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Thirty-five years of synthetic studies directed towards the histrionicotoxin family of alkaloids†

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This article brings together for the first time reviews of all the synthetic attempts towards the spirocyclic histrionicotoxin alkaloids published since the discovery of the group in 1971. This covers 5 total syntheses of the fully unsaturated parent alkaloid HTX-283A, 7 total syntheses of perhydrohistrionicotoxin, 15 total syntheses of other members of this alkaloid family, 25 formal syntheses, and 19 partial syntheses involving the successful formation of the core azaspirocyclic structure but lacking advancement towards the target structure.

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† The authors would like to dedicate this review to Professor Timothy Gallagher, on the occasion of his 50th birthday.

1 Introduction

The histrionicotoxins (HTX) are a family of spirocyclic alkaloids originally isolated from skin extracts of the Colombian poison

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Alex Sinclair

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Robert Stockman was born in Castle Cary, Somerset, UK in 1971. He obtained a BSc (Hons) in Chemistry at the University of Bath in 1994, which incorporated a year spent in the Process Chemistry group at SmithKline Beecham in Great Burgh. He then moved to the University of Bristol to undertake a PhD in the group of Professor Tim Gallagher, studying the utility of pyrrolidin-3-ones as building blocks for the synthesis of indolizidines and phakellin. In January 1998, he moved to work as a postdoctoral fellow with Professor Philip Magnus, FRS, at the University of Texas at Austin, where he worked on the syntheses of nakadomarin and manzamine A. In July 1999 he was appointed as Lecturer in Organic Chemistry at the University of East Anglia. His research interests encompass the development of new methods for the asymmetric synthesis of functionalised heterocycles and the use of combined two-directional synthesis/cascade approaches for target- and diversity-oriented synthesis.

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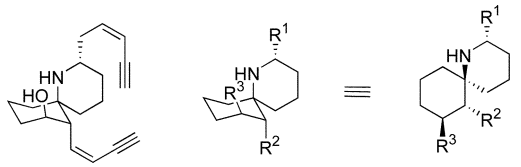
arrow frog *Dendrobates histrionicus.* In 1971, Witkop *et al.* isolated 200 mg of a mixture of six alkaloids from the skin extracts of 1110 frogs, and the chemical structures of the two major fractions (HTX-283A **1** and HTX-285A **3**) were identified by a combination of mass spectrometry, NMR and X-ray crystal analysis.[1] Since this time, the other members of this alkaloid family have also been identified,[2] and their structures are summarised in Table 1 (compounds **1–15**). Also included are four synthetic derivatives (Table 1, compounds **16–19**), which we will also cover in this review. The compounds of this family share the unique core spiropiperidine structure, and vary only in the length and degree of saturation present in the two side chains, with the exception of the three deoxygenated members (Table 1, entries 13–15).

Table 1 Structures of the histrionicotoxins



HTX 283A **1**

Alkaloid	R^1	R^2	R^3
Histrionicotoxin (HTX-283A) **1**			OH
Dihydrohistrionicotoxin (HTX-285E) **2**			OH
Isodihydohistrionicotoxin (HTX-285A) **3**			OH
Neodihydrohistrionicotoxin (HTX-285B) **4**			OH
Allodihydrohistrionicotoxin (HTX-285C) **5**			OH
Tetrahydrohistrionicotoxin (HTX-287B) **6**			OH
Isotetrahydrohistrionicotoxin (HTX-287A) **7**			OH
Allotetrahydrohistrionicotoxin (HTX-287D) **8**			OH
Octahydrohistrionicotoxin (oHTX) **9**			OH
Δ^{17}-*trans*-HTX **10**			OH
(HTX-259A) **11**			OH
(HTX-235A) **12**			OH
(HTX-219A) **13**			H
(HTX-243A) **14**			H
(HTX-269B) **15**			H
Perhydrohistrionicotoxin (pHTX) **16**			OH
7-Debutyl-perhydrohistrionicotoxin **17**		H	OH
2-Depentyl-perhydrohistrionicotoxin **18**	H		OH
2-Depentyl-7-debutyl-perhydrohistrionicotoxin **19**	H	H	OH

Significant biological interest has been shown in this family of compounds due to their unusual effects as selective non-competitive inhibitors of the neuromuscular, ganglionic and central neuronal nicotinic acetylcholine receptors, and thus they have become important as neurophysiological research tools.[3]

The histrionicotoxins are found at extremely low natural abundances (<180 μg per frog). Attempts to breed the frogs in captivity in order to determine a plausible biosynthetic pathway have failed to date. Captive frogs do not secrete these toxins, indicating that the frogs probably accumulate these alkaloids from as yet unknown dietary sources, such as ants and mites.[4] The frogs are now protected under the Convention on International Trade in Endangered Species (CITES).

The unique neurophysiological properties of the histrionicotoxin group, when coupled with their intriguing structure, have prompted a large number of synthetic approaches towards the core spiropiperidine ring system, along with a number of successful total syntheses of both the parent HTXs and synthetic derivatives. This review summarises the synthetic approaches, covering the key total syntheses mentioned in previous reviews[5] and those published thereafter.

The synthetic approaches will be classified according to the last bond formed in order to generate the core spiropiperidine system, with any stereo- and regiochemical control being discussed on an individual basis. The first set of approaches (Fig. 1, A–D) start from a functionalised carbocyclic system to which the heterocyclic ring is fused to form the core spirocycle. The second set of approaches (Fig. 1, E and F) start with a heterocyclic system, and the carbocyclic ring is then fused onto this, generating the core spirocycle. Where these classes are excessively large, they are further sub-classified according to the nitrogen functionality prior to the spirocyclisation step.

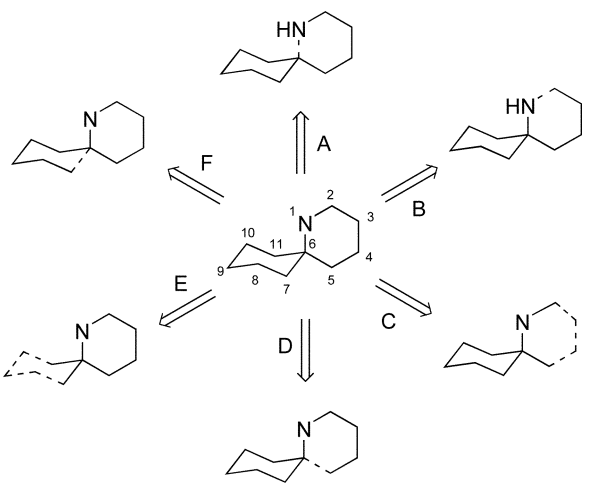
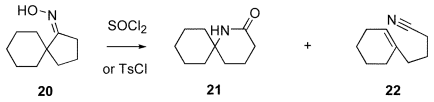


Fig. 1 Classification of synthetic approaches to the histrionicotoxins.

2 Approach A: formation of the N1–C6 bond

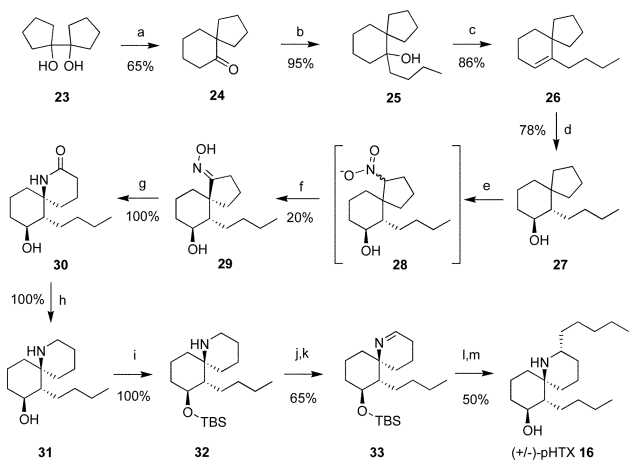
2.1 Oximes: the Beckmann rearrangement

The Beckmann rearrangement from an oxime to an amide has been used on numerous occasions as a tool for the ring expansion of cyclic ketones. The first example of it being used to generate an azaspirocyclic system was in 1960 when Hill *et al.* showed that it was possible to convert oxime **20** into a 1 : 1 mixture of spirolactam **21** and nitrile **22**, which gave a 32% yield of lactam **21** after separation by recrystallisation (Scheme 1).[6]



Scheme 1 Hill's 1960 Beckmann spirolactamisation.

In 1975, Corey *et al.* used the Beckmann rearrangement as a key step in the first total synthesis of (±)-pHTX **16**, showing that this method was an efficient means to generate the core azaspirocycle (Scheme 2).[7] The bicyclopentyldiol **23** was converted to spiroketone **24** by a pinacol rearrangement, producing the required quaternary carbon. A nucleophilic addition of butyllithium then formed the tertiary alcohol **25**, which was dehydrated with thionyl chloride to give olefin **26**. Hydroboration followed by oxidation then gave alcohol **27** as a single diastereomer. The nitrogen functionality was then introduced by first converting the alcohol to nitrite ester **28** with nitrosyl chloride. This compound was then immediately submitted to Barton's irradiation conditions, promoting controlled decomposition to give a mixture of oxime **29** and an isomeric oxime produced from nitrate functionalisation of the *n*-butyl side chain. These two oximes were separated, giving the desired oxime **29** in 20% yield. The key Beckmann rearrangement was then carried out, giving spirocyclic lactam **30** as the major product. The carbonyl function was subsequently reduced to give amine **31**. Protection of the hydroxyl function of **31** was followed by conversion to the *N*-bromoamine, with subsequent dehydrobromination generating imine **33**. The C2 pentyl side chain was then installed by reaction with pentyllithium, which gave a 1 : 1 mixture of epimers. Chromatographic separation then allowed the desired epimer to be isolated and deprotected to give (±)-pHTX **16** in thirteen steps. This first synthesis of pHTX used state-of-the-art synthetic methodologies of the time, a feature which would lead



Scheme 2 Corey's 1975 (±)-pHTX total synthesis. *Reagents and conditions*: (a) conc. H_2SO_4; (b) BuLi, hexane–Et_2O, reflux, repeat three times; (c) $SOCl_2$, pyridine, −78 °C, 6 h; (d) hydroboration, basic H_2O_2; (e) NOCl, pyridine, 0 °C; (f) *hv*; (g) TsCl, pyridine, 12 h; (h) $LiAlH_4$, 36 h; (i) TBSCl, NaH, 2 h; (j) NBS, 1 h; (k) KCO_2tBu, −40 °C; (l) $C_5H_{11}Li$, 12 h; (m) TBAF.

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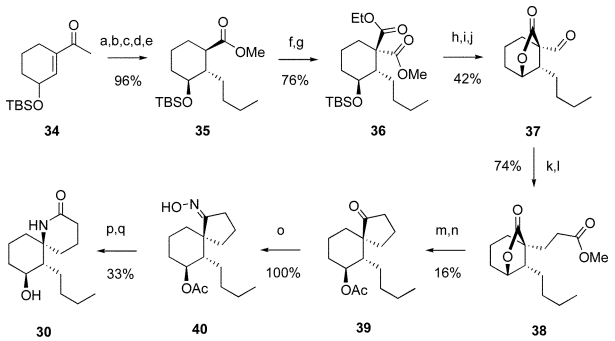
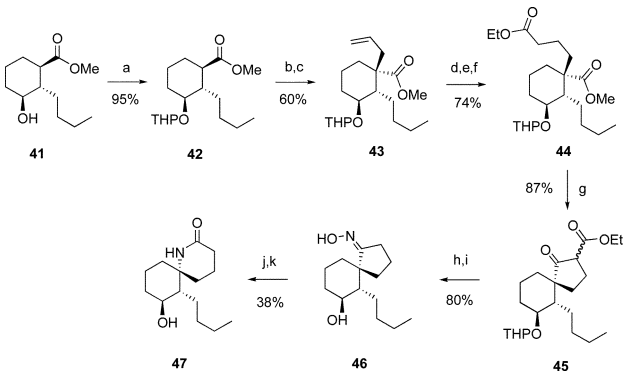
to this synthesis being incorporated in many chemistry degree courses and textbooks.

The Beckmann rearrangement was revisited in 1981 by Ibuka *et al.* in an alternative route to the key spirocyclic lactam **30**, starting from the TBS-protected cyclohexene **34** (Scheme 3).[8] The relative stereochemistry was set up in the initial step by a facially selective alkylation of the α,β-unsaturated ketone, which was then subsequently converted to ester **35**. Deprotonation followed by carboxylation gave an unstable acid that was immediately alkylated with diazoethane to give the much more stable diester **36**. Exposure of this compound to dilute HCl then promoted lactonisation to give bicyclic lactone **37**. The remaining ester function was reduced and re-oxidised to give aldehyde **37**, allowing a Horner–Wadsworth–Emmons olefination to be carried out. The resulting alkene was then reduced by catalytic hydrogenation to give ester **38**. The key spirocyclisation was effected by an acyloin condensation, giving a mixture of the desired spirocycle and its acetoxyketone. This mixture was then reduced with zinc/acetic acid to give a good yield of the acyl-protected spirocyclic ketone **39**. Condensation with hydroxylamine then installed the oxime function, and the key Beckmann rearrangement was carried out to give the Corey lactam **30** in a moderate yield after deprotection, constituting a formal synthesis of (±)-pHTX **16** (Scheme 3).



Scheme 3 Ibuka's 1981 (±)-pHTX formal synthesis. *Reagents and conditions*: (a) $BuCuAlCl_3$; (b) LDA, −40 °C; (c) TMSCl, NEt_3, −10 °C; (d) O_3, −70 °C; (e) N_2CH_2; (f) LDA, THF; CO_2; (g) N_2CHMe; (h) HCl, H_2O, 50 °C; (i) DIBAL, hexane–toluene, −70 °C; (j) PCC, DCM; (k) $(MeO)_2(O)PCHCO_2Me$, benzene, Et_2O, 0 °C; (l) H_2, PtO_2; (m) Na, TMSCl, toluene, reflux; HCl, 0 °C; Ac_2O, pyridine, DMAP, $CHCl_3$; (n) Zn, AcOH; (o) $NH_2OH{\cdot}HCl$, $NaHCO_3$, MeOH; (p) *p*TsCl, pyridine; (q) NaOMe, MeOH.

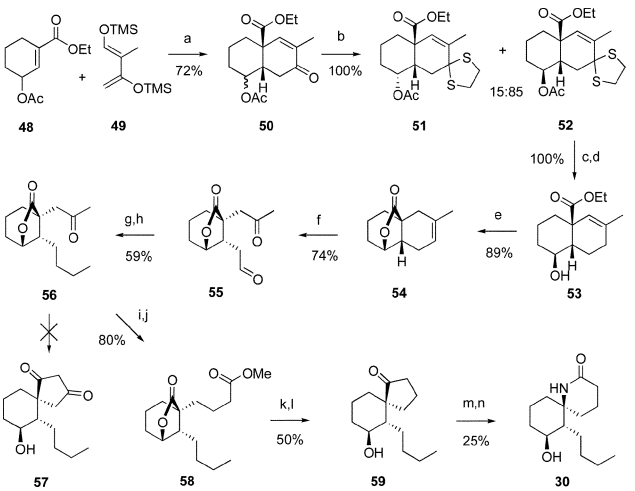
Ibuka adapted this procedure in order to selectively synthesise a racemic mixture of the unnatural 6-*epi* isomer of **30** where the stereochemistry around the spirocyclic core had been reversed (Scheme 4).[9] The previously synthesised ester **41** underwent a hydroxyl protecting group exchange followed by deprotonation and alkylation with allyl bromide. Unfortunately the acidic work-up required for this reaction resulted in hydroxyl deprotection, requiring reprotection to give the inverted ester **43**. Osmium-catalysed olefin cleavage generated the aldehyde, allowing chain extension by a Horner–Wadsworth–Emmons reaction. Hydrogenation of the resulting alkene then gave **44**, which underwent an intramolecular Dieckmann cyclisation to give spirane **45**. Decarboxylation followed by condensation to give oxime **46** then allowed the key Beckmann rearrangement to occur, constituting



Scheme 4 Ibuka's 1981 (±)-*rel*-(6*R*)-pHTX formal synthesis. *Reagents and conditions*: (a) DHP, H^+; (b) $KN(TMS)_2$, THF; allylmagnesium bromide, THF; HCl, H_2O; (c) DHP, H^+; (d) OsO_4, $NaIO_4$, THF; (e) $(MeO)_2(O)P{=}CHCO_2Me$, benzene, Et_2O, 0 °C; (f) H_2, PtO_2; (g) KH, THF; (h) DMSO, H_2O, LiCl, $NaHCO_3$, 150 °C; (i) $NH_2OH{\cdot}HCl$, $NaHCO_3$, MeOH; (j) *p*TsCl, pyridine; (k) sodium naphthalenide, THF.

a formal synthesis of the *rel*-(6*R*)-pHTX. The stereochemistry of the azaspirocycle was determined by X-ray analysis of **47**.

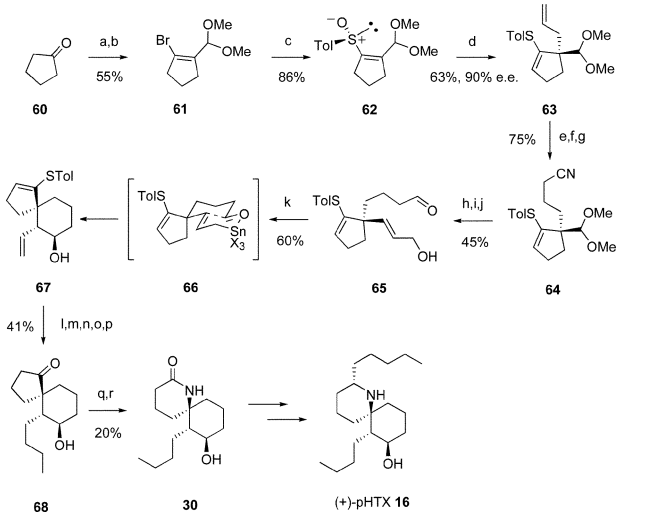
Ibuka also developed an alternative route to lactam **30** in 1982.[10] This started with an initial Diels–Alder reaction between **48** and **49** to give bicyclic enone **50** as an inseparable mixture of *O*-acyl epimers (Scheme 5). This mixture was then converted into its respective thioketals giving a separable 85 : 15 mixture in favour of the desired epimer **52**. Desulfurisation followed by acetal hydrolysis then gave the hydroxy ester **53**, which was readily converted to lactam **54** in an 89% yield by thermodynamic double bond migration. Oxidative cleavage of the alkene **52** then gave keto aldehyde **55**, which readily underwent a chemoselective Wittig homologation to furnish keto lactone **56** after hydrogenation. The planned intramolecular Claisen addition unfortunately failed to give diketone **57**, and they were forced to investigate alternative routes. It was found that methoxycarbonylation of the kinetic



Scheme 5 Ibuka's 1982 (±)-pHTX formal synthesis. *Reagents and conditions*: (a) 190 °C; HCl, H_2O; (b) $HS(CH_2)SH$; (c) Raney Ni; (d) KOH, H_2O; (e) *p*TsOH, toluene, reflux; (f) OsO_4, $NaIO_4$, THF, −50 °C; (g) ethyltriphenylphosphonium bromide, NaH, −50 °C; (h) H_2, PtO_2; (i) Whitlock methoxycarbonylation; (j) $NaBH_4$, MeOH, −40 °C; MsCl, pyridine; DBU, Et_3N; H_2, PtO_2; (k) KOH, THF; (l) DABCO, xylene, reflux; (m) $NH_2OH{\cdot}HCl$, $NaHCO_3$, MeOH; (n) TsCl.

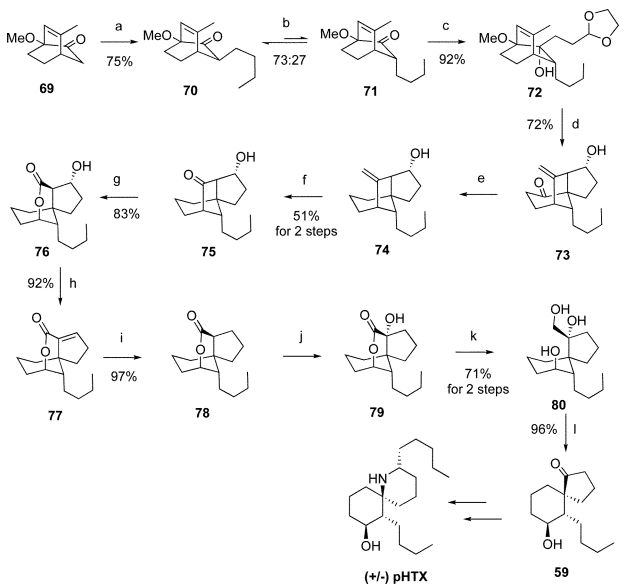
enolate of **56**, followed by reduction of the resulting ketone, successfully yielded methyl ester **58**. A Dieckmann condensation followed by removal of the redundant methoxycarbonyl group using DABCO in refluxing xylene gave spirocyclic hydroxy ketone **59**. This was converted to lactam **30** using the previously developed conditions for the key Beckmann rearrangement.

A synthesis of the enantiomerically pure (+)-form of the Corey intermediate **30** was reported in 1994 by Iwata, constituting a formal synthesis of the unnatural (+)-pHTX **16** (Scheme 6).[11] Cyclopentanone **60** was converted to bromide **61** following known procedures. Bromide **61** was then subjected to a halogen–lithium exchange and reacted with (−)-menthyl-(*S*)-toluene-*p*-sulfinate to give chiral vinylic sulfoxide **62**. A Pummerer-type nucleophilic addition of allylmagnesium bromide then gave the (*S*)-vinylic sulfide **63** with a 90% enantiomeric excess. This could be readily converted to nitrile **64** by hydroboration–oxidation, conversion of the resulting alcohol to a mesylate and displacement with cyanide. Hydrolysis of acetal **64** followed by a Wittig olefination of the resulting aldehyde exclusively produced a *cis*-alkene, which was then isomerised to the *trans* isomer before nitrile reduction gave the hydroxyl aldehyde **65**. The key diastereoselective spirocyclisation step was then attempted using a Lewis acid-catalysed ene reaction, which gave a spirocyclic compound as a single isomer. However, this was found to be the unwanted C6 epimer of **67**. They next investigated a palladium-catalysed intramolecular carbonyl allylation, which was thought to proceed through the sterically minimised transition state **66**, yielding the desired **67** as a single epimer. Compound **67** was then submitted to a sequence of hydroboration–oxidation, tosylation, ethylation and deprotection, followed by the key Beckmann rearrangement to give (+)-**30**.



Scheme 6 Iwata's 1994 (+)-pHTX formal synthesis. *Reagents and conditions*: (a) PBr_3, DMF, $CHCl_3$; (b) $CH(OMe)_3$, MeOH; (c) *n*BuLi, (*S*)-(−)-methyl-*p*-toluenesulfinate, THF, −78 °C; (d) allylmagnesium bromide, THF; (e) 9-BBN, THF; 3 M NaOH, H_2O_2; (f) MsCl, Et_3N, DCM; (g) KCN, 18-crown-6, MeCN, H_2O, reflux; (h) *p*TsOH, acetone; (i) $(EtO)_2P(O)CH_2CO_2Et$, *t*BuOK, THF, −40 °C; (j) DIBAL, toluene, −78 °C; (k) $PdCl_2(PhCN)_2$, $SnCl_2$, THF, H_2O; (l) methoxymethyl chloride, *i*Pr_2EtN, DCM, DMAP; (m) 9-BBN, THF; 3 M NaOH, H_2O_2; (n) *p*TsCl, pyridine, DMAP, DCM; (o) Et_2CuLi, Et_2O, −40 °C; (p) HCl, MeCN, 60 °C; (q) $MeCO_2Na$, $NH_2OH{\cdot}HCl$, MeOH; (r) *p*TsCl, pyridine, benzene.

Between 1997 and 2000, the group of Kim utilised a series of tandem pinacol rearrangement strategies directed towards a formal synthesis of the Corey intermediate **30** (Scheme 7).[12,13] Stereoselective alkylation of the known Diels–Alder adduct **69** with butyl iodide produced the *exo* product **70**. This compound was epimerised under basic conditions to give a chromatographically separable 27 : 73 mixture of the desired *endo* isomer **71** and the undesired *exo* isomer **70**. Exposure of **71** to the Grignard reagent derived from (bromoethyl)dioxolane under Barbier conditions led to the stereospecific formation of *endo* alcohol **72**. The antiperiplanar relationship between the olefinic bridge and the hydroxyl function of **72** was now stereoelectronically favourable for the desired pinacol rearrangement. Treatment with *p*TsOH in refluxing acetone resulted in the formation of a bicyclo[3.2.1]octane intermediate, which spontaneously underwent an ene reaction to give tricyclic alcohol **73** in an 89 : 11 ratio with its hydroxyl epimer. A modified Wolff–Kishner reduction was then carried out, reducing the carbonyl function to yield tricyclic alkene **74**, which was then exposed to ozonolysis conditions, generating ketone **75**. A Baeyer–Villiger oxidation of ketone **75** yielded **76** with an extremely high regioselectivity due to a combination of high facial selectivity and a more conformationally stable transition state. Dehydration of the β-hydroxyl function, followed by hydrogenation of the resulting olefin and an oxaziridine-mediated α-hydroxylation, gave lactone **79**. Finally, reductive opening of this lactone, followed by an oxidative cleavage of the resulting diol, resulted in keto alcohol **59**, which had previously been converted to **30** by the Ibuka group.



Scheme 7 Kim's 2000 (±)-pHTX formal synthesis. *Reagents and conditions*: (a) LHMDS, THF, HMPA, *n*BuLi; (b) NaOH, MeOH; (c) 2-(2-bromoethyl)-1,3-dioxolane, Mg, $Br(CH_2)Br$; (d) TsOH, acetone, reflux; (e) NH_2NH_2, KOH, $HO(CH_2)_2OH$, 2-methylenepropane-1,3-diol; (f) O_3.EtOAc; (g) *m*CPBA, $NaHCO_3$, DCM; (h) TsCl, DMAP, Et_3N, DCM; (i) H_2, Pd/C, EtOH; (j) KHMDS, Davis' oxaziridine, THF, −78 °C; (k) $LiAlH_4$, THF; (l) $NaIO_4$, acetone, H_2O.

In summary, the Beckmann rearrangement has been a well-investigated method for the generation of an aza-spirocyclic

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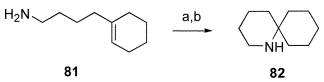
system, although it is compromised by the competing formation of nitriles similar to **22**, giving undesirable low yields in some cases.

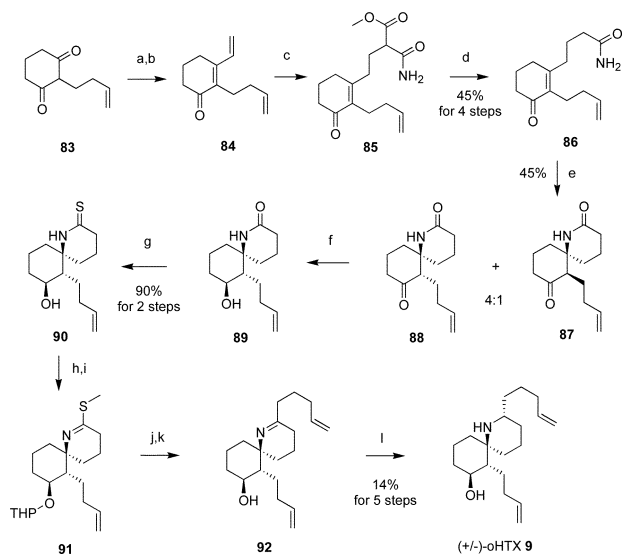
2.2 The Michael addition and intramolecular ene reaction of amines

In 1972, Lattes *et al.* reported the formation of 1-azaspiro-[5,5]-undecane **82** by an intramolecular aminomercuration–demercuration reaction from amine **81** using mercuric acetate (Scheme 8).[14]



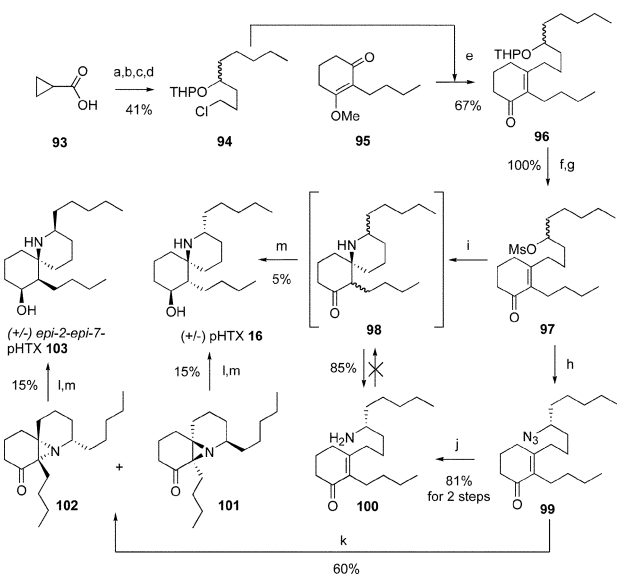
Scheme 8 Lattes' 1972 spiroamine formation. *Reagents and conditions*: (a) $Hg(OAc)_2$; (b) $NaBH_4$.

In 1975, Kishi *et al.* utilised this method as the key step in a total syntheses of oHTX **9** (Scheme 9).[15] This route started with the treatment of diketone **83** with acidic ethanol, followed by reaction with vinylmagnesium bromide. The resulting vinylcyclohexanone **84** was then exposed to the anion of methyl malonamate, giving ester-amide **85**, which was immediately decarboxylated to give the keto amide **86**. An acid-catalysed intramolecular Michael addition of **86** was carried out to form the key spirocycle as an epimeric mixture of **87** and **88** in a 2 : 1 ratio, unfortunately in favour of the undesired C7 epimer **87**. This mixture was then equilibrated using sodium methoxide to give a much more acceptable 4 : 1 ratio in favour of the desired C7 epimer **88**. Chromatographic separation, followed by lithium reduction in liquid ammonia, gave lactamol **89**, which was further converted to thiolactam **90**. Tetrahydropyran protection of the hydroxyl function of **90** then allowed the α-thioimidate to be formed and trapped as the methyl thioimidate **91**. Reaction of **91** with pent-5-enyllithium and DIBAL installed the pentenyl side chain, to give **92**. Hydroxyl deprotection and $LiAlH_4$ reduction then gave a chromatographically separable mixture of the target oHTX **9** and its C7 epimer in a favourable 6 : 1 ratio.



Scheme 9 Kishi's 1975 (±)-oHTX total synthesis. *Reagents and conditions*: (a) EtOH, H^+; (b) vinylmagnesium bromide; (c) $NH_2COCH_2CO_2Me$, NaOMe; (d) HCl, dioxane, 100 °C; (e) $HC(OEt)_3$, H^+; NaOMe; (f) Li/NH_3; (g) Ac_2O, P_2S_5, NaOH, reflux; (h) DHP, H^+; (i) $Me_3O^+ BF_4^-$; (j) $CH_2{=}CH(CH_2)_3Li$, DIBAL; (k) H^+, H_2O; (l) $LiAlH_4$.

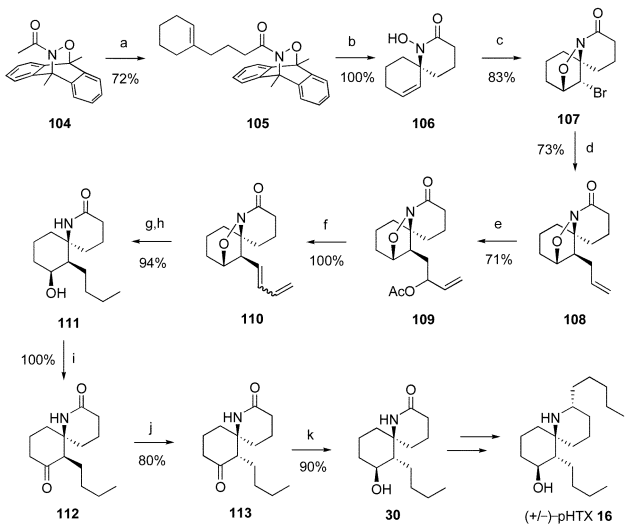
Corey also utilised the 1,4-intramolecular Michael addition methodology to generate (±)-pHTX **16** directly from mesylate **97**, albeit in a low yield (Scheme 10).[16] Firstly, cyclohexanone **95** was reacted with the lithium anion of THP-protected 1-chloro-4-nonanol **94** to give enone **96** in good yield. This was then deprotected to generate the key mesylate **97** in quantitative yield. It was initially attempted to form azaspirocycle **98** by heating this mesylate in a saturated aqueous ammonia solution in order to promote a Michael-type addition. IR analysis of the crude mixture indicated the presence of the desired Michael adduct **98**, but all attempts to isolate this compound were unsuccessful, resulting only in the isolation of free amine **100**. An attempted *in situ* reduction of this crude mixture with sodium borohydride generated a complex mixture of products, from which it was eventually found possible to isolate a sample of (±)-pHTX **16**, albeit in a low 5% yield. Attempts to improve on this yield were unsuccessful and an alternative route was then sought. Conversion of the mesylate intermediate **97** to azide **99** then allowed a Lindlar hydrogenation to be carried out, forming amine **100** in good yield. A large number of conditions were screened in order to convert this amine directly to the desired spirocycle **98**, but all attempts were unsuccessful. Subsequently, an intramolecular [3 + 2] cycloaddition of azide **99** to form a triazoline was investigated. This reaction was found to give a mixture of the aziridine isomers **101** and **102**, presumably through initial triazoline formation followed by nitrogen extrusion. This mixture of aziridines, upon reduction, gave a 1 : 1 mixture of (±)-pHTX **16** and (±)-2-*epi*-7-*epi*-pHTX **103**, which were fortunately found to be chromatographically separable. Optimisation of this cycloaddition was investigated, and it was found to be possible



Scheme 10 Corey's 1976 (±)-pHTX total synthesis. *Reagents and conditions*: (a) $C_5H_{11}Li$, Et_2O, 0 °C; (b) HCl, Et_2O; (c) $LiAlH_4$, Et_2O; (d) DHP, TsOH, DCM; (e) Li, Et_2O, THF, 0 °C; (f) AcOH, H_2O, THF, 50 °C; (g) MsCl, Et_3N, DCM, −20 °C; (h) LiN_3, THF, H_2O; (i) NH_3, EtOH, 60 °C; $NaBH_4$, MeOH; (j) H_2, $Pd/CaCO_3$–Pb; (k) xylene, reflux; (l) Li/NH_3, Et_2O, reflux; (m) $NaBH_4$, MeOH, −40 °C.

to generate the desired aziridine isomer **101**, leading to a selective synthesis of (±)-pHTX **16**.

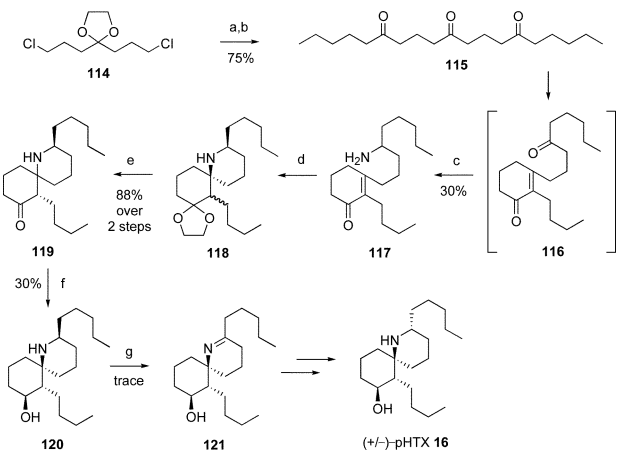
The group of Keck *et al.* developed a novel intramolecular ene reaction in order to generate an azaspirocyclic core, which was successfully advanced to the Corey lactam **30** (Scheme 11).[17]



Scheme 11 Keck's 1982 (±)-pHTX formal synthesis. *Reagents and conditions*: (a) LDA, THF, HMPA, −78 °C; 1-(2-iodoethyl)cyclohexene; (b) reflux, tolune; (c) NBS, CH_2Cl_2, 0 °C; (d) allyltri(*n*-butyl)tin, benzene, reflux; (e) OsO_4, THF, 0 °C; vinylmagnesium bromide, THF, −78 °C; acetic anyhdride; (f) $Pd(OAc)_2$, PPh_3, dioxane, reflux; (g) H_2, Adams catalyst, EtOAc; (h) Na–Hg, isopropanol; (i) DMSO, oxalyl chloride; (j) NaOMe, reflux; (k) Li/NH_3, −78 °C.

Compound **104** was initially alkylated with the cyclohexene moiety to give **105**. Thermolysis of this compound triggered a retro-Diels–Alder reaction, and the resulting acylnitroso compound spontaneously underwent an ene reaction to give *N*-hydroxylactam **106**. The *N*-hydroxyl group was then utilised to install the C8 hydroxyl function with the desired stereochemistry by intramolecular attack on a bromonium species formed by addition of *N*-bromosuccinimide to **106**, giving bromoisoxazolidine **107**. The C7 side chain was then readily introduced using allyltri(*n*-butyl)tin to yield alkene **108** as a single stereoisomer. Unfortunately, this product was found to be the undesired equatorial C7 epimer, but as **87** could successfully be epimerised to the axial **88** (as Kishi had previously demonstrated during his (±)-oHTX synthesis), this wasn't seen as a major stumbling block. Oxidative cleavage of the olefin function in **108** then allowed chain extension to proceed by reaction with vinylmagnesium bromide, followed by acyl protection of the resulting hydroxyl function, to give **109**. Allylic acetate **109** was then converted to diene **110** by a palladium-catalysed elimination of acetic acid. A palladium-catalysed hydrogenation followed by a sodium amalgam reduction yielded hydroxylactam **111** in excellent yield. Swern oxidation of alcohol **111** generated **112**, which was epimerised by refluxing with sodium methoxide to give **113**, and this was converted to the Corey lactone **30** by diastereoselective reduction of the ketone.

The Winterfeldt group published an investigation into the spirocyclisation of triketone **115** in 1982 (Scheme 12).[18] This straight-chain ketone was chosen as a possible equivalent to the common biological precursor for both the histrionicotoxin and



Scheme 12 Winterfeldt's 1982 (±)-pHTX formal synthesis. *Reagents and conditions*: (a) 2-amyl-1,3-dithiane, BuLi, THF, −30 °C; (b) OHC–CO_2H, MeCN, HCl; (c) $MeCO_2^-NH_4^+$, $NaBH_3CN$, MeOH; (d) $(HOCH_2)_2$, *p*TsOH, benzene, reflux; (e) HCl, THF, MeCN, H_2O, 65 °C; *t*BuOK, *t*BuOH, toluene, reflux; (f) $LiAlH_4$, Et_2O; (g) *tert*-butyl hypochloride, Et_2O, *t*BuOK.

gephyrotoxin alkaloids.[19] This ketone was synthesised by thioketal alkylation of dichloroketal **114** followed by ketone deprotection. This triketone was found to readily cyclise to a complex mixture of cyclic ketones due to the similar pK_a values of the protons adjacent to the carbonyl functions. Reductive amination of this mixture then generates a range of amines and cyclic imines that contain the core carbon framework of a number of different alkaloids, one of which is **117**, formed through intermediate **116**. Unfortunately, all attempts to further cyclise this mixture by a Michael addition were unsuccessful, so they masked the carbonyl function as an acetal in an attempt to alter the cyclisation equilibrium. Reaction of **117** with ethylene glycol and catalytic acid in benzene at reflux promoted acetal formation as well as spirocyclisation to give a complex mixture of spirocyclic stereoisomers in good yield. These were found to equilibrate to a single thermodynamic isomer **118** when heated further in toluene. Acetal deprotection was carried out, but again gave a complex mixture of stereoisomers, which were converted into a single thermodynamic spirocycle **119** with well-defined relative stereochemistry by treatment with *tert*-butoxide in toluene at reflux. Unfortunately, the thermodynamic product of this reaction contained the wrong configuration at C2, which would need to be corrected later in the synthesis. Reduction of the ketone function of **119** generated a mixture of the two epimeric alcohols. These were separated by exposure of the mixture to phosgene, which converted only the desired *cis*-amino-hydroxy compound to its cyclic urethane, which was isolated and hydrolysed to give alcohol **120**. This was then converted to the cyclic imine **121** by treatment with *tert*-butyl hypochlorite, albeit in a low yield, constituting a formal synthesis, as this compound had been previously converted to (±)-pHTX **16** by the Kishi group.

In 1983, the groups of Carruthers and Godleski simultaneously published syntheses of (±)-2-depentyl-pHTX **18** utilising very similar Michael addition methodology (Scheme 13).[20–23]

The Carruthers group started with cyclohexenone **122** and treated it with the Grignard reagent derived from 4-chlorobutan-1-ol. After acidic workup the resulting hydroxyl function was protected to give tosylate **123**. Borohydride reduction of the

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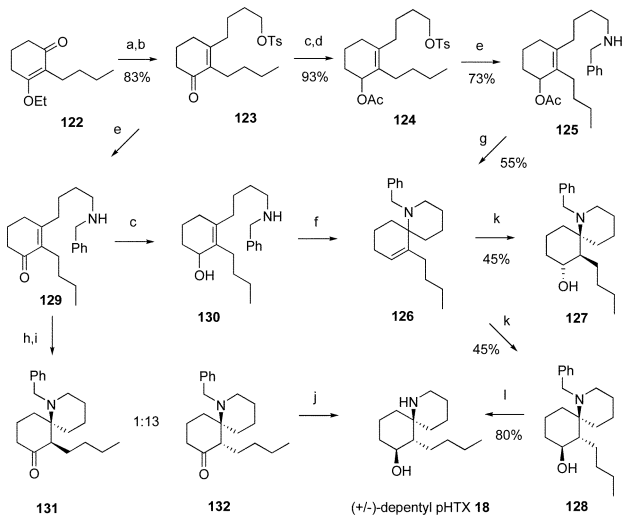
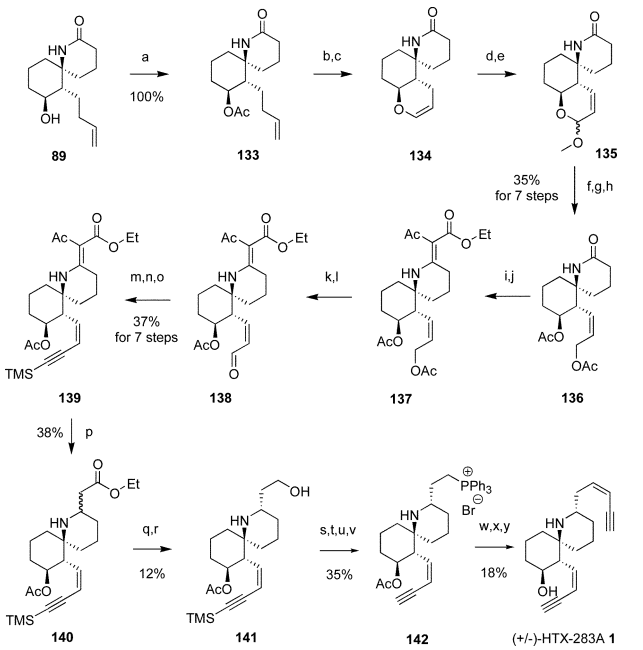


Scheme 13 Carruthers' and Godleski's 1983 (±)-depentyl-pHTX total syntheses. *Reagents and conditions*: (a) $ClMg(CH_2)_4OMgCl$, THF, −20 °C; H^+, H_2O, THF; (b) TsCl, pyridine, −10 °C; (c) DIBAL, toluene, −50 °C; (d) Ac_2O, Et_3N, DCM; (e) $PhCH_2NH_2$, NaI, DMSO; (f) Me_3SiI, Et_3N, DCM, −20 °C; (g) $Pd(PPh_3)_4$, MeCN; (h) Me_3SiI, Et_3N, DCM, 0 °C; (i) NaOMe, DCM; (j) Li/NH_3, MeOH; (k) $BH_3{\cdot}Me_2S$, hexane, THF, 40 °C; diglyme, NaOH, H_2O_2, H_2O, 80 °C; (l) H_2, Pd/C, EtOH.

ketone function followed by acyl protection gave **124**, and the tosyloxy function was then displaced with benzylamine to give amine **125**. This compound was cyclised with catalytic tetrakis(triphenylphosphine)palladium to produce the key spirocycle **126** in 55% yield. Anti-Markovnikov hydration, using hydroboration and subsequent oxidation, was then expected to be directed by the proximal nitrogen to give the required axial hydroxyl. However, after peroxide oxidation, the resulting product was found to be an epimeric mixture of compounds **127** and **128**. After isolation of the desired epimer **128**, the benzyl protecting group was removed using palladium-catalysed hydrogenation to yield (±)-2-depentyl-pHTX **18**.

The Godleski group explored a very similar route, but also investigated a second route in which they chose to install the benzyl-protected amine before reduction of the ketone, thus forming **129** directly from **123**. The key Michael addition was then found to give a 5 : 1 mixture of the desired product **132** and the epimeric **131**, respectively. This ratio could be further enhanced to 13 : 1 by base-catalysed epimerisation, and palladium-catalysed hydrogenation then gave the desired (±)-2-depentyl-pHTX **18**. It was also found that Carruthers' undesired epimer **127** could be re-oxidised and epimerised to give the Godleski azaspirocycle **132**, effectively recycling this unwanted epimer.

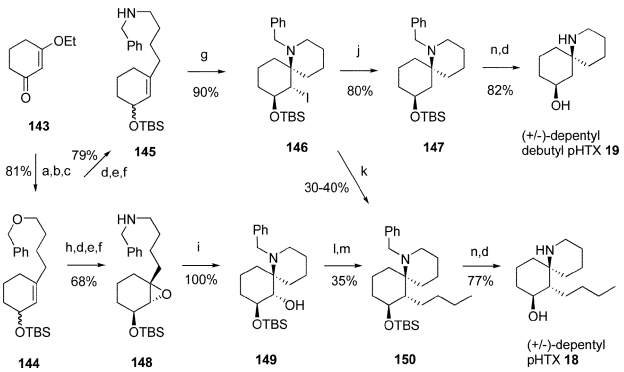
The Kishi group demonstrated in 1985 that their previously synthesised lactam **89** could also be utilised in a total synthesis of the fully unsaturated (±)-HTX-283A **1** (Scheme 14).[24] The acyl derivative **133** was first formed quantitatively by treatment with acetic anhydride. This was then converted to the cyclic enol ether **134** by an oxidative cleavage, promoting intramolecular addition, followed by a base-catalysed deprotection and dehydration. Bromination followed by dehydrobromination in methanol was then found to give an epimeric mixture of unsaturated methoxyacetals **135** in good yield. This mixture was hydrolysed, reduced and acetylated to provide diacetate **136**. Conversion of the lactam into



Scheme 14 Kishi's 1985 (±)-HTX total synthesis. *Reagents and conditions*: (a) Ac_2O, pyridine; (b) OsO_4, $NaIO_4$; (c) NaOH, MeOH; Ac_2O, pyridine, reflux; (d) Br_2, MeOH; (e) DBU, DMSO, reflux; (f) Ac_2O, H_2O; (g) $NaBH_4$, THF; (h) Ac_2O, pyridine; (i) P_2S_5, pyridine, 80 °C; (j) $MeCOCHBrCO_2Et$, $NaHCO_3$; (k) NaOH, MeOH, −20 °C (l) PCC, DCM; (m) $Ph_3P^+CH_2ClCl^-$, BuLi, THF, −78 °C; (n) NaOEt, EtOH, 50 °C; (o) MeLi, TMSCl, THF; (p) $NaBH_3CN$, hexane; (q) $LiAlH_4$, THF; (r) NaOH, MeOH, 0 °C; (s) TBAF, THF; (t) MsCl, Et_3N, DCM; HCl, EtOH; (u) LiBr, DMF, 50 °C; (v) Ph_3P, MeCN, 160 °C; (w) LDA, THF; TBDMS–C≡C–CHO; (x) TBAF, THF; (y) NaOH, MeOH.

a thiolactam followed by condensation with ethyl bromoacetate then gave **137**. Selective deprotection of the allylic alcohol followed by oxidation gave aldehyde **138**. A Wittig reaction then generated a chloroalkene, which, upon base-promoted elimination of HCl, gave a terminal alkyne, which was subsequently protected with a trimethylsilyl group, giving **139**. This potentially unstable enyne group was found to survive the long series of reactions needed in order to further develop the C2 side chain. The olefinic function of **139** was first reduced using cyanoborohydride, before the resulting ester **140** was further reduced to an epimeric mixture of alcohols. A retro-Michael addition was then performed under basic conditions at low temperature, successfully epimerising this compound to give the desired epimer **141**. A reaction with triphenylphosphine then generated phosphonium salt **142**, and a Wittig reaction could then be performed to attach the silyl-protected *cis*-ene-yne function, which was then deprotected to yield the target (±)-HTX 283A **1**.

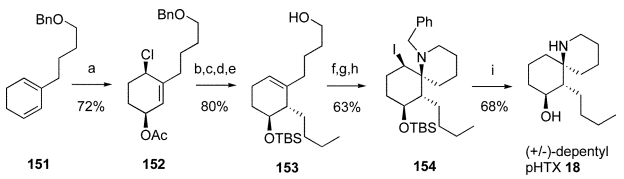
In 1986, Tanner and Somfai presented two routes to access both depentyl-debutyl-pHTX **19** and debutyl-pHTX **18** from benzyl ether **144** and its enol enone precursor **143** (Scheme 15).[25,26] They first exchanged the benzyloxy group for a benzyl amine, giving **145**, which was then subjected to an iodine-promoted spirocyclisation, which, due to the steric bulk of the silyl protecting group, was found to be entirely facially stereospecific, resulting in the formation of **146** as a single diastereomer. A free-radical dehalogenation then gave azaspirocycle **147**, which upon hydroxyl and amino deprotection gave (±)-depentyl-debutyl-pHTX **19**. It was also found possible to perform an iodine–lithium exchange



Scheme 15 Tanner's 1986 (±)-dependyl-pHTX total synthesis. *Reagents and conditions*: (a) $PhCH_2O(CH_2)_4MgBr$, THF; H^+, H_2O; (b) DIBAL, toluene; (c) TBSCl, DMF; (d) H_2, $Pd(OH)_2/C$, EtOH; (e) TsCl, pyridine; (f) $PhCH_2NH_2$, NaI, DMSO; (g) I_2, DCM; (h) *m*CPBA, CH_2Cl_2, $NaHCO_3$, H_2O; (i) toluene, reflux; (j) Bu_3SnH, benzene; (k) *t*BuLi, Et_2O; BuOTs, HMPT; (l) MeLi, MsCl, Et_2O; LiOH, THF; (m) MeLi, MsCl, Et_2O; Bu_2CuLi, Et_2O; (n) TBAF, THF.

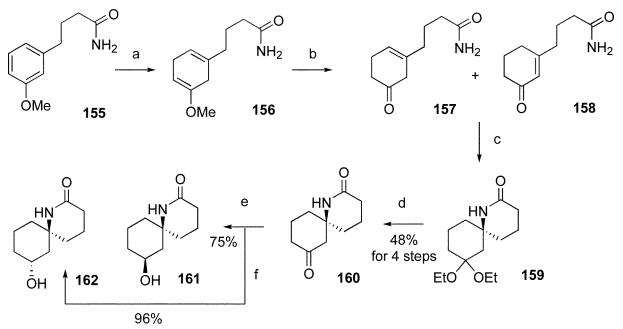
on **146**, allowing alkylation with butyl tosylate to give **150** in modest yield. This material was easily deprotected to give (±)-dependyl-pHTX **18**. Epoxidation of benzyl ether **144** was also found to proceed with excellent facial selectivity, to give epoxide **148** as a single isomer. Spirocyclisation was then carried out in quantitative yield by a regio- and stereospecific intramolecular epoxide opening to give **149**. The resulting hydroxyl function could then be mesylated and displaced with hydroxide, followed by a second mesylation and displacement with an organocuprate to retain the desired side chain stereochemistry. This gave **150** in a slightly better yield than the route from **147**, and **150** was converted as before to give (±)-dependyl-pHTX **18**.

The Tanner group developed a rapid route to (±)-dependyl-pHTX **18**, generating the azaspirocyclic core by a stereoselective iodocyclisation (Scheme 16).[27] They started with a stereoselective conversion of diene **151** to acetoxy-chloride **152** using Backvall's methodology. The butyl side chain was then introduced with complete stereocontrol using organocuprate chemistry. Hydroxyl protecting group exchange, followed by a dissolving metal reduction, generated cyclic alkene **153** in excellent yield. Conversion of the primary hydroxyl function of **153** to a benzyl amine, followed by iodocyclisation, formed the key spirocycle **154**, which was deprotected by palladium-catalysed hydrogenation to give (±)-dependyl-pHTX **18** in excellent yield.



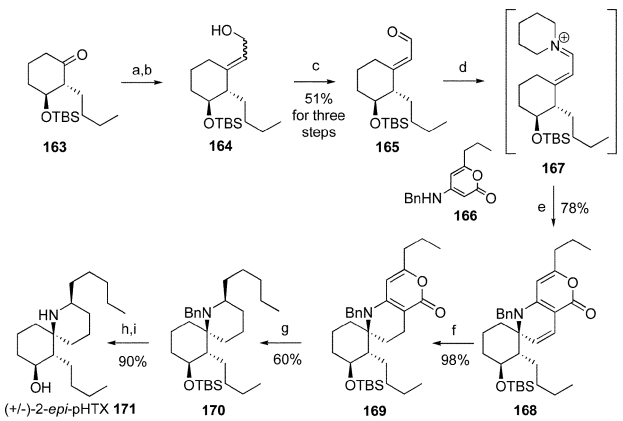
Scheme 16 Tanner's 1989 (±)-dependyl-pHTX total synthesis. *Reagents and conditions*: (a) $Pd(OAc)_2$, LiOAc, LiCl, benzoquinone, acetone, AcOH; (b) *n*BuMgBr, CuCN, Et_2O; (c) K_2CO_3, MeOH, H_2O; (d) TBSCl, imidazole, DMF; (e) Na/NH_3, −78 °C; (f) TsCl, pyridine; (g) $BnNH_2$, NaI, DMSO; (h) I_2, $NaHCO_3$, DCM; (i) H_2, $Pd(OH)_2/C$, MeOH.

In 1989, the Magnus group developed a novel Birch reduction–Michael addition method to efficiently and selectively generate the 7-debutyl-pHTX precursors **161** and **162** (Scheme 17).[28] The amide **155** was reduced under standard Birch conditions, which, upon hydrolysis, gave a mixture of **157** and **158**. This mixture was treated with triethyl orthoformate in the presence of an acid catalyst, generating a single azaspirocycle **159**, which was immediately hydrolysed to give ketone **160**. Reduction of this ketone to either of the hydroxyl diastereomers was found to be possible by careful choice of reaction conditions. A great advantage of this method is that none of the intermediates need to be isolated, making this an extremely efficient approach. Unfortunately, advancing these intermediates on to 7-debutyl-pHTX **17** using Corey's procedures produced an inseparable mixture of C2 epimers.



Scheme 17 Magnus' 1989 (±)-debutyl-pHTX formal synthesis. *Reagents and conditions*: (a) Na, *t*BuOH, Et_2O; (b) 1 M HCl, THF; $NaHCO_3$; (c) $HC(OEt)_3$, EtOH, camphorsulfonic acid; (d) HCl, DCM; (e) L-(*S*)-Selectride, DCM, −78 °C; (f) $NaBH_4$, MeOH.

The Hsung group developed a rapid novel total synthesis of (±)-2-*epi*-pHTX **192** by an annelation reaction between an α,β-unsaturated iminium salt and a vinylogous amide (Scheme 18).[29] Starting from cyclohexanone **163**, a Horner–Wadsworth–Emmons reaction followed by reduction of the ester gave the α-allylic alcohol **164**. The alcohol was re-oxidised to give aldehyde **165** which, upon condensation with piperidine, gave the iminium ion intermediate **167**, which was trapped with aminopyrone **166** to give the key spirocycle **168** by a Knoevenagel condensation and 6π-electron electrocyclic ring closure of the resulting azatriene intermediate. The alkene function of **168** was



Scheme 18 Hsung's 2002 (±)-2-*epi*-pHTX total synthesis. *Reagents and conditions*: (a) NaH, $(EtO)_2POCH_2CO_2Et$, THF, reflux; (b) DIBAL, DCM, 0 °C; (c) Dess–Martin periodinone, DCM; (d) piperidine, Ac_2O; (e) **166**, toluene, 150 °C; (f) Pd/C, H_2, EtOH; (g) $LiAlH_4$, EtOH; Pd/C, H_2, EtOH; (h) HCl, MeOH, H_2O, reflux; (i) H_2, $Pd(OH)_2$, MeOH.

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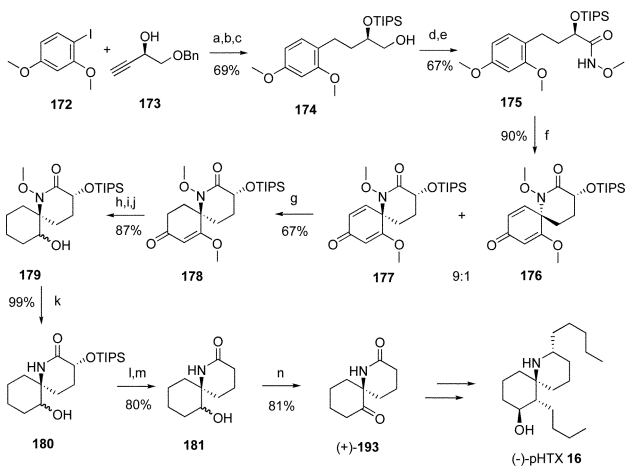
now reduced by palladium-catalysed hydrogenation to give **169**. Treatment of **169** with $LiAlH_4$ effected decarboxylation of the pyrone, exposing the future pentyl side chain as a diene. This crude intermediate was then immediately exposed to a palladium-mediated hydrogenation, providing the pentyl side chain with high stereocontrol, unfortunately in favour of the wrong C2 epimer **170**. Deprotection then yielded a total synthesis of (±)-2-*epi*-pHTX **171**.

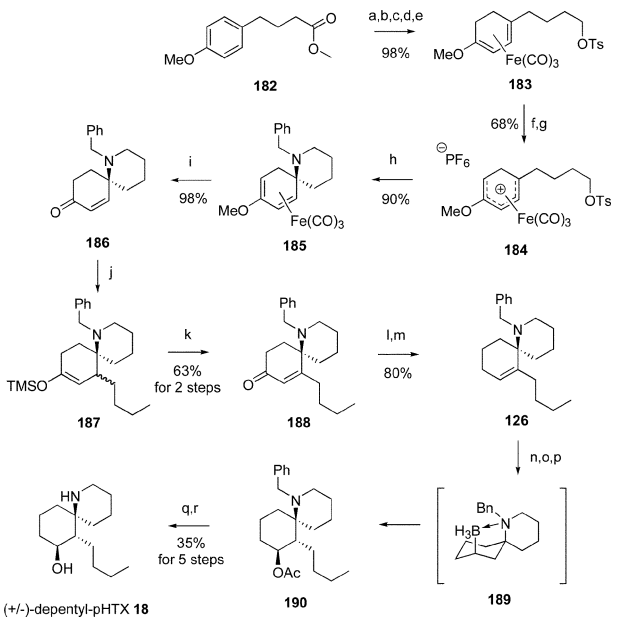
In 2004, Wardrop's group developed a stereoselective nitrenium ion-mediated synthesis of the (+)-Kishi lactam **193** (Scheme 19).[30] A Sonagashira coupling of iodoarene **172** and (*R*)-4-benzyloxy-3-hydroxy-1-butyne **173** gave alcohol **174** after debenzylation. This was oxidised to the carboxylic acid using Jones' reagent before being converted to the Weinreb amide **175**. The key spirocyclisation was initiated with phenyliodonium bis(trifluoroacetate) to give a 9 : 1 mixture of C6 epimers **177** and **176**, with the desired **177** as the major product. This selectivity was thought to be due to steric interactions between the TIPS group and the *ortho*-methoxy group directing the facial selectivity of the amide attack. This mixture of spirodienones was then hydrogenated over PtO_2 to give a mixture of the desired enol ether **178** and the over-reduced cyclohexanone. Careful optimisation of the reaction time allowed **178** to be isolated as the major product in a 67% yield. Luche reduction followed by another hydrogenation then gave the respective ketone as a single diastereomer. In order to avoid the reductive cleavage of the nitrogen–C6 bond, this ketone was reduced with sodium borohydride, to give alcohol **179** as a 3 : 1 mixture of *syn* and *anti* diastereomers. It was then attempted to cleave both the TIPS and the N–O bond in one pot using samarium diiodide, but these conditions only resulted in N–O cleavage, giving **180** in high yield. The TIPS group was removed using TBAF, and exposure of this compound to a second equivalent of SmI_2 in the presence of propionic acid successfully yielded **181** as a single diastereoisomer. Swern oxidation then provided the optically pure (+)-**193**, constituting a formal synthesis of (−)-pHTX **16**.



Scheme 19 Wardrop's 2004 (−)-pHTX formal synthesis. *Reagents and conditions*: (a) $PdCl_2$, PPh_3, CuI, Et_3N, ultrasonication, 40 °C; (b) TIPSCl, imidazole, DMAP, DMF; (c) H_2, Pd/C, EtOAc; (d) CrO_3, H_2SO_4, acetone; (e) *i*BuOCOCl, Et_3N, −20 °C; $H_2NOMe{\cdot}HCl$, Et_3N; (f) $PhI(OCOCF_3)_2$, CH_2Cl_2, MeOH, −78 °C; (g) H_2, PtO_2, EtOAc; (h) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C; 1 M HCl, THF; (i) H_2, Pd/C, EtOAc; (j) $NaBH_4$, MeOH, DCM, 0 °C; (k) SmI_2, THF, HMPA; (l) TBAF, THF; (m) SmI_2, $EtCO_2H$, THF, ultrasonication; (n) $(COCl)_2$, DMSO, DCM, −60 °C; Et_3N.

2.3 Organometallic-mediated cyclisation

The use of organometallic complexes in natural product synthesis is commonplace, due to their often excellent ability to control the relative stereochemistry of reactions. There have, however, been relatively few organometallic reactions developed that can generate an azaspirocyclic core. In 1980, Pearson *et al.* used an organoiron complex to generate the spirocyclic enone **186**.[31] They subsequently showed that it was possible to advance this intermediate towards a total synthesis of (±)-dependyl-pHTX **18** (Scheme 20).[32] The aromatic **182** was first reduced under Birch conditions, before being coupled with the ferric tricarbonyl ligand. The ester function was then reduced to the alcohol, and converted to tosylate **183**. Regiospecific hydride abstraction, followed by formation of the hexafluorophosphate salt, then gave **184**. The key spirocyclisation was achieved by stirring in a solution of benzylamine to give spirocycle **185** as a single regioisomer. The iron ligand was removed and an acid-catalysed hydrolysis gave the azaspirocyclic enone **186** in excellent yield. An organocuprate addition of the C7 alkyl chain was then carried out, followed by silyl trapping of the resultant enol to give **187**. A phenylselenyl chloride-mediated oxidation of enol ether **187** gave enone **188**, which was reduced with sodium borohydride, yielding the Godleski spirocyclic alkene **126**. Hydroboration was then carried out followed by oxidation, but initially the major product isolated was that of the wrong C8 hydroxyl epimer. After re-examination of the reaction mixture, they were able to isolate a non-polar compound that was identified as alkylborane intermediate **189**. This compound had resisted the oxidation

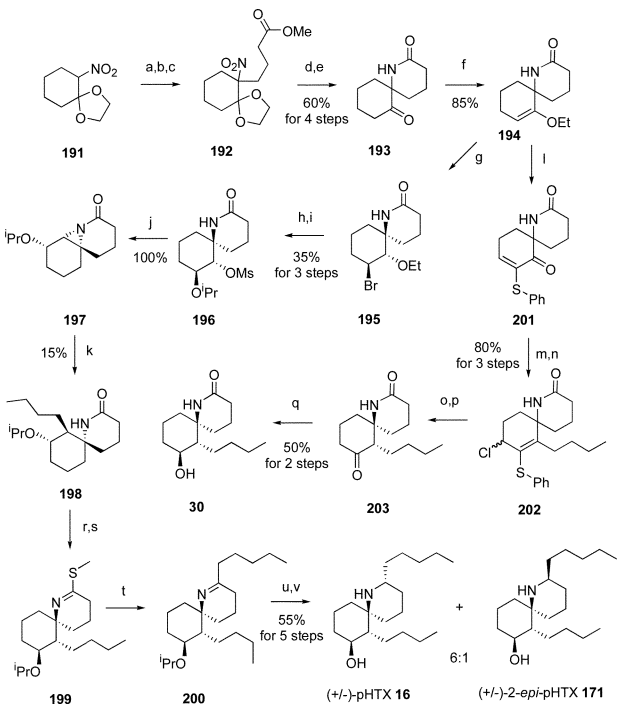


Scheme 20 Pearson's 1980 (±)-depentyl-pHTX total synthesis. *Reagents and conditions*: (a) Li/NH_3, *t*BuOH; (b) $DMSO_4$, K_2CO_3, acetone, reflux; (c) $Fe(CO)_5$, Bu_2O, reflux; (d) DIBAL, THF, −78 °C (e) TsCl, pyridine, 0 °C; (f) Ph_3C^+ BF_4^-, DCM, reflux; (g) NH_4^+ PF_6^-, DCM, H_2O; (h) $PhCH_2NH_2$, $MeNO_2$; (i) Me_3NO, benzene; $(CO_2H)_2$, MeOH, H_2; (j) Bu_2CuLi, THF, −25 °C; TMSCl, Et_3N; (k) PhSeCl, THF, −78 °C; H_2O_2, AcOH; (l) $NaBH_4$, MeOH; (m) $AlCl_3$, Et_2O, $LiAlH_4$; (n) $NaBH_4$, $BF_3{\cdot}OEt_2$; (o) NaOH, H_2O_2, THF, H_2O; (p) AcCl, pyridine; (q) NaOH, MeOH; (r) H_2, Pd/C, EtOH.

conditions, presumably due to the presence of the dative N–B bond. Subsequent treatment of this isolated material with alkaline hydrogen peroxide then led to the formation of the desired epimer as the major product. This mixture was acetylated and the two epimers were separated to give pure **190**, albeit in moderate yield. Deprotection was then carried out to give the target (±)-dependyl-pHTX **18**.

3 Approach B: formation of the N1–C2 bond

In 1957, Hill showed that it was possible to form spirolactams by the Raney nickel-catalysed hydrogenation of nitroesters.[33] This observation remained relatively overlooked, however, until it was re-investigated in 1975 by the Kishi group, who were able to successfully adapt it toward the formation of the core spirolactam **193**, which was subsequently advanced to give a total synthesis of (±)-pHTX **16** (Scheme 21).[34] The ketal-protected nitrocyclohexanone **191** was alkylated with methyl acrylate which, after ester hydrolysis, gave the carboxylic acid. This was then homologated using Arndt–Eistert conditions to give nitroester **192**. A catalytic hydrogenation then promoted the spirocyclisation, and this was followed by acetal deprotection to give the key spirocycle **193** in good yield. Ketone **193** was then reacted with triethyl orthoformate to give enol ether **194**. Reaction of **194** with bromide followed by a borohydride reduction gave bromide **195** as a single stereoisomer, which was further converted to mesylate

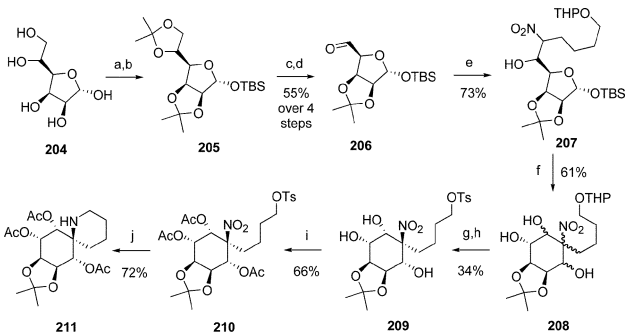


Scheme 21 Kishi's 1975 (±)-pHTX total synthesis. *Reagents and conditions*: (a) CH_2=CHCOOMe, Triton B , *t*BuOH; (b) NaOH, MeOH; (c) $SOCl_2$, benzene, 50 °C; CH_2N_2, Et_2O; $AgBF_4$, Et_3N, MeOH, 0 °C; (d) H_2, Raney Ni, MeOH, 50 °C; (e) TFA, H_2O, 75 °C; (f) $CH(OEt)_3$, H^+, reflux; (g) Br_2; $NaBH_4$; (h) *i*PrONa, *i*PrOH; (i) MsCl, pyridine; (j) NaH, benzene; (k) Bu_2CuLi, THF; (l) PhSCl, DCM; (m) BuMgCl, THF; (n) $SOCl_2$; (o) Zn, HCl; (p) HBr, H_2O; NaOMe, DCM; (q) Li/NH_3, −78 °C; (r) P_2S_5, benzene, reflux; (s) Me_3O^+ BF_4^-; (t) $C_5H_{11}Li$, DIBAL, Et_2O; (u) BBr_3, DCM; (v) AlH_3, cyclohexane.

196. An intramolecular aziridination was then promoted by the action of sodium hydride, giving spirocyclic aziridine **197** in a quantitative yield. The C7 alkyl chain was now selectively installed by organocuprate aziridine opening to give spirocyclic lactam **198** in a modest yield. Lactam **198** was converted to the thiolactam by exposure to P_2S_5 in refluxing benzene, before being further converted to the thioimidate **199**. Reaction with pentyllithium and diisobutylaluminium hydride then installed the C2 alkyl chain to yield imine **200**. A separable 6 : 1 mixture of the target pHTX **16** and its C2 epimer **171** was then generated in good yield by the action of boron tribromide and lithium aluminium hydride.

A second, more efficient route, involving the formation of thiophenyl ether **201** from the previously synthesised enol ether **194**, was also published in the same paper. Installation of the C2 side chain was now achieved by reaction of butylmagnesium chloride with **201**, followed by a thionyl chloride-promoted dehydration to give chloride **202**. A zinc-mediated reduction of the chloride of **202** then gave a phenyl vinylic sulfide, which was immediately exposed to HBr-mediated hydrolysis and epimerisation, yielding a 4 : 1 mixture of spiroketolactam **203** and its C2 epimer. The desired epimer was isolated and reduced with lithium in liquid ammonia to exclusively give the Corey intermediate **30**, delivering a second formal synthesis of (±)-pHTX **16**.

The Harrison group published an enantioselective route towards the azaspirocyclic HTX core structure based on the use of carbohydrate starting materials (Scheme 22).[35] Starting from D-mannose **204**, hydroxyl protection gave **205**, which was selectively deprotected at the 5- and 6-positions to yield a diol, which, upon periodate-mediated oxidative cleavage, gave aldehyde **206**. An intermolecular Henry reaction was now carried out, generating nitroalkane **207**. Exposure to tetrabutylammonium fluoride cleaved the silyl protecting group, promoting a second intramolecular Henry reaction that generated the nitrocyclohexane **208** as a mixture of isomers. Attempts to utilise the reversibility of the Henry reaction in order to epimerise this mixture to the single thermodynamic product were unsuccessful, so this mixture was treated with aqueous acetic acid in order to cleave the THP group. Selective tosylation of the generated primary alcohol was then carried out, and the resulting epimeric mixture could now be resolved to give the major desired isomer **209** in 34% yield. Attempts to perform the spirocyclisation of this compound by treatment with aluminium amalgam resulted in complete



Scheme 22 Harrison's 1987 HTX approach. *Reagents and conditions*: (a) acetone, H^+; (b) TBDMSCl, DMF, imidazole; (c) H^+, THF, H_2O; (d) $NaIO_4$, EtOH, H_2O; (e) $O_2N(CH_2)_5OTHP$, KOH, EtOH; (f) TBAF, THF; (g) AcOH; (h) TsCl, pyridine; (i) Ac_2O, pyridine; (j) Al–Hg.

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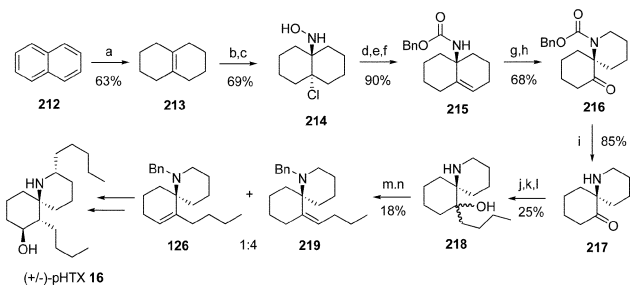
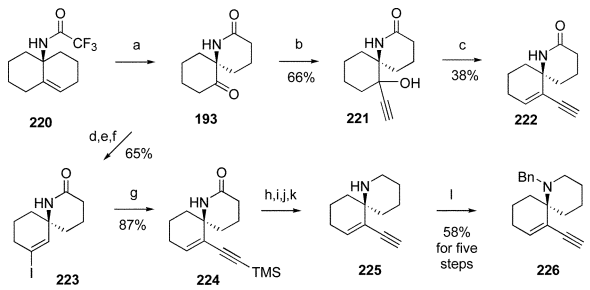
decomposition. Triacetate **210** was therefore formed, and this was found to spontaneously cyclise on exposure to aluminium amalgam to give the desired spirocycle **211** in good yield. This route was unfortunately not progressed further towards the target natural products, but demonstrates the potential of using carbohydrate starting materials in the synthesis of enantiomerically pure azaspirocycles.

In 1984, the Holmes group developed a formal synthesis of (±)-pHTX using the Godleski intermediate **126** (Scheme 23).[36] Starting from naphthalene **212**, dissolving metal reduction gave bicycle **213**, which was converted to the nitrosyl chloride adduct **214**. Elimination of HCl from **214** and subsequent formation of the benzyl carbamate **215** was followed by ozonolysis of the alkene to give a keto aldehyde. The generated aldehyde intermediate spontaneously underwent an intramolecular condensation with the amino group to give a cyclic imine, which was converted to azaspirocycle **216** in good yield by hydrogenation. The piperidine nitrogen of **216** was deprotected giving **217**, and a variety of conditions were then investigated in order to install the C7 alkyl chain. Eventually it was found that a modest yield of the isomeric alcohols **218** could be achieved after the repetitive addition of *n*-butyllithium, followed by quenching with methanol. Dehydration of this mixture gave an inseparable mixture of exocyclic and endocyclic alkenes, and these were converted to the *N*-benzyl derivatives in order to aid identification. The mixture was found to contain a 4 : 1 ratio of the undesired exocyclic isomer **219** and the desired endocyclic **126** respectively. It was then attempted to isomerise this mixture to the desired product, based on the established preference for endocyclic double bonds within six-membered rings. A large number of isomerisation conditions were attempted but unfortunately were found to be unsuccessful, and in some cases, were found to push the equilibrium further in favour of the undesired exocyclic alkene. They concluded that this unexpected thermodynamic preference for the exocyclic double bond is due to the ring strain caused by having the cyclic double bond α to the spirocyclic centre.



Scheme 23 Holmes' 1984 (±)-pHTX formal synthesis. *Reagents and conditions*: (a) Li, $EtNH_2$, Me_2NH; (b) isoamyl nitrate, HCl; (c) H_2, Pt, EtOH; (d) NaOMe, MeOH; (e) Al–Hg, THF, H_2O, reflux; (f) $PhCH_2OCOCl$; (g) O_3, DCM, −78 °C; Me_2S; (h) H_2, PtO_2, EtOH; (i) Me_3SiI, MeCN; (j) *n*BuLi; (k) MeOH; (l) repeat last two steps five times; (m) $KHSO_4$, 170 °C; (n) $PhCH_2Br$, KI, *i*Pr_2NEt, MeCN.

The Holmes group then published an approach towards the side-chain-unsaturated histrionicotoxins in 1988 (Scheme 24).[37] This route started with the ruthenium tetraoxide-mediated cleavage of cyclic alkene **220**, which generated the azaspirocyclic keto lactam **193**. Treatment of this compound with lithium acetylide gave the acetylenic carbinol **221** as a single indeterminable isomer. A

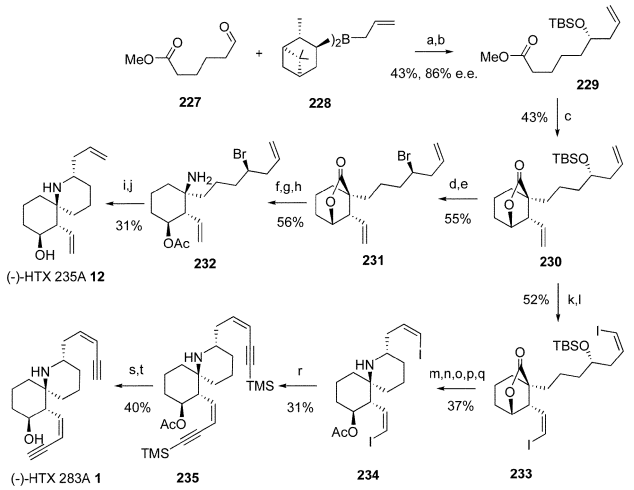


Scheme 24 Holmes' 1988 (±)-pHTX formal synthesis. *Reagents and conditions*: (a) RuO_4, $NaIO_4$, THF; (b) LiC≡CH, THF, −78 °C; (c) $SOCl_2$, pyridine; (d) $N_2H_4{\cdot}H_2O$, 100 °C; (e) I_2, TMG, THF; (f) TMG, 90 °C; (g) Me_3Si–C≡CH, $Pd(PPh_3)_4$, CuI, *n*$BuNH_2$, benzene; (h) Lawesson's reagent, toluene, 100 °C; (i) $Me_3O^+\ BF_4^-$, DCM; (j) $NaBH_4$, MeOH, −78 °C; (k) Na_2CO_3, MeOH; (l) BnBr, NaI, MeCN, *i*Pr_2NEt.

variety of standard conditions were then attempted to dehydrate this tertiary alcohol, but it was found to be surprisingly resistant, presumably due to the unfavourable energetics involved in the formation of the endocyclic double bond. Eventually, they found that exposure of this alcohol to thionyl chloride generated the unsaturated azaspirocycle **222** in a moderate 38% yield.

A second approach towards the unsaturated spirocycles was also mentioned in this paper, again utilising spirocycle **193**. This was first converted to its hydrazone before being transformed to the vinyl iodide **223** by the action of iodine in the presence of tetramethylguanidine. A palladium-mediated Sonogashira coupling was then carried out to install the enyne side chain, generating **224**, which could be desilylated to form the previously generated **222**. Alternatively, **224** could be reacted with Lawesson's reagent, followed by Meerweins reagent, to give the corresponding thioamino ether. A sodium borohydride-mediated reduction was then carried out to yield spirocyclic amine **225** in high yield, with no sign of allylic rearrangement. Unfortunately, partial desilylation of the enyne was found to occur under these conditions, so this deprotection was taken to completion by the action of sodium carbonate in methanol to give the unsaturated azaspirocycle **225**. This was then converted to the *N*-benzyl derivative **226**, in order to enable purification and full characterisation.

The Stork group were able to develop a pair of impressive asymmetric total syntheses of both (−)-HTX 283A **1** and (−)-HTX 235A **12**, from enantiomerically pure starting materials (Scheme 25).[38] Silyl ether **229** was isolated as a single enantiomer upon the reaction of the (−)-α-pinene-derived borane **228** with aldehyde **227** and subsequent silyl protection. Alkylation of this compound with LDA and *trans*-(2*S*,3*S*)-3-(3-bromopropyl)-2-ethenyloxirane prompted a spontaneous intramolecular cyclisation to yield lactone **230** as a single enantiomer, possessing three correctly set stereogenic centres. Desilylation of the hydroxyl function using dilute HCl was now performed, followed by conversion to bromide **231** using carbon tetrabromide and triphenylphosphine. The construction of the piperidine ring required the conversion of the lactone carbonyl to an amino function, which was achieved by the action of trimethylaluminium and ammonium chloride followed by the addition of acetic anhydride, to give the crude acetoxy amide, which underwent a Hoffmann rearrangement promoted by phenyliodonium bis(trifluoroacetate) to give amine **232**. The desired cyclisation was found to not

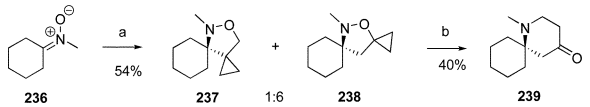


Scheme 25 Stork's 1990 (−)-HTX 283A total synthesis. *Reagents and conditions*: (a) −78 °C to rt; (b) *t*BuMe$_2$SiCl, imidazole, DCM, DMAP; (c) LDA, HMPA, THF, *trans*-(2*S*,3*S*)-3-(3-bromopropyl)-2-ethenyloxirane, −78 °C; LDA, −78 °C to rt; (d) HCl, THF; (e) PPh$_3$, CBr$_4$, Et$_2$O; (f) NH$_4$Cl, AlMe$_3$, benzene, 50 °C; (g) Ac$_2$O, pyridine, DMAP; (h) PhI(CO$_2$CF$_3$)$_2$, MeCN, H$_2$O; (i) Et$_3$N, DCE, 70 °C; (j) MeOH, aq. Na$_2$CO$_3$; (k) O$_3$, PPh$_3$; (l) (Ph$_3$P$^+$CH$_2$I) I$^-$, NaN(TMS)$_2$, HMPA, THF; (m) HCl, THF; (n) PPh$_3$, CBr$_4$, Et$_2$O; NH$_4$Cl, AlMe$_3$, benzene; (o) Ac$_2$O, pyridine, DMAP; (p) PhI(CO$_2$CF$_3$)$_2$, MeCN, H$_2$O; (q) Et$_3$N, DCE, 70 °C; (r) Pd(PPh$_3$)$_4$, CuI, benzene, Me$_3$Si–C≡CH; (s) TBAF; (t) aq. K$_2$CO$_3$, MeOH.

occur spontaneously, but instead required heating at 55 °C in the presence of triethylamine, which promoted the key intramolecular elimination, yielding the desired azaspirocycle. Removal of the acetate protecting group then yielded the target enantiomerically pure (−)-HTX 235A **12** in 10 steps from **227** in an overall yield of 1.8%.

Stork and co-workers then attempted to synthetically elaborate HTX 235A **12** towards its longer side chain relative HTX 283A **1**. They had previously developed a methodology for transforming aldehydes into their respective (*Z*)-vinyl iodides, which could then undergo a palladium-catalysed coupling to give the desired (*Z*)-enynes.[39] In order to convert the terminal olefins in HTX 235A **12** to their respective (*Z*)-vinyl iodides, the amino and hydroxyl functions needed to be protected, and this was found to be extremely difficult in the case of the highly hindered secondary amine, which led to this approach being abandoned. They then postulated that the vinyl iodide motifs could to be installed earlier in the synthetic route, as long as they could survive the chemical transformations needed to generate the target core structure. The dialkenyl lactone **230** was transformed to the dialdehyde by ozonolysis, and the previously developed Stork–Wittig conditions were applied to generate the bis-(*Z*)-vinyl iodide **233**. This intermediate was then successfully converted to the azaspirocycle **234** using conditions similar to those used for the synthesis of HTX 235A **12**. A palladium-catalysed Sonogashira coupling was then performed to yield bis-enyne **235** in adequate yield, which was then deprotected to generate the enantiomerically pure (−)-HTX 283A **1** in 13 steps from **227**.

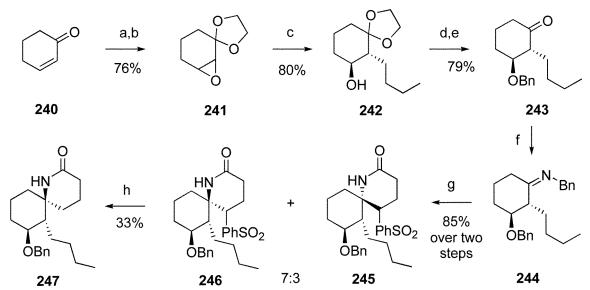
As part of their extensive investigations of the 1,3-dipolar cycloaddition of nitrones and methylenecyclopropanes, and the subsequent thermal rearrangements of the generated isoxazolidines, in 1992 the Brandi group published an application of their approach that generated an azaspirocyclic system similar to that of the HTX core structure (Scheme 26).[40]



Scheme 26 Brandi's 1992 spirocycle formation. *Reagents and conditions*: (a) methylenecyclopropane, benzene, sealed tube, 80 °C; (b) FVT, 400 °C, 10^{-3} mmHg.

When the cyclohexanone-derived *N*-methylnitrone **236** was heated in a sealed tube with methylenecyclopropane, a 6 : 1 mixture of the regioisomeric isoxazolidines **237** and **238** were formed. When the major isomer, **238**, was subsequently exposed to thermal rearrangement conditions, the sole isolable product was the azaspirocycle **239** in 40% yield. This relatively low yield is ascribed to the generation of volatile decomposition products, which could only be detected by GC-MS. This methodology for the rapid generation of the azaspirocyclic systems has yet to be developed further towards the HTX alkaloid family.

The Thompson group also published work in 1992 describing their investigations towards the azaspirocyclic core structure of the HTX alkaloids (Scheme 27).[41] Their approach started with cyclohexanone **240**, which was protected as a ketal before being converted to epoxide **241**. A regioselective alkylation was then achieved using boron trifluoride etherate and butyllithium, which generated alcohol **242** in good yield. The high regioselectivity was thought to be due to chelation between the lithium and the ketal oxygens, directing the organometallic attack towards the α-ketal position. Protection of the hydroxyl as its benzyl ether, followed by acetal deprotection, gave ketone **243**, which was quantitatively converted to imine **244**. Activation of this imine with boron trifluoride etherate allowed it to react with the dianion of 4-(benzenesulfonyl)butanoic acid to give a 7 : 3 mixture of azaspirocycles **246** and **245** respectively. A number of methods were then attempted to cleave the sulfone group, but these were all found to give high yields of ring-opened products. The best conditions found for this sulfone cleavage were found to be sodium amalgam in methanol, which generated the advanced azaspirocycle **247** in a modest 33% yield.



Scheme 27 Thompson's 1992 HTX approach. *Reagents and conditions*: (a) TsOH, $(HOCH_2)_2$, toluene; (b) *m*CPBA, NaHCO$_3$, DCM; (c) BF$_3$·Et$_2$O, *n*BuLi, THF; (d) BnBr, NaH, DMF; (e) HCl, H$_2$O, THF; (f) BnNH$_2$, benzene; (g) BF$_3$·Et$_2$O, 4-phenylsulfonylbutanoic acid, *n*BuLi, THF, −78 °C; (h) Na–Hg, MeOH, 0 °C.

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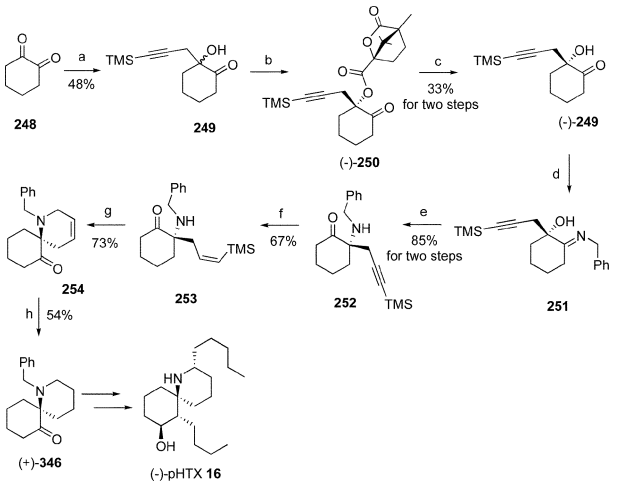
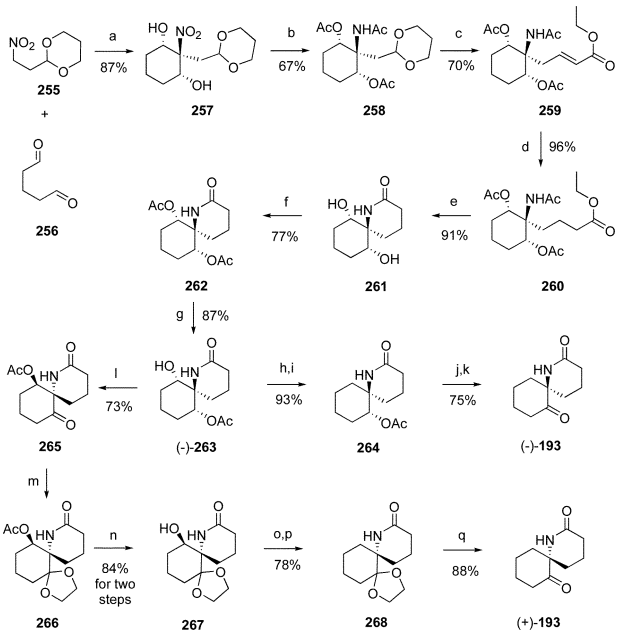
In 1996, the Vatele group published a formal synthesis of (−)-pHTX **16** utilising an iminium–vinylsilane cyclisation as the key step in the formation of the spirocyclic system (Scheme 28).[42] Starting from cyclohexanedione **248**, initial conversion to its trimethylsilyl enol ether, followed by addition of the alkyne side chain by a Grignard reaction, gave the racemic α-hydroxyl ketone **249**. This racemic mixture was converted into the camphanate ester **250**, allowing the two diastereomers to be separated by column chromatography. Deprotection then gave the desired α-hydroxyl ketone enantiomer (−)-**249** with an ee of 96%. Condensation of **249** with benzylamine then gave **251**, which, upon heating, underwent a rearrangement to give the α-amino ketone **252** in 84% yield. A Lindlar hydrogenation then generated the *Z*-alkene **253**, which was treated with paraformaldehyde, generating an intermediate iminium ion that underwent cyclisation to give the key spirocycle **254**. Chemoselective hydrogenation was then carried out using Adam's catalyst, giving (+)-**346** in 54% yield and concluding the asymmetric formal synthesis of pHTX **16**.



Scheme 28 Vatele's 1996 (+)-pHTX formal synthesis. *Reagents and conditions*: (a) TMSCl, Et_3N, DCM; −40 °C, $LiCH_2C{\equiv}C{-}SiMe_3$; HCl; (b) (−)-camphanic acid chloride, DMAP, DCM, 0 °C; (c) $n$$Bu_4NOH$, H_2O, DCM; (d) benzylamine, toluene, reflux; (e) diglyme, reflux: (f) H_2, $Pd/BaSO_4$, EtOH; (g) paraformaldehyde, camphorsulfonic acid, MeCN, 70 °C; (h) PtO_2, H_2, EtOH.

The Luzzio group described their successful synthetic approach towards both (+)- and (−)-pHTX **16**, utilising an enzymatic desymmetrisation and a double Henry reaction as the key steps in the synthesis of both antipodes of the enantiomerically pure Kishi lactone **193** (Scheme 29).[43] Their route started with a double Henry condensation between glutaraldehyde **256** and nitroacetal **255** which readily formed the crystalline nitrodiol **257** in good yield. Triacetyl protection then gave **258**, and this was followed by a tandem ultrasound-promoted acetal deprotection/Wittig homologation to yield the α,β-unsaturated ester **259** in 70% yield. Catalytic hydrogenation of **259** gave the saturated ester **260**. Acid-mediated hydrolysis of the acetyl functions resulted in a crude dihydroxyamino acid, which was exposed to a DCC-mediated lactamisation to efficiently generate the core azaspirocyclic diol **261** in excellent yield. Several enzymatic desymmetrisations were then explored for the preparation of optically pure monoacetate **263**. The first of these to be investigated was the regioselective



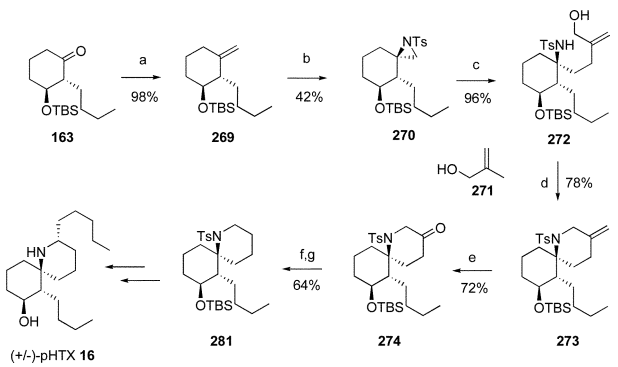
Scheme 29 Luzzio's 1999 (+)- and (−)-pHTX total synthesis. *Reagents and conditions*: (a) TMG, THF; (b) Al–Hg, THF, Raney Ni, H_2; Et_3N, ultrasound, Ac_2O, pyridine; (c) AcOH, H_2O, ultrasound; $EtOCOCH_2PPh_3^+$ Br^-, Et_3N; (d) H_2, Pd/C, MeOH; (e) 1.2 M HCl, reflux; DCC, DMAP, pyridine; (f) AcCl, DMAP, DCM; (g) pig liver esterase, pH 7; (h) PhOCSCl, DMAP, DCM; (i) Bu_3SnH, AIBN, toluene, 95 °C; (j) NaOMe, MeOH; (k) $(COCl)_2$, DMSO, DCM: (l) DMSO, DCC, H_3PO_4; (m) $HOCH_2CH_2OH$, TsOH, toluene; (n) NaOMe, MeOH; (o) PhOCSCl, DMAP, DCM; (p) Bu_3SnH, AIBN, toluene, 95 °C; (q) AcOH, TFA, H_2O.

monoacylation of achiral spirodiol **263** using vinyl acetate and a range of esterases and lipases. Unfortunately, all the attempted conditions failed to produce any acylated products. They next formed the *meso*-diacetylated compound **262** by chemical methods and then attempted an enzymatic mono-hydrolysis using a range of enzymes. The use of porcine liver esterase at pH 7.5 allowed them to isolate the crystalline (−)-monoacetate **263** in 87% yield and 93% ee as determined by ^{19}F NMR analysis of the Mosher ester derivative. They also attempted this enzymatic hydrolysis on triacetate **258**, but found this to be completely resistant to all the attempted conditions. The enantiomerically pure alcohol **263** was then converted to its methylcarbonate and phenylthiocarbonates, with the aim of performing a free-radical deoxygenation. Treatment of the methylcarbonate with tri-*n*-butyltin hydride and AIBN only resulted in complete recovery of the alcohol **263**. Treatment of the phenylthiocarbonate under the same conditions, however, resulted in the generation of the desired dehydroxy acetate **264** in an excellent 93% yield. Deacylation followed by a Moffat oxidation then yielded the enantiomerically pure Kishi lactam (−)-**193** in 75% yield.

It was then attempted to generate the (+) antipode of **193** from the enantiomerically pure monoacetate **263**, and this was found to be mostly a matter of protecting group manipulation. Moffat oxidation of **263** gave keto acetate **265** in good yield, and this was then converted to ketalacetate **266** by the action of ethylene glycol. Deacylation then gave **267** and this was followed by a free-radical deoxygenation, using the same conditions utilised before,

to yield spirolactam **268**. A simple acid-mediated deprotection then yielded the enantiomerically pure (+)-**193** in excellent yield.

In 2006, the Harrity group reported a formal synthesis of (±)-pHTX **16** based on a stepwise [3 + 3] annelation strategy (Scheme 30).[44] Starting from TBS-protected hydroxy ketone **163**, the ketone function was first methylated using Nysted's reagent (cyclo-dibromo-di-μ-methylene-[μ-(tetrahydrofuran)]trizinc) to give alkene **269**. A number of methods were then investigated for the diastereoselective aziridination to give **270**. Eventually, it was determined that Sharpless' conditions generated the desired aziridine, containing the required stereochemistry, in 42% yield. They next investigated a direct [3 + 3] cycloaddition in order to access the spirocyclic piperidine directly. This was unfortunately found to be unsuccessful, so they turned their attention to a stepwise addition/cyclisation sequence. A double deprotonation of methallyl alcohol **271**, followed by the addition of magnesium bromide, provided a reagent that underwent efficient addition to the aziridine of **270** to provide sulfonamide **272**. This then cyclised in the presence of titanium isopropoxide and a palladium catalyst to give spirocycle **273** in excellent yield. The remainder of the synthesis involved straightforward functional group interconversions. Firstly, an oxidative cleavage of the olefin function gave ketone **274**, which was then reduced to the hydroxyl followed by a Barton–McCombie type deoxygenation to give the Tanner spirocycle **281**, completing the formal synthesis of (±)-pHTX **16**.

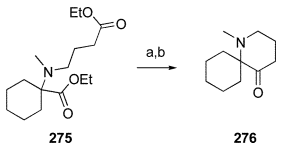


Scheme 30 Harrity's 2006 (±)-pHTX formal synthesis. *Reagents and conditions*: (a) Nysted's reagent, $TiCl_4$, THF, 0 °C; (b) $TsClN^-\ Na^+$, NBS, MeCN; (c) $CH_2{=}C(Me)CH_2OH$, *n*BuLi, TMEDA, $MgBr_2$, Et_2O, THF; (d) $Pd(OAc)_2$, PPh_3, $Ti(O\textit{i}Pr)_4$, toluene, reflux; (e) OsO_4, NMO; $NaIO_4$, acetone, H_2O; (f) $NaBH_4$, MeOH; (g) NaH, CS_2, MeI, THF; AIBN, $n Bu_3SnH$, benzene, reflux.

4 Approach C: formation of the C2–C3, C3–C4 or C4–C5 bond

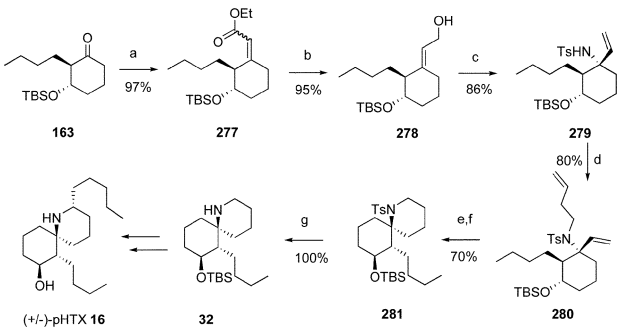
This approach involves the carbocyclic core being formed with the quaternary centre already present. Standard carbon–carbon bond forming reactions are then used to close the second ring to form the azaspirocycle. Due to the inherent difficulties in forming quaternary centres, as well those associated with handling free amines, there have been relatively few examples of the preparation of a spirocyclic system using this approach.

The first of these, carried out by the Schipper group in the 1960s, generated spirocycle **276** by Dieckmann condensation of tertiary amine **275**, followed by decarboxylation (Scheme 31).[45] Unfortunately, this precursor lacks any of the substitution required in order to successfully convert it into the HTX skeleton, as well as presenting the problem of demethylating the nitrogen function.



Scheme 31 Schipper's 1961 spirocyclisation. *Reagents and conditions*: (a) $NaBH_4$, THF, EtOH, −78 °C; (b) NaH, THF.

Later, in 1999, Tanner *et al.* developed a formal synthesis of (±)-pHTX **16**, utilising a [2,3]-sigmatropic rearrangement and ring-closing metathesis strategy (Scheme 32).[46] Starting with the ketone **163**, formed from the respective epoxide, a Peterson olefination yielded the α,β-unsaturated ester **277** as a 2 : 1 mixture of *E* and *Z* isomers. This mixture was then reduced to the corresponding mixture of allylic alcohols, and the desired *E*-isomer **278** was isolated in a 61% yield. This alcohol was treated with *N*-(phenylseleno)phthalimide (NPS) and tributylphosphine to form the allylic selenide intermediate, which was immediately treated with chloramine-T to induce the [2,3]-sigmatropic rearrangement, giving **279** as a single diastereomer in an impressive 86% yield. They then encountered problems installing the requisite four-carbon chain, and after extensive experimentation, eventually found that exposure of the *N*-anion to the triflate of 3-buten-1-ol induced the conversion to **280** in an isolated yield of 80%. The crucial ring-closing metathesis step was also found to be troublesome, and acceptable yields could only be achieved by prolonged heating in toluene at 90 °C using 20 mol% of Grubbs' second-generation catalyst. This produced the azaspirocycle **281** in 80% yield, and subsequent catalytic hydrogenation yielded the Corey intermediate **32** in 85% yield.



Scheme 32 Tanner's 1999 (±)-pHTX formal synthesis. *Reagents and conditions*: (a) lithium trimethylsilylacetic acid ethyl ester; (b) DIBAL; (c) NPS, Bu_3P; chloramine-T; (d) BuLi, THF, HMPA; $CH_2(CH_2)_2OTf$; (e) Grubbs' catalyst, toluene, 90 °C; (f) H_2, Adams catalyst; (g) TBAF, H^+.

5 Approach D: formation of the C5–C6 bond

The potential of intramolecular [2 + 2] cycloaddition for the rapid generation of the spirocyclic systems was first demonstrated in 1984 by the group of Smith, in an unsuccessful approach towards the Ibuka intermediate **39** (Scheme 33).[47] Starting from

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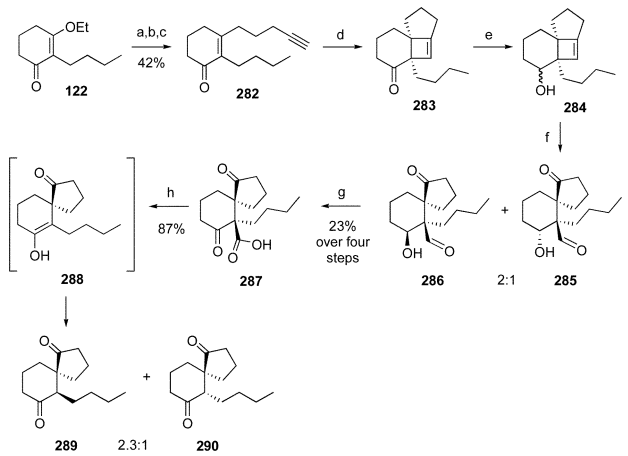
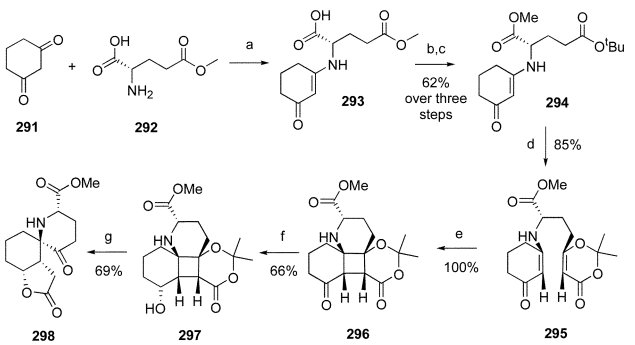


Scheme 33 Smith's 1984 (±)-pHTX formal synthesis. *Reagents and conditions*: (a) $IMg(CH_2)_3C{\equiv}C–TMS$, THF; (b) HCl, THF; (c) TBAF, THF; (d) *hv*, MeOH, NaOAc; (e) $NaBH_4$, MeOH; (f) O_3, DCM, −78 °C; (g) $NaIO_4$, RuO_4, H_2O, CCl4; (h) toluene, reflux; *p*TsOH, THF, reflux.

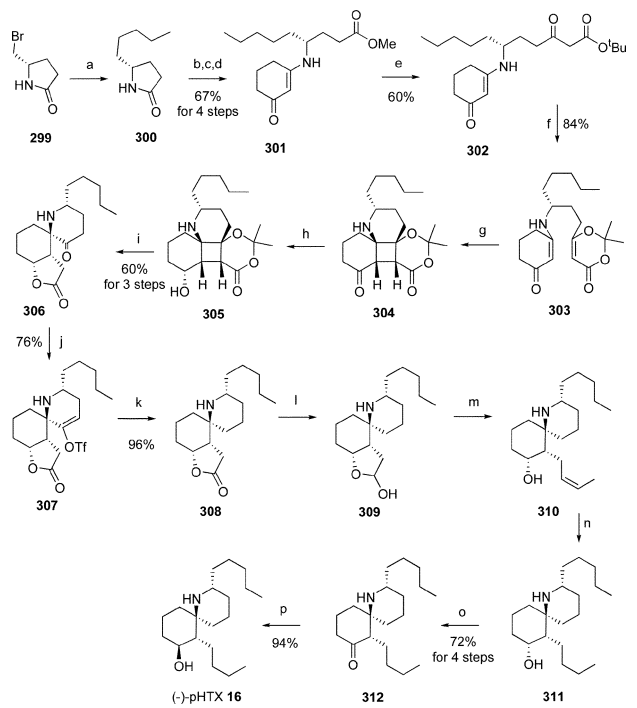
the enol ether **122**, they performed a Grignard addition, followed by hydrolysis and silyl deprotection, to give alkyne **282** in 42% yield. Attempts to improve upon this yield were unsuccessful, so they decided to carry on and investigate the [2 + 2] cycloaddition process. Irradiation of alkyne **282** through uranium glass, in methanol buffered with sodium acetate, yielded the desired crude tricycle **283**. However, attempts to purify this compound only resulted in decomposition, presumably due to the inherent strain present in the ring system. An *in situ* sodium borohydride reduction of the crude ketone yielded an inseparable mixture of the more stable epimeric alcohols **284**. These crude alcohols were exposed to ozonolysis conditions, followed by a reductive work-up, to generate the aldehydes **285** and **286** as a mixture of hydroxyl epimers. Conversion to the acetates then allowed these isomers to be isolated, and they were determined to have a 2 : 1 ratio in favour of the unwanted hydroxyl epimer **286**. Unfortunately, attempts to decarboxylate the desired epimer **285** with Wilkinson's reagent under a wide variety of conditions led to either decomposition or recovery of the starting material. Smith then decided to investigate the decarboxylation of the mixture in the assumption that the C6 stereochemistry could be controlled at a later stage. A RuO_4-mediated oxidation of the epimeric mixture obtained directly from the [2 + 2] cyclisation was then carried out, yielding the crystalline carboxylic acid **287**. The thermal decarboxylation of this compound was found to proceed smoothly, giving a 10 : 1 mixture of epimeric spirodienones. Stereochemical assignments of these two compounds were carried out, and the minor isomer was found to correlate with an authentic sample of **290**, formed through chemical modification of a known sample of intermediate **39** obtained from the Ibuka group. The unfortunate bias in favour of the undesired epimer prompted an investigation of the re-equilibration of this mixture, in order to effect a more efficient advancement to the HTX alkaloids. They found that the ratio could be made more favourable by the use of acid-catalysed re-equilibration under thermal conditions, although they were only able to improve this ratio to 2.3 : 1 in favour of the undesired isomer **289**. This route was therefore not advanced further due to this unfortunate inefficiency at this late stage in the synthesis.

The Winkler group had more success developing a similar cycloaddition methodology towards the HTX alkaloids, and published an elegant approach towards an enantiomerically pure advanced intermediate in 1986 (Scheme 34).[48] Cyclohexane-1,3-dione **291** was condensed with methyl L-glutamate **292** to yield the optically pure vinylogous amine **293**. Without further purification, this product was treated with the lithium enolate of *tert*-butyl acetate to form the β-keto ester **293**, the carboxylic acid function of which was immediately converted to the methyl ester **294** by the action of diazomethane. Dioxolenone formation was then accomplished using a mixture of trifluoroacetic anhydride and trifluoroacetic acid in acetone, which gave the key photosubstrate **295** in excellent yield. Irradiation of this compound promoted the desired [2 + 2] cycloaddition, generating **296** as the single photoadduct in quantitative yield. The exclusive formation of **296** can be explained by the lower steric hindrances present in the transition state when the methyl ester group adopts a pseudo-equatorial configuration, as opposed to the large steric clashes present in the pseudo-axial transition state. A facially selective borohydride reduction was then carried out, yielding alcohol **297** as the single product. Deprotonation of this hydroxyl function promoted lactone formation to furnish the enantiomerically pure azaspirocyclic lactone **298**, which possesses three of the four stereocentres required for advancement to the HTX alkaloids.



Scheme 34 Winkler's 1986 HTX approach. *Reagents and conditions*: (a) benzene, reflux; (b) $MeCO_2tBu$, BuLi, THF, −78 °C; (c) CH_2N_2, THF, 0 °C; (d) trifluoroacetic anhydride, TFA, acetone; (e) *hv*, MeCN, 0 °C; (f) $NaBH_4$, THF, EtOH, −78 °C; (g) NaH, THF.

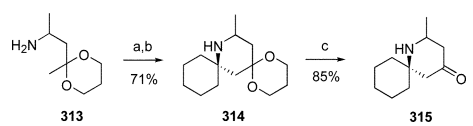
The Winkler group continued to work on this elegant stereoselective methodology, and in 1989 they published a modification of the previous route that resulted in the first stereoselective synthesis of (−)-pHTX (Scheme 35).[49] The reaction of enantiomerically pure bromo pyrrolidinone **299** (derived from L-glutamic acid) with butyl organocuprate resulted in the generation of alkyl pyrrolidinone **300**. Acid hydrolysis liberated the amino acid, which was immediately condensed with cyclohexane-1,3-dione and converted to the methyl ester vinylogous amide **301**. Conversion to the photoadduct **303** was carried out as before, and irradiation to promote the core cycloaddition was again found to give a single product, forming **304** in near-quantitative yield. A stereoselective reduction to form **305** was then carried out, followed by an intramolecular lactone formation to yield **306**. Conversion of this lactone to the enol triflate **307** was carried out using LDA and *N*-phenyltrifluoromethanesulfonimide, and palladium-catalysed hydrogenation of the crude product yielded the fully saturated azaspirocycle **308**. DIBAL reduction then yielded the lactol **309**,



Scheme 35 Winkler's 1989 (−)-pHTX total synthesis. *Reagents and conditions*: (a) nBu$_2$CuLi, Et$_2$O; (b) 6 M HCl; (c) 1,3-cyclohexanedione, benzene; (d) DCC, DMAP, MeOH; (e) LDA, tBuOCOMe, THF; (f) acetone, $(CF_3CO)_2O$, CF_3CO_2H; (g) $h\nu$, MeCN; (h) $NaBH_4$, EtOH; (i) NaH, THF; (j) LDA, Tf_2NPh, THF; (k) H_2, PtO_2, EtOH; (l) $LiAl(OBu)_3H$, THF; (m) nBuLi, $Ph_3P^+MeBr^-$, THF; (n) H_2, PtO_2, EtOH; (o) Dess–Martin periodinane, DCM; (p) $LiAl(OtBu)_3H$, THF.

which was immediately exposed to a Wittig olefination to give **310** as a 1 : 1 mixture of olefin isomers. A second palladium-catalysed hydrogenation reduced this double bond to generate the C8 epimer of pHTX **311**. Dess–Martin oxidation yielded the azaspirocyclic ketone **312**, and a number of reduction conditions were then screened in order to stereoselectively generate the required axial hydroxyl function. Reduction using lithium in liquid ammonia was found to exclusively give the undesired equatorial C8 epimer **311**. Treatment with an excess of lithium tri-*tert*-butoxyaluminium hydride in THF, however, gave a quantitative yield of a 19 : 1 mixture in favour of the desired isomer. Purification then furnished (−)-pHTX **16**, giving a highly impressive enantioselective total synthesis in 16 steps with an overall yield of 9%.

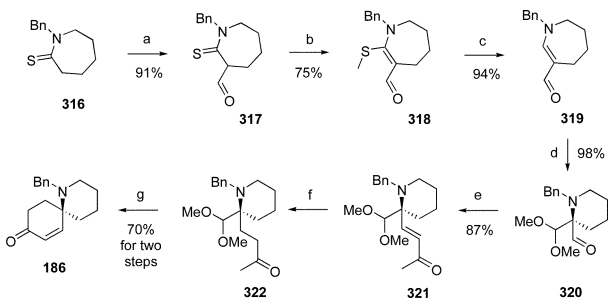
The Troin group published a spirocyclisation route involving an intramolecular Mannich reaction in 2001, which shows potential for further development towards the HTX core structure (Scheme 36).[50] Condensation of α-methylamine **313** with cyclohexanone produced an intermediate imine, which when exposed to boron trifluoride etherate, underwent an intramolecular Mannich reaction to yield azaspirocycle **314** in good yield, which was subsequently deprotected to give **315**.



Scheme 36 Troin's 2001 spirocyclisation. *Reagents and conditions*: (a) *p*TsOH, cyclohexanone, DCM; (b) $BF_3{\cdot}Et_2O$; (c) HCl, acetone.

6 Approach E: formation of either C7–C8, C8–C9, C9–C10 or C10–C11 bonds

This approach involves the formation of a piperidine ring with a quaternary centre situated α to the nitrogen. Conventional carbon–carbon bond forming reactions are then utilised in order to complete the spirocyclic ring system. A number of approaches involving this methodology have been based on the ring contraction of cyclic enamino aldehydes in order to generate the quaternary piperidine ring rapidly. The first group to utilise this approach was that of Duhamel in 1986, in a formal synthesis of (±)-pHTX **16** (Scheme 37).[51] Formylation of thiolactam **316** with Bredereck's reagent, followed by hydrolysis, yielded aldehyde **317** in excellent yield. Treatment of this aldehyde with methyl triflate, followed by a triethylamine-mediated deprotonation, generated the methylthioaldehyde **318**. This underwent a Raney nickel-mediated desulfurisation to yield the enamino aldehyde **319**. Upon treatment with bromine and triethylamine in methanol, the desired ring-contraction proceeded in near-quantitative yield, to afford the acetal **320**. Condensation with acetone gave the unsaturated keto acetal **321**, which could then undergo palladium-catalysed hydrogenation to yield intermediate **322**. Acetal hydrolysis then promoted the spontaneous cyclisation to yield the Pearson intermediate **186**.



Scheme 37 Duhamel's 1986 (±)-pHTX formal synthesis. *Reagents and conditions*: (a) tBuOCH$(NMe_2)_2$, 140 °C; (b) $MeOSO_2F$, CH_2Cl_2, Et_3N; (c) Raney Ni, acetone; (d) Br_2, Et_2O, −70 °C; MeOH, Et_3N, −70 °C; (e) tBuOK, acetone, THF, −10 °C; (f) H_2, Pd/C, KOH, EtOH, EtOAc; (g) 3 M HCl, reflux.

Over the next few years, the Duhamel group were able to expand upon this methodology, culminating in a total synthesis of (±)-pHTX **16** in 1989 (Scheme 38).[52] Starting from cyclic ketone **323**, which already contains the future C2 pentyl side chain, they generated benzyl-protected lactam **324** by an acid-catalysed Beckmann-type ring expansion. Application of their previously developed methodology then generated the pentyl analogue of **319**. When this compound was exposed to the key ring contraction step, however, the major product was found to contain an undesired *trans* relationship between the aldehyde and pentyl side chains. Further investigation revealed that when the methyl ester **325** was used instead, the ring contraction proceeded to exclusively give the desired *cis* isomer **326** in an almost quantitative yield. A Wittig reaction then advanced this intermediate to the α,β-unsaturated ketone **327**, and hydrogenation yielded the saturated ester **328**. DIBAL reduction of ester **328** gave aldehyde **329**, which underwent a base-promoted internal condensation to give spirocycle **330**. A methodology analogous to that used

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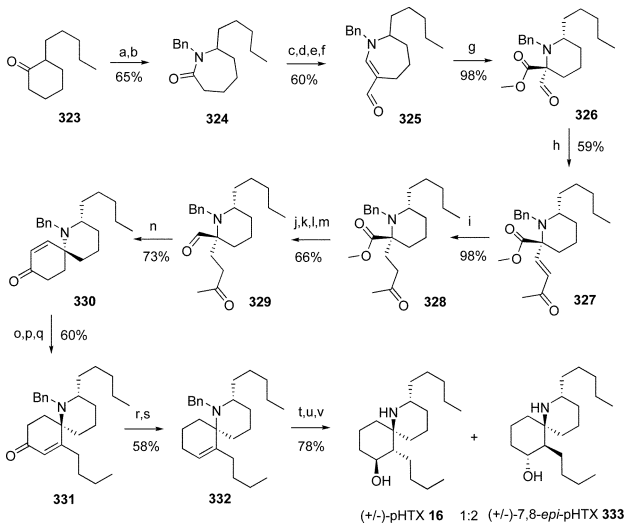
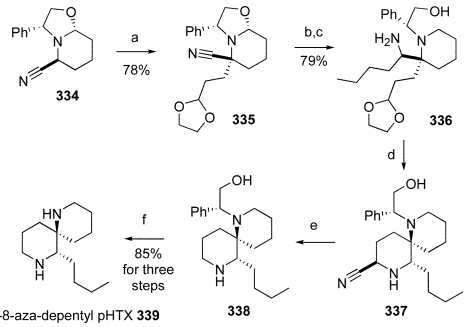


Scheme 38 Duhamel's 1989 (±)-pHTX total synthesis. *Reagents and conditions*: (a) H_2NOSO_3H, HCO_2H; (b) *t*BuOK, $PhCH_2Br$; (c) Lawesson's reagent; (d) *t*BuOCH$(NMe_2)_2$; (e) $MeOSO_2F$; (f) Raney Ni; (g) Br_2, Et_2O, −70 °C; MeOH, Et_3N, −70 °C; (h) $Ph_3P{=}CHCOMe$, *t*BuOK, THF, −5 °C; (i) H_2, Pd/C; (j) $(CH_2OH)_2$, *p*TsOH, toluene; (k) DIBAL, Et_2O; (l) $(COCl)_2$, DMSO, Et_3N; (m) 3 M HCl, reflux; (n) *t*BuOK, THF; (o) Bu_2CuLi, Et_3N, TMSCl, Et_2O; (p) PhSeCl, THF; (q) H_2O_2, AcOH; (r) $NaBH_4$, MeOH; (s) $LiAlH_4$, $AlCl_3$, Et_2O; (t) BH_3, Me_2S, THF; (u) H_2O_2, NaOH; (v) H_2, Pd/C.

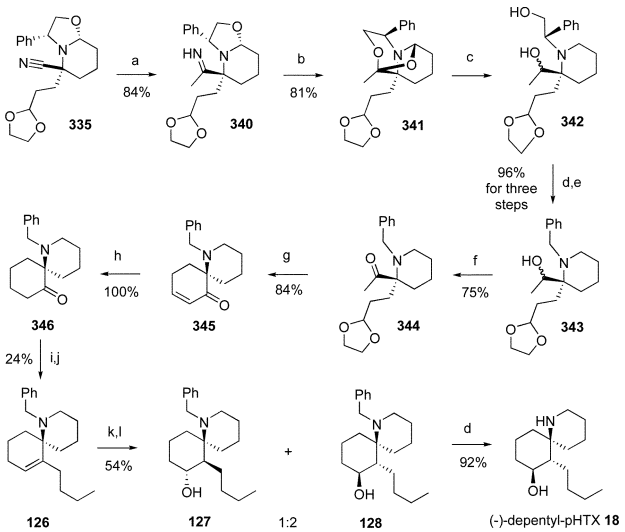
by Pearson[32] was then utilised to complete the synthesis, but the 1,4-organocuprate addition was found to produce an unsatisfactory amount of the 1,2-addition side-product. The desired transformation was eventually accomplished by initial addition of triethylamine and chlorotrimethylsilane to the organocuprate before addition of the enone. The resulting intermediate was directly treated with benzeneselenyl chloride, followed by hydrogen peroxide in acetic acid, to yield the desired butyl enone **331** in a 60% yield. Borohydride reduction then removed the redundant ketone function to give **332**. Godleski's hydroboration–oxidation procedure was then carried out, generating a mixture of alcohols that were debenzylated and separated to yield a 1 : 2 mixture of (±)-pHTX **16** and its 7,8-epimer **333**.

The Husson group reported an approach towards the 8-aza analogue **339** of (+)-dependyl-pHTX **18** in 1989 (Scheme 39).[53] Starting with the chiral nitrile **334**, a stereoselective allylation was performed to yield the ketal **335** as a single isomer. This compound was then submitted to a second alkylation step, using butyllithium to fabricate the imine, which was then reduced to give a 95 : 5 mixture of the desired (*R*)-amine **336** and its unwanted (*S*)-enantiomer. A one-step acetal deprotection/reductive amination was then attempted, but unfortunately this reaction failed to proceed under a range of conditions, with the only product isolated being that from the condensation between the aldehyde and the piperidine nitrogen. A stepwise approach was next investigated. An intermediate iminium ion was generated by an acid-catalysed cyclisation, and this was immediately trapped with potassium cyanide to furnish the unstable amino-nitrile **337**. Borohydride reduction yielded the more stable spirodiamine **338**, and the chiral auxiliary was then removed by palladium-catalysed hydrogenation to yield the target (+)-8-azadependyl-pHTX **339** in an excellent overall yield.



Scheme 39 Husson's 1991 (+)-8-azadependyl-pHTX total synthesis. *Reagents and conditions*: (a) LDA, THF, −78 °C; 2-(2-bromoethyl)-1,3-dioxolane, THF; (b) BuLi, Et_2O, −78 °C; (c) $NaBH_4$, MeOH; (d) HCl, KCN, DCM, H_2O; (e) $NaBH_4$, MeOH; (f) H_2, Pd/C, MeOH.

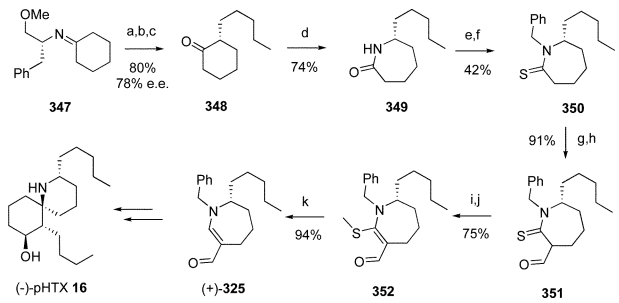
Husson *et al.* then reapplied their methodology towards an asymmetric synthesis of (−)-dependyl-pHTX **18**, which also constituted a formal synthesis of (−)-pHTX **16** (Scheme 40).[54] The previously generated chiral nitrile **335** was alkylated with methyllithium, generating the imine **340**, which was immediately hydrolysed under acidic conditions. The expected free ketone was not formed, however, and instead they isolated the tricyclic ketal **341**. Reduction of this unexpected cyclic ether system was carried out using lithium aluminium hydride and aluminium trichloride to generate an epimeric mixture of alcohols **342**. The chiral auxiliary was then removed by hydrogenation and replaced with a benzyl function, yielding **343**. Swern oxidation of **343** yielded the crude ketone **344**, which was readily converted to the spirocyclic enone **345** by refluxing in HCl. A 1,4-reduction was then carried out using a $BaSO_4$-poisoned catalyst to prevent removal of the benzyl protecting group, giving spirocycle **346**. Alkylation of the resulting ketone was then investigated. Both Grignard and cerium reagents failed to produce the desired product, and eventually the best conditions found used a butyllithium alkylation to yield an



Scheme 40 Husson's 1991 (−)-dependyl-pHTX total synthesis. *Reagents and conditions*: (a) MeLi, Et_2O, −78 °C; (b) citric acid, H_2O_2, DCM; (c) $LiAlH_4$, $AlCl_3$, THF, −40 °C; (d) H_2, Pd/C, MeOH; (e) $PhCH_2Br$, DMF, $NaHCO_3$, 80 °C; (f) oxalyl chloride, DMSO, Et_3N; (g) 1.5 M HCl, reflux; (h) H_2, Pd, $BaSO_4$, EtOAc; (i) BuLi, Et_2O; (j) HI, benzene, reflux; (k) $BH_3{\cdot}Me_2S$, THF, reflux; (l) NaOH, H_2O_2, diglyme, 80 °C.

intermediate alcohol in a poor 37% yield. Reaction with hydrogen iodide in refluxing benzene then promoted a dehydration, producing a single enantiomer of the Godleski endocycle **126**. The previously described hydroboration–oxidation was then carried out to yield a separable 2 : 1 mixture of the desired **128** and its C7,C8 epimer **127**. Finally, hydrogenation of the benzyl function yielded (−)-depentyl-pHTX **18** in good yield.

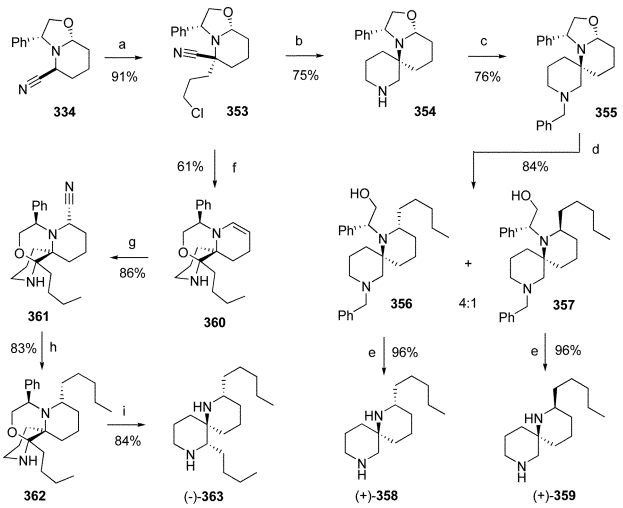
In 1991, the Duhamel group reported a second expansion of their previous methodology, describing the generation of the optically pure (+)-enamine **325**, constituting a formal synthesis of (−)-pHTX **16** (Scheme 41).[55] Condensation of cyclohexanone with 2(*R*)-amino-3-phenylpropan-1-ol, followed by methylation of the latent oxygen function, resulted in the auxiliary-bound imine **347**. Deprotonation, followed by a facially selective alkylation with pentyl iodide, resulted in the formation of chiral ketone **348** with a 78% ee after cleavage of the chiral auxiliary. This was advanced using their previously developed methodology to generate the enantiomerically pure (+)-**325**.



Scheme 41 Duhamel's 1991 (−)-pHTX formal synthesis. *Reagents and conditions*: (a) LDA; (b) $C_5H_{11}I$; (c) AcOH, H_2O; (d) H_2NOSO_3H, HCO_2H; (e) *t*BuOK, $PhCH_2Br$; (f) Lawesson's reagent; (g) *t*BuOCH$(NMe_2)_2$; (h) 2 M HCl; (i) $MeOSO_2F$; (j) Et_3N; (k) Raney Ni.

A further modification of the Husson group's methodology was reported in 1993, describing a total asymmetric synthesis of (−)-8-aza-pHTX **363** and (+)-8-azadebutyl-pHTX **358** (Scheme 42).[56] Starting with chiral nitrile **334**, alkylation with the Grignard reagent of 1-chloro-3-iodopropane yielded the chloronitrile **353** as a single isomer. A lithium aluminium hydride reduction of the axial nitrile then promoted an intramolecular cyclisation to give spirodiamine **354**, which was subsequently benzyl-protected to give **355**. The reaction with *n*-pentylmagnesium bromide then produced a 4 : 1 separable mixture of spirocycles **356** and **357**, respectively. When these two epimeric compounds were individually subjected to palladium-catalysed hydrogenation, the benzyl function was cleaved, resulting in the total synthesis of (+)-8-aza-7-debutyl-pHTX **358** and (+)-8-aza-7-debutyl-2-*epi*-pHTX **359** in good yields.

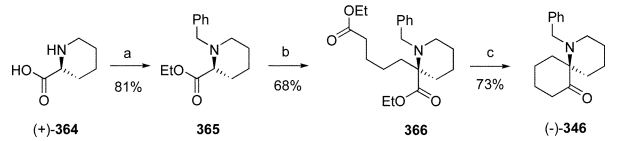
In order to generate the dialkylated aza analogue of pHTX **16**, the Husson group had to develop a method to install the C7 butyl chain. A butyllithium addition to the cyanide function of **353** was found to produce an intermediate imine anion that underwent an intramolecular cyclisation with the proximal alkyl chloride to yield a spirocyclic imine, which, on exposure to a second equivalent of butyllithium, underwent an elimination, opening the oxazolidine ring to give an enamine alkoxide. The resulting oxygen anion then underwent intramolecular addition to the imine function, resulting in the formation of tricycle **360**. This



Scheme 42 Husson's 1993 (−)-8-aza-pHTX total synthesis. *Reagents and conditions*: (a) LDA, THF, −78 °C; $Cl(CH_2)_3I$, THF; (b) $LiAlH_4$, Et_2O; (c) $PhCH_2Br$, NaI; (d) $C_5H_{11}MgBr$, Et_2O, THF; (e) H_2, Pd/C; (f) BuLi, THF, Et_2O; (g) KCN, citric acid; (h) $C_5H_{11}MgBr$, AcOH; (i) H_2, Pd/C.

unstable compound was then transformed into amino nitrile **361** using KCN in an acidic biphasic medium. Nitrile **361** was formed as a single axial isomer due to stereoelectronic control. It was attempted to introduce the C2 alkyl chain by deprotonation next to the nitrile and alkylation but all attempts failed, presumably due to steric hindrance. They then attempted to introduce the side chain by Grignard displacement of the nitrile, but this approach only led to poor yields, which they thought might be the result of deprotonation of the putative iminium species, forming an enamine. Eventually, the problem was solved by recycling any enamine by repeated additions of acetic acid, to reform an iminium species, followed by addition of the Grignard nucleophile, and this resulted in the formation of the dialkyl tricycle **362** as a single isomer in 83% yield. Catalytic hydrogenation resulted in reductive cleavage of the benzyl scaffold and the isolation of the desired (−)-8-aza-pHTX analogue **363**.

In 1995, Vatèle and co-workers developed a convenient and rapid three-step route to the Husson spiroaminoketone **346** from the relatively inexpensive (±)-pipecolinic acid **364** (Scheme 43).[57] Generation of the acid chloride with *in situ* quenching in ethanol, followed by *N*-benzylation, yielded piperidine **365**. Deprotonation followed by addition of the ethyl ester of 5-bromopentanoic acid resulted in formation of the desired quaternary centre α to the piperidine nitrogen, yielding diester **366**. Finally, a Dieckmann cyclisation furnished a crude β-keto ester, which was converted to the Husson spiropiperidine (−)-**346** in good yield.



Scheme 43 Vatele's 1995 (−)-depentyl-pHTX formal synthesis. *Reagents and conditions*: (a) $SOCl_2$, EtOH, reflux; Et_3N, *O*-benzyl-*N*,*N*-dicyclohexylurea; (b) LDA, THF, −78 °C; HMPA, $Br(CH_2)_4CO_2Et$; (c) NaH, THF, reflux; 4 M HCl, reflux.

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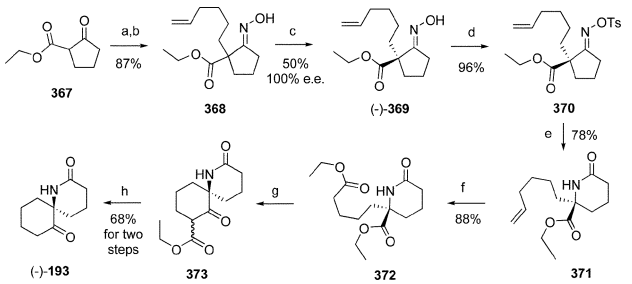
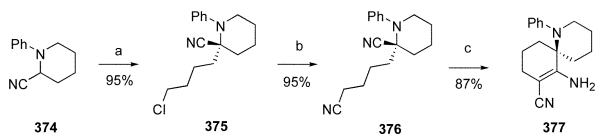
The Westermann group reported a formal synthesis of (−)-pHTX **16** in 2002, wherein they described a general method to obtain enantiomerically pure oxime esters by enzymatic kinetic resolution (Scheme 44).[58] Alkylation of cyclopentanone **367** with bromohexene, followed by oxime formation, resulted in oxime ester **368**. The group screened a large number of enzymes for the kinetic resolution, and found the optimum conditions were when using lipase PS and vinyl acetate in a 1 : 1 mixture of *tert*-butanol and isopropyl ether. Using these conditions, they were able to perform a quantitative resolution, allowing the isolation of (−)-**369** in 50% yield and 100% ee. Tosylation of this enantiomerically pure substrate then resulted in the formation of **370**, which underwent a Beckmann rearrangement to give piperidine **371** when stirred with silica gel. Ozonolysis in alkaline ethanol then successfully converted the terminal olefin to ester **372**, which underwent a Dieckmann cyclisation when treated with *tert*-butoxide, yielding the spirocyclic ester **373**. An acid-catalysed decarboxylation was then carried out in refluxing xylene to yield the enantiomerically pure Kishi spirocycle (−)-**193** in good yield.



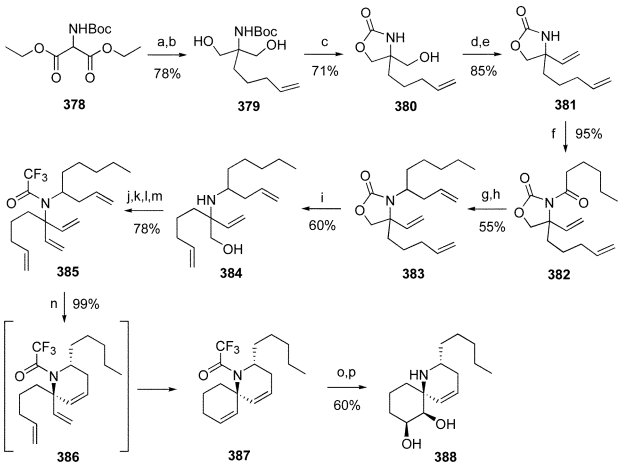
Scheme 44 Westermann's 2002 (−)-pHTX formal synthesis. *Reagents and conditions*: (a) NaH, $CH_2{=}CH(CH_2)_4Br$, THF; (b) $NH_3OH{\cdot}HCl$, pyridine, EtOH; (c) Lipase PS, vinyl acetate, *n*BuOH, *i*Pr_2O; (d) TsOH, pyridine; (e) SiO_2, DCM; (f) O_3, NaOH, EtOH; (g) *t*BuOK, pyridine; (h) *p*TsOH, xylene, reflux.

In 2003, a Thorpe–Ziegler annulation was reported by the Hurvois group as a potential methodology for accessing the core spirocyclic structure of the HTX alkaloids (Scheme 45).[59] Aminonitrile **374** was alkylated with bromochlorobutane, giving chloronitrile **375** in excellent yield. This was converted to dinitrile **376**, before exposure to LDA promoted an intramolecular annulation to yield the aminonitrile spirocycle **377** in high yield.



Scheme 45 Hurvois' 2003 HTX approach. *Reagents and conditions*: (a) LDA, THF, $Cl(CH_2)_4Br$; (b) NaCN, DMSO, *n*Bu_4NI, 70 °C; (c) LDA, THF, −78 °C.

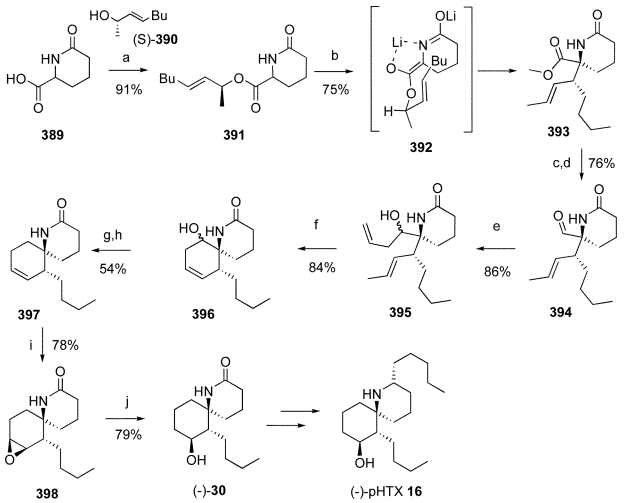
In 2004, a diastereoselective tandem ring-closing metathesis strategy was reported by the Harrity group (Scheme 46).[60] Boc-protected amidomalonate **378** was first alkylated with bromopentene, followed by reduction, giving the pseudo C_2-symmetric diol **379**. This was desymmetrised by intramolecular cyclisation to give the oxazolidinone **380**. A Swern oxidation of the remaining hydroxyl function, followed by a Wittig reaction, then generated



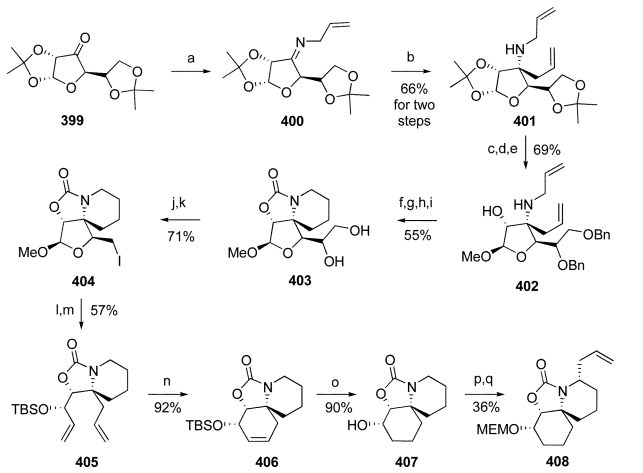
Scheme 46 Harrity's 2004 HTX approach. *Reagents and conditions*: (a) NaOEt, EtOH, $CH_2{=}CH(CH_2)_3Br$; (b) $LiAlH_4$, THF; (c) NaH, THF; (d) DMSO, $(COCl)_2$, DCM; (e) $Ph_3P{=}CH_2$, THF; (f) BuLi, THF, −78 °C; $C_5H_{11}COCl$; (g) DIBAL, DCM, −100 °C; TMSOTf, 2,6-lutidine; (h) $CH_2CHCH_2SiMe_3$, $BF_3{\cdot}Et_2O$, DCM; (i) MeLi, Et_2O, −78 °C; NaOH, H_2O, EtOH, 80 °C; (j) TFA, DCM, 0 °C; (k) DMSO, $(COCl)_2$, DCM; (l) $Ph_3P{=}CH_2$, THF; (m) trifluoroacetic anhydride, Et_3N, Et_2O; (n) Grubbs' II catalyst, DCM, 40 °C; (o) $NaBH_4$, EtOH; (p) OsO_4, TMEDA, −78 °C; MeOH, HCl.

the diene **381** in excellent yield. The future C2 pentyl side chain was installed by acylation to give **382**. A third terminal alkene chain was then installed by partial DIBAL reduction and trapping to give the TMS ether, and a Lewis acid-mediated allylation then proceeded smoothly to give **383**. Cleavage of the oxazolidinone function by the addition of methyllithium, followed by hydrolysis, then gave the hydroxylamine **384**. A second Swern/Wittig combination of reactions, followed by *N*-protection, then gave the trifluoroacetamide **385**. Exposure of this tetraene to ruthenium-catalysed ring-closing metathesis (RCM) conditions gave **387**, demonstrating the remarkable selectivity that can be achieved with this reaction. Thorpe–Ingold effects were found to promote RCM to occur with preference for the initial formation of the heterocyclic ring, as opposed to the carbocyclic ring, and this was supported by the isolation of piperidine **386** as the only monocyclic product. The relative stereochemistry was also effectively controlled during this reaction, due to steric interactions between the pentene side chain and the trifluoroacetate group, resulting in the exclusive *cis* axial relationship between the two pentyl chains. The second carbocyclic RCM then occurred, resulting in the isolation of spirocyclic diene **387** in an excellent 99% yield. A regio- and stereoselective alkene functionalisation was achieved by the action of TMEDA–OsO_4, directing the dihydroxylation successfully to give the spirocyclic diol **388** as a single diastereomer. Elaboration of this key intermediate towards the target natural product has yet to be reported.

The Kim group reported a formal synthesis of (−)-pHTX **16** in 2005, utilising a Claisen rearrangement of a cyclic amino acid ester enolate as the key step (Scheme 47).[61] Oxopipecolic acid **389** was first coupled with the enantiomerically pure allylic alcohol (*S*)-**390** to give ester **391**. A Lewis acid-mediated Claisen reaction was then carried out to form the required quaternary centre, generating **393** with 98% ee. Reduction of the ester, followed by re-oxidation to the aldehyde, gave **394**, which was immediately



Scheme 47 Kim's 2005 (−)-pHTX formal synthesis. *Reagents and conditions*: (a) DCC, DMAP, DCM; (b) LDA, $ZnCl_2$, THF; (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, H_2O; (d) Dess–Martin periodinane, $NaHCO_3$, DCM; (e) allylmagnesium bromide, THF, 0 °C; (f) Grubbs' catalyst, DCM, 40 °C; (g) Im_2CS, DMAP, DCM; (h) Bu_3SnH, AIBN, toluene, reflux; (i) Oxone, $NaHCO_3$, $MeCOCF_3$, Na_2EDTA, H_2O, DCM, 0 °C; (j) DIBAL, THF.



Scheme 48 Bera's 2005 HTX approach. *Reagents and conditions*: (a) allylamine, benzene; (b) allyl phenyl ether, lithium, biphenyl, THF; (c) H_2SO_4, MeOH; (d) benzyl bromide, NaH, TBAI, THF; (e) H_2SO_4, MeOH, reflux; (f) Boc_2O, DMAP, Et_3N, DCM, 0 °C; (g) NaOH, THF, MeOH; (h) Grubbs' II catalyst, benzene, reflux; (i) H_2, Pd/C, AcOH, EtOH; (j) $NaIO_4$, DCM, 0 °C; $NaBH_4$, THF; (k) TPP, I_2, imidazole, toluene, reflux; (l) Zn, allyl bromide, sonication, 40 °C; (m) TBDMSOTf, lutidine, DCM, 0 °C; (n) Grubbs' II catalyst, DCM, reflux; (o) H_2, Pd/C, AcOH, EtOH; (p) NaH, MEMCl, THF, DMF, 0 °C; (q) BuLi, allyl bromide, THF, 0 °C.

reacted with allylmagnesium bromide to form alcohol **395** as an epimeric mixture. It was then attempted to remove the hydroxyl function using a Barton–McCombie deoxygenation, but this was found to be unsuccessful, so the planned ring-closing metathesis reaction was now carried out, leaving the deoxygenation until a later stage. Azaspirocycle **396** was obtained in an 84% yield after exposure to Grubbs' second-generation catalyst. The Barton–McCombie deoxygenation was now found to be successful, yielding spirocycle **397** in a 54% yield. Reaction of **397** with Oxone® and trifluoroacetone then yielded epoxide **398** with a high 30 : 1 selectivity in favour of the desired enantiomer. Finally, reduction using DIBAL successfully opened up the epoxide ring in a regioselective manner, generating the enantiomerically pure Corey intermediate **30**.

Also in 2005, Bera published an enantioselective approach towards the core HTX structure starting from D-(+)-glucose-derived substrate **399** (Scheme 48).[62] Condensation with allylamine generated imine **400**, which was then reacted with allyl phenyl ether in the presence of lithium metal to install the alkyl chain on the top face, giving diene **401**. A series of protecting group modifications then gave the dibenzyl diene **402** in good yield. Boc protection of the amine was carried out, followed by base hydrolysis to promote cyclisation to form an oxazolidinone. This could now be exposed to RCM conditions to generate the desired piperidine ring, and palladium-catalysed hydrogenation simultaneously cleaved the benzyl groups while reducing the alkene, to give tricycle **403**. Oxidative cleavage of the diol function to the aldehyde, followed by reduction and alcohol-to-iodide conversion, yielded iodide **404**. A domino reaction was then carried out using allyl bromide in the presence of zinc dust and water, which successfully cleaved both the carbon–iodine bond and the cyclic ether linkage. This resulted in the formation of a hemiacetal, which was hydrolysed to an aldehyde, which in turn underwent nucleophilic attack by allylzinc bromide to give diene **405** after hydroxyl protection. A second RCM reaction was then carried out in order to furnish the carbocyclic portion of the azaspirocyclic system, giving **406**, which, upon a palladium-catalysed hydrogenation, gave **407**. The hydroxyl function was then reprotected as its MEM ether before C2 alkylation was carried out using allyl bromide. Unfortunately, the desired compound **408** could only be isolated in a 44% yield, and has yet to be advanced further towards the target compound.

7 Approach F: formation of either C6–C7 or C6–C11 bonds

7.1 Nitrones: oxidative cyclisation with activated olefins

The first example of nitrone cyclisation methodology being applied towards the formation of an azaspirocyclic system was the pioneering work of Tufariello in 1974, in an unsuccessful synthetic attempt toward (±)-pHTX **16** (Scheme 49).[63] Starting with (hydroxymethyl)tetrahydropyran **409**, they exposed it to thionyl chloride, and the resulting chloride was immediately reduced with sodium in liquid ammonia to give hexynol **410** in good yield. THP protection of the hydroxyl function, followed by alkyne alkylation with methyl chloroformate and subsequent THP cleavage, yielded alkyne **411**. A Lindlar hydrogenation was then carried out to generate the *cis*-olefin, and this was followed by conversion of the hydroxyl function to the acid chloride **412**. Addition of the four-carbon segment was then achieved by organocuprate alkylation, to generate the unstable keto alcohol **413**, which was immediately converted to the nitroketone **414** by a series of standard functional group transformations. Exposure of this compound to ammonium chloride and zinc in aqueous methanol promoted nitro-group reduction to a hydroxylamine and an intramolecular condensation to form a cyclic nitrone intermediate. This nitrone was expected to undergo spontaneous intramolecular cyclisation under the reaction conditions, and

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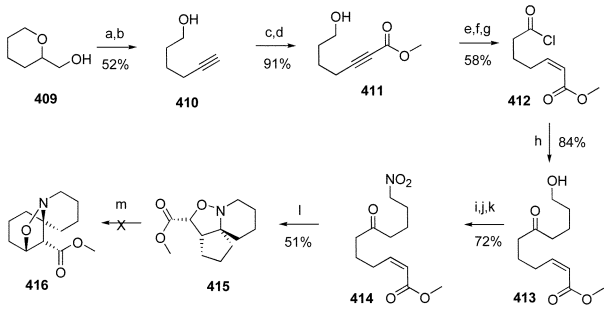
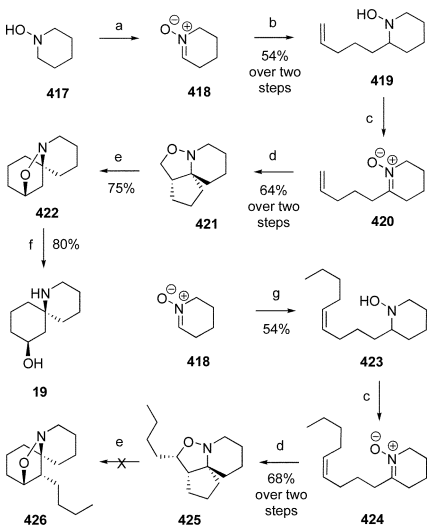


Scheme 49 Tufariello's 1974 HTX approach. *Reagents and conditions*: (a) $SOCl_2$, pyridine; (b) $NaNH_2$, $Fe(NO_3)_3{\cdot}9H_2O$, NH_3, −78 °C; (c) HCl, DHP; $NaHCO_3$, H_2O; (d) *n*BuLi, THF, MeCOCl, −78 °C; *p*TsOH, MeOH; (e) H_2, Lindlar catalyst, quinoline, MeOH; (f) CrO_3, acetone, H_2SO_4; (g) $(COCl)_2$, benzene; (h) CuI, HMPA, Et_2O, $EtOCH(CH_3)O(CH_2)_4Li$, −78 °C; HCl, THF; (i) MsCl, DCM, 0 °C; (j) LiBr, acetone; (k) H_2NCONH_2, $NaNO_3$, DMSO; (l) NH_4Cl, Zn, MeOH; (m) toluene, reflux.

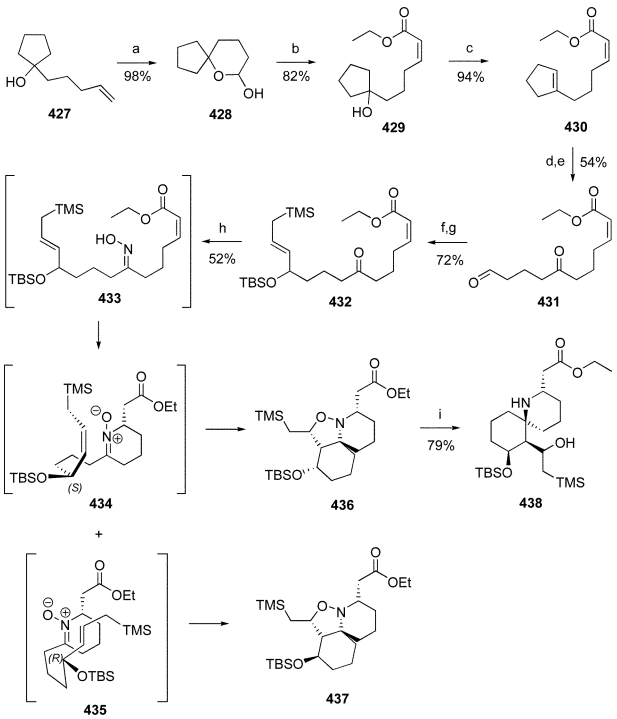
on work-up of the reaction they were able to isolate a basic product which they assumed to be the expected **416**. However, on further spectroscopic and chemical analysis, this compound was actually determined to be the regioisomer **415**, formed from an α-addition to the unsaturated ester, rather than the expected β-addition. Attempts to convert **415** to the desired theoretically more thermodynamically stable ring system **416** were unsuccessful, and this was ascribed to steric interactions between the methoxy ester and the side chain methylene groups in the desired transition state, as opposed to the transition state leading to **415**, where the steric interactions are minimised.

The Gössinger group then reported their results in 1975, involving a similar methodology which had been investigated in parallel to those of the Tufariello group (Scheme 50).[64] Cyclic nitrone **418** was generated by the oxidation of piperidinol **417**. Installation of the terminal olefin side chain was achieved using a Grignard reaction, to give **419**, which was oxidised to give nitrone **420**. Heating this nitrone in refluxing toluene promoted cyclisation to the 6,5,5-kinetic adduct **421**. Further heating of this in a sealed tube at 195 °C then promoted a retrocyclisation to form the desired thermodynamic adduct **422**. Raney nickel hydrogenation then converted this to (±)-2-dependyl-7-debutyl-pHTX **19**. This scheme was then re-applied towards the synthesis of (±)-2-dependyl-pHTX **18** by the use of the butyl-substituted olefin. Nitrone **418** was converted to olefin **423** through an analogous Grignard reaction and again oxidised to form the key nitrone **424**. Heating this compound as before again generated the 6,5,5-kinetic adduct **425**, but all attempts to convert this to the desired 6,6,5-thermodynamic adduct **426** failed, presumably due to the same steric impediments discovered by the Tufarello group, showing that the transition state for the desired β-addition can only be achieved when steric interactions are minimised.

The next group to investigate nitrone cyclisations leading to azaspirocyclic systems was that of Parsons, who reported their work involving a tandem Michael addition/nitrone cyclisation in 1993 (Scheme 51).[65] Ozonolysis of cyclopentanol **427**, followed by a reductive work-up, yielded lactol **428** in near-quantitative yield. This was then converted to the α,β-unsaturated ester **429** by Wittig homologation, before dehydration with phosphorous oxychloride generated cyclopentene **430**. Epoxidation followed by



Scheme 50 Gossinger's 1975 (±)-2-dependyl-7-debutyl-pHTX total synthesis. *Reagents and conditions*: (a) HgO, $CHCl_3$; (b) $BrMg(CH_2)_3CH{=}CH_2$, Et_2O, reflux; (c) HgO, Et_2O; (d) toluene, reflux; (e) toluene, 195 °C; (f) H_2, Raney Ni, EtOH; (g) $BrMg(CH_2)_3CH{=}CH(CH_2)_3Me$, Et_2O, reflux.

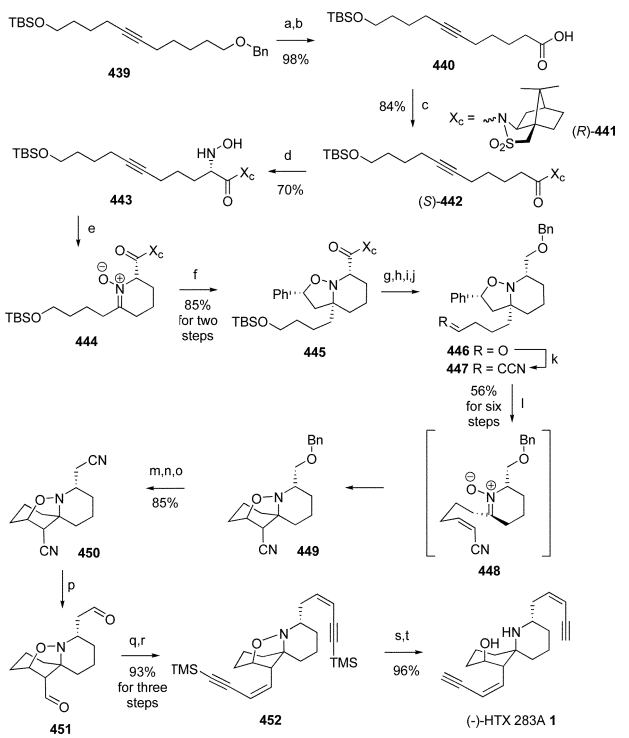


Scheme 51 Parsons' 1993 HTX approach. *Reagents and conditions*: (a) O_3, DCM, −78 °C; PPh_3; (b) $Ph_3P{=}CHCO_2Et$, DCM; (c) $POCl_3$, pyridine, reflux; (d) *m*CPBA, DCM; (e) H_5IO_6, THF, H_2O; (f) (3-bromoallyl)trimethylsilane, $CrCl_2$, $NiCl_2$, DMF; (g) TBSCl, DMF, DMAP, imidazole; (h) $NH_2OH{\cdot}HCl$, NaOAc, toluene, H_2O, sealed tube, 150 °C; (i) H_2, Pd, EtOH.

periodate cleavage then converted this to keto aldehyde **431**. A chromium-mediated addition of (3-bromoallyl)trimethylsilane to aldehyde **431**, followed by TBS protection, yielded the cyclisation precursor **432** as a mixture of OTBS epimers. Condensation with hydroxylamine generated the intermediate oxime **433**, which spontaneously underwent a Michael addition to produce a nitrone

intermediate. This intermediate now underwent the key nitrone cycloaddition through two sterically minimised transition states **434** and **435**, depending on the stereochemistry of the OTBS centre, to produce the separable isoxazolidines **436** and **437** respectively. The presence of the OTBS group, and its high preference for an equatorial conformation, effectively locks the alkene arm into a configuration by which only the desired 6,6-spirocycles can be formed. The relative stereochemistries of both adducts were confirmed by NOE studies, and the desired epimer **436** was then reductively cleaved to yield spirocycle **438**, which contains the correct relative stereochemistry at three of the four chiral centres needed in order to be advanced to the HTX alkaloids.

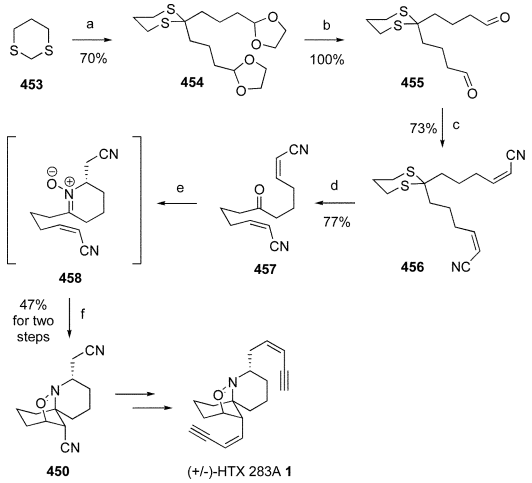
In 1999, the Holmes group published an enantioselective total synthesis of (−)-HTX 283A **1** utilising an intramolecular [3 + 2] nitrone cycloaddition as the key step (Scheme 52).[66] Starting with the debenzylation of the known acetylenic diol **439**, followed by oxidation to the corresponding acid **440**, allowed the incorporation of Oppolzer's (+)-(*R*)-2,10-camphorsultam chiral auxiliary **441**, yielding the (*S*)-enantiomer **442** as the sole product. Diastereoselective installation of the hydroxylamine was achieved by the reaction of the sodium enolate of **442** with 1-chloro-1-nitrosocyclohexane under acidic conditions, forming **443** as a single stereoisomer. Michael addition was now carried out by refluxing in toluene to afford nitrone **444**, which was then masked



Scheme 52 Holmes' 1999 (−)-HTX 283A total synthesis. *Reagents and conditions*: (a) BCl_3·DMS, DCM; (b) Jones' reagent, acetone; (c) Et_3N, pivaloyl chloride; **441**, *n*BuLi, THF, −78 °C; (d) $NaN(TMS)_2$, THF; 1-chloro-1-nitrosocyclohexane, THF, HCl; (e) toluene, 80 °C; (f) styrene, 75 °C; (g) $LiAlH_4$, THF, 0 °C; (h) NaH, BnBr, THF; (i) HF, MeCN; (j) TPAP, NMO; (k) Me_3SiCH_2CN, *n*BuLi, THF, $B(OiPr)_3$, −78 °C; (l) toluene, 190 °C; (m) BCl_3·Me_2S, DCM; (n) MsCl, Et_3N, DMAP, DCM; (o) NaCN, DMSO, 55 °C; (p) DIBAL, toluene, −78 °C; (q) $KN(TMS)_2$, $[Ph_3P^+CH_2I\,I^-]$, THF, −78 °C; (r) $Pd(PPh_3)_4$, CuI, Et_2NH, Me_3Si–C≡CH; (s) Zn, acetic acid; (t) K_2CO_3, MeOH.

by an intermolecular cycloaddition with styrene to generate isoxazolidine **445** as a single regio- and stereoisomer. The now redundant chiral auxiliary was removed by reductive cleavage, and the resultant alcohol was protected as its benzyl ether, before desilylation and oxidation of the other hydroxyl function formed aldehyde **446**. This was converted to the *cis*-α,β-unsaturated nitrile **447** by Peterson olefination. After heating this adduct in toluene at 190 °C in a sealed tube, a retro-[3 + 2] cycloaddition liberated the styrene moiety, generating the key nitrone intermediate **448**, which then underwent a second cycloaddition, this time intramolecularly, to produce the desired thermodynamic cycloadduct **449**. The low steric hindrance of the nitrile function, when compared to the ester and alkyl chains used by Tufariello and Gossinger, finally allows access to the thermodynamic transition state **448** required for formation of the HTX core structure. This tricycle was converted to the crystalline dinitrile **450** by nucleophilic substitution of the mesylate intermediate, allowing both arms to be developed simultaneously. DIBAL reduction to the dialdehyde **451** was achieved quantitatively, before a Stork–Wittig procedure generated the bis-iodoalkene, which was immediately subjected to Sonogashira coupling to generate the TMS-protected bis-enyne **452**. The strained N–O bond was reduced using activated zinc dust in acetic acid, before TMS deprotection yielded the target (−)-HTX 283A **1** in an impressive overall yield of 16%. They also achieved a total synthesis of (−)-HTX 235A **12** by zinc reduction of the intermediate bis-iodoalkene, demonstrating the potential of this route for the generation of other members of the HTX family.

In 2000, Stockman reported an alternative route to Holmes' dinitrile intermediate **450**, again utilising a tandem oxime formation/Michael addition and nitrone cycloaddition to form the azaspirocyclic skeleton, this time from a C_2-symmetric acyclic precursor, greatly enhancing the synthetic accessibility of this intermediate (Scheme 53).[67] 1,3-Dithiane **453** was doubly alkylated by successive addition of *n*-butyllithium followed by 2-(3′-chloropropyl)-1,3-dioxolane to give C_2-symmetric diacetal **454**. Deprotection yielded the dialdehyde **455** in quantitative yield by stirring in HCl and THF, and this was then converted to the



Scheme 53 Stockman's 2000 (±)-HTX 283A formal synthesis. *Reagents and conditions*: (a) *n*BuLi, THF, HMPA, −78 °C; 2-(3-chloropropyl)-1,3-dioxolane; (b) HCl, THF, H_2O; (c) Me_3SiCH_2CN, THF, *n*BuLi, −78 °C; (d) NCS, $AgNO_3$, MeCN; (e) NH_2OH·HCl, NaOAc, MeOH; (f) toluene, 160 °C, sealed tube.

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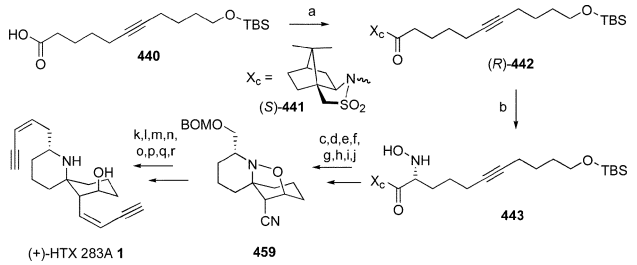
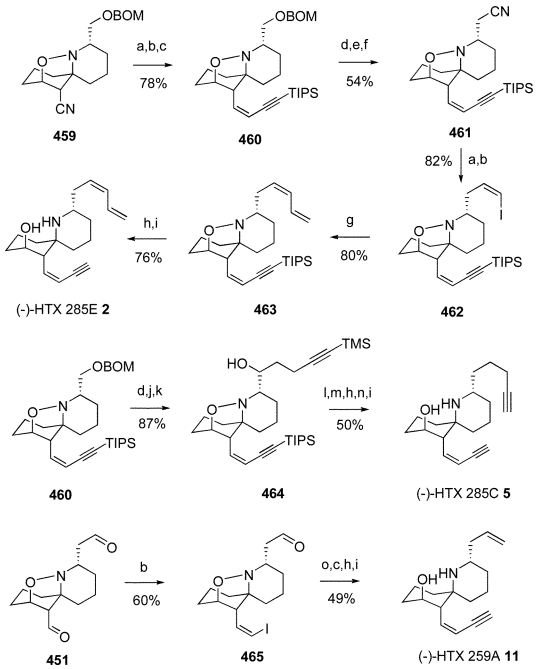
cis,*cis*-dinitrile **456** in good yield by double Peterson olefination. Removal of the dithiane functionality was achieved using NCS and silver nitrate to give the key C_2-symmetric ketone **457**. This was condensed with hydroxylamine to form the nitrone intermediate **458** after a spontaneous Michael addition. Heating a toluene solution of this nitrone in a sealed tube at 160 °C then converted it to the Holmes dinitrile **450**, thus constituting a formal synthesis of (±)-HTX 283A **1** and (±)-HTX 235A **12**.

The Holmes group then published an extensive paper, describing their investigations into the electronic and steric interactions involved within transition states such as **448** and the respective selectivity for either the kinetic 6,5,5-cycloadduct or the thermodynamic 6,6,5-adduct, in which was also published a total synthesis of (+)-HTX 283A **1** using a modification of their previous route (Scheme 54).[68] Acid **440** was this time coupled with Oppolzer's (−)-(*S*)-2,10-camphorsultam chiral auxiliary **441** in order to generate the opposite (*R*)-enantiomer of **442**. Installation of the hydroxylamine function was again achieved with complete stereocontrol to yield **443**, and this was advanced to the natural product target as before, with the one exception being that a BOM protecting group was used instead of a benzyl, due to the milder detachment conditions involved.



Scheme 54 Holmes' 2002 (+)-HTX 283A total synthesis. *Reagents and conditions*: (a) Et_3N, pivaloyl chloride; X_cH, *n*BuLi, THF, −78 °C; (b) $NaN(TMS)_2$, THF; 1-chloro-1-nitrosocyclohexane, THF, HCl; (c) toluene, 80 °C; (d) styrene, 75 °C; (e) $LiAlH_4$, THF, 0 °C; (f) $i Pr_2EtN$, BOMCl, nBu_4NI, toluene, 65 °C; (g) HF, MeCN; (h) TPAP, NMO; (i) Me_3SiCH_2CN, *n*BuLi, THF, $B(OiPr)_3$, −78 °C; (j) toluene, 190 °C; (k) Amberlyst-15, MeOH; (l) MsCl, Et_3N, DMAP, DCM; (m) NaCN, DMSO, 55 °C; (n) DIBAL, toluene, −78 °C; (o) $KN(TMS)_2$, $Ph_3P^+CH_2I\,I^-$, THF, −78 °C; (p) $Pd(PPh_3)_4$, CuI, Et_2NH, Me_3Si–C≡CH; (q) Zn, AcOH; (r) K_2CO_3, MeOH.

The Holmes group also published a further expansion of their methodology in the same year, describing the total synthesis of the 'unsymmetrical' alkaloids (−)-HTX 259A **11**, (−)-HTX 285C **5** and (−)-HTX 285E **2** by stepwise introduction of the different side chains (Scheme 55).[69] The previously synthesised BOM nitrile tricycle **459** was utilised as the starting point for the synthesis, due to the differentiation already present between the two side chains. The C7 nitrile was first converted to the *cis*-iodoalkene using the previously developed methodology. Sonogashira coupling was then carried out to give the TIPS-protected *cis*-enyne **460**. The C2 side chain was deprotected and converted to give nitrile **461**, again using the previously developed methodology. This was converted to the *cis*-iodoalkene **462**, which was subjected to a Stille coupling with vinyltributyltin to yield *cis*-diene **463**. This was subjected to a reductive N–O bond cleavage, followed by TBAF-mediated desilylation to afford the enantiomerically pure (−)-HTX 285E **2**.

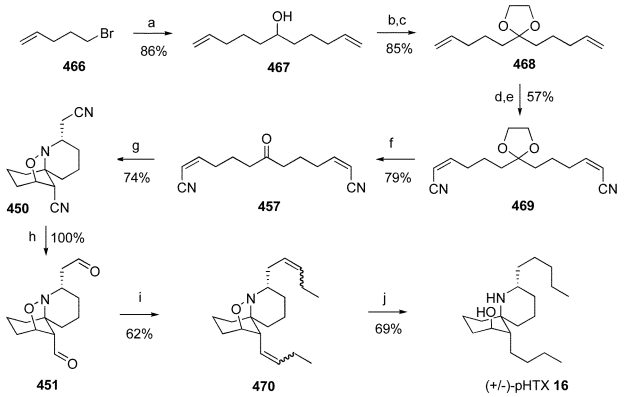


Scheme 55 Holmes' 2002 (−)-HTX 259A, (−)-HTX 285C and (−)-HTX 285E total syntheses. *Reagents and conditions*: (a) DIBAL, toluene, −78 °C; (b) $KN(TMS)_2$, $Ph_3P^+CH_2I\,I^-$, THF, −78 °C; (c) $Pd(PPh_3)_4$, CuI, Et_2NH, iPr_3Si–C≡CH; (d) Amberlyst-15, MeOH; (e) MsCl, Et_3N, DMAP, DCM; (f) NaCN, DMSO, 55 °C; (g) tributylvinyltin, $PdCl_2(MeCN)_2$, DMF; (h) Zn, AcOH; (i) TBAF, THF; (j) IBX, DMSO; (k) Me_3Si–C≡$C(CH_2)_2MgBr$, THF, 0 °C; (l) NaH, 0 °C; CS_2, MeI, THF; (m) Bu_3SnH, AIBN, benzene, 80 °C; (n) K_2CO_3, MeOH; (o) Cp_2TiMe_2, toluene, 110 °C.

BOM-protected enyne tricycle **460** was also oxidised with IBX, generating the aldehyde, and allowing a Grignard addition of (4-bromobut-1-ynyl)trimethylsilane to afford dialkyne **464** in good yield. Xanthate formation, followed by a Barton–McCombie free-radical deoxygenation, yielded an intermediate, which upon reductive N–O cleavage and desilylation generated an enantiomerically pure sample of (−)-HTX 285C **5**.

The third total synthesis mentioned within this paper was brought about by the expedient observation that dialdehyde **451** can undergo a regioselective Stork–Wittig reaction at the C7 aldehyde. This is remarkable, since the C7 aldehyde appears to be the more sterically hindered aldehyde, but its enhanced reactivity can be explained by the presence of the two diaxial heteroatom bonds causing a greater electron deficiency within this aldehyde. The less reactive aldehyde can now be methylated using the Petasis reagent to complete the C2 allyl side chain. A Sonogashira coupling followed by N–O cleavage and desilylation then yielded (−)-HTX 259A **11**.

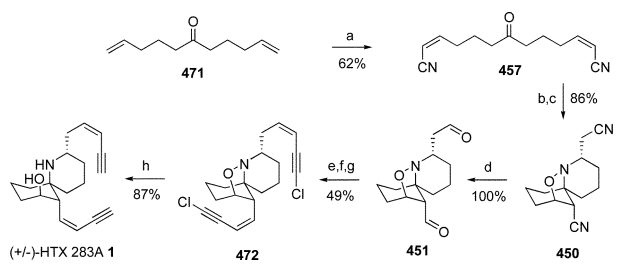
The Stockman group reported an entirely two-directional synthesis of (±)-pHTX **16** in 2004 (Scheme 56).[70] The synthesis started with a Grignard reaction between two equivalents of bromopentene **466** and ethyl formate to generate the C_2-symmetric alcohol **467**. A pyridinium chlorochromate-mediated oxidation was then carried out followed by ketal protection to yield acetal **468** in good yield. The terminal olefins were then cleaved using osmium tetraoxide, and a Peterson homologation was carried out to give a 13 : 1 mixture of the desired *cis*,*cis*-diene **469** and the unwanted *cis*,*trans*-diene. Separation of these isomers was



Scheme 56 Stockman's 2004 (±)-pHTX total synthesis. *Reagents and conditions*: (a) Mg, Et_2O, ethyl formate; (b) PCC, SiO_2, DCM; (c) $HO(CH_2)_2OH$, benzene, *p*TsOH, reflux; (d) OsO_4, $NaIO_4$, THF, H_2O; (e) $TMSCH_2CN$, *n*BuLi, THF, −78 °C; (f) HCl, THF, H_2O; (g) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, MeCN; toluene, 185 °C, sealed tube; (h) DIBAL, toluene, −78 °C; (i) BuLi, $Ph_3P^+(CH_2)_2Me\ Br^-$, THF, −40 °C; (j) H_2, Pd/C, MeOH.

followed by acetal deprotection to yield the key C_2-symmetric cyclisation precursor **457**. This was condensed with hydroxylamine and heated to promote the tandem Michael addition/nitrone cyclisation, yielding the Holmes dinitrile **450** in good yield. Reduction of the nitrile functions to the dialdehyde **451** followed by a Wittig homologation yielded diene **470** as a mixture of *cis* and *trans* isomers. This mixture then underwent palladium-catalysed hydrogenation to effect both the N–O bond cleavage and olefin reduction, yielding the target (±)-pHTX **16**.

Subsequently, the Stockman group in collaboration with the Fuchs group described the development of a second entirely two-directional total synthesis, this time of the fully unsaturated parent (±)-HTX 283A **1** (Scheme 57).[71] This synthesis started with the cross-metathesis of dialkene **471** with acrylonitrile using the Grubbs–Hoveyda catalyst to directly generate dinitrile **457** in a 60% yield. This was converted to the Holmes dinitrile **450** and the subsequent dialdehyde **451** using their previously developed methodology. The resulting dialdehyde was then exposed to a Wittig reaction with (trichloropropyl)triphenylphosphonium chloride to generate the two trichlorobutene side chains, which are then submitted to a series of base-promoted HCl eliminations, to yield the chloro-protected *cis*-enyne side chains present in **472**. The N–O groups and the chloro-alkynes are then simultaneously

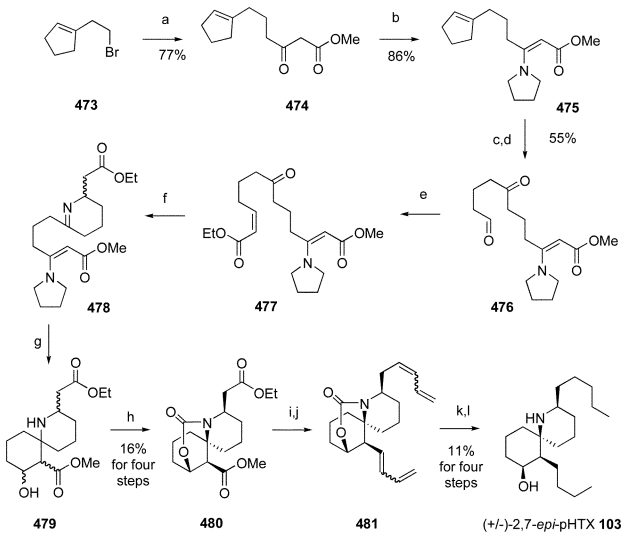


Scheme 57 Stockman and Fuchs' 2006 (±)-HTX 283A total synthesis. *Reagents and conditions*: (a) CH_2=CHCN, THF, Grubbs–Hoveyda catalyst, MW; (b) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, MeCN; (c) sealed tube, toluene, 190 °C; (d) DIBAL, toluene, −78 °C; (e) $Cl_3C(CH_2)_2PPh_3^+\ Cl^-$, NaHMDS, THF, −40 °C; (f) DBU, $CHCl_3$; (g) NaHMDS, THF; (h) $CrCl_2$, *n*PrSH, DMF.

reduced by the action of chromium dichloride and propyl thiol to yield the target (±)-HTX 283A **1** in 87% yield after purification. This results in a total synthesis of (±)-HTX 283A **1** in 8 steps from **471** in an overall yield of 24%.

7.2 Imines: the Mannich reaction and acyliminium ion–olefin cyclisations

The potential of the Mannich reaction for the generation of an azaspirocyclic core was first investigated by Corey *et al.* in 1975 and was used in a total synthesis of 2-*epi*-7-*epi*-(±)-pHTX **103** (Scheme 58).[72] Bromocyclopentene **473** was first treated with the lithium anion of methyl acetoacetate to yield the β-keto ester **474**. This was condensed with pyrrolidine in refluxing benzene to generate the enamine ester **475**. Hydroxylation with osmium tetraoxide, followed by oxidative cleavage, then formed keto aldehyde **476**, which was subjected to a Wittig homologation to yield the crude α,β-unsaturated ester **477**. This was treated with liquid ammonia in a sealed tube at room temperature to effect quantitative conversion to the cyclic imine **478** as a mixture of C2 epimers. The key Mannich reaction was then promoted with *p*-TsOH, and the crude product was immediately reduced with sodium borohydride to form the spirocycle **479** as a complex mixture of epimers. Exposure to phosgene promoted the formation of the urethane **480**, allowing isolation of the desired hydroxyl regioisomer. X-Ray crystallography confirmed the *epi*-configuration at both the C2 and C6 positions. This diester was now reduced using DIBAL to generate the dialdehyde, followed by a double Wittig olefination with (allyldimethylphenyl)phosphonium bromide, to afford bis-diene **481**. Palladium-catalysed hydrogenation then reduced the alkene functions, before cleavage of the urethane linkage was achieved with lithium in monomethylamine, to yield the target (±)-2-*epi*-7-*epi*-pHTX **103**.



Scheme 58 Corey's 1975 (±)-2-*epi*-7-*epi*-pHTX total synthesis. *Reagents and conditions*: (a) methyl acetoacetate, LDA, HMPA, THF; (b) pyrrolidine, AcOH, benzene, reflux; (c) OsO_4, pyridine, Et_2O; aq. sodium bisulfite; (d) Ag_2CO_3, benzene, reflux; (e) LDA, triethyl phosphonoacetate, THF, −30 °C; (f) liquid NH_3, sealed tube, 20 °C; (g) *p*TsOH, DCM; $NaBH_4$, EtOH, −20 °C; (h) phosgene, DCM, 0 °C; pyridine; (i) DIBAL, DCM; (j) allyldimethylphenylphosphonium bromide, potassium methylsulfinylmethylide, THF, DMSO; (k) H_2, Pd/C, THF; (l) Li/$MeNH_2$, −78 °C.

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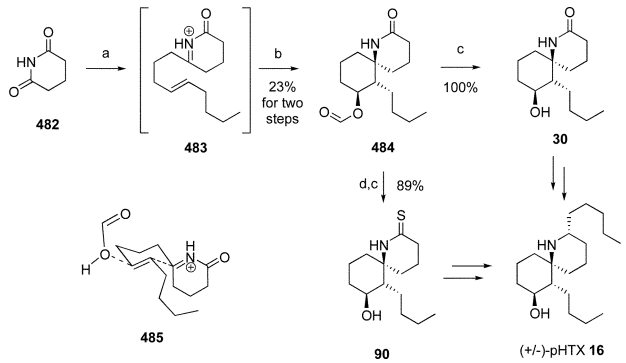
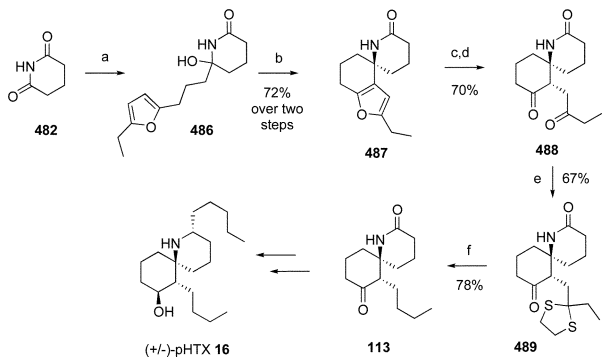
In the late 1970s, the groups of Speckamp and Evans both independently developed an extremely rapid stereoselective formal synthesis of both the Corey lactone **30** and the Kishi thiolactone **90** utilising an acyliminium ion–olefin cyclisation to achieve two formal syntheses of (±)-pHTX **16** (Scheme 59).[73–75] The core spirocycle **484** was rapidly formed by an initial Grignard reaction on glutarimide **482**, forming an acyliminium ion intermediate **483**, which underwent an olefin cyclisation to give **484** when exposed to formic acid. Although low-yielding, this cyclisation was found to proceed with high regio- and stereoselectivity when a *trans* olefin was used. This selectivity was later shown by Speckamp to be due to the stability of the chair-like transition state **485**, in which the butyl chain adopts an equatorial configuration.[76] Hydrolysis of spirocycle **484** was then found to give the Corey lactone **30** in a quantitative yield, whereas conversion to the thiolactone before hydrolysis yields the Kishi thiolactone **90**.



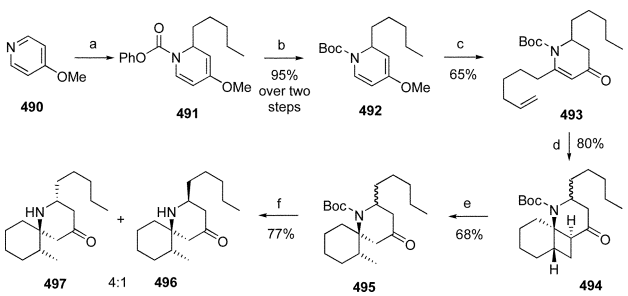
Scheme 59 Evans' and Speckamp's 1979 (±)-pHTX formal syntheses. *Reagents and conditions*: (a) (*E*)-non-4-enylmagnesium bromide, THF; (b) HCOOH; (c) KOH, EtOH, H_2O; (d) P_2S_5, benzene, reflux.

The Tanis group were able to develop another formal synthesis of (±)-pHTX **16** using a similar strategy, but involving a furan-terminated cyclisation (Scheme 60).[77] Glutarimide **482** was first reacted with the Grignard of 1-bromo-3-(5-ethyl-2-furyl)propane, to afford the carbinolamide **486**. This was cyclised, without purification, to give a high 72% yield of the spirocycle **487**. This increase in yield can be ascribed to the smaller number of transition state conformers which the furan ring can adopt when compared to the acyclic system present in the Speckamp/Evans route. Oxidative cleavage of the furan ring was then achieved with mCPBA to yield an unstable ene-dione, which was immediately reduced to the more stable diketone **488**. In order to differentiate between the two ketone functions, so that the side chain ketone can be selectively removed, diketone **488** was exposed to both thermodynamic ethylene ketalisation and Noyori kinetic ketalisation conditions. The thermodynamic conditions, involving ethylene glycol in refluxing benzene, unfortunately led to complete reversion to furan **487**. The kinetic Noyori conditions, using the bis-TMS ether of ethylene glycol and TMS triflate, however, showed a huge preference for ketalisation at the side chain ketone. Exposing diketone **488** to the bis-TMS ether of ethanedithiol and TMS triflate resulted in kinetic dithioketalisation, and selectively provided the desired monoketone **489** as the sole product. A Raney nickel reduction then cleanly removed the thioketal, generating the Kishi lactone **113** in good yield.



Scheme 60 Tanis' 1987 (±)-pHTX formal synthesis. *Reagents and conditions*: (a) MeMgI, THF; 3-(5-ethylfur-2-yl)propylmagnesium bromide, THF; (b) HCOOH, benzene; (c) *m*CPBA; $NaHCO_3$, H_2O; (d) H_2, Pd/C, EtOAc; (e) $Me_3Si–SCH_2CH_2S–SiMe_3$, TMSOTf; (f) Raney Ni, EtOH, reflux.

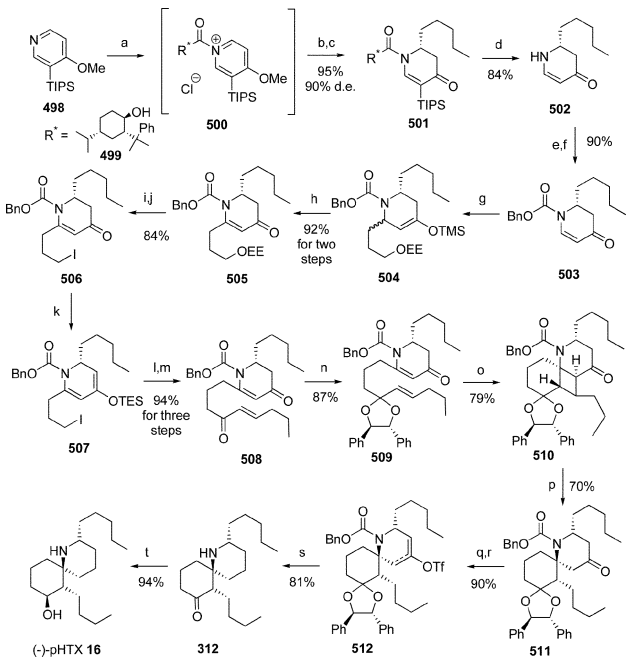
The Comins group reported the development of a novel intramolecular [2 + 2] cycloaddition approach towards the spirocyclic core structure (Scheme 61).[78] Phenyl chloroformate was first added to 4-methoxypyridine **490** to form an acylpyridinium intermediate, which provided dihydropyridine **491** upon addition of *n*-pentylmagnesium bromide. This crude product was then treated with *t*-BuOK, to yield the *N*-Boc derivative **492**. C6 lithiation, followed by alkylation with iodohexene, provided the cyclisation precursor **493**. This was exposed to photolytic irradiation to provide tricycle **494** as an inseparable mixture of C2 epimers. This mixture was treated with samarium iodide to effect a regioselective cyclobutane ring opening, yielding spirocycle **495**, which contains the desired C7 stereochemistry. Boc deprotection allowed the C2 isomers to be separated, providing the desired isomer **497** in a 4 : 1 ratio with the undesired C2 epimer **496**.



Scheme 61 Comins' 1994 HTX approach. *Reagents and conditions*: (a) PhOCOCl, THF, −23 °C; $C_5H_{11}MgBr$; (b) *t*BuOK, THF; (c) *n*BuLi, TMEDA, THF; $CH_2{=}CH(CH_2)_4I$; (d) *hv*, acetone; (e) SmI_2, DMPU, THF; (f) TFA, THF.

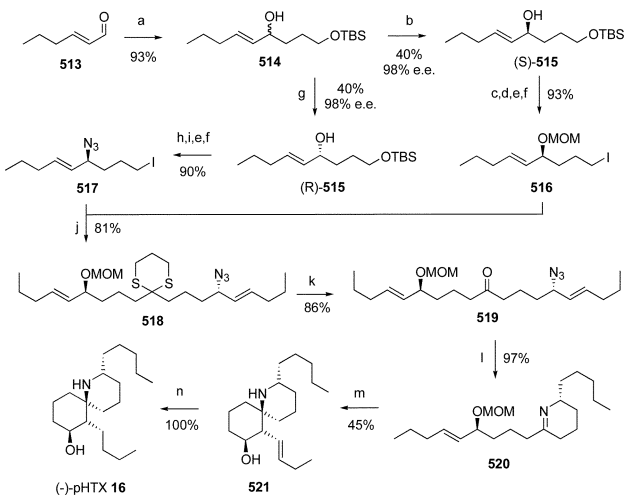
This methodology continued to be investigated by the Comins group, and in 1998 they reported a chiral auxiliary-mediated asymmetric synthesis of (−)-pHTX (Scheme 62).[79] The enantiopure acylpyridinium salt **500**, prepared *in situ* from TIPS-methoxypyridine **498** and (−)-(1*R*,2*S*,4*R*)-2(α-cumyl)-4-isopropylcyclohexanol **499**, was treated with *n*-pentylmagnesium bromide to provide dihydropyridone **502** with a 90% de. This was further purified by chiral HPLC to afford the enantiomerically pure **501** in a 95% yield. Treatment with sodium methoxide, followed by acidification, yielded the unprotected dihydropyridone **502**, enabling the chiral auxiliary to be recovered in 95% yield.

Acylation with benzyl chloroformate then provided the enantiopure carbamate **503**, which was alkylated by a copper-mediated 1,4-conjugate Grignard addition to provide the crude silyl enol ether **504**. This was immediately oxidised using palladium acetate to provide dihydropyridone **505** in 92% yield. Hydroxyl deprotection, followed by conversion to iodide **506**, allowed the C4 carbonyl to be protected as the triethylsilyl enol ether **507**. The alkyl chain was extended using the anion of 2-(trimethylsilyloxy)hept-3-enenitrile, to afford enone **508**, which was then selectively protected as a ketal. On exposure to the photolysis conditions, an inseparable 7 : 1 mixture of photoadducts was produced. In order to improve upon the facial selectivity of this reaction, they reverted back to enone **508** and selectively protected it by transketalisation with an enantiomerically pure bis-TMS ether to yield the auxiliary-bound ketal **509**. Photolysis now proceeded with complete selectivity for the least hindered olefin face, yielding tricycle **510** as the sole product in 79% yield. Regioselective cyclobutane ring opening was then effected with samarium diiodide, forming spirocyclic ketone **511**, which was converted to a mixture of vinyl triflates **512** using LHMDS and *N*-(5-chloro-2-pyridyl)triflimide. Palladium-catalysed hydrogenation then simultaneously reduced the vinyl triflate moiety, cleaved the ketal, and deprotected the nitrogen to yield the Winkler spirocycle **312** in excellent yield. The asymmetric total synthesis was then completed following Winkler's procedure to generate the target (−)-pHTX **16** in 14% overall yield.



Scheme 62 Comins' 1998 (−)-pHTX total synthesis. *Reagents and conditions*: (a) (−)-(1*R*,2*S*,4*R*)-2-(cumyl)-4-isopropylcyclohexanol chloroformate; (b) $C_5H_{11}MgCl$; (c) H_3O^+; (d) NaOMe, MeOH; HCl; (e) *n*BuLi; (f) $ClCO_2Bn$; (g) $(CH_2CHOCHCH_3)O(CH_2)_3MgBr$, CuBr, TMSCl; (h) $Pd(OAc)_2$, MeCN; (i) oxalic acid; (j) NIS, PPh_3; (k) NaHMDS, TMSCl; (l) 2-(trimethylsilyloxy)hept-3-enenitrile, LHMDS, THF; (m) HCl; NaOH; (n) (*S*)-1,2-diphenyl-1,2-bis(trimethylsilyloxy)ethane, TMSOTf; (o) *hν*, acetone; (p) SmI_2, THF, DMPU; (q) LHMDS, THF; (r) *N*-(5-chloro-2-pyridyl)triflimide; (s) H_2, $Pd(OH)_2$, Li_2CO_3, EtOH; (t) $LiAl(OtBu)_3H$.

In 1998, the Tanner group reported the use of a Lewis acid-mediated intramolecular imine ene reaction as the key spirocyclisation step in another synthesis of enantiomerically pure (−)-pHTX **16** (Scheme 63).[80] The racemic allyl alcohol **514** was readily formed by an organolithium alkylation of allyl aldehyde **513**. This alcohol was then subjected to two Sharpless kinetic resolutions involving (−)- and (+)-DIPT to obtain the both the (*S*)- and (*R*)-enantiomers of **515** in over 98% ee for either resolution. The (*S*)-enantiomer of **515** was then converted to the MOM ether, desilylated, and the resultant hydroxyl function was then transformed to the iodide, yielding **516** in an excellent 94% yield. A catalytic hydrogenation of the (*R*)-enantiomer of **515** was followed by a Mitsunobu reaction to install the azide function with complete stereochemical inversion. The primary alcohol was then converted to the iodide, as before, giving **517** in 90% yield. Dithiane **453** was sequentially alkylated with **516** followed by **517**, to yield the coupled product **518**. The thioketal was hydrolysed using NCS and silver nitrate to afford the key azido ketone **519**. Conversion to the cyclic imine **520** was achieved using triphenylphosphine in refluxing benzene, and a brief screen of Lewis acids and solvents allowed the optimum spirocyclisation conditions to be obtained. Thus, a 45% yield of spirocycle **521** could be obtained as a single diastereomer when imine **520** was exposed to dichlorotitanium diisopropoxide in toluene/ether. The MOM protecting group was also conveniently removed during this step, allowing the total synthesis to be completed by quantitative hydrogenation to yield the target (−)-pHTX **16** as a single enantiomer.



Scheme 63 Tanner's 1998 (−)-pHTX total synthesis. *Reagents and conditions*: (a) 3-(*tert*-butyldimethylsilyloxy)propyllithium, Et_2O, pentane; (b) $Ti(OiPr)_4$, (−)-DIPT, TBHP, DCM, −20 °C; (c) MOMCl, iPr_2NEt, DCM; (d) TBAF, cat. HOAc, THF; (e) TsCl, DMAP, Et_3N, DCM; (f) NaI, acetone; (g) $Ti(OiPr)_4$, (+)-DIPT, TBHP, DCM, −20 °C; (h) H_2, PtO_2, hexane; (i) HN_3, PPh_3, DEAD, THF; TBAF; (j) 2,2-bis(tributylstannanyl)-[1,3]dithiane, BuLi, THF; (k) NCS, $AgNO_3$, H_2O, MeCN; (l) PPh_3, benzene, 60 °C; (m) $TiCl_2(OiPr)_2$, toluene, Et_2O; (n) H_2, PtO_2, EtOH.

The Lhommet group reported an *N*-acyliminium ion approach towards the spirocyclic HTX skeleton, based on a similar methodology to that of the Tanis group (Scheme 64).[81] The monocyclic enamine **522** was first converted to the bicyclic enamine **523** by reductive cyclisation. This enamine was then readily substituted

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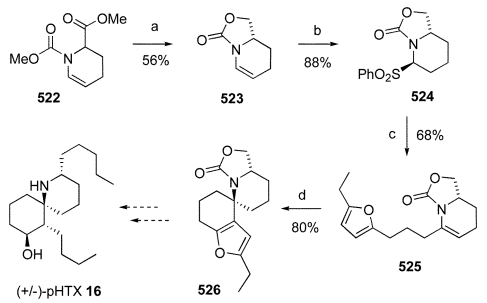
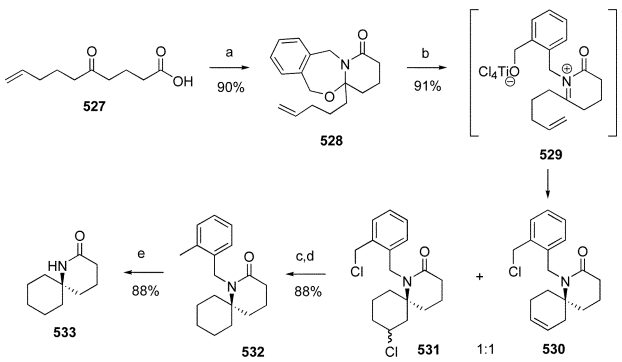


Scheme 64 Lhommet's 2001 HTX approach. *Reagents and conditions*: (a) $NaBH_4$, MeOH, DME, 90 °C; (b) $PhSO_2H$, DCM; (c) LDA, HMPA, THF, 2-(3-bromopropyl)-5-ethylfuran; TFA, DCM.

when exposed to benzenesulfinic acid in dichloromethane, yielding sulfone **524** in an 88% yield. A range of unsaturated alkyl chains were then systematically installed and exposed to the acyliminium ion cyclisation conditions. The most effective of these were found to be the furan-containing chains, analogous to the results found by the Tanis group. Ethylfuran **525** was synthesised and cyclised to provide azaspirocycle **526** in an excellent yield. This compound possesses the required carbon skeleton and relative stereochemistry to be advanced further towards the HTX alkaloids, but as yet these results have not been published.

The Kibayashi group published a Lewis acid-mediated olefin–iminium cyclisation leading to azaspirocycles, which shows potential to be adapted further towards existing HTX intermediates (Scheme 65).[82] The condensation of the unsaturated keto acid **527** with (2-(aminomethyl)phenyl)methanol yields the tricyclic *N*-acyl-*N*,*O*-acetal **477**. Exposure to titanium tetrachloride then generated an intermediate iminium **529**, which underwent a chloride-initiated cyclisation to give a 1 : 1 mixture of spirocyclic alkene **530** and spirocyclic chloride **531**. Palladium-catalysed hydrogenation, followed by free-radical dechlorination, then successfully converted this mixture to the single spirocycle **532** in high yield. This compound was debenzylated to generate the azaspirocycle **533**. Further exploration of this method towards the synthesis of the histrionicotoxins has not been reported.



Scheme 65 Kibayashi's 2001 spirocyclisation. *Reagents and conditions*: (a) toluene, (2-(aminomethyl)phenyl)methanol, reflux; (b) $TiCl_4$, CH_2Cl_2; (c) H_2, Pd/C, EtOH; (d) Bu_3SnH, AIBN, benzene, 80 °C; (e) Na/NH_3, EtOH, −78 °C.

8 Conclusions

In conclusion, since the discovery of the first histrionicotoxins 35 years ago, they have become a popular and rigorous test-bed for state-of-the-art methodologies and strategies. They have, and continue to, inspire organic chemists the world over to develop new and exciting solutions to the problems for formation of quaternary centres, contiguous stereogenic centres, spirocyclic ring systems and highly unsaturated chains. This retrospective of synthetic approaches to the histrionicotoxins forms a chronological catalogue of synthetic methods, and no doubt additional installments will be provided as chemist's imaginations continue to be piqued by these compelling compounds.

9 Acknowledgements

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