CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Sulfinyl-mediated stereoselective functionalization of acyclic conjugated dienes.

Authors: Roberto Fernández de la Pradilla, Ignacio Colomer, Mercedes Ureña, and Alma Viso

To be cited as: *Chem. Eur. J.* 10.1002/chem.201905742

Link to VoR: http://dx.doi.org/10.1002/chem.201905742

Supported by
ACES

WILEY-VCH

10.1002/chem.201905742

WILEY-VCH

FULL PAPER

Sulfinyl-mediated stereoselective functionalization of acyclic conjugated dienes.

Ignacio Colomer, Mercedes Ureña, Alma Viso, and Roberto Fernández de la Pradilla*[a]

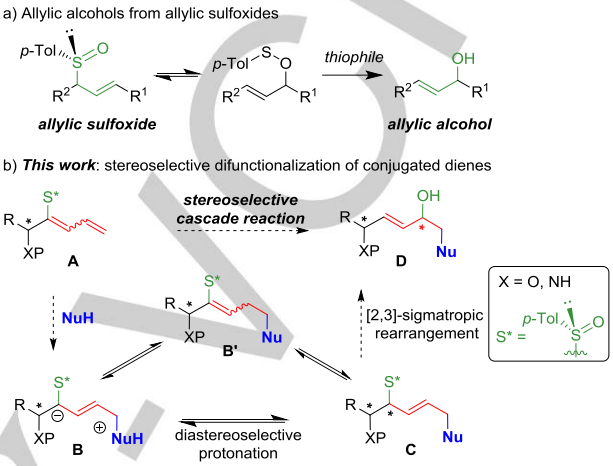
Abstract: The chemo- and stereocontrolled functionalization of conjugated sulfinyl dienes in a cascade process that involves a conjugate addition, diastereoselective protonation and a [2,3]-sigmatropic rearrangement is reported. Enantioenriched 1,4-diol and 1,4-aminoalcohol derivatives are obtained in a very straightforward manner. Further functionalization of these structures, including highly stereoselective epoxidation, dihydroxylation and the stereodivergent synthesis of several polyols in a controlled fashion is described.

Introduction

The chemo- and stereocontrolled functionalization of acyclic molecules still remains a major challenge in synthetic organic chemistry. Conjugated dienes have attracted the attention of different groups and this has led to a variety of useful strategies within this field.[1] Readily available enantiopure sulfoxides are also suitable precursors for acyclic stereocontrol,[2] and the [2,3]-sigmatropic rearrangement of allylic sulfoxides stands out as a promising strategy to contribute in solving this problem.[3] This rearrangement, discovered independently by Mislow, Braverman and Evans,[4] allows for the transformation of allylic sulfoxides into rearranged sulfenates that, in the presence of a thiophile, lead irreversibly to allylic alcohols (Scheme 1a).

In connection with our interest in the development of stereocontrolled methodologies using enantiopure sulfinyl auxiliaries,[5] and our interest in acyclic stereocontrol, we considered that functionalized sulfinyl dienes **A** could undergo a conjugate addition of an appropriate nucleophile,[6] to generate intermediate **B** (Scheme 1b). Subsequent protonation, either to alkenyl sulfoxides **B'** with ensuing isomerization, or to allylic sulfoxides **C**, controlled by the preexisting contiguous chiral center, would eventually trigger the highly selective [2,3]-sigmatropic rearrangement to produce unsaturated 1,4-diol or 1,4-aminoalcohol derivatives **D**, after sulfenate cleavage by excess nucleophile acting as thiophile.[7]

The 1,4-aminoalcohol and 1,4-diol are motifs found in a wide range of natural and bioactive products, such as, halicholactone, amphidinolide H and meglumine antimoniate, a treatment for leishmaniasis (Figure 1).[8] However, the development of new methods to access these substructures has attracted much less attention than the related 1,2-, 1,3-, or 1,5- compounds.



Scheme 1. [2,3]-Sigmatropic rearrangement of allylic sulfoxides and proposed cascade processes for the synthesis of 1,4-diol and 1,4-aminoalcohol derivatives.

Existing approaches to prepare unsaturated 1,4-diols rely on nucleophilic additions,[9] reductions or metathesis,[10] of adequately functionalized precursors and suitable transformations carried out on oxiranes,[11] dienes and alkenes.[12] In contrast, the synthesis of the related 2-ene-1,4-aminoalcohol derivatives is comparatively less well-developed involving Pd-catalyzed allylic substitutions, alkylations of aminoaldehydes or reductive cleavage of 1,2-oxazines obtained by [4+2] cycloaddition.[13] A recent report exemplifies the synthesis of unsaturated 1,4-diols, 1,4-aminoalcohols and 1,4-diamines from α-thioaldehydes.[14]

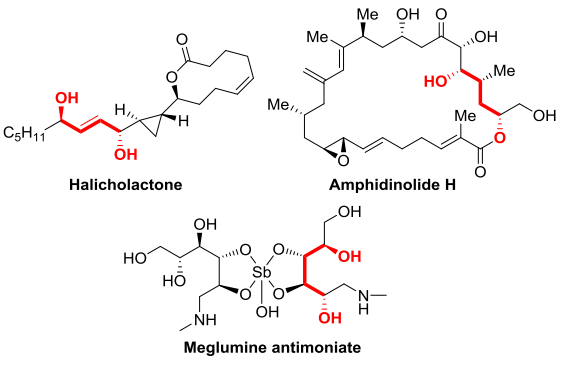


Figure 1. Natural and bioactive products containing the 1,4-diol substructure.

We present herein a full account of the results of our study on the stereoselective functionalization of acyclic sulfinyl 1,3-dienes to

[a] Dr. I. Colomer, Dr. M. Ureña, Dr. A. Viso, Prof. R. Fernández de la Pradilla
Instituto de Química Orgánica General, CSIC. Juan de la Cierva 3, 28006 Madrid (Spain)
E-mail: rfpradilla@iqog.csic.es

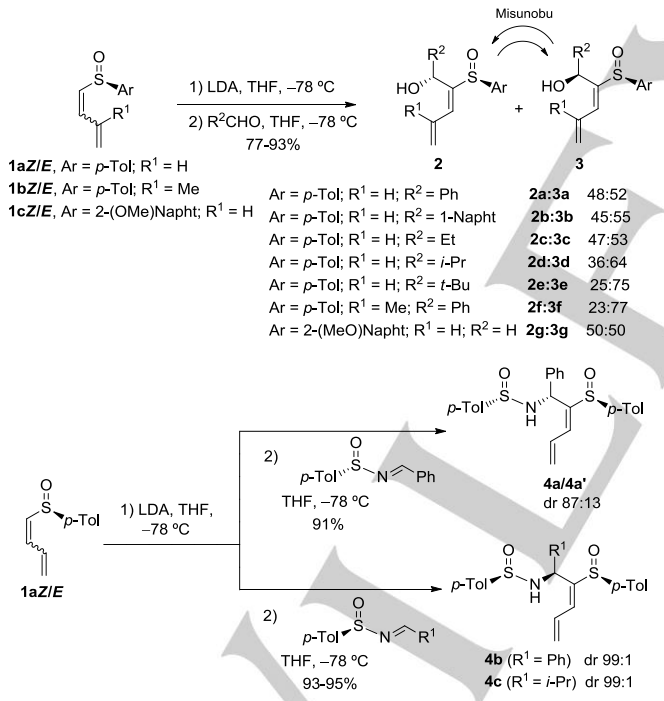
Supporting information and the ORCID identification number(s) for the author(s) of this article is available on the WWW under

10.1002/chem.201905742

produce highly enantioenriched 1,4-diols and 1,4-aminoalcohols, via [2,3]-sigmatropic rearrangement of an in-situ generated allylic sulfoxide (Scheme 1).[15] This transformation renders a net chemo- and stereoselective 1,2-difunctionalization of the terminal double bond in a sulfinyl 1,3-diene, along with removal of the chiral auxiliary.

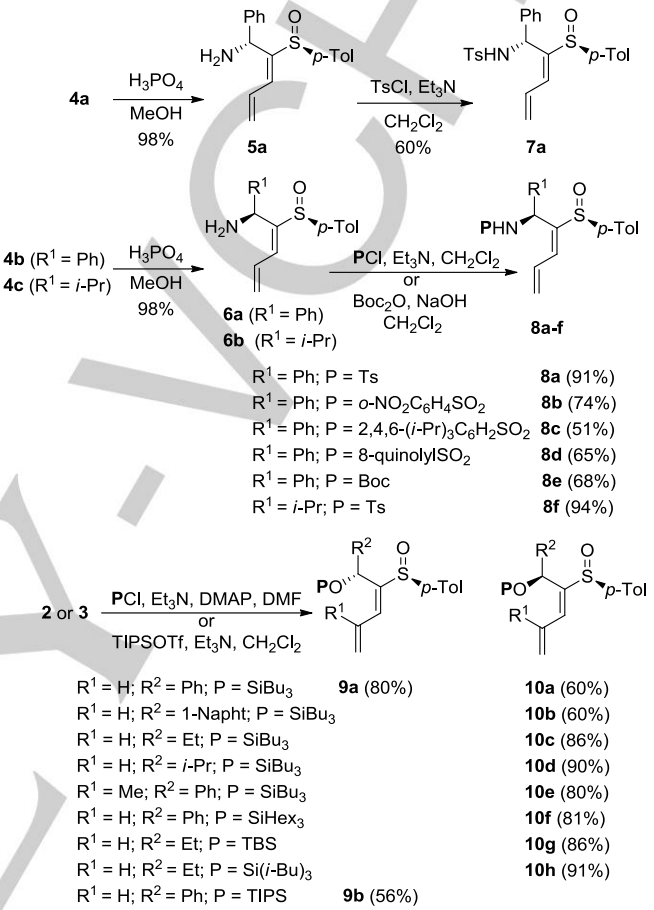
Results and Discussion

Synthesis of starting materials: Enantiopure sulfinyl dienes **1a–c** were prepared as a mixture of *Z*/*E* isomers from the corresponding menthyl sulfinate (Scheme 2).[16] Lithiation of the *Z*/*E* mixture of **1a–c** at low-temperature took place with concomitant isomerization to the *E* lithiated sulfinyl alkenes that were trapped with the appropriate aldehydes to provide the corresponding α-hydroxy sulfinyl dienes **2a–g** and **3a–g** in good yields with low to moderate diastereoselectivity. A simple chromatographic purification allowed for the separation of **2a–g** and **3a–g**. Moreover, it is worth noting that the configuration of the allylic center that supports the hydroxyl group has been successfully inverted in many examples using Mitsunobu conditions.[17]



Scheme 2. Synthesis of α-hydroxy and α-sulfinamido dienyl sulfoxides.

Analogous α-amino sulfinyl dienes were prepared following a similar strategy, in a process that involves lithiation of *Z*/*E* sulfinyl diene **1a** and trapping with the appropriate sulfinimine to obtain sulfinamides **4a-c** with high stereocontrol.[18] Subsequent deprotection (Scheme 3) affords amines **5a**, **6a** and **6b**. Finally, installing different protecting groups on nitrogen gives rise to a variety of dienyl sulfoxides **7a** and **8a-f**. On the other hand, protection of diastereoisomeric alcohols **2** and **3** affords silyl ethers **9** and **10**, respectively, with very good yields, using the appropriate silyl chloride or triflate and Et_3N.



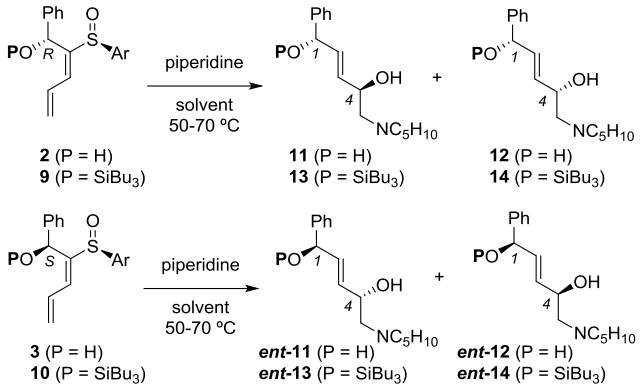
Scheme 3. Synthesis of α-amido and α-silyloxy dienyl sulfoxides.

Searching for optimal conditions: Our study started by examining the reactivity of diastereomeric α-hydroxy dienes with an aromatic allylic substituent, **2a** (Table 1, entries 1-3) and **3a** (Table 1, entries 4-6), using different solvents (ethanol, toluene and DMF). At this stage, we selected piperidine for its versatile role as a good nucleophile to trigger the initial step, but also as an excellent thiophile to promote sulfenate cleavage in the final stage. In all cases we observed the expected 1,4-diol product in good to excellent yields. Using the *S* isomer, **3a**, an almost equimolecular mixture of *anti*/*syn* 1,4-diols was obtained, regardless of the solvent (Table 1, entries 4-6). In sharp contrast, the *R* isomer, **2a**, in toluene afforded a 90:10 ratio of diastereoisomers, with *anti* **11a** being the major one (Table 1, entry 2).

10.1002/chem.201905742

FULL PAPER

Table 1. Screening of solvents and sulfinyl substitution.



entry	SM (Ar, P)	Solvent	Major Product	*anti*/*syn* dr[a] (yield %)[b]
1	**2a** (*p*-Tol, H)	EtOH	**11a**	60:40 (89)
2		toluene	**11a**	90:10 (97)
3		DMF	**11a**	80:20 (72)
4	**3a** (*p*-Tol, H)	EtOH	***ent*-11a**	55:45 (90)
5		toluene	***ent*-12a**	35:65 (78)
6		DMF	***ent*-12a**	40:60 (90)
7	**9a** (*p*-Tol, $SiBu_3$)	EtOH	**13a**	60:40 (88)
8		toluene	**13a**	60:40 (93)
9		DMF	**13a**	82:18 (91)
10	**10a** (*p*-Tol, $SiBu_3$)	EtOH	***ent*-13a**	90:10 (92)[c]
11		toluene	***ent*-13a**	85:15 (92)
12		DMF	***ent*-13a**	78:22 (92)
13	**2g** (2-MeONaph, H)	EtOH	**12a**	40:60 (89)
14		toluene	**11a**	75:25 (90)
15	**3g** (2-MeONaph, H)	EtOH	***ent*-12a**	25:75 (95)
16		toluene	***ent*-11a**	60:40 (92)

[a] Ratio determined by ^{1}H NMR analysis. [b] Combined yield. [c] Absolute configuration at C-4 was determined by derivatization as (*S*)-MPA esters **15** and **16** (see Supporting Information for details).

To evaluate the effect that protecting the hydroxyl moiety could have on the outcome of the reaction, silyl ethers **9a** (Table 1, entries 7-9) and **10a** (Table 1, entries 10-12) were tested using the same solvents. For the *R* isomer **9a**, a low diastereoselectivity (d.r. 60:40) was observed both in ethanol and toluene, while this stereocontrol is increased up to 82:18 in DMF. Interestingly, the *S* isomer, **10a**, participated in a remarkably stereoselective process in ethanol, leading to monoprotected *anti* 1,4-diol ***ent*-13a** in 90:10 dr (Table 1, entry 10). Finally, to examine the influence that the substitution on the sulfinyl group could have on the stereoselection, 2-methoxynaphthylsulfinyl derivatives **2g** and **3g** were prepared. Unfortunately, they did not improve the results mentioned above (Table 1, entries 13-16).[19] In summary, *anti* 1,4-diol **11** can be obtained in very high yield and stereoselectivity from dienol **2** using toluene (Table 1, entry 2). Alternatively, the monoprotected enantiomer ***ent*-13** can be accessed by reacting silyl ether **10** in ethanol (Table 1, entry 10).

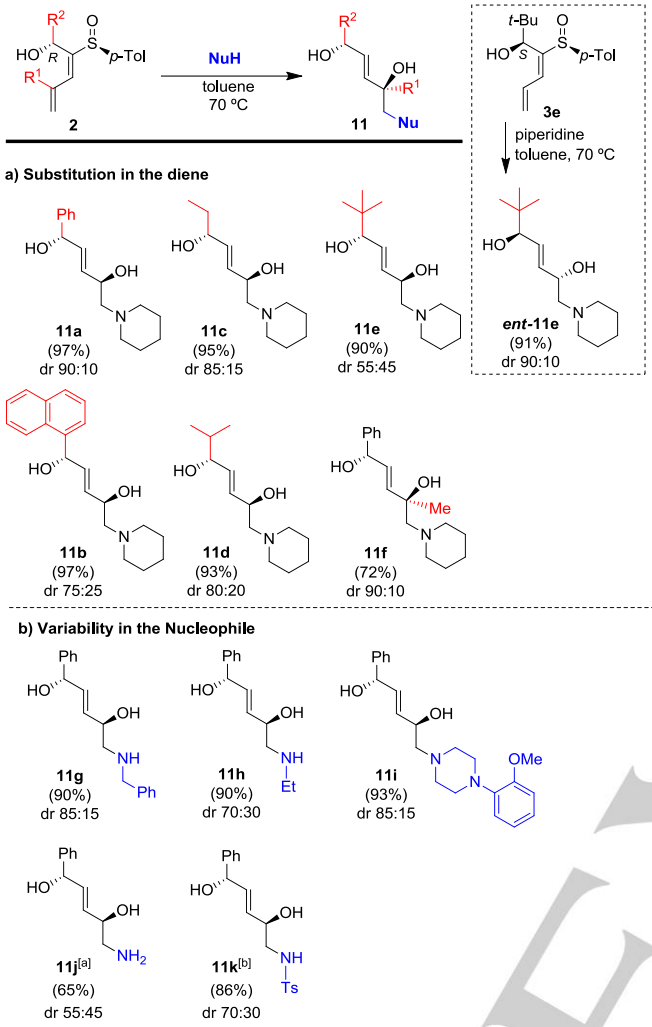
It should be pointed out that, through these preliminary studies, at short reaction times, small amounts of alkenyl sulfoxides of general structure **B'** (Scheme 1) were frequently isolated, leading to 1,4-diol derivatives **D** under the reaction conditions.

Scope of the reaction: With these optimal conditions in hand, we examined the scope of this new transformation. We first evaluated the effect of substitution at the allylic carbon (R^2) and at the internal position of the diene (R^1) using the *R* isomer of α-hydroxy dienes **2** in toluene (Scheme 4). The transformation is compatible with aromatic allylic substitution such as a phenyl ring for model substrate (**11a**) and a 1-naphthyl moiety as well, although with some loss of stereoselectivity (**11b**). Regarding aliphatic substitution, both linear (**11c**, R^2 = Et) and branched aliphatic chains (**11d**, R^2 = *i*-Pr) can be introduced with high yields and moderate stereocontrol. Bulkier aliphatic substitution (**11e**, R^2 = *t*-Bu) does not prevent the reaction but the stereoselectivity of the process is severely reduced. Interestingly, diastereoisomeric substrate **3e** afforded the complementary *anti* 1,4-diol ***ent*-11e** with remarkable selectivity.

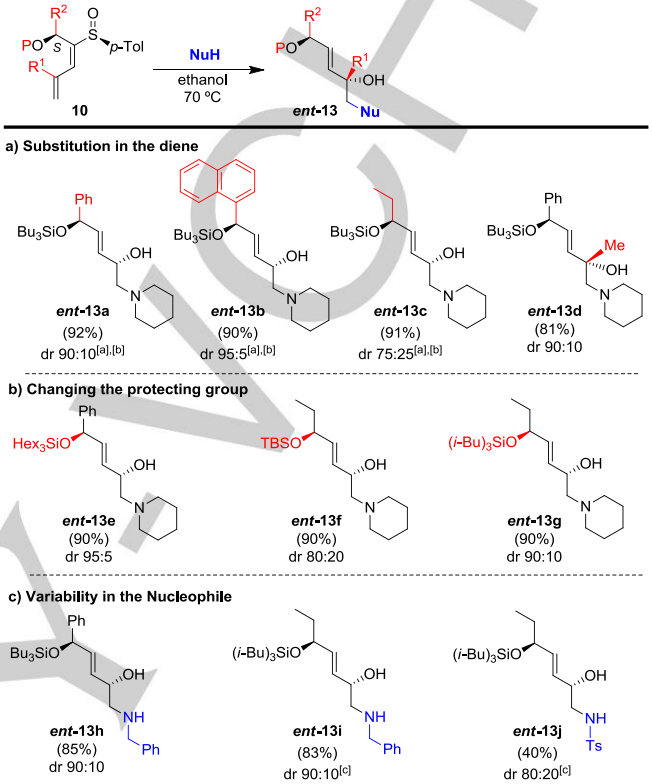
Regarding internal substitution at the diene (R^1 = Me), tertiary alcohol **11f** was obtained with excellent yield and stereoselectivity. This result increases the utility of this method, considering the challenging preparation of optically pure tertiary alcohols.

We then turned our attention to study the scope of the nucleophile that triggers the cascade reaction by initial conjugate addition onto the dienyl sulfoxide. Primary amines, such as benzylamine or ethylamine, as well as functionalized secondary amines are well tolerated, providing *anti* 1,4-diols **11g**, **11h** and **11i** respectively in very good yields with slightly diminished diastereoselectivity (Scheme 4). The challenging use of *p*-toluenesulfonamide, with reduced nucleophilicity, or aqueous ammonia allows to expand the scope of the method, although the latter lacks the desired level of stereoselectivity, probably due to the highly polar aqueous co-solvent introduced (Scheme 4, **11j** and **11k**).

10.1002/chem.201905742



Scheme 4. Scope for the synthesis of *anti* 5-amino-1,4-diols **11** from dienols **2**. [a] THF was used as solvent. [b] DMF was used as solvent.



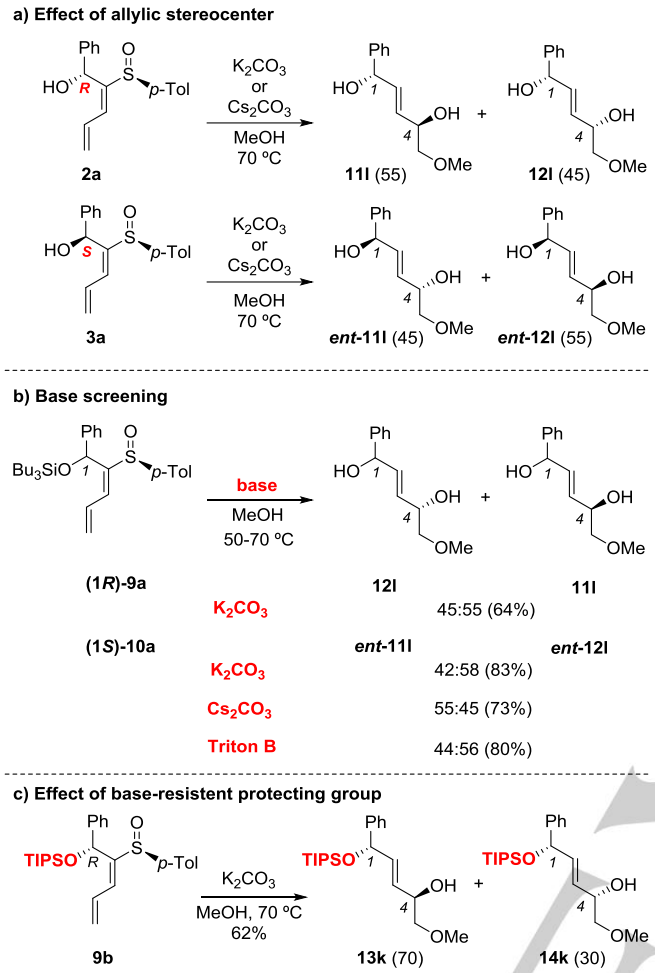
Scheme 5. Scope for the synthesis of monoprotected *anti* 1,4-diols ***ent*-13** from silyloxy dienes **10**. [a] Desilylation of ***ent*-13a-c** provides ***ent*-11a-c** in good yields. [b] The absolute configuration was determined from the MPA esters **15** and **16**. (see Supporting Information). [c] 3 equiv of DBU was added.

Turning our attention to the *S* isomer of silyloxy dienes **10**, and carrying out the reaction in ethanol, both aromatic and aliphatic groups at the allylic position are well tolerated (Scheme 5). Besides the model substrate with a phenyl ring (Scheme 5, ***ent*-13a**), the 1-naphthyl derivative shows an extremely high stereocontrol (Scheme 5, ***ent*-13b**). Aliphatic substitution brings about a significant erosion of the diastereomeric ratio (Scheme 5, ***ent*-13c**). Nevertheless, this problem can be overcome by using a more hindered silyl-protecting group, increasing the diastereoselectivity from 75:25 up to 90:10 ratio (Scheme 5, ***ent*-13c** vs ***ent*-13f** and ***ent*-13g**). Similarly, the size of the silyloxy group leads to higher diastereoselectivity (95:5) for aromatic substituted substrates (Scheme 5, ***ent*-13a** vs ***ent*-13e**). As a remarkable example, enantiopure tertiary alcohol ***ent*-13d** can be obtained in good yield and selectivity.

Finally using benzylamine and *p*-toluenesulfonamide, either with aromatic or aliphatic derivatives, smoothly led to the desired silyloxy amino alcohols in high yield and stereoselectivity (Scheme 5 ***ent*-13h**, ***ent*-13i** and ***ent*-13j**).

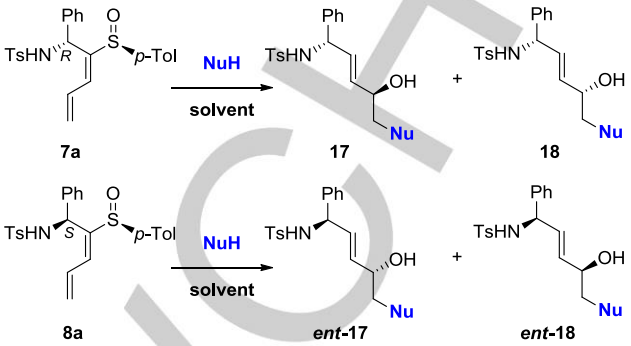
In an effort to extend this method to other nucleophiles, we explored the use of alcohols as solvents and as the nucleophilic initiators of the cascade process under basic conditions. The treatment of diastereomers **2a** and **3a** in MeOH with the addition of inorganic bases (K_2CO_3 or Cs_2CO_3) produced the expected 1,4-diols **11** and **12**, however with no diastereocontrol (Scheme 6a). Inspired by the results presented above, where silyloxy dienes **10** in EtOH gave the best results with amines (Scheme 5), we examined the reaction of silyl ethers **9a** and **10a** under identical conditions. Although the reactions worked nicely, unfortunately we obtained, an equimolecular mixture of diastereoisomers of the same 1,4-diols, presumably as a result of initial deprotection of the silyl ether to generate alcohols **2a** and **3a** and subsequent cascade reaction (Scheme 6b). Exploring different organic or inorganic bases did not overcome this problem (Triton B, NaOMe, DABCO, etc.). However, the use of a more robust protecting group **9b** (TIPS) avoids the undesired deprotection, and the monoprotected *anti* 1,4-diol **13k** is obtained in good yield with improved stereocontrol (Scheme 6c).

10.1002/chem.201905742



Scheme 6. Scope for the synthesis of 5-methoxy 1,4-diols **11-14** from dienols **2-3** and silyloxy dienes **9-10**.

Table 2. Screening of solvents and nucleophiles for the synthesis of 1,4-aminoalcohols.



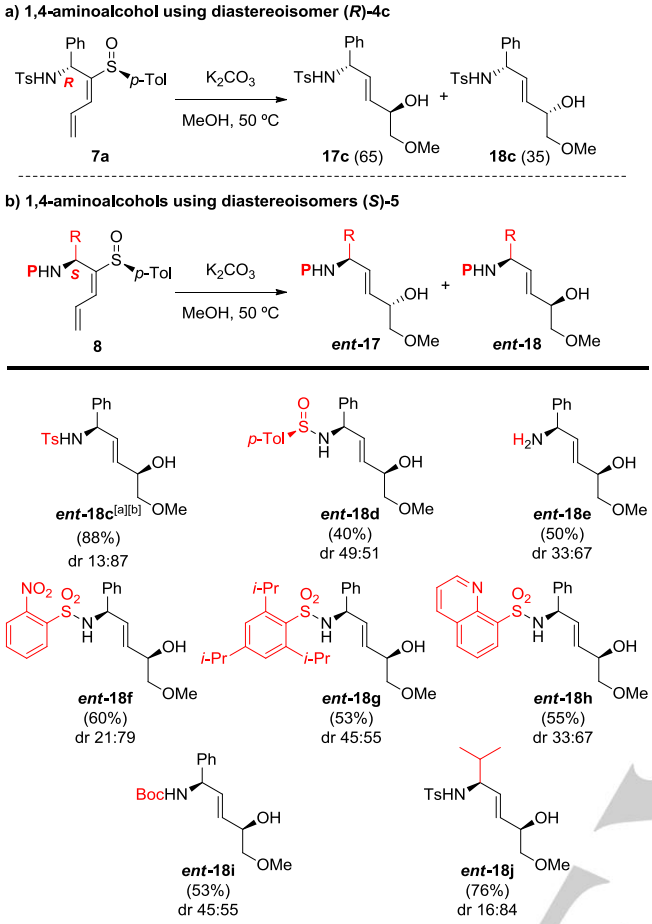
entry	SM	NuH	Solvent	Major Product	*anti*/*syn* dr (yield %)[a], [b]
1	**7a**	Piperidine	toluene	**17a**	83:17 (70) [c]
2	**8a**			***ent*-17a**	70:30 (79)
3	**7a**		EtOH	**17a**	64:36 (85)
4	**8a**			***ent*-17a**	60:40 (88)
5	**7a**	$BnNH_2$	EtOH	**17b**	78:22 (73)
6	**8a**			***ent*-18b**	43:57 (94)

[a] Ratio determined by ^1H NMR analysis. [b] Combined yield. [c] Absolute configuration at C-4 was determined by derivatization with (*S*)-MPA to **15** and **16** (see Supporting Information).

While we have shown that it is possible to access a wide number of 1,4-diols starting from readily available α-hydroxy sulfinyl dienes, we thought that this method could be even more general and powerful by installing different functional groups at the allylic position. For example, from the related α-amino sulfinyl dienes we could access the challenging and much less explored 1,4-aminoalcohol motif. Thus, we performed a quick screening of solvents and nucleophiles on both diastereoisomers of *N*-tosyl aminodienes (**7a** and **8a**). The reaction with piperidine as nucleophile, for both isomers, led to the *anti* 1,4-aminoalcohols (**17** and ***ent*-17** respectively) as the major products in high yields with moderate to good diastereocontrol (Table 2, entries 1-4). The reactions in toluene showed better selectivities than those in ethanol (Table 2, entries 1-2 vs entries 3-4), with a clear reinforcing effect for the *R* isomer, **7a**, compared to the *S* isomer, **8a** (Table 2, entry 1 vs 2). This effect becomes more pronounced when using $BnNH_2$ as nucleophile in EtOH (Table 2, entries 5-6).

Turning our attention to the use of methanol under basic conditions, as a model of oxygen-based nucleophiles, and using aminodiene **7a** we observed an enriched mixture of the expected *anti* 1,4-aminoalcohol **17c** (Scheme 7a). However, when reacting its diastereoisomer **8a**, *syn* 1,4-aminoalcohol ***ent*-18c** was unexpectedly obtained with a remarkably reinforcing effect (judged by the high 13:87 dr vs. 65:35 for **17c**). Having established the viability of this new method to achieve the synthesis of 1,4-aminoalcohols, we examined the effect that the protecting group on nitrogen could have on the outcome of the reaction (Scheme 7b). Modifying the *N*-Ts protecting group and using other sulfonamides ***ent*-18f-h**, sulfinamide ***ent*-18d**, carbamate ***ent*-18i** or the free amine ***ent*-18e** do not improve the diastereoselectivity of the process. Finally keeping the *N*-Ts protecting group we evaluated aliphatic substitution at the allylic position with similar results to the aromatic one (Scheme 7b, ***ent*-18j**).

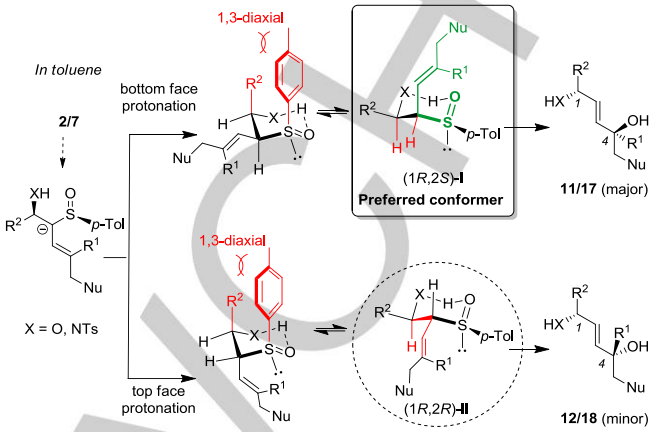
10.1002/chem.201905742



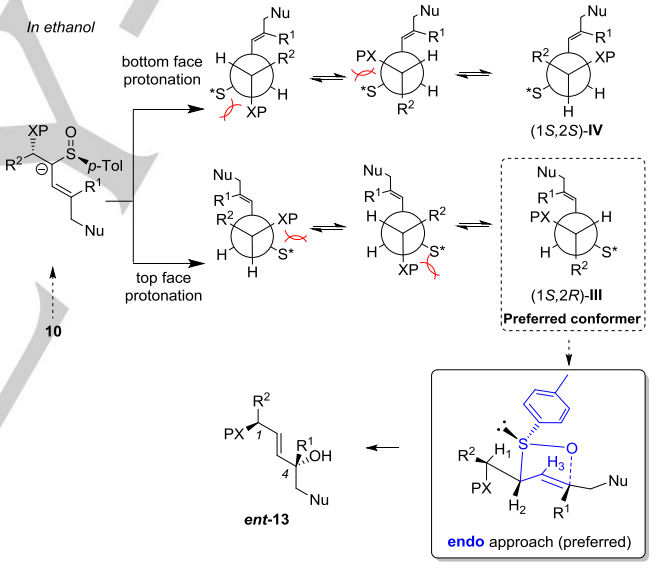
Scheme 7. Scope for the synthesis of 5-methoxy *syn* 1,4-aminoalcohols ***ent*-18** from aminodienes **8**. [a] The absolute configuration at C4 was determined by derivatization with (*S*)- or (*R*)-MPA to afford **15** and **16**. [b] Mono- and bis-acetylation of ***ent*-18c** yielded **19** and **19'** used for structural elucidation (see Supporting Information).

Stereochemical outcome: Our proposal to account for the stereochemical outcome of the process for the synthesis of *anti* 1,4-diols **11** and *anti* 1,4-aminoalcohols **17** starting from (*R*) dienes (**2** or **7a** respectively), is shown in Scheme 8. In toluene, an intramolecular hydrogen bond between the sulfoxide and the OH/NHTs group would determine the major chair-like six-membered conformation for the allylic sulfoxides generated from **2/7**, resulting in conformer (1*R*,2*S*)-**I** being more favored than (1*R*,2*R*)-**II**. Subsequent sigmatropic rearrangement would lead predominantly to *anti* 1,4-diols **11**, or *anti*-1,4-aminoalcohol **17c**.[20]

Our rationalization for the results obtained from silyl ethers **10** is shown in scheme 9. In ethanol, gauche interactions between the groups on the C1-C2 bond would be responsible for the relative stability of silylated allylic sulfoxides (1*S*,2*R*)-**III** vs. (1*S*,2*S*)-**IV**. In addition, the strain is minimized in reactive conformer (1*S*,2*R*)-**III**, by eclipsing H_3 and H_1 and the position of the sulfur *p*-tolyl group leads to a more favored endo approach for the subsequent sulfoxide-sulfenate rearrangement to give *anti* ***ent*-13** with high diastereoselectivity (Scheme 9).



Scheme 8. Stereochemical outcome for the synthesis of 1,4-diols **11**.

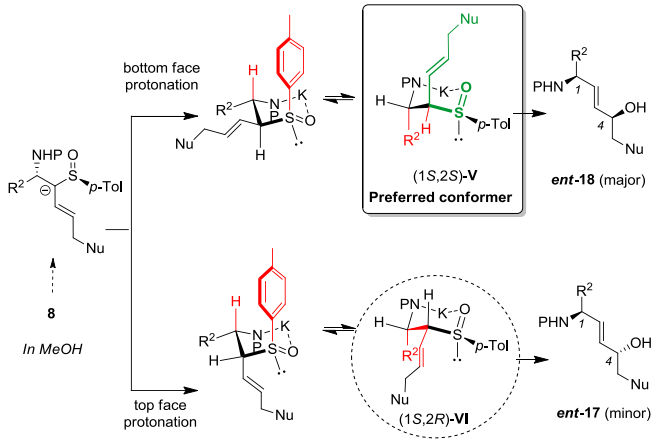


Scheme 9. Stereochemical outcome for the synthesis of 1,4-silyloxyalcohols ***ent*-13**.

Finally, the *syn* selective synthesis of 1,4-aminoalcohols ***ent*-18** from (*S*) amino dienes **8** in MeOH with K_2CO_3 could be understood by considering the acidity of the sulfonamide proton, and the ability to form a chelated transition state, involving the sulfoxide, the nitrogen and the cation (K^+). While amino diene **7a** would represent the non-reinforcing isomer, following the outcome in Scheme 8, leading to anti 1,4-aminoalcohol **17c**, diastereomeric aminodiene **8** is the reinforcing isomer. The major chair-like six-membered conformation for the allylic sulfoxides generated from **8**, results in conformer (1*R*,2*S*)-**V** to be more favored than (1*R*,2*R*)-**VI** (Scheme 10). Subsequent sigmatropic

10.1002/chem.201905742

rearrangement would lead predominantly to *syn* 1,4-aminoalcohol ***ent*-18**.

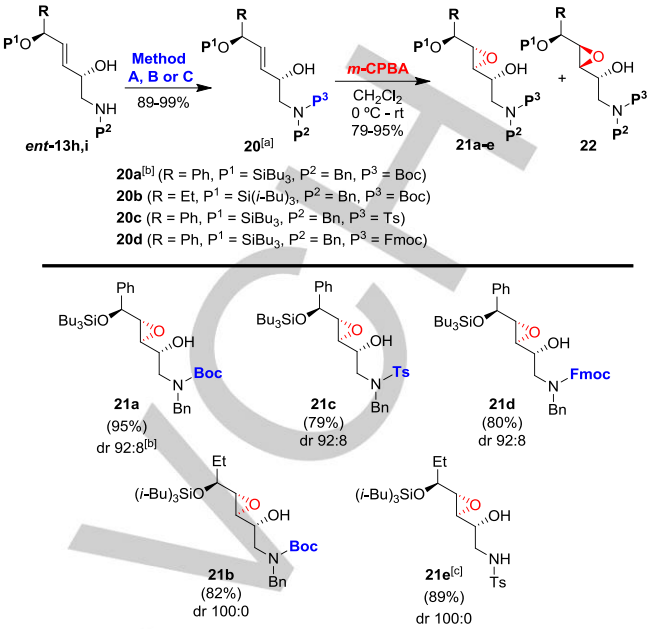


Scheme 10. Stereochemical outcome for the synthesis of 1,4-aminoalcohols ***ent*-18**.

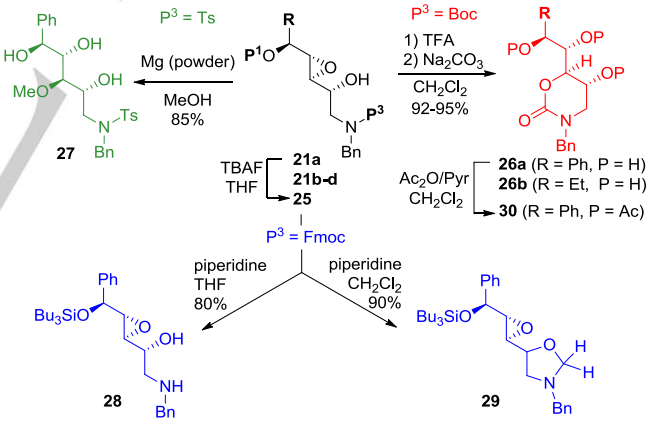
Reactivity of 1,4-diols: To take advantage of these valuable densely functionalized structures we decided to explore the reactivity of the double bond in two fundamental processes in organic chemistry such as epoxidation and dihydroxylation. We selected monoprotected *anti* 1,4-diols ***ent*-13h** and ***ent*-13i** (with aromatic and aliphatic allylic substitution, respectively) as representative examples. We first explored the viability of protecting the amine as carbamate (**20a**, **20b** and **20d**) or sulfonamide (**20c**) under standard conditions (Scheme 11). The epoxidation was examined next and the treatment of **20a**, **20c** and **20d** (with aromatic allylic substitution) with *m*-CPBA afforded epoxides **21a**, **21c** and **21d** with high stereocontrol (dr 92:8) and excellent yields (Scheme 11). Epoxidation of *N*-Boc carbamate **20b** and *N*-Ts monoprotected 1,4-diol ***ent*-13j** under the same conditions gave epoxides **21b** and **21e** in good yields, as single detectable diastereoisomers.[21]

Encouraged by the synthetic potential of these highly functionalized epoxy diol derivatives **21**, we examined further stereoselective modifications at the epoxide and amino moieties. Thus, treatment of **21a**, **21b** and desilylated **25** with TFA and then with base provided 1,3-oxazin-2-ones **26a,b** regio- and stereoselectively, via a nucleophilic attack of the carbamate oxygen onto the epoxide (Scheme 12).[22] Acetylation of **26a** under standard conditions gave peracetylated compound **30** that was useful to assign the relative stereochemistry. Alternative treatment of **21c** with Mg (powder) in MeOH resulted in silyl ether deprotection followed by regio- and stereoselective epoxide opening, presumably by $Mg(OMe)_2$ formed in situ, via a chelated intermediate, to afford monoprotected polyol **27** (Scheme 12).

Finally, deprotection of the Fmoc derivative **21d** under standard conditions with piperidine in THF gave amine **28** in good yields. In sharp contrast, the use of piperidine in CH_2Cl_2, unexpectedly, led to oxazolidine **29**, in excellent yield with incorporation of the methylene unit from the solvent under mild conditions.[23]



Scheme 11. Protection of *anti* 1,4-diols ***ent*-13** and highly stereoselective epoxidation. Method A: Boc_2O, DIPEA, MeCN. Method B: Fmoc-Cl, Et_3N, CH_2Cl_2. Method C: TsCl, Et_3N, THF. [a] Minor diastereoisomer **20'** was also isolated. [b] To support structural elucidation, **20a** was acetylated and desilylated to render **23a** and **24** (see Supporting Information). [c] ***ent*-13j** was used as starting material.

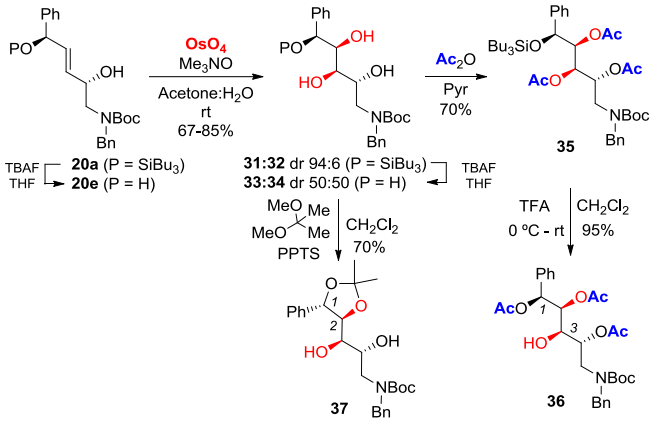


Scheme 12. Reactivity of 2,3-epoxy 1,4-diol derivatives.

Alternatively, the dihydroxylation of **20a**, for which a nonreinforcing array of allylic oxygenated stereocenters was initially expected, under standard conditions, gave triol **31** with excellent yield and very high diastereoselectivity (**31**:**32**, 94:6, Scheme 13).[24] This selectivity in the dihydroxylation of an acyclic substrate is remarkable particularly compared with the analogous dihydroxylation of 1,4-diol **20e** (prepared by deprotection of **20a**) that affords **33** and **34** as a 50:50 mixture of diastereoisomers (Scheme 13). A reasonable explanation for this result, based on steric effects, could be found in a zig-zag arrangement of the carbon chain, where the bulky silyl group would be in the same

10.1002/chem.201905742

plane of the chain. In that scenario, OsO_4 would approach from the opposite face of the hydroxy group at C-4, in an *anti* fashion. In order to confirm the configuration of the new stereocenters cyclic 1,3-dioxolane **37** was synthesized and a detailed NMR study was performed,[25] in which the coupling constant ($J_{1,2}$ = 8.9 Hz) revealed a *trans* configuration at C1-C2.[26] It is important to emphasize that **31** presents a complementary relative stereochemistry to that of **27** (Scheme 12). This stereodivergency is a noteworthy accomplishment of our methodology.



Scheme 13. Highly stereoselective dihydroxylation of 1,4-diol derivatives.

Finally, acetylation of triol **31** gave peracetylated compound **35** that, under acidic conditions seeking concurrent *N*-Boc cleavage and silyl deprotection, interestingly, gave rise to mono unprotected polyol **36**, by selective silyl ether deprotection and an unexpected complete acetyl migration from C3 to C1.
It is worth emphasizing the importance of these methodologies that allow for the full functionalization of dienes **10** in a very short and straightforward sequence (2-3 steps) and in a highly stereoselective manner (4 new C-heteroatom bonds and 3 stereogenic centers).[27]

Conclusions

In summary, a new general method for the synthesis of 1,4-diols and 1,4-aminoalcohols from conjugated sulfinyl dienes has been reported. This is the result of a cascade reaction encompassing a conjugate addition followed by diastereoselective protonation to an allylic sulfoxide and a [2,3]-sigmatropic rearrangement. The process has been studied in depth and the advantages and limitations for a numerous collection of compounds covering a wide structural scope have been defined. This process is compatible with both aliphatic and aromatic substitution in the diene moiety, and both oxygen- and nitrogen-based nucleophiles are competent initiators of the sequence. Furthermore, the reactivity of the resulting unsaturated 1,4-diols towards epoxidation and dihydroxylation has been explored with excellent results.

Experimental Section

General procedure for the synthesis of 5-amino-1,4-diols.

To a solution of 1.0 equiv of α-hydroxy sulfinyl diene in toluene, ethanol or DMF, 5.0 equiv of amine (NuH) were added. The mixture was stirred at 70 ºC and monitored by TLC until completion. Then, the solvent was evaporated under reduced pressure to give the corresponding alcohol that was purified by chromatography on silica gel using the appropriate mixture of eluents.

Synthesis of (–)-(1*S*,2*E*,4*R*)-1-Phenyl-5-(piperidin-1-yl)pent-2-ene-1,4-diol, 11a, and (1*S*,2*E*,4*S*)-1-Phenyl-5-(piperidin-1-yl)pent-2-ene-1,4-diol, 12a.

From α-hydroxy sulfinyl diene **2a** (45 mg, 0.15 mmol, 1.0 equiv) and piperidine (75 µL, 64 mg, 0.75 mmol, 5.0 equiv), in toluene, according to the general procedure (2 d) and after chromatographic purification (CH_2Cl_2 – 50% EtOH-CH_2Cl_2), a 90:10 mixture of alcohols **11a:12a** was obtained as a yellow oil (37 mg, 97%). Data for **11a** (from the mixture): R_f 0.20 (50% EtOH-CH_2Cl_2). **[α]$^{20}_D$** –13.3 (*c* = 0.50). **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 1.38-1.44 (m, 2 H, CH_2 piperidine), 1.49-1.60 (m, 4 H, 2 x CH_2 piperidine), 2.23-2.32 (m, 3 H, H-5a + CH_2 piperidine), 2.34 (dd, 1 H, *J* = 12.4, 3.7 Hz, H-5b), 2.57 (br s, 2 H, CH_2 piperidine), 4.15-4.18 (m, 1 H, H-4), 5.19 (d, 1 H, *J* = 6.1 Hz, H-1), 5.70 (ddd, 1 H, *J* = 15.5, 6.0, 1.2 Hz, H-3), 5.95 (ddd, 1 H, *J* = 15.4, 6.1, 1.2 Hz, H-2), 7.23-7.26 (m, 1 H, Ph), 7.30-7.35 (m, 4 H, Ph). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 24.2 (CH_2 piperidine), 26.0 (2 x CH_2 piperidine), 54.4 (2 x CH_2 piperidine), 64.3 (C-5), 66.6 (C-4), 74.3 (C-1), 126.30 (2 x Ph), 127.6 (Ph), 128.46 (2 x Ph), 131.3 (C-3), 133.7 (C-2), 142.7 (Ph). **IR** (film): 3391, 2938, 1639, 1562, 1493, 1452, 1413, 1267, 1034, 973, 758, 736, 701 cm^{-1}. **HRMS** (ES) m/z calcd for $C_{16}H_{24}NO_2$ $[M+H]^+$ 262.1807, found 262.1804. Partial data for **12a** (from the mixture): R_f 0.20 (50% EtOH-CH_2Cl_2). The NMR signals overlapped with those of **11a**, except for **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 5.67 (ddd, 1 H, *J* = 15.5, 6.0, 1.2 Hz, H-3), 5.94 (ddd, 1 H, *J* = 15.4, 6.1, 1.2 Hz, H-2). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 64.27 (C-5), 66.7 (C-4), 74.4 (C-1), 127.57 (Ph), 128.4 (2 x Ph), 133.9 (C-2).

General procedure for the synthesis of 5-amino-1-silyloxy-4-alcohols.

To a solution of 1.0 equiv of α-silyloxy sulfinyl diene in ethanol, toluene or DMF, 5.0 equiv of amine (NuH) was added. The mixture was stirred at 70 ºC and monitored by TLC until completion. Then, the solvent was evaporated under reduced pressure to give the corresponding alcohol, that was purified by chromatography on silica gel using the appropriate mixture of eluents.

Synthesis of (+)-(2*S*,3*E*,5*R*)-5-Phenyl-1-(piperidin-1-yl)-5-(tributylsilyloxy)pent-3-en-2-ol, *ent*-13a, and (2*R*,3*E*,5*R*)-5-Phenyl-1-(piperidin-1-yl)-5-(tributylsilyloxy)pent-3-en-2-ol, *ent*-14a.

From α-silyloxy sulfinyl diene **10a** (40 mg, 0.09 mmol, 1.0 equiv) and piperidine (45 µL, 38 mg, 0.45 mmol, 3.0 equiv), in ethanol, according to the general procedure (5 d) and after chromatographic purification (CH_2Cl_2 – 10% EtOH-CH_2Cl_2), a 90:10 mixture of alcohols ***ent*-13a:*ent*-14a** was obtained as a colorless oil (29 mg, 92%). Data for ***ent*-13a** (from the mixture): R_f 0.29 (5% EtOH-CH_2Cl_2). **[α]$^{20}_D$** +22.6 (*c* = 0.27). **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 0.51-0.58 (m, 6 H, 3 x CH_2 *n*-Bu), 0.82 (t, 9 H, *J* = 6.8 Hz, 3 x CH_3 *n*-Bu), 1.19-1.28 (m, 12 H, 6 x CH_2 *n*-Bu), 1.39-1.45 (m, 2 H, CH_2 piperidine), 1.51-1.62 (m, 4 H, 2 x CH_2 piperidine), 2.25-2.35 (m, 4 H, CH_2 piperidine + H-1), 2.59 (m, 2 H, CH_2 piperidine), 4.15 (m, 1 H, H-2), 5.13 (d, 1 H, *J* = 6.1 Hz H-5), 5.61 (ddd, 1 H, *J* = 15.3, 6.1, 1.1 Hz, H-3), 5.81 (ddd, 1 H, *J* = 15.4, 6.1, 1.0 Hz, H-4), 7.18-7.21 (m, 1 H, Ph), 7.26-

7.31 (m, 4 H, Ph). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 13.7 (3 x CH_2 *n*-Bu), 13.8 (3 x CH_3 *n*-Bu), 24.1 (CH_2 piperidine), 25.4 (3 x CH_2 *n*-Bu), 25.9 (2 x CH_2 piperidine), 26.6 (3 x CH_2 *n*-Bu), 54.5 (2 x CH_2 piperidine), 64.4 (C-1), 66.7 (C-2), 74.8 (C-5), 126.1 (2 x Ph), 127.0 (Ph), 128.1 (2 x Ph), 129.7 (C-3), 135.2 (C-4), 143.8 (Ph). **IR** (film): 3420, 2958, 2925, 2856, 2802, 1670, 1492, 1454, 1407, 1377, 1261, 1190, 1080, 1026, 963, 887, 797, 698 cm^{-1}. **MS** (ES) m/z 460 $[M+H]^+$ (100%). Partial data for ***ent*-14a** (from the mixture): ***R*$_f$** 0.29 (5% EtOH-CH_2Cl_2). The NMR signals overlapped with those of ***ent*-13a**, except for **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 5.59 (ddd, 1 H, *J* = 15.3, 6.1, 1.1 Hz, H-3), 5.83 (ddd, 1 H, *J* = 15.4, 6.1, 1.0 Hz, H-4). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 126.2 (2 x Ph), 129.5 (C-3).

General procedure for the synthesis of 5-amino-1,4-aminoalcohols.

To a solution of 1.0 equiv of dienyl sulfonamide in toluene or ethanol, 5.0 equiv of amine (NuH) was added. The mixture was stirred at 70 ºC and monitored by TLC until completion. Then, the solvent was evaporated under reduced pressure to give the corresponding alcohol that was purified by chromatography on silica gel using the appropriate mixture of eluents.

Synthesis of (–)-*N*-[(1*S*,2*E*,4*R*)-4-Hydroxy-1-phenyl-5-(piperidin-1-yl)pent-2-en-1-yl]-*p*-tolylsulfonamide, 17a, and *N*-[(1*S*,2*E*,4*S*)-4-Hydroxy-1-phenyl-5-(piperidin-1-yl)pent-2-en-1-yl]-*p*-tolylsulfonamide, 18a.

From sulfonamide **7a** (34 mg, 0.075 mmol, 1.0 equiv) and piperidine (37 µL, 32 mg, 0.38 mmol, 5.0 equiv), in toluene, according to the general procedure (2 d) and after chromatographic purification (CH_2Cl_2 – 20% EtOH-CH_2Cl_2), an 83:17 mixture of alcohols **17a:18a** was obtained as a yellow oil (22 mg, 70%). Data for **17a** (from the mixture): ***R*$_f$** 0.14 (20% EtOH-CH_2Cl_2). **$[\alpha]^{20}_D$** –16.2 (*c* = 1.79). **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 1.41 (m, 2 H, CH_2 piperidine), 1.49-1.58 (m, 4 H, 2 x CH_2 piperidine), 2.04 (ap t, 1 H, *J* = 11.4 Hz, H-5a), 2.14 (dd, 1 H, *J* = 12.4, 3.7 Hz, H-5b), 2.26 (m, 2 H, CH_2 piperidine), 2.37 (s, 3 H, CH_3 *p*-Tol), 2.53 (m, 2 H, CH_2 piperidine), 4.02 (m, 1 H, H-4), 4.91 (d, 1 H, *J* = 6.5 Hz, H-1), 5.38 (dd, 1 H, *J* = 15.4, 5.6 Hz, H-3), 5.76 (dd, 1 H, *J* = 15.4, 5.5 Hz, H-2), 7.08-7.11 (m, 2 H, Ph), 7.16-7.19 (m, 5 H, Ph + Ts), 7.60 (d, 2 H, *J* = 8.3 Hz, Ts). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 21.5 (CH_3 *p*-Tol), 24.1 (CH_2 piperidine), 26.0 (2 x CH_2 piperidine), 54.4 (2 x CH_2 piperidine), 59.0 (C-1), 64.0 (C-5), 66.3 (C-4), 127.0 (2 x Ts), 127.17 (2 x Ts), 127.6 (Ph), 128.5 (2 x Ph), 129.4 (2 x Ph), 130.1 (C-2), 133.2 (C-3), 137.69 (Ar), 139.46 (Ar), 143.1 (Ar). **IR** (film): 3272, 3062, 2937, 2857, 1598, 1566, 1494, 1454, 1411, 1325, 1267, 1158, 1093, 1042, 969, 814, 736, 701, 666 cm^{-1}. **HRMS** (ES) m/z calcd for $C_{23}H_{31}N_2O_3S[M+H]^+$ 415.2055, found 415.2062. Partial data for **18a** (from the mixture): ***R*$_f$** 0.14 (20% EtOH-CH_2Cl_2). The NMR signals overlapped with those of **17a**, except for **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 2.15 (dd, 1 H, *J* = 12.4, 3.7 Hz, H-5b), 4.93 (d, 1 H, *J* = 5.9 Hz, H-1), 5.41 (dd, 1 H, *J* = 15.4, 5.6 Hz, H-3), 5.77 (dd, 1 H, *J* = 15.4, 5.5 Hz, H-2). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 58.9 (C-1), 64.0 (C-5), 127.1 (Ts x 2), 127.16 (Ts x 2), 127.6 (Ph), 132.9 (C-3), 137.74 (Ar), 139.54 (Ar).

General procedure for the synthesis of 5-methoxy-1,4-aminoalcohols.

To a solution of 1.0 equiv of amide or amine **7/8** in methanol, 3.0 equiv of Cs_2CO_3 or K_2CO_3 was added. The mixture was stirred at 50 ºC and monitored by TLC until completion. Then, the solvent was evaporated under reduced pressure to give the alcohol **17/18** that was purified by chromatography on silica gel using the appropriate mixture of eluents.

Synthesis of (+)-*N*-[(1*R*,2*E*,4*R*)-4-Hydroxy-5-methoxy-1-phenylpent-2-en-1-yl]-*p*-tolylsulfonamide, *ent*-17c, and *N*-[(1*R*,2*E*,4*S*)-4-Hydroxy-5-methoxy-1-phenylpent-2-en-1-yl]-*p*-tolylsulfonamide, *ent*-18c.

From sulfonamide **8a** (40 mg, 0.09 mmol, 1.0 equiv) and Cs_2CO_3 (87 mg, 0.27 mmol, 3.0 equiv), according to the general procedure (5 d) and after chromatographic purification (30 – 80% EtOAc-CH_2Cl_2), a 22:78 mixture of alcohols ***ent*-17c:*ent*-18c** was obtained as a colorless oil (28 mg, 88%). Further crystallization (1:2 EtOAc-hexane) of the fraction yielded a diastereomerically enriched mixture of alcohols (13:87). Data for ***ent*-18c** (from the mixture): ***R*$_f$** 0.17 (30% EtOAc-CH_2Cl_2). **$[\alpha]^{20}_D$** +24.6 (*c* = 0.39). **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 1.62 (br s, 1 H, OH), 2.38 (s, 3 H, Me *p*-Tol), 3.09 (dd, 1 H, *J* = 9.5, 8.1 Hz, H-5a), 3.28 (dd, 1 H, *J* = 9.5, 3.3 Hz, H-5b), 3.34 (s, 3 H, OMe), 4.19-4.22 (m, 1 H, H-4), 4.81 (d, 1 H, *J* = 7.0 Hz, NH), 4.93 (ap t, 1 H, *J* = 6.5 Hz, H-1), 5.51 (ddd, 1 H, *J* = 15.4, 5.6, 1.5 Hz, H-3), 5.81 (ddd, 1 H, *J* = 15.4, 6.1, 1.5 Hz, H-2), 7.03-7.10 (m, 2 H, Ar), 7.18-7.22 (m, 5 H, Ar), 7.61 (dt, 2 H, *J* = 8.3, 1.7 Hz, Ar). **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 21.5 (Me *p*-Tol), 58.9 (C-1), 59.0 (OMe), 70.2 (C-4), 76.1 (C-5), 127.0 (2 x Ar), 127.2 (2 x Ar), 127.8 (Ar), 128.7 (2 x Ar), 129.4 (2 x Ar), 130.9 (C-3), 131.2 (C-2), 137.7 (Ar), 139.4 (Ar), 143.2 (Ar). **IR** (film): 3272, 2925, 1598, 1453, 1326, 1158, 1092, 969, 814, 752 cm^{-1}. **MS** (ES) m/z 384 $[M+Na]^+$ (100%). Partial data for ***ent*-18c** (from the mixture): ***R*$_f$** 0.17 (30% EtOAc-CH_2Cl_2). The NMR signals overlapped with those of ***ent*-17c**, except for **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 5.48 (ddd, 1 H, *J* = 15.4, 5.6, 1.5 Hz, H-3).

General procedure for Boc protection of amines.

To a cold solution (0 ºC) of the starting material in CH_3CN (10 mL/mmol) was added DIPEA (1.5 equiv) and Boc_2O (1.2 equiv). The mixture was allowed to warm up to rt and monitored by TLC, until completion (1 h). The crude was concentrated, and then was purified by column chromatography on silica gel using a gradient of the appropriate solvents.

Synthesis of (+)-*tert*-Butyl benzyl [(2*S*,3*E*,5*R*)-2-hydroxy-5-phenyl-5-(tributylsilyloxy)pent-3-en-1-yl]carbamate, 20a, and *tert*-Butyl benzyl [(2*R*,3*E*,5*R*)-2-hydroxy-5-phenyl-5-(tributylsilyloxy)pent-3-en-1-yl]carbamate, 20a'.

From a 90:10 mixture of amino alcohols ***ent*-13h**:***ent*-14h** (172 mg, 0.36 mmol) in CH_3CN (3.6 mL), DIPEA (0.12 mL, 93 mg, 0.72 mmol, 2.0 equiv) and Boc_2O (94.0 mg, 0.43 mmol, 1.2 equiv), following the general procedure, and after chromatographic purification (10-60% EtOAc-hexane) a pure fraction of **20a** (181 mg, 88%) and a mixture of **20a**:**20a'** (10 mg, 4%) was obtained as orange oils. Data for **20a**: ***R*$_f$** 0.34 (20% EtOAc-hexane). **$[\alpha]^{20}_D$** +85.4 (*c* = 2.08). **^{1}H NMR ($CDCl_3$, 400 MHz, 50 ºC)** δ 0.49-0.53 (m, 6 H, 3 x CH_2 *n*-Bu), 0.79 (t, 9 H, *J* = 6.9 Hz, 3 x CH_3 *n*-Bu), 1.17-1.24 (m, 12 H, 6 x CH_2 *n*-Bu), 1.41 (s, 9 H, 3 x CH_3 *t*-Bu), 3.20 (dd, 1 H, *J* = 14.1, 3.1 Hz, H-1a), 3.25-3.45 (m, 1 H, H-1b), 3.45 (br s, 1 H, OH), 4.28 (ddd, 1 H, *J* = 15.5, 10.2, 4.9 Hz, H-2), 4.34-4.48 (m, 2 H, CH_2 benzyl), 5.11 (d, 1 H, *J* = 5.6 Hz, H-5), 5.60 (ddd, 1 H, *J* = 15.4, 5.7, 1.2 Hz, H-3), 5.80 (dd, 1 H, *J* = 15.3, 5.4 Hz, H-4), 7.13-7.16 (m, 2 H, Ar), 7.17-7.21 (m, 1 H, Ar), 7.22 (m, 1 H, Ar), 7.23-7.28 (m, 6 H, Ar). **^{13}C NMR ($CDCl_3$, 100 MHz, 50 ºC)** δ 13.7 (3 x CH_2 *n*-Bu and 3 x CH_3 *n*-Bu), 25.3 (3 x CH_2 *n*-Bu), 26.6 (3 x CH_2 *n*-Bu), 28.3 (3 x CH_3 *t*-Bu), 52.5 (CH_2 benzyl), 53.5 (C-1), 71.7 (C-2), 74.6 (C-5), 80.7 (C *t*-Bu), 126.1 (2 x Ar), 127.1 (4 x Ar), 127.2 (Ar), 128.1 (Ar), 128.5 (2 x Ar), 129.2 (C-3), 135.1 (C-4), 138.1 (Ar), 143.8 (Ar), 157.7 (C=O). **IR** (film): 3434, 3087, 3064, 3030, 2957, 2924, 2871, 1695, 1494, 1455, 1412, 1366, 1297, 1246, 1168, 1130, 1079, 1028, 967, 888, 758, 733, 699 cm^{-1}. **HRMS** (ES) m/z calcd for $C_{35}H_{55}NNaO_4Si$ $[M+Na]^+$ 604.3798, found 604.3816. Partial data for **20a'** (from the mixture): ***R*$_f$** 0.36 (20% EtOAc-hexane).

General procedure for the epoxidation of alkenes.

To a solution of the alkene at 0 ºC in CH_2Cl_2 (10 mL/mmol) *m*-CPBA (70% purity) was added slowly, and the mixture was warmed up to rt. This

mixture was stirred until disappearance (monitored by TLC) of the starting material. The *m*-chlorobenzoic acid (white solid) generated in the reaction was filtered. The resulting solution was treated with a saturated $NaHCO_3$ solution (5 mL/mmol) and H_2O (5 mL/mmol) and diluted with EtOAc (10 mL/mmol). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL/mmol), the combined organic extracts were washed with a saturated $NaHCO_3$ solution (5 mL/mmol), H_2O (5 mL/mmol) and finally with a saturated NaCl solution. The mixture was dried over Na_2SO_4 and was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using a gradient of the appropriate solvents.

Synthesis of (+)-*tert*-Butyl benzyl[(2*R*,3*S*,4*S*,5*S*)-2-hydroxy-5-phenyl-5-(tributylsilyloxy)-3,4-(oxiranyl)pentyl]carbamate, 21a, and *tert*-Butyl benzyl[(2*R*,3*R*,4*R*,5*S*)-2-hydroxy-5-phenyl-5-(tributylsilyloxy)-3,4-(oxiranyl)pentyl]carbamate, 22a.

From carbamate **20a** (46 mg, 0.079 mmol) and *m*-CPBA (21.0 mg, 0.09 mmol, 1.2 equiv) in CH_2Cl_2, according to the general procedure (4 h) and after chromatographic purification (5-50% EtOAc-hexane) a pure fraction of **21a** (42 mg, 89%) and **22a** (3 mg, 6%) was obtained as colorless oils. Data for **21a**: R_f 0.30 (20% EtOAc-hexane). **[α]$^{20}_D$** +35.8 (*c* = 0.21). **^{1}H NMR (CDCl$_3$, 400 MHz, 40 ºC)** δ 0.48-0.53 (m, 6 H, 3 x CH_2 *n*-Bu), 0.81 (t, 9 H, *J* = 6.8 Hz, 3 x CH_3 *n*-Bu), 1.15-1.28 (m, 12 H, 6 x CH_2 *n*-Bu), 1.43 (s, 9 H, 3 x CH_3 *t*-Bu), 3.02-3.05 (m, 2 H, H-3 and H-4), 3.23 (dd, 1 H, *J* = 14.3, 3.5 Hz, H-1a), 3.28-3.47 (br, 1 H, H-1b), 3.72-3.79 (m, 1 H, H-2), 4.34 (m, 2 H, CH_2 benzyl), 4.69 (d, 1 H, *J* = 3.3 Hz, H-5), 7.12-7.19 (m, 2 H, Ar), 7.21-7.32 (m, 8 H, Ar). **^{13}C NMR (CDCl$_3$, 100 MHz, 40 ºC)** δ 13.7 (3 x CH_2 *n*-Bu and 3 x CH_3 *n*-Bu), 25.3 (3 x CH_2 *n*-Bu), 26.5 (3 x CH_2 *n*-Bu), 28.4 (3 x CH_3 *t*-Bu), 49.9 (C-1), 50.5 (CH_2 benzyl), 56.8 and 56.9 (C-3 and C-4), 69.7 (C-2), 72.7 (C-5), 80.6 (C *t*-Bu), 126.4 (2 x Ar), 127.3 (4 x Ar), 127.8 (2 x Ar), 128.3 (Ar), 128.6 (Ar), 138.1 (Ar), 141.3 (Ar), 157.9 (C=O). **IR** (film): 3364, 3065, 2957, 2924, 2872, 1674, 1575, 1488, 1454, 1367, 1251, 1142, 1076, 1028, 888, 753, 701 cm^{-1}. **HRMS** (ES) m/z calcd for $C_{35}H_{55}NNaO_5Si$ [M+Na]$^+$ 620.3747, found 620.3736. Partial data for **22a**: R_f 0.35 (20% EtOAc-hexane). **^{1}H NMR (CDCl$_3$, 400 MHz, 40 ºC)** δ 0.49-0.53 (m, 6 H, 3 x CH_2 *n*-Bu), 0.82 (t, 9 H, *J* = 6.8 Hz, 3 x CH_3 *n*-Bu), 1.17-1.27 (m, 12 H, 6 x CH_2 *n*-Bu), 1.43 (s, 9 H, 3 x CH_3 *t*-Bu), 3.02-3.05 (m, 2 H, H-3 and H-4), 3.23 (dd, 1 H, *J* = 14.5, 3.7 Hz, H-1a), 3.28-3.47 (br, 1 H, H-1b), 3.72-3.79 (m, 1 H, H-2), 4.37-4.51 (m, 2 H, CH_2 benzyl), 4.69 (d, 1 H, *J* = 3.2 Hz, H-5), 7.12-7.19 (m, 2 H, Ar), 7.21-7.32 (m, 8 H, Ar).

General procedure for the synthesis of 1,3-oxazin-2-ones via epoxide opening.

To a solution of the epoxy carbamate at 0 ºC in CH_2Cl_2 (10 mL/mmol) TFA was added slowly. This mixture was stirred until disappearance (monitored by TLC) of the starting material. The resulting solution was treated with a solution of Na_2CO_3 or NaOH (5 mL/mmol) until basic pH=11, and diluted with CH_2Cl_2 (10 mL/mmol). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL/mmol). The mixture was dried over Na_2SO_4 and was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using a gradient of the appropriate solvents.

Synthesis of (+)-(5*R*,6*R*)-3-Benzyl-6-[(1*S*,2*S*)-1,2-dihydroxy-2-phenylethyl]-5-hydroxy-1,3-oxazin-2-one, 26a.

From epoxy carbamate **21a** (32 mg, 0.054 mmol) in CH_2Cl_2 (0.6 mL) and TFA (12 µL, 18 mg, 0.16 mmol, 3.0 equiv), according to the general procedure and after chromatographic purification (5-50% Et_2O-CH_2Cl_2), **26a** was obtained as a white solid (17 mg, 95%). Data for **26a**: R_f 0.20 (10% Et_2O-CH_2Cl_2). **[α]$^{20}_D$** +65.4 (*c* = 0.12). **mp** 145 ºC. **^{1}H NMR (CD$_3$OD, 500 MHz)** δ 3.12 (ddd, 1 H, *J* = 12.4, 3.9, 1.5 Hz, H-4a), 3.58 (dd, 1 H, *J* = 12.3, 3.9 Hz, H-4b), 3.95 (t, 1 H, *J* = 5.8 Hz, H-1'), 4.16 (ddd, 1 H, *J* = 5.8, 3.7, 1.4 Hz, H-6), 4.28 (q, 1 H, *J* = 3.8 Hz, H-5), 4.42 (d, 1 H, *J* = 15.2 Hz, Ha CH_2 Bn), 4.66 (d, 1 H, *J* = 15.2 Hz, Hb CH_2 Bn), 4.79 (d, 1 H, *J* = 5.7 Hz, H-2'), 7.24-7.27 (m, 2 H, Ar), 7.30-7.34 (m, 6 H, Ar), 7.43-7.45 (m, 2 H, Ar). **^{13}C NMR (CD$_3$OD, 125 MHz)** δ 50.7 (C-4), 53.6 (CH_2 benzyl), 62.0 (C-5), 75.2 (C-2'), 75.7 (C-1'), 83.0 (C-6), 128.7 (4 x Ar), 128.9 (2 x Ar), 129.1 (2 x Ar), 129.7 (2 x Ar), 137.9 (Ar), 142.4 (Ar), 155.8 (C=O). **NOESY 1D (CD$_3$OD, 500 MHz)**: between H2'-H1' 2.5%, between H2'-H5 1.6%, between H2'-H6 0.8%, between H1'-H6 2.5%, between H1'-H5 0.7%, between H1'-H4b 2.8%, between H5-H6 1.4%, between H5-H4a 1.7%, between H5-H4b 4.2%, between H4a-H4b 22.0%, between H4a-HBna 1.3%, between H4b-HBnb 2.2%. **IR** (CH_2Cl_2): 3368, 2925, 1671, 1487, 1452, 1362, 1249, 1144, 1076, 1026, 864, 755, 700 cm^{-1}. **HRMS** (ES): calcd for $C_{19}H_{22}NO_5$ [M+H]$^+$ 344.1498, found 344.1493.

Synthesis of (+)-*N*-Benzyl-*N*-(2*R*,3*R*,4*S*,5*S*)-2,4,5-trihydroxy-3-methoxy-5-phenylpentyl)tosylsulfonamide, 27.

To a cold solution of 1.0 equiv of epoxy sulfonamide **21c** (8 mg, 0.012 mmol, 1.0 equiv) in MeOH, was added Mg powder (2 mg, 0.086 mmol, 7.0 equiv). The mixture was stirred from rt to 50 ºC and monitored by TLC until completion (1 d). The solvent was evaporated and the crude was purified by chromatography on silica gel (5-50% Et_2O-CH_2Cl_2) to obtain a pure fraction of **27** as a colorless oil (5 mg, 85%). Data for **27**: R_f 0.20 (10% Et_2O-CH_2Cl_2). **[α]$^{20}_D$** +21.5 (*c* = 0.32). **^{1}H NMR (CDCl$_3$, 500 MHz)** δ 2.10 (d, 1 H, *J* = 6.4 Hz, OH), 2.43 (s, 3 H, CH_3 Ts), 2.91 (d, 1 H, *J* = 5.3 Hz, OH), 3.14 (s, 3 H, OMe), 3.15 (dd, 1 H, *J* = 13.2, 6.4 Hz, H-1a), 3.30 (dd, 1 H, *J* = 14.9, 8.2 Hz, H-1b), 3.36 (td, 1 H, *J* = 6.8, 1.5 Hz, H-3), 3.71-3.80 (m, 2 H, H-2 and H-4), 4.19 (d, 1 H, *J* = 6.6 Hz, H-5), 4.29 (d, 1 H, *J* = 14.6 Hz, Ha Bn), 4.35 (d, 1 H, *J* = 14.6 Hz, Hb Bn), 7.20-7.22 (m, 2 H, Ar), 7.28-7.38 (m, 10 H, Ar), 7.70 (d, 2 H, *J* = 8.3 Hz, Ts). **^{13}C NMR (CDCl$_3$, 125 MHz)** δ 21.5 (CH_3 Ts), 51.7 (C-1), 54.0 (CH_2 Bn), 56.7 (OMe), 68.9 (C-2), 70.7 (C-3), 74.4 (C-4), 85.1 (C-5), 127.3 (2 x Ar), 127.9 (2 x Ar), 128.0 (Ar), 128.3 (Ar), 128.47 (2 x Ar), 128.53 (2 x Ar), 128.7 (2 x Ar), 129.9 (2 x Ar), 135.9 (Ar), 136.1 (Ar), 137.6 (Ar), 143.7 (Ar). **IR** (film): 3410, 3032, 2957, 2925, 2872, 2858, 1667, 1466, 1455, 1417, 1367, 1297, 1249, 1169, 1137, 1080, 964, 889, 700 cm^{-1}. **HRMS** (ES) m/z calcd for $C_{26}H_{32}NO_6S$ [M+H]$^+$ 486.1945, found 486.1950.

Synthesis of (+)-(2*R*,3*S*,4*S*,5*S*)-1-(Benzylamino)-3,4-(oxiranyl)-5-phenyl-5-[(tributylsilyloxy]pentan-2-ol, 28.

To a solution of 1.0 equiv of carbamate **21d** (7.0 mg, 0.01 mmol) in THF (0.1 mL) was added 5.0 equiv of piperidine (5 µL, 4 mg, 0.047 mmol). The mixture was stirred at rt and monitored by TLC until completion (1 d). The crude was concentrated and purified by chromatography on silica gel (20-80% EtOAc-CH_2Cl_2) to obtain a pure fraction of **28** as a colorless oil (4 mg, 80%). Data for **28**: R_f 0.20 (80% EtOAc-CH_2Cl_2). **[α]$^{20}_D$** +69.5 (*c* = 1.15). **^{1}H NMR (CDCl$_3$, 500 MHz)** δ 0.48-0.53 (m, 6 H, 3 x CH_2 *n*-Bu), 0.80 (t, 9 H, *J* = 6.9 Hz, 3 x CH_3 *n*-Bu), 1.17-1.25 (m, 12 H, 6 x CH_2 *n*-Bu), 1.88 (br s, 2 H, OH and NH), 2.72 (dd, 1 H, *J* = 12.1, 6.8 Hz, H-1a), 2.75 (dd, 1 H, *J* = 12.2, 5.0 Hz, H-1b), 3.08 (dd, 1 H, *J* = 3.8, 2.2 Hz, H-4), 3.10 (dd, 1 H, *J* = 3.9, 2.2 Hz, H-3), 3.63 (ddd, 1 H, *J* = 6.8, 4.9, 4.0 Hz, H-2), 3.74 (d, 1 H, *J* = 13.3 Hz, Ha Bn), 3.77 (d, 1 H, *J* = 13.3 Hz, Hb Bn), 4.66 (d, 1 H, *J* = 3.8 Hz, H-5), 7.23-7.30 (m, 10 H, Ar). **^{13}C NMR (CDCl$_3$, 125 MHz)** δ 13.6 (3 x CH_2 *n*-Bu), 13.7 (3 x CH_3 *n*-Bu), 25.2 (3 x CH_2 *n*-Bu), 26.5 (3 x CH_2 *n*-Bu), 52.0 (C-1), 53.6 (CH_2 Bn), 57.4 (C-4), 58.9 (C-3), 68.3 (C-2), 72.7 (C-5), 126.3 (2 x Ar), 127.1 (Ar), 127.8 (Ar), 128.1 (2 x Ar), 128.3 (2 x Ar), 128.5 (2 x Ar), 139.7 (Ar), 141.3 (Ar). **NOESY 1D (CD$_3$OD, 500 MHz)**: between H5-H4 4.0%, between H1-H3 2.0%, between H1-H2 4.0%. **IR** (film): 2917, 2849, 1682, 1461, 1373, 1265, 1206, 1138, 1080, 742 cm^{-1}. **HRMS** (ES) m/z calcd for $C_{30}H_{48}NO_3Si$ [M+H]$^+$ 498.3398, found 498.3392.

10.1002/chem.201905742

FULL PAPER

Synthesis of (+)-(5*R*)-3-Benzyl-5-[(1*S*,2*S*,3*S*)-1,2-epoxy-3-phenyl-3-tributylsilyloxy]oxazolidine, 29.

To a solution of 1.0 equiv of carbamate **21d** (7.0 mg, 0.01 mmol) in CH_2Cl_2 (0.1 mL) was added 2.0 equiv of piperidine (2 µL, 2 mg, 0.02 mmol). The mixture was stirred at rt and monitored by TLC until completion (1 day). The crude was concentrated and purified by chromatography on silica gel (20-80% EtOAc-CH_2Cl_2) to obtain a pure fraction of **29** as a colorless oil (4.5 mg, 90%). Data for **29**: R_f 0.40 (80% EtOAc-CH_2Cl_2). $[\alpha]^{20}_D$ +50.3 (*c* = 0.85). **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 0.49-0.53 (m, 6 H, 3 x CH_2 *n*-Bu), 0.80 (t, 9 H, *J* = 6.9 Hz, 3 x CH_3 *n*-Bu), 1.17-1.26 (m, 12 H, 6 x CH_2 *n*-Bu), 2.78 (dd, 1 H, *J* = 11.4, 7.2 Hz, H-4a), 3.05 (dd, 1 H, *J* = 12.0, 7.2 Hz, H-4b), 3.06 (dd, 1 H, *J* = 3.7, 2.2 Hz, H-2´), 3.15 (dd, 1 H, *J* = 4.6, 2.1 Hz, H-1´), 3.66 (d, 1 H, *J* = 13.0 Hz, Ha Bn), 3.70 (d, 1 H, *J* = 13.0 Hz, Hb Bn), 3.92 (td, 1 H, *J* = 7.2, 4.6 Hz, H-5), 4.29 (d, 1 H, *J* = 5.4 Hz, H-2a), 4.32 (d, 1 H, *J* = 5.4 Hz, H-2b), 4.68 (d, 1 H, *J* = 3.6 Hz, H-3´), 7.28-7.31 (m, 10 H, Ar). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 13.6 (3 x CH_2 *n*-Bu), 13.7 (3 x CH_3 *n*-Bu), 25.2 (3 x CH_2 *n*-Bu), 26.5 (3 x CH_2 *n*-Bu), 54.5 (C-4), 56.3 (C-1´), 58.2 (CH_2 Bn), 59.5 (C-2´), 72.6 (C-3´), 73.8 (C-5), 87.1 (C-2), 126.3 (2 x Ar), 127.3 (Ar), 127.8 (Ar), 128.3 (2 x Ar), 128.4 (2 x Ar), 128.8 (2 x Ar), 138.7 (Ar), 141.4 (Ar). **IR** (film): 3088, 3064, 3030, 2956, 2924, 2871, 1660, 1495, 1455, 1409, 1376, 1297, 1197, 1080, 1028, 998, 887, 746, 699 cm^{-1}. **HRMS** (ES) m/z calcd for $C_{31}H_{48}NO_3Si$ $[M+H]^+$ 510.3398, found 510.3422.

General procedure for the dihydroxylation of alkenes.

To a cold solution (0 ºC) of the carbamate in a 9:1 mixture of acetone-water (10 mL/mmol) $Me_3NO{\cdot}2H_2O$ (4.0 equiv) and 5% mol of OsO_4 (2.5% wt in *t*-BuOH) was added slowly, and the mixture was warmed to rt until disappearance of the starting material (monitored by TLC). The crude was evaporated, dissolved in EtOAc and filtered through a pad of silica gel, concentrated and purified by chromatography on silica gel using a gradient of the appropriate solvents.

Synthesis of (+)-*tert*-Butyl benzyl [(2*R*,3*R*,4*R*,5*S*)-5-phenyl-5-(tributylsilyloxy)-2,3,4-trihydroxypentyl]carbamate, 31, and *tert*-Butyl benzyl [(2*R*,3*S*,4*S*,5*S*)-5-phenyl-5-(tributylsilyloxy)-2,3,4-trihydroxypentyl]carbamate, 32.

From carbamate **20a** (120 mg, 0.206 mmol) in 2.1 mL of acetone-H_2O (9:1) $Me_3NO{\cdot}2H_2O$ (92.0 mg, 0.824 mmol, 4.0 equiv) and OsO_4 (130 µL, 3.0 mg, 0.010 mmol, 0.05 equiv), according to the general procedure (1 d) and after chromatographic purification (20-80% Et_2O-hexane) a pure fraction of **31** (102.0 mg, 80%) and **32** (6.5 mg, 5%) was obtained as colorless oils. Data for **31**: R_f 0.42 (60% Et_2O-hexane). $[\alpha]^{20}_D$ +92.6 (*c* = 1.34). **^{1}H NMR ($CDCl_3$, 400 MHz, 50 ºC)** δ 0.44-0.51 (m, 6 H, 3 x CH_2 *n*-Bu), 0.81 (t, 9 H, *J* = 6.7 Hz, 3 x CH_3 *n*-Bu), 1.14-1.28 (m, 12 H, 6 x CH_2 *n*-Bu), 1.37 (s, 9 H, 3 x CH_3 *t*-Bu), 2.99 (s, 1 H, OH), 3.05 (t, 1 H, *J* = 8.1 Hz, H-3), 3.31-3.51 (m, 2 H, H-1), 3.54-3.66 (m, 1 H, OH), 3.74-3.79 (m, 1 H, H-2), 3.85-3.89 (m, 1 H, H-4), 4.39 (d, 1 H, *J* = 15.8 Hz, Ha Bn), 4.48 (d, 1 H, *J* = 15.7 Hz, Hb Bn), 4.79 (d, 1 H, *J* = 7.7 Hz, H-5), 7.15-7.17 (m, 2 H, Ar), 7.22-7.29 (m, 6 H, Ar), 7.33-7.35 (m, 2 H, Ar). **^{13}C NMR ($CDCl_3$, 100 MHz, 50 ºC)** δ 13.6 (3 x CH_2 *n*-Bu), 13.8 (3 x CH_3 *n*-Bu), 25.3 (3 x CH_2 *n*-Bu), 26.5 (3 x CH_2 *n*-Bu), 28.3 (3 x CH_3 *t*-Bu), 50.56 (C-1), 50.6 (CH_2 benzyl), 65.9 (C-3), 70.0 (C-2), 72.9 (C-4), 74.7 (C-5), 80.7 (C *t*-Bu), 127.2 (2 x Ar), 127.4 (4 x Ar), 128.0 (2 x Ar), 128.3 (Ar), 128.5 (Ar), 138.3 (Ar), 141.0 (Ar), 158.4 (C=O). **IR** (film): 3410, 3088, 3065, 3032, 2957, 2925, 2872, 2858, 1667, 1606, 1587, 1496, 1466, 1455, 1417, 1367, 1297, 1249, 1169, 1137, 1080, 1028, 964, 889, 853, 828, 761, 732, 700 cm^{-1}. **HRMS** (ES) m/z calcd for $C_{35}H_{57}NO_6Si$ $[M+H]^+$ 616.4033, found 616.4033. Partial data for **32**: R_f 0.15 (60% Et_2O-hexane). **^{1}H NMR ($CDCl_3$, 400 MHz, 50 ºC)** δ 0.48-0.54 (m, 6 H, 3 x CH_2 *n*-Bu), 0.80 (t, 9 H, *J* = 6.8 Hz, 3 x CH_3 *n*-Bu), 1.18-1.25 (m, 12 H, 6 x CH_2 *n*-Bu), 1.42 (s, 9 H, 3 x CH_3 *t*-Bu), 3.25 (dd, 1 H, *J* = 14.9, 4.4 Hz, H-1a), 3.34-3.49 (m, 1 H, H-1b), 3.65-3.70 (m, 2 H, H-3 and H-4), 3.78-3.82 (m, 1 H, H-2), 4.23-4.25 (m, 2 H, CH_2 benzyl), 4.79 (d, 1 H, *J* = 5.9 Hz, H-5), 7.17-7.19 (m, 2 H, Ar), 7.26-7.32 (m, 8 H, Ar). **HRMS** (ES) m/z calcd for $C_{35}H_{57}NO_6Si$ $[M+H]^+$ 616.4033, found 616.4028.

Synthesis of (+)-(2*R*,3*R*,4*R*,5*S*)-1-[Benzyl(*tert*-butoxycarbonyl)amino]-3-hydroxy-1-phenylpentane-2,4,5-triyl triacetate, 36.

To a cold solution (0 ºC) of 1.0 equiv of silyloxy triacetate **35** (32 mg, 0.054 mmol) in CH_2Cl_2 (0.6 mL) was added TFA (12 µL, 18 mg, 0.16 mmol, 3.0 equiv). The mixture was stirred from 0 ºC to rt and monitored by TLC until completion (1 d). The crude was treated with Na_2CO_3, extracted with EtOAc, concentrated and purified by chromatography on silica gel (5-50% Et_2O-CH_2Cl_2) to obtain a pure fraction of **36** as a colorless oil (17 mg, 95%). Data for **36**: R_f 0.40 (40% EtOAc-hexane). $[\alpha]^{20}_D$ +51.4 (*c* = 0.86). **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 1.25 (s, 9 H, 3 x CH_3 *t*-Bu), 1.92 (s, 3 H, CH_3 Ac), 1.97 (s, 3 H, CH_3 Ac), 2.07 (s, 3 H, CH_3 Ac), 3.11 (dd, 1 H, *J* = 15.9, 3.0 Hz, H-1a), 3.30 (ddd, 1 H, *J* = 10.0, 4.7, 1.6 Hz, H-3), 3.91 (d, 1 H, *J* = 15.7 Hz, H-1b), 4.00 (d, 1 H, *J* = 15.9 Hz, Ha Bn), 4.49 (d, 1 H, *J* = 15.9 Hz, Hb Bn), 4.74 (dt, 1 H, *J* = 9.9, 3.0 Hz, H-2), 5.11 (d, 1 H, *J* = 4.5 Hz, OH), 5.42 (d, 1 H, *J* = 9.1 Hz, H-4), 6.16 (d, 1 H, *J* = 9.7 Hz, H-5), 6.96 (d, 2 H, *J* = 7.7 Hz, Ar), 7.20-7.36 (m, 6 H, Ar), 7.51 (d, 2 H, *J* = 7.0 Hz, Ar). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 20.8 (CH_3 Ac), 20.9 (CH_3 Ac), 21.0 (CH_3 Ac), 28.2 (3 x CH_3 *t*-Bu), 46.3 (C-1), 53.3 (CH_2 Bn), 66.4 (C-3), 71.9 (C-2), 73.0 (C-4), 75.6 (C-5), 81.4 (C *t*-Bu), 126.9 (2 x Ar), 127.3 (Ar), 127.8 (2 x Ar), 128.5 (3 x Ar), 128.6 (2 x Ar), 136.8 (Ar), 137.4 (Ar), 157.8 (C=O Boc), 169.7 (C=O Ac), 170.0 (C=O Ac), 170.6 (C=O Ac). **IR** (film): 3357, 2926, 2855, 1739, 1668, 1456, 1438, 1373, 1239, 1179, 1120, 1084, 1029, 723, 697 cm^{-1}. **HRMS** (ES) m/z calcd for $C_{29}H_{37}NNaO_9$ $[M+Na]^+$ 566.2361 found 566.2381.

Synthesis of (+)-*tert*-Butyl benzyl{(2*R*,3*R*)-3-[(4*R*,5*S*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-2,3-dihydroxypropyl}carbamate, 37.

To a cold solution (0 ºC) of 1.0 equiv of triol **31** (15 mg, 0.025 mmol) in CH_2Cl_2 (0.3 mL) was added 2.0 equiv of 2,2-dimethoxypropane (6 µL, 5.0 mg, 0.050 mmol) and 0.1 equiv of PPTS (1.0 mg, 0.003 mmol). The mixture was stirred at rt and monitored by TLC until completion (1 day). The crude was concentrated and purified by chromatography on silica gel (5-60% Et_2O-hexane) to obtain a pure fraction of **37** as a colorless oil (8.0 mg, 70%). Data for **37**: R_f 0.38 (20% Et_2O-hexane). $[\alpha]^{20}_D$ +30.6 (*c* = 0.11). **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 1.40 (s, 9 H, 3 x CH_3 *t*-Bu), 1.50 (s, 3 H, CH_3), 1.53 (s, 3 H, CH_3), 2.88 (br d, 1 H, *J* = 9.1 Hz, OH-C3), 3.32 (td, 1 H, *J* = 9.0, 1.3 Hz, H-3), 3.40 (dd, 1 H, *J* = 14.7, 2.0 Hz, H-1a), 3.50-3.62 (m, 1 H, H-1b), 3.67-3.72 (m, 1 H, H-2), 3.91 (br s, 1 H, OH-C2), 4.15 (br d, 1 H, *J* = 8.3 Hz, H-4), 4.38 (d, 1 H, *J* = 15.7 Hz, Ha Bn), 4.51 (d, 1 H, *J* = 15.6 Hz, Hb Bn), 5.02 (d, 1 H, *J* = 8.8 Hz, H-5), 7.17-7.19 (m, 2 H, Ar), 7.28-7.39 (m, 8 H, Ar). **^{13}C NMR ($CDCl_3$, 125 MHz)** δ 27.0 (CH_3), 27.3 (CH_3), 28.3 (3 x CH_3 *t*-Bu), 50.7 (C-1), 52.6 (CH_2 benzyl), 68.3 (C-3), 73.3 (C-2), 78.8 (C-5), 81.0 (C *t*-Bu), 81.3 (C-4), 109.3 (C ketal), 126.8 (2 x Ar), 127.3 (2 x Ar), 127.4 (Ar), 127.7 (Ar), 128.3 (Ar), 128.5 (2 x Ar), 128.6 (2 x Ar), 137.9 (Ar), 158.4 (C=O). **NOESY 1D ($CDCl_3$, 500 MHz)**: between H5-ArH 2.5%, between H5-H4 0.2%, between H5-H3 1.3%, between H5-OH3 0.3%, between CH_3-H5 0.75%. **IR** (film): 3410, 3088, 3065, 3032, 2957, 2925, 1667, 1606, 1587, 1496, 1466, 1455, 1417, 1367, 1297, 1249, 1169, 1137, 1080, 1028, 964, 889, 853, 828, 761, 732, 700 cm^{-1}. **HRMS** (ES): calcd for $C_{26}H_{36}NO_6$ $[M+H]^+$ 458.2543, found 458.2547.

Acknowledgements

This research was supported by CTQ2016-77555-C2-2-R and MICINN (CTQ2009-07752). We also thank CM for additional support to MU and MEC for a fellowship to I.C.

Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,4-aminoalcohols • 1,4-diols • [2,3]-sigmatropic rearrangement • sulfenate • sulfoxide

[1] a) J.-J. Feng, Y. Xu, M. Oestreich, *Chem. Sci.* **2019**, *10*, 9679-9683; b) E. McNeill, T. Ritter, *Acc. Chem. Res.* **2015**, *48*, 2330-2343; c) N. Herrmann, D. Vogelsang, A. Behr, T. Seidensticker, *Chem. Cat. Chem.* **2018**, *10*, 5342-5365; d) Y. Liu, D. Fiorito, C. Mazet, *Chem. Sci.* **2018**, *9*, 5284-5288; e) J.-E. Bäckvall, R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **1998**, *98*, 2291-2312, and references therein.

[2] For a recent review, see: a) D. Kaiser, I. Klose, R. Oost, J. Neuhaus, N. Maulide, *Chem. Rev.* **2019**, *119*, 8701-8780. For leading reports, see: b) B. Wang, X. Wang, X. Yin, W. Yu, Y. Liao, J. Ye, M. Wang, J. Liao, *Org. Lett.* **2019**, *21*, 3913-3917; c) D. Kobayashi, M. Miura, M. Toriyama, S. Motohashi, *Tetrahedron Lett.* **2019**, *60*, 120-123; d) X. Wang, B. Wang, X. Yin, W. Yu, Y. Liao, J. Ye, M. Wang, L. Hu, J. Liao, *Angew. Chem.* **2019**, *131*, 12392-12398; *Angew. Chem. Int. Ed.* **2019**, *58*, 12264-12270; e) D. Kaldre, I. Klose, N. Maulide, *Science* **2018**, *361*, 664-667; f) R. I. Rodríguez, E. Ramírez, J. A. Fernández-Salas, R. Sánchez-Obregón, F. Yuste, J. Alemán, *Org. Lett.* **2018**, *20*, 8047-8051; g) C. Bauder, *Eur. J. Org. Chem.* **2018**, 4874-4899; h) B. Chen, P. Cao, Y. Liao, M. Wang, J. Liao, *Org. Lett.* **2018**, *20*, 1346-1349.

[3] For a review, see: a) I. Colomer, M. Velado, R. Fernández de la Pradilla, A. Viso, *Chem. Rev.* **2017**, *117*, 14201-14243. For recent reports, see: b) J. R. Walker, J. E. Merit, R. Thomas-Tran, D. T. Y. Tang, J. Du Bois, *Angew. Chem.* **2019**, *131*, 1703-1707; *Angew. Chem. Int. Ed.* **2019**, *58*, 1689-1693; c) R. Yalla, S. Raghavan, *Org. Biomol. Chem.* **2019**, *17*, 4572-4592; d) F. Tang, Y. Yao, Y.-J. Xu, C.-D. Lu, *Angew. Chem.* **2018**, *130*, 15809-15812; *Angew. Chem. Int. Ed.* **2018**, *57*, 15583-15586.

[4] a) D. R. Rayner, E. G. Miller, P. Bickart, A. J. Gordon, K. Mislow, *J. Am. Chem. Soc.* **1966**, *88*, 3138-3139; b) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, K. Mislow, *J. Am. Chem. Soc.* **1968**, *90*, 4869-4876; c) S. Braverman, Y. Stabinsky, *Chem. Commun.* **1967**, 270-271; d) D. A. Evans, G. C. Andrews, C. L. Sims, *J. Am. Chem. Soc.* **1971**, *93*, 4956-4957; e) D. A. Evans, G. C. Andrews, *Acc. Chem. Res.* **1974**, *7*, 147-155.

[5] a) R. Fernández de la Pradilla, A. Castellanos, I. Osante, I. Colomer, M. I. Sánchez, *J. Org. Chem*. **2009**, *74*, 170-181; b) A. Viso, R. Fernández de la Pradilla, M. Ureña, I. Colomer, *Org. Lett.* **2008**, *10*, 4775-4778.

[6] The conjugate addition of nucleophiles to vinyl sulfoxides has been reported: a) S. G. Pyne, P. Bloem, R. Griffith, *Tetrahedron* **1989**, *45*, 7013-7022; b) S. G. Pyne, P. Bloem, S. L. Chapman, C. E. Dixon, R. Griffith, *J. Org. Chem*. **1990**, *55*, 1086-1093; c) D. Craig, K. Daniels, A. R. MacKenzie, *Tetrahedron* **1992**, *48*, 7803-7816; d) F. Brebion, B. Delouvrié, F. Nájera, L. Fensterbank, M. Malacria, J. Vaissermann, *Angew. Chem.* **2003**, *115*, 5500-5503; *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 5342-5345. For conjugate additions of lithiated protected cyanohydrins to a dienyl sulfoxide, see: e) E. Guittet, S. Julia, *Synth. Commun.* **1981**, *11*, 697-708; f) E. Guittet, S. Julia, *Synth. Commun.* **1981**, *11*, 709-722. For some examples of remote nucleophilic epoxidation of dienyl sulfoxides, see: g) R. Fernández de la Pradilla, P. Manzano, C. Montero, J. Priego, M. Martínez-Ripoll, L. A. Martínez-Cruz, *J. Org. Chem*. **2003**, *68*, 7755-7767.

[7] a) M. Motofumi, M. Toriyama, T. Kawakubo, K. Yasukawa, T. Takido, S. Motohashi, *Org. Lett.* **2010**, *12*, 3882-3885; b) S. Raghavan, V. Vinoth Kumar, L. Raju Chowhan, *Synlett* **2010**, 1807-1810; c) S. Raghavan, M. K. R. Yelleni, *J. Org. Chem.* **2016**, *81*, 10912-10921; d) The SPAC (Sulfoxide Piperidine And Carbonyl) reaction involves the isomerization from vinyl to allylic sulfoxides, followed by [2,3]-sigmatropic rearrangement in acyclic systems. For leading references, see: e) Z. Du, T. Kawatani, K. Kataoka, R. Omatsu, J. Nokami, *Tetrahedron* **2012**, *68*, 2471-2480; f) J. Nokami, K. Kataoka, K. Shiraishi, M. Osafune, I. Hussain, S.-I. Sumida, *J. Org. Chem.* **2001**, *66*, 1228-1232; g) V. Guerrero de la Rosa, M. Ordóñez, J. M. Llera, *Tetrahedron: Asymmetry* **2001**, *12*, 1089-1094; h) E. Domínguez, J. C. Carretero, *Tetrahedron Lett.* **1990**, *31*, 2487-2490. For some diastereoselective examples of this process, see: i) B. M. Trost, T. A. Grese, *J. Org. Chem.* **1991**, *56*, 3189-3192; j) K. Burgess, J. Cassidy, I. Henderson, *J. Org. Chem.* **1991**, *56*, 2050-2058; k) K. Burgess, I. Henderson, *Tetrahedron* **1991**, *47*, 6601-6616; l) B. M. Trost, L. Dong, G. M. Schroeder, *J. Am. Chem. Soc.* **2005**, *127*, 10259-10268.

[8] For a synthesis of halicholactone, see; a) Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, T. Ibuka, H. Ohishi, Y. Takemoto, *J. Org. Chem.* **2001**, *66*, 81-88. For a synthesis of amphidinolide H, see: b) A. Fürstner, L. C. Bouchez, J.-A. Funel, V. Liepins, F.-H. Porée, R. Gilmour, F. Beaufils, D. Laurich, M. Tamiya, *Angew. Chem.* **2007**, *119*, 9425-9430; *Angew. Chem. Int. Ed.* **2007**, *46*, 9265-9270. For a review on drugs for tropical diseases, see: c) J. N. Burrows, R. L. Elliott, T. Kaneko, C. E. Mowbray, D. Waterson, *Med. Chem. Commun.* **2014**, *5*, 688-700. For selected examples of these structural motifs in natural products, see: d) C. M. König, B. Gebhardt, C. Schleth, M. Dauber, U. Koert, *Org. Lett.* **2009**, *11*, 2728-2731; e) H. C. Kim, S. H. Kang, *Angew. Chem.* **2009**, *121*, 1859-1861; *Angew. Chem. Int. Ed.* **2009**, *48*, 1827-1829; f) A. Robinson, V. K. Aggarwal, *Org. Biomol. Chem.* **2012**, *10*, 1795-1801; g) M.-C. Lin, B.-W. Chen, C.-Y. Huang, C.-F. Dai, T.-L. Hwang, J.-H. Sheu, *J. Nat. Prod.* **2013**, *76*, 1661-1667; h) S. N. Greszler, J. T. Malinowski, J. S. Johnson, *Org. Lett.* **2011**, *13*, 3206-3209; i) D. E. Williams, C. M. Sturgeon, M. Roberge, R. J. Andersen, *J. Am. Chem. Soc.* **2007**, *129*, 5822-5823.

[9] a) W. R. Roush, P. T. Grover, *Tetrahedron* **1992**, *48*, 1981-1998; b) S. Vettel, P. Knochel, *Tetrahedron Lett*. **1994**, *35*, 5849-5852; c) Bloch, R.; Brillet, C. *Tetrahedron: Asymmetry* **1992**, *3*, 333-336; d) M. Binanzer, G. Y. Fang, V. K. Aggarwal, *Angew. Chem.* **2010**,*122*, 4360-4364; *Angew. Chem. Int. Ed.* **2010**, *49*, 4264-4268; e) D. R. Williams, B. A. Atwater, S. A. Bawel, P. Ke, O. Gutierrez, D. J. Tantillo, *Org. Lett.* **2014**, *16*, 468-471; f) M. Amador, X. Ariza, J. García, J. Ortiz, *Tetrahedron Lett*. **2002**, *43*, 2691-2694; g) R. S. Diez, B. Adger, E. M. Carreira, *Tetrahedron* **2002**, *58*, 8341-8344.

[10] a) M. J. Burk, J. E. Feaster, R. L. Harlow, *Tetrahedron: Asymmetry* **1991**, *2*, 569-592; b) G. Solladié, N. Huser, J. L. García-Ruano, J. Adrio, M. C. Carreño, A. Tito, *Tetrahedron Lett.* **1994**, *35*, 5297-5300; c) G. A. Molander, K. L. Bobbitt, *J. Org. Chem.* **1994**, *59*, 2676-2678; d) J. Bach, R. Berenguer, J. García, T. Loscertales, J. Manzanal, J. Vilarrasa, *Tetrahedron Lett*. **1997**, *38*, 1091-1094; e) J. Bach, R. Berenguer, J. García, M. López, J. Manzanal, J. Vilarrasa, *Tetrahedron* **1998**, *54*, 14947-14962; f) Y. Hayashi, H. Yamaguchi, M. Toyoshima, S. Nasu, K. Ochiai, M. Shoji, *Organometallics* **2008**, *27*, 163-165; g) Z. Liu, R. Bittman, *Org. Lett.* **2012**, *14*, 620-623; h) G. Sabitha, C. N. Reddy, P. Gopal, J. S. Yadav, *Tetrahedron Lett.* **2010**, *51*, 5736-5739.

[11] a) D. M. Hodgson, C. D. Bray, N. D. Kindon, *Org. Lett.* **2005**, *7*, 2305-2308. b) M. Tortosa, *Angew. Chem.* **2011**, *123*, 4036-4039; *Angew. Chem. Int. Ed.* **2011**, *50*, 3950-3953; c) Y.-Q. Zhang, N. Funken, P. Winterscheid, A. Gansäuer, *Angew. Chem.* **2015**, *127*, 7035-7038;

Angew. Chem. Int. Ed. **2015**, *54*, 6931-6934; d) N. Funken, F. Mühlhaus, A. Gansäuer, *Angew. Chem.* **2016**, *128*, 12209-12213; *Angew. Chem. Int. Ed.* **2016**, *55*, 12030-12034; e) J. Liu, H. Yao, C. Wang, *ACS Catal.* **2018**, *8*, 9376-9381.

[12] a) H. E. Burks, L. T. Kliman, J. P. Morken, *J. Am. Chem. Soc.* **2009**, *131*, 9134-9135; b) R. J. Ely, J. P. Morken, *Org. Lett.* **2010**, *12*, 4348-4351; c) T. Hashimoto, D. Hirose, T. Taniguchi, *Angew. Chem.* **2014**, *126*, 2768-2772; *Angew. Chem. Int. Ed.* **2014**, *53*, 2730-2734.

[13] a) C. N. Farthing, P. Kočovský, *J. Am. Chem. Soc.* **1998**, *120*, 6661-6672; b) J.-E. Bäckvall, J.-E. Nyström, R. E. Nordberg, *J. Am. Chem. Soc.* **1985**, *107*, 3676-3686; c) S. G. Pyne, Z. Dong, *Tetrahedron Lett*. **1999**, *40*, 6131-6134; d) N. Maezaki, Y. Hirose, T. Tanaka, *Org. Lett.* **2004**, *6*, 2177-2180; e) C. Lutz, V. Lutz, P. Knochel, P. *Tetrahedron* **1998**, *54*, 6385-6402; f) S. F. Martin, M. Hartmann, J. A. Josey, *Tetrahedron Lett.* **1992**, *33*, 3583-3586; g) L. Werner, J. R. Hudlicky, M. Wernerova, T. Hudlicky, *Tetrahedron* **2010**, *66* 3761-3769. For other approaches, see: h) J. Llaveria, Á. Beltrán, W. M. C. Sameera, A. Locati, M. M. Díaz-Requejo, M. I. Matheu, S. Castillón, F. Maseras, P. J. Pérez, *J. Am. Chem. Soc.* **2014**, *136*, 5342-5350; i) S. Tsuzaki, S. Usui, H. Oishi, D. Yasushima, T. Fukuyasu, T. Oishi, T. Sato, N. Chida, *Org. Lett.* **2015**, *17*, 1704-1707.

[14] T. Kano, R. Sakamoto, K. Maruoka, *Chem. Commun.* **2014**, *50*, 942-944.

[15] For a preliminary communication, see: a) R. Fernández de la Pradilla, I. Colomer, M. Ureña, A. Viso, *Org. Lett.* **2011**, *13*, 2468-2471. For related research, see: b) R. Fernández de la Pradilla, M. Velado, I. Colomer, C. Simal, A. Viso, H. Gornitzka, C. Hemmert, *Org. Lett.* **2014**, *16*, 5200-5203; c) C. Simal, R. H. Bates, M. Ureña, I. Giménez, C. Koutsou, L. Infantes, R. Fernández de la Pradilla, A. Viso, *J. Org. Chem.* **2015**, *80*, 7674-7692; d) R. Fernández de la Pradilla, N. Lwoff, A. Viso, *Eur. J. Org. Chem.* **2009**, 2312-2322 and references cited therein.

[16] D. Craig, K. Daniels, A. R. MacKenzie, *Tetrahedron* **1993**, *49*, 11263-11304.

[17] R. Fernández de la Pradilla, A. Castellanos, *Tetrahedron Lett.* **2007**, *48*, 6500-6504 and ref. 5a.

[18] A. Viso, R. Fernández de la Pradilla, M. Ureña, R. H. Bates, M. A. del Águila, I. Colomer, *J. Org. Chem.* **2012**, *77*, 525-542 and ref. 5b.

[19] Addition of $ZnBr_2$ to promote intramolecular chelation did not improve previous results. See Supporting information.

[20] a) D. K. Jones-Hertzog, W. L. Jorgensen, *J. Am. Chem. Soc.* **1995**, *117*, 9077-9078; b) D. K. Jones-Hertzog, W. L. Jorgensen, *J. Org. Chem.* **1995**, *60*, 6682-6683.

[21] For similar results on *m*-CPBA epoxidation of 1,4-silyloxyalcohols: a) M. Uchiyama, Y. Kimura, A. Ohta, *Tetrahedron Lett.* **2000**, *41*, 10013-10017; b) C. R. Johnson, M. W. Miller, *J. Org. Chem.* **1995**, *60*, 6674-6675; c) S. Saito, H. Itoh, Y. Ono, K. Nishioka, T. Moriwake, *Tetrahedron: Asymmetry* **1993**, *4*, 5-8 and references therein.

[22] a) M. Yoshida, M. Ohshima, T. Toda, *Heterocycles* **1993**, *35*, 623-626; b) C. Vanucci, X. Brusson, V. Verdel, F. Zana, H. Dhimane, G. Lhommet, *Tetrahedron Lett.* **1995**, *36*, 2971-2974; c) H. Urabe, Y. Aoyama, F. Sato, *Tetrahedron* **1992**, *48*, 5639-5646.

[23] 1,2-Aminoalcohols have been reported to react with CH_2Cl_2 in a high-pressure reactor under high temperatures. See: a) C. Hajji, M. L. Testa, R. de la Salud-Bea, E. Zaballos-García, J. Server-Carrió, J. Sepúlveda-Arques, *Tetrahedron* **2000**, *56*, 8173-8177; b) C. Hajji, M. L. Testa, E. Zaballos-García, R. J. Zaragozá, J. Server-Carrió, J. Sepúlveda-Arques, *Tetrahedron* **2002**, *58*, 3281-3285; c) A. Hamdach, E. M. El Hadrami, C. Hajji, E. Zaballos-García, J. Sepúlveda-Arques, R. J. Zaragozá, *Tetrahedron* **2004**, *60*, 10353-10358. For CH_2Cl_2 as alkylating agent or in Mannich reaction see: d) K. Matsumoto, *Angew. Chem.* **1982**, *94*, 937-937; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 922-922; e) W. J. Spillane, P. O. Burke, *Synthesis* **1986**, 1021-1024; f) J. M. Concellón, P. L. Bernad, J. A. Pérez-Andrés, *Tetrahedron Lett.* **2000**, *41*, 1231-1234.

[24] For related dihydroxylations of nonreinforcing cyclic substrates, see: a) O. Arjona, A. de Dios, R. Fernández de la Pradilla, J. Plumet, *Tetrahedron Lett.* **1991**, *32*, 7309-7312; b) O. Arjona, A. Candilejo, A. de Dios, R. Fernández de la Pradilla, J. Plumet, *J. Org. Chem.* **1992**, *57*, 6097-6099; c) O. Arjona, A. de Dios, J. Plumet, B. Saez, *J. Org. Chem.* **1995**, *60*, 4932-4935; d) B. M. Trost, M. L. Crawley, C. B. Lee, *Chem. Eur. J.* **2006**, *12*, 2171-2187.

[25] For a full discussion see the Supporting Information.

[26] It has been reported that vicinal coupling constants for *trans*-1,3-dioxolanes (8.0-9.0 Hz) are higher than for *cis* isomers (6.0-7.0 Hz). See: a) F. A. L. Anet, *J. Am. Chem. Soc.* **1962**, *84*, 747-752; b) M. Adamczeski, E. Quiñoá, P. Crews, *J. Am. Chem. Soc.* **1988**, *110*, 1598-1602; c) M. Adamczeski, E. Quiñoá, P. Crews, *J. Am. Chem. Soc.* **1989**, *111*, 647-654.

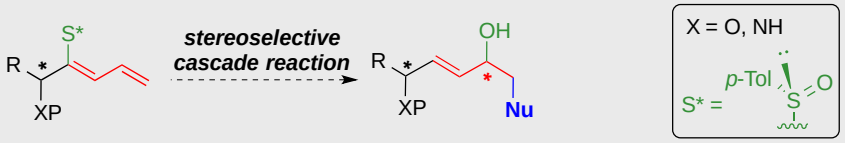
[27] For a recent approach to related amino 1,4-diol derivatives, see: S. K. Liew, S. J. Kaldas, A. K. Yudin, *Org. Lett.* **2016**, *18*, 6268-6271.

10.1002/chem.201905742

WILEY-VCH

Entry for the Table of Contents

FULL PAPER



*Ignacio Colomer, Mercedes Ureña, Alma Viso, and Roberto Fernández de la Pradilla**

Page No. – Page No.

Sulfinyl-mediated stereoselective functionalization of acyclic conjugated dienes

A new methodology to prepare acyclic unsaturated 1,4-diol derivatives from conjugated sulfinyl dienes has been developed. A cascade process that entails nucleophilic addition to produce a functionalized allylic sulfoxide, followed by [2,3]-sigmatropic rearrangement and sulfenate cleavage renders the target molecules with high yields and selectivities.