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Asymmetric Total Synthesis of (−)-Stenine and 9a-*epi*-Stenine

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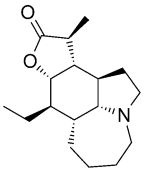
Abstract: A route for the asymmetric synthesis of (−)-stenine, a member of the *Stemona* alkaloid family used as folk medicine in Asian countries, is described. The key features of the sequence employed include stereoselective transformations on a cyclohexane ring controlled by a chiral auxiliary unit and an intramolecular Mitsunobu reaction to construct the perhydroindole ring system. By using an intermediate in the route to (−)-stenine, an asymmetric synthesis of 9a-*epi*-stenine was also executed. The C(9a) stereocenter in 9a-*epi*-stenine was installed by using a Staudinger/aza-Wittig reaction of a keto–azide precursor followed by reduction of the resulting imine. The results of this effort demonstrate the applicability of the chiral auxiliary based strategy to the preparation of naturally occurring alkaloids that contain highly functionalized cyclohexane cores.

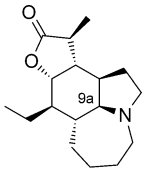
Keywords: alkaloids · asymmetric synthesis · chiral auxiliary · natural products · stenine

Introduction

Extracts from the roots and rhizomes of plants in the Stemonaceae family (*Stemona* and *Croomia* spieces) have long been used in Asian countries as remedies for the treatment of respiratory diseases and as anthelmintics. These extracts were found to be rich *Stemona* alkaloids, which possess polycyclic structures containing multiple stereogenic centers. The structures of most of the alkaloids in this family contain a pyrrolo[1,2-*a*]azepine nucleus with different connection sites between the basic ring system and side chains that serve as the foundation of subcategorization of members of this family.[1] Stenine, a member of this group of alkaloids, was isolated from the roots of *Stemona tuberosa*.[2] The structure of this alkaloid contains a fully substituted cyclohexane core unit fused to three other rings along with seven contiguous stereogenic centers. This substance has attracted considerable attention among synthetic chemists. For example, Hart, Padwa, and Aubé have developed routes for the total syntheses of racemic stenine,[3–5] and several other investigations have been carried out by exploring general approaches to prepare this target.[6] To date, three asymmetric syntheses of stenine have been described, including those of Wipf and Morimoto that employ relatively lengthy sequences.[7,8] Recently, Zhang devised a highly concise enantioselective synthesis of this target that was based on an asymmetric double Michael reaction.[9] Owing to its range of potent biological activities and its structural complexity, stenine continues to serve as a challenging synthetic target. Below, we describe the results of an investigation that has led to the development of a stereocontrolled total synthesis of stenine and its C(9a) epimer, 9a-*epi*-stenine, that utilizes a novel chiral auxiliary based strategy.



(−)-stenine



9a-*epi*-stenine

The most demanding task in the synthesis of stenine is the stereoselective construction of its densely substituted cyclohexane core. In the course of recent efforts focusing on asymmetric reactions using chiral acetals derived from C_2-symmetric diols,[10] we developed a new asymmetric desymmetrization strategy that employs intramolecular haloetherification reactions of cyclohexadiene acetals **1** to generate substituted cyclohexenes **2** (Scheme 1).[11] This process, which enables installation of multiple chiral centers in cyclohexane rings, proceeds via a rigid cationic intermediate (Scheme 1) and utilizes the chiral auxiliary as a template that remains in the product. We have already demonstrated the usefulness of this haloetherification methodology by its application to the synthesis of biologically active natural products containing substituted cyclohexane frameworks.[12]

Synthetic plan: The plan we have devised for the asymmetric synthesis of (−)-stenine and 9a-*epi*-stenine employs the

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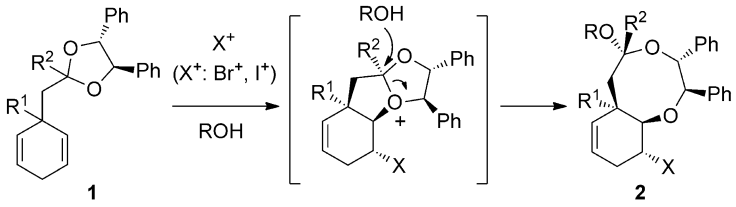
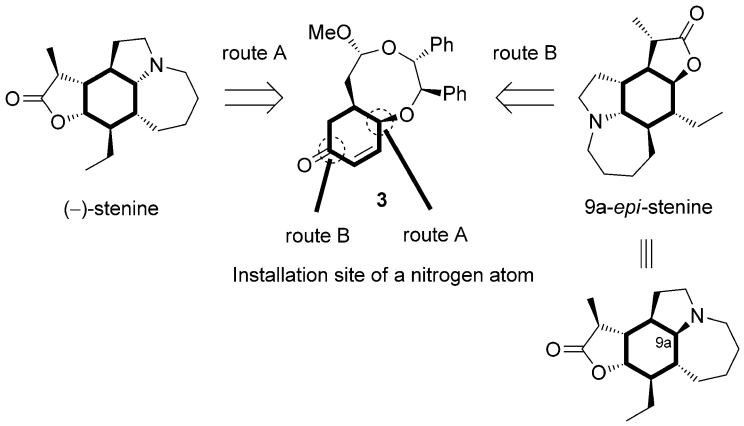


Scheme 1. Intramolecular haloetherification of cyclohexadiene acetals **1**.



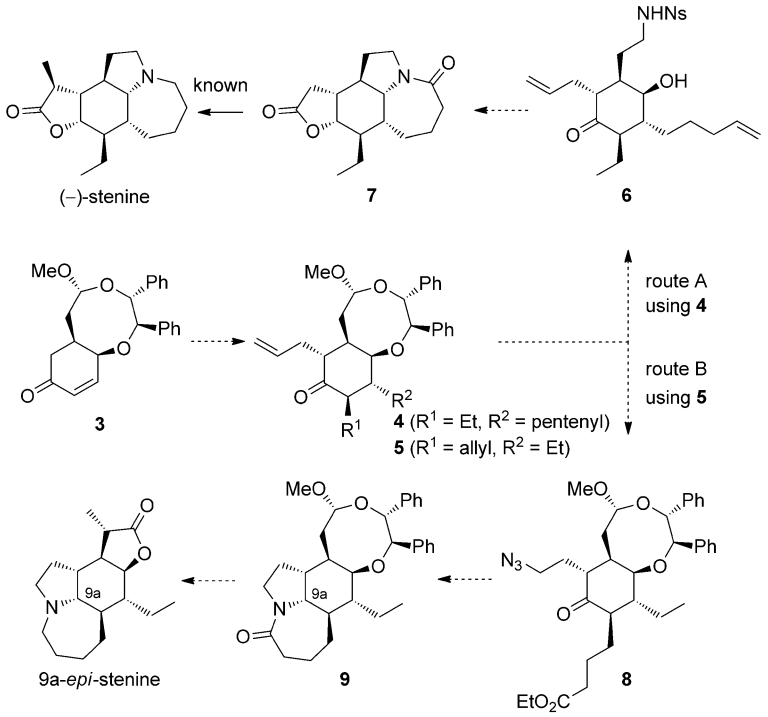
Scheme 2. Synthetic strategy for the preparation of (−)-stenine and 9a-*epi*-stenine by using the common intermediate **3**.

common intermediate **3** (Scheme 2), which can be obtained by hydroboration and subsequent oxidation of the cyclohexane derivative **2** ($R^1=R^2=H$, R = Me, X = Br in Scheme 1).[12b] We postulated that this enone would serve as a suitable precursor for a variety of highly functionalized cyclohexanes containing multiple asymmetric centers because it possesses a variety of functional groups that can undergo nucleophilic and electrophilic addition reactions. Furthermore, we believed that the sterically bulky auxiliary present in **3** would govern the conformation of the cyclohexene ring and guide the stereochemical course of ensuing transformations. Finally, we envisaged that two different routes would exist to convert **3** to (−)-stenine (Scheme 2, route A) and 9a-*epi*-stenine (route B), through processes that lead to installation of the nitrogen center.

The synthetic plans for the preparation of (−)-stenine and 9a-*epi*-stenine, outlined in Scheme 3, begin with a set of stereoselective alkylation reactions of the cyclohexene core of **3**, guided by the steric environment provided by the eight-membered acetal. These processes will produce the cyclohexanone derivatives **4** and **5**. In the pathway for synthesis of (−)-stenine, the tetracyclic lactam **7** would be produced by using a 2-nitrobenzenesulfonamide ($NsNH_2$)-based intramolecular Mitsunobu reaction[13] of alcohol **6**, prepared from **4**, followed by manipulation of the two terminal olefin moieties. Importantly, previous studies have shown that lactam **7** can be transformed to stenine through sequential α-methylation of the lactone ring and reduction of the lactam moiety.[5b,c,9] In contrast, the C(9a) stereocenter in 9a-*epi*-stenine would be installed by employing a Staudinger/aza-Wittig reaction of keto azide **8** and subsequent stereoselective reduction of the resulting imine. Finally, 9a-*epi*-stenine would then be generated from lactam **9** through conversion of the 8-membered acetal to the required lactone.

Results and Discussion

Synthesis of (−)-stenine: The first phase of the synthetic approach to stenine focused on the stereoselective introduction of alkyl side chains on the cyclohexane ring of enone **3**. We observed that allylation at the α′-position of **3** takes place readily to afford **10** in 92% yield (Scheme 4). CuCN-promoted Michael addition of 4-pentenyl magnesium bromide to **10** and a subsequent aldol reaction of the resulting enolate with acetaldehyde gave alcohol **11** in 84% yield.[14] Conventional two-step reduction of the alcohol moiety in **11** led to formation of the desired α-ethylcyclohexanone **4** as a



Scheme 3. Detailed plan for the syntheses of (−)-stenine and 9a-*epi*-stenine. Ns = 2-nitrobenzenesulfonyl.

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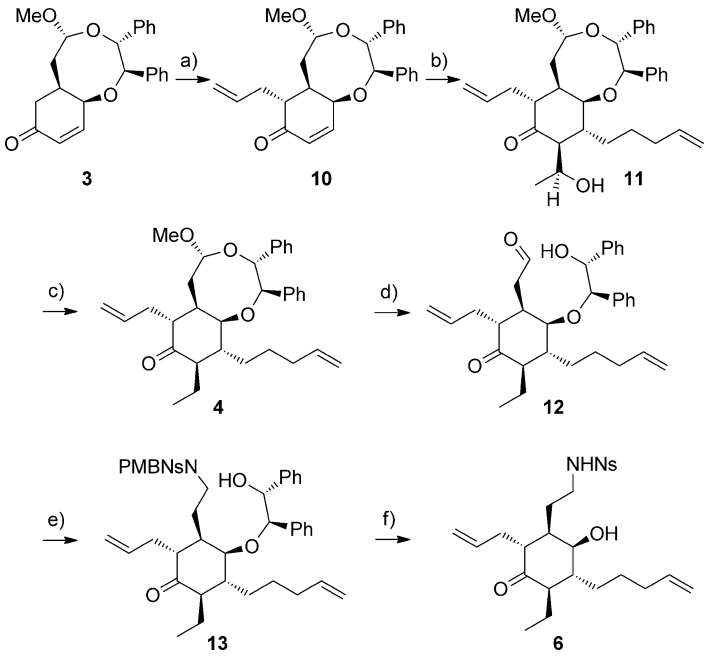
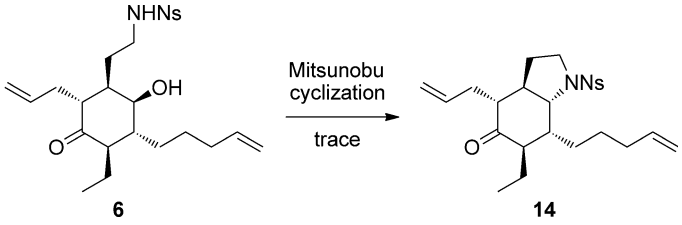


Scheme 4. Synthesis of alcohol **6**: a) LHMDS (1.2 equiv), allyl iodide (3.0 equiv), HMPA (10 equiv), THF, −78 °C, 3 h, 92 %; b) 4-pentenyl magnesium bromide (2.0 equiv), CuCN (0.2 equiv), THF, −78 °C, 1 h, then CH_3CHO (1.5 equiv), −78 °C, 1 h, 84 %; c) i) *O*-phenyl chlorothionoformate (5.0 equiv), DMAP (1.0 equiv), pyridine, RT, 12 h; ii) AIBN (0.1 equiv), Bu_3SnH (3.0 equiv), benzene, 80 °C, 1 h; d) DDQ (0.5 equiv), CH_3CN/H_2O 10:1, RT, 4 h, 85 % (3 steps); e) i) 4-methoxybenzylamine (1.1 equiv), $NaBH(OAc)_3$ (2.0 equiv), 1,2-DCE, RT, 1.5 h; ii) 2-nitrobenzenesulfonyl chloride (1.5 equiv), Et_3N (2.0 equiv), CH_2Cl_2, RT, 30 min, 72 % (2 steps); f) CAN (5.0 equiv), CH_3CN/H_2O 2:1, RT, 5 h, 68 %. AIBN = azobisisobutyronitrile, CAN = cerium(IV) ammonium nitrate, 1,2-DCE = 1,2-dichloroethane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = *N*,*N*-4-dimethylaminopyridine, HMPA = hexamethylphosphoramide, LHMDS = lithium bis(trimethylsilyl)amide, PMB = *para*-methoxybenzyl.

single diastereomer. Unfortunately, direct ethylation adjacent to the ketone did not proceed at all. An initial attempt to hydrolyze the acetal group in **4**, employing standard Brønsted acid based procedures, gave aldehyde **12** in only modest yields. However, when **4** was treated with a catalytic amount of DDQ,[15] aldehyde **12** was obtained in high yield (85 %, three steps). Reductive amination of the aldehyde moiety in **12** by using 4-methoxybenzylamine and $NaBH(OAc)_3$,[16] followed by protection of the amine as a 2-nitrobenzenesulfonamide provided **13** in 72 % yield (two steps). Removal of the PMB and 2-hydroxyethyl groups in **13** was accomplished by using CAN[17] and gave the desired alcohol **6** in 68 % yield.

Methods to bring about Mitsunobu-type cyclization of **6** to construct the nitrogen-containing bicyclic system in stenine was next examined (Scheme 5). However, extensive efforts to promote the conversion of **6** to **14** were not successful because under a variety of Mitsunobu cyclization conditions either elimination of the hydroxyl group in **6** occurred or starting material **6** was recovered. We reasoned that the conformation of the cyclohexane ring in **6** was the factor



Scheme 5. Mitsunobu cyclization of alcohol **6**.

preventing Mitsunobu cyclization that would need to proceed through S_N2 displacement of the hydroxyl group. Because this hydroxyl moiety is located in an axial position, a severe 1,3-diaxial interaction exists between it and the 1,3-disposed ethyl group (Figure 1).

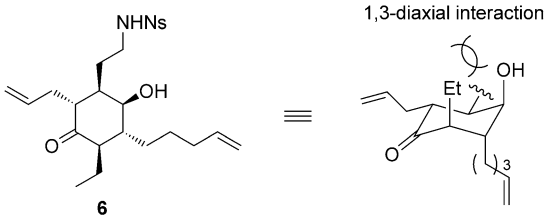


Figure 1. Proposed conformation of alcohol **6**.

This reasoning led to a modification of the strategy in which the Mitsunobu reaction would be conducted on alcohol **18**, which does not suffer from this bad hydroxyl–ethyl group interaction. To explore this proposal, alcohol **18** was generated by using a procedure that is similar to the one employed to prepare **6** (Scheme 6). Michael addition of 4-pentenyl magnesium bromide to the enone **10** afforded **15** in 90 % yield. DDQ-mediated hydrolysis of the acetal group in **15**, followed by reductive amination of the resulting aldehyde **16** and protection of the amine as a Ns group led to formation of cyclohexanone derivative **17** in 61 % yield (three steps). Treatment of **17** with CAN then furnished the target alcohol **18** in 62 % yield.

An investigation of the Mitsunobu cyclization of **18** led to the results summarized in Table 1. Under standard conditions (PPh_3, DEAD, THF, or benzene), **18** reacted to form **19** in rather low yield (Table 1, entries 1 and 2). Also, when $n Bu_3P$ instead of PPh_3 was used to promote this process, only elimination of the alcohol group took place (Table 1, entry 3). Finally, changing the solvent to 1,4-dioxane with DIAD gave a higher yield of **19** (55 % yield, entry 4).[18] The presence of a *trans* ring fusion in **19** was demonstrated by observing coupling constants of 11.2 and 4.0 Hz (shown in Table 1, right figure).[19]

After having developed a route to prepare **19**, attention then focused on the assembly of the polycyclic framework of stenine. α-Ethylation of **19** by using LHMDS and EtI provided **14** in 80 % yield (based on the recovered starting material). As anticipated, this process took place selectively from the β face of the cyclohexanone ring system (i.e., *trans*

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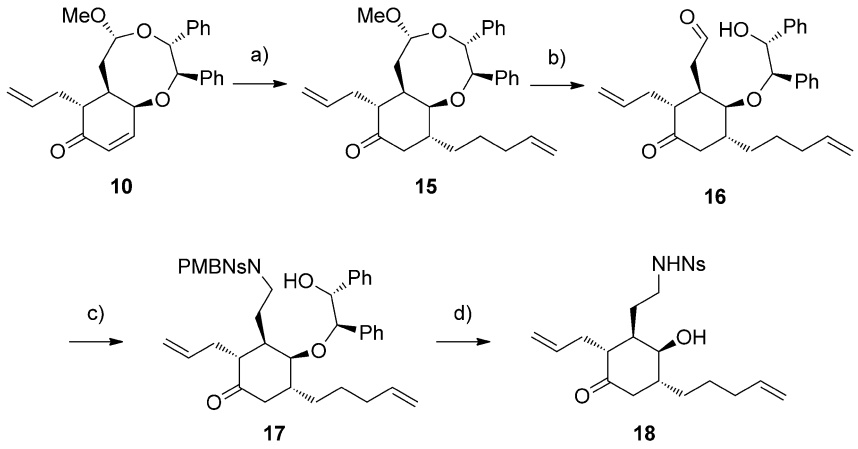
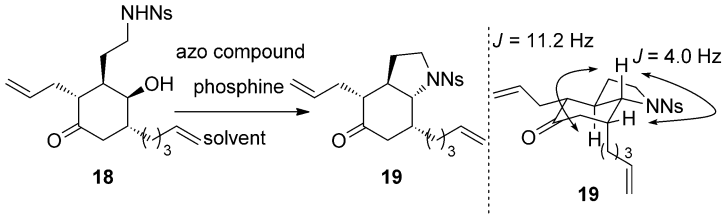


Scheme 6. Synthesis of alcohol **18**: a) 4-pentenyl magnesium bromide (2.0 equiv), CuI (0.5 equiv), THF, −78 °C, 3 h, 90 %; b) DDQ (0.5 equiv), CH_3CN/H_2O 10:1, RT, 4 h, 84 %; c) i) 4-methoxybenzylamine (1.1 equiv), $NaBH(OAc)_3$ (2.0 equiv), 1,2-DCE, RT, 1.5 h; ii) 2-nitrobenzenesulfonyl chloride (1.5 equiv), Et_3N (2.0 equiv), CH_2Cl_2, RT, 30 min, 73 % (2 steps); d) CAN (5.0 equiv), CH_3CN/H_2O 2:1, RT, 5 h, 62 %.

Table 1. Mitsunobu cyclization of alcohol **18** to form **19**.[a]

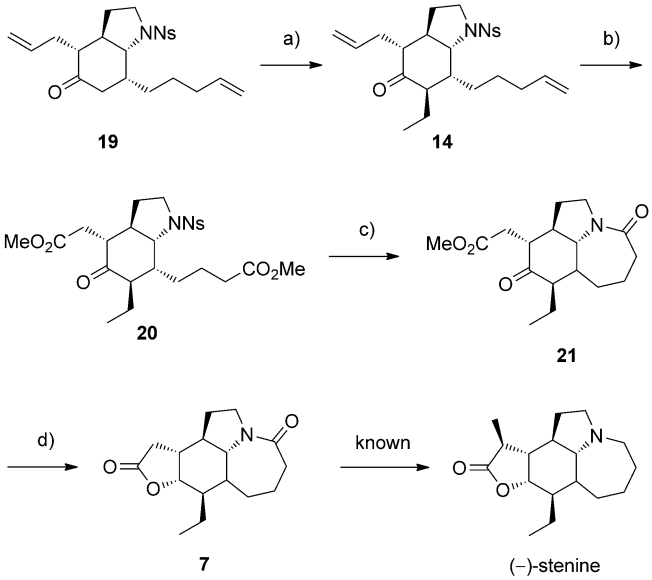


Entry	Azo compound	Solvent	Time	Yield [%][e]
1[b]	DEAD	THF	1 h	18
2[b]	DEAD	benzene	1 h	19
3[c]	DEAD	THF	24 h	n.d.[f]
4[d]	DEAD	1,4-dioxane	15 min	47
5[d]	DIAD	1,4-dioxane	15 min	55
6[d]	DTAD	1,4-dioxane	15 min	28

[a] Unless otherwise noted, reactions were performed by using PPh_3 (2.0 equiv) and azo compound (2.0 equiv) at room temperature. [b] The reaction was performed at 0 °C. [c] nBu_3P was used instead of PPh_3. [d] 1.5 equivalents of PPh_3 and the azo compound were used. [e] Isolated yield. [f] Compound **19** was not detected. DEAD = diethyl azodicarboxylate, DIAD = diisopropyl azodicarboxylate, DTAD = di-*tert*-butyl azodicarboxylate.

to the pre-existing pentenyl group). Conversion of **14** to ester **20** was effected in 57 % overall yield by using a sequence of reactions involving ozonolysis, PDC oxidation, and trimethylsilyldiazomethane-promoted esterification.[20] Removal of the Ns group in **20**, by employing standard conditions (PhSH, $CsCO_3$), followed by lactam ring formation in toluene heated at reflux gave the desired tricyclic lactam **21** in 95 % yield. Finally, $NaBH_4$-mediated reduction of the ketone moiety in **21** afforded lactone **7**, which has been previously employed by Aubé[5b,c] and Zhang[9] as an intermediate in their total syntheses of stenine. All spectroscopic data of **7** matched those reported by these workers.[5b,c,9] Consequently, the route we have developed, which efficiently and stereoselectively installs all stereogenic centers in the cyclohexane ring, serves as an alternative for synthesis of enantiomerically pure (−)-stenine (Scheme 7).

Synthesis of 9a-*epi*-stenine: A synthetic route to 9a-*epi*-stenine was also developed by employing intermediate **3** used in the approach to (−)-stenine. Accordingly, enone **3** reacted with EtMgBr in the presence of CuI, followed by TMSCl and Et_3N-promoted silylation of the resulting enolate to afford silyl enol ether **22** (Scheme 8). Double α,α′-allylation of **22** was achieved by using an excess of MeLi and allyl iodide to provide **5**, in which three stereocenters have been installed, in 44 % overall yield. In this process, a dianion intermediate is generated through reaction of **22** with MeLi, serving as a strong base. Reduction of the ketone group in **5** with $LiAlH_4$ occurred selectively from the α face to generate alcohol **23**.[21] Alcohol **23**, containing a small amount of a minor diastereoisomer, was purified by acetylation and a $LiAlH_4$ reduction process. Oxidative cleavage of both terminal olefin moieties in **23**, carried out by using the Le-



Scheme 7. Total synthesis of (−)-stenine: a) LHMDS (1.5 equiv), ethyl iodide (10 equiv), HMPA (10 equiv), THF, −78 °C to RT, 24 h, 57 % (80 % brsm); b) i) O_3, CH_2Cl_2, −78 °C, 15 min, then PPh_3 (8.0 equiv), RT, 1 h, 81 %; ii) PDC (10 equiv), DMF, RT, 24 h; iii) $TMSCHN_2$ (2.5 equiv), benzene/MeOH 4:1, RT, 30 min, 70 % (2 steps); c) i) $CsCO_3$ (3.0 equiv), PhSH (1.5 equiv), CH_3CN, RT, 12 h; ii) toluene, reflux, 24 h, 95 % (2 steps); d) $NaBH_4$ (3.0 equiv), MeOH, 0 °C, 1.5 h, 64 %. PDC = pyridinium dichromate.

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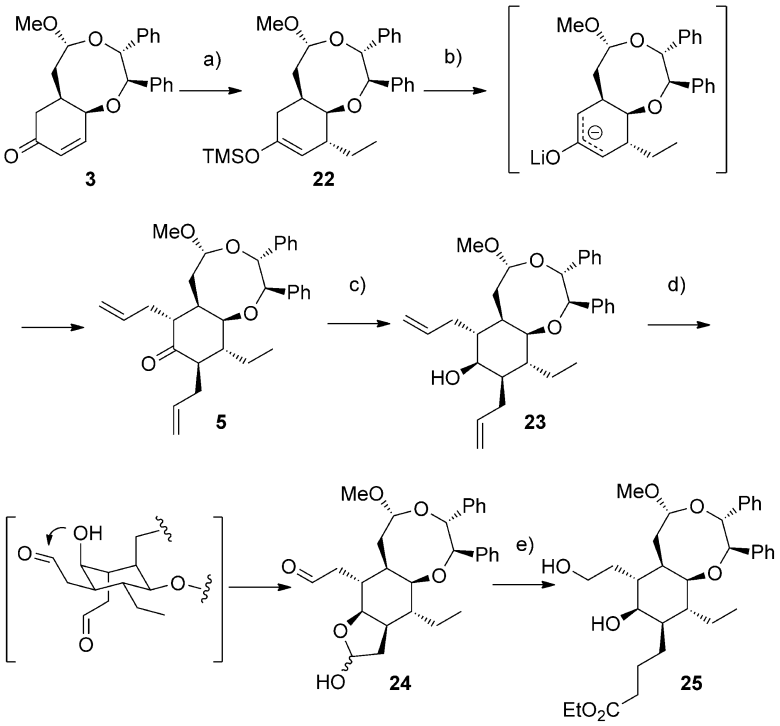
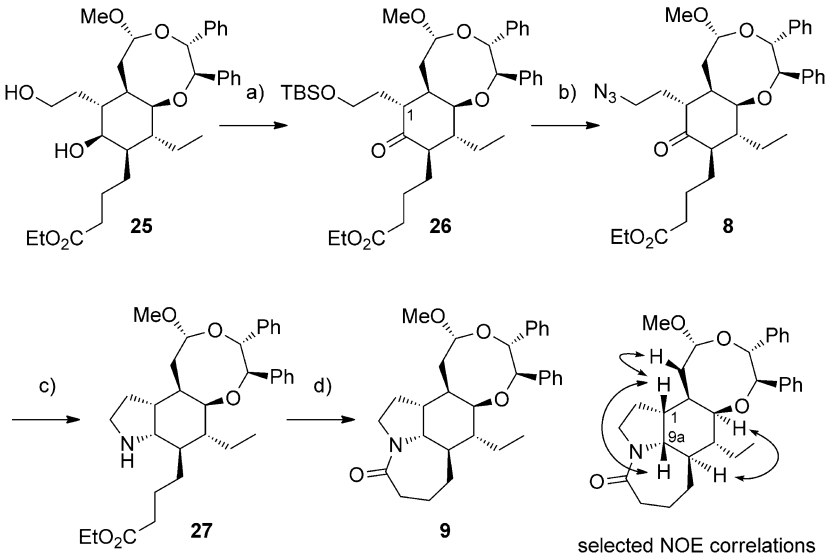


Scheme 8. Synthesis of diol **25**: a) i) EtMgBr (5.0 equiv), CuI (cat.), THF, −78 °C, 30 min; ii) TMSCl (8.0 equiv), Et_3N (9.0 equiv), HMPA (4.0 equiv), THF, 0 °C to RT, 30 min; b) i) MeLi (3.5 equiv), DME, −15 °C, 15 min; ii) allyl iodide (4.0 equiv), 1 h, 0 °C, 44 % (3 steps); c) i) $LiAlH_4$ (1.2 equiv), THF, 0 °C to RT, 99 % (9:1 d.r.); ii) Ac_2O, DMAP, pyridine; iii) $LiAlH_4$ (2 equiv), THF, 0 °C to RT, 85 %; d) OsO_4 (cat.), $NaIO_4$ (4.2 equiv), THF/H_2O 1:1, 1 h, 69 % (d.r. 2.5:1); e) i) DIBAL (3.0 equiv), toluene, −78 °C, 1 h, 77 % (d.r. 2.5:1); ii) $Ph_3P{=}CHCO_2Et$ (1.5 equiv), benzene, reflux, 3 h; iii) Pd/C (cat.), H_2, AcOEt, RT, 2 h, 92 % (2 steps). DIBAL = diisobutylaluminum hydride; DME = 1,2-dimethoxyethane.

mieux–Johnson procedure,[22] gave the monoacetal **24** exclusively as a result of selective addition of the alcohol to the equatorial aldehyde group in the intermediate dialdehyde. Conversion of the lactol **24** to the corresponding ester **25** was accomplished by utilizing a three-step sequence, including DIBAL reduction of the free aldehyde group, Horner–Wasworth–Emmons reaction of the lactol, and hydrogenetion of the olefin moiety.

Sequential TBS protection of the primary alcohol group and oxidation of the secondary alcohol in **25** gave rise to the cyclohexanone derivative **26** in 95 % overall yield (Scheme 9). Owing to its basicity, tetra-*n*-butylammonium fluoride (TBAF), employed for deprotection of the TBS group, promoted undesired epimerization at C(1).[19] In contrast, the desired primary alcohol was obtained in 75 % yield by treatment with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F), a milder reagent for silyl ether deprotection.[23] Alcohol to azide conversion was performed by using Mitsunobu conditions to give **8** in 91 % yield. A Staudinger reaction of the keto azide **8** occurred by using Et_3P and was followed by an intramolecular aza-Wittig reaction that gave the corresponding imine, which was reduced by using $NaBH_4$ from the convex face to produce amine **27**. When we conducted the Staudinger/aza-Wittig reaction by using PPh_3, the high temperature brought about a slight degree of epimerization. In toluene heated at reflux, **27** was transformed to lactam **9** in 53 % overall yield. The stereochemical assignment of **9** was based on the results of ^1H NMR spectroscopic experiments, which showed that an NOE interaction exists between H(1) and



Scheme 9. Synthesis of lactam **9**: a) i) TBSCl (1.2 equiv), imidazole (2.4 equiv), DMF, RT, 1 h, 100 %; ii) PDC (1.3 equiv), CH_2Cl_2, RT, overnight, 95 %; b) i) TAS-F (2.1 equiv), DMF/H_2O 20:1, RT, 24 h, 75 %; ii) PPh_3 (2.4 equiv), DEAD (2.4 equiv), DPPA (1.2 equiv), THF, RT, 1 h, 91 %; c) i) Et_3P (1.2 equiv), THF, RT, 3 h; ii) $NaBH_4$ (2.0 equiv), MeOH, 0 °C, 1 h; d) toluene, reflux, 2 h, 53 % (3 steps). DPPA = diphenylphosphoryl azide, TAS-F = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

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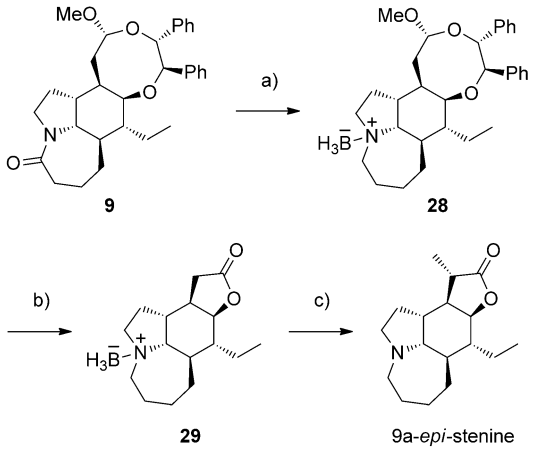
H(9a) and, therefore, that the five-membered ring is fused to the cyclohexane ring in a *cis* manner.

In the final stage of the synthesis of 9a-*epi*-stenine, reduction of lactam **9** was achieved by employing BH_3·THF to afford aminoborane intermediate **28** (Scheme 10). The



Scheme 10. Total synthesis of 9a-*epi*-stenine: a) BH_3·THF (5.0 equiv), THF, RT, 3 h; b) i) Ca, NH_3, EtOH, −78 °C, 1 h; ii) PDC (2.0 equiv), CH_2Cl_2, overnight, 37% (3 steps); c) i) LDA (8.4 equiv), MeI (30 equiv), HMPA (10 equiv), −78 °C, 1 h; ii) Na_2CO_3, MeOH, reflux, 1 h, 65% (2 steps). LDA = lithium diisopropylamide.

eight-membered cyclic acetal moiety in **28** was then converted to the corresponding lactol under Birch reduction conditions. In addition, oxidation of the lactol with PDC gave lactone **29** in 37% yield (three steps). Finally, α-methylation of **29** followed by deboration furnished 9a-*epi*-stenine in 65% overall yield.

Conclusion

In the investigation described above, stereocontrolled syntheses of (−)-stenine and 9a-*epi*-stenine were achieved by using strategies that rely on the common intermediate **3**. This effort showed that enone **3** serves as a useful intermediate in the preparation of complex naturally occurring alkaloids, like stenine, that contain densely substituted cyclohexane cores. In the routes developed, all six stereogenic centers in the cyclohexane rings of the targets are introduced with a high degree of stereoselectivity by employing an intramolecular bromoetherification reaction of cyclohexadiene acetal **1** and efficient transformations of the chiral auxiliary containing enone **3**.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were measured by JEOL JNM-AL 500, JEOL JNM-ECS 400, JEOL JNM-EX 300, and JEOL JNM-EX 270 spectrometers with tetramethylsilane as an internal standard. IR spectra were recorded by Shimadzu FTIR 8400 and IRAffinity-1 by using a diffuse reflectance measurement of samples dispersed in KBr powder. Optical rotations were measured by JASCO P-1020. HRMS and elemental analysis were performed by the Elemental Analysis Section of Graduate School of Pharmaceutical Sciences in Osaka University. Melting points were measured on Yanagimoto Micro Melting Point Apparatus and were uncorrected. Column chromatography was performed with SiO_2 (Merck Silica Gel 60 (230–400 mesh) or Kanto Chemical Silicagel 60 (spherical, 63–210 μm). The organic layer was dried over Na_2SO_4 or $MgSO_4$.

(1*R*,3*R*,4*R*,6*R*,8*R*)-6-Methoxy-3,4-diphenyl-2,5-dioxabicyclo[6.4.0]dodec-11-en-10-one (**3**) was prepared according to the known procedure.[12b]

(1*R*,3*R*,4*R*,6*R*,8*R*,9*R*)-9-Allyl-6-methoxy-3,4-diphenyl-2,5-dioxabicyclo-[6.4.0]dodec-11-en-10-one (10): LHMDS (1.0 M in THF, 5.5 mL, 5.53 mmol) was added to a stirred solution of **3** (1.68 g, 4.61 mmol) in THF (46 mL) at −78 °C under N_2 and the resulting mixture was stirred for 1 h. HMPA (8.0 mL, 46.1 mmol) and allyl iodide (1.26 mL, 13.8 mmol) were added at −78 °C and the resulting mixture was stirred at −78 °C for 3 h. The reaction was quenched with sat. aq. NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 5:1) to give **10** (1.72 g, 92%) as a colorless amorphous solid. $[\alpha]_D^{27.4} = +50.4$ ($c = 1.04$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.74$ (1H, ddd, $J = 11.9$, 8.2, 3.7 Hz), 2.22 (1H, dt, $J = 13.5$, 5.0 Hz), 2.30–2.50 (3H, m), 3.27 (3H, s), 3.31 (1H, brs), 4.40 (1H, A in ABq, $J = 6.9$ Hz), 4.44 (B in ABq, $J = 6.9$ Hz), 4.71 (1H, dd, $J = 2.7$, 2.3 Hz), 5.17 (1H, d, $J = 16.9$ Hz), 5.22 (1H, d, $J = 10.1$ Hz), 5.29 (1H, dd, $J = 5.0$, 3.2 Hz), 5.82–5.90 (1H, m), 5.95 (1H, dd, $J = 10.1$, 1.8 Hz), 6.74 (1H, d, $J = 10.1$ Hz), 6.94 (2H, d, $J = 6.0$ Hz), 6.99 (2H, d, $J = 6.0$ Hz), 7.17–7.21 ppm (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.9$, 36.4, 38.2, 51.1, 54.8, 75.0, 88.07, 88.11, 105.3, 117.4, 127.2, 127.5, 127.75, 127.79, 127.84, 127.9, 128.0, 135.5, 137.6, 138.3, 147.6, 200.1; IR (KBr): $\tilde{\nu} = 2907$, 1678, 1092 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{26}H_{29}O_4$: 405.2066 $[M+H]^+$; found: 405.2067.

(1*R*,3*R*,4*R*,6*R*,8*R*,9*R*,12*R*)-9-Allyl-6-methoxy-12-(pent-4-en-1-yl)-3,4-diphenyl-2,5-dioxabicyclo[6.4.0]dodecan-10-one (15): 4-Pentenyl magnesium bromide (1.0 M in THF, 2.7 mL, 2.74 mmol) was added to a stirred suspension of **10** (555 mg, 1.37 mmol) and CuI (131 mg, 0.686 mmol) in THF (14 mL) at −78 °C under Ar and the resulting mixture was stirred at −78 °C for 3 h. The reaction was quenched with sat. aq. NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 5:1) to give **15** (586 mg, 90%) as a colorless amorphous solid. $[\alpha]_D^{27.7} = -50.8$ ($c = 1.41$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.10$–1.52 (4H, m), 1.87–2.00 (3H, m), 2.11–2.19 (3H, m), 2.37–2.44 (1H, m), 2.48–2.63 (2H, m), 2.67–2.75 (2H, m), 3.24 (3H, s), 3.99 (1H, dd, $J = 6.9$, 2.3 Hz), 4.42 (2H, s), 4.92–4.97 (2H, m), 5.10–5.15 (2H, m), 5.27 (1H, dd, $J = 8.2$, 2.7 Hz), 5.66–5.84 (2H, m), 6.91 (2H, dd, $J = 6.4$, 1.4 Hz), 7.00 (2H, dd, $J = 6.4$, 1.4 Hz), 7.13–7.22 ppm (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.7$, 31.9, 33.6, 33.7, 37.0, 38.0, 39.6, 41.6, 51.9, 54.6, 81.2, 87.9, 89.4, 105.1, 114.7, 117.2, 127.0, 127.5, 127.7, 127.8, 127.9, 135.3, 137.9, 138.4, 138.9, 211.9 ppm; IR (KBr): $\tilde{\nu} = 2926$, 1709, 1121, 1088 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{31}H_{39}O_4$: 475.2848 $[M+H]^+$; found: 475.2864.

2-{(1*R*,2*R*,5*R*,6*S*)-2-Allyl-6-[(1*R*,2*R*)-2-hydroxy-1,2-diphenylethoxy]-3-oxo-5-(pent-4-en-1-yl)cyclohexyl}acetaldehyde (16): DDQ (76.8 mg, 0.338 mmol) was added to a stirred solution of **15** (321 mg, 0.676 mmol) in CH_3CN/H_2O (6.8 mL, v/v = 10:1) at room temperature and the resulting mixture was stirred at this temperature for 4 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 3:1) to give **16** (262 mg, 84%) as a colorless oil. $[\alpha]_D^{29.5} = -17.9$ ($c = 1.33$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.02$–1.41 (4H, m), 1.85–2.24 (5H, m), 2.34–2.70 (4H, m), 2.85 (1H, dd, $J = 17.4$, 6.9 Hz), 3.05 (1H, d, $J = 3.2$ Hz), 3.68 (1H, dd, $J = 4.6$, 2.7 Hz), 4.33 (1H, d, $J = 7.3$ Hz), 4.80 (1H, dd, $J = 7.3$, 2.7 Hz), 4.93–5.04 (4H, m), 5.64–5.76 (2H, m), 6.89–7.22 (10H, m), 9.77 ppm (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.6$, 31.2, 31.9, 33.3, 34.8, 39.1, 41.1, 42.8, 50.2, 78.5, 86.4, 114.8, 117.3, 126.8, 127.7, 127.8, 128.0, 128.15, 128.20, 134.9, 138.2, 138.4, 139.8, 201.5, 210.9 ppm;

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IR (KBr): $\tilde{\nu}$ = 3422, 2928, 1709, 1074 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{30}H_{36}O_4Na$: 483.2511 $[M+Na]^+$; found: 483.2527.

***N*-{2-[(1*R*,2*R*,5*R*,6*S*)-2-Allyl-6-[(1*R*,2*R*)-2-hydroxy-1,2-diphenylethoxy]-3-oxo-5-(pent-4-en-1-yl)cyclohexyl}ethyl)-*N*-(4-methoxybenzyl)-2-nitrobenzenesulfonamide (17)**: 4-Methoxybenzylamine (13.6 μL, 0.105 mmol) and $NaBH(OAc)_3$ (40.5 mg, 0.191 mmol) were added to a solution of **16** (44.0 mg, 0.0955 mmol) in 1,2-DCE (1.0 mL) at 0 °C under N_2 and the resulting mixture was stirred at room temperature for 1.5 h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried and concentrated in vacuo. 2-Nitrobenzenesulfonyl chloride (31.7 mg, 0.143 mmol) and Et_3N (26.5 μL, 0.191 mmol) were added to a solution of residue in CH_2Cl_2 (1.0 mL) at 0 °C under N_2 and the resulting mixture was stirred at room temperature for 30 min. The mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 2:1) to give **17** (51.6 mg, 73 %) as a colorless amorphous soild. $[\alpha]_D^{27.8} = -12.7$ (*c* = 0.66 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88–1.38 (5H, m), 1.86–2.07 (8H, m), 2.37–2.43 (2H, m), 3.15 (1H, d, *J* = 1.4 Hz), 3.24 (1H, ddd, *J* = 14.7, 9.6, 5.0 Hz), 3.51–3.62 (2H, m), 3.75 (3H, s), 4.40 (1H, d, *J* = 8.2 Hz), 4.49 (1H, A in ABq, *J* = 15.2 Hz), 4.58 (1H, B in ABq, *J* = 15.2 Hz), 4.80 (1H, dd, *J* = 8.2, 2.7 Hz), 4.84 (1H, br s), 4.92–4.96 (3H, m), 5.50–5.59 (1H, m), 5.67–5.76 (1H, m), 6.81 (2H, d, *J* = 8.7 Hz), 7.01–7.05 (4H, m), 7.14–7.20 (8H, m), 7.63–7.73 (3H, m), 8.05 ppm (1H, d, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 21.0, 25.6, 31.4, 33.4, 38.7, 41.2, 45.7, 50.6, 55.2, 60.4, 78.7, 113.9, 114.1, 114.7, 117.0, 124.2, 127.17, 127.21, 127.6, 127.8, 128.0, 128.1, 128.3, 129.6, 129.7, 131.0, 131.8, 133.4, 133.7, 135.2, 138.3, 139.4, 147.9, 159.4, 211.5 ppm; IR (KBr): $\tilde{\nu}$ = 3563, 2907, 1705, 1543 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{44}H_{50}N_2O_8SNa$: 789.3185 $[M+Na]^+$; found: 789.3185.

***N*-{2-[(1*R*,2*R*,5*R*,6*S*)-2-Allyl-6-hydroxy-3-oxo-5-(pent-4-en-1-yl)cyclohexyl]ethyl}-2-nitrobenzenesulfonamide (18)**: CAN (404 mg, 0.737 mmol) was added to a solution of **17** (113 mg, 0.147 mmol) in CH_3CN/H_2O (1.5 mL, v/v = 2:1) at room temperature and the resulting mixture was stirred at room temperature for 5 h. The mixture was diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 1:1) to give **18** (41.0 mg, 62 %) as a colorless oil. $[\alpha]_D^{25.7} = -18.0$ (*c* = 1.87 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11–2.22 (12H, m), 2.16 (1H, dd, *J* = 13.7, 5.0 Hz), 2.73 (1H, dd, *J* = 13.7, 5.5 Hz), 3.11–3.25 (2H, m), 3.94 (1H, br s), 4.93–5.02 (4H, m), 5.63–5.80 (3H, m), 7.74–7.87 (3H, m), 8.12–8.14 ppm (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.0, 28.5, 31.1, 31.3, 33.5, 39.6, 40.7, 41.4, 42.5, 49.8, 69.9, 114.9, 116.9, 125.3, 131.1, 132.8, 133.56, 133.58, 135.4, 138.2, 148.0, 211.2 ppm; IR (KBr): $\tilde{\nu}$ = 3339, 2928, 1701, 1541, 1167 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{22}H_{31}N_2O_6S$: 451.1921 $[M+H]^+$; found: 451.1912.

(3a*R*,4*R*,7*R*,7a*R*)-4-Allyl-1-[(2-nitrophenyl)sulfonyl]-7-(pent-4-en-1-yl)-hexahydro-1*H*-indol-5(6*H*)-one (19): DIAD (1.9 M in toluene, 0.15 mL, 0.272 mmol) and PPh_3 (71.3 mg, 0.272 mmol) were added to a solution of **18** (81.7 mg, 0.181 mmol) in 1,4-dioxane (3.6 mL) at room temperature under N_2 and the resulting mixture was stirred at room temperature for 15 min. The mixture was concentrated in vacuo. The residue was purified by SiO_2 column chromatography (benzene/AcOEt = 10:1) to give **19** (43.3 mg, 55 %) as a colorless oil. $[\alpha]_D^{25.9} = -177.7$ (*c* = 0.77 in $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.82–1.98 (9H, m), 1.87 (1H, dt, *J* = 11.4, 5.0 Hz), 2.20–2.26 (1H, m), 2.30 (1H, dd, *J* = 14.7, 5.5 Hz), 2.37–2.43 (1H, m), 2.59 (1H, dd, *J* = 14.7, 2.3 Hz), 2.66 (1H, br s), 3.34 (1H, dt, *J* = 11.2, 5.9 Hz), 3.78 (1H, dd, *J* = 11.0, 4.1 Hz), 3.89 (1H, dd, *J* = 10.5, 8.7 Hz), 5.11–5.16 (4H, m), 5.75–5.85 (1H, m), 5.94–6.05 (1H, m), 6.78 (1H, dt, *J* = 7.8, 1.4 Hz), 6.88 (1H, dt, *J* = 7.8, 1.4 Hz), 6.95 (1H, dt, *J* = 7.8, 1.4 Hz), 7.90 ppm (1H, dt, *J* = 7.8, 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 26.8, 28.6, 31.3, 33.7, 37.2, 43.3, 43.8, 51.0, 53.3, 67.1, 114.5, 116.9, 124.3, 131.0, 131.6, 132.0, 133.8, 135.5, 138.3, 148.4, 208.5 ppm; IR (KBr): $\tilde{\nu}$ = 2928, 1713, 1547, 1373, 1167 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{22}H_{29}N_2O_5S$: 433.1772 $[M+H]^+$; found: 433.1785.

(3a*R*,4*R*,6*R*,7*R*,7a*R*)-4-Allyl-6-ethyl-1-[(2-nitrophenyl)sulfonyl]-7-(pent-4-en-1-yl)hexahydro-1*H*-indol-5(6*H*)-one (14): LHMDS (1.0 M in THF, 0.21 mL, 0.208 mmol) was added to a stirred solution of **19** (74.8 mg, 0.173 mmol) in THF (1.7 mL) at −78 °C under Ar and the resulting mixture was stirred for 1 h. HMPA (0.32 mL, 1.73 mmol) and ethyl iodide (0.14 mL, 1.73 mmol) were added at −78 °C. The resulting mixture was stirred and then allowed to warm to room temperature over 5 h. The reaction was quenched with sat. aq. NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 5:2) to give **5** (45.8 mg, 57 %) as a colorless oil and **14** (21.4 mg, 29 %) was recovered. $[\alpha]_D^{24.4} = -110.4$ (*c* = 0.55 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (3H, t, *J* = 7.3 Hz), 1.33–1.78 (7H, m), 1.87 (2H, d, *J* = 6.9 Hz), 2.00–2.12 (2H, m), 2.26–2.48 (5H, m), 3.47 (1H, dd, *J* = 11.0, 5.5 Hz), 3.92 (1H, dd, *J* = 11.0, 8.7 Hz), 3.98 (1H, dd, *J* = 11.0, 4.1 Hz), 4.88–5.05 (4H, m), 5.62–5.82 (2H, m), 7.67–7.75 (3H, m), 8.07 ppm (1H, dd, *J* = 6.9, 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 25.4, 26.8, 27.0, 28.7, 31.4, 33.8, 40.9, 44.3, 50.4, 50.8, 55.7, 64.4, 114.5, 116.8, 124.4, 131.1, 131.5, 132.6, 133.7, 135.7, 138.4, 148.3, 211.6 ppm; IR (KBr): $\tilde{\nu}$ = 2930, 1705, 1543, 1371, 1362, 1165 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{24}H_{33}N_2O_5S$: 461.2110 $[M+H]^+$; found: 461.2093.

Methyl 4-{(3a*R*,4*R*,6*R*,7*R*,7a*R*)-6-ethyl-4-(2-methoxy-2-oxoethyl)-1-[(2-nitrophenyl)sulfonyl]-5-oxooctahydro-1*H*-indol-7-yl}butanoate (20): A solution of **14** (21.0 mg, 0.0456 mmol) in CH_2Cl_2 (1.0 mL) was bubbled with ozone at −78 °C for 15 min. The reaction was quenched with PPh_3 (95.7 mg, 0.365 mmol) at −78 °C and allowed to warm to room temperature. The mixture was stirred for 1 h and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 1:2) to give aldehyde **30** (17.2 mg, 81 %) as a colorless oil. PDC (100 mg, 0.267 mmol) was added to a suspension of **30** (12.4 mg, 0.0267 mmol) and Celite in DMF (0.3 mL) at room temperature under N_2 and the resulting mixture was stirred at room temperature for 24 h. Et_2O and $MgSO_4$ were added, and the solution was filtered and concentrated in vacuo. $TMSCHN_2$ (2.0 M in Et_2O, 33.4 μL, 0.0667 mmol) was added to a solution of the residue in benzene/MeOH (0.5 mL, v/v = 4:1) at 0 °C under N_2 and the resulting mixture was stirred at room temperature for 15 min and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 1:2) to give **20** (9.8 mg, 70 %) as a colorless oil. $[\alpha]_D^{22.8} = -105.3$ (*c* = 0.28 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (3H, t, *J* = 7.3 Hz), 1.52–1.90 (9H, m), 2.03–2.14 (1H, m), 2.20 (2H, t, *J* = 7.8 Hz), 2.24 (1H, dd, *J* = 16.5, 4.6 Hz), 2.33–2.41 (2H, m), 2.70 (1H, dd, *J* = 16.9, 7.8 Hz), 2.95 (1H, ddd, *J* = 12.8, 7.8, 5.0 Hz), 3.47 (1H, dt, *J* = 11.4, 5.9 Hz), 3.65 (3H, s), 3.66 (3H, s), 3.88 (1H, dd, *J* = 10.5, 8.7 Hz), 4.00 (1H, dd, *J* = 11.4, 4.1 Hz), 7.67–7.78 (3H, m), 8.04–8.07 ppm (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.3, 22.9, 25.4, 26.5, 28.3, 31.6, 34.0, 41.1, 44.3, 47.2, 50.6, 51.5, 51.8, 55.2, 64.1, 124.4, 129.5, 131.2, 131.6, 133.9, 148.4, 172.4, 173.6, 210.3 ppm; IR (KBr): $\tilde{\nu}$ = 2953, 2934, 1732, 1713, 1549, 1371, 1167 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{24}H_{33}N_2O_9S$: 525.1907 $[M+H]^+$; found: 525.1912.

Methyl 2-(5*R*,7a*R*,8*R*,10*R*,10a*R*)-10-ethyl-4,9-dioxododecahydroazipino-[3,2,1*h,i*]indol-8-yl)acetate (21): PhSH (2.8 μL, 0.0280 mmol) and $CsCO_3$ (18.3 mg, 0.0560 mmol) were added to a solution of **20** (9.8 mg, 0.0187 mmol) in CH_3CN (0.3 mL) at 0 °C under N_2 and the resulting mixture was stirred at room temperature for 12 h. Sat. aq. $NaHCO_3$ was added and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was dissolved in toluene (1.0 mL) and stirred at reflux for 24 h. After cooling, the mixture was concentrated in vacuo. The residue was purified by SiO_2 column chromatography (AcOEt/MeOH = 10:1) to give **21** (5.5 mg, 95 %) as a colorless oil. $[\alpha]_D^{17.4} = -45.8$ (*c* = 0.17 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (3H, t, *J* = 7.3 Hz), 1.39–1.50 (2H, m), 1.66–2.08 (7H, m), 2.27–2.50 (5H, m), 2.59 (1H, dd, *J* = 16.0, 5.5 Hz), 2.76 (1H, dd, *J* = 16.0, 5.5 Hz), 3.47–3.55 (2H, m), 3.68 (3H, s), 3.72 ppm (H, dd, *J* = 11.9, 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4, 22.3, 22.6, 25.2, 26.7, 31.9, 34.4, 37.9, 42.4, 46.7, 49.1, 51.9, 53.2, 62.2, 170.9, 171.7, 212.8 ppm; IR (KBr): $\tilde{\nu}$ = 2926, 2855, 1736, 1715, 1632, 1261 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{26}NO_4$: 308.1862 $[M+H]^+$; found: 308.1860.

13-Desmethyl-5-oxostenine (7): $NaBH_4$ (1.8 mg, 0.0488 mmol) was added to a solution of **21** (5.0 mg, 0.0162 mmol) in MeOH (0.3 mL) at 0 °C

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under N_2 and the resulting mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with aq. 1 N HCl and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (AcOEt/MeOH = 10:1) to give **7** (2.9 mg, 64 %) as a white solid. M.p. 140 °C; $[\alpha]_D^{19.2} = -67.4$ ($c = 0.13$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.97$ (3H, t, $J = 7.3$ Hz), 1.44–1.68 (7H, m), 1.88–2.07 (4H, m), 2.30–2.57 (4H, m), 2.80 (1H, dd, $J = 17.9$, 9.6 Hz), 3.40–3.75 (3H, m), 4.57 ppm (1H, dd, $J = 11.9$, 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.2$, 22.4, 22.9, 27.8, 33.1 (2C), 35.5, 37.4, 42.5, 44.2, 46.7, 60.6, 81.5, 171.0, 176.0 ppm; IR (KBr): $\tilde{\nu} =$ 2961, 2928, 1775, 1634, 1263 cm^{-1}; HRMS (EI): m/z calcd for $C_{16}H_{23}NO_3$: 277.1687 $[M]^+$; found: 277.1678; the spectroscopic data were identical to the reported data.[5b,c,9]

(1*R*,3*R*,4*R*,6*R*,8*R*,9*R*,11*R*,12*R*)-9,11-Diallyl-12-ethyl-6-methoxy-3,4-diphenyl-2,5-dioxabicyclo[6.4.0]dodecan-10-one (5): EtMgBr (1.02 M in THF, 3.4 mL, 3.50 mmol) was added to a stirred suspension of **3** (255 mg, 0.700 mmol) and CuI (10.0 mg, 0.0525 mmol) in THF (7.0 mL) at −78 °C under Ar and the resulting mixture was stirred for 30 min at −78 °C and then allowed to warm to 0 °C. TMSCl (0.72 mL, 5.67 mmol), Et_3N (0.87 mL, 6.24 mmol), and HMPA (0.50 mL, 2.87 mmol) were added to the mixture at 0 °C and the resulting mixture was allowed to warm to room temperature and concentrated in vacuo. *n*-Pentane was then added and the mixture was filtered and concentrated in vacuo. MeLi (1.14 M in Et_2O, 2.2 mL, 2.51 mmol) was added to a solution of the residue in DME (7.0 mL) at −10 °C under Ar and the resulting mixture was stirred for 15 min at −15 °C and allowed to warm to 0 °C. Allyl iodide (0.25 mL, 2.73 mmol) was added at 0 °C and the resulting mixture was stirred for 1 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ and extracted with Et_2O. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 15:1) to give **5** (145 mg, 44 %) as a colorless oil. $[\alpha]_D^{24.7} = -76.9$ ($c = 1.90$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.81$ (3H, t, $J = 7.3$ Hz), 1.38–1.43 (1H, m), 1.45–1.65 (1H, m), 1.84–2.04 (3H, m), 2.20–2.51 (5H, m), 2.60–2.67 (2H, m), 3.21 (3H, s), 4.09 (1H, dd, $J =$ 6.0, 2.3 Hz), 4.38 (2H, s), 4.80–4.86 (2H, m), 5.07–5.13 (2H, m), 5.22 (1H, dd, $J = 8.6$, 2.8 Hz), 5.72 (2H, m), 6.82–7.21 ppm (10H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 9.9$, 23.3, 32.4, 35.4, 36.9, 37.6, 44.7, 48.4, 51.2, 54.6, 79.7, 87.5, 90.0, 105.6, 116.2, 117.4, 127.0, 127.4, 127.5, 127.7, 127.8, 128.0, 135.0, 136.3, 137.9, 138.7, 213.2 ppm; IR (KBr): $\tilde{\nu} =$ 3034, 1713, 1455, 1121 cm^{-1}; elemental analysis calcd (%) for $C_{31}H_{38}O_4$: C 78.45, H 8.07; found: C 78.44, H 8.08.

(1*R*,3*R*,4*R*,6*R*,8*R*,9*R*,10*R*,11*R*,12*R*)-9,11-Diallyl-12-ethyl-6-methoxy-3,4-diphenyl-2,5-dioxabicyclo[6.4.0]dodecan-10-ol (23): $LiAlH_4$ (21.2 mg, 0.556 mmol) in THF (3.0 mL) was added to a solution of **5** (220 mg, 0.464 mmol) in THF (3.0 mL) at 0 °C under N_2 and the resulting mixture was allowed to warm to room temperature. The reaction was quenched with 15 % aq. NaOH and filtered and concentrated in vacuo to give **23** containing the minor isomer (218 mg, 99 %, d.r. 9:1). The obtained **23** was acetylated by Ac_2O (1 mL), DMAP (cat.), and pyridine (2 mL) at room temperature for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 8:1) to afford the acetylated **23** (199.4 mg, 85 %). $LiAlH_4$ (29.7 mg, 0.78 mmol) in THF (1.5 mL) was added to a solution of the acetylated **23** (199.4 mg, 0.39 mmol) in THF (3.0 mL) at 0 °C under N_2 and the resulting mixture was allowed to warm to room temperature. The reaction was quenched with 15 % aq. NaOH and filtered and concentrated in vacuo to give **23** (185.4 mg, 99 %). ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 0.82$ (3H, br s), 1.15–1.18 (2H, m), 1.57–1.64 (2H, m), 1.92–2.41 (8H, m), 3.23 (3H, s), 3.67 (1H, d, $J = 7.4$ Hz), 3.90 (1H, br s), 4.34 (1H, d, $J = 9.1$ Hz), 4.48 (1H, d, $J = 9.1$ Hz), 4.96–5.13 (4H, m), 5.27 (1H, dd, $J = 7.7$, 1.3 Hz), 5.70–5.89 (2H, m), 6.89–7.00 (4H, m), 7.12–7.19 ppm (6H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.1$, 22.6, 31.5, 33.9, 35.9, 36.8, 37.4, 39.7, 43.6, 54.4, 70.4, 88.4, 89.6, 106.3, 115.9, 116.7, 126.9, 127.1, 127.3, 127.5, 127.6, 127.7, 127.9, 128.0, 136.7, 137.4, 137.9, 138.8 ppm; IR (KBr): $\tilde{\nu} = 3472$, 2934, 1455, 1121 cm^{-1}; elemental analysis calcd (%) for $C_{31}H_{40}O_4$: C 78.11, H 8.46; found: C 77.96, H 8.40.

Ethyl 4-[(1*S*,3*R*,4*R*,6*R*,8*R*,9*R*,10*R*,11*R*,12*R*)-12-ethyl-10-hydroxy-9-(2-hydroxyethyl)-6-methoxy-3,4-diphenyl-2,5-dioxabicyclo[6.4.0]dodecan-11-yl]butanoate (25): A catalytic amount of OsO_4 was added to a solution of **23** (136 mg, 0.286 mmol) in THF/H_2O (16 mL. v/v = 1:1) at room temperature and the resulting mixture was stirred at room temperature for 15 min. $NaIO_4$ (256 mg, 1.20 mmol) was added in several portions and the resulting mixture was stirred for 1 h. The mixture was diluted with water and AcOEt and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 1:1) to give aldehyde **24** (95.0 mg, 69 %, d.r. 2.5:1) as a colorless oil. DIBAL-H (0.95 M in hexane, 0.26 mL) was added to a solution of **24** (39.0 mg, 0.0812 mmol) in toluene (1.5 mL) at −78 °C under N_2 and the resulting mixture was stirred at −78 °C for 1 h. The reaction was quenched with MeOH and then allowed to warm to room temperature. Aq. 2 N NaOH was added and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 1:3) to give alcohol **31** (30.3 mg, 77 %, 2.5:1 d.r.) as a colorless oil. $Ph_3P{=}CHCO_2Et$ (19.9 mg, 0.0572 mmol) was added to a solution of **31** (18.4 mg, 0.0381 mmol) in benzene (0.4 mL) at room temperature under N_2 and the resulting mixture was stirred at reflux for 3 h. After cooling, the mixture was concentrated in vacuo. A catalytic amount of 10 % Pd/C was added to a solution of the residue in AcOEt (0.5 mL) at room temperature and the resulting mixture was stirred at room temperature for 2 h under H_2. The mixture was filtered and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 1:2) to give **25** (19.5 mg, 92 %) as a colorless oil. $[\alpha]_D^{24.5} = +4.8$ ($c = 1.01$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.82$ (3H, br s), 1.13–2.08 (15H, m), 1.23 (3H, t, $J = 7.2$ Hz), 2.04–2.33 (3H, m), 3.22 (3H, s), 3.66 (1H, br s), 3.82 (2H, t, $J = 7.2$ Hz), 3.94 (1H, br s), 4.12 (2H, q, $J = 7.1$ Hz), 4.32 (1H, d, $J = 8.9$ Hz), 4.50 (1H, d, $J = 8.9$ Hz), 5.24 (1H, dd, $J = 6.4$, 3.0 Hz), 6.90–6.99 (4H, m), 7.16–7.19 ppm (6H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.2$, 22.7, 28.6, 34.3, 35.3, 37.0, 37.3, 39.6, 40.9, 54.5, 60.2, 61.2, 71.1, 77.2, 88.6, 89.6, 106.3, 126.9, 127.4, 127.7, 127.9, 128.1, 127.9, 128.1, 137.9, 138.8, 173.8 ppm; IR (KBr): $\tilde{\nu} = 3478$, 2934, 1732, 1075, 1057 cm^{-1}; HRMS (FAB): m/z calcd for $C_{33}H_{47}O_7$: 555.3322 $[M+H]^+$; found: 555.3341.

Ethyl 4-[(1*S*,3*R*,4*R*,6*R*,8*R*,9*R*,11*R*,12*R*)-9-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}-12-ethyl-6-methoxy-10-oxo-3,4-diphenyl-2,5-dioxabicyclo[6.4.0]dodecan-11-yl]butanoate (26): Imidazole (62.2 mg, 0.914 mmol) and TBSCl (68.8 mg, 0.457 mmol) were added to a stirred solution of **25** (211 mg, 0.381 mmol) in DMF (0.8 mL) at room temperature under N_2 and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. aq. NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 4:1) to give TBS ether **32** (254 mg, 99 %) as a colorless oil. A suspension of PDC (180 mg, 0.478 mmol) in CH_2Cl_2 (2.0 mL) was added to a suspension of **32** (242 mg, 0.362 mmol) and Celite in CH_2Cl_2 (1.5 mL) at room temperature under N_2 and the resulting mixture was stirred at room temperature overnight. Et_2O was then added, the solution filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 5:1) to give **26** (230 mg, 95 %) as a colorless oil. $[\alpha]_D^{27.3} = -32.6$ ($c = 1.64$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.05$ (3H, s), 0.06 (3H, s), 0.79 (3H, t, $J = 8.2$ Hz), 0.90 (9H, s), 1.21 (3H, t, $J = 7.1$ Hz), 1.25–2.55 (14H, m), 2.50–2.60 (1H, m), 2.65–2.80 (1H, m), 3.18 (3H, s), 3.62 (2H, t, $J = 6.5$ Hz), 4.00–4.15 (2H, m), 4.36 (2H, s), 5.18 (1H, d, $J = 5.6$ Hz), 6.75–7.25 ppm (10H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = -5.4$, −5.3, 10.3, 14.2, 18.3, 22.8, 23.7, 26.0, 28.1, 33.7, 34.4, 36.9, 39.4, 46.2, 47.5, 48.5, 54.6, 60.1, 60.9, 80.5, 87.8, 90.1, 105.7, 127.0, 127.4, 127.6, 127.7, 127.8, 127.9, 137.9, 138.8, 173.4, 214.1 ppm; IR (KBr): $\tilde{\nu} = 2928$, 1736, 1711, 1090 cm^{-1}; elemental analysis calcd (%) for $C_{39}H_{58}O_7Si$: C 70.23, H 8.77; found: C 70.42, H 8.72.

Ethyl 4-[(1*S*,3*R*,4*R*,6*R*,8*R*,9*R*,11*R*,12*R*)-9-(2-azidoethyl)-12-ethyl-6-methoxy-10-oxo-3,4-diphenyl-2,5-dioxabicyclo[6.4.0]dodecan-11-yl]butanoate (8): TAS-F (199 mg, 0.724 mmol) was added to a stirred solution of **26** (230 mg, 0.345 mmol) in DMF/H_2O (3.0 mL, v/v = 20:1) at 0 °C. The resulting mixture was gradually allowed to warm to room temperature

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and was then stirred for 24 h. The reaction was quenched with sat. aq. NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 1:1) to give alcohol **33** (143 mg, 75%) as a colorless oil. PPh_3 (133 mg, 0.508 mmol), DEAD (50% in toluene, 0.22 mL, 0.508 mmol), and DPPA (55.0 μL, 0.254 mmol) were added to a stirred solution of **33** (117 mg, 0.212 mmol) in THF (1.2 mL) at 0 °C under N_2. The resulting mixture was gradually allowed to warm to room temperature and stirred for 1 h at room temperature. MeOH was added and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 4:1) to give **8** (111 mg, 91%) as a colorless oil. $[\alpha]_D^{26.3} = -23.8$ ($c = 1.68$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.84$ (3H, t, $J = 7.3$ Hz), 1.22 (3H, t, $J = 7.2$ Hz), 1.26–2.20 (14H, m), 2.45–2.47 (1H, m), 2.76 (1H, td, $J = 8.7$, 4.9 Hz), 3.20 (3H, s), 3.35–3.41 (2H, m), 4.08 (2H, q, $J = 7.2$ Hz), 4.38 (1H, A in ABq, $J = 9.0$ Hz), 4.42 (1H, B in ABq, $J = 9.0$ Hz), 5.20 (1H, dd, $J = 7.1$, 3.6 Hz), 6.84–7.20 ppm (10H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 10.6$, 14.1, 22.7, 24.1, 28.6, 29.2, 34.1, 36.8, 39.5, 46.7, 47.5, 49.3, 49.3, 54.5, 60.0, 81.0, 88.2, 89.9, 105.4, 126.9, 127.4, 127.6, 127.7, 127.8, 137.7, 128.6, 173.2, 213.4 ppm; IR (KBr): $\tilde{\nu} = 2878$, 2098, 1731, 1709 cm^{-1}; elemental analysis calcd (%) for $C_{33}H_{43}N_3O_6$: C 68.61, H 7.50, N 7.27; found: C 68.79, H 7.62, N 7.16.

(7a*R*,8*R*,8a*S*,10*R*,11*R*,13*R*,14a*R*,14b*R*,14c*S*)-8-Ethyl-13-methoxy-10,11-diphenyltetradecahydroazepino[3,2,1-*hi*][1,4]dioxocino[6,5-*e*]indol-4(5*H*)one (9): Et_3P (20% in toluene, 90 μL, 0.157 mmol) was added to a stirred solution of **8** (75.5 mg, 0.131 mmol) in THF (1.3 mL) at room temperature under N_2 and the resulting mixture was stirred at room temperature for 3 h. MeOH (1.3 mL) was added and then $NaBH_4$ (10.0 mg, 0.264 mmol) was added at 0 °C and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was dissolved in toluene (4.0 mL) and stirred at reflux for 2 h. After cooling, the mixture was concentrated in vacuo. The residue was purified by SiO_2 column chromatography (AcOEt) to give **9** (34.0 mg, 53%) as a colorless oil. $[\alpha]_D^{26.2} = -34.9$ ($c = 1.14$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.62$ (3H, t, $J = 7.3$ Hz), 1.21–2.50 (15H, m), 1.26 (3H, t, $J = 7.2$ Hz), 2.48 (2H, t, $J = 5.0$ Hz), 2.79 (1H, br s), 3.32 (1H, dd, $J = 11.7$, 6.9 Hz), 3.27 (3H, s), 3.65 (1H, dd, $J = 11.7$, 8.3 Hz), 3.71–3.77 (1H, m), 4.39 (1H, A in ABq, $J = 9.3$ Hz), 4.41 (1H, B in ABq, $J = 9.3$ Hz), 5.34 (1H, dd, $J = 8.9$, 3.8 Hz), 6.90–7.19 ppm (10H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 9.1$, 20.6, 23.8, 28.3, 35.2, 36.1, 37.7, 38.2, 40.2, 44.1, 45.2, 54.6, 60.5, 77.2, 78.2, 86.4, 89.3, 105.3, 127.1, 127.4, 127.5, 127.6, 127.8, 127.9, 138.0, 138.8, 174.3 ppm; IR (KBr): $\tilde{\nu} = 3033$, 1646, 1455, 1211, 1055 cm^{-1}; HRMS (FAB): m/z: calcd for $C_{31}H_{40}NO_4$: 490.2958 $[M+H]^+$; found: 490.2952.

(7a*R*,8*R*,8a*S*,11a*R*,11b*R*,11c*R*)-8-Ethyldodecahydroazepino[3,2,1-*hi*]furo-[3,2-*e*]indol-10(2*H*)-one BH_3 complex (29): BH_3·THF (1.0 M in THF, 0.35 mL, 0.350 mmol) was added to a stirred solution of **9** (34.0 mg, 0.0694 mmol) in THF (1.0 mL) at 0 °C under N_2. The resulting mixture was gradually allowed to warm to room temperature and stirred for 3 h. EtOH (0.3 mL) was added and the mixture was added to liq. NH_3 at −78 °C. Calcium (30.0 mg, 0.749 mmol) was added at −78 °C and the resulting mixture was stirred at −78 °C for 1 h. The reaction was quenched with sat. aq. NH_4Cl and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1.0 mL) and the mixture was added to the suspension of PDC (50.0 mg, 0.133 mmol) and Celite in CH_2Cl_2 (0.5 mL) at room temperature. The resulting mixture was stirred at room temperature overnight. Et_2O was added, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (benzene/AcOEt = 4:1) to give **29** (7.2 mg, 37%) as a glassy powder. $[\alpha]_D^{25.3} = +15.5$ ($c = 1.32$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (3H, t, $J = 7.5$ Hz), 1.24–2.05 (13H, m), 2.27–2.42 (3H, m), 2.69–2.87 (5H, m), 3.17–3.25 (2H, m), 3.59 (1H, t, $J = 7.9$ Hz), 4.46 ppm (1H, dd, $J = 8.1$, 6.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 8.9$, 22.4, 24.1, 27.6, 28.5, 30.5, 34.6, 35.3, 35.8, 39.8, 41.7, 61.9, 63.2, 77.8, 81.6, 175.6 ppm; IR (KBr): $\tilde{\nu} = 2965$, 2382, 1782, 1165 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{28}BNO_2$: C 69.32, H 10.18, N 5.05; found: C 69.11, H 9.99, N 4.94.

9a-*epi*-Stenine: A solution of **29** (6.6 mg, 0.0238 mmol) in THF (1.0 mL) was added to a solution of LDA (1.0 M in THF, 0.20 mL, 0.200 mmol) at −78 °C under N_2 and the resulting mixture was stirred at −78 °C for 30 min. HMPA (40.0 μL, 0.230 mmol) and MeI (50.0 μL, 0.803 mmol) were added and the resulting mixture was stirred at −78 °C for 1 h. The reaction was quenched with sat. aq. NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was dissolved in MeOH (1.0 mL) and Na_2CO_3 (19.0 mg, 0.179 mmol) was added and the resulting mixture was stirred at reflux for 1 h. After cooling, H_2O was added and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 10:1) to give 9a-*epi*-stenine (4.3 mg, 65%) as a glassy powder. $[\alpha]_D^{25.8} = +14.7$ ($c = 0.83$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.92$ (3H, t, $J = 7.1$ Hz), 1.22–2.49 (18H, m), 1.34 (3H, d, $J = 7.5$ Hz), 3.16–3.40 (2H, m), 4.53 ppm (1H, t, $J = 7.2$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 9.3$, 16.6, 22.4, 25.3, 27.6, 29.6, 29.7, 38.5, 40.7, 42.3, 55.9, 57.4, 68.5, 71.1, 77.2, 81.6, 180.1 ppm; IR (KBr): $\tilde{\nu} = 2931$, 1769, 1219, 1188 cm^{-1}; HRMS (FAB): m/z calcd for $C_{17}H_{28}NO_2$: 278.2120 $[M+H]^+$; found: 278.2121.

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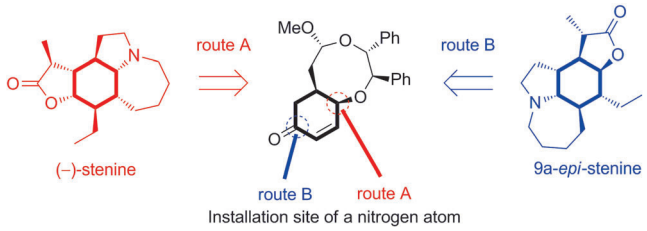

Alkaloids

H. Fujioka, K. Nakahara, N. Kotoku, Y. Ohba, Y. Nagatomi, T.-L. Wang, Y. Sawama, K. Murai, K. Hirano, T. Oki, S. Wakamatsu, Y. Kita* ..... ▮▮▮▮–▮▮▮▮

Asymmetric Total Synthesis of (−)-Stenine and 9a-*epi*-Stenine

Stereocontrolled synthesis: Stereocontrolled syntheses of (−)-stenine and 9a-*epi*-stenine have been developed by using a common cyclohexenone intermediate (see scheme). All six stereogenic centers in the cyclohexane ring were introduced with a high degree of stereoselectivity.

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