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SYNTHESIS OF TWO NEUROKININ NK1 RECEPTOR ANTAGONISTS: (+)-L-733,060 AND (–)-L-733,061

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Abstract – This review describes synthetic approaches to (+)-L-733,060 and (–)-L-733,061 reported since 1994, focusing on methods allowing the construction and control of the two stereogenic centers. The methods are divided into three groups: (1) resolution of racemates (chemical or enzymatic resolution), (2) diastereoselective reactions using chiral pools or auxiliaries, and (3) enantioselective reactions (aminohydroxylation, epoxidation, deprotonation, allylic amination, aza-Henry reaction, vinylogous aldolization).

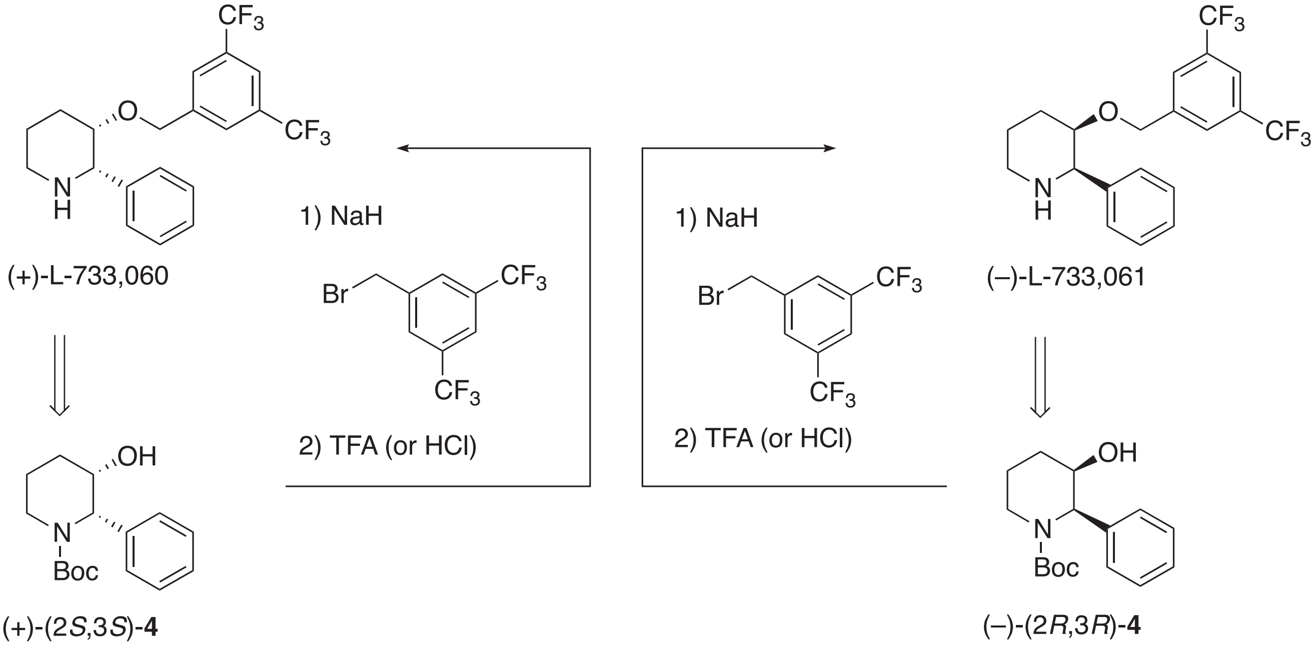
CONTENTS

Dedicated to Prof. Ei-ichi Negishi on the occasion of his 77th birthday.

1. INTRODUCTION

The neurokinin Substance P (SP),[1] an 11 amino-acid peptide, has been associated with a variety of biological effects such as smooth muscle contraction, neurological inflammation,[2] gain transmission and regulation of the immune response.[3] Thus, Substance P antagonists may be useful in a variety of disorders including migraine,[4] rheumatoid arthritis,[5] and pain.[6] It has been reported that (2*S*,3*S*)-2-phenyl-3-[(3,5)-bis(trifluoromethyl)benzyloxy]piperidine, (+)-L-733,060, has a better affinity for the hNK1 receptor stably expressed in CHO cells than (2*R*,3*R*)-2-phenyl-3-[(3,5)-bis(trifluoromethyl)-benzyloxy]piperidine, (–)-L-733,061 (IC_{50}= 1 nM *versus* IC_{50}= 300 nM).[7] These affinities were determined by competition with ^{125}I-SP.[8]

In view of the potential pharmacological applications, several syntheses of enantiomers (+)-L-733,060 and (–)-L-733,061 have been reported, both in racemic and optically active forms. As (+)-L-733,060 is more biologically active than (–)-L-733,061, only a few syntheses of this latter compound have been realized. Different strategies have been utilized to access these two compounds; however, most of the reports deal with classical resolution of racemates (chemical and enzymatic resolution), use of chiral pool, chiral auxiliaries, enantioselective reagents or catalysts to produce one of the enantiomer. In most cases, the precursor of (+)-L-733,060 [or (–)-L-733,061] is *N*-Boc piperidin-3-ol (+)-**4** [or (–)-**4**], which is transformed to the desired NK1 receptor antagonist in two steps. The first step is an etherification of the hydroxyl group in (+)-**4** [or (–)-**4**] with 3,5-bistrifluoromethylbenzyl bromide under basic conditions, followed by the cleavage of the *N*-*t*-butyl carbamate using trifluoroacetic acid (or HCl) (Scheme 1).



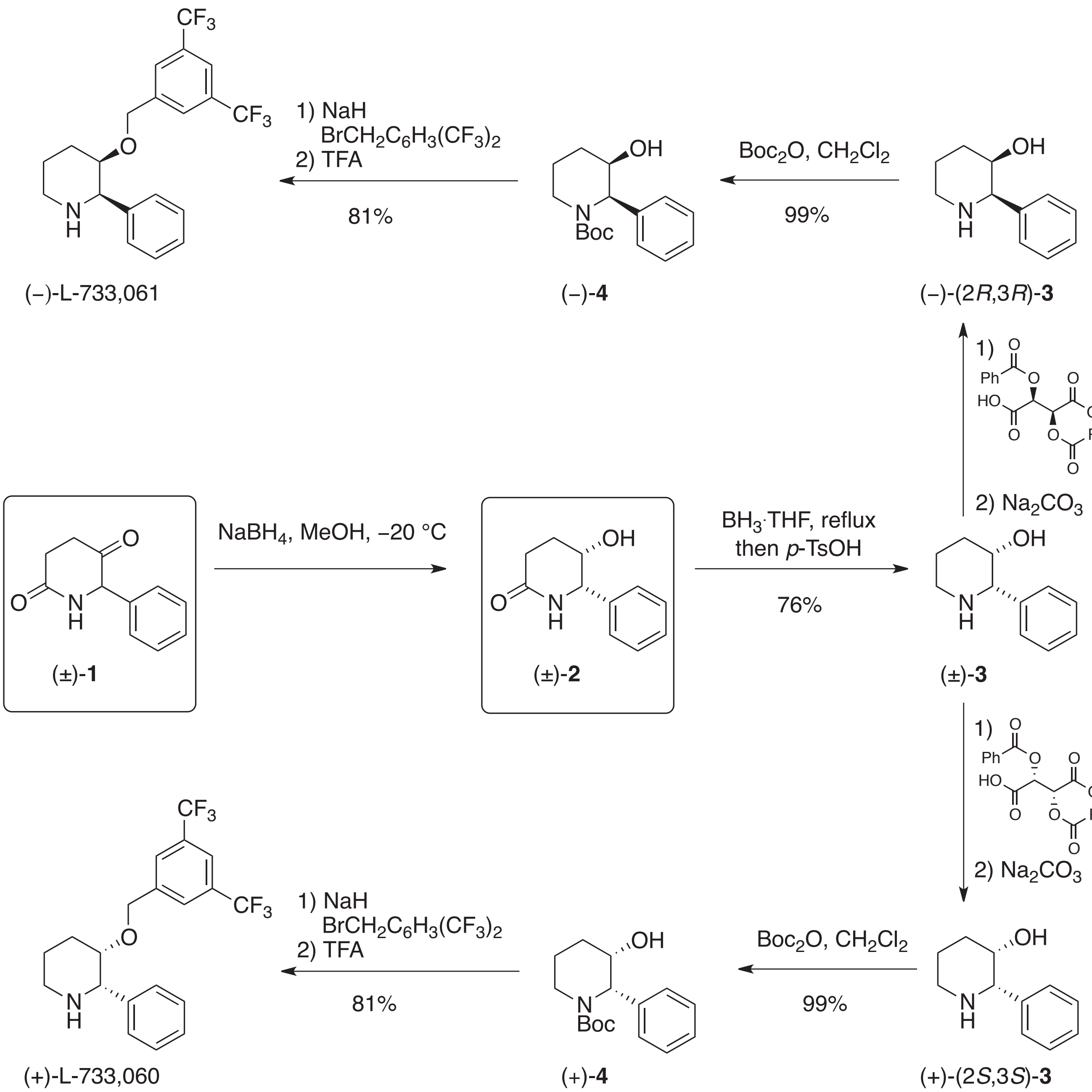
Scheme 1. Synthesis of (+)-L-733,060 and (–)-L-733,061 from piperidin-3-ols (+)-**4** and (–)-**4**

2. RESOLUTION OF RACEMATES

In order to obtain the two enantiomers (+)-L-733,060 and (–)-L-733,061 and to compare their biological activities, the resolution of a racemate was performed.

2-1. Chemical Resolution

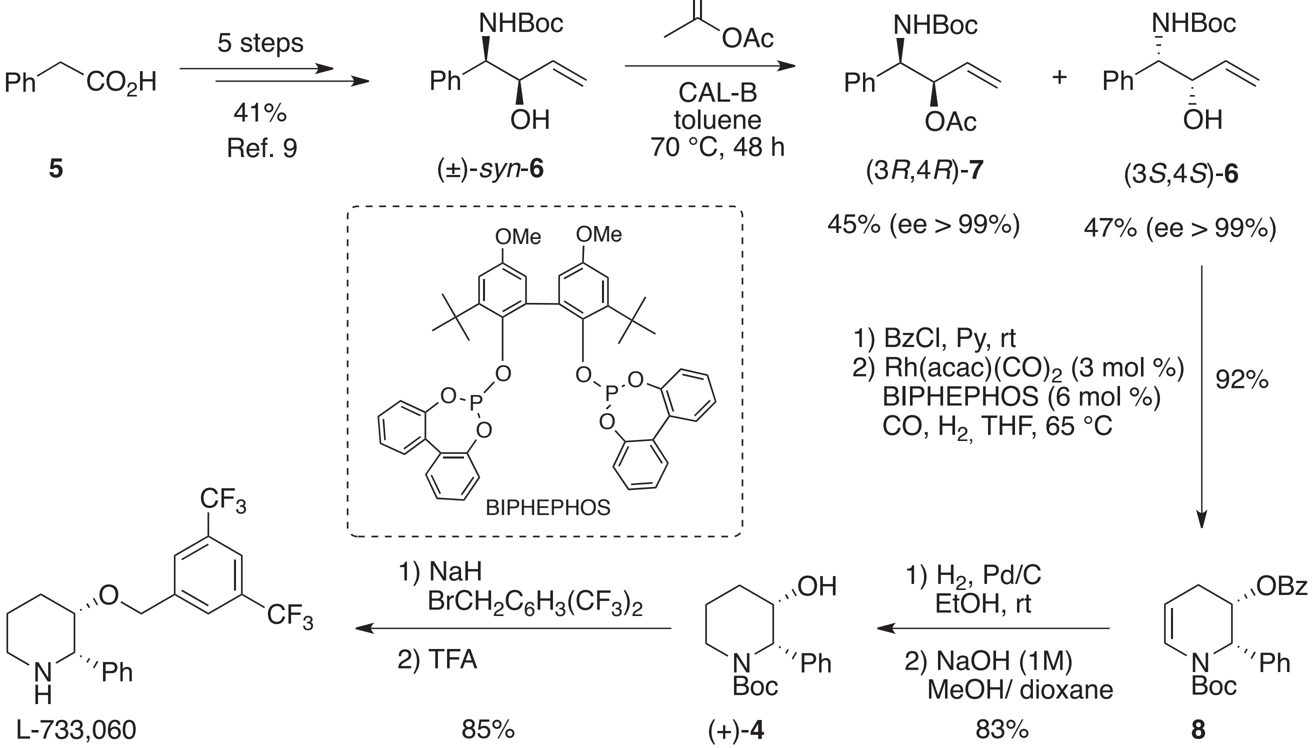
The first synthesis of L-733,060 and L-733,061 was performed at Merck in 1994.[7] The synthesis of these two compounds started from keto lactam (±)-**1** which was reduced ($NaBH_4$, –20 °C) to provide hydroxyl lactam (±)-**2**. This lactam was then reduced with borane to produce *cis*-disubstituted piperidine (±)-**3** which after resolution using (–)- and (+)-dibenzoyl tartaric acid led respectively to (+)-**3** and (–)-**3**. The individual enantiomers were then converted to *N*-Boc protected piperidines (+)-**4** and (–)-**4,** which were then converted in the previously described two-step sequence (etherification, deprotection, see Scheme 1) to L-733,060 and L-733,061 respectively (Scheme 2).



Scheme 2. Synthesis of L-733,060 and L-733,061 by Harrison *et al.*

2-2. Enzymatic Resolution

As *N*-protected amino alcohols can be efficiently resolved by lipase catalyzed kinetic resolution, this process was successfully applied to amino alcohol (±)-**6**[9] to access L-733,060. Amino alcohol (±)-**6** was prepared in five steps from 2-phenylethanoic acid **5** and then stirred with 2-propenyl acetate in toluene with particles of CAL-B at 70 °C. A clean acetylation of one enantiomer afforded acetylated (3*R*,4*R*)-**7** with excellent enantiomeric purity (ee > 99%). Furthermore, unreacted amino alcohol (3*S*,4*S*)-**6** also showed an excellent enantiomeric excess (ee > 99%). Due to the enzymatic resolution of amino alcohol (±)-*syn*-**6**, both L-733,060 and L-733,061 were obtained. The synthesis of L-733,060 was the only one reported. Thus, after benzoylation of (3*S*,4*S*)-**6** (BzCl, pyridine, rt), the piperidine framework of L-733,060 was constructed through a Rh-catalyzed hydroformylation [Rh(acac)(CO)$_2$ (3 mol %), BIPHEPHOS (6 mol %), 5 atm of CO–H$_2$ (1:1)] providing enamide **8** (92%). Hydrogenation of **8** followed by alkaline hydrolysis [(1M) NaOH/MeOH/1,4-dioxane (2:3:6)] gave piperidine (+)-**4**, which was transformed in two steps to L-733,060 (etherification, deprotection, 85%) (Scheme 3).[10]



Scheme 3. Synthesis of L-733,060 by Mandai *et al.*

3. DIASTEREOSELECTIVE REACTIONS

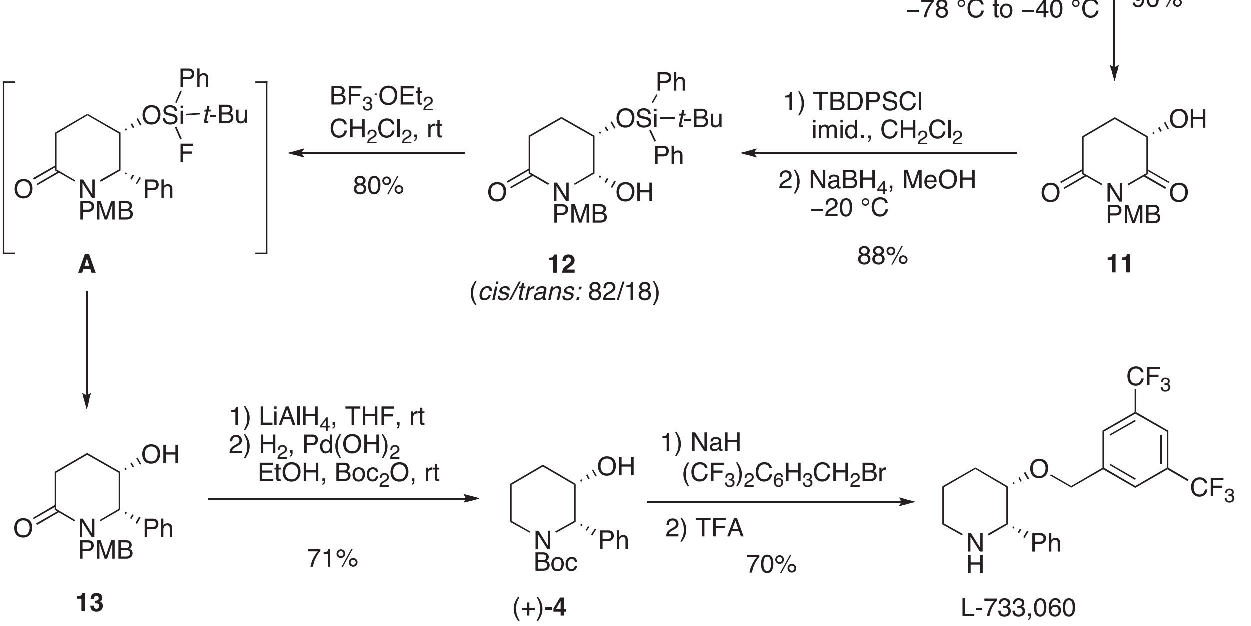
The control of the C3 stereogenic center in L-733,060 and L-733,061 was realized by applying diastereoselective reactions to derivatives issued from natural amino acids and optically active amines in which the stereogenic center corresponds to the C2 stereogenic center present in L-733,060 and L-733,061.

3-1. From Amino Acids

L-Glutamic acid is a versatile starting material which allowed the synthesis of L-733,060 as well as L-733,061. Three other natural amino acids, L-phenylglycine, L-pyroglutamic acid, and L-proline were also used as precursors of L-733,060.

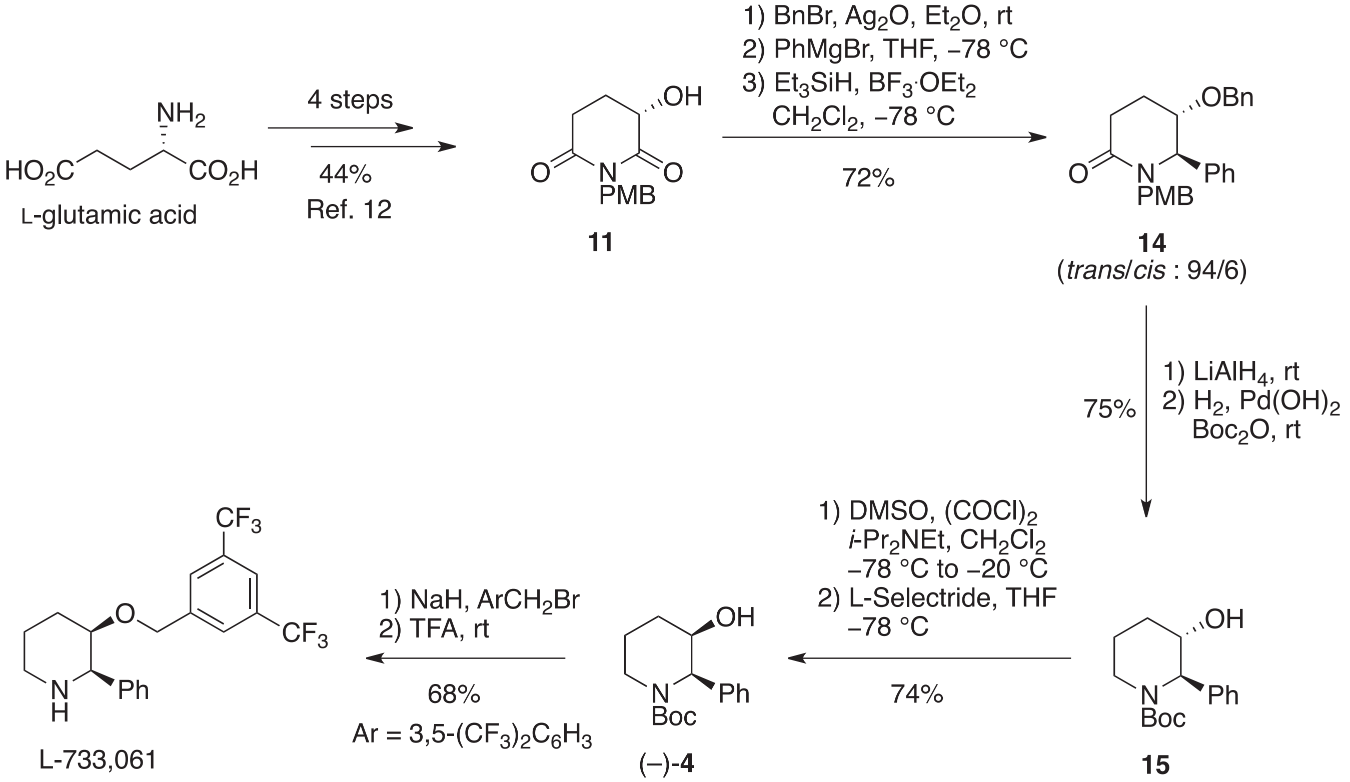
3-1-1. L-Glutamic Acid

A common precursor to L-733,060 and L-733,061 was the optically active glutarimide **11** which was synthesized in four steps from L-glutamic acid. At first, L-glutamic acid was transformed to γ-lactone carboxylic acid **9** by using a diazotation (H_2SO_4, $NaNO_2$).[11] Treatment of **9** with thionyl chloride and then *p*-methoxybenzylamine afforded lactone amide **10** (70% for the two steps). The ring expansion to convert **10** to glutarimide **11**, precursor of L-733,060 and L-733,061, was achieved by treatment with *t*-BuOK at –78 °C (90%, ee = 98%).[12] To realize the transformation of **11** to L-733,060, **11** was protected with *t*-butyldiphenylsilyl chloride (TBDPSCl, imidazole, CH_2Cl_2) and the resulting protected glutarimide was reduced with $NaBH_4$ (–20 °C to –10 °C) to afford two separable diastereomers in a 82/18 ratio in favor of *cis*-isomer **12**. The key step in the synthesis of L-733,060 is an intramolecular deoxygenative phenylation of **12** which was realized using $BF_3{\cdot}OEt_2$ (CH_2Cl_2, rt) to produce the desired *cis*-disubstituted piperidine **13** in 80% yield *via* intermediate **A**. After reduction of **13** ($LiAlH_4$, THF, rt) and a one-pot deprotection/protection sequence, (+)-**4** was isolated in 71% yield and then transformed to L-733,060 in two steps (Scheme 4).[12]



Scheme 4. Synthesis of L-733,060 by Huang *et al*.

In the synthesis of L-733,061, in order to control the (*R*)-configuration at C2, glutarimide **11** was protected as a benzyl ether. After reductive alkylation with phenylmagnesium bromide, and treatment with an excess of $BF_3 \cdot OEt_2$ (3 equiv) and triethylsilane, the predominantly *trans*-**14** isomer (*trans*/*cis* = 94:6) was isolated with a global yield of 72%. After reduction and a one-pot hydrogenolysis/*N*-Boc protection sequence, the (2*R*,3*S*)-disubstituted piperidine **15** was isolated (75%). As the configuration of the hydroxyl group at C3 has to be inverted, a Swern oxidation followed by a selective reduction with L-selectride was conducted to lead to the desired L-733,061 precursor, compound (–)-**4** (74% yield). Compound (–)-**4** was transformed to L-733,061 by using the two usual final steps (Scheme 5).[13]

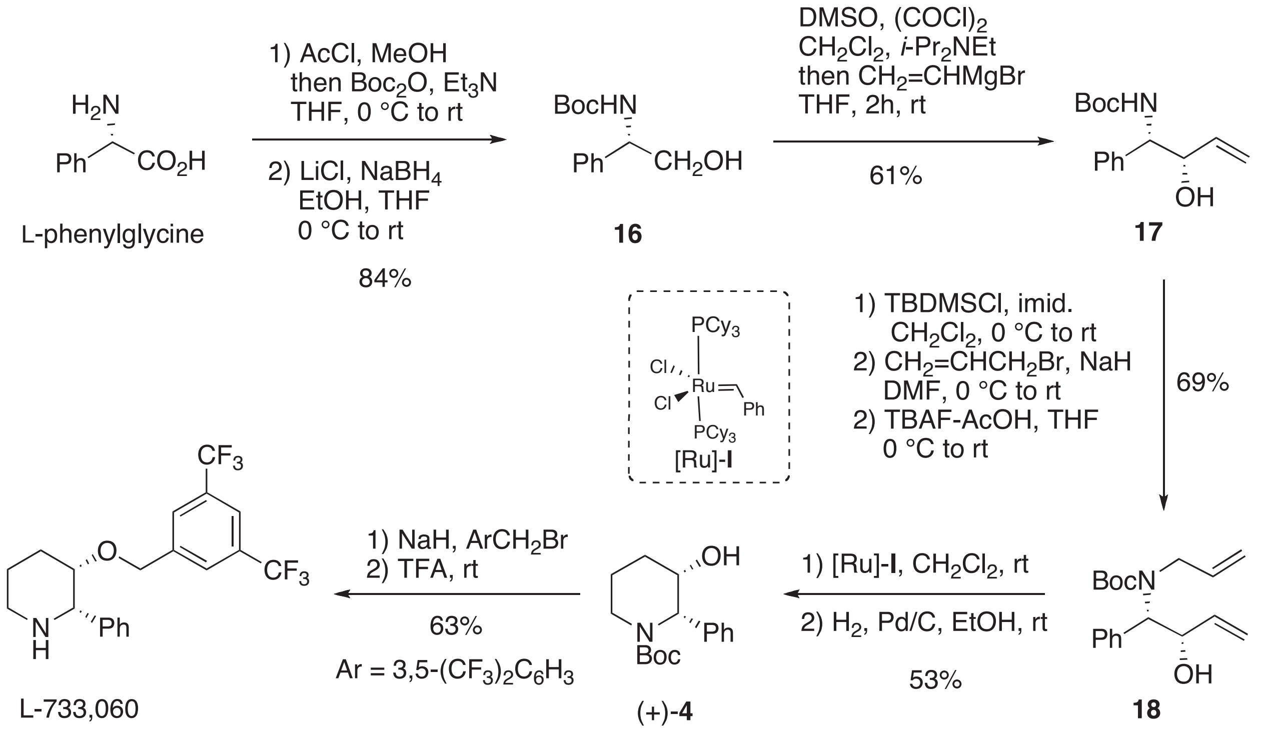


Scheme 5. Synthesis of L-733,061 by Huang *et al.*

3-1-2. L-Phenylglycine

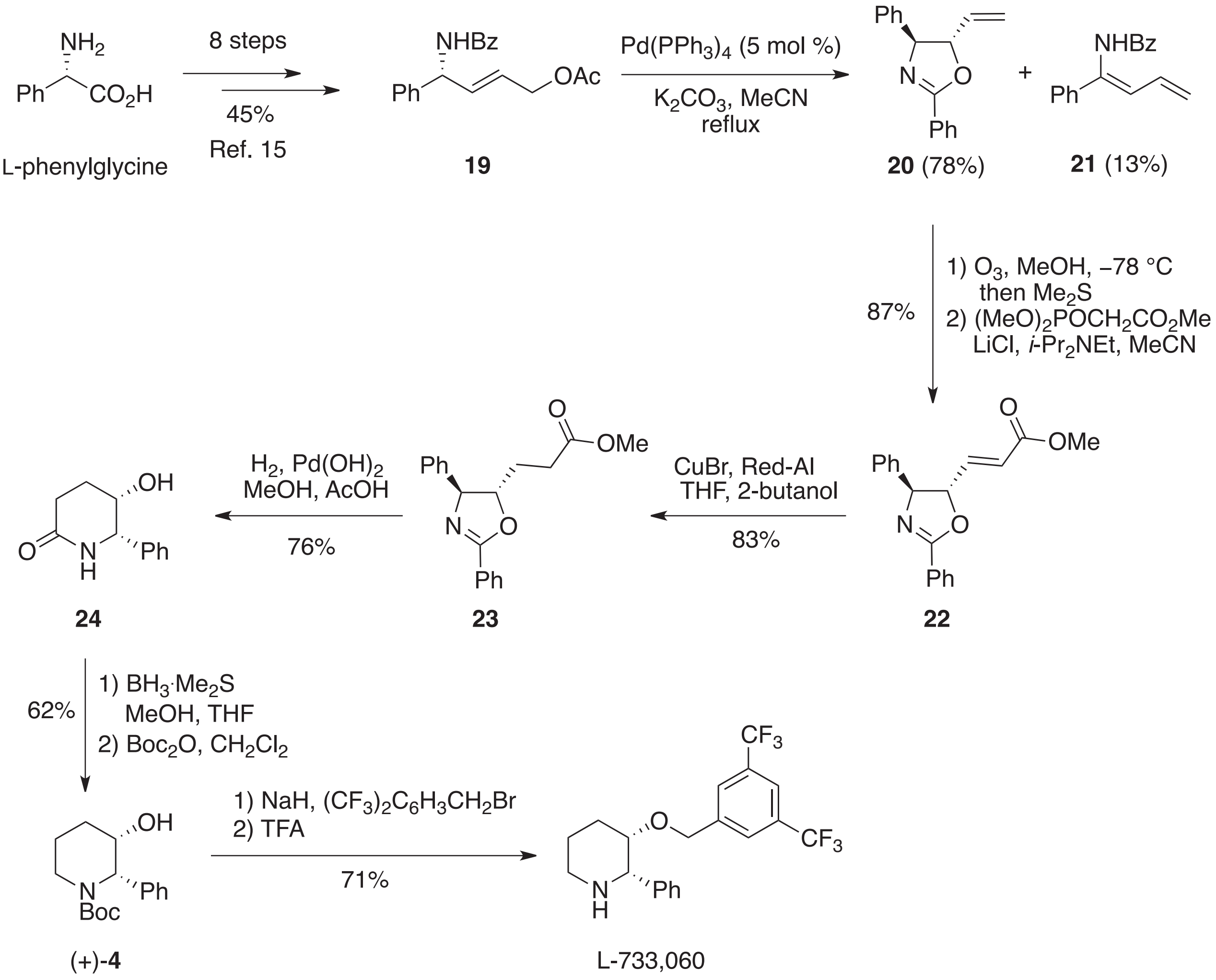
L-733,060 was synthesized from L-phenylglycine using a ring-closing metathesis (RCM)[14] to construct the piperidine framework. The synthesis of L-733,060 started from commercially available L-phenylglycine, which was transformed to *syn*-1,2-amino alcohol **17** in four steps. L-Phenylglycine was converted to an *N*-Boc methyl ester (AcCl, MeOH, then Boc_2O, Et_3N, THF) which was reduced to alcohol **16** ($NaBH_4$, LiCl, Et_2O/THF, 84%). The obtained alcohol was then oxidized (Swern conditions) and the resulting aldehyde was treated *in situ* with vinylmagnesium bromide, yielding the corresponding allylic alcohol **17** with good diastereoselectivity (90/10) in favor of the *syn*-isomer according to a

Cram-chelate model. After protection of the hydroxyl group (TBDMSCl, imidazole), an *N*-allylation was performed (NaH, allylBr, DMF) and, after desilylation (TBAF-AcOH), the obtained dienic compound **18** was involved in a RCM and then in a hydrogenation to produce piperidine (+)-**4**. This piperidine was then transformed to L-733,060 by the usual procedure (etherification, deprotection) (Scheme 6).[15]



Scheme 6. Synthesis of L-733,060 by Rao *et al.*

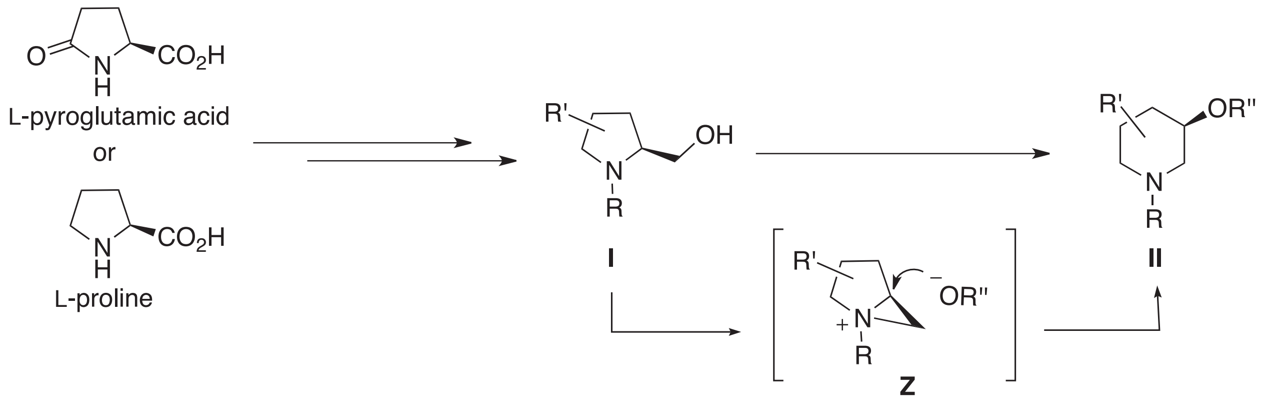
A second synthesis of L-733,060 was realized from L-phenylglycine *via* a *trans*-vinyloxazoline intermediate. L-Phenylglycine was transformed to allylic benzamide **19**, precursor of *trans*-vinyloxazoline **22**, in eight steps.[15] Acyclic allylic benzamide **19** was treated with Pd(0) [$Pd(PPh_3)_4$] under basic conditions (K_2CO_3, CH_3CN, reflux) to obtain *trans*-vinyloxazoline **20** (78%).[16] It is worth noting that under these conditions an elimination product, conjugated enamide **21**, was formed in 13% yield. After ozonolysis of **20**, the obtained aldehyde was reacted with methyl trimethylphosphonoacetate to yield α,β-unsaturated methyl ester **22** (87%). 1,4-Reduction of **22** with copper bromide, Red-Al, and 2-butanol gave saturated methyl ester **23** (83%). Hydrogenation of **23** with $Pd(OH)_2$ in AcOH/MeOH was performed under 70 psi of H_2 at room temperature followed by solvolysis of the resulting oxazolidine to directly afford hydroxypiperidinone **24**. Reduction of **24** using borane-methyl sulfide complex and protection with Boc_2O led to (+)-**4**, which was then transformed to L-733,060 using the two usual final steps (Scheme 7).[17]



Scheme 7. Synthesis of L-733,060 by Ham *et al*.

3-1-3. L-Pyroglutamic Acid and L-Proline

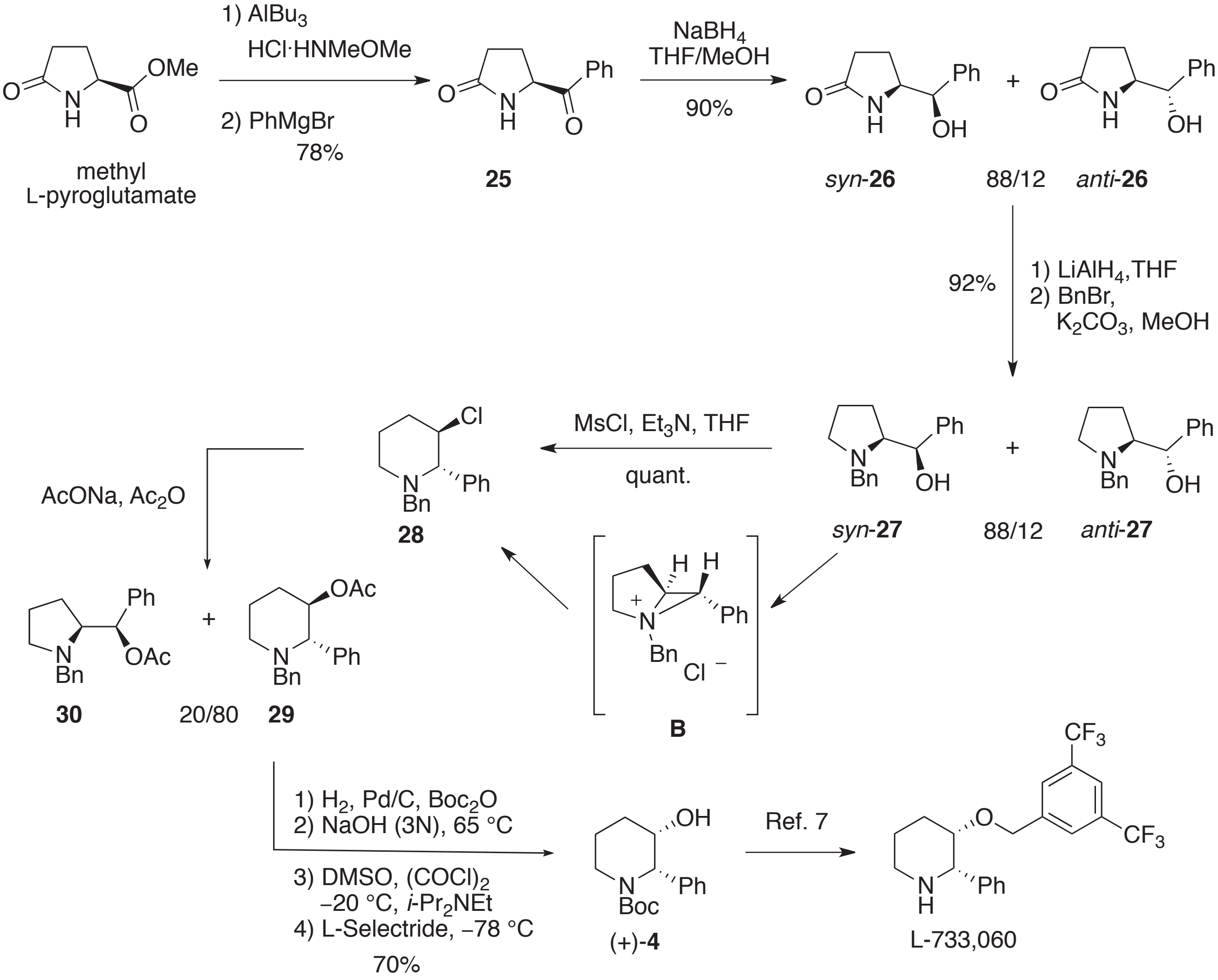
L-733,060 and L-733,061 were obtained using a ring enlargement of pyrrolidine methanols **I** as the key step to form 3-hydroxypiperidines **II** *via* aziridinium **Z** intermediates.[18] Pyrrolidine methanols **I** were obtained either from L-pyroglutamic acid or L-proline (Scheme 8).



Scheme 8. Ring expansion of prolinols to form 3-hydroxypiperidines

3-1-3-1. L-Pyroglutamic Acid

The synthesis of L-733,060 started with the transformation of methyl L-pyroglutamate, which was prepared from L-pyroglutamic acid, to the Weinreb amide which was treated with phenylmagnesium bromide to furnish phenyl ketone **25**. To access pyrrolidine methanol *syn*-**26**, precursor of the 3-hydroxypiperidine core, phenyl ketone **25** was reduced with $NaBH_4$ (THF, MeOH, 90%) to furnish a mixture of pyrrolidines *syn*-**26** and *anti*-**26** in a ratio 88/12.[19] After treatment of the mixture with $LiAlH_4$ and *N*-benzylation, prolinols *syn*-**27** and *anti*-**27** were formed and separated. The ring expansion of *syn*-**27** was then performed with mesyl chloride (Et_3N, THF) to afford 3-chloropiperidine **28** quantitatively *via* aziridinium **B**. *N*-Benzyl-3-chloropiperidine **28** was then heated with AcONa-Ac_2O to produce the corresponding 3-acetoxypiperidine **29** as well as acetoxymethylpyrrolidine **30** in a ratio 80/20.[20] In order to obtain (+)-**4** with the (*R*)-configuration at C3, an inversion of the stereogenic center had to be realized. Thus, after hydrogenolysis in the presence of Boc_2O (H_2, Pd/C, Boc_2O), acetolysis (NaOH 3N, 65 °C), Swern oxidation, and stereoselective reduction of the ketone with L-selectride, the precursor of L-733,060, piperidine (+)-**4**[7] was isolated with an overall yield of 70% (4 steps) (Scheme 9).[21]

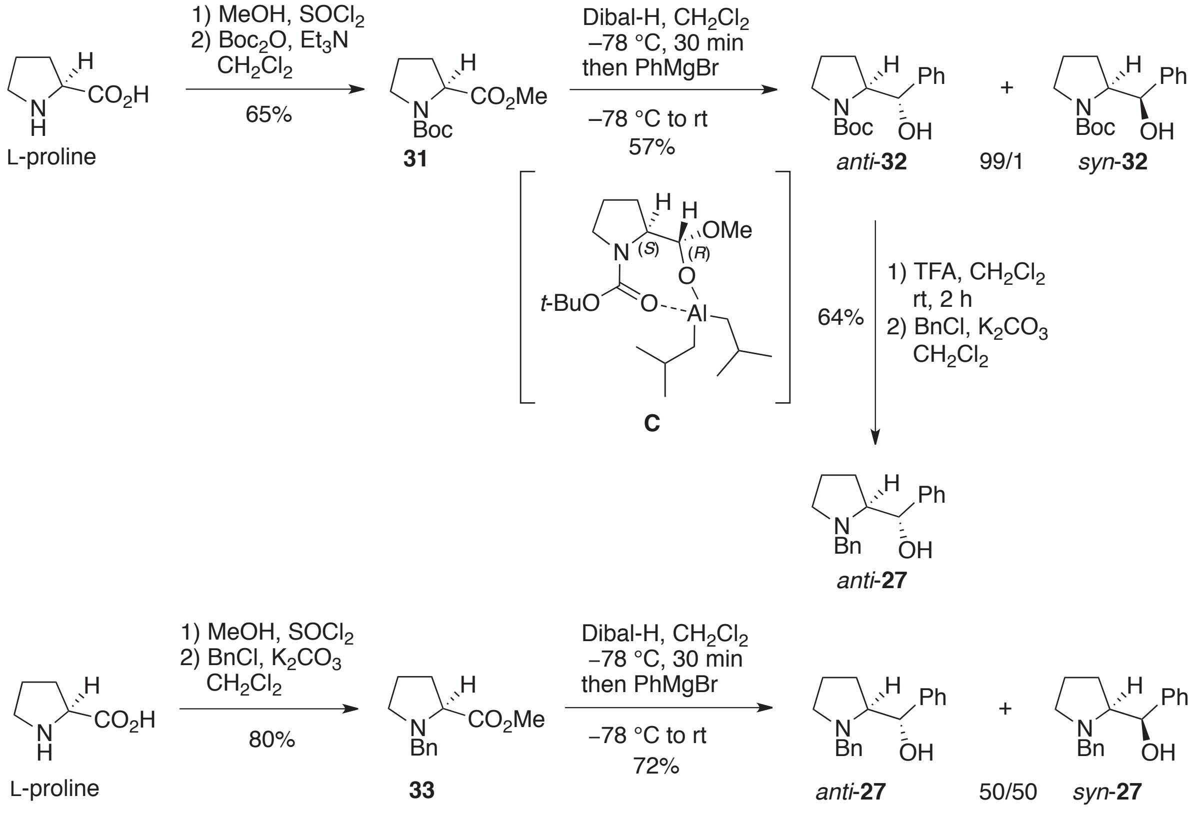


Scheme 9. Synthesis of L-733,060 by Langlois et *al*.

3-1-3-2. L-Proline

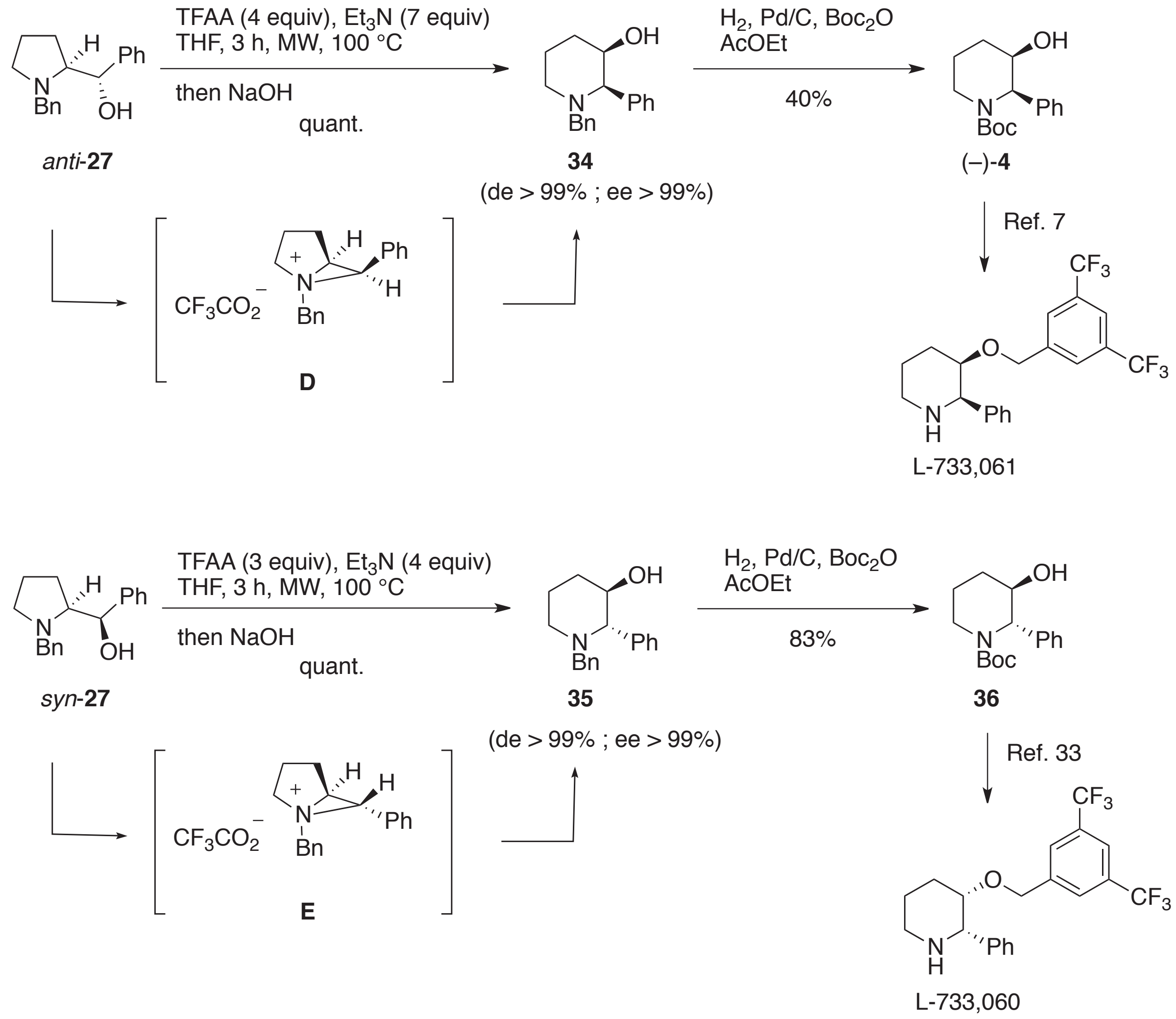
The syntheses of L-733,060 and L-733,061 were realized from L-proline by utilizing a ring enlargement of prolinols with TFAA[22] to access 3-hydroxypiperidine precursors (–)-**4** and **36** (Scheme 11).

L-Proline was transformed to *N*-Boc proline methyl ester **31** which was then transformed to the corresponding amino alcohols *anti*-**32** and *syn*-**32** with excellent diastereoselectivity (de = 98%), in favor of the isomer *anti*-**32**, using Dibal-H followed by the addition of phenylmagnesium bromide (CH_2Cl_2, –78 °C to rt). This excellent diastereoselectivity is probably due to the complexation of aluminium with the *N*-Boc group (intermediate **C**). It is worth pointing out that when an *N*-benzyl group is present instead of a Boc group, no diastereoselectivity was observed. Indeed, treatment of *N*-benzylproline methyl ester **33** with Dibal-H followed by the addition of phenylmagnesium bromide (CH_2Cl_2, –78 °C to rt) afforded two separable diastereomers *anti*-**27** and *syn*-**27** in a 50/50 ratio with a yield of 72%. After a deprotection/protection sequence, amino alcohol *anti*-**32** was transformed to *anti*-**27** (64%) (Scheme 10).[23]



Scheme 10. Synthesis of prolinols **27** from L-proline

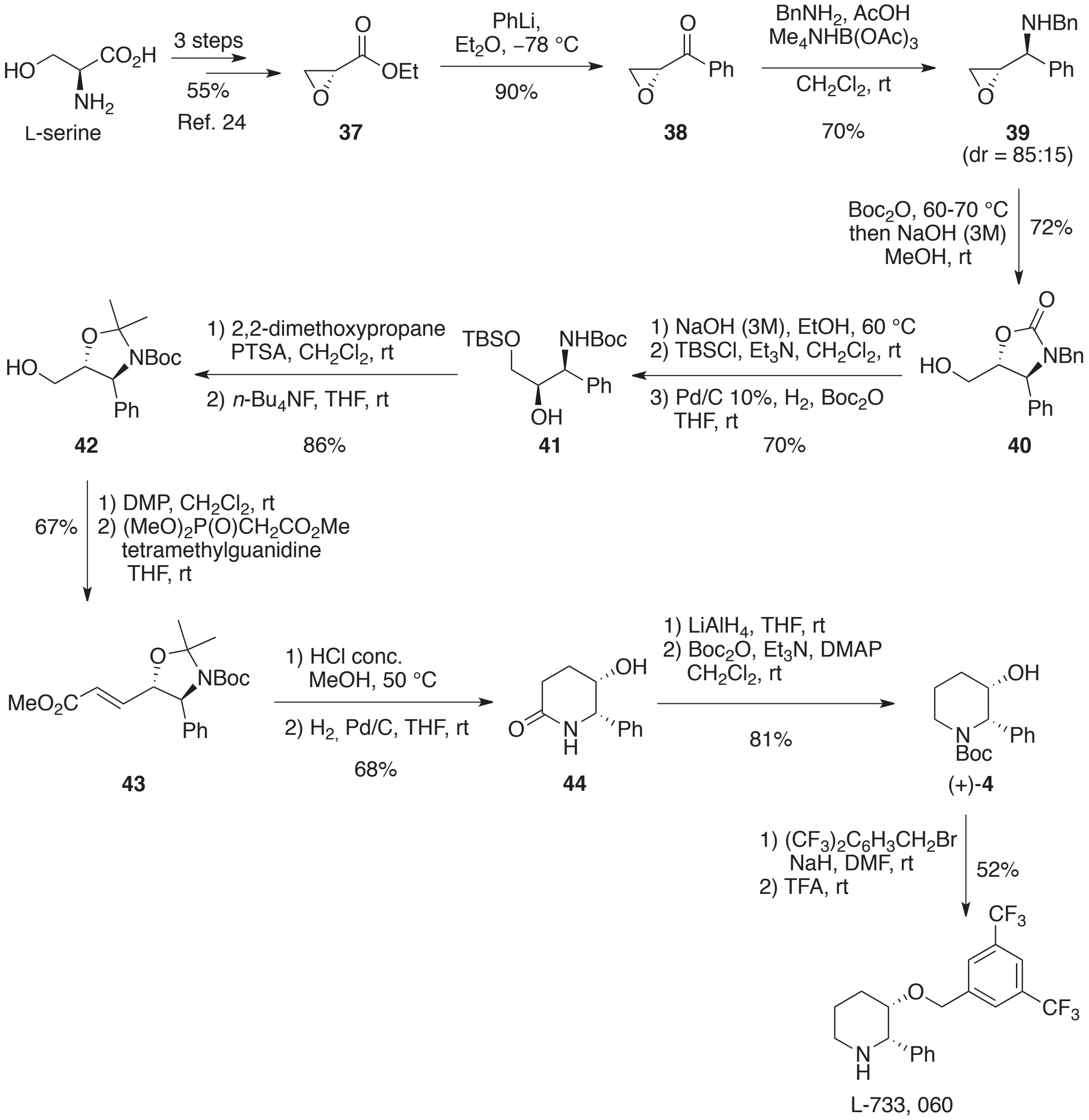
Amino alcohols *anti*-**27** and *syn*-**27** were respectively treated with TFAA/Et_3N and then with NaOH to afford, *via* aziridiniums **D** and **E** respectively, piperidinols **34** and **35** with excellent diastereoselectivities (de > 99%) and enantioselectivities (ee > 99%). The transformation of **34** to (–)-**4**[7] and **35** to **36**,[21,33] precursors of L-733,061 and L-733,060 respectively, was realized in a two-step one-pot sequence hydrogenolysis/*N*-Boc protection (Scheme 11).[23]



Scheme 11. Synthesis of L-733,061 and L-733,060 by Cossy *et al.*

3-1-4. L-Serine

Ethyl glycidate, which was prepared from L-serine,[24] was transformed to L-733,060. This transformation began with the addition of phenyllithium to ester **37**.[25] Subsequent diastereoselective reductive amination of obtained ketone **38** led to *anti*-**39**/*syn*-**39** in a ratio of 85/15. After separation of the two diastereomers, *anti*-**39** was converted to oxazolidinone **40** by a regioselective intramolecular epoxide opening upon treatment with di-*tert*-butyldicarbonate.[26] As oxidation difficulties were encountered due to the presence of the *N*-benzyl protecting group, the benzyl group was replaced by a *N*-Boc protecting group. Thus, **40** was treated with NaOH, the primary hydroxyl group was protected as a TBS-ether and after a hydrogenolysis/protection sequence (H_2, Pd/C then Boc_2O), carbamate alcohol **41** was isolated in 70% yield. In order to oxidize the primary alcohol, **41** was treated with dimethoxypropane (PTSA, CH_2Cl_2, rt), and the deprotection of the primary alcohol was realized affording oxazolidine **42**. A Dess-Martin oxidation followed by a Horner-Wadsworth-Emmons reaction led to α,β-unsaturated ester **43** (67% overall yield). After cyclization of **43** by treatment under acidic conditions followed by hydrogenation (H_2, Pd/C, THF), lactam **44** was isolated (68%) and transformed to (+)-**4** after reduction ($LiAlH_4$) and *N*-Boc protection (Boc_2O, Et_3N, DMAP, CH_2Cl_2) in 81% overall yield (Scheme 12).[27]



Scheme 12. Synthesis of L-733,060 by Haddad *et al.*

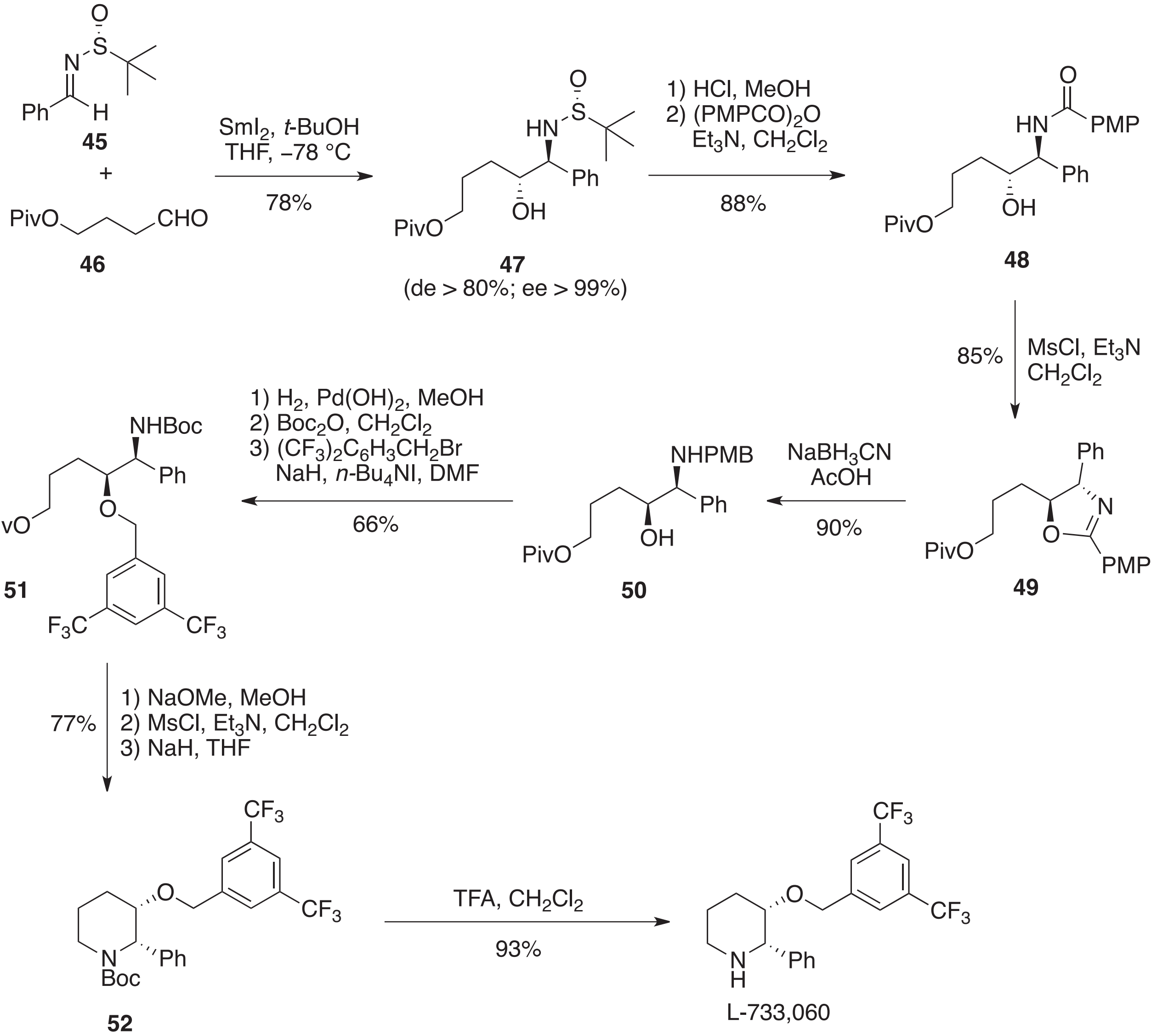
3-2. From Chiral Inductors: Optically Active Sulfinyl Amides and Amines

Optically active sulfinyl amides and amines were used to synthesize L-733,060 either to introduce the nitrogen of the piperidine ring or used to synthesize L-733,061 as a chiral auxiliary.

3-2-1. Optically Active Sulfinyl amides

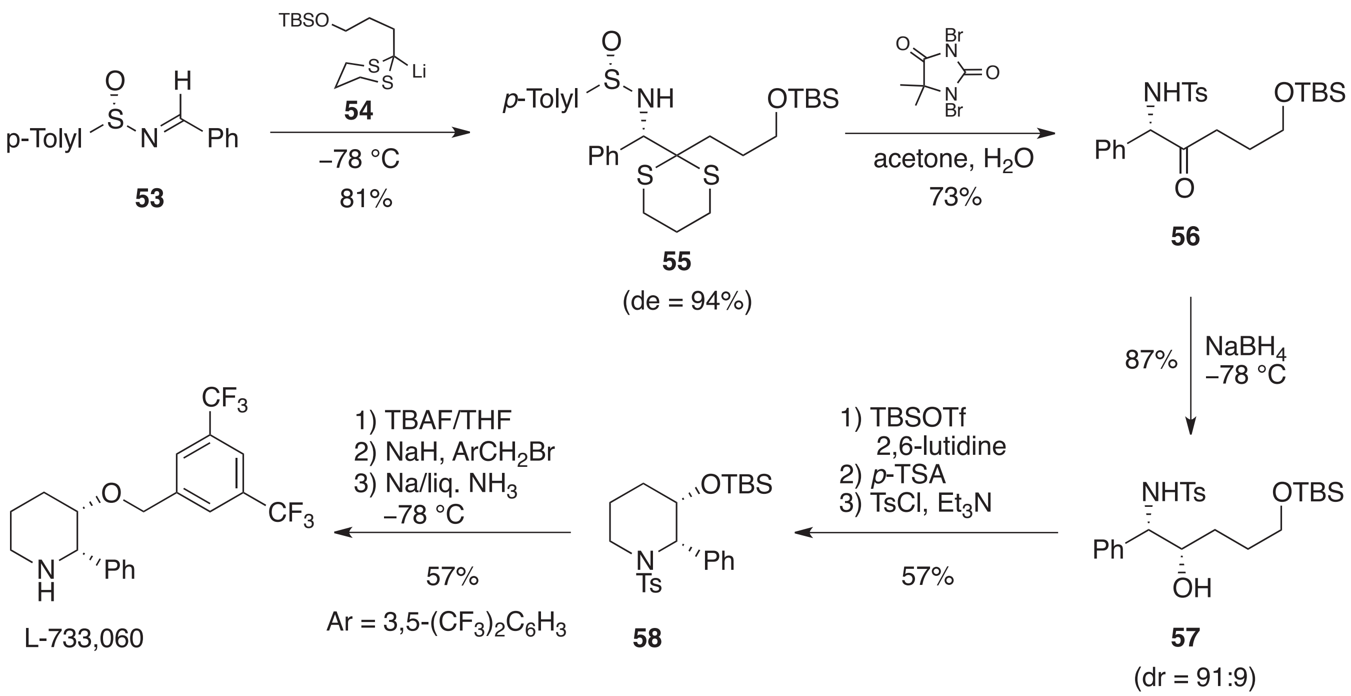
Three syntheses of L-733,060 were easily realized diastereo- and enantioselectively from (*R*)-*tert*-butylsulfinyl amide. The addition of ketyl radicals or organometallics onto optically active sulfinyl imines allows the synthesis of protected 1,2-amino alcohols in good diastereoselectivies.

One route to access L-733,060 featured the SmI_2-induced reductive coupling of *N*-*tert*-butanesulfinyl imine **45** with aldehyde **46** to lead to protected *anti*-1,2-amino alcohol **47** with excellent diastereoselectivity (de > 80%) and excellent enantiomeric excess (ee > 99%). As an inversion of the hydroxyl group is necessary to access L-733,060, hydrolysis of the sulfinyl amine (HCl, MeOH) followed by selective *N*-acylation with 4-methoxybenzoic anhydride were applied to **47**, leading to amide **48** (88%). Upon treatment of **48** with MsCl/Et_3N, oxazoline **49** was obtained with complete inversion of configuration at C2. Reductive ring-opening of oxazoline ($NaBH_3CN$, AcOH) gave *syn*-1,2-amino alcohol **50** (90%). Due to deprotection problems of the *para*-methoxybenzyl (PMB) group at the ultimate stage of the synthesis of L-733,060, the PMB group was replaced by an *N*-Boc group and, after a selective *O*-benzylation [3,5-$(CF_3)_2C_6H_3CH_2Br$, NaH, TBAI], **51** was formed (66% for the 3 steps). Routine removal of the pivaloyl group and ring-closure afforded *N*-Boc protected piperidine **52**, which after removal of the Boc group led to L-733,060 (Scheme 13).[28]



Scheme 13. Synthesis of L-733,060 by Lin *et al*.

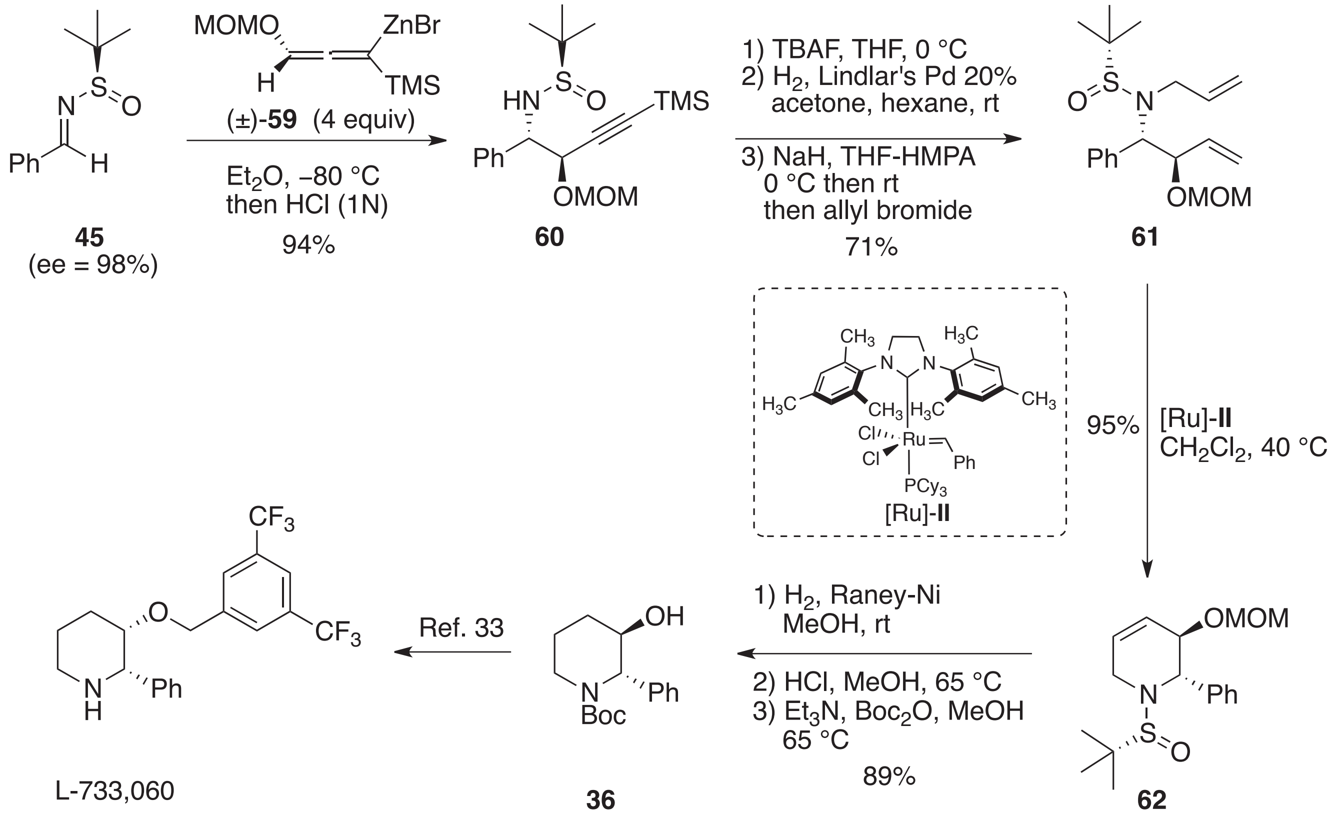
(+)-(*S*)-(*N*-Benzylidene)-*p*-toluenesulfinamide **53** was transformed to protected *syn*-1,2-amino alcohol **57** in three steps. Addition of lithium-1,3-dithiane **54** to **53** gave **55** in 94% de and 81% yield for the major diastereomer. Hydrolysis and oxidation of the sulfonyl group in **55** by 1,3-dibromo-5,5-dimethylhydantoin in acetone/H_2O afforded **56**. A diastereoselective reduction of amino ketone **56** with $NaBH_4$ gave the protected *syn*-1,2-amino alcohol **57** (dr = 91:9). After a protection/deprotection/tosylation sequence, piperidine **58** was formed (57% yield). Piperidine **58** was then transformed to L-733,060 after deprotection of the hydroxy group, *O*-benzylation, and *N*-tosyl deprotection with Na/NH_3(liq.) at –78 °C (Scheme 14).[29]



Scheme 14. Synthesis of L-733,060 by Davis *et al.*

A third synthesis of L-733,060 was realized from *N*-*tert*-butanesulfinyl imine **45**, which was transformed to a protected *anti*-1,2-amino alcohol **60** by addition of the allenyl zinc **59**. This protected amino alcohol was then transformed to piperidine **36**. This represents a formal synthesis of L-733,060.

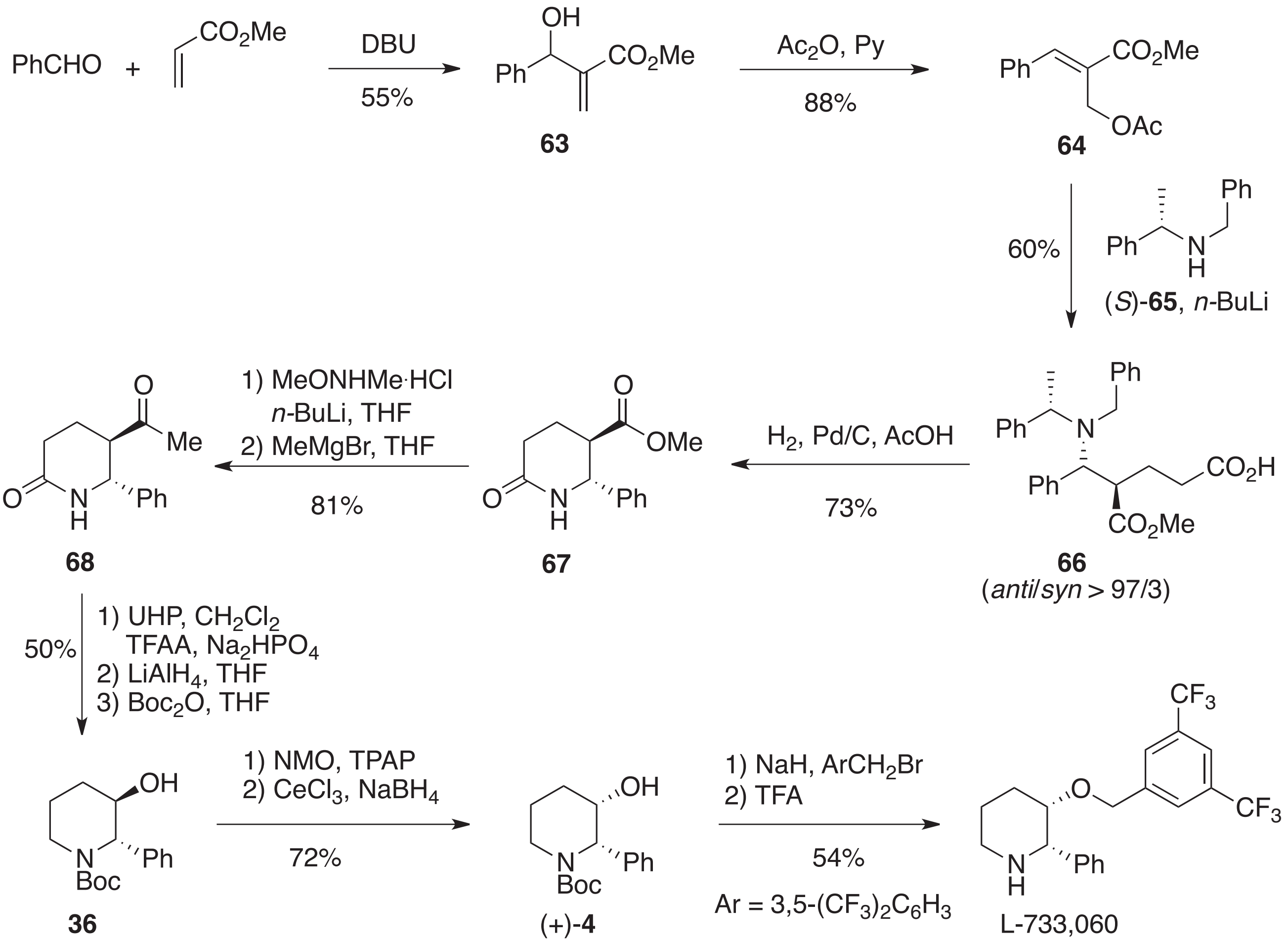
The synthesis of L-733,060 began with the addition of racemic allenyl zinc (±)-**59** (4 equiv) to *N*-*tert*-butylsulfinyl imine **45**[30] to produce protected *anti*-1,2-amino alcohol **60** as a single isomer. This protected *anti*-1,2-amino alcohol was transformed to diene **61** after protodesilylation of the acetylenic group by TBAF, hydrogenation with Lindlar catalyst and *N*-allylation (NaH, AllylBr, THF/HMPA). To construct the piperidine core, **61** was subjected to a ring-closing metathesis (RCM) using Grubbs second generation catalyst (95% yield). After hydrogenation of the olefin using Raney nickel (MeOH, rt), acidic removal of the *tert*-butylsulfoxide group and concomitant MOM-ether cleavage, then *N*-Boc protection, **36** which represents a precursor of L-733,060, was isolated in 89% yield (Scheme 15).[31]



Scheme 15. Synthesis of L-733,060 by Chemla *et al.*

3-2-2. Optically Active Phenylethylamine

The synthesis of L-733,060 started from Baylis-Hillman adduct **63** formed from benzaldehyde and methyl acrylate. The obtained hydroxyl α,β-unsaturated ester **63** was transformed to acetyl derivative **64** by treatment with Ac_2O and pyridine. When **64** was treated with chiral lithium amide (*S*)-**65**, a domino reaction featuring a stereoselective Ireland-Claisen rearrangement and an asymmetric Michael addition[32] took place to produce **66** in 60% yield with good diastereoselectivity (dr > 97/3). Hydrogenolysis of δ-amino acid **66** (H_2 50psi, Pd/C in AcOH) induced a subsequent lactamization and gave piperidinone **67** which was transformed to methyl ketone **68** in two steps, *via* a Weinreb amide using MeONHMe·HCl and *n*-BuLi as the base followed by the addition of MeMgBr in THF. A Baeyer-Villiger oxidation [urea hydrogen peroxide (UHP), TFAA], then reduction of the lactam ($LiAlH_4$) and *N*-Boc protection provided **36**. The synthesis of L-733,060 required the inversion of the hydroxy group at C3 in **36**. This inversion was realized after TPAP-oxidation followed by stereoselective reduction of the formed ketone using $CeCl_3/NaBH_4$. Piperidine (+)-**4** was obtained in 72% yield and then transformed to L-733,060 in two steps (etherification, deprotection) (Scheme 16).[33]

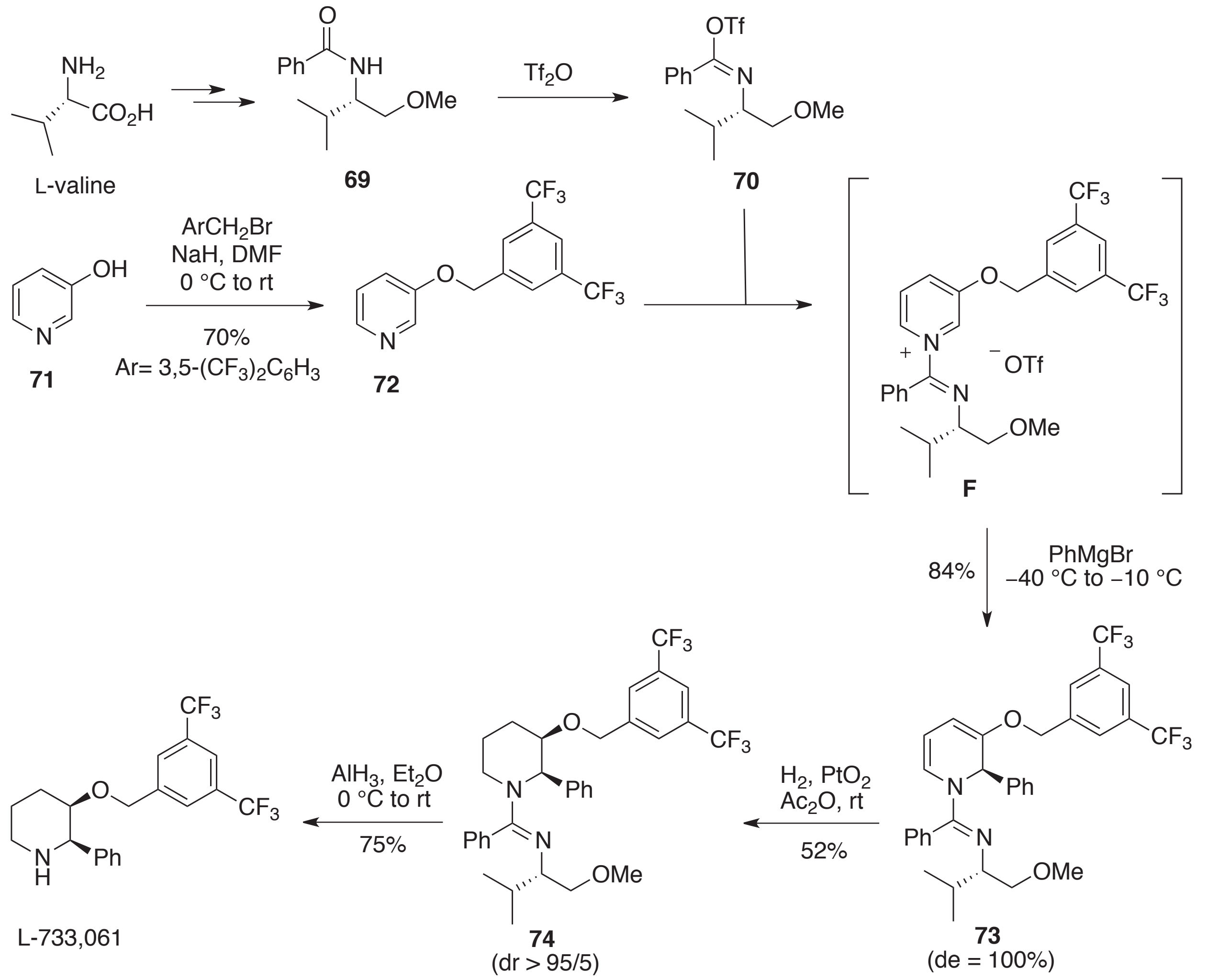


Scheme 16. Synthesis of L-733,060 by Garrido *et al.*

3-3-3. Using Amino Chiral Auxiliary

L-Valine can be transformed easily to amide **69**, which was used as a chiral auxiliary in the preparation of a pyridinium salt that was transformed to an optically active 2,3-disubstituted 1,2-dihydropyridine.

The synthesis of L-733,061 started with the deprotonation of 3-hydroxypyridine **71** (NaH, DMF), followed by the addition of 3,5-bis(trifluoromethyl)benzyl bromide allowing the formation of pyridine **72** (70% yield). The addition of phenylmagnesium bromide to pyridinium salt **F** derived from amide **69** *via* **70** and pyridine **72** produced 1,2-dihydropyridine **73** (84%). The diastereoselective hydrogenation of **73** from the opposite face of the phenyl ring at C2 afforded piperidine **74** as a single diastereomer (dr > 95/5) in 52% yield. Finally, alane reduction of the amidine led to L-733,061 (75% yield) (Scheme 17).[34]



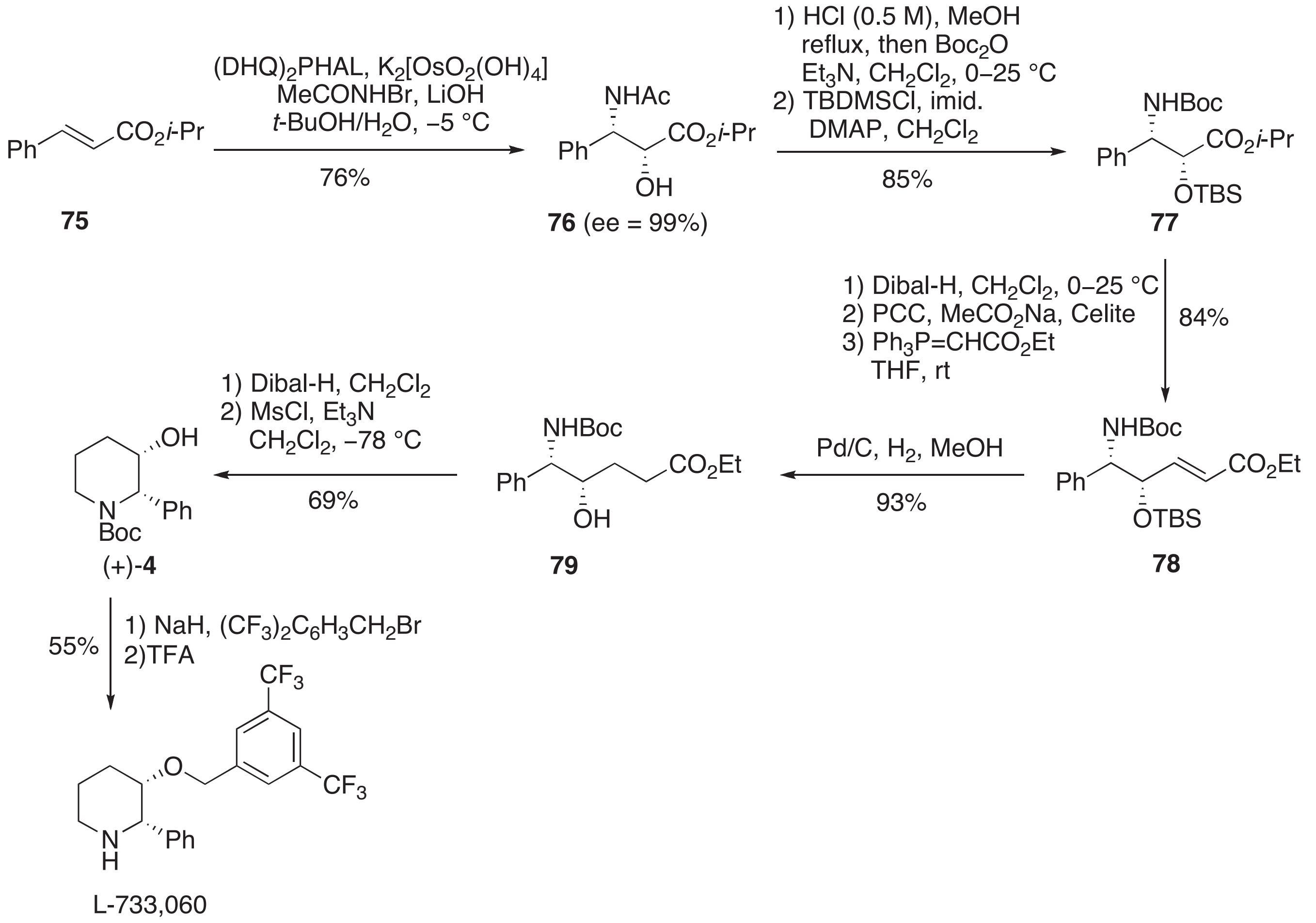
Scheme 17. Synthesis of L-733,061 by Charette *et al.*

4. ENANTIOSELECTIVE REACTIONS

As enantioselective reactions can be versatile, both enantiomers L-733,060 and L-733,061 can be obtained easily.

4-1. Sharpless Asymmetric Aminohydroxylation

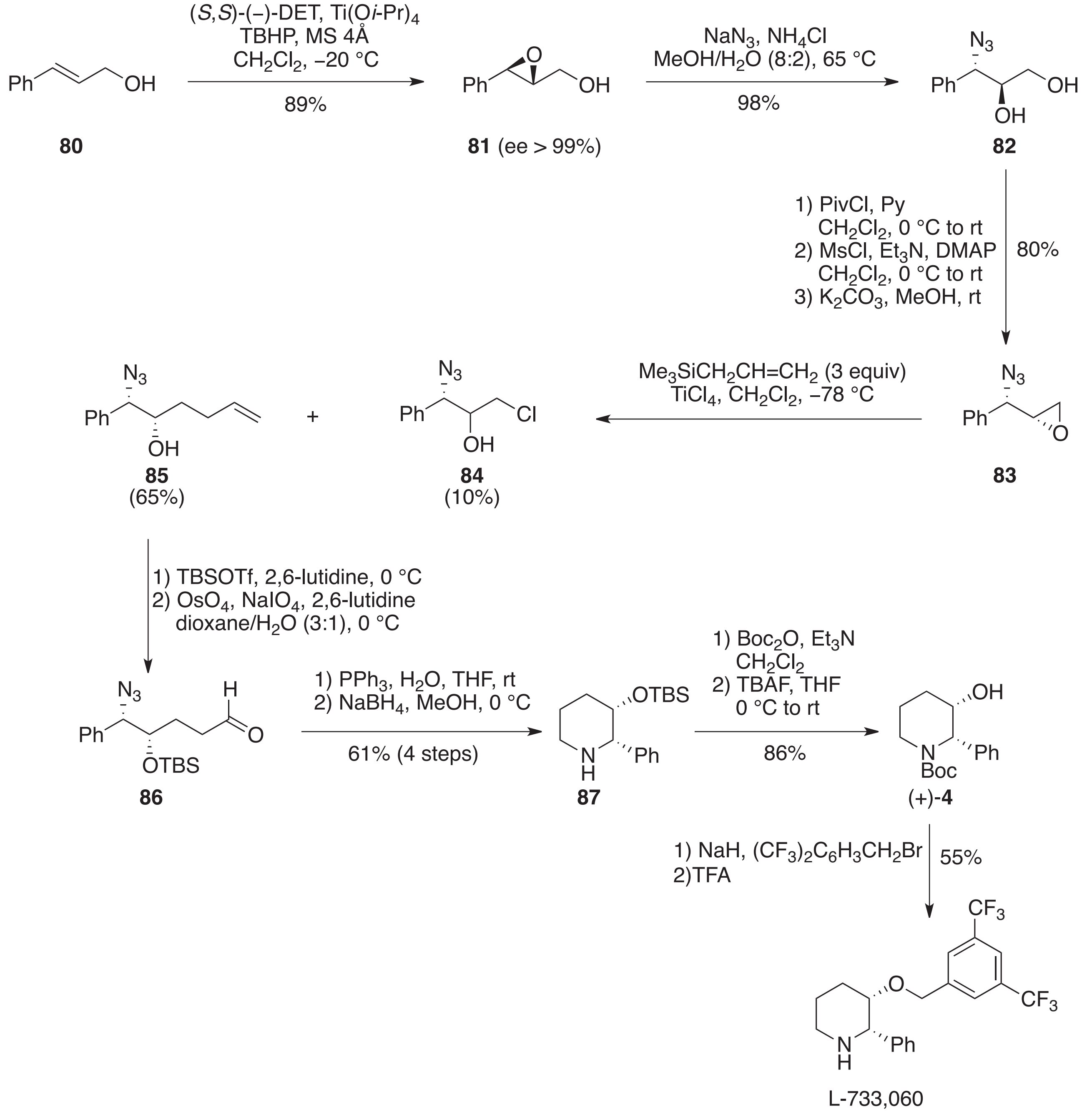
L-733,060 was synthesized by applying an aminohydroxylation of an unsaturated ester by utilizing $(DHQ)_2PHAL$ as the chiral inductor. The synthesis of L-733,060 started from isopropyl cinnamate **75** which was subjected to a Sharpless asymmetric aminohydroxylation[35] using $(DHQ)_2PHAL$, potassium osmate as the oxidant and *N*-bromoacetamide as the nitrogen source to produce desired protected amino alcohol **76** in 76% yield with excellent enantiomeric excess (superior to 99%). In order to access (+)-**4**, precursor of L-733,060, a deprotection/protection sequence was applied to **76** to produce **77**. This compound was then subjected to a reduction/oxidation sequence to produce an aldehyde, which on a subsequent Wittig reaction gave α,β-unsaturated ester **78**. Olefin reduction and concomitant deprotection of the hydroxyl group furnished hydroxyl ester **79**. After reduction of the ester with Dibal-H, the resulting alcohol was transformed to the mesylate to furnish (+)-**4**, which was transformed to L-733,060 (Scheme 18).[36]



Scheme 18. First synthesis of L-733,060 by Kumar *et al.*

4-2. Sharpless Asymmetric Epoxidation

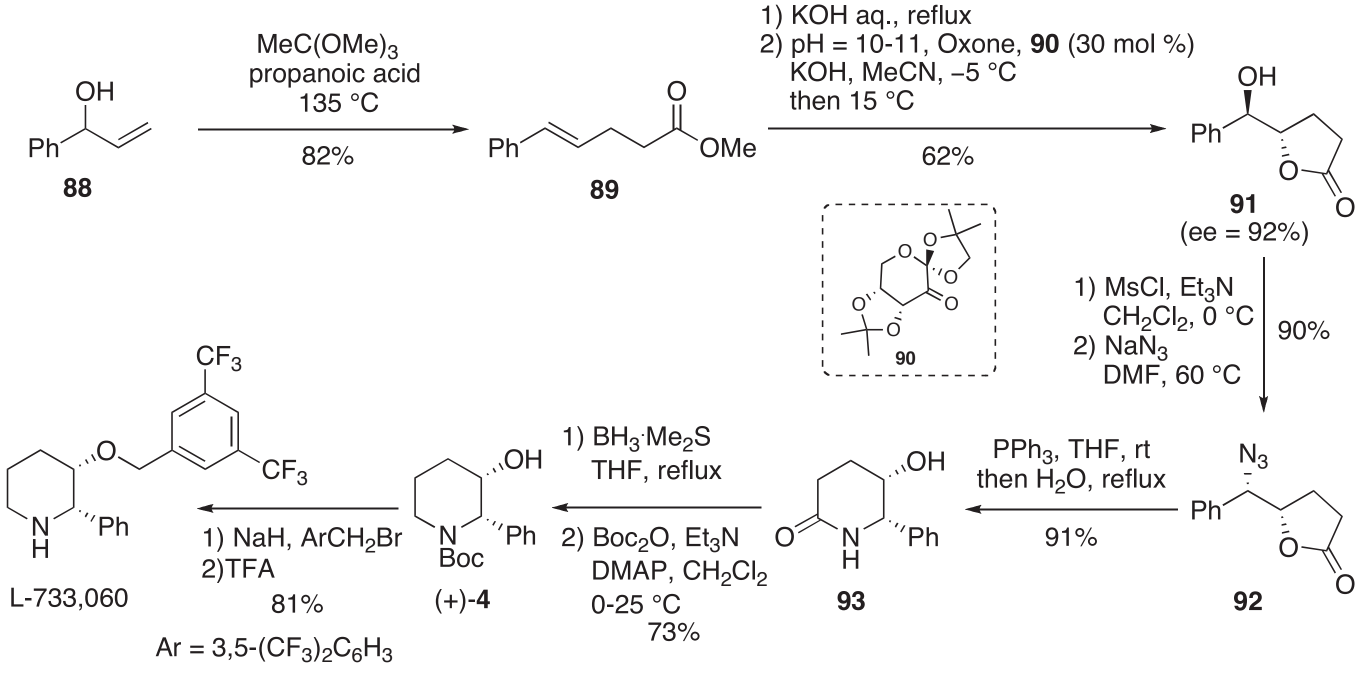
As the Sharpless epoxidation is versatile and the epoxide ring-opening can be regioselective, these reactions can be used to synthesize L-733,060 and L-733,061. The starting material to access L-733,060 was (*E*)-cinnamyl alcohol **80**, which was epoxidized according to Sharpless conditions using (*S*,*S*)-(–)-DET as the chiral inductor. The regioselective epoxide opening of **81** with NaN$_3$ gave a single regioisomer in excellent yield (98%). To obtained the desired *syn* configuration of the azido alcohol to access L-733,060, epoxy alcohol **81** was transformed to azido epoxide **83** in a three-step sequence involving a chemoselective pivaloylation of diol **82**, mesylation of the secondary alcohol (MsCl, Et$_3$N, DMAP) and treatment of the mesylate with K$_2$CO$_3$ in MeOH. In order to construct the carbon skeleton of L-733,060, epoxide **83** was then treated with allylsilane (3 equiv) and TiCl$_4$ in CH$_2$Cl$_2$ at –78 °C. After elimination of byproduct **84**, azido alcohol **85** was protected (TBSOTf, 2,6-lutidine). After oxidative cleavage of the double bond (OsO_4, $NaIO_4$), **86** was isolated without further purification. When a one-pot Staudinger/aza-Wittig reaction was applied to **86**, an intramolecular condensation took place to produce a six-membered imine that was reduced ($NaBH_4$) *in situ* to produce **87**. The resulting piperidine **87** was then protected as an *N*-Boc derivative and the TBS protecting group was cleaved to furnish (+)-**4**, a precursor of L-733,060. The usual two final reactions (etherification/deprotection) applied to (+)-**4** afforded L-733,060 (Scheme 19).[37]



Scheme 19. Second synthesis of L-733,060 by Kumar *et al.*

4-3. Shi Asymmetric Epoxidation

The Shi epoxidation was used as an alternative to the Sharpless epoxidation to access L-733,060, using a D-fructose dioxirane derivative. The synthesis of L-733,060 started with a Johnson-Claisen [3,3]-sigmatropic rearrangement applied to allylic alcohol **88** [$MeC(OMe)_3$, $EtCO_2H$, 135 °C] to construct its carbon backbone, and led exclusively to (*E*)-homoallylic ester **89** (82% yield).[38] After alkaline hydrolysis of the ester, the potassium carboxylate was subjected to Shi epoxidation[39] using D-fructose-derivative ketone **90** as the chiral catalyst (30 mol %), and oxone (2 $KHSO_5$-$KHSO_4$-K_2SO_4) as the stoichiometric oxidant to afford hydroxylactone **91** in 62% yield and 92% ee. Mesylation of the alcohol, followed by treatment of the obtained mesylate with NaN_3, afforded azidolactone **92** with inversion of configuration. Reduction of the azide under Staudinger conditions (PPh_3, THF, H_2O) produced lactam **93** (91% yield) *via* presumably intramolecular *O*-to-*N*-ring expansion by the amine generated *in situ*. Reduction of lactam **93** with $BH_3{\cdot}SMe_2$ in THF followed by protection of the secondary amine with Boc_2O gave the *cis*-amino alcohol (+)-**4** (73% yield over the two steps), which was transformed to L-733,060 (Scheme 20).[40]

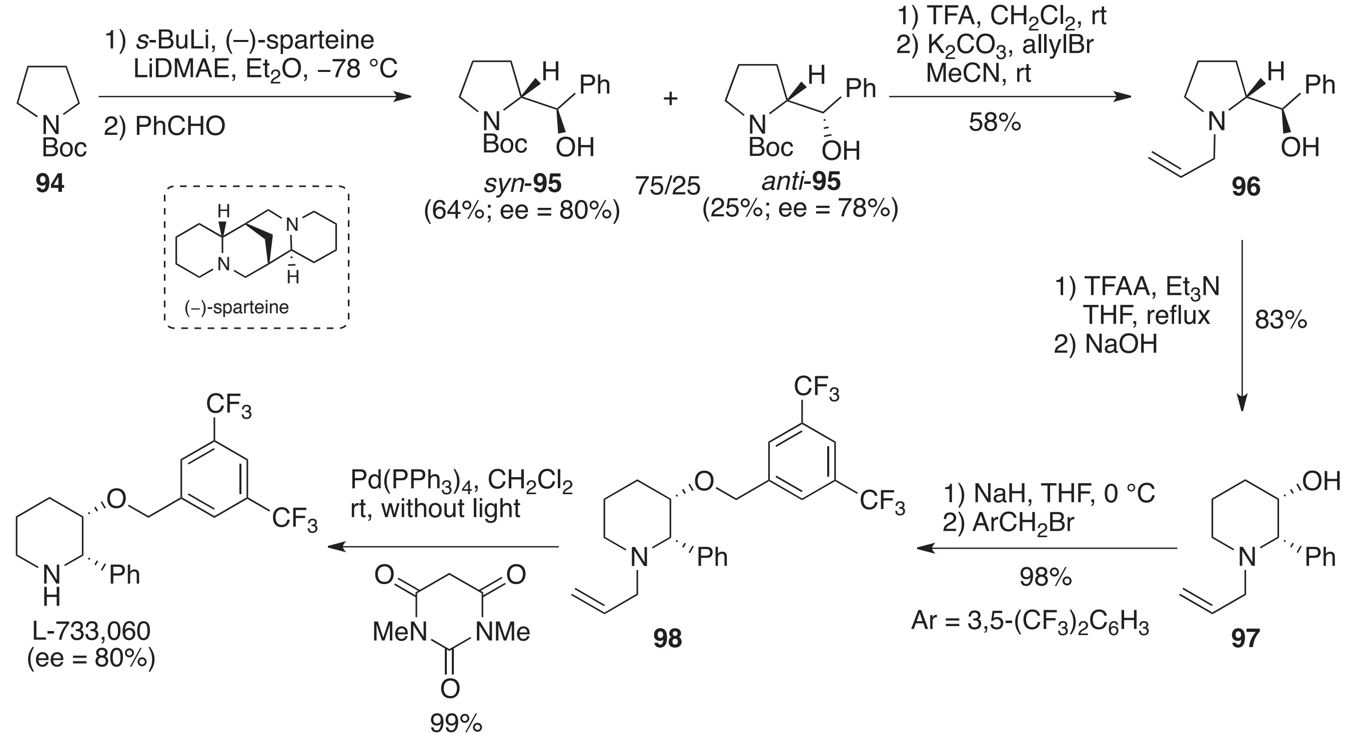


Scheme 20. Synthesis of L-733,060 by Sudalai *et al.*

Four other enantioselective reactions were utilized to access L-733,060 and L-733,061: an enantioselective deprotonation/ring-expansion, an enantioselective allylic amination, an enantioselective aza-Henry reaction, and an enantioselective organo-catalyzed direct vinylogous aldolization.

4-4. Enantioselective Deprotonation and Ring-Expansion

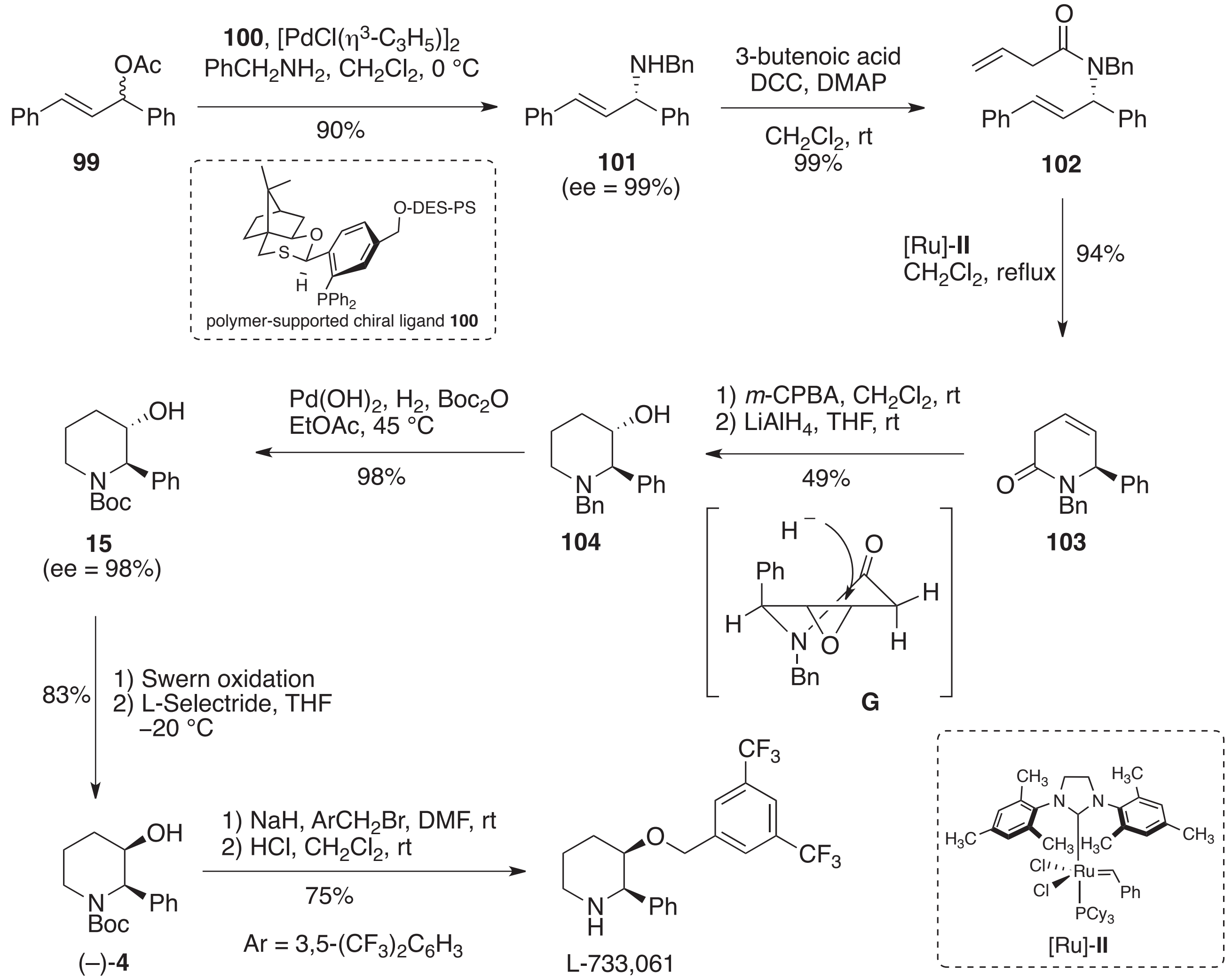
A catalytic asymmetric deprotonation step of *N*-Boc pyrrolidine **94** using *s*-BuLi, (–)-sparteine in the presence of lithiated 2-dimethylaminoethanol (LiDMAE) led after addition of benzaldehyde to prolinols *syn*-**95** and *anti*-**95** in a ratio of 75/25. Prolinol *syn*-**95** was isolated in 64% yield with an ee of 80% and the isomer *anti*-**95** was isolated in 25% yield with an ee of 78%. After separation of *syn*-**95** and *anti*-**95**, *syn*-**95** was *N*-deprotected and converted to *N*-allyl-2-hydroxymethylpyrroline **96** that was subjected to a ring expansion leading to piperidine **97** using TFAA/ET$_3$N, then NaOH.[22] The remaining two steps proceeded in high yield. *O*-Benzylation of **97** was achieved by using a NaH deprotonation followed by alkylation of the alcoholate with functionalized benzyl bromide. Finally, treatment of obtained **98** with Pd(0) and *N,N'*-dimethylbarbituric acid produced a deallylation to give L-733,060 with an enantiomeric ratio of 90:10 (Scheme 21).[41]



Scheme 21. Synthesis of L-733,060 by O'Brien *et al.*

4-5. Enantioselective Allylic Amination

A palladium-catalyzed enantioselective allylic amination has been used as the key step in the synthesis of L-733,061. Pd-catalyzed asymmetric allylic amination of allyl acetate **99** using chiral ligand **100** afforded allyl amine **101** in 90% yield and 99% ee.[42] Compound **101** was then converted to diene **102** by treatment with 3-butenoic acid (DCC, DMAP, CH$_2$Cl$_2$). A RCM applied to **102**, using the second-generation Grubbs catalyst, afforded the desired unsaturated 2-phenylpiperidinone **103** (94% yield). The 3-hydroxy group of L-733,061 was introduced by epoxidation of **103** (*m*-CPBA). Reduction with LiAlH$_4$ allowed the reduction of the amide and the regioselective ring-opening of the epoxide. This regioselective ring-opening occurred probably *via* conformer **G**, in which the steric interaction between the benzyl group on the nitrogen and the phenyl group at C2 is minimal. Then, the hydride anion can attack from the β-axial site at C4, affording desired *trans*-product **104**, which was then converted to *N*-Boc product **15** [$Pd(OH)_2$, H_2, Boc_2O, EtOAc, 45 °C]. After four steps, **15** was transformed to L-733,061 by inversion of the configuration of the stereogenic center at C3. After Swern oxidation, stereoselective reduction of the formed ketone by L-Selectride (THF, –20 °C), *O*-benzylation of the hydroxyl group in (–)-**4** (NaH, 3,5-bistrifluoromethylbenzyl bromide), and *N*-Boc cleavage, L-733,061 was isolated with an overall yield of 63% (4 steps) (Scheme 22).[43]

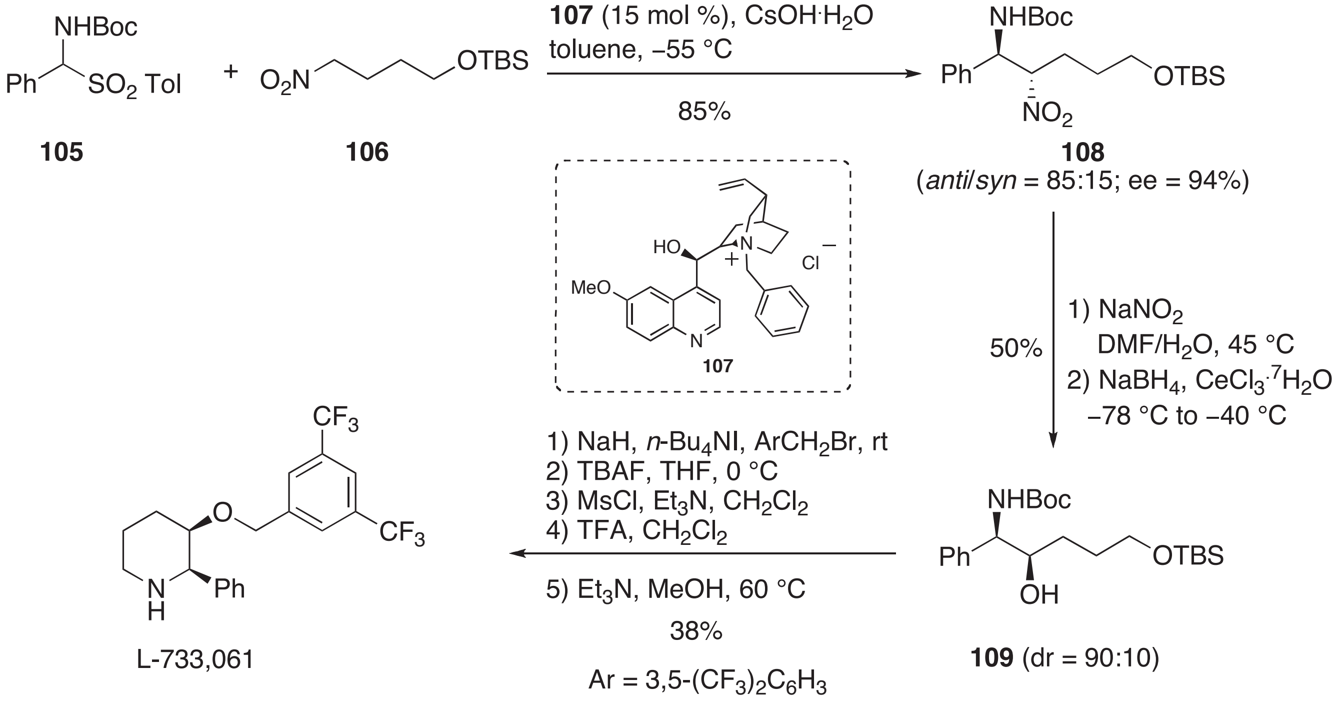


Scheme 22. Synthesis of L-733,061 by Nakano *et al.*

4-6. Enantioselective Aza-Henry Reaction

Recently, an efficient enantioselective synthesis of L-733,061 was accomplished using an organo-catalyzed enantioselective aza-Henry reaction.

The reaction of *N*-Boc sulfone **105** with nitro compound **106** employing CsOH·H_2O and phase transfer catalyst quinidine salt **107** (15 mol %) in toluene at –55 °C for 44 h resulted in product **108** in 85% yield with an *anti*/*syn* ratio of 85:15 in favor of the *anti*-isomer with an ee of 94%. After oxidation of the nitro functionality of **108** to a ketone ($NaNO_2$, DMF/H_2O) and reduction with $NaBH_4$/$CeCl_3$, the *syn*-selective secondary alcohol **109** was obtained with a dr of 90/10. The secondary alcohol was then *O*-benzylated with 3,5-bis-trifluoromethylbenzyl bromide under basic conditions, and after cleavage of the TBS group, the resulting primary alcohol was mesylated and the amine deprotected (TFA). When the resulting TFA ammonium salt was treated under basic conditions (Et_3N, MeOH, 2h, 60 °C), the desired L-733,061 was isolated in 38% overall yield (5 steps) (Scheme 23).[44]

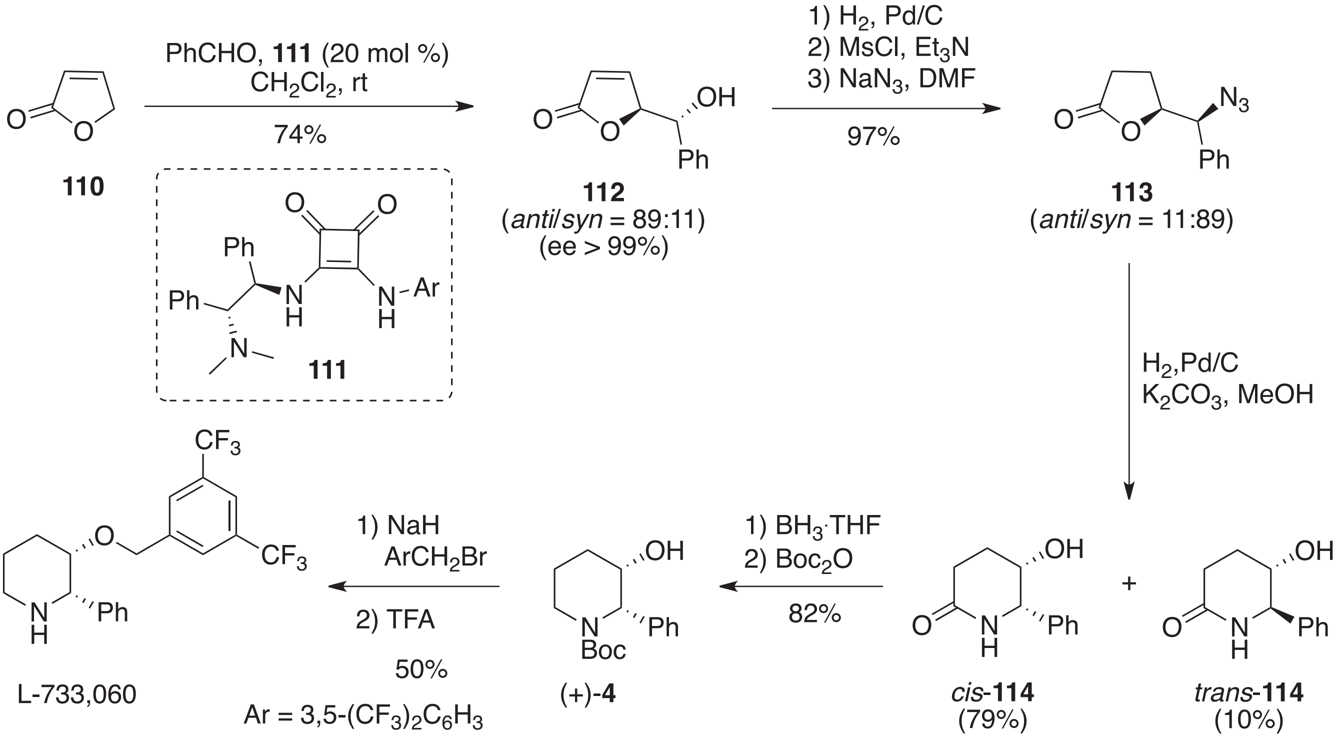


Scheme 23. Synthesis of L-733,061 by Kumaraswamy *et al*.

4-7. Enantioselective Organo-catalytic Direct Vinylogous Aldolization

L-733,060 was synthesized by applying an enantioselective organo-catalyzed direct vinylogous aldolization to γ-crotonolactone[45] by utilizing a chiral aminosquaramide as the inductor.

The synthesis of L-733,060 started from γ-crotonolactone **110**. The direct vinylogous aldolization of this γ-crotonolactone with benzaldehyde in the presence of aminosquaramide catalyst **111** provided butenolide **112** in 74% yield, with good diastereoselectivity (*anti*/*syn*: 89/11) and excellent enantiomeric excess (ee >99% for the *anti*-diastereomer). The diastereomeric mixture **112** was converted to lactam **114** *via* a series of simple transformations. After hydrogenation of the double bond in **112**, subsequent mesylation of the secondary alcohol, and displacement of the mesylate by an azide anion with inversion of configuration, azido butyrolactone **113** was isolated. Reduction of the azide in **113** (H_2, Pd/C) in the presence of a base (K_2CO_3, MeOH), *via* an intramolecular *N*-acylation of the *in situ* generated amino butyrolactone, led to required piperidones **114**. At this stage, *cis*-**114** was separated from minor diastereomer *trans*-**114**. After reduction of piperidone *cis*-**114** with borane, the corresponding piperidine was formed and converted to *N*-Boc derivative (+)-**4** in 82% yield. Compound (+)-**4** was then transformed (etherification, deprotection) to L-733,060 by the two usual final reactions (Scheme 24).[46]



Scheme 24. Synthesis of L-733,060 by Pansare *et al.*

5. CONCLUSION

This review described the syntheses of two enantiomeric neurokinin NK1 receptor antagonists (+)-L-733,060 and (–)-733,061 reported up to date. As most of the syntheses are versatile, library of (+)-L-733,060 and (–)-733,061 should be obtained for biological tests.

REFERENCES

1. U. S. von Euler and J. H. Gaddum, *J. Physiol.*, 1931, **72**, 74; M. M. Chang, S. E. Leeman, and H. D. Niall, *Nat. New Biol.*, 1971, **232**, 86.
2. M. Lotz, J. H. Vaughan, and D. A. Carson, *Science*, 1988, **241**, 1218.
3. A. Perianan, R. Synderman, and B. Malfroy, *Biochem. Biophys. Res. Commun.*, 1989, **161**, 520.
4. M. A. Moskowitz, *Trends Pharmacol. Sci.*, 1992, **13**, 307.

5. M. Lotz, D. A. Carson, and J. H. Vaughan, *Science*, 1987, **235**, 893.
6. M. Otsuka and M. Yanagisawa, *J. Physiol.*, 1988, **395**, 255.
7. T. Harrison, B. J. Williams, C. J. Swain, and R. G. Ball, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 2545.
8. T. M. Fong, S. A. Anderson, H. Yuh, R. R. C. Huang, and C. D. Strader, *Mol. Pharm.*, 1992, **41**, 24; A. M. Cascieri, E. Ber, T. M. Fong, S. Sadowski, A. Bansal, C. Swain, E. Seward, B. Frances, D. Burns, and C. D. Strader, *Mol. Pharm.*, 1992, **42**, 458.
9. T. Oshitari and T. Mandai, *Synlett*, 2003, 2374.
10. T. Oshitari and T. Mandai, *Synlett*, 2006, 3395.
11. O. H. Gringore and F. P. Rouessac, '*Organic Syntheses,*' Coll. Vol. VII, ed. by J. P. Freeman, John Wiley & Sons, New York, 1990, pp. 99.
12. P.-Q. Huang, L.-X. Liu, B.-G. Wei, and Y.-P. Ruan, *Org. Lett.*, 2003, **5**, 1927.
13. L.-X. Liu, Y.-P. Ruan, Z.-Q. Guo, and P.-Q. Huang, *J. Org. Chem.*, 2004, **69**, 6001.
14. For recent review see: P. Merino, T. Tejero, G. Greco, E. Marca, I. Delso, A. Gomez-SanJuan, and R. Matute, *Heterocycles*, 2012, **84**, 75 and references therein.
15. G. Bhaskar and B. V. Rao, *Tetrahedron Lett.*, 2003, **44**, 915.
16. K. Y. Lee, Y. H. Kim, M. S. Park, and W. H. Ham, *Tetrahedron Lett.*, 1998, **39**, 8129; K. Y. Lee, Y. H. Kim, M. S. Park, C. Y. Oh, and W. H. Ham, *J. Org. Chem.*, 1999, **64**, 9450.
17. Y.-J. Yoon, J.-E. Joo, K.-Y. Lee, Y.-H. Kim, C.-Y. Oh, and W.-H. Ham, *Tetrahedron Lett.*, 2005, **46**, 739.
18. For reviews; J. Cossy and D. Gomez Pardo, *Chemtracts*, 2002, **15**, 579; J. Cossy and D. Gomez Pardo, '*Targets in Heterocyclic Systems*,' Vol. 6, ed. by O. A. Attanasi and D. Spinelli, Italian Society of Chemistry, Rome, 2002, pp. 1; J. Cossy, D. Gomez Pardo, C. Dumas, O. Mirguet, I. Déchamps, T.-X. Métro, B. Burger, R. Roudeau, J. Appenzeller, and A. Cochi, *Chirality*, 2009, **21**, 850.
19. A. Ookawa and K. Soai, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1465; K. Soai and K. Ohi, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 1601; K. Soai, A. Ookawa, T. Kaba, and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111.
20. O. Calvez, A. Chiaroni, and N. Langlois, *Tetrahedron Lett.*, 1998, **39**, 9447.
21. O. Calvez and N. Langlois, *Tetrahedron Lett.*, 1999, **40**, 7099.
22. J. Cossy, C. Dumas, and D. Gomez Pardo, *Tetrahedron Lett.*, 1995, **36**, 549; J. Cossy, C. Dumas, and D. Gomez Pardo, *Synlett*, 1997, 905; J. Cossy, C. Dumas, and D. Gomez Pardo, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1343; J. Wilken, M. Kossenjans, W. Saak, D. Haase, S. Pohl, and J. Martens, *Liebigs Ann./Recl.*, 1997, 573; N. Langlois and O. Calvez, *Synth. Commun.*, 1998, **28**, 4471; P. W. Davis, S. A. Osgood, N. Hébert, K. G. Sprankle, and E. E. Swayze, *Biotechnol. Bioeng.*, 1999, **28**,

4471; J. Cossy, C. Dumas, and D. Gomez Pardo, *Eur. J. Org. Chem.*, 1999, 1693; P. Michel and A. Rassat, *J. Org. Chem.*, 2000, **65**, 2572; J. Cossy, O. Mirguet, and D. Gomez Pardo, *Synlett*, 2001, 1575; A. Brandi, S. Cicchi, V. Paschetta, D. Gomez Pardo, and J. Cossy, *Tetrahedron Lett.*, 2002, **43**, 9357; A. Deyine, J.-M. Delcroix, and N. Langlois, *Heterocycles*, 2004, **64**, 207; I. Déchamps, D. Gomez Pardo, P. Karoyan, and J. Cossy, *Synlett*, 2005, 1170; R. Roudeau, D. Gomez Pardo, and J. Cossy, *Tetrahedron*, 2006, **62**, 2388; M. Mena, J. Bonjoch, D. Gomez Pardo, and J. Cossy, *J. Org. Chem.*, 2006, **71**, 5930; I. Déchamps, D. Gomez Pardo, and J. Cossy, *ARKIVOC*, 2007, **v**, 38; I. Déchamps, D. Gomez Pardo, and J. Cossy, *Tetrahedron*, 2007, **63**, 9082; T.-X. Métro, D. Gomez Pardo, and J. Cossy, *J. Org. Chem.*, 2007, **72**, 6556; T.-X. Métro, D. Gomez Pardo, and J. Cossy, *Synlett*, 2007, 2888; A. Rives, Y. Génisson, V. Faugeroux, N. Saffon, and M. Baltas, *Synthesis*, 2009, 3251.

23. A. Cochi, B. Burger, C. Navarro, D. Gomez Pardo, J. Cossy, Y. Zhao, and T. Cohen, *Synlett*, 2009, 2157.
24. Y. Petit and M. Larchevêque, '*Organic Syntheses,*' Vol. 75, ed. by A. B. Smith, III, John Wiley & Sons, New York, 1998, pp. 37.
25. L. Pégorier, Y. Petit, A. Mambu, and M. Larchevêque, *Synthesis*, 1994, 1403.
26. M. Haddad and M. Larchevêque, *Tetrahedron Lett.*, 1996, **37**, 4525.
27. S. Prévot, P. Phansavath, and M. Haddad, *Tetrahedron: Asymmetry*, 2010, **21**, 16.
28. R.-H. Liu, K. Fang, B. Wang, M.-H. Xu, and G.-Q. Lin, *J. Org. Chem.*, 2008, **73**, 3307.
29. F. A. Davis and T. Ramachandar, *Tetrahedron Lett.*, 2008, **49**, 870.
30. F. Ferreira, C. Botuha, F. Chemla, and A. Pérez-Luna, *Chem. Soc. Rev.*, 2009, **38**, 1162.
31. B. Hélal, F. Ferreira, C. Botuha, F. Chemla, and A. Pérez-Luna, *Synlett*, 2009, 3115.
32. N. M. Garrido, M. Garcia, D. Diez, M. R. Sanchez, F. Sanz, and J. G. Urones, *Org. Lett.*, 2008, **10**, 1687.
33. N. M. Garrido, M. Garcia, M. R. Sanchez, D. Diez, and J. G. Urones, *Synlett*, 2010, 387.
34. A. Lemire, M. Grenon, M. Pourasharf, and A. B. Charette, *Org. Lett.*, 2004, **6**, 3517.
35. G. Li, H. H. Angert, and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2813; M. Bruncko, G. Schlingloff, and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1483; S. H. Lee, J. Yoon, S. H. Chung, and Y. S. Lee, *Tetrahedron*, 2001, **57**, 2139.
36. S. R. V. Kandula and P. Kumar, *Tetrahedron: Asymmetry*, 2005, **16**, 3579.
37. S. K. Cherian and P. Kumar, *Tetrahedron: Asymmetry*, 2007, **18**, 982.
38. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.*, 1970, **92**, 741; K. Mori, T. Nukada, and T. Ebata, *Tetrahedron*, 1981, **37**, 1343.

39. D. J. Ager, K. Anderson, E. Oblinger, Y. Shi, and J. VanderRoest, *Org. Process Res. Dev.*, 2007, **11**, 44.

40. L. Emmanuvel and A. Sudalai, *Tetrahedron Lett.*, 2008, **49**, 5736.

41. J. L. Bilke, S. P. Moore, P. O'Brien, and J. Gilday, *Org. Lett.*, 2009, **11**, 1935.

42. H. Nakano, K. Takahashi, Y. Suzuki, and R. Fujita, *Tetrahedron: Asymmetry*, 2005, **16**, 609.

43. K. Takahashi, H. Nakano, and R. Fujita, *Tetrahedron Lett.*, 2005, **46**, 8927.

44. G. Kumaraswamy and A. Pitchaiah, *Tetrahedron*, 2011, **67**, 2536.

45. H. Ube, N. Shimada, and M. Terada, *Angew. Chem. Int. Ed.*, 2010, **49**, 1858; Y. Yang, K. Zheng, J. Zhao, J. Shi, L. Lin, X. Liu, and X. Feng, *J. Org. Chem.*, 2010, **75**, 5382; S. V. Pansare and E. K. Paul, *Chem. Commun.*, 2011, **47**, 1027.

46. S. V. Pansare and E. K. Paul, *Org. Biomol. Chem.*, 2012, **10**, 2119.

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