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# Enantioselective Total Syntheses of the Proposed and Revised Structures of Methoxystemofoline: A Stereochemical Revision

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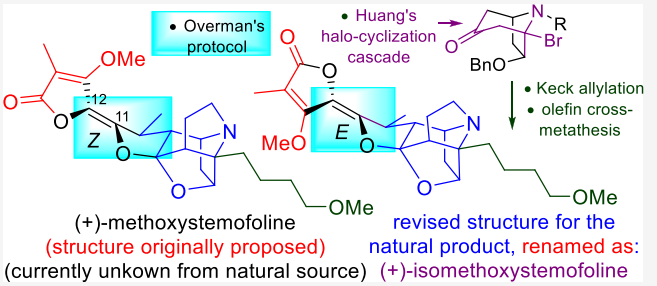
**ABSTRACT:** This article describes the full details of our synthetic efforts toward the enantioselective total synthesis of the complex alkaloid methoxystemofoline. The enantioselective construction of the tetracyclic core features: (1) the Keck allylation at the *N*-$\alpha$ bridgehead carbon to forge the tetrasubstituted stereocenter; (2) an olefin cross-metathesis reaction for the side-chain elongation that is amenable for the synthesis of congeners and analogues; and (3) a regioselective aldol addition reaction with methyl pyruvate that ensured the subsequent regioselective cyclization reaction to construct the fourth ring. Overman's method was employed to install the 5-(alkoxyalky1idene)-3-methyl-tetronate moiety. In the last step, a nonstereoselective reaction resulted in the formation of both the proposed structure of methoxystemofoline and its *E*-stereoisomer, the natural product (revised structure), in a 1:1 ratio. We suggest to rename the natural product as isomethoxystemofoline, and report for the first time the complete $^1$H NMR data for this natural product.






## INTRODUCTION

*Stemona* plants (Stemonaceae) have been used as folk medicine in Asian countries China, Japan, Vietnam, and Thailand for thousands of years as insecticides in agriculture, as anthelmintic agents on domestic animals, and as anticough agents for humans.[1] Known as "Bai Bu" in the traditional Chinese medicine, the roots, stems, and leaves of *S. tuberosa* Lour., *S. sessilifolia* (Miq.) Miq., *S. japonica* (Blume) Miq. *S. parviflora* Wright, C. H., and related *Stemona* species have been used as antitussive agents and as pesticides.[2a] Three species of the above-mentioned *Stemona* genus have been listed since 1985's edition of the "Chinese Pharmacopoeia" as cough remedies.[2b] To date, over 220 *Stemona* alkaloids have been isolated from plants of genus *Stemona* (family *Stemonaceae*).[1a]

Stemofoline alkaloids are a subfamily of *Stemona* alkaloids comprising over 20 members.[1a] Stemofoline (**1** in Figure 1), the first member of this subfamily of alkaloid was isolated in 1970 by Irie and co-workers from the stems and leaves of *Stemona japonica* Miq.[3] Its structure including absolute configuration was unambiguously determined by the X-ray crystallographic analysis of single crystals of stemofoline hydrobromide monohydrate. In 1991, Xu and co-workers reported the isolation of two new stemofoline alkaloids named oxystemofoline (**3**) and methoxystemofoline (**4**), along with the known stemofoline (**1**) as minor stemofoline alkaloids from the roots of *S. parviflora* Wright, C. H.,[4a] an herb used by the Li ethnic group in Hainan Island, China. The structures of oxystemofoline (**3**) and methoxystemofoline (**4**) were assigned by means of IR, MS, and 2D NMR techniques, and by the

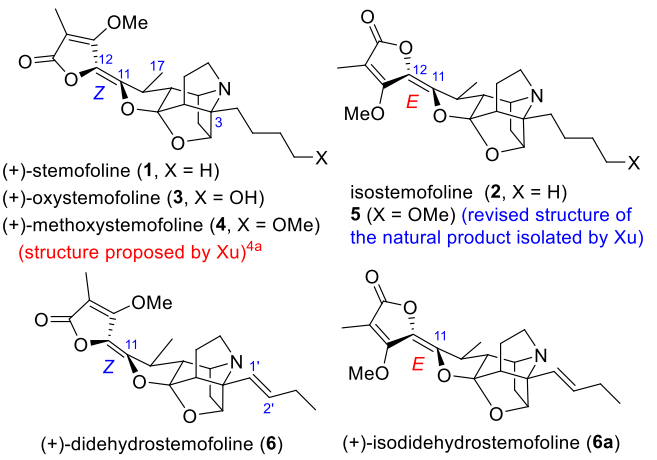



**Figure 1.** Structures and proposed structure (for **4**) of representative stemofoline alkaloids.

conversion of oxystemofoline (**3**) to **4** via *O*-methylation. The authors claimed that the specific optical rotation and CD spectra implied that the three alkaloids have the same absolute

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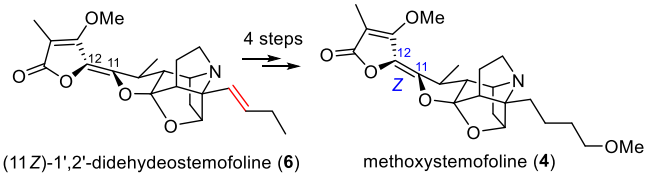
configuration, and the IR, specific optical rotation, $^1$H NMR, and other physicochemical data were in agreement with those reported by Irie et al. for the stemofoline isolated from *Stemona japonica*. However, for methoxystemofoline (**4**), only $^1$H NMR signals of the methyl groups and H-7 were reported, and for stemofoline (**1**), the optical rotation data was not described. Moreover, the reported CD spectrum of methoxystemofoline (**4**) is actually different from those of oxystemofoline (**3**) and stemofoline (**1**).[4a] In 2016, from the same species, 8 new and 17 known *Stemona* alkaloids including the above-mentioned three alkaloids were isolated.[4b] In that report, for the known compounds including oxystemofoline (**3**), methoxystemofoline (**4**), and stemofoline (**1**), their structures were determined by comparing the NMR and MS data with those reported in the literature, but the data were not reported.

Due to the intricate structure featuring the pentacyclic cage-type core, seven contiguous stereogenic centers, and the 5-(1-alkoxyalkylidene)tetronate moiety with hard to control geometry, the total synthesis of stemofoline group alkaloids presents a formidable challenge. Hence, although tremendous synthetic efforts have been consecrated since the early 1980s which have resulted in several valuable strategies,[5−7] the first racemic total synthesis of isostemofoline (**2**) was not accomplished until 1999 by Kende and co-workers.[6] In 2003, Overman and co-workers disclosed an elegant total synthesis of (±)-didehydrostemofoline (**6**) and (±)-isodidehydrostemofoline (**6a**).[7] The enantioselective formal total synthesis of didehydrostemofoline and isodidehydrostemofoline was reported in 2012 by Martin and co-workers through an elegant catalytic dipolar cycloaddition cascade.[5k,l] Important contributions also came from the group of Ye,[8a] and in particular from Pyne and co-workers,[8b,d] who undertook systematic phytochemical and semisynthetic studies, which culminated in the isolation and synthesis of a series of stemofoline alkaloids and unnatural analogues[8c,b,d] including oxystemofoline (**3**) and methoxystemofoline (**4**) (Scheme 1). However, the total

**Scheme 1. Pyne's Semisynthesis of Methoxystemofoline (4) by Side-Chain Modification of (11*Z*)-1′,2′-Didehydeostemofoline (6)**

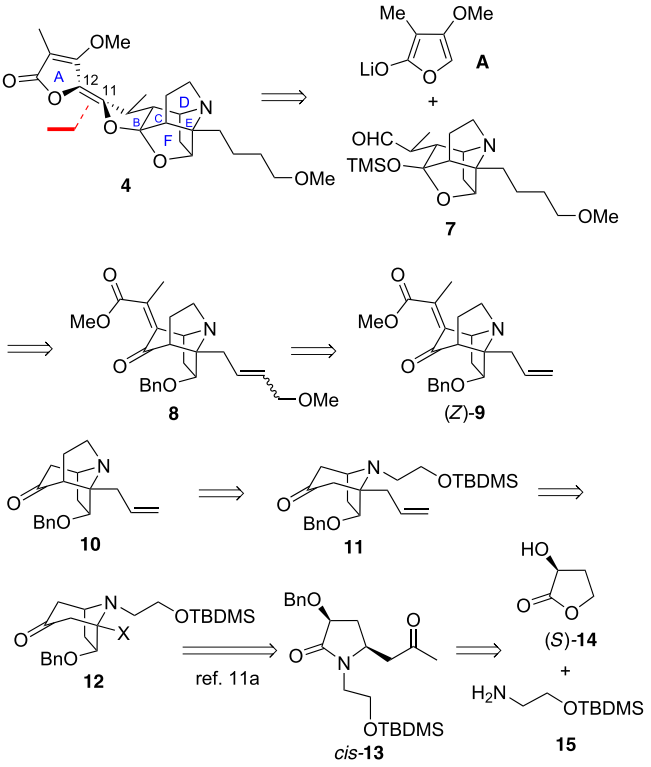



synthesis of methoxystemofoline (**4**) has not yet been reported.[14a] Many stemofoline alkaloids and analogues showed remarkable bioactivities including insecticidal,[9a,b] acetylcholinesterase (AChE)-inhibitory, nematicidal,[4b] and anti-inflammatory activities.[9c] In this regard, employing stemofoline (**1**) as a lead compound, the scientists at Bayer CropScience AG, and at Syngenta have developed Sivanto (common name: flupyradifurone, FPF)[9d] and cyanotropanes[9e] as two classes of commercial insecticides. Significantly, stemofoline and analogues have been shown to possess effective MDR reversing activities, and may be used in the cancer chemotherapy.[10]

In continuation of our programs aimed at both the development of efficient synthetic methodologies,[11] and the total synthesis[12] of polycyclic natural products,[13] we have been engaged in the enantioselective total synthesis of stemofoline alkaloids,[14a] and disclosed very recently the enantioselective total synthesis of (+)-stemofoline (**1**).[14b] We report herein the full account of the enantioselective total synthesis of both the proposed and revised structures of methoxystemofoline (**4**).

**Retrosynthetic Analysis.** Our retrosynthetic analysis of the originally proposed structure of methoxystemofoline (**4**) is outlined in Scheme 2. A retro-vinylogous aldol disconnection[6,7] suggests aldehyde **7** as the advanced intermediate and enolate of methyl α-methyltetronate (**A**) as the nucleophilic partner. Compound **7** should be available from tropin-3-one derivative **8** via hydrogenation/hydrogenolysis, *O*-protection of hemiacetal and reduction of ester. A retro-olefin cross-metathesis[15] disconnection implied allylic compound (*Z*)-**9** as another key intermediate. A retro-aldol condensation disconnection leads to tropin-3-one derivative **10**, which could be available from compound **11**. The latter is anticipated to be synthesized from 1-bromotropin-3-one derivative **12**. By the tandem triflic anhydride ($Tf_2O$)-mediated amide-activation−halide-promoted halo-tropinonation method developed from our laboratory,[11a] **12** could be readily constructed from keto-lactam *cis*-**13**, which could in turn be synthesized from commercially available α-hydroxy-γ-lactone (*S*)-**14** and protected 2-aminoethanol **15**.

**Scheme 2. Retrosynthetic Analysis of Originally Proposed Structure for Methoxystemofoline (4)**




## RESULTS AND DISCUSSION

Our total synthesis started from the commercially available (*S*)-α-hydroxy-γ-lactone **14**, which can also be prepared from L-malic acid by a known procedure.[16] *O*-Benzylation of hydroxylactone **14** (BnBr, $Ag_2O$, rt) gave the known (*S*)-α-benzyloxy-γ-lactone **16**,[17] which was subjected to aminolysis with protected β-amino alcohol **15** to give hydroxyamide **17** in 81% overall yield (Scheme 3). It was expected that oxidation of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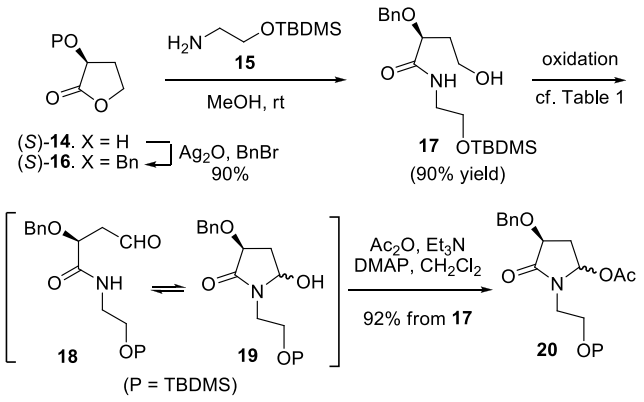
**Scheme 3. Synthesis of Chiral Precursor 20**




the alcohol would lead, via aldehyde−amide **18**, to the formation of tautomeric hemiaminal **19**. However, oxidation of hydroxyamide **17** with IBX,[18] Parikh−Doering reagent,[19] or Dess−Martin periodinane[20] yielded, in all three cases, an inseparable mixture of **18** and **19** (Table 1, entries, 1−3).

**Table 1. Reaction Optimization for the Formation of 19**

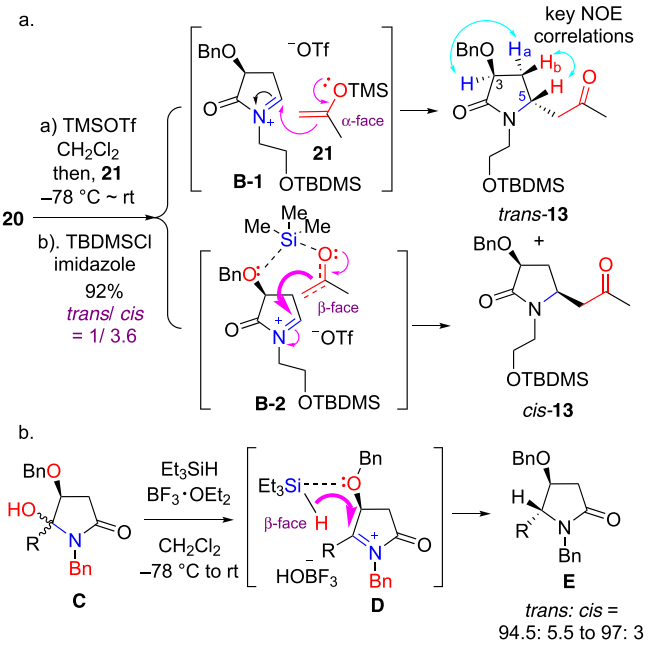
| entry | reaction conditions | yield[a] (%) | ratio (**18**:**19**)[b] |
|---|---|---|---|
| 1 | IBX (3.0 equiv), DMSO, rt, 2 h | 57 | 20:1 (0:100)[c] |
| 2 | $SO_3$·py (4.0 equiv), $Et_3N$ (7.0 equiv), DMSO, rt, 1 h | 78 | 1:2.5 (0:100)[c] |
| 3 | DMP (1.3 equiv), $CH_2Cl_2$, rt, 2.5 h | 85 | 5:1 (0:100)[c] |
| 4 | DMP (1.5 equiv), $CH_2Cl_2$, rt, 2.5 h | 70[d] | 5:1 (0:100)[c] |
| 5 | $(COCl)_2$ (1.1 equiv), DMSO (2.2 equiv), $Et_3N$ (5.0 equiv), $CH_2Cl_2$, −78 °C, 2.5 h | 95[d] | 0:100[c] |

[a]Isolated yield. [b]Ratio determined by $^1H$ NMR of the crude product. [c]Ratio obtained after refluxing with $SiO_2$ in MeOH for 3 h. [d]Yield at a 3 g scale.

Delightedly, it was uncovered that after stirring the crude products with silica gel in MeOH at reflux for 3 h, the aldehyde−amide **18** tautomerized completely to **19**. Although the Dess−Martin oxidation of **17** produced **18** and **19** in a high yield (85%, Table 1, entry 3), the yield decreased to 70% upon scaling up to a 3.0 g scale (Table 1, entry 4). Moreover, the solids formed during the oxidation brought up a trouble of separation. These problems were solved by employing the Swern oxidation,[21] which provided the desired hemiaminal **19** in 95% yield (Table 1, entry 5). Significantly, the reaction can be scaled up to a 17 g scale, and after a routine workup, the crude product was completely tautomerized ($SiO_2$, MeOH, reflux, 3 h) to give hemiaminal **19** as an inseparable diastereomeric mixture in a ratio of 57:43. The diastereomeric mixture **19**, without separation, was acetylated ($Ac_2O$, DMAP, $NEt_3$) to give acetate **20** as an inseparable diastereomeric mixture (ratio = 1.3:1, stereochemistries not determined) in a combined yield of 92% from **17**. Because the subsequent Lewis acid-mediated α-amidoalkylation reaction[22] was believed to pass through an *N*-acyliminium intermediate[22] (cf. **B-1** in Scheme 4), the diastereomeric mixture **20** was used in the next step without separation.

Indeed, exposing the diastereomeric mixture of **20** to silyl enol ether of acetone (**21**) and TMSOTf in $CH_2Cl_2$ (−78 °C, 2 h, then warm to rt, overnight) yielded the α-amidoalkylation

**Scheme 4. (a) Synthesis of Keto-Lactams and Rationalization of the Stereochemical Outcome; (b) Our Previous Stereoselective Reaction**




products containing both the desired one (**13**) and that with concomitant *O*-desilylation. Without separation, the resultant mixture was treated with TBDMSCl (imidazole, rt) to give keto-lactam **13** in an overall yield of 92% from **20** as a 3.6:1 diastereomeric mixture in favor of the desired *cis*-diastereomer (Scheme 4). The stereochemistry of the minor diastereomer was determined to be *trans* by the observed strong correlations between H-3 and H-4a, and between H-4b and H-5 in the NOESY spectrum of *trans*-**13** (see *trans*-**13** in Scheme 4 and Supporting Information).[23] Thus, the stereochemistry of the major diastereomer was deduced to be *cis*-**13**. The similar 1,3-*cis*-diastereoselective α-amidoalkylation reactions have been reported by Seebach.[22d] The observed *cis*-diastereoselectivity could be understood by taking into account the *N*-acyliminium intermediate **B-1** and transition state **B-2**. The steric bias on the α-face of **B-1** would lead to a *trans*-addition of silyl enol ether **21** to yield *trans*-**13**. However, the observed *cis*-diastereoselective addition implies another fact that dominates over the steric effect. The transition state **B-2** features a weak interaction between the silicon atom and oxygen atom in OBn, and thus the hinge effect is suggested to account for the observed *cis*-selectivity. Previously, to account for the highly *trans*-diastereoselective reductive dehydroxylation of hemiaminal **C** to give **E**, we have suggested a similar transition state **D** as a working model.[22a]

Next, we proceeded to construct the tropin-3-one skeleton **12** by the method we developed recently.[11a] Thus, keto-lactam *cis*-**13** was exposed to TMSOTf and $Et_3N$ in $CH_2Cl_2$ at 0 °C to form the silyl enol ether **22** (Scheme 5). Treating the latter to $Tf_2O$/DTBMP and $ZnBr_2$ ($CH_2Cl_2$, −78 °C to rt) afforded, via the intramolecular Mannich-type reaction of the intermediate **F**, the desired cyclization product 1-bromotropin-3-one **12** in 78% yield from *cis*-**13**.

Now we were in a position to investigate the introduction of an allyl group at C1 of **12** to build the bridgehead tetrasubstituted stereocenter (α-chiral amine). In our previous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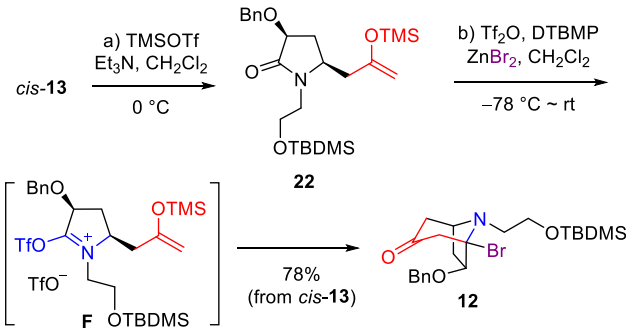
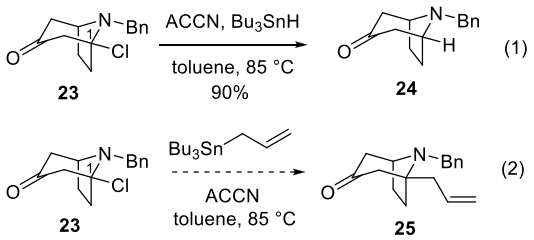
**Scheme 5. Two-Step Synthesis of Chiral Bicyclic Core**



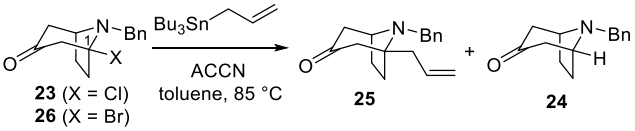

investigation, we have developed a method for the reductive dehalogenation of 1-chlorotropin-3-one **23** under radical conditions (eq 1).[11a] Inspired by that work, we envisioned




that if tributyltin hydride is replaced by allyltributyltin, it would be possible to achieve a radical allylation reaction (Keck allylation[24]) (eq 2). It is worth mentioning that both the bridgehead radicals[25] and the C−C bond formation based on $\alpha$-aminoalkyl radicals are well documented.[26] However, very few examples of the generation - reduction of bridgehead *N*-$\alpha$-carbon radicals have been reported,[27,11a] and to our knowledge, the Keck allylation has not been applied to the bridgehead $\alpha$-aminoalkyl radicals.

As a model study, we first investigated the radical allylation of 1-chlorotropin-3-one **23**. When a mixture of 1-chlorotropin-3-one **23** (1.0 equiv), 1,1′-azobis(cyclohexanecarbonitrile) (ACCN)[28] (1.2 equiv), and $AllylBu_3Sn$ (2.0 equiv) in toluene was stirred at 85 °C for 20 h, the desired product **25**[29] was obtained in 24% yield, along with the reduced product **24** in 47% yield (Table 2, entry 1). The formation of a substantial amount of **24** may reasonably be ascribed to a hydrogen abstraction of the presumed radical intermediate **G** (Figure 2) from the solvent (toluene). We envisaged that this problem

**Table 2. Radical Dehalogenative Allylation (Keck Allylation) of 1-Halo-tropin-3-ones**




| entry | halide (X) | ACCN (equiv) | $AllylBu_3Sn$ (equiv) | product **25** (yield)[a] (%) |
|---|---|---|---|---|
| 1 | **23** (Cl) | 1.2 | 2.0 | 24 |
| 2 | **23** (Cl) | 1.2 | 10.0 | 52 |
| 3 | **26** (Br) | 1.2 | 10.0 | 76 |
| 4 | **26** (Br) | 0.2 | 10.0 | 71 |
| 5 | **26** (Br) | 0.2 | 2.0 | 5 |

[a]Isolated yield.

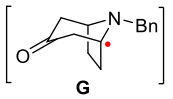
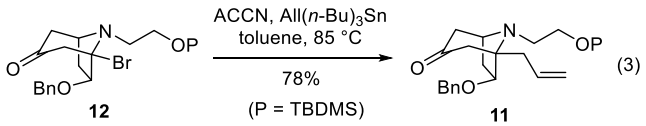



**Figure 2.** Presumed bridgehead $\alpha$-aminoalkyl radical.

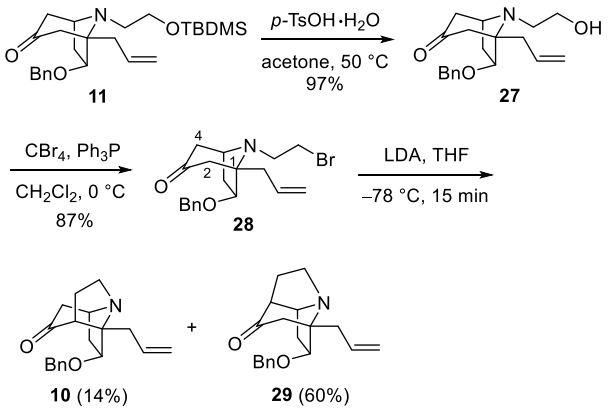
could be tackled by increasing the amount of $AllylBu_3Sn$. Indeed, by employing 10.0 equiv of $AllylBu_3Sn$, the yield of **25** was improved to 52% (entry 2). Moreover, the use of the corresponding bromide **26**[11a] allowed further improving the yield of **25** to 76% (entry 3). It was observed that even with 0.2 equiv of ACCN, a 71% yield of **25** was obtained (entry 4), while using fewer equivalents of $AllylBu_3Sn$ (2.0 equiv) led to a dramatic drop of yield to 5% (entry 5).

With the conditions defined for the debrominative allylation at the bridgehead carbon, its application to substrate **12** was examined. In the event, a mixture of allyltributyltin, ACCN, and 1-bromotropinone **12** in toluene was heated at 85 °C for 18 h that produced the desired allylation product **11** in 78% yield (eq 3).




**Initial Attempts for the Regioselective Construction of the Tricyclic Core 10.** Our first approach to the tricyclic core **10** is shown in Scheme 6. Silyl ether **11** was converted to

**Scheme 6. Attempted Synthesis of the Tricyclic Core 10**




bromide **28** by *O*-desilylation (*p*-TsOH·$H_2O$, acetone, 50 °C) and bromination ($Ph_3P$, $CBr_4$, $CH_2Cl_2$, 0 °C). Treating tropin-3-one bromide **28** with LDA in THF for 15 min at −78 °C produced two regioisomeric cyclization products **10** and **29** in a combined yield of 74%. Unfortunately, the desired compound **10** turned out to be the minor regioisomer that was formed in only 14% yield. The major regioisomer **29**, obtained in 60% yield, was assumed to be formed from the enolate generated from deprotonation at the less hindered C-4.

To create a molecular environment favoring a selective deprotonation at C-2, a change of the *O*-protecting group from benzyl to a chelating one was envisaged, and MOM was selected for this purpose (Scheme 7). Thus, the ketone group in **11** was protected in situ in form of enolate[30] by treating with LDA at −25 °C. The resultant enolate was exposed to lithium naphthalenide (LN) for 10 min to cleave the *O*-benzyl group, which delivered compound **30** in 81% yield after workup.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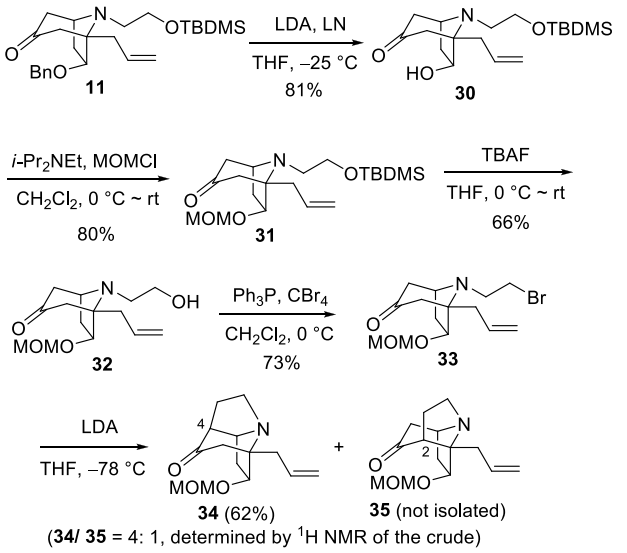
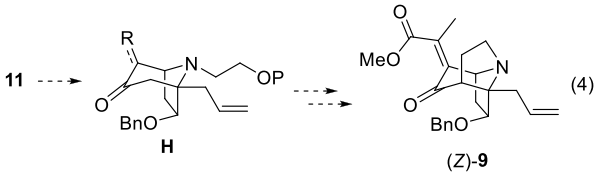
**Scheme 7. Further Attempted Synthesis of the Tricyclic Core 35**




Successive *O*-reprotection (*i*-$Pr_2NEt$, MOMCl, $CH_2Cl_2$, 0 °C to rt), *O*′-desilylation (TBAF, THF, 0 °C to rt), and bromination ($Ph_3P$, $CBr_4$, $CH_2Cl_2$, 0 °C) produced the desired tropin-3-one derivative **33** in an overall yield of 39%. Disappointedly, treatment of **33** with LDA at −78 °C produced a regioisomeric mixture of cyclization products in a 4:1 ratio as determined by $^1H$ NMR analysis of the crude product, from which the undesired regioisomer **34** was isolated once again as the major diastereomer in 62% yield.

**Construction of the Tricyclic Core by a Modified Strategy.** Although we were unable to perform a regioselective intramolecular alkylation at C-2 from either **28** or **33**, the results were still encouraging considering the possibility to undertake a regioselective enolization at C-4. It is reasonable to expect that the first-functionalization at C-4 would not only proceed regioselectively to yield **H**, but also ensure the subsequent cyclization to be occurred at C-2 (eq 4). Thus, a




modification of the synthetic sequence (cf. Scheme 2) by changing the order of C−C bond formations at C-2 and C-4 was envisioned. We first attempted an alkylation at C-4 of tropinone **11**. However, we were unable to undertake the desired alkylation by successive treatment of **11** with a base (LDA, or NaHMDS, or KHMDS) and an ethyl haloacetate ($Br/ICH_2CO_2Et$). On the other hand, an aldol reaction with ethyl glyoxalate was tried. Disappointedly, treatment of tropinone **11** with $TiCl_4$, (*i*-Pr)$_2$NEt and ethyl glyoxalate in $CH_2Cl_2$ at −78 °C to rt produced a complex mixture. We next investigated the use of less reactive methyl pyruvate[31] as a partner for the aldol reaction under basic conditions, and the results are summarized in Table 3. Deprotonation of tropinone **11** with NaHMDS at −78 °C followed by exposing the resulted enolate to methyl pyruvate yielded regioselectively the desired C-4 aldol adduct **36** as a mixture of four diastereomers (dr = 23:10:33:33) in a combined yield of 81% (Table 3, entry 1). No regioisomer **37** was observed. Using LDA as the base for the deprotonation yielded, in addition to four diastereomers of **36** in 62% combined yield, regioisomer **37** in 16% yield (entry 2). When KHMDS or LiHMDS was used as the base, and the reaction mixture was warmed up to room temperature, a substantial amount of starting material was recovered (entries 3 and 4). Surprisingly, when the LDA-mediated reaction was warmed-up to room temperature, the yield of **36** decreased to 10%, and a 74% yield of the starting material **11** was obtained (entry 5). These results implied that **36** and **37** have a propensity of retro-aldol reaction at rt. Thus, the conditions highlighted in entry 2 was employed for the subsequent dehydration reaction.

For the dehydration of the aldol adduct **36**, several protocols were attempted, including acidic elimination ($H_2SO_4$, 0.5 M in THF; $H_2SO_4$/HCOOH), elimination via mesyl/trifluoroacetyl esters, and Martin's sulfurane-mediated reaction.[32] However, all failed to give the desired product **38** or **39**. Interestingly, when a solution of **36** and *p*-TsOH in toluene was heated at reflux for 3 h, **40** and **41** were obtained both in 34% yield (Scheme 8). The structure of **41** was determined by X-ray diffraction analysis (Figure 3, see the SI for detailed X-ray crystallography data).[33] Although the desired product **38** or **39** was not obtained, the formation of **40** and **41** in good combined yield is interesting, because their formation implied several reactions occurred in tandem, which include the desired dehydration, *O*-desilylation, enolization, butenolide ring formation (for **40**), and ketalization (for **41**).

The selective dehydration was finally achieved by exposing **36** to $POCl_3$/pyridine at 0 °C to rt,[34] which produced the *α*,*β*-unsaturated ester **38** in 76% yield as a geometric mixture (ratio = 3.6:1) in favor of *Z*-isomer (Scheme 9). The stereochemistry of (*Z*)-**38** was determined by means of NOESY technique. A NOE correlation was observed between the protons of the *α*-methyl group (*δ* 1.94 ppm) and H-5 (*δ* 4.26 ppm) of the major diastereomer, which indicated that the latter being the desired *Z*-isomer [(*Z*)-**38**] (see: Supporting Information). Our next task was the construction of the third bridge ring. For this purpose, diastereomer (*Z*)-**38** was subjected to *O*-desilylation (*p*-TsOH, acetone, 50 °C) and bromination ($Ph_3P$, $CBr_4$), which afforded bromide **42** in 97% over two steps. Surprisingly, treatment of enone bromide **42** with LDA in THF at −78 °C for 20 min afforded compounds **43** and **44** in 48% and 21% yield, respectively. The use of NaH as the base (0 °C to rt) led to the desired cyclization product (*Z*)-**9** in 34% yield, along with its isomer **44** in 10% yield. In this regard, NaOMe turned out to be a superior base. Thus, exposing keto-bromide derivative **42** to NaOMe (1.1 equiv) in THF at 0 °C yielded the cyclization products (*Z*)-**9** and **44** in 68% and 27% yield, respectively (combined yield: 95%). Further efforts to improve the regioselectivity of the reaction were unfruitful.

**Formation of the Advanced Intermediate 7.** With the tricyclic core (*Z*)-**9** in hand, our next task was the elongation of the side chain at C-1. The olefin cross-metathesis reaction[16] was used for this aim, and compound **11** was selected for a model study (Scheme 10, a). Considering the basicity of the substrate,[35] Ti(O*i*-Pr)$_4$[35] was used as an additive to ensure a smooth olefin cross-metathesis reaction. Hence a mixture of **11**, (*Z*)-1,4-dimethoxybut-2-ene (5.0 equiv), Grubbs second generation catalyst (20% equiv), and Ti(O*i*-Pr)$_4$ (1.0 equiv) was heated in toluene at 60 °C for 1.5 h. The desired olefin cross-metathesis reaction proceeded smoothly to give the chain


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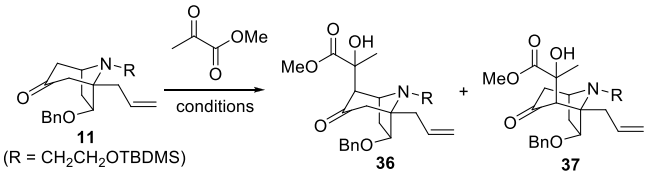
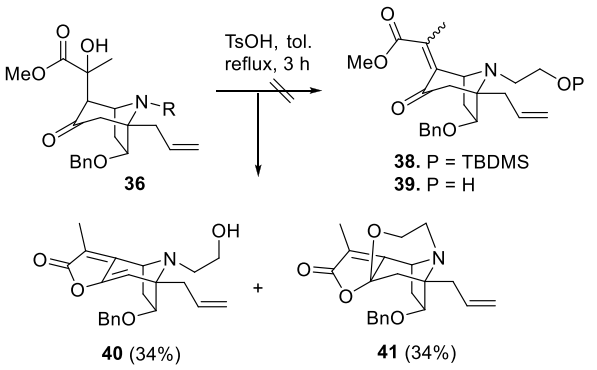
**Table 3. Optimization of the Aldol Reaction of Tropin-3-one 11 with Methyl Pyruvate**




| | | | 36 | | 37 | |
|---|---|---|---|---|---|---|
| entry | base | temperature (time) | yield[a] (%) | dr[b] | yield[a] (%) | recovered **11**[c] (%) |
| 1 | NaHMDS | −78 °C (2.5 h) | 81 | 23:10:33:33 | – | 5 |
| 2 | LDA | −78 °C (1.5 h) | 62 | N.D.[c] | 16 | 17 |
| 3 | KHMDS | −78 °C (2 h) to rt | 34 | 43:4:43:9 | – | 32 |
| 4 | LiHMDS | −78 °C (2 h) to rt | 40 | 29:71 | 8 | 40 |
| 5 | LDA | −78 °C (2 h) to rt | 10 | – | – | 74 |

[a]Isolated yield. [b]Ratio determined by $^1$H NMR of the crude product. [c]No determined.

**Scheme 8. Attempted Dehydration of Hydroxyketone 36**



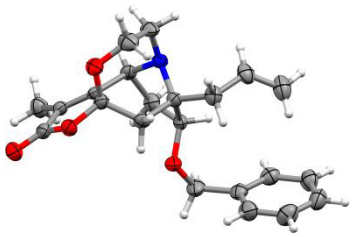
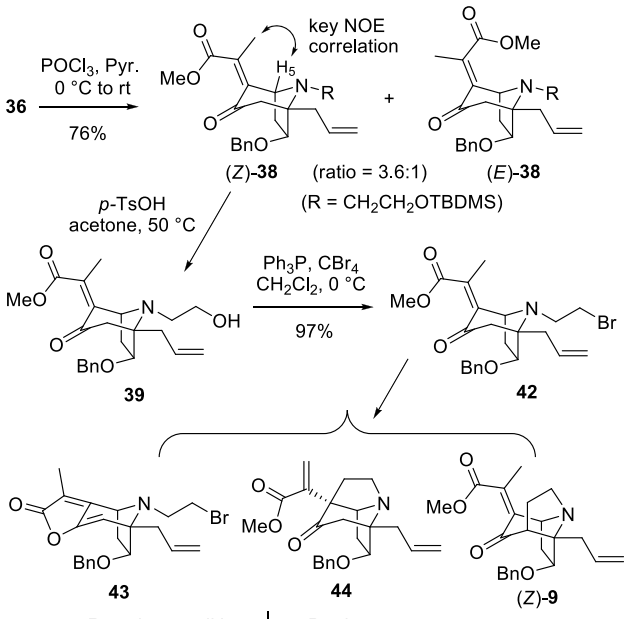



**Figure 3.** X-ray crystal structure of compound **41** (ORTEP ellipsoids are depicted at the 50% level).

**Scheme 9. Synthesis of Fully Functionalized Tricyclic Core 9**




| Reaction conditions | Products |
|---|---|
| LDA, THF, −78 °C | **43** (48%) + **44** (21%) |
| NaH, THF, 0 °C to rt | *Z*-**9** (34%) + **44** (10%) |
| NaOMe | **Z-9** (68%) + **44** (27%) |

elongation product **46** in 56% yield as a 12:1 *E*/*Z* geometric mixture. Surprisingly, under the same conditions, the reaction of (*Z*)-**9** failed to give the desired product, and only a 32% of the starting material was recovered. The failure was attributed to the rigidity of the tricyclic tropinone (*Z*)-**9**, which renders the lone electron pair of nitrogen more exposed, and compound (*Z*)-**9** is thus more basic. Consequently, Ti(O*i*-Pr)$_4$ can only partially prevent its toxication toward the Grubbs catalyst. To overcome this problem, the use of a salt of amine (*Z*)-**9** was envisaged.[35c] Indeed, upon heating a mixture of a hydrochloride salt of (*Z*)-**9**, the Grubbs second generation catalyst, and (*Z*)-1,4-dimethoxybut-2-ene in toluene at 60 °C, the desired cross-coupling product **8a** was obtained in 56% yield as a 6.5:1 *E*/*Z* geometric mixture. Unexpectedly, an enone-ester moiety isomerized compound **8b** (*E*/*Z* = 6.5:1) was also obtained as a side product in 14% yield (Scheme 10, b). A possible scenario for the formation **8b** may be that under acidic conditions, a dienol-formation occurred, then retauto-merization took place to yield both enone-esters **8a** and **8b**.

With compound **8a** in hand, we next addressed the catalytic hydrogenation. To our surprise, catalytic hydrogenation of **8a** in the presence of HCl gave complex products (Scheme 10, b-**A**). Pleasantly, in the absence of HCl, the two olefin bonds were saturated smoothly to give **48** as a single diastereomer, which without purification, was further subjected to catalytic hydrogenolysis under acidic conditions (Pd/C, $H_2$, HCl) to give the hemiacetal **47** in 81% yield over two steps (Scheme 10, b-**B**). Encouraged by this result, a one-pot protocol was developed (Scheme 10, b-**C**). Thus, the geometric isomer mixture of **8a** was subjected to catalytic hydrogenation. After completing the transformation of **8a** to **48** as indicated by TLC monitoring, 2 equiv of a 2 M HCl was added, and the resulting mixture was stirred at rt for 48 h to give, in one pot, compound **47** in 85% yield as a single diastereomer. The structure of **47** was determined by X-ray analysis (Figure 4, see the SI for detailed X-ray crystallography data).[33] In light of these results,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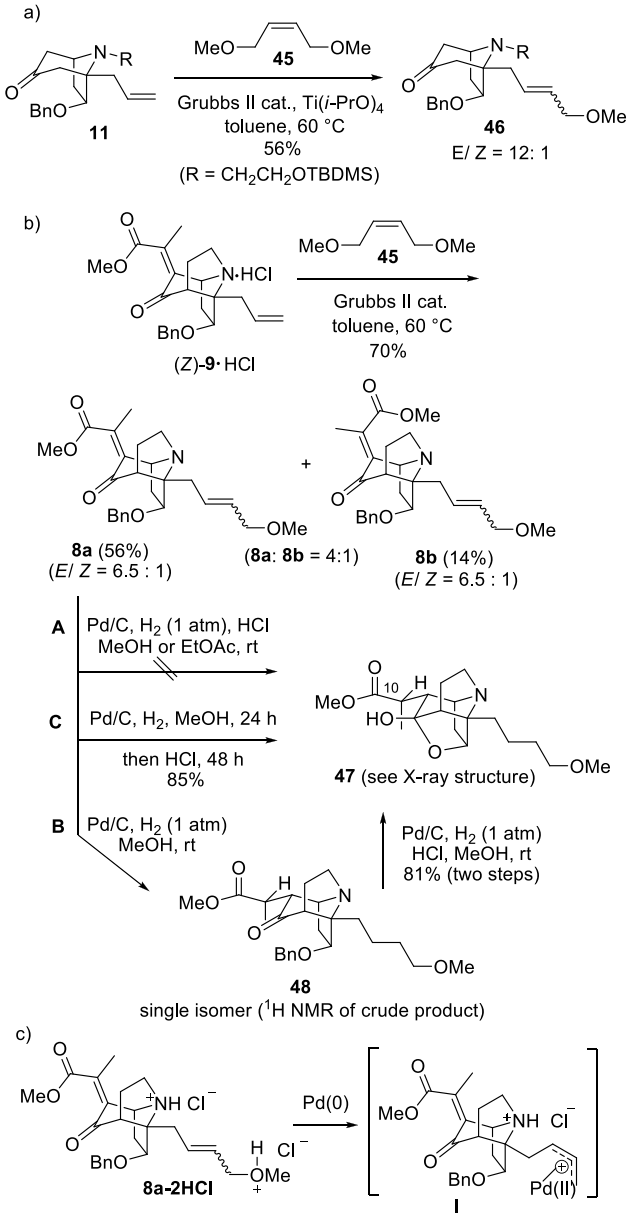
**Scheme 10. Synthesis of the Functionalized Tetracyclic Core 47**



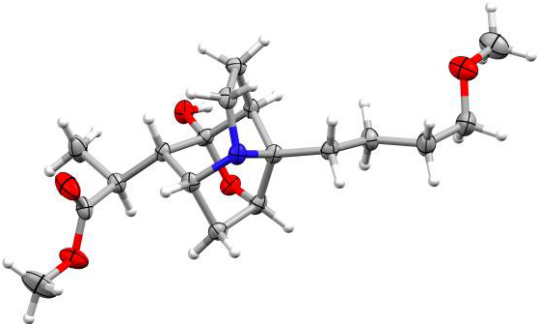
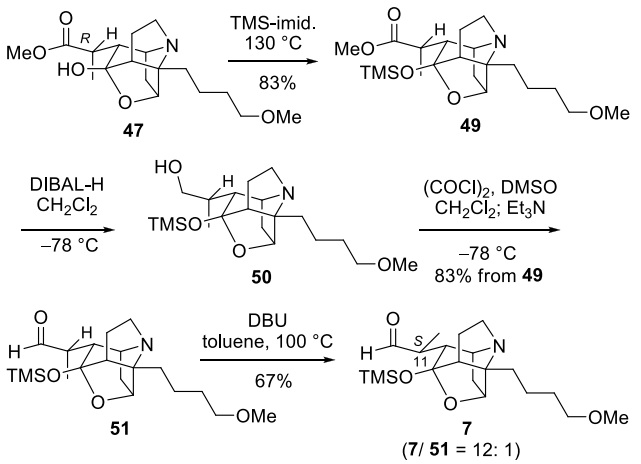



**Figure 4.** X-ray crystal structure of compound **47** (ORTEP ellipsoids are depicted at the 50% level).

the complex products formed under the conditions shown in Scheme 10, b-**A** is attributable to the formation of $\pi$-allylpalladium intermediate **I** (Scheme 10, c) followed by Tsuji–Trost reactions.[36]

Because compound **47** possesses an *R*-configuration at C-10, whereas that of the natural product is *S*, a correction of stereochemistry at C-10 was necessary. This was achieved by employing Overman's protocol.[7] Thus, compound **47** was *O*-silylated (TMS-imid., 130 °C)[7] to give acetal-ester **49** (Scheme 11). The latter was subjected to reduction with DIBAL-H

**Scheme 11. Synthesis of the Advanced Intermediate 7 (from *Z*-38)**




($CH_2Cl_2$, −78 °C), and the resultant crude alcohol **50**, without purification, was subjected to Swern oxidation to give aldehyde **51** in 83% yield over two steps. Treatment of aldehyde **51** with DBU (4 equiv) in toluene at 100 °C for 2 h gave rise to the epimerized diastereomer **7** along with the recovered aldehyde **51** in a 12:1 ratio with a combined yield of 67%.

**Convergent Transformation of the Minor Geometric Isomer (*E*)-38 into the Advanced Intermediate 7.** To improve the overall efficiency of our total synthesis, after achieving the transformation of the major geometric isomer (*Z*)-**38** into **7** (Schemes 9–11), the transformation of (*E*)-**38** into **7** was also investigated (Scheme 12). Thus, following the procedures described for (*Z*)-**38**, diastereomer (*E*)-**38** was subjected to desilylation (*p*-TsOH, acetone 50 °C), bromination ($PPh_3$, $CBr_4$, $CH_2Cl_2$, 0 °C), cyclization (NaOMe, THF, 0 °C), and cross-olefin metathesis with (*Z*)-1,4-dimethoxybut-2-ene to give **8a** (*E*/*Z* = 6.2:1) and **8b** (*E*/*Z* = 6.2:1) in an overall yield of 43% from (*E*)-**38** (Scheme 12). It is interesting to note that the results we obtained here is quite similar to those we obtained in Scheme 10, namely, the cross-metathesis reaction of either geometric isomer (*Z*)-**9** or (*E*)-**9** yielded **8a** and **8b** in either 4:1 or 1:4 ratio depending on the geometry of the starting **9**. The geometric ratios of the nonconjugated olefin were also similar: 6.5:1 versus 6.2:1.

Since the isomer **8a** has been converted into aldehyde **7** (Schemes 10 and 11), similar transformation for its isomer **8b** was pursued. Under the conditions defined for the one-pot transformation of **8a** to **47** (Scheme 10), and followed by *O*-silylation (TMS-imid., 130 °C), compound **8b** was converted into compound **54** in an overall yield of 77%. Since compound **54** possessed the correct stereochemistry at C-10, it was directly converted to aldehyde **7** by the reduction with DIBAL-H followed by Swern oxidation (cf. **49** to **51** in Scheme 11). The aldehyde **7** obtained herein was identical in all aspects to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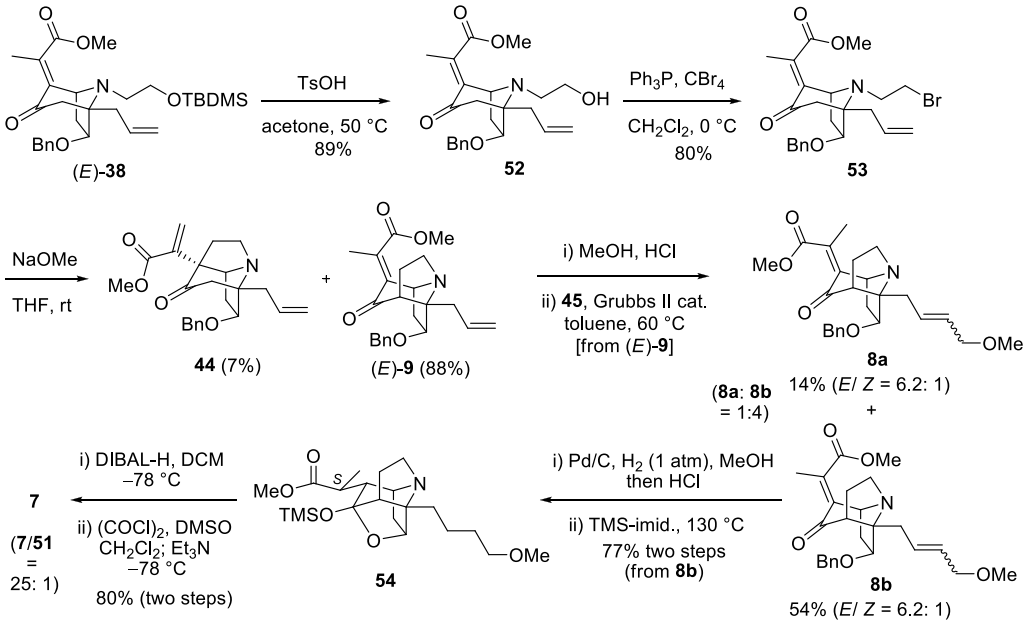
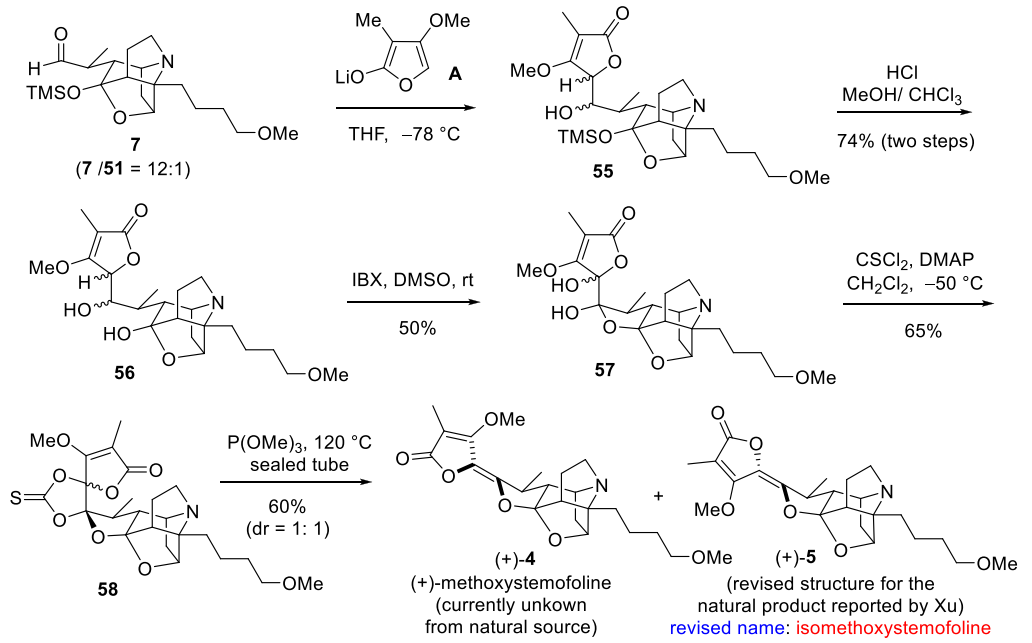
**Scheme 12. Synthesis of the Advanced Intermediate 7 from the Minor Diastereomer (*E*)-38**




**Scheme 13. Completion of the Total Synthesis of Both the Suggested and Revised Structures of Methoxystemofoline**




that formed in Scheme 11 except that the ratio of **7**:**51** was improved to 25:1. The presence of a small amount of epimer **51** in **7** indicated that little epimerization (3.8%) occurred during the transformation of **54** to **7**. Thus, we have taken full use of both geometric isomers of **38**, formed during the dehydration of **36** (Scheme 9) and of **8a**/**8b**, formed during the olefin cross-metathesis of **9** (Schemes 10 and 12), in the diastereoconvergent synthesis of the key intermediate **7**.

**Completion of the Total Synthesis of the Proposed Structure of Methoxystemofoline (4) and Revision of Its Stereo Structure.** With the advanced intermediate **7** in hand, the remaining task was the installation of the 5-(alkoxyalky1i-dene)-3-methyl-tetronate moiety, for which Overman's strategy[7] was adopted. Thus, the diastereomeric mixture of aldehydes **7**/**51** (dr = 12:1) was subjected to react with vinylogous lithium enolate **A** at −78 °C, which gave the adduct **55** (Scheme 13). Partial desilylation was observed during the purification of **55** by column chromatography on $SiO_2$. The resulting mixture was treated with a 1 M HCl in MeOH/$CHCl_3$ to yield the vinylogous hemiacetal **56** as a complex diastereomeric mixture in 74% yield from **7**. Without separation, the diastereomeric mixture of **56** was oxidized with IBX in DMSO[7,37] at rt to give directly a diastereomeric mixture of hemiacetal **57**. The latter was further treated with thiophosgene (DMAP, $CH_2Cl_2$, −50 °C)[38] to afford compound **58** as yet another diastereomeric mixture. Finally, heating a mixture of **58** and $P(OMe)_3$ (40 equiv) in a sealed tube at 120 °C for 12 h provided the desired proposed structure of methoxystemofoline (**4**), along with its (*E*)-geometric isomer **5** in a ratio of 1:1 and with a combined yield


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Table 4. Characteristic Spectral and Physiochemical Data of *Z*- and *E*-Stereoisomers of Methoxystemofoline

| compound | $\delta_{Me\text{-}17}$ | $[\alpha]_D$ | original (revised) name/structure |
|---|---|---|---|
| our synthetic product **4** | 1.37 (d, *J* = 6.5 Hz, 3H) | $[\alpha]_D^{20}$ +220−226 (*c* 0.1, $CH_3OH$) | methoxystemofoline/**4** |
| our synthetic product **5** | 1.44 (d, *J* = 6.7 Hz, 3H) | $[\alpha]_D^{20}$ +71−85 (*c* 0.1, $CH_3OH$) | isomethoxystemofoline/**5** |
| natural product (Xu;[4a] Dai/Zhao[4b]) | 1.44 (d, *J* = 6.7 Hz, 3H)[4a] | $[\alpha]_D^{21.6}$ + 75.6 (*c* 0.037, $CH_3OH$)[4a] | methoxystemofoline/**4** (isomethoxystemofoline/**5**) |
| semisynthetic product (Pyne[8c]) | 1.37 (d, *J* = 6.0 Hz, 3H) | $[\alpha]_D^{25}$ +249 (*c* 0.29, $CH_3OH$) | methoxystemofoline/**4** |

of 60%. The physical {**4**: $[\alpha]_D^{20}$ + 220−226 (*c* 0.1, $CH_3OH$); lit.[8c] $[\alpha]_D^{25}$ +249 (*c* 0.29, $CH_3OH$); **5**: $[\alpha]_D^{20}$ +71−85 (*c* 0.1, $CH_3OH$); lit.[4a] $[\alpha]_D^{21.6}$ +75.6 (*c* 0.037, $CH_3OH$)} and spectral ($^1H$ and $^{13}C$ NMR) data of our synthetic compounds **4** and **5** are consistent with those reported by Pyne[8c] and Xu,[4a] respectively.

Concerning the geometry of the deoxygenated olefinic bond at C11−C12 of the stemofoline group alkaloids, it has been reported that (11*E*)-1′,2′-didehydrostemofoline and its 11*Z*-isomer[39] can be distinguished by the $^1H$ NMR spectra: chemical shift of the C-17 methyl proton appears at downfield ($\delta$ 1.46) for 11*E*-isomer compared with that of the 11*Z*-isomer ($\delta$ 1.38).[40] According to this empirical rule, the geometry of the olefinic bond at C11−C12 of our products were assigned as 11*E*-isomer **5** with an olefinic resonance at $\delta_{Me\text{-}17}$ 1.44 (d, *J* = 6.7 Hz, 3H), and 11*Z*-isomer **4** with an olefinic resonance at $\delta_{Me\text{-}17}$ 1.37 (d, *J* = 6.5 Hz, 3H), which correspond to the natural product reported by Xu [$\delta_{Me\text{-}17}$ 1.44 (d, *J* = 6.7 Hz, 3H)],[4a] and to the unnatural semisynthetic product reported by Pyne [$\delta_{Me\text{-}17}$ 1.37 (d, *J* = 6.0 Hz, 3H)],[8c] respectively.

Another diagnostic parameter for distinguishing 11*Z*- and 11*E*-stemofoline group alkaloids is the specific optical rotation data. The (11*Z*)-stemofoline group alkaloids typically have specific rotations around 200.[1f,8c] A comparison of the above-mentioned specific optical rotation data of our synthetic products **4** and **5** with those of Xu[4a] and Pyne[8c] (Table 4) confirms once again that our synthetic products **4** and **5** correspond to the products obtained by Pyne,[8c] and Xu,[4a] respectively.

On the basis of these results, we came to a conclusion that the natural product isolated[4a,b] and named by Xu as methoxystemofoline[4a] is actually compound **5** with an 11*E*-stereochemistry, and the semisynthetic product obtained by Pyne[8c] is the 11*Z*-stereoisomer **4** (Table 4). Because in the stemofoline group alkaloids, the stemofoline series possesses an 11*Z*-stereochemistry, and the isostemofoline series has an 11*E*-stereochemistry, we suggest to rename the natural product isolated by Xu as isomethoxystemofoline (**5**). On the basis of biosynthetic consideration, we believe that the 11*Z*-stereoisomer, namely, methoxystemofoline (**4**), is plausibly a natural product yet to be discovered. We thus suggest to retain the name for the semisynthetic product obtained by Pyne as methoxystemofoline (**4**).

## CONCLUSION

In summary, we have accomplished the first total synthesis of the originally proposed structure of (+)-methoxystemofoline (**4**). The nonstereoselective reaction of the last step allowed us to obtain **4** along with its 11*E*-stereoisomer **5** in a 1:1 ratio. This was, in fact, critical for us to find the wrong assignment about the stereo structure of the natural product, and to revise the originally proposed structure **4** to **5**. It is worth noting that thanks to the nonstereoselective reaction of the last step, we were able to obtain the natural product **5** without any additional step. According to the naming system of the stemofoline group alkaloids, we suggest renaming the natural product as (+)-isomethoxystemofoline (**5**). We also predict that methoxystemofoline (**4**) with a 11*Z*-stereochemistry is an undiscovered natural product. Through this work, the relative and absolute configuration of the natural product isomethoxystemofoline (**5**) was determined as (11*E*,13*E*,2*S*,3*S*,7*R*,8*S*,9*R*,9a*S*,10*S*). On the other hand, the key features of our strategy to the challenging tetracyclic core include: (1) a high-yielding protocol to construct the enantiopure 1-bromotropin-3-one skeleton; (2) a radical C−C bond-forming reaction (Keck allylation) at the *N*-$\alpha$ bridgehead carbon to forge the tetrasubstituted stereocenter at C-1; (3) the olefin cross-metathesis reaction for the side-chain elongation; and (4) a regioselective aldol addition reaction with methyl pyruvate that ensured the subsequent regioselective cyclization reaction to construct the third ring. The route is flexible and should be amenable to the preparation of congeners and analogues bearing different side-chains at C-3.

## EXPERIMENTAL SECTION

**General Methods.** NMR spectra were recorded on a Bruker AV 400, AV 500 spectrometer at 25 °C in the solvents indicated. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts ($\delta$) are reported in ppm and referenced to internal standard $Me_4Si$ and solvent signals ($Me_4Si$, 0 ppm for $^1H$ NMR, and $CDCl_3$, 77.0 ppm for $^{13}C$ NMR). Structural assignments were made with additional information from NOESY experiments. Melting points were determined on a Büchi M560 Automatic Melting Point apparatus and are uncorrected. HRMS spectra were recorded on a 7.0 T FT-MS apparatus using an ICR analyzer. Infrared spectra were measured with a Nicolet Avatar 330 FT-IR spectrometer using film KBr pellet technique. Silica gel (200−300 mesh) was used for flash column chromatography (FC), eluting (unless otherwise stated) with ethyl EtOAc/*n*-hexane mixture. All other commercially available compounds were used as received. THF and toluene were distilled over sodium benzophenone ketyl under $N_2$.

*(4S)-4-(Benzyloxy)-1-[2-(tert-butyldimethylsilyloxy)ethyl]-5-oxopyrrolidin-2-yl acetate (**20**).* To a cooled solution (−78 °C) of oxalyl chloride(4.26 mL, 49.7 mmol) in $CH_2Cl_2$ (110 mL) under $N_2$ was added dropwise a solution of DMSO (7.04 mL, 99.4 mmol) in $CH_2Cl_2$(23 mL). After being stirred for 15 min at −78 °C, a solution of compound **17**[14a] (16.57 g, 45.1 mmol) in $CH_2Cl_2$(45 mL) was added dropwise, and the resulting mixture was stirred at the same temperature for 30 min, $Et_3N$ (31.4 mL, 226 mmol) was added, and the reaction was kept stirred for 2.5 h at −78 °C. The reaction was quenched with ice−water (50 mL). The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was diluted with MeOH (100 mL), and silica gel (5 g) was added. The suspension was refluxed at 75 °C (oil bath) for 2 h, then silica gel was filtered and solvent was removed under reduced pressure to give hemiacetal **19**, which was used in the next step without purification. The crude hemiacetal **19** and DMAP (100 mg) was dissolved in $CH_2Cl_2$ (230 mL) under $N_2$, and cooled to 0 °C. Then $Et_3N$ (15.7 mL, 112.9 mmol) and $Ac_2O$ (8.48 mL, 90.3 mmol) were added successively. After being stirred at room temperature overnight, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL). The organic layer


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was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/6) to give compound **20** (16.9 g, yield: 92% from **17**) as an inseparable diastereomeric mixture in a ratio of 57:43 ($^1$H NMR), which was used in the next step without further separation. Colorless oil. IR (film) $\nu_{max}$ 2953, 2929, 2856, 1716, 1453, 1423, 1362, 1237, 1192, 1102, 1010, 923, 836, 778, 736, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$, data read from the diastereomeric mixture) $\delta$ (major diastereomer) 7.40−7.24 (m, 5H), 6.21 (dd, $J$ = 6.4, 1.7 Hz, 1H), 4.93 (d, $J$ = 12.0 Hz, 1H), 4.75 (d, $J$ = 12.0 Hz, 1H), 4.02 (dd, $J$ = 8.3, 3.0 Hz, 1H), 3.81−3.60 (m, 4H), 2.69−2.57 (m, 1H), 2.08 (s, 3H), 2.01−1.94 (m, 1H), 0.86 (s, 9H), 0.03 (s, 6H); $\delta$ (minor diastereomer) 7.40−7.24 (m, 5H), 6.30 (d, $J$ = 5.7 Hz, 1H), 5.01 (d, $J$ = 11.9 Hz, 1H), 4.77 (d, $J$ = 11.9 Hz, 1H), 4.32 (dd, $J$ = 8.2, 8.2 Hz, 1H), 3.81−3.60 (m, 2H), 3.20−3.10 (m, 2H), 2.35 (dd, $J$ = 14.0, 7.8 Hz, 1H), 2.28−2.14 (m, 1H), 2.02 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$, data read from the diastereomeric mixture) $\delta$ (major diastereomer) 172.6, 170.3, 137.5, 128.3 (2C), 127.9 (2C), 127.7, 83.1, 73.2, 72.0, 60.5, 42.9, 33.8, 25.7 (3C), 21.0, 18.0, −5.6 (2C); $\delta$ (minor diastereomer) 174.3, 170.3, 137.5, 128.3 (2C), 127.9 (2C), 127.8, 83.0, 72.9, 72.2, 60.8, 43.2, 34.6, 25.7 (3C), 21.0, 18.0, −5.5 (2C). HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ Calcd for $C_{21}H_{33}NO_5SiNa$ 430.2020, found 430.2023.

*1-Allyl-8-benzyl-8-azabicyclo[3.2.1]octan-3-one (**25**).* To a solution of bromide **26** (46 mg, 0.157 mmol) and 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) (46 mg, 0.188 mmol) in anhydrous toluene (0.8 mL) was added allyltributyltin (0.49 mL, 1.57 mmol). After being stirred overnight at 85 °C (oil bath), the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/15) to give compound **25** (31 mg, yield: 76%) as a colorless oil. IR (film) $\nu_{max}$ 2950, 1711, 1453, 1347, 1335, 1229, 1141, 914, 740, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.46−7.25 (m, 5H), 5.98−5.84 (m, 1H), 5.17 (br s, 1H), 5.16−5.11 (m, 1H), 3.98 (d, $J$ = 13.5 Hz, 1H), 3.72 (d, $J$ = 13.5 Hz, 1H), 3.49−3.43 (m, 1H), 2.73 (dd, $J$ = 15.7, 4.3 Hz, 1H), 2.52 (d, $J$ = 15.4 Hz, 1H), 2.45 (dd, $J$ = 14.3, 6.5 Hz, 1H), 2.38 (dd, $J$ = 14.3, 7.8 Hz, 1H), 2.27 (dd, $J$ = 15.4, 1.7 Hz, 1H), 2.06 (dt, $J$ = 15.7, 1.8 Hz, 1H), 1.98−1.85 (m, 2H), 1.68−1.58 (m, 1H), 1.52−1.42 (m, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 209.8, 139.3, 133.47, 128.44 (2C), 128.39 (2C), 127.1, 118.1, 64.6, 56.4, 49.2, 47.5, 42.6, 41.7, 33.5, 27.5. HRMS (ESI-TOF) $m/z$ [M + H]$^+$ Calcd for $C_{17}H_{22}NO$ 256.1696, found 256.1696.

*(1S,5S,7S)-1-Allyl-7-(benzyloxy)-8-[2-(tert-butyldimethylsilyloxy)-ethyl]-8-azabicyclo[3.2.1]octan-3-one (**11**).* To a solution of 1-bromotropin-3-one **12**[14b] (3.67 g, 7.84 mmol) and 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) (2.30 g, 9.43 mmol) in anhydrous toluene (26 mL) was added allyltributyltin (24.4 mL, 78.6 mmol), and the mixture was stirred overnight at 85 °C (oil bath). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (EtOAc/PE = 1/15) to give compound **11** (2.63 g, yield: 78%) as a colorless oil. $[\alpha]_D^{20}$ −1.4 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2952, 2927, 2855, 1715, 1471, 1462, 1453, 1255, 1155, 1099, 1005, 835, 776, 735, 697 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.22 (m, 5H), 5.81−5.67 (m, 1H), 5.05−4.98 (m, 1H), 4.97−4.89 (m, 1H), 4.55 (d, $J$ = 12.1 Hz, 1H), 4.34 (d, $J$ = 12.1 Hz, 1H), 3.82 (dd, $J$ = 9.8, 3.4 Hz, 1H), 3.79−3.72 (m, 3H), 2.85−2.75 (m, 3H), 2.60 (d, $J$ = 16.1 Hz, 1H), 2.33−2.20 (m, 3H), 2.11 (d, $J$ = 16.6 Hz, 1H), 2.09 (d, $J$ = 16.1 Hz, 1H), 1.35 (dd, $J$ = 13.4, 3.4 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 6H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 208.5, 138.4, 133.0, 128.2 (2C), 127.4 (3C), 117.9, 80.2, 71.4, 67.0, 62.9, 55.4, 45.0, 43.7, 41.7, 39.9, 35.4, 25.9 (3C), 18.2, −5.41, −5.43. HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ Calcd for $C_{25}H_{39}NO_3SiNa$ 452.2591, found 452.2599.

*(1S,5S,7S)-1-Allyl-7-(benzyloxy)-8-(2-hydroxyethyl)-8-azabicyclo-[3.2.1]octan-3-one (**27**).* A solution of compound **11** (266 mg, 0.62 mmol) and PTSA ($p$-toluenesulfonic acid monohydrate) (471 mg, 2.48 mmol) in acetone (6.2 mL) was stirred at 50 °C for 2 h. To the resulting mixture was added a saturated aqueous $NaHCO_3$ until pH = 8. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/PE = 2/1) to give alcohol **27** (190 mg, yield: 97%) as a colorless oil. $[\alpha]_D^{20}$ +9.6 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 3447, 2918, 2850, 1709, 1637, 1384, 1143, 1027, 911, 734, 695 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.22 (m, 5H), 5.80−5.67 (m, 1H), 5.08−5.00 (m, 1H), 5.00−4.91 (m, 1H), 4.56 (d, $J$ = 12.1 Hz, 1H), 4.35 (d, $J$ = 12.1 Hz, 1H), 3.88 (dd, $J$ = 9.7, 3.3 Hz, 1H), 3.75−3.60 (m, 3H), 2.93 (ddd, $J$ = 12.9, 9.4, 5.2 Hz, 1H), 2.80 (dt, $J$ = 12.9, 3.7 Hz, 1H), 2.72−2.62 (m, 2H), 2.60−2.52 (m, 1H), 2.35−2.22 (m, 3H), 2.21−2.14 (m, 1H), 2.09 (d, $J$ = 16.2 Hz, 1H), 1.41 (dd, $J$ = 13.5, 3.4 Hz, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 207.6, 138.1, 132.3, 128.3 (2C), 127.5, 127.4 (2C), 118.6, 80.3, 71.4, 66.6, 59.0, 53.8, 44.1, 44.0, 41.5, 39.8, 35.4. HRMS (ESI-TOF) $m/z$ [M + H]$^+$ Calcd for $C_{19}H_{26}NO_3$ 316.1907, found 316.1908.

*(1S,5S,7S)-1-Allyl-7-(benzyloxy)-8-(2-bromoethyl)-8-azabicyclo-[3.2.1]octan-3-one (**28**).* To a cooled solution (0 °C) of alcohol **27** (154 mg, 0.49 mmol) in anhydrous $CH_2Cl_2$ (5 mL) were added $CBr_4$ (208 mg, 0.64 mmol) and $PPh_3$(192 mg, 0.73 mmol). The resulting mixture was stirred at 0 °C for 30 min and then concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/PE = 1/8) to give bromide **28** (160 mg, yield: 87%) as a colorless oil. $[\alpha]_D^{20}$ −14.0 ($c$ 2.0, $CHCl_3$). IR (film) $\nu_{max}$ 2918, 1713, 1658, 1620, 1384, 1092, 799 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.22 (m, 5H), 5.80−5.67 (m, 1H), 5.08−5.00 (m, 1H), 5.00−4.91 (m, 1H), 4.53 (d, $J$ = 12.1 Hz, 1H), 4.33 (d, $J$ = 12.1 Hz, 1H), 3.84 (dd, $J$ = 9.7, 3.4 Hz, 1H), 3.70−3.62 (m, 1H), 3.47−3.32 (m, 2H), 3.13−2.95 (m, 2H), 2.69−2.59 (m, 2H), 2.35−2.22 (m, 3H), 2.16 (br d, $J$ = 16.6 Hz, 1H), 2.05 (d, $J$ = 16.1 Hz, 1H), 1.36 (dd, $J$ = 13.4, 3.4 Hz, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 207.4, 138.1, 132.6, 128.2 (2C), 127.4, 127.3 (2C), 118.2, 80.3, 71.3, 66.8, 54.8, 45.1, 43.9, 41.6, 39.9, 35.3, 30.6. HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ Calcd for $C_{19}H_{24}BrNO_2Na$ 400.0888 and 402.0868, found 400.0889 and 402.0870.

*(1R,4R,5S,7S,7aS)-7a-Allyl-7-(benzyloxy)hexahydro-1H-1,5-ethanopyrrolizin-9-one (**10**) and (1S,4R,5S,6S,7aS)-5-Allyl-6-(benzyloxy)hexahydro-1H-1,5-ethanopyrrolizin-9-one (**29**).* To a cooled solution (−78 °C) of bromide **28** (53 mg, 0.141 mmol) in anhydrous THF (1.4 mL) was added a freshly prepared LDA (0.282 mL, 0.282 mmol, 1 M in THF). After being stirred at the same temperature for 15 min, the reaction was quenched with a saturated aqueous $NH_4Cl$ (3 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 2/1) to give compound **10** (6 mg, yield: 14%) and compound **29** (25 mg, yield: 60%).

Compound **10**: Colorless oil. $[\alpha]_D^{20}$ −50.0 ($c$ 0.5, $CHCl_3$). IR (film) $\nu_{max}$ 2920, 2850, 1720, 1453, 1383, 1351, 1096, 1073, 1027, 736, 697 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.22 (m, 5H), 5.80−5.67 (m, 1H), 5.05 (dd, $J$ = 10.1, 1.0 Hz, 1H), 4.97 (dd, $J$ = 17.0, 1.0 Hz, 1H), 4.54 (d, $J$ = 12.2 Hz, 1H), 4.40 (d, $J$ = 12.2 Hz, 1H), 4.09 (d, $J$ = 8.4 Hz, 1H), 3.50 (t, $J$ = 6.0 Hz, 1H), 3.20−3.05 (m, 2H), 2.80 (d, $J$ = 6.6 Hz, 1H), 2.52 (dd, $J$ = 17.0, 6.0 Hz, 1H), 2.28−2.12 (m, 5H), 1.76−1.64 (m, 2H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 208.3, 138.1, 133.0, 128.3 (2C), 127.5, 127.4 (2C), 118.1, 81.0, 78.7, 71.8, 60.4, 56.4, 46.1, 40.6, 38.5, 38.0, 30.6. HRMS (ESI-TOF) $m/z$ [M + H]$^+$ Calcd for $C_{19}H_{24}NO_2$ 298.1802, found 298.1803.

Compound **29**: Colorless oil. $[\alpha]_D^{20}$ +19.0 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2919, 2852, 1712, 1452, 1411, 1384, 1352, 1094, 1025, 740, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.22 (m, 5H), 5.88−5.73 (m, 1H), 5.05 (dd, $J$ = 10.1, 0.8 Hz, 1H), 1.46 (dd, $J$ = 13.8, 6.2 Hz, 1H), 4.97 (br d, $J$ = 17.0 Hz, 1H), 4.55 (d, $J$ = 11.9 Hz, 1H), 3.91 (dd, $J$ = 9.6, 6.2 Hz, 1H), 4.39 (d, $J$ = 11.9 Hz, 1H), 3.46 (dd, $J$ = 7.9, 3.5 Hz, 1H), 3.20−3.00 (m, 2H), 2.72−2.66 (m, 1H), 2.60 (d, $J$ = 16.2 Hz, 1H), 2.37 (dt, $J$ = 13.8, 8.8 Hz, 1H), 2.28−2.04


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(m, 3H), 1.90 (d, $J$ = 16.2 Hz, 1H), 1.82 (ddd, $J$ = 13.2, 8.5, 4.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 210.4, 138.2, 133.0, 128.2 (2C), 127.6 (2C), 127.5, 118.0, 80.8, 71.5, 69.0, 65.4, 56.0, 44.4, 42.0, 40.0, 32.0, 29.3. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ Calcd for $C_{19}H_{24}NO_2$ 298.1802, found 298.1805.

*(1S,5S,7S)-1-Allyl-8-[2-(tert-butyldimethylsilyloxy)ethyl]-7-hydroxy-8-azabicyclo[3.2.1]octan-3-one (**30**).* To a cooled solution (−25 °C) of compound **11** (406 mg, 0.94 mmol) in anhydrous THF (10.0 mL) was added a freshly prepared LDA (1.88 mL, 1.88 mmol, 1 M in THF). The reaction mixture was stirred at the same temperature for 1 h. Then a solution of lithium naphthalenide (7.52 mL, 7.52 mmol, 1 M in THF) was added in one portion and the resulting mixture was stirred for 15 min. The reaction was quenched with a saturated aqueous $NH_4Cl$ (10 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/4) to give compound **30** (258 mg, yield: 81%) as a white solid. Mp 65−71 °C. $[\alpha]_D^{20}$ −30.3 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 3409, 2953, 2926, 2853, 1705, 1462, 1415, 1384, 1359, 1254, 1150, 1100, 1081, 919, 835, 775 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.91−5.80 (m, 1H), 5.21−5.12 (m, 2H), 4.12 (dt, $J$ = 10.5, 4.0 Hz, 1H), 3.77 (t, $J$ = 6.2 Hz, 2H), 3.75−3.70 (m, 1H), 2.87−2.78 (m, 3H), 2.54 (dd, $J$ = 16.1, 1.5 Hz, 1H), 2.51−2.43 (m, 1H), 2.38−2.30 (m, 1H), 2.26−2.19 (m, 1H), 2.18−2.08 (m, 2H), 1.22 (dd, $J$ = 13.8, 3.9 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 209.1, 133.1, 118.7, 75.1, 67.6, 63.0, 55.6, 45.4, 43.2, 42.0, 40.6, 38.1, 25.9 (3C), 18.2, −5.39, −5.41. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ Calcd for $C_{18}H_{34}NO_3Si$ 340.2302, found 340.2312.

*(1S,5S,7S)-1-Allyl-8-[2-(tert-butyldimethylsilyloxy)ethyl]-7-(methoxymethoxy)-8-azabicyclo[3.2.1]octan-3-one (**31**).* To a cooled solution (0 °C) of alcohol **30** (258 mg, 0.76 mmol) in anhydrous $CH_2Cl_2$ (8.0 mL) was added $i$-$Pr_2NEt$ (0.33 mL, 1.90 mmol) and the resulting mixture was stirred for 15 min. Then a chloromethyl methyl ether (MOMCl) (0.115 mL, 1.52 mmol) was slowly added. After being stirred 1 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for 5 h. The reaction was quenched with a saturated aqueous $NH_4Cl$ (10 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/8) to give compound **31** (233 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ −17.0 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2952, 2927, 2854, 1716, 1462, 1254, 1146, 1103, 1045, 917, 835, 776 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.90−5.77 (m, 1H), 5.15−5.05 (m, 2H), 4.60 (d, $J$ = 6.8 Hz, 1H), 4.55 (d, $J$ = 6.8 Hz, 1H), 3.99 (dd, $J$ = 10.1, 3.6 Hz, 1H), 3.82−3.70 (m, 3H), 3.33 (s, 3H), 2.85−2.75 (m, 3H), 2.51 (dd, $J$ = 16.3, 1.4 Hz, 1H), 2.40−2.30 (m, 1H), 2.28 (d, $J$ = 7.1 Hz, 2H), 2.11 (d, $J$ = 16.3 Hz, 2H), 1.32 (dd, $J$ = 13.6, 3.7 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 208.7, 133.0, 118.1, 96.1, 79.1, 66.9, 62.8, 55.6, 55.3, 45.0, 43.9, 41.8, 39.5, 35.9, 25.9 (3C), 18.3, −5.39, −5.42. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ Calcd for $C_{20}H_{38}NO_4Si$ 384.2565, found 384.2572.

*(1S,5S,7S)-1-Allyl-8-(2-hydroxyethyl)-7-(methoxymethoxy)-8-azabicyclo[3.2.1]octan-3-one (**32**).* To a cooled solution (0 °C) of compound **31** (156 mg, 0.41 mmol) in anhydrous THF (2.0 mL) was added tetra-$n$-butylammonium fluoride (0.81 mL, 0.81 mmol). After being stirred 30 min at 0 °C, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with a saturated aqueous $NH_4Cl$ (3 mL) and the aqueous layer was separated and extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/1) to give compound **32** (72 mg, yield: 66%) as a colorless oil. $[\alpha]_D^{20}$ −7.7 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 3439, 2918, 2849, 1712, 1442, 1408, 1217, 1145, 1106, 1042, 916 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.90−5.76 (m, 1H), 5.18−5.10 (m, 2H), 4.62 (d, $J$ = 6.8 Hz, 1H), 4.56 (d, $J$ = 6.8 Hz, 1H), 4.06 (dd, $J$ = 10.1, 3.5 Hz, 1H), 3.80−3.60 (m, 3H), 3.34 (s, 3H), 2.95 (ddd, $J$ = 13.0, 9.4, 5.1 Hz, 1H), 2.82 (dt, $J$ = 12.9, 3.7 Hz, 1H), 2.72−2.64 (m, 1H), 2.59 (dd, $J$ = 16.1, 1.2 Hz, 1H), 2.44−2.34 (m, 1H), 2.34−2.28 (m, 2H), 2.17 (d, $J$ = 16.6 Hz, 1H), 2.11 (d, $J$ = 16.1 Hz, 1H), 1.39 (dd, $J$ = 13.7, 3.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 207.8, 132.3, 118.9, 79.2, 96.1, 66.6, 59.0, 55.7, 53.8, 44.3, 44.1, 41.7, 39.5, 35.9. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ Calcd for $C_{14}H_{24}NO_4$270.1700, found 270.1704.

*(1S,5S,7S)-1-Allyl-8-(2-bromoethyl)-7-(methoxymethoxy)-8-azabicyclo[3.2.1]octan-3-one (**33**).* To a cooled solution (0 °C) of alcohol **32** (90 mg, 0.34 mmol) in anhydrous $CH_2Cl_2$ (3.5 mL) were added $CBr_4$ (142 mg, 0.44 mmol) and $PPh_3$(132 mg, 0.50 mmol). The reaction mixture was stirred at 0 °C for 30 min and then concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/PE = 1/4) to give bromide **33** (80 mg, yield: 73%) as a colorless oil. $[\alpha]_D^{20}$ −28.6 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2944, 2918, 2848, 1713, 1441, 1415, 1216, 1145, 1106, 1043, 916 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.90−5.76 (m, 1H), 5.18−5.09 (m, 2H), 4.60 (d, $J$ = 6.8 Hz, 1H), 4.55 (d, $J$ = 6.8 Hz, 1H), 4.01 (dd, $J$ = 10.2, 3.7 Hz, 1H), 3.70−3.60 (m, 1H), 3.50−3.37 (m, 2H), 3.32 (s, 3H), 3.16−2.98 (m, 2H), 2.72−2.62 (m, 1H), 2.56 (dd, $J$ = 16.1, 1.4 Hz, 1H), 2.44−2.34 (m, 1H), 2.30 (d, $J$ = 7.0 Hz, 2H), 2.17 (dt, $J$ = 16.4, 1.5 Hz, 1H), 2.07 (d, $J$ = 16.1 Hz, 1H), 1.35 (dd, $J$ = 13.7, 3.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 207.7, 132.6, 118.5, 96.1, 79.2, 66.7, 55.7, 54.8, 45.2, 44.1, 41.8, 39.6, 35.8, 30.5. HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ calcd for $C_{14}H_{22}BrNO_3Na$ 354.0681 and 356.0660, found 354.0676 and 356.0664.

*(1S,4R,5S,6S,7aS)-5-Allyl-6-(methoxymethoxy)hexahydro-1H-1,5-ethanopyrrolizin-9-one (**34**).* To a cooled solution (−78 °C) of bromide **33** (45 mg, 0.17 mmol) in anhydrous THF (1.4 mL) was added a freshly prepared solution of LDA (0.27 mL, 0.27 mmol, 1 M in THF). The reaction mixture was stirred at the same temperature for 30 min, then was quenched with a saturated aqueous $NH_4Cl$ (3 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 2/1) to give compound **34** (21 mg, yield: 62%) as a colorless oil. $[\alpha]_D^{20}$ +0.3 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2952, 2921, 2891, 1712, 1451, 1414, 1269, 1214, 1144, 1116, 1098, 1069, 1042, 1017, 916 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.98−5.83 (m, 1H), 5.17−5.05 (m, 2H), 4.62 (d, $J$ = 6.8 Hz, 1H), 4.59 (d, $J$ = 6.8 Hz, 1H), 4.08−4.00 (m, 1H), 3.47 (dd, $J$ = 7.9, 3.7 Hz, 1H), 3.34 (s, 3H), 3.18−3.05 (m, 2H), 2.74−2.67 (m, 1H), 2.56−2.42 (m, 2H), 2.27−2.20 (m, 2H), 2.18−2.06 (m, 1H), 1.92 (d, $J$ = 16.1 Hz, 1H), 1.83 (ddd, $J$ = 13.4, 8.5, 4.7 Hz, 1H), 1.47 (ddd, $J$ = 14.0, 6.3, 1.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 210.6, 133.0, 118.2, 96.1, 79.8, 69.0, 65.5, 56.1, 55.6, 44.4, 42.0, 39.7, 31.9, 29.9. HRMS (ESI-TOF) $m/z$ $[M + Na]^+$ calcd for $C_{14}H_{21}NO_3Na$ 274.1414, found 274.1421.

*Methyl (R/S)-2-{(1S,2R/S,5S,6S)-5-allyl-6-(benzyloxy)-8-[2-(tert-butyldimethylsilyloxy)ethyl]-3-oxo-8-azabicyclo[3.2.1]octan-2-yl}-2-hydroxypropanoate (**36**) and Methyl 2-{(1S,5S,7S)-1-allyl-7-(benzyloxy)-8-[2-(tert-butyldimethylsilyloxy)ethyl]-3-oxo-8-azabicyclo[3.2.1]octan-2-yl}-2-hydroxypropanoate (**37**).* To a cooled solution (−78 °C) of a freshly prepared solution of LDA (20 mL, 4.77 mmol, 0.24 M in THF) was added a solution of compound **11** (1023 mg, 2.38 mmol) in anhydrous THF (5 mL). The reaction mixture was stirred at the same temperature for 1 h, then methyl pyruvate (0.68 mL, 7.14 mmol) was slowly added. After being stirred for 1.5 h, the reaction was quenched with a saturated aqueous $NH_4Cl$ (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/8) to give two regioisomeric fractions **36** (785 mg, combined yield: 62%) and **37** (201 mg, yield: 16%). Fraction **36** is a mixture of four diastereomers, which was used in the next step without further separation. Repeated flash


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chromatography of **36** allowed separation of three fractions **36a,b** (containing two diastereomers), **36c**, and **36d** for characterization. The regioisomeric fraction **37** contained substantially one diastereomer of unknown configuration.

**36a,b**: White solid. IR (film) $\nu_{max}$ 3345, 2953, 2914, 1743, 1737, 1442, 1159, 1109, 1098, 833, 779 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$, data read from the diastereomeric mixture) $\delta$ 7.37−7.23 (m, 5H), 5.92−5.66 (m, 1H), 5.20−4.90 (m, 2H), 4.60−4.50 (m, 1H), 4.44−4.26 (m, 1H), 3.92−3.66 (m, 6H), 3.52−3.34 (m, 1H), 3.06−2.80 (m, 1H), 2.80−2.54 (m, 3H), 2.50−2.04 (m, 3H), 1.43−1.34 (m, 1H), 1.32 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, data read from the diastereomeric mixture) $\delta$ 207.6, 175.7, 138.4, 137.9, 132.9, 132.1, 128.4 (2C), 128.2, 127.7, 127.4 (2C), 127.3, 119.4, 118.0, 83.4, 80.8, 76.9, 73.4, 72.7, 71.2, 68.5, 67.9, 63.1, 61.7, 61.1, 60.9, 57.0, 53.5, 52.8, 52.3, 49.7, 48.3, 45.0, 44.0, 39.8, 39.0, 34.5, 32.2, 26.0 (3C), 25.9 (3C), 24.9, 23.7, 18.5, 18.2, −5.25, −5.29, −5.36, −5.42. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{29}H_{46}NO_6Si$ 532.3089, found 532.3087.

**36c**: Colorless oil. $[\alpha]_D^{20}$ +65.7 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 3339, 2952, 2928, 2883, 2856, 1757, 1731, 1712, 1462, 1454, 1256, 1189, 1156, 1098, 836, 778 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.22 (m, 5H), 6.36 (br s, 1H), 5.87−5.74 (m, 1H), 5.16−5.06 (m, 2H), 4.55 (d, $J$ = 12.1 Hz, 1H), 4.39 (d, $J$ = 12.1 Hz, 1H), 4.09 (br d, $J$ = 8.3 Hz, 1H), 3.87 (dd, $J$ = 9.7, 4.7 Hz, 1H), 3.80 (t, $J$ = 5.8 Hz, 2H), 3.72 (s, 3H), 2.98 (dt, $J$ = 12.9, 5.8 Hz, 1H), 2.76 (d, $J$ = 17.0 Hz, 1H), 2.72−2.58 (m, 2H), 2.54 (s, 1H), 2.45−2.36 (m, 2H), 2.31 (dd, $J$ = 15.0, 7.9 Hz, 1H), 1.56 (s, 3H), 1.40 (ddd, $J$ = 14.3, 4.7, 0.9 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 208.7, 174.5, 138.0, 132.3, 128.4 (2C), 127.6, 127.3 (2C), 119.3, 83.6, 72.7, 68.1, 62.9, 62.6, 57.9, 52.3, 49.5, 47.5, 39.1, 34.6, 26.0, 25.9 (3C), 18.3, −5.4 (2C). HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{29}H_{46}NO_6Si$ 532.3089, found 532.3083.

**36d**: Colorless oil. $[\alpha]_D^{20}$ −25.5 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 3441, 2953, 2928, 2856, 1729, 1712, 1462, 1454, 1384, 1361, 1253, 1164, 1099, 836, 777 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.24 (m, 5H), 5.80−5.66 (m, 1H), 5.01 (br d, $J$ = 10.3 Hz, 1H), 4.95 (dd, $J$ = 17.1, 1.4 Hz, 1H), 4.53 (d, $J$ = 12.0 Hz, 1H), 4.30 (d, $J$ = 12.0 Hz, 1H), 3.83 (s, 1H), 3.80−3.65 (m, 6H), 3.46 (dd, $J$ = 7.4, 3.1 Hz, 1H), 3.11 (br s, 1H), 2.90−2.77 (m, 2H), 2.60 (d, $J$ = 14.6 Hz, 1H), 2.24 (d, $J$ = 7.2 Hz, 2H), 2.18−2.05 (m, 2H), 1.89 (dd, $J$ = 14.0, 3.8 Hz, 1H), 1.63 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 207.9, 174.5, 138.4, 132.8, 128.2 (2C), 127.4 (3C), 118.1, 80.5, 75.5, 71.3, 68.7, 62.0, 59.1, 54.3, 52.4, 45.2, 45.0, 39.4, 32.2, 26.8, 25.9 (3C), 18.4, −5.27, −5.29. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{29}H_{46}NO_6Si$ 532.3089, found 532.3090.

**37**: Colorless oil. $[\alpha]_D^{20}$ +2.0 ($c$ 0.9, $CHCl_3$). IR (film) $\nu_{max}$ 3406, 2952, 2928, 2883, 2856, 1747, 1721, 1462, 1454, 1251, 1178, 1145, 1103, 835, 778 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.07 (br s, 1H), 7.37−7.22 (m, 5H), 5.82−5.66 (m, 1H), 5.08−4.95 (m, 2H), 4.43 (d, $J$ = 11.9 Hz, 1H), 4.32 (d, $J$ = 11.9 Hz, 1H), 3.93−3.82 (m, 2H), 3.82−3.74 (m, 2H), 3.70 (s, 3H), 3.43 (br s, 1H), 2.97 (dt, $J$ = 12.7, 5.5 Hz, 1H), 2.86 (dd, $J$ = 15.3, 3.4 Hz, 1H), 2.66−2.55 (m, 1H), 2.50−2.28 (m, 4H), 1.57 (br d, $J$ = 14.0 Hz, 1H), 1.26 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 205.9, 177.1, 137.8, 132.7, 128.3 (2C), 127.49, 127.46 (2C), 118.0, 84.4, 74.6, 72.6, 72.3, 62.9, 58.3, 57.0, 52.4, 50.1, 49.3, 37.4, 34.1, 28.5, 25.9 (3C), 18.2, −5.4, −5.5. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{29}H_{46}NO_6Si$ 532.3089, found 532.3085.

*(4S,6S,7S)-7-Allyl-6-(benzyloxy)-9-(2-hydroxyethyl)-3-methyl-4,5,6,7-tetrahydro-2H-4,7-epiminocyclohepta[b]furan-2-one (**40**) and (9S,10aS)-8-Allyl-9-(benzyloxy)-1-methyl-5,6,8,9,10,10a-hexahydro-2H-3a,8-methanofuro[3,2-f]pyrrolo[1,2-d][1,4]oxazepin-2-one (**41**).* A solution of the diastereoisomeric mixture **36** (74 mg, 0.14 mmol) and PTSA ($p$-toluenesulfonic acid monohydrate) (106 mg, 0.56 mmol) in toluene (7.0 mL) was refluxed for 3 h. After being cooled to room temperature, a saturated aqueous $NaHCO_3$ was added until pH = 8. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/2) to give compound **40** (18 mg, yield: 34%) and alcohol **41** (18 mg, yield: 34%).

Compound **40**: Pale yellow oil. $[\alpha]_D^{20}$ −133.4 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 3436, 2921, 1768, 1651, 1453, 1377, 1286, 1205, 1025, 871, 698 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.39−7.26 (m, 5H), 5.86−5.72 (m, 1H), 5.44 (s, 1H), 5.13 (br d, $J$ = 10.2 Hz, 1H), 5.06 (br d, $J$ = 17.1 Hz, 1H), 4.55 (d, $J$ = 12.0 Hz, 1H), 4.42 (d, $J$ = 12.0 Hz, 1H), 4.30 (d, $J$ = 7.7 Hz, 1H), 4.17 (dd, $J$ = 8.8, 3.8 Hz, 1H), 3.63−3.53 (m, 2H), 2.74 (ddd, $J$ = 13.6, 8.7, 5.5 Hz, 1H), 2.65−2.54 (m, 2H), 2.45 (dd, $J$ = 14.7, 6.2 Hz, 1H), 2.38 (td, $J$ = 13.3, 3.6 Hz, 1H), 1.92 (s, 3H), 1.47 (dd, $J$ = 13.1, 3.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 171.1, 149.6, 147.9, 137.8, 131.8, 128.4 (2C), 127.79, 127.77 (2C), 119.8, 119.2, 107.7, 82.7, 71.9, 66.4, 59.4, 54.3, 45.5, 38.6, 35.0, 8.2. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{22}H_{26}NO_4$ 368.1856, found 368.1864.

Compound **41**: White solid. Mp 159−167 °C. $[\alpha]_D^{20}$ −25.7 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2919, 1767, 1330, 1303, 1254, 1213, 1165, 1102, 1074, 1011, 974, 931, 752, 701 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.20 (m, 5H), 5.79−5.65 (m, 1H), 5.06 (br d, $J$ = 10.1 Hz, 1H), 5.00 (br d, $J$ = 17.1 Hz, 1H), 4.50 (d, $J$ = 12.0 Hz, 1H), 4.41 (d, $J$ = 12.0 Hz, 1H), 4.14 (d, $J$ = 7.5 Hz, 1H), 3.95−3.82 (m, 2H), 3.82−3.73 (m, 1H), 3.29−3.17 (m, 1H), 3.00 (td, $J$ = 15.3, 4.3 Hz, 1H), 2.78 (d, $J$ = 14.8 Hz, 1H), 2.54−2.36 (m, 3H), 2.25 (d, $J$ = 14.8 Hz, 1H), 1.81 (s, 3H), 1.38 (dd, $J$ = 12.7, 2.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 172.4, 164.0, 137.9, 132.6, 128.4 (2C), 127.8, 127.6 (2C), 121.0, 118.4, 103.2, 79.9, 71.7, 63.0, 62.3, 56.9, 47.1, 41.9, 37.1, 37.0, 8.5. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{22}H_{26}NO_4$ 368.1856, found 368.1869.

*Methyl (Z)-2-{(1S,5S,6S)-5-allyl-6-(benzyloxy)-8-[2-(tert-butyldimethylsilyloxy)ethyl]-3-oxo-8-azabicyclo[3.2.1]octan-2-ylidene}propanoate [(Z)-**38**] and Methyl (E)-2-{(1S,5S,6S)-5-allyl-6-(benzyloxy)-8-[2-(tert-butyldimethylsilyloxy)ethyl]-3-oxo-8-azabicyclo[3.2.1]octan-2-ylidene}propanoate [(E)-**38**].* To a cooled solution (0 °C) of the diastereoisomeric mixture **36** (1743 mg, 3.28 mmol) in anhydrous pyridine (16.4 mL) was slowly added phosphorus oxychloride (1.53 mL, 16.4 mmol). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with a saturated aqueous $NH_4Cl$ (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/15) to give compound (*E*)-**38** (280 mg, yield: 17%) and compound (*Z*)-**38** (1000 mg, yield: 59%).

(*Z*)-**38**: Pale yellow oil. $[\alpha]_D^{20}$ −33.7 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2926, 2855, 1731, 1693, 1625, 1462, 1433, 1383, 1241, 1189, 1153, 1102, 918, 835, 777, 738 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.22 (m, 5H), 5.85−5.70 (m, 1H), 5.01 (dd, $J$ = 10.2, 1.0 Hz, 1H), 4.93 (dd, $J$ = 17.1, 1.0 Hz, 1H), 4.53 (d, $J$ = 12.0 Hz, 1H), 4.33 (d, $J$ = 12.0 Hz, 1H), 4.26 (d, $J$ = 7.6 Hz, 1H), 3.91 (dd, $J$ = 9.4, 3.1 Hz, 1H), 3.76 (s, 3H), 3.68 (t, $J$ = 6.4 Hz, 2H), 2.84−2.70 (m, 2H), 2.68−2.57 (m, 1H), 2.45−2.32 (m, 1H), 2.28−2.22 (m, 2H), 2.19 (d, $J$ = 17.6 Hz, 1H), 1.94 (s, 3H), 1.48 (dd, $J$ = 13.4, 3.1 Hz, 1H), 0.90 (s, 9H), 0.06 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 198.0, 171.5, 138.2, 137.3, 135.8, 133.0, 128.3 (2C), 127.5, 127.4 (2C), 118.0, 80.1, 71.5, 66.3, 63.1, 57.5, 52.3, 45.5, 43.0, 40.1, 35.4, 26.0 (3C), 18.5, 15.8, −5.3 (2C). HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{29}H_{44}NO_5Si$ 514.2983, found 514.2979.

(*E*)-**38**: Pale yellow oil. $[\alpha]_D^{20}$ +2.8 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2952, 2926, 2854, 1721, 1691, 1462, 1383, 1229, 1186, 1149, 1099, 916, 835, 777 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.24 (m, 5H), 5.87−5.72 (m, 1H), 5.01 (dd, $J$ = 10.1, 1.0 Hz, 1H), 4.92 (dd, $J$ = 17.1, 1.0 Hz, 1H), 4.54 (d, $J$ = 12.0 Hz, 1H), 4.34 (d, $J$ = 12.0 Hz, 1H), 4.30 (d, $J$ = 7.7 Hz, 1H), 3.87 (dd, $J$ = 9.6, 3.5 Hz, 1H), 3.77 (s, 3H), 3.71−3.56 (m, 2H), 2.86−2.71 (m, 2H), 2.61 (ddd, $J$ = 12.5, 7.2, 5.2 Hz, 1H), 2.44−2.32 (m, 1H), 2.28−2.18 (m, 3H), 2.17 (s, 3H), 1.49 (dd, $J$ = 13.8, 3.5 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.9, 169.5, 147.5, 140.3, 138.3, 135.0, 133.1, 128.3 (2C), 127.5, 127.4 (2C), 117.9, 80.1, 71.4, 66.8, 61.8, 59.7, 52.0, 45.6, 39.8, 35.4, 26.0 (3C), 18.4, 16.9, −5.31,


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−5.35. HRMS (ESI-TOF) $m/z$ [M + H]$^+$ calcd for $C_{29}H_{44}NO_5Si$ 514.2983, found 514.2980.

*Methyl (Z)-2-{(1S,5S,6S)-5-allyl-6-(benzyloxy)-8-(2-hydroxyethyl)-3-oxo-8-azabicyclo[3.2.1]octan-2-ylidene}propanoate (**39**).* A solution of compound (Z)-**38** (1.00 g, 1.95 mmol) and PTSA (*p*-toluenesulfonic acid monohydrate, 928 mg, 7.80 mmol) in acetone (20 mL) was stirred at 50 °C (oil bath) for 30 min. To the resulting mixture was added a saturated aqueous $NaHCO_3$ until pH = 8. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/1) to give alcohol **39** (738 mg, yield: 95%) as a colorless oil. $[\alpha]_D^{20}$ −22.7 (*c* 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 3435, 2917, 2849, 1728, 1692, 1620, 1433, 1407, 1383, 1296, 1279, 1240, 1189, 1151, 1119, 1090, 1045, 1028, 992, 918, 738, 693 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.20 (m, 5H), 5.80−5.65 (m, 1H), 5.09−5.02 (m, 1H), 5.01−4.92 (m, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.28 (d, *J* = 7.8 Hz, 1H), 3.97 (dd, *J* = 9.3, 3.2 Hz, 1H), 3.76 (s, 3H), 3.67−3.57 (m, 2H), 2.94−2.82 (m, 2H), 2.65 (td, *J* = 12.9, 3.2 Hz, 1H), 2.42 (ddd, *J* = 13.6, 9.3, 7.8 Hz, 1H), 2.35−2.15 (m, 3H), 1.94 (s, 3H), 1.54 (dd, *J* = 13.6, 3.2 Hz, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.2, 171.3, 137.9, 136.6, 136.2, 132.2, 128.3 (2C), 127.6, 127.5 (2C), 118.8, 79.9, 71.5, 66.0, 59.1, 55.6, 52.3, 44.7, 42.9, 39.8, 35.4, 15.8. HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{23}H_{29}NO_5Na$ 422.1938, found 422.1942.

*Methyl (Z)-2-{(1S,5S,6S)-5-allyl-6-(benzyloxy)-8-(2-bromoethyl)-3-oxo-8-azabicyclo[3.2.1]octan-2-ylidene}propanoate (**42**).* To a cooled solution (0 °C) of alcohol **39** (712 mg, 1.78 mmol) in anhydrous $CH_2Cl_2$ (18 mL) were added $CBr_4$ (759 mg, 2.32 mmol) and $PPh_3$(700 mg, 2.67 mmol). After being stirred at 0 °C for 30 min, the resulting mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/PE = 1/6) to give bromide **42** (799 mg, yield: 97%) as a colorless oil. $[\alpha]_D^{20}$ −48.5 (*c* 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2917, 2849, 1728, 1693, 1620, 1432, 1383, 1277, 1237, 1188, 1151, 1118, 1027, 992, 738, 697 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.20 (m, 5H), 5.84−5.70 (m, 1H), 5.08−5.01 (m, 1H), 5.01−4.93 (m, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.28 (d, *J* = 7.7 Hz, 1H), 3.93 (dd, *J* = 9.4, 3.3 Hz, 1H), 3.76 (s, 3H), 3.44−3.30 (m, 2H), 3.05 (td, *J* = 14.6, 7.4 Hz, 1H), 2.95−2.80 (m, 2H), 2.44 (ddd, *J* = 13.5, 9.4, 7.7 Hz, 1H), 2.33−2.21 (m, 2H), 2.17 (d, *J* = 17.6 Hz, 1H), 1.96 (s, 3H), 1.50 (dd, *J* = 13.5, 3.3 Hz, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 171.2, 137.9, 136.5, 136.2, 132.5, 128.2 (2C), 127.5, 127.4 (2C), 118.3, 79.9, 71.4, 66.3, 56.7, 52.3, 45.4, 42.9, 40.0, 35.3, 31.0, 15.8. HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{23}H_{28}BrNO_4Na$ 484.1099 and 486.1079, found 484.1095 and 486.1069.

*(4S,6S,7S)-7-Allyl-6-(benzyloxy)-9-(2-bromoethyl)-3-methyl-4,5,6,7-tetrahydro-2H-4,7-epiminocyclohepta[b]furan-2-one (**43**) and Methyl 2-((1R,4R,5S,7aS)-5-allyl-6-(benzyloxy)-9-oxohexahydro-1H-1,5-ethanopyrrolizin-1-yl)acrylate (**44**).* To a cooled solution (−78 °C) of bromide **42** (38 mg, 0.08 mmol) in anhydrous THF (1.0 mL) was added a freshly prepared solution of LDA (0.46 mL, 0.16 mmol, 0.36 M in THF). After being stirred at the same temperature for 20 min, the reaction was quenched with a saturated aqueous $NH_4Cl$ (3 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/5) to give compound **43** (17 mg, yield: 48%) and compound **44** (6.5 mg, yield: 21%).

Compound **43**: Colorless oil. $[\alpha]_D^{20}$ −148.0 (*c* 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2919, 2849, 1769, 1650, 1453, 1397, 1376, 1285, 1189, 1127, 1092, 1050, 1020, 916, 873, 737, 698 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.24 (m, 5H), 5.86−5.72 (m, 1H), 5.42 (s, 1H), 5.13−5.08 (m, 1H), 5.08−5.02 (m, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.29 (d, *J* = 7.6 Hz, 1H), 4.13 (dd, *J* = 8.8, 3.7 Hz, 1H), 3.36−3.24 (m, 2H), 2.91 (dt, *J* = 14.5, 7.4 Hz, 1H), 2.65−2.50 (m, 3H), 2.49−2.40 (m, 1H), 1.92 (s, 3H), 1.42 (dd, *J* = 13.1, 3.7 Hz, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 171.1, 149.4, 148.1, 137.9, 132.1, 128.4 (2C), 127.8, 127.7 (2C), 119.8, 118.9, 107.9, 82.8, 71.9, 66.6, 55.2, 46.3, 38.7, 35.1, 30.7, 8.3. HRMS (ESI-TOF) $m/z$ [M + Na]$^+$ calcd for $C_{22}H_{24}BrNO_3Na$ 452.0837 and 454.0817, found 452.0844 and 454.0822.

Compound **44**: Colorless oil. $[\alpha]_D^{20}$ −28.0 (*c* 0.5, $CHCl_3$). IR (film) $\nu_{max}$ 2920, 2849, 1725, 1709, 1625, 1453, 1435, 1414, 1383, 1352, 1322, 1197, 1171, 1126, 1096, 1027, 736, 695 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.22 (m, 5H), 6.25 (s, 1H), 5.87−5.73 (m, 1H), 5.34 (s, 1H), 5.10−5.03 (m, 1H), 5.03−4.94 (m, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.36 (d, *J* = 11.9 Hz, 1H), 3.92 (dd, *J* = 9.4, 6.1 Hz, 1H), 3.74 (s, 3H), 3.67 (d, *J* = 7.7 Hz, 1H), 3.22−3.09 (m, 2H), 2.72−2.60 (m, 2H), 2.41 (ddd, *J* = 13.8, 9.4, 8.3 Hz, 1H), 2.32−2.20 (m, 2H), 2.11 (d, *J* = 15.3 Hz, 1H), 2.07−1.97 (m, 1H), 1.36 (ddd, *J* = 13.8, 6.1, 1.3 Hz, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 207.2, 167.3, 140.4, 138.1, 132.9, 128.3 (2C), 127.63 (2C), 127.58, 123.6, 118.1, 80.5, 71.5, 70.2, 67.8, 64.3, 51.9, 44.1, 42.1, 39.7, 39.0, 29.4. HRMS (ESI-TOF) $m/z$ [M + H]$^+$ calcd for $C_{23}H_{28}NO_4$ 382.2013, found 382.2018.

*Methyl (Z)-2-[(1R,4R,5S,7S,7aS)-7a-allyl-7-(benzyloxy)-9-oxohexahydro-1H-1,5-ethanopyrrolizin-8-ylidene]propanoate [(Z)-**9**].* To a cooled solution (0 °C) of bromide **42** (738 mg, 1.60 mmol) in anhydrous THF (32 mL) was added a freshly prepared solution of NaOMe (3.36 mL, 0.5 M in THF and MeOH). After being stirred at the same temperature for 20 min, the reaction was quenched with a saturated aqueous $NH_4Cl$ (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 2/1) to give compound (Z)-**9** (427 mg, yield: 68%) and compound **44** (164 mg, yield: 27%). (Z)-**9**: colorless oil. $[\alpha]_D^{20}$ −78.5 (*c* 0.5, $CHCl_3$). IR (film) $\nu_{max}$ 2946, 2923, 2846, 1730, 1705, 1630, 1453, 1432, 1279, 1241, 1150, 1089, 1071, 1027, 761, 736, 697 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.20 (m, 5H), 5.80−5.65 (m, 1H), 5.10−5.02 (m, 1H), 5.02−4.94 (m, 1H), 4.53 (d, *J* = 12.3 Hz, 1H), 4.36 (d, *J* = 12.3 Hz, 1H), 4.15 (d, *J* = 7.9 Hz, 1H), 4.07 (d, *J* = 6.1 Hz, 1H), 3.77 (s, 3H), 3.12−2.95 (m, 2H), 2.86 (d, *J* = 6.3 Hz, 1H), 2.31−2.11 (m, 4H), 1.96−1.85 (m, 4H), 1.72 (d, *J* = 13.2 Hz, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 171.3, 138.0, 137.3, 135.8, 132.9, 128.2 (2C), 127.39, 127.35 (2C), 118.2, 81.0, 78.7, 71.7, 63.3, 55.8, 52.3, 46.3, 38.3, 37.7, 30.0, 15.8. HRMS (ESI-TOF) $m/z$ [M + H]$^+$ calcd for $C_{23}H_{28}NO_4$ 382.2013, found 382.2023.

*(1S,5S,7S)-7-(Benzyloxy)-8-[2-(tert-butyldimethylsilyloxy)ethyl]-1-[(E)-4-methoxybut-2-en-1-yl]-8-azabicyclo[3.2.1]octan-3-one and its Z-isomer (**46**).* To a solution of compound **11** (54 mg, 0.17 mmol) and commercially available (Z)-1,4-dimethoxy-but-2-one (73 mg, 0.63 mmol) in anhydrous toluene (2.4 mL) was added successively titanium(IV) isopropoxide (0.037 mL, 0.17 mmol) and a solution of Grubbs second catalyst (21 mg, 0.025 mmol) in toluene (0.5 mL). After being stirred at 60 °C (oil bath) for 1.5 h, the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/10) to compound **46** (31 mg, yield: 56%) as an inseparable geometric mixture in the ratio of *E*/*Z* = 12:1. Pale yellow oil. IR (film) $\nu_{max}$ 2952, 2927, 2855, 1716, 1462, 1454, 1360, 1255, 1190, 1155, 1100, 972, 835, 777, 736, 697 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$, data of *E*-isomer read from the geometric mixture) $\delta$ 7.35−7.22 (m, 5H), 5.66−5.56 (m, 1H), 5.44 (dt, *J* = 15.5, 6.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 3.82−3.73 (m, 6H), 3.25 (s, 3H), 2.85−2.74 (m, 3H), 2.59 (dd, *J* = 16.0, 1.0 Hz, 1H), 2.33−2.20 (m, 3H), 2.14−2.06 (m, 2H), 1.35 (dd, *J* = 14.6, 3.9 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 6H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$, data of *E*-isomer read from the geometric mixture) $\delta$ 208.5, 138.3, 129.8, 128.3, 128.2 (2C), 127.44 (2C), 127.41, 80.3, 72.8, 71.3, 66.9, 62.9, 57.7, 55.4, 44.9, 43.6, 41.7, 38.5, 35.3, 25.9 (3C), 18.2, −5.4 (2C). HRMS (ESI-TOF) $m/z$ [M + H]$^+$ calcd for $C_{27}H_{44}NO_4Si$ 474.3034, found 474.3034.

*Methyl (Z)-2-{(1R,4R,5S,7S,7aS)-7-(benzyloxy)-7a-[(E)-4′-methoxybut-2′-en-1-yl]-9-oxohexahydro-1H-1,5-ethanopyrrolizin-8-ylidene}propanoate (**8a**) and 2′(Z)-isomer and Methyl (E)-2-{(1R,4R,5S,7S,7aS)-7-(benzyloxy)-7a-[(E)-4′-methoxybut-2′-en-1-*


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*yl]-9-oxohexahydro-1H-1,5-ethanopyrrolizin-8-ylidene}-propanoate (**8b**) and 2′(Z)-isomer.* To a cooled (0 °C) solution of compound (*Z*)-**9** (370 mg, 0.97 mmol) in MeOH (10 mL) was added 2 M HCl (0.97 mL, 1.94 mmol). After being stirred at the same temperature for 20 min, the solvent was removed under reduced pressure, and the resultant amine hydrochloride salt was dissolved in anhydrous toluene (19.4 mL), then (*Z*)-1,4-dimethoxy but-2-one (1.12 g, 9.7 mmol) and a solution of Grubbs second catalyst (165 mg, 0.194 mmol) in toluene (2 mL) were added successively. After being stirred at 60 °C (oil bath) for 1.5 h, the mixture was cooled to 0 °C and quenched with a saturated aqueous $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/1) to give compound **8a** (231 mg, yield: 56%) and its isomer **8b** (57 mg, yield: 14%), both as an inseparable geometric mixture in a ratio of *E*/*Z* = 6.5:1.

**8a** (*E*/*Z* = 6.5:1): Light brown oil. IR (film) $\nu_{max}$ 2928, 2854, 1784, 1730, 1706, 1630, 1454, 1433, 1280, 1243, 1192, 1152, 1111, 1071, 1026, 973, 737, 698 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$, data of *E*-isomer read from the geometric mixture) $\delta$ 7.35−7.21 (m, 5H), 5.70−5.56 (m, 1H), 5.50 (dt, *J* = 15.4, 5.9 Hz, 1H), 4.53 (d, *J* = 12.3 Hz, 1H), 4.34 (d, *J* = 12.3 Hz, 1H), 4.14 (d, *J* = 7.8 Hz, 1H), 4.07 (d, *J* = 6.0 Hz, 1H), 3.81 (d, *J* = 5.8 Hz, 2H), 3.77 (s, 3H), 3.26 (s, 3H), 3.11−2.95 (m, 2H), 2.85 (d, *J* = 6.3 Hz, 1H), 2.30−2.12 (m, 4H), 1.95−1.85 (m, 4H), 1.72 (d, *J* = 13.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, data of *E*-isomer read from the geometric mixture) $\delta$ 197.3, 171.3, 137.9, 137.3, 135.8, 130.1, 128.3, 128.2 (2C), 127.43, 127.40 (2C), 81.1, 78.7, 72.7, 71.8, 63.3, 57.7, 55.7, 52.3, 46.3, 37.7, 36.8, 29.9, 15.8. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{32}NO_5$ 426.2275, found 426.2277.

**8b** (*E*/*Z* = 6.5:1): Light brown oil. IR (film) $\nu_{max}$ 2925, 2852, 1725, 1702, 1631, 1454, 1434, 1380, 1353, 1281, 1231, 1190, 1165, 1147, 1110, 1069, 1028, 972, 737, 698 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$, data of *E*-isomer read from the geometric mixture) $\delta$ 7.36−7.24 (m, 5H), 5.68−5.57 (m, 1H), 5.48 (dt, *J* = 15.3, 6.0 Hz, 1H), 4.58 (d, *J* = 12.2 Hz, 1H), 4.35 (d, *J* = 12.2 Hz, 1H), 4.13 (d, *J* = 8.2 Hz, 1H), 4.11−4.06 (m, 1H), 3.82−3.79 (m, 2H), 3.78 (s, 3H), 3.25 (s, 3H), 3.07−2.98 (m, 2H), 2.90 (d, *J* = 6.3 Hz, 1H), 2.34−2.10 (m, 7H), 1.80 (d, *J* = 13.6 Hz, 1H), 1.74−1.66 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, data of *E*-isomer read from the geometric mixture) $\delta$ 200.1, 169.5, 139.8, 137.9, 135.7, 130.0, 128.22, 128.18 (2C), 127.4, 127.3 (2C), 80.8, 79.2, 72.7, 71.6, 66.3, 57.8, 57.6, 52.0, 46.2, 37.5, 36.7, 29.8, 16.9. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{32}NO_5$ 426.2275, found 426.2278.

*Methyl (R)-2-{(2R,2aR,2a$^1$S,5R,6S,7aS,8R)-2-hydroxy-2a$^1$-(4′-methoxybutyl)octahydro-2,6-methanofuro[2,3,4-gh]pyrrolizin-8-yl}propanoate (**47**).* A suspension of the geometric mixture **8a** (*E*/*Z* = 6.5:1) (254 mg, 0.598 mmol) and 10% Pd/C (127 mg) in methanol (10 mL) was stirred under an atmosphere of $H_2$ for 24 h at room temperature. Then a solution of 2 M HCl (0.60 mL, 1.20 mmol) was added and the resulting mixture was stirred for 48 h. The mixture was filtered through a Celite pad washing with methanol. The solvent was removed under reduced pressure. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH= 20:1) to afford compound **47** (172 mg, yield: 85%) as a single isomer. White solid. Mp 114−116 °C. $[\alpha]_D^{20}$ −20.3 (*c* 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 3343, 2931, 2873, 1734, 1456, 1435, 1317, 1289, 1258, 1244, 1192, 1157, 1121, 1081, 1039, 979, 946, 855, 767 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.29 (s, 1H), 4.11 (br s, 1H), 3.67 (s, 3H), 3.37 (td, *J* = 6.4, 1.3 Hz, 2H), 3.32 (s, 3H), 3.15−3.10 (m, 1H), 3.08−2.95 (m, 2H), 2.95−2.85 (m, 1H), 2.13−2.07 (m, 1H), 1.99 (d, *J* = 12.0 Hz, 1H), 1.92 (dd, *J* = 8.7, 3.4 Hz, 1H), 1.90−1.81 (m, 2H), 1.66−1.22 (m, 10H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 176.6, 106.2, 81.5, 80.1, 72.5, 63.5, 58.5, 56.8, 51.5, 47.1, 42.7, 38.4, 33.7, 31.5, 30.0, 26.3, 21.8, 18.6. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{30}NO_5$ 340.2118, found 340.2119.

*Methyl (R)-2-{(2S,2aR,2a$^1$S,5R,6S,7aS,8R)-2a$^1$-(4′-methoxybutyl)-2-(trimethylsilyloxy)octahydro-2,6-methanofuro[2,3,4-gh]-pyrrolizin-8-yl}propanoate (**49**).* A neat mixture of hemiacetal **47** (221 mg, 0.65 mmol) and (trimethylsilyl)imidazole (3.9 mL, 26 mmol) was heated at 130 °C (oil bath) for 20 min. The reaction mixture was then cooled to 0 °C and purified by flash chromatography (eluent: EtOAc/hexane = 1:1, containing 3% of $Et_3N$) to provide compound **49** (222 mg, yield: 83%) as a colorless oil. $[\alpha]_D^{20}$ −26.2 (*c* 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2928, 2856, 1737, 1455, 1327, 1250, 1191, 1155, 1120, 1085, 1039, 985, 955, 893, 875, 845, 757 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.26 (br s, 1H), 3.64 (s, 3H), 3.37 (t, *J* = 6.5 Hz, 2H), 3.32 (s, 3H), 3.09−3.04 (m, 1H), 3.04−2.95 (m, 2H), 2.86−2.77 (m, 1H), 2.21−2.17 (m, 1H), 1.94 (d, *J* = 12.0 Hz, 1H), 1.90−1.78 (m, 3H), 1.64−1.56 (m, 2H), 1.54−1.40 (m, 4H), 1.39−1.24 (m, 4H), 0.15 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 176.5, 107.6, 81.1, 80.2, 72.5, 63.6, 58.5, 56.4, 51.3, 47.3, 43.7, 38.9, 34.0, 31.7, 30.0, 26.6, 21.7, 19.5, 1.8 (3C). HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{38}NO_5Si$ 412.2514, found 412.2510.

*(R)-2-{(2S,2aR,2a$^1$S,5R,6S,7aS,8R)-2a$^1$-(4′-Methoxybutyl)-2-(trimethylsilyloxy)octahydro-2,6-methanofuro[2,3,4-gh]pyrrolizin-8-yl}propanal (**51**).* To a cooled (−78 °C) solution of ester **49** (110 mg, 0.27 mmol) in $CH_2Cl_2$ (3 mL) was added a 1 M solution of DIBAL-H in toluene (1.0 mL, 1.0 mmol), and the mixture was stirred at the same temperature for 30 min. Then the reaction was quenched with MeOH (2 mL) and a saturated aqueous solution of potassium sodium tartrate (2 mL), then warmed to room temperature and stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure to give a crude alcohol **50**, which was used in the next step without purification.

To a cooled solution (−78 °C) of oxalyl chloride (0.055 mL, 0.64 mmol) in $CH_2Cl_2$ (4.0 mL) under $N_2$ was added dropwise a solution of DMSO (0.09 mL, 1.28 mmol) in $CH_2Cl_2$(1.0 mL). After being stirred for 15 min at −78 °C, a solution of the crude alcohol **50** in $CH_2Cl_2$(1.0 mL) was added dropwise. After being stirred at the same temperature for 30 min, $Et_3N$ (0.45 mL, 3.2 mmol) was added, and the reaction was kept stirred for 2 h at −78 °C. The reaction was quenched with 5 mL of ice−water at 0−5 °C. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH = 40:1) to provide aldehyde **51** (85 mg, yield: 83% from **49**) as a colorless oil. $[\alpha]_D^{20}$ −46.0 (*c* 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2925, 2854, 1723, 1666, 1598, 1461, 1326, 1250, 1192, 1119, 1038, 961, 893, 872, 845 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.78 (d, *J* = 2.8 Hz, 1H), 4.29 (br s, 1H), 3.38 (td, *J* = 6.5, 0.9 Hz, 2H), 3.32 (s, 3H), 3.22−3.17 (m, 1H), 3.10−2.90 (m, 2H), 2.85−2.75 (m, 1H), 2.26 (t, *J* = 3.4 Hz, 1H), 2.06−2.01 (m, 1H), 1.89−1.83 (m, 3H), 1.65−1.56 (m, 2H), 1.54−1.24 (m, 5H), 1.22 (d, *J* = 6.9 Hz, 3H), 0.16 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 205.4, 107.3, 81.5, 79.9, 72.5, 63.0, 58.5, 56.2, 47.4, 44.5, 43.5, 33.8, 31.8, 30.0, 26.8, 21.7, 13.8, 1.8 (3C). HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{36}NO_4Si$ 382.2408, found 382.2409.

*(S)-2-{(2S,2aR,2a$^1$S,5R,6S,7aS,8R)-2a$^1$-(4′-Methoxybutyl)-2-(trimethylsilyloxy)octahydro-2,6-methanofuro[2,3,4-gh]pyrrolizin-8-yl}propanal (**7**).* To a solution of aldehyde **51** (100 mg, 0.26 mmol) in toluene (5.0 mL) was added DBU (0.20 mL, 1.3 mmol), and the resulting mixture was stirred at 100 °C (oil bath) for 2 h. The resulting mixture was cooled to 0 °C, and quenched with a saturated aqueous $NH_4Cl$ (5 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH = 40:1) to provide epimerized aldehyde **7** (67 mg, combined yield: 67%) as an inseparable epimeric mixture (7:**51** = 12:1). Colorless oil. $[\alpha]_D^{20}$ −29.5 (*c* 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2926, 2854, 1723, 1678, 1460, 1327, 1250, 1192, 1119, 1044, 983, 965, 894, 872, 847, 763 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$, data of the major diastereomer read from


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the diastereoisomeric mixture) $\delta$ 9.53 (d, $J$ = 3.9 Hz, 1H), 4.25 (br s, 1H), 3.36 (t, $J$ = 6.5 Hz, 2H), 3.30 (s, 3H), 3.20−3.15 (m, 1H), 3.08−2.90 (m, 2H), 2.67−2.57 (m, 1H), 2.25−2.20 (m, 1H), 2.03 (dd, $J$ = 10.3, 3.6 Hz, 1H), 1.86−1.76 (m, 3H), 1.63−1.40 (m, 6H), 1.36−1.25 (m, 1H), 0.93 (d, $J$ = 7.3 Hz, 3H), 0.09 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, data of the major diastereomer read from the diastereoisomeric mixture) $\delta$ 204.1, 106.7, 81.4, 79.7, 72.5, 62.2, 58.5, 54.9, 47.5, 43.0, 41.7, 33.7, 31.8, 30.0, 26.5, 21.7, 11.8, 1.6 (3C). HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{20}H_{36}NO_4Si$ 382.2408, found 382.2408.

*Methyl (E)-2-{(1S,5S,6S)-5-allyl-6-(benzyloxy)-8-(2-hydroxyethyl)-3-oxo-8-azabicyclo[3.2.1]octan-2-ylidene}propanoate (**52**).* A solution of (*E*)-**38** (1.63 g, 3.18 mmol) and PTSA (*p*-toluenesulfonic acid monohydrate, 2.4 g, 12.7 mmol) in acetone (30 mL) was stirred at 50 °C (oil bath) for 30 min. To the resulting mixture was added a saturated aqueous $NaHCO_3$ until pH = 8. The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/2) to give compound **52** (1.13g, yield: 89%) as a colorless oil. $[\alpha]_D^{20}$ +20.0 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 3437, 2951, 1725, 1690, 1639, 1435, 1407, 1352, 1273, 1232, 1187, 1149, 1118, 1067, 1045, 993, 916, 739, 699 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.24 (m, 5H), 5.79−5.67 (m, 1H), 5.07−5.01 (m, 1H), 5.00−4.92 (m, 1H), 4.56 (d, $J$ = 12.3 Hz, 1H), 4.36 (d, $J$ = 12.3 Hz, 1H), 4.33 (d, $J$ = 7.9 Hz, 1H), 3.93 (dd, $J$ = 9.6, 3.5 Hz, 1H), 3.78 (s, 3H), 3.67−3.51 (m, 2H), 2.92−2.82 (m, 2H), 2.65 (dt, $J$ = 12.8, 3.3 Hz, 1H), 2.46−2.35 (m, 2H), 2.29 (dd, $J$ = 14.6, 8.1 Hz, 1H), 2.25−2.14 (m, 5H), 1.54 (dd, $J$ = 13.9, 3.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.2, 169.6, 138.8, 138.0, 135.7, 132.2, 128.3 (2C), 127.6, 127.5 (2C), 118.7, 79.9, 71.4, 66.6, 59.0, 58.5, 52.2, 45.7, 44.6, 39.6, 35.3, 16.9. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{23}H_{30}NO_5$ 400.2118, found 400.2121.

*Methyl (E)-2-{(1S,5S,6S)-5-allyl-6-(benzyloxy)-8-(2-bromoethyl)-3-oxo-8-azabicyclo[3.2.1]octan-2-ylidene}propanoate (**53**).* To a cooled solution (0 °C) of alcohol **52** (1090 mg, 2.73 mmol) in anhydrous $CH_2Cl_2$ (27 mL) was added $CBr_4$ (1340 mg, 4.10 mmol) and $PPh_3$ (1431 mg, 5.46 mmol). The reaction mixture was stirred at 0 °C for 30 min and then concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/10) to give bromide **53** (1007 mg, yield: 80%) as a colorless oil. $[\alpha]_D^{20}$ +12.5 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2950, 2922, 2856, 1726, 1692, 1639, 1454, 1435, 1408, 1351, 1272, 1232, 1186, 1150, 1117, 1087, 1072, 1028, 992, 918, 738, 698 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.22 (m, 5H), 5.82−5.70 (m, 1H), 5.07−5.01 (m, 1H), 5.01−4.93 (m, 1H), 4.54 (d, $J$ = 12.0 Hz, 1H), 4.35 (d, $J$ = 12.0 Hz, 1H), 4.33 (d, $J$ = 7.7 Hz, 1H), 3.89 (dd, $J$ = 9.6, 3.7 Hz, 1H), 3.79 (s, 3H), 3.45−3.30 (m, 2H), 3.01 (ddd, $J$ = 13.2, 8.7, 7.1 Hz, 1H), 2.91 (ddd, $J$ = 13.2, 8.2, 5.1 Hz, 1H), 2.84 (d, $J$ = 16.5 Hz, 1H), 2.40 (ddd, $J$ = 13.8, 9.6, 8.0 Hz, 1H), 2.32−2.20 (m, 2H), 2.17 (d, $J$ = 16.5 Hz, 1H), 2.17 (s, 3H), 1.48 (dd, $J$ = 13.8, 3.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.3, 169.4, 139.3, 138.1, 135.1, 132.6, 128.3 (2C), 127.53, 127.47 (2C), 118.3, 80.1, 71.5, 66.9, 59.1, 52.1, 46.0, 45.5, 39.6, 35.2, 30.4, 16.8. HRMS (ESI-TOF) $m/z$ $[M + Na^+]$ calcd for $C_{23}H_{28}BrNO_4Na$ 484.1099 and 486.1079, found 484.1102 and 486.1082.

*Methyl (E)-2-{(1R,4R,5S,7S,7aS)-7a-allyl-7-(benzyloxy)-9-oxohexahydro-1H-1,5-ethanopyrrolizin-8-ylidene}propanoate [(E)-**9**].* To a cooled solution (0 °C) of bromide **53** (830 mg, 1.80 mmol) in anhydrous THF (36 mL) was added a freshly prepared solution of NaOMe (1.98 mL, 1.0 M in THF and MeOH). The reaction mixture was stirred at the same temperature for 20 min before being quenched with a saturated aqueous $NH_4Cl$ (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/PE = 1/4) to give compound (*E*)-**9** (603 mg, yield: 88%) and compound **44** (48 mg, yield: 7%). (*E*)-**9**: Colorless oil. $[\alpha]_D^{20}$ −30.2 ($c$ 0.5, $CHCl_3$). IR (film) $\nu_{max}$ 2925, 2850, 1726, 1702, 1638, 1454, 1438, 1353, 1280, 1256, 1232, 1148, 1110, 1069, 1028, 995, 973, 738, 698 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.23 (m, 5H), 5.80−5.65 (m, 1H), 5.08−5.02 (m, 1H), 5.01−4.92 (m, 1H), 4.58 (d, $J$ = 12.3 Hz, 1H), 4.37 (d, $J$ = 12.3 Hz, 1H), 4.15 (d, $J$ = 8.2 Hz, 1H), 4.09 (d, $J$ = 6.3 Hz, 1H), 3.77 (s, 3H), 3.07−3.00 (m, 2H), 2.91 (d, $J$ = 6.3 Hz, 1H), 2.32−2.10 (m, 7H), 1.80 (d, $J$ = 13.6 Hz, 1H), 1.75−1.66 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.2, 169.7, 139.9, 138.0, 135.8, 132.9, 128.3, 127.4, 127.3, 118.2, 80.8, 79.2, 71.7, 66.4, 57.9, 52.0, 46.3, 38.2, 37.6, 29.9, 17.0. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{23}H_{28}NO_4$ 382.2013, found 382.2017.

Similar to the procedure described for the transformation of (*E*)-**9** to **8a**/**8b**, 583 mg of compound (*E*)-**9** was converted to 88 mg of **8a** (*E*/*Z* = 6.2/1) and 350 mg of **8b** (*E*/*Z* = 6.2/1) in 14% and 54% yield, respectively.

*Methyl (S)-2-{(2S,2aR,2a$^1$S,5R,6S,7aS,8R)-2a$^1$-(4-methoxybutyl)-2-(trimethylsilyloxy)octahydro-2,6-methanofuro[2,3,4-gh]pyrrolizin-8-yl}propanoate (**54**).* A suspension of the geometric mixture **8b** (*E*/*Z* = 6.2:1, 108 mg, 0.25 mmol) and 10% Pd/C (54 mg) in methanol (5 mL) was stirred under an atmosphere of $H_2$ for 24 h at room temperature. Then 2 M HCl (0.25 mL, 0.5 mmol) was added and the resulting mixture was stirred for 48 h. The mixture was filtered through a Celite pad washing with methanol. The solvent was removed under reduced pressure to give a crude hemiacetal which was used in the next step without purification. A neat of crude hemiacetal and (trimethylsilyl)imidazole (1.5 mL, 9.9 mmol) was heated to 130 °C (oil bath) for 20 min. The reaction mixture was then cooled to 0 °C, and the mixture was purified by flash chromatographed (EtOAc/hexane = 1:1, containing 3% of $Et_3N$) to provide compound **54** (81 mg, yield: 77%) as a single diastereomer. Colorless oil. $[\alpha]_D^{20}$ −9.6 ($c$ 1.0, $CHCl_3$). IR (film) $\nu_{max}$ 2949, 2881, 1740, 1460, 1434, 1329, 1315, 1249, 1192, 1162, 1119, 1087, 1043, 1030, 980, 895, 845, 757 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.20 (br s, 1H), 3.61 (s, 3H), 3.34 (t, $J$ = 6.4 Hz, 2H), 3.29 (s, 3H), 3.18−3.13 (m, 1H), 2.99 (t, $J$ = 7.5 Hz, 2H), 2.71−2.62 (m, 1H), 2.25−2.17 (m, 2H), 1.90−1.72 (m, 2H), 1.69 (d, $J$ = 11.7 Hz, 1H), 1.62−1.38 (m, 6H), 1.35−1.23 (m, 1H), 1.03 (d, $J$ = 7.3 Hz, 3H), 0.07 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 177.5, 107.0, 81.5, 79.3, 72.5, 62.1, 58.5, 55.0, 51.3, 47.5, 41.3, 36.7, 33.7, 31.8, 30.0, 26.4, 21.7, 14.9, 1.6 (3C). HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{21}H_{38}NO_5Si$ 412.2514, found 412.2517.

Similar to the procedure described for the transformation of **49** to **7**, 75 mg of compound **54** was converted to 55 mg of compound **7** (**7**/**25** = 25/1) in 80% yield over two steps.

*Compound **56**.* To a cooled (−78 °C) solution of 4-methoxy-3-methylfuran-2(5*H*)-one (195 mg, 1.52 mmol) in anhydrous THF (5 mL) was added dropwise *n*-BuLi (0.51 mL, 2.4 M in hexane, 1.22 mmol). The reaction mixture was stirred at the same temperature for 30 min, then a solution of aldehyde **7** (116 mg, 0.30 mmol) in THF (1 mL) was added dropwise. After being stirred at −78 °C for 1 h, the reaction was quenched with a saturated aqueous $NH_4Cl$ (5 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure to give a crude adduct **55**, which was quickly purified by flash chromatography (eluent $CH_2Cl_2$/MeOH = 10:1). The complex adduct **55** was further dissolved in MeOH (4.0 mL) and $CHCl_3$ (0.70 mL), then aqueous HCl (1 M, 1.0 mL, 1.0 mmol) was added. After being stirred at room temperature for 3 h, $K_2CO_3$ (3.4 g) was added and the suspension was stirred vigorously for 1 h. The solvents then were removed in vacuo, $CHCl_3$ (20 mL) was added and the suspension was stirred for 1 h. The solids were removed by filtration and the filtrate was concentrated to give diol **56** (98 mg, yield: 74% from **7**/**51** (12:1)) as a mixture of several diastereoisomers, which was used in the next step without further separation. White solid. IR (film) $\nu_{max}$ 3339, 2931, 1749, 1667, 1455, 1390, 1337, 1232, 1112, 1043, 986 $cm^{-1}$. The $^1H$ NMR spectrum of the diastereomeric mixture is too complex to analyze in detail. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, data read from the diastereomeric mixture) $\delta$ 175.6, 175.2, 174.2, 173.9, 172.0, 171.8, 105.6, 98.1, 97.99, 97.96,


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81.5, 81.4, 81.3, 80.0, 79.5, 79.2, 78.3, 78.1, 77.2, 74.1, 73.9, 72.4, 72.3, 64.4, 63.7, 63.2, 59.3, 58.8, 58.7, 58.3, 55.6, 53.3, 47.0, 41.3, 40.2, 35.2, 35.1, 35.0, 34.2, 33.7, 32.4, 31.3, 29.8, 29.5, 26.3, 26.2, 21.7, 14.6, 14.2, 14.1, 8.3. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{23}H_{36}NO_7$ 438.2486, found 438.2489.

*Compound* ***57***. A solution of the diastereomeric mixture of diol **56** (52 mg, 0.119 mmol), IBX (267 mg, 0.95 mmol) and DMSO (2.5 mL) was heated to 55 °C (oil bath) for 6 h. After being cooled to room temperature, a saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was stirred for 2 h. The resulting mixture was extracted with $CHCl_3$ (5 × 30 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH = 10:1) to provide diol **57** (26 mg, yield: 50%) as a mixture of several diastereoisomers, which was used in the next step without further separation. Pale yellow oil. IR (film) $\nu_{max}$ 3351, 2922, 2851, 1757, 1673, 1462, 1389, 1329, 1262, 1118, 1021, 943 $cm^{-1}$. The $^1H$ NMR spectrum of the diastereomeric mixture is too complex to analyze in detail. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, data read from the diastereomeric mixture) $\delta$ 172.5, 167.8, 111.2, 101.8, 99.9, 82.9, 78.6, 77.2, 72.5, 60.8, 58.9, 58.6, 50.7, 49.8, 47.4, 45.9, 35.8, 32.9, 31.6, 30.0, 26.2, 21.9, 12.4, 8.5. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{23}H_{34}NO_8$ 452.2279, found 452.2280.

*Compound* ***58***. To a cooled (−50 °C) solution of the diastereomeric mixture of diol **57** (24.0 mg, 0.053 mmol) in $CH_2Cl_2$ (0.8 mL) were added successively a solution of DMAP (63.0 mg, 516 mmol) in $CH_2Cl_2$ (1.0 mL), and a solution of thiophosgene in $CCl_4$ (1.5 M, 0.212 mL, 0.318 mmol) (over 30 min). The mixture was stirred at −50 °C for 2 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ (5.0 mL) and the resulting mixture was allowed warming up to room temperature. The mixture was extracted with $CHCl_3$ (5 × 30 mL), the combined organic phases were dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography ($CH_2Cl_2$/MeOH = 10:1) to provide compound **58** (17 mg, yield: 65%) as a mixture of two diastereomers in a ratio of 3:1 ($^1H$ NMR), which was used in the next step without further separation. Colorless oil. IR (film) $\nu_{max}$ 2937, 1796, 1682, 1456, 1390, 1336, 1270, 1211, 1153, 1115, 1065, 1026, 995, 892, 879, 750 $cm^{-1}$. The $^1H$ NMR spectrum of the diastereomeric mixture is too complex to analyze in detail. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, data of the major diastereomer read from the diastereomeric mixture) $\delta$ 185.5, 168.2, 162.6, 117.1, 112.5, 105.8, 103.0, 82.1, 78.6, 72.5, 60.5, 59.8, 58.6, 50.1, 47.5, 44.6, 39.3, 32.9, 31.6, 30.0, 26.3, 21.8, 11.2, 8.6. HRMS (ESI-TOF) $m/z$ $[M + H]^+$ calcd for $C_{24}H_{32}NO_8S$ 494.1843, found 494.1849.

*Methoxystemofoline (****4****) and Isomethoxystemofoline (****5****).* A solution of the diastereomeric mixture of thiocarbonate **58** (10 mg, 0.02 mmol) in $P(OMe)_3$ (1.0 mL, 8.5 mmol) was heated to 120 °C (oil bath) in a sealed tube for 12 h. After cooling to room temperature, the mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (5.0 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and the solvents and $P(OMe)_3$ were removed under reduced pressure. The residue was purified by preparative thin layer chromatography (silica gel, $CH_2Cl_2$/MeOH = 20:1) to provide isomethoxystemofoline (**5**) (2.6 mg, yield: 31%) and methoxystemofoline (**4**) (2.5 mg, yield: 29%).

Isomethoxystemofoline (**5**): Colorless oil. $[\alpha]_D^{20}$ +71−85 ($c$ 0.1, $CH_3OH$) {lit. [data reported for the natural product isolated by Xu, and named as methoxystemofoline (**4**)][4a] $[\alpha]_D^{21.6}$ + 75.6 ($c$ 0.037, $CH_3OH$)}. IR (film) $\nu_{max}$ 2926, 2853, 1745, 1693, 1619, 1454, 1396, 1365, 1239, 1157, 1139, 1121, 1068, 1025, 1000, 968 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.27 (br s, 1H), 4.10 (s, 3H), 3.46 (br s, 1H), 3.38 (t, $J$ = 6.3 Hz, 2H), 3.32 (s, 3H), 3.22−3.08 (m, 2H), 3.04−2.95 (m, 1H), 2.68 (d, $J$ = 6.0 Hz, 1H), 2.03 (s, 3H), 1.96 (d, $J$ = 12.2 Hz, 1H), 1.93−1.86 (m, 1H), 1.85−1.77 (m, 1H), 1.75−1.65 (m, 2H), 1.64−1.50 (m, 5H), 1.44 (d, $J$ = 6.7 Hz, 3H), 1.39−1.32 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta$ 170.5, 163.3, 149.9, 128.8, 113.6, 98.6, 82.7, 78.7, 72.5, 60.8, 59.4, 58.5, 50.1, 47.5, 46.0, 36.3, 33.1, 31.7, 30.0, 26.7, 21.9, 16.2, 8.7. HRMS (ESI-TOF) $m/z$ $[M + H^+]$ calcd for $C_{23}H_{32}NO_6$ 418.2224, found 418.2226.

Methoxystemofoline(**4**): Colorless oil. $[\alpha]_D^{20}$ +220−226 ($c$ 0.1, $CH_3OH$) {lit. [data of the semisynthetic product reported by Pyne et al.][8c] $[\alpha]_D^{25}$ +249 ($c$ 0.29, $CH_3OH$)}. IR (film) $\nu_{max}$ 2922, 2851, 1745, 1619, 1458, 1396, 1366, 1140, 1117, 1058, 1007, 988, 966 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 4.26 (br s, 1H), 4.13 (s, 3H), 3.45 (br s, 1H), 3.37 (t, $J$ = 6.4 Hz, 2H), 3.32 (s, 3H), 3.15−3.05 (m, 2H), 3.02−2.96 (m, 1H), 2.69 (d, $J$ = 6.0 Hz, 1H), 2.06 (s, 3H), 1.94 (d, $J$ = 12.2 Hz, 1H), 1.92−1.87 (m, 1H), 1.85−1.78 (m, 2H), 1.73−1.68 (m, 1H), 1.64−1.55 (m, 4H), 1.53−1.45 (m, 1H), 1.37 (d, $J$ = 6.5 Hz, 3H), 1.35−1.31 (m, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) $\delta$ 169.9, 163.0, 148.6, 128.1, 112.9, 98.8, 83.0, 78.7, 72.7, 61.1, 59.0, 58.8, 50.2, 47.8, 47.7, 34.7, 33.5, 31.9, 30.2, 26.8, 22.0, 18.5, 9.3. HRMS (ESI-TOF) $m/z$ $[M + H^+]$ calcd for $C_{23}H_{32}NO_6$ 418.2224, found 418.2225.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02667.

Tables of comparison of NMR data and copies of $^1H$ NMR, $^{13}C$ NMR, NOESY spectra; X-ray crystallographic data for compounds **41** and **47** (PDF)

### Accession Codes

CCDC 2040695 and 2041067 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

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