ORGANIC LETTERS

2002
Vol. 4, No. 9
1427−1430

Synthesis of an Influenza Neuraminidase Inhibitor Intermediate via a Highly Diastereoselective Coupling Reaction

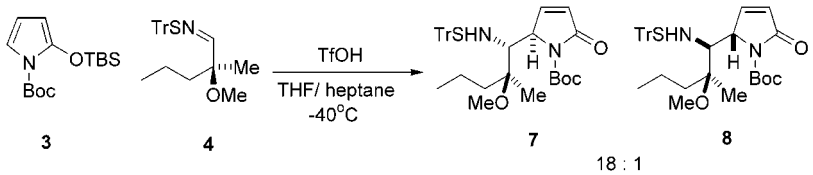
David M. Barnes,[†] Maureen A. McLaughlin,*[,†] Tetsuro Oie,[‡] Michael W. Rasmussen,[†] Kent D. Stewart,[‡] and Steven J. Wittenberger[†]

Global Pharmaceutical R&D, Process Research & Development, Abbott Laboratories, 1401 Sheridan Road, D-R450, Bldg. R8, North Chicago, Illinois 60064-4000, and Department of Structural Biology, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, Illinois 60064-6100

maureen.mclaughlin@abbott.com

Received December 19, 2001 *(Revised Manuscript Received March 21, 2002)*

ABSTRACT



A highly diastereoselective coupling reaction between TBSOP (3) and trityl sulfenimine 4 was developed which provided influenza neuraminidase inhibitor intermediate 7 in 80% yield and >99% de after crystallization. The reaction was shown to be reversible with the high diastereoselectivity resulting from a favorable H-bonding interaction in the major diastereomer.

The influenza virus infects between 25 and 75 million people annually in the United States and results in estimated health care and lost productivity costs of over 10 billion dollars per year.[1] In recent years, significant advances in the understanding of the virus and its replication process have resulted in the identification of the influenza neuraminidase enzyme as a promising target for pharmaceutical intervention. Inhibition of neuraminidase results in the inability of the newly produced virus to be released from the infected cell, disrupting viral replication.[2]

Abbott's influenza neuraminidase inhibitor A-315675 (**1**) is a potent inhibitor of influenza viral replication.[3] Upon undertaking process optimization of the current route to this compound (Scheme 1),[4b] it was immediately recognized that development of a highly selective coupling reaction (**3** + **4**) and the isolation of a single diastereomer of intermediate **2** from the reaction mixture would be imperative to the success of this route.[4c] Therefore, initial efforts focused on understanding the factors which affect the selectivity of the

[†] Global Pharmaceutical R&D, Process Research & Development.
[‡] Department of Structural Biology.

(1) Service, R. F. *Science* **1997**, *275*, 756.

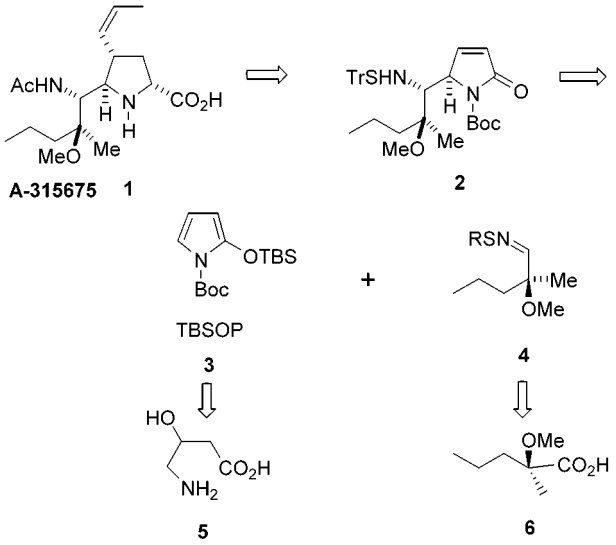
(2) (a) Varghese, J. N. *Drug Dev. Res.* **1999**, *46*, 176 and references therein. (b) Palese, P.; Jobita, K.; Ueda, M.; Compans, R. W. *Virology* **1974**, *61*, 397. (c) Liu, C.; Eichelberger, M. C.; Compans, R. W.; Air, G. M. *J. Virol.* **1995**, *69*, 1099.

(3) Maring, C.; McDaniel, K.; Krueger, A.; Zhau, C.; Sun, M.; Madigan, D.; DeGoey, D.; Chen, H.-J.; Yeing, M. C.; Flosi, W.; Grampovnik, D.; Kati, W.; Klein, L.; Stewart, K.; Stoll, V.; Saldivar, S.; Montgomery, D.; Carrick, R.; Steffy, K.; Kempf, D.; Molla, A.; Kohlbrenner, W.; Kennedy, A.; Herrin, T.; Xu, Y.; Laver, W. G. Presented at the 14th International Conference on Antiviral Research, *Antiviral Res.* **2001**, *50*, A76; Abstract 129.

(4) (a) For X-ray crystallographic data for compounds **7** and **11** see ref 4b, supplementary data. (b) DeGoey, D. A.; Chen, H.-J.; Flosi, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. *J. Org. Chem.* **2002**, *ASAP article*. (c) A manuscript describing the process research and initial scale-up is in preparation. For a presentation of this synthesis, see: Bhagavatula, L.; Chen, H.-J.; DeGoey, D.; DeMattei, J.; Flosi, W. J.; Grampovnik, D.; Gupta, A.; Hill, D.; Klein, L.; Kurukulasuriya, R.; Manna, S.; McLaughlin, M.; Nichols, P.; Oie, T.; Premchandran, R.; Rasmussen, M.; Stewart, K.; Tian, Z.; Wittenberger, S. J. Abstract Prepared for Presentation at ChiraSource2001, Philadelphia, PA, Nov 2001.

10.1021/ol017268v CCC: $22.00
Published on Web 04/03/2002

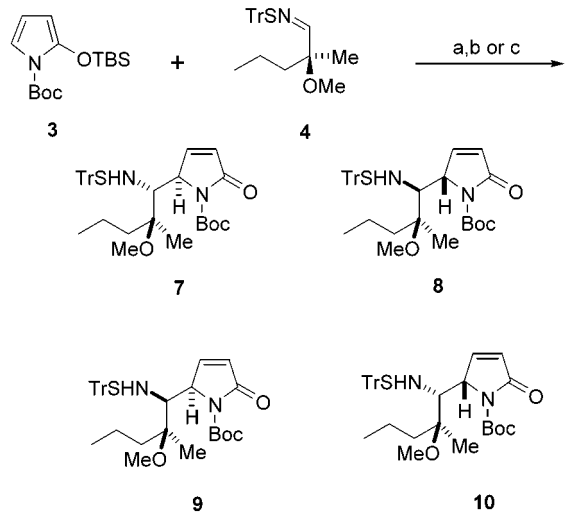
Scheme 1



reaction, which would also facilitate product isolation through crystallization.

Furan-, pyrrole-, and thiophene-based siloxydienes have been shown to undergo highly selective aldol-type reactions with a variety of chiral substrates to yield an array of highly functionalized molecules in high enantiomeric and diastereomeric purity.[5] In our case, coupling of *N*-*tert*-butoxycarbonyl-2-(*tert*-butyldimethylsiloxy)pyrrole[6,7] (**3**, TBSOP, 1.5 equiv) with *S*-trityl sulfenimine **4**[8] using $BF_3{\cdot}OEt_2$ (2 equiv) in THF at −78 °C resulted in a 4−5:1 ratio of C4−C5 erythro diastereomers **7** and **8** (Scheme 2).[4b] Notably, C5−C6 threo diastereomers **9** and **10** were not observed. The structure of major isomer **7**[9] was identified by X-ray crystallographic analysis, and minor isomer **8**,[10] isolated by chromatography as an oil, was also characterized by X-ray analysis after

Scheme 2[a]



[a] (a) $BF_3{\cdot}OEt_2$ (2 equiv), Et_2O, −78 °C, 4−5:1 (ratio **7**:**8**); (b) TMSOTf (2 equiv), THF, −78 °C, 5:1; (c) TfOH (0.8 equiv), THF/heptane, −40 °C, 18:1.

conversion to acetate **11**[4a,b] (Figure 1). A screen of various Lewis acids ($BF_3{\cdot}OEt_2$, $ZnCl_2$, $Ti(OiPr)_4$, $Yb(OTf)_3$, $Cu(OTf)_2$, $TiCl_4$, TMSOTf, TBSOTf, TIPSOTf, Et_2AlCl) indicated this ratio could be slightly increased to 5−6:1 by using TMSOTf in Et_2O or THF.

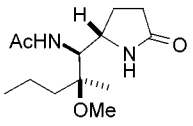


Figure 1. Derivative of minor diastereomer **8**, structurally characterized by X-ray crystallographic analysis.

While optimizing the reaction stoichiometry and solvent composition using TMSOTf, two important observations were made. First, the diastereomer ratio increased slightly as the reaction proceeded, possibly indicating a reversible reaction. To further investigate this observation, the reaction was carried out with TMSOTf (1.5 equiv) either at −78 °C for extended reaction times (18 h) or at higher temperature (−40 °C). In the reaction carried out at −78 °C, the diastereomeric ratio increased from 4:1 (**7** to **8**) at 3 h to 11:1 after stirring for 18 h (HPLC assay yield = 83%). Similarly, in the −40 °C reaction the ratio increased from 9:1 at 1 h to a 19:1 ratio after 6 h (HPLC assay yield = 88%). These results strongly suggest that the reaction is reversible and equilibrates to a thermodynamic mixture.

(5) (a) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333. (b) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 6307. (c) Rassu, G.; Auzzas, L.; Pinna, L.; Zanardi, F.; Battastini, L.; Casiraghi, G. *Org. Lett.* **1999**, *1*, 1213.

(6) (a) Bocchi, V.; Chierici, L.; Gardini, G. P.; Mondelli, R. *Tetrahedron* **1970**, *26*, 4073. (b) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L. *J. Org. Chem.* **1992**, *57*, 3760.

(7) The literature procedure for preparation of TBSOP was unsuitable for large scale preparation so an alternate synthesis was developed. The results will be published shortly.

(8) For preparation and use of sulfenimine, sulfinimine, and sulfonimines, see: (a) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13. (b) Branchaud, B. P. *J. Org. Chem.* **1983**, *48*, 3531. (c) Davis, F. A.; Slegeir, W. A. R.; Evans, S.; Schwartrz, A.; Goff, D. L.; Palmer, R. *J. Org. Chem.* **1973**, *38*, 2809.

(9) ***tert*-Butyl (2*R*)-2-((1*R*,2*S*)-2-methoxy-2-methyl-1-(((tritylsulfenyl)amino)pentyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (7):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, J = 2.0, 6.1 Hz, 1H), 7.29−7.19 (m, 15 H), 6.02 (dd, J = 1.4, 6.1 Hz, 1H), 4.83 (m, 1H), 3.86 (dd, J = 3.1, 11.5 Hz, 1H), 3.05 (s, 3H), 2.62 (d, J = 11.2 Hz, 1H), 1.62−0.98 (m, 4H), 1.36 (s, 9H), 0.92 (t, J = 6.66 Hz, 3H), 0.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 150.5, 148.2, 144.8, 130.1, 127.6 (2C), 126.6, 82.4, 79.2, 71.1, 66.9, 64.6, 48.9, 38.7, 27.9, 19.2, 17.1, 14.9. HRMS *m*/*z* [M + H] calcd for $C_{35}H_{43}N_2O_4S$, 587.2944; found, 587.2953.

(10) ***tert*-Butyl (2*S*)-2-((1*S*,2*S*)-2-methoxy-2-methyl-1-(((tritylsulfenyl)amino)pentyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (8)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.18 (m, 16H), 6.02 (dd, J = 1.7, 6.1 Hz, 1H), 4.90 (m, 1H), 3.89 (dd, J = 2.0, 11.5 Hz, 1H), 3.06 (s, 3H), 2.42 (d, J = 11.5 Hz, 1H), 1.54 (s, 9H), 1.28−0.85 (m, 4H), 1.16 (s, 3H), 0.57 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ168.6, 150.1, 148.2, 144.3, 129.9, 128.1, 127.7, 126.5, 82.6, 79.1, 71.8, 67.1, 65.3, 49.2, 37.3, 28.2, 20.9, 17.5, 14.7.

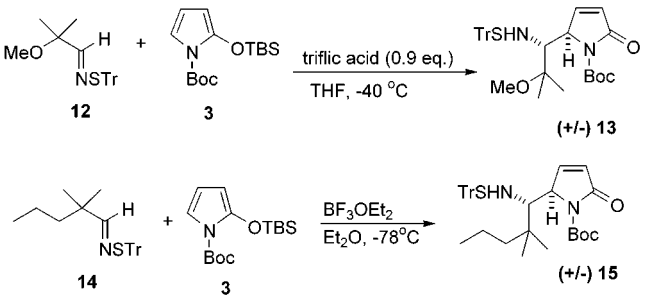
To confirm this hypothesis, the two diastereomers were separated by chromatography and subjected to the reaction conditions (**7** or **8**, 0.5−2 equiv of TBSOP, 1−2 equiv of TMSOTF in THF/heptane at −40 °C). The major diastereomer **7** was converted to a 93:7 mixture of **7** to **8** whereas minor diastereomer **8** was converted to a 74:26 mixture of diastereomers. Complete conversion to the thermodynamic ratio was not achieved since both reactions were complicated by the formation of a significant amount of the product resulting from loss of Boc group from **7**. However, these results clearly illustrate the reversibility of the reaction.[11]

The second observation was that although the reaction proceeded smoothly to completion on small (50−100 mg) scale, on a larger scale significant amounts (30−50%) of imine starting material were recovered. Attempts to push the reaction to completion through longer reaction times, higher temperatures, or excess Lewis acid were unsuccessful and resulted in product decomposition and low yields. This dependence on reaction scale suggested that the larger relative amount of water present in the smaller scale reaction, perhaps leading to hydrolysis of TMSOTf, might have facilitated the conversion. The ensuing experiment demonstrated that the reaction was more effectively carried out with triflic acid. Subsequent investigation of the reaction parameters showed that the ratio could be reliably improved to 18:1, with an HPLC assay yield of 95% of desired isomer **7**, by performing the reaction with triflic acid (0.8 equiv) in THF/heptane at −40 °C.[12] The reaction typically shows complete conversion to a 4:1 ratio of diastereomers within 15 min, and then equilibration to 18:1 over approximately 2 h.

Initial attempts at isolation of **7** in high enantiomeric and isomeric purity were very promising. After washing the crude reaction mixture with 0.5 M $NaHCO_3$ followed by brine, a solvent switch to heptane (<1% THF by GC) and crystallization afforded **7** in 80−85% isolated yield, >99% de and >99% ee (ee = 89% for imine **4**).[12a,b] Since it had not yet been demonstrated whether optical purity could be raised in subsequent purifications, isolation of **7** with high ee was key to the success of this route. However, while investigating lots of imine **4** with lower ee (80%) it was discovered that these lots provided product of equal or lower ee than the incoming imine. Further studies showed the presence of a racemic crystal form of slightly lower solubility, identified by X-ray powder pattern, which prevented any enhancement of ee at this stage of the synthesis. Therefore an alternate synthesis that provided imine of >95% ee was developed so that coupled product **7** could be obtained in >95% ee.[4c]

To investigate the source of the high selectivity achieved in the coupling reaction, two imine analogues, **12** and **14** (Scheme 3), were prepared. When subjected to the reaction

Scheme 3



conditions (0.9 equiv of triflic acid, THF, −40 °C), imine **12** cleanly provided adduct (±)-**13** as a single diastereomer in 70% yield. Conversely, when the reaction was carried out on imine **14**, the reaction mixture consisted of primarily starting material after 2 h. Closer examination revealed that the pyrrole enantiomers (±)-**15** were unstable under the reaction conditions and rapidly reverted to starting material. However, by carrying out the reaction with $BF_3{\cdot}OEt_2$ at −78 °C for 30 min, pyrrole (±)-**15** was isolated as a single diastereomer. The threo diastereomer was not detected by LC-MS or ^1H NMR in either reaction. Furthermore, the decreased stability of (±)-**15** relative to (±)-**13** and **7** suggests the presence of the side chain methoxy group has a significant impact on the outcome of the reaction.

To further elucidate the source of the unexpectedly high selectivity of the reaction of TBSOP (**3**) with imine **4**, the reaction was examined by molecular modeling of the four possible diastereomeric ammonium salts corresponding to **7**−**10**. Energy minimization using a Hartree−Fock 6-31G* basis set showed that all low energy conformations contained a hydrogen bond between the trityl thioamine group and the methoxy oxygen. The distance between the side chain N ($\delta+$) and the ring pyrrolidine nitrogen ($\delta-$) as well as the size of the alkyl group proximal to sulfur (methyl or propyl) also impacted the relative energies of the four diastereomers. Thus, isomers **9** and **10** which show a trans (N−N distance = 3.8 Å) relationship about the C5−C6 bond are significantly higher in energy (ΔE >5 kcal/mol) than **7** and **8** which show a gauche (N−N distance = 2.8 Å) conformation, due to a

(11) The formation of imine **4** was observed by HPLC during the course of the equilibrations, further implicating the reversibility of the reaction rather than another mechanism of interconversion.

(12) (a) **Sample experimental for 7:** To a solution of imine (**4**, 30.4 g, 75.3 mmol) and TBSOP (**3**, 31.3 g, 105 mmol, 1.4 equiv) in heptane/THF (1:4, 520 mL) at −40 °C was added triflic acid (5.33 mL, 60.2 mmol, 0.8 equiv) dropwise at a rate to maintain T = −35 °C. The reaction was maintained at −40 °C and monitored by HPLC. After 1.5 h, HPLC showed 8 peak area % imine remaining (diastereomer ratio = 12:1). Additional triflic acid (0.15 equiv) was added and the reaction stirred for 2.5 h at which time HPLC showed 4 peak area % imine remaining (diastereomer ratio = 19:1). The reaction was poured into 0.5 M $NaHCO_3$ (500 mL) stirred for 10 min; the layers were separated. The organics were washed with brine (200 mL) and dried over Na_2SO_4. Yield = 96% (HPLC assay yield of THF/heptane solution). HPLC conditions: Zorbax SB-C8 4.6 × 250 mm 5-μm column; 1.5 mL/min flow rate; mobile phase 50:50 water (0.1% H_3PO_4): acetonitrile gradient over 15 min to 10:90, hold 5 min; column temperature 35 °C; UV detection at 230 nm. Retention times: TBSOP (**3**) 14.2 min; imine **4** 15.5 min; major diastereomer **7** 16.0 min; minor diastereomer **8** 15.2 min. The solvent was switched to heptane (<1 peak area % THF by GC) by distillation under low vacuum (T = 30−40 °C), maintaining solvent level at 400 mL until distillation was complete. The product begins to crystallize out during distillation. The suspension was distilled to a volume of 240 mL and allowed to cool to room temperature and stir overnight. The solid was filtered and washed with heptane (2 × 30 mL). The solid was dried in vacuo at 40 °C to give **4** (37.6 g, 85.2%, de>99%): mp 150−152 °C. See footnote 10 for NMR data. (b) Chiral HPLC conditions for major diastereomer **7**: Chiralpak AD 4.6 × 250 mm column; 1 mL/min flow rate; isocratic mobile phase 97:3 hexane:isopropanol; column temperature ambient; UV detection at 210 nm. Retention times: 4.6, 5.2 min.

favorable electrostatic interaction between the two charged atoms. Furthermore, the five-membered ring formed by the hydrogen-bonding interaction required a steric interaction between the sulfur atom and the C7 substituent, favoring isomer **7** (methyl) over isomer **8** (propyl). These calculations predict a ΔE of 0.5 kcal/mol between **7** and **8** which at −40 °C translates to a thermodynamic distribution of 70:30 between isomers **7** and **8** with ≪1% of **9** and **10** (ΔE >5 kcal/mol). This prediction is in qualitative agreement with the experimentally observed ratio of 95:5 (isomers **9** and **10** not observed).

In conclusion, a highly diastereoselective route to prepare a key intermediate in the synthesis of A-315675 has been developed. The coupling of TBSOP and *S*-trityl sulfenimine with triflic acid followed by crystallization afforded **7** in 80−85% yield and >99% de and has been demonstrated in the preparation of >3 kg of **7**. The reaction has been shown to be reversible with the high selectivity arising from a favorable H-bonding interaction in the major diastereomer.

Acknowledgment. The authors thank the Structural Chemistry department at Abbott Laboratories for spectroscopic data and Rebekah Dobrin for preparation of adduct **15**.

OL017268V