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COMMUNICATION

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Multi-Gram Scale Synthesis of Chiral 3-Methyl-2,5-*trans*-tetrahydrofurans

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In this article, we report the rapid and facile synthesis of chiral 3-methyl-2,5-*trans*-tetrahydrofurans. This reaction utilizes cheap and easily available starting materials. A domino hydrolysis and intramolecular *Michael*-type ring closure reaction was the key step. As a result, synthesis of the desired 3-methyl-2,5-*trans*-tetrahydrofurans could be achieved in gram-scale over seven linear steps with high chemical yield and high diastereoselectivity.

Keywords: 3-methyl-2,5-*trans*-tetrahydrofurans, ring closure, gram-scale syntheses, diastereoselectivity, synthetic methods.

Introduction

3-Methyl-2,5-*trans*-tetrahydrofurans are critical structural elements for various natural products, biologically active compounds, and pharmaceuticals.[1–7] For instance, natural products chagosensine,[8,9] cationomycin,[10,11] amphidinolides C, C2, C3, and F[12–15] possess such *trans*-tetrahydrofuran substructures (*Figure 1*). As a consequence, many methodologies have been developed for the construction of this type of heterocycle.[16–22]

Among them, intramolecular conjugated addition of an oxygen nucleophile is often used for the formation of 3-methyl-2,5-*trans*-tetrahydrofurans (*Scheme 1,a*), which inspired us to identify suitable conditions to obtain useful amount of 3-methyl-2,5-*trans*-tetrahydrofurans intermediates for further studies on total synthesis of natural products.[23,24] Herein, we report a rapid and facile process to access gram-scale quantities of 3-methyl-2,5-*trans*-tetrahydrofurans in just seven linear steps. A domino hydrolysis and diastereoselective intramolecular *Michael*-type ring closure strategy is the key step (*Scheme 1,b*).

Results and Discussion

As depicted in *Scheme 2*, our synthetic route began with diazotization of inexpensive starting material, L-glutamic acid **1**, using $NaNO_2$ in HCl aqueous solution to provide lactone **2**. Reduction of the carboxyl group of lactone **2** with borane followed by protection of the primary alcohol **3** with TBSCl led to lactone **4**. Selective methylation of **4** using LiHMDS and MeI delivered **5** as

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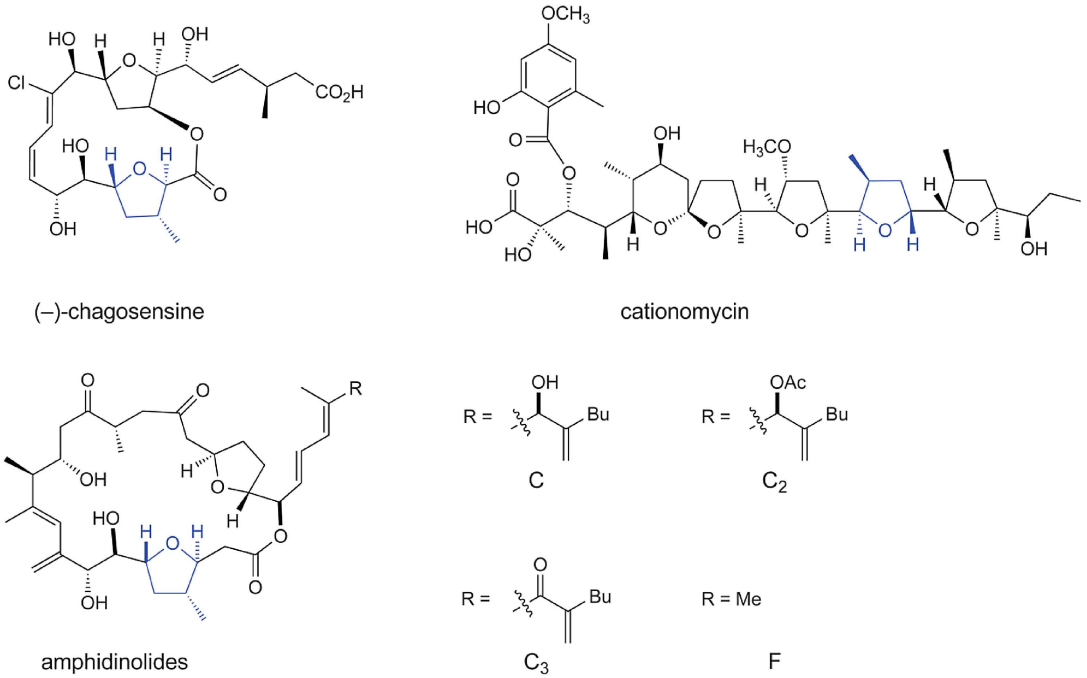
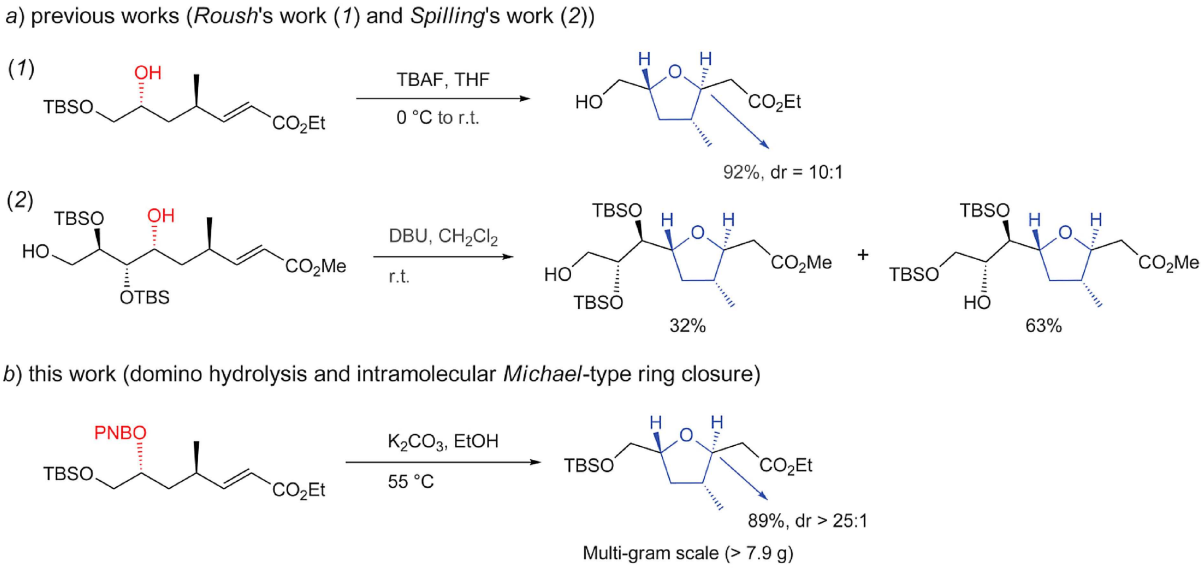


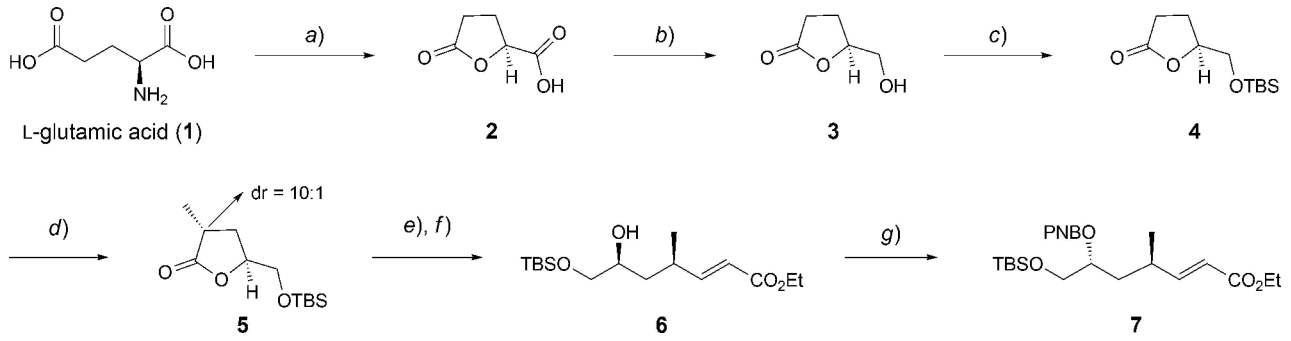
Figure 1. Representative natural products and bioactive compounds containing a 3-methyl-2,5-*trans*-tetrahydrofurans core.



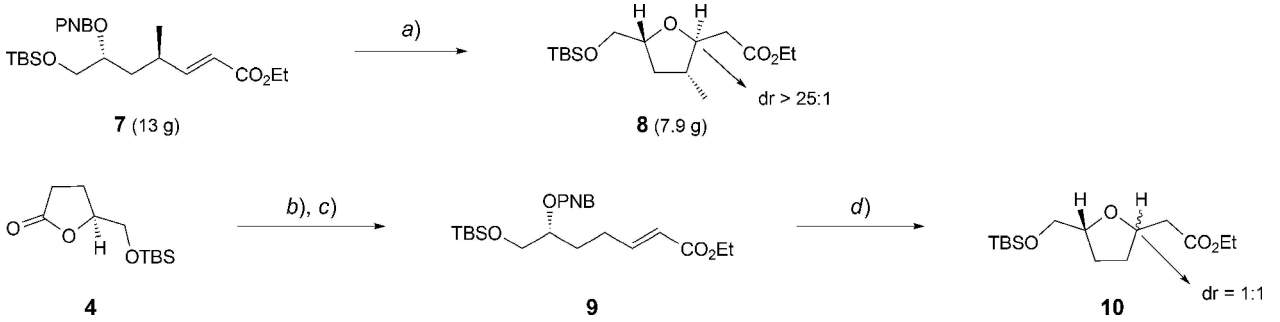
Scheme 1. Synthesis of 3-methyl-2,5-*trans*-tetrahydrofurans.

a mixture of two diastereoisomers (dr = 10:1). Although the two stereoisomers of **5** could be separated by chromatography on silica gel, purification would be very time-consuming due to the similar polarity of the two isomers. Hence, we used the mixture directly for the next step, and easy separation of isomeric products was performed at a later stage. With the mixture of two stereoisomers of **5** in hand, DIBAL reduction followed by *Wittig* reaction produced the pure conjugated ester **6** with an isolated yield over 85% of two steps. Subsequent *Mitsunobu* reaction of hydroxyl group in **6** delivered PNB ester **7**.

Following successful preparation of ester precursor **7**, the 3-methyl-2,5-*trans*-tetrahydrofuran **8** was formed through a domino hydrolysis and intramolecular *Michael*-type ring closure process using K_2CO_3 as



Scheme 2. The synthesis of intermediate **7**. Reagents and conditions: *a*) $NaNO_2$, HCl, H_2O, 0 °C to r.t.; *b*) $BH_3 \cdot SMe_2$, THF, 0 °C; *c*) TBSCl, imidazole, DMAP, CH_2Cl_2, r.t., 42% over three steps; *d*) LiHMDS, MeI, THF, −78 °C, 80%; *e*) DIBAL, −78 °C; *f*) $(Ph_3P)_3PCHCO_2Et$, PhMe, 80 °C, 85% over two steps; *g*) Ph_3P, DIAD, *p*-nitrobenzoic acid, THF, 0 °C, 74% over three steps.



Scheme 3. Domino hydrolysis and intramolecular *Michael*-type ring closure reaction. Reagents and conditions: *a*) K_2CO_3, EtOH, 55 °C, 89%; *b*) DIBAL, −78 °C; *c*) $(Ph_3P)_3PCHCO_2Et$, PhMe, 80 °C; *d*) K_2CO_3, EtOH, 55 °C.

base with multi-gram scale (7.9 g). Notably, the methyl-bearing stereogenic center played a very important role in controlling the stereochemical outcome of the ring closure reaction (*Scheme 3*). Under the same conditions, the ester **10** was obtained from the cyclization of **9**, which was synthesized from lactone **4** using the same synthetic route as described in *Scheme 2*, but with no diastereocontrol (*dr* = 1:1).

Conclusions

In summary, we have developed a domino hydrolysis and intramolecular *Michael*-type ring closure strategy to prepare 3-methyl-2,5-*trans*-tetrahydrofurans. It uses the readily-available chiral pool material L-glutamic acid as starting material. The required 3-methyl-2,5-*trans*-tetrahydrofuran was obtained with high chemical yield (18.8% overall yield) and high diastereoselectivity (*dr* > 25:1) over seven steps. The process was also efficiently realized on multi-gram scale. Furthermore, the *trans*-tetrahydrofurans intermediate **8** can be subjected to further chain extension in either direction, which might be useful for the synthesis of various natural products and biologically active compounds.[25–29]

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Author Contribution Statement

S. Qin and *Y. Cao* are contributed equally to this work. *S. Qin*, *Y. Cao*, and *Y. Luo* performed the experiments, analyzed the data. Prof. *S. Jiang* and Prof. *J. S. Clark* gave important suggestion for this project and help improved the language. Prof. *X. Wang* and Dr. *G. Yang* designed the experiments and wrote the manuscript.

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