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# Total synthesis of the lupin alkaloid cytisine: comparison of synthetic strategies and routes

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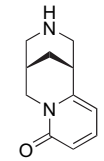
**Contents**

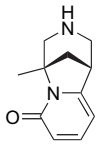


## 1. Discovery and isolation

(−)-Cytisine is a naturally occurring lupin alkaloid found in the seeds of the *Laburnum anagyroides* and other *Leguminosae*.[1] In 1862, Husemann and Marmé isolated (−)-cytisine in a pure form.[2] The late 19th and early 20th centuries saw work to determine the structure of (−)-cytisine by chemical means. This was conducted by the groups of Partheil,[3] Freund,[4] Späth,[5] Ewins[6] and Ing.[7,8] Finally, in 1932, Ing proposed the correct structure of cytisine **1**,[8] updating a previously reported erroneous proposal, pyridone **2**.[7]



(–)-cytisine **1**



**2**

(−)-Cytisine is a significant constituent of the seeds of some *Leguminosae*[9,10] and can be easily obtained on a multi-gram scale by extraction of *L. anagyroides* seeds using a mixture of aqueous ammonia in MeOH and $CH_2Cl_2$.[11,12] A simple acid/base extraction followed by recrystallisation from either acetone or toluene typically gives ~5 g of pure (−)-cytisine from ~600 g of *L. anagyroides* seeds, providing a cheap source of (−)-cytisine.[12]

## 2. Biological activity

(−)-Cytisine shows significant biological activity, specifically at neuronal nicotinic acetylcholine receptors (nAChRs)[13] and, as a consequence, the biological activity of the analogues of (−)-cytisine has been investigated in recent years.[14–19] Neuronal nAChRs are distributed widely throughout the peripheral and central nervous systems and a number of subtype receptors exist. (−)-Nicotine, the addictive component of tobacco, binds to the α4β2 subtype receptor with high affinity ($K_i$=0.95 nM, rat cortex) and subtype specificity (for α3β4 and α7, $K_i$=840 and 4200 nM, respectively).[17] At the α4β2 subtype receptor, (−)-nicotine

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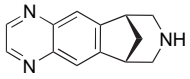
exhibits a full agonist profile, resulting ultimately in the release of dopamine, a chemical associated with the sensation of pleasure. The stimulation of a dopaminergic response is a significant factor in nicotine addiction.[20] (−)-Cytisine exhibits an even higher affinity and similar selectivity for the α4β2 subtype nAChR ($K_i$=0.17 nM).[17] Unlike (−)-nicotine, however, (−)-cytisine only displays a partial agonist profile at the α4β2 subtype receptor. Researchers at Pfizer speculated that such a biological profile could make (−)-cytisine a useful staring point for developing a smoking cessation drug.[17] Thus, (−)-cytisine would selectively bind to the α4β2 receptor in the presence of (−)-nicotine as it has a higher affinity for the receptor, thus preventing nicotine binding. As (−)-cytisine is a partial agonist of the α4β2 receptor, it would trigger a much reduced dopaminergic response, compared to (−)-nicotine, which would have the potential of overcoming the cravings associated with nicotine withdrawal. Despite its profile at the receptor, (−)-cytisine shows little efficacy in vivo,[21] due to two bioavailability issues: (i) poor absorption[22] and (ii) poor brain penetration at the blood–brain barrier, due to the basic nitrogen being protonated at physiological pH.[23] In recent work, the Pfizer group disclosed their modifications to (−)-cytisine with the aim of maintaining the in vitro activity, but increasing the in vivo availability. This led to the development of varenicline **3**, which has now been approved as a smoking cessation drug.



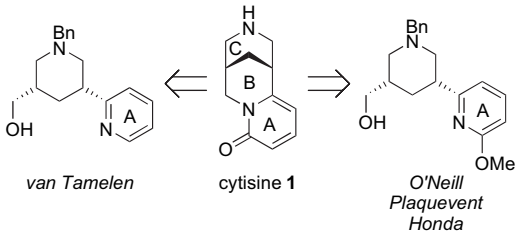
**3**

## 3. Total synthesis of cytisine

To date, 10 distinct, total syntheses of cytisine **1** and one formal synthesis have been reported. The first total synthesis of (±)-cytisine was accomplished by van Tamelen in 1955[24,25] and this was closely followed by Bohlmann's[26] and Govindachari's[27] syntheses in the late 1950s. After a hiatus of nearly 50 years, the identification of (−)-cytisine's biological activity led to renewed interest from industry and academia. Two new routes to (±)-cytisine were reported by chemists at Pfizer in 2000 (O'Neill[28] and Coe[29]) as a prelude to their development of varenicline **3**. Subsequently, Gallagher[30] and our own group[31] also completed the syntheses of (±)-cytisine. The first asymmetric synthesis of (−)-cytisine was described by Lesma[32] in 2004 and was closely followed by the syntheses of (+)-cytisine (Honda[33] and Gallagher[34]). The key details of these synthetic approaches are summarised and compared in the following sections. There is a particular emphasis on the strategies adopted in the syntheses and they are therefore not presented in chronological order.

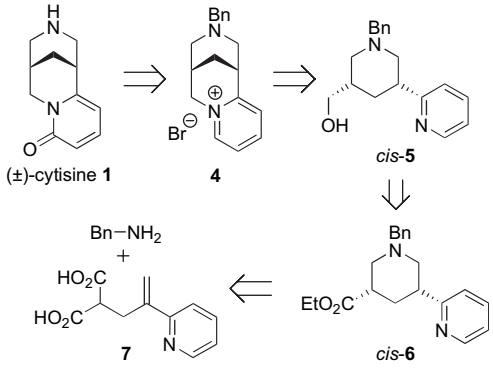
### 3.1. Synthesis using a pyridine-derived A-ring

In four of the synthetic approaches to cytisine **1**, a pyridine derivative was used as a precursor of the pyridone A-ring of cytisine (Scheme 1). van Tamelen's route used a monosubstituted pyridine, whilst the approach pioneered by O'Neill (and subsequently exploited by other groups) employed a methoxy-substituted pyridine, thus avoiding the need for an oxidation step to produce the pyridone ring. In each of these synthetic routes, a *cis*-3,5-disubstituted piperidine needs to be constructed.




**Scheme 1**. Strategy: pyridine-derived A-ring.

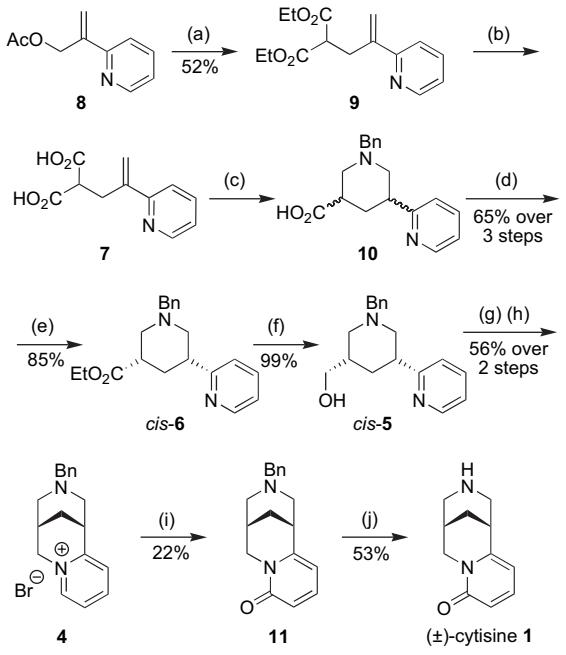
The retrosynthetic analysis of the first synthesis of (±)-cytisine, reported by van Tamelen and Baren in 1955,[24,25] is shown in Scheme 2. In this case, cytisine was obtained from pyridinium salt **4** by hydrolysis and oxidation. Pyridinium salt **4** was generated by the cyclisation of alcohol *cis*-**5** (after conversion into the corresponding bromide) obtained by the reduction of the ester in piperidine *cis*-**6**. Piperidine *cis*-**6** was generated by the reaction of benzylamine with vinylpyridine **7**. The required cis relative stereochemistry in alcohol *cis*-**5** was obtained by the base-mediated epimerisation of a mixture of esters *cis*- and *trans*-**6**.




**Scheme 2**. van Tamelen's retrosynthetic analysis of (±)-cytisine.

The forward synthesis of van Tamelen's approach is shown in Scheme 3.[24,25] The first step of the synthesis was the formation of malonate **9**. This was achieved by the substitution of allyl 2-(2-pyridyl)-acetate **8** with the sodium enolate of diethyl malonate to give malonate **9** in 52% yield. The reaction presumably proceeds either via an allyl cation intermediate or by a conjugate addition–elimination pathway. Then, malonate **9** was saponified using refluxing aqueous NaOH and the crude malonic acid **7** was immediately used in the next step. The conversion of malonic acid **7** into piperidine *cis*-**6** started with a Mannich reaction between the enol of **7** and the Mannich base of benzylamine and formaldehyde. Presumably, this was followed by decarboxylation of one of the acid groups, as indicated by the evolution of $CO_2$ in the initial stages of heating, and it was shown (by UV spectroscopy) that intramolecular conjugate addition onto the vinylpyridine functionality to form the piperidine ring required at least 4 h. This produced the corresponding acid **10**, which was esterified to give ester **6**. Based on the yields

of the subsequent ester reduction and cyclisation, it was deduced that ester **6** comprised a significant amount of the unwanted diastereomeric ester *trans*-**6**. Thus, it was necessary to introduce an epimerisation step to improve the overall yield. Epimerisation of the mixture of esters *cis*- and *trans*-**6** using NaOEt in refluxing EtOH gave the thermodynamically more stable piperidine *cis*-**6** (in which both substituents are equatorial) in 55% yield over four steps from malonic acid **7**.

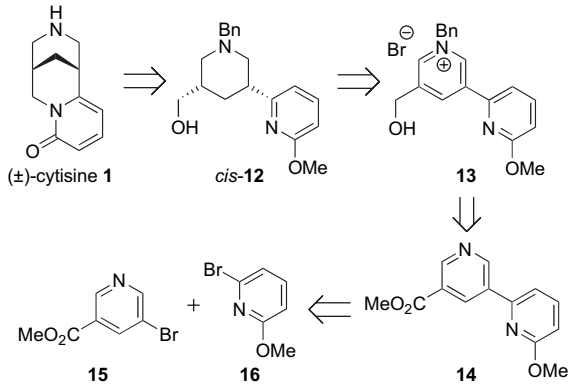



**Scheme 3**. Reagents and conditions: (a) NaH, diethyl malonate, DMF/benzene, reflux; (b) 4 M $NaOH_{(aq)}$, reflux; (c) HCl, $BnNH_2$, $HCHO_{(aq)}$, reflux, 16 h; (d) HCl, EtOH; (e) Na, EtOH; (f) $LiAlH_4$, $Et_2O$; (g) $HBr_{(aq)}$, (h) benzene, reflux; (i) $NaOH_{(aq)}$, $K_3Fe(CN)_6$, 100 °C, 16 h; (j) HI, phenol, $NH_4I$, 5% auric chloride solution, 150 °C, 0.5 h.

Ester reduction of *cis*-**6** using $LiAlH_4$ gave alcohol *cis*-**5**. Conversion of alcohol *cis*-**5** into pyridinium salt **4** was achieved by first treating the alcohol *cis*-**5** with HBr and then heating the crude bromide in benzene to induce cyclisation to give pyridinium salt **4** in 56% yield over the two steps. Oxidation of pyridinium salt **4** using aqueous NaOH and $K_3Fe(CN)_6$ generated the pyridone ring of *N*-benzyl cytisine **11** in a slightly disappointing 22% yield. The final step in the synthesis was debenzylation and this was carried out using HI at 150 °C to give (±)-cytisine **1** in 53% yield.

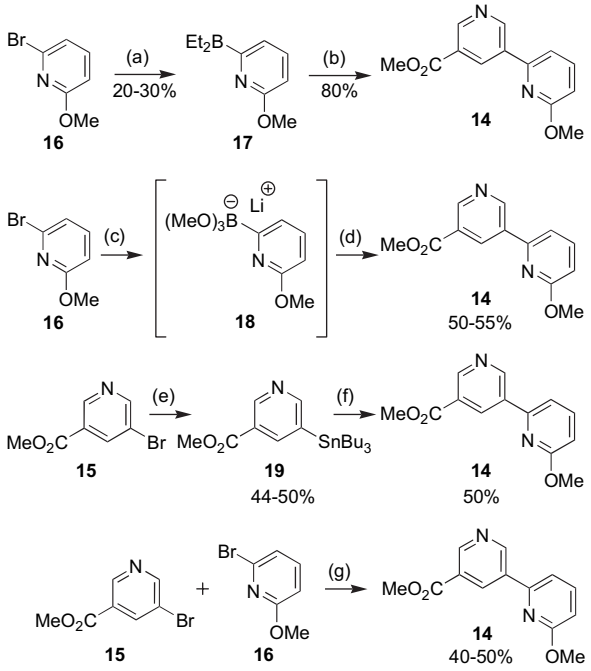
To summarise, van Tamelen's synthesis of cytisine was completed in seven steps from allyl 2-(2-pyridyl)-acetate **8** in 2% overall yield.[24,25] Additionally, van Tamelen also reported[25] the resolution of (±)-cytisine using *d*-camphor-10-sulfonic acid to give the corresponding sulfonate salt of (−)-cytisine, which was identical to the *d*-camphor-10-sulfonate salt of natural (−)-cytisine based on melting point and optical rotation.

The first stage of O'Neill's retrosynthetic analysis[28] (Scheme 4) is reminiscent of the van Tamelen route,[24,25] disconnecting the pyridone carbon–nitrogen bond to give a *cis*-3,5-disubstituted piperidine **12**. A key difference to van Tamelen's route at this stage is the presence of the methoxypyridine in *cis*-**12**, which removes the need for a late-stage oxidation of the pyridine to the pyridone. Piperidine *cis*-**12** was obtained by the hydrogenation of the corresponding pyridinium salt **13**, which was obtained from bis-pyridine **14**. The aryl–aryl bond in **14** was constructed through a palladium(0)-mediated coupling process and bis-pyridine **14** was ultimately derived from bromopyridines **15** and **16**.




**Scheme 4**. O'Neill's retrosynthetic analysis of (±)-cytisine.

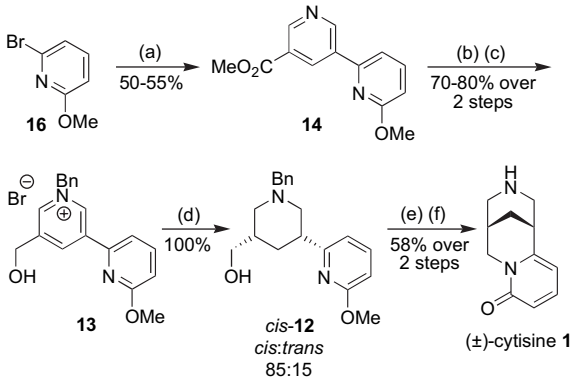
Various combinations and conditions for Suzuki and Stille cross-coupling reactions were investigated by O'Neill and co-workers for the synthesis of bis-pyridine **14** (Scheme 5). Lithium–halogen exchange of the bromide in **16** followed by borane trapping afforded a low yield (20–30%) of borane **17**. This was unfortunate since borane **17** was a particularly efficient Suzuki-coupling partner with bromopyridine **15**




**Scheme 5**. Reagents and conditions: (a) (i) *n*-BuLi, $Et_2O$, −40 °C; (ii) $BEt_3$; (iii) $I_2$; (b) cat. $Pd(PPh_3)_4$, **15**; (c) (i) *n*-BuLi, $Et_2O$, −40 °C; (ii) $B(OMe)_3$, $Et_2O$; (d) cat. $Pd(PPh_3)_4$, **15**, 2 equiv CsF, DME, 85 °C, 12 h; (e) $BnPd(Ph_3P)_2Cl$, $^nBu_3SnSn^nBu_3$; (f) cat. $Pd(PPh_3)_4$, **16**; (g) $BnPd(Ph_3P)_2Cl$, $^nBu_3SnSn^nBu_3$, DMF, 130 °C, 1 h.

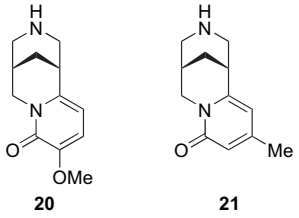
(80% yield of bis-pyridine **14**). A higher overall yield of bis-pyridine **14** (50–55%) was obtained when borate ester **18** (generated in situ from **16**) was coupled with bromopyridine **15**. Ultimately, this approach proved to be the most efficacious way of generating bis-pyridine **14** for cytisine total synthesis (vide infra). Stille coupling was also relatively successful. Thus, stannane **19** could be produced in 44–50% yield from a palladium(0)-mediated reaction of bromopyridine **15** with hexabutylditin. Then, Stille coupling was used to produce bis-pyridine **14** in 50% yield. Finally, a rather unusual 'one-pot' stannylation-Stille coupling approach to **14** (40–50% yield) was accomplished by mixing bromopyridines **15** and **16** with hexabutylditin under palladium(0) catalysis. The expected homodimer products were not generated in significant quantities.

With an appropriate method for preparing bis-pyridine **14** in place, O'Neill completed a total synthesis of cytisine, as outlined in Scheme 6. Thus, bis-pyridine **14** was generated in 50–55% yield using the optimised palladium(0)-coupling protocol. The selective reduction of one of the pyridine rings in 3,5-disubstituted pyridines such as **14** is linked to the oxidation level of the substituents. It was found that the ester in **14** had to be reduced to a primary alcohol prior to benzylation. After reduction, chemoselective benzylation of the least sterically hindered pyridine nitrogen gave the pyridinium salt **13** in 70–80% yield, providing the required activation for selective hydrogenation using $H_2$ and $PtO_2$. In this way, a quantitative yield of an 85:15 mixture of piperidines *cis*- and *trans*-**12** was obtained.

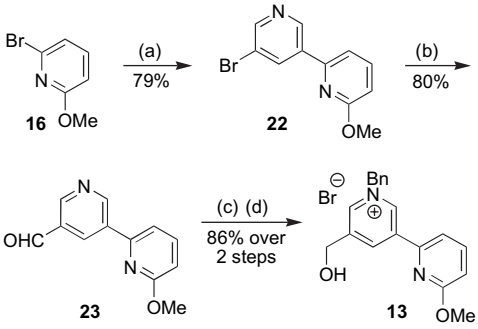



**Scheme 6**. Reagents and conditions: (a) (i) *n*-BuLi, $Et_2O$, −40 °C; (ii) $B(OMe)_3$; (iii) **15**, cat. $Pd(PPh_3)_4$, 2 equiv CsF, DME, 85 °C, 12 h; (b) $LiAlH_4$, $Et_2O$; (c) BnBr, MeCN; (d) $H_2$, $PtO_2$, $Et_3N$/MeOH; (e) (i) MsCl, $Et_3N$, $CH_2Cl_2$; (ii) toluene, reflux; (f) $H_2$, $Pd(OH)_2$, $NH_4^+HCOO^-$, MeOH.

O'Neill's intermediate, piperidine *cis*-**12**, is similar to van Tamelen's intermediate *cis*-**6**, but there is no need for an oxidation process in O'Neill's case. Thus, mesylation of the hydroxyl group in *cis*-**12** followed by heating in toluene induced cyclisation to give *N*-benzyl cytisine. *N*-Debenzylation to (±)-cytisine was achieved by transfer hydrogenolysis using $Pd(OH)_2$ and ammonium formate (58% yield from *cis*-**12**). This total synthesis of cytisine is the shortest (five steps) and highest yielding (25% overall yield) reported to date.[28] Furthermore, O'Neill and Kozikowski have demonstrated that this is a useful approach to cytisine analogues such as **20**[28] and **21**.[19] A limitation of this route to analogues of cytisine, however, is that they commence with suitably functionalised pyridines and the preparation of each analogue requires an essentially complete total synthesis.



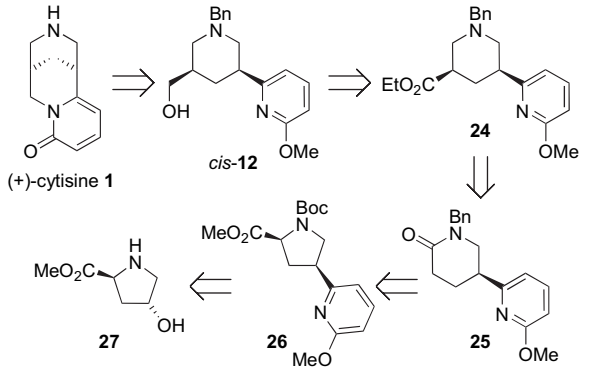

Plaquevent has reported an alternative cross-coupling approach to O'Neill's intermediate, pyridinium salt **13**, thus completing a formal synthesis of (±)-cytisine.[35] In this case, Plaquevent used a Negishi-coupling protocol with 3,5-dibromopyridine (Scheme 7). Thus, lithium–halogen exchange of bromopyridine **16** with *n*-BuLi and subsequent transmetallation from lithium to zinc using $ZnCl_2$ provided the acceptor for the Negishi coupling. The organozinc reagent thus formed was coupled with 3,5-dibromopyridine using 1 mol % $Pd(PPh_3)_4$ in refluxing THF to give the desired bis-pyridine **22** in 79% yield. The use of 2 equiv of 3,5-dibromomopyridine was required to minimise a second Negishi reaction between the organozinc reagent and bis-pyridine **22**. The next step involved a second lithium–halogen exchange and trapping with DMF. The conditions that proved to be the most efficient were lithium–halogen exchange of the bromide in bis-pyridine **22** with *n*-BuLi in $Et_2O$ followed by reaction with DMF in THF, all at −78 °C. In this way, aldehyde **23** was isolated in 80% yield. Next, aldehyde **23** was reduced to the primary alcohol using $NaBH_4$ (94% yield), which was converted into pyridinium salt **13** (92% yield) upon treatment with an excess of benzyl bromide. This completed a formal synthesis of (±)-cytisine[35] and, although Plaquevent's route to pyridinium salt **13** is one step longer than O'Neill's, the overall yield is ~10 to 15% higher. Consequently, Plaquevent's Negishi approach to pyridinium salt **13** and O'Neill's subsequent steps represent the most efficient way of achieving the total synthesis of (±)-cytisine.




**Scheme 7**. Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 °C; (ii) $ZnCl_2$, −78 °C→rt; (iii) 1 mol % $Pd(PPh_3)_4$, 2 equiv 3,5-dibromopyridine, THF, reflux, 24 h; (b) (i) *n*-BuLi, $Et_2O$, −78 °C, 1 h; (ii) 5 equiv DMF, THF, −78 °C→rt, 16 h; (c) $NaBH_4$, EtOH, rt; (d) 3 equiv BnBr, MeOH.

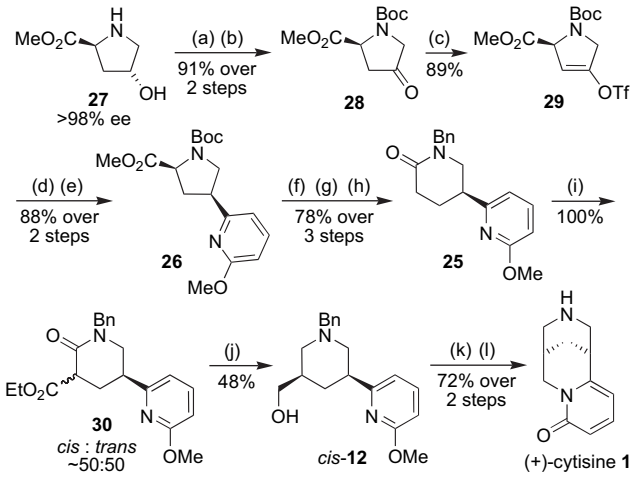
Honda has recently disclosed an enantioselective entry into piperidine alcohol *cis*-**12**, a key intermediate in O'Neill's route. In fact, Honda's approach delivered the first asymmetric synthesis of (+)-cytisine[33] as well as the total syntheses of

(+)-kuraramine and (+)-jussiaeiine, which are presumed metabolites of *N*-methylcytisine.[36,37] Honda's retrosynthetic analysis is shown in Scheme 8. O'Neill's key intermediate was prepared from piperidine ester **24**, obtained from lactam **25**. One of the key steps in Honda's route was the ring expansion of pyrrolidine **26** to lactam **25** via a $SmI_2$-promoted reduction of the carbon–nitrogen bond and subsequent lactamisation. Pyrrolidine **26** was generated from hydroxyproline derivative **27** in a few steps.




**Scheme 8**. Honda's retrosynthetic analysis of (+)-cytisine.

Honda's forward synthesis (Scheme 9) began with *N*-protection of hydroxyproline derivative **27** under standard conditions. Then, Swern oxidation to ketone **28** was followed by LHMDS-mediated deprotonation and O-triflylation using *N*-(5-chloro-2-pyridyl)triflimide to give enol triflate **29** in 81% yield over three steps from hydroxyproline **27**. Stille coupling between enol triflate **29** and 2-tributylstannyl-6-methoxypyridine (catalysed by $Pd(PPh_3)_4$ in the presence of LiCl/CuI at 65 °C in THF) was used to install the 2-methoxypyridine moiety. This produced an intermediate vinylpyridine that was hydrogenated under standard conditions



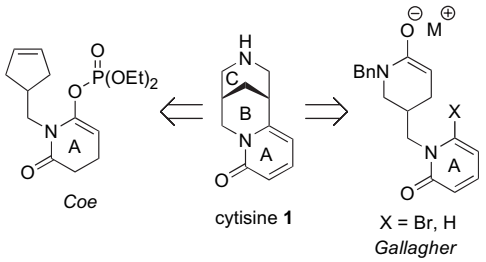

**Scheme 9**. Reagents and conditions: (a) $Boc_2O$, $Et_3N$, $CH_2Cl_2$, rt; (b) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −40 °C to rt; (c) LHMDS, *N*-(5-chloro-2-pyridyl)triflimide, THF, −78 °C to −20 °C; (d) $Pd(PPh_3)_4$, LiCl, CuI, 2-tributylstannyl-6-methoxypyridine, THF, 65 °C; (e) $H_2$, Pd/C, MeOH, rt, 100%; (f) TFA, $CH_2Cl_2$, 0 °C; (g) $SmI_2$, THF/HMPA, MeOH, 0 °C to rt; (h) NaH, BnBr, THF/HMPA, THF, 0 °C to rt; (h) LDA, $ClCO_2Et$, THF, −78 °C; (i) $LiAlH_4$, THF, 0 °C to rt; (j) (i) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C; (ii) toluene, reflux; (k) $Pd(OH)_2$, $NH_4^+HCOO^-$, MeOH, reflux.

to deliver **26** in 88% yield for this two-step sequence. Presumably, the cis-stereoselectivity arises from hydrogenation on the least sterically hindered face, opposite to the ester substituent. After Boc-deprotection of **26** using TFA, reaction with $SmI_2$ effected reductive deamination (carbon–nitrogen bond cleavage) of the α-amino ester to the δ-amino ester, which cyclises to the lactam. Subsequent N-benzylation (NaH, benzyl bromide) generated the lactam **25** in 78% yield over the three steps.

Next, generation of the enolate of lactam **25** using LDA and electrophilic trapping with ethyl chloroformate gave a ~50:50 mixture of esters *cis*- and *trans*-**30** in quantitative yield. In contrast to van Tamelen's results (see Scheme 3), all attempts for epimerisation of β-keto ester **30** to the desired *cis*-3,5-disubstituted piperidine ester were unsuccessful. Nevertheless, reduction of the ~50:50 mixture of esters *cis*- and *trans*-**30** using $LiAlH_4$ gave a separable mixture of alcohols *cis*- and *trans*-**12**, from which *cis*-**12** was isolated in 48% yield (43% yield of the unwanted *trans*-**12**). The last two steps of the synthesis were completed in 72% yield using O'Neill's conditions to give (+)-cytisine. Honda's synthesis proceeds in 19% overall yield (11 steps from hydroxyproline **27**).[33] This is a rather lengthy, but particularly efficient, synthesis, especially when one considers that it was not possible to epimerise the ~50:50 mixture of esters *cis*- and *trans*-**30** towards the desired diastereomer.

### 3.2. Synthesis using a glutarimide- or pyridone-derived A-ring

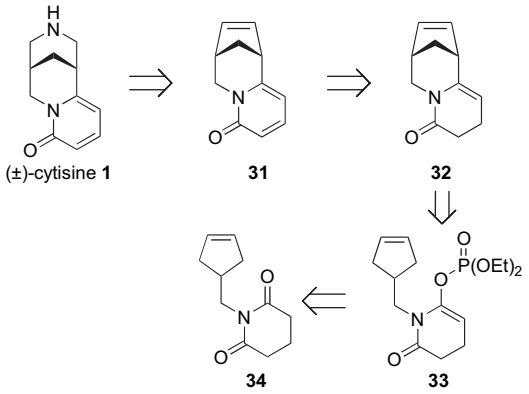
The routes presented in Section 3.1 all relied on a late-stage, intramolecular pyridine N-alkylation to form the B-ring of cytisine. In the synthetic routes to cytisine described by Coe and Gallagher (Scheme 10), a different pyridone disconnection was envisaged in which the B-ring of cytisine would be formed by a palladium(0)-mediated intramolecular process. In fact, in Gallagher's second-generation approach (X=H), addition of the enolate directly to the pyridone was used to close the ring. Gallagher's approach also enabled the pyridone A-ring of cytisine to be intact throughout the synthesis. A final advantage of these strategies for cytisine synthesis is that they remove the need for a *cis*-3,5-disubstituted piperidine.




**Scheme 10**. Strategy: glutarimide- or pyridone-derived A-ring.

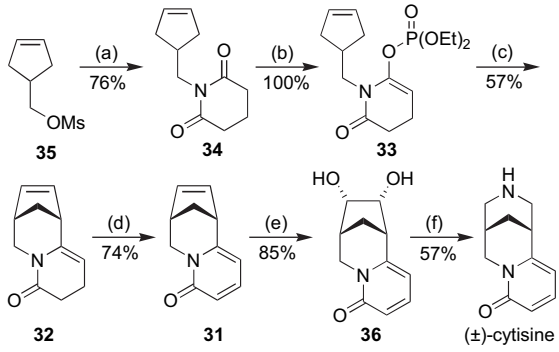
The retrosynthetic analysis adopted by Coe is shown in Scheme 11.[29] (±)-Cytisine was derived from pyridone **31** by oxidative cleavage of the alkene to a bis-aldehyde and successive reductive amination with ammonia. Pyridone **31** was obtained by oxidation of lactam **32**, which was produced from an intramolecular Heck reaction with enol phosphate

**33**. Enol phosphate **33** was generated by O-phosphorylation of the enolate derived from *N*-alkylated glutarimide **34**.




**Scheme 11**. Coe's retrosynthetic analysis of (±)-cytisine.

Coe's synthesis of (±)-cytisine[29] (Scheme 12) starts with N-alkylation of glutarimide via deprotonation and reaction with mesylate **35** in the presence of $^{n}Bu_4N^+I^-$ and DMF to give imide **34** in 76% yield. Initial efforts for the projected intramolecular Heck reaction centred around the formation of an enol triflate from imide **34**. Unfortunately, these attempts were low yielding and attention was then switched to the use of an enol phosphate. Thus, deprotonation of imide **34** using LHMDS and subsequent reaction with diethyl chlorophosphate furnished enol phosphate **33** in quantitative yield. The key intramolecular Heck reaction of enol phosphate **33** was accomplished under standard conditions (2 mol % $Pd(OAc)_2$, 4 mol % P(*o*-tol)$_3$ and 1.5 equiv of $Et_3N$, MeCN, 83 °C, 24 h) to give lactam **32** in 57% yield.

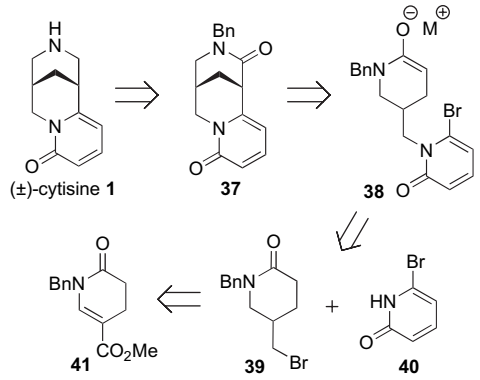



**Scheme 12**. Reagents and conditions: (a) (i) glutarimide, *t*-BuOK, 68 °C, THF, 1 h; (ii) mesylate **35**, cat. DMF, cat. $^{n}Bu_4NI$, 76%; (b) (i) LHMDS, THF, −78 to 23 °C; (ii) $ClP(O)(OEt)_2$; (c) 1.5 equiv $Et_3N$, 2.0 mol % $Pd(OAc)_2$, 4 mol % P(*o*-tol)$_3$, MeCN, 60 °C, 24 h; (d) 10–20 equiv $MnO_2$, benzene, 80 °C, 3 h; (e) $Me_3NO\cdot 2H_2O$, cat. $OsO_4$, $CH_2Cl_2$; (f) (i) 1 equiv $NaIO_4$, EtOH/$H_2O$, 30 min; (ii) $NH_4OH$, $H_2$, $Pd(OH)_2$, 48–72 h.

The remaining steps of this synthesis, including oxidation to the pyridone, alkene oxidative cleavage and amination, proceeded uneventfully and in good yield. Thus, the dihydropyridone in lactam **32** was successfully oxidised to the desired pyridone **31** (74% yield) using $MnO_2$ in refluxing benzene. The use of DDQ for oxidation of lactam **32** was unsuccessful. Dihydroxylation of the alkene in pyridone **31** was achieved using $OsO_4$/NMO to give the diol **36** as a single diastereomer in 85% yield, presumably as a result of preferential reaction on the *exo*-face of the alkene. Finally, cleavage of the 1,2-diol in **36** using $NaIO_4$ gave a bis-aldehyde, which was subjected to double reductive amination using ammonia solution and $Pd(OH)_2$/hydrogen to complete the synthesis of (±)-cytisine (57% over two steps). Coe's synthesis of (±)-cytisine proceeds over six steps in 16% overall yield[29] and is a particularly attractive synthesis, as it does not require the use of any protecting groups.

A brief study by Coe on an enantioselective version of the Heck reaction **33**→**32** using a chiral phosphine ligand was not very successful. Using one of Pfaltz's chiral oxazoline-phosphine ligands, a Heck reaction of enol phosphate **33** gave lactam **32** in 22% ee, although it did enable Coe to complete a synthesis of enantio-enriched (+)-cytisine via this approach.

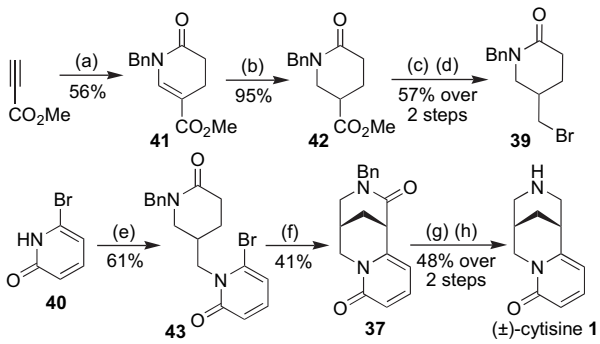
The retrosynthetic analysis of Gallagher's first-generation route to (±)-cytisine is summarised in Scheme 13.[30] In this case, cytisine is derived from lactam **37** by amide reduction. Using a pyridone disconnection analogous to Coe's, lactam **37** was constructed by a palladium(0)-mediated intramolecular arylation of enolate **38**. The amide precursor to enolate **38** was constructed by the union of bromide **39** with bromopyridone **40** (via pyridone N-alkylation). Bromide **39** was generated starting from unsaturated lactam **41**.




**Scheme 13**. Gallagher's first-generation retrosynthetic analysis of (±)-cytisine.

The first step in Gallagher's synthesis (Scheme 14) was the preparation of unsaturated lactam **41**. This was achieved using a multi-component procedure reported by Stille,[38] which involved a conjugate addition of benzylamine onto methyl propiolate, N-acylation with acryloyl chloride and cyclisation. In this way, unsaturated lactam **41** was obtained in 56% yield. Hydrogenation of the unwanted double bond gave lactam **42** in high yield (95%). Reduction of the ester functionality in lactam **42** using $LiAlH_4$ and reaction of the intermediate alcohol with $PBr_3$ in refluxing toluene gave the bromide **39** in 57% yield over two steps.

Unfortunately, selective N-alkylation of bromopyridone **40** with bromide **39** proved difficult, since O-alkylation and, to a lesser extent, elimination from bromide **34** were competitive. After much optimisation, suitable conditions for satisfactory N-alkylation were found (bromopyridone **40**, 2 equiv NaH, 4 equiv LiBr, 24:1 DME/DMF, rt, 10 days) and, under these conditions, a 61% yield of the desired

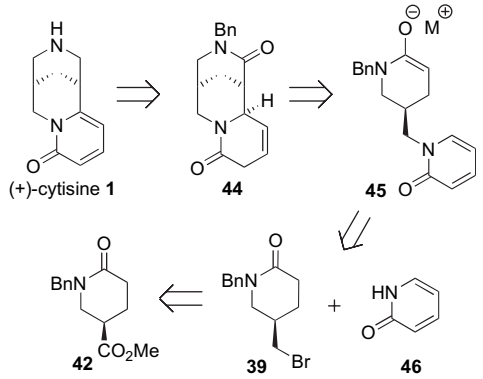


**Scheme 14**. Reagents and conditions: (a) (i) $BnNH_2$, $Et_2O$, rt; (ii) acryloyl chloride, THF, 70 °C; (b) $H_2$, Pd/C, $Na_2CO_3$, EtOH, 20 °C; (c) $LiAlH_4$, THF, −10 °C; (d) $PBr_3$, toluene, 110 °C; (e) 2 equiv NaH, 4 equiv LiBr, DME/DMF (24:1), bromide **39**, 10 days; (f) 5 mol % $Pd(OAc)_2$, 7.5 mol % (±)-BINAP, 2 equiv KHMDS, THF, 70 °C; (g) $BH_3$·THF, 0 °C to rt; (h) 1 equiv HCl in MeOH, $H_2$, $Pd(OH)_2$/C, MeOH.

pyridone lactam **43** was obtained. Next, the key bispidine-forming step via an intramolecular lactam α-arylation was investigated. Pyridone lactam **43** was deprotonated with KHMDS and subsequent reaction in the presence of $Pd(OAc)_2$ and (±)-BINAP facilitated the α-arylation process to give lactam **37** in an unoptimised 44% yield. To complete the synthesis of cytisine, the lactam was reduced using $BH_3$·THF and N-debenzylation was achieved using $Pd(OH)_2$ and hydrogen (48% yield over two steps). To summarise, Gallagher's route is eight steps and generates (±)-cytisine in 4% overall yield.[30]

Gallagher also briefly investigated the asymmetric hydrogenation of unsaturated lactam **41**, but, using Ru[(*R*,*R*)-Me-Duphos]cod·$BF_4$ as the chiral catalyst, lactam **42** was generated in a disappointing 24% ee. As outlined below, however, an efficient way of generating enantio-enriched lactam **42**, via enzymatic resolution, has now been optimised by Gallagher's group.

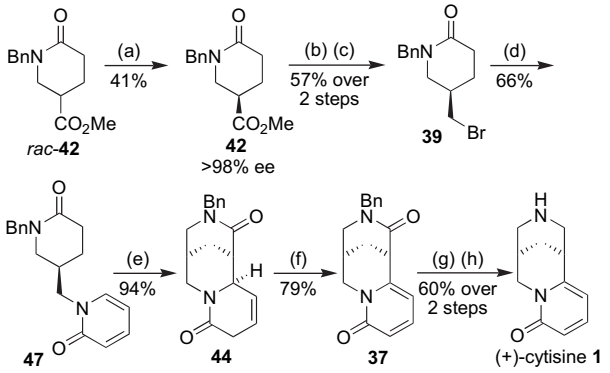
More recently, Gallagher has reported a second-generation approach to cytisine and the key features of the retrosynthetic analysis are presented in Scheme 15.[34] The key difference in this new approach is that the bispidine is formed via direct, intramolecular conjugate addition of an enolate onto the pyridone (**45**→**44**). As a result, subsequent oxidation of



**Scheme 15**. Gallagher's second-generation retrosynthetic analysis of (+)-cytisine.

the dihydropyridone in **44** to the pyridone in cytisine is required. The lactam precursor to enolate **45** was prepared by N-alkylation of 2-pyridone **46** using bromide **39** in a similar fashion to the previous route. Furthermore, the new approach delivered (+)-cytisine, since an efficient method for the preparation of enantio-enriched lactam **42** was devised.

In Gallagher's second-generation route to (+)-cytisine (Scheme 16), lactam ester *rac*-**42** was prepared in two steps (53% overall yield) from methyl propiolate using the previously described approach (see Scheme 14). Enzymatic resolution of *rac*-**42** was achieved by ester hydrolysis using aqueous α-chymotrypsin to give a 41% yield of ester (*R*)-**42** in >98% ee and a 48% yield of the corresponding (*S*)-carboxylic acid in 64% ee. The remainder of the synthesis was carried out using lactam **42** (>98% ee). First of all, lactam **42** was converted into bromide **39** by reduction with $LiAlH_4$ and bromination using $PBr_3$ (57% yield over two steps). Selective N-alkylation of 2-pyridone **46** under the conditions optimised for N-alkylation of the more sterically encumbered bromopyridone **40** delivered pyridone lactam **47** in 66% yield.



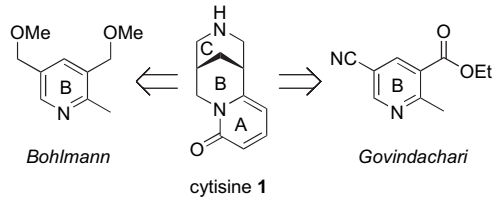
**Scheme 16**. Reagents and conditions: (a) α-chymotrypsin, 0.1 M phosphate buffer, acetone, pH 7.4; (b) $LiAlH_4$, THF, −10 °C; (c) $PBr_3$, toluene, 110 °C; (d) 2-pyridone **46**, $K_2CO_3$, $^nBu_4N^+Br^-$, water, toluene, reflux; (e) 2 equiv LHMDS, THF, 70 °C, 15 h; (f) $MnO_2$, $CH_2Cl_2$; (g) $BH_3$·THF, 0 °C to rt; (h) $Pd(OAc)_2$, HCl, MeOH, $H_2$.

Next, the key cyclisation was studied. It was found that the deprotonation of pyridone lactam **47** with LHMDS and subsequent heating at 70 °C in a sealed tube allowed efficient cyclisation to give a single diastereomer of dihydropyridone **44** in an impressive 94% yield. Such 1,6-additions onto pyridones are rare and Gallagher also exploited this type of process as a key step in the total synthesis of the related alkaloids, (±)-anagyrine and (±)-thermopsin.[34] $MnO_2$ oxidation of dihydropyridone **44** then restored the pyridone oxidation level and gave pyridone **37** in 79% yield. Pyridone **37** was converted into (+)-cytisine by reduction with $BH_3$·THF and hydrogenolysis using $Pd(OAc)_2$ and hydrogen (60% yield over two steps). To summarise, Gallagher's synthesis of (+)-cytisine was accomplished over 11 steps and in 4% overall yield.[34]

### 3.3. Synthesis using a pyridine-derived B-ring

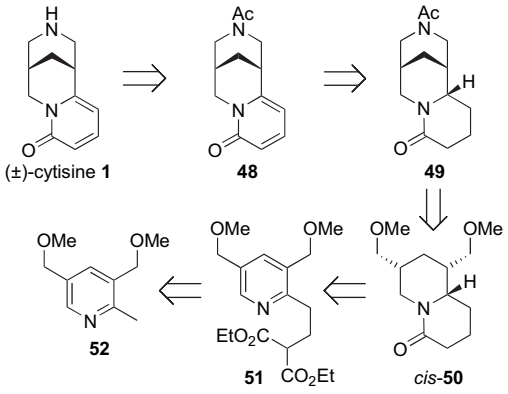
The use of a substituted pyridine as a precursor to the B-ring of cytisine was explored by Bohlmann and Govindachari

(Scheme 17). In each synthetic route, hydrogenation of a 3,5-disubstituted pyridine (after construction of the pyridone A-ring) was used to establish the cis stereochemistry required for the preparation of the bispidine.



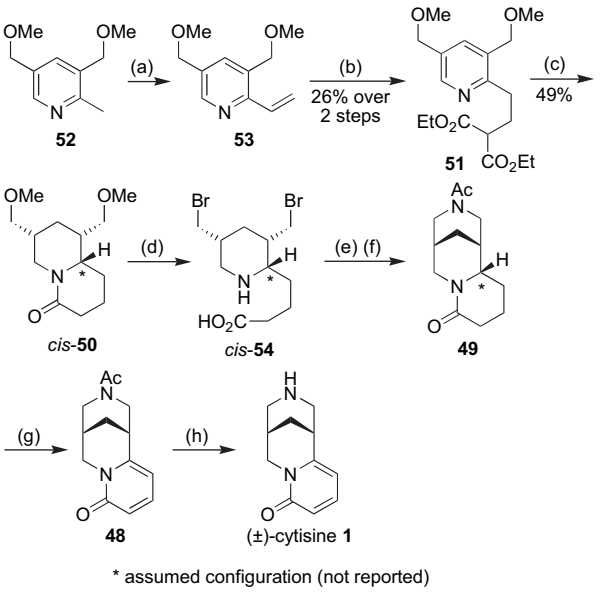

**Scheme 17**. Strategy: pyridine-derived B-ring.

Bohlmann investigated several approaches to a variety of precursors to cytisine[39,40] but the retrosynthetic analysis of the most successful approach is shown in Scheme 18.[26] Dehydrogenation of lactam **49** was used to form the pyridone ring in pyridone **48**. Lactam **49** was formed by the reaction of the dibromide derived from bis-methyl ether *cis*-**50** with ammonia. The cis stereochemistry in *cis*-**50** was set up by the hydrogenation of pyridine **51**, derived from the substituted 2-methylpyridine **52**.



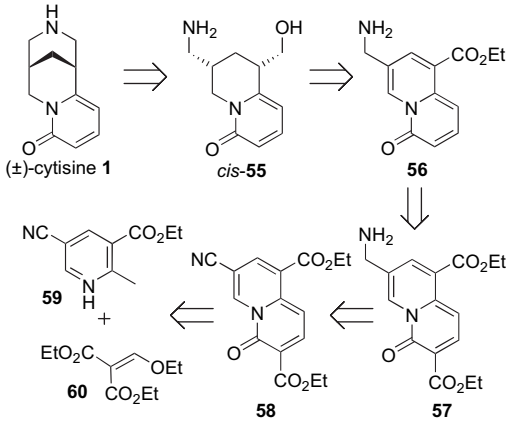

**Scheme 18**. Bohlmann's retrosynthetic analysis of (±)-cytisine.

Bohlmann's forward synthesis[26] (Scheme 19) commenced with homologation of the 2-methyl substituent of pyridine **52**. Thus, 2-methylpyridine **52** was converted into vinylpyridine **53** by heating **52** in aqueous formaldehyde. Then, Michael addition of the enolate derived from diethyl malonate onto vinylpyridine **53** gave malonate **51** in 26% yield over two steps. Rather harsh conditions (Raney nickel, dioxane, 180 °C, 200 atm hydrogen) were required to effect hydrogenation of the pyridine ring in malonate **51**. In this way, the desired 3,5-cis-stereochemistry in lactam *cis*-**50** was set up, although the indicated configuration at the remaining stereogenic centre is assumed (from cis-delivery of hydrogen). The hydrogenation was accompanied by subsequent piperidine cyclisation onto one of the ester groups, with decarboxylation of the remaining ester to give *cis*-**50**. The methyl ethers in *cis*-**50** were transformed into bromides upon treatment with hydrogen bromide. Unfortunately, under these conditions, lactam hydrolysis also occurred to give the amino acid *cis*-**54**. A three-step sequence was used to convert amino acid *cis*-**54** into cytisine-like lactam **49**. Thus, cyclisation to the bispidine required treatment with ammonia and heating. Next, the pyridone ring was constructed by double dehydrogenation, which was brought about by heating **49** over 10% Pd/C in a metal bath to give only an 11% yield of *N*-acylcytisine **48** (~80% purity). Finally, amide hydrolysis was carried out using hydrochloric acid to give (±)-cytisine via an eight-step route.[26] It is not possible to calculate an overall yield for this route, since the yields for some of the steps were not reported.



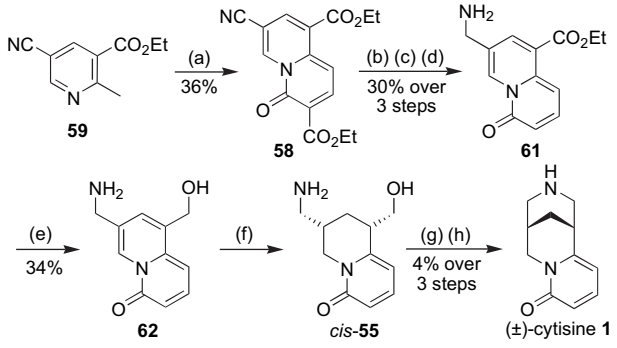

**Scheme 19**. Reagents and conditions: (a) $HCHO_{(aq)}$, 140 °C, 2 h; (b) NaOEt, $H_2C(CO_2Et)_2$, EtOH, reflux, 1 h; (c) Raney Ni, dioxane, 185 °C, 200 atm $H_2$, 2 h; (d) concd HBr, 5 h, 120 °C; (e) (i) $NH_3$, EtOH, 0 °C; (ii) 100 °C, 10 h, autoclave; (iii) methylnaphthalene, 200 °C, MeOH, 2 h; (f) $Ac_2O$, rt, 16 h, 100 °C, 30 min; (g) Pd/C, metal bath, 4.5 h; (h) HCl.

The retrosynthetic analysis of Govindachari's cytisine synthesis is summarised in Scheme 20.[27] In this case, cytisine was obtained by the cyclisation of the amino alcohol *cis*-**55**, derived from partial regioselective hydrogenation of quinolizinone **56**. Quinolizinone **56** was, in turn, generated from **57** and nitrile **58**. Nitrile **58** was obtained from nicotinate **59** via deprotonation of the methyl group, conjugate addition onto Michael acceptor **60**, elimination and amide formation.




**Scheme 20**. Govindachari's retrosynthetic analysis of (±)-cytisine.

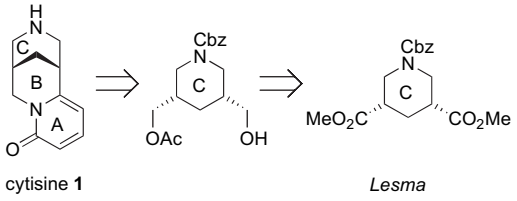
Starting from nicotinate **59**, Govindachari's route to cytisine (Scheme 21) initially involved conversion into the bis-ester **58** via reaction of **59** with Michael acceptor **60** and KOEt in EtOH (36% yield). This reaction presumably proceeds by methyl group deprotonation, Michael addition and ethoxide elimination to give an intermediate in which the pyridine nitrogen cyclises onto one of the esters to ultimately form quinolizinone **58**. Chemoselective reduction of the nitrile to a primary amine gave an aminoquinolizinone, in which one of the ester groups was removed by hydrolysis (6 M $HCl_{(aq)}$) and decarboxylation upon heating. The crude amino acid was then re-esterified using HCl in EtOH to give the amino ester **61** in 30% yield over three steps. $LiAlH_4$ reduction was used to convert the ester into a primary alcohol **62**. Chemoselective reduction of the pyridine ring in **62** (leaving the pyridone ring intact) was accomplished using hydrogen/$PtO_2$ to give *cis*-**55**. Then, crude *cis*-**55** was treated with $PBr_3$ to transform the hydroxyl group into a bromide and cyclisation was carried out by heating at 100 °C with $K_2CO_3$ in a sealed tube to give a 4% yield of (±)-cytisine over these last three steps. In summary, Govindachari's synthesis delivers (±)-cytisine in 0.03% overall yield through a six-isolation-step route from nicotinate **59**.[27]




**Scheme 21**. Reagents and conditions: (a) diethyl ethoxymethylenemalonate **60**, KOEt/EtOH, reflux, 4 h; (b) $PtO_2$, $H_2$, EtOH; (c) 6 M $HCl_{(aq)}$, reflux, 1 h; (d) HCl, EtOH; (e) $LiAlH_4$, $Et_2O$; (f) $PtO_2$, $H_2$; (g) $PBr_3$, benzene, 100 °C, 4 h; (h) $K_2CO_3$, 18 h, sealed tube, 100 °C.

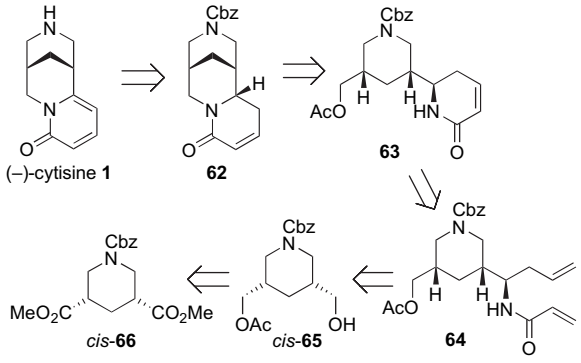
### 3.4. Synthesis using a piperidine-derived C-ring

The only synthetic approach to cytisine that has involved the construction of the C-ring from a piperidine was reported by Lesma. This route involved starting with the C-ring intact and then elaborating a desymmetrised *cis*-piperidine alcohol to complete the first asymmetric synthesis of (−)-cytisine (Scheme 22).



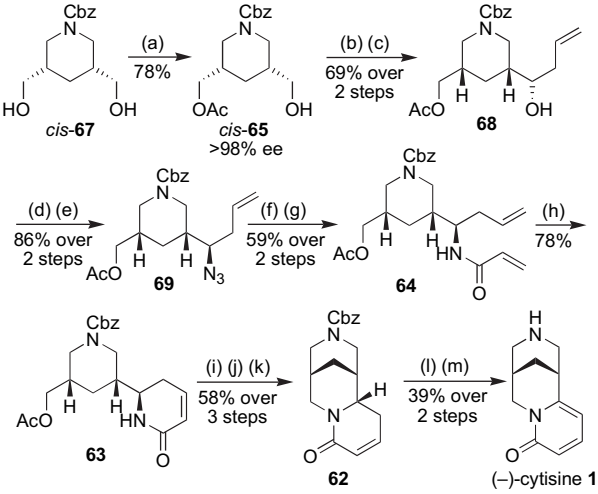

**Scheme 22**. Strategy: piperidine-derived C-ring.

The complete retrosynthetic analysis of Lesma's synthesis of (−)-cytisine is shown in Scheme 23.[32] Thus, (−)-cytisine was generated by the oxidation of dihydropyridone **62** and *N*-deprotection. Dihydropyridone **62** was derived from *cis*-piperidine **63** by the conversion of the acetate in **63** into a suitable leaving group and an intramolecular $S_N2$ reaction. The pyridone precursor **63** was constructed from diene **64** via a ring-closing metathesis. Diene **64** was obtained from piperidine monoacetate *cis*-**65**. Enzymatic desymmetrisation of a diol obtained by the reduction of bis-ester *cis*-**66** was the source of enantioselectivity in this asymmetric synthesis of (−)-cytisine.




**Scheme 23**. Lesma's retrosynthetic analysis of (−)-cytisine.

Lesma's synthesis of (−)-cytisine (Scheme 24) starts from diol *cis*-**67**, which was prepared by the reduction of the corresponding bis-ester *cis*-**66** (presumably obtained from the known[41] *N*-benzyl-protected *cis*-piperidine). Enzymatic acetylation of the diol *cis*-**67** using *Pseudomonas fluorescens* lipase (PFL) and vinyl acetate generated piperidine monoacetate *cis*-**65** in 78% yield and with >98% ee.[42,43] Swern oxidation of **65** generated the corresponding aldehyde (91% yield) and allyl addition under reagent control using Brown's (−)-allyldiisopinocampheylborane was required to achieve a high degree of stereocontrol, generating alcohol **68**



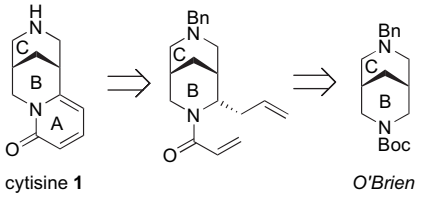

**Scheme 24**. Reagents and conditions: (a) *Pseudomonas fluorescens* lipase (PFL), vinyl acetate, rt, 6 h; (b) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$; (c) (−)-allyldiisopinocampheylborane, allyl MgBr, $Et_2O$, −78 °C then NaOH, $H_2O_2$; (d) MsCl, $Et_3N$, $CH_2Cl_2$; (e) $NaN_3$, DMF, 80 °C; (f) $PPh_3$, THF then water; (g) acryloyl chloride, $Et_3N$, $CH_2Cl_2$; (h) Ru(=CHPh)$(PCy_3)_2Cl_2$, $CH_2Cl_2$, reflux; (i) NaOH, THF; (j) MsCl, $Et_3N$, $CH_2Cl_2$; (k) NaH, THF, rt; (l) DDQ, 1,4-dioxane, reflux; (m) 6 M, HCl, reflux.

in 76% yield (10:1 mixture of diastereomers). Although this diastereocontrol was ultimately of no consequence, as the stereogenic centre would be oxidised to the pyridone, asymmetric allyl boronation was used, as it was easier to progress a single diastereomer through the remainder of the synthesis. The required amine was then introduced by mesylation of alcohol **68** and reaction with $NaN_3$ in DMF, which gave azide **69** in 86% yield over the two steps. Azide reduction and acylation with acryloyl chloride produced diene **64** (59% yield), which was reacted with Grubbs' first-generation catalyst to achieve ring-closing metathesis to **63** (76% yield).

Creation of the bispidine framework was accomplished before aromatisation to the pyridone ring. Thus, acetate hydrolysis of **63** was followed by mesylate activation and cyclisation was carried out via NaH deprotonation of the NH of the amide. This produced dihydropyridone **62** in 58% yield over the three steps. Attempted oxidation of **62** to the *N*-Cbz-protected cytisine using $MnO_2$, as previously employed by Coe (see Scheme 12), was unsuccessful. It was found, however, that DDQ smoothly oxidised **62** to the desired pyridone and subsequent acid-mediated *N*-deprotection afforded (−)-cytisine in 39% yield over two steps. To summarise, the first total synthesis of (−)-cytisine, reported by Lesma, proceeded in 13 steps from piperidine diol *cis*-**67** in 7% overall yield.[32]

### 3.5. Synthesis via initial construction of the bispidine core (BC-rings)

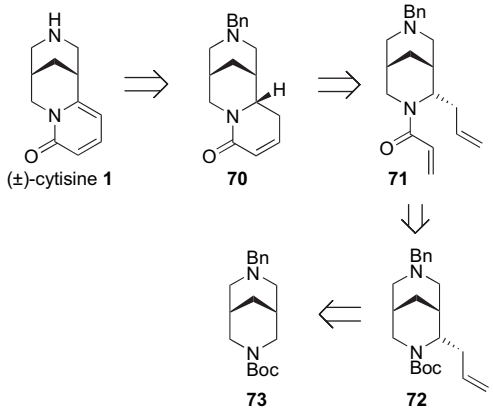
A previously unexplored strategy for cytisine synthesis, namely construction of the bispidine core (BC-rings) and subsequent elaboration of the pyridone ring, has recently been developed by our group (Scheme 25). One of the main advantages of this approach is that it circumvents the need to form a *cis*-piperidine. Instead, in the first two steps, a bispidine is formed via a double-Mannich reaction of a 4-piperidinone and ketone removal.




**Scheme 25**. Strategy: initial construction of BC-rings.

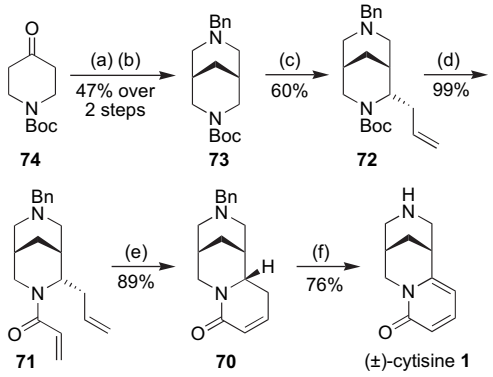
The retrosynthetic analysis of our synthesis of (±)-cytisine is shown in Scheme 26.[31] Thus, cytisine was obtained by oxidation and N-debenzylation of dihydropyridone **70**. Dihydropyridone **70** was generated by ring-closing metathesis of diene **71**, obtained by elaboration of allylated *N*-Boc bispidine **72**. A key step in this route was the grafting of the allyl group onto bispidine **73**. This was achieved by lithiation at the position α to the *N*-Boc group in **73** and subsequent electrophilic trapping.

The forward synthesis of our synthesis of (±)-cytisine (Scheme 27) commenced with the double-Mannich reaction of *N*-Boc piperidone **74** with benzylamine and paraformaldehyde, which gave the corresponding bispidinone. The




**Scheme 26**. O'Brien's retrosynthetic analysis of (±)-cytisine.

resulting carbonyl group was removed via the formation of the tosyl hydrazone and reduction with $NaBH_4$ to give bispidine **73** in 47% yield over two steps. Construction of the pyridone ring started with allylation of **73**. Thus, deprotonation of bispidine **73** at the position α to the *N*-Boc group was accomplished satisfactorily using *s*-BuLi/TMEDA in $Et_2O$ at −78 °C for 7 h. Allylation was only successful if the organolithium was transmetallated to the monoalkyl-cyanocuprate and then trapped with allyldiphenyl phosphate. In this way, allylated *N*-Boc bispidine **72** was produced in 60% yield. The use of other organocuprates or other allylating reagents was either totally unsuccessful or lower yielding. Although of no synthetic consequence, it is interesting to note that **72** was generated as a single diastereomer, which is believed to arise by preferential equatorial lithiation and retention of configuration through subsequent processes (transmetallations and electrophilic trapping).




**Scheme 27**. Reagents and conditions: (a) $BnNH_2$, AcOH, $(CHO)_n$, MeOH, reflux, 5 h; (b) (i) $TsNHNH_2$, EtOH, reflux, 2 h; (ii) $NaBH_4$, 4:1 THF/water, rt, 16 h then reflux, 3 h; (c) (i) 1.6 equiv *s*-BuLi/TMEDA, $Et_2O$, −78 °C, 7 h; (ii) 1.0 equiv CuCN·2LiCl, THF; (iii) 2.2 equiv allyldiphenyl phosphate; (d) (i) 1:1 TFA/$CH_2Cl_2$, 0 °C, 2 h; (ii) 10% $NaOH_{(aq)}$, $CH_2Cl_2$, rt, 1 h; (e) Ru(=CHPh)$(PCy_3)_2Cl_2$, toluene, reflux, 15 min; (f) 10% Pd/C, 2:1 toluene/cyclohexene, 100 °C, 12 h.

Next, allylated *N*-Boc bispidine **72** was efficiently converted into diene **71** by TFA deprotection and acylation with acryloyl chloride (99% overall yield). Ring-closing metathesis was then used to form the dihydropyridone ring. Reaction of diene **71** with Grubbs' first-generation catalyst in toluene at reflux generated dihydropyridone **70** (89% yield) in 15 min. The efficiency of this ring-closing metathesis

was attributed to the rigidity of the bispidine framework. Optimisation of the oxidation of dihydropyridone **70** to form the pyridone ring led to a one-pot process in which the oxidation was accompanied by in situ N-debenzylation. Starting from **71**, the oxidation–debenzylation was achieved using 20 mol % Pd/C in the presence of cyclohexene to give cytisine in 76% yield. This tandem oxidation–debenzylation process is assumed to hinge on the ability of cyclohexene to initially act as a hydrogen acceptor to regenerate the catalyst for the pyridone oxidation, but then to switch its role to a hydrogen donor to facilitate debenzylation. In summary, our synthesis of (±)-cytisine was completed in six steps with an overall yield of 19%.

## 4. Conclusions and outlook

Of all of the known syntheses of cytisine, the routes to *racemic* cytisine reported by O'Neill (including Plaquevent's modifications), Coe and ourselves are the most efficient in terms of overall yield (16–35%) and the shortest number of steps (five or six steps). These approaches represent the best way of preparing (±)-cytisine and its analogues for biological evaluation. Indeed, the O'Neill route has been used exactly for that purpose, although the preparation of each analogue of cytisine required a separate total synthesis. Thus, there is still a need to develop an approach to cytisine that delivers a late-stage intermediate that is equipped with the appropriate functionality for analogue preparation. It is also important to stress van Tamelen's pioneering contribution to cytisine synthesis, as this early synthetic work underpins the O'Neill–Plaquevent route. In addition, Coe's route is notable, as it does not employ any protecting groups. Furthermore, an efficient asymmetric synthesis of cytisine is still required, since each of the three asymmetric routes to (−)- or (+)-cytisine has limitations. Hopefully, this review will stimulate further studies into the development of new asymmetric routes to (−)- and (+)-cytisine, which will be suitable for the easy generation of cytisine analogues.

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**Biographical sketch**

**Peter O'Brien** was born in South Manchester in 1970 and went on to study Natural Sciences at the University of Cambridge. He graduated in 1992 and remained in Cambridge carrying out a Ph.D. on *Enantio- and Diastereoselective Reaction with Phosphine Oxides* under the supervision of Dr. Stuart Warren. After the award of his Ph.D. in 1995, he moved to The University of York as a Royal Commission for the Exhibition of 1851 Research Fellow and initiated research into chiral bases. In March 1996, he was appointed as a lecturer in organic chemistry at The University of York. In 1999, he was awarded one of the Royal Society of Chemistry's Meldola medals and prizes and in 2000, a GlaxoWellcome award for innovative organic chemistry. He was promoted to Senior Lecturer in 2002 and Reader in 2005. He has been an Associate Editor for *Tetrahedron* since 1998 and is currently Secretary of The Royal Society of Chemistry's Heterocyclic and Synthesis Group (2005–2008). His research focuses on the synthesis of new chiral bases (e.g., the (+)-sparteine surrogate), the development of new synthetic methodology and the total synthesis of biologically interesting natural products.

**Darren Stead** was born in South Yorkshire in 1982 and went on to study Chemistry at the University of York. This included a year in industry working as a medicinal chemist at Merck Sharp Dohme. He graduated in 2004 and remained in York, carrying out a Ph.D. (sponsored by Lilly) on the total synthesis of cytisine and organolithium-mediated asymmetric synthesis of other naturally occurring alkaloids, under the supervision of Dr. Peter O'Brien.