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# Total Synthesis of A-315675: A Potent Inhibitor of Influenza Neuraminidase

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***Abstract:*** A concise, stereocontrolled, and practical synthesis of a neuraminidase inhibitor consisting of a highly functionalized D-proline scaffold is described. Key features involve a stereocontrolled addition of a propiolate ester to a chiral nonracemic nitrone derived originally from D-serine and the manipulation of acyclic and cyclic motifs en route to the target in 12.8% overall yield over 22 steps. Several crystalline intermediates were suitable for single-crystal X-ray analysis.

## Introduction

Headlines announcing the approach of the "flu season" are causes of major health concerns affecting millions of people worldwide. Despite major efforts at thwarting annual epidemics, the prospects of morbidity and mortality resulting from such respiratory tract infections are significant.[1] Until recently, therapeutic options against the influenza virus consisted of vaccination,[2] and the use of two closely related drugs, amantadine or rimantadine.[3] However, mutations in the antigenic components of viral surface proteins have curtailed the widespread use of *anti*-flu vaccines except for a segment of the population. While effective against influenza A virus, the utility of amantadine or rimantadine has been hampered by the rapid emergence of resistance in viral strains, and the lack of efficacy against influenza B virus.[4] Their specific activity against influenza A virus has been attributed to an ion channel blocking of a specific viral protein.

The influenza RNA virus expresses two glycoproteins on its surface that are essential for its replication and infectivity.[5] The cycle of infection starts in the epithelial cells of the upper respiratory tract by binding of virus particles to cell surface receptor glyconconjugates, which is followed by endocytosis.[6] The viral glycoprotein hemagglutinin[7] mediates the binding to the receptor on the host cell and the process of endocytosis. After replication, new virus particles are released with the aid of a second glycoprotein, neuraminidase,[8] which cleaves terminal *N*-acetyl neuraminic acid units from the cell surface glycoconjugate, thus sparing the virus from being entrapped by aggregation. The infective virus will then propagate through the respiratory tract, a process that is also facilitated by further neuraminidase-mediated cleavages at the mucosal level.[6a,9] The catalytic action of neuraminidase is therefore responsible for the replication, infectivity, and propagation of the influenza virus. Elegant X-ray crystallographic[10] structural studies have revealed that the catalytic active site of influenza neuraminidases A and B, consisting of 18 amino acid residues is highly conserved.

The realization that *N*-acetyl neuraminic acid (NANA) **1** is a weak inhibitor of the enzyme led to the design of closely related analogues, such as the 2,3-didehydro analogue DANA (**2**), which is about 1000 times more active as an inhibitor (Figure 1).[11] The structural information on the enzyme has spurned several new inhibitors of which two are presently marketed. Zanamivir (Relenza) (**3**), a 4-deoxy-4-guanidino analogue of **2**, is administered by nasal inhalation, since it is of low bioavailability when given orally, and it is rapidly eliminated.[12] Tamiflu (Oseltamivir)[13] is a carbocyclic ester analogue of GS-4071 that is highly

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(1) (a) Monto, A. S.; Iacuzio, I. A.; La Montagne, J. R. *J. Infect. Dis.* **1997**, *176*, 51. (b) Service, R. F. *Science* **1997**, *275*, 756. (c) Saul, H. *New Scientist* **1995**, 26. (d) Lui, K.-J.; Kendal, A. P. *Am. J. Public Health* **1987**, *77*, 712. (e) Glezen, W. P. *Epidemiol. Rev.* **1982**, *4*, 25.
(2) Hayden, F. G.; Belshe, R. B.; Clover, R. D.; Hay, A. J.; Oakes, M. G.; Soo, N. *N. Engl. J. Med.* **1989**, *321*, 1696.
(3) Hayden, F. G.; Couch, R. B. *Rev. Med. Virol.* **1992**, *2*, 89.
(4) Hay, A. J.; Wolstenholme, A. J.; Skehel, J. J.; Smith, M. H. *EMBO J.* **1985**, *4*, 3021.
(5) (a) Air, G. M.; Laver, W. G. *Proteins: Struct. Funct. Genet.* **1989**, *6*, 348. (b) Liu, C.; Eichelberger, M. C.; Compans, R. W.; Air, G. M. *J. Virol.* **1995**, *69*, 1099. (c) Klenk, H.-D.; Rott, R. *Adv. Virus Res.* **1988**, *34*, 247. (d) Paleso, P.; Compans, R. W. *J. Gen. Virol.* **1976**, *33*, 159.
(6) (a) Liu, C.; Eichelberger, M. C.; Compans, R. W.; Air, G. M. *J. Virol.* **1995**, *69*, 1099. (b) Meanwell, N. A.; Krystal, M. *Drug Dis. Today* **1996**, *1*, 316.
(7) (a) Sauter, N. K.; Hanson, J. E.; Click, G. D.; Brown, J. H.; Crowther, R. L.; Park, S. J.; Skehel, J. J.; Wiley, D. C. *Biochemistry* **1992**, *31*, 9609. (b) Mammen, M.; Dahmann, G.; Whitesides, G. *J. Med. Chem.* **1995**, *38*, 4179.
(8) Colman, P. M. In *The Influenza Viruses: Influenza Virus Neuraminidase, Enzyme and Antigen*; Krug, R. M., Ed.; Plenum: New York, 1989, pp 175−218. Colman, P. M. *Protein Sci.* **1994**, *3*, 1657.
(9) Klenk, H. D.; Rott, R. *Adv. Virus Res.* **1988**, *34*, 247.
(10) (a) Burmeister, W. P.; Ruigrok, R. W. H.; Cusack, S. *EMBO J.* **1992**, *11*, 49. (b) Bossart-Whitaker, P.; Carson, M.; Babu, Y. S.; Smith, C. D.; Laver, W. G.; Air, G. M. *J. Mol. Biol.* **1993**, *232*, 1069. (c) Varghese, J. H.; Colman, P. M. *J. Mol. Biol.* **1995**, *221*, 473. (d) Janakiraman, M. N.; White, C. L.; Laver, W. G.; Air, G. M.; Luo, M. *Biochemistry* **1994**, *33*, 8172. (e) Varghese, J. N.; McKimm-Breschkin, J. L.; Caldwell, J. B.; Kortt, A. A.; Colman, P. M. *Proteins: Struct. Funct. Genet.* **1992**, *14*, 327. (f) Tulip, W. R.; Varghese, J. N.; Laver, W. G.; Colman, P. M. *J. Mol. Biol.* **1992**, *227*, 122. (g) Varghese, J. N.; Epa, V. C.; Colman, P. M. *Protein Sci.* **1995**, *4*, 1081. (h) Air, G. M.; Laver, W. G.; Luo, M.; Stray, S. J.; Legrone, G.; Webster, R. G. *Virology* **1990**, *177*, 578.
(11) (a) Meindl, P.; Bodo, G.; Palese, P.; Schulman, J.; Tuppy, H. *Virology* **1974**, *58*, 457. (b) Holzer, C. T.; von Itzstein, M.; Jin, B.; Pegg, M. S.; Stewart, W. P.; Wu, W.-Y. *Glyconj. J.* **1993**, *10*, 40.


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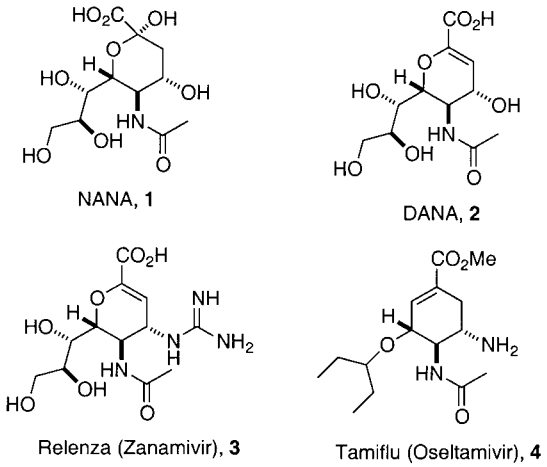



***Figure 1.*** Inhibitors of neuraminidase.

active against influenza A and B viruses, and effective orally. A cyclopentane variant, BCX-1812 (**5**), has been recently shown to be a potent and selective neuraminidase inhibitor.[14] Scientists at Abbott Laboratories have also discovered inhibitors based on a pyrrolidine motif such as **6**.[15] Refinements in structure-based inhibitor design uncovered a novel trisubstituted pyrrolidine carboxylic acid, A-315675 (**7**), that is highly active against neuraminidases (Figure 2).[16] Initially, **7** was synthesized by Abbott scientists as the racemate, and subsequently resolved to afford the desired enantiomer. An enantioselective synthesis of **7** has been reported in preliminary form.[17]

The interaction of Zanamivir, GS-4071, BCX-1812, and related inhibitors within the catalytic site of neuraminidase is well-known from X-ray crystallographic studies. Thus, four subsites in the enzyme interact with requisite polar and hydrophobic groups in the inhibitors leading to effective binding.[13,15] The mandatory presence of a carboxylic acid in all these inhibitors and an acetylamino group two or three carbon atoms away across a ring structure fits well with interactions with positively charged arginines (Arg 118, 292, 371) and hydrophobic interactions with aromatic and aliphatic chains (Trp 180, Ile 224), respectively.[13] The replacement of the triol unit

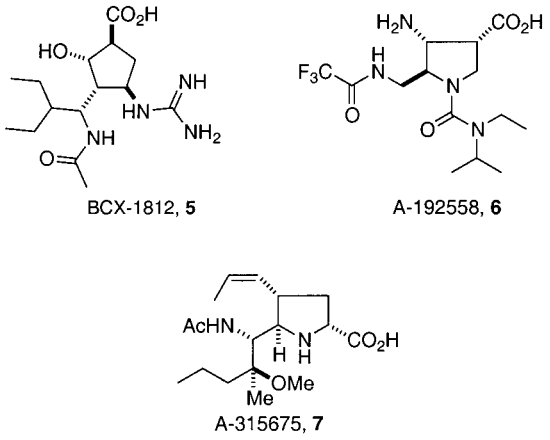



***Figure 2.*** Second-generation inhibitors of neuraminidase.

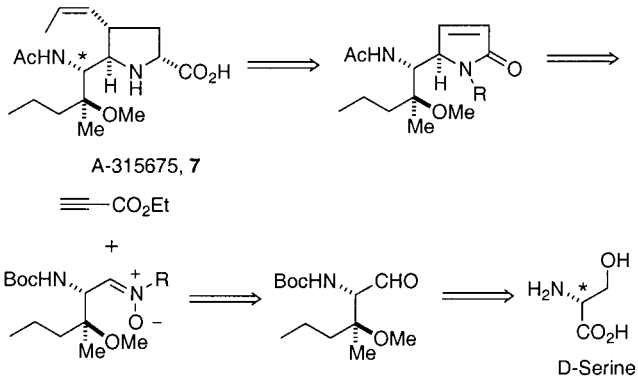



***Figure 3.*** Disconnective analysis for A-315675.

in **1** or **2** with an hydrophobic ether unit as in **4** was most revealing, and paved the way to further probe productive interactions with aliphatic parts of amino acid side chains.[13] The fourth site is uniformly occupied by a basic group such as an amine or guanidine in all known inhibitors that have been structurally based on the compounds shown in Figure 1.[10,13,15] An important demarcation from these structural and functional requirements was the discovery that a basic group normally required to interact with Glu 119, Glu 227, and Asp 151 could be replaced by a *cis*-propenyl group in A-315675, where hydrophobic contact with the aliphatic chain in Glu was found to be beneficial.[16]

We report herein a concise, stereocontrolled, and practical total synthesis of A-315675. Consideration of the structure reveals a number of challenges associated mainly with the creation of four contiguous stereogenic centers on a scaffold that can be formally related to D-proline (Figure 3). Rather than starting with the functionally versatile D-pyroglutamic acid as a chiral template, and elaborating the intended functionality, we opted for a strategy that builds the pyrrolidine ring from D-serine (Figure 3). Conversion to a nitrone intermediate and C−C bond formation[18] capitalizing on internal resident chirality was expected to produce an acyclic construct that could be cyclized and further manipulated en route to the desired target.

Extensive studies by Merino,[19] Vallée,[20] and their co-workers have delineated functional and stereochemical requirements for

(12) von, Itzstein, M.; Wu, Y.; Kok, G. B.; Pegg, M. S.; Dyason, J. C.; Jiu, B.; Van Phan, T.; Synthe, M. L.; White, H. F.; Oliver, S. W.; Colman, P. G.; Varghese, V. J.; Cameron, J. M.; Penn, C. R. *Nature* **1993**, *363*, 418.

(13) (a) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H. T.; Zhang, L. J.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681. (b) Lew, W.; Chen, X.; Kim, C. U. *Curr. Med. Chem.* **2000**, *7*, 663.

(14) Babu, Y. S.; Chand, P.; Bantia, S.; Kotian, P.; Dehghani, A.; El-Kattan, Y.; Liu, T.-H.; Hutchinson, T. L.; Elliott, A. J.; Parker, C. D.; Ananth, S. L.; Horn, L. L.; Laver, G. W.; Montgomery, J. A. *J. Med. Chem.* **2000**, *43*, 3482.

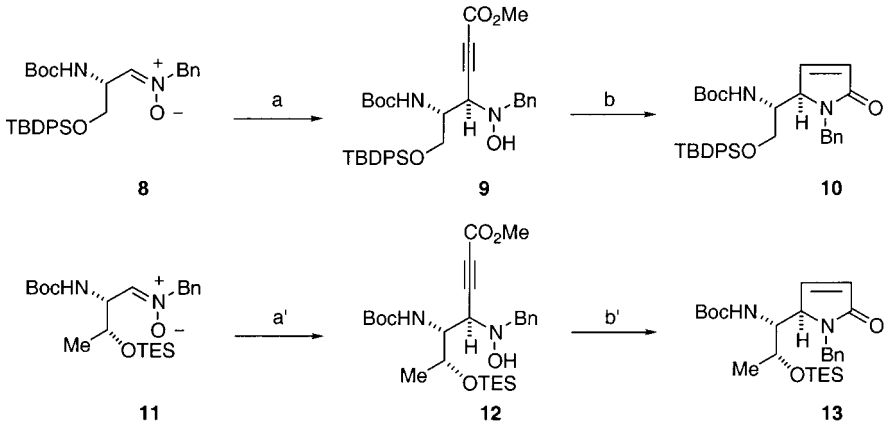
(15) Wang, G. T.; Chen, Y.; Wang, S.; Gentles, R.; Sowin, T.; Kati, W.; Muchmore, S.; Giranda, V.; Stewart, K.; Sham, H.; Kempf, D. I.; Laver, W. G. *J. Med. Chem.* **2001**, *44*, 1192.

(16) (a) Maring, C.; McDaniel, K.; Krueger, A.; Zhao, C.; Sun, M.; Madigan, D.; DeGoey, D.; Chen, H.-J.; Yeung, M. C.; Flosi, W.; Grampovnik, D.; Kati, W.; Klein, L.; Stewart, K.; Stoll, V.; Saldivar, A.; 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 Research, 2001, Vol. 50, A76, Abstract 129. (b) Zhao, C.; Maring, C.; Sun, M.; Stewart, K.; Stoll, V.; Xu, Y.; Gu, Y.; Krueger, A.; Herrin, T.; Herrin, T.; Sham, H.; Laver, W. G.; Madigan, D.; Kennedy, A.; Kati, W.; Montgomery, D.; Saldivar, A.; Kempf, D.; Kohlbrenner, W. Design, Synthesis and Activity of Substituted Pyrrolidine Influenza Neuraminidase Inhibitors; Thirteenth International Conference on Antiviral Research, Baltimore, MD, April; Antiviral Research 2000, Vol. 46, p A53, Abstract 58.

(17) DeGoey, D. A.; Flosi, W. J.; Grampovnik, D.-J.; Yeung, C. M.; Klein, L.; Kempf, D. J. Enantioselective Synthesis of Anti-Influenza Compound ABT-675; Presented at the 221st National Meeting of the American Chemical Society, San Diego, CA, April 2001; Paper ORGN 320.

(18) (a) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1. For recent reviews on nitrones, see: (b) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (c) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon: New York, 1991; Vol. 4, p 1069.

***Scheme 1***[a]




[a] Conditions: (a or a′) methyl propiolate, *n*-BuLi, −78 °C, 65−72%; (b or b′) zinc, AcOH/MeOH, 60 °C, 70−75%.

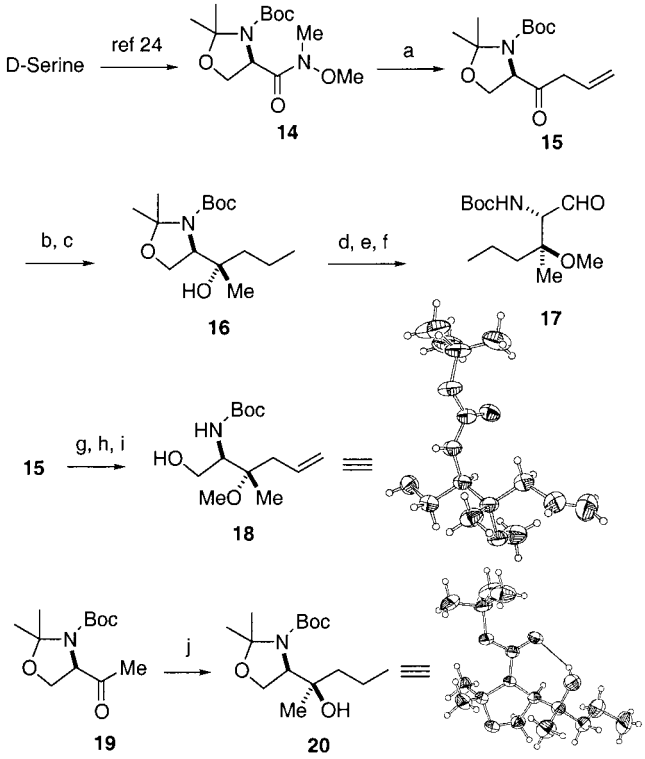
the addition of lithium acetylides, as well as alkyl and aryl Grignard reagents to *N*-protected α-amino nitrones. *N*-Benzyl nitrones derived from *N*-Boc *N*,*O*-isopropylidene L-serinal[21] react with Li TMS acetylide to afford the *syn*-diastereomer almost exclusively.[19b] On the other hand, the *N*-benzyl nitrone prepared from *N*-Boc-*O*-*tert*-butyldiphenylsilyl-L-serinal leads to an 85:15 mixture of diastereomers with the *anti*-diastereomer predominating. Vallée and co-workers[20a] obtained the *syn*-diastereomer with the above-mentioned cyclic *N*-benzyl nitrone with the lithium anion of *tert*-butyl propiolate. The Merino group[19] has rationalized these results, based on models proposed by Houk[22] on the addition of nucleophilic reagents to double bonds. They have further proposed that such additions proceed via a product-like transition state based on X-ray structural analysis of related products.

On the basis of these precedents we hoped that nucleophilic addition of a lithium propiolate to an as yet untested $\beta$-methoxy nitrone shown in Figure 3 would indeed afford the desired *anti*-vicinal diamine intermediate needed in our synthesis. We therefore undertook a brief study with nitrones **8**[19a] and **11** prepared from L-serine and L-threonine, respectively, as representative models (Scheme 1). Treatment of **8** and **11** individually with the lithium salt of methyl propiolate afforded **9** and **12**, respectively, as observed in related cases.[19] Selective reduction with zinc and acetic acid gave the lactams **10** and **13** in excellent yields. [23]

Although the observed *anti*-selectivity in the model compounds **9** and **12** was very encouraging, we had to rely on experimentation to assess the role that the $\beta$-methoxy group could play in the stereochemical course of acetylide addition to a branched $\beta$-substituted nitrone (Figure 3). Our first objective was to devise an efficient and stereocontrolled synthesis of an aldehyde precursor as shown in Scheme 2.

The readily available *N*-methyl-*N*-methoxy *N*-Boc-*N*,*O*-isopropylidene-D-serine,[24] **14**, was treated with allylmagnesium bromide to give the allylic ketone **15** in excellent yield. The same ketone has been previously prepared[25] by a two-step sequence from Garner's aldehyde.[21] On the other hand, except for methyllithium, treatment of **14** with ethyllithium, vinyllithium ,or their Grignard reagent counterparts gave the corresponding ketones in low yield.[26] Hydrogenation and reaction with methylmagnesium bromide, followed by methylation of the resulting tertiary alcohol, afforded **16** as a single diastere-

***Scheme 2***[a]




[a] Conditions: (a) allylMgBr, THF, −78 °C, 93%; (b) $H_2$, MeOH, Pd/C, 99%; (c) MeMgBr, THF, −78 °C, 92%; (d) NaH, MeI, DMF, $Bu_4NI$, 99%; (e) pTsOH, MeOH, 90%; (f) $SO_3$-pyridine, DMSO, $Et_3N$; (g) MeMgCl, THF, −78 °C, 48% and 40% of **15**; (h) NaH, MeI, THF, 87%; (i) pTsOH, MeOH, 90%; (j) PrMgCl, THF, −78 to −20 °C, 84%.

(19) (a) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 629. (b) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 5627. (c) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442.

(20) (a) Denis, J.-N.; Tchertchian, S.; Tomassini, A.; Vallée, Y. *Tetrahedron Lett.* **1997**, *38*, 5503. (b) Dagoneau, C.; Denis, J.-N.; Vallée, Y. *Synlett*, **1999**, 602.

(21) Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18.

(22) For a review, see: Houk, K. N.; Paddow-Row, N. M.; Rondan, N. G.; Wu, Y.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. J.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108.

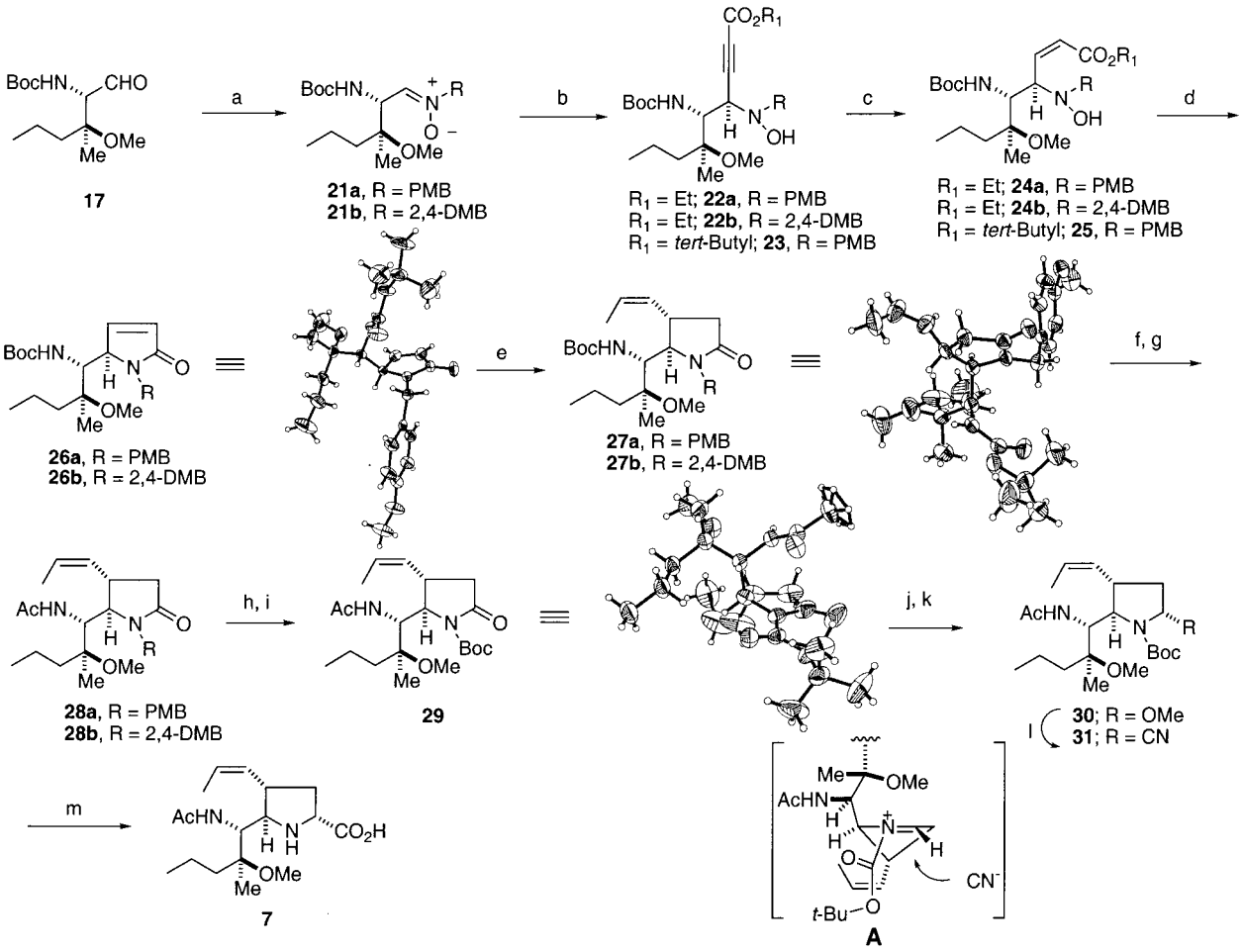
(23) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1996**, *61*, 9028.

(24) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707.

(25) Kobayashi, J.; Ishibashi, M.; Doi, Y. *Tetrahedron* **1996**, *62*, 4573.

(26) (a) Ageno, G.; Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Riva, R.; Rocca, V. *Tetrahedron* **1995**, *51*, 8121. See also: (b) Laïb, T.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1998**, *63*, 1709. (c) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. (d) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.

***Scheme 3***[a]




[a] Conditions: (a) *p*-methoxybenzylNHOH or 2,4-dimethoxybenzylNHOH, $CH_2Cl_2$, $MgSO_4$, 90%; (b) ethyl or *tert*-butyl propiolate, *n*-BuLi, $BF_3{\cdot}Et_2O$, −78 °C, 90−95%; (c) $H_2$, Lindlar's; (d) $Mo(CO)_6$, $MeCN/H_2O$, 75% from **23**; (e) *cis*-1-propenyllithium, $CuBr{\cdot}Me_2S$, TMSCl, DMPU, −78 to −20 °C, 91% (f) TFA, $CH_2Cl_2$; (g) $Ac_2O$; (h) CAN, $MeCN/H_2O$; (i) $Boc_2O$, $Et_3N$, MeCN, 77% from **27a**; (j) Super-H, THF, −78 °C; (k) pTsOH, MeOH; (l) TMSCN, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, −78 to −50 °C, 64% from **29**; (m) HCl, AcOH, 65−70%.

omer as evidenced by $^1H$ and $^{19}F$ NMR data of the corresponding Mosher ester. An X-ray crystal structure determination of the corresponding unsaturated alcohol **18** confirmed the assignment (Scheme 2).

Mild acid hydrolysis of **16** gave the *N*-Boc alcohol, which was oxidized according to Parikh and Doering[27] to afford the corresponding aldehyde **17**. The undesired diastereomer could be obtained by reversing the order of Grignard additions. Thus, when the methyl ketone **19** was treated with propylmagnesium bromide, the resulting tertiary alcohol **20** was found to be epimeric at the tertiary center as evidenced by an X-ray crystal structure (Scheme 2). These results can be easily rationalized by assuming a chelated Cram-type transition state model where the aldehyde carbonyl and the α-nitrogen are chelated to magnesium as reported in numerous well-established precedents.[26a,28]

Nitrones **21a** and **21b** were easily obtained by treatment of the aldehyde **17** with *p*-methoxybenzylhydroxylamine[29] and 2,4-dimethoxybenzylhydroxylamine, respectively, under dehydrating conditions.[30] Addition of the lithium anion of ethyl or *tert*-butyl propiolate in the presence of $BF_3{\cdot}Et_2O$ to **21a** led to **22a** and **23**, respectively, in 90−95% yield. Stereochemistry was ascertained from spectroscopic data and an X-ray structure of an advanced analogue (see below). Addition of ethyl propiolate to **21b** led to the adduct **22b** as expected. Lewis acids such as magnesium bromide,[20] zinc bromide,[31] or diethylaluminum chloride[31] are known to influence the *syn/anti* stereoselectivity in the reaction of organometallic reagents with nitrones derived

(27) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(28) For pertinent reviews, see: (a) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121. (b) Juckzak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556 and references therein. For α-*N*-Boc amino aldehydes, see, for example: (d) Bigi, F.; Casnati, G.; Sartori, G.; Araldi, G.; Bocelli, G. *Tetrahedron Lett.* **1989**, *30*, 1121. (e) Melnick, M. J.; Bisaha, S. N.; Gammill, R. B. *Tetrahedron Lett.* **1990**, *31*, 961. (f) De Camp, A. E.; Kawaguchi, A. I.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867. (g) Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939. (h) Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021. (i) Reetz, M. T.; Rölfing, K.; Grienbenow, N. *Tetrahedron Lett.* **1994**, *35*, 1969. For α-*N*-Boc oxazolidine aldehydes, see, for example: (j) Beaulieu, P. L. *Tetrahedron Lett.* **1991**, *32*, 1031. (k) Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697. (l) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Jouillé, M. M. *Tetrahedron* **1996**, *52*, 11673. For α-alkoxy aldehydes, see, for example: (m) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (n) Wolfrom, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800. Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1978**, *19*, 2745. (o) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035. (p) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031.

(29) Baldwin, J. E.; Cha, J. K.; Kruse, L. I. *Tetrahedron* **1985**, *41*, 5241.

(30) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2537.

(31) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1759. See also: Fujisawa, T.; Nagai, M.; Koike, Y.; Shimizu, M. *J. Org. Chem.* **1994**, *59*, 5865.

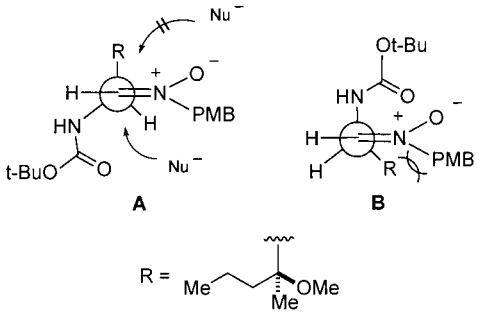



***Figure 4.*** Proposed models for Li acetylide attack.

from L-serine. The present case is of interest because of the high stereoselectivity observed with $\beta$-alkoxy-$\alpha$-amino nitrone derivatives such as **21a** or **21b** as well as the effectiveness of $BF_3{\cdot}Et_2O$ as a promoter (Scheme 3). Eventually, the sequence with *tert*-butyl propiolate was abandoned in favor of the much cheaper ethyl ester. Figure 4 illustrates a model that rationalizes the results of acetylide anion addition to nitrones **21a** or **21b**. Although all possible rotameric conformations are subject to 1,3-allylic strain, conformer A is a plausible model in which a *pro-R* attack may also benefit from a coordinative anchoring of the lithium acetylide to the nitrone oxygen atom.[32]

The next objective was to effect chemoselective reductions of the triple bond and the *N*-hydroxy group en route to cyclic lactams **26a** and **26b**. Two protocols were studied based on our own models and literature precedents to evaluate the compatibility of functional groups. In the first, **22a** was treated with excess zinc in methanol containing acetic acid at reflux to give directly the intended $\alpha,\beta$-unsaturated lactam **26a** in 60−65% yield, accompanied by the corresponding *trans*-$\alpha,\beta$-unsaturated ester (~10−15%). In the case of **22b**, ring closure required refluxing in 2-propanol containing acetic acid. These results were rewarding considering the reported failure of *N*-4-methoxybenzyl-*N*-hydroxy acetylenic adducts prepared from $\alpha$-alkyl nitrones[33] to undergo cyclization. Since the corresponding *N*-benzyl analogue was successfully cyclized to the $\alpha,\beta$-unsaturated lactam under the same conditions (zinc/methanol-AcOH, 9:1, 60 °C),[33] the authors assumed that the presence of the 4-methoxy group rendered the nitrogen atom more basic, hence more efficiently protonated. This presumption may have some validity, since in the "more basic" 2,4-dimethoxybenzyl case **22b**, no cyclization took place in refluxing methanol unlike the higher boiling 2-propanol. The successful cyclizations of our *N*-monomethoxy and *N*-dimethoxy intermediates formed from **22a** and **22b** compared to the $\alpha$-alkyl analogues[33] could also be due to a proximity effect.[34] Thus, the $\beta$-methoxy group can act as a coordinating site[35] for the *N*-bound zinc, thus diminishing its basicity as shown in Figure 5.

A second method of chemoselective reduction of **22a** and **22b** relied on a stepwise process, eliminating the use of excess zinc. Thus, reduction of **22a** or **22b** under Lindlar conditions afforded the *cis*-$\alpha,\beta$-unsaturated *N*-hydroxy ester analogues **24a** and **24b**, respectively. Reductive cleavage of the *N*-hydroxy

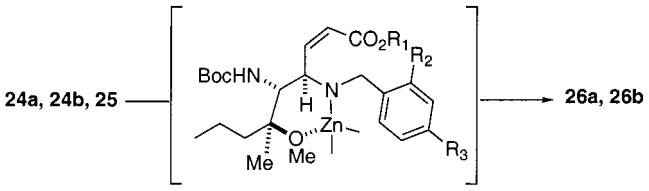



***Figure 5.*** Proposed model for lactam formation.

group by treatment with molybdenum hexacarbonyl in aqueous acetonitrile[36] led to the crystalline pyrrolidinones **26a** and **26b**, respectively, in 75% yield. The structure of **26a** was ascertained by single-crystal X-ray analysis, confirming its absolute configuration.

The next stereochemical and functional hurdle was the introduction of the *cis*-propenyl group. After considerable experimentation, it was found that good-quality *cis*-propenyllithium[37] could be transformed into the corresponding cuprate reagent by treatment with cuprous bromide−dimethyl sulfide complex. Conjugate addition to the $\alpha,\beta$-unsaturated lactam **26a** in THF in the presence of TMSCl and DMPU under temperature-controlled conditions afforded the crystalline adduct **27a** in 91% yield. An X-ray structure analysis confirmed the expected orientation of the *cis*-propenyl group, resulting from an *anti*-attack relative to the bulky side chain at C-5 of the lactam. The same results were obtained with the *N*-2,4-dimethoxybenzyl analogue **26b** to afford **27b.** Fortunately, internal coordination of the reagent with electron-rich functionality in these substrates did not adversely affect the yield or the stereochemical outcome of the reactions. Conjugate addition of organocuprates to $\alpha,\beta$-unsaturated amides[38] or bicyclic lactams[39] usually necessitates the presence of an electron-withdrawing group on the nitrogen atom or next to the carbonyl. However, certain nonactivated bicyclic $\alpha,\beta$-unsaturated lactams are known to undergo highly efficient and stereocontrolled conjugate addition with lower order Gilman-type organocuprates in ether as solvent in the absence of Lewis acids.[40] The effect of additives such as TMSCl is known to enhance the reactivity of $\alpha,\beta$-unsaturated carbonyl compounds toward organocuprates.[41] Inclusion of HMPA as activator is also known to enhance the efficiency of conjugate additions.[42] In the case of **26a**, conjugate addition with *cis*-propenyl cuprate in THF was only possible in the presence of 5 mmol equiv each of TMSCl and DMPU as additives. In the absence of additives, the reaction was extremely slow and impractical to pursue.

With all but the carboxyl group remaining to be introduced, we proceeded toward that goal, hoping to maintain the delicate

(32) See, for example: Villamena, F. A.; Crist, D. R. *J. Chem. Soc., Dalton Trans.* **1998**, 4055.
(33) Dagoneau, C.; Denis, J.-N.; Vallée, Y. *Synlett* **1999**, 602.
(34) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.
(35) (a) Nyzam, V.; Beland, C.; Zammattio, F.; Villieras, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1835. (b) Knochel, P.; Almena Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275. (c) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: New York, 2000.
(36) (a) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351. (b) Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1996**, *37*, 5273. (c) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Perkin Trans. I* **1985**, 1401.
(37) (a) Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379. (b) Linstrumelle, G.; Krieger, J. K.; Whitesides, G. M. *Org. Synth.* **1976**, *55*, 103.
(38) (a) Hagen, T. J. *Synlett* **1990**, 63. (b) Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, *26*, 657.
(39) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814.
(40) (a) Hanessian, S.; Ratovelomanana, V. *Synlett* **1990**, 501. (b) Hanessian, S.; Ratovelomanana, V.; Couture, C. *Synlett* **1991**, 222.
(41) See, for example: (a) Corey, E. J.; Boaz, N. *Tetrahedron Lett.* **1985**, *26*, 6019. (b) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047. (c) Horgachi, Y.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025. (d) Dorigo, A. E.; Morokuma, K, *J. Am. Chem. Soc.* **1989**, *111*, 6524.
(42) (a) Mpango, G. B.; Mahalanabis, K. K.; Madhavi-Danghani, Z.; Snieckus, V. *Tetrahedron Lett.* **1980**, *21*, 4823. (b) Nakamura, E.; Matsuzawa, S.; Horigachi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029. (c) Bussanne, I.; Roger, J. *Tetrahedron Lett.* **1998**, *39*, 845.

balance of functionality at other centers. Removal of the *N*-Boc group from **27a** and *N*-acetylation proceeded uneventfully to give **28**. Initially cleavage of the *N*-PMB group with ceric ammonium nitrate (CAN) in aqueous acetonitrile at reflux temperature caused partial isomerization of the *cis*-propenyl group to the *trans*-isomer, as shown by an X-ray crystal structure of the rearranged product. On the other hand, cleavage of the *N*-2,4-dimethoxybenzyl group in **27b** with CAN was accomplished at room temperature. However, optimization of the conditions of cleavage of the *N*-PMB group allowed us to develop a reproducible method simply by conducting the reaction at 45 °C instead of 60 °C with no detectable isomerization of the *cis*-propenyl group as evidenced by NMR. In this manner, we could avoid the use of the more expensive *N*-2,4-dimethoxybenzyl hydroxylamine.

Since the introduction of the latent C-2 carboxyl group was based on *N*-acyliminium ion chemistry,[43] it was necessary to protect the pyrrolidine nitrogen as the *N*-Boc derivative, which was accomplished under standard conditions, affording a nicely crystalline product. An X-ray crystal structure ascertained the structural and stereochemical integrity of this product, including the maintenance of the *cis*-propenyl geometry. There are several examples of introduction of a 2-cyano group in *N*-Boc 2-pyrrolidinones en route to the corresponding carboxylic acid derivatives. The protocol calls for the formation of *N*-Boc iminium ions and the addition of TMSCN in the presence of a Lewis acid.[44] Addition of a vinyl or propenylcuprate to iminium ions derived from *N*-Boc 2-pyrrolidinones also has precedence.[45] In these cases, an oxidative cleavage would be necessary to convert the olefin to the desired carboxylic acid.

We opted for introducing a cyano group being cognizant that high stereochemical control many not be assured in the absence of a vicinal steric bias[44,46] or a favorable stereoelectronic control.[47] In the event, reduction of **29** with lithium triethylborohydride[48] and conversion of the hemiaminal intermediate to the corresponding *O*-methyl derivative **30** was realized in good yield. Treatment of **30** with TMSCN in methylene chloride in the presence of $BF_3 \cdot Et_2O$ at −78 to −50 °C led to the desired 2-cyano *N*-Boc pyrrolidine derivatives **31** accompanied by the 2-epimer as a minor product (5:1), which was easily separated by chromatography. The bulkier C-4 side chain (pyrrolidine numbering) may exert a stereodirecting influence in shielding the $\beta$-face of the iminium **A** as illustrated in Scheme 3. Hydrolysis of the cyano group with concomitant removal of the *N*-Boc group necessitated a study of several acidic conditions.[49] Eventually, 12 N HCl in acetic acid afforded the desired product **7** as a white solid, with physical and spectral properties identical with data provided by Abbott laboratories.[50]

We have described a highly stereocontrolled total synthesis of a novel neuraminidase inhibitor **7** in 12.8% overall yield covering 22 steps from D-serine. Clearly, the resident stereogenic center of the amino acid was primarily responsible for the creation of an adjacent tertiary alcohol as in **16**, and possibly for the highly diastereoselective acetylide addition to the nitrones **21a** and **21b**. Once assembled as a 5-substituted $\alpha,\beta$-unsaturated lactam **26a** or **26b**, the subsequent introduction of appropriate functionality was based on a chiral template effect in which steric orientation and favorable coordination with polar functionality may have worked to advantage. Among other attributes of this total synthesis of A-315675 are the crystallinity of crucial intermediates, consistently high yields for individual steps, and practicality.

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**Supporting Information Available:** Experimental procedures, selected $^1H$, $^{13}C$ spectra, and X-ray structures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(43) (a) Speckamp, N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) Hiemstra, H.; Speckamp, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, p 1047.

(44) (a) Arndt, H.-A.; Polborn, K.; Koert, U. *Tetrahedron Lett.* **1997**, *38*, 3879. (b) Langlois, N.; Rojas-Rousseau, A. *Tetrahedron* **1993**, *49*, 77. (c) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron Lett.* **1993**, *34*, 5743.

(45) (a) McClure, K. F.; Renold, P.; Kemp, D. S. *J. Org. Chem.* **1995**, *60*, 454. (b) Pedregal, C.; Ezquerra, J.; Collado, I. *J. Org. Chem.* **1995**, *60*, 5011. (c) Wistrand, L.-G.; Skrinjar, M. *Tetrahedron* **1991**, *47*, 573. For earlier reports on the addition of carbon nucleophiles to acyl iminium ions, see: (d) Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1704. (e) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590.

(46) See, for example: (a) Durand, J.-O.; Larcheveque, M.; Petit, Y. *Tetrahedron Lett.* **1998**, *39*, 5473. (b) Dhimane, H.; Vanucci, C.; Lhommet, G. *Tetrahedron Lett.* **1997**, *38*, 1415. (c) Thanning, M.; Wistrand, L. G. *Acta Chem. Scand.* **1989**, *43*, 290.

(47) Stork, G. *Pure Appl. Chem.* **1989**, *61*, 439.

(48) Pedergal, C.; Ezquerra, J.; Escribano, A.; Carreno, M. C.; Garcia Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053. For recent applications, see: (a) Hanessian, S.; McNaughton-Smith, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567. (b) Hanessian, S.; Balaux, E.; Musil, D.; Olsson, L.-L.; Nilsson, I. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 243. (c) Zanardi, F.; Battistini, L.; Rassu, G.; Auzzus, L.; Pinna, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 2048.

(49) Among the conditions studied: 12 N HCl in MeOH, or dioxane; 2-propanol/acetyl chloride, MeOH/TMSCl led to the corresponding esters, contaminated with variable amounts of amide, carboxylic acid, and unidentified byproducts. For related cases, see refs 44b and 46a.

(50) The $^1H$ and $^{13}C$ NMR spectra characteristics were in accord with data provided by Abbott Laboratories for comparison. The presence of the corresponding amide (undetected by $^1H$ NMR) could only be observed by HPLC analysis. We thank Dr. Steven Wittenberger, Abbott Laboratories, for this analysis. For the conversion of primary amides to esters, see: Greenlee, W. J.; Thorsett, E. D. *J. Org. Chem.* **1981**, *46*, 5351 (as cited in ref 46a). For further details on the conversion of **30**, obtained by a different synthetic strategy, to **7**, see ref 17.