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Total synthesis of (±)-stemonamide and (±)-isostemonamide

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Abstract—Two different approaches to the alkaloids stemonamide and isostemonamide using *N*-acyliminium chemistry are described. The approach using an aldol spirocyclization to construct the second contiguous spirocenter was successful. The total synthesis of these products was completed by 1,4-addition of an appropriate side chain, α-methylenation by Mannich reaction, double bond isomerization and closure of the azepine ring.

1. Introduction

Alkaloids from *Stemona* plants have been used in Chinese and Japanese folk medicine as cough-relief agents and insecticides. The alkaloids of this family, having relatively complex polycyclic structures, have been classified into six groups according to their structural features.[1] Five of these groups, containing the pyrrolo[1,2-*a*]azepine nucleus characteristic of the majority of the *Stemona* alkaloids, receive the name of the simplest member: stenine (**I**), stemoamide (**II**), tuberostemospironine (**III**), stemonamine (**IV**) and parvistemoline (**V**), while the sixth group comprises eight alkaloids (e.g. stemofoline **VI**), some of them lacking the mentioned nucleus (Fig. 1).

Our group has been interested in the total synthesis of

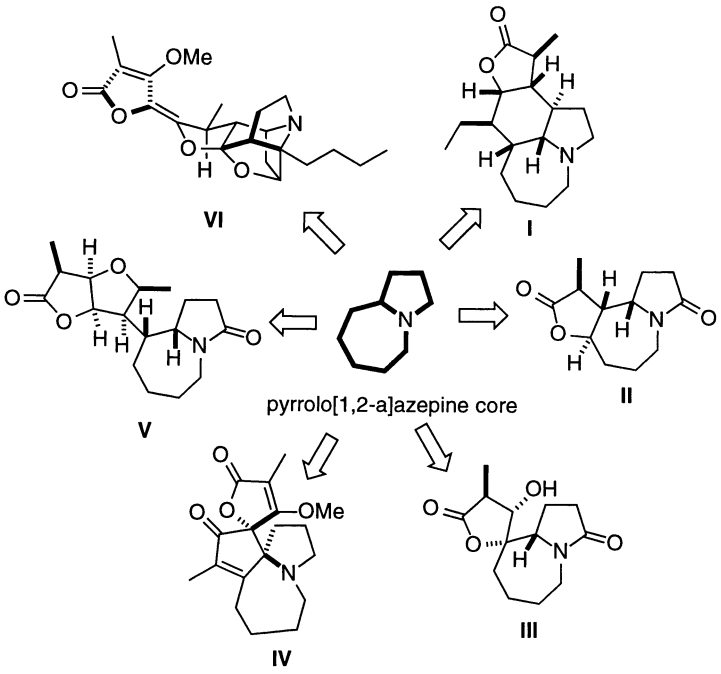

Figure 1.

Keywords: stemonamide; isostemonamide; acyliminium; aldol spirocyclization; Mannich reaction.

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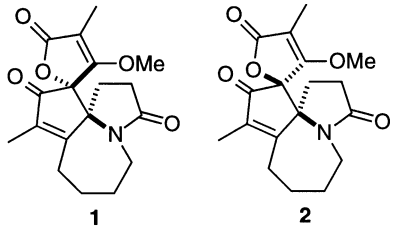
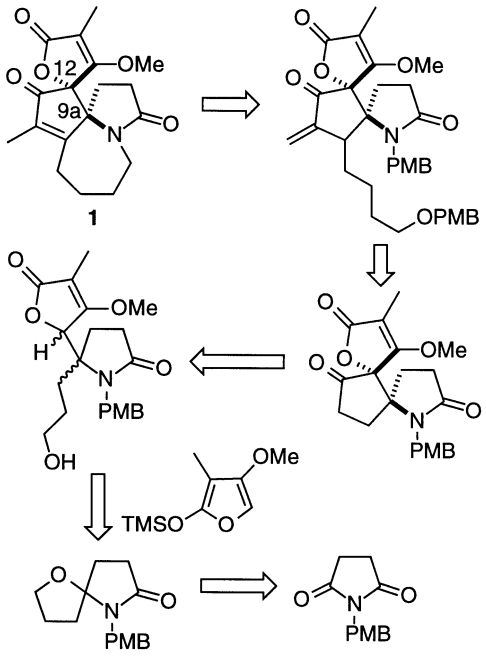


Figure 2. Stemonamide (**1**) and isostemonamide (**2**).



Scheme 1. Retrosynthetic analysis.

Stemona alkaloids[2] and has already reported the total synthesis of isostemofoline.[3] Herein we would like to report the first total synthesis of another two members of this family: (±)-stemonamide (**1**) and (±)-isostemonamide (**2**).[4,5] These two compounds were isolated by Xu et al.[6] in 1994 from the roots of *Stemona japonica*. They present the tetracyclic core characteristic of the stemonamine[7] group (**IV**, Fig. 1) with two contiguous spirocyclic quaternary centers; their structures are depicted in Fig. 2.

Stemonamide (**1**) differs from isostemonamide (**2**) only in the relative stereochemistry at the quaternary centers; while in stemonamide (**1**) the heteroatoms are in *anti* disposition, in isostemonamide (**2**) they are *syn*.

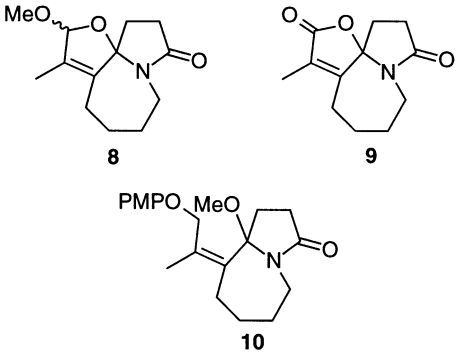


Figure 3.

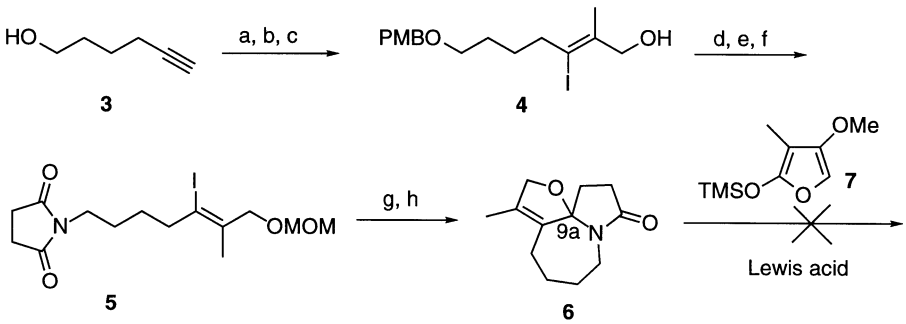
Our synthesis relies on the addition of a silyloxyfuran to an *N*-acyliminium ion[8] to create the first quaternary center (Scheme 1), followed by aldol spirocyclization to construct the tricyclic core of the stemonamine group. The remaining carbons needed to complete the framework were installed by 1,4-addition of an appropriate Grignard reagent and by a Mannich reaction. The seven-membered ring was closed by intramolecular nucleophilic displacement.

2. Results and discussion.

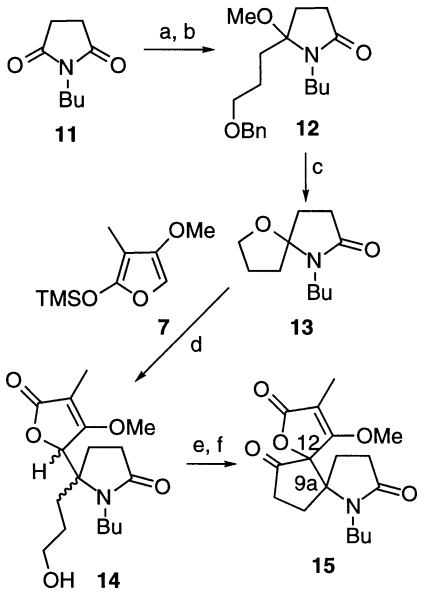
2.1. Limitations of the acyliminium approach

We approached the synthesis of stemonamide in two different ways using *N*-acyliminium chemistry.[9] In the first, a convenient funtionalized chain **4**[10] was attached to succinimide by Mitsunobu reaction, and the seven-membered ring was formed by intramolecular cyclization promoted by *n*-BuLi transmetallation[11] (Scheme 2).

The resulting hemiaminal under acid catalysis gave the tricyclic aminal **6**. This compound **6** was treated, in the presence of the silyloxyfuran **7**, with several Lewis acids[9] ($BF_3{\cdot}Et_2O$, TMSOTf, $TiCl_4$) to generate the *N*-acyliminium ion and create the C-9a quaternary center having in place adequate functionalization to close the fourth ring of stemonamide. Unfortunately these attempts to form the quaternary center were unsuccessful (Scheme 2).



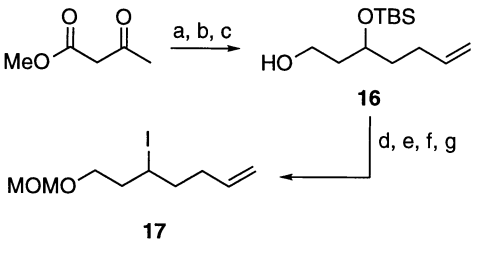
Scheme 2. *Reagents and conditions*: (a) NaH, PMBBr, 0°C to rt, 66%; (b) *n*-BuLi, $(HCHO)_n$, THF, −78°C to rt, 74%; (c) MeMgCl, CuI, 0°C to rt then I_2, 0°C to rt, 71%; (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0°C to rt, 93%; (e) CAN, CH_3CN–H_2O (2:1), 0°C, 80%; (f) succinimide, DEAD, Ph_3P, 0°C to rt, 80%; (g) *n*-BuLi, THF, −78°C to rt; (h) PPTS, MeOH, rt, 49% (2 steps).



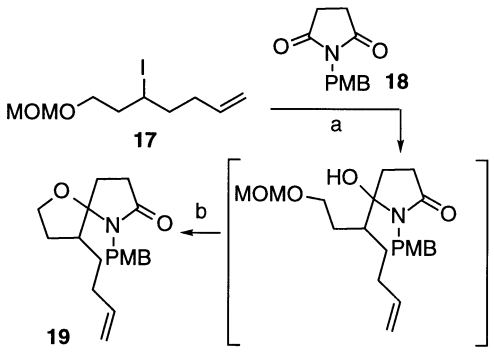
Scheme 3. *Reagents and conditions*: (a) $BnO(CH_2)_3MgBr$, Et_2O, 0°C to rt; (b) *p*-TsOH, MeOH, reflux, 76% (2 steps); (c) H_2, 10%Pd/C, MeOH, rt, 81%; (d) $BF_3{\cdot}Et_2O$, **7**, CH_2Cl_2, −78°C to rt, 27% (41% SM); (e) Dess–Martin periodinane, CH_2Cl_2, rt, 53% (25% SM); (f) DBU, CH_2Cl_2, rt then Dess–Martin periodinane, rt, 56%.

The compounds **8**, **9** and **10** were prepared in an analogous way (Fig. 3). Treatment of **8** with TMSOTf in the presence of the silyloxyfuran **7** gave a complex mixture of products; under the same conditions, **9** was recovered mostly unreacted. In the case of **10**, the major compound seemed to come from 1,4-addition of **7** to the conjugated acyliminium ion formed.

In the second approach the tricyclic ketones **15** were prepared as a model (Scheme 3). Grignard addition of (3-benzyloxypropyl) magnesium bromide to the succinimide **11** and protection, as methoxyaminal **12**, followed by hydrogenation gave the spiro compound **13**. When **13** was treated with the silyloxyfuran **7** in the presence of boron trifluoride, the isomeric mixture of alcohols **14** was obtained in modest yield (27%) together with 41% of recovered starting material. This mixture of alcohols **14** was oxidized with Dess–Martin periodinane to the corresponding mixture of aldehydes (53% with 25%SM), which upon intramolecular aldol reaction[12] followed by oxidation provided the



Scheme 4. *Reagents and conditions*: (a) NaH, *n*-BuLi, allyl bromide, THF, 0°C to rt, 83%; (b) $NaBH_4$, MeOH, 0°C, 78%; (c) TBSCl, Im, DMF, rt, 90%; (d) LAH, Et_2O, −60°C, 79%; (e) *i*-$PrNEt_2$, MOMCl, CH_2Cl_2, 0°C to rt; (f) TBAF, THF, rt, 86% (2 steps); (g) Ph_3P, HMPA, 2,6-lutidine, I_2, benzene, 80°C, 80%.



Scheme 5. *Reagents and conditions*: (a) SmI_2, NiI_2, THF, rt to reflux; (b) conc. HCl, MeOH, 60°C, 9% (2 steps).

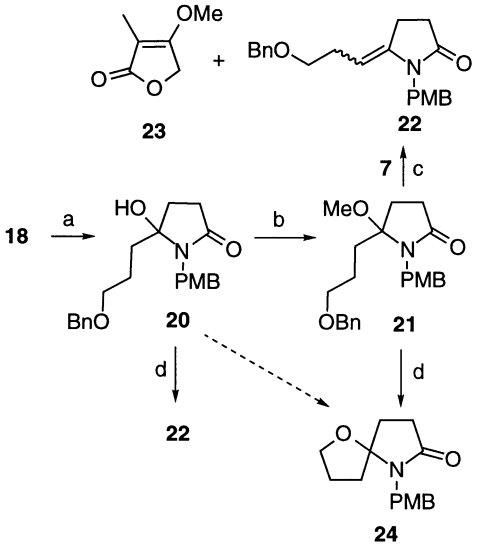
ketones **15** as a 1:1 mixture of diastereomers in 56% yield (Scheme 3).

With a feasible route to the tricyclic core of the stemonamine family in hand, we explored the possibility of incorporating in the Grignard reagent the four-carbon side chain needed to close the seven-membered ring. With this purpose, the iodide **17** was prepared starting from methyl acetoacetate. Dianion chemistry was used to introduce the allyl chain, and a sequence of trivial functional group manipulations led to **17** in 32% overall yield (Scheme 4).

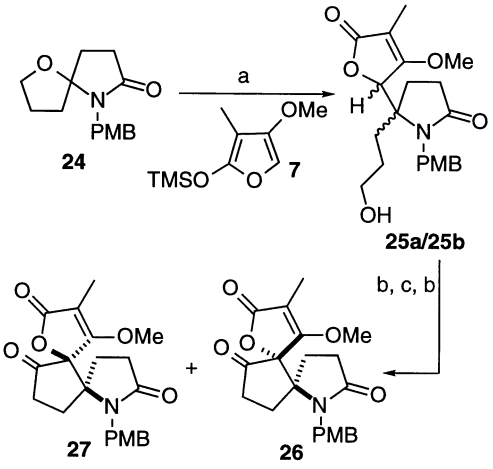
However, addition of the Grignard reagent derived from **17** to the imide **18** failed under several conditions. Only a Barbier-type reaction, mediated by a samarium(II) iodide/catalytic nickel iodide system,[13] allowed the isolation of the expected compound **19**, but in very low yield (Scheme 5).

2.2. Productive acyliminium addition and aldol spirocyclization

Our failure to improve the yield of this addition directed us to the earlier approach, using an appropriate protecting group for the imide. The *N*-(4-methoxybenzyl)succinimide

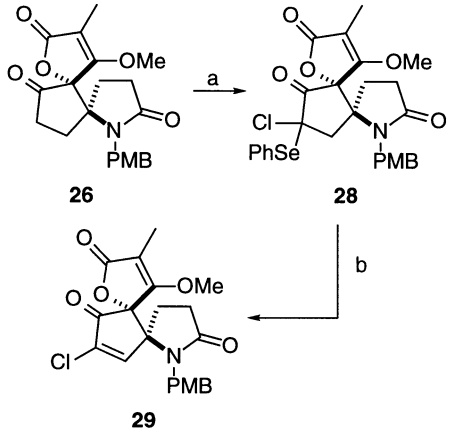


Scheme 6. *Reagents and conditions*: (a) $BnO(CH_2)_3MgBr$, Et_2O, reflux; (b) PPTS, MeOH, rt, 90% (**18→21**); (c) $BF_3{\cdot}Et_2O$ or TMSOTf, CH_2Cl_2 or CH_3CN; (d) H_2, 10%Pd/C, MeOH, rt, 90% (**21→24**), 86% (**18→22**).

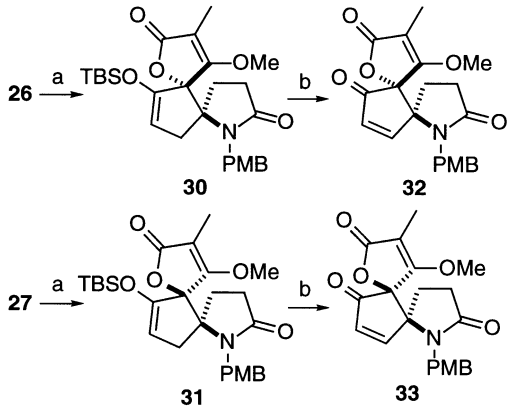


Scheme 7. *Reagents and conditions*: (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 40 min, 82%; (b) $(COCl)_2$, DMSO, TEA, CH_2Cl_2; (c) DBU, CH_2Cl_2, overnight, rt 70% (**25a/25b→26**+**27**).

18 was reacted with (3-benzyloxypropyl) magnesium bromide, in ether at reflux for 30 min, and the resulting hemiaminal **20** was protected as its methoxy derivative **21** in 90% overall yield by treatment with PPTS in methanol at room temperature (Scheme 6). The intermediate hemiaminal **30** and its methoxy derivative **31** proved to be prone to elimination and they gave the exocyclic enamide **22** (single isomer, the geometry of the double bond was not determined) in halogenated solvents. To skip one synthetic step, we explored the possibility of generating the acyliminium ion by treatment of **21** with either $BF_3{\cdot}Et_2O$ or TMSOTf in the presence of the silyloxyfuran **7**, but the enamide **22** and the tetronic acid derivative **23** were the only products of the reaction (Scheme 6). Thus it was necessary to form the spiro compound **24** prior to the addition of the silyloxyfuran. Hydrogenolysis of the benzyl group in **21** with palladium on carbon in methanol proceeded smoothly, through the primary alcohol, to the expected compound **24** in 90% yield. An attempt to obtain the spiro compound by direct hydrogenolysis of the hemiaminal **20** also failed, and the enamide **22** was obtained after 1–2 h of reaction (Scheme 6).



Scheme 8. *Reagents and conditions*: (a) PhSeCl, Amberlite® IR120, EtOAc, rt, 37%; (b) $NaIO_4$, $NaHCO_3$, MeOH–H_2O, rt, 64%.



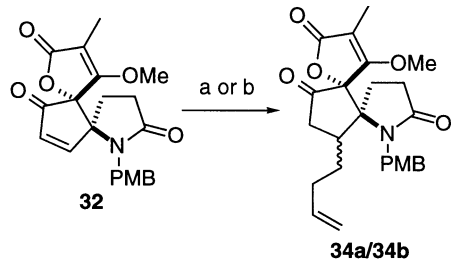
Scheme 9. *Reagents and conditions*: (a) TBDMSOTf, collidine, toluene, 7 h, 0°C to rt, 80% (**30**), 68% (**31**); (b) $Pd(OAc)_2$, O_2, DMSO, 80°C, 24–48 h, 93% (**32**), 89% (**33**).

Finally, addition of a solution of silyloxyfuran **7** to a stirred mixture of $BF_3{\cdot}Et_2O$ and the spiro compound **24** in dichloromethane at room temperature afforded the diastereomeric mixture of alcohols **25a/25b** (ratio 1:2) in 80% yield (Scheme 7). A small amount of this mixture was separated for characterization purposes. Oxidation of the mixture **25** under Swern conditions gave the corresponding aldehydes, which were used directly in the DBU-mediated aldol spirocyclization to obtain the corresponding aldols. These aldols were oxidized using a Swern protocol to afford the tricyclic ketones **26** and **27** as a 1:1 diastereomeric mixture in 70% isolated yield (Scheme 7). The ketones **26** and **27** were easily separated by column chromatography. The faster eluting isomer **26** possessed the relative stereochemistry of stemonamide (**1**) while the slower eluting isomer **27** corresponded to isostemonamide (**2**), as shown by the X-ray crystal structures of these targets.

2.3. Dehydrogenation of the tricyclic ketolactams

To install the double bond required to attach the four-carbon side chain, we first explored the use of selenium chemistry. However, treatment with PhSeCl of the lithium enolate of **26**[14] or its trimethylsilyl enol ether[15] gave the expected selenide only in very low yield, and a considerable amount of starting material was recovered. The use of Sharpless conditions[16] (PhSeCl, Amberlite® IR120, EtOAc) afforded the α-chloro-α-selenoderivative **28** in 37% yield. This upon oxidation with sodium periodate in MeOH–H_2O and elimination led to the α-chloroenone **29** in 64% yield (Scheme 8). Presumably the selenyl derivative reacts with a second molecule of PhSeCl in which the chlorine acts as an electrophile, as suggested in the literature.[17]

The above problems were circumvented by palladium(II) acetate dehydrogenation of the silyl enol ethers derived from **26** and **27**. The action of $Pd(OAc)_2$ (0.5 equiv.) and *p*-benzoquinone (0.5 equiv.) in CH_3CN[18] on the trimethylsilyl enol ether derived from **26** did not afford satisfactory results. Formation of the TMS silyl enol ether could not be followed by TLC and the expected enone **32** had the same R_f as ketone **26**. The TBDMS enol ethers **30** and **31** were prepared by treatment of **26** and **27** with TBDMSOTf (3.2 equiv.) and collidine (10 equiv.) in dry toluene[19] at rt

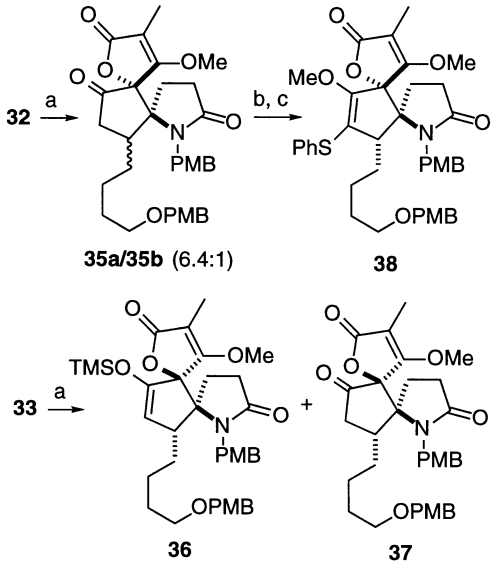


Scheme 10. *Reagents and conditions*: (a) $CH_2{=}CH(CH_2)_2MgBr$, $CuBr{\cdot}Me_2S$, THF, −78°C; (b) $CH_2{=}CH(CH_2)_2MgBr$, 5% $CuBr{\cdot}Me_2S$, TMSCl, HMPA, THF, −40°C.

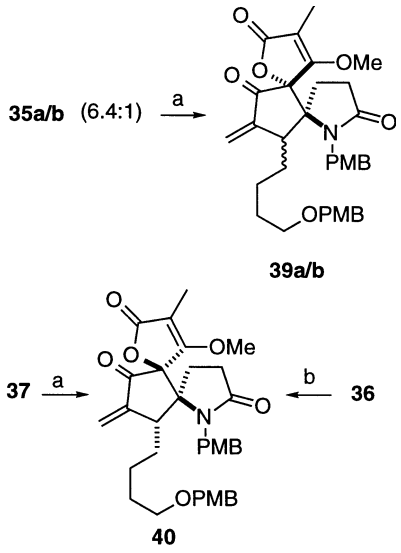
for 7–8 h in 84 and 68% isolated yields, respectively (Scheme 9). We tried Larock's modification[20] of the Saegusa reaction (10% $Pd(OAc)_2$, O_2 in DMSO) hoping to reduce the amount of metal used, but unfortunately with our substrate we needed 0.85 equiv. of $Pd(OAc)_2$ and 45–53 h to consume all the starting material. Nevertheless the enones **32** and **33** were isolated under these conditions in high yields, 93 and 89%, respectively (Scheme 9).

2.4. Conjugate addition and α-methylenation

With the enones **32** and **33** in hand we were ready to attach the missing four-carbon segment of the azepine ring of these alkaloids. Our first approach used 4-bromo-1-butene; hydroboration of the terminal olefin and activation of the alcohol were planned for the final ring closure. The 1,4-addition to **32** proved to be difficult and the use of an excess of cuprate reagent[21] only afforded the expected products **34a/b** in 18% yield (4:1 diastereomeric mixture), together with recovered starting material (32%). When $CuBr{\cdot}Me_2S$ was substituted by the more soluble $[n\text{-}Bu_3P{\cdot}CuI]_4$[22,23]only unreacted material **32** (88%) was isolated even after 7 h at rt. However the use of the Grignard reagent and catalytic amounts of $CuBr{\cdot}Me_2S$ with HMPA and TMSCl as additives[24] proved beneficial, and in their presence the reaction proceeded in good yields: 69% of **34a/b** (ratio 1:1.6) and 19% of **32** (Scheme 10).



Scheme 11. *Reagents and conditions*: (a) $PMBO(CH_2)_4MgBr$, $CuBr{\cdot}Me_2S$, TMSCl, HMPA, THF, −78°C; (b) LDA, THF, −78°C then $PhSSO_2Ph$, rt; (c) NaH, THF, rt then MeI.

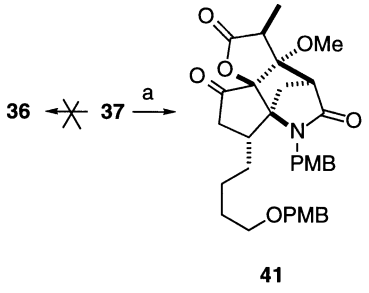


Scheme 12. *Reagents and conditions*: (a) KH, THF then $Me_2N^+{=}CH_2{\cdot}CF_3COO^-$, rt; (b) $Me_2N^+{=}CH_2{\cdot}CF_3COO^-$, CH_2Cl_2, rt.

At this time a second generation of the Grignard reagent had been prepared incorporating the required oxygen functionality. Thus the 1,4-addition of 4-(4-methoxybenzyloxybutyl)magnesium bromide took place under the above conditions in good yields. Addition occurred mainly *anti* to the C–N bond in the stemonamide series, and exclusively *anti* in the isostemonamide series (no other isomer was detected by ^1H NMR). Examination of molecular models suggests that the steric hindrance of the *N*-PMB group is responsible for the observed stereoselectivity in the cuprate addition,[25] although another factor that could contribute to this *anti*-diastereoselectivity is the use of TMSCl.[26] Even in the presence of these additives, an excess of the Grignard reagent was necessary to complete the reaction, along with careful control of the reaction time to prevent undesired 1,2-additions to the lactone and the lactam. The reactions were carried out with 4.0 equiv. of Grignard reagent at −78°C for 30 min. Ketone **35** was obtained in 74% yield, and in the isostemonamide series, silyl enol ether **36** was isolated in 57% yield together with ketone **37** in 32% yield (Scheme 11).

In order to introduce the methyl group and regenerate the double bond, **35a** was deprotonated with LDA at −78°C and the enolate was quenched with phenyl benzenethiosulfonate[27] at 20°C to give the expected α-sulfide in 45% yield. Further treatment with sodium hydride and methyl iodide[28] afforded only the O-alkylation product **38** in 61% yield and no C-alkylation products were observed (Scheme 11). Possibly the O-alkylation is favored to avoid eclipsing interactions in the heavily substituted cyclopentanone.

Finally the methyl group and a double bond were installed in one step by a Mannich reaction.[29a] Use of s-trioxane and *N*-methylanilinium trifluoroacetate,[29b] known to afford directly α-methylene ketones, led to recovery of the starting material in almost quantitative yield. However treatment of



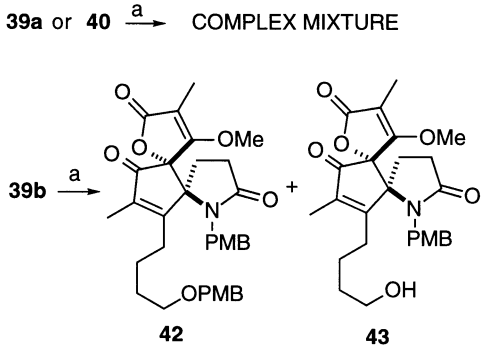
Scheme 13. *Reagents and conditions*: TMSOTf, Et_3N, THF, 0°C, 3 h, 24% (53% recovered **37**).

a solution of **35** in THF with an excess of potassium hydride (1 h, 20°C) followed by addition of the Mannich reagent *N*,*N*-dimethylformaldimmonium trifluoroacetate[30,31] directly afforded, after overnight stirring, the α-methylene ketone **39** in 67% yield. Under the same conditions, ketone **37** gave the expected product **40** in 85% yield. When silyl enol ether **36** was reacted with an excess of this reagent using Danishefsky conditions,[32] **40** was obtained as the only product in 96% yield. Under the experimental conditions, namely excess of *N*,*N*-dimethylformaldimmonium trifluoroacetate, the intermediate Mannich bases must undergo quaternization, followed by elimination, affording the α-methylene ketones **39** and **40** (Scheme 12).

2.5. An unexpected cyclization

The formation of the silyl enol ethers of **35** and **37** was investigated since α-methylenation gave a higher yield from the silyl enol ether than through the potassium enolate. Thus ketolactam **37** was treated in THF with TMSOTf (2.75 equiv.) and Et_3N (10 equiv.) at 0°C and generation of a faster eluting product was observed, as expected. The reaction was quenched before completion after 3 h at 0°C and to our surprise the less polar product was not the silyl enol ether **36** but the tetracyclic compound **41** (Scheme 13).

The structure of **41** was elucidated by ^1H and ^{13}C NMR and confirmed by single-crystal X-ray analysis (Fig. 4).[33] Tetracyclic **41** is the product of a 1,4-addition from the α-position of the lactam to the tetronate moiety.



Scheme 14. *Reagents and conditions*: $RhCl_3{\cdot}xH_2O$, EtOH–H_20 (10:1), reflux.

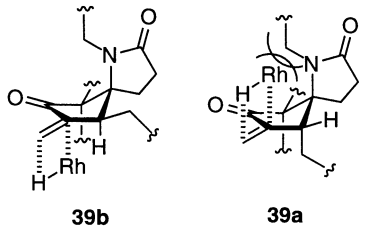


Figure 5.

2.6. Alkene isomerization and final ring closure

Our first attempts to isomerize the exocyclic double bond in **39a** and **40** with rhodium trichloride hydrate[34] failed, and only complex mixtures were obtained. The main components of these mixtures derived from deprotection of the PMB group of the alcohol and addition of the solvent to the enone. It is important to point out in contrast that the minor isomer **39b** underwent isomerization in ca. 60% yield concurrently with partial loss of the PMB group (Scheme 14).

This result suggested that steric factors may be responsible for the lack of reactivity. The accepted mechanism for this type of reaction implies the formation of a σ-alkyl complex between the olefin and the metal followed by abstraction of a *syn* proton.[35] In the case of the minor isomer **39b**, the complex forms on the α-face of the molecule (Fig. 5).

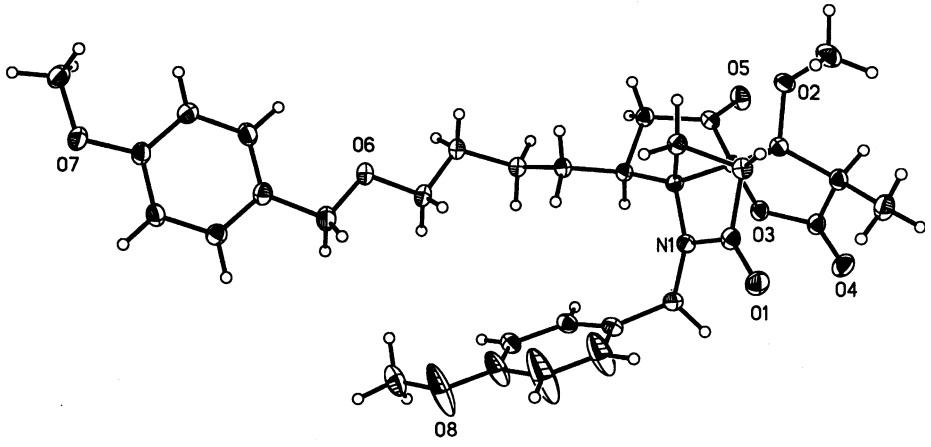
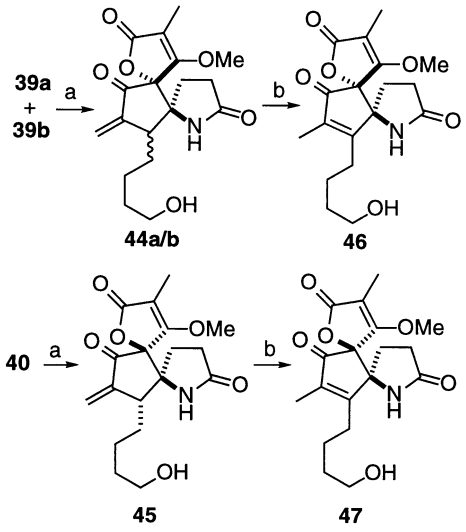
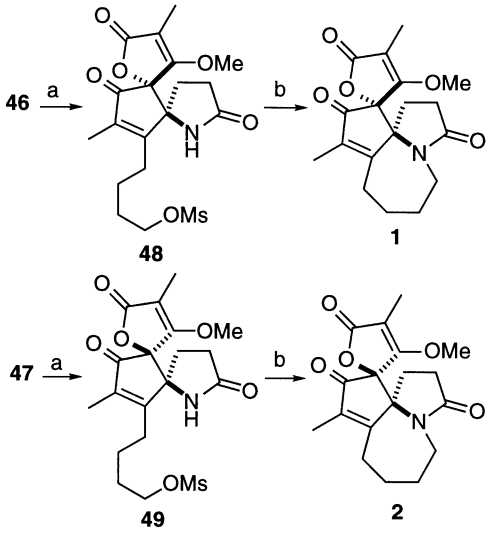


Figure 4.



Scheme 15. *Reagents and conditions*: (a) CAN, $CH_3CN–H_20$ (3:1), rt; (b) $RhCl_3{\times}H_2O$, EtOH–H_2O (10:1), reflux.



Scheme 16. *Reagents and conditions*: (a) MsCl, DMAP, py, CH_2Cl_2 0°C, 1 h (**46**), 4 h (**47**); (b) NaH, THF, rt, 30 h (**48**), 5 h (**49**).

However in the major isomers **39a** and **40**, for the reaction to take place, the complex needs to form on the β-face which is hindered by the large *N*-PMB substituent.

This assumption was confirmed, after removal of both protecting groups with cerium(IV) amonium nitrate,[36] whereupon the isomerization was achieved in all the isomers under the same conditions to obtain **46** in 66% yield and **47** in 69% yield (Scheme 15).

These alcohols **46** and **47** were converted to the corresponding mesylates **48** and **49** in 71 and 83% yield, respectively. Finally, intramolecular displacement under basic conditions[5,37] (NaH, THF, rt) allowed us to obtain stemonamide (**1**) in 46% yield, together with 14% of recovered mesylate. In a similar way, isostemonamide (**2**) was prepared in 70% yield (Scheme 16).

The structures of **1** and **2** were corroborated by NMR comparison[38] and by single-crystal X-ray determinations[39] (Fig. 6). The structures are in agreement with those proposed by Xu et al.[6] for the natural products.

3. Conclusion

We have completed the first total syntheses of (±)-stemonamide **1** and (±)-isostemonamide **2** in 15 steps from *N*-(4-methoxybenzyl)succinimide in 4 and 7% overall yield, respectively. Slight differences in reactivity have been observed in the synthetic route for the two series.

4. Experimental

4.1. General

Experiments that required an inert atmosphere were carried out under dry argon in a flame-dried glass system. Solvents and reagents used in this work were purified according to standard literature techniques and stored under argon. THF and Et_2O were freshly distilled from sodium/benzophenone and transferred via syringe. Methylene chloride and acetonitrile were distilled from CaH_2. Melting points are

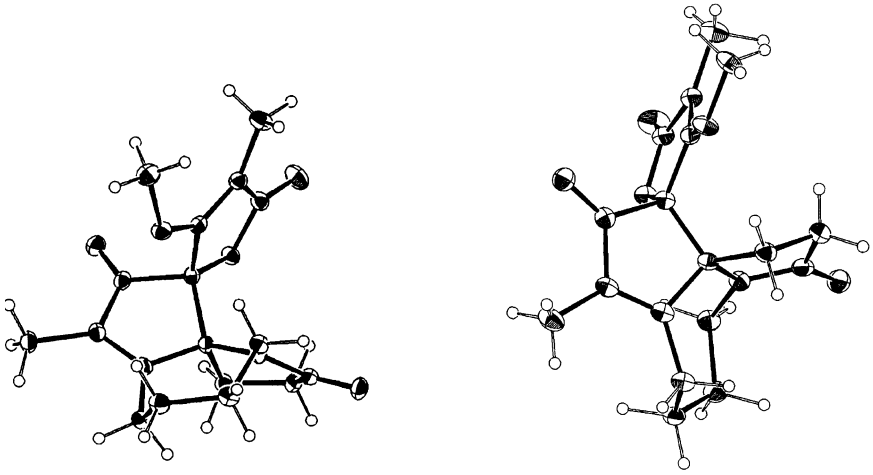


Figure 6. X-Ray structures of (±)-stemonamide (**1**) (left) and (±)-isostemonamide (**2**) (right).

uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 FTIR instrument as films on sodium chloride plates. ^{1}H and ^{13}C NMR spectra were obtained on Bruker AMX 400 and Avance 400 instruments in the solvent indicated at 400 and 100 MHz, respectively. Chemical shifts are expressed in ppm downfield from TMS. The ^{1}H NMR data are presented in the order: δ value of the signal, integrated number of protons, peak multiplicity (abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet) and coupling constants in Hertz. Mass spectra were recorded on a Hewlett Packard 110 MSD using APCI or API-ES mode. High resolution mass analyses were carried out by UC Riverside Mass Spectrometry Department (DCI/NH_3, CI/NH_3 or FAB as indicated). Elemental analyses were performed by Galbraith Laboratories. Flash chromatographies were run on silica gel (Natland, 200–400 mesh) with the solvent mixture indicated. TLC was performed on commercial silica gel glass plates (Baker Si500F) that were developed by immersion in the most appropriate of the following systems: 20% phosphomolybdic acid in ethanol, 5% H_2SO_4 in ethanol, 5% anisaldehyde+5% H_2SO_4 in ethanol and 0.6% $KMnO_4$+6% K_2CO_3 in water.

4.1.1. Methoxyaminal 21. To a stirred mixture of magnesium turnings (1.89 g, 77.9 mmol) and a catalytic amount of I_2 in dry Et_2O (40 mL) under reflux, some drops of a solution of 1-[(3-bromopropoxy)methyl]-benzene (11.9 g, 51.9 mmol) in Et_2O (40 mL) were added. Once the iodine color disappeared, the remaining bromide solution was added dropwise (approx. 1 h). When the addition was finished the reaction mixture was stirred for an additional 20 min. The Grignard reagent formed was added dropwise to a stirred suspension of *N*-(4-methoxybenzyl)succinimide **18** (5.68 g, 26.0 mmol) in Et_2O (200 mL) under reflux. After 30 min the reaction was cooled to rt, quenched with saturated aqueous NH_4Cl solution (150 mL) and extracted with EtOAc+1% Et_3N. The combined organic layers were washed with brine and dried (anhydrous K_2CO_3). Evaporation of the solvents under reduced pressure afforded 8.85 g of crude hemiaminal. This crude hemiaminal was dissolved in MeOH (250 mL) and PPTS (327 mg, 1.3 mmol) was added. The reaction mixture was stirred for 1.5 h at rt. Methanol was evaporated under reduced pressure, and the residue was dissolved in EtOAc+1% Et_3N, washed with H_2O, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried (anhydrous K_2CO_3). The solvents were evaporated and the residue was chromatographed (hexanes/EtOAc 2:1+2% Et_3N then EtOAc+2% Et_3N) to afford 8.96 g (90%) of **21** and 250 mg (3%) of **22**. **21**: mp 81–83°C (heptane/ethyl acetate). IR (film): 2933, 1692, 1612, 1513, 1453, 1400, 1357, 1246, 1178, 1072, 1033, 734, 698 cm^{-1}. ^{1}H NMR (CD_3OD): 1.16–1.24 (1H, m); 1.42–1.50 (2H, m); 1.73–1.78 (1H, m); 2.01–2.05 (2H, m); 2.31–2.47 (2H, m); 2.94 (3H, s); 3.09–3.19 (2H, m); 3.73 (3H, s); 3.98 (1H, d, J=15.0 Hz); 4.25 (1H, d, J=12.0 Hz); 4.29 (1H, d, J=12.0 Hz); 4.45 (1H, d, J=15.0 Hz); 6.74 (2H, d, J=8.5 Hz); 7.13–7.24 (7H, m) ppm. ^{13}C NMR (CD_3OD): 24.9, 26.4, 30.6, 37.3, 42.8, 49.5, 55.7, 70.9, 73.8, 98.5, 114.8 (2C), 128.6, 128.7 (2C), 129.4 (2C), 130.7 (2C), 131.5, 139.8, 160.4, 178.4 ppm. APCI(+): 384 ([MH]$^+$, 72), 352 (65), 350 (100), 121 (52), 60 (88). HRMS (DCI/NH_3): calcd for $C_{23}H_{30}NO_4$ *m/z* 384.2175; found 384.2162.

4.1.2. Spiro compound 24. To a stirred solution of **21** (5.40 g, 14.0 mmol) in methanol (100 mL), was added a catalytic amount of 10%Pd/C. The reaction mixture was stirred for 2 h under hydrogen atmosphere. When the hydrogenolysis of the benzyl group was completed (TLC), the hydrogen atmosphere was changed to argon, and the reaction was stirred for an additional 3 h. The catalyst was removed by filtration through a pad of silica gel using EtOAc as eluent. The solvents were removed under vacuum and the residue was chromatographed on silica gel (hexanes/EtOAc 1:1 then 1:2) to give 3.25 g (90%) of **24**. **24**: mp 49–51°C (heptane/ethyl acetate). IR (film): 2953, 1698, 1613, 1513, 1398, 1357, 1303, 1247, 1176, 1046, 916, 889, 818 cm^{-1}. ^{1}H NMR (CD_3OD): 1.84–2.05 (4H, m); 2.12–2.17 (2H, m); 2.41 (1H, ddd, J=5.0, 8.2, 17.2 Hz); 2.53 (1H, td, J=8.5, 17.2 Hz); 3.74–3.80 (1H, m); 3.76 (3H, s); 3.92 (1H, q, J=6.8 Hz); 4.17 (1H, d, J=15.5 Hz); 4.57 (1H, d, J=15.5 Hz); 6.84 (2H, d, J=8.8 Hz); 7.19 (2H, d, J=8.8 Hz) ppm. ^{13}C NMR (CD_3OD): 26.5, 30.1, 34.7, 35.3, 43.0, 55.7, 69.0, 102.7, 114.8 (2C), 129.4 (2C), 131.5, 160.3, 178.0 ppm. API-ES(+): 545 ([2M+Na]$^+$, 100), 284 ([M+Na]$^+$, 50). HRMS (CI/NH_3): calcd for $C_{15}H_{20}NO_3$ *m/z* 262.1443; found 262.1450. Elemental analysis. Calculated C, 68.94; H, 7.33. Found C, 68.88; H, 7.54.

4.1.3. Addition of the silyloxyfuran 7 to 24. To a stirred solution of **24** (4.29 g, 16.4 mmol) and $BF_3{\cdot}Et_2O$ (4.2 mL, 32.8 mmol) in dry CH_2Cl_2 (38.0 mL), neat silyloxyfuran **7** (freshly prepared from 48.2 mmol of 4-methoxy-3-methyl-2(5*H*)-furanone) was added dropwise. After 40 min of stirring at rt, the reaction mixture was cooled to 0°C, quenched with saturated $NaHCO_3$ solution, and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, and dried (Na_2SO_4) and the solvents were evaporated to give a residue that upon purification (silica gel, EtOAc then EtOAc/2-propanol 4:1) afforded 5.23 g (82%) of a 1:2 diastereomeric mixture of alcohols **25a** and **25b**. **25a** (faster eluting isomer): mp 152–153°C heptane/ethyl acetate. IR (film): 3424, 2954, 1755, 1667, 1612, 1585, 1514, 1454, 1392, 1342, 1246, 1178, 1061, 978, 892, 820, 756, 735, 701, 666 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.08–1.17 (1H, m); 1.39–148 (1H, m); 1.73–1.96 (4H, m); 1.96 (3H, bs); 2.33 (1H, ddd, J=7.9, 9.7, 17.5 Hz); 2.42 (1H, ddd, J=5.3, 10.3, 17.5 Hz); 3.35–3.39 (2H, m); 3.79 (3H, s); 4.04 (3H, s); 4.32 (1H, d, J=15.2 Hz); 4.56 (1H, d, J=15.2 Hz); 4.58 (1H, bs); 6.83 (2H, d, J=8.6 Hz); 7.29 (2H, d, J=8.6 Hz) ppm. ^{13}C NMR ($CDCl_3$): 8.4, 23.8, 25.6, 29.3, 30.6, 43.4, 54.9, 58.9, 61.5, 67.8, 79.7, 98.9, 113.2 (2C), 129.5 (2C), 129.9, 158.4, 170.8, 173.7, 176.0 ppm. API-ES(+): 801 ([2M+Na]$^+$, 56), 428 ([M+K]$^+$, 100), 412 ([M+Na]$^+$, 79). HRMS(FAB+): Calcd for $C_{21}H_{27}NO_6Na$ *m/z* 412.1736; found 412.1722. Elemental analysis. Calcd C, 64.77; H, 6.99; found C, 64.62; H, 7.25. **25b** (slower eluting isomer): mp 139–141°C (heptane/ethyl acetate). IR (film): 3418, 2936, 1748, 1667, 1613, 1585, 1514, 1455, 1392, 1338, 1246, 1178, 1061, 990, 888, 820, 757, 736, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.20–1.27 (1H, m); 1.43–1.55 (1H, m); 1.68–1.97 (4H, m); 1.89 (3H, d, J=1.0 Hz); 2.40 (1H, ddd, J=5.7, 10.8,

17.2 Hz); 2.52 (1H, ddd, J=6.7, 10.8, 17.2 Hz); 3.40–3.50 (2H, m); 3.78 (3H, s); 4.07 (3H, s); 4.34 (1H, d, J=15.3 Hz); 4.44 (1H, d, J=15.3 Hz); 4.52 (1H, d, J=1.0 Hz); 6.82 (2H, d, J=8.6 Hz); 7.28 (2H, d, J=8.6 Hz) ppm. ^{13}C NMR ($CDCl_3$): 8.4, 23.2, 25.6, 29.4, 30.6, 42.9, 54.8, 58.9, 61.4, 67.9, 80.4, 99.2, 113.2 (2C), 129.2 (2C), 129.5, 158.4, 170.5, 173.5, 175.8 ppm. API-ES(+): 801 ($[2M+Na]^+$, 100), 428 ($[M+K]^+$, 46), 412 ($[M+Na]^+$, 85). HRMS (FAB+): Calcd for $C_{21}H_{27}NO_6Na$ m/z 412.1736; found 412.1746. Elemental analysis. Calcd C, 64.77; H, 6.99; found C, 64.61; H, 7.22.

4.1.4. The tricyclic core: ketones 26 and 27. To a stirred solution of DMSO (0.27 mL, 3.74 mmol) in dry CH_2Cl_2 (5 mL) at −60°C, oxalyl chloride (0.78 mL of a 2 M solution in CH_2Cl_2) was added. After 30 min a solution of the mixture of alcohols **25a/25b** (404 mg, 1.04 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred for 30 min at −60°C, then Et_3N (0.87 mL, 6.24 mmol) was added and the reaction mixture was quickly placed at 0°C. After 30 min the reaction was diluted with CH_2Cl_2 and poured into ice-cold water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1N HCl solution, saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). The solvents were removed under reduced pressure and the crude product was used without further purification in the next step. The crude aldehydes were dissolved in dry CH_2Cl_2 (10 mL), and DBU (0.18 mL, 1.22 mmol) was added at rt. The reaction mixture was stirred overnight at rt, diluted with CH_2Cl_2 and washed with 1N HCl solution, saturated $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4), and the solvents were evaporated under reduced pressure to afford a residue that was submitted to Swern conditions. The mixture of aldols was oxidized following the procedure described earlier (DMSO: 0.20 mL, 2.87 mmol; $(COCl)_2$: 0.72 mL, 1.44 mmol; Et_3N: 0.60 mL, 4.32 mmol in 7 mL of CH_2Cl_2) to provide, after chromatography on silica gel (hexanes/EtOAc 1:2 then EtOAc), 195 mg (70%) of a 1:1 mixture of ketones **26** and **27**. **26** (faster eluting isomer): mp 101–104°C (heptane/ethyl acetate). IR (film): 2958, 1770, 1694, 1660, 1613, 1586, 1514, 1462, 1390, 1326, 1248, 1204, 1104, 1076, 969, 941, 895, 878, 816, 752, 662 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.73 (1H, ddd, J=2.4, 8.8, 12.8 Hz); 1.83 (1H, td, J=10.6, 13.3 Hz); 1.84 (3H, s); 2.39–2.62 (4H, m); 2.72–2.81 (2H, m); 3.80 (3H, s); 4.02 (3H, s); 4.14 (1H, d, J=15.8 Hz); 4.84 (1H, d, J=15.8 Hz); 6.85 (2H, d, J=8.7 Hz); 7.11 (2H, d, J=8.7 Hz) ppm. ^{13}C NMR ($CDCl_3$): 8.6, 29.1, 29.2, 31.7, 33.4, 43.1, 55.1, 59.5, 70.9, 89.5, 99.8, 113.7 (2C), 127.6 (2C); 129.7, 158.5, 167.7, 172.2, 176.3, 206.3 ppm. APCI(+): 386 ($[MH]^+$, 100), 278 (15), 121 (35). HRMS (DCI/NH_3). Calcd for $C_{21}H_{24}NO_6$ m/z 386.1604; found 386.1601. **27** (slower eluting isomer): mp 183–185°C (pentane/ethyl ether/CH_2Cl_2). IR (film): 2926, 1770, 1694, 1661, 1612, 1513, 1443, 1392, 1323, 1248, 1177, 1152, 1055, 1008, 948, 896, 810, 734 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.92–1.98 (2H, m); 2.06 (3H, s); 2.32–2.54 (6H, m); 3.79 (3H, s); 3.91 (1H, d, J=16.3 Hz); 4.13 (3H, s); 5.16 (1H, d, J=16.3 Hz); 6.83 (2H, d, J=8.6 Hz); 7.15 (2H, d, J=8.6 Hz). ^{13}C NMR ($CDCl_3$): 8.8, 28.8, 29.1, 30.3, 31.2, 33.7, 43.9, 55.0, 59.7, 70.0, 88.3, 99.5, 113.7 (2C), 127.8 (2C), 158.6, 168.7, 172.0, 175.2, 207.9 ppm. APCI(+): 386 ($[MH]^+$, 100), 278 (20), 121 (50). HRMS (DCI/NH_3). Calcd for $C_{21}H_{24}NO_6$ m/z 386.1604; found 386.1598.

4.1.5. α-Chloroenone 29. To a solution of **26** (54 mg, 0.14 mmol) in EtOAc (2.0 mL), Amberlite IR120 (15 mg) and phenylselenyl chloride (268 mg, 1.4 mmol) were added. After the first 24 h, identical amounts of phenylselenyl chloride and Amberlite IR120 were added. The reaction mixture was stirred for 2 days. Then the reaction was diluted with EtOAc and washed with H_2O, saturated Na_2CO_3 solution, brine and dried (Na_2SO_4). Chromatography on silica gel (hexanes/EtOAc 1:1 then EtOAc) afforded 30 mg (37%) of the chloro-selenide and 15 mg (28%) of **26**. The chloro-selenide was dissolved in 1.4 mL of the mixture MeOH–H_2O (6:1) and was treated with $NaIO_4$ (27 mg, 0.13 mmol) and $NaHCO_3$ (5 mg, 0.064 mmol). The reaction mixture was stirred vigorously for 4 h, diluted with EtOAc, washed with saturated $NaHCO_3$ solution, H_2O and brine, and dried (Na_2SO_4). After removing the solvents the residue was chromatographed on silica gel (hexanes/EtOAc 1:1) to obtain 15 mg (64%) of **29**. **29**: IR (film): 2934, 1772, 1752, 1703, 1664, 1513, 1457, 1386, 1327, 1249, 1146, 1059, 949, 771, 732 cm^{-1}. ^{1}H NMR ($CDCl_3$): 2.00 (3H, s); 2.06 (1H, ddd, J=9.0, 12.0, 13.0 Hz); 2.41 (1H, dd, J=9.0, 16.8 Hz); 2.51 (1H, dd, J=8.0, 13.0 Hz); 2.64 (1H, ddd, J=8.0, 12.0, 16.8 Hz); 3.82 (3H, s); 3.94 (3H, s); 4.05 (1H, d, J=15.5 Hz); 4.95 (1H, d, J=15.5 Hz); 6.88 (2H, d, J=8.6 Hz); 7.02 (1H, s); 7.09 (2H, d, J=8.6 Hz) ppm. ^{13}C NMR ($CDCl_3$): 9.1, 29.5, 32.5, 44.5, 55.3, 59.7, 72.1, 88.4, 100.4, 114.3 (2C), 128.6 (2C), 129.7, 135.4, 156.0, 159.1, 167.8, 172.0, 175.6, 189.8 ppm. APCI(+): 420 ($[M'H]^+$, 22), 418 ($[MH]^+$, 64), 312 (5), 310 (15), 121 (100).

4.1.6. The TBDMS enol ethers 30 and 31. To a stirred solution of **26** (2.21 g, 5.74 mmol) and collidine (7.6 mL, 57.4 mmol) in dry toluene (32 mL) at 0°C, TBDMSOTf (4.2 mL, 18.4 mmol) was added. The reaction mixture was allowed to warm to rt, and was stirred for 8 h, then was cooled at 0°C, diluted with Et_2O and some brine was added. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with 0.3N HCl solution, saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). The solvents were evaporated and the residue afforded upon chromatography (hexanes/EtOAc 1:2 then 1:3) 2.40 g (84%) of **30** and 105 mg (4%) of **26**. **30**: IR (film): 2932, 1760, 1698, 1666, 1513, 1389, 1337, 1247, 1130, 838 cm^{-1}. ^{1}H NMR (C_6D_6): 0.05 (3H, s); 0.10 (3H, s); 0.86 (9H, s); 1.34 (1H, ddd, J=9.4, 11.2, 13.0 Hz); 1.64 (3H, s); 1.79 (1H, dd, J=2.5, 15.2 Hz); 2.07 (1H, ddd, J=1.3, 9.4, 16.8 Hz); 2.48 (1H, ddd, J=8.6, 11.2, 16.8 Hz); 2.52 (1H, dd, J=2.5, 15.2 Hz); 2.63 (1H, ddd, J=1.3, 8.6, 13.0 Hz); 3.22 (3H, s); 3.31 (3H, s); 4.14 (1H, d, J=15.6 Hz); 4.67 (1H, t, J=2.5 Hz); 5.06 (1H, d, J=15.6 Hz); 6.79 (2H, d, J=8.6 Hz); 7.21 (2H, d, J=8.6 Hz) ppm. ^{13}C NMR (C_6D_6): −4.9, −4.8, 8.7, 18.1, 25.5 (3C), 30.0, 32.1, 37.4, 44.1, 54.8, 58.5, 73.9, 92.4, 100.1, 106.5, 114.2 (2C), 128.6 (2C), 132.1, 150.0, 159.2, 169.9, 172.4, 175.7 ppm. APCI(+): 500 ($[MH]^+$, 100). HRMS (DCI/NH_3). Calcd for $C_{27}H_{38}NO_6Si$ m/z 500.2468; found 500.2454. Elemental analysis. Calcd C, 64.90; H, 7.46; found C, 64.96; H, 7.84.

Under the same conditions **31** was obtained in 68% isolated yield. **31**: mp 114–115°C (heptane/ethyl acetate). IR (film): 2931, 2857, 1762, 1694, 1666, 1612, 1513, 1463, 1392, 1321, 1248, 1175, 1132, 1024, 974, 940, 839 cm^{-1}. ^1H NMR (C_6D_6): 0.04 (3H, s); 0.15 (3H, s); 0.89 (9H, s); 1.51 (1H, td, *J*=9.5, 11.9 Hz); 1.76 (3H, s); 2.02 (1H, dd, *J*=2.2, 15.8 Hz); 2.02–2.08 (1H, m); 2.12–2.16 (2H, m); 2.36 (1H, dd, *J*=2.8, 15.8 Hz); 3.27 (3H, s); 3.32 (3H, s); 4.21 (1H, d, *J*=15.6 Hz); 4.60 (1H, t, *J*=2.5 Hz); 5.44 (1H, d, *J*=15.6 Hz); 6.79 (2H, d, *J*=8.6 Hz); 7.34 (2H, d, *J*=8.6 Hz) ppm. ^{13}C NMR (C_6D_6): −4.9, −4.6, 8.7, 18.1, 25.5 (3C), 29.9, 30.0, 38.7, 44.7, 54.8, 58.4, 71.8, 91.4, 99.0, 106.3, 114.1 (2C), 129.2 (2C), 132.6, 149.4, 159.2, 170.7, 172.3, 174.8 ppm. APCI(+): 500 ($[MH]^+$, 100), 392 (7). HRMS (DCI/NH_3). Calcd for $C_{27}H_{38}NO_6Si$ *m/z* 500.2468; found 500.2450. Elemental analysis. Calcd C, 64.90; H, 7.46; found C, 64.98; H, 7.67.

4.1.7. Installation of the double bond to yield 32 and 33. The TBDMS enol ethers (2.4 g, 4.81 mmol of **30**; 3.0 g, 6.13 mmol of **31**) were dissolved in dry DMSO (20 mL/mmol) and 10%$Pd(OAc)_2$ was added. The reaction mixture was stirred at 80°C under oxygen atmosphere for 45 h (**30**) and for 53 h (**31**). Additional amounts of $Pd(OAc)_2$ were added up to 0.85 equiv. The reaction mixture was cooled to rt and diluted with EtOAc and saturated $NaHCO_3$ solution was added. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with H_2O, brine and dried (Na_2SO_4). Chromatography on silica gel (hexanes/EtOAc 1:2 for **32** or EtOAc for **33**) afforded 1.7 g (93%) of **32** and 2.1 g (89%) of **33**. **32**: mp 142–143°C (heptane/ethyl acetate). IR (film): 2940, 1769, 1732, 1704, 1662, 1514, 1386, 1343, 1248, 1144, 1070 cm^{-1}. ^1H NMR ($CDCl_3$): 1.95 (3H, s); 2.03 (1H, ddd, *J*=8.9, 12.1, 13.0 Hz); 2.35 (1H, dd, *J*=8.9, 16.8 Hz); 2.44 (1H, dd, *J*=7.9, 13.0 Hz); 2.64 (1H, ddd, *J*=7.9, 12.1, 16.8 Hz); 3.78 (3H, s); 3.87 (3H, s); 4.10 (1H, d, *J*=15.6 Hz); 4.88 (1H, d, *J*=15.6 Hz); 6.33 (1H, d, *J*=6.3 Hz); 6.84 (2H, d, *J*=8.6 Hz); 7.07 (2H, d, *J*=8.6 Hz); 7.21 (1H, d, *J*=6.3 Hz) ppm. ^{13}C NMR ($CDCl_3$): 8.9, 29.4, 32.8, 44.4, 55.2, 59.3, 73.4, 89.5, 99.7, 114.0 (2C), 128.4 (2C), 129.8, 132.5, 158.9, 162.5, 168.1, 172.6, 176.0, 195.4 ppm. APCI (+): 384 ($[MH]^+$, 100), 276 (25), 121 (55). HRMS (DCI/NH_3). Calcd for $C_{21}H_{22}NO_6$ *m/z* 384.1447; found 384.1434. Elemental analysis. Calcd C, 65.79; H, 5.52. Found C, 65.97; H, 5.69. **33**: mp 153–154°C (heptane/ethyl acetate/CH_2Cl_2). IR (film): 2925, 1770, 1732, 1698, 1662, 1514, 1389, 1321, 1247, 1176, 1063 cm^{-1}. ^1H NMR ($CDCl_3$): 2.08 (3H, s); 2.11–2.19 (1H, m); 2.31–2.54 (3H, m); 3.64 (1H, d, *J*=15.9 Hz); 3.79 (3H, s); 4.09 (3H, s); 5.13 (1H, d, *J*=15.9 Hz); 6.26 (1H, d, *J*=6.1 Hz); 6.79 (2H, d, *J*=8.6 Hz); 7.02 (1H, d, *J*=6.1 Hz); 7.05 (2H, d, *J*=8.6 Hz) ppm. ^{13}C NMR ($CDCl_3$): 8.8, 27.7, 29.2, 44.1, 55.1, 59.5, 72.0, 85.9, 98.9, 113.8 (2C), 129.0 (2C), 129.7, 133.7, 158.7, 163.6, 169.2, 172.4, 174.5, 197.9 ppm. APCI (+): 384 ($[MH]^+$, 100), 276 (52), 121 (45). HRMS (DCI/NH_3). Calcd for $C_{21}H_{22}NO_6$ *m/z* 384.1447; found 384.1449. Elemental analysis. Calcd C, 65.79; H, 5.52. Found C, 64.12; H, 5.49.

4.1.8. 1,4-Addition to 32 and 33. To a stirred mixture of magnesium turnings (101 mg, 4.16 mmol) and a catalytic amount of I_2 in dry THF (2.0 mL) under reflux, some drops of a solution of 1-[(4-bromobutoxy)methyl]-4-methoxy-benzene (568 mg, 2.08 mmol) in THF (2.0 mL) were added. Once the iodine color disappeared, the remaining bromide solution was added dropwise (5–10 min), and the reaction mixture was stirred for an additional 20–25 min. The Grignard reagent was added dropwise to a stirred suspension of $CuBr{\cdot}Me_2S$ (5.0 mg, 0.024 mmol) and HMPA (0.23 mL, 1.30 mmol) in THF (1.0 mL) at −78°C. After 10 min, a solution of **32** (200 mg, 0.52 mmol) and TMSCl (0.13 mL, 1.04 mmol) in THF (9.0 mL) was added dropwise at −78°C. The reaction mixture was stirred vigorously for 30 min then quenched with saturated NH_4Cl solution (10 mL) and diluted with Et_2O. The layers were separated, the aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine and dried (Na_2SO_4). The solvents were evaporated under reduced pressure, and the residue was chromatographed (hexanes/EtOAc 1:1 then 1:2) to obtain 223 mg (74%) of a 6.4:1 mixture of **35a/b**. **35a**: IR (film): 2935, 2860, 1770, 1694, 1660, 1612, 1585, 1514, 1456, 1390, 1322, 1247, 1175, 1070, 1033, 873, 819, 753 cm^{-1}. ^1H NMR ($CDCl_3$): 0.85–0.95 (1H, m); 0.99–1.06 (2H, m); 1.20–1.40 (3H, m); 1.75 (3H, s); 1.97–2.09 (3H, m); 2.36 (1H, ddd, *J*=2.6, 9.7, 17.1 Hz); 2.74 (1H, t, *J*=9.7 Hz); 2.76 (1H, dd, *J*=9.2, 19.7 Hz); 2.93–3.02 (1H, m); 3.33 (2H, dt, *J*=2.1, 6.2 Hz); 3.76 (3H, s); 3.81 (3H, s); 3.98 (3H, s); 4.21 (1H, d, *J*=15.6 Hz); 4.38 (1H, d, *J*=11.6 Hz); 4.42 (1H, d, *J*=11.6 Hz); 4.68 (1H, d, *J*=15.6 Hz); 6.83 (2H, d, *J*=8.6 Hz); 6.89 (2H, d, *J*=8.6 Hz); 7.13 (2H, d, *J*=8.6 Hz); 7.25 (2H, d, *J*=8.6 Hz) ppm. ^{13}C NMR ($CDCl_3$): 8.8, 23.2, 25.0, 29.1, 29.2, 29.8, 35.9, 40.2, 43.1, 55.2 (2C), 59.7, 69.5, 72.5, 74.7, 90.9, 100.3, 113.7 (2C), 113.8 (2C), 128.5 (2C), 129.3 (2C), 130.1, 130.5, 158.8, 159.2, 167.8, 172.1, 176.8, 205.9 ppm. APCI(+): 578 ($[MH]^+$, 100), 458 (45), 121 (40). HRMS (DCI/NH_3). Calcd for $C_{33}H_{40}NO_8$ *m/z* 578.2754; found 578.2741.

Under the same conditions, from 1.4 g (3.68 mmol) of **33** were obtained 1.37 g (57%) of **36** and 674 mg (32%) of **37** (chromatography on silica gel (hexanes/EtOAc 1:2 then EtOAc)). **36**: ^1H NMR ($CDCl_3$): 0.17 (9H, s); 0.69–0.75 (1H, m); 0.99–1.05 (1H, m); 1.17–1.31 (4H, m); 1.87–1.95 (1H, m); 1.97 (3H, s); 2.02–2.19 (2H, m); 2.23–2.29 (1H, m); 2.63–2.67 (1H, m); 3.20–3.25 (2H, m); 3.67 (3H, s); 3.73 (3H, s); 4.04 (3H, s); 4.12 (1H, d, *J*=15.8 Hz); 4.31 (2H, s); 4.99 (1H, d, *J*=2.5 Hz); 5.02 (1H, d, *J*=15.8 Hz); 6.73 (2H, d, *J*=8.4 Hz); 6.81 (2H, d, *J*=8.6 Hz); 7.13 (2H, d, *J*=8.6 Hz); 7.17 (2H, d, *J*=8.4 Hz) ppm. ^{13}C NMR ($CDCl_3$): −0.3 (3C), 8.6, 24.0, 24.5, 29.3 (2C), 30.1, 44.2, 44.8, 54.9 (2C), 59.1, 69.4, 72.1, 74.8, 93.3, 99.9, 111.3, 113.4 (4C), 128.5 (2C), 128.9 (2C), 130.3, 131.3, 147.9, 158.3, 158.8, 169.9, 172.4, 175.8 ppm. APCI(+): 650 ($[MH]^+$, 100), 578 (20). **37**: mp 147–148°C (heptane/CH_2Cl_2). IR (film): 2934, 2858, 1768, 1694, 1661, 1612, 1585, 1514, 1456, 1393, 1334, 1303, 1247, 1178, 1098, 1035, 1006, 930, 909, 820, 753, 735, 668 cm^{-1}. ^1H NMR ($CDCl_3$): 0.60–0.69 (1H, m); 0.73–0.80 (1H, m); 0.88–0.98 (1H, m); 1.10–1.19 (2H, m); 1.20–1.29 (1H, m); 1.92–2.01 (2H, m); 2.05 (3H, s); 2.20 (1H, ddd, *J*=3.2, 7.7, 13.0 Hz); 2.35–2.50 (2H, m); 2.76–2.87 (2H, m); 3.20–3.27 (2H, m); 3.74 (3H, s); 3.82 (3H, s); 4.14 (3H, s); 4.34 (1H, d, *J*=15.4 Hz); 4.36 (1H, d, *J*=11.6 Hz); 4.38 (1H, d, *J*=11.6 Hz); 5.04 (1H, d, *J*=15.4); 6.79 (2H, d, *J*=8.6 Hz);

6.89 (2H, d, J=8.6 Hz); 7.23 (2H, d, J=8.6 Hz); 7.27 (2H, d, J=8.6 Hz) ppm. ^{13}C NMR ($CDCl_3$): 9.3, 20.5, 24.8, 28.8, 29.0, 29.5, 39.4, 40.6, 44.3, 55.0, 55.1, 59.7, 69.4, 72.3, 73.5, 89.9, 103.1, 113.6 (4C), 129.0 (2C), 129.4 (2C), 130.4, 130.6, 158.8, 159.0, 168.2, 170.8, 176.3, 204.7 ppm. APCI(+): 578 ($[MH]^+$, 100), 458 (5), 408 (8), 241 (9), 121 (10). HRMS (DCI/NH_3). Calcd for $C_{33}H_{40}NO_8$ m/z 578.2754; found 578.2750.

4.1.9. *O*-Alkylation of 35a to yield 38. To a stirred solution of **35a** (48 mg, 0.083 mmol) in dry THF (1.0 mL) at −78°C, was added dropwise 0.15 mL of a 0.65 M solution of LDA in THF (freshly prepared). The reaction mixture was stirred for 1 h at −78°C then a solution of phenyl benzenethiosulfonate (42 mg, 0.17 mmol) in THF (0.5 mL) was added. The −78°C bath was changed to an ice bath and the reaction was stirred for an additional 1 h. After quenching with saturated NH_4Cl solution and extracting with EtOAc, the combined organic layers were washed with 1N HCl solution, saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). Chromatography on silica gel (hexanes/EtOAc 1:1) afforded 26 mg (45%) of the α-sulfide and 10 mg (21%) of **35a**. 19 mg (0.028 mmol) of the above sulfide were dissolved in THF (1.0 mL), and deprotonated with an excess of 80% NaH at rt. After 40 min, an excess of MeI was added, and the reaction mixture was stirred for 9 h then was poured into cold water, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried (Na_2SO_4). The residue was chromatographed on silica gel (hexanes/EtOAc 1:1 then 1:2) to afford 12 mg (61%) of **38**. **38**: ^{1}H NMR ($CDCl_3$): 0.50–0.60 (1H, m); 1.05–1.10 (1H, m); 1.20–1.38 (4H, m); 1.84 (3H, s); 2.06 (1H, td, J=10.0, 13.3 Hz); 2.33 (1H, bdd, J=10.0, 16.9 Hz); 2.50 (1H, bdd, J=10.0, 13.3 Hz); 2.64 (1H, td, J=10.0, 16.9 Hz); 3.01 (1H, dd, J=4.1, 7.2 Hz); 3.19 (2H, bt, J=6.0 Hz); 3.74 (3H, s); 3.81 (3H, s); 3.89 (3H, s); 4.04 (3H, s); 4.19 (1H, d, J=15.9 Hz); 4.30 (1H, d, J=11.6 Hz); 4.36 (1H, d, J=11.6 Hz); 4.72 (1H, d, J=15.9 Hz); 6,79 (2H, d, J=8.7 Hz); 6.87 (2H, d, J=8.7 Hz); 7.03 (2H, d, J=8.7 Hz); 7.15–7.26 (7H, m) ppm. ^{13}C NMR ($CDCl_3$): 8.8, 24.9, 25.1, 28.9, 29.3, 30.0, 43.8, 46.1, 55.3 (2C), 59.2, 59.7, 69.7, 72.4, 77.1, 92.3, 100.4, 112.0, 113.7 (2C), 113.8 (2C), 126.1, 127.8 (2C), 127.9 (2C), 129.0 (2C), 129.2 (2C), 130.1, 130.7, 135.7, 155.7, 158.6, 159.1, 169.5, 172.7, 177.1 ppm.

4.1.10. Mannich reaction to yield 39a/b and 40. From the ketones **35a/b** or **37**: to a stirred suspension of 35% KH (10–20-fold excess) in dry THF, a solution of the ketone in dry THF was added dropwise at 0°C. The reaction mixture (0.04 M) was stirred for 1 h at 0°C then an excess of dimethylmethyleneammonium trifluoroacetate was added (5.0–10.0 mL/mmol). The reaction was stirred overnight at rt, and was quenched with 10% Na_2CO_3 solution at 0°C and extracted with EtOAc. The combined organic layers were washed with brine and dried (Na_2SO_4). The solvents were evaporated, and the residue was chromatographed on silica gel (hexanes/EtOAc 1:2 then 1:3) to obtain **39a/b** in 67% yield or **40** in 85% yield.

From the silyl enol ether **36**: to a stirred solution of **36** (802 mg, 1.24 mmol) in dry CH_2Cl_2 (20 mL), an excess of dimethylmethyleneammonium trifluoroacetate was added (0.80 mL/mmol) at rt. The reaction was stirred for 3 h, and was quenched with 10% Na_2CO_3 solution at 0°C and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried (Na_2SO_4). The solvents were evaporated, and the residue was chromatographed on silica gel (hexanes/EtOAc 1:2) to give 703 mg (96%) of **40**.

39a: IR (film): 2934, 1767, 1697, 1661, 1612, 1513, 1457, 1388, 1322, 1248, 1176, 1148, 1034, 819 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.66–0.76 (1H, m); 1.12–1.24 (1H, m); 1.27–1.50 (4H, m); 1.72 (3H, s); 1.82 (1H, td, J=10.0, 13.5 Hz); 1.96 (1H, ddd, J=2.3, 10.0, 13.5 Hz); 2.32 (1H, ddd, J=2.3, 10.0, 17.2 Hz); 2.68 (1H, td, J=10.0, 17.2 Hz); 3.28–3.38 (3H, m); 3.72 (3H, s); 3.76 (3H, s); 3.93 (3H, s); 4.17 (1H, d, J=15.7 Hz); 4.37 (2H, s); 4.68 (1H, d, J=15.7 Hz); 5.54 (1H, d, J=3.5 Hz); 6.25 (1H, d, J=3.5 Hz); 6.80 (2H, d, J=8.5 Hz); 6.85 (2H, d, J=8.6 Hz); 7.08 (2H, d, J=8.6 Hz); 7.22 (2H, d, J=8.5 Hz) ppm. ^{13}C NMR ($CDCl_3$): 8.7, 23.4, 25.5, 28.1, 29.0, 29.9, 42.5, 43.1, 55.1 (2C), 59.5, 69.1, 72.4, 73.6, 89.6, 100.3, 113.6 (2C), 113.7 (2C), 121.7, 128.2 (2C), 129.1 (2C), 129.6, 130.3, 144.1, 158.7, 159.0, 168.1, 172.2, 176.8, 195.0 ppm. APCI(+): 590 ($[MH]^+$, 100), 470 (56), 362 (8), 241 (6), 121 (28). HRMS (DCI/NH_3). Calcd for $C_{34}H_{40}NO_8$ m/z 590.2754; found 590.2753.

40: IR (film): 2934, 2361, 1766, 1737, 1696, 1612, 1513, 1458, 1392, 1333, 1246, 1176, 1097, 1035, 987, 818 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.30–0.40 (1H, m); 1.00 (1H, dt, J=4.7, 12.8 Hz); 1.12–1.34 (4H, m); 1.80 (1H, td, J=10.2, 13.6 Hz); 2.02 (3H, s); 2.09 (1H, ddd, J=2.8, 8.1, 13.6 Hz); 2.30–2.45 (2H, m); 3.13–3.26 (3H, m); 3.69 (3H, s); 3.76 (3H, s); 4.11 (3H, s); 4.32 (1H, d, J=15.7 Hz); 4.33 (2H, s); 5.01 (1H, d, J=15.7 Hz); 5.51 (1H, d, J=3.0 Hz); 6.21 (1H, d, J=3.4 Hz); 6.76 (2H, d, J=8.5 Hz); 6.84 (2H, d, J=8.4 Hz); 7.19 (2H, d, J=8.4 Hz); 7.20 (2H, d, J=8.5 Hz) ppm. ^{13}C NMR ($CDCl_3$): 9.3, 21.1, 25.2, 27.8, 29.0, 29.9, 44.3, 44.9, 55.0, 55.1, 59.7, 69.2, 72.3, 72.4, 88.8, 103.1, 113.5 (2C), 113.6 (2C), 121.7, 129.0 (4C), 130.2, 130.3, 144.6, 158.8, 159.0, 168.3, 170.9, 176.5, 193.8 ppm. APCI(+): 590 ($[MH]^+$, 100). HRMS (DCI/NH_3). Calcd for $C_{34}H_{40}NO_8$ m/z 590.2754; found 590.2738.

4.1.11. Unexpected cyclization to form 41. To a stirred solution of **37** (115 mg, 0.20 mmol) and Et_3N (0.28 mL, 2.0 mmol) in dry THF (5.0 mL), TMSOTf (0.1 mL, 0.55 mmol) was added at 0°C. The reaction mixture was stirred under argon at 0°C for 3 h then quenched with saturated $NaHCO_3$ solution, and diluted with Et_2O. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue chromatographed on silica gel (hexanes/EtOAc 1:2 then 1:3) to afford 28 mg (24%) of **41** and 61 mg (53%) of **37**. **41**: mp 168–169°C (heptane/CH_2Cl_2). IR (film): 2932, 1795, 1756, 1704, 1588, 1513, 1462, 1302, 1247, 1176, 1096, 1038, 821 cm^{-1}. ^{1}H NMR (C_6D_6): 0.35–0.44 (1H, m); 0.54–0.67 (2H, m); 0.82–0.94 (1H, m); 1.13–1.18 (2H, m); 1.42 (1H, d, J=10.2 Hz); 1.48 (3H, d, J=7.5 Hz); 1.56 (1H, dd, J=11.5, 18.5 Hz); 1.68 (1H, d, J=10.2 Hz); 1.90–1.98 (1H, m); 2.26 (1H, dd, J=7.8, 18.5 Hz); 2.67 (3H, s); 2.76 (1H, q, J=7.5 Hz); 2.92 (1H, bs); 3.11–3.15 (2H, m); 3.28 (3H, s); 3.30 (3H, s); 3.66 (1H, d,

J=15.5 Hz); 4.29 (1H, d, J=11.6 Hz); 4.33 (1H, d, J=11.6 Hz); 5.18 (1H, d, J=15.5 Hz); 6.69 (2H, d, J=8.6 Hz); 6.84 (2H, d, J=8.6 Hz); 7.03 (2H, d, J=8.6 Hz); 7.25 (2H, d, J=8.6 Hz) ppm. ^{13}C NMR (C_6D_6): 12.3, 24.9, 29.9, 31.0, 34.1, 38.7, 42.4, 43.8, 44.8, 50.1, 52.0, 54.8 (2C), 69.7, 72.7, 77.3, 91.3, 92.6, 114.0 (2C), 114.1 (2C), 129.3 (2C), 129.4 (2C), 131.0, 131.2, 159.4, 159.7, 174.1, 174.3, 204.7 ppm. APCI(+): 578 ([MH]$^+$, 100), 536 (14), 327 (38), 121 (30). HRMS (DCI/NH_3). Calcd for $C_{33}H_{40}NO_8$ m/z 578.2754; found 578.2733. Elemental analysis. Calcd C, 68.61; H, 6.80. Found C, 68.23; H, 6.93. X-Ray analysis: The crystal structure has been deposited at the Cambridge Crystallographic Data Centre. Deposition number: CCDC 171377.

4.1.12. Removal of PMB groups to yield 44a/b and 45. To a stirred solution of the α-methylene ketone **39a/b** or **40** in the mixture CH_3CN–H_2O (3:1) (40 mL/mmol), was added CAN (6.0 equiv.) at rt. The mixture was stirred for 1.5 h then was poured into water, and extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). The residue was chromatographed on silica gel (EtOAc/2-propanol 8:1 then 4:1) to afford **44a/b** in 80% yield or **45** in 75% yield.**44a**: IR (film): 3250, 2935, 1767, 1698, 1660, 1326, 1042 cm^{-1}. ^{1}H NMR (CD_3OD): 1.51–1.80 (6H, m); 1.97 (1H, ddd, J=3.0, 9.9, 13.3 Hz); 2.02 (3H, s); 2.02–2.11 (1H, m); 2.28 (1H, ddd, J=3.0, 9.9, 17.2 Hz); 2.45 (1H, td, J=9.9, 17.2 Hz); 3.36–3.41 (1H, m); 3.60 (2H, t, J=5.9 Hz); 4.15 (3H, s); 5.68 (1H, d, J=2.0 Hz); 6.27 (1H, d, J=2.0 Hz) ppm. ^{13}C NMR (CD_3OD): 11.1, 26.5, 28.6, 31.2, 33.7, 36.2, 47.9, 63.2, 64.8, 72.9, 94.6, 101.5, 124.4, 148.6, 173.4, 178.0, 183.1, 199.2 ppm. APCI(+): 350 ([MH]$^+$, 100), 222 (13), 156 (8), 122 (36). HRMS (DCI/NH_3). Calcd for $C_{18}H_{24}NO_6$ m/z 350.1604; found 350.1599.

45: IR (film): 3251, 2934, 1760, 1697, 1661, 1455, 1338, 1102, 998, 734 cm^{-1}. ^{1}H NMR (CD_3OD): 1.49–1.75 (6H, m); 1.97–2.04 (1H, m); 2.07 (3H, s); 2.21–2.32 (3H, m); 3.10–3.15 (1H, m); 3.59 (2H, t, J=6.3 Hz); 4.21 (3H, s); 5.68 (1H, d, J=3.5 Hz); 6.25 (1H, d, J=3.5 Hz) ppm. ^{13}C NMR (CD_3OD): 9.1, 21.7, 26.0, 28.0, 31.0, 33.8, 47.5, 60.8, 62.5, 70.6, 88.3, 103.9, 121.9, 146.5, 170.1, 173.8, 180.5, 196.1 ppm. APCI(+): 350 ([MH]$^+$, 100), 222 (10). HRMS (DCI/NH_3). Calcd for $C_{18}H_{24}NO_6$ m/z 350.1604; found 350.1603.

4.1.13. Isomerization of the double bond, mesylation and ring closure. A stirred mixture of **44a/b** or **45** and a catalytic amount of rhodium trichloride hydrate in EtOH–H_2O (10:1) (10 mL/mmol) was kept under reflux for 36 or 24 h, respectively. The reaction mixture was allowed to cool to rt and the solvents were evaporated under reduced pressure. The residue was chromatographed on silica gel (EtOAc/2-propanol 4:1) to give **46** in 66% yield or **47** in 69% yield. These compounds were characterized as the corresponding mesylates.

4.1.14. Less polar mesylate 48. To a stirred solution of **46** (43 mg, 0.12 mmol), pyridine (0.20 mL, 2.48 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (1.0 mL), MsCl (0.1 mL, 1.29 mmol) was added at 0°C. The reaction mixture was stirred for 1 h at 0°C then was quenched with saturated $NaHCO_3$ solution, and was stirred for an additional 10 min. CH_2Cl_2 was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1N HCl solution, saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). The solvents were evaporated under reduced pressure and the residue was chromatographed on silica gel (EtOAc then EtOAc/2-propanol 16:1) to afford 36 mg (71%) of **48**. **48**: IR (film): 3206, 2937, 1766, 1699, 1662, 1456, 1390, 1350, 1329, 1255, 1174, 1150, 1075, 980, 930, 850, 802, 731 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.64–1.74 (2H, m); 1.76–1.86 (2H, m); 1.81 (3H, s); 1.98–2.07 (1H, m); 2.00 (3H, s); 2.27 (1H, dd, J=9.6, 16.8 Hz); 2.35–2.40 (2H, m); 2.45–2.61 (2H, m); 3.03 (3H, s); 4.01 (3H, s); 4.22–4.30 (2H, m); 7.53 (1H, bs) ppm. ^{13}C NMR ($CDCl_3$): 8.7, 8.8, 24.2, 25.6, 29.0, 29.5, 30.7, 37.4, 59.7, 69.2, 69.6, 90.3, 97.9, 137.2, 168.0, 171.0, 173.5, 179.1, 194.9 ppm. APCI(+): 428 ([MH]$^+$, 100), 332 (15), 122 (12).

4.1.15. More polar mesylate 49. To a stirred solution of **47** (62 mg, 0.18 mmol), pyridine (0.20 mL, 2.48 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (3.0 mL), MsCl (0.1 mL, 1.29 mmol) was added at 0°C. The reaction mixture was stirred for 4 h at 0°C then was quenched with saturated $NaHCO_3$ solution, and was stirred for an additional 10 min. CH_2Cl_2 was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1N HCl solution, saturated $NaHCO_3$ solution, brine and dried (Na_2SO_4). The solvents were evaporated under reduced pressure. 64 mg (83%) of **49** were isolated after chromatography (EtOAc/2-propanol 8:1). **49**: IR (film): 3341, 2935, 1765, 1704, 1662, 1451, 1390, 1347, 1173, 1109, 1073, 1003, 934, 860, 801, 731 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.65–1.75 (3H, m); 1.84 (3H, s); 1.84–1.90 (1H, m); 2.08 (3H, s); 2.15 (1H, td, J=9.3, 13.4 Hz); 2.29 (1H, td, J=9.0, 17.1 Hz); 2.37–2.46 (2H, m); 2.48–2.58 (2H, m); 3.05 (3H, s); 4.14 (3H, s); 4.28 (2H, t, J=6.1 Hz); 6.41 (1H, bs) ppm. ^{13}C NMR ($CDCl_3$): 8.8, 9.2, 24.7, 26.0, 27.7, 29.2, 37.4, 59.7, 68.8, 69.7, 77.2, 85.3, 101.9, 137.6, 168.5, 171.6, 172.3, 177.3, 196.1 ppm. APCI(+): 428 ([MH]$^+$, 100), 332 (15).

4.1.16. Stemonamide (1). To a stirred suspension of NaH (15-fold excess, previously washed with dry hexane) in THF (0.5 mL), a solution of **48** (36 mg, 0.084 mmol) in dry THF (3.5 mL) was added. The reaction mixture was stirred at rt for 2 days then at 0°C was diluted with Et_2O, and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine and dried (Na_2SO_4). After removal of the solvents, the residue was chromatographed on silica gel (EtOAc/2-propanol 16:1) to afford 13 mg (46%) of (±)-**1** and 5 mg (14%) of **48**. (±)-**1**: colorless crystals, mp 240–241°C (EtOAc/CH_2Cl_2). IR (film): 2925, 1765, 1698, 1661, 1456, 1389, 1326, 1145, 1075, 1006, 858 cm^{-1}. ^{1}H NMR ($CDCl_3$): 1.22–1.44 (2H, m); 1.81 (1H, bd, J=17.0 Hz); 1.84 (3H, s); 1.93 (1H, dt, J=8.8, 12.5 Hz); 1.99 (3H, s); 2.05–2.16 (2H, m); 2.27 (1H, dd, J=8.8, 16.6 Hz); 2.34 (1H, dd, J=7.8, 12.5 Hz); 2.58 (1H, ddd, J=7.8, 12.5, 16.6 Hz); 2.82 (1H, bt, J=13.0 Hz); 2.97 (1H, bdd, J=5.8, 12.8 Hz); 3.97 (3H, s); 4.16 (1H, bd, J=14.4 Hz) ppm. ^{13}C NMR ($CDCl_3$): 8.4, 9.1, 27.3, 27.4, 29.8, 30.1, 31.9, 41.2,

59.2, 74.5, 90.1, 99.6, 136.9, 168.6, 170.9, 172.9, 175.8, 196.5 ppm. APCI(+): 663 ($[2MH]^+$, 10), 332 ($[MH]^+$, 100), 207 (9), 125 (12). HRMS (DCI/NH_3). Calcd for $C_{18}H_{22}NO_5$ *m/z* 332.1498; found 332.1507. Elemental analysis. Calcd C, 65.24; H, 6.39. Found C, 65.53; H, 6.58. X-Ray analysis: the crystal structure has been deposited at the Cambridge Crystallographic Data Centre. Deposition number: CCDC 171376.

4.1.17. Isostemonamide (2). A solution of **49** (64 mg, 0.15 mmol) in dry THF (6.0 mL) was added over a stirred suspension of NaH (15-fold excess, previously washed with dry hexane) in THF (2.0 mL). The reaction mixture was stirred at rt for 5 h then at 0°C diluted with Et_2O, and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc, and the combined organic layers washed with brine and dried (Na_2SO_4). After removal of the solvents, the residue was chromatographed on silica gel (EtOAc/2-propanol 16:1) to afford 35 mg (70%) of (±)-**2**. (±)-**2**: colorless crystals, mp 225–227°C (EtOAc/CH_2Cl_2). IR (film): 2926, 2360, 1766, 1698, 1661, 1450, 1393, 1331, 1248, 1165, 1126, 1073, 1036, 1006, 963, 734 cm^{-1}. ^1H NMR ($CDCl_3$): 1.22–1.43 (2H, m); 1.76 (1H, bd, *J*=14.2 Hz); 1.84 (3H, s); 1.90 (1H, dt, *J*=9.1, 13.0 Hz); 2.05 (3H, s); 2.01–2.04 (2H, m); 2.24 (1H, ddd, *J*=7.1, 13.0, 16.5 Hz); 2.33 (1H, dd, *J*=9.1, 16.5 Hz); 2.59 (1H, dd, *J*=7.1, 13.0 Hz); 2.90–2.98 (2H, m); 4.13 (3H, s); 4.14 (1H, bd, *J*=15.0 Hz) ppm. ^{13}C NMR ($CDCl_3$): 8.3, 9.2, 26.9, 27.6, 27.9, 29.4, 29.7, 42.3, 59.8, 73.5, 86.4, 102.7, 136.6, 168.7, 171.7, 172.6, 174.6, 196.9 ppm. APCI(+): 663 ($[2MH]^+$, 16), 332 ($[MH]^+$, 100). HRMS (DCI/NH_3). Calcd for $C_{18}H_{22}NO_5$ *m/z* 332.1498; found 332.1495. Elemental analysis. Calcd C, 65.24; H, 6.39. Found C, 65.36; H, 6.59. X-Ray analysis: the crystal structure has been deposited at the Cambridge Crystallographic Data Centre. Deposition number: CCDC 171378.

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