Natural Product Synthesis

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Enantioselective Formal Total Syntheses of Didehydrostemofoline and Isodidehydrostemofoline through a Catalytic Dipolar Cycloaddition Cascade**

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Plants of the *Stemonacea* family, which are indigenous to a number of areas in Southeast Asia, have long been used in traditional oriental medicine for treating a variety of ailments.[1] Extraction of the roots and leaves of these plants have yielded a number of biologically active alkaloids that have been targets of many synthetic investigations.[2] Arguably the most complex members of the *Stemona* alkaloids are those belonging to the stemofoline family, which are characterized by a densely functionalized, caged hexacyclic architecture and differ in the geometry of the C11–C12 double bond and the oxidation state of the butyl side chain at C3 (Figure 1). These alkaloids, which were first reported by Irie and co-workers in 1970[3] and later isolated from other *Stemona* species,[4–6] exhibit strong insecticidal activity because they act as insect acetylcholine receptor antagonists.[7] Didehydrostemofoline (**1**) is not only the most potent acetylcholine receptor antagonist,[8] but it also exhibits in vivo anti-oxytocin activity as well as antitumor activity against gastric carcinoma.[4,9] A recent study has shown that stemofoline (**2**) increases the sensitivity of anticancer drugs such as vinblastine, paclitaxel, and doxorubicin by reversal of P-glycoprotein mediated multi-drug resistance.[10] A number of semisynthetic analogs of these alkaloids have been prepared and found to exhibit acetylcholinesterase inhibitory activity.[8,11]

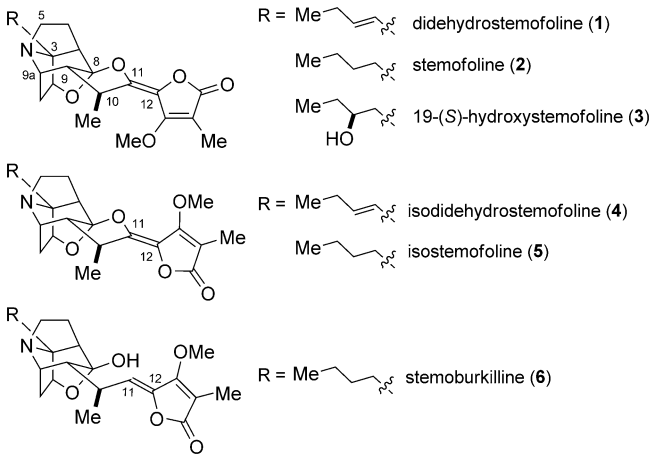

Figure 1. The stemofoline family of natural products.

Because of their complex polycyclic structures and their biological activities, there has been considerable interest in the synthesis of the stemofoline alkaloids. Despite these efforts,[12,13] the only total syntheses are Kende's synthesis of (±)-isostemofoline (**5**) in 1999[14] and Overman's syntheses of (±)-**1** and (±)-**4** in 2003.[15] Each of the Kende and the Overman strategies relied upon clever cascade processes to construct the bridged polycyclic core of these alkaloids. However, because neither of these approaches is enantioselective, we queried whether we might be able to achieve an enantioselective synthesis of selected members of the stemofoline alkaloids using a single, enantiomerically pure starting material as the sole source of chirality.

Examination of the structures of didehydrostemofoline (**1**) and isodidehydrostemofoline (**4**) reveals a bicyclic γ-ylidenetetronate moiety that is fused to a tetracyclic, cage-like framework. The problem of creating this array was solved by Overman by coupling **7** with **8** (Scheme 1), followed by two additional operations to furnish an intermediate diol that was subjected to a Corey–Winter olefination to give a mixture of (±)-**1** and (±)-**4**.[15] Given that the synthesis of **8** would thus represent formal syntheses of **1** and **4**, we were attracted by the prospect that we might be able to prepare **8** through an approach that featured an intramolecular [3+2] cycloaddition of an azomethine ylide. Indeed, we had previously demonstrated that such reactions can be used to create the tricyclic core of the stemofoline alkaloids, but we had encountered difficulties with either poor regioselectivity in the cycloaddition or with refunctionalizing the cycloadduct in ways that might lead to **8**.[13] These studies, however, did suggest that the presence of an electron-withdrawing group at C5 and a protected alcohol at C8 (didehydrostemofoline numbering) on an azomethine ylide such as **10** would preferentially afford the cycloadduct **9**. We envisioned that **10** might be generated in situ from the diazo imine **11**, which in turn would be accessible from commercially available 2-deoxy-D-ribose (**12**). Herein, we report the enantioselective formal syntheses of **1** and **4** by using an intramolecular dipolar cycloaddition cascade as a key step to rapidly assemble the tricyclic core.

The synthesis commenced with transforming **12** through a one-pot Wittig olefination and iodination sequence to give

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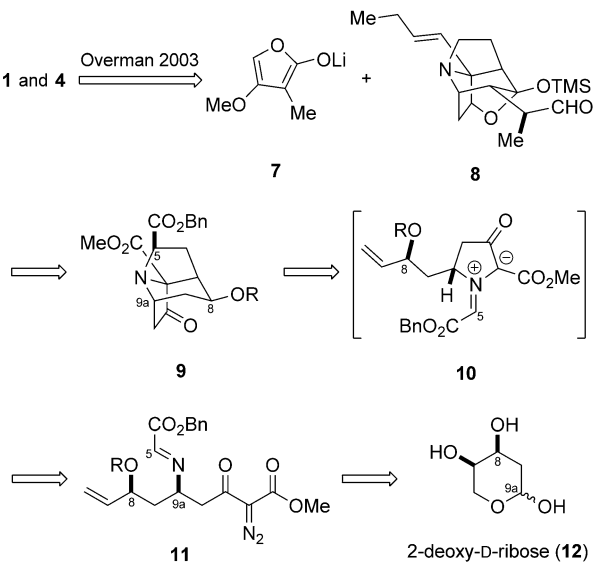
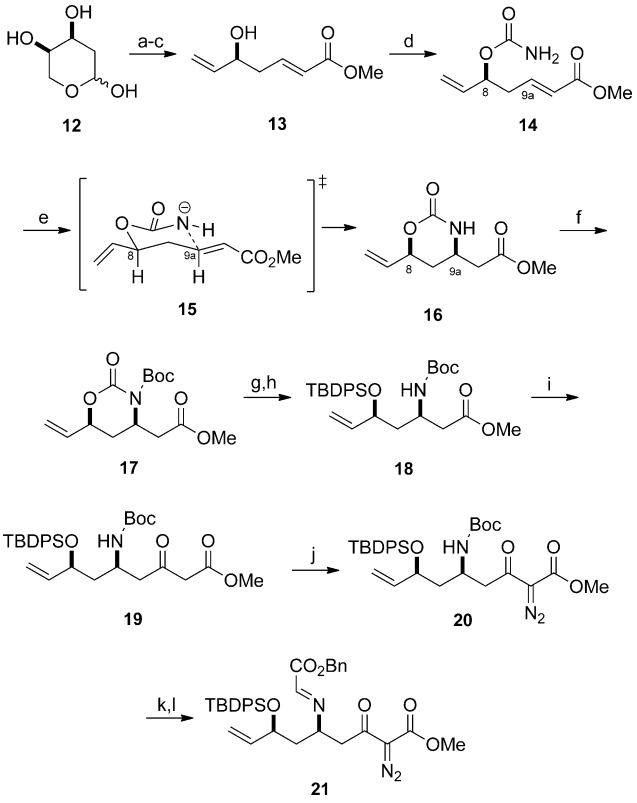


Scheme 1. Retrosynthesis of didehydrostemofoline and isodidehydrostemofoline. TMS = trimethylsilyl, Bn = benzyl.



Scheme 2. Synthesis of cycloaddition precursor **21**. Reagents and conditions: a) Ph_3PCHCO_2Me, THF, reflux; I_2, Ph_3P, imidazole; b) Ac_2O, pyridine, DMAP, CH_2Cl_2, 87% (two steps); c) Zn granules, MeOH, reflux, 62%; d) $ClSO_2NCO$, CH_2Cl_2; H_2O, 99%; e) NaH, CH_2Cl_2, −10°C, 80% (d.r. = 8:1 *cis*:*trans*); f) Boc_2O, NEt_3, DMAP, CH_2Cl_2, 87%; g) Cs_2CO_3, MeOH; h) TBDPS-Cl, imidazole, DMAP, CH_2Cl_2, 80% (two steps); i) $MeCO_2Me$, NaHMDS, THF, −78°C to −10°C, 75% (+ 17% recovered **18**); j) *p*-ABSA, NEt_3, MeCN, 92%; k) TFA, CH_2Cl_2; l) BnO_2CCHO, NEt_3, 4 Å MS, CH_2Cl_2, 99% (two steps). DMAP = 4-dimethylaminopyridine, Boc = *tert*-butoxycarbonyl, TBDPS = *tert*-butyl diphenylsilyl, NaHMDS = sodium hexamethyldisilazide, *p*-ABSA = *p*-acetamidobenzenesulfonyl azide, TFA = trifluoroacetic acid.

an intermediate iodo diol that was not isolated but was acetylated directly to give an iodo bis-acetate. This compound was then treated immediately with zinc granules in refluxing methanol to effect both a Boord elimination and a transesterification to furnish the allylic alcohol **13** in 54% overall yield from **12** (Scheme 2).[16] The physical nature of zinc metal used to induce the Boord elimination was important, as zinc dust led to a lower yield (46% vs. 62%). The optimized process for synthesizing **13** did not require chromatographic purification of any intermediate and was easily executed on > 100 g scale. The allylic alcohol **13** was then converted into carbamate **14** in quantitative yield, thereby setting the stage for a key Hirama–Ito cyclization,[17] which transferred the chirality at C8 to C9a preferentially through the transition state **15** to give the key intermediate **16** as the major product. When this reaction was performed in THF using NaH as the base at room temperature, **16** was isolated in 75% yield and moderate diastereoselectivity (d.r. ≈ 4:1). However, when the reaction was conducted in CH_2Cl_2 at −10°C, **16** was isolated in 80% yield and improved diastereoselectivity (d.r. ≈ 8:1).

The cyclic carbamate **16** was transformed into the imide **17**, which underwent regioselective, methoxide-induced cleavage to give an intermediate alcohol that was protected as the silyl ether **18**. The subsequent Claisen condensation of **18** with the sodium enolate of methyl acetate provided the β-ketoester **19** in 75% yield together with recovered **18** (ca. 17%). When the corresponding lithium enolate was employed, the Claisen reaction proceeded to give **19** in significantly lower yields (35–60%). β-Ketoester **19** was then converted into the diazo-β-ketoester **20** by using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) as the diazo transfer reagent. Acid-induced deprotection of **20** with trifluoroacetic acid gave an ammonium salt that was condensed in situ with benzyl glyoxylate; subsequent removal of the solvent under reduced pressure gave the crude diazo imine **21**, which was contaminated with an approximately equimolar amount of TFA·NEt_3 (^{1}H NMR spectrum) and several minor impurities.

Having thus prepared **21**, we were anxious to determine whether it might be induced to undergo the much anticipated cascade of reactions to deliver the tricyclic core of the stemofoline alkaloids as depicted in Scheme 1. Some support for the possible efficacy of this conversion is found in previous work of Padwa et al.,[18] although a sequence in which all reactions proceed through an intramolecular manifold is unprecedented. Owing to our zeal to quickly put our plan to the test, we used the crude diazo imine **21** in initial experiments. As will become evident, this was a most fortuitous decision. In the event, crude **21** was heated in refluxing xylenes in the presence of $Rh_2(OAc)_4$ (3 mol%) to give the desired azatricycle **22** in 75% yield as a single regioisomer and stereoisomer (Scheme 3). We quickly learned, however, that this reaction sequence was considerably more complex than we had initially envisioned. Namely, in an effort to improve the yield of this pivotal cascade process, the imine **21** was purified by column chromatography using basic alumina to remove TFA·NEt_3 and the other minor impurities. Surprisingly, when pure **21** was heated in refluxing xylenes

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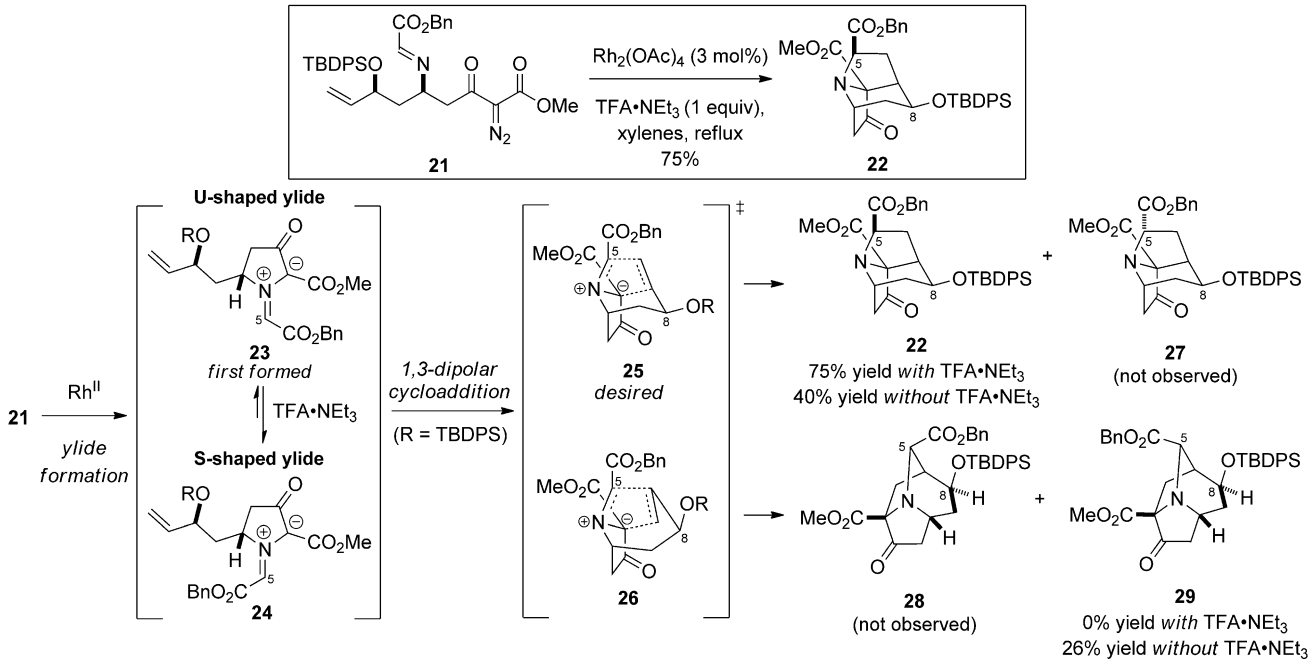

Scheme 3. Rhodium-catalyzed diastereoselective dipolar cycloaddition cascade and mechanistic rationale for the observed selectivity.

in the presence of $Rh_2(OAc)_4$ (3 mol%), a mixture (1.5:1) of the regioisomers **22** and **29** was obtained in 66% combined yield.

The divergent results obtained with crude and purified **21** beg an explanation. We envision that the rhodium carbene formed upon diazo decomposition of **21**, which presumably has the imine stereochemistry shown, undergoes cyclization to generate the U-shaped azomethine ylide **23**. This intermediate may then either undergo dipolar cycloaddition or isomerization, which appears to be accelerated by the presence of a weak acid, to form the more stable S-shaped azomethine ylide **24**. The two regioisomeric transition states for the cycloaddition of **23** and **24** are depicted by **25** and **26**, wherein the stereochemistry at C5 in **25** and **26** is dictated by the stereochemistry at C5 in **23** or **24**. The dipolar cycloaddition of **23** through transition state **25** will furnish **27**, which was not detected, whereas cycloaddition of **23** through transition state **26** will provide **29**, which was only isolated when the reaction was conducted in the absence of acid. The cycloaddition of the diastereomeric azomethine ylide **24** through transition state **25** generates the desired adduct **22**, whereas cycloaddition of **24** by the regioisomeric transition state **26** will give **28**, which was not observed. Examination of transition-state models reveals that those leading to **27** and **28** are much more hindered than those leading to **22** and **29**. In the presence of acid, it thus appears that isomerization of **23** to **24** is more facile than the cyclization of **23** through the slightly less favorable transition state shown in **26** to give **29**. This remarkably efficient cascade reaction is notable because the tricyclic core of the stemofoline alkaloids is generated with high stereoselectivity and regioselectivity in a single chemical operation from an acyclic precursor.

Having thus generated the key tricyclic intermediate **22**, the stage was set to complete the formal syntheses of **1** and **4** (Scheme 4). Stereoselective hydride reduction of the ketone moiety in **22** delivered the requisite *endo*-alcohol, which was subsequently protected as MOM ether **30**. Hydrogenolysis of the benzyl ester **31** afforded the amino acid, which was subjected directly to a modified Barton decarboxylation protocol using $CHCl_3$ as the solvent to give **31** in 63% yield from **30**.[19] The butenyl side chain was then introduced by DIBAL-H reduction of **31**, followed by a Julia–Kocienski olefination[20] of the intermediate aldehyde **32** to furnish **33**. TBAF-mediated removal of the TBDPS group from **33** and subsequent Parikh–Doering oxidation[21] of the secondary alcohol thus formed afforded ketone **34**. The alkylation of the enolate derived from **34** with ICH_2CO_2Et provided the axial-alkylated product **35**. Base-mediated epimerization of **35** provided the equatorially substituted product, which was treated with TFA to effect deprotection of the MOM group and furnish the hemiketal **36** in 29% overall yield from **31**. The spectral data of synthetic **36** thus obtained are consistent with those reported by Overman et al. for racemic **36** that was subsequently elaborated into didehydrostemofoline (**1**) and isodidehydrostemofoline (**4**).[15] Accordingly, preparation of enantiomerically pure **36** completes the formal enantioselective syntheses of **1** and **4**. It also completes enantioselective syntheses of stemofoline (**2**) and stemoburkilline (**6**) because these two compounds were recently prepared from **1** by semisynthesis.[6b]

In summary, the tricyclic compound **36**, a key intermediate in Overman's elegant synthesis of didehydrostemofoline (**1**) and isodidehydrostemofoline (**4**), has been prepared in enantiomerically pure form, thereby completing the first enantioselective approach to these alkaloids. Inasmuch as **1** has also been transformed into other stemofoline alkaloids,[6b] this accomplishment also constitutes a formal synthesis of many other members of the stemofoline family of natural products. The synthesis begins with commercially available 2-deoxy-D-ribose and features a novel cascade of

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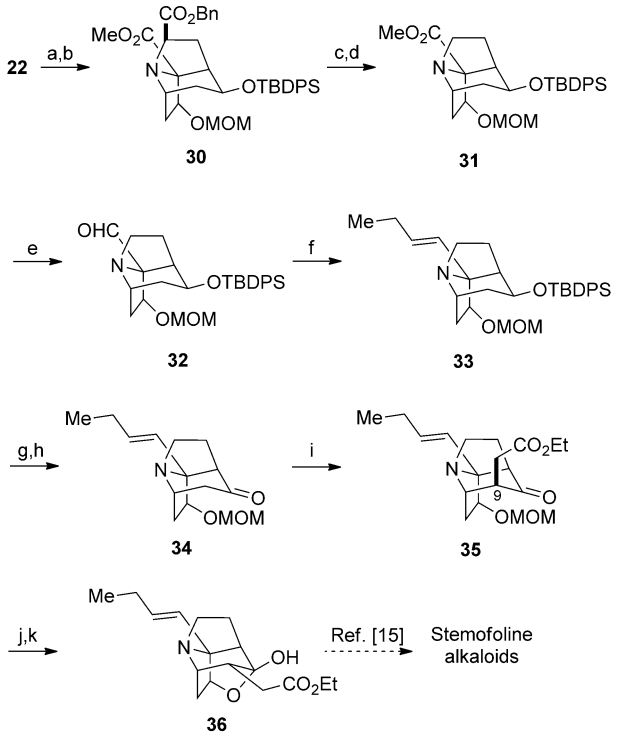

Scheme 4. Completion of the formal total synthesis. Reagents and conditions: a) $NaBH_4$, MeOH, −30 °C; b) MOM-Cl, NE*t*Pr_2, DMF, 50 °C, 75% (two steps); c) Pd/C, H_2, EtOH; d) 2-mercaptopyridine-*N*-oxide, DCC, DMAP, *t*BuSH, $CHCl_3$, *hν* (250 W tungsten), 63% (two steps); e) DIBAL-H, CH_2Cl_2, −78 °C, 90%; f) Ph-N_4CSO_2-*n*Pr, KHMDS, DME, −55 °C, 89%; g) TBAF, THF, 50 °C, 95%; h) SO_3·py, NEt_3, DMSO, CH_2Cl_2, 77%; i) LDA, ICH_2CO_2Et, THF, −10 °C, 62%; j) DBU, toluene, 130 °C; k) TFA, CH_2Cl_2, 81% (two steps). MOM = methoxymethyl, DMF = *N*,*N*-dimethylformamide, DCC = dicyclohexylcarbodiimide, DIBAL-H = diisobutylaluminum hydride, KHMDS = potassium hexamethyldisilazide, DME = dimethoxyethane, TBAF = tetrabutylammonium fluoride, DMSO = dimethylsulfoxide, LDA = lithium diisopropylamide, DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene.

reactions that culminates in the intramolecular dipolar cycloaddition of an acyclic diazo imine intermediate to form the cage-like, tricyclic core of the stemofoline alkaloids. Further applications of similar cascade reactions to complex molecule synthesis are in progress as is the use of **22** as an intermediate in even shorter routes to the stemofoline alkaloids. The results of these investigations will be reported in due course.

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