A Facile Access to Antiflu Agent Tamiflu/Oseltamivir

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Abstract: A practical approach to Tamiflu is developed featuring the construction of the carbocycle core of the target molecule through a Diels–Alder reaction with concurrent introduction of one of the nitrogen atoms. Incorporation of another nitrogen atom was achieved via a high-yielding regioselective ring opening of a cyclic sulfite.

Key words: Diels–Alder reactions, eliminations, enantiomeric resolution, epoxides, antiviral agents

Over the last decade the avian flu virus H5N1 has gradually developed into a serious life threat around the world.[1] Although now the patients can be treated effectively by oral administration of Tamiflu [**1**, the phosphate of Oseltamivir (**2**)], an inhibitor of neuraminidase, the supply of the semisynthetic drug apparently cannot meet the massive and still increasing global demand because the starting material (–)-shikimic acid (**3**) itself is a limited natural resource (Figure 1).

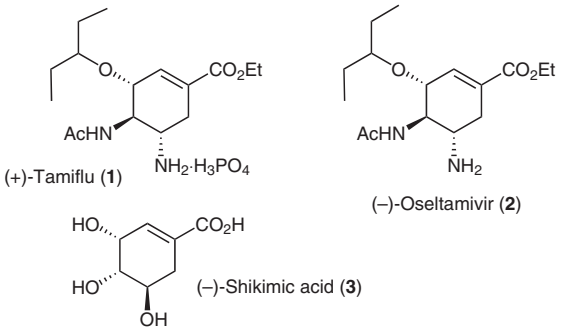
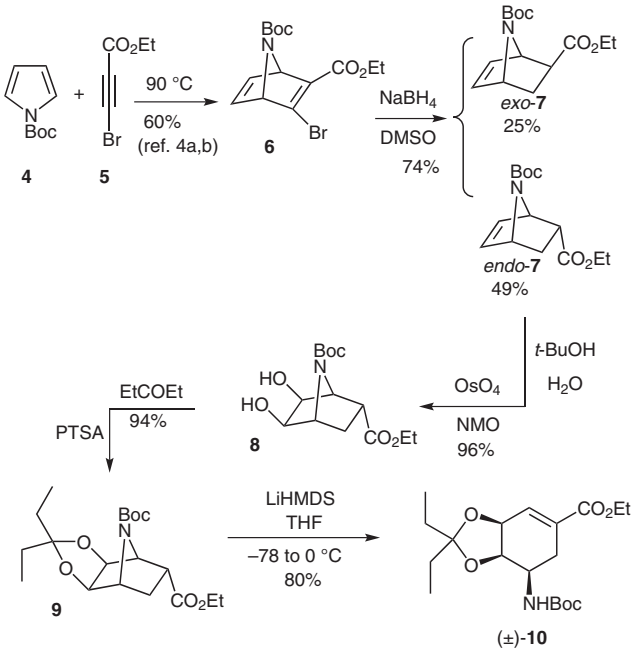


Figure 1 The structures of Tamiflu and shikmic acid

In world-wide exhaustive efforts to gain facile access to Tamiflu an array of synthetic routes[2] has been developed. However, while all these approaches demonstrate certain interesting novel chemistries many of them involved expensive/toxic reagents or starting materials that are not readily available. It appears that an ideal synthesis of Tamiflu is still to be found. Further investigations are warranted, especially now when swine flu (A-H1N1) takes tighter grips worldwide. Herein, we wish to report a Diels–Alder reaction based new approach which would allow for synthesis of racemic Tamiflu in twelve steps and 12% overall yield if using the last four steps in Kann's[2k] and Corey's[2c] route, respectively. In combination of resolution of a key intermediate (**10**), enantiopure (+)-Tamiflu would be also obtainable in comparable yields.

The Diels–Alder reaction between pyrrole and acrylate was recognized as a rapid entry into the desired molecular architecture at an early stage of development of Tamiflu.[3] However, because the cycloaddition failed to take place as anticipated, this seemingly highly straightforward strategy was completely abandoned by subsequent investigators. We were deeply impressed by the potentially high efficiency of the Diels–Alder approach and felt that it deserved further investigations. In a literature study we noticed that Rainier[4a] and Trudell[4b] had reported a similar Diels–Alder addition, where a bromo-substituted acetylenecarboxylate was utilized. Although the product carried an unwanted bromine atom, it might be conveniently removed with $NaBH_4$ in DMSO when saturation of the C–C double bond in conjugate with the ester group as observed with some more or less related molecular setups.[4c,5] If this debromination really worked out, it would be possible to reactivate the abandoned cycloaddition



Scheme 1

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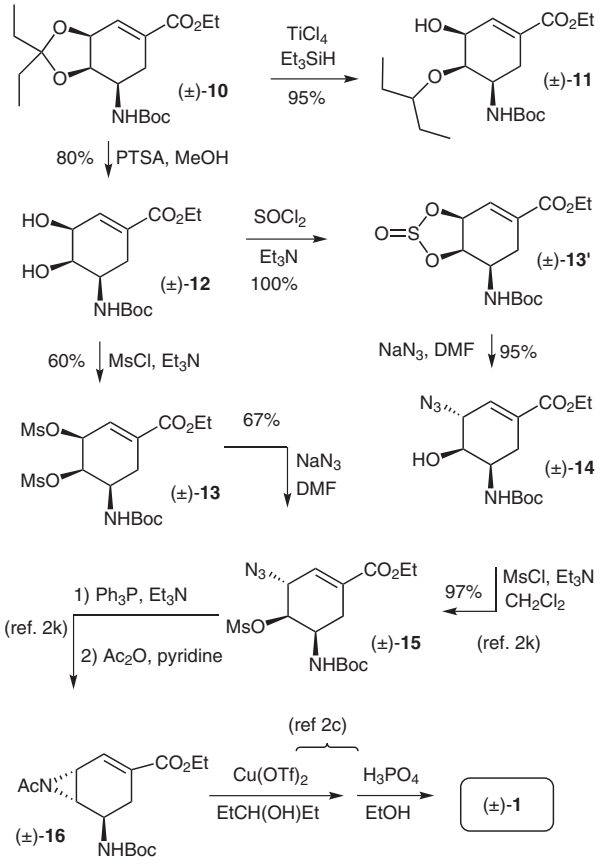
strategy. With these thoughts in mind, we began the explorations on the new approach.

Our synthesis emerged with the facile cycloaddition between the **4**[6] and **5**[7] as described in the literature[4] (Scheme 1). To our delight, the bromine atom indeed could be removed with $NaBH_4$/DMSO[5] when saturating the conjugated C–C double bond, giving *endo*-**7**[4c] and *exo*-**7** formed in 49% and 25% isolated yield, respectively. The isolated major isomer *endo*-**7** was then exposed to OsO_4/NMO (*N*-methylmorpholine *N*-oxide) in *t*-BuOH–H_2O to afford the corresponding *endo*-diol **8** (96%). Further treatment of **8** with 3-pentanone in the presence of a catalytic amount of PTSA led to ketal **9** (94%), which on exposure to LiHMDS in THF at –78 to 0 °C led to the key intermediate racemic **10** in 80% yield.[8] In preparative runs, the diastereomeric mixtures of **7**, **8**, and **9** could be used without need for separation of the isomers and the racemic **10** was isolated in a comparable overall yield (24%) by only one column chromatography at the end of the whole sequence.

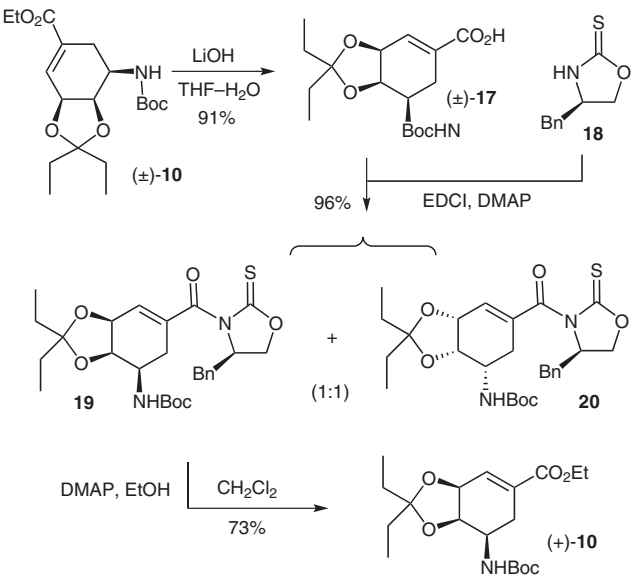


Scheme 2

In an attempt to make full use of the 3-pentylidene protecting group, we tried to cleave the ketal functionality by reduction with $TiCl_4/Et_3SiH$[9] (Scheme 2), which was expected to result in a 3-pentyl ether motif. A clean reaction was indeed observed under such conditions. However, the 3-pentyl group turned out to be on a wrong hydroxyl group (**11**). We suspected that the undesired selectivity might stem from the steric crowding associated with the neighboring NHBoc group. However, use of protecting groups of smaller sizes (such as acetyl or trifluoroacetyl group) or simply an unprotected amino group still failed to raise the content of the desired isomer in the product mixtures to more than 50%. For this reason, we next switched to the alternative strategy in Scheme 2, leaving construction of the 3-pentyl ethereal linkage to a later stage.

The new plan started with removal of the ketal protecting group in **10** with PTSA in MeOH. The resulting diol **12** was converted into dimesylate **13** with $MsCl/Et_3N$ in CH_2Cl_2, which on treatment with NaN_3/DMF led to the known azide **15**, an advanced intermediate in Kann's[2k] synthesis. As the yields of these steps were not satisfactory, we also examined an alternative route to **15**.

In the event, the diol **12** was converted into cyclic sulfite **13′** via reaction with $SOCl_2$. The nitrogen atom was then introduced by a regioselective opening of the cyclic sulfite[10] at the allylic position with azide anion giving **14**, also an advanced intermediate in Kann's[2k] synthesis. Thus, starting from **14** using the remaining steps of Kann[2k] and Corey,[2c] racemic Tamiflu [(±)-**1**] would be obtained in twelve steps from **4** and **5** with 12% overall yield.



Scheme 3

Access to (+)-**10** was gained through the sequence shown in Scheme 3. Separation of the enantiomers was achieved through derivation with optically active chiral auxiliary **18**. Thus, hydrolysis of the ester functionality led to the corresponding free carboxylic acid (±)-**17**. Catenation of **17** with **18**[11] was achieved with the aid of EDCI [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide] and DMAP. The resulting diastereomers **19** and **20** were readily separated by column chromatography on silica gel. The isomer with desire stereochemistry (**19**) was then transformed (+)-**10** through a DMAP-mediated ethanolysis.[12] With

(+)-**10** in lieu of (±)-**10** through the relevant steps in Scheme 2, optically active Tamiflu [(+)-**1**] should be attainable in a comparable yield.[13]

In conclusion, a novel approach to the core structure of antiflu agent Tamiflu/Oseltamivir is developed. A literature Diels–Alder reaction was employed as a rapid entry into the desired fully functionalized cyclohexene architecture, which opens up a previously unreachable possibility of using pyrrole nitrogen as the source of the amino group in the end product. Such a strategy was made feasible here mainly because of successful realization of removal of the superfluous alkenyl bromine atom in the Diels–Alder product with $NaBH_4$ along with selective saturation of the C–C double bond conjugated to the ester functionality and the β-elimination of the *N*-Boc that collapsed the bridged framework into the fully functionalized cyclohexene. Apart from the conciseness of the synthetic sequence, the present approach is also merited by the fact that all the steps up to (±)-**10** could be completed with only one chromatography at the end of the sequence. Another noteworthy feature of the present approach is the use of cyclic sulfite instead of epoxide as substrate in the introduction of the second nitrogen atom because the yields with the cyclic sulfite were apparently higher. From the known (±)-**14** following the literature steps it should be possible to obtain (±)-**1** in 12% overall yield in totally twelve steps. The (±)-**10** could also be resolved into optically active components via corresponding *N*-acyl oxazolidin-2-thione. Use of (+)-**10** in lieu of (±)-**10** in the same synthetic sequence should allow for the synthesis of optically active Tamiflu [(+)-**1**]. Compared the existing routes in the literature, the present one is remarkably practical because of use of common/inexpensive starting materials and reagents. It should make a good complement to its precedents.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) The absolute configuration of (+)-**10** was established by comparison of the spectroscopic data of the **15** thus derived with those reported in the literature (ref. 2k).