Drug Synthesis

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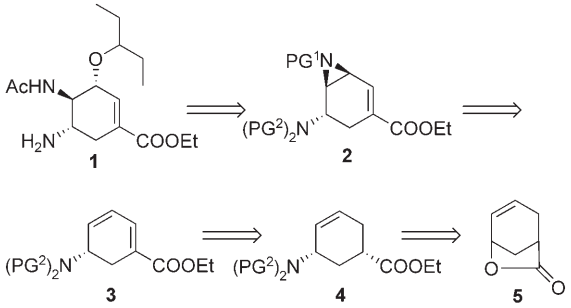
A Concise Synthesis of (−)-Oseltamivir**

Barry M. Trost and Ting Zhang*

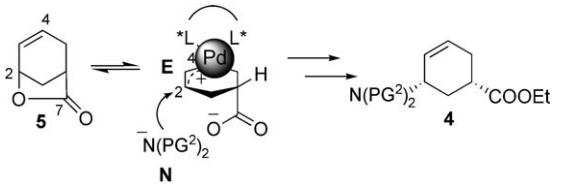
Since its first isolation from a human patient a decade ago, the avian flu virus H5N1 has caused pandemic life-threatening influenza outbreaks in multiple areas around the world.[1] Efforts to find an orally active neuraminidase inhibitor were fruitful upon the discovery of Tamiflu ((−)-oseltamivir phosphate, **1**·H_3PO_4) by Gilead Sciences.[2] However, the daily dose of 150 mg per patient requires large quantities of the drug to meet the global need, especially that from the developing world.[3] Currently, tamiflu is marketed by Roche and is prepared by a semisynthetic approach starting from (−)-shikimic acid, which is still a limited resource given the massive demand.[4] Therefore, the development of alternative synthetic approaches, which start from simple materials, has drawn extensive attention from the chemical community. Despite numerous reports on the development of chemical syntheses of tamiflu from simple starting materials,[5] to date, enhanced efficiency in its synthesis remains a challenge. We took on the challenge and herein report our success in the development of a concise and efficient synthesis of (−)-oseltamivir (**1**).

As shown by our retrosynthetic analysis (Scheme 1), we envisioned the installation of the alkoxy group towards the end of the synthetic sequence, with a direct opening of aziridine **2** as the most efficient option.[2,4,5] In our approach, a direct but unprecedented chemo-, regio-, and stereoselective aziridination of diene **3** was envisioned. Furthermore, diene **3** could be quickly obtained from intermediate **4** by using sulfoxide elimination chemistry that was developed by our research group.[6] Finally, a novel palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) reaction in which a nitrogen-centered nucleophile, was used to directly open racemic *cis*-lactone **5** was proposed to set the requisite stereochemistry for the entire synthesis.



Scheme 1. Retrosynthetic analysis of (−)-oseltamivir. PG = protecting group.

Commercially available lactone **5** was chosen as the starting material on account of its six-membered carbon backbone, its relative stereochemistry, and its potential to deracemize. A palladium-catalyzed AAA process was proposed to open the lactone and thus install an amino-group equivalent onto the ring enantioselectively. Different from common lactone-opening procedures, where nucleophiles would usually attack C7, the Pd-AAA process would result in a nucleophilic addition at C2 or C4 (Scheme 2). Uniquely for **5**, with the tethered carboxylate as a leaving group, the requisite carboxylic ester moiety could also be revealed by the Pd-AAA reaction. A proof of principle for this approach was obtained from our previous work with carbon-centered nucleophiles.[7] Surprisingly and in contrast to that work, the use of imides as nucleophiles (for example, $NHBoc_2$, $NHCbz_2$, $NH(CHO)_2$, and phthalimide; Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl), with or without the addition of bases, failed to give any Pd-AAA reaction product. Revisiting the reaction mechanism gave rise to a few conclusions and postulates:[7a] a) the full or partial deprotonation of the nitrogen-centered nucleophile was necessary to increase its nucleophilicity; b) the approach of an anionic nucleophile **N** towards intermediate **E** could induce repulsion between the negative charge on the nitrogen atom and that on the carboxylate group thus inhibiting the nucleophilic addition (Scheme 2); c) the conversion of intermediate **E** back into starting material **5** is dominant over the nucleophilic attack of the imide anion. Therefore, to overcome the repulsion, the



Scheme 2. Palladium-catalyzed asymmetric allylic alkylation. L = ligand.

[*] Prof. B. M. Trost, T. Zhang
Department of Chemistry
Stanford University
Stanford, CA 94305 (USA)
Fax: (+1) 650-725-0002
E-mail: bmtrost@stanford.edu
Homepage: http://www.stanford.edu/group/bmtrost/

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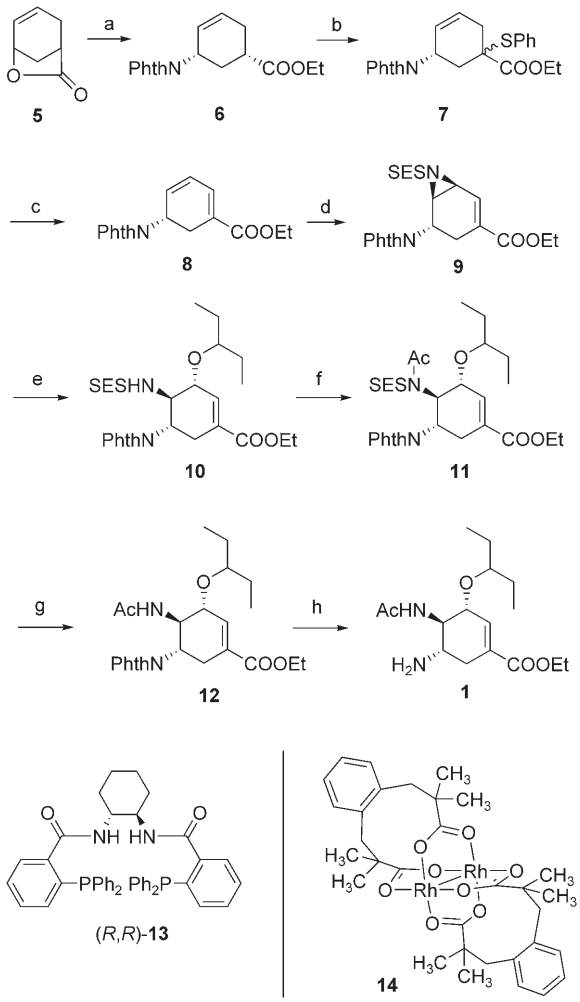
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

carboxylate anion must be trapped as it is formed without diminishing the nucleophilicity of the nitrogen-centered nucleophile. On the basis of the above analysis, we proposed using a trimethylsilyl (TMS) group, whose oxophilicity would result in a selective trapping of the carboxylate oxygen atom over the nitrogen atom. Furthermore, the TMS group could alternatively be introduced attached to the nitrogen-centered nucleophile, wherein silyl transfer should capture the carboxylate moiety while simultaneously revealing the imide anion. Consequently, we chose commercially available TMS-phthalimide as the nitrogen-centered nucleophile. Utilizing another advantage of introducing the TMS group, that is, its susceptibility to acid hydrolysis, esterification could be carried out in the same pot, thus revealing the carboxylic ethyl ester functionality. To our delight, and in stark contrast to using phthalimide itself, the use of $[(\eta^3\text{-}C_3H_5PdCl)_2]$ and the Trost ligand (*R*,*R*)-**13** as the catalyst, and with TMS-phthalimide as the nucleophile, the racemic lactone **5** was opened and desymmetrized. The resulting TMS-carboxylate was converted into the ethyl ester with ethanol in situ to afford **6** in 84% yield and 98% *ee* in one pot (Scheme 3).

Sulfenylation of **6** with $PhSSO_2Ph$ and KHMDS as the base gave an approximate 1:1 diasteromeric mixture of α-thioester **7** in 94% yield.[6] Oxidation of this diastereomeric mixture with *m*CPBA resulted in the corresponding sulfoxide intermediate, which underwent thermal elimination in situ to give diene **8**[8] as well as a small amount of the corresponding 1,4-diene. DBU was used as an additive to slightly increase the regioselectivity in the elimination process. After chromatography, **8** was obtained as a 10:1 regioisomeric mixture in 85% yield, and was carried through as a mixture to the next step.

An unexpected difficulty arose in the selective aziridination step. Copper catalysts, despite their popularity in common aziridination reactions,[9] showed virtually no selectivity between the α,β double bond and the γ,δ double bond of **8**, despite the extensive screening of ligands. In this case, changing Cu to a larger metal such as Ag or Au resulted in low reactivity, although only one isomer, the desired γ,δ-aziridine **9**, was obtatined.[10] Recently Guthikonda, Du Bois, and co-workers reported a Rh-catalyzed intermolecular aziridination reaction, which highlights the generation of a nitrene species in situ and with the olefin being the limiting reagent.[11] When their exact reagents and reaction conditions were applied to our substrate **8**, only the ring-opened product of the presumed vinylaziridine was obtained.[12] Thus, finding a stablizing yet easy to remove protecting group on the aziridine was important. Aryl sulfonyl groups were shown to be problematic: tosyl and benzenesulfonyl groups were difficult to remove later in the synthesis, whereas *p*-nitrobenzenesulfonyl-protected aziridine was unstable and readily decomposed either after a prolonged reaction time or during chromatography. Finally, the 2-(trimethylsilyl)ethanesulfonyl (SES) group was found to be the best choice. Further optimization of the reaction showed that $[Rh_2(esp)_2]$ (bis-[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)], **14**),[13] a new catalyst for C–H insertion reactions reported by Du Bois and co-workers, gave better conversion compared to $[Rh_2(O_2CCPh_3)_4]$, $[Rh_2(O_2CCMe_3)_4]$, and $[Rh_2(CF_3CONH)_4]$ for the aziridination reactions of **8** with $PhI(OAc)_2$ and $SESNH_2$ as the nitrene source. Moreover, by changing the oxidant from $PhI(OAc)_2$ to $PhI(O_2CCMe_3)_2$ an even better conversion was achieved. Most satisfyingly, γ,δ-aziridine **9** was observed as the only product in all cases. In the end, with chlorobenzene as the solvent,[14] $PhI(O_2CCMe_3)_2$ and $SESNH_2$ as the nitrene source, $[Rh_2(esp)_2]$ as the catalyst, and MgO as the base and dessicant, the single isomer **9** was obtained in 86% yield from the diene mixture **8**.[15]

The remaining transformations were straightforward. Opening aziridine **9** with $BF_3{\cdot}Et_2O$ in 3-pentanol gave **10** in 65% yield.[16] Acylation of **10** in Ac_2O with DMAP and



Scheme 3. Synthesis of (−)-oseltamivir. Reagents and conditions: a) 2.5 mol% $[(\eta^3\text{-}C_3H_5PdCl)_2]$, 7.5 mol% (*R*,*R*)-**13**, 1.5 equiv trimethylsilylphthalimide, THF, 40°C, then $TsOH{\cdot}H_2O$, EtOH, reflux, 84%, 98% *ee*; b) 1.5 equiv KHMDS, 1.8 equiv $PhSSO_2Ph$, THF, −78°C to RT, 94%; c) 1 equiv *m*CPBA, 2 equiv $NaHCO_3$, 0°C, then 1 equiv DBU, 60°C, toluene, 85%; d) 2 mol% **14**, 1.1 equiv $SESNH_2$, 1.3 equiv $PhI(O_2CCMe_3)_2$, 2.3 equiv MgO, PhCl, 0°C to RT, 86%; e) 1.5 equiv $BF_3{\cdot}Et_2O$, 3-pentanol, 75°C, 65%; f) 2 equiv DMAP, 20 equiv pyridine, Ac_2O, MW, 150°C, 1 h, 84%; g) 2 equiv TBAF, THF, RT, 95%; h) 5 equiv NH_2NH_2, EtOH, 68°C, quant. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, *m*CPBA = *meta*-chloroperbenzoic acid, MW = microwave, Phth = phthaloyl, SES = 2-(trimethylsilyl)ethanesulfonyl, TBAF = *tetra*-*n*-butylammonium fluoride, Ts = *para*-toluenesulfonyl.

pyridine was accelerated by a microwave reactor and yielded **11** (84%) at 150°C after 1 hour.[17] Once acylated, the SES protecting group could be easily removed by treatment with TBAF to afford **12** in 95% yield.[17] Finally, heating **12** in ethanolic hydrazine yielded **1** in quantitative yield.

In summary, we have successfully synthesized (−)-oseltamivir. The synthesis features a novel palladium-catalyzed deracemizing lactone reaction with a nitrogen-centered nucleophile as well as an unprecedented Rh-catalyzed chemo-, regio-, and stereoselective direct aziridination reaction on an electron-deficient conjugated diene system. This azide-free synthesis required just eight steps from commercially available starting materials and proceeded with an overall yield of 30%,[18] which to our knowledge represents the shortest synthesis to date.

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[8] A similar diene intermediate, bearing an NH-Boc group rather than an *N*-phthaloyl group, was reported by Corey and coworkers (Ref. [5a]). In their approach, the synthesis of the diene required eight steps, whereas in our approach, **8** was prepared in only three steps. From the conjugate diene, they applied a two-step haloamination–S_N2 displacement sequence to form the desired aziridine while we developed a direct aziridination process.

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[12] See the Supporting Information for details.

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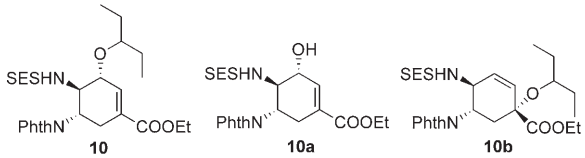
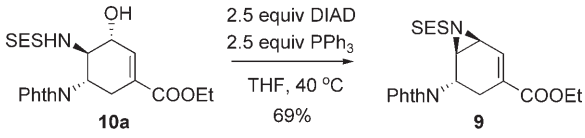
[14] Optimization studies showed that instead of dry chlorobenzene, dry isopropyl acetate (a non-halogenated solvent) could give the same result under otherwise identical reaction conditions, but with a slight inconvenience during the workup; see the Supporting Information for details. J. Chan, K. D. Baucom, J. A. Murry, *J. Am. Chem. Soc.* **2007**, *129*, 14106–14107.

[15] See the Supporting Information for selected optimized reaction conditions for aziridination.

[16] The modest yield of **10** resulted from the formation of two by-products, **10a** and **10b** (the stereochemistry of **10b** has not been verified), which are separable from **10** and from each other. It



turned out to be extremely difficult to convert **10a** into **10** through alkylation reactions. However, converting **10a** into **9** was successful. An unoptimized reaction condition is shown below. DIAD = diisopropylazodicarboxylate.



[17] At room temperature **11** existed as an approximately 4:1 rotameric mixture in $CDCl_3$. NMR spectroscopy studies in C_6D_6 showed the two sets of rotameric signals of **11** to gradually coalesce as the temperature increased and became one set of resonances upon reaching 80°C. The same effect was observed for **12**. See the Supporting Information for details.

[18] The overall yield would be higher if **10a** were to be recycled as indicated in Ref. [16].

