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One-Step Stereospecific Strategy for the Construction of the Core Structure of the 5,11-Methanomorphanthridine Alkaloids in Racemic as well as in Optically Pure Form: Synthesis of (±)-Pancracine and (±)-Brunsvigine

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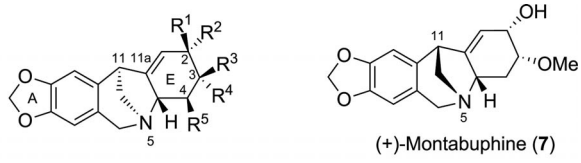
The unique core structure of the complex pentacyclic 5,11-methanomorphanthridine has been constructed stereospecifically in one step by an intramolecular [3+2] cycloaddition of a non-stabilized azomethine ylide (AMY), generated by the sequential double desilylation of **14** using $Ag^{I}F$ as a one-electron oxidant. The formation of the single diastereomer in the key step is explained by the preferred transition state produced by *endo* attack of the AMY on the "*Re*" face of the dipolarophile. An asymmetric version of the cycloaddition using a chiral dipolarophile was applied to construct the core structure **68** with 63 % *ee*. This strategy was successfully applied to the formal synthesis of (±)-pancracine and the total synthesis of (±)-brunsvigine. An unprecedented and interesting skeletal rearrangement product **49** was observed during the attempted assembly of the E ring from **46** through Horner–Wadsworth–Emmons reactions. Mechanisms involving azetidinium salt formation or the Grob-type fragmentation are advanced to explain the observed rearrangement.

Introduction

The *Amaryllidaceae* alkaloids[1] have long been a source of structurally intriguing target molecules due to their architectural diversity, limited supply and wide range of promising biological activities that continue to challenge the capabilities of contemporary organic synthesis. These alkaloids encompass functionally and structurally diverse pentacyclic 5,11-methanomorphanthridine frameworks and were first isolated by Wildman and Brown[2] in 1955 from various plant species such as Pancratium, Narcissus and Brunsvigia. In general, the alkaloids of this group, such as (–)-pancracine (**1**),[2] (–)-brunsvigine (**2**),[3] (–)-montanine (**3**),[4] (–)-coccinine (**4**),[4] (–)-manthine (**5**),[4] (–)-nangustine (**6**)[5] and (+)-montabuphine (**7**),[6] possess identical structural features except for the oxygen substitutions in the E ring (i.e., methoxy or hydroxy) and the stereochemistry at C-2 and C-3, except for (–)-nangustine (**6**), as shown in Figure 1. These alkaloids have been shown to display anxiolytic, anti-depressive, anti-convulsive and weak hypotensive activities.[7] Owing to the unique structural features and important biological activities associated with these alkaloids, considerable synthetic efforts have been directed towards their syntheses, but an efficient and conceptually new route has remained elusive.



	R^1	R^2	R^3	R^4	R^5	
1	H	OH	OH	H	H	(–)-Pancracine
2	H	OH	H	OH	H	(–)-Brunsvigine
3	H	OMe	OH	H	H	(–)-Montanine
4	OMe	H	OH	H	H	(–)-Coccinine
5	H	OMe	OMe	H	H	(–)-Manthine
6	H	H	H	OH	OH	(–)-Nangustine

Figure 1. Members of the montanine type of alkaloids.

Scrutiny of the literature revealed that construction of the core pentacyclic 5,11-methanomorphanthridine skeleton **8** has mainly been achieved through only three strategies, such as the Pictet–Spengler reaction from **9**, the intramolecular amination of **10** and the intramolecular radical cyclization of **11** (Figure 2). Hoshino and co-workers[8] accomplished the synthesis of **1**–**4** in racemic form from a precursor of type **10**, obtained by the Pictet–Spengler reaction of the corresponding cyclohexane derivative. Jin and Weinreb[9] also used a similar cyclization protocol starting from a compound of type **10** in their synthesis of (–)-pancracine (**1**) and (–)-coccinine (**4**). In another approach, Hoshino and co-workers[10] used radical cyclization of a

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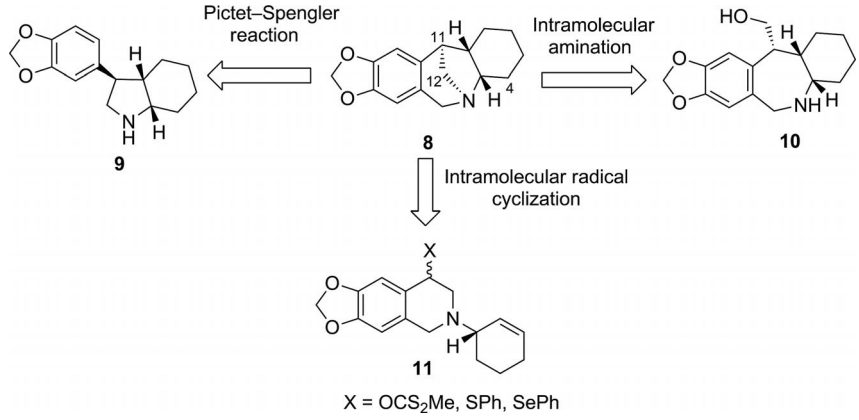
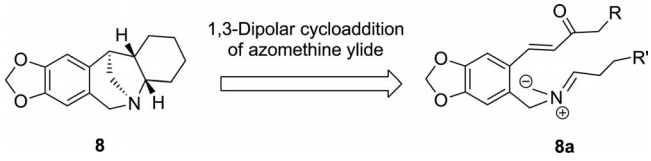


Figure 2. Main strategies adopted for the synthesis of the 5,11-methanomorphanthridine alkaloid skeleton.

precursor of type **11** to construct skeleton **8**. Overman,[11] Pearson,[12] Ikeda,[13] Sha,[14] Banwell,[15] Chang,[16] Hashimoto[17] and Pansare[18] and their co-workers all used precursors of type **9** in their respective elaborations of these alkaloids. However, in all these strategies, the syntheses were elaborated from a precursor having the desired stereochemistry at C-4a and C-11a and relative disposition of the methylene bridge of **8**, which involved its construction in a stepwise manner.

We viewed the synthesis of **8** from an entirely different angle (Scheme 1), employing the [3+2] cycloaddition of a non-stabilized azomethine ylide (AMY, **8a**) for the construction of the core-substituted CD-ring system, which on further elaboration by employing a suitable C–C bond-forming reaction would provide the E ring.



Scheme 1. Retrosynthetic analysis.

In this article we present the full details[19] of our concept and the development of a strategy that leads to the total synthesis of montanine-type *Amaryllidaceae* alkaloids.

Results and Discussion

Background and Concept

Our continuing interest in exploring the application of non-stabilized azomethine ylides (AMYs), generated by sequential double desilylation of α,α′-bis(trimethylsilyl)-substituted alkyl(methyl)amines using Ag^IF as a one-electron oxidant,[20] for the total synthesis of architecturally complex alkaloids[21] led us to envisage the intramolecular 1,3-dipolar cycloaddition of AMYs of type **8a** for the stereospecific construction of the critical CD ring of 5,11-methanomorphanthridine alkaloids in a single step. While designing the synthetic route, it was very clear to us from the beginning that intramolecular *endo* attack (**A**) of AMY **14a** on the "*Re*" face of the α,β-unsaturated carbonyl moiety would be energetically more favoured than *exo* attack (**B**) due to steric repulsion (Figure 3). Such a cycloaddition was also expected to fulfil all the stereochemical requirements of **8** in a single step without using a starting material with fixed stereocentres.

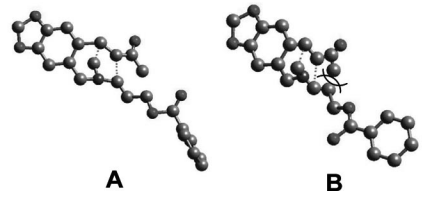


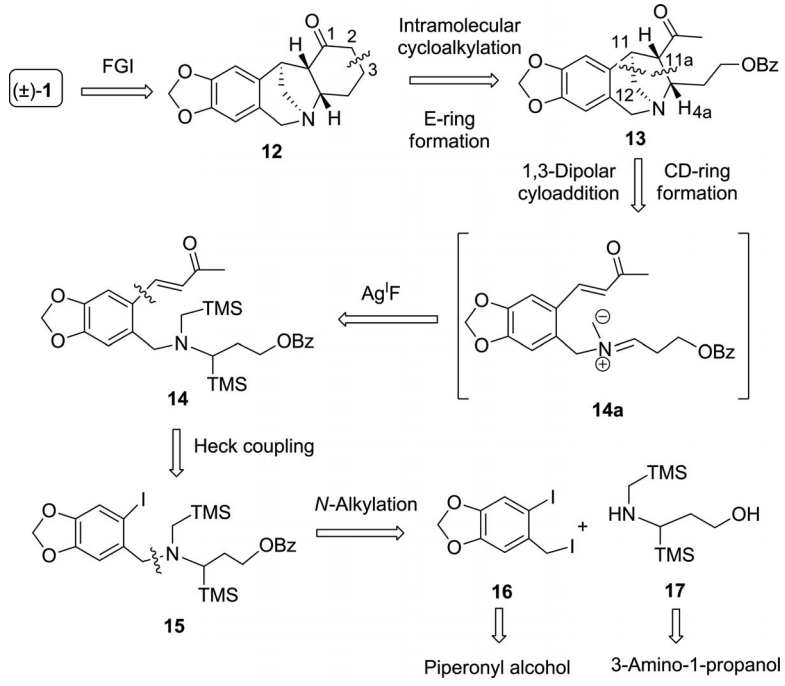
Figure 3. Empirical view of transition state **14a** (hydrogen atoms have been omitted for simplicity).

Enthused by the above concept and design, we pursued our initial retrosynthetic plan for (±)-pancracine (**1**), which is shown in Scheme 2.

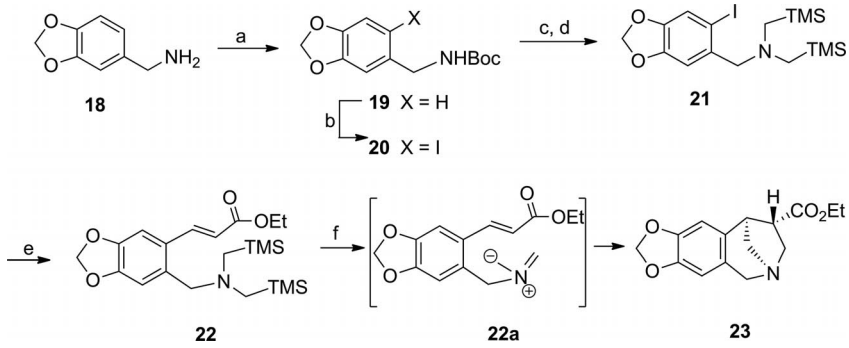
Model Studies

To check the feasibility of our proposed strategy, we studied the intramolecular [3+2] cycloaddition of non-stabilized azomethine ylide **22a**, as shown in Scheme 3. Key precursor **22** was easily prepared in 72% yield by the Heck coupling of **21** with ethyl acrylate (8 equiv.). Compound **21** was prepared in 78% yield by the deprotection of the *N*-Boc moiety of **20** using TFA followed by *N*-alkylation with (iodomethyl)trimethylsilane in the presence of excess K_2CO_3 in dry CH_3CN under reflux. The crucial cycloaddition step involved the dropwise addition of **22** to a stirred heterogeneous mixture of flame-dried Ag^IF (2.5 equiv.) in dry CH_3CN at room temperature. Chromatographic purification of the crude mass gave the expected tetracyclic core **23** of 5,11-methanomorphanthridine in 65% yield, which was fully characterized by IR, ^1H and ^{13}C NMR, and mass spectral analyses. The relative stereochemistry of **23** was confirmed by 2D NMR studies.

Inspired by the success of this strategy for the construction of the ABCD-ring system of 5,11-methanomor-



Scheme 2. Initial retrosynthetic plan for the synthesis of pancracine (**1**).



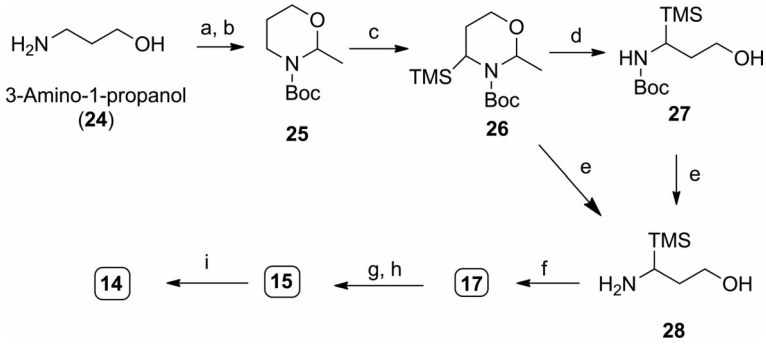
Scheme 3. Reagents and conditions: (a) $(Boc)_2O$, NaOH, H_2O, 0 °C to room temp., overnight, 90%; (b) I_2, CF_3COOAg, $CHCl_3$, 1 h, 70%; (c) TFA, CH_2Cl_2, 0 °C to room temp., 4 h, quant.; (d) ICH_2TMS, K_2CO_3, CH_3CN, reflux, 10 h, 78%; (e) ethyl acrylate, $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, reflux, 10 h, 72%; (f) Ag^IF, CH_3CN, room temp., 12 h, 65%.

phanthridine skeleton **23**, we proceeded with the proposed synthesis of montanine-type alkaloids by this strategy.

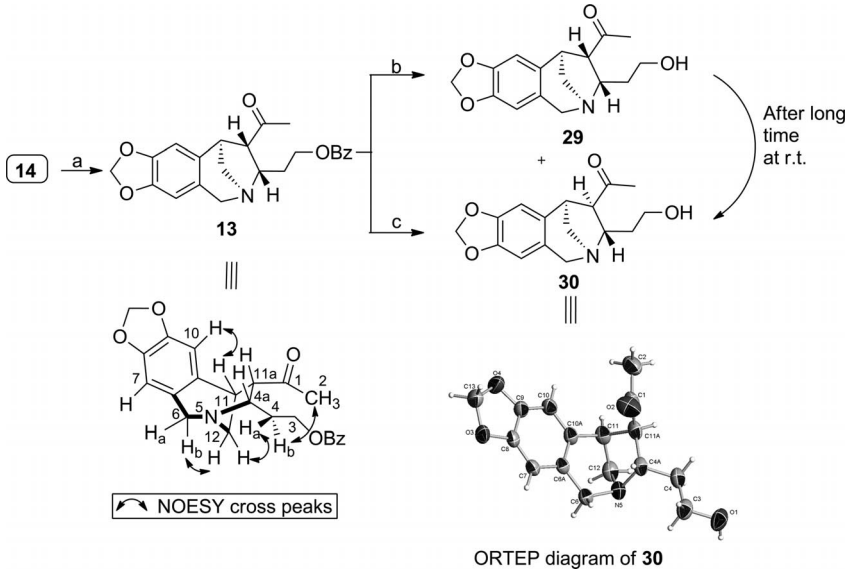
Formal Total Synthesis of (±)-Pancracine (1)

Initially, we focused our attention on synthesizing **12**, an advanced intermediate used by Overman and Shim[11] in the total synthesis of (±)-pancracine (**1**), by the intramolecular cycloalkylation of cycloadduct **13**. The cycloaddition precursor **14** was prepared (60%) by Heck coupling of **15** with methyl vinyl ketone (MVK, 8 equiv.). Compound **15** was synthesized in 81% yield by *N*-alkylation of **17** with **16** in CH_3CN at reflux in the presence of activated K_2CO_3 followed by simple benzoylation of the primary hydroxy group. The bis(silylated) secondary amine **17** was synthesized (61% overall yield) easily by starting from 3-propan-1-ol (**24**) as shown in Scheme 4.

The cycloaddition reaction of the AMY **14a**, generated from **14** according to the standard cycloaddition protocol, gave **13** (56% isolated yield) as a single diastereoisomer (Scheme 5). The stereochemistry of **13** was assigned on the basis of extensive COSY, NOESY and HETCOR NMR spectral studies.[22] With fused tetracyclic intermediate **13** in hand, the only task remaining to complete the formal synthesis of **1** was the construction of the E ring, which we had envisaged by a cycloalkylation strategy. Whereas debenzoylation of **13** by stirring with LiOH/MeOH at room temperature resulted in unexpected epimerized alcohol **30** in 98% yield (confirmed by X-ray crystallography),[23] reaction at 0 °C gave **29** (Scheme 5). However, because the stereochemistry at C-11a at this stage was irrelevant for accomplishing the synthesis of the final natural product, we continued with **30**. Cycloalkylation of the corresponding mesylate derivative of **30** by using LDA/THF[24] at –78 °C produced



Scheme 4. Reagents and conditions: (a) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C to room temp., 36 h; (b) $CH_3CH(OEt)_2$, PPTS, benzene, reflux, 10 h, 90% over two steps; (c) *s*BuLi, TMEDA, THF, –78 °C, 4 h then TMSCl, 2 h, 92%; (d) *p*-TsA, MeOH/H_2O, room temp., 4 h, quant.; (e) 1 N HCl, dioxane, 45 min, reflux, 92%; (f) ICH_2TMS, K_2CO_3, CH_3CN, reflux, 10 h, 80%; (g) **16**, K_2CO_3, CH_3CN, reflux, 10 h; (h) BzCl, Et_3N, CH_2Cl_2, 0 °C to room temp., 6 h, 81%; (i) $Pd(OAc)_2$, PPh_3, K_2CO_3, MVK, CH_3CN, reflux, 12 h, 60%.



Scheme 5. Reagents and conditions: (a) Ag^IF, CH_3CN, room temp., 12 h, 56%; (b) LiOH/MeOH, at 0 °C; (c) LiOH/MeOH, room temp., 3 h, 98%.

the rearranged product **34** in 65% yield. The formation of **34** indicated the possible involvement of the thermodynamic enolate **32** in this rearrangement (Scheme 6).

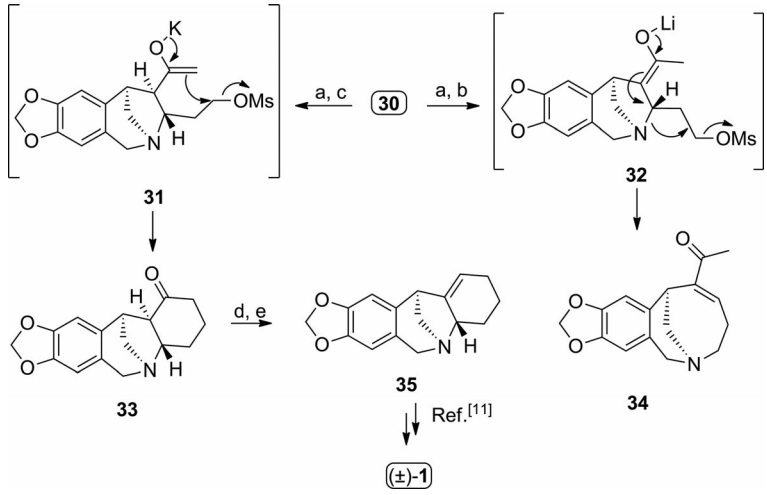
This unexpected setback led us to explore an alternative strategy of generating the kinetic enolate from **30** by using KHMDS/THF[25] at –78 °C, which produced the expected cyclized product **33** (11a-*epi*-**12**) in 58% yield. To complete the formal total synthesis of **1**, compound **33** was transformed into **35** by reductive elimination of the corresponding enol triflate by using $[Pd(PPh_3)_4]/Et_3SiH$ in THF[26] (71% yield). The required enol triflate was generated from **33** by the reaction of the corresponding lithium enolate of **33** with Comins reagent.[27]

After accomplishing the synthesis of **35**,[19] an advanced intermediate used by Overman and Shim[11] in the synthesis of **1**, we realized the limitation of this approach for the synthesis of other members of this class of alkaloids. Therefore, we turned our attention towards designing a general route that would allow the synthesis of other alkaloids of this class. Because there are a variety of oxygen substituents at C-2 and C-3 in the E ring, it was essential to consider building a regioselective double bond (masked oxygen functionality) in the E ring. In this context, we envisioned **36** as an ideal precursor, which in turn we visualized could be obtained from **37** by employing a suitable method (Scheme 7).

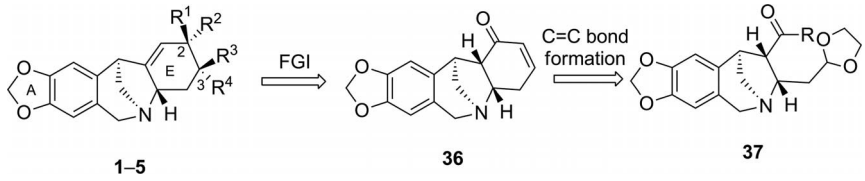
Towards this end, different approaches were attempted, and their failures and successes are presented in chronological order of the development.

First-Generation Approach – Intramolecular Mukaiyama-Type Aldol Reaction

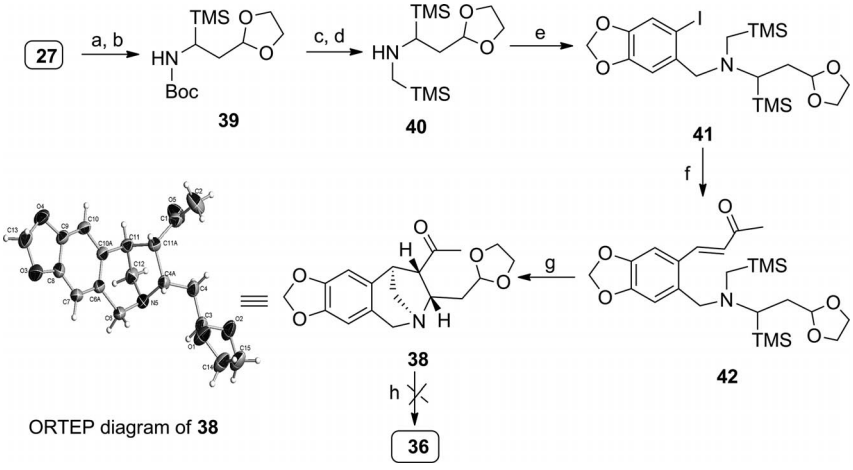
Initially, we planned to synthesize enone **36** from cycloadduct **38**, which is appropriately equipped with a ketone as well as an acetal, by an intramolecular Mukai-



Scheme 6. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C to room temp., 15 min, quant.; (b) LDA, THF, –78 °C to room temp., 5 h, 65%; (c) KHMDS, THF, –78 °C to room temp., 5 h, 58%; (d) LDA, THF, Comins reagent, –78 °C to room temp., 6 h; (e) [Pd-(PPh_3)$_4$], Et_3SiH, LiCl, THF, 60 °C, 24 h, 71% over two steps.



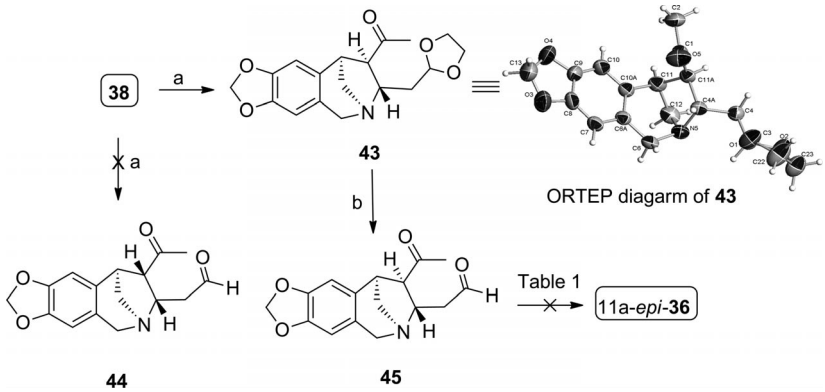
Scheme 7. General route for the synthesis of **1**–**5**.



Scheme 8. Reagents and conditions: (a) Iodoxybenzoic acid, ethyl acetate, reflux, 10 h, quant.; (b) ethylene glycol, *p*-TsA, benzene, Dean–Stark, overnight, 90%; (c) TFA, CH_2Cl_2, 0 °C to room temp., 4 h, quant.; (d) ICH_2TMS, K_2CO_3, CH_3CN, reflux, 10 h, 77%; (e) **16**, K_2CO_3, CH_3CN, reflux, 10 h, 85%; (f) $Pd(OAC)_2$, PPh_3, K_2CO_3, MVK, CH_3CN, reflux, 12 h, 65%; (g) Ag^IF, CH_3CN, room temp., 12 h, 53%; (h) TMSOTf, 2,6-lutidine, –20 °C, THF.

yama-type aldol reaction.[28] Based upon the above premise, **38** was synthesized (53% isolated yield) as a single diastereomer from **42** according to the usual cycloaddition procedure. The synthesis of **42** along with its cycloaddition reaction is depicted in Scheme 8. The structure and stereochemistry of **38** were confirmed by single-crystal X-ray crystallography as well as detailed 2D ^1H NMR spectral analyses.[29]

We attempted first the aldol reaction of **38** by subjecting it to TMSOTf (2 equiv.) and 2,6-lutidine (3 equiv.)[30] at –20 °C in THF; however, **36** could not be obtained, and instead we ended up with an unidentifiable product. This un-anticipated failure led us to try the classic acid/base-catalysed intramolecular aldol reaction[31] with the unmasked aldehyde. Towards this end, we initially attempted to deprotect the dioxolane moiety of **38** under mild reaction condi-



Scheme 9. Reagents and conditions: (a) 3 N HCl, THF/H_2O, room temp., 8 h, 90%; (b) 3 N HCl, THF/H_2O, reflux. 10 h, 88%.

Table 1. Reaction conditions employed in the attempts to perform the aldol reaction.

Entry	Starting material	Conditions	Inference
1	**38**	2,6-lutidine, TMSOTf, –20 °C[30]	unidentified
2	**38**	3 N HCl, THF, room temp., overnight	**43**
3	**38**	3 N HCl, THF, reflux, 10 h	**45**
4	**43**	KHMDS, TMSOTf, THF, –78 °C	starting material
5	**43**	KHMDS, Bu_2BOTf, DME, –78 °C	starting material
6	**43**	LiHMDS, $TiCl_4$, CH_2Cl_2, –78 °C	starting material
7	**45**	3 N HCl, THF/H_2O, reflux	complex mixture
8	**45**	Camphorsulfonic acid/xylene, reflux[36]	complex mixture
9	**45**	NaOMe/MeOH, room temp.[37]	complex mixture
10	**45**	KOH/MeOH, room temp.	complex mixture
11	**45**	DBU, toluene, reflux	complex mixture

tions, namely by using (a) *p*-TsA, acetone, (b) PPh_3, CBr_4, THF, 0 °C,[32] (c) DDQ, CH_3CN/H_2O (9:1), room temp.[33] and (d) TMSI, CH_3CN,[34] etc.; however, no reaction was observed. Furthermore, stirring **38** with 3 N HCl in THF/H_2O (1:1) at room temperature produced only epimerized product **43** instead of the expected aldehyde **44**. The stereochemistry of **43** was confirmed by spectroscopic analysis and single-crystal X-ray crystallography (Scheme 9).[35]

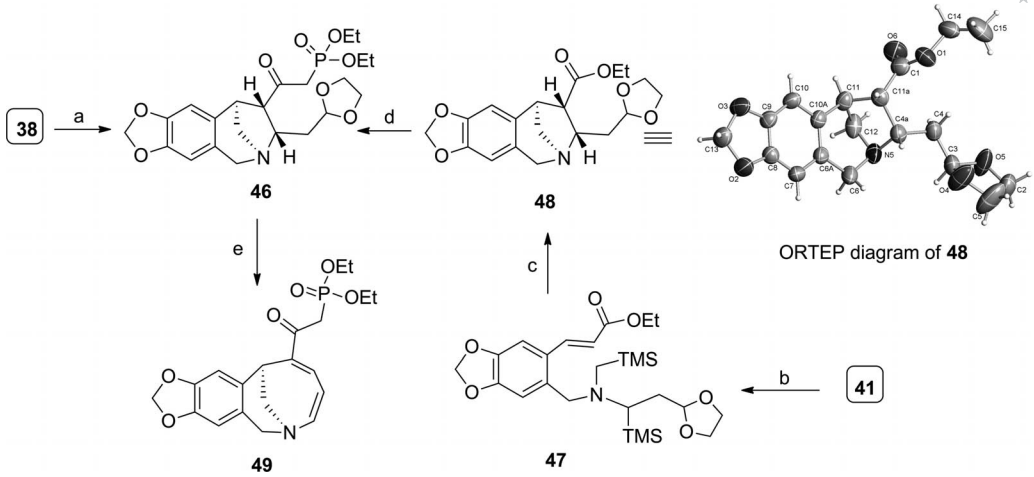
Finally, aldehyde **45** was obtained by heating **43** at reflux with 3 N HCl for 10 h, which was then subjected to different acid- as well as base-catalysed aldol reactions (Table 1, Entries 7–11), but all attempts failed to deliver any identifiable product. Furthermore, we tried to obtain the aldol reaction product from **38** as well as **43** (11a-*epi*-**38**) under various reaction conditions (Table 1), but again all our attempts failed to deliver the corresponding enone.

Second-Generation Approach – Horner–Wadsworth–Emmons (HWE) Reaction

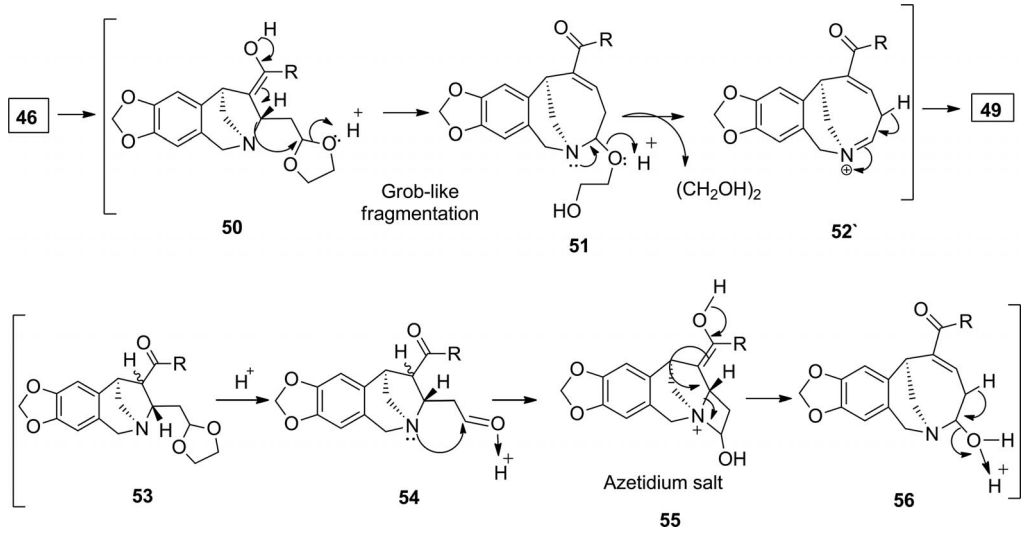
After these frustrating and unanticipated hurdles in obtaining **36** or 11a-*epi*-**36** by the aldol reaction, we evaluated the intramolecular HWE reaction[38] of substrate **46**. We initially tried to synthesize **46** by treating **38** with diethyl chlorophosphonate in the presence of KHMDS at –78 °C; however, this approach gave product **46** in very poor yield (12%). Therefore, we proceeded with compound **48**, and its reaction with the lithium salt of diethyl methylphosphonate gave **46** in 92% yield (Scheme 10). Compound **48** was easily synthesized (39% yield) in two steps by starting from **41** using an identical cycloaddition reaction. The structure of compound **48** was unambiguously confirmed by 1D and 2D NMR analyses as well as by single-crystal X-ray crystallography.[39]

Attempted deprotection of the acetal moiety of **46** under a variety of acidic conditions (3 N HCl/THF/H_2O, oxalic acid/THF/H_2O) prior to executing the HWE reaction resulted only in the rearranged product **49** in 68% yield along with some unidentifiable product. The formation of **49** may be rationalized by invoking the intermediacy of the thermodynamic enol ether followed by rearrangement by Grob-type fragmentation[40] or by the azetidium salt intermediate **55**, as shown in Scheme 11. This rearranged skeletal product supports our earlier observation for the formation of **34**.

After all these failures, we reached the conclusion that both **38** and **46** during dioxolane deprotection under thermodynamic reaction conditions either rearrange from a five- to a seven-membered ring to relieve strain or it stops with the epimerization at the C-11a centre to reduce the steric congestion between the ketone and the acetal, which in turn probably does not allow it to form the cyclic enone because it would lead to a conformationally strained system with three sp^2-hybridized carbon atoms in the E ring.



Scheme 10. Reagents and conditions: (a) KHMDS, $ClPO(OEt)_2$, THF, –78 °C to room temp., 2 h, 12%; (b) $Pd(OAc)_2$, PPh_3, K_2CO_3, ethyl acrylate, CH_3CN, reflux, 12 h, 70%; (c) Ag^IF, CH_3CN, room temp., 12 h, 56%; (d) $CH_3PO(OEt)_2$, *n*BuLi, –78 °C, then 48, 2 h, THF, 92%; (e) oxalic acid, THF/H_2O (1:1), reflux, 10 h, 68%.



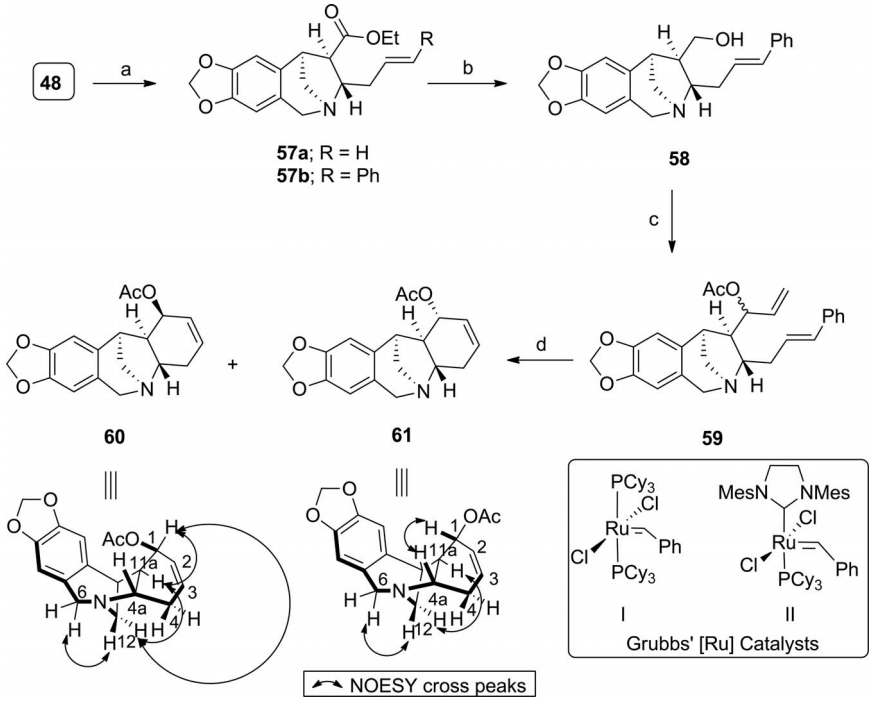
Scheme 11. Plausible mechanism for the formation of **49** [R = $CH_2P(O)(OEt)_2$].

Third-Generation Approach – Ring-Closing Metathesis (RCM) Approach

With the above disappointing results, we envisaged to install the C-2=C-3 double bond by ring-closing metathesis (RCM) of a substrate of type **59**, which can be synthesized by starting from **48**. Because our initial attempt to synthesize **57a** by one-carbon Wittig olefination of the corresponding aldehyde, obtained by hydrolysis of **48** using methylenetriphenylphosphorane, was found to be low-yielding (45%), **57b** was obtained in 68% yield by using benzylidenetriphenylphosphorane. DIBAl-H reduction of **57b** gave **58** in 96% yield, which on Swern oxidation followed by reaction with vinylmagnesium bromide (1 M solution in THF) gave the corresponding alcohol, purified as the acetate derivative **59** (95% yield, *dr* = 2.5:1). RCM of **59** by using either Grubbs' catalysts (first or second generation)[41] in CH_2Cl_2 or benzene (room temperature to reflux) failed to give the expected cyclized product (Scheme 12).

This observation was not very surprising as it is known that a free/unprotected amine coordinates to the ruthenium atom and reduces the catalytic activity of the catalyst. Fortunately, it has also been established that ammonium salts are tolerated very well by the ruthenium catalyst.[42] Therefore, the metathesis of **59** in the presence of different acids such as *p*-TsA,[43] $Ti(OiPr)_4$[44] and HCl[45] by using Grubbs' second-generation catalyst in boiling benzene for 10–15 h was examined. The best cyclization results were obtained by using **59**·HCl, which produced a mixture of **60** and **61** in 93% yield (*dr* = 2.5:1). Both diastereomers **60** and **61** were isolated pure by column chromatography and were characterized by ^1H and ^{13}C NMR spectroscopy. The stereochemistry at C-1 was assigned on the basis of extensive COSY and NOESY studies.

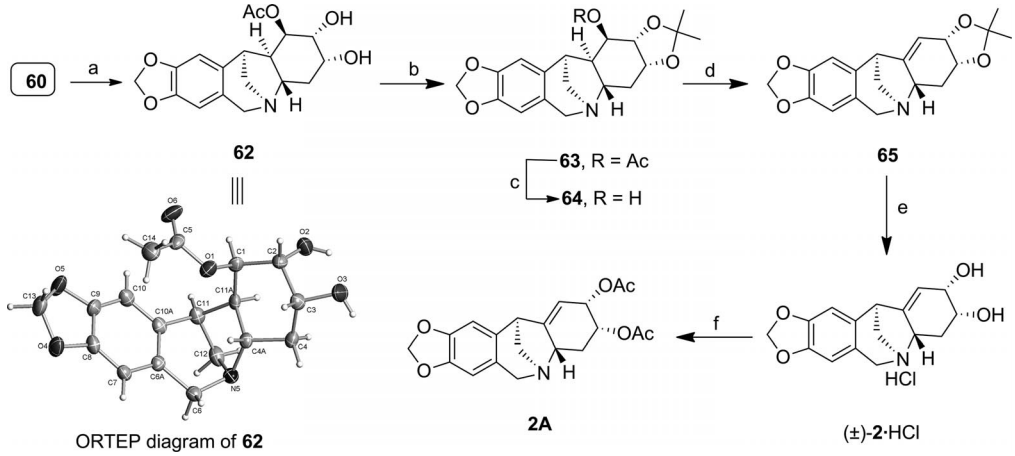
At this stage, we realized the potential of both **60** and **61** for the synthesis of natural products **1**–**5** by functional-group interconversions, exploiting the stereochemistry of the allylic acetoxy functionality for directing the hydroxylation of the double bond.



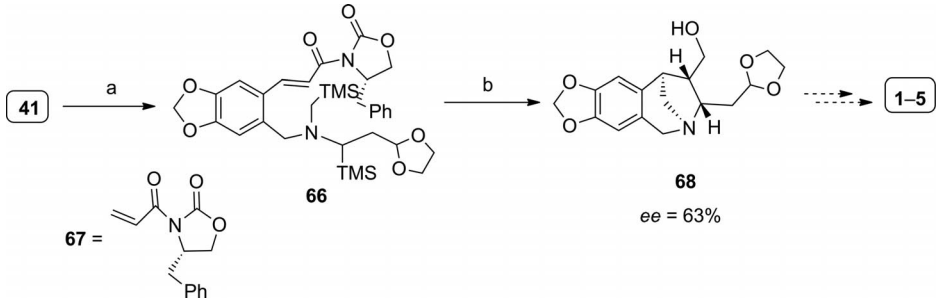
Scheme 12. Reagents and conditions: (a) (i) oxalic acid, THF/H_2O (1:1), reflux, 24 h; (ii) benzylidenediphenylphosphorane, *n*BuLi then aldehyde, 0 °C to room temp., overnight, 68%; (b) DIBAl-H, CH_2Cl_2, –78 °C to room temp., 1 h, 96%; (c) (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 2 h then TEA, quant.; (ii) vinylmagnesium bromide, THF, 0 °C to room temp., 6 h, quant.; (iii) Ac_2O, TEA, DMAP, CH_2Cl_2, 0 °C to room temp., 4 h, 94%; (d) **59**·HCl, Grubbs' 2nd generation catalyst (10 mol-%), benzene, reflux, 12 h, 93%.

Total Synthesis of (±)-Brunsvigine (2)

To achieve a total synthesis of **2**, the major diastereomer **60** was subjected to dihydroxylation (OsO_4, trimethylamine *N*-oxide, pyridine, *t*BuOH/H_2O) to afford **62** as a single diastereomer in quantitative yield. The stereochemical outcome was confirmed by single-crystal X-ray analysis.[46] Installation of the pivotal $\Delta^{1,11a}$ double bond required to complete the total synthesis of **2** was initially attempted by deacetylation[47] of the acetonide-protected dihydroxy compound **63** using DBU at an elevated temperature, but this failed to yield the desired compound **65**. Therefore, we first deprotected the acetate moiety to the corresponding alcohol **64** (NaOMe/MeOH, 91% yield) and then mesylated it. The corresponding mesyl derivative of **64** was heated at reflux with DBU in toluene (2 d) to afford **65** in 89% yield. Acetonide deprotection by passing HCl (gas) into a methanolic solution of **65** afforded the (±)-brunsvigine·HCl (**2**·HCl) salt in quantitative yield (Scheme 13). For better purification and characterization, **2**·HCl was transformed into the corresponding diacetate derivative **2A** by using Ac_2O in pyridine. Note that compound **2A** can be synthesized from



Scheme 13. Reagents and conditions: (a) OsO_4, trimethylamine *N*-oxide, pyridine, *tert*-butanol/H_2O, 18 h, quant.; (b) 2,2-dimethoxypropane, *p*-TsA, acetone, room temp., 6 h, 95%; (c) NaOMe, MeOH, room temp., 4 h, 91%; (d) (i) MsCl, TEA, DMAP, CH_2Cl_2, 0 °C to room temp., 5 h, quant.; (ii) DBU, toluene, 110 °C, 2 d, 89%; (e) $HCl_{(gas)}$, MeOH, 30 min, quant.; (f) Ac_2O, DMAP, pyridine, 20 h, quant.



Scheme 14. Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, K_2CO_3, **67**, CH_3CN, reflux, 12 h, 65%; (b) (i) Ag^IF, CH_3CN, room temp., 18 h; (ii) LAH, THF, 0 °C to room temp., 46% over two steps.

60 without purification of any intermediate in 80% overall yield. The spectroscopic data for compounds **65** and **2A** were found to be in excellent agreement with those reported.[14]

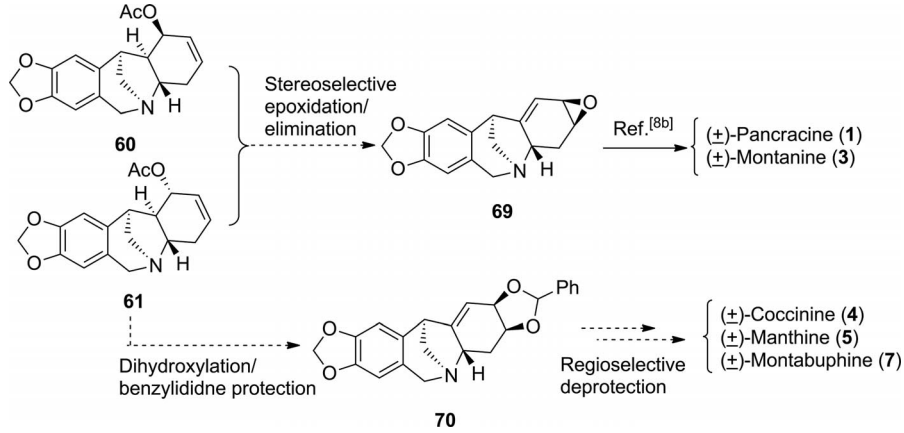
Development of a Chiral Auxiliary Based Asymmetric 1,3-Dipoar Cycloaddition Strategy for the Synthesis of the Enantiomerically Enriched 5,11-Methanomorphanthridine Skeleton

After succeeding in synthesizing 5,11-methanomorphanthridine alkaloids in racemic form, we turned our attention towards developing a conceptually new and general protocol for the synthesis of these alkaloids in enantiomerically enriched form. Most of the asymmetric approaches known for the synthesis of montanine alkaloids are mainly based on chiral-pool strategies except for two recent reports on the formal synthesis of pancracine[17,18] based on organocatalytic approaches. The asymmetric 1,3-dipolar cycloaddition of azomethine ylides to a variety of alkenes has emerged as one of the most powerful strategies for the construction of enantiopure pyrrolidine ring systems.[48,49] Therefore, developing an asymmetric [3+2] cycloaddition approach for assembling the 5,11-methanomorphanthridine framework appeared to be worth exploring as this would be an entirely new concept in this area.

In this regard, we designed our strategy starting from the same intermediate **41** and equipped it with Evans' oxazolidinone chiral auxiliary **67** by the Heck coupling reaction to obtain **66** in 65% yield (Scheme 14).[50] Intramolecular cycloaddition of **66** gave the corresponding cycloadduct, which was subjected to LAH reduction without purification and characterization to give **68** (*ee* = 63% after crystallization)[51] in 46% yield over two steps. Compound **68** can easily be converted into RCM products **60** and **61** via **59** as demonstrated earlier in Scheme 12.

Conclusions

We have successfully developed a conceptually novel and efficient protocol featuring a one-step stereospecific construction of the core structure of the 5,11-methanomorphanthridine alkaloid by the 1,3-dipolar cycloaddition of a non-stabilized AMY, and this strategy was elegantly applied to the formal synthesis of (±)-pancracine. To develop a general and versatile route to the synthesis of these types of alkaloids, different protocols, such as Mukaiyama-type aldol, Horner–Wadsworth–Emmons (HWE) and RCM reactions, were attempted for the efficient construction of the E ring. An RCM protocol was found to be a robust strategy for assembling the E ring with a double bond at the appropriate position. This strategy was successfully used for the total synthesis of (±)-brunsvigine. We have also envisaged extending the use of the RCM products **60/61** to the total synthesis of other members of this class by stereoselective functionalization of the double bond and exploiting the stereochemistry of the acetoxy/hydroxy functionality at the allylic position, as shown in Scheme 15.



Scheme 15. Outlines of the synthesis of other montanine alkaloids.

We have also developed an asymmetric route to the construction of the 5,11-methanomorphanthridine framework through a chiral auxiliary based intramolecular asymmetric 1,3-dipolar cycloaddition of a non-stabilized azomethine ylide. This methodology not only has potential to be extremely useful in the synthesis of natural-product targets, but also provides a new entry to the field of intramolecular asymmetric 1,3-dipolar cycloaddition reactions.

Experimental Section[52]

General: All reactions requiring anhydrous conditions were performed under a positive pressure of argon by using oven-dried glassware (110 °C), which were cooled under argon. Solvents for anhydrous reactions were dried according to Perrin and coworkers.[37] Benzene, CH_2Cl_2, and triethylamine were distilled from CaH_2 and stored over molecular sieves and KOH, respectively. THF and diethyl ether were distilled from sodium benzophenone ketyl. Solvents used for chromatography were distilled at their respective boiling points according to known procedures. Petroleum ether used in the experiments had a boiling range of 60–80 °C. All commercial reagents were obtained from Sigma–Aldrich and Lancaster Chemical Co. (U.K.). *n*-Butyllithium and *s*-butyllithium were titrated by using diphenylacetic acid as indicator. TMSCl and MsCl were distilled before use. The progress of reactions was monitored by TLC, performed on aluminium sheets precoated with silica gel 60 (Merck, 230–400 mesh). Compounds were visualized by heating after dipping in an alkaline solution of $KMnO_4$ and $(NH_4)_6Mo_7O_{24}$ (6.25 g) in aqueous H_2SO_4 (250 mL). Column chromatography was performed on silica gel (60–120/100–200/230–400 mesh). Typical syringe and cannula techniques were used to transfer air- and moisture-sensitive reagents. All melting points were recorded with Thermonik and Büchi melting-point instruments. IR spectra were recorded with Perkin–Elmer 599-B IR and 1620 FT-IR spectrometers. ^{1}H NMR spectra were recorded with Bruker ACF 200, AV 400 and DRX 500 instruments by using deuteriated solvents. Chemical shifts are reported in ppm, proton coupling constants (J) are reported as absolute values in Hz, and multiplicity is given as follows: br., broadened; s, singlet; d, doublet; t, triplet; dt, doublet of triplets; td, triplet of doublets; ddd, doublet of doublet of doublets; m, multiplet). ^{13}C NMR spectra were recorded with Bruker ACF 200, AV 400 and DRX 500 instruments operating at 50, 100 and 125 MHz, respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ = 77.0 ppm). Mass spectra were recorded with a PE SCIEX API QSTAR pulsar spectrometer (LC-MS), automated GC–MS with a solid-probe facility mass spectrometer and high-resolution mass spectrometry (HRMS) were recorded with an MSI (U.K.) Autoconcept instrument with ionization by electron impact, achieved at an ionization potential of 70 eV. X-ray data for four compounds were collected at T = 296 K with a SMART APEX CCD single-crystal X-ray diffractometer by using Mo-K_α radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°. The structures were solved by direct methods using SHELXTL.[53] All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (SHELXTL) was used for structure solution and full-matrix least-squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. The refinements were carried out by using SHELXL-97. Microanalysis data were obtained by using a Carlo–Erba CHNS-O EA 1108 Elemental Analyser at National Chemical Laboratory.

(6-Iodo-1,3-benzodioxol-5-yl)-*N*,*N*-bis[(trimethylsilyl)methyl]-methanamine (21): A 100 mL round-bottomed flask, equipped with an argon gas balloon and a magnetic stirring bar was charged with a solution of **20** (4 g, 10.61 mmol) in dry CH_2Cl_2 (40 mL) and cooled to 0 °C. Trifluoroacetic acid (6.05 g, 53.05 mmol) was introduced dropwise into the stirring solution through a syringe at 0 °C, and then the mixture was warmed to room temp. and stirred for a further 4 h. The reaction mixture was recooled to 0 °C and basified with an aqueous NaOH solution (pH = 10). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with brine, dried with Na_2SO_4, and concentrated to give the crude amine, which was used without further purification in the next step. (Iodomethyl)trimethylsilane (3.15 mL, 21.22 mmol) was added to a stirred heterogeneous solution of the crude amine and K_2CO_3 (3.75 g, 26.25 mmol) in CH_3CN (60 mL), and the mixture was heated at reflux for 10 h. The reaction mixture was cooled to room temp., and K_2CO_3 was filtered off by using suction. The filtrate was concentrated under reduced pressure to give a pasty mass, which was dissolved in ethyl acetate and washed with water (2 × 20 mL), brine (20 mL), dried with Na_2SO_4, and concentrated again to afford a yellow oil, which was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5) to obtain **21** as a pale-yellow oil (3.5 g, 78%). R_f = 0.4 (petroleum ether/ethyl acetate, 9:1). IR (neat): $\tilde{\nu}_{max}$ = 2954, 2925, 2358, 1502, 1475, 1247, 1103, 1041 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.22 (s, 1 H), 7.12 (s, 1 H), 5.97 (s, 2 H), 3.37 (s, 2 H), 1.97 (s, 4 H), 0.05 (s, 18 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 148.0 (C), 146.7 (C), 135.6 (C), 117.7 (CH), 109.7 (CH), 100.9 (CH_2), 86.4 (C), 69.4 (CH_2), 50.3 (CH_2), –1.5 [$Si(CH_3)_3$] ppm. MS: m/z = 450.34 [M + 1]$^+$. $C_{16}H_{28}INO_2Si_2$ (449.48): calcd. C 42.75, H 6.28, N 3.12; found C 42.56, H 6.07, N 3.28.

Ethyl (*E*)-3-[6-({Bis[(trimethylsilyl)methyl]amino}methyl)-1,3-benzodioxol-5-yl]acrylate (22): Ethyl acrylate (1.74 mL, 16.03 mmol) was added to a mixture of K_2CO_3 (0.55 g, 4.00 mmol), $Pd(OAc)_2$ (0.04 g, 0.16 mmol), PPh_3 (0.09 g, 0.32 mmol) and **21** (1.00 g, 2.00 mmol) in dry CH_3CN (15 mL). The mixture was purged with argon to degas it properly. The reaction mixture was stirred at room temp. for 1 h and heated at reflux under argon for an additional 12 h. The volatile material was removed under reduced pressure, the whole dark-brown mass was dissolved in CH_2Cl_2, and the organic layer was washed with 0.1 N HCl (3 × 10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were washed with brine, dried with Na_2SO_4, concentrated under reduced pressure, and the residue was purified by column chromatography (petroleum ether/ethyl acetate, 95:5) to give 0.61 g (72%) of **22** as a yellow liquid. R_f = 0.3 (petroleum ether/ethyl acetate, 9:1). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2954, 2898, 2360, 1712, 1631, 1504, 1485, 1257, 1176, 1041 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, J = 15.9 Hz, 1 H), 7.01 (s, 1 H), 6.97 (s, 1 H), 6.14 (d, J = 15.9 Hz, 1 H), 5.95 (s, 2 H), 4.20 (q, J = 7.1 Hz, 2 H), 3.46 (s, 2 H), 1.85 (s, 4 H), 1.54 (t, J = 7.1 Hz, 3 H), 0.27 (s, 18 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.0 (CO), 149.2 (C), 146.9 (C), 141.8 (CH), 135.3 (C), 127.6 (C), 117.4 (CH), 110.4 (CH), 105.6 (CH), 101.2 (CH_2), 63.2 (CH_2), 60.2 (CH_2), 50.7 (CH_2), 14.3 (CH), –1.1 [$Si(CH_3)_3$] ppm. MS: m/z = 422.12 [M + 1]$^+$. $C_{21}H_{35}NO_4Si_2$ (421.68): calcd. C 59.81, H 8.37, N 3.32; found C 59.63, H 8.19, N 3.11.

Ethyl 4,5-Methylenedioxy-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene-11-carboxylate (23): A solution of **22** (0.50 g, 1.90 mmol) in dry CH_3CN (30 mL) was added slowly to an argon-flushed 100 mL two-necked flask containing vacuum-dried Ag^IF (0.590 g, 4.7 mmol) in dry CH_3CN (30 mL) at room temp. The colour of the

reaction mixture gradually turned to dark brown with concomitant deposition of silver on the surface of the flask in the form of a mirror. The reaction was monitored periodically by TLC. After stirring for 12 h, the reaction mixture was filtered through a small plug of basic alumina, and the solvent was evaporated to give a crude brown residue, which was purified by silica gel column chromatography (petroleum ether/acetone, 55:45) to give **23** (0.21 g, 65%) as a white solid. R_f = 0.3 (petroleum ether/acetone, 6:4); m.p. 260–262 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2360, 1730, 1586, 1481, 1380 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.47 (s, 1 H), 6.36 (s, 1 H), 5.79 (br. s, 2 H), 4.24 and 3.83 (ABq, J = 17.0 Hz, 2 H), 4.06 (q, J = 7.3 Hz, 2 H), 3.37 (dd, J = 12.8, 4.1 Hz, 1 H), 3.20 (br. d, J = 1.8 Hz, 1 H), 3.12 (br. dd, J = 11.4, 1.8 Hz, 1 H), 3.04 (dd, J = 11.5, 2.3 Hz, 1 H), 2.98 (d, J = 11.5 Hz, 1 H), 2.96 (dd, J = 10.0, 4.3 Hz, 1 H), 1.17 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.9 (CO), 146.5 (C), 145.8 (C), 133.9 (C), 124.1 (C), 106.7 (CH), 106.3 (CH), 100.6 (CH_2), 60.7 (CH_2), 59.0 (CH_2), 57.4 (CH_2), 55.3 (CH_2), 53.7 (CH), 42.0 (CH), 13.3 (CH_3) ppm. MS: m/z = 276.32 $[M + 1]^+$. $C_{15}H_{17}NO_4$ (275.30): calcd. C 65.44, H 6.22, N 5.09; found C 65.34, H 6.18, N 5.19.

***tert*-Butyl *N*-[2-(1,3-Dioxolan-2-yl)-1-(trimethylsilyl)ethyl]carbamate (39):** A mixture of **27** (5 g, 20.2 mmol) and iodoxybenzoic acid (8.5 g, 30 mmol) in ethyl acetate (70 mL) was heated at reflux under argon overnight. After cooling to room temp., the reaction mixture was passed through a pad of Celite and concentrated under vacuum to produce the corresponding aldehyde, which was pure enough to be used in the next step. For characterization, it was passed through a small column of silica gel. R_f = 0.3 (petroleum ether/ethyl acetate, 9:1). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3389, 1720, 1643, 1465, 1313, 1176 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.81 (br. s, 1 H), 4.53 (br. s, 1 H), 3.51 (m, 1 H), 2.52 (m, 2 H), 1.41 (s, 9 H), 0.01 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.0 (CO), 156.2 (CO), 80.3 (C), 45.1 (CH_2), 37.1 (CH), 28.3 (CH_3), –4.3 [$Si(CH_3)_3$] ppm. MS (MALDI-TOF): m/z = 246 $[M + H]^+$. A mixture of aldehyde (5 g, 20 mmol), ethylene glycol (1.5 g, 25 mmol) and *p*-TsA (0.25 g) was heated at reflux in benzene (80 mL) under Dean–Stark conditions for 8–10 h. The solvent was evaporated under reduced pressure, and the whole residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with water (2 × 25 mL), brine, and dried with Na_2SO_4. Column chromatography (petroleum ether/ethyl acetate, 95:5) of the crude reaction mixture afforded **39** (4.5 g, 90% yield over two steps) as a white crystalline solid. R_f = 0.3 (petroleum ether/ethyl acetate, 9:1); m.p. 57–59 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3440, 3357, 1693, 1500, 1390, 1365, 1249, 1170, 1043, 1027 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.86 (t, J = 4.7 Hz, 1 H), 4.46 (br. d, J = 9.0 Hz, 1 H), 3.83 (m, 2 H), 3.77 (m, 2 H), 3.23 (m, 1 H), 1.68 (dd, J = 9.4, 4.3 Hz, 2 H), 1.37 (s, 9 H), –0.02 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.3 (CO), 103.9 (CH), 79.1 (C), 65.1 (CH_2), 64.6 (CH_2), 37.6 (CH), 35.8 (CH_2), 28.6 (CH_3), –3.2 [$Si(CH_3)_3$] ppm. LC–MS: m/z = 290 $[M + H]^+$. $C_{13}H_{27}NO_4Si$ (289.45): calcd. C 53.94, H 9.40, N 4.84; found C 53.96, H 9.38, N 4.70.

2-(1,3-Dioxolan-2-yl)-1-(trimethylsilyl)-*N*-[(trimethylsilyl)methyl]-ethanamine (40): A 100 mL round-bottomed flask equipped with an argon gas balloon and a magnetic stirring bar was charged with a solution of **39** (5 g, 16.77 mmol) in dry CH_2Cl_2 (50 mL) and cooled to 0 °C. TFA (7.7 mL, 100.62 mmol) was introduced dropwise to the stirred mixture through a syringe. The mixture was stirred further until the disappearance of the starting material (approx. completed in 4 h). The volatile material was evaporated under reduced pressure, and the reduced mass was dissolved in dry CH_3CN. The reaction mixture was then cooled to 0 °C and basified by slow addition of excess activated K_2CO_3 (pH = 10). (Iodomethyl)trimethylsilane (2.3 mL, 15.10 mmol) was added to this solution, which was heated at reflux for 10 h. The reaction mixture was cooled to room temp., and K_2CO_3 was filtered off under suction. The filtrate was concentrated under vacuum to remove CH_3CN. The resultant pasty mass was dissolved in ethyl acetate and washed with water (2 × 20 mL). The water extract was partitioned by ethyl acetate again (2 × 20 mL), and the combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, and concentrated under vacuum to give **40** as a reddish yellow oil (3.7 g, 77% yield over two steps). This material can be used in the next step without further purification. An analytically pure sample was obtained by passing the oil through a small silica gel column. R_f = 0.2 (petroleum ether/ethyl acetate, 9:1). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3346, 3166, 2954, 2896, 1679, 1612, 1415, 1253, 1192, 1132, 1041 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.95 (dd, J = 4.7, 3.5 Hz, 1 H), 3.99 (m, 2 H), 3.78 (m, 2 H), 2.66 (br. d, J = 9.5 Hz, 1 H), 2.26 (d, J = 13.7 Hz, 1 H), 2.04–1.96 (m, 2 H), 1.81 (m, 1 H), 1.43 (m, 1 H), 0.08 (s, 9 H), 0.06 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 104.3 (CH), 65.1 (CH_2), 64.9 (CH_2), 48.3 (CH), 37.9 (CH_2), 30.9 (CH_2), –2.4 [$Si(CH_3)_3$], –2.7 [$Si(CH_3)_3$] ppm. LC–MS: m/z = 276 $[M + H]^+$. $C_{12}H_{29}NO_2Si_2$ (275.54): calcd. C 52.31, H 10.61, N 5.08; found C 52.56, H 10.48, N 4.94.

2-(1,3-Dioxolan-2-yl)-*N*-[(6-iodo-1,3-benzodioxol-5-yl)methyl]-1-(trimethylsilyl)-*N*-[(trimethylsilyl)methyl]ethanamine (41): K_2CO_3 (3.58 g, 25.87 mmol) and **16** (6.7 g, 17.5 mmol) were added to a solution of **40** (5 g, 17.5 mmol) in dry CH_3CN (50 mL). The progress of the reaction was monitored by TLC (completed in approximately 10 h). On completion of the reaction, the mixture was cooled, filtered, and the solvent evaporated under vacuum. The resultant pasty mass was taken up in ethyl acetate and washed with water (2 × 25 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were washed with brine (40 mL), dried with Na_2SO_4, and concentrated under vacuum to give a brown mass, which was purified by column chromatography (petroleum ether/ethyl acetate, 98:2) to give **41** as a pale-yellow oil (8 g, 85%). R_f = 0.4 (petroleum ether/ethyl acetate, 9.2:0.8). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2950, 2891, 1502, 1469, 1245, 1130, 1103 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.20 (s, 1 H), 7.10 (s, 1 H), 5.95 (s, 2 H), 5.05 (dd, J = 6.3, 3.9 Hz, 1 H), 3.94 (m, 2 H), 3.84 (m, 2 H), 3.60 and 3.48 (ABq, J = 15.3 Hz, 2 H), 2.45 (dd, J = 8.6, 5.7 Hz, 1 H), 2.18 (d, J = 14.5 Hz, 1 H), 2.05 (d, J = 14.5 Hz, 1 H), 2.01 (m, 1 H), 1.65 (m, 1 H), 0.13 (s, 9 H), 0.05 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 148.7 (C), 147.3 (C), 136.1 (C), 118.3 (CH), 110.2 (CH), 104.1 (CH), 101.6 (CH_2), 87.0 (C), 64.4 (CH_2), 64.9 (CH_2), 64.8 (CH_2), 50.8 (CH), 45.1 (CH_2), 31.5 (CH_2), –0.7 [$Si(CH_3)_3$], –0.9 [$Si(CH_3)_3$] ppm. MS (MALDI-TOF): m/z = 536.1190 $[M + H]^+$. $C_{20}H_{34}INO_4Si_2$ (535.57): calcd. C 44.85, H 6.40, N 2.62; found C 44.63, H 6.31, N 2.81.

(*E*)-4-[6-({[2-(1,3-Dioxolan-2-yl)-1-(trimethylsilyl)ethyl][(trimethylsilyl)methyl]amino}methyl)-1,3-benzodioxol-5-yl]but-3-en-2-one (42): The experimental procedure was the same as that used for **15**, and the product mixture was purified by column chromatography (petroleum ether/ethyl acetate, 96:4) to give pure **42** in 65% yield as a yellow solid. R_f = 0.3 (petroleum ether/ethyl acetate, 9.2:0.8); m.p. 105–107 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2850, 2593, 2360, 2341, 1666, 1593, 1479, 1251, 1039 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, J = 15.6 Hz, 1 H), 7.02 (s, 1 H), 6.92 (s, 1 H), 6.38 (d, J = 15.6 Hz, 1 H), 5.89 (s, 1 H), 5.88 (s, 1 H), 4.86 (dd, J = 5.5, 4.1 Hz, 1 H), 3.83–3.80 (m, 2 H), 3.72–3.65 (m, 3 H), 3.47 (d, J = 14.2 Hz, 1 H), 2.27 (dd, J = 7.8, 5.5 Hz, 1 H), 2.26 (s, 3 H), 2.10–1.90 (m, 3 H), 1.60–1.50 (m, 1 H), 0.00 (s, 9 H), –0.04 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.7 (CO), 149.4 (C), 146.5 (C), 140.0 (CH), 135.7 (C), 126.8 (CH), 126.2 (C), 109.8 (CH), 105.3

(CH), 103.6 (CH), 101.0 (CH_2), 64.4 (CH_2), 64.3 (CH_2), 55.9 (CH_2), 49.5 (CH), 44.5 (CH_2), 30.3 (CH_2), 27.5 (CH_3), –0.8 [$Si(CH_3)_3$], –1.4 [$Si(CH_3)_3$] ppm. MS (MALDI-TOF): *m*/*z* = 478.2465 $[M + H]^+$. $C_{24}H_{39}NO_5Si_2$ (477.75): calcd. C 60.34, H 8.23, N 2.93; found C 60.26, H 8.20, N 2.73.

1-[10-(1,3-Dioxolan-2-ylmethyl)-4,5-methylenedioxy-9-azatricyclo-[7.2.1.0^{2,7}]dodeca-2,4,6-trien-11α-yl]ethanone (38): The experimental procedure applied for **38** was identical to that for **13**, and the product was purified by silica gel column chromatography (petroleum ether/acetone, 80:20) followed by crystallization from ethanol to give **38** in 53% isolated yield as a white crystalline solid. R_f = 0.3 (petroleum ether/acetone, 8:2); m.p. 154–156 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2958, 1708, 1483, 1359, 1139, 1039 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.37 (s, 1 H), 6.34 (s, 1 H), 5.78 (br. s, 2 H), 4.97 (dd, *J* = 6.9, 2.3 Hz, 1 H), 4.18 and 3.63 (ABq, *J* = 17.0 Hz, 2 H), 3.87–3.82 (m, 2 H), 3.77–3.73 (m, 2 H), 3.53 (td, *J* = 8.7, 3.7 Hz, 1 H), 3.33 (d, *J* = 8.7 Hz, 1 H), 3.26 (dd, *J* = 11.2, 2.5 Hz, 1 H), 2.97 (d, *J* = 2.5 Hz, 1 H), 2.87 (d, *J* = 11.5 Hz, 1 H), 2.06 (s, 3 H), 1.81–1.79 (m, 1 H), 1.40 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.6 (CO), 146.3 (C), 145.5 (C), 134.9 (C), 125.3 (C), 106.6 (CH), 106.3 (CH), 103.5 (CH), 100.4 (CH_2), 64.6 (CH), 64.5 (CH), 64.3 (CH_2), 64.3 (CH_2), 59.9 (CH_2), 53.9 (CH_2), 43.4 (CH), 35.7 (CH_2), 32.2 (CH_3) ppm. MS (MALDI-TOF): *m*/*z* = 332.1489 $[M + H]^+$. $C_{18}H_{21}NO_5$ (331.37): calcd. C 65.24, H 6.39, N 4.23; found C 65.14, H 6.47, N 4.11.

1-[10-(1,3-Dioxolan-2-ylmethyl)-4,5-methylenedioxy-9-azatricyclo-[7.2.1.0^{2,7}]dodeca-2,4,6-trien-11β-yl]ethanone (43): A mixture of **38** (0.1 g, 0.3 mmol) and 3 N HCl (1 mL) in THF (3 mL) was stirred at room temp. for 8–10 h. The solvent was evaporated under reduced pressure, and the whole residue was dissolved in CH_2Cl_2 (8 mL). The organic layer was washed with saturated $NaHCO_3$ solution (2 × 3 mL) and water (3 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and column chromatography (chloroform/methanol, 9:1) afforded 0.09 g of **43** (90%) as a white solid. R_f = 0.25 ($CHCl_3$/MeOH, 9:1); m.p. 165–167 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.38 (s, 1 H), 6.28 (s, 1 H), 5.81 (s, 2 H), 4.85 (dd, *J* = 5.4, 3.3 Hz, 1 H), 4.26 (d, *J* = 16.8 Hz, 1 H), 3.87–3.77 (m, 3 H), 3.75–3.63 (m, 3 H), 3.24 (br. d, *J* = 9.0 Hz, 3 H), 3.06 (d, *J* = 2 Hz, 1 H), 2.20–2.11 (m, 1 H), 2.05 (s, 3 H), 1.74–1.60 (m, 1 H) ppm. MS (MALDI-TOF): *m*/*z* = 332.1489 $[M + H]^+$. $C_{18}H_{21}NO_5$ (331.37): calcd. C 65.24, H 6.39, N 4.23; found C 65.12, H 6.42, N 4.14.

(11β-Acetyl-4,5-methylenedioxy-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-trien-10-yl)acetaldehyde (45): A mixture of **38** or **43** (0.2 g, 0.6 mmol) and 3 N HCl (1 mL) in THF (4 mL) was heated at reflux for 10 h. The solvent was evaporated under reduced pressure, and the whole residue was taken up in CH_2Cl_2 (8 mL). The organic layer was washed with saturated $NaHCO_3$ solution (2 × 3 mL) and water (2 × 3 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic extracts were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure to give **45** (0.18 g, 88% yield) as a brown paste. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2921, 1721, 1342, 1041 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.76 (dd, *J* = 2.0, 1.6 Hz, 1 H), 6.45 (s, 1 H), 6.37 (s, 1 H), 5.87 (br. s, 2 H), 4.26 and 3.91 (ABq, *J* = 17.2 Hz, 1 H), 4.00 (m, 1 H), 3.72–3.59 (m, 1 H), 3.34 (m, 1 H), 3.24–3.04 (m, 2 H), 2.77–2.63 (m, 1 H), 2.49–2.38 (m, 1 H), 2.15 (s, 3 H) ppm. MS (ESI): *m*/*z* = 320.23 $[M + CH_3OH + 1]^+$.

Ethyl (*E*)-3-[6-({[2-(1,3-Dioxolan-2-yl)-1-(trimethylsilyl)ethyl][(trimethylsilyl)methyl]amino}methyl)-1,3-benzodioxol-5-yl]acrylate (47): The experiment was performed by using the same procedure as described for **42** but by using ethyl acrylate instead of methyl vinyl ketone (MVK) to give **47** in 70% yield as a yellow amorphous solid after silica gel column chromatography (petroleum ether/ethyl acetate, 95:5). R_f = 0.3 (petroleum ether/ethyl acetate, 9:1); m.p. 101–103 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3054, 2954, 1706, 1618, 1504, 1479, 1402, 1265, 1178, 1041 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 15.8 Hz, 1 H), 7.08 (s, 1 H), 7.00 (s, 1 H), 6.16 (d, *J* = 15.8 Hz, 1 H), 5.96 (br. s, 2 H), 4.94 (dd, *J* = 5.8, 4.3 Hz, 1 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 3.95–3.77 (m, 5 H), 3.56 (d, *J* = 14.1 Hz, 1 H), 2.33 (dd, *J* = 8.2, 5.3 Hz, 1 H), 2.17 (d, *J* = 14.5 Hz, 1 H), 2.01 (d, *J* = 14.5 Hz, 1 H), 2.11–2.00 (m, 1 H), 1.65–1.53 (m, 1 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 0.08 (s, 9 H), 0.05 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.1 (CO), 149.4 (C), 146.8 (C), 141.7 (CH), 135.4 (C), 127.2 (C), 117.4 (CH), 110.0 (CH), 105.6 (CH), 103.8 (CH), 101.3 (CH_2), 64.7 (CH_2), 64.6 (CH_2), 60.3 (CH_2), 56.3 (CH_2), 49.5 (CH), 44.7 (CH_2), 30.6 (CH_2), 14.4 (CH_3), 0.5 (CH_3), –1.1 (CH_3) ppm. HRMS (EI): calcd. for $C_{25}H_{41}NSi_2O_6$ $[M]^+$ 507.24753; found 507.24753.

Ethyl (6*R*,7*S*,8*S*,9*R*)-7-[(1,3-Dioxolan-2-yl)methyl]-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*c*]azepine-8-carboxylate (48): The experiment was performed by using the same procedure as described for **23** to give **48** in 56% yield as a white crystalline solid after silica gel column chromatography (petroleum ether/acetone, 8:2). R_f = 0.3 (petroleum ether/acetone, 7.5:2.5); m.p. 129–131 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2972, 2892, 1727, 1670, 1610, 1507, 1484, 1399, 1373, 1233, 1155, 1038 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.48 (s, 1 H), 6.41 (s, 1 H), 5.86 (br. s, 2 H), 5.08 (dd, *J* = 7.3, 2.7 Hz, 1 H), 4.24 and 3.68 (ABq, *J* = 17.0 Hz, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 3.99–3.80 (m, 4 H), 3.55 (ddd, *J* = 11.9, 8.4, 3.0 Hz, 1 H), 3.38 (dd, *J* = 11.5, 2.8 Hz, 1 H), 3.17 (dd, *J* = 8.8, 1.2 Hz, 1 H), 3.15 (br. d, *J* = 2.6 Hz, 1 H), 2.98 (td, *J* = 11.5, 1.2 Hz, 1 H), 1.80 (br. s, 1 H), 1.52 (br. s, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.2 (CO), 146.5 (C), 145.6 (C), 134.7 (C), 125.6 (C), 107.0 (CH), 106.4 (CH), 103.8 (CH), 100.6 (CH_2), 64.8 (CH_2), 64.6 (CH_2), 64.5 (CH), 60.3 (CH_2), 60.2 (CH_2), 57.9 (CH), 54.29 (CH_2), 43.6 (CH), 36.0 (CH_2), 14.1 (CH_3) ppm. HRMS (EI): calcd. for $C_{19}H_{23}NO_6$ $[M]^+$ 361.15254; found 361.15344.

Diethyl (2-{(6*R*,7*S*,8*S*,9*R*)-7-[(1,3-Dioxolan-2-yl)methyl]-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*c*]azepin-8-yl}-2-oxoethyl)phosphonate (46): *n*BuLi in hexane (0.85 mL, 1.6 mmol) was added dropwise to a stirred solution of diethyl methylphosphonate (0.27 mL, 1.8 mmol) in dry THF (2 mL) at –78 °C under argon over a period of 15 min. The resulting reaction mixture was stirred at the same temperature for an additional 1 h. Compound **48** (0.13 g, 0.36 mmol) in dry THF (2 mL) was added dropwise to the resulting reaction mixture and allowed to react at –78 °C for 1 h. After 1 h, the mixture was warmed to room temperature over a period of 2 h. A saturated solution of NH_4Cl was added to the reaction mixture, which was then extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated under vacuum to obtain a viscous brown residue, which was purified by silica gel chromatography (petroleum ether/acetone, 6:4) to afford **46** (0.156 g, 92%) as a brown viscous paste. R_f = 0.2 (petroleum ether/acetone, 6:4). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2925, 2851, 1701, 1607, 1505, 1485, 1435, 1399, 1247, 1182, 1038 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.51 (s, 1 H), 6.41 (s, 1 H), 5.85 (br. s, 2 H), 5.01 (dd, *J* = 7.1, 2.3 Hz, 1 H), 4.26 and 3.71 (ABq, *J* = 17.2 Hz, 2 H), 4.20–4.06 (m, 4 H), 3.95–3.78 (m, 4 H), 3.69–3.53 (m, 2 H), 3.38 (dd, *J* = 11.5, 2.9 Hz, 1 H), 3.23 (d, *J* = 13.4 Hz, 0.5 H), 3.12 (d, *J* = 13.4 Hz, 0.5 H), 3.11 (d, *J* = 2.9 Hz, 1 H), 3.26–3.02 (m, 2 H), 2.99–2.94 (m, 1 H), 2.88 (d, *J* = 11.6 Hz, 1 H), 1.82–1.99 (m, 1 H),

1.38–1.49 (m, 1 H), 1.32 (t, J = 7.0 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4 (CO), 146.9 (C), 134.5 (C), 124.8 (C), 107.2 (CH), 106.5 (CH), 103.3 (CH), 100.8 (CH_2), 64.9 (CH), 64.9 (CH_2), 64.6 (CH_2), 60.1 (CH_2), 54.0 (CH_2), 53.2 (CH), 53.2 (CH), 53.0 (CH), 52.9 (CH), 44.6 (CH), 44.2 (CH_2), 43.2 (CH_2), 36.0 (CH), 31.9 (CH), 29.1 (CH), 22.7 (CH), 14.1 (CH_3) ppm. MS (ESI): m/z = 468.24 $[M + H]^+$. $C_{22}H_{30}NO_8P$ (467.45): calcd. C 56.53, H 6.47, N 3.00; found C 56.37, H 6.58, N 2.86.

Diethyl {2-[(6*S*,11*S*)-5,11-Dihydro-6,11-methano[1,3]dioxolo[4′,5′:4,5]-benzo[1,2-*c*]azonin-10-yl]-2-oxoethyl}phosphonate (49): Oxalic acid (0.4 g, 3.2 mmol) was added to a stirred solution of **46** (0.150 g, 0.32 mmol) in THF/H_2O (1:1; 6 mL), and the mixture was heated at 80 °C for 10 h. After completion of the reaction, the mixture was cooled to room temp. The volatile material was evaporated under reduced pressure, the residue diluted with ethyl acetate and basified by slow addition of saturated $NaHCO_3$ (pH = 8). The aqueous layer was separated in a separating funnel and washed with ethyl acetate (2 × 10 mL); the combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (petroleum ether/acetone, 4:6) to give **49** as a yellow paste (0.088 g, 68%). R_f = 0.3 (petroleum ether/acetone, 2:3). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2983, 1607, 1504, 1486, 1439, 1265, 1243, 1191, 1038 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35 (m, 1 H), 7.10 (br. d, J = 7.5 Hz, 1 H), 6.78 (td, J = 7.5, 3.8 Hz, 1 H), 6.49 (s, 1 H), 6.38 (s, 1 H), 5.85 and 5.84 (ABq, J = 1.3 Hz, 2 H), 4.27–4.15 (m, 9 H), 3.31 (br. s, 2 H), 1.26 (t, J = 7.1 Hz, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.1 (C), 160.1 (C), 146.5 (C), 146.4 (C), 135.6 (CH), 131.9 (CH), 131.4 (CH), 131.3 (CH), 128.6 (CH), 118.6 (CH), 118.4 (CH), 109.3, 105.8 (CH), 100.7 (CH_2), 62.5 (CH_2), 62.4 (CH_2), 47.9 (CH_2), 47.5 (CH_2), 29.7 (CH_2), 16.2 (CH_3), 16.2 (CH_3) ppm. MS (ESI): m/z = 406.34 $[M + H]^+$. $C_{20}H_{24}NO_6P$ (405.39): calcd. C 59.26, H 5.97, N 3.46; found C 59.37, H 6.08, N 3.58.

Ethyl (6*R*,7*S*,8*R*,9*R*)-7-Cinnamyl-5,7,8,9-tetrahydro-6,9-methano-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*c*]azepine-8-carboxylate (57b): Oxalic acid (3.5 g, 27.7 mmol) was added to a stirred solution of the pure cycloadduct **48** (1 g, 2.7 mmol) in THF/H_2O (1:1; 50 mL), and the reaction mixture was heated at reflux for 24 h. The reaction mixture was cooled to room temp., and THF was evaporated under reduced pressure at 45 °C, the residue diluted with ethyl acetate and basified by slow addition of a saturated $NaHCO_3$ solution (pH = 10) at 0 °C. The organic layer was separated in a separating funnel, and the aqueous layer was again washed with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure to give the aldehyde as a brown residue, which was used in the Wittig olefination reaction without further purification. The Wittig ylide was generated by slow addition of *n*BuLi (1.6 N in hexane, 1.87 mL, 3 mmol) to a suspension of the corresponding salt (benzylidenetriphenylphosphorane; 1.6 g, 3.78 mmol) in dry THF (12 mL) under a positive pressure of argon at 0 °C. The appearance of an orange colour indicated the generation of the ylide, which was stirred at the same temperature for another 30 min and then slowly introduced into the solution of the aldehyde (0.8 g, 2.5 mmol) in dry THF (3 mL) over a period of 10 min. The reaction mixture was warmed to room temp. and stirred overnight before the addition of a saturated NH_4Cl solution. The aqueous layer was separated and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated to obtain a viscous brown mass, which was purified by column chromatography (petroleum ether/acetone, 8:2) to yield **57b** as a pale-yellow paste (0.66 g, 68%). R_f = 0.3 (petroleum ether/acetone, 7:3). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2929, 1731, 1502, 1482, 1232, 1038 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.09 (m, 5 H), 6.45 (dd, J = 14.5, 3.3 Hz, 1 H), 6.43 (s, 1 H), 6.4 (s, 1 H), 6.25–6.10 (m, 1 H), 5.85 (br. s, 2 H), 4.25 and 3.76 (ABq, J = 17.1 Hz, 2 H), 3.89 (q, J = 7.1 Hz, 2 H), 3.48 (dd, J = 6.8, 6.7, Hz, 1 H), 3.19 (dd, J = 5.2, 2.4 Hz, 1 H), 3.15 (dd, J = 11.5, 2.3 Hz, 1 H), 3.06 (d, J = 11.5 Hz, 1 H), 2.91 (dd, J = 6.0, 5.4 Hz, 1 H), 2.53–2.47 (m, 1 H), 2.50–2.22 (m, 2 H), 1.13 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6 (CO), 146.9 (C), 145.4 (C), 137.54 (C), 132.2 (CH), 131.0 (C), 132.1 (CH), 128.6 (CH), 128.5 (CH), 127.4 (CH), 127.1 (CH), 126.1 (CH), 108.3 (CH), 106.4 (CH), 100.6 (CH_2), 66.3 (CH), 60.9 (CH_2), 60.9 (CH_2), 55.7 (CH_2), 43.8 (CH), 39.7 (CH_2), 14.2 (CH_3) ppm. HRMS (EI): calcd. for $C_{24}H_{25}NO_4$ $[M]^+$ 391.17836; found 391.17956.

[(6*R*,7*S*,8*R*,9*R*)-7-Cinnamyl-5,7,8,9-tetrahydro-6,9-methano[1,3]-dioxolo[4′,5′:4,5]benzo[1,2-*c*]azepin-8-yl]methanol (58): DIBAl-H (1.46 N in toluene, 2.1 mL, 3.2 mmol) was added slowly over a period of 10 min to a stirred solution of **57b** (0.5 g, 1.2 mmol) in dry CH_2Cl_2 at –78 °C. After completion of the addition, the reaction mixture was warmed to room temp. over 1 h. The reaction mixture was diluted with CH_2Cl_2, a few drops of Na,K tartarate were added, and the mixture was stirred for an additional 1 h, dried with Na_2SO_4, passed through a small pad of Celite and concentrated under reduced pressure to obtain the reduced product **58** as a white paste (0.431 g, 96%), which was pure enough to be used in the next step. R_f = 0.25 (petroleum ether/acetone, 3:2). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3421, 3053, 2926, 2893, 2307, 1481, 1265, 1236, 1039 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.14 (m, 5 H), 6.55 (s, 1 H), 6.46 (d, J = 15.9 Hz, 1 H), 6.44 (s, 1 H), 6.33–6.19 (m, 1 H), 6.84 (br. s, 2 H), 4.26 and 3.64 (ABq, J = 17.0 Hz, 2 H), 3.47 (dd, J = 10.4, 5.3 Hz, 1 H), 3.18 (d, J = 9.1 Hz, 1 H), 3.12 (dd, J = 9.1, 2.4 Hz, 1 H), 3.05 (br. s, 1 H), 3.04–2.90 (m, 1 H), 2.61–2.29 (m, 4 H), 2.0 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5 (C), 145.4 (C), 137.5 (C), 131.8 (CH), 131.7 (CH), 128.4 (CH), 127.9 (CH), 127.0 (CH), 126.0 (CH), 125.9 (CH), 108.6 (CH), 106.4 (CH), 100.6 (CH_2), 67.7 (CH), 62.8 (CH_2), 60.9 (CH_2), 58.2 (CH), 55.1 (CH_2), 42.1 (CH), 39.8 (CH_2) ppm. HRMS (EI): calcd. for $C_{22}H_{23}NO_3$ $[M]^+$ 349.16776; found 349.16859.

1-[(6*R*,7*S*,8*R*,9*R*)-7-Cinnamyl-5,7,8,9-tetrahydro-6,9-methano[1,3]-dioxolo[4′,5′:4,5]benzo[1,2-*c*]azepin-8-yl)allyl Acetate (59): Dry DMSO (0.09 mL, 1.29 mmol) was added under argon to a stirred solution of oxalyl chloride (0.1 mL, 1.29 mmol) in CH_2Cl_2 (2 mL) at –78 °C. After 15 min, a solution of alcohol **58** (0.3 g, 0.86 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise to the reaction mixture, which was stirred at the same temperature for another 2 h. Excess TEA (0.6 mL, 4.3 mmol) was added to the reaction mixture, which was gradually warmed to room temp. over 30 min. The resulting reaction mixture was diluted with CH_2Cl_2 and extracted with water. The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated under vacuum to obtain the crude aldehyde quantitatively, which was pure enough to be used in the Grignard reaction with vinylmagnesium bromide. For characterization, it was purified by flash chromatography (petroleum ether/acetone, 4:1). R_f = 0.3 (petroleum ether/acetone, 3:2). IR ($CHCl_3$): $\tilde{\nu}$ = 2953, 2887, 1714, 1481, 1340, 1230, 1140, 1037 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.33 (d, J = 2.7 Hz, 1 H), 7.29–7.16 (m, 5 H), 6.40 (d, J = 15.8 Hz, 1 H), 6.39 (s, 1 H), 6.38 (s, 1 H), 6.14 (app. ddd, J = 15.8, 7.3, 6.4 Hz, 1 H), 5.82 and 5.81 (ABq, J = 1.4 Hz, 2 H), 4.27 and 3.74 (ABq, J = 17.2 Hz, 2 H), 3.36 (app. q, J = 7.0 Hz, 1 H), 3.29 (br. d, J = 5.0 Hz, 1 H), 3.07 (br. s, 2 H), 2.8 (app. td, J = 6.3, 2.7 Hz, 1 H), 2.4 (m, 1 H), 2.2 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.8 (CO), 147.2 (C), 145.9 (C), 137.3 (C), 137.0 (C), 132.5 (CH), 132.0 (CH), 128.6 (CH),

128.5 (CH), 127.2 (CH), 126.8 (CH), 126.1 (C), 108.0 (CH), 106.9 (CH), 100.8 (CH_2), 67.6 (CH), 65.0 (CH), 60.7 (CH_2), 55.9 (CH_2), 43.1 (CH), 39.5 (CH_2) ppm. MS (ESI): *m*/*z* = 348 $[M + 1]^+$, 380.40 $[M + CH_3OH + 1]^+$. Vinylmagnesium bromide (VMB, 1 M in THF, 2.6 mL, 2.6 mmol) was added slowly to a stirred solution of the aldehyde (0.3 g, 0.86 mmol) in dry THF (3 mL) at –78 °C under a positive pressure of argon over a period of 10 min. The resulting reaction mixture was stirred at room temp. overnight before quenching with water. The aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine and concentrated under reduced pressure to give the allylic alcohol as a brown paste in quantitative yield, which was isolated after acetate protection of the alcohol. Ac_2O (0.1 mL, 1 mmol) was added dropwise to a stirred solution of the above alcohol (0.3 g, 0.86 mmol), DMAP (10 mg), and TEA (0.18 mL, 1.29 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C, and the mixture was stirred at room temp. for 6 h. After completion of the reaction, water (3 mL) was added, and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and concentrated under reduced pressure to give a brown mass, which was purified by column chromatography (petroleum ether/acetone, 4:1) to yield **59** (94% combined yield of two diastereomers). R_f = 0.4 (petroleum ether/acetone, 7:3). For characterization, the major isomer was isolated by slowly passing 20% acetone/petroleum ether through the column. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3024, 2977, 1738, 1503, 1482, 1372, 1234, 1038 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 7.4 Hz, 2 H), 7.29 (dd, *J* = 7.7, 7.4 Hz, 2 H), 7.20 (dd, *J* = 7.4, 7.2 Hz, 1 H), 6.52–6.36 (m, 4 H), 5.90 (ABq, *J* = 1.5 Hz, 2 H), 5.82 (ddd, *J* = 17.4, 10.5, 6.9 Hz, 1 H), 5.27 (dd, *J* = 16.0, 8.2 Hz, 2 H), 4.80 (dd, *J* = 10.4, 6.8 Hz, 1 H), 4.32 and 3.75 (ABq, *J* = 16.9 Hz, 2 H), 3.16 (dd, *J* = 11.3, 2.0 Hz, 1 H), 3.01 (d, *J* = 11.3 Hz, 1 H), 2.87–2.80 (m, 2 H), 2.52 (m, 1 H), 2.41–2.33 (m, 2 H), 1.98 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (CO), 147.1 (C), 145.5 (C), 137.6 (C), 135.7 (C), 135.5 (CH), 131.6 (CH), 130.8 (CH), 128.5 (CH), 128.3 (CH), 127.1 (CH), 126.1 (CH), 118.8 (CH_2), 108.7 (CH), 106.6 (CH), 100.8 (CH_2), 76.4 (CH), 69.6 (CH), 61.0 (CH_2), 59.1 (CH), 55.4 (CH_2), 42.0 (CH), 40.2 (CH_2), 21.2 (CH_3) ppm. HRMS (EI): calcd. for $C_{26}H_{27}NO_4$ $[M]^+$ 417.19401; found 417.19417.

(6*R*,6a*S*,10a*R*,11*R*)-5,6a,7,10,10a,11-Hexahydro-6,11-methano[1,3]-dioxolo[4′,5′:4,5]benzo[1,2-*e*]benzo[*b*]azepin-10-yl Acetate (60 and 61): The mixture of isomers of **59** (0.2 g, 0.48 mmol) was dissolved in dry CH_2Cl_2 (3 mL) under argon and saturated with dry $HCl_{(gas)}$ at 0 °C to give the hydrochloride salt. After 30 min at 0 °C, CH_2Cl_2 was removed under argon, freshly distilled benzene was added to **59**·HCl, and the mixture degassed thoroughly for 10 min. Grubbs second-generation catalyst (80 mg, 10 mol-%) was added in two portions, and the mixture was again degassed for 10–15 min. The reaction mixture was then heated at reflux for 6 h. After completion of the reaction, the mixture was diluted with ethyl acetate and washed with a saturated K_2CO_3 solution. The aqueous layer was washed with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure to give cyclized products **60** and **61** as a yellowish oil (mixture of diastereomers), which were separated by flash column chromatography in 93% combined yield [eluent: 2 and 4–5% MeOH/CH_2Cl_2 for the minor (40 mg) and major (100 mg) isomers, respectively].

Major Diastereomer (60): R_f = 0.25 (CH_2Cl_2/MeOH, 4:1; eluted with 4–5%). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2926, 2360, 1726, 1483, 1240, 1040 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.46 (br. s, 2 H), 5.92 (m, 1 H), 5.84 (br. s, 1 H), 5.73–5.60 (m, 2 H), 4.22 and 3.80 (ABq, *J* = 16.4 Hz, 2 H), 3.17 (br. d, *J* = 10.8 Hz, 1 H), 3.07 (td, *J* = 11.0, 4.6 Hz, 1 H), 3.00 (d, *J* = 11.0 Hz, 1 H), 2.95 (br. s, 1 H), 2.63 (dt, *J* = 17.0, 4.9 Hz, 1 H), 2.2–2.1 (m, 2 H), 1.54 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4 (CO), 146.4 (C), 145.5 (C), 132.4 (CH), 131.3 (CH), 127.0 (CH), 108.9 (CH), 106.9 (CH), 100.7 (CH_2), 67.5 (CH), 62.0 (CH_2), 60.0 (CH), 58.6 (CH_2), 56.6 (CH), 40.1 (CH), 33.3 (CH_2), 20.7 (CH_3) ppm. ^1H NMR (400 MHz, C_6D_6): δ = 6.50 (s, 1 H), 6.32 (s, 1 H), 5.82–5.76 (m, 2 H), 5.70–5.66 (m, 1 H), 5.38 (br. s, 2 H), 4.02 and 3.49 (ABq, *J* = 16.3 Hz, 2 H), 3.04 (td, *J* = 11.0, 4.8 Hz, 1 H), 3.17 (dd, *J* = 11.0, 1.3 Hz, 1 H), 3.00 (d, *J* = 11.0 Hz, 1 H), 2.49 (dt, *J* = 17.0, 4.8 Hz, 1 H), 2.43 (br. s, 1 H), 2.07–1.97 (m, 1 H), 1.71 (dt, *J* = 11.0, 3.5 Hz, 1 H), 1.55 (s, 3 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 169.6 (CO), 146.6 (C), 145.7 (C), 132.5 (CH), 132.3 (CH), 127.2 (CH), 109.0 (CH), 106.9 (CH), 100.3 (CH_2), 67.5 (CH), 62.2 (CH_2), 60.0 (CH), 58.6 (CH_2), 56.9 (CH), 40.1 (CH), 33.7 (CH_2), 20.4 (CH_3) ppm. HRMS (EI): calcd. for $C_{18}H_{19}NO_4$ $[M]^+$ 313.13141; found 313.13631.

Minor Diastereomer (61): R_f = 0.3 (CH_2Cl_2/MeOH, 8:2; eluted with 2–3%). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3381, 2949, 2924, 2554, 1737, 1732, 1485, 1371, 1240, 1037 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.46 (br. s, 2 H), 5.90 (ABq, *J* = 1.4 Hz, 2 H), 5.80–5.70 (m, 1 H), 5.55 (dt, *J* = 10.1, 1.7 Hz, 1 H), 5.03 (m, 1 H), 4.22 and 3.73 (ABq, *J* = 16.2 Hz, 2 H), 3.21 (br. d, *J* = 11.2 Hz, 1 H), 3.07 (d, *J* = 11.2 Hz, 1 H), 2.98 (br. s, 1 H), 2.67 (td, *J* = 11.0, 4.4 Hz, 1 H), 2.51 (dt, *J* = 15.7, 5.0 Hz, 1 H), 2.30–2.20 (m, 2 H), 2.12 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.4 (CO), 147.1 (C), 146.1 (C), 129.9 (CH), 129.1 (CH), 109.2 (CH), 107.0 (CH), 100.9 (CH_2), 72.0 (CH), 63.7 (CH), 61.6 (CH_2), 57.8 (CH_2), 57.7 (CH), 39.2 (CH), 31.9 (CH_2), 21.2 (CH_3) ppm. ^1H NMR (500 MHz, C_6D_6): δ = 6.70 (s, 1 H), 6.29 (s, 1 H), 5.67 (app. dt, *J* = 10.1, 1.7 Hz, 1 H), 5.56–5.53 (m, 1 H), 5.40 and 5.32 (ABq, *J* = 1.4 Hz, 2 H), 5.36–5.33 (m, 1 H), 4.02 and 3.40 (ABq, *J* = 16.2 Hz, 2 H), 2.94 (br. d, *J* = 11.0 Hz, 1 H), 2.78 (d, *J* = 11.2 Hz, 1 H), 2.66 (br. s, 1 H), 2.52 (m, 1 H), 2.30 (app. dt, *J* = 15.7, 5.0 Hz, 1 H), 1.93 (m, 1 H), 1.85 (m, 1 H), 1.81 (s, 3 H) ppm. HRMS (EI): calcd. for $C_{18}H_{19}NO_4$ $[M]^+$ 313.13141; found 313.13631.

(6*R*,6a*S*,8*R*,9*R*,10*R*,10a*R*,11*R*)-8,9-Dihydroxy-5,6a,7,8,9,10,10a,11-octahydro-6,11-methano[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*e*]benzo[*b*]azepin-10-yl Acetate (62): Trimethylamine *N*-oxide dihydrate (27 mg, 0.24 mmol) was added to a solution of **60** (50 mg, 0.16 mmol) in a mixture of *t*BuOH (0.5 mL), pyridine (30 μL) and water (30 μL). The solution was stirred until all solids had dissolved, and a crystal of OsO_4 was added at room temp. The resulting solution was stirred for 18 h. A pinch of Na_2SO_3 was added to the reaction mixture, which was stirred for an additional 30 min. The solvent was removed by rotary evaporation, and the residue was dissolved in CH_2Cl_2 (5 mL) and partitioned with brine (2 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the organic layers were dried with Na_2SO_4, concentrated and recrystallized from ethanol to obtain **62** as a white crystalline solid as a single diastereomer. R_f = 0.25 (CH_2Cl_2/MeOH, 9:1); m.p. 293–295 °C. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3385, 3081, 2976, 2928, 1734, 1375, 1246, 1217, 1047 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 6.62 (s, 1 H), 6.49 (s, 1 H), 5.90 (br. s, 2 H), 5.43 (br. s, 1 H), 4.33 and 4.03 (ABq, *J* = 15.6 Hz, 2 H), 3.70–3.64 (m, 1 H), 3.62 (br. s, 1 H), 3.41 (d, *J* = 10.5 Hz, 1 H), 3.25–3.18 (m, 1 H), 3.09 (br. s, 1 H), 2.65 (d, *J* = 11.4 Hz, 1 H), 2.35–2.26 (m, 1 H), 2.08–2.00 (m, 1 H), 1.88 (app. q, *J* = 11.5 Hz, 1 H), 1.51 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 172.0 (CO), 149.2 (C), 148.5 (C), 132.2 (C), 125.8 (C), 110.4 (CH), 109.0 (CH), 103.3 (CH_2), 72.6 (CH), 72.4 (CH), 71.2 (CH), 62.6 (CH_2), 61.5 (CH), 60.7 (CH_2), 54.1 (CH), 42.0 (CH), 36.2 (CH_2), 21.5 (CH_3) ppm. HRMS (EI): calcd. for $C_{18}H_{21}NO_6$ $[M]^+$ 347.13689; found 347.13667.

(3a*R*,4a*S*,5*R*,12*R*,12a*R*,13*R*,13a*R*)-2,2-Dimethyl-3a,4,4a,6,12,12a,13,13a-octahydro-5,12-methano[1,3]dioxolo[4′,5′:4,5]benzo-[1,2-*b*][1,3]dioxolo[4′,5′:4,5]benzo[1,2-*e*]azepin-13-yl Acetate (63): 2,2-Dimethoxypropane (0.1 mL, 0.8 mmol) was added to a solution of **62** (50 mg, 0.15 mmol), *p*-TsA (43 mg, 0.22 mmol) and molecular sieves in dry acetone (0.5 mL) at room temperature, and the progress of the reaction was monitored by TLC. After completion of the reaction (6 h), the volatile material was evaporated under reduced pressure, and the residue was diluted with CH_2Cl_2 and washed with water. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated by rotary evaporation. The crude product was pure enough to be used in the next step. For analytical data, the product was purified by column chromatography (CH_2Cl_2/MeOH, 9:1) to give **63** as a yellow paste (50 mg, 95%). R_f = 0.3 (CH_2Cl_2/MeOH, 95:5). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2928, 2857, 1745, 1481, 1374, 1239, 1070 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.47 (s, 1 H), 6.43 (s, 1 H), 5.86 and 5.85 (ABq, J = 1.2 Hz, 2 H), 5.77 (app. t, J = 1.8 Hz, 1 H), 4.29–4.14 (m, 1 H), 4.19 and 3.75 (ABq, J = 16.5 Hz, 2 H), 3.81 (ddd, J = 2.7, 2.1, 2.0 Hz, 1 H), 3.22 (br. d, J = 10.8 Hz, 1 H), 2.99 (d, J = 11.1 Hz, 1 H), 2.93 (app. t, J = 10.7 Hz, 1 H), 2.87 (br. s, 1 H), 2.48 (m, 1 H), 2.40 (app. dt, J = 10.7, 2.7 Hz, 1 H), 1.51 (s, 3 H), 1.50 (s, 3 H), 1.29 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5 (CO), 146.5 (C), 145.7 (C), 108.6 (CH), 107.0 (CH), 100.8 (CH_2), 76.5 (CH), 74.5 (CH), 67.9 (CH), 61.9 (CH_2), 59.1 (CH), 59.0 (CH_2), 54.6 (CH), 40.1 (CH), 37.0 (CH_2), 28.3 (CH_3), 26.3 (CH_3), 20.4 (CH_3) ppm. MS (ESI): m/z = 388.0495 $[M + 1]^+$. $C_{21}H_{26}NO_6$ (388.44): calcd. C 65.10, H 6.50, N 3.62; found C 65.23, H 6.38, N 3.49.

(3a*R*,4a*S*,5*R*,12*R*,12a*R*,13*R*,13a*S*)-2,2-Dimethyl-3a,4,4a,6,12,12a,13,13a-octahydro-5,12-methano[1,3]dioxolo[4′,5′:4,5]benzo-[1,2-*b*][1,3]dioxolo[4′,5′:4,5]benzo[1,2-*e*]azepin-13-ol (64): NaOMe (20 mg, 0.77 mmol) was added to a stirred solution of **63** (30 mg, 0.08 mmol) in distilled MeOH (0.5 mL), and the mixture was stirred at room temp. for 4 h. After completion of the reaction, the methanol was evaporated, and the residue was redissolved in CH_2Cl_2 and washed with water. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated to give a white paste, which was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 85:15) to yield pure alcohol **64** as a white viscous material in 91% yield. R_f = 0.2 (CH_2Cl_2/MeOH, 9:1). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3337, 3018, 2926, 2399, 2360, 2333, 1506, 1485, 1387, 1240, 1215, 1068 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.61 (s, 1 H), 6.52 (s, 1 H), 5.92 (ABq, J = 1.4 Hz, 2 H), 4.59 (br. s, 1 H), 4.30 (m, 1 H), 4.23 and 3.77 (ABq, J = 16.3 Hz, 2 H), 3.95 (d, J = 3.3 Hz, 1 H), 3.30 (d, J = 10.5 Hz, 1 H), 3.04 (d, J = 10.5 Hz, 1 H), 3.05 (br. s, 1 H), 2.52–2.48 (m, 1 H), 2.41–2.38 (m, 1 H), 1.67 (ddd, J = 11.8, 10.5, 10.4 Hz, 1 H), 1.49 (s, 3 H), 1.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4 (C), 146.8 (C), 130.4 (C), 108.9 (C), 108.0 (CH), 107.0 (CH), 101.2 (CH_2), 78.1 (CH), 74.5 (CH), 68.5 (CH), 61.6 (CH_2), 58.8 (CH_2), 58.1 (CH), 57.0 (CH), 40.4 (CH), 37.2 (CH_2), 28.3 (CH_3), 26.3 (CH_3) ppm. HRMS (EI): calcd. for $C_{19}H_{23}NO_5$ $[M]^+$ 345.15762; found 345.15728.

(3a*R*,4a*S*,5*R*,12*S*,13a*S*)-2,2-Dimethyl-3a,4,4a,6,12,13a-hexahydro-5,12-methano[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*b*][1,3]dioxolo[4′,5′:4,5]benzo[1,2-*e*]azepine (65): Mesyl chloride (8 μL, 0.09 mmol) was added to a stirred solution of **64** (10 mg, 0.03 mmol), DMAP (2 mg) and TEA (12 μL, 0.09 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred at room temp. for 10 h and then diluted with water (1 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was used in the next step without purification. The residue (12 mg) was heated at reflux with freshly distilled DBU (0.04 mL) in dry toluene (0.5 mL) at 110 °C for 2 d. After completion of the reaction, monitored by analytical HPLC, the volatile material was evaporated, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 97:3) to give **65** (8 mg, 89% yield). R_f = 0.4 (CH_2Cl_2/MeOH, 95:5). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2975, 2925, 2853, 1735, 1628, 1480, 1376, 1260, 1041 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.55 (s, 1 H), 6.46 (s, 1 H), 5.87 (ABq, J = 1.5 Hz, 2 H), 5.70 (dd, J = 2.2 Hz, 1 H), 4.48–4.45 (m, 1 H), 4.34 and 3.78 (d, J = 17.0 Hz, 2 H), 4.27 (ddd, J = 11.6, 5.6, 5.6 Hz, 1 H), 3.33–3.30 (m, 1 H), 3.12 (dd, J = 10.8, 2.2 Hz, 1 H), 3.08 (m, 1 H), 3.04 (d, J = 10.8 Hz, 1 H), 2.28 (m, 1 H), 1.46 (s, 3 H), 1.35 (s, 3 H),1.32 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.6 (C), 146.8 (C), 146.1 (C), 132.4 (C), 124.5 (C), 112.3 (CH), 109.5 (C), 107.2 (CH), 106.8 (CH), 100.8 (CH_2), 73.9 (CH), 71.8 (CH), 62.2 (CH), 61.0 (CH_2), 55.2 (CH_2), 45.4 (CH), 33.2 (CH_2), 27.9 (CH_3), 25.3 (CH_3) ppm. HRMS (EI): calcd. for $C_{19}H_{21}NO_4$ $[M]^+$ 327.14726; found 327.14706.

(6*R*,6a*S*,8*R*,9*S*,11*S*)-5,6a,7,8,9,11-Hexahydro-6,11-methano[1,3]-dioxolo[4′,5′:4,5]benzo[1,2-*e*]benzo[*b*]azepine-8,9-diol·HCl (Brunsvigine·HCl, 2·HCl): HCl gas was passed through a solution of **65** (10 mg, 0.03 mmol) in dry methanol at 0 °C for 15 min. The reaction mixture was stirred at the same temperature for an additional 30 min. The volatile material was evaporated under reduced pressure to give the HCl salt of brunsvigine (**2**) in quantitative yield. ^1H NMR (500 MHz, D_2O): δ = 6.82 (s, 1 H), 6.71 (s, 1 H), 5.95 and 5.94 (ABq, J = 1.0 Hz, 2 H), 5.95 (m, 1 H), 4.75 merged with the D_2O peak, 4.45 (d, J = 15.6 Hz, 1 H), 4.17 (t, J = 3.9 Hz, 1 H), 4.12–4.09 (m, 1 H), 3.97 (d, J = 2.8 Hz, 1 H), 3.76–3.71 (m, 1 H), 3.69 (d, J = 11.0 Hz, 1 H), 3.56 (dd, J = 11.0, 2.0 Hz, 1 H), 3.33 (br. s, 1 H), 2.37 (ddd, J = 8.5, 5.2, 3.3 Hz, 1 H), 1.76 (ddd, J = 11.9, 11.9, 11.9 Hz, 1 H) ppm. HRMS (EI): calcd. for $C_{16}H_{17}NO_4$ 287.1158; found 287.11472.

(6*R*,6a*S*,8*R*,9*S*,11*S*)-5,6a,7,8,9,11-Hexahydro-6,11-methano[1,3]-dioxolo[4′,5′:4,5]benzo[1,2-*e*]benzo[*b*]azepine-8,9-diyl Diacetate (2A): Acetic anhydride (250 μL, 0.210 mmol) was added to a stirred solution of the HCl salt of brunsvigine (10 mg, 0.028 mmol) and DMAP (2 mg, 0.016 mmol) in dry pyridine (2 mL) at room temp., and the resulting reaction mixture was stirred for 20 h. Pyridine was evaporated under reduced pressure, and the residue was purified by chromatography through a silica gel column (CH_2Cl_2/MeOH, 97:3) to give **2A** in 95% yield as a white crystalline solid. R_f = 0.4 (CH_2Cl_2/MeOH, 98:2); m.p. 183–185 °C (ref.[14] 184 °C). IR (neat): $\tilde{\nu}_{max}$ = 2932, 2875, 1735, 1528, 1482, 1241, 1048 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.54 (s, 1 H), 6.48 (s, 1 H), 5.89 and 5.86 (ABq, J = 1.2 Hz, 2 H), 5.55 (br. s, 1 H), 5.47 (dd, J = 4.0, 4.0 Hz, 1 H), 4.94 (ddd, J = 12.2, 4.0, 4.0 Hz, 1 H), 4.36 and 3.87 (ABq, J = 16.5 Hz, 1 H), 3.36–3.34 (m, 2 H), 3.09 (ABq, J = 11.0 Hz, 2 H), 3.06 (d, J = 11.0 Hz, 2 H), 2.22–2.20 (m, 1 H), 2.08 (s, 3 H), 2.00 (s, 3 H),1.80 (ddd, J = 11.6, 11.6, 11.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.5 (CO), 170.0 (CO), 156.6 (C), 147.0 (C), 146.1 (C), 131.5 (C), 124.5 (C), 112.1 (CH), 107.5 (CH), 106.9 (CH), 100.8 (CH_2), 68.8 (CH), 66.1 (CH), 63.0 (CH), 61.2 (CH_2), 56.0 (CH_2), 45.4 (CH), 30.2 (CH_2), 21.0 (CH_3), 20.9 (CH_3) ppm. HRMS (EI): calcd. for $C_{20}H_{21}NO_6$ $[M]^+$ 371.1369; found 371.13504.

(4*S*)-3-{(*E*)-3-[6-({[2-(1,3-Dioxolan-2-yl)-1-(trimethylsilyl)ethyl][(trimethylsilyl)methyl]amino}methyl)-1,3-benzodioxol-5-yl]acryloyl}-4-benzyloxazolidin-2-one (66): Evans' acryloyloxazolidinone **67** (2.13 gm, 9.18 mmol) was added to a mixture of K_2CO_3 (2.53 g,

18.36 mmol), $Pd(OAc)_2$ (0.164 g, 0.73 mmol), PPh_3 (0.385 g, 1.46 mmol) and **41** (5 g, 9.18 mmol) in dry CH_3CN (40 mL). The mixture was degassed several times with argon, stirred for 1 h, and then heated at reflux under argon for 12 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, and washed with 0.1 N HCl (3 × 20 mL) followed by brine. The combined organic layers were concentrated under reduced pressure, and the residue was purified by column chromatography (petroleum ether/ethyl acetate, 85:15) to give 3.8 g (65%) of **66** as a viscous pale-yellow liquid. R_f = 0.25 (petroleum ether/ethyl acetate, 9:1). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2925, 1778, 1703, 1600, 1041 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.22 (d, J = 15.4 Hz, 1 H), 7.59 (d, J = 15.4 Hz, 1 H), 7.27–7.05 (m, 7 H), 5.92 (s, 2 H), 4.92 (m, 1 H), 4.71 (m, 1 H), 4.13 (m, 2 H), 3.84 (m, 2 H), 3.74 (m, 3 H), 3.53 (d, J = 14.0 Hz, 1 H), 3.28 (dd, J = 13.4, 3.0 Hz, 1 H), 2.77 (dd, J = 13.4, 9.6 Hz, 1 H), 2.32 (br. t, J = 5.9 Hz, 1 H), 2.13 (d, J = 13.9 Hz, 1 H), 1.96 (m, 1 H), 1.93 (d, J = 13.9 Hz, 1 H), 1.59 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5 (CO), 165.2 (CO), 153.6 (C), 149.9 (C), 146.9 (C), 143.4 (CH), 136.4 (C), 135.5 (C), 129.5 (CH), 128.9 (CH), 127.4 (CH), 115.9 (CH), 109.9 (CH), 106.1 (CH), 103.9 (CH), 101.4 (CH_2), 66.1 (CH_2), 64.7 (CH_2), 64.6 (CH_2), 56.4 (CH_2), 55.4 (CH), 49.7 (CH), 44.7 (CH_2), 38.0 (CH_2), 30.5 (CH_2), 0.5 [$Si(CH_3)_3$], –1.0 [$Si(CH_3)_3$] ppm. MS (MALDI-TOF): m/z = 639 $[M + H]^+$. $C_{33}H_{46}N_2O_7Si_2$ (638.91): calcd. C 62.04, H 7.26, N 4.38; found C 62.18, H 7.33, N 4.52.

{(6*R*,7*S*,8*S*,9*R*)-7-[(1,3-Dioxolan-2-yl)methyl]-5,7,8,9-tetrahydro-6,9-methano[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*c*]azepin-8-yl}methanol (68): A cycloaddition reaction was performed as described for compound **23**. After the disappearance of the starting material, the reaction mixture was filtered through a small plug of basic alumina and eluted with methanol. The solvent was evaporated completely to give a crude brown residue, which was redissolved in dry THF, and the resulting solution was added to a suspension of $LiAlH_4$ in dry THF at 0 °C and the reaction mixture stirred at room temp. for 4 h. After completion of the starting material, as monitored by TLC, the reaction mixture was quenched with a saturated aqueous Na_2SO_4 solution and stirred for a further 1 h. The reaction mixture was filtered through small pad of Celite, the solvent was evaporated, and the crude mass was purified by column chromatography (CH_2Cl_2/MeOH, 9:1) to give chiral alcohol **68** (46% yield over two steps) as a white solid. R_f = 0.25 (CH_2Cl_2/MeOH, 9:1); m.p. 168–170 °C. $[a]_D^{27}$ = +10.5 (c = 0.45, MeOH). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3431, 3053, 2985, 1635, 1404, 1265, 1236, 1040 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.51 (s, 1 H), 6.42 (s, 1 H), 5.85 (br. s, 2 H), 5.08 (dd, J = 6.9, 2.6, Hz, 1 H), 4.22 and 3.70 (ABq, J = 16.7 Hz, 2 H), 3.99–3.80 (m, 4 H), 3.77–3.62 (m, 1 H), 3.50 (dd, J = 9.0, 10.6 Hz, 1 H), 3.29 (dd, J = 11.4, 8.1, 3.6 Hz, 1 H), 3.01 (dd, J = 2.7 Hz, 1 H), 2.95 (d, J = 2.7 Hz, 1 H), 2.85 (d, J = 11.4 Hz, 1 H), 2.55–2.44 (m, 1 H), 2.08 (br. s, 1 H), 1.85–1.58 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.2 (C), 145.7 (C), 135.9 (C), 125.2 (C), 107.1 (CH), 106.5 (CH), 104.0 (CH), 100.6 (CH_2), 64.9 (CH_2), 64.6 (CH_2), 62.9 (CH), 61.4 (CH_2), 60.5 (CH_2), 55.9 (CH), 52.5 (CH_2), 42.5 (CH), 34.7 (CH_2) ppm. MS (ESI): m/z = 320 $[M + H]^+$. HRMS (EI): calcd. for $C_{17}H_{21}NO_5$ 319.1419; found 319.1473.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all synthetic compounds, HPLC spectrum for **68**.

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