Original Article: A Novel Approach for Total Synthesis of *Stemona* Alkaloid: Tuberostemonamide

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ABSTRACT

Stemona alkaloids are structurally complex and polycyclic alkaloids, obtained from a novel class of natural plants which are extracted, separated, and purified from *Stemonaceae* family. They are abundantly and more exclusively obtained from the renowned three classes, namely *Stemona, Stichoneuron,* and *Croomia* of monocotyledonous family *Stemonaceae*. They are structurally distinguished by the presence of a central pyrroloazepine core. By 2019, almost 215 *Stemona* alkaloids were isolated from nature. More than 80 members have already been discovered and many more are in pipeline likely to be isolated. Traditionally, their roots have been used for centuries in Chinese medicine for a variety of purposes including (but not limited to): Treatment of bronchitis, tuberculosis, pertussis, as well as anti-parasitic agents. By rational comparing and contrasting, the multidimensional bioactivities of *Stemona* alkaloids specifically stemofoline-type derivatives are the most promising compounds representing many lead structures for further development of commercial agents used in pharmaceutical and chemical industries. Here, on our total synthesis proposal, we vividly explained step by step the total synthesis procedure to get the *Stemona* alkaloid: Tuberostemonamide. This renowned *Stemona* alkaloid has potent pharmaceutical effects in the treatment of different neurodegenerative diseases and inflammatory conditions. For such fascinating future work and robust research scope, we proposed and worked on a unique and effective total synthetic pathway for the Tuberostemonamide synthesis, which can be used in the synthetic organic lab. It is hoped that the proposed synthetic process discussed here would be utilized efficiently and give the highest possible yield (%).

Introduction

Nowadays natural plants are playing a vital role in the synthesis of a wide variety of safest drugs. Due to the various emergent side effects in the human body with synthetic and semisynthetic drugs, scientists are more interested in developing Phyto-based drugs. The importance of natural components in traditional medicine has been

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well recognized and the concept is used to develop many outstanding lifesaving drugs, which either possess the whole structure of core natural product or incorporate through chemical modifications (usually straightforward). At present, medicinally and clinically important natural products are considerably invented through phenotypic or simply target-based screening.

Natural plants have been used extensively as medicine throughout the world for many centuries, [1–3] and so is the total synthetic process of plant-based natural products to become a reliable means of inventing new components with known detailed functional characteristics of novel compounds, which ultimately promote them to new drug discovery [4–6]. *Stemonaceae* plant products have a wonderful prestigious timeline of utilization medicinally to manage pertussis, tuberculosis, anthelmintics, and bronchitis in Japan and China [7]. Almost 215 multi-dimensional alkaloids have been isolated to date [8]. although very small parts of *Stemona* alkaloids have been asymmetrically synthesized [7–9]. Alkaloid extract from *S. tuberosa* showed very potent anticough activity in guinea pigs [10-11]. Various *Stemona* alkaloids have been found to show antitussive and insecticidal activities [12–14]. At present, over 80 *Stemona* alkaloids have been identified separated from *Stemona* species, which can structurally be categorized into six different simple groups namely, the stemoamide group, stenine groups, tuberostemospironine groups, stemonamine group, parvistemoline group, and miscellaneous group, respectively [15]. Chemical diversification and variability were highly prominent in *S. tuberosa.* [16] In search for biologically active alkaloids of *S. tuberosa*, four new *stemona* alkaloids were isolated and identified, including didehydrotuberostemonine A (1), stemoninone (2), tuberostemospiroline (3), and tuberostemonine L (4), accompanied by the seven known alkaloids 2-oxostenine (5), tuberostemonine (6), sessilifoliamide H (7), tuberostemonone (8), didehydrotuberostemonine (9), bisdehydrostemoninine (10), and tuberostemoamide (11), taken from the roots of this plant.

Many recent studies on *S. tuberosa* of various localities have already isolated more than 80 prominent alkaloids, [17] which are divided into tuberostemoninetype, [18–22] stemoninine-type, [23–24], and croomine-type.[25–26] Some main alkaloids in Baibu, such as neotuberostemonine and neostenine have been proved to exhibit antitussive potency comparable to codeine [21]. Stemoninine and bisdehydrostemoninine have shown significant anticough activity in the guinea pig after cough induction by citric acid aerosol stimulation [23-24].

More interestingly, *Stemona* alkaloids have been also evaluated in insects on their nicotinic acetylcholine receptors. Cholinergic receptors are stimulated by the binding of acetylcholine (Ach). In humans, the blocking of AchE (acetylcholine esterase) prolongs the duration of action of acetylcholine (Ach), which is very helpful for the treatment of renowned Alzheimer's disease (AD) of aged patients. Already, many alkaloids have been found to be effective as AchE inhibitors. The life-threatening Alzheimer's disease drugs are galantamine, rivastigmine, donepezil, and memantine [27]. Thus, *Stemona* alkaloids have medicinal potentials in humans to treat AD [28].

It is known that biologically effective natural products are most discovered rather than synthetic substances for the healing of human diseases, interestingly even in lacking extensive information about the purpose of the natural products in their original biological setting. The success of such relentless efforts of some researchers has led to suggest that scaffolds of natural products may lead to useful chemical libraries. Unfortunately, one single *Stemona* alkaloidal component is barely developed for the next investigational medicinal use. It happens prominently due to the lack of extensive biological profiling, which is extensively affected by accurate separation as well as proper synthetic access process. Two *Stemona* components, namely tuberostemoamide and sessilifoliamide A, were separated by Lin [29-30] and Takeya, [31]

respectively, which first presented their total synthesis and medicinal evaluation. Structurally speaking, these two naturally obtaining alkaloidal components have the same 5/7/5 tricyclic skeleton, which is why it is highly reasonably acceptable to present direct structural modification at the ester portion, which would be an innovative synthetic plan for the abovementioned two tetracyclic alkaloidal substances. Based on the excellent work of Dai [32] and Chida–Sato, [33] and at the same time proper utilization of structural activity relationship of the stemoamide-group alkaloids, scientists have proposed corresponding retrosynthetic breakdowns as well as total synthesis strategy, for both Tuberostemoamide and Sessilifoliamide A. In our total synthesis proposal for the Tuberostemonamide *Stemona* alkaloid, we also discussed the possible complete retrosynthetic analysis and synthetic pathways for easy understanding and ultimate efficient synthesis of the final product.

Retrosynthetic Analysis

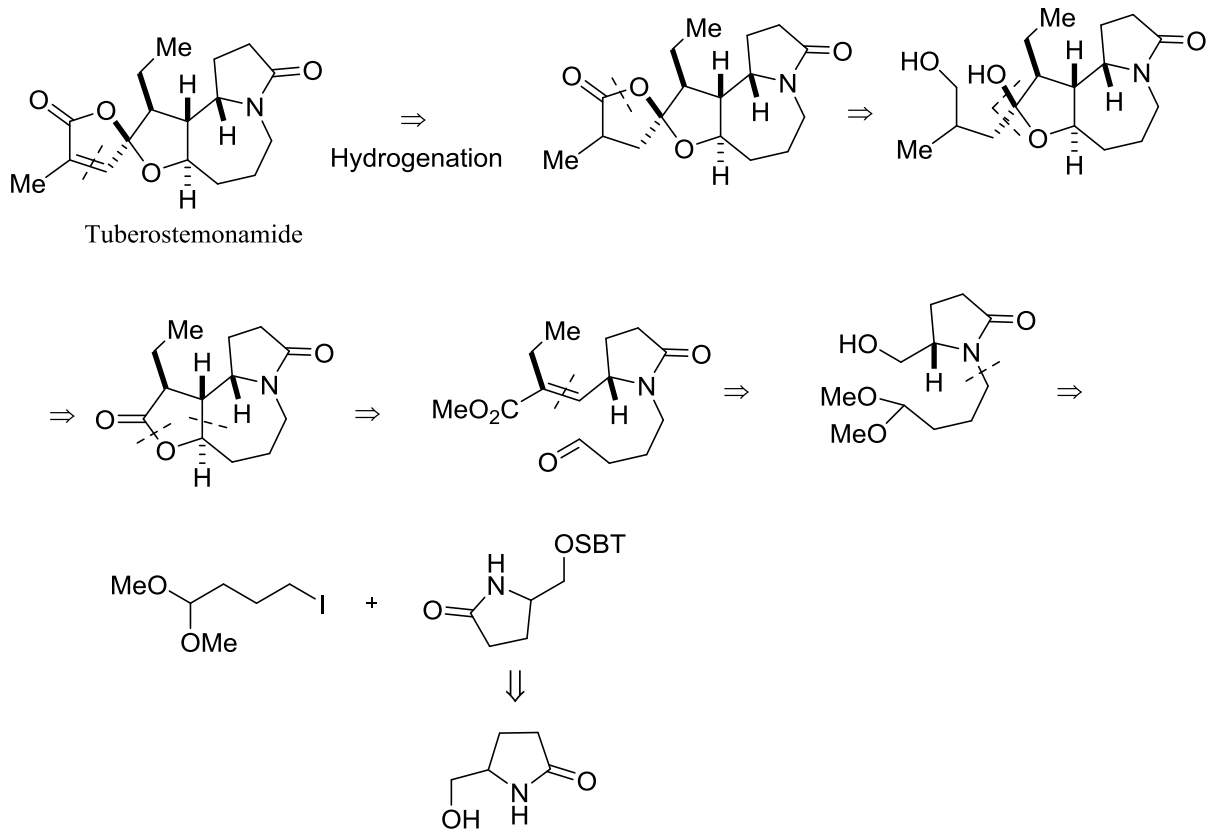

Figure 1. Retrosynthetic analysis of Tuberostemonamide

In Figure 1 above, we can see our proposed Retrosynthetic analysis. At first, Tuberostemonamide undergoes hydrogenation then the lactone ring broke up to get hydroxyl compound. Next, we obtain a keto compound. After subsequent disassembly by oxidation, we get TBSO -pyroglutamic derivative. But this TBSO compound is not commercially available, so we proceed further conversion to achieve a very cheap and commercially available compound: (R)-(-)-5-(Hydroxymethyl)-2-pyrrolidinone.

Forward Synthesis Pathways

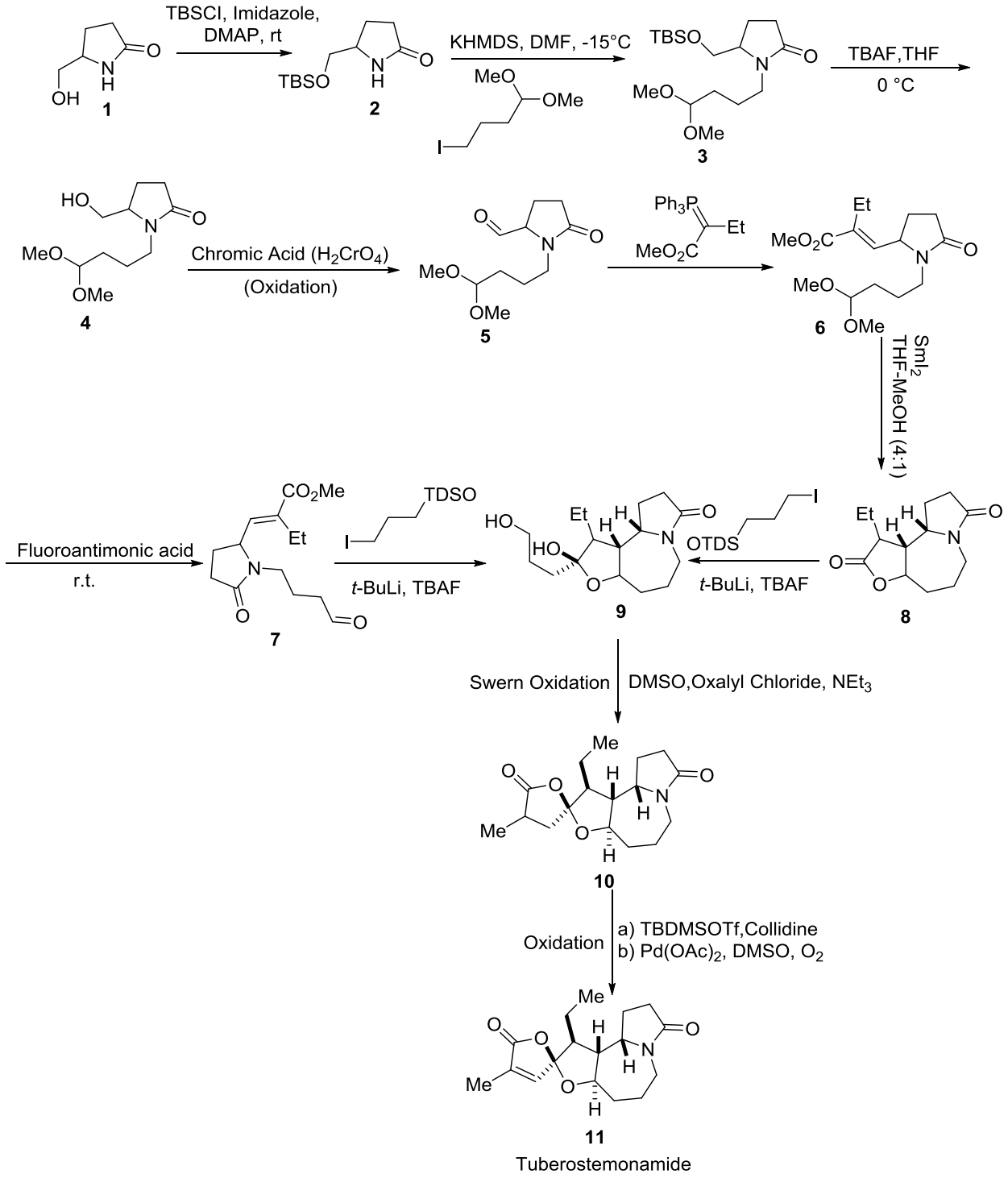

Figure 2. Proposed forward synthesis of Tuberostemonamide

In Figure 2, the total forward synthesis pathways are illustrated step by step to reach our desired product "Tuberostemonamide". At first, we initiate our total synthesis process with the commercially available starting reagent: (R)-(-)-5-(Hydroxymethyl)-2-pyrrolidinone. This reagent is treated with TBSCI along with Imidazole in the presence of DMAP to obtain the compound (2). Thus, we can protect the Hydroxyl group of the compound (1). Then, the compound (2) reacts with the iodide compound in presence of KHMDS to produce compound (3), which ultimately produces the alcoholic compound (4)

by treating TBAF and THF. Then, this compound produces keto compound (5) by oxidation process with Chromic acid. The compound (5) reacts with a butanoate reagent to generate compound (6). Then, Strong Fluoroantimonic acid reacts with compound (6) to produce a keto compound (7). Subsequently, the compound undergoes samarium (II) iodide (SmI_2) mediated cyclization reaction to make a cyclic product (8). Then, the compound (8) reacts with an iodide reagent in presence of t-BuLi to generate compound (9). By renowned "Swern oxidation", the compound (9) is converted to compound (10). Finally, by the further oxidation process, we can produce our desired final product, i.e. Tuberostemonamide (11).

Commercial Sources

Our starting reagent is (R)-(−)-5-(Hydroxymethyl)-2-pyrrolidinone, (M.W.:115.13; Chemical Formula: $C_5H_9NO_2$), which is readily available in Sigma-Aldrich Inc. (Product number: 366358, CAS number: 66673-40-3, 1 g: $72.10). Again DMAP [4-(Dimethylamino) pyridine] (Product number: 107700, CAS number: 1122-58-3, 5 g: $18.60) and Imidazole (Product number: I2399, CAS number: 288-32-4, 100 g: $43.30) are also cheaply available in Sigma-Aldrich Inc.

Conclusion

In conclusion, by adopting more convenient and cheapest synthetic pathways, we proposed our total plausible synthesis of Tuberostemonamide. It is, based on the current study, that the synthetic strategy would result in the highest yield (%) of the product. As the recent synthetic world is always evolving, so any synthetic chemist may follow this synthetic procedure and can modify as necessary to produce other *Stemona* alkaloids that would be used in different human diseases. One of the highly helpful tips for the future of new phyto-based drug discovery is that, by considering and exploiting the versatility of the tricyclic intermediates of this *Stemona*, total synthesis of similar 5/7/5 tricycle bearing alkaloidal molecules are presently in pipeline and are widely growing, which, coupled with our innovative synthetic research process, will definitely potentiate future biosynthetic medicinal, and clinical explorations of such highly fascinating as well as attractive alkaloidal natural components.

Competing interest declaration

There is no potential competing interest related to this manuscript.

Grants

None.

Author contributions

None except listed.

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