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Asymmetric formal total synthesis of the stemofoline alkaloids: the evolution, development, and application of a catalytic dipolar cycloaddition cascade

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ABSTRACT

A formal synthesis of didehydrostemofoline and isodidehydrostemofoline has been accomplished by preparing an intermediate in the Overman synthesis of these alkaloids from commercially available 2-deoxy-D-ribose. The work presented in this account chronicles the evolution of our explorations to identify the optimal steric and electronic control elements necessary to generate the tricyclic core structure of these alkaloids in a single operation from an acyclic precursor. The key step in the synthesis is a novel dipolar cycloaddition cascade sequence that is initiated by cyclization of a rhodium-derived carbene onto the nitrogen atom of a proximal imine group to generate an azomethine ylide that then undergoes spontaneous cyclization via dipolar cycloaddition. The synthesis features several other interesting reactions, including a Boord elimination to prepare a chiral allylic alcohol, a highly diastereoselective Hirama–Itô cyclization, and a useful modification of the Barton decarboxylation protocol.

1. Introduction

1.1. Isolation and biological activity

The *Stemonacea* family is a small group of flowering plants native to various regions of Southeast Asia.[1] Herbal extracts from a variety of these plants have been used for centuries as pesticidal agents and to treat respiratory diseases. These plant extracts have yielded a number of biologically active alkaloids that have been the focus of extensive biological and medical research.[2] Arguably the most complex members of the *Stemona* family of alkaloids are those of the stemofoline family, which are characterized by a caged hexacyclic architecture and differ in the geometry of the C(11)–C(12) double bond and the oxidation state of the four-carbon side chain R (Fig. 1). Three species of the *Stemona* genus (*Stemona tuberosa*, *Stemona japonica*, and *Stemona sessilifolia*) are officially listed in the modern edition of the Pharmacopoeia of the People's Republic of China as herbal antitussive agents, and the ground up roots of these plants are still sold in local markets and herb shops for medicinal and agricultural purposes.[1] Owing to the similar appearance of many of the *Stemona* species and their visual similarities to plants belonging to other genera, the incorrect common

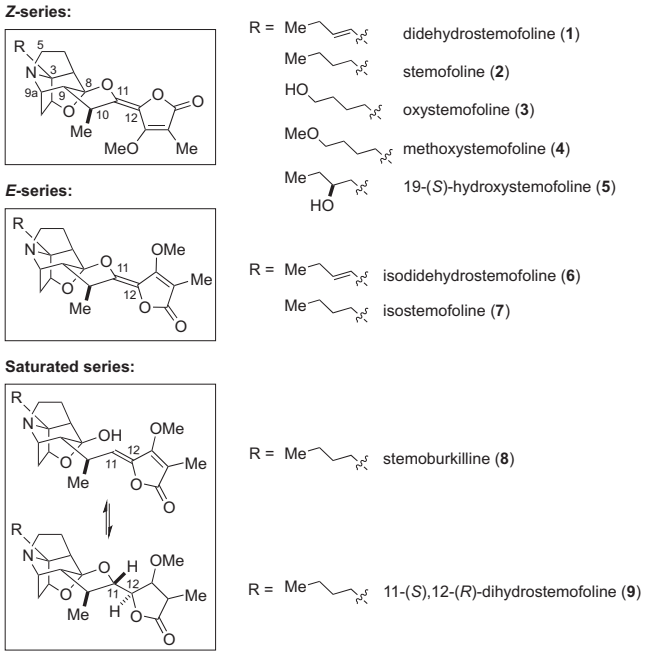

Fig. 1. The stemofoline alkaloids.

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names are often used at these markets to sell plants that do not contain the active principles found in the *Stemona* species. Accordingly, one must be vigilant when studying or using the plant materials for medical or research applications. In fact, didehydrostemofoline (**1**) was first erroneously reported to be isolated from *Asparagus racemosus* and originally named asparagamine A.[3] The roots of *A. racemosus*, which are also sold as an herbal antitussive remedy, bear a striking resemblance to the roots of the *Stemona* plants, thereby giving rise to an early suspicion that **1** actually originated from a *Stemona* plant. Corroborating this hypothesis, **1** was later isolated from *Stemona collinsae*,[4] and a recent report confirmed that **1** is not present in *A. racemosus* altogether.[5]

The stemofoline alkaloids were first isolated by Irie and coworkers from *S. japonica*,[6] and they were later isolated from other *Stemona* species.[7] Many of these alkaloids exhibit strong insecticidal activity because of their activity as insect acetylcholine (AChE) receptor antagonists.[8] In a recent screen for AChE inhibitory activity, didehydrostemofoline (**1**) was found to be among the most potent of the stemofoline alkaloids.[9] Didehydrostemofoline also exhibits in vivo anti-oxytocin activity and antitumor activity against gastric carcinoma,[4,10] whereas stemofoline (**2**) has been shown to be effective at increasing the sensitivity of clinically used anticancer drugs such as paclitaxel, vinblastine, and doxorubicin by reversing P-glycoprotein mediated multi-drug resistance.[11] Continued interest in these alkaloids is reflected in more recent work in which a number of semisynthetic analogs were prepared and found to possess potent AChE inhibitory activity.[9,12]

The complex molecular architecture coupled with the diverse biological activities of these alkaloids has inspired considerable interest from the synthetic community.[1,13,14] However, despite considerable effort, the only two accounts of the total syntheses of these alkaloids are Kende's synthesis of (±)-isostemofoline (**7**)[15] and Overman's syntheses of (±)-**1** and (±)-**6**.[16] Other interesting approaches toward these alkaloids have also been reported.[13] For example, Thomas applied an intramolecular Mannich reaction to construct the skeleton of stemofoline (**2**),[13d,e] and Gin prepared the core structure of stemofoline by a novel process that featured an intramolecular dipolar cycloaddition.[13a,e]

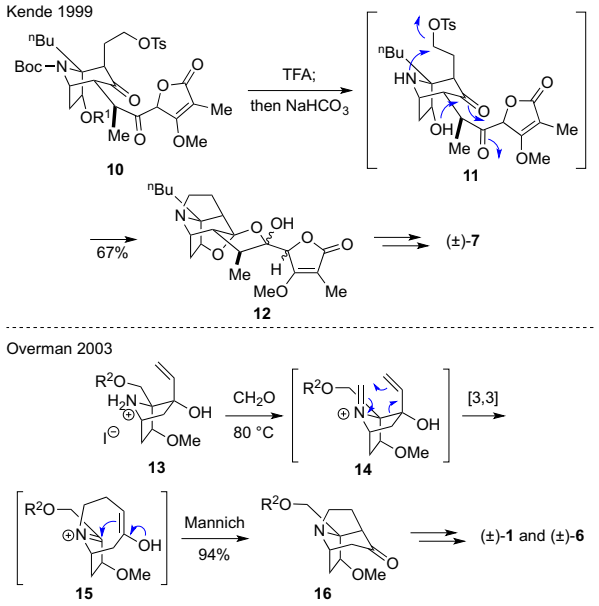
1.2. Total syntheses of the stemofoline alkaloids

Both the Overman and Kende approaches to the stemofoline alkaloids relied upon the use of impressive cascade processes to construct the bridged polycyclic core (Scheme 1). In Kende's synthesis of (±)-isostemofoline (**7**),[15] the core structure was constructed at an advanced stage by a sequence that was initiated by treating the azabicycle **10** with TFA to effect MOM and BOC-deprotection and liberate the intermediate aminoalcohol **11**, which spontaneously collapsed to the pentacyclic amine **12**. The Overman approach[16] to racemic **1** and **6** relied on the use of their prototypal aza-Cope–Mannich methodology in which **13** was heated with paraformaldehyde to generate the iminium ion **14**, which underwent an aza-Cope reaction to give **15** that cyclized via an intramolecular Mannich reaction to deliver the tricycle **16**.

Although the Kende and Overman syntheses set a high bar for the construction of the stemofoline core, the completed total syntheses were long requiring >30 steps. Furthermore, neither of these total syntheses was enantioselective. We thus believed that there was considerable opportunity to develop new chemistry that would lead to the first enantioselective syntheses of the *Stemofoline* alkaloids by a shorter sequence of reactions.

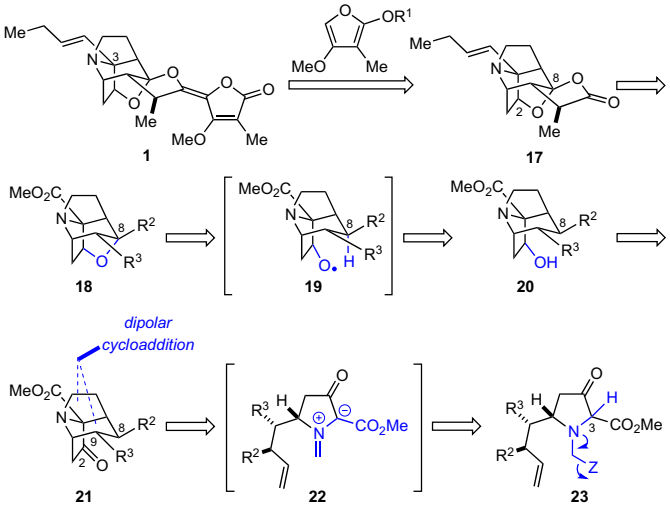
1.3. Initial planning

Members of the *Stemona* alkaloids have long been a focus of attention in our group because of the many challenges associated



Scheme 1. Prior approaches to the stemofoline core as applied to total synthesis (R^1=MOM, R^2=TIPS).

with fabricating the polycyclic cores of these naturally occurring bases. Our first introduction to these alkaloids resulted in an extraordinarily concise synthesis of croomine[17] using sequential vinylogous Mannich reactions.[18] We were similarly intrigued by the obvious challenges associated with developing short, enantioselective syntheses of representative members of the even more complex stemofoline group. Although the details of our plans to access these alkaloids have progressed through a number of iterations, the critical elements of our approach have remained the same (Scheme 2). In our original plan, we envisioned that the lactone **17** would serve as a key intermediate, and a number of tactics were envisioned for its conversion into didehydrostemofoline (**1**). A key step in producing **17** would involve the remote functionalization of the C(8)-position by a hydroxy radical **19** at C(2)[19] that would be derived from the *endo*-alcohol **20** by reaction with hypervalent iodine as prescribed by seminal work from Suárez.[20] Alcohol **20** would be derived from the stereoselective reduction of ketone **21** by attack of a hydride reagent from the least hindered face of the ketone. The critical disconnection in the overall strategy, however, involved forming the tricyclic core of the stemofoline alkaloids by the intramolecular 1,3-dipolar cycloaddition of an olefinic

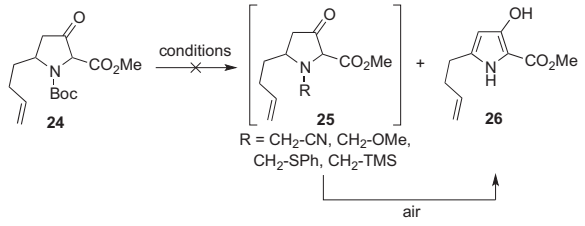


Scheme 2. Novel 1,3-dipolar cycloaddition approach to stemofoline core.

azomethine ylide of the general form **22**. The key challenge was to identify an azomethine ylide **22** that was suitably substituted so it would undergo a highly regioselective dipolar cycloaddition to give **21** (Scheme 2). However, the path to identifying the optimal azomethine ylide **22** and its precursor **23** was fraught with unanticipated pitfalls. It was necessary to prepare and investigate several functionalized pyrrolidine derivatives **23** having various alkyl and heteroatom substituents at R^2 and R^3 and a number of different Z groups. The precise nature of the azomethine ylide precursor **23** therefore underwent a series of iterations that were guided by an evolving understanding of this cycloaddition.

1.4. First generation approach

We first envisioned that the azomethine ylide **22** might be generated by expelling the leaving group Z from pyrrolidinone **23**, followed by deprotonation of the resulting iminium ion (Scheme 2). In order to test the feasibility of this plan, we used pyrrolidinone **24** as a model to screen conditions for azomethine ylide formation (Scheme 3). However, our efforts were quickly derailed when we discovered that all attempts to replace the Boc-protecting group of **24** with a variety of functionalized methylene groups gave the pyrrole **26** as the only identifiable product.



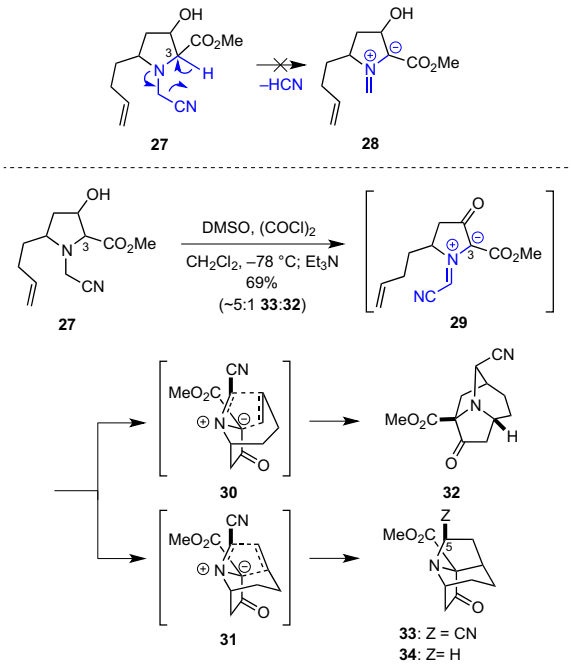
Scheme 3. Initial attempts to form precursors of azomethine ylides.

We reasoned that the enol form of **25** (R=H) underwent rapid and unavoidable oxidation, so we decided to reduce the ketone moiety in **24** to obviate any possibility of enolization during the process of refunctionalizing the nitrogen atom. In the event, **24** was reduced, and the requisite α-amino nitrile moiety was installed by removing the Boc-protecting group and subjecting the intermediate secondary amine to a Strecker reaction to provide **27** (Scheme 4). As we had predicted, the amino nitrile **27** did not undergo aromatization to a pyrrole, but all attempts to convert **27** into the corresponding azomethine ylide **28** by the net loss of HCN were unsuccessful.

Generation of an azomethine ylide **28** from **27** requires ionization by loss of cyanide ion and the proton at C(3) (Scheme 4). We thus queried whether azomethine ylide generation might be facilitated by increasing the acidity of this proton by oxidation of the alcohol moiety. Accordingly, **27** was oxidized by a Swern oxidation with careful exclusion of oxygen to avoid pyrrole formation. Much to our surprise, we isolated a mixture (ca. 5:1) of cycloadducts **33** and **32** in 69% combined yield; *both of these cycloadducts retained cyano group*.[14a,21] We believe this unusual transformation involved formation of the cyano-azomethine ylide **29** that then underwent cycloaddition by the two regioisomeric transition states **30** and **31** to furnish **32** and **33**, respectively. Although this reaction sequence provided compelling support for the viability of our approach to the stemofoline core, we were unable to decyanate **33** to provide **34**. We were thus obliged to modify the strategy in order to access a tricyclic intermediate without the superfluous functionality at C(5).

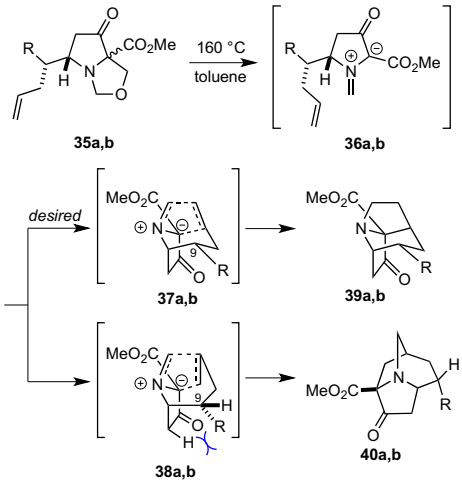
1.5. Second generation approach

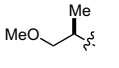
Our second approach (Scheme 5) was inspired by work reported by Joucla,[22] who had shown that flash vacuum thermolysis of



Scheme 4. Discovery of oxidative azomethine ylide formation.

oxazolidines generated azomethine ylides that underwent dipolar cycloadditions with olefinic partners. We thus discovered that heating the oxazolidine **35a** in a sealed tube gave a mixture (1:3) of the regioisomeric cycloadducts **39a** and **40a** in 96% combined yield,[21] presumably via the corresponding transition states **37a** and **38a** (Scheme 5). Although the yield of this transformation was high, the undesired regioisomer **40a** was favored. As a possible tactic to enhance formation of the desired regiochemistry in the cycloaddition, we explored the possibility that the undesired transition state **38b** might be destabilized by the presence of a bulky substituent R at C(9). In order to test this hypothesis, **35b** was prepared and subjected to thermolysis to provide a slightly more favorable mixture (1:1) of cycloadducts **39b** and **40b** in 95% yield.[21]



Entry	R	Yield (%) (39:40)
a	H	96 (1:3)
b		95 (1:1)

Scheme 5. Effect of steric factors on dipolar cycloaddition.

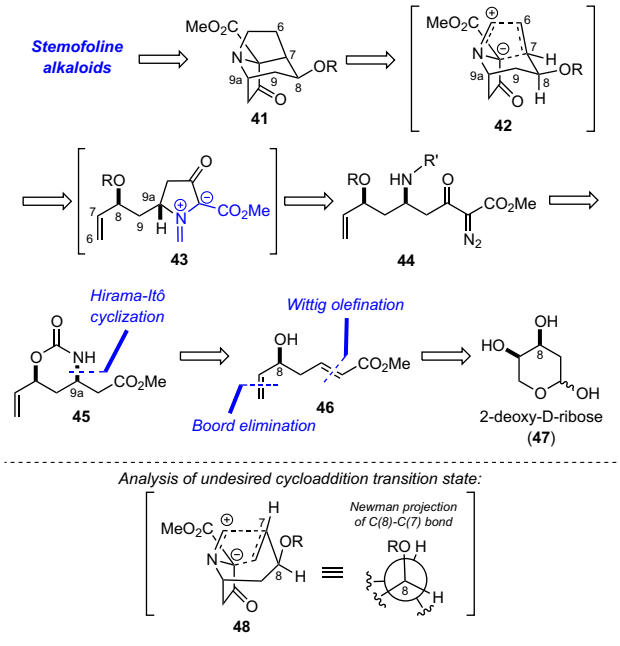
The results of the cycloadditions of the azomethine ylides **36a** and **36b** validated our hypothesis that steric effects can be exploited to favorably affect the regiochemical course of the cycloaddition. The modest increase in selectivity that was observed, however, was insufficient for the purpose of a total synthesis. Accordingly, we continued our search to identify what structural modifications to the azomethine ylide precursor were required to further enhance the selectivity.

2. Results and discussion

2.1. Development of a new synthetic plan

Our early work established the underlying viability of the key cycloaddition strategy for constructing the core of the stemofoline alkaloids.[14a,b] It also provided some direction as to how steric and electronic parameters influenced the regioselectivity of the cycloaddition. An important goal in refining our approach was to enable an enantioselective synthesis of the tricyclic core utilizing a starting material from the 'chiral pool' as the sole source of chirality. Remaining stereocenters would be introduced by diastereoselective transformations that would be subject to substrate-controlled reactions. We reasoned that such a strategy would likely increase the overall efficiency of the synthesis by decreasing the number of synthetic operations and the need for using multiple stoichiometric chiral auxiliaries that characterized our initial efforts.

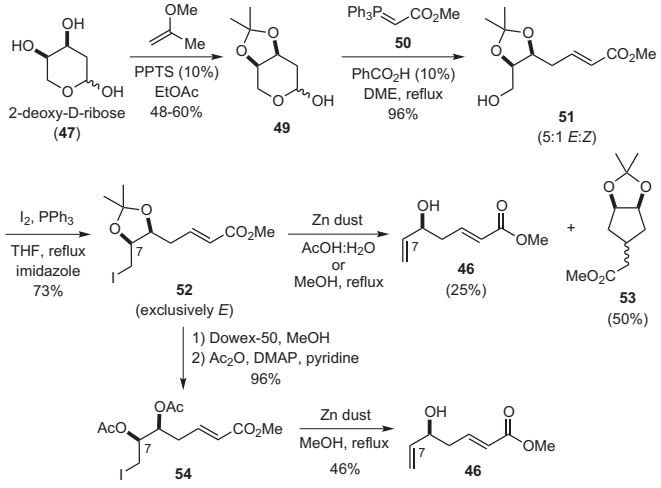
Toward this end, we viewed commercially available 2-deoxy-D-ribose (**47**) as a suitable starting material because it possesses the resident chirality, and it contains five of the nine carbon atoms found in the tricyclic core of the stemofoline alkaloids. The essential features of our new strategy are outlined in retrosynthetic format in Scheme 6. The first stage of the synthesis would thus involve converting 2-deoxy-D-ribose into the allylic alcohol **46** utilizing sequential Wittig olefination and Boord elimination reactions. The chirality of the allylic alcohol at C(8) would then be exploited to stereoselectively establish the amino functionality at C(9a) to provide **45** via a diastereoselective, intramolecular aza-Michael reaction. Elaboration of **45** via a Claisen condensation followed by diazo transfer and refunctionalization of the aminoalcohol leads to **44**, the immediate precursor of the azomethine ylide **43**. The critical question was whether the presence of a protected hydroxyl group at C(8) would disfavor the transition state **48** leading to the undesired regioisomer and preferentially deliver **41** via transition state **42**.



Scheme 6. Revised retrosynthesis of didehydrostemofoline.

2.2. 2-Deoxy-D-ribose as a chiral starting material for allylic alcohol 46

There was some precedent for preparing the allylic alcohol **46** from 2-deoxy-D-ribose (**47**),[23] but **46** had only been isolated as a byproduct of another process. A reliable means for preparing **46** had thus not appeared in the prior art. Accordingly, we sought to develop a concise and effective process to synthesize **46**. The first generation route to **46** commenced with protecting 2-deoxy-D-ribose (**47**) by treatment with 2-methoxypropene in the presence of PPTS to give acetonide **49** (Scheme 7).[24] In order to obtain reproducible yields, it was necessary to perform the reaction at a concentration of 0.3 M rather than at 0.8 M as described in the literature; however, the product was always accompanied by the formation (>20%) of the protected furanoside (five-membered, α and β) forms of the sugar, which were separated by chromatography. The protected hemiacetal **49** was then subjected to a Wittig olefination to provide enoate **51** as an *E*/*Z*-mixture (5:1) of olefin isomers in 96% yield. We had previously shown that use of a tri-*n*-butylphosphine derived Wittig reagent enhanced the diastereoselectivity in related olefinations,[25] and application of this modification to **49** afforded a markedly improved *E*/*Z*-ratio of ~9:1. The disadvantage of this procedure is that the requisite Wittig reagent is more expensive.

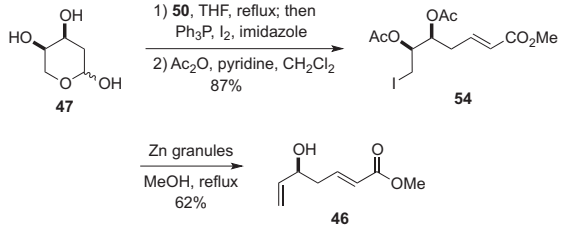


Scheme 7. Initial synthetic efforts to prepare **46**.

It was also known that molecular iodine can catalyze the thermodynamic equilibrations of enones and enoates.[26] Because the next step in the sequence would involve the use of iodine to convert the primary alcohol into an iodide, we queried whether the presence of an excess of iodine might effect concomitant epimerization of the undesired *Z*-enoate. In the event, reaction of a *E*/*Z*-mixture (5:1) of **51** with triphenylphosphine and a 10 mol % excess of iodine provided exclusively the *E*-iodoenoate **52** in 73% yield. Upon treatment with activated Zn (dust)/AcOH, compound **52** underwent facile Boord elimination[27] to give a mixture (1:2) of the desired allylic alcohol **46** and the cyclopentane **53** in a combined 75% yield. Although samarium iodide mediated radical cyclizations of substrates like **52** to give cyclopentanes such as **53** are known,[23] the reaction of zinc metal with **52** was expected to give predominately the elimination product **46** rather than **53**.

This route to the alcohol **46** thus proceeded in 10% overall yield from 2-deoxy-D-ribose by a sequence that required four synthetic steps and four chromatographic purifications. However, there are some obvious deficiencies, and we set to the task of developing a more efficient process. Toward this end, we reasoned that the yield of the Boord elimination might be improved by refunctionalizing the diol to increase the leaving group ability of the secondary alcohol at C(7), thereby favoring elimination over cyclization (Scheme 7). Acetonide **52** was thus converted into iodo diacetate **54** in 96% yield by sequential treatment with Dowex/MeOH and acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP). When the iodide **54** was treated with Zn (dust) in methanol, the ratio of elimination to cyclization improved, and the alcohol **46**, which was formed by transesterification under the reaction conditions, was isolated in 46% yield. This alternate route provided **46** in a slightly improved 16% overall yield, but six synthetic operations and four chromatographic purifications were now required. However, a key discovery was that the Boord elimination could be improved by enhancing the leaving group ability of the oxygen function at C(7).

In the interest of further streamlining the synthesis of **46**, the diol protection strategy was more closely scrutinized. Because unprotected 2-deoxy-D-ribose (**47**) was known to undergo olefination,[28] it was first allowed to react with Wittig reagent **50**, and the resulting mixture of enoates was treated directly with Ph_3P/I_2 to effect iodination (Scheme 8). The reaction was subjected to an aqueous workup, and the crude mixture of iodo diols was acetylated to provide the iodo diacetate **54** in 87% over two steps. Although **54** could be readily purified by chromatography, simple filtration through a plug of silica gel provided material that was sufficiently pure for the next step. After additional experimentation to optimize the Boord elimination, we discovered that the yield of product was improved significantly by the use of Zn granules rather than Zn dust. Under these modified conditions, the allylic alcohol **46** was formed in 62% yield.

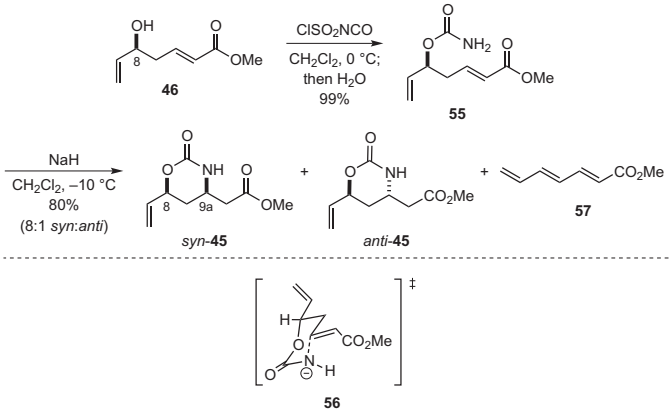


Scheme 8. Optimized synthesis of **46** (three steps, one column, 54% overall yield).

This result is somewhat surprising because there is no apparent reason that the *physical state* of the Zn metal should so drastically affect the product distribution. On the other hand, the presence of trace metal impurities in the Zn dust might catalyze the conjugate addition, thereby placing importance on the source and purity of the zinc metal. However, the assay on the batches of Zn dust and Zn granules that were used did not reveal any differences in impurity profiles. This uncertainty notwithstanding, it was possible to perform this reaction reproducibly on scales up to 100 g. We were now able to prepare **46** in 54% overall yield by a process that required three chemical operations and only one chromatographic purification.

2.3. Application of Hirama–Itô cyclization

With an efficient and scalable route to the allylic alcohol **46**, we were positioned to probe the efficacy of the Hirama–Itô cyclization,[29] which involves an intramolecular Michael addition of *O*-tethered carbamates to α,β-unsaturated carbonyl compounds. The allylic alcohol **46** was first treated with chlorosulfonylisocyanate to give the primary carbamate **55** in nearly quantitative yield after a hydrolytic workup (Scheme 9). Reaction of **55** with NaH in THF at room temperature gave the cyclic carbamate **45** as a mixture (4:1) of *syn*- and *anti*-diastereomers in 75% yield via the preferred transition state **56** in which the vinyl group resided in an equatorial orientation. This experiment clearly established that the stereochemistry at C(8) could be exploited in a substrate-controlled reaction to create the stereocenter at C(9a). Despite this swift success, it was apparent that further experimentation would be needed to improve the diastereoselectivity of this intramolecular aza-Michael reaction. Toward this goal, the work of Hirama and Itô offered little encouragement because results of those studies suggested that varying reaction parameters would not likely have a significant impact upon the yield and diastereoselectivities of the process. Undaunted, we discovered that a number of variables impacted the yield and diastereoselectivity of this specific conversion.



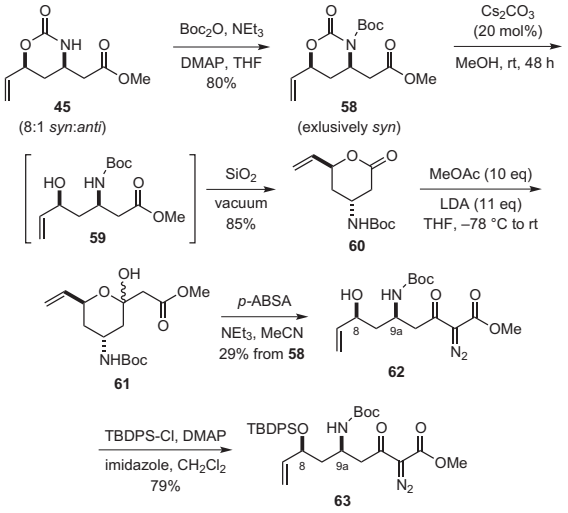
Scheme 9. Application of the Hirama–Itô cyclization reaction.

Although not reported by Hirama and Itô, the elimination product **57** often accounted for 10–20% of the product mixture upon cyclization of **55** (Scheme 9). We discovered that the extent of this elimination increased when more polar solvents were employed, and the use of DMF provided as much as 20% of **57**. The use of NaH in THF did not provide appreciable conversion at temperatures of 0 °C or below, but when CH_2Cl_2 was used as the solvent, the reaction was complete within 2 h at −10 °C with only trace amounts of **57** being formed. We examined the effects of changing the cationic counterion and found that more Lewis acidic counterions led to increasing amounts of elimination, but the Lewis acidities had no influence on the diastereoselectivity. For example, the use of KO*t*-Bu in THF at −20 °C gave nearly 20% of **57**; however, the use of LiO*t*-Bu under the same conditions provided the triene **57** almost exclusively. Varying the temperature of the reaction had little effect on the amount of elimination, but the diastereoselectivity was sensitive to changes in temperature. For example, at temperatures below −20 °C, the use of freshly sublimed KO*t*-Bu in THF gave a mixture (10:1) of *syn*- and *anti*-**45** in 78% yield. When the reaction was performed at −10 °C using NaH as the base in CH_2Cl_2, a slightly less favorable mixture (8:1) of *syn*- and *anti*-**45** was obtained in 80% yield. However, under these conditions the reaction mixture was contaminated with fewer impurities, and the desired **45** could be readily isolated by a single recrystallization as an inseparable mixture (8:1) of diastereomers. Accordingly, these conditions were adopted as the standard for preparing **45**.

2.4. Elaboration of 45 to precursor of the cycloaddition

The next stage of the synthesis involved converting **45** into an orthogonally protected aminoalcohol of the general form **44**

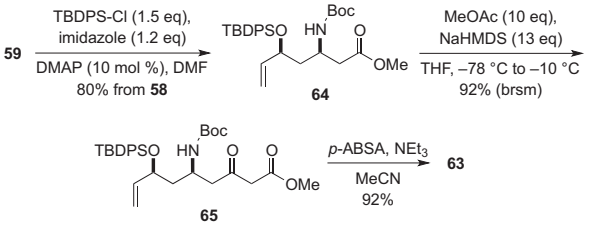
(Scheme 6) that bore the required diazo-β-ketoester moiety, and several approaches were examined. Carbamates such as **45** are known to be difficult to cleave directly, but the corresponding *N*-acyl derivatives can be readily opened by nucleophilic attack. Accordingly, the carbamate moiety in **45** was activated by N-acylation, and the *syn* Boc-carbamate **58** thus obtained underwent facile methanolysis using Cs_2CO_3/MeOH to deliver the amino-alcohol **59** (Scheme 10). Although **59** could be isolated in relatively pure form, we found that it cyclized readily to give the lactone **60** on attempted purification and thus decided to test **60** as an intermediate. Toward this end, it was necessary to optimize the conversion of **59** into **60**, and we found that this was most conveniently achieved by adsorbing crude **59** onto dry silica gel, followed by column chromatography to provide lactone **60** in 80% yield from **58**.



Scheme 10. Synthesis of diazoacetoacetate **63** from cyclic carbamate **45**.

The cross Claisen reaction of lactone **60** with the enolate of methyl acetate gave the hemiacetal **61**, but the yield was invariably low. We examined a number of experimental variants, including the use of *tert*-butyl acetate to minimize the amount of homo-Claisen product formed, but the yield of **61** could not be improved. We also found that performing the Claisen reaction on crude **59** provided **61** directly, albeit also in modest yield. That the lactone **60** was a likely intermediate in this transformation is supported by the independent observation that treatment of **59** with excess LDA gave **60**. In practice, using **59** as the substrate for the Claisen reaction was a more convenient process for preparing **61**. We then found that **61**, which is presumably in equilibrium with its acyclic form, could be readily converted into **62** by diazo transfer using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) to give the diazo compound **62** in three steps and 29% overall yield from **58**. Subsequent protection of the hydroxyl group as its TBDPS-ether proceeded in 79% yield to provide the key diazoacetoacetate intermediate **63**.

This route to **63** did provide small quantities of material for exploring subsequent reactions, but the conversion of **60** into **63** was sufficiently laborious that we decided to develop a more expedient route that avoided the intermediate hemiacetal **61**. We found after some experimentation that crude **59** underwent facile silylation using TBDPS–Cl (1.5 equiv) and imidazole (1.2 equiv) to give **64** in 80% yield from **59** (Scheme 11). The yields were consistently higher when the TBDPS–Cl was premixed with imidazole in DMF for 15–20 min prior to addition of **59**. If imidazole was used in excess of the silyl chloride, only the lactone **60** was isolated.

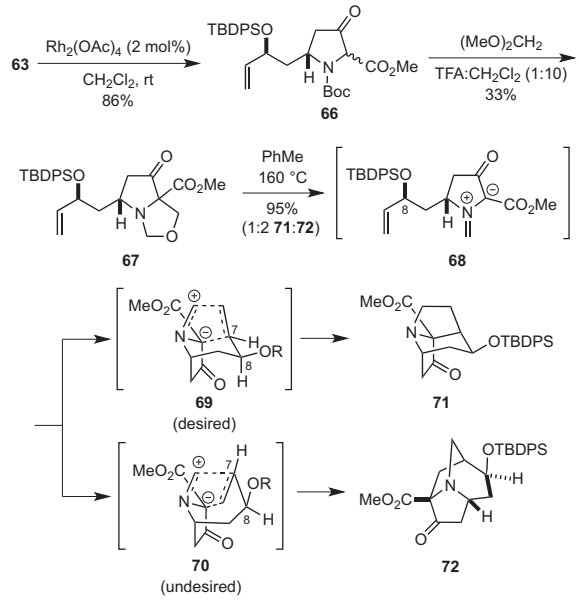


Scheme 11. Optimized Claisen condensation.

When **64** was subjected the Claisen reaction conditions that were originally developed to prepare **61**, the β-ketoester **65** was isolated in 60% yield (Scheme 11). However, loss of the *N*-Boc-protecting group from product **65** occurred as a significant side reaction, providing 20–30% of the free amine as a side product. After performing several control experiments, we determined that the *N*-Boc-group in **65** was not stable in the presence of excess LDA. Fortunately, we also discovered that use of NaHMDS as a base was not plagued by this side reaction, and **64** was thus transformed into the desired β-ketoester **65** in 75% yield; 17% of **64** was also recovered. The reaction of **65** with *p*-ABSA then furnished the requisite diazoacetoacetate **63** in 92% yield. The synthesis of **63** from commercially available 2-deoxy-D-ribose was thus accomplished in 10 synthetic steps and in 21% overall yield. This process for preparing **63**, which has been reproduced multiple times on a decagram scale, requires only four chromatographic purifications.

2.5. Development of a regioselective cycloaddition

With significant quantities of the diazoacetoacetate **63** in hand, the stage was set to examine the pivotal dipolar cycloaddition step. Toward this end, the diazo compound **63** was first converted into pyrrolidinone **66** in 86% yield by a rhodium catalyzed NH-insertion according to a protocol we had previously utilized (Scheme 12).[14] When **66** was allowed to react with dimethoxymethane in the presence of trifluoroacetic acid (TFA), the oxazolidine **67** was formed in 33% yield. We tentatively attributed the low yield in this transformation to loss of the silyl protecting group and reasoned that this problem could be eventually be solved with a different protecting group. In the end, this was not necessary because thermolysis of **67** delivered an unfavorable mixture (1:2) of regioisomers **71** and **72**. This discouraging experiment revealed



Scheme 12. Oxazolidine thermolysis of a C(8)-substituted precursor.

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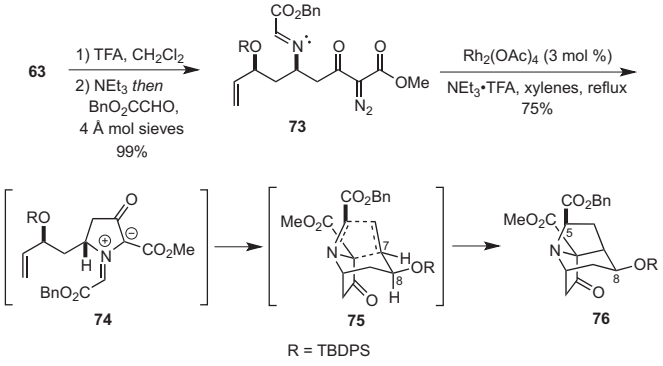
that the protected hydroxyl group at C(8) was not as effective in directing the regiochemical outcome of the dipolar cycloaddition as was a substituent at C(9) (cf. **35b**→**39b**+**40b**, Scheme 5).

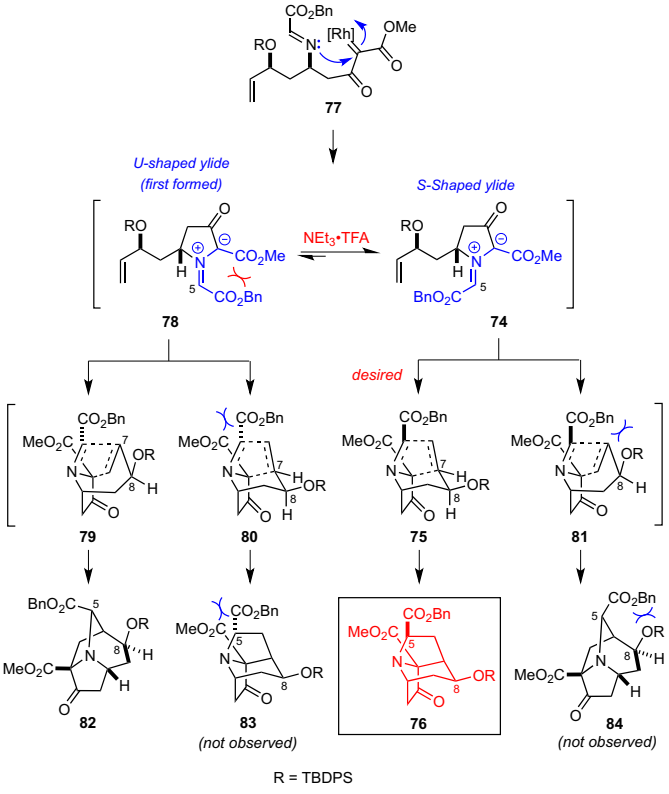
At this juncture, it was apparent that the mere presence of substituents at C(8) and C(9) was not sufficient to guarantee high regioselectivity in the dipolar cycloaddition. Indeed, the only azomethine ylide that underwent a cycloaddition with a significant level of regioselectivity had an electron-withdrawing group at C(5) (cf. **29**). We therefore turned our attention to generating an azomethine ylide bearing a readily removable, electron-withdrawing group at this position. After considering several options, we decided to examine the approach outlined in Scheme 13. This unusual sequence was inspired by the knowledge that stabilized metal carbenes can react with imines via intermolecular processes to generate azomethine ylides.[30] The reactions of metal carbenes to form azomethine ylides in an intramolecular sense, however, are not well known.[31] Moreover, the formation of an azomethine ylide by such a cyclization has only been studied in intermolecular dipolar cycloaddition reactions with highly active dipolarophiles.[31] In a considerably more ambitious adaptation of this reaction, we envisioned that the reaction of diazoacetoacetate **73** with a rhodium catalyst would initiate a novel cascade of reactions in which the initially formed metal carbene would cyclize onto the nitrogen atom of the proximal imine group to generate the azomethine ylide **74** that would then undergo spontaneous cyclization via a dipolar cycloaddition to deliver the desired adduct **76**.



Scheme 13. Dipolar cycloaddition cascade approach to the stemofoline core.

As the first step toward implementing this new plan, carbamate **63** was converted into diazoimine **73** by removing the Boc-group and treating the intermediate ammonium salt with NEt_3 and benzyl glyoxylate to provide the diazoimine **73** in quantitative yield (Scheme 13). Anxious to test the feasibility of the key cascade sequence, crude **73**, which contained an equimolar amount of NEt_3·TFA, was used in initial experiments. As will soon be appreciated, this was a fortunate decision with unanticipated consequences. In the event, the crude diazoimine **73** thus obtained was heated in refluxing benzene in the presence of $Rh_2(OAc)_4$ (5 mol %) to give the tricycle **76** in 35% yield; none of the regioisomeric cycloadduct was isolated, although a mixture of a number of other side products was obtained. Based upon mechanistic considerations and the ^1H NMR spectrum of the mixture, we surmised that at least some of these compounds were isomeric aziridines. Because aziridines are known to undergo thermal ring opening to generate azomethine ylides,[32] we conducted the reaction at higher temperature in refluxing xylenes and obtained **76** in 75% yield. In this case, the reaction mixture was considerably cleaner than at lower temperature, and the putative isomeric aziridines were no longer observed in the reaction mixture. The catalyst loading could be lowered to 3 mol % without deterioration in yield. This remarkably efficient cascade reaction sequence 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.

Toward improving the overall yield of **76** from **63**, the intermediate diazoimine **73** was purified by column chromatography on basic alumina. Surprisingly, however, when the pure sample of **73** was heated in refluxing xylenes in the presence of $Rh_2(OAc)_4$, a mixture (1.5:1) of cycloadducts **76** and **82** was obtained in 66% combined yield (Scheme 14).



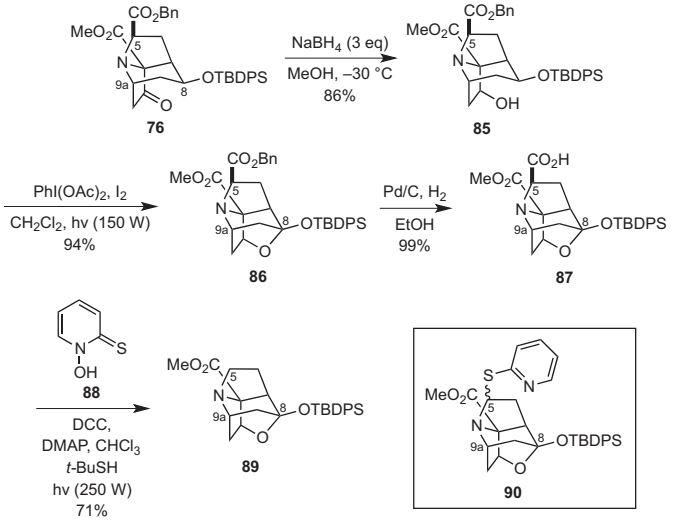
Scheme 14. Mechanistic rationale for observed cycloaddition selectivity.

The divergent results obtained with crude and purified **73** beg an explanation (Scheme 14). One reasonable possibility is that the rhodium carbene that is generated from **73**, which presumably has the imine stereochemistry shown in **77**, undergoes kinetic cyclization to form the U-shaped azomethine ylide **78**. This intermediate may either undergo dipolar cycloaddition via the cis-regioisomeric transition states **79** or **80** or isomerize to the S-shaped ylide **74**, which should be more stable owing to reduced steric $A^{1,3}$-interactions. The observed effect of the presence of NEt_3·TFA during the sequence suggests that the isomerization of **78** to **74** may be acid-catalyzed. The S-shaped ylide **74** may undergo cyclization via the two competing, regioisomeric transition states **75** and **81** to give **76** and **84**, respectively; whereas **78** can lead to **82** and **83** via the corresponding transition states **79** and **80**. Adducts **83** and **84** were not observed, presumably because of the unfavorable interactions between the two ester groups in transition state **80** and the ester and the protected alcohol in transition state **81**. The cycloadduct **82** was only isolated if the reaction was conducted in the absence of NEt_3·TFA. It thus tentatively appears that the isomerization of **78** to **74** in the presence of acid is more facile than the cyclization of **78** to give **82**.

2.6. Removing the now superfluous ester group at C(5)

Inasmuch as the ester group had now served its critical role of guiding the regiochemistry of the dipolar cycloaddition reaction, it

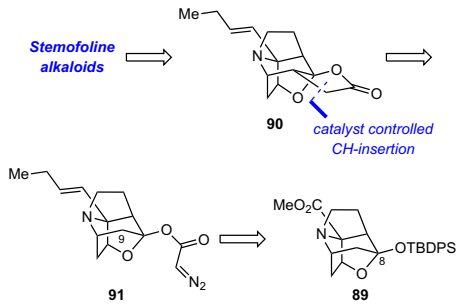
was time to examine tactics to effect its removal from **76**. Toward the dual objectives of removing the ester at C(5) and oxidizing C(8) by remote functionalization, the keto function in **76** was reduced with $NaBH_4$ in methanol at −30 °C to provide the endocyclic alcohol **85** in 86% yield as the only diastereomer (Scheme 15). When **85** was subjected to the Suárez protocol for remote radical functionalization,[20] the tetracycle **86** was obtained in 94% yield. Hydrogenolysis of the benzyl ester moiety in **86** provided the amino acid **87** in virtually quantitative yield. Williams and coworkers had recently reported that chloroform could be used as a hydrogen atom donor in developing a one-step, Barton decarboxylation process that seemed nicely suited to the task at hand.[33] Indeed, after forming the Barton ester derived from amino acid **87** using *N*-hydroxy-2-pyridinethione (**88**) and dicyclohexylcarbodiimide (DCC) in $CHCl_3$, the reaction mixture was irradiated with a tungsten filament light bulb (250 W) for ~1 h at room temperature to furnish the decarboxylated tricycle **89** in 40% yield. The major byproduct obtained was pyridyl sulfide **90**, which was also observed in the absence of a suitable hydrogen donor by Barton.[34] Toward improving the yield of **89**, more reactive H-atom donors were examined as additives, and we eventually discovered that use of *tert*-BuSH (10 equiv) increased the yield of **89** to 71%.



Scheme 15. Advancement of cycloadduct and decarboxylation of core.

2.7. Completion of formal total synthesis

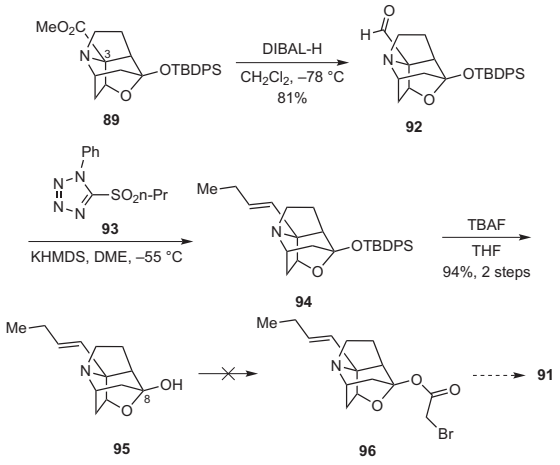
With the advanced intermediate **89** in hand, a number of endgames were contemplated. One attractive strategy featured the formation of the lactone ring in **90** via a dirhodium catalyzed, regioselective C–H insertion to directly functionalize the C(9)-position of the stemofoline core (Scheme 16). Such reactions are known to favor insertion into 3° C–H bonds over 2° C–H bonds, but



Scheme 16. Retrosynthetic analysis inspired by regioselective C–H insertion.

it is possible to use chiral catalysts in simpler, cyclohexanol-derived systems to override this innate preference.[35] Because C–H insertions of this type had never been applied to a substrate as complex as **91**, there was a significant opportunity to advance this methodology.

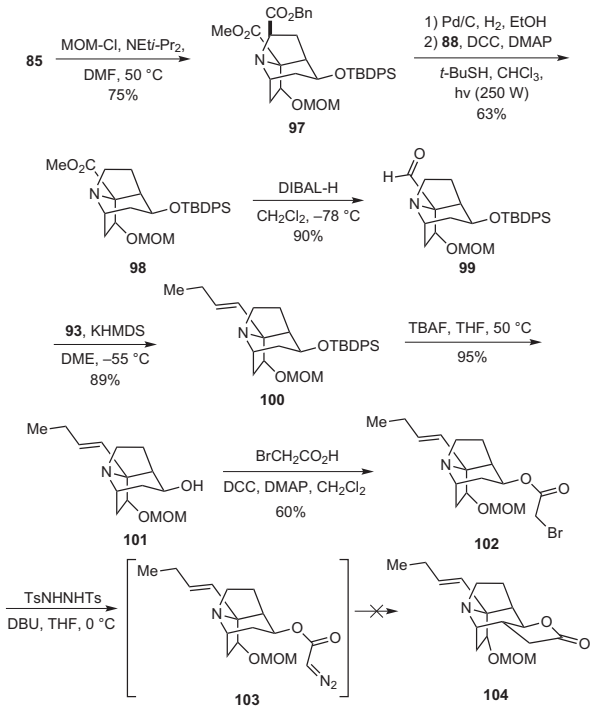
In order to assess the viability of the endgame strategy outlined in Scheme 16, the ester function at C(3) of **89** was reduced with DIBAL–H to provide aldehyde **92** in 81% yield (Scheme 17). When **92** was subjected to a Julia–Kocienski olefination with tetrazole **93** in the presence of KHMDS,[36] the crude olefin **94** that was obtained was directly subjected to desilylation with tetra-*n*-butylammonium fluoride (TBAF) to afford hemiketal **95** in 94% yield over the two-step sequence. Initial attempts to acylate the hemiketal hydroxy group to directly generate the requisite diazoacetate **91** involved use of *p*-toluenesulfonylhydrazone of glyoxylic acid chloride according to procedures reported by House[37] and Corey.[38] We were attracted to this route because we had employed this reagent with considerable success in the past.[39] However, despite repeated attempts, we were not able to access the diazoacetate **91** from hemiketal **95**. Fukuyama had reported an alternative method for generating diazoacetates from bromoacetates,[40] so we turned our attention to converting **95** into **96**. Unfortunately, use of a number of reagent combinations (i.e., bromoacetylbromide/base, bromoacetylbromide/HBr, and bromoacetic anhydride/DMAP) all failed to give significant quantities of **96**.



Scheme 17. Advancement of decarboxylated core.

We reasoned that the hemiketal nature of the tertiary-like hydroxyl group at C(8) might be adversely affecting its reactivity, so we decided to switch to a modified substrate in which the hydroxyl group at C(8) was a simple secondary alcohol. In the event, protection of the tricyclic alcohol **85** as its MOM ether furnished **97** in 75% yield (Scheme 18). Hydrogenolysis of the benzyl ester in **97** afforded the free carboxylic acid, which was then subjected to the same modified Barton decarboxylation protocol used previously (see Scheme 15, **87**→**89**) to give **98** in 63% overall yield from **97**. Reduction of the ester group in **98** followed by a Julia–Kocieński olefination gave **100** in 80% yield from **98**. Desilylation of the TBDPS-ether **100** afforded alcohol **101** in 95% yield. After screening several reaction conditions to acylate the C(8) alcohol of **101**, we found that bromoacetate **102** was best prepared using the esterification conditions developed by Steglich (bromoacetic acid, DCC, DMAP).[41] Bromoacetate **102** was then subjected to conditions developed by Fukuyama (TsNHNHTs, DBU)[40] to prepare diazoacetate **103**.

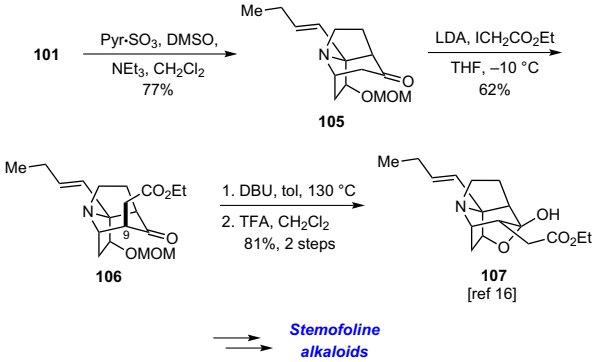
Although this conversion had been reported to work well with a number of simple compounds,[40] we discovered that the reaction of **102** to give **103** was highly problematic, and the major product



Scheme 18. Attempted C–H insertion.

was invariably **101**. The diazoacetate **103** was also surprisingly unstable, and all attempts to purify it led to significant losses of material. Consequently, crude **103** that had simply been filtered through a short pad of neutralized silica gel was used in attempts to functionalize the C(9)-position of **103** by C–H insertion, and we were able to screen several rhodium catalysts using this material. However, exposure of **103** to $Rh_2(OAc)_4$, $Rh_2(5(S)\text{-MEPY})_4$, and $Rh_2(5(R)\text{-MEPY})_4$ did not provide any detectable quantity of the desired lactone **104**. Given the difficulties we encountered in trying to prepare the sufficient amounts of diazo compound **103** for C–H insertion experiments, we turned our attention to an alternate approach in which we would convert **101** into an intermediate in Overman's syntheses of racemic stemofoline alkaloids.[16]

We thus subjected **101** to a Parikh–Doering oxidation to afford ketone **105**,[42] the enolate of which was alkylated with ICH_2CO_2Et to provide the *axial*-alkylated product **106**. Epimerization of **106** under basic conditions followed by treatment with TFA delivered the hemiketal **107** in 81% yield over the two steps. Because racemic **107** has been converted into didehydrostemofoline (**1**) and isodidehydrostemofoline (**6**) by Overman, its preparation completes the formal enantioselective syntheses of these alkaloids. The spectral data of our synthetic (+)-**107** is consistent with those reported by Overman for (±)-**107**[16] (Scheme 19).



Scheme 19. Advancing cycloadduct to a formal total synthesis.

3. Conclusion

In summary, a formal synthesis of didehydrostemofoline (**1**) and isodidehydrostemofoline (**6**) has been accomplished by preparing a key intermediate in the Overman synthesis of these alkaloids from commercially available 2-deoxy-D-ribose. The work presented in this account chronicles the evolution of our explorations to identify the optimal steric and electronic control elements necessary to generate the tricyclic core structure of these alkaloids in a single operation from an acyclic precursor. The key step in the synthesis is a novel cascade reaction sequence that is initiated by cyclization of a rhodium-derived carbene onto the nitrogen atom of a proximal imine group to generate an azomethine ylide that then undergoes spontaneous cyclization via dipolar cycloaddition. The synthesis features several other interesting reactions, including a Boord elimination to prepare a chiral allylic alcohol, a highly diastereoselective Hirama–Itô cyclization, and a useful modification of the Barton decarboxylation protocol. Further applications of cascade reactions to natural product synthesis are underway in our group, and will be reported in due course.

4. Experimental

4.1. General

Solvents and reagents were reagent grade and used without purification unless otherwise noted. Zn granules were activated by stirring with 1 M HCl for 10 min, filtering, rinsing with deionized H_2O, MeOH, then Et_2O, and drying under vacuum before use. Dichloromethane (CH_2Cl_2) and triethylamine (Et_3N) were distilled from calcium hydride and stored under nitrogen and methyl acetate was purified before each use by first drying over $MgSO_4$ and then distilling from P_2O_5. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were passed through a column of neutral alumina and stored under argon. Methanol (MeOH) and dimethylformamide (DMF) were passed through a column of molecular sieves and stored under argon. Toluene was passed through a column of Q5 reactant and stored under argon. ^1H nuclear magnetic resonance (NMR) spectra were obtained at 400 or 500 MHz as indicated. Chemical shifts are reported in parts per million (ppm, δ) and referenced to the solvent. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as: s, singlet; d, doublet; t, triplet; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons; br, broad; and br s, broad singlet. Infrared (IR) spectra were obtained using a Perkin–Elmer FTIR 1600 spectrophotometer on sodium chloride plates and reported as wavenumbers (cm^{-1}). Low-resolution chemical ionization mass spectra were obtained on a Finnigan TSQ-70 instrument, and high-resolution measurements were obtained on a VG Analytical ZAB2-E instrument. Analytical thin layer chromatography was performed using Merck 250 micron 60F-254 silica plates. The plates were visualized with UV light, *p*-anisaldehyde, and potassium permanganate. Flash column chromatography was performed according to Still's method using ICN Silitech 32-63 D 60A silica gel.[43]

4.2. (*E*)-Methyl 4-((4*S*,5*S*)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate (52)

Iodine (0.764 g, 3.01 mmol) was added to a solution of triphenylphosphine (0.781 g, 2.98 mmol) and imidazole (0.270 g, 3.96 mmol) in THF (15 mL) and the reaction mixture was stirred at room temperature for 10 min. A solution of **51** (0.457 g, 1.98 mmol) in THF (6.5 mL) was added and the solution was heated under reflux for 3.5 h until complete consumption of **51** was observed by TLC. The reaction mixture was cooled to room temperature, and poured into a stirred solution of aq $Na_2S_2O_3$ (5% w/w, 25 mL). EtOAc (25 mL)

was added, and the organic layer was removed. The aqueous layer was then extracted with CH_2Cl_2 (2×15 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude residue was dissolved in Et_2O (50 mL) and the precipitate was removed by filtration and rinsed with an additional portion of Et_2O (50 mL). After concentrating the filtrate and washings, the crude residue was purified by flash chromatography eluting with hexanes/Et_2O (4:1) to give 0.490 g (73% yield) of **52** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03–6.95 (m, 1H), 5.95 (dt, J=15.6, 1.2 Hz, 1H), 4.41 (app q, J=5.2 Hz, 1H), 4.27 (app p, J=4.0 Hz, 1H), 3.73 (s, 3H), 3.23–3.10 (m, 2H), 2.56–2.42 (m, 2H), 1.47 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.2, 144.2, 123.2, 108.8, 77.8, 76.0, 51.4, 32.2, 28.2, 25.5, 2.3; IR (neat) 2987, 2948, 1721, 1660, 1436, 1381, 1041 cm^{-1}; HRMS (ESI) 363.0080 [$C_{11}H_{17}INaO_4$ $(M+Na)^+$ requires 363.0064].

4.3. Methyl (2*E*,5*S*,6*S*)-5,6-bis(acetyloxy)-7-iodohept-2-enoate (54)

A solution of 2-deoxy-D-ribose **47** (25.0 g, 186.4 mmol) and methyl(triphenylphosphoranylidene)acetate **50** (74.8 g, 223.6 mmol) in THF (750 mL) was heated under reflux for 6 h and then cooled to room temperature. Imidazole (25.4 g, 372.7 mmol), PPh_3 (53.8 g, 205 mmol), and I_2 (54.4 g, 214.3 mmol) were then added sequentially to the reaction, and the mixture was stirred overnight in the dark at room temperature. The reaction was quenched with 10% aq $Na_2S_2O_3$ (500 mL) and diluted with EtOAc (250 mL). The resulting layers were separated and the aqueous layer extracted with CH_2Cl_2 (2×150 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude residue was dissolved in CH_2Cl_2 (375 mL), and then acetic anhydride (57.1 g, 559.1 mmol, 52.9 mL), DMAP (2.28 g, 18.7 mmol), and pyridine (44.2 g, 559.1 mmol, 45.2 mL) were added and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then poured into a separatory funnel, and washed with 1 M aq HCl (2×35 mL), saturated aq $NaHCO_3$ (1×35 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Trituration of the residue with Hex/Et_2O (100 mL, 8:1) precipitated out the Ph_3P=O byproduct formed during the olefination step. The precipitate was removed by filtration, and rinsed with Hex/Et_2O (150 mL, 8:1). The filtrate was then concentrated, redissolved in Et_2O (100 mL), and vacuum filtered through a 2.5 in pad of SiO_2 using a 3 in diameter fritted funnel. Once the initial filtrate had adsorbed onto the silica, the silica pad was rinsed with Et_2O (3×100 mL). The combined filtrate and washings were concentrated to give 62.3 g (87%) of **54** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.89–6.81 (m, 1H), 5.88 (dt, J=15.6, 1.2 Hz, 1H), 5.18–5.14 (m, 1H), 5.00–4.96 (m, 1H), 3.73 (s, 3H), 3.38–3.23 (m, 2H), 2.61–2.47 (m, 2H), 2.12 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.50, 169.45, 165.9, 142.4, 123.9, 72.1, 71.5, 51.4, 32.4, 20.6, 20.6, 2.1; IR (neat) 2952, 1747, 1660, 1436, 1372, 1223, 1040 cm^{-1}; HRMS (ESI) m/z 406.9962 [$C_{12}H_{17}INaO_6$ $(M+Na)^+$ requires 406.9962].

4.4. Methyl (2*E*,5*S*)-5-hydroxyhepta-2,6-dienoate (46)

A mixture of **54** (62.3 g, 162.2 mmol) and freshly activated Zn granules (53.0 g, 810.9 mmol) in anhyd MeOH (635 mL) was heated under reflux for 16 h. After cooling the reaction mixture to room temperature, the suspension was filtered through a pad of Celite then rinsed with MeOH (190 mL). The combined filtrate and washings were concentrated and the crude residue was purified by flash chromatography eluting with Hex/EtOAc (2:1) to give 15.7 g (62%) of **46** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.01–6.93 (m, 1H), 5.94–5.84 (comp, 2H), 5.27 (dt, J=17.6, 1.2 Hz, 1H), 5.15 (dt, J=10.4, 1.2 Hz, 1H), 4.27 (q, J=6.0 Hz, 1H), 3.72 (s, 3H), 2.72 (br s, 1H), 2.45 (td, J=7.2, 1.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 145.0, 139.7, 123.3, 115.3, 71.3, 51.4, 39.7; IR (neat) 3428, 2951, 1722, 1660, 1436 cm^{-1}; HRMS (CI) m/z 157.0864 [$C_8H_{13}O_3$ (M+1) requires 157.0865].

4.5. Methyl (2*E*,5*S*)-5-(carbamoyloxy)hepta-2,6-dienoate (55)

Chlorosulfonylisocyanate (15.7 g, 110.5 mmol) was added dropwise to solution of **46** (15.7 g, 100.5 mmol) in CH_2Cl_2 (1 L) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h, at which time H_2O (300 mL) was added. The reaction flask was then equipped with a short-path distillation apparatus and heated to 60 °C (bath temperature) until all of the CH_2Cl_2 had distilled. The remaining aqueous mixture was extracted with EtOAc (325 mL), and the combined organic layers were washed with saturated aq $NaHCO_3$ (1×25 mL), brine (1×25 mL), dried (Na_2SO_4), filtered, and concentrated to give 20.3 g (99%) of **55** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.90 (dt, J=15.6, 7.2, 1H), 5.90 (dt, J=15.6, 1.2 Hz, 1H), 5.80 (ddd, J=16.8, 10.8, 6.4 Hz, 1H), 5.33–5.20 (comp, 3H), 4.94 (br s, 2H), 3.74 (s, 3H), 2.62–2.49 (comp, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 156.1, 143.4, 135.4, 123.8, 117.2, 73.3, 51.5, 36.9; IR (neat) 3474, 3364, 3203, 2953, 2925, 1714, 1660, 1604, 1438, 1384, 1320, 1041 cm^{-1}; HRMS (CI) m/z 200.0925 [$C_9H_{14}NO_4$ $(M+H)^+$ requires 200.0923].

4.6. Methyl 2-[(4*R*,6*S*)-6-ethenyl-2-oxo-1,3-oxazinan-4-yl]acetate (45)

Compound **55** (20.3 g, 101.5 mmol) was dissolved in dry CH_2Cl_2 (895 mL) and cooled to −10 °C (bath temperature) in an ice/brine bath. NaH (4.31 g, 180.1 mmol, 60% w/w dispersion in mineral oil) was added in one portion, and the mixture was stirred under an atmosphere of N_2 (g) at −10 °C for 1.5 h. The reaction was quenched by the slow addition of saturated aq NH_4Cl (650 mL), and the aqueous layer was extracted with CH_2Cl_2 (4×300 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was then purified by recrystallization from methyl *tert*-butylether to give 17.09 g (85%) of **45** as a crystalline mixture (dr=8:1) of diastereomers: ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) δ 6.48 (br s, 1H), 5.92–5.83 (m, 1H), 5.41 (d, J=17.2 Hz, 1H), 5.27 (d, J=10.8 Hz, 1H), 4.75 (q, J=5.6 Hz, 1H), 3.98–3.91 (m, 1H), 3.72 (s, 3H), 2.57 (dd, J=4.4, 3.2 Hz, 2H), 1.60–1.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 153.8, 134.7, 117.4, 76.6, 51.9, 47.0, 39.9, 33.1; IR (neat) 3428, 2951, 1722, 1660, 1436 cm^{-1}; HRMS (CI) m/z 200.0924 [$C_9H_{14}NO_4$ (M+H) requires 200.0923].

4.7. *tert*-Butyl (4*R*,6*S*)-6-ethenyl-4-(2-methoxy-2-oxoethyl)-2-oxo-1,3-oxazinane-3-carboxylate (58)

A solution of **45** (17.1 g, 85.5 mmol), Boc_2O (37.4 g, 170.9 mmol), NEt_3 (26.0 g, 256.9 mmol, 258.1 mL), and DMAP (1.03 g, 8.55 mmol) in CH_2Cl_2 (430 mL) was stirred at room temperature overnight. The reaction was quenched with 1 M aq HCl (340 mL), and the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (2×500 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give 22.2 g (80%) of *syn*-**58** as a colorless oil. Major diastereomer (*syn*-**58**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.82 (ddd, J=17.2, 10.8, 6.0 Hz, 1H), 5.38 (d, J=17.2 Hz, 1H), 5.26 (d, J=10.8 Hz, 1H), 4.67–4.61 (m, 1H), 4.48 (dddd, J=8.8, 8.8, 8.8, 2.8 Hz, 1H), 3.66 (s, 3H), 2.92 (dd, J=16.0, 2.8 Hz, 1H), 2.57 (dd, J=16.0, 8.8 Hz, 1H), 2.54–2.48 (m, 1H), 2.74 (ddd, J=14.0, 11.6, 8.8 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5, 151.9, 150.6, 133.4, 118.3, 83.7, 76.0, 51.8, 50.3, 40.0, 34.8, 27.9; IR (neat) 2982, 2955, 1792, 1759,

1736, 1438, 1393, 1370, 1307, 1160 cm^{-1}; HRMS (CI) 300.1453 [$C_{14}H_{22}NO_6$ (M+H) requires 300.1447].

Minor diastereomer (*anti*-**58**): ^1H NMR ($CDCl_3$, 400 MHz) δ 5.87 (ddd, J=17.6, 10.4, 6.0 Hz, 1H), 5.41 (d, J=17.6 Hz, 1H), 5.30 (d, J=10.4 Hz, 1H), 4.93–4.87 (m, 1H), 4.67 (ddd, J=14.4, 6.0, 3.6 Hz, 1H), 3.72 (s, 3H), 2.86 (dd, J=16.0, 3.2 Hz, 1H), 2.65 (dd, J=16.0, 10.0 Hz, 1H), 2.19 (app dt, J=14.4, 3.2 Hz, 1H), 2.08 (ddd, J=14.4, 10.0, 5.2 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 151.6, 148.5, 134.4, 117.9, 84.2, 74.9, 52.0, 49.6, 37.7, 31.2, 27.8; IR (neat) 2982, 2955, 1792, 1759, 1736, 1438, 1393, 1370, 1307, 1160 cm^{-1}; HRMS (CI) 300.1453 [$C_{14}H_{22}NO_6$ $(M+H)^+$ requires 300.1447].

4.8. *tert*-Butyl (4*R*,6*S*)-2-oxo-6-vinyltetrahydro-2*H*-pyran-4-ylcarbamate (60)

A solution of **58** (0.150 g, 0.500 mmol) and Cs_2CO_3 (20 mg, 0.100 mmol) in MeOH (20 mL) was stirred at room temperature for 24 h. The reaction mixture was concentrated and a slurry of the crude residue and SiO_2 (0.150 g) was created and the suspension was concentrated to dryness. The substrate adsorbed on silica was dried under high vacuum for 1 h, and then purified by column chromatography eluting with hexanes/EtOAc (2:1) to give 0.103 g (85%) of **60** as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 5.93–5.85 (m, 1H), 5.36 (d, J=17.2 Hz, 1H), 5.29 (d, J=9.6 Hz, 1H), 5.08–5.03 (m, 1H), 4.99 (br s, 1H), 4.09 (br s, 1H), 2.87 (dd, J=17.6 Hz, 6.8 Hz, 1H), 2.52 (dd, J=17.6, 6.8 Hz, 1H), 2.08–1.97 (m, 2H), 1.47 (s, 9H); LRMS (CI) m/z 241 [$C_{12}H_{19}NO_4$ (M+1) requires 241].

4.9. (5*R*,7*S*)-Methyl 5-(*tert*-butoxycarbonylamino)-2-diazo-7-hydroxy-3-oxonon-8-enoate (62)

A solution of **58** (0.388 g, 1.30 mmol) and Cs_2CO_3 (0.052 g, 0.259 mmol) in MeOH (52 mL) was stirred at room temperature for 24 h, and then the reaction mixture was concentrated to dryness. In a separate flask, methyl acetate (0.577 g, 7.80 mmol) was added dropwise to a freshly prepared solution of LDA (7.80 mmol) in THF (7.4 mL) at −78 °C and the solution was stirred for 1 h. The enolate solution was then cannulated into a flask containing a solution of the crude residue from the previous step that had been precooled to 0 °C. The resulting solution was stirred at 0 °C for 1 h then it was warmed to room temperature and stirred for an additional 1 h. The reaction was quenched with saturated aq NH_4Cl (40 mL) and diluted with EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated, and the crude residue was purified by flash chromatography eluting with Hex/EtOAc (4:1) to give ~0.144 g of **61** as crude oil contaminated with 10–20% methyl acetoacetate. The crude residue, *p*-acetamidobenzenesulfonyl azide (*p*-ABSA, 0.127 g, 0.546 mmol), and NEt_3 (0.254 g, 2.52 mmol) in MeCN (5 mL) were stirred at room temperature overnight. The reaction mixture was concentrated, triturated with Et_2O (20 mL), filtered, and concentrated. The crude residue was purified by column chromatography eluting with Hex/EtOAc (1:1) to give 0.045 g (29%) of **62** as a yellow oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 5.93–5.85 (m, 1H), 5.27 (dt, J=17.2, 1.2 Hz, 1H), 5.12 (dt, J=10.4, 1.2 Hz, 1H), 5.08 (br s, 1H), 4.25–4.22 (m, 1H), 4.21–4.13 (m, 1H), 3.84 (s, 3H), 3.14 (dd, J=15.6, 4.0 Hz, 1H), 3.02 (dd, J=15.8, 6.0 Hz, 1H), 2.61 (br s, 1H), 1.86–1.71 (comp, 2H), 1.42 (s, 9H); LRMS (CI) m/z 342 [$C_{15}H_{24}N_3O_6$ (M+1) requires 342].

4.10. Methyl (3*R*,5*S*)-3-{[(*tert*-butoxy)carbonyl]amino}-5-[(*tert*-butyldiphenylsilyl)oxy]hept-6-enoate (64)

A solution of *syn*-**58** (22.22 g, 74.2 mmol) and Cs_2CO_3 (2.86 g, 14.8 mmol) in MeOH (370 mL) was stirred at room temperature for 48 h. The reaction mixture was then concentrated under reduced pressure to provide 20.3 g of crude **59** as a colorless oil that was used in the next step without further purification. A solution of crude **59** (20.3 g, 74.2 mmol) in DMF (50 mL) was added to a solution of TBDPS–Cl (30.6 g, 111.3 mmol), imidazole (6.57 g, 96.46 mmol), and DMAP (0.091 g, 0.742 mmol) in DMF (320 mL), and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with 1 M aq HCl (300 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3×150 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (5:1) to give 30.4 g (80%, from **58**) of **64** as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.70–7.63 (comp, 4H), 7.47–7.33 (comp, 6H), 5.85 (ddd, J=17.2, 10.2, 6.4 Hz, 1H), 5.10–5.03 (comp, 2H), 4.41 (app d, J=8.8 Hz, 1H), 4.17 (app q, J=6.0 Hz, 1H), 3.91–3.81 (m, 1H), 3.60 (s, 3H), 2.40 (app d, J=4.8 Hz, 2H), 1.62 (app t, J=6.4 Hz, 2H), 1.36 (s, 9H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 171.8, 154.8, 139.4, 135.90, 135.87, 134.1, 133.7, 129.8, 129.6, 127.6, 127.4, 115.5, 79.0, 72.2, 51.5, 44.2, 42.3, 39.6, 28.3, 27.0, 19.2; IR (neat) 3423, 2959, 2932, 2858, 1737, 1716, 1502, 1170, 1111 cm^{-1}; HRMS (ESI) 512.2830 [$C_{29}H_{42}NO_5Si$ $(M+H)^+$ requires 512.2754].

4.11. Methyl (5*R*,7*S*)-5-{[(*tert*-butoxy)carbonyl]amino}-7-[(*tert*-butyldiphenylsilyl)oxy]-3-oxonon-8-enoate (65)

A solution of freshly distilled methyl acetate (4.75 g, 64.1 mmol) in THF (128 mL) was added dropwise via syringe pump to a solution of NaHMDS (83.33 mmol, 1.8 M in hexane) in THF (167 mL) at −78 °C. After 30 min, a solution of **64** (3.28 g, 6.41 mmol) in THF (13 mL) was added dropwise to the reaction via syringe pump. During the syringe pump additions the metal needle used to transfer the substrate solutions was passed through a −78 °C bath to precool the solutions before introduction into the reaction flask. After 1 h at −78 °C, the reaction mixture was warmed to −10 °C (ice/brine bath) and stirred for 6 h. The reaction was then quenched by addition of saturated aq NH_4Cl (300 mL) and warmed to room temperature. The reaction mixture was extracted with EtOAc (5×100 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with hexanes/EtOAc (using a gradient from 9:1 to 5:1) to give 3.55 g (75%) of **65** as a colorless oil along with 0.56 g (17%) of recovered starting material **64**: ^1H NMR ($CDCl_3$, 400 MHz, rotamers) δ 7.69–7.62 (comp, 4H), 7.47–7.33 (comp, 6H), 5.83 (ddd, J=17.1, 10.4, 6.4 Hz, 1H), 5.10–5.03 (comp, 2H), 4.37 (app d, J=8.0 Hz, 1H), 4.15 (app q, J=4.0 Hz, 1H), 3.92–3.83 (m, 1H), 3.70 (s, 3H), 3.37 (s, 2H), 2.61 (app d, J=2.8 Hz, 2H), 1.68–1.61 (m, 2H), 1.35 (s, 9H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 172.6, 167.6, 154.9, 139.4, 135.9, 135.8, 134.0, 133.6, 129.8, 129.6, 127.6, 127.4, 115.5, 79.0, 72.3, 52.2, 49.0, 47.9, 43.9, 42.1, 28.2, 26.9, 19.1; IR (neat) 3417, 2957, 2932, 2858, 1746, 1715, 1714, 1502, 1246, 1169, 1111 cm^{-1}; HRMS (ESI) 576.2750 [$C_{31}H_{43}NNaO_6Si$ $(M+Na)^+$ requires 576.2757].

4.12. Methyl (5*R*,7*S*)-5-{[(*tert*-butoxy)carbonyl]amino}-7-[(*tert*-butyldiphenylsilyl)oxy]-2-diazo-3-oxonon-8-enoate (63)

A solution of **65** (3.55 g, 1.97 mmol), *p*-ABSA (0.708 g, 2.95 mmol), and NEt_3 (0.598 g, 5.91 mmol) in MeCN (6.6 mL) was stirred at room temperature for 16 h. The reaction mixture was then concentrated and the crude residue was triturated with Et_2O (25 mL). The precipitate was filtered and rinsed with Et_2O/CH_2Cl_2 (25 mL, 2:1), and the combined filtrate and washings were concentrated under reduced pressure. The crude residue was purified by column chromatography eluting with Hex/EtOAc (2:1) to give 1.14 g (92%) of **63** as a yellow oil: ^1H NMR ($CDCl_3$, 400 MHz,

rotamers) δ 7.71–7.63 (comp, 4H), 7.46–7.33 (comp, 6H), 5.83 (ddd, *J*=17.0, 10.2, 6.4 Hz, 1H), 5.10–5.03 (comp, 2H), 4.31 (app d, *J*=9.6 Hz, 1H), 4.21–4.13 (m, 1H), 3.99–3.92 (m, 1H), 3.81 (s, 3H), 2.96–2.83 (comp, 2H), 1.71–1.56 (comp, 2H), 1.34 (s, 9H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, rotamers) δ 190.6, 161.6, 154.9, 139.4, 135.9, 134.1, 133.7, 129.7, 129.6, 128.2, 127.5, 127.4, 115.4, 78.8, 76.2, 72.2, 52.1, 45.6, 44.5, 42.7, 28.2, 26.9, 19.1; IR (neat) 3417, 2959, 2932, 2856, 2136, 1716, 1655, 1500, 1313, 1171, 1112 cm^{-1}; HRMS (ESI) 580.2838 [$C_{31}H_{42}N_3O_6Si$ $(M+H)^+$ requires 580.2843].

4.13. Methyl (5*R*)-5-[(2*S*)-2-[(*tert*-butyldiphenylsilyl)oxy]but-3-en-1-yl]-7-oxo-hexahydropyrrolo[1,2-*c*][1,3]oxazole-7a-carboxylate (67)

A mixture of **63** (0.190 g, 0.328 mmol) and $Rh_2(OAc)_4$ (0.007 g, 0.016 mmol) in CH_2Cl_2 (6.6 mL) was stirred at room temperature for 16 h. The reaction mixture was concentrated and the crude residue purified by column chromatography eluting with Hex/EtOAc (5:1) to give 0.181 g (86%) of **66** as a mixture (1:1) of diastereomers and rotamers. The crude residue and dimethoxymethane (0.138 g, 1.82 mmol) in TFA/CH_2Cl_2 (1:10, 8.6 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into a separatory funnel, diluted with CH_2Cl_2 (30 mL), and washed with saturated aq $NaHCO_3$ (2×15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated and the crude residue was then purified by column chromatography eluting with Hex/EtOAc (using a gradient elution from 1:0 to 6:1) to give 0.017 g (33%) of **67** as a mixture (1:1) of diastereomers as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68–7.60 (comp, 4H), 7.47–7.33 (comp, 6H), 5.86–5.78 (m, 1H), 5.05 (dt, *J*=17.2, 1.2 Hz, 1H), 5.03 (dt, *J*=10.4, 1.2 Hz, 1H), 4.51 (d, *J*=7.2 Hz, 1H), 4.23 (dt, *J*=6.4, 4.8 Hz, 1H), 4.15 (d, *J*=7.2 Hz, 1H), 4.08 (d, *J*=9.2 Hz, 1H), 3.92 (d, *J*=9.2 Hz, 1H), 3.73 (s, 3H), 3.08–3.01 (m, 1H), 2.26 (d, *J*=7.2 Hz, 1H), 2.25 (d, *J*=10.0 Hz, 1H), 1.98 (ddd, *J*=13.8, 6.4, 3.6 Hz, 1H), 1.72 (ddd, *J*=13.8, 9.4, 4.8 Hz, 1H), 1.07 (s, 9H); LCMS (ESI) *m*/*z* 494.87 [$C_{28}H_{36}NO_5Si$ (M+H) requires 494.67].

4.14. Methyl 3-[(*tert*-butyldiphenylsilyl)oxy]-9-oxo-7-azatricyclo[5.3.0.0^{4,8}]decane-8-carboxylate (71)

A solution of **67** (19 mg, 0.038 mmol) in toluene (3.8 mL) in a sealed tube reaction vessel was heated to 160 °C for 4 h. The reaction mixture was cooled to room temperature, concentrated, and the crude residue was then purified by column chromatography eluting with Hex/EtOAc (1:1) to give 5.6 mg (32%) of **71** as a colorless oil along with 11 mg (62%) of **72** as a colorless oil. Minor regioisomer (**71**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62–7.58 (comp, 4H), 7.46–7.34 (comp, 6H), 3.96–3.91 (m, 1H), 3.75 (s, 3H), 3.55–3.52 (m, 1H), 3.14 (ddd, *J*=13.4, 11.4, 4.4 Hz, 1H), 3.02 (dt, *J*=8.4, 6.0 Hz, 1H), 2.97 (dd, *J*=6.2, 3.6 Hz, 1H), 2.66–2.60 (m, 1H), 2.36 (ddd, *J*=13.4, 8.8, 4.4 Hz, 1H), 1.84 (d, *J*=18.0 Hz, 1H), 1.71 (ddd, *J*=18.2, 11.0, 5.2 Hz, 1H), 1.65–1.57 (comp, 1H), 1.37–1.32 (comp, 1H), 1.05 (s, 9H); LRMS (CI) *m*/*z* 464 [$C_{27}H_{34}NO_4Si$ (M+H) requires 464].

Major regioisomer (**72**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64–7.60 (comp, 4H), 7.46–7.35 (comp, 6H), 3.85–3.79 (comp, 3H), 3.74 (s, 3H), 2.81 (dd, *J*=15.8, 6.8 Hz, 1H), 2.63–2.54 (comp, 2H), 2.28–2.24 (m, 1H), 2.05 (d, *J*=15.6 Hz, 1H), 1.66–1.60 (m, 1H), 1.51 (d, *J*=14.4 Hz, 1H), 1.08 (s, 9H), 0.9 (ddd, *J*=15.6, 9.0, 5.2 Hz, 1H); LRMS (CI) *m*/*z* 464 [$C_{27}H_{34}NO_4Si$ (M+H) requires 464].

4.15. Methyl (5*R*,7*S*)-5-[(*E*)-[2-(benzyloxy)-2-oxoethylidene]amino]-7-[(*tert*-butyldiphenylsilyl)oxy]-2-diazo-3-oxonon-8-enoate (73)

Trifluoroacetic acid (0.315 g, 2.76 mmol) was added to a pre-cooled solution of **63** (0.160 g, 0.276 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 2 h. The reaction mixture was then concentrated to dryness and pumped down under high vacuum for 2 h to ensure the removal of all excess TFA. Molecular sieves of 4 Å (0.100 g) were added to a solution of the crude residue in CH_2Cl_2 (1.5 mL) and the mixture was cooled to 0 °C. NEt_3 (0.028 g, 0.276 mmol) was then added dropwise, and upon completion of the addition, the reaction mixture was warmed to room temperature. A 1 M solution of benzyl glyoxylate (0.41 mL, 0.414 mmol) in toluene was then added, and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was then passed through a short pad of oven dried basic alumina, rinsing with anhyd CH_2Cl_2 (10 mL), and the combined filtrate and washings were concentrated under reduced pressure to give 0.173 g (99%) of **73** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (s, 1H), 7.63–7.59 (comp, 4H), 7.39–7.28 (comp, 11H), 5.75–5.67 (m, 1H), 5.27 (s, 2H), 4.93 (app d, *J*=10.4 Hz, 1H), 4.84 (app d, *J*=17.2 Hz, 1H), 4.10–4.05 (m, 1H), 4.04–3.96 (m, 1H), 3.79 (s, 3H), 3.31 (dd, *J*=18.0, 9.2 Hz, 1H), 2.82 (dd, *J*=16.0, 3.6 Hz, 1H), 1.95–1.88 (m, 1H), 1.84–1.77 (m, 1H), 1.04 (s, 9 H).

4.16. 6-Benzyl-8-methyl-(6*R*)-3-[(*tert*-butyldiphenylsilyl)oxy]-9-oxo-7-azatricyclo[5.3.0.0^{4,8}]decane-6,8-dicarboxylate (76)

Trifluoroacetic acid (1.58 mL, 20.7 mmol) was added to a pre-cooled solution of **63** (1.20 g, 2.07 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then concentrated to dryness and pumped down under high vacuum for 2 h to ensure the removal of all excess TFA. Molecular sieves of 4 Å (1.2 g) were added to a solution of the crude residue in CH_2Cl_2 (6 mL) and the mixture was cooled to −20 °C. NEt_3 (0.32 mL, 2.28 mmol) was then added dropwise, and upon complete of the addition, the reaction mixture was warmed to room temperature. A 1 M solution of benzyl glyoxylate (3.11 mL, 3.11 mmol) in CH_2Cl_2 was then added, and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was filtered through Celite and rinsed with CH_2Cl_2 (12 mL) to give **73** as a colorless oil along with an equimolar amount of NEt_3·TFA. The crude residue was dissolved in xylenes (40 mL), $Rh_2(OAc)_4$ (0.027 g, 0.062 mmol) was added, and the mixture was heated under reflux for 24 h. The reaction mixture was concentrated to under reduced pressure, and the crude residue was purified by column chromatography eluting with Hex/EtOAc (3:1 to 1:1, with 1% v/v NEt_3) to give 0.93 g (75%) of **76** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59–7.55 (comp, 4H), 7.45–7.35 (comp, 11H), 5.28 (d, *J*=3.2 Hz, 2H), 4.15 (app q, *J*=6.0 Hz, 1H), 4.08–4.04 (m, 1H), 3.94–3.89 (m, 1H), 3.72 (s, 3H), 2.96 (app q, *J*=3.2 Hz, 1H), 2.68 (dd, *J*=13.6, 5.6 Hz, 1H), 2.61 (dd, *J*=16.0, 6.4 Hz, 1H), 2.15–2.07 (m, 1H), 1.80 (d, *J*=17.6 Hz, 1H), 1.35–1.19 (comp, 2H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.0, 172.5, 169.7, 167.4, 135.5, 135.5, 135.3, 134.7, 133.5, 133.0, 130.0, 129.9, 128.6, 128.5, 127.8, 127.6, 82.4, 67.0, 66.2, 62.3, 54.2, 53.1, 49.7, 44.0, 33.6, 27.0, 26.8, 19.0; IR (neat) 2953, 2857, 1738, 1741, 1428, 1228, 1112 cm^{-1}; HRMS (ESI) *m*/*z* 598.2614 [$C_{35}H_{40}NO_6Si$ (M+H) requires 598.2625].

4.17. 6-Benzyl-8-methyl-(6*R*)-3-[(*tert*-butyldiphenylsilyl)oxy]-9-hydroxy-7-azatricyclo[5.3.0.0^{4,8}]decane-6,8-dicarboxylate (85)

A solution of **76** (0.085 g, 0.142 mmol) in MeOH (4.7 mL) was cooled to −30 °C and $NaBH_4$ (0.016 g, 0.426 mmol) was added in one portion. The reaction mixture was stirred at −30 °C for 2 h then warmed slowly to room temperature over the course of 1 h. The reaction was quenched with aq 1 M HCl (4 mL), and the resulting mixture was concentrated to remove all MeOH. The crude aq mixture was neutralized with solid K_2CO_3, and then extracted with EtOAc (4×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by column chromatography eluting with 4:1 Hex/EtOAc to give

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0.063 g (86%) of **85** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67–7.61 (comp, 4H), 7.44–7.31 (comp, 11H), 5.24 (q, J=13.2 Hz, 2H), 4.77–4.72 (m, 1H), 4.37 (dd, J=10.4, 3.2 Hz, 1H), 4.30 (dd, J=11.2, 5.6 Hz, 1H), 3.70 (s, 3H), 3.67–3.62 (m, 1H), 2.66 (dd, J=14.0, 5.6 Hz, 1H), 2.51 (dd, J=6.0, 3.2 Hz, 1H), 2.43–2.35 (m, 1H), 1.97–1.88 (comp, 2H), 1.64–1.57 (m, 1H), 1.43–1.35 (m, 1H), 1.33–1.09 (comp, 1H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.3, 170.9, 135.75, 135.66, 135.6, 134.4, 134.2, 129.5, 129.5, 128.52, 128.48, 128.3, 127.4, 127.4, 80.5, 73.2, 66.7, 65.8, 61.6, 57.0, 52.4, 46.4, 37.4, 35.0, 27.3, 26.9, 19.1; IR (neat) 3233, 2955, 2892, 2857, 1736, 1471, 1225, 1108 cm^{-1}; HRMS (ESI) m/z 600.2777 [$C_{35}H_{42}NO_6Si$ (M+H) requires 600.2781].

4.18. 4-Benzyl-2-methyl-(4*R*)-7-[(*tert*-butyldiphenylsilyl) oxy]-11-oxa-3-azatetracyclo[5.3.1.0^{2,6}.0^{3,9}]undecane-2,4-dicarboxylate (86)

A solution of **85** (32 mg, 0.0534 mmol), $PhI(OAc)_2$ (0.026 g, 0.0800 mmol), and I_2 (13.6 mg, 0.0534 mmol) in CH_2Cl_2 (2.7 mL) was irradiated with tungsten filament light bulb (150 W) at room temperature for 1.5 h. The reaction was quenched with 10% aq sodium thiosulfate (3 mL), and extracted with EtOAc (4×5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by column chromatography eluting with Hex/EtOAc (1:1) to give 29 mg (94%) of **86** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74–7.69 (comp, 4H), 7.44–7.32 (comp, 11H), 5.16 (app q, J=8.4 Hz, 2H), 4.64 (app t, J=2.4 Hz, 1H), 4.29 (app t, J=9.2 Hz, 1H), 3.69 (s, 3H), 3.68–3.64 (m, 1H), 2.73 (m, 1H), 2.15–2.10 (comp, 2H), 1.73–1.66 (comp, 1H), 1.59 (d, J=11.6 Hz, 1H), 1.60–1.54 (comp, 1H), 1.32 (d, J=13.6 Hz, 1H), 1.27–1.24 (m, 1H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 170.3, 136.0, 135.9, 135.4, 134.3, 134.2, 129.6, 129.6, 128.5, 128.4, 127.33, 127.29, 106.3, 85.0, 79.5, 77.2, 66.7, 63.7, 57.2, 56.9, 52.4, 37.9, 35.7, 29.4, 26.9, 19.1; IR (neat) 2955, 2858, 1736, 1457, 1214 cm$^{-1;}$ HRMS (ESI) m/z 598.2623 [$C_{35}H_{40}NO_6Si$ (M+H) requires 598.2625].

4.19. Methyl 7-[(*tert*-butyldiphenylsilyl)oxy]-11-oxa-3-azatetracyclo [5.3.1.0^{2,6}.0^{3,9}]undecane-2-carboxylate (89)

A suspension of benzyl ester **86** (0.419 g, 0.701 mmol) and 10% w/w Pd/C (112 mg) in EtOH (14 mL) was stirred under an atmosphere of H_2 (gas) at room temperature for 16 h. The mixture was filtered through a short pad of Celite, which was rinsed with EtOH (30 mL), and the combined filtrate and washings were concentrated to dryness to give 0.358 g (>99%) of acid **87** as an amorphous solid. A mixture of crude acid **87** (0.193 g, 0.424 mmol), 1-hydroxypyridine-2(1*H*)-thione (**88**, 0.073 g, 0.570 mmol), DCC (0.118 g, 0.570 mmol), and DMAP (0.047 g, 0.424 mmol) was dissolved in $CHCl_3$ (4.0 mL). The resulting canary yellow solution was treated with *t*-BuSH (0.43 mL, 0.424 mmol) and immediately irradiated with a tungsten filament light bulb (250 W) at room temperature for 1 h. The reaction mixture was then concentrated, and the crude residue was directly purified by column chromatography eluting with hexanes/EtOAc (as a gradient from 3:1 →1:1 →1:5 with 1% v/v Et_3N) to give 0.126 g (71%) of **89** as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77–7.72 (comp, 4H), 7.45–7.34 (comp, 6H), 4.65 (s, 1H), 3.71 (s, 3H), 3.23 (m, 1H), 3.13 (ddd, J=12.9, 9.0, 6.0 Hz, 1H), 2.93 (ddd, J=13.5, 7.8, 5.7 Hz, 1H), 2.78–2.76 (m, 1H), 1.83–1.71 (comp, 2H), 1.65–1.60 (comp, 3H), 1.39 (d, J=16.2 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 136.0, 136.0, 134.6, 134.4, 129.6, 129.6, 127.4, 127.3, 106.3, 83.9, 80.3, 61.1, 60.4, 58.3, 52.3, 49.5, 38.1, 35.4, 26.9, 26.6, 21.0, 19.1, 14.2; IR (neat) 2953, 1740, 1430, 1276, 1218, 1109 cm^{-1}; HRMS (ESI) m/z 464.2256 [$C_{27}H_{34}NO_4Si$ (M+H) requires 464.2252].

4.20. 2-[(1*E*)-But-1-en-1-yl]-11-oxa-3-azatetracyclo [5.3.1.0^{2,6}.0^{3,9}]undecan-7-ol (95)

DIBAL–H (0.41 mL, 1.0 M in hexanes, 0.41 mmol) was added dropwise to solution of **89** (0.126 g, 0.272 mmol) in CH_2Cl_2 (5 mL) at −78 °C and the reaction mixture was stirred for 3 h. The reaction was quenched with MeOH (0.3 mL) and half saturated potassium sodium tartrate solution (5 mL) at −78 °C, and the reaction mixture was warmed to room temperature and stirred vigorously until the organic layer became clear. The separated aqueous layer was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and then concentrated. The crude residue was purified by column chromatography eluting with EtOAc/MeOH (5:1) with 1% v/v Et_3N to give 0.096 g (81%) of **92** as a light yellow oil.

To a stirred solution of **92** (0.096 g, 0.221 mmol) and 1-phenyl-1*H*-tetrazol-5-yl sulfone **93** (0.168 g, 0.664 mmol) in DME (7.4 mL) at −55 °C was added KHMDS (1.8 mL, 0.5 M in toluene, 0.884 mmol) dropwise. The resulting solution was stirred for 1 h at −55 °C and warmed to room temperature. After stirring for 1 h at room temperature, the reaction mixture was quenched with saturated NaCl solution (5 mL). The separated aqueous layers were extracted with EtOAc (3×10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and then concentrated to give ~0.102 g of **94** as a crude oil. To a stirred solution of crude **94** (~0.102 g, 0.221 mmol) in THF (4.4 mL) at room temperature was added TBAF (0.209 g, 0.663 mmol). The resulting solution was stirred for 4 h at room temperature before it was filtered through a pad of silica gel, and washed with CH_2Cl_2/MeOH (2:1, 40 mL) containing 1% v/v Et_3N. The combined solution was concentrated, and the crude residue was purified by column chromatography eluting with hexanes/EtOAc (1:1) to remove the nonpolar impurities followed by EtOAc/MeOH (5:1) with 1% v/v Et_3N to give 0.046 g (94%) of **95** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70 (dt, J=15.6, 6.0 Hz, 1H), 4.48 (d, J=15.6 Hz, 1H), 4.30 (d, J=1.8 Hz, 1H), 3.39 (m, 1H), 3.30 (comp, 2H), 2.38 (m, 1H), 2.09–2.04 (comp, 2H), 1.86–1.80 (comp, 5H), 1.62 (d, J=13.2 Hz, 1H), 0.99 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.4, 127.4, 105.0, 82.7, 82.4, 60.8, 56.7, 48.2, 37.8, 34.5, 26.5, 25.4, 13.6; IR (neat) 3337, 2959, 2878, 1350, 1328, 1056, 977 cm^{-1}; HRMS (ESI) m/z 222.1487 [$C_{13}H_{20}NO_2$ (M+H) requires 222.1489].

4.21. 6-Benzyl-8-methyl-(6*R*)-3-[(*tert*-butyldiphenylsilyl) oxy]-9-methyloxymethyloxy-7-azatricyclo[5.3.0.0^{4,8}]decane-6,8-dicarboxylate (97)

To a stirred solution of **85** (0.624 g, 2.04 mmol) in DMF (10 mL) were sequentially added MOM–Cl (0.79 mL, 10.4 mmol) and N(*i*-Pr)$_2$Et (3.62 mL, 20.8 mmol) at room temperature. The resulting solution was heated to 50 °C and stirred for 16 h at 50 °C. The reaction was quenched with MeOH (1.0 mL), diluted with H_2O (50 mL), and extracted with EtOAc (4×20 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and the crude residue was purified by column chromatography eluting with hexanes/EtOAc (as a gradient from 2:1 to 1:2) with 1% v/v Et_3N to give 0.502 g (75%) of **97** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69–7.61 (comp, 4H), 7.41–7.32 (comp, 11H), 5.24 (q, J=12.0 Hz, 2H), 4.68–4.62 (m, 1H), 4.28 (d, J=1.2 Hz, 2H), 4.32–4.26 (m, 1H), 4.03 (dd, J=11.1, 6.0 Hz, 1H), 3.72–3.71 (m, 1H), 3.71 (s, 3H), 3.06 (s, 3H), 2.79 (dd, J=6.3, 3.3 Hz, 1H), 2.61 (dd, J=13.8, 5.7 Hz, 1H), 2.48–2.38 (m, 1H), 2.08–1.99 (m, 1H), 1.33–1.09 (comp, 3H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.0, 170.8, 135.8, 135.7, 134.6, 134.1, 129.5, 128.5, 128.5, 128.3, 127.4, 96.1, 80.0, 78.3, 76.6, 66.7, 66.1, 61.3, 57.1, 55.3, 52.5, 45.9, 37.4, 34.9, 27.6, 26.9, 19.1; IR (neat) 2953, 2893, 2857, 1739, 1225, 1111, 1040, 702 cm^{-1}; HRMS (ESI) m/z 644.3037 [$C_{37}H_{46}NO_7Si$ (M+H) requires 644.3038].

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4.22. Methyl 3-[(*tert*-butyldiphenylsilyl)oxy]-9-methyloxymethyloxy-7-azatricyclo[5.3.0.0^{4,8}]-decane-8-carboxylate (98)

A suspension of **97** (0.340 g, 0.528 mmol) and 10% w/w Pd/C (84 mg) in EtOH (11 mL) was stirred under an atmosphere of H_2 (gas) at room temperature for 16 h. The mixture was filtered through a short pad of Celite, which was rinsed with EtOH (30 mL), and the combined filtrate and washings were concentrated to dryness to give 0.292 g (100%) of the corresponding carboxylic acid as an amorphous solid. The acid thus obtained (0.292 g, 0.528 mmol), 1-hydroxypyridine-2(*1H*)-thione (**88**, 0.101 g, 0.881 mmol), DCC (0.163 g, 0.881 mmol), and DMAP (0.064 g, 0.528 mmol) were dissolved in $CHCl_3$ (5.3 mL). *t*-BuSH (0.59 mL, 5.28 mmol) was added to the solution, and the solution was immediately irradiated with a tungsten filament light bulb (250 W) at room temperature for 1 h. The reaction mixture was concentrated, and the residue was purified by column chromatography eluting with hexanes/EtOAc (as a gradient from 2:1 to 0:1) with 1% v/v Et_3N to give 0.170 g (63%) of **98** as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71–7.66 (comp, 4H), 7.42–7.34 (comp, 6H), 4.72–4.64 (m, 1H), 4.36–4.29 (comp, 2H), 3.72 (s, 3H), 3.22–3.18 (m, 1H), 3.10 (s, 3H), 2.93 (dd, *J*=10.5, 4.2 Hz, 1H), 2.84 (dd, *J*=8.4, 5.4 Hz, 1H), 2.77 (dd, *J*=5.7, 3.9 Hz, 1H), 2.48–2.38 (m, 1H), 2.31–2.22 (m, 1H), 1.66–1.58 (m, 1H), 1.52–1.48 (m, 1H), 1.41–1.35 (comp, 2H), 1.13 (dd, *J*=16.2, 2.4 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.7, 135.9, 135.8, 134.8, 134.3, 129.5, 127.4, 127.4, 96.0, 79.3, 78.8, 77.2, 66.4, 60.3, 55.3, 52.4, 47.4, 46.6, 37.7, 34.7, 27.0, 24.7, 19.2; IR (neat) 2951, 2889, 2857, 1737, 1428, 1262, 1229, 1107, 1044 cm^{-1}; HRMS (ESI) *m*/*z* 510.2673 [$C_{29}H_{40}NO_5Si$ (M+H) requires 510.2670].

4.23. 3-[(*tert*-Butyldiphenylsilyl)oxy]-9-(methyloxymethyloxy)-7-azatricyclo[5.3.0.0^{4,8}]decane-8-carbaldehyde (99)

DIBAL–H (0.74 mL, 1.0 M in hexanes, 0.74 mmol) was added dropwise to solution of **98** (0.251 g, 0.492 mmol) in CH_2Cl_2 (10 mL) at −78 °C and the reaction mixture was stirred for 2 h. The reaction was quenched with MeOH (0.5 mL) and half saturated potassium sodium tartrate solution (5 mL) at −78 °C, and the reaction mixture was warmed to room temperature and stirred vigorously until the organic layer became clear. The separated aqueous layer was extracted with CH_2Cl_2 (2×10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and then concentrated. The crude residue was purified by column chromatography eluting with hexanes/EtOAc (as a gradient from 1:1 to 1:5) with 1% v/v Et_3N to give 0.212 g (90%) of **99** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.30 (s, 1H), 7.70–7.65 (comp, 4H), 7.42–7.33 (comp, 6H), 4.61 (m, 1H), 4.30–4.23 (comp. 3H), 3.21–3.19 (m, 1H), 3.04 (s, 3H), 2.88–2.73 (comp, 2H), 2.62 (dd, *J*=5.7, 3.3 Hz, 1H), 2.48–2.38 (m, 1H), 2.26 (ddd, *J*=13.5, 9.0, 5.1 Hz, 1H), 1.62–1.52 (comp, 2H), 1.47–1.40 (m, 1H), 1.32–1.25 (m, 1H), 1.21 (d, *J*=13.8, 2.7 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.5, 135.9, 135.8, 127.5, 127.4, 96.0, 82.3, 75.4, 66.3, 61.0, 55.3, 47.7, 43.2, 38.2, 35.3, 27.0, 24.7, 19.2; IR (neat) 2933, 2887, 2857, 1731, 1111, 1088, 1045, 703 cm^{-1}; HRMS (ESI) *m*/*z* 480.2562 [$C_{28}H_{38}NO_4Si$ (M+H) requires 480.2565].

4.24. 8-[(1*E*)-But-1-en-1-yl]-3-[(*tert*-butyldiphenylsilyl)oxy]-9-(methyloxymethyloxy)-7-azatricyclo[5.3.0.0^{4,8}]decane (100)

KHMDS (3.52 mL, 0.5 M in toluene, 11.76 mmol) was added dropwise to a solution of **99** (0.212 g, 0.44 mmol) and 1-phenyl-5-propylsulfonyl-1*H*-tetrazole (0.335 g, 1.33 mmol) in DME (15 mL) at −55 °C and the reaction mixture was stirred for 1 h at −55 °C then for 1 h at room temperature. The reaction mixture was quenched with saturated aq NaCl solution (5 mL), the layers separated, and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated, and the crude residue was purified by column chromatography eluting with hexanes/EtOAc (as a gradient from 3:1→1:1→0:1) with 1% v/v Et_3N to give 0.240 g (89%) of **100** as colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72–7.66 (comp, 4H), 7.41–7.33 (comp, 6H), 5.54 (dt, *J*=15.6, 6.3 Hz, 1H), 5.26 (d, *J*=15.6 Hz, 1H), 4.66–4.60 (m, 1H), 4.35 (d, *J*=6.6 Hz, 1H), 4.32 (d, *J*=6.6 Hz, 1H), 3.95 (dd, *J*=10.5, 3.0 Hz, 1H), 3.14–3.07 (m, 1H), 3.09 (s, 3H), 2.88–2.68 (m, 3H), 2.36–2.29 (m, 1H), 2.22 (dd, *J*=6.0, 3.6 Hz, 1H), 2.12 (ddd, *J*=12.9, 8.4, 4.5 Hz, 1H), 2.00 (dt, *J*=7.5, 1.5 Hz, 2H), 1.61–1.51 (m, 2H), 1.42–1.36 (m, 1H), 1.07 (s, 9H), 0.95 (t, *J*=7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.9, 135.8, 132.4, 130.9, 129.3, 127.4, 96.0, 82.1, 75.7, 66.9, 60.3, 55.1, 47.4, 47.0, 37.3, 35.2, 27.0, 25.5, 24.8, 19.2, 13.7; IR (neat) 2958, 2932, 2886, 2857, 1472, 1428, 1106, 1043, 703 cm^{-1}; HRMS (ESI) *m*/*z* 506.3092 [$C_{31}H_{44}NO_3Si$ (M+H) requires 506.3085].

4.25. 8-[(1*E*)-But-1-en-1-yl]-9-(methyloxymethyloxy)-7-azatricyclo[5.3.0.0^{4,8}]decan-3-ol (101)

A solution of **100** (0.130 g, 0.256 mmol), and TBAF (0.487 g, 1.54 mmol) in THF (5.0 mL) was stirred at 50 °C for 16 h. The reaction mixture was cooled to room temperature and Et_3N (0.2 mL) was added. The reaction mixture was concentrated and the crude residue was purified by column chromatography eluting with hexanes/EtOAc (3:1) to remove the nonpolar impurities and then with EtOAc/MeOH (10:1) with 1% v/v Et_3N to give 0.065 g (95%) of **101** as a light yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.68 (dt, *J*=15.6, 6.6 Hz, 1H), 5.48 (d, *J*=15.6 Hz, 1H), 4.65–4.54 (comp, 3H), 4.14 (dd, *J*=10.5, 2.7 Hz, 1H), 3.35 (s, 3H), 3.29–3.26 (m, 1H), 2.91–2.82 (m, 1H), 2.71 (ddd, *J*=14.1, 8.7, 5.4 Hz, 1H), 2.55–2.45 (m, 1H), 2.32 (dd, *J*=6.0, 3.6 Hz, 1H), 2.09–1.97 (m, 2H), 1.85 (ddd, *J*=13.2, 8.7, 5.4 Hz, 1H), 1.66–1.56 (m, 2H), 1.45–1.36 (m, 2H), 0.97 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.1, 131.5, 96.4, 82.1, 75.8, 65.0, 60.2, 55.4, 47.3, 46.9, 37.3, 34.3, 25.5, 24.6, 13.7; IR (neat) 3368, 2957, 2886, 1454, 1151, 1097, 1042, 961 cm^{-1}; HRMS (ESI) *m*/*z* 268.1910 [$C_{15}H_{26}NO_3$ (M+H) requires 268.1907].

4.26. 8-[(1*E*)-But-1-en-1-yl]-9-(methyloxymethyloxy)-7-azatricyclo[5.3.0.0^{4,8}]decan-3-one (105)

Et_3N (0.068 mL, 0.486 mmol) and SO_3·Py (0.039 g, 0.243 mmol) were sequentially added to a solution of **101** (0.013 g, 0.049 mmol) in CH_2Cl_2 (1 mL) and DMSO (0.5 mL) at room temperature and the reaction mixture was stirred for 4 h. The reaction mixture was diluted with saturated aq $NaHCO_3$ solution (2 mL), the layers separated, and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated, and the crude residue was purified by column chromatography eluting with hexanes/EtOAc (as a gradient from 1:1 to 0:1) with 1% v/v Et_3N to give 0.010 g (77%) of **105** as colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.74 (dt, *J*=15.9, 6.9 Hz, 1H), 5.41 (dt, *J*=15.9, 1.5 Hz, 1H), 4.59 (s, 2H), 4.21 (d, *J*=8.7 Hz, 1H), 3.53 (t, *J*=6.3 Hz, 1H), 3.33 (s, 3H), 3.16–3.00 (m, 2H), 2.85 (d, *J*=6.6 Hz, 1H), 2.58–2.50 (m, 1H), 2.45–2.36 (m, 1H), 2.19–2.11 (m, 1H), 2.07 (comp, 3H), 1.69–1.60 (comp, 2H), 0.99 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.3, 132.2, 129.9, 95.8, 82.0, 79.7, 60.4, 56.9, 55.6, 46.6, 41.2, 38.6, 30.9, 25.5, 13.6; IR (neat) 2958, 2893, 1722, 1106, 1091, 1040 cm^{-1}; HRMS (ESI) *m*/*z* 266.1754 [$C_{15}H_{24}NO_3$ (M+H) requires 266.1751].

4.27. Ethyl 2-{8-[(1*E*)-but-1-en-1-yl]-9-(methyloxymethyloxy) 3-oxo-7-azatricyclo[5.3.0.0^{4,8}]decan-2-yl}acetate (106)

Freshly prepared LDA (0.42 mL, 0.2 M in THF, 0.084 mmol) was added to a solution of **105** (0.016 g, 0.060 mmol) in THF (1.2 mL) at −10 °C, and the reaction mixture was stirred for 1 h at −10 °C. Ethyl

iodoacetate (0.011 mL, 0.090 mmol) was then added at −10 °C, and the reaction was continued for 30 min. DABCO (20 mg) was added, and the solution was warmed to room temperature. Saturated aq NaCl (5 mL) and EtOAc (5 mL) were added, the layers were separated, and the aqueous layer extracted with EtOAc (2×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and then concentrated under reduced pressure, and the crude residue was purified by column chromatography eluting with hexanes/EtOAc (as a gradient from 1:1 to 0:1) with 1% v/v Et_3N to give 0.013 g (62%) of **106** as colorless oil along with 0.003 g (16%) of starting material **105**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.72 (dt, J=15.6, 6.3 Hz, 1H), 5.41 (d, J=15.6 Hz, 1H), 4.57 (s, 2H), 4.22–4.14 (comp, 3H), 3.40 (d, J=5.7 Hz, 1H), 3.33 (s, 3H), 3.18–3.07 (m, 2H), 2.88–2.75 (comp, 3H), 2.54 (dd, J=15.6, 10.8 Hz, 1H), 2.41–2.32 (m, 1H), 2.19–2.02 (comp, 3H), 1.74 (d, J=12.9 Hz, 1H), 1.70–1.62 (m, 1H), 1.27 (t, J=7.2 Hz, 3H), 0.99 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.4, 171.7, 132.3, 129.3, 95.6, 82.2, 78.9, 63.0, 60.9, 56.6, 55.7, 48.3, 45.7, 41.8, 38.9, 30.2, 25.5, 14.2, 13.6; IR (neat) 2960, 1732, 1715, 1151, 1106, 1039 cm$^{-1;}$ HRMS (ESI) m/z 352.2123 [$C_{19}H_{30}NO_5$ (M+H) requires 352.2119].

4.28. Ethyl 2-{2-[(1*E*)-but-1-en-1-yl]-7-hydroxy-11-oxa-3-azatetracyclo[5.3.1.0^{2,6}.0^{3,9}]undecan-8-yl}acetate (107)

A solution of **106** (0.014 g, 0.040 mmol) and DBU (0.024 mL, 0.16 mmol) in toluene (0.4 mL) was heated at 130 °C (bath temperature) for 4 h in a screw-capped vial. The reaction mixture was cooled to room temperature and filtered through a pad of silica gel (first with EtOAc then EtOAc/MeOH 10:1) to afford the 0.014 g of the epimerized product as yellow oil. The crude residue was dissolved in CH_2Cl_2 (0.4 mL) and TFA (0.31 mL, 4.0 mmol) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was sequentially diluted with 5 M aq NaOH (1 mL), CH_2Cl_2 (5 mL), and $NaHCO_3$ (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by column chromatography eluting with EtOAc with 1% v/v Et_3N to give 0.010 g (81%) of **107** as light yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.72 (dt, J=15.5, 6.0 Hz, 1H), 5.48 (d, J=15.5 Hz, 1H), 5.36 (br s, 1H), 4.25 (br s, 1H), 4.19 (qd, J=7.0, 2.0 Hz, 2H), 3.19 (br s, 1H), 3.06–2.96 (m, 2H), 2.92 (dd, J=17.0, 9.5 Hz, 1H), 2.45 (t, J=3.5 Hz, 1H), 2.23–2.19 (m, 2H), 2.09–2.03 (m, 2H), 1.89–1.81 (comp, 3H), 1.64 (dt, J=12.0, 3.0 Hz, 1H), 1.28 (t, J=7.0 Hz, 3H), 0.99 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.6, 132.6, 127.2, 104.8, 82.3, 81.6, 65.3, 61.5, 56.0, 47.8, 36.9, 33.2, 32.5, 26.8, 25.4, 14.1, 13.6; IR (neat) 3349, 2962, 1733, 1325, 1273, 1227, 1179, 1038, 972 cm^{-1}; HRMS (ESI) m/z 308.1859 [$C_{17}H_{26}NO_4$ (M+H) requires 308.1856]; $[\alpha]_D^{25}$ +17.3 (c 0.5, $CHCl_3$).

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21. The ratio of **39** and **40** was based on an analysis of the ^{1}H NMR spectrum of the crude reaction mixture and confirmed by the isolated yields of both regioisomers. The ratio based on the ^{1}H NMR spectrum relies upon the relative integrations of the diagnostic *endo*-C(1)–H_a proton of **39** and the *endo*-C(1)–H_a proton of **40**. These protons appear as well resolved, sharp doublets between 1. 5 and 2.2 ppm in all cycloadducts, with the signal from the desired cycloadducts **33**, **39a**, **39b**, **67**, and **72** always being upfield from the undesired regioisomers **32**, **40a**, **40b**, **68**, and **77**. The C(1)–Ha protons of **33**, **39a**, **39b**, **67**, and **72** have geminal coupling constants of 18.0 Hz (±0.1 Hz), whereas the coupling constants for the C(1)–Ha protons of **32**, **40a**, **40b**, **68**, and **77** are 15. 6 Hz (±0.1 Hz).

39 40

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