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COMMUNICATION

Synthesis of the anti-influenza agent (−)-oseltamivir free base and (−)-methyl 3-*epi*-shikimate†

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A new enantioselective synthesis of the anti-influenza agent (−)-oseltamivir free base (7.1% overall yield; 98% ee) and (−)-methyl 3-*epi*-shikimate (16% overall yield; 98% ee) has been described from readily available raw materials. Sharpless asymmetric epoxidation and diastereoselective Barbier allylation of an aldehyde are the key reactions employed in the incorporation of chirality, while the cyclohexene carboxylic ester core was constructed through a ring closing metathesis reaction.

Introduction

Oseltamivir phosphate (Tamiflu, **1**) is an orally effective neuraminidase inhibitor,[1] widely used for the treatment and prevention of human influenza (H1N1) and avian influenza (H5N1) infections.[2] The anti-influenza drug **1** was initially discovered by Gilead Sciences and subsequently licensed to Roche for production. The commercial manufacturing process of Tamiflu employs (−)-shikimic acid,[3] a natural product isolated from the Chinese star anise plant, as the raw material. However, the supply of (−)-shikimic acid of consistent purity is problematic due to seasonal and geographical constraints. As a consequence, several methods for its synthesis have been documented in the literature.[3–5] Among the strategies reported, the one from Hayashi's group (9 steps, 57% yield) turns out to be the best so far.[6] However, some of the existing routes are less attractive due to certain drawbacks such as use of expensive starting materials, chiral building blocks and low yields. In order to meet the increasing demand for Tamiflu **1** worldwide, its alternative synthesis from readily available and less expensive starting materials is mandatory.

In continuation of our interest in the asymmetric synthesis of bioactive molecules,[7] we report, in this communication, an efficient synthesis of (−)-oseltamivir free base and (−)-methyl 3-*epi*-shikimate **2**, a unnatural methyl ester of shikimic acid, from readily available starting materials by employing Sharpless asymmetric epoxidation (AE), diastereoselective Barbier allylation and ring closing metathesis (RCM) as the key reactions.

Based on retrosynthetic analysis, we visualized that epoxide **3** can be considered as the key precursor in the synthesis of Tamiflu **1** and (−)-methyl 3-*epi*-shikimate **2** (Fig. 1).

Results and discussion

Initially, epoxy aldehyde **(−)-7**[8] was prepared in 64.5% yield from commercially available *cis*-2-butene-1,4-diol **4** in three steps: (i) monosilylation of diol **4** (TBSCl, imid., 73%), (ii) AE of allylic alcohol **5** [$Ti(OiPr)_4$, (−)-DET, anhydrous TBHP, 93%], (iii) oxidation of epoxy alcohol **(+)-6** (TEMPO, BAIB, 95%) (Scheme 1). Wittig olefination of **(−)-7** with

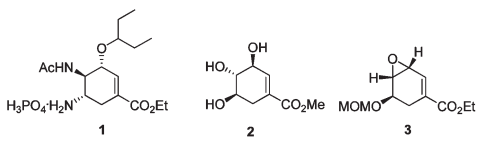
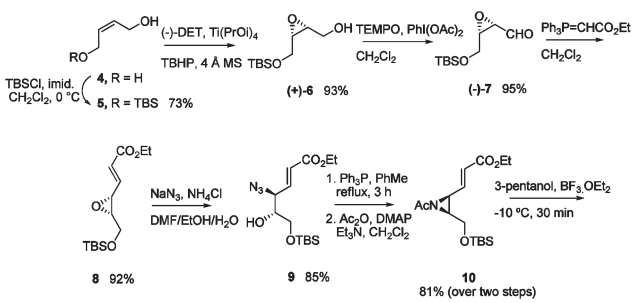


Fig. 1 Oseltamivir phosphate (**1**), methyl 3-*epi*-shikimate (**2**) and their precursor **3**.



Scheme 1 Initial efforts in the synthesis of **1**.

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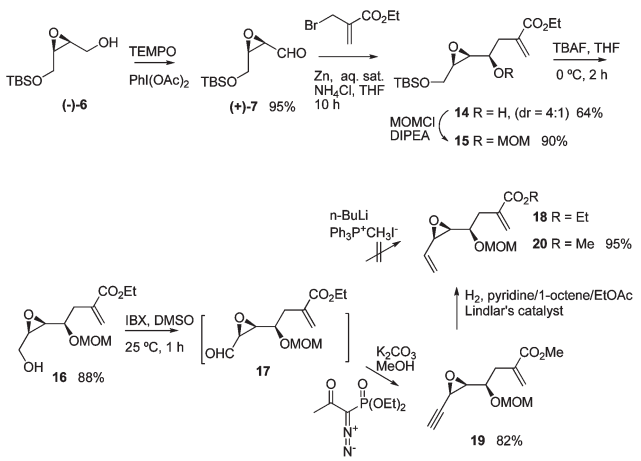
$Ph_3P{=}CHCO_2Et$ gave α,β-unsaturated epoxy ester **8** in 92% yield. Regioselective ring opening of **8** at the allylic position, with azide ion in the presence of NH_4Cl, was accomplished in 85% yield to give azido alcohol **9**. Staudinger reaction (Ph_3P, toluene) followed by *N*-acetylation (Ac_2O, DMAP, Et_3N) afforded protected aziridine **10** in 81% yield. Regioselective ring opening of **10** with 3-pentanol in presence of 1.5 equivalent of $BF_3{\cdot}OEt_2$ proceeded smoothly to furnish α,β-unsaturated epoxy ester **11** as the exclusive product in 75% yield. On desilylation with TBAF, **11** unexpectedly gave the furan derivative **12**,[9] a Michael adduct, as the major product (65%) along with the desired alcohol **13** in minor amounts (17% yield). Since the yield of **13** was miserably low, an alternative route to **1** was undertaken as shown in Scheme 2.

In the second approach, antipode epoxy alcohol **(−)-6** was readily prepared in 96% ee[10] in two steps as described above: (i) monosilylation, (ii) AE using (+)-DET as chiral source (Scheme 2). Oxidation of **(−)-6** (TEMPO, BAIB) gave the aldehyde **(+)-7**, which was subjected to Barbier allylation with ethyl 2-(bromomethyl)acrylate to afford the homoallylic alcohol **14** in 64% yield (dr = 4 : 1). The *syn*-stereochemistry in **14** was established unambiguously from 2D NMR studies.[11]

The hydroxyl group in **14** was then protected (MOMCl, DIPEA, 90%) and the TBS group in **15** deprotected (TBAF, THF) to produce **16**, which was then subjected to oxidation (IBX/DMSO) to give the labile aldehyde **17**. Several attempts to perform Wittig olefination (*n*-BuLi, $PPh_3{}^{+}CH_3I^{-}$, THF) of **17** to produce diene **18** were quite unsuccessful, due to its rapid decomposition under the strongly basic conditions.

Alternatively, the crude aldehyde **17** was subjected to Seyferth–Gilbert homologation using the Bestman–Ohira reagent[12] in the presence of K_2CO_3 and MeOH, which gave the terminal alkyne **19** in 82% yield with a completely transesterified methyl ester in 2 h. To prevent the transesterification process, the Seyferth–Gilbert homologation was carried out in EtOH; however no reaction took place even after 6 h.

Next, a systematic study of selective catalytic hydrogenation [H_2 (1 atm), Lindlar's catalyst, additives, solvents] of alkyne **19** to alkene **20** was undertaken and the results are summarized in Table 1. As can be seen, the ethyl acetate and pyridine

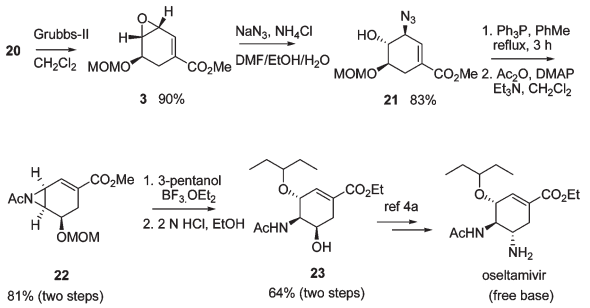


Scheme 2 Synthesis of dienic epoxy ester **20**.

Table 1 Optimization studies for selective catalytic hydrogenation of alkyne **19**: role of additives[a]

Entry	Solvent	Additives	Yield of **20**[b] (%)
1	MeOH	Quinoline (10 mol%)	26
2		Quinoline (1.2 equiv.)	23
3		Pyridine (1.2 equiv.)	34
4	DMF	Quinoline (1.2 equiv.)	22
5		Pyridine (1.2 equiv.)	16
6		1,10-Phenanthroline (1.2 equiv.)	14
7	EtOAc	Quinoline (1.2 equiv.)	57
8		Pyridine (1.2 equiv.)	64
9[c]		Pyridine–1-octene	95
10	Benzene	Pyridine (1.2 equiv.)	33

[a] H_2 (1 atm), Lindlar's catalyst (5 wt%), dry solvent, 25 °C, 6 h. [b] Isolated yield. [c] py–1-octene–EtOAc (1 : 1 : 10).

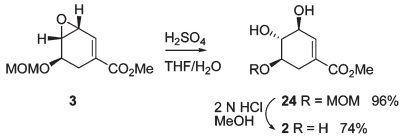


Scheme 3 Synthesis of oseltamivir free base.

combination gave good yields (64%) of diene **20**; however higher selectivity (95%) to **20** could be achieved with a pyridine–1-octene combination. The cyclohexene core **3** was then constructed smoothly in 90% yield *via* a RCM strategy using Grubbs II catalyst under high dilution (Scheme 3). Conversion of **3** to aziridine **22** was achieved in three steps as before (see Scheme 1) with an overall yield of 67%: (i) epoxide opening with azide, (ii) formation of aziridine and (iii) its *N*-acetylation.

Regioselective ring opening of aziridine **22** with 3-pentanol followed by simultaneous MOM deprotection and transesterification using 2 N HCl in EtOH afforded the key amino alcohol **23**, whose spectral data were in complete agreement with reported values.[4a,g] Amino alcohol **23** was then converted to oseltamivir free base in three steps by following the reported procedures:[4a] (i) mesylation of alcohol **23**, (ii) displacement of mesylate with azide ion, (iii) reduction of azide with Lindlar's catalyst.

Several epimers of shikimic acid (*e.g.* methyl 3-*epi*-shikimate **2**) form the constituents of various natural products of biological importance and their syntheses have attracted considerable attention.[13a] We thus envisioned that, the cyclic epoxide **3** could be considered as an important precursor for the synthesis of **2**. Thus, **3** was readily converted into the desired triol **2** through a two step reaction sequence: (i) epoxide opening (H_2SO_4, THF–H_2O); (ii) MOM deprotection of **24** (2 N HCl, MeOH) (Scheme 4). The comparison of spectral data of **2** with the reported values[13b,c] further establishes the absolute configuration of cyclic epoxide **3**.



Scheme 4 Synthesis of methyl 3-*epi* shikimate **2**.

Conclusion

In conclusion, we have described a new enantioselective synthesis of the anti-influenza agent (−)-oseltamivir free base (7.1% overall yield; 98% ee) and (−)-methyl 3-*epi*-shikimate 2 (16% overall yield; 98% ee) starting from readily available *cis*-1,4-butene diol. Key steps employed are the AE, diastereoselective Barbier allylation and RCM. This method comprises of operationally simple yet efficient reactions with the use of inexpensive and non-toxic reagents, amenable for commercial exploitation.

Acknowledgements

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References

1 (*a*) A. L. Cheam, I. G. Barr, A. W. Hampson, J. Mosse and A. C. Hurt, *Antiviral Res.*, 2004, **63**, 177; (*b*) B. J. Smith, J. L. McKimm-Breshkin, M. McDonald, R. T. Fernley, J. N. Varghese and P. M. Colman, *J. Med. Chem.*, 2002, **45**, 2207; (*c*) C. U. Kim, W. Lew, M. A. Williams, H. Wu, L. Zhang, X. Chen, P. A. Escarpe, D. B. Mendel, W. G. Laver and R. C. Stevens, *J. Med. Chem.*, 1998, **41**, 2451; (*d*) C. U. Kim, W. Lew, M. A. Williams, H. Liu, L. Zhang, S. Swaminathan, N. Bischofberger, M. S. Chen, D. B. Mendel, C. Y. Tai, W. G. Laver and R. C. Stevens, *J. Am. Chem. Soc.*, 1997, **119**, 681.

2 (*a*) A. C. Hurt, P. Selleck, N. Komadina, R. Shaw, L. Brown and I. G. Barr, *Antiviral Res.*, 2007, **73**, 228; (*b*) L. Werner, A. Machara, B. Sullivan, I. Carrera, M. Moser, D. R. Adams and T. Hudlicky, *J. Org. Chem.*, 2011, **76**, 10050; (*c*) A. Abbott, *Nature*, 2005, **435**, 407; (*d*) G. Laver and E. Garman, *Science*, 2001, **293**, 1776; (*e*) J. D. Bloom, L. I. Gong and D. Baltimore, *Science*, 2010, **328**, 1272.

3 (*a*) J. C. Rohloff, K. M. Kent, M. J. Postish, M. W. Becker, H. H. Chapman, D. E. Kelly, W. Lew, M. S. Louie, L. R. McGee, E. J. Prisbe, L. M. Schultze, R. H. Yu and L. Zhang, *J. Org. Chem.*, 1998, **63**, 4545; (*b*) M. Federspiel, R. Fisher, M. Henning, H. J. Mair, T. Oberhauser, G. Rimmler, T. Albiez, J. Bruhin, H. Estermann, C. Gandert, V. Gockel, S. Gotzo, U. Hoffmann, G. Huber, G. Janatsch, S. Lauper, O. Rockel-Stabler, R. Trussardi and A. G. Zwahlen, *Org. Process Res. Dev.*, 1999, **3**, 266; (*c*) M. Karpf and R. Trussardi, *J. Org. Chem.*, 2001, **66**, 2044 and references cited therein; (*d*) P. J. Harrington, J. D. Brown, T. Foderaro and R. C. Hughes, *Org. Process Res. Dev.*, 2004, **8**, 86.

4 (*a*) X. Lu, F.-F. Wang, N. Quan, X.-X. Shi and L.-D. Nie, *Tetrahedron: Asymmetry*, 2011, **22**, 1692; (*b*) S. Raghavan and V. S. Babu, *Tetrahedron*, 2011, **67**, 2044; (*c*) B. M. Trost and T. Zhang, *Chem.–Eur. J.*, 2011, **17**, 3630; (*d*) T. Tanaka, Q. Tan, H. Kawakubo and M. Hayashi, *J. Org. Chem.*, 2011, **76**, 5477; (*e*) H. Ishikawa, B. Bondzic and Y. Hayashi, *Eur. J. Org. Chem.*, 2011, 6020; (*f*) M. Trajkovic, Z. Z. Ferjancic and R. N. Saicic, *Org. Biomol. Chem.*, 2011, **9**, 6927; (*g*) D. S. Gunasekera, *Synlett*, 2012, 573; (*h*) H.-K. Kim and K.-J. J. Park, *Tetrahedron Lett.*, 2012, **53**, 1561 and references cited therein.

5 For review articles on synthetic strategies to oseltamivir, see: (*a*) J. Magano, *Tetrahedron*, 2011, **67**, 7875; (*b*) J. Magano, *Chem. Rev.*, 2009, **109**, 4398; (*c*) M. Shibasaki and M. Kanai, *Eur. J. Org. Chem.*, 2008, 1839; (*d*) V. Farina and J. D. Brown, *Angew. Chem., Int. Ed.*, 2006, **45**, 7330.

6 H. Ishikawa, T. Suzuki and Y. Hayashi, *Angew. Chem., Int. Ed.*, 2009, **48**, 1304.

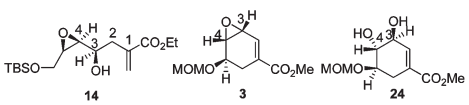
7 (*a*) V. Rawat, P. V. Chouthaiwale, V. B. Chavan, G. Suryavanshi and A. Sudalai, *Tetrahedron Lett.*, 2010, **51**, 6565; (*b*) I. N. Chaithanya Kiran, R. S. Reddy, G. Suryavanshi and A. Sudalai, *Tetrahedron Lett.*, 2011, **52**, 438; (*c*) D. Devalankar, P. V. Chouthaiwale and A. Sudalai, *Tetrahedron: Asymmetry*, DOI: 10.1016/j.tetasy.2012.02.004.

8 The Jorgensen's asymmetric epoxidation proceeded in poor yields (15%) to give **(−)-7**; M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang and K. A. Jorgensen, *J. Am. Chem. Soc.*, 2005, **127**, 6964.

9 G. Reddipalli, M. Venkataiah, M. K. Mishra and N. W. Fadnavis, *Tetrahedron: Asymmetry*, 2009, **20**, 1802.

10 See ESI.†.

11 The relative stereochemistry of **14**, **3** and **24** was confirmed by COSY and NOESY studies. A significant COSY and NOESY correlation was observed between H_4 and H_3 in **14** and **3**, while no correlation is observed between H_4 and H_3 in **24**.



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12 S. Müller, B. Liepold, G. J. Roth and H. J. Bestmann, *Synlett*, 1996, 521.

13 (*a*) L. Sánchez-Abella, S. Fernández, N. Armesto, M. Ferrero and V. Gotor, *J. Org. Chem.*, 2006, **71**, 5396; (*b*) R. Brettle, R. Cross, M. Frederickson, E. Haslam, F. S. MacBeath and G. M. Davies, *Tetrahedron*, 1996, **52**, 10547; (*c*) N. Armesto, M. Ferrero, S. Fernández and V. Gotor, *Tetrahedron Lett.*, 2000, **41**, 8759.

