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# Enantioselective Organocatalytic Partial Transfer Hydrogenation of Lactone-Fused Quinolines

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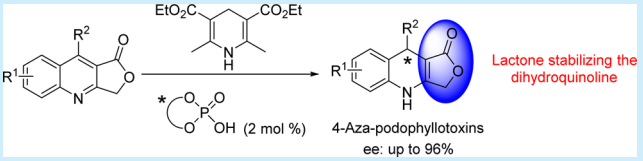
Supporting Information

**ABSTRACT:** The first enantioselective synthesis of 4-aza-podophyllotoxin derivatives by partial transfer hydrogenation of lactone-fused quinolines was achieved using a chiral Brønsted acid catalyst. This reaction was extended to a large scope of substrates with good yields and enantioselectivities.




Catalytic asymmetric transformations have become an essential part of contemporary organic synthesis. Over the past decades, the field of organocatalysis has emerged and grown dramatically with many new applications.[1] In an international context oriented toward the development of eco-friendly processes, the use of nonmetallic catalysts has proven to be a good alternative in organic synthesis.

In this wide area, chiral Brønsted acids are frequently utilized to catalyze asymmetric reactions.[2] In particular, the use of chiral phosphoric acids in the presence of organic hydrides was successfully applied to the enantioselective reduction of nitrogen-containing substrates[3] such as imines,[4] enamines,[5] benzoxazines,[6] benzodiazepines,[7] pyridines[8] and quinolines.[9] To our knowledge, when this biomimetic approach was carried out with substituted quinolines, only the tetrahydro adducts, resulting from a double addition of hydride, were isolated. More recently, this complete reduction was also observed in an asymmetric relay catalysis Friedländer condensation/transfer hydrogenation.[10]

The mechanism reported by Rueping for the exclusive formation of tetrahydroquinolines describes the formation of the highly reactive dihydro intermediate which undergoes the second reduction step via an enamine protonation.[9a]

Besides this, since the synthesis of the first 4-aza-2,3-didehydro-4-deoxypodophyllotoxin **1** and the report of its potent anticancer activity,[11] many researchers have studied with interest these dihydroquinoline derivatives.[12] From a pharmaceutical point of view, these molecules belong to the lignan family and are structurally close to podophyllotoxin **2** and the commercially available topoisomerase II inhibitors, etoposide **3a** and teniposide **3b**, widely used in medicine as anticancer agents (Figure 1).[13]

Despite the substantial medical application of the 4-aza-podophyllotoxins and given that it was proven that one enantiomer is much more biologically active than the

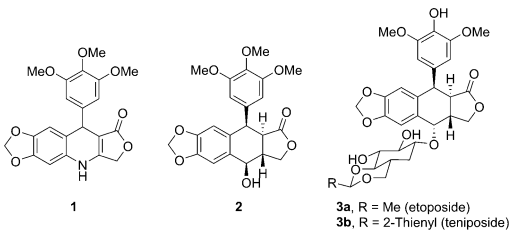



**Figure 1.** Podophyllotoxin derivatives.

other,[12e,14] none of the reported syntheses controlled the stereogenic center at the C1 position.

In this context, we describe in this paper the first enantioselective synthesis of aza-podophyllotoxins by partial transfer hydrogenation of lactone-fused quinolines.[12h]

Hence, our initial investigations were focused on finding the appropriate chiral phosphoric acid catalyst **7** for the reduction of quinoline **4a** in the presence of Hantzsch ester **6** (Table 1, entries 1−9). Among the commercially available chiral phosphoric acids, we focused our attention on the phosphoric acid derivatives of BINOL (**7a**−**e**), H8-BINOL (**7f**−**g**), and VAPOL (**7h**) (Figure 2).

Following this survey, we were pleased to find that, as suspected, the lactone moiety prevents the second reduction step from occurring, allowing thus the isolation of the dihydroquinoline **5a**. Interestingly, partial hydrogenations were already reported on pyridine and benzopyrylium ions.[8,15]

Among the catalysts used, the phosphoric acid **7a** was found to be the best for this transformation with respect to reactivity and enantioselectivity with a 92% yield and 92% ee (Table 1, entry 1).[16] The treatment of **4a** with the catalyst antipode

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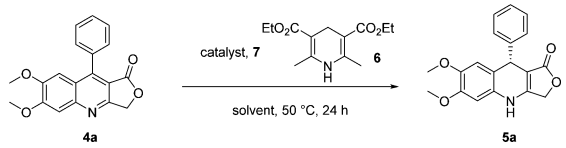
**Table 1. Optimization of the Reaction Conditions**




| entry[a] | catalyst (mol %) | solvent | yield (%)[b] | ee (%)[c,d] |
|---|---|---|---|---|
| 1 | **7a** (10) | toluene | 92 | 92 |
| 2 | **7a** (10) | toluene | 88 | −84[e] |
| 3 | **7b** (10) | toluene | 86 | 88 |
| 4 | **7c** (10) | toluene | 93 | 1 |
| 5 | **7d** (10) | toluene | 95 | 3 |
| 6 | **7e** (10) | toluene | 87 | 1 |
| 7 | **7f** (10) | toluene | 98 | 25 |
| 8 | **7g** (10) | toluene | 93 | 91 |
| 9 | **7h** (10) | toluene | 97 | 35 |
| 10 | **7a** (10) | benzene | 99 | 91 |
| 11 | **7a** (10) | $CH_2Cl_2$ | 62 | 95 |
| 12 | **7a** (10) | $CHCl_3$ | 42 | 90 |
| 13 | **7a** (10) | acetonitrile | 71 | 90 |
| 14 | **7a** (10) | tetrahydrofuran | 77 | 95 |
| 15 | **7a** (10) | MTBE[f] | 79 | 95 |
| 16 | **7a** (10) | DMC[g] | 82 | 93 |
| 17 | **7a** (5) | toluene | 92 | 93 |
| 18 | **7a** (2) | toluene | 91 | 93 |
| 19 | **7a** (1) | toluene | 87 | 93 |
| 20 | **7a** (0.1) | toluene | 28 | 88 |
| 21 | **7a** (2)[h] | toluene | 65 | 93 |
| 22 | **7a** (2)[i] | toluene | 85 | 93 |

[a]General conditions: 1 equiv of quinoline and 2 equiv of Hantzsch ester. [b]Isolated yields. [c]Determined by chiral-phase HPLC analysis. [d]See ref 16. [e]Opposite catalyst enantiomer was employed. [f]Methyl *tert*-butyl ether. [g]Dimethyl carbonate. [h]Reaction conducted at 30 °C. [i]Reaction conducted at 70 °C.

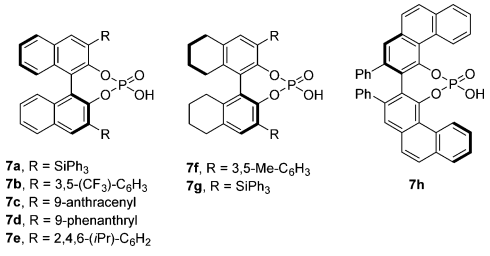



**Figure 2.** Chiral phosphoric acid catalysts.

resulted in the formation of the opposite dihydroquinoline enantiomer (Table 1, entry 2).

After observing that the nature of the organic hydride had no significant effect on the reactivity or the enantioselectivity,[17] further studies using catalyst **7a** were oriented toward the solvent employed.

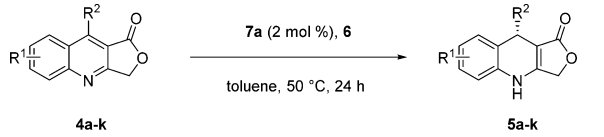
It is worth noting that the nature of the solvent had a major effect on the product yield but not on the enantioselectivity. The best reactivity was observed in aromatic nonpolar solvents (Table 1, entries 1 and 10). Chlorinated solvents resulted in decreased product yields (Table 1, entries 11 and 12). Interestingly, dimethyl carbonate, considered as a green solvent, gave a rather good yield and selectivity (82% yield, 93% ee) (Table 1, entry 16).

Further experimentations revealed that the catalyst loading could be lowered to 1 mol % without significant loss of reactivity or selectivity (Table 1, entry 19). When 0.1 mol % of catalyst **7a** was used, the product yield dramatically dropped to 28% (Table 1, entry 20). Additionally, when 2 mol % of catalyst was used, it was determined that 50 °C was the optimal temperature for the activity (Table 1, entry 18 vs entries 21 and 22).

These preliminary studies revealed that the best conditions for the transfer hydrogenation of quinoline **4a** were 2 equiv of dihydropyridine **6** and 2 mol % of catalyst **7a** at 50 °C in toluene for 24 h.

Under these optimized conditions, we explored the scope of the Brønsted acid catalyzed monohydrogenation for the formation of various aza-podophyllotoxin derivatives (Table 2).

**Table 2. Scope of the Transfer Hydrogenation Reaction**




| entry[a] | substrate, **4** | $R^1$ | $R^2$ | product, **5** | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **4a** | | | **5a** | 91 | 93 |
| 2 | **4b** | | | **5b** | 89 | 91 |
| 3 | **4c** | | | **5c** | 90 | 88 |
| 4 | **4d** | | | **5d** | 76 | 89 |
| 5 | **4e** | | | **5e** | 23 | 93 |
| 6 | **4f** | | | **5f** | 92 | 95 |
| 7 | **4g** | | | **5g** | 49 | 86 |
| 8 | **4h** | | | **5h** | 58 | 71 |
| 9 | **4i** | | | **5i** | 37 | 72 |
| 10 | **4j** | | | **5j** | 84 | 27 |
| 11 | **4k** | | | **5k** | 57 | 96 |

[a]General conditions: 1 equiv of quinoline and 2 equiv of Hantzsch ester. [b]Isolated yields. [c]Determined by chiral-phase HPLC analysis.

In this survey, we considerably changed the nature of the substituent $R^2$. In order to fit the biological requirements, we have tested the dimethoxy and the methylene dioxy groups for $R^1$.[18] To our satisfaction, high enantioselectivities and good yields were generally observed. Surprisingly, the replacement of the dimethoxy substituents $R^1$ on the quinoline ring by a methylene dioxy moiety generally induced a significant decrease of the enantioselectivity (Table 2, entries 1 vs 8, 4 vs 9, and 5 vs 10). Arising from a relatively minor structural change in these substrates, this difference in enantioselectivity is intriguing and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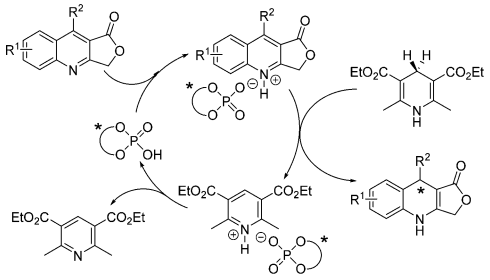
still remains to be clarified. Although it has to be emphasized that the best enantioselectivity was observed when such a dioxolane $R^1$ group was combined with a methoxy dioxolane aryl subunit as $R^2$ (product **4k**, 96% ee) (Table 2, entry 11), only a moderate yield of 57% was obtained.

Based on the literature precedent,[9a] the mechanism suggested for the transfer hydrogenation of lactone-fused quinolines involves an initial protonation of the quinoline. Subsequent hydride transfer results in the formation of the stable 1,4-dihydroquinoline (Scheme 1).

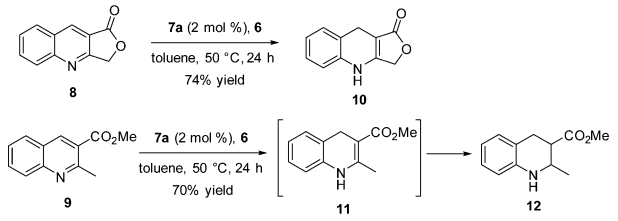
**Scheme 1. Proposed Mechanism for the Brønsted Acid Catalyzed Transfer Hydrogenation of Lactone-Fused Quinolines**



After the optimization and the extension of the reaction scope, we focused our interest on the particular reactivity of the lactone-fused dihydroquinolines.

In order to explain their nonreactivity toward a Brønsted acid in the presence of **6**, we have initially assumed that the mesomeric electron-withdrawing group in the *β*-position of the nitrogen could stabilize the enamine. For this purpose, we performed the transfer hydrogenation on both quinolines **8** and **9** bearing in position 3 a similar electron-withdrawing substituent (Scheme 2)

**Scheme 2. Transfer Hydrogenation of Quinolines 8 and 9**



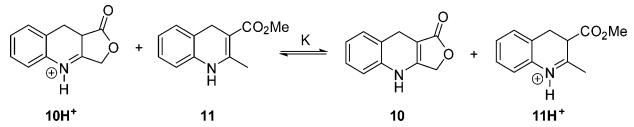

Whereas the formation of the dihydroadducts **10** and **11** was expected in both the cases, ester derivative **9** underwent a complete reduction furnishing the tetrahydroquinoline **12** in 70% yield.

Therefore, a DFT-based study was conducted on dihydroquinolines **10** and **11** using the *ω*B97X-D functional[19] and a PCM model[20] for the solvent.[21]

First, in order to evaluate their difference of reactivity toward a proton, a proton exchange between **10** and **11** was studied (Scheme 3).

Highlighting the much easier protonation of dihydroquinoline **11**, an equilibrium constant $K$ of $3.5 \times 10^{15}$ was calculated for this transformation.[22] This result is in good agreement with the experimental observation, as **11** leads to the tetrahydroadduct after protonation. In order to understand such a difference of reactivity between **10** and **11** toward a proton, we

**Scheme 3. Proton Exchange between 10 and 11**[a]




[a]In toluene.

decided to go further with the structural analysis of both dihydroquinolines.

The optimization of the structures **10** and **11** revealed a significant difference of geometry (Figure 3). Indeed, while the

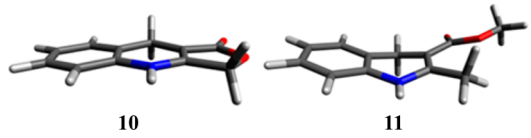



**Figure 3.** Optimized structures for **10** and **11**.

dihydroquinoline ring system **10** is nearly planar, a curved shape is adapted by **11**.[23] Related to this, the out-of-plane angle of the N−H bond is higher in the molecule **11** than in the lactone-fused derivative. These structural differences are in correlation with a higher nitrogen lone-pair delocalization and consequently a higher double bond character in the N−C and C−C bonds of the enamine moiety in the lactone-fused dihydroquinoline **10**.[24] Thus, by increasing the strength of the enamine double bond, the reactivity of **10** toward a proton is considerably affected in comparison to the molecule **11**. This is also supported by the fact that the carbon in the *β*-position of the nitrogen in the lactone-fused dihydroquinoline **10** has a lower electron density than in dihydroquinoline **11**.[25]

This study revealed the crucial role played by the five-membered ring lactone moiety in the particular reactivity of the starting quinolines **4** and **8** in the transfer hydrogenation reaction.

In summary, we have developed the first organocatalytic enantioselective transfer hydrogenation of lactone-fused quinolines to obtain various aza-podophyllotoxin derivatives. The exclusive formation of stable 1,4-dihydroquinolines was rationalized by computational studies highlighting the higher stability of the enamino-lactone toward protonation.

## ■ ASSOCIATED CONTENT

### Supporting Information

Full experimental details and analytical data including NMR spectra and chiral HPLC analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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(16) As no single crystals have been obtained, assignment of the absolute configuration was based and extrapolated from the chiral HPLC of the compound **5k** described in ref 14.

(17) Results not reported here. Hantzsch esters with various esters groups (methyl, isopropyl, benzyl, allyl) gave the same yield and enantioselectivity for the reaction reported in Table 1. Benzothiazolines were also tested but did not allow any conversion: Zhu, C.; Akiyama, T. *Org. Lett.* **2009**, *11*, 4180.

(18) Additionnally, the synthesis of quinolines **4** bearing an electron-withdrawing group in $R_1$ position can not be realized.

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(21) See Supporting Information for more details.

(22) Determined from the calculated Gibbs energy variation of $\Delta_r G^\circ = -19.4$ kcal/mol.

(23) Maximum dihedral angles of the nitrogen-containing ring is 3° for **10** and 28° for **11**.

(24) N–C bond lengths: 1.352 Å for **10** and 1.377 Å for **11**. C–C bond lengths: 1.342 Å for **10** and 1.360 Å for **11**.

(25) APT charges: −0.65 and −0.74 in **10** and **11** respectively.



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