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A chemoenzymatic synthesis of the anti-influenza agent Tamiflu®

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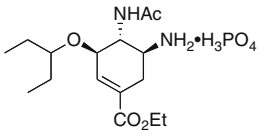
ABSTRACT

The anti-influenza drug Tamiflu® is synthesized from enzymatically derived, enantiomerically pure, and readily available *cis*-1,2-dihydrocatechol.

Tamiflu® (**1**, also known as oseltamivir phosphate) is marketed by Roche, and is used as an orally available agent for both the treatment and the prevention of infections due to influenza viruses.[1] In vivo, the compound undergoes esterase-mediated hydrolysis to the corresponding carboxylic acid, which is a potent inhibitor of neuraminidases A and B, key enzymes required for viral replication. While certain of its derivatives have recently been found to be more efficacious,[2] and may exhibit reduced side-effects,[3] Tamiflu® remains a frontline agent for the treatment of human influenza. It is also active against the avian virus H5N1.[4] Accordingly, and given the continuous threat of the outbreak of influenza pandemics, officially sanctioned stockpiling of the drug has taken place in a number of countries.[5] As a result, concerns have been raised about the capacity of the existing production process to meet peak demand.[6] These arise because the current industrial synthesis[7] starts from shikimic acid, a compound that is not always readily available in consistently pure form.[6] The need to use potentially hazardous azides in the production process[7] represents another drawback associated with the existing synthesis.[6] Consequently, there has been a significant number of recent efforts directed toward the development of alternative and robust routes to Tamiflu®.[8] Among the various approaches pursued, some have involved the use of Diels–Alder chemistry to assemble the cyclohexene core of target **1**.[9] Catalytic enantioselective variants of this basic strategy have recently been described by both the Corey and co-workers[10] and Fukuyama groups.[11] In an alternative approach, the meso-trick[12] has been used to prepare various enantiopure cyclohexane precursors[13,14] while both a metal-mediated[15] and an elegant metal-catalyzed[16] routes to Tamiflu® have also been described. The recent disclosure, by Fang et al.,[17] of two syntheses of the title compound from the readily available and enantiomerically pure *cis*-1,2-dihydrocatechol **2**[18] prompts us to report our own efforts in the area.



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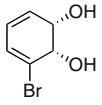

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The route we have used in establishing a formal total synthesis of Tamiflu® (**1**) is shown in Scheme 1, and it begins with the stereoselective conversion of compound **2** into the previously reported PMP-acetal **3**.[19] Reductive cleavage of the latter material with DIBAL-H resulted in a ca. 6:1 and inseparable mixture of compound **4** and its regio-isomer (85% combined yield from compound **2**). In anticipation of effecting a copper-catalyzed intramolecular aziridination reaction of a type recently described by Fleming and co-workers,[20] compound **4** was treated successively with 1,1′-carbonyldiimidazole (CDI) and hydroxylamine (generated in situ by reacting the corresponding hydrochloride salt with imidazole). In this manner, a chromatographically separable mixture of the PMB ether of *o*-bromophenol (21% at 88% conversion) and the desired *N*-hydroxycarbamate **5** (56% at 88% conversion) was obtained. The structure of compound **5** was confirmed by single-crystal X-ray analysis, details of which will be presented elsewhere. *O*-Tosylation of compound **5** using *p*-toluenesulfonyl chloride and triethylamine then gave compound **6** which could be obtained in

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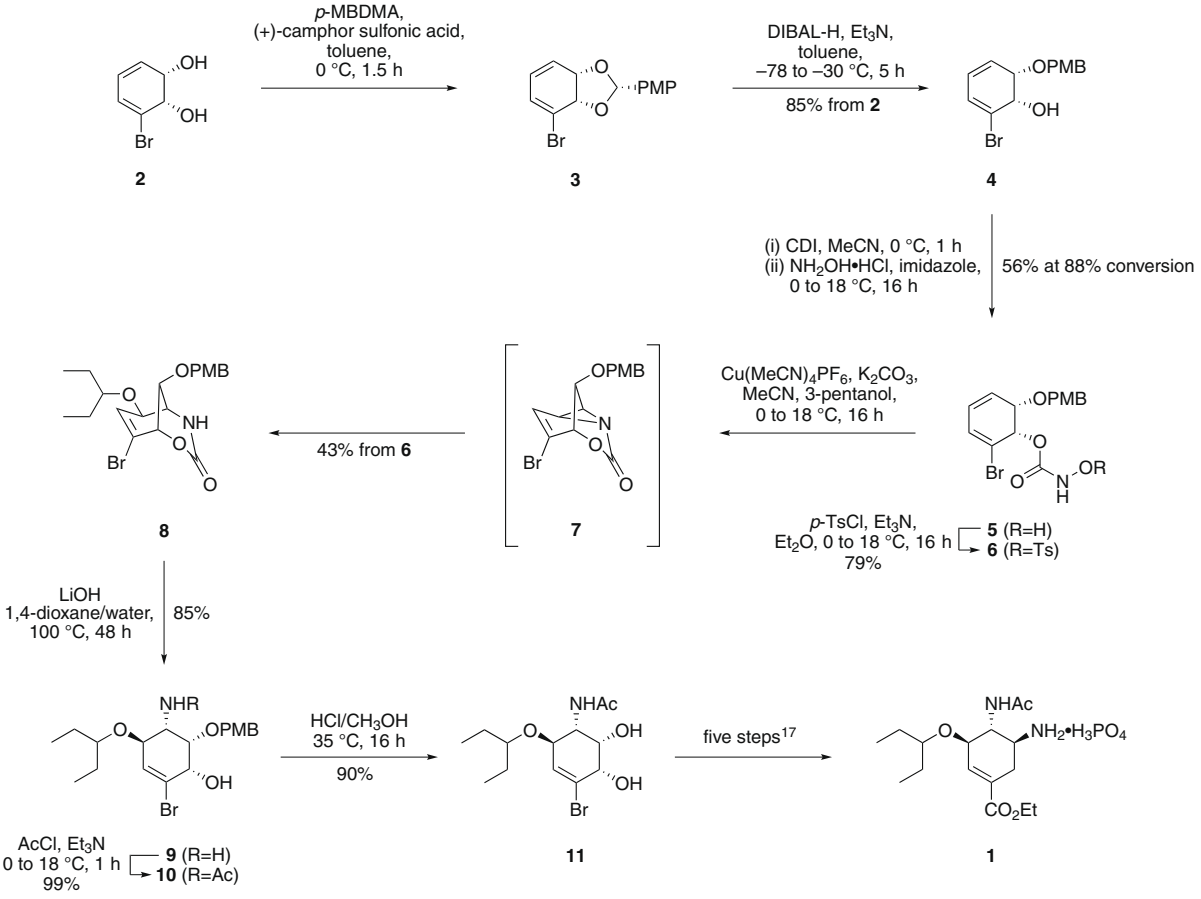

Scheme 1.

pure form and in 79% yield after column chromatography. In the pivotal step of the reaction sequence, a solution of *N*-tosyloxy carbamate **6** in a 1.5:1 v/v mixture of 3-pentanol and acetonitrile was treated with potassium carbonate and with a catalytic amount of $Cu(CH_3CN)_4PF_6$,[21] and the ensuing mixture maintained at 25 °C for 16 h. After workup and flash chromatography, the cyclic carbamate **8** was obtained in 43% yield. Presumably, this product is generated through the regioselective nucleophilic ring-opening of the intermediate and highly strained acylaziridine **7** by 3-pentanol.

While compound **8** could be *N*-acylated using acetyl chloride in the presence of Hünig's base, the product of this process could not be ring-opened in the desired manner using any one of a number of nucleophiles including ammonia. As a result, carbamate **8** was treated with lithium hydroxide in 1,4-dioxane/water at 100 °C for 48 h. In this way, the amino alcohol **9** was obtained in 85% yield. *N*-Acylation of compound **9** was accomplished under standard conditions to give acetamide **10** in 99% yield, and the PMB group within the latter compound was then cleaved with aqueous acid to give diol **11** (90%).[22] The spectral data recorded on this compound matched those reported by Fang et al.,[17] but final confirmation of its structure followed from a single-crystal X-ray analysis.[23] The derived ORTEP plot is shown in Figure 1.

The acquisition of compound **11** constitutes a formal total synthesis of Tamiflu® (**1**) because it is a key intermediate associated with both of Fang's routes[17] to this target. Thus, this group was selectively able to remove the allylic hydroxyl within compound **11** and then convert, with accompanying inversion of stereochemistry, the remaining hydroxyl residue into an azido group. Ni[0]-promoted carboethoxylation of the alkenyl bromide moiety followed by hydrogenolytic cleavage of the azido group, and reaction of the resulting primary amine with phosphoric acid then gave Tamiflu®. A related azide-free synthesis, again using compound **11** as an intermediate and involving the same number of steps, has also been described by Fang and co-workers.[17] On this basis, the present work represents a 16 step and enantioselective synthesis of Tamiflu® from bromobenzene, the precursor to *cis*-1,2-dihydro-

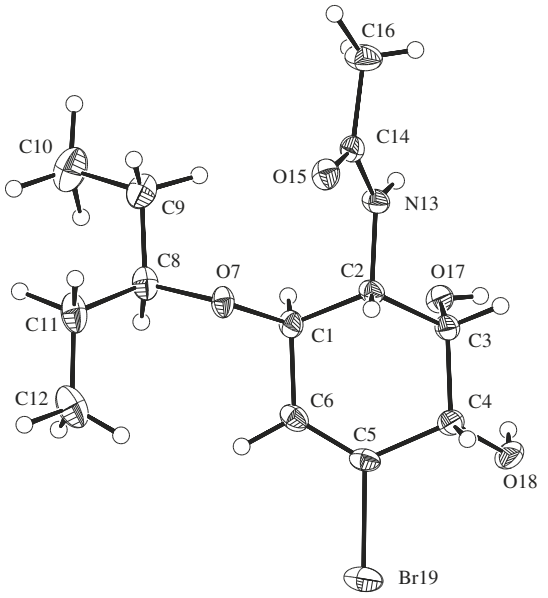

Figure 1. Structure of compound **11** with labelling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

catechol **2**. Given the capacity for the large-scale production of diol **2** from this arene,[24] the present work has the potential to provide a useful new route to compound **1**. We are currently working on a second generation synthesis of Tamiflu® that exploits the capacity of the route described here to deliver selectively the mono-protected forms **9** and **10** of diol **11**. Results will be reported in due course.

Acknowledgments

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Supplementary data

Experimental procedures, product characterization, and ^{1}H or ^{13}C NMR spectra for compounds **4**–**6** and **8**–**11** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.130.

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18. Compound **2** can be obtained from the Aldrich Chemical Co. (Catalogue Number 489492) or from Questor, Queen's University of Belfast, Northern Ireland (see: http://questor.qub.ac.uk/newsite/contact.htm). For reviews on methods for generating *cis*-1,2-dihydrocatechols by microbial dihydroxylation of the corresponding aromatics, as well as on the synthetic applications of these metabolites, see: (a) Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichim. Acta* **1999**, *32*, 35; (b) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Vögtle, M. *Pure Appl. Chem.* **2003**, *75*, 223; (c) Johnson, R. A. *Org. React.* **2004**, *63*, 117.
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21. Various copper catalysts were examined for their capacity to effect this transformation, and $Cu(CH_3CN)_4PF_6$ proved to be the most effective.
22. Selected physical and spectral data for compound **11** are presented in the Supplementary data.
23. X-ray crystal data for compound **11**: $C_{13}H_{22}BrNO_4$, $M = 336.23$, $T = 200(1)$ K, monoclinic, space group $P2_1$, $Z = 2$, $a = 8.1118(3)$, $b = 6.9730(2)$, $c = 13.3490(4)$ Å, $\beta = 98.0424(17)^\circ$ $V = 747.64(4)$ Å^3, $D_x = 1.493$ g cm^{-3}, 3414 unique data ($2\theta_{max} = 55^\circ$); $R = 0.025$ [for 2899 with $I > 2.0\sigma(I)$]; $Rw = 0.044$ (all data), $S = 0.99$. Images were measured on a Nonius Kappa CCD diffractometer (MoKα, graphite monochromator, $\lambda = 0.71073$ Å). Crystallographic data for compound **11** have been deposited with the Cambridge Crystallographic Data Center (CCDC no. 701227). These data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: data_request@ccdc.cam.ac.uk, fax: +44 1223 336033, or via http://www.ccdc.cam.ac.uk/data_request/cif).
24. See, for example: Ballard, D. G. H.; Courtis, A.; Shirley, I. M.; Taylor, S. C. *Macromolecules* **1988**, *21*, 294.