Tetrahedron: *Asymmetry* 21 (2010) 1147–1153

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Tetrahedron: *Asymmetry* report number 133

Allenylzincs and *tert*-butylsulfinylimines: a fruitful marriage for synthesis

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ARTICLE INFO

Article history:
Received 2 April 2010
Accepted 19 April 2010
Available online 21 June 2010

Dedicated to Henri Kagan on the occassion of his 80th birthday

ABSTRACT

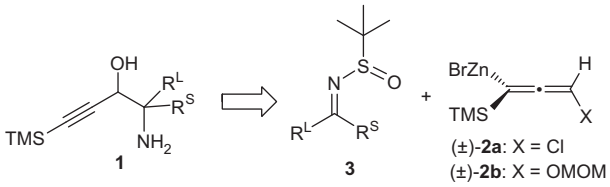
The stereoselective synthesis of alkynyl 1,2-amino alcohols by the addition of 3-chloro- and 3-methoxymethoxy- allenylzincs to chiral *tert*-butylsulfinylimines is described. The methodology is applicable to the preparation of alkynyl 2-amino-1,3-diols (*O*,*N*,*O* stereotriads) using α-alkoxy *tert*-butylsulfinylimines as chiral starting materials. The scope and limitations of the methodology along with recent applications to the efficient asymmetric syntheses of natural and/or bioactive alkaloids and polyhydroxylated alkaloids are presented.

Contents

1. Introduction

The 1,2-amino alcohol pattern is found in a number of naturally occurring and/or biologically active molecules such as alkaloids, antibiotics, aminosugars, and enzyme inhibitors. As a consequence, methods for its stereoselective preparation have been the subject of frequent publications.[1] By contrast, despite their high synthetic potential, little is reported on the stereoselective synthesis of highly functionalized alkynyl 1,2-amino alcohols. Commonly, these compounds are obtained by the addition of propargyl/allenylmetals to α-amino aldehydes.[2,3]

Over the past 10 years, our group has been involved in the development of new methods for the stereoselective preparation of synthetically useful compounds.[4] In a continuation of this work, we reasoned that alkynyl 1,2-amino alcohols of structure **1** could be obtained stereoselectively by the addition of 3-heterosubstituted allenylzincs (±)-**2** to enantiopure *tert*-butylsulfinylimines **3** where R^L is the large substituent and R^S the small one (Scheme 1).



Scheme 1. Retrosynthetic scheme for alkynyl 1,2-amino alcohols.

Herein, we report our advances in this area and some recent applications in natural product synthesis.

2. Synthesis of alkynyl 1,2-amino alcohols

2.1. By ring-opening of alkynyl aziridines

Aziridines are well documented to undergo in most cases regio- and stereoselective nucleophile ring-opening reactions.[5] We have previously shown that racemic alkynyl aziridines[6] could be easily obtained by the stereoselective addition of 3-chloro allenylzinc (±)-**2a** to achiral imines.[4c] In our ongoing works, we then wished to take advantage of the high electrophilicity of these aziridines

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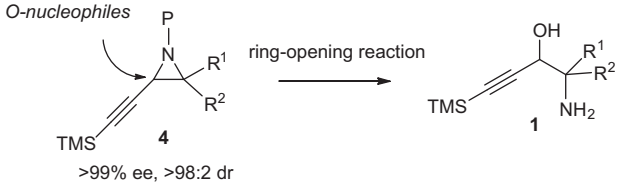
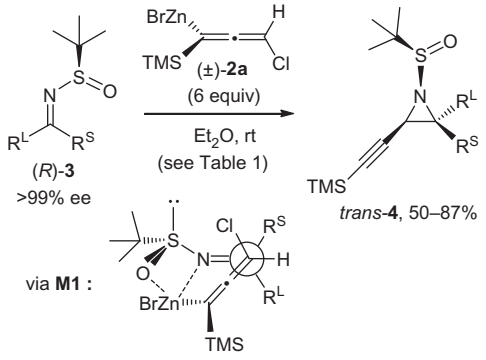
doi:10.1016/j.tetasy.2010.04.044

to produce alkynyl 1,2-amino alcohols **1** by the regio- and stereoselective ring-opening reaction (at the propargylic position) of diastereo- and enantioenriched alkynyl aziridines **4** with *O*-nucleophiles (Scheme 2).[7]



Scheme 2. Alkynyl 1,2-amino alcohols from aziridines.

With the aim of synthesizing alkynyl aziridines **4** in diastereo- and enantiopure form, we thus studied the stereoselective addition of 3-chloro allenylzinc (±)-**2a** to enantiopure imines **3** (Scheme 3).[8] Since allenylzinc (±)-**2a** could only be prepared in a racemic form by the deprotonation (*n*-BuLi, 1 equiv of TMEDA, Et_2O, −80 °C, 15 min) of 3-chloro-1-trimethylsilylprop-1-yne and subsequent transmetallation of the intermediate allenyllithium ($ZnBr_2$, Et_2O, −80 °C, 10 min), we investigated conditions for achieving a kinetic resolution. We found that 6 equiv of (±)-**2** in Et_2O at room temperature were necessary to obtain aziridines **4** with excellent *trans:cis* ratios (up to 94:6) from enantiopure imines **3** (Table 1). In all cases, the stereoselectivity was very close to that observed with racemic imines[9] (corresponding to the upper limit ratio according to Hoffmann's studies on the configurational stability of organometallic reagents[10]) which strongly suggests that (±)-**2a** could be regarded as partially configurationally stable with respect to the time scale defined by the reaction rate. Thus, under these conditions, *trans* alkynyl aziridines **4** were isolated as diastereomerically (>98:02 dr) and enantiomerically (>99% ee) pure compounds in good isolated yields (50–87%) after silica gel chromatography.[11]



Scheme 3. Synthesis of *trans* aziridines.

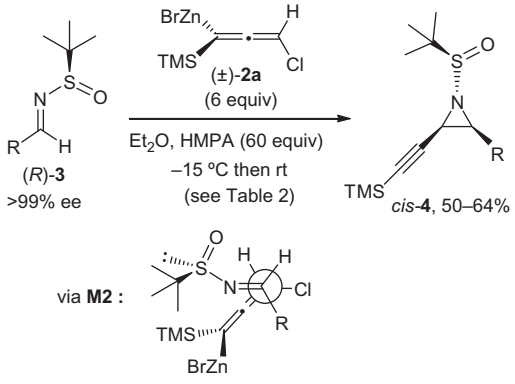
Table 1
Synthesis of aziridines *trans*-**4** produced via Scheme 3

Entry	Imine	R^L	R^S	*trans:cis*[a]	Yield[b] (%)
1	**3a**	*n*-Pr	H	89:11 (90:10)	61
2	**3b**	(*E*)-Crotyl	H	90:10 (94:06)	64
3	**3c**	*i*-Pr	H	94:06 (96:04)	69
4	**3d**	*c*-Hexyl	H	90:10 (90:10)	58
5	**3e**	Ph	H	86:14 (91:09)	50
6	**3f**	Ph	Me	90:10 (91:09)	69
7	**3g**	*n*-Pent	*n*-Pent	—	87

[a] Selectivities were measured by ^1H NMR on the crude reaction mixtures. Selectivities obtained with racemic imines **3** are indicated in parentheses. Dr values of the major *trans* isomers measured by ^1H NMR were >98:02.
[b] Isolated yields in purified major *trans* isomers.

The high *trans* selectivity was assumed to result from the nucleophilic attack of the (a*S*)-enantiomer of allenylzinc (±)-**2a** from the less hindered *si* face of imine (*R*)-**3** through the chelated transition state model **M1** (Scheme 3) wherein the zinc atom of the metallic species is coordinated (in a four-membered metallacycle) by both the nitrogen and the oxygen atoms of the sulfinyl auxiliary.

We further reasoned that using Lewis acids could have some influence on the stereoselective outcome of the reaction by preventing the coordination of the zinc atom. Unfortunately, pre-coordination of imines with various Lewis acids afforded either aziridines *trans*-**4** (with $ZnBr_2$, $BF_3{\cdot}Et_2O$, or MAD[12]) or unidentified by-products (with $TiCl_4$). We then proceeded under the assumption that HMPA[13] would be able to coordinate the zinc atom of (±)-**2a** (Scheme 4).[14] To our delight, when reacting imine **3a** with 1 equiv of (±)-**2a** in Et_2O in the presence of 8 equiv of HMPA, a 49:51 *trans:cis* ratio was obtained suggesting that, under these conditions, allenylzinc (±)-**2a** is configurationally stable with respect to the time scale defined by the reaction rate (Table 2, entry 1). Using larger amounts of HMPA allowed the stereoselectivity to be improved. The best result was observed when 60 equiv of HMPA were used leading to a 34:66 *trans:cis* mixture (Table 2, entry 2). Everything then proceeded as if the rate of racemization of (±)-**2a** were higher in the presence of 60 equiv of HMPA than in the presence of 8 equiv. As expected,[10] employing 6 equiv of (±)-**2a** allowed a high dynamic kinetic resolution to take place giving a 16:84 *trans:cis* mixture of aziridines (Table 2, entry 3). Under the best conditions (6 equiv of (±)-**2a**, 60 equiv of HMPA, Et_2O, from −15 °C to rt), imines **3** possessing primary R substituents were easily converted into the corresponding aziridines with fair to high selectivities in favor of the *cis* isomers (up to 89:11 dr). In all the cases, the major aziridines *cis*-**4** were isolated as diastereomerically (>98:02 dr) and enantiomerically (>99% ee) pure compounds in



Scheme 4. Synthesis of *cis* aziridines.

Table 2
Synthesis of aziridines *cis*-**4** produced via Scheme 4

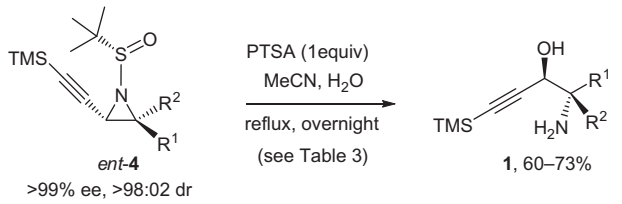
Entry	Imine	R	*trans:cis*[a]	Yield[b] (%)
1	**3a**	*n*-Pr	49:51[c]	nd
2	**3a**	*n*-Pr	34:66[d]	nd
3	**3a**	*n*-Pr	16:84	54
4	**3b**	(*E*)-Crotyl	16:84	55
5	**3h**	Me	11:89	64
6	**3i**	*n*-Hept	22:78	56
7	**3j**	(*E*)-$nC_5H_{11}CH{=}CH$	29:71	62
8	**3k**	(*E*)-PhCH=CH	13:87	56
9	**3l**	$Ph(CH_2)_2$	29:71	50
10	**3m**	(*E*)-$nC_5H_{11}C{\equiv}C$	27:73	60

[a] Selectivities measured by ^1H NMR on the crude reaction mixtures. Dr values of the major *cis* isomers measured by ^1H NMR were >98:02.
[b] Isolated yields in purified major *cis* isomers.
[c] Reaction run with 1 equiv of (±)-**2a** in the presence of 8 equiv of HMPA.
[d] Reaction run with 1 equiv of (±)-**2a** in the presence of 60 equiv of HMPA.

good yields (50–64%) after silica gel chromatography.[15] It is worth noting that no reaction occurred with secondary R substituents under these conditions (Scheme 4).

The formation of the major *cis* isomers under the above-mentioned conditions has been explained by the synclinal transition state model **M2** in which the imine adopts its most stable conformation due to an important $n_N \rightarrow \sigma^*_{S-O}$ hyperconjugative interaction (Scheme 4). In such a situation, the (a*S*)-enantiomer of allenylzinc (±)-**2a** approaches from the *re* face of imine (*R*)-**3** by minimizing the steric interaction between the chlorine atom and the sulfinyl auxiliary.

Having in hands a general method for the stereoselective preparation of either *trans* or *cis* alkynyl aziridines, we then undertook studies on their ring-opening reactions with oxygen nucleophiles. Running the reaction with TFA/H_2O,[16] $BF_3{\cdot}Et_2O$ then H_2O, or $HClO_4/H_2O$[17] failed to produce the desired alkynyl 1,2-amino alcohols. By contrast, treating alkynyl aziridines *ent*-**4** overnight with 1 equiv of PTSA in a refluxing 7:1 MeCN/H_2O mixture[18] directly afforded the corresponding alkynyl 1,2-amino alcohols **1** as the result of the aziridine-ring opening with H_2O and concomitant nitrogen deprotection (Scheme 5).



Scheme 5. Aziridine ring-opening reaction.

The reaction occurred in a highly regio- and stereoselective manner (⩾95:05) in the case of 2,3-disubtituted aziridines which possess only saturated R^1 or R^2 = H substituents (Table 3). In all these cases, 1,2-amino alcohols **1** were formed through the nucleophilic attack of H_2O at the propargylic carbon (which is the more electrophilic center) of the aziridines. Thus, under these conditions, isomers *anti*-**1** and *syn*-**1** were obtained selectively from *trans*-**4** and *cis*-**4** aziridines, respectively, in good isolated yields (60–73%). On the other hand, with 2,3,3-trisubstituted aziridines (R^1 and $R^2 \neq$ H) low regioselectivity was observed, whereas aziridines bearing unsaturated R^1 or R^2 substituents only led to unidentified products.[19]

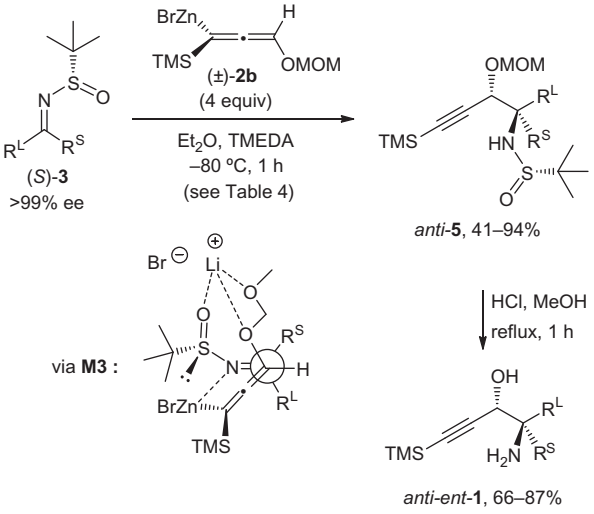
Table 3
Synthesis of 1,2-amino alcohols **1** produced via Scheme 5

Entry	*ent*-**4**	R^1	R^2	**1**[a]	Yield[b] (%)
1	*trans*-**3a**	*n*-Pr	H	*anti*-**1a**	66
2	*cis*-**3a**	H	*n*-Pr	*syn*-**1a**	71
3	*trans*-**3c**	*i*-Pr	H	*anti*-**1c**	70
4	*trans*-**3d**	*c*-Hexyl	H	*anti*-**1d**	73
5	*trans*-**3h**	Me	H	*anti*-**1h**	64
6	*cis*-**3h**	H	Me	*syn*-**1h**	66
7	*trans*-**3i**	*n*-Hept	H	*anti*-**1i**	60
8	*cis*-**3i**	H	*n*-Hept	*syn*-**1i**	66

[a] Regio- and stereoselectivities measured by ^{1}H NMR on the crude reaction mixtures were ⩾95:05.
[b] Isolated yields in purified products **1**.

2.2. By direct addition to *tert*-butylsulfinylimines

The stereoselective preparation of alkynyl 1,2-amino alcohols **1** through the addition of 3-chloro allenylzinc (±)-**2a** to imines **3** and subsequent ring opening of the resulting aziridines **4** thus appeared to be synthetically useful with a wide range of imines. However, this methodology failed when applied to imines substituted with vinylic or aromatic side chains, or bearing a quaternary carbon at the propargylic position. We then investigated an alternative method applicable to such unsaturated and hindered imines using 3-methoxymethoxy allenylzinc (±)-**2b** (Scheme 6, 1st step).[20] In all the cases, the reaction was run with 4 equiv of (±)-**2b** generated in situ in racemic form by the deprotonation of the corresponding alkynyl ether (*s*-BuLi, TMEDA, Et_2O, −80 °C, 1 h) and subsequent transmetallation ($ZnBr_2$, Et_2O, −80 °C, 15 min). This afforded 1,2-sulfinamido alkyl ethers **5** with high stereoselectivity (>98:02) in favor of the *anti* isomers from imines **3** (Table 4). Under these conditions, TMEDA used for the deprotonation step was demonstrated to have a great influence on both the kinetics and the stereoselectivity of the reaction. Indeed, when performing the reaction in the presence of 4 equiv of TMEDA (Method A), only a conversion of 47% was reached within 3 h at −80 °C from imine **3a**, albeit with a >98:02 dr (Table 4, entry 1). Conversely, the use



Scheme 6. Synthesis of *anti*-1,2-amino alcohols.

Table 4
Synthesis of 1,2-amino alcohols *ent*-**1** produced via Scheme 6

Entry	Imine	R^L	R^S	Method[a]	Yields[b] (%)
1	**3a**	*n*-Pr	H	A	47[c]
2	**3a**	*n*-Pr	H	B	100[d]
3	**3a**	*n*-Pr	H	C	82 (78)
4	**3b**	(*E*)-crotyl	H	B	77 (73)
5	**3c**	*i*-Pr	H	B	83 (81)
6	**3d**	*c*-Hexyl	H	B	81 (86)
7	**3e**	Ph	H	B	94 (86)
8	**3f**	Ph	Me	B	41 (87)
9	**3h**	Me	H	C	94[e]
10	**3l**	$Ph(CH_2)_2$	H	C	78 (66)
11	**3n**	$TBSOCH_2$	H	C	84 (81)[f]
12	**3o**	$MeO_2C(CH_2)_3$	H	B	88
13	**3p**	$Cl(CH_2)_4$	H	B	90[g]

[a] Method for the first step. *Method A*: reaction run in the presence of 4 equiv of TMEDA with rapid (<2 min) addition of imine **3**. *Method B*: reaction run in the presence of 0.4 equiv of TMEDA with rapid (<2 min) addition of imine **3**. *Method C*: reaction run in the presence of 0.4 equiv of TMEDA with slow addition of imine **3** over a period of 45 min.
[b] Isolated yields in purified products **5** from **3**. In parentheses are given the isolated yields in **1** from **5**. Stereoselectivities measured by ^{1}H NMR on the crude reaction mixtures were >98:02 unless otherwise stated.
[c] Converion based on recovered starting imine **3** after 3 h of stirring at −80 °C.
[d] The stereoselectivity was 89:11.
[e] The stereoselectivity was 93:07.
[f] The second reaction was run for 2 h at reflux. The TBS–ether was concomitantly deprotected giving the free primary alcohol.
[g] The stereoselectivity was 96:4.

of 0.4 equiv of TMEDA (Method B) allowed complete conversion to be attained within 1 h at −80 °C, but with a lower 89:11 stereoselectivity (Table 4, entry 2).

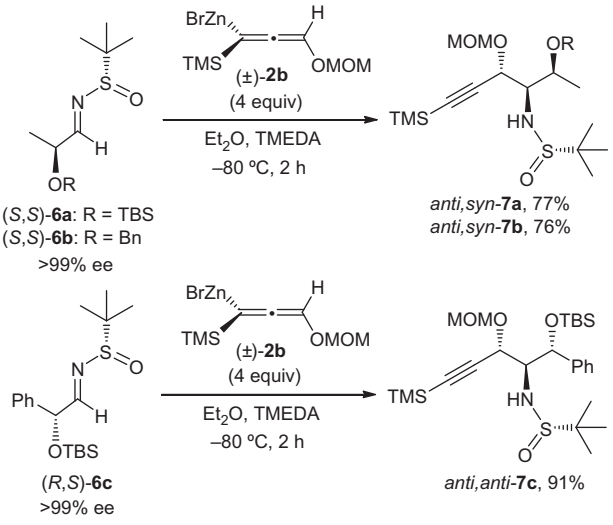
Finally, the best results were obtained when imine **3a** was slowly added at −80 °C over a period of 45 min (Method C) to an etheral solution of allenylzinc (±)-**2b**. Thus, both complete conversion and high stereoselectivity were observed within 1 h at −80 °C (Table 4, entry 3).

All of these observations suggest that allenylzinc (±)-**2b** is not completely configurationally stable in the time scale defined by the rate of its reaction with imine **3a** under these conditions.[10] The same process (Method C) was applied to other primary imines in order to produce the corresponding *anti* isomers **5** with high stereoselectivity (Table 4, entries 9–11). By contrast, with all other less reactive imines, no slow addition was necessary to reach an excellent *anti* stereoselectivity (Table 4, entries 4–8, 12, and 13). In all the cases, alkynyl 1,2-sulfinamido alkyl ethers *anti*-**5** were isolated in good to excellent yields (41–94%) with high stereoselectivity (⩾ 93:7 dr: >99% ee) after silica gel chromatography (>98:02 dr and >99% ee).

The stereoselectivity of the reaction was assumed to arise from transition state model **M3** wherein the imine adopts its less energetic conformation. In **M3**, because of the possible chelation of a lithium cation by both the oxygen atoms of the MOM-ether moiety and the sulfinyl auxiliary, the (a*S*)-enantiomer of (±)-**2b** approaches from the *si* face of imine (*S*)-**3** which corresponds to an *anti* relationship between the R^L substituent of the imine and the MOM-ether moiety (Scheme 6). Surprisingly, and opposite to what we had previously observed with (±)-**2a**, using HMPA in the reaction of (±)-**2b** with imines **3** did not allow the stereoselectivity to be switched in favor of the isomeric *syn*-1,2-sulfinamido alkyl ethers.

Alkynyl 1,2-amino alcohols were finally obtained by treating compounds **5** with methanolic HCl at reflux (Scheme 6, 2nd step). Usual basic work-up then allowed crude 1,2-amino alcohols *ent*-**1** to be obtained in high purity (>90%). They were further isolated in good to excellent yields (66–87%) as diastereo- and enantiopure products after chromatography over silica gel (Table 4).[21]

The methodology was generalized to α-chiral imines in order to access to 2-amino-1,3-diol subunits which constitute an important pattern found in many natural molecules of biological interest, such as indolizidine and pyrrolizidine alkaloids. Thus, performing the reaction between α-alkoxy imines **6** and 4 equiv of (±)-**2b** (Et_2O, 0.4 equiv of TMEDA, −80 °C, 2 h) afforded the expected *O,N,O*-stereotriads **7** in a highly stereoselective manner (Scheme 7).[22]

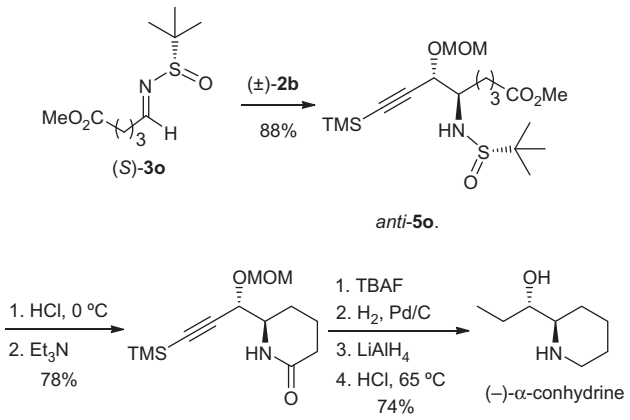


Scheme 7. Access to *O,N,O*-stereotriads.

In all the cases, the stereoselectivity of the addition was excellent and independent of the α stereocenter configuration, whatever the protecting group (TBS or Bn) on the oxygen atom. With imines **6a** and **6b**, the stereoselectivity (explained by a transition state model analogous to **M3**) is consistent with the inherent selectivity provided both by the sulfinyl group and the Felkin–Ahn model which furnishes Felkin adducts *anti,syn*-**7a** and **7b** through the nucleophilic attack of (±)-**2b** from the *si* face of the imine. Interestingly, under the same conditions, the *si* face of diastereoisomeric imine **6c** is also attacked by (±)-**2b** giving the *anti*-Felkin product *anti,anti*-**7c** with a high selectivity, which indicates that the inherent diastereofacial selectivity of the chiral auxiliary overrides the selectivity provided by Felkin–Anh control.

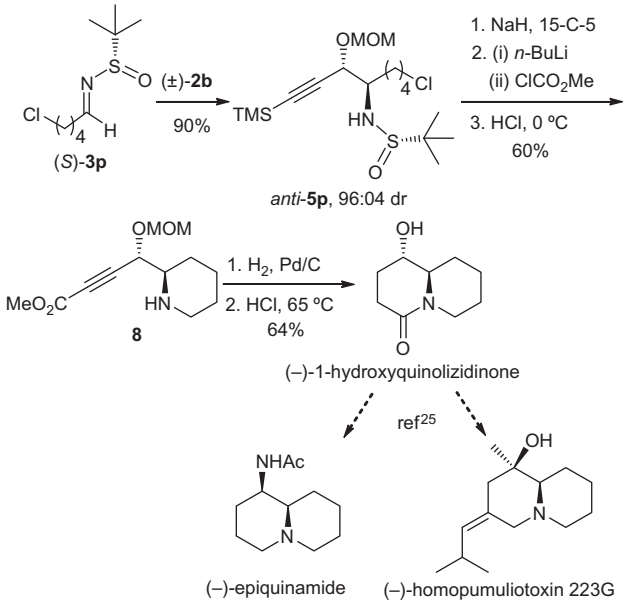
3. Synthetic applications

Having in hands an efficient method for the stereoselective synthesis of highly functionalized alkynyl 1,2-amino alcohols, we investigated the synthesis of natural and/or bioactive products in which the 1,2-amino alcohol motif can be found. The first synthesis that we reported was that of (−)-α-conhydrine, a piperidine alkaloid isolated from the seeds and leaves of hemlock *Conium maculatum* L.[23] The key step of our synthesis was the high yielding stereoselective preparation of alkynyl 1,2-sulfinamido alkyl ether **5o** (see Table 4, entry 12) which possesses the two stereogenic centers of the target molecule. The piperidine ring was elaborated through the selective deprotection of the nitrogen atom of **5o** with methanolic HCl at 0 °C and subsequent condensation of the resulting free amine onto the ester moiety under basic treatment. Classical chemical transformations then allowed (−)-α-conhydrine to be obtained in 7 steps and 41% overall yield (Scheme 8).[24]



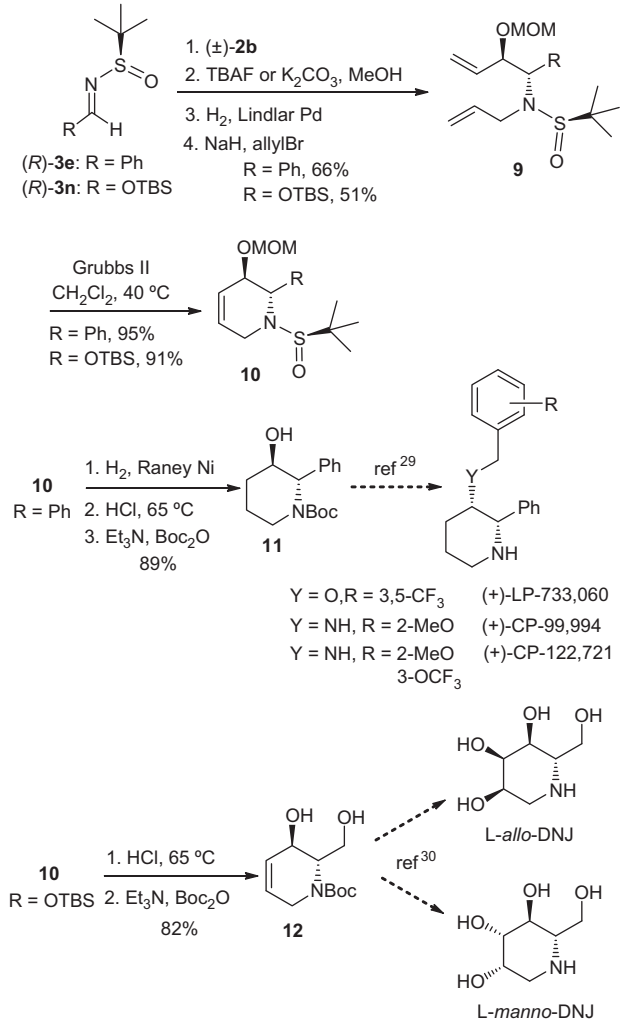
Scheme 8. Synthesis of (−)-α-conhydrine.

It is also possible to functionalize the alkynyl moiety for homologation of the carbon chain through reaction with a chloroformate. This was exemplified by the synthesis of (−)-1-hydroxyquinolizidinone, an intermediate[25] of (−)-epiquinamide, a potential lead for the development of new therapeutics for neuronal receptors,[26,27] and (−)-homopumiliotoxin 223G, which exhibits myotonic and cardiotonic activity[26] (Scheme 9). The key step of this synthesis was the formation of 1,2-sulfinamido alkyl ether **5p** (see Table 4, entry 13) with a high stereoselectivity (96:04 dr). The bicyclic core of the target molecule was then constructed by the intramolecular displacement of the chlorine atom by the sodium amide, generated upon treatment of **5p** with NaH/15-crown-5 ether, and then condensation of the free secondary amine of **8** to the propiolic ester moiety. Following this synthetic scheme, (−)-1-hydroxyquinolizidinone was obtained in 6 steps and 34% overall yield.[28]



Scheme 9. Synthesis of (−)-1-hydoxyquinolizidinone.

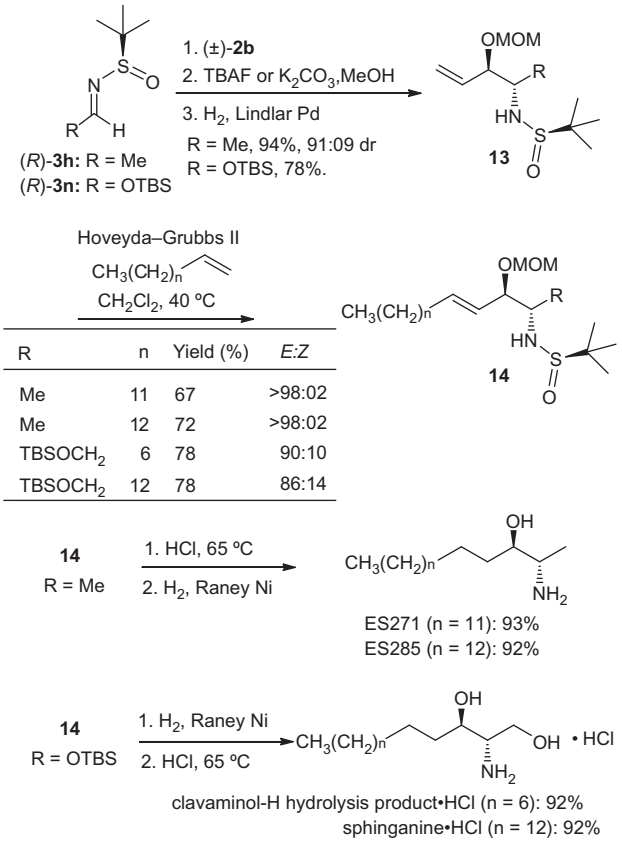
More recently we reported the synthesis of a known advanced key intermediate of various human non-peptide NK-1 receptors,[29]



Scheme 10. Syntheses of human non-peptide NK-1 receptors and L-DNJ.

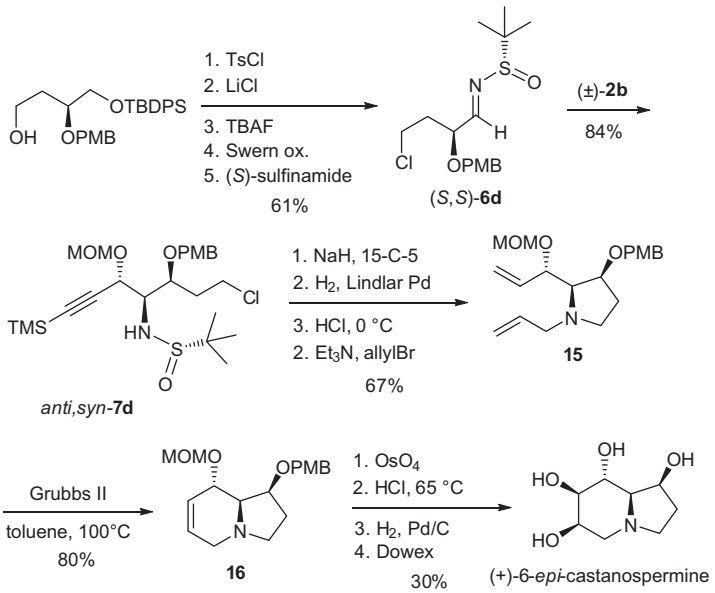
and the formal synthesis of L-1-deoxynojirimycins (L-DNJ), inhibitors of human lysosomal α-mannosidases,[30] by combining our methodology with the ring-closing metathesis reaction. The two key steps of both syntheses were the highly stereoselective formation of 1,2-sulfinamido alkyl ethers **5e** and **5n** (see Table 4, entries 7 and 11) and the ring-closing metathesis reaction of *N*-allylamines **9** using Grubbs 2nd generation catalyst at 40 °C in CH_2Cl_2 (Scheme 10). This allowed to access compound **11** in 7 steps and 56% yield,[31] and compound **12** in 6 steps and 38% yield[32] using mainstream chemistry.

Our methodology was also successfully applied in combination with the cross-metathesis reaction in the synthesis of four sphingoid-type bases. These compounds are found in a number of bioactive products and more particularly in ceramides and sphingolipids.[33] Amongst them, sphinganine is of particular interest as the biogenetical precursor of sphingosine, the most prevalent sphingoid base.[34] The hydrolysis product of clavaminol-H, like almost all of its congeners, has been recently discovered and has been shown to possess high cytotoxic properties against a wide range of tumor cell lines.[35] The same promising cytotoxic activity has also been reported for unnatural and natural spisulosines ES271 and ES285.[36] We have succeeded into developing a straightforward synthesis of these compounds in which the long carbon chain is elaborated by cross-metathesis employing Hoveyda–Grubbs 2nd generation catalyst and the appropriate terminal long-chain alkenes at 40 °C in CH_2Cl_2. Following our synthetic scheme, all of these sphingoid-type bases have been prepared in 6 steps from imines **3h** and **3n** (see Table 4, entries 9 and 11) in >56% overall yields (Scheme 11).[37]



Scheme 11. Syntheses of sphingoid-type bases.

Very recently, we have undertaken the stereoselective formation of 2-amino-1,3-diols for the synthesis of bioactive polyhydroxylated alkaloids, such as indolizidine and pyrrolizidine



Scheme 12. Synthesis of (+)-6-*epi*-castanospermine.

alkaloids, in which such an *O,N,O*-stereotriad is found. In this context, we have developed a synthesis of (+)-6-*epi*-castanospermine, extracted from *Castanospermum Australe*, and which has been thoroughly studied for its biological properties such as its potency to inhibit α-glycosidases.[38] In our synthesis, the key step corresponded to the stereoselective preparation of alkynyl *anti,syn*-2-amino-1,2-diol **7d** from α-alkoxy imine **6d**. The indolizidine core of the target molecule was constructed through the intramolecular displacement of the chlorine atom of **7d** (as described in the synthesis of (−)-1-hydroxyquinolizidinone, see Scheme 9) and subsequent ring-closing metathesis conducted on pyrrolidine **15** using Grubbs 2nd generation catalyst at 100 °C in toluene. The two last stereocenters were created by the stereoselective dihydroxylation of the cyclic alkene function of **16**. The overall synthesis then allowed us to isolate (+)-6-*epi*-castanospermine in 15 steps and 8.5% yield (Scheme 12).[39]

4. Conclusion

In conclusion, we have disclosed new efficient methodologies for the stereoselective preparation of synthetically useful alkynyl 1,2-amino alcohols and 2-amino-1,3-diols through the addition of 3-chloro- and 3-methoxymethoxy-allenylzinc reagents to chiral *tert*-butylsulfinylimines. The high synthetic potential of these new methodologies has been demonstrated by developing several asymmetric syntheses of naturally occurring and/or bioactive alkaloids. Further efforts in the synthesis of polyhydroxylated alkaloids will be reported in due course.

Acknowledgments

The authors are indebted to all the former collaborators who participated in the works presented in this paper. The authors also cordially thank UPMC, CNRS, and the JCEMolChem project for financial support, GlaxoSmithKline for a Ph.D grant to J. Louvel, and Dr E. Demont (GSK) for fruitful discussions.

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