor activity in a broad range of solid and hematologic malignancies in clinical trials. SCH 66336 (lonafarnib) **1**, a trihalo benzocycloheptapyridine tricyclic compound, is a potent inhibitor of farnesyl protein transferase possessing oral and cellular antitumor activity.[2] During structure−activity relationship studies leading to SCH 66336, 10-bromo benzocycloheptapyridyl FTIs were found to be more potent than analogous compounds lacking the 10-bromo substitution. This phenomenon was believed to be due in part to an increase in conformational rigidity as the 10-bromine substituent in the molecule could restrict the conformation of the C-11 piperidyl group in an axial orientation.[3] Introduction of a bromo group at the C-10 position of the tricyclic benzocycloheptapyridine had already been achieved in the discovery synthesis by nitration, reduction, bromination, and deamination starting from loratadine (**2**). A less expensive ketone (**3**), available in large quantities from Schering-Plough production, was proposed as an alternative starting material for SCH 66336 (Scheme 1).[4]

Treatment of **3** with $HNO_3-H_2SO_4$ at 0−5 °C specifically nitrates the phenyl ring to provide a mixture of 9-nitro (**4a**) and 7-nitro (**4b**) regioisomers in a ratio of about 6.5:1 in high chemical yield.[5] Separation of the isomeric mixture was not necessary since the nitrogen function was removed from the C-ring in latter steps. The preparation of **7** using discovery chemistry involved reduction of the 7(9)-nitro-8-chloroketones (**4a** and **4b**) with iron filings in the presence of acetic acid as the first step. Filtration through Celite followed by an extractive workup with several citric acid washes offered a mixture of amino ketones (**5a** and **5b**). This mixture was treated with Br_2 to provide **6a** and **6b** which were subsequently deaminated with $NaNO_2$ and H_3PO_2 to give the desired product **7** in ∼55% isolated yield (Scheme 2).

Several issues with this three-step route needed to be addressed before scale-up. The iron reduction of the nitro group to amine gave a thick slurry that was difficult to filter. The aqueous layer was dark, making it hard to distinguish between the two phases. Addition of the iron powder was very exothermic, presenting a process safety concern. For these reasons, a more efficient process was required to produce large quantities of **7** to support the delivery of SCH 66336 drug substance for toxicological and clinical studies. We report herein an efficient one-pot process for the synthesis of **7** from **4**.

Results and Discussion

Attempts to selectively reduce the nitro function in the presence of the ketone with zinc were unsuccessful. Hydrogenation with Pd/C, PtO_2, Raney Ni, etc. also reduced both the ketone and nitro groups to form an amino alcohol. Although the over-reduced amino alcohols **8a**−**b** could be

* To whom correspondence should be addressed. E-mail: xiaoyong.fu@spcorp.com.

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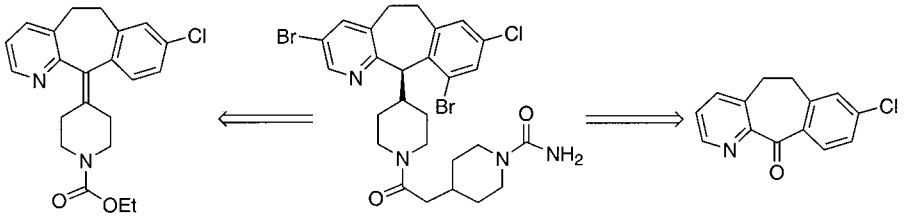
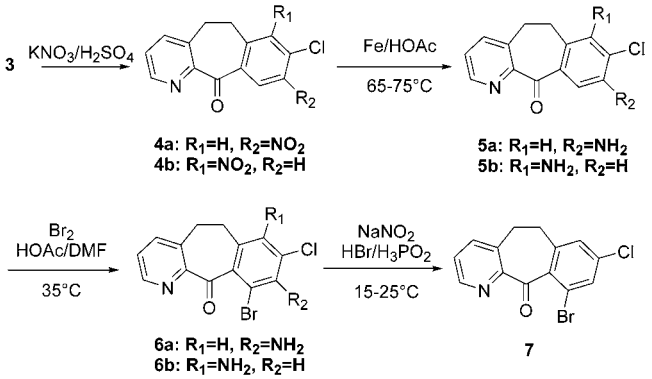
Scheme 1



2 (Loratadine) **1 (SCH 66336)** **3**

Scheme 2



4a: R_1=H, R_2=NO_2
4b: R_1=NO_2, R_2=H

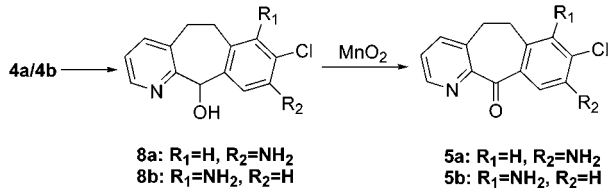
5a: R_1=H, R_2=NH_2
5b: R_1=NH_2, R_2=H

6a: R_1=H, R_2=NH_2
6b: R_1=NH_2, R_2=H

7

oxidized to regenerate the desired amino ketones **5a**−**b** (Scheme 3) with MnO_2, this added an extra step, reducing process efficiency.

Scheme 3



8a: R_1=H, R_2=NH_2
8b: R_1=NH_2, R_2=H

5a: R_1=H, R_2=NH_2
5b: R_1=NH_2, R_2=H

One of the conventional methods in the literature for selectively reducing aromatic nitro groups in the presence of a carbonyl function to amines involved the use of stannous chloride ($SnCl_2$).[6] Indeed, when the mixture of **4a**,**b** was treated with $SnCl_2$ in hydrochloric acid at 0−25 °C for up to 48 h, the nitro group was selectively reduced while the ketone function was left intact. Since the reduction took a long time to complete, numerous solvents (DMF, AcOH, EtOH, MeOH, IPA, THF, CH_3CN, etc.) were screened to facilitate the reaction rate. The best solvent was acetonitrile which furnished **5** in >97% (peak area) by HPLC analysis (>95% solution yield of **5a**,**b**). The reaction was complete in 2−3 h at 70 °C with 4 equiv of $SnCl_2 \cdot 2H_2O$. After quenching with aqueous NaOH, the two layers were cleanly separated, and the $SnCl_4$ was hydrolyzed to $Sn(OH)_4$, which was removed in the aqueous layer. To demonstrate the feasibility of incorporating the Sn(II) reduction in the synthesis, the mixture of amino ketones **5a** and **5b** in DMF was treated with bromine at 0−5 °C in the presence of acetic acid. The isolated mixture of regioisomers of **6** was deaminated, and the desired product **7** was isolated in ∼70% overall yield. These encouraging results prompted us to streamline the process. However, when the reaction mixture containing regioisomers of **6** was subjected to the deamination procedure, significant amounts of **5a**−**b** were observed after charging hypophosphorous acid due to debromination.[7] We speculated that the residual bromide ion present could assist the debromination. Thus, replacement of bromine with other brominating agents, such as NBS, should not only eliminate the use of toxic bromine but also minimize the debromination. Indeed, NBS in the presence of a catalytic amount of acid ($HClO_4$ or other acid) proved to be a clean and efficient alternative reagent to Br_2 for the conversion of aminoketones **5a**−**b** to 10-bromo derivative **6a**−**b**. It should be pointed out that bromination with NBS did not produce the debromo compound as the byproduct during or after charging hypophosphorous acid as monitored by HPLC. The overall yield of **7** from **4** was greater than 70% in three steps.

Although the chemistry described above worked well with the 5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one system, the following problems became evident during further developmental work. The residual Cl^- ion from the reduction mixture reacted with the diazonium intermediate to generate up to 2−3% of 8,10-dichloroketone[8] **9** in the subsequent steps. Although the level of **9** was limited to below 1% by introducing aqueous NaOH workup after the reduction, the workup and distillation of the reduction mixture required a long process time. A possible pathway for the formation of the trace amount of **9** is depicted in Scheme 4 (**9** can also be formed from the minor C-7 diazonium intermediate). Since it was difficult to remove this impurity **9** by recrystallization, it was necessary to avoid its formation.

It is obvious that replacing stannous chloride ($SnCl_2$) with stannous bromide[9] ($SnBr_2$) would eliminate the chloride source for the formation of **9**. However, $SnBr_2$ is a more expensive reagent[10] than $SnCl_2$. An inexpensive alternative is to generate $SnBr_2$ in situ from stannous sulfate ($SnSO_4$)[11]

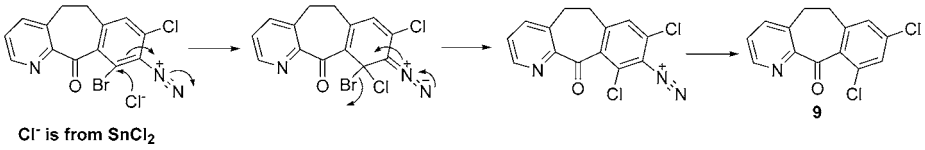
(6) Buck, J. S.; Ide, W. S. *Org. Synth.* **1933**, *13*, 28−30. Stipanovic, R. D.; Steidl, J. *Synth. Commun.* **1986**, *16*, 1809−13. Dixon, R. P.; Snyder, J. S.; Bradley, L.; Linnenbrink, J. *Org. Prep. Proced. Int.* **2000**, *32*, 573−577. Sakowski, J.; Boehm, M.; Sattler, I.; Dahse, H.-M.; Schlitzer, M. *J. Med. Chem.* **2001**, *44*, 2886−2899. Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839−42. Satoh, T.; Mitsuo, N.; Nishiki, M.; Inoue, Y.; Ooi, Y. *Chem. Pharma. Bull.* **1981**, *29*, 1443−5.

(7) The debrominated byproduct was observed in as much as 50% when H_3PO_2 was charged directly into the bromination mixture. However, the level of the impurity could be controlled to below 5% by adjusting the pH of the mixture to 4 before the H_3PO_2 addition.

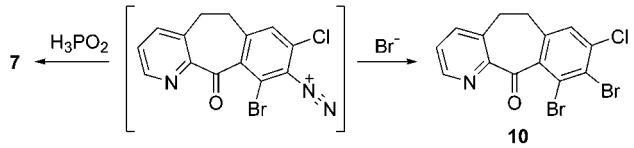
(8) The structure of impurity **9** was proposed by HPLC−MS analysis of the 8-chloro-10-bromoketone **7**.

(9) Borchardt, R. T.; Huber, J. H.; Houston, M. *J. Med. Chem.* **1982**, *25*, 258−63. Kasai, T.; Nakamori, T.; Furugaki, K. *Nippon Kagaku Kaishi* **1981**, *(4)*, 536−43.

Scheme 4



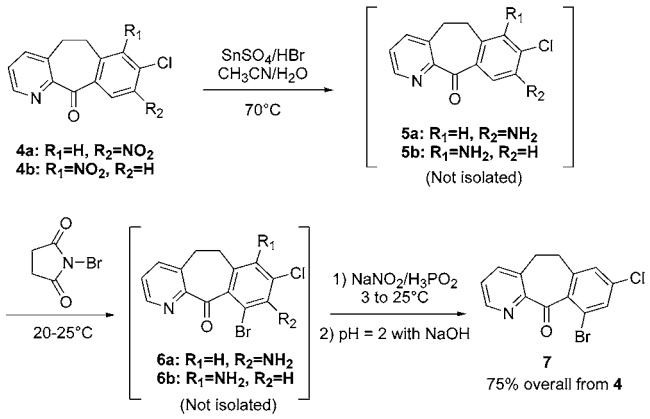
Scheme 5



and 48% aqueous HBr. Indeed, the $SnSO_4$/HBr reduction gave a mixture of **5a**−**b** in >97% (combined peak area) by HPLC analysis. It was noted that this new procedure produced a thick slurry. After cooling to room temperature, the reaction mixture was filtered. The cake generated contained mostly inorganic tin salts but can trap as much as 10 to 20% of the desired product. Initial attempts to wash the cake with 4−6 × 1:1 CH_3CN/H_2O led to inconsistent recovery of the product in the filtrate. Washing the cake with aqueous acetonitrile containing hypophosphorous acid (1.5×) was more efficient in recovering the mixture of **5a**−**b**. The combined filtrate and washes were directly subjected to bromination (NBS) and deamination (7.5 × volume H_3PO_2 and 1 × 30% $NaNO_2$). The desired product **7** was isolated in greater than 70% overall yield by adjusting the pH to 2.0 with 50% caustic to effect the crystallization of the product. It should be noted that attempts to increase the volumetric efficiency by reducing the amount of H_3PO_2 resulted in a higher level of a dibromo impurity proposed to be dibromoketone **10**,[12] which is formed from a competing side reaction of bromide with the diazonium intermediate (Scheme 5). For example, the dibromo impurity (**10**) was detected in about 1% by HPLC with 9 volumes of H_3PO_2. The level of **10** increased to 2.5% with 6 volumes of H_3PO_2 and 4% with 3 volumes.

Difficulties were encountered during filtration after the $SnSO_4$ reduction in our pilot-plant scale-up. Greater than 10% of the over-reduced byproduct **8** was observed by HPLC analysis. Although impurity **8** was subsequently removed during the crystallization step, the chemical yield was significantly lower (58% vs 73%). Since over-reduction could only be reproduced in the laboratory by aging the filtrate and washes in the presence of hypophosphorous acid, the filtration of inorganic tin salts followed by hypophosphorus acid/CH_3CN wash was reexamined. Careful analysis suggested that the desired product **7** crystallizes at around pH 2, while the inorganic salts remain in solution at pH <3. By taking advantage of the solubility difference, the deamination could be executed in a homogeneous solution with the increased amount of hypophosphorous acid without the filtration of tin salts after the reduction. This would eliminate the slow filtration procedure and also reduce the 9,10-dibromo impurity **10**. The volumetric efficiency of the process would improve since the washes are eliminated. With the above analysis in mind, the mixture of starting nitro compounds **4a**−**b** was smoothly reduced with $SnSO_4$ in the presence of 48% aqueous HBr in CH_3CN. The heterogeneous mixture was further treated with NBS. After the bromination, 13 × volume 50% hypophosphorus acid was added, followed by the addition of 30% aqueous $NaNO_2$ to effect the deamination. The pH of the reaction mixture was adjusted to 2.0 with aqueous NaOH, and the product **7** crystallized out. Since the reaction mixture turned to a homogeneous solution before the crystallization of **7** began, the product was obtained in high yield and purity. Washing the wet cake with 5% aqueous acetic acid was more effective in removing the inorganic Sn salts than with pure water. The product **7** was isolated in about 75% overall yield (Scheme 6). A typical plant batch of **7** was found to contain 0.25% residual Sn[13] which had no detrimental effects either on the latter processing steps or final product quality. Insufficient removal of tin salts during wet cake washing would make subsequent layer separations extremely difficult.

Scheme 6



Conclusions

In summary, we have developed an efficient, high-yielding one-pot (three steps) process for the conversion of a mixture of 7(9)-nitroketone **4a**−**b** to 10-bromo-8-chloroketone **7** in 75% isolated yield. The process involved a Sn(II)-induced selective reduction of the aromatic nitro group to amino ketones **5a**−**b** in the presence of a ketone function. The heterogeneous reaction mixture was directly treated with NBS to introduce the 10-bromo substituent to afford **6a**−**b**. The amino group in **6** was then removed through a diazonium intermediate. The desired product **7** was isolated via crystal-

(10) Aldrich (2003−2004): tin(II) bromide $72.20/50 g, tin(II) chloride $74.10/500 g, and tin(II) sulfate $73.30/500 g.

(11) Tin(II) oxide was also effective for this reduction in the presence of 48% HBr.

(12) The structure of impurity **10** was proposed by HPLC−MS analysis of the 8-chloro-10-bromoketone **7**. The other potential dibromo impurity resulting from the minor C-7 dianzonium intermediate was not identified.

(13) The residual Sn analysis was performed by QTI (Quantitative Technologies Inc.).

lization by adjusting the pH of the reaction mixture to about 2 with NaOH. The process was scaled up (77-kg scale of **4**) in our plant multiple times to produce **7** in reproducible yields and purity.

Experimental Section

The starting regioisomeric mixture of 7(9)-nitro-8-chloroketones **4a** and **4b** (HPLC ratio: ~6.5:1 for **4a**/**4b**) was manufactured in our commercial plant in Ireland. All other chemicals or reagents were commercially available. The reactions were monitored by HPLC analysis (Waters Symmetry C18 4.6 mm i.d. × 25 cm column maintained at a temperature of about 30 °C, 55:45 CH_3CN/H_2O as mobile phase at 1.0 mL/min, UV detector at 254 nm). The approximate retention times (min) for the starting materials, intermediates and products are **4a** = 6.3, **4b** = 7.1, **5a** = 4.7, **5b** = 4.5, **6** = 5.8, and **7** = 9.5 min. Molar yields were calculated based on the starting compound and product purities, as determined by HPLC using the above conditions. The melting point was recorded on an Electrothermal "MelTemp" and uncorrected. NMR spectroscopic data were recorded on a Bruker NMR spectrometer. Mass spectra were acquired by on the JEOL MStation mass spectrometer operating in the FAB ionization mode.

10-Bromo-8-chloro-5,6-dihydro-benzo[5,6]cyclohepta-[1,2-*b*]pyridin-11-one 7. A mixture of 8-chloro-5,6-dihydro-9-nitro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one (**4a**) and 8-chloro-5,6-dihydro-7-nitro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one (**4b**) (77 kg, 266 mol) was gradually added to a solution of water (270 L), tin sulfate (231 kg, 1074 mol) and hydrobromic acid (77 L, 681 mol) in acetonitrile (303 kg) while maintaining the internal temperature below 5 °C. The mixture was heated to 68−72 °C over a period of about 1.5 h and held at this temperature for about 2 h until reduction to the aminoketone **5**[14] was complete as monitored by HPLC. The mixture was cooled to a temperature between 20 and 25 °C and diluted with methanol (231 L). The reaction was further cooled to about 10 °C and *N*-bromosuccinimide (NBS, 100 kg, 561 mol) was charged over a period of about 30 min, while maintaining the temperature below 25 °C. On complete formation of the bromoamine **6**[15] by HPLC analysis (additional NBS may be charged as needed), the reaction mixture was cooled to about 0 °C, and hypophosphorous acid (1278 kg) was slowly charged over a period of about 3 h while maintaining the reaction temperature below 5 °C. After cooling, a solution of sodium nitrite (25 kg, 362 mol) in water (55 L) was gradually added while maintaining the temperature below 3 °C. The reaction was warmed to 20−25 °C over about 1.5 h and aged for about 1 h until the reaction completion by HPLC analysis. The pH was adjusted to about 2.2 by slowly charging approximately 450 L of 50% NaOH while maintaining the reaction temperature below 40 °C. The slurry was cooled to a temperature between 20 and 25 °C and held for about 30 min. The solid was filtered and washed with warm aqueous acetic acid (1500 L, 5% HOAc in H_2O) followed by water (770 L). The wet cake was dried at 65−75 °C to provide 67.2 kg (75%) of product with a purity of 96%; mp 184−185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, J_1 = 4.46 Hz, J_2 = 1.11 Hz, 1H), 7.60 (dd, J_1 = 7.86 Hz, J_2 = 1.49 Hz, 1H), 7.56 (d, J = 1.89 Hz, 1H), 7.40 (dd, J_1 = 7.87 Hz, J_2 = 4.52 Hz, 1H), 7.23 (d, J = 1.85 Hz, 1H), 3.26 (m, 2H), 3.15 (m, 2H). ^{13}C NMR (100.62 MHz, $CDCl_3$) 196.06, 152.48, 149.01, 141.66, 140.28, 139.58, 136.97, 136.77, 132.00, 127.33, 126.56, 120.46, 33.57, 32.48. FAB-MS (*m*/*z*) 322 ($M^+ + H$), 304 (MH − H_2O), 292 (MH − CH_2O), 286 (MH − HCl), 242 (MH − HBr), 214 (MH − HBr − H_2CN), 213 (MH − HBr − CHO), 180 (MH − HBr − Cl − HCN), 178 (MH − HBr − HCl − H_2CN), 177 (MH − HBr − HCl − CHO), 152 (MH − HBr − Cl − HCN − CO), 151 (MH − HBr − HCl − HCN − CO). FAB-HRMS Calcd for $C_{14}H_{10}ONClBr$: 321.9634, observed: 321.9623. Anal. Calcd for $C_{14}H_9BrClNO$: C, 52.13; H, 2.81; N, 4.34. Found: C, 52.03; H, 2.58; N, 4.24.

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(14) **5a** (as a major component 80% in the mixture):^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, J_1 = 4.60 Hz, J_2 = 1.56 Hz, 1H), 7.62 (dd, J_1 = 4.02 Hz, J_2 = 1.45 Hz, 1H), 7.51 (s, 1H), 7.36 (dd, J_1 = 7.72 Hz, J_2 = 4.68 Hz, 1H), 7.15 (s, 1H), 4.16 (br s, 2H), 3.13 (s, 4H). ^{13}C NMR (100.62 MHz, $CDCl_3$) 194.07, 154.92, 148.95, 142.17, 137.75, 137.30, 136.69, 132.43, 126.28, 124.49, 117.98, 33.93, 33.28. **5b** (as a minor component 20% in the mixture): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, J_1 = 4.74 Hz, J_2 = 1.49 Hz, 1H), 7.63 (dd, J_1 = 4.02 Hz, J_2 = 1.45 Hz, 1H), 7.45 (d, J = 8.52 Hz, 1H), 7.35 (dd, J_1 = 7.71 Hz, J_2 = 5.16 Hz, 1H), 7.31 (d, J = 8.53 Hz, 1H), 4.19 (br s, 2H), 3.20 (m, 2H), 2.99 (m, 2H). ^{13}C NMR (100.62 MHz, $CDCl_3$) estimated from APT experiment: 194.07, 157.36, 149.10, 142.17, 141.48, 137.30, 136.43, 134.55, 127.82, 126.28, 124.49, 117.98, 30.70, 30.50. FAB-MS (mixture of **5a**/**5b**) (*m*/*z*) 259 ($M^+ + 1$), 241, 229, 223, 195, 194, 178, 167, 166, 140, 139. FAB-HRMS (mixture of **5a**/**5b**): Calcd for $C_{14}H_{12}ON_2Cl$: 259.0638, observed: 259.0634; mp 195−197 °C.

(15) **6a**/**6b** (80/20 mixture): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, J_1 = 4.45 Hz, J_2 = 1.37 Hz, 1H), 7.57 (dd, J_1 = 7.82 Hz, J_2 = 1.22 Hz, 1H), 7.46 (s, 1H, **6b** minor), 7.37 (dd, J_1 = 7.88 Hz, J_2 = 4.52 Hz, 1H), 7.16 (s, 1H, **6a** major), 4.64 (br s, 2H), 3.21 (m, 2H), 3.05 (m, 2H). FAB-MS (mixture of **6a**/**6b**) (*m*/*z*) 337 ($M^+ + 1$), 320, 319, 307, 301, 257, 229, 228, 194, 192, 166. FAB-HRMS (mixture of **6a**/**6b**) Calcd for $C_{14}H_{11}ON_2ClBr$: 336.9743, observed: 336.9737; mp 155−158 °C.