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Tailored Synthesis of Skeletally Diverse *Stemona* Alkaloids through Chemoselective Dyotropic Rearrangements of β-Lactones

*Zhen Guo, Ruiyang Bao, Yuanhe Li, Yunshan Li, Jingyang Zhang, and Yefeng Tang**

Abstract: Collective synthesis of skeletally diverse *Stemona* alkaloids has been achieved, featuring tailored dyotropic rearrangements of β-lactones as key elements. Specifically, three typical 5/7/5 tricyclic skeletons associated with stemoamide, tuberostemospiroline and parvistemonine were first accessed through chemoselective alkyl-, hydrogen-, and aryl-migration dyotropic rearrangements of β-lactones, respectively. With rational manipulations of substrate structures and reaction conditions, these dyotropic rearrangements proceeded with excellent efficiency, good chemoselectivity and high stereospecificity. Furthermore, several polycyclic *Stemona* alkaloids including saxorumamide, isosaxorumamide, stemonine and bisdehydroneostemoninine were obtained from the aforementioned tricyclic skeletons through late-stage derivatizations. Along the total synthesis tour, a novel visible-light photoredox-catalyzed formal [3+2] cycloaddition was also developed, which offers a valuable tool for accessing oxaspirobutenolide and related scaffolds.

Introduction

Stemona alkaloids, primarily isolated from the *Stemonaceae* plants, constitute a salient class of natural products displaying remarkable structural and biological diversity.[1] So far, more than 200 *Stemona* alkaloids have been identified, which could be divided into eight groups based on Pilli's classification.[1b] Among them, stemoamide-type alkaloids arguably represent the largest one. Structurally, stemoamide-type alkaloids feature a 5/7/5 tricyclic core in which an oxygenated five-membered ring (C ring) is *trans*-fused to the pyrrolo[1,2-α]-azepine nucleus (A/B rings), as exemplified by stemoamide (**1**) (Figure 1).[2] Other representative members include saxorumamide (**2a**), isosaxorumamide (**2b**) and stemocochinin (**3**),[3] which bear one or two additional γ-lactone moieties on the A and C rings. Besides stemoamide-type alkaloids, there also exist another group of compounds displaying a characteristic 5/7/5 tricyclic framework, as shown in tuberostemospiroline (**4**),[4] croomine (**5**)[5] and dehydrocroomine (**6**).[6] Different from stemoamide-type alkaloids, their C ring is *spiro*-fused to the A/B ring system. Interestingly, in addition to the variation of ring-conjunction patterns, some *Stemona* alkaloids, such as parvistemonine A (**7**),[7] bisdehydroneostemoninine (**8**) and bisdehydrostemoninine (**9**),[8] feature a partially aromatized 5/7/5-fused tricyclic core, with their A ring existing in a form of pyrrole.

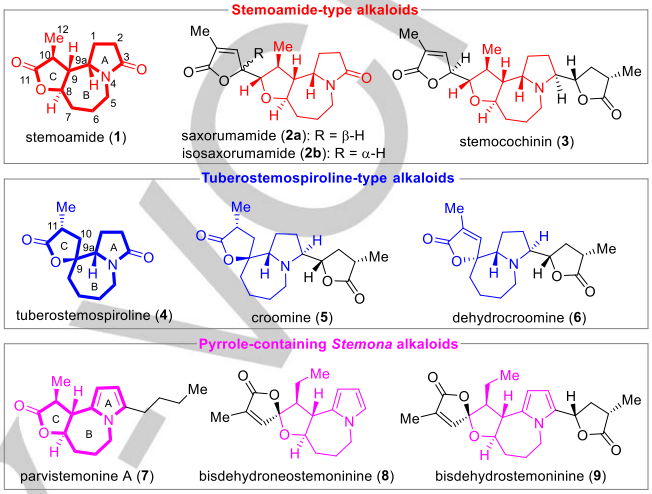

Figure 1. Representative *Stemona* alkaloids featuring 5/7/5 tricyclic cores.

Owing to their attractive molecular architectures and appealing biomedical potential, *Stemona* alkaloids have emerged as popular synthetic targets for decades.[1a,1b,9] Particularly, great effort has been devoted towards the synthesis of stemoamide-type alkaloids. Indeed, over 20 total syntheses of **1** have been completed so far, rendering it the most extensive explored target in this family.[10] Recently, significant progress has also been made on the synthesis of structurally more complicated polycyclic congeners. For instance, Chida, Sato and co-workers completed the collective synthesis of a series of tetra- or pentacyclic stemoamide-type alkaloids (e.g. **2a/b** and **3**) through chemoselective introduction of different γ-lactone moieties onto the tricyclic core of stemoamide.[11] Besides, Wang and co-workers reported the asymmetric synthesis of another two tetracyclic stemoamide-type alkaloids tuberostemoamide and sessilifoliamide.[12] Sharing considerable structural resemblance to stemoamide-type alkaloids, tuberostemospiroline-type alkaloids have also attracted considerable attention from synthesis community, with a series of seminal works completed by the Williams,[13] Martin,[14] Figueredo,[15] and Yang[16] groups. Comparably, the pyrrole-containing *Stemona* alkaloids have not succumbed to total synthesis until 2018 when the first total synthesis of bisdehydroneostemoninine (**8**) and bisdehydrostemoninine (**9**) was disclosed by Dai and co-workers.[17a] Later on, the Dai group also realized the late-stage conversion of some pyrrole-containing *Stemona* alkaloids into the corresponding γ-lactam-containing congeners.[17b]

Our interest in *Stemona* alkaloids was motivated by a long-term project directed towards the development of mechanistically interesting and practically useful dyotropic rearrangement of β-lactones.[18] Since its first discovery in the late of 1970s,[19] this unique reaction has been explored intermittently by different groups, mostly on a methodological level.[20] Despite a seemingly

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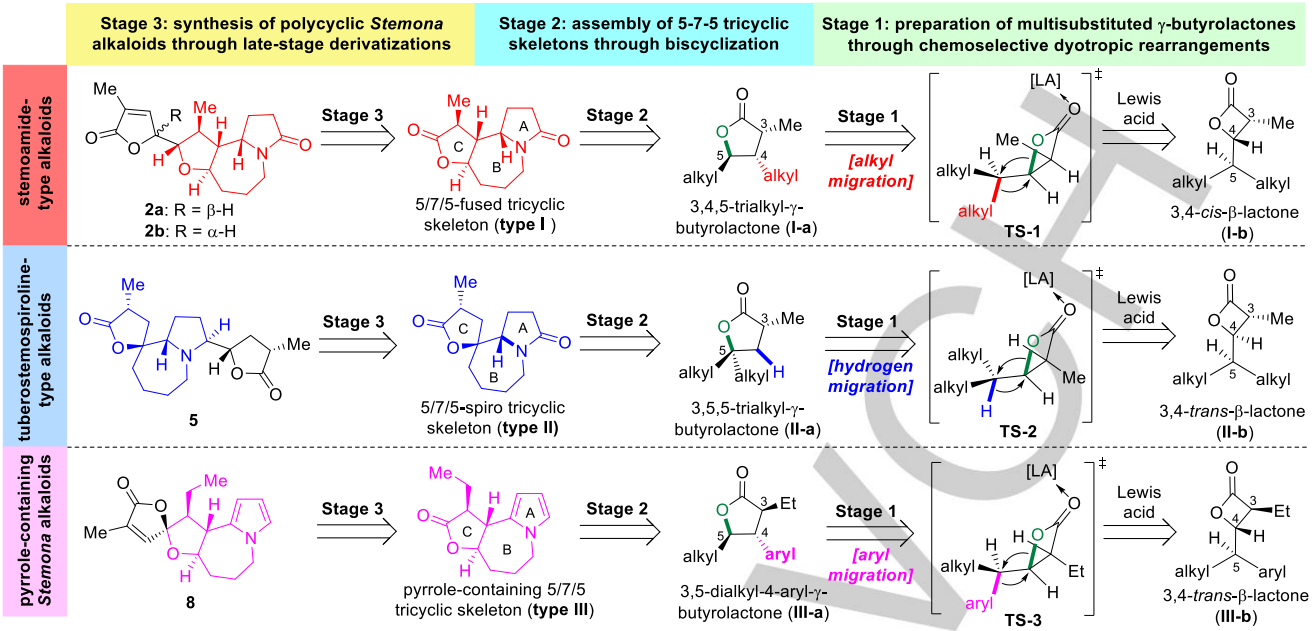

Scheme 1. Overall research plan for accessing skeletally diverse *Stemona* alkaloids through chemoselective dyotropic rearrangements of β-lactones.

useful method for the access of multisubstituted γ-butyrolactones, its synthetic potential has remained underdeveloped, particularly in natural product synthesis,[20o,20q] This is partially because its complicated reactivity and selectivity issues, which are largely dependent on substrate structures as well as reaction conditions, make it less predictable and controllable in practice. In recent years, our group has been striving to unearth the synthetic potential of this class of reactions.[21] For examples, in 2012 we reported a chemoselective and stereospecific dyotropic rearrangement using 3,4-*cis*-disubstituted β-lactones as substrates, which has been successfully applied to the collective synthesis of various xanthanolides.[21a] Very recently, we further extended dyotropic rearrangement to a new class of substrates, namely α-methylene-β-lactones, which provided an enabling method for the synthesis of α-methylene-γ-butyrolactone-containing natural products.[21c] Benefited from such experience, we recognized that both the reactivity and selectivity of dyotropic rearrangement of β-lactones could be rationally controlled by judicious manipulation of substrate structures and reaction conditions. Naturally, *Stemona* alkaloids caught our eyes since their molecular architectures are rich in multisubstituted γ-butyrolactone moieties and represent an ideal platform to showcase the great potential of chemoselective dyotropic rearrangements of β-lactones. Overall, our synthesis blueprint could be divided into three stages depicted in Scheme 1. We envisioned that most of the polycyclic *Stemona* alkaloids outlined in Figure 1 could be derived from three basic 5/7/5 tricyclic skeletons (type **I**-**III**) through late-stage derivatizations (stage 3). In turn, these tricyclic skeletons could be traced back to the corresponding precursors **Ia**-**IIIa** that equipped with the necessary functionalities for subsequent assembly of the A/B rings (stage 2). Furtherly disentangling the structures of **Ia**-**IIIa** suggested that their major differences stem from the substitution pattern and stereochemistry, which, we expected, could be ideally addressed through tailored dyotropic rearrangements of β-lactones in a predictable and controllable manner. Specifically, 3,4,5-trialkyl-γ-butyrolatone **I-a** could be obtained from 3,4-*cis*-disubstituted β-lactone **I-b** through an alkyl-migration dyotropic rearrangement. The prearrangement of C-3 and C-4 substituents in a *cis*-configuration warrants the reaction to proceed through the favorable transition state **TS-1** because it shows the minimal *syn*-pentane interaction between the C-3 Me and C-5 substitutes (Me → H vs Me → alkyl or allyl). As result, only the alkyl group displaying an anti-coplanar alignment with the C4-O1 bond will engage in migration to afford 3,4,5-trisubstituted γ–butyrolactone **I-a**. Moreover, the concerted and stereospecific nature of dyoptropic rearrangement would secure the *trans*-configuration of C-4 and C-5 substituents. For 3,5,5-trisalkyl-γ-butyrolatone **II-a**, a hydrogen-migration dyotropic rearrangement could be employed, which necessitates 3,4-*trans*-β-lactone **II-b** as the precursor. Compared to **I-b**, **II-b** shows a less conformational constraint along the C4-C5 single bond and thus the electronic instead of steric factor would play a crucial role in determining the reaction pathways. Since C-H bond generally has a higher σ orbital than C-C bond, hydrogen migration should take place preferentially through the transition state **TS-2**, thus resulting in 3,5,5-trisubstituted-γ-butyrolatone **II-a**. Finally, to access 3,5-dialkyl-4-aryl-γ-butyrolatone **IIIa**, we would like to utilize an aryl-migration dyotropic rearrangement that entails 5-aryl-3,4-*trans*-β-lactone **III-b** as the substrate. In this scenario, aryl migration should occur preferentially through **TS-3** due to its greater migration aptitude than hydrogen and alkyl groups.

Of note, although significant advances have been made on the total synthesis of *Stemona* alkaloids, there is still a lack of unified strategy enabling the facile access of all three groups of *Stemona* alkaloids outlined in Figure 1. In this article, we report a flexible and controllable strategy that can ideally meet this grand challenge. Hinging on three rationally designed tailored dyotropic rearrangements of β-lactones, the present work has culminated in the collective synthesis of a number of skeletally diverse *Stemona* alkaloids with high efficiency.

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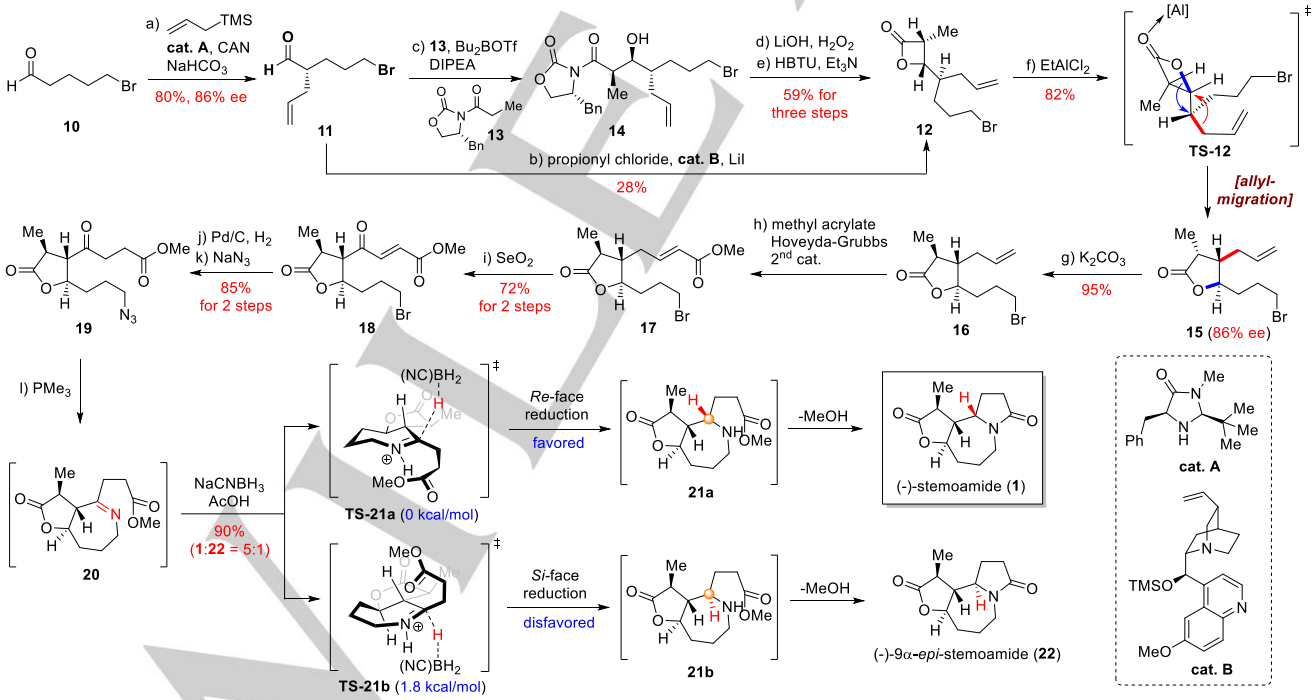
Results and Discussion

Synthesis of 5/7/5-fused tricyclic skeleton through alkyl-migration dyotropic rearrangement. Our study commenced from the synthesis of type I tricyclic skeleton associated with stemoamide (**1a**). Based on our design, a 3,4-cis-disubstituted β-lactone should be used as the precursor of alkyl-migration dyotropic rearrangement. For this end, chiral aldehyde **11** (80% yield, 85% ee) was prepared from **10** through MacMillan's asymmetric α-allylation of aldehyde via organo-SOMO catalysis.[22] With **11** in hand, we attempted to prepare 3,4-cis-β-lactone **12** through Nelson's cinchona alkaloid-catalyzed acyl halide-aldehyde cyclocondensation.[23] To our disappointment, while the reaction did work, the desired product was only obtained in a low yield. Further optimization failed to give a promising result.[24] Thus, a stepwise protocol was adopted to access **12**, featuring sequential Evans' asymmetric *syn*-aldol reaction[25] as the key step. Having **12** available in a scalable manner, we moved to explore the crucial dyotropic rearrangement. Delightfully, under the previously identified optimal conditions ($EtAlCl_2$, toluene),[21a] the reaction proceeded smoothly, leading to allyl-migration product **15** as a single diastereoisomer in 82% yield. No hydrogen- or alkyl-migration product was detected in the reaction. Moreover, the enantiopurity of **15** was also examined based on its derivative (for details, see Supporting Information), which turned out to be identical to that of compound **11**. Of note, since the stereochemistry of C-10 stereogenic center was opposite to that of natural target, it was inverted through a base-promoted epimerization. With 3,4,5-trialkyl-γ-butyrolatone **16** in hand, we then moved to assemble the remaining A/B rings. To this end, a cross-metathesis reaction followed by allylic oxidation was used to introduce the C9a-C3 side chain. Subsequently, hydrogenation of the C1=C2 double bond followed by the replacement of bromide with sodium azide led to the key precursor **19**. With all requisite functionalities set up, the A/B rings were constructed through a one-pot reaction involving Staudinger/aza-Wittig reaction, Borch reductive amination[26] and lactam formation, which gave (-)-stemoamide (**1**) and (-)-9a-*epi*-stemoamide[27] (**22**) in excellent combined yield (90%) and good diastereoselectivity (dr 5:1). To get deep insight into the stereochemical outcome of the transformation, we carried out a computational study to search for the optimal transition-state conformation for the Borch reduction. Conformational searches were carried out and the optimal transition states were located at PWPB95-D3/def2-QZVPP//PBE0/def-TZVP level with SMD solvation in reaction solvent. In the optimal transition state leading to **21a** (**TS-21a**), the seven-membered ring bears a chair-like conformation, in which the side-chain is folded towards the α-face, probably driven by an electrostatic-dominated interaction between the ester group and the iminium moiety. Thus, the reducing agent preferentially approaches the imine moiety from the *Re* face to give (-)-stemoamide. Comparably, for the optimal transition state leading to **21b** (**TS-21b**), the seven-membered ring needs to adopt a twisted-boat-like conformation with the side-chain disposed towards the β-face. Calculation shows that **TS-21b** has a higher Gibbs free energy than **TS-21a** (ΔG = 1.8 kcal/mol), which is in agreement with the experimental results.



Scheme 2. Total synthesis of (-)-stemoamide. Reagents and conditions: a) $NaHCO_3$ (1.5 equiv), CAN (2.5 equiv), **cat. A** (0.2 equiv), H_2O, DME, -70 °C; then allyltrimethylsilane (2.5 equiv), -20 °C, 8 h, 80%, 86% ee; b) propionyl chloride (4.0 equiv), LiI (2.5 equiv), **cat. B** (1.0 equiv), DIPEA (5.0 equiv), DCM, Et_2O, -40 °C, 10 h, 28%; c) **13** (1.0 equiv), Bu_2BOTf (1.1 equiv), DIPEA (1.2 equiv), DCM, -78 to 0 °C, 3 h, 84%; d) LiOH (1.6 equiv), H_2O_2, THF/H_2O (4/1), RT, 3 h, 95%; e) HBTU (1.2 equiv), Et_3N (4.0 equiv), DCM, RT, 16 h, 73%; f) $EtAlCl_2$ (2.0 equiv), toluene, 1 min, RT, 82%; g) K_2CO_3 (1.5 equiv), MeOH, 50 °C, 40 min, 95%; h) Hoveyda-Grubbs 2nd cat. (0.05 equiv), methyl acrylate (10.0 equiv), DCM, 10 h, 90%; i) SeO_2 (2.0 equiv), 1,4-dioxane, 90 °C, microwave, 1 h, 80%; j) Pd/C, H_2, THF, 1 h, RT, 95%; k) NaN_3 (2.0 equiv), DMF, 85°C, 90%; l) PMe_3 (1.1 equiv), THF; then $NaCNBH_3$ (2.0 equiv), MeCN, HOAc, 20 h, RT, 90%, dr. = 5:1. CAN = ceric ammonium nitrate, DME = dimethoxyethane, DIPEA = N,N-diisopropylethylamine, DCM = dichloromethane, HBTU = 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, DMF = N,N-dimethylformamide, THF = tetrahydrofuran.

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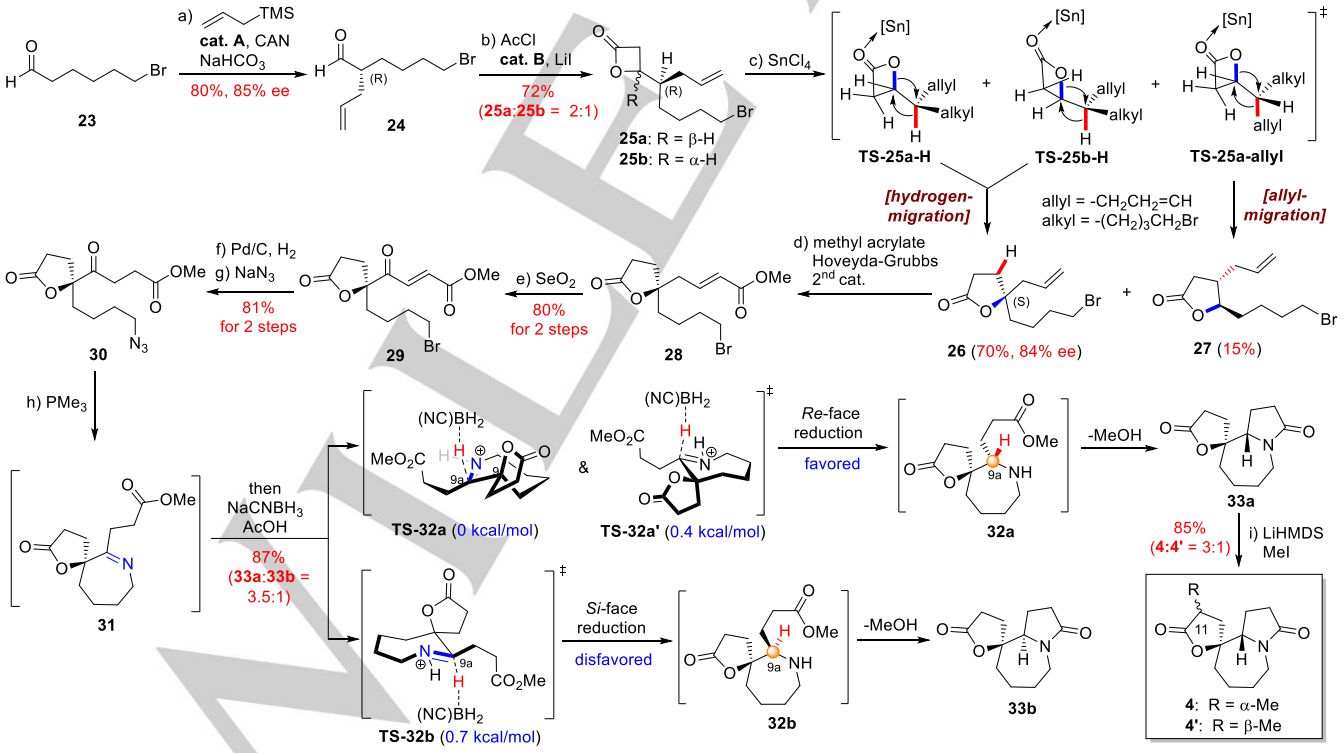
Synthesis of 5/7/5-spiro tricyclic skeleton through hydrogen-migration dyotropic rearrangement. This part of work also started from the preparation of chiral aldehyde **24** (80% yield, 85% ee) through MacMillan's asymmetric α-allylation reaction.[22a] To obtain the requisite 3,4-*trans*-β-lactone for hydrogen-migration dyotropic reaction, we first attempted the *trans*-selective asymmetric [2+2] cyclocondensation developed by Peters and co-workers.[28] However, the reaction did not work well for the substrate **24**, only resulting in a poor yield of the desired product (not shown). Thus, we turned to employ Nelson's cinchona alkaloid-catalyzed asymmetric [2+2] cyclocondensation reaction with acetyl chloride as a reactant partner,[23] which afforded β-lactones **25a** and **25b** as a pair of diastereoisomers (dr 2:1) in 72% combined yield. While the diastereoselectivity of the reaction appeared to be moderate, in theory, both of these diastereoisomers should lead to an identical product through hydrogen-migration dyotropic rearrangement. Therefore, we chose to directly use the mixtures of **25a/b** in the following step in practice. It turned out that the reaction did work with $EtAlCl_2$ as promoter. However, only a moderate yield (37%) of the desired product **26** was obtained, together with substantial amounts (17%) of allyl-migration product **27**. Apparently, in the absence of notable steric factor, the reaction pathways were mainly determined by the migration aptitude of C-5 substitutes. Although some previous studies[20a,21c] indicated that hydrogen displays a greater migratory capability than alkyl groups, allyl migration takes place as a competing reaction in the current scenario due to its increased migratory capability. To improve the selectivity of the reaction, we conducted an extensive condition optimization (for details, see Supporting Information). We found that the usage of relatively weak Lewis acids (e.g. $MgBr_2$, $SnCl_4$) and nonpolar solvents (e.g. toluene, pentane) had a beneficial effect on the selectivity. Pleasingly, an acceptable result was obtained with the combination of $SnCl_4$/pentane, which afforded **26** as the major product in 70% yield, together with a small amount of **27** (ca 15%). Moreover, it was found that **26** display nearly equal enantiopurity to that of compound **24** (for details, see Supporting Information). To get deep insight into the present dyotropic rearrangements, we also performed the reactions using the pure samples of **25a** or **25b**. As expected, under the optimal conditions both **the** reactions of **25a** and **25b** led to **26** as the major product. Differently, while substantial amounts of allyl-migration product **27** could be observed in the former reaction (**26**:**27** = 2.4:1), the latter one displayed a higher chemoselectivity (ca. 6:1), with only a tiny amount of the corresponding allyl-migration product detected. Having **26** in hand, the B/C rings were then constructed through the similar sequence applied for stemoamide (**1**). As shown, **26** underwent cross-metathesis reaction followed by allylic oxidation to give **29** in an excellent yield (80%). Reduction of the double bond of **29** followed by a SN2 substitution provided the key precursor **30**. Treatment of **30** with PMe_3 led to the formation of imine species **31**, which then underwent sequential imine reduction and lactam formation to yield **33a** and **33b** as a pair of diastereoisomers in an excellent yield (87%) and acceptable diastereoselectivity (dr 3.5:1). The diastereoselectivity of Borch reduction could also be rationalized by the calculation study performed by us. As shown, there are two optimal transition states (**TS-32a** and **TS-32a'**) that may lead to the formation of **32a**, both



Scheme 3. Total synthesis of (-)-tuberostemospiroline. Reagents and conditions: a) $NaHCO_3$ (1.5 equiv), CAN (2.5 equiv), **cat. A** (0.2 equiv), H_2O, DME, -70 °C; then allyltrimethylsilane (2.5 equiv), -20 °C, 8 h, 80%, 85% ee; b) acetyl chloride (4.0 equiv.), LiI (2.5 equiv.), **cat. B** (0.5 equiv.), DIPEA (5.0 equiv), DCM, Et_2O, -40 °C, 5 h, 72%; c) $SnCl_4$ (1.1 equiv.), pentane, 30 min, 70%; d) Hoveyda-Grubbs 2nd cat. (0.05 equiv), methyl acrylate (10.0 equiv), DCM, 10 h, 92%; e) SeO_2 (2.0 equiv), 4 Å molecular sieve, 1,4-dioxane, 150 °C, sealed tube, 5 h, 87%; f) Pd-C, H_2, EtOAc, 12 h, RT, 90%; g) NaN_3 (2.0 equiv), NaI (0.2 equiv), DMF, 85 °C, 1 h, 89%; h) PMe_3 (1.1 equiv), THF; then $NaCNBH_3$ (20.0 equiv), MeCN, HOAc, 20 h, RT, 87%, dr. = 3.5:1; i) LiHMDS (1.3 equiv), MeI (4.0 equiv), THF, -78 to -20 °C, 3 h, 64%. LiHMDS = lithium bis(trimethylsilyl)amide.

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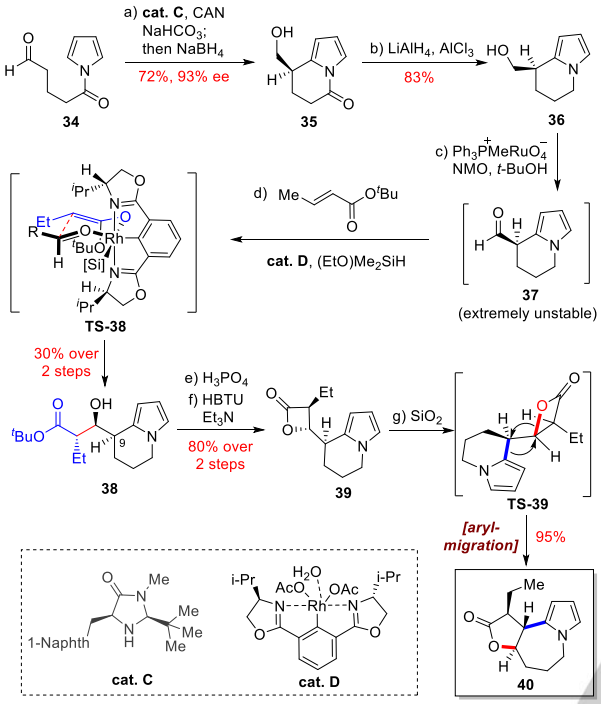
of which display lower Gibbs free energies than that one (**TS-32b**) associated with **32b** (for details, see SI). Finally, chemoselective α-methylation of **33a** afforded tuberostemospiroline (**4**) and its C-11 epimer (**4'**) in a combined yield of 85%, favoring the former as the major product (*dr* 3:1).[16]



Scheme 4. Synthesis of pyrrole-containing 5/7/5 tricyclic skeleton. Reagents and conditions: a) **cat. C** (0.2 equiv), $NaHCO_3$ (5.0 equiv), CAN (2.0 equiv), NaO_2CCF_3 (2.0 equiv), H_2O (1.0 equiv), DME, -78 to -30 °C, 24 h; then $NaBH_4$, 72%, 93% ee; b) $LiAlH_4$ (10.0 equiv), $AlCl_3$ (10.0 equiv), THF, 60 °C, 3 h, 83%; c) MTP3 (0.2 equiv), NMO (1.5equiv), *t*-BuOH (20.0 equiv), DCM, 5 min; d) *tert*-butyl crotonate (1.5 equiv), **cat. D** (0.01 equiv), $(EtO)Me_2SiH$ (1.6 equiv), toluene, 50 °C, 5 h, 30% over 2 steps; e) H_3PO_4, toluene, 6 h; f) HBTU (1.0 equiv), Et_3N (4.0 quiv), DCM, 16 h, 80% over 2 steps; g) silica gel, DCM, 30 min, 95%.

Synthesis of pyrrole-containing 5/7/5 tricyclic skeleton through aryl-migration dyotropic rearrangement. In this part of work, the known compound **36** was used as starting material, which could be readily prepared from **34** through two steps following the procedure reported by the MacMillan group.[22b] Albeit seemingly straightforward, the transformation from **36** to **37** turned out be rather challenging. Indeed, the reaction outcomes varied dramatically dependent on the reaction conditions and work-up procedure, mainly attributed to the fragile nature of the resulting product. After extensive tries, we found that the modified Ley-Griffith oxidation could serve this goal, with the commonly used *tetra-n*-propylammonium perruthenate (TPAP) replaced by methyltriphenylphoshonium perruthenate (MTP3).[29] Moreover, the usage of excess amounts of *t*-BuOH in the reaction was necessary in order to inhibit the erosion in enantiopurity of the resulting product. It is also noteworthy that **37** had to be used directly in the next step without chromatography or long-time storage. To make the desired 3,4-*trans*-β-lactone, a mild Rh-catalyzed anti-selective reductive aldol reaction[30] was employed, which delivered β-hydroxyester **38** as a major product in 30% overall yield over two steps, together with a small amount (ca 5%) of another unidentified product (most likely the C-9 epimer of **38**). The stereochemical outcome of the reductive aldol reaction could be rationalized by a Zimmerman-Traxler-type transition state (**TS-38**), in which the Rh-(*E*)-enolate species prefers to attack the Re face of the coordinating benzaldehyde (**37**) due to catalyst control. Subsequently, hydrolysis of **38** followed by lactonization gave 3,4-*trans*-β-lactone **39** in 80% yield over two steps. Serendipitously, we discovered that **39** readily advanced to a new spot on the TLC plate, which was determined to be tricyclic compound **40**. This discovery was interesting, since it indicated that the aryl-migration dyotropic rearrangement could occur in the absence of Lewis acid. To the best of our knowledge, this is the first example of Lewis-acid-free dyotropic rearrangement of β-lactone. We attributed this unique reactivity to the great migration capability of the electron-rich pyrrole ring. Based on this discovery, we conducted the dyotropic rearrangement with silica gel as promoter, which gave rise to **40** in a nearly quantitative yield (>95%). In this way, the enantioselective synthesis of pyrrole-containing tricyclic skeleton was achieved from the known compound **36** in a highly concise manner (5 steps and two chromatographic operations).

Synthesis of polycyclic stemona alkaloids through late-stage derivatizations. The facile access of three key 5/7/5 tricyclic skeletons of *Stemona* alkaloids paved the way to access those polycyclic congeners outlined in Figure 1. Strategically, these targets could be obtained from the corresponding tricyclic precursors through introducing one or two oxygenated five-membered rings (e.g. γ-butenolide or γ-butyrolactone) onto their A and C rings. As a proof-of-concept case, the total synthesis of saxorumamide (**2a**) and isosaxorumamide (**2b**) was first undertaken by us. Based on the inspiring work reported by Chida, Sato and co-workers,[11b] a one-pot reaction involving chemoselective reduction of the lactone moiety of **1** followed by $BF_3{\cdot}Et_2O$-mediated vinylogous Mukaiyama reaction with 2-siloxyfuran **42a** was adopted, which furnished four diastereoisomeric products without obvious diastereoselectivity. Fortunately, we found that direct treatment of the resulting mixture with DBU in toluene at 130 °C led to the formation of two natural products saxorumamide (**2a**) and isosaxorumamide (**2b**) in 30% and 37% isolated yields, respectively.[31] This result indicated that the unnatural diastereoisomers could convert to the thermodynamically more stable natural products through a base-promoted ring-opening/ring closing equilibrium (retro-1,6-/1,6-conjugation addition), with the bulky γ-butenolide moiety arranged in the opposite orientation of the adjacent C-10 methyl group.

In parallel, we also completed the total synthesis of another tetracyclic natural product stemonine (**47**). Strategically, key to the success of relied on the chemoselective functionalization of the lactam moiety of stemoamide (**1**). Inspired by the pioneering works reported by Huang and co-workers,[32] we first attempted to achieve this goal through a one-pot amide bond activation/vinylogous Mannich reaction. Thus, upon the treatment with Tf_2O/DTBMP, stemoamide (**1**) was converted to the Vilsmeier−Haack-type intermediate **44**, which then underwent vinylogous Mannich reaction with 2-siloxyfuran **42b** to give the tetracyclic compound **45** as a single isomer. Reduction of the C3=C18 double bond of **45** with $NaBH_3CN$/AcOH led to the formation of the desired products **46a** and **46b** in a moderate yield (ca. 40%, dr 1.2:1), together with some unidentified compounds. To improve the efficiency of the synthesis, an alternative protocol reported by the Chida/Sato group[11a] was also examined by us, hinging on an iridium-

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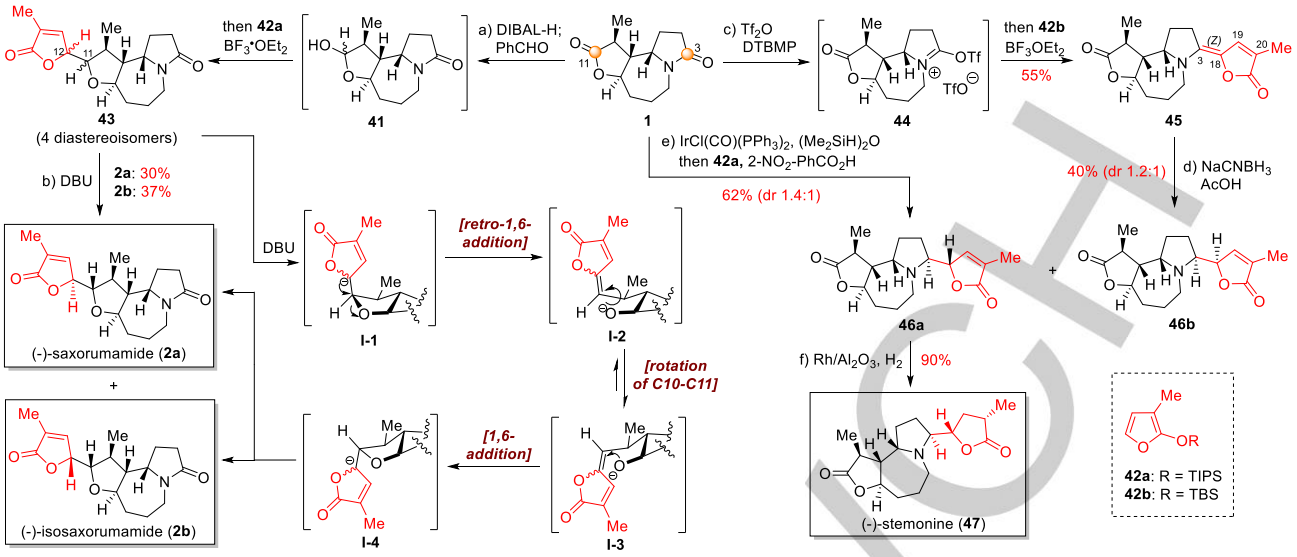
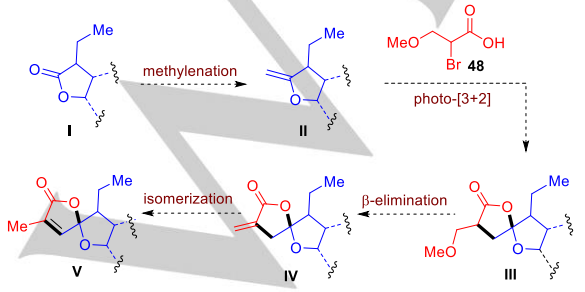


Scheme 5. Total synthesis of (-)-saxorumamide, (-)-isosaxorumamide and (-)-stemonine. Reagents and conditions: a) DIBAL-H (3.0 equiv.), DCM, -78 °C, 1 h; then PhCHO (2.1 equiv), **42a** (6.0 equiv), $BF_3{\cdot}OEt_2$ (4.0 equiv), -50 °C to RT, 24 h; b) DBU (2.0 equiv.), toluene, 130 °C, 12 h, **2a** (30%) + **2b** (37%); c) Tf_2O (1.5 equiv), DTBMP (1.5 equiv), DCE, 0 °C, 2 min; **42b** (4.0 equiv), 0 °C ,10 h, 55%; d) $NaCNBH_3$ (3.0 equiv), AcOH (10.0 equiv), DCM, 0 °C, 6 h, 40% (**46a/b**, dr 1.2:1); e) $IrCl(CO)(PPh_3)_2$ (0.01 equiv), $(Me_2SiH)_2O$ (1.5 equiv), toluene, RT, 1 h; **42a** (3 equiv), 2-NO_2-$PhCO_2H$ (5 equiv), CH_3CN, 24 h, 62% (dr 1.4:1); f) Rh/Al_2O_3, H_2, EtOH, 3 h, 90%.

catalyzed amide-bond reductive nucleophilic addition reaction[33]. The reaction worked smoothly, affording **46a** and **46b** in an improved yield and diastereoselectivity (62%, dr 1.4:1). Finally, hydrogenation of the C19=C20 double bond of **46a**[11a] furnished stemonine (**47**) as a single diastereoisomer in 90% yield.

At the end of the present work, the total synthesis of bisdehydroneostemoninine (**8**) was undertaken by us. Structurally, the C/D rings of **8** features a unique 5/5-oxaspirobutenolide motif.[34] Initially, we planned to construct this structural motif through the sequence depicted in Scheme 6. Thus, alkyl enol ether **II**, readily accessible from lactone **I** through methylenation, could engage in an atom transfer radical addition[35] with 2-bromo-3-methoxy propionic acid (**48**), thus resulting in 5/5-oxaspirolactone **III**. After a base-promoted β-elemination followed by isomerization, **III** could convert into the desired 5/5-oxaspirobutenolide motif **V**.

Guided by this design, we first conducted a model study using **48** and 2-ethoxypropene (**49a**) as reaction pairs (Table 1). At first, the reaction was conducted under the conditions reported by Curran and co-workers.[35a] As shown, while the reaction did work, only a low yield of the γ-butyrolactone **50a** was isolated (entry 1, Table 1). To improve the reaction, a series of bases and solvents were evaluated, among which the best result was obtained with

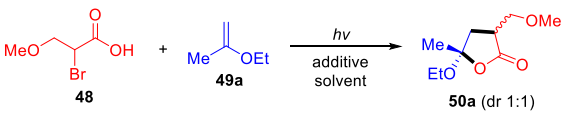


Scheme 6. Proposed strategy for synthesis of the 5/5-oxaspirobutenolide motif of bisdehydroneostemoninine.

the combination of DIPEA and acetone (entry 4), which furnished **50a** in 42% yield. Given that visible-light photoredox-catalyzed [3+2] cycloaddition of alkene and α-halogenated acid has also been well established recently,[36] we turned to perform the reaction using photoredox catalyst. After a simple evaluation of the reaction parameters (entries 6-9), we found that the transformation worked well in DMF with $Ru(bpy)_3Cl_2$ as photocatalyst and blue LED as light resource, which delivered **50a** in an excellent yield of 83%.

Encouraged by the result of model study, we moved to apply the photoredox-catalyzed formal [3+2] cycloaddition to the synthesis of bisdehydroneostemoninine (**8**). To this end, tricyclic compound **40** was first converted to enol ether **51** through Petasis methylenation.[37] Subsequently, the photoredox catalyzed-[3+2] cycloaddition of **51** with **48** was conducted under the optimal conditions, which afforded two pairs of

Table 1. Model study of the formal [3+2] cycloaddition[a]



entry	light resource	base	catalyst	solvent	yield of **50a**[b]
1	254nm	Et_3N	---	benzene	21%
2	254nm	Et_3N	---	acetone	31%
3	254nm	Et_3N	---	MeCN	25%
4	254nm	DIPEA	---	acetone	42%
5	254nm	DABCO	---	acetone	22%
6[c]	blue LED	DIPEA	$Ru(bpy)_3Cl_2$	DMF	50%
7	blue LED	DIPEA	$Ru(bpy)_3Cl_2$	DMF	83%[d]
8	blue LED	DIPEA	*fac*-Ir(ppy)$_3$	DMF	79%
9	blue LED	DIPEA	thioxanthone	DMF	11%

[a]Reaction conditions: **49a** (1.0 equiv.), **48** (10 equiv.), and base (12.0 equiv.) in DMF, 4-24 h. [b] Yield determined by ^1H NMR with mesitylene as an internal standard. [c] **49a** (1.0 equiv.), **48** (10 equiv.), and base (5.0 equiv.). [d] Yield of the isolated product.

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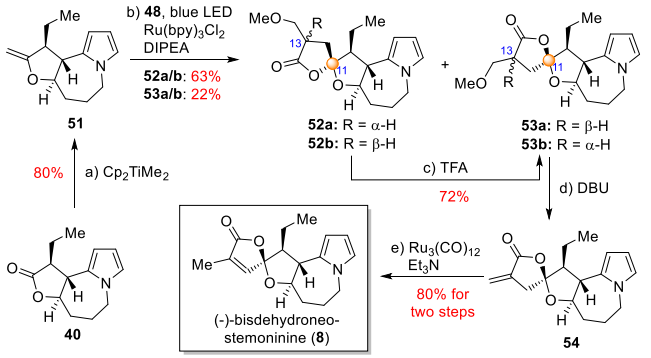


Scheme 7. Total synthesis of (-)-bisdehydroneostemoninine. Reagents and conditions: a) Cp_2TiMe_2 (2.5 equiv), toluene, 105 °C, 2h, 80%; b) blue LED lamp, $Ru(bpy)_3Cl_2$ (0.01equiv), **48** (10.0 equiv), DIPEA (12.0 equiv), DMF, 24 h, 63% (**52a/b**) and 22% (**53a/b**); c) TFA (1.0 equiv), DCM, 10 min, 72%; d) DBU (1.5 equiv), toluene, DCM, 120 °C, 24 h; e) $Ru_3(CO)_{12}$ (0.1 equiv), Et_3N (1.1 equiv), dioxane, 100 °C, 1 h, 80% over 2 steps.

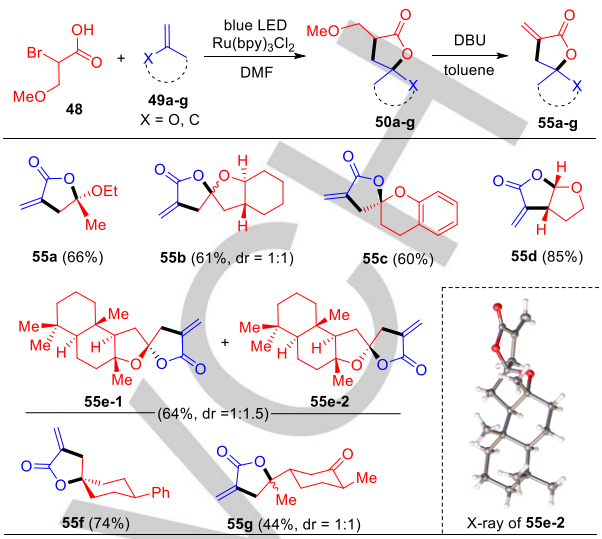
diastereoisomeric oxaspirolactones **52a/b** and **53a/b** in 63% and 22% yields, respectively (for a full rationalization of the stereochemical outcome of this transformation, see Supporting Information). While **52a/b** bear incorrect stereochemistry at the C-11 position, we were pleased to find that they could convert to **53a/b** through an acid-facilitated ring-opening/ring-closing equilibrium, indicating the latter products are thermodynamically more stable. This assumption was substantiated by a calculation study which showed that both **53a** and **53b** bear lower Gibbs free energies than **52a** and **52b**, respectively. Finally, **53a/b** could convert to bisdehydroneostemoninine (**8**) through a base-promoted β-elimination followed by Ru_3-$(CO)_{12}$-catalyzed double isomerization.[17a]

Scope of the visible-light photoredox-catalyzed [3+2]-cycloaddition. Beyond its application to the above-mentioned specific substrate, we also evaluated the generality of the newly developed visible-light photoredox-catalyzed formal [3+2]-cycloaddition with a variety of other alkene components. To simply the synthesis, we conducted the photocycloaddition and β-elimination consecutively, without isolating the intermediates. As shown, all of the examined enol ethers (**49a–e**) worked well with the reactions, affording α-methylene-γ-butyrolactones (**55a-e**) in good to excellent overall yields.[38] Moreover, 1,1-dialkylsubstituted alkenes (e.g. **49f** and **49g**) also turned out to be amenable to the reactions, as witnessed in the cases leading to **55f** and **55g**. Given that α-methylene-γ-butyrolactones represent a highly important class of structural element in natural products and pharmaceutical agents,[39] we anticipate that this photocycloaddition may find widespread application in organic synthesis and medicinal chemistry.

Conclusion

In summary, we have completed the collective synthesis of a series of *Stemona* alkaloids including stemoamide, tuberostemospiroline, saxorumamide, isosaxorumamide, stemonine and bisdehydroneostemoninine. Key to our success relies on the tailored synthesis of three typical 5/7/5 tricyclic skeletons of *Stemona* alkaloids through a unified strategy hinging on the chemoselective hydrogen-, alkyl-, and aryl-migration dyotropic rearrangements of β-lactones. The present work shows that the versatile reactivities of dyotropic rearrangements of β-lactones, combined with sophisticate manipulation of substrate structures and reaction conditions, could be utilized to access skeletally diverse natural products in a predictable and controllable manner. While such great potential has been largely underestimated over the past decades, we hope that the present work could stimulate more research interest on this old but venerable reaction.

Table 2. Application of the formal [3+2] cycloaddition for the synthesis of α-methylene-γ-lactones[a],[b],[c]



[a]Reaction conditions: **49a-g** (1.0 equiv.), **48** (10.0 equiv.) DIPEA (12.0 equiv.) in DMF, blue LED; then DBU (1.5 equiv.) in toluene; [b]yield of the isolated product; [c]d.r. value was determined by ^{1}H NMR.

Acknowledgements

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Keywords: natural product • total synthesis • alkaloid • dyotropic rearrangement • photoredox catalyst

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[38] CCDC 2064037 (**55e-2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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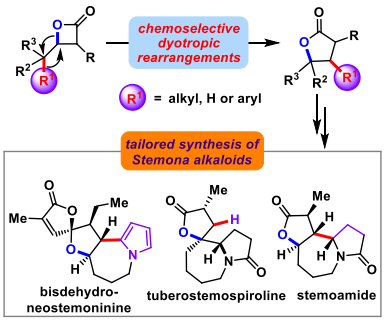
RESEARCH ARTICLE

Entry for the Table of Contents

Three types of multisubstituted chiral γ-butyrolactones have been constructed in a predictable and controllable manner through chemoselective alkyl-, hydrogen-, and aryl-migration dyotropic rearrangements of β-lactones, which paves the way to the tailored synthesis of a series of skeletally diverse *Stemona* alkaloids with high efficiency.



*Zhen Guo, Ruiyang Bao, Yuanhe Li, Yunshan Li, Jingyang Zhang, and Yefeng Tang**

Page No. – Page No.
Tailored Synthesis of Skeletally Diverse *Stemona* Alkaloids through Chemoselective Dyotropic Rearrangements of β-Lactones