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[2,3]-Sigmatropic Rearrangements of 3-Sulfinyl Dihydropyrans: Application to the Syntheses of the Cores of *ent*-Dysiherbaine and Deoxymalayamicin A

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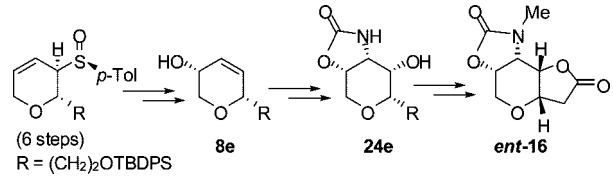

The [2,3]-sigmatropic rearrangement of a variety of configurationally stable diastereomeric allylic sulfinyl dihydropyrans, produced by base-promoted cyclization of sulfinyl dienols, has been studied. In some cases, the efficient transformation of these substrates into dihydropyranols required an in-depth study of reaction conditions, with the preferred protocol relying on the use of DABCO in warm toluene. This methodology has been applied to the syntheses of the cores of *ent*-dysiherbaine and deoxymalayamicin A by means of efficient tethered aminohydroxylations.

Introduction

The[2,3]-sigmatropic rearrangement of allylic sulfoxides to allylic sulfenates originally developed by Mislow,[1] Braverman,[2] and Evans[3] is a reversible process that can cause the racemization of allylic sulfoxides **I**, via the intermediate sulfenate esters **II**, that can transform into enantiomeric sulfoxides **III** (Scheme 1).[4] The presence of a suitable thiophile can cleave the O−S bond in the sulfenate intermediate, rendering the process irreversible by removing the sulfur atom and leading to an allylic alcohol **IV**. Allylic alcohols are important substructures in many bioactive products and also key building blocks in organic synthesis since they can be involved in a variety of stereocontrolled chemical transformations that allow for the creation of new functionalities.[5] The conversion of sulfoxides into allylic alcohols has been widely used with synthetic purposes since it may benefit from the chiral auxiliary properties of sulfoxides, and represents an easy procedure for removal of the sulfur moiety which usually is not present in final synthetic targets.[6]

During the past few years our group has developed the stereocontrolled cyclization of hydroxy sulfinyl dienes with different bases depending on the diene geometry to obtain configurationally stable sulfinyl dihydropyrans **3**−**6** with 2,3-*trans* and 2,3-*cis* relative configuration (Scheme 2).[7] These substrates present a peculiar arrangement of functionalities that suggests that different reactivities should be considered, for instance, under basic reaction conditions; these include oxygen β-elimination and cleavage of the dihydropyran ring, epimerization α to the sulfoxide, and for 2,3-*trans* substrates the possible pyrolitic *syn*-elimination of the sulfoxide moiety.

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(3) Evans, D. A.; Andrews, G. C.; Sims, C. L. *J. Am. Chem. Soc.* **1971**, *93*, 4956–4957.

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(6) Recent examples: (a) Fernández de la Pradilla, R.; Lwoff, N. *Tetrahedron Lett.* **2008**, *49*, 4167–4169. (b) Fernández de la Pradilla, R.; Lwoff, N.; Viso, A. *Tetrahedron Lett.* **2007**, *48*, 8141–8144. (c) Brebion, F.; Nàjera, F.; Delouvrié, B.; Lacôte, E.; Fensterbank, L.; Malacria, M. *Synthesis* **2007**, 2273–2278. (d) Pelc, M. J.; Zakarian, A. *Tetrahedron Lett.* **2006**, *47*, 7519–7523. (e) Koprowski, M.; Krawczyk, E.; Skowrońska, A.; McPartlin, M.; Choi, N.; Radojevic, S. *Tetrahedron* **2001**, *57*, 1105–1118. For an example retaining the sulfur atom see: (f) Satoh, T.; Miyagawa, T. *Tetrahedron Lett.* **2006**, *47*, 1981–1983.

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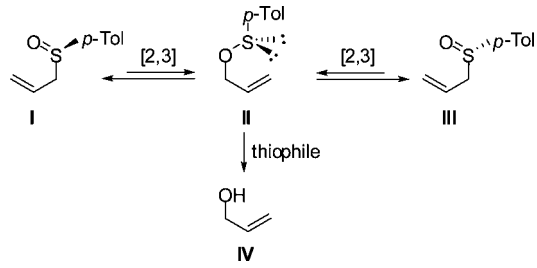
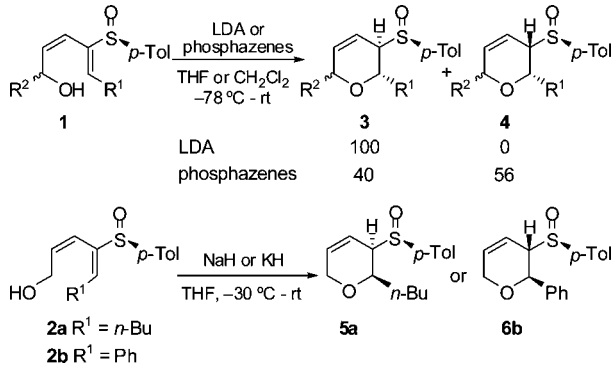
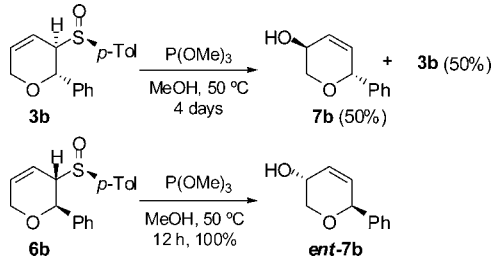
SCHEME 1. Sigmatropic Rearrangement of Allylic Sulfoxides



SCHEME 2. Base-Mediated Cyclization of Hydroxy Sulfinyl Dienes



SCHEME 3. Sigmatropic Rearrangement of Allylic Sulfoxides

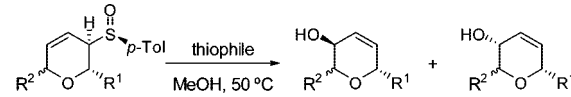


Moreover, the intrinsic configurational stability of the majority of these allylic sulfoxides suggests that the [2,3]-sigmatropic rearrangement is not a favored pathway for these substrates. In this paper we report in full our studies on the reactivity of these allylic sulfoxides in the [2,3]-sigmatropic rearrangement under different conditions. In addition, the application of this methodology to the syntheses of the cores of *ent*-dysiherbaine and deoxymalayamicin A by means of efficient tethered aminohydroxylations is also described.

Results and Discussion

Sigmatropic Rearrangement of 2,3-*trans* Sulfinyl Dihydropyrans. Within the context of exploring the reactivity of our sulfinyl dihydropyrans, we first studied the sigmatropic rearrangement of diastereomeric 2,3-*trans* substrates **3b** and **6b** under standard conditions [$P(OMe)_3$/MeOH] to obtain the corresponding 3,6-*trans* allylic alcohols. For substrate **6b** the reaction worked well in 12 h, while diastereomer **3b** afforded poor yields and long reaction times were required (Scheme 3). Sulfinyl dihydropyrans **3b** and **6b** are enantiomeric except for the configuration at sulfur, and yet they adopt different preferred conformations; this suggests that conformational factors could also be determinant for the viability of the sigmatropic process.

TABLE 1. Sigmatropic Rearrangement Using $P(OMe)_3$ and Et_2NH as Thiophiles



3a R^1 = *n*-Bu, R^2 = H; **3b** R^1 = Ph, R^2 = H; **3c** R^1 = Ph, R^2 = (*S*)-Me; **3d** R^1 = Ph, R^2 = (*R*)-Me

7a R^1 = *n*-Bu, R^2 = H; **7b** R^1 = Ph, R^2 = H; **7c** R^1 = Ph, R^2 = (*S*)-Me; **7d** R^1 = Ph, R^2 = (*R*)-Me

8a R^1 = *n*-Bu R^2 = H; **8b** R^1 = Ph, R^2 = H; **8c** R^1 = Ph, R^2 = (*S*)-Me; **8d** R^1 = Ph, R^2 = (*R*)-Me

entry	substrate	thiophile	**7**:**8** ratio	yield
1	**3a**	$P(OMe)_3$	100:0	19%
2	**3a**	Et_2NH	89:11	85%
3	**3b**	$P(OMe)_3$	100:0	50%[a]
4	**3b**	Et_2NH	85:15	60%
5	**3c**	$P(OMe)_3$	100:0	27%
6	**3c**	$P(OMe)_3$	100:0	22%[b]
7	**3c**	Et_2NH	73:27	91%[c]
8	**3d**	$P(OMe)_3$	100:0	72%

[a] 50% of starting material recovered. [b] Temperature 60 °C, 39% of a mixture of intermediates formed by MeOH capture was isolated (see Supporting Information). [c] 8% of vinyl sulfoxide is isolated.

To the moment, these conformational factors that may cause such a great difference in reactivity have been scarcely documented for this process probably due to the intrinsic configurational instability at sulfur of most allylic sulfoxides. Since our methodology provided all four diastereomers of substituted 3-sulfinyl dihydropyrans in some cases and they were configurationally stable to a certain extent, we had a unique opportunity to examine the behavior of all possible diastereomers in the [2,3]-sigmatropic rearrangement. Therefore, we decided to carry out a thorough study of the process with different substrates and conditions with the intent of finding optimized conditions to obtain synthetically useful dihydropyranols in a relatively short reaction sequence.

Trying to improve the process for less reactive substrates like **3b**, we tried other thiophilic agents such as Et_2NH, improving yields, but obtaining mixtures of 3,6-*trans* and 3,6-*cis* diastereomers, **7** and **8** (Table 1). For aliphatic substrate **3a** the reaction with $P(OMe)_3$ afforded only the expected *trans* alcohol **7a** but in low yield (Table 1, entry 1). The use of Et_2NH improved the yield but a mixture of isomers was obtained (Table 1, entry 2). The behavior was similar for substrate **3b** with an aromatic substituent (Table 1, entries 3 and 4) and also for 2,6-disubstituted sulfinyl dihydropyran **3c** (Table 1, entries 5 and 7). When the rearrangement of **3c** with $P(OMe)_3$ was carried out at higher temperature, a mixture of products resulting from capture of the intermediates with MeOH was obtained along with the product (Table 1, entry 6). In contrast, diasteromeric substrate **3d** afforded **7d** as a single isomer and in good yield by reaction with $P(OMe)_3$ (Table 1, entry 8). The different selectivities found for Et_2NH relative to $P(OMe)_3$ suggested that different reaction pathways were operative for these thiophiles.

These results may be rationalized qualitatively on the basis of the relative ease of attaining the reactive conformations that place the sulfoxide in a pseudoaxial position with the oxygen atom oriented toward the double bond for different diastereomeric allylic sulfoxides. The conformational analysis of the substrates based on chemical shifts and coupling constants show that the preferred conformations for **6b** and **3d** place the sulfoxide in a pseudoequatorial position (Figure 1, conformers **V** and **VII**), while isomers **3a**−**c** locate the sulfoxide in a

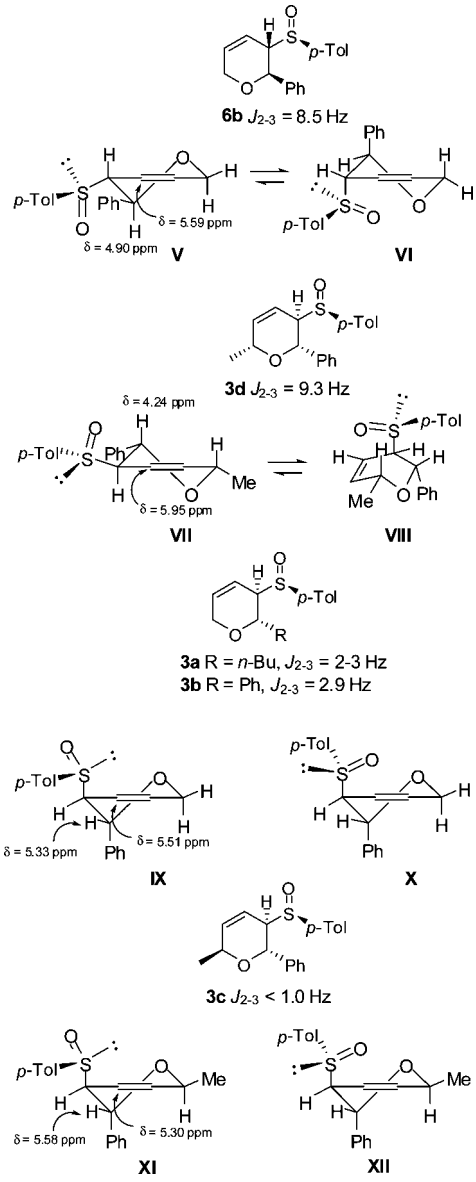


FIGURE 1. Proposed reactive conformations for **6b** and **3a**−**d**.

pseudoaxial arrangement (Figure 1, conformers **IX** and **XI**).[7b,8] In addition, the chemical shift patterns for H-2 and H-4 in the case of isomers **3a**−**c** suggest that the preferred conformer may place the oxygen atom away from the allylic moiety.

In the case of **6b** and **3d**, a simple conformational change from one chair conformer to the alternative chair (**6b**) or to a boat conformer (**3d**) would lead to the required pseudoaxial arrangements (Figure 1, conformers **VI** and **VIII**),[9] with the *p*-tolyl group away from the dihydropyran ring in both cases. It should be noted that the alternative chair conformer for **3d** (not shown) would present severe 1,3-diaxial interactions. For substrates **3a**−**c**, a conformational change around the carbon−sulfur bond would be required to reach the reactive conformation. The resulting reactive conformers for **3a**,**b** (Figure 1, conformer **X**) and for **3c** (Figure 1, conformer **XII**) would place the bulky *p*-tolyl group pointing toward the dihydropyran ring in an unfavorable scenario.[10]

We then studied another known thiophile, $Na_2S\cdot 9H_2O$ in MeOH, and found interesting results which were complementary to those previously obtained (Table 2).[11] For all substrates the major product was 3,6-*cis* allylic alcohol **8** in similar ratios for all types of substitution with the minor product *ent*-**7** presenting enantiomeric configuration at C-6. For substrates **3e** and **3f** (prepared to study synthetic applications of this process, see below), the silyl protecting group was cleaved in the presence of $Na_2S\cdot 9H_2O$ (entries 4, 5) both in the presence or absence of an excess of base in the reaction media. Since the [2,3]-sigmatropic rearrangement of allylic sulfoxides occurs as a concerted process and the facial selectivity is determined by the configuration of the sulfur-bearing center, from 2,3-*trans* substrates **3** it would be expected to obtain 3,6-*trans* alcohols. Therefore the results obtained with $Na_2S\cdot 9H_2O$ implied that an alternative reaction pathway was operative. The enantiomeric purity of some of the alcohols obtained was evaluated by derivatization with methoxyphenylacetic acid (see below).[12]

We hypothesized that formation of the major *cis* products and products of the enantiomeric configuration at C-6, could imply an epimerization at position 3 and/or a ring opening-closing sequence (Scheme 4), which would give rise to the formation of *cis* isomers **4** which are known to transform into alcohols **8** easily.[7b] Therefore, to address this possibility, we examined the behavior of dienyl sulfoxides **1**, precursors of dihydropyrans **3**, under these reaction conditions. Interestingly it was possible to carry out the cyclization and sigmatropic rearrangement in one step for all substrates studied, obtaining slightly different selectivities from the process with sulfinyl dihydropyrans **3**. Changing from MeOH to an aprotic solvent like DMF (Table 2, entry 7), improved the selectivity but with diminished yield due to formation of a considerable amount of the corresponding vinyl sulfoxide.[13] The use of lower excess of reagent did not have much effect on the selectivity (Table 2, entry 8). For *Z,E* diene **2b** (not shown) in DMF, a complex reaction mixture was recovered along with starting material.

The slightly different selectivities found for *ent*-**7a**−**b** and **8a**−**b** when carrying out the reaction from **3a**−**b** or from **1a**−**b** is likely to reflect the possibility of at least two potential reaction pathways for the process supporting the hypothesis of coexistence of epimerization at C-3 and ring opening-closing sequences. The minor *trans* product *ent*-**7a** obtained from the reaction of diene **1a** (Table 2, entry 6) was not enantiomerically pure (50% ee, see below). The fact that products of the enantiomeric series were obtained suggested the possibility of formation of both diastereomers of *cis* and *trans* dihydropyrans under the reaction conditions, each of them evolving preferentially through the most reactive isomers (Scheme 4). A tentative rationalization of these results may even involve a partial isomerization of the diene **1** to the *Z,E* isomer **2** and subsequent cyclization to obtain dihydropyrans with enantiomeric configuration at C-2, **5** or **6**

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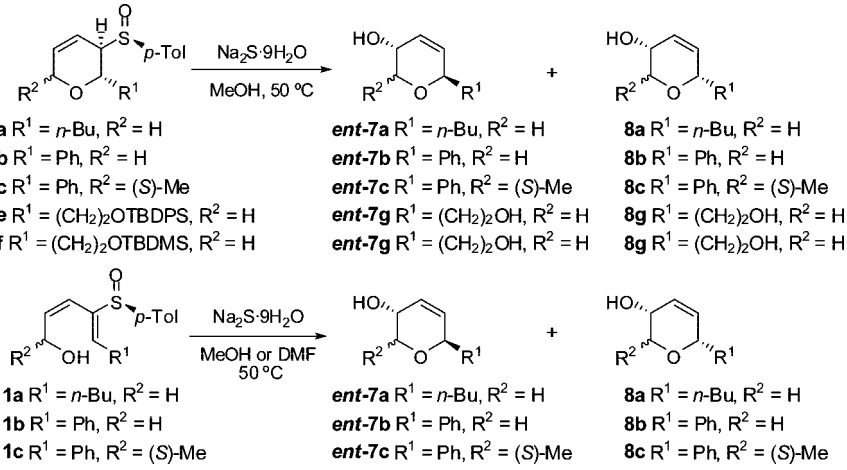
(10) The conformation around the sulfur atom could also be influenced by coordination of the sulfinyl and ring oxygens with the solvent thus increasing the steric bulk around those atoms. See: (a) McNelis, B. J.; Sternbach, D. D.; MacPhail, A. T. *Tetrahedron* **1994**, *50*, 6767–6782. (b) Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989–8992.

(11) Evans, D. A.; Bryan, C. A.; Sims, C. L. *J. Am. Chem. Soc.* **1972**, *94*, 2891–2892.

(12) Supporting Information. See: (a) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569–8577. For a review on the determination of absolute configuration by NMR, see: (b) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–118.

(13) Stereochemistry of vinyl sulfoxide could not be determined.

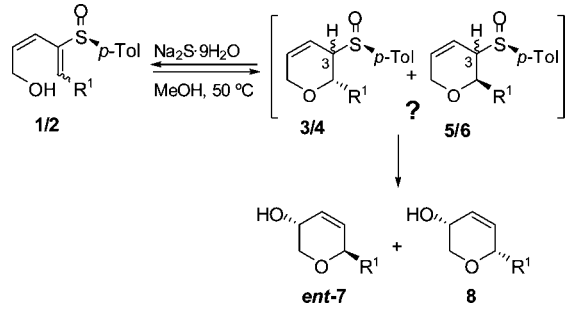
TABLE 2. Cyclization and Sigmatropic Rearrangement with $Na_2S \cdot 9H_2O$



entry	substrate	*ent*-**7**:**8** ratio	yield
1	**3a**	19:81	68%
2	**3b**	11:89	89%
3	**3c**	0:100	100%
4	**3e**	6:94	89%[a]
5	**3f**	0:100	100%[a]
6	**1a**	30:70	79%
7	**1a**	5:95	53%[b]
8	**1b**	34:66	96%[c]
9	**1c**	6:94	75%

[a] Deprotected alcohols **8g** and *ent*-**7g** were obtained. [b] Reaction carried out in DMF; ^{1}H NMR of the crude product was a 70:4:26 mixture of **8a**, *ent*-**7a** and the corresponding vinyl sulfoxide (8% isolated yield) (not shown, see Supporting Information). [c] Reaction carried out with 6.7 equiv of $Na_2S \cdot 9H_2O$.

SCHEME 4. Possible Reaction Pathway for the Formation of Alcohols 8 and *ent*-7



or simply that the cyclizations of dienols **1** have diminished selectivities under these conditions. Furthermore, it appears that Na_2S is sufficiently basic to promote epimerization at C-3 and/or ring-cleavage for sulfinyl dihydropyrans **3** leading to dienols **1** or **2**.

At this stage, we had not found a satisfactory solution for the sigmatropic rearrangement of 2,3-*trans* substrates **3**, the most readily available diastereomers from our methodology. Therefore, we explored other possibilities that could solve this problem and lead to an improvement of the process for these substrates. It has been reported that solvent effects have a profound influence on the rate of [2,3]-sigmatropic rearrangements.[1b,14] Usually, polar solvents stabilize sulfoxides by solvation decreasing the sulfoxide-sulfenate conversion rate. There are examples in the literature where a change of solvent modulates the reactivity of allylic sulfoxides, from obtaining the pyrolitic *syn*-elimination product in MeOH to affording the [2,3]-sigmatropic rearrangement product in benzene.[9b,15]

In addition to the thiophiles already mentioned, many different thiophilic bases, such as piperidine, K_2CO_3, $Mg(OMe)_2$, or DABCO, have been used in the past to carry out the conversion of allylic sulfoxides to allylic alcohols with variable results.[16] In the context of previous studies on the cyclization of hydroxy sulfinyl dienes with phosphazenes in different solvents, we had obtained small amounts of rearrangement product (allylic alcohol) so we decided to explore the use of hindered bases as thiophilic agents for the process.[7b] A change of solvent from MeOH to toluene, which allowed for an increase in the reaction temperature from 50 to 70 °C and at the same time might influence the viability and rate of the process, perhaps favoring the desired [2,3]-sigmatropic rearrangement, led us from 2,3-*trans* sulfoxides **3** to *trans* allylic alcohols **7** with complete stereoselectivity and good yields. We studied several hindered bases under the new conditions and the results are gathered in Table 3. The use of BEMP apparently caused some epimerization of the starting material, affording *trans* alcohols and a small amount of *cis* isomer (Table 3, entry 1). Amine and amidine type bases such as DABCO (Table 3, entries 2−5), DBU (Table 3, entries 6, 7 and 8), DBN (Table 3, entry 9) or quinuclidine (Table 3, entry 10), afforded the expected product with complete selectivity for substrates bearing aromatic and aliphatic substituents as well as for the C-4 substituted derivative **3h**.[17,18] In contrast, the yield for the reaction with $P(OMe)_3$ was only

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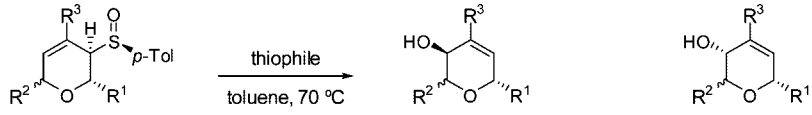
(15) Posner, G. H.; Haces, A.; Harrison, W.; Kinter, C. M. *J. Org. Chem.* **1987**, *52*, 4836–4841.

(16) (a) Evans, D. A.; Andrews, G. C. *J. Am. Chem. Soc.* **1972**, *94*, 3672–3674. (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Restelli, A. *Gazz. Chim. Ital.* **1985**, *115*, 637–641.

TABLE 3. Sigmatropic Rearrangement with Hindered Bases



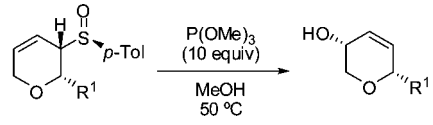
3a R^1 = *n*-Bu, R^2 = H, R^3 = H
3b R^1 = Ph, R^2 = H, R^3 = H
3e R^1 = $(CH_2)_2$OTBDPS, R^2 = H, R^3 = H
3h R^1 = *n*-Bu, R^2 = H, R^3 = Me

7a R^1 = *n*-Bu, R^2 = H, R^3 = H
7b R^1 = Ph, R^2 = H, R^3 = H
7e R^1 = $(CH_2)_2$OTBDPS, R^2 = H, R^3 = H
7h R^1 = *n*-Bu, R^2 = H, R^3 = Me

8a R^1 = *n*-Bu, R^2 = H, R^3 = H
8b R^1 = Ph, R^2 = H, R^3 = H
8e R^1 = $(CH_2)_2$OTBDPS, R^2 = H, R^3 = H
8h R^1 = *n*-Bu, R^2 = H, R^3 = Me

entry	substrate	base	**7**:**8** ratio	yield
1	**3a**	BEMP	97:3	84%
2	**3a**	DABCO	100:0	77%
3	**3b**	DABCO	100:0	90%
4	**3e**	DABCO	100:0	93%
5	**3h**	DABCO	100:0	41%
6	**3a**	DBU	100:0	53%
7	**3b**	DBU	100:0	92%
8	**3e**	DBU	100:0	70%
9	**3b**	DBN	100:0	67%
10	**3b**	Quinuclidine	100:0	69%
11	**3a**	$P(OMe)_3$	100:0	42%
12	**3a**	Et_2NH	100:0	83%

SCHEME 5. Sigmatropic Rearrangement of *cis* Isomers 4



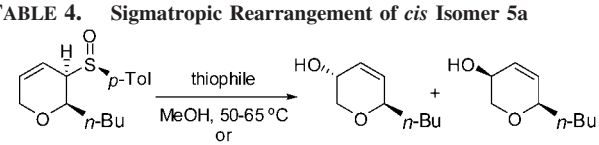
4a R^1 = *n*-Bu 6 h **8a** R^1 = *n*-Bu, 60%
4b R^1 = Ph 7 h **8b** R^1 = Ph, 63%
4e R^1 = $(CH_2)_2$OTBDPS 4 h **8e** R^1 = $(CH_2)_2$OTBDPS, 83%

improved slightly with the new conditions (Table 3, entry 11). It appears that the effect of the solvent is the main cause for the improvement in the stereoselectivity, as the reaction of **3a** with Et_2NH in toluene yields only *trans* product (Table 3, entry 12; compare to Table 1, entry 2). We hypothesized that toluene would minimize solvation of the oxygen atoms and therefore would lead to less restricted conformations around the sulfur−carbon bond, allowing for the oxygen to be placed in the appropriate position to interact with the allylic center.

Sigmatropic Rearrangement of 2,3-*cis* Sulfinyl Dihydropyrans. The reaction of 2,3-*cis* isomers **4** with $P(OMe)_3$ in MeOH proceeded smoothly for substrates with aliphatic and aromatic substituents (Scheme 5), leading to the expected 3,6-*cis* alcohols **8** as single isomers in moderate to good yields. The conformational analysis for **4a**−**b** suggested a pseudoaxial arrangement of the sulfoxide, with the oxygen oriented toward the double bond and the *p*-tolyl group facing away from the ring (Figure 2). Since it seems that no change of conformation is required to adopt the required conformation, the process is likely to have a lower activation energy which would explain the fact that these substrates rearrange almost spontaneously at room temperature in CH_2Cl_2 solution.

In contrast, diastereomeric 2,3-*cis* substrate **5a** was not reactive with $P(OMe)_3$ (Table 4, entry 1). When the conditions were changed to Et_2NH at 65 °C, we obtained a mixture of

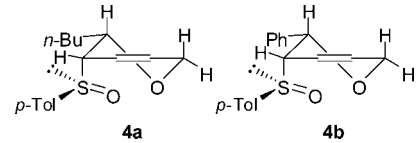
TABLE 4. Sigmatropic Rearrangement of *cis* Isomer 5a



5a ***ent*-7a** ***ent*-8a**

entry	thiophile agent	*ent*-**7a**:*ent*-**8a** ratio	yield
1	$P(OMe)_3$	−	−[a]
2	Et_2NH	72:28	100%[a]
3	$Na_2S \cdot 9H_2O$	100:0	70%[a]
4	DABCO	0:100	48%[b]
5	Et_2NH	0:100	53%[c]

[a] Reaction carried out in MeOH. [b] Reaction carried out in toluene. [c] Reaction carried out in toluene; 13% of vinyl sulfoxide isolated.



4a **4b**

FIGURE 2. Proposed conformations for **4a**−**b**.

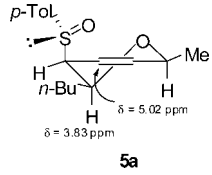
isomers with the *trans* isomer ***ent*-7a** as the major product (note that the main product should be *cis* as the process is expected to occur with retention of configuration). This suggests a possible epimerization at position 3 of the sulfoxide to give a reactive *trans* substrate similar to **6b** that would rearrange easily to form the *trans* allylic alcohol. The low value of the optical rotation of diastereomerically pure ***ent*-7a** derived from 2,3-*cis* substrate **5a** (Table 4, entry 3, see Supporting Information) suggests that, to some extent, the reaction pathway in this case involves a ring-cleavage followed by cyclization and rearrangement.

In contrast, under the new conditions, 2,3-*cis* sulfoxide **5a** gave the expected *cis* isomer ***ent*-8a** as a single product, but only in moderate yields (Table 4, entries 4 and 5). The reactive conformation for **5a** (Figure 3) would place the *p*-tolyl group pointing toward the dihydropyran ring thus leading to strong steric interactions with the *cis* side chain at C-2.

Stereochemical Assignments. Since the spectroscopic data for ***ent*-7b** was ambiguous ($J_{2ax\text{-}3}$ = 5.4 Hz, $J_{2eq\text{-}3}$ = 4.4 Hz) we prepared acetate ***ent*-9b** by acetylation and the inversion product

(17) Bicyclic amidines DBU and DBN have been termed as "nonnucleophilic strong bases" but numerous examples have been reported which demonstrate that they can also act as nucleophiles. For examples, see: Baidya, M.; Mayr, H. *Chem. Commun* **2008**, 1792–1794, and references therein.

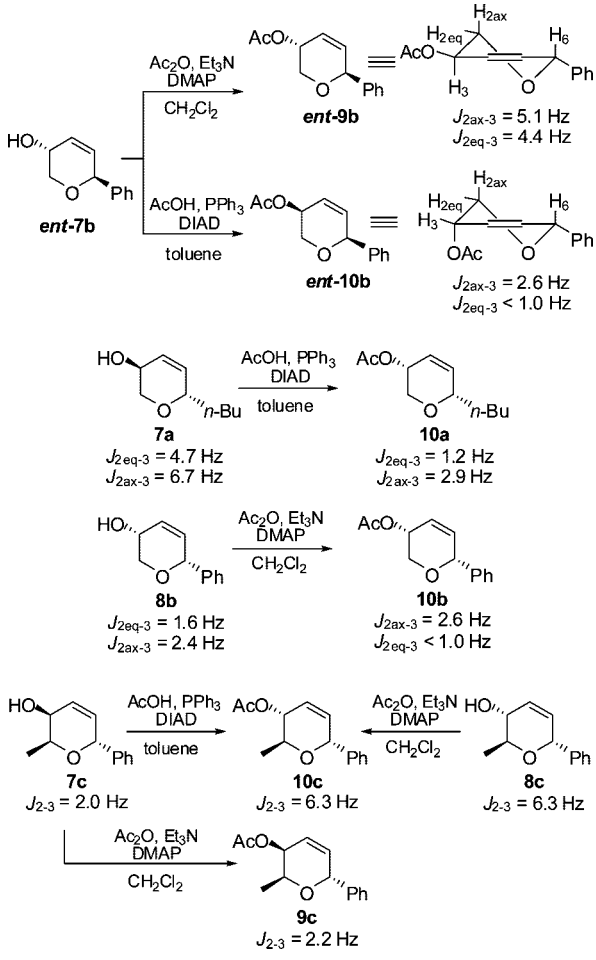
(18) The reaction mixture had to be carefully degassed before closing the system and heating at 70 °C for the yields to be reproducible.



5a

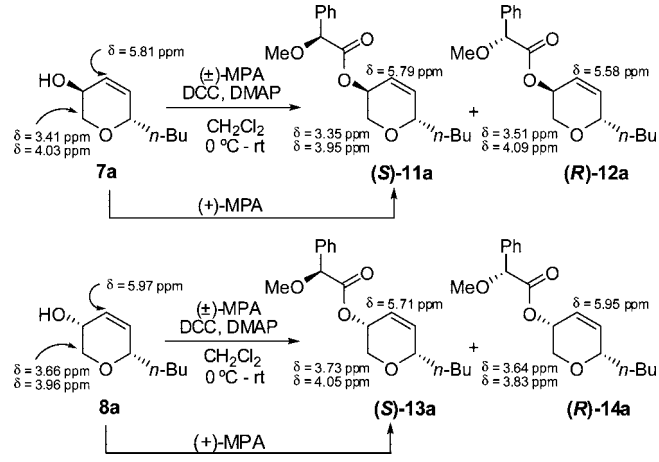
FIGURE 3. Proposed reactive conformer for **5a**.

SCHEME 6. Acetylation and Mitsunobu Reactions

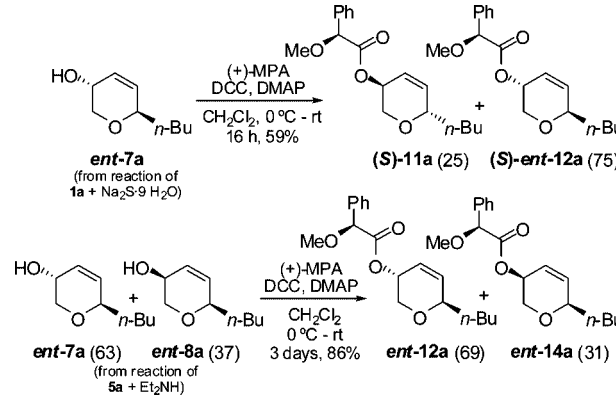


ent-**10b** by a Mitsunobu protocol.[19] The coupling constants between H_3-H_{2eq} and H_3-H_{2ax} indicated a pseudoaxial arrangement for H_3 for *ent*-**9b** and pseudoequatorial in *ent*-**10b**. This represented a 3,6-*trans* relative stereochemistry for acetate *ent*-**9b** and therefore for the precursor alcohol *ent*-**7b**. Based on coupling constants values for H_2 and H_3 we could determine the preferred conformation for alcohols **7a**−**e**, where the hydroxyl group is in a pseudoequatorial position ($J_{2eq-3} = 4.7$ Hz, $J_{2ax-3} = 6.7$ Hz) except for **7c** where the methyl substituent in C-2 is pseudoequatorial, with the phenyl and hydroxyl groups pseudoaxial. For **8a**−**e** the hydroxyl groups were pseudoaxial, except for alcohol **8c** which adopted a conformation where both methyl and hydroxyl substituents had a pseudoequatorial arrangement. To confirm the stereochemistry assigned to **7a** and **8b** they were converted into acetates **10a** and **10b** by Mitsunobu inversion and acetylation respectively (Scheme 6), that had coupling constants values similar to those obtained for *ent*-**10b**. The same procedures were followed for alcohols **7c** and **8c** both affording acetate **10c**, and diastereomeric acetate **9c** by acetylation of **7c**.

SCHEME 7. Derivatization of 7a and 8a



SCHEME 8. Derivatization of *ent*-7a and *ent*-8



The absolute stereochemistry of allylic alcohols **7a** (from **3a** and DABCO) and **8a** (from **3a** and Na_2S and independently, from **4a** and $P(OMe)_3$) was determined by the preparation of the (*S*) and (*R*)-methoxyphenyl acetates **11**, **12**, **13** and **14** (Scheme 7).[12] In addition, we have examined several derivatizations of products obtained with other thiophiles to gain insight on their absolute configurations, and therefore on the possible reaction pathways (Scheme 8).

The reaction with (+)-MPA of practically diastereomerically pure *ent*-**7a**, derived from the cyclization and rearrangement of **1a** with $Na_2S\cdot 9H_2O$, afforded only two diastereomers in 25:75 ratio, indicating that *ent*-**7a** had 50% ee (Scheme 8), and also that alcohol *ent*-**7a** obtained in this manner had enantiomeric configuration at C-6, thus supporting the hypothesis of ring opening-closing sequence. Shielding effects observed on H-4 showed that the assignment for the alcohols was in agreement with the results observed. On the other hand, a 63:37 diastereomeric mixture of *ent*-**7a** and *ent*-**8a**, obtained from the reaction of **5a** with Et_2NH, was derivatized with (+)-MPA to afford a 69:31 mixture of diastereomers *ent*-**12a** and *ent*-**14a** along with recovered starting material and traces of **13a**. This showed that the alcohols were epimers at C-3, and that more than one mechanism could be operating in the reaction, since a small amount of **13a** of the enantiomeric series was observed in the mixture.

Finally, 2,6-disubstituted alcohols **7c**, **7d** and **8c** were also derivatized with (+)-MPA to confirm their enantiomeric purity to produce esters **11c**, **11d** and **13c** respectively as single isomers (Scheme 9). Due to lack of sufficient amounts of these samples

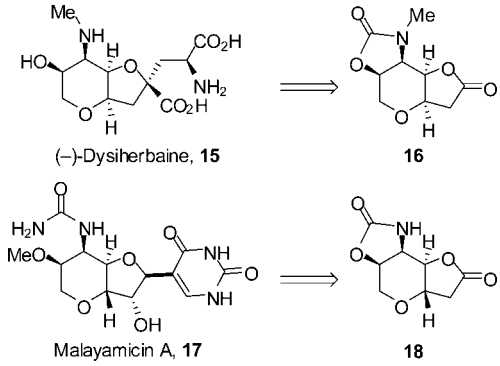
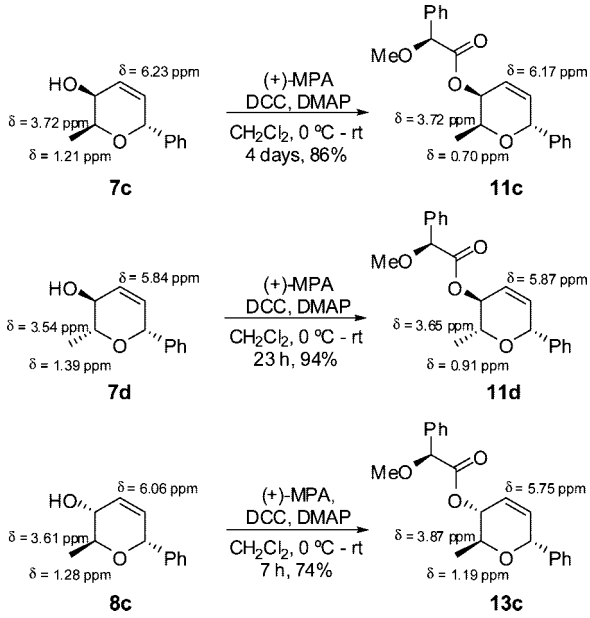


FIGURE 4. Structure of (−)-dysiherbaine and malayamicin A.

SCHEME 9. Derivatization of 7c, 7d, and 8c



we could not carry out the reaction with (±)-MPA, so strictly, the absolute configuration for these alcohols could not be confirmed. However, a spectroscopic analysis related to the previous one was done for all 2-methoxy-2-phenylacetic derivatives, observing that the methyl group at C-2 in **11c** and **11d** was shielded while H-4 was shielded in **13c** relative to the precursor alcohols. These results were similar to those observed for alcohols **7a** and **8a** and their corresponding methoxyphenyl acetates. Therefore assuming a similar behavior for alcohols **7c-d** and **8c** we tentatively assigned the absolute configurations shown in Scheme 9.

Synthetic Applications. Having developed efficient conditions to perform the [2,3]-sigmatropic rearrangement of 2,3-*trans* substrates **3** in good yields and selectivities, we addressed the synthetic applications of the process. We focused our attention in natural products such as (−)-dysiherbaine **15** and malayamicin A **17** (Figure 4) with a bicyclic tetrahydropyran-tetrahydrofuran core. (−)-Dysiherbaine is a neurotoxic aminoacid first isolated in 1997 from the marine sponge *Dysidea herbacea* that presents very interesting biological activity as a potent agonist of non-NMDA type glutamate receptors in the central nervous system.[20] The structure of **15** was determined by extensive spectroscopic studies to be an unprecedented diamino dicarboxylic acid, which is characterized by a structurally novel *cis*-fused hexahydrofuro[3,2-*b*]pyran ring system containing a glutamate substructure. The potent biological

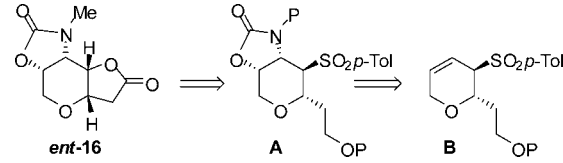
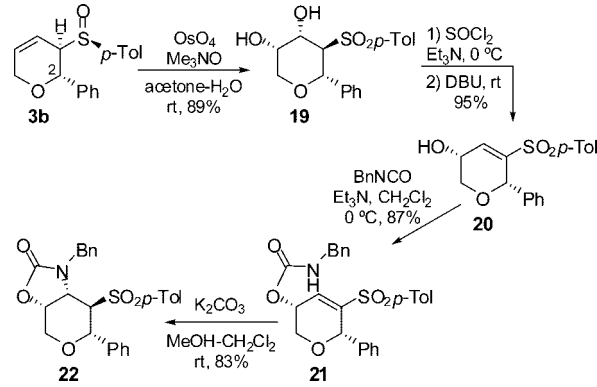


FIGURE 5. Initial retrosynthetic scheme.

SCHEME 10. Model Studies for the Initial Approach to *ent*-16



activity and structural novelty has led to many approaches toward the synthesis of dysiherbaine.[21] On the other hand, malayamicin A **17**, a bicyclic *C*-nucleoside that exhibits fungicide activity, was isolated from the soil organism *Streptomyces malaysiensis*, and its structure was proposed by detailed NMR studies and by degradation. The structure and stereochemistry of **17** was confirmed by a stereocontrolled total synthesis from D-ribonolactone,[22] and that methodology has been used to prepare semisynthetic analogues, *N*-malayamicin A and related purine and pyrimidine nucleosides.[23] In view of this background, we considered exploring an approach to the synthesis of ***ent*-16**, the enantiomer of a known intermediate in the total synthesis of (−)-dysiherbaine,[21e] and to tricyclic intermediate **18**, the core of deoxymalayamicin A (Figure 4). We report herein a full account of our studies toward the synthesis of *ent*-dysiherbaine,[6b] based on the [2,3]-sigmatropic rearrangement of sulfinyl dihydropyrans and a Donohoe tethered aminohydroxylation.[24] This last strategy has also been used by other groups to install the amino diol and create the four contiguous stereocenters in the tetrahydropyran ring of (−)-dysiherbaine.[21e,k]

Our initial retrosynthetic analysis implied the formation of a carbamate derivative **A** that could be obtained from an allylic sulfone **B** with the appropriate functionalization at C-2. (Figure 5). At this stage, we chose to carry out a model study to test the viability of the early steps of the sequence (Scheme 10).

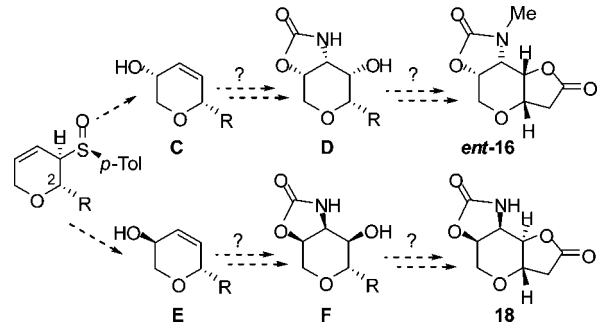
Readily available allylic sulfinyl dihydropyran **3b** (Scheme 10)[7] was subjected to dihydroxylation affording sulfonyl diol **19** and elimination to obtain vinyl sulfone **20**. Formation of benzyl carbamate **21** and cyclization under basic conditions afforded oxazolidinone **22** in excellent yield.[8] This model substrate presented the relative stereochemistry enantiomeric to dysiherbaine aside from the sulfone-bearing center. A reasonable option to convert a structure related to **22** into the required functionality would imply the transformation of the sulfone moiety into a carbonyl group,[25] and a straightforward reduction to the desired α-hydroxyl functionality. Typically this transformation requires a metalation at the sulfone-bearing center and capture of the anion with an oxygen-based electrophile. The structure of these intermediates, with two good leaving groups

flanking the reactive metalated sulfone, suggested that competing β-eliminations could be important in this case. These considerations, along with the considerable length of the synthetic plan, prevented us from pursuing this route further.

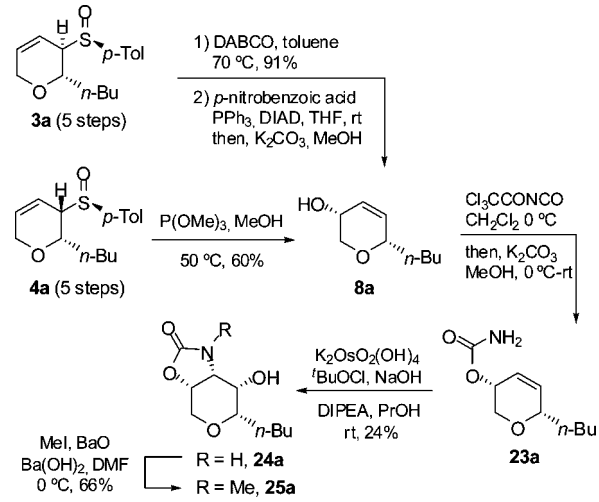
Taking advantage of the possibility of obtaining 3,6-*cis* and *trans* dihydropyranols from a common sulfinyl dihydropyran, we evaluated an alternative approach starting from an allylic sulfoxide related to **3b** with the appropriate functionalization at C-2 that could be transformed into alcohols **C** and **E** by a [2,3]-sigmatropic rearrangement in the presence of a thiophile,[6] and subsequently into **D** and **F** respectively by a tethered aminohydroxylation protocol (Scheme 11). Structure **D** after transformations of the side chain at C-2 could be converted into *ent*-**16**, enantiomer of the intermediate used in a total synthesis of (−)-dysiherbaine.[21c] From intermediate **F** a similar strategy could be applied to prepare **18** which presents the bicyclic core and functionality of deoxymalayamicin A.

To test the viability of the initial part of the synthetic scheme for *ent*-**16**, we focused on the known and easily available compound **3a** (Scheme 12) that underwent a smooth sigmatropic rearrangement under the new conditions, to produce the corresponding *trans* allylic alcohol stereoselectively that was converted into *cis* isomer **8a** by a Mitsunobu reaction.[19] As already discussed, the less readily available sulfoxide **4a** could be directly transformed into **8a** in one step and in good yield. Treatment of allylic alcohol **8a** with trichloroacetylisocyanate followed by aqueous K_2CO_3 in MeOH afforded carbamate **23a** in excellent yield. Aminohydroxylation of carbamate **23a**, under the conditions originally described by Donohoe,[24a] gave the

SCHEME 11. Synthetic Strategy for the Syntheses of *ent*-16 and 18



SCHEME 12. Model Study for the Synthesis of *ent*-16



desired product **24a** in 21−24% yield, along with 15−33% recovered starting material.[26,27] All efforts to improve the yield of this transformation, including a change of ligand to $(DHQ)_2PHAL$, changes of the batches and sources of reagents, etc., proved to be fruitless. Nonetheless, this model study was completed by *N*-methylation to afford **25a** in 66% yield.

At this stage we decided to carry on with the formal synthesis of *ent*-dysiherbaine, with the expectation that the outcome of the aminohydroxylation could be improved for the precise substrate required and our efforts are gathered in Scheme 13. We started the synthesis from commercially available 4-(*tert*-butyldimethylsilyloxy)-1-butyne **27f** in order to prepare sulfinyl dihydropyran **3f**. The synthesis of the corresponding alkynyl sulfoxide took place in very low yield, and the sigmatropic rearrangement of **3f** with $Na_2S\cdot 9H_2O$ (Table 2, entry 5) planned to obtain **8f**, led to the 3,6-*cis* deprotected derivative **8g** as we have already discussed. Unfortunately selective protection of the primary alcohol to generate **8f** was not efficient and therefore we considered using the TBDPS derivative instead, expecting it to be stable in the sigmatropic rearrangement step.[28] Therefore

(19) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164.

(20) Sakai, R.; Kamiya, H.; Murata, M.; Shimamoto, K. *J. Am. Chem. Soc.* **1997**, *119*, 4112–4116.

(21) Total syntheses: (a) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2000**, *2*, 635–638. (b) Sasaki, M.; Koike, T.; Sakai, R.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 3923–3926. (c) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *J. Am. Chem. Soc.* **2000**, *122*, 5216–5217. (d) Phillips, D.; Chamberlin, A. R. *J. Org. Chem.* **2002**, *67*, 3194–3201. (e) Takahashi, K.; Matsumura, T.; Ishihara, J.; Hatakeyama, S. *Chem. Commun.* **2007**, 4158–4160. (f) Sasaki, M.; Tsubone, K.; Aoki, K.; Akiyama, N.; Shoji, M.; Oikawa, M.; Sakai, R.; Shimamoto, K. *J. Org. Chem.* **2008**, *73*, 264–273. Partial and formal syntheses: (g) Naito, T.; Nair, J. S.; Nishiki, A.; Yamashita, K.; Kiguchi, T. *Heterocycles* **2000**, *53*, 2611–2615. (h) Miyata, O.; Iba, R.; Hashimoto, J.; Naito, T. *Org. Biomol. Chem.* **2003**, *1*, 772–774. (i) Kang, S. H.; Lee, Y. M. *Synlett* **2003**, 993–994. (j) Huang, J.-M.; Xu, K.-C.; Loh, T.-P. *Synthesis* **2003**, 755–764. (k) Cohen, J. L.; Chamberlin, A. R. *Tetrahedron Lett.* **2007**, *48*, 2533–2536. (l) See also ref 6a. Related studies: (m) Lygo, B.; Slack, D.; Wilson, C. *Tetrahedron Lett.* **2005**, *46*, 6629–6632. (n) Cohen, J. L.; Limon, A.; Miledi, R.; Chamberlin, A. R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2189–2194. (o) Sasaki, M.; Tsubone, K.; Shoji, M.; Oikawa, M.; Shimamoto, K.; Sakai, R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5784–5787. (p) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 9373–9381.

(22) Hanessian, S.; Marcotte, S.; Machaalani, R.; Huang, G. *Org. Lett.* **2003**, *5*, 4277–4280.

(23) (a) Hanessian, S.; Huang, G.; Chenel, C.; Machaalani, R.; Loiseleur, O. *J. Org. Chem.* **2005**, *70*, 6721–6734. (b) Hanessian, S.; Marcotte, S.; Machaalani, R.; Huang, G.; Pierron, J.; Loiseleur, O. *Tetrahedron* **2006**, *62*, 5201–5214.

(24) (a) Donohoe, T. J.; Johnson, P. D.; Helliwell, M.; Keenan, M. *Chem. Commun.* **2001**, 2078–2079. (b) Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934–12935. (c) Donohoe, T. J.; Johnson, P. D.; Pye, R. J. *Org. Biomol. Chem.* **2003**, *1*, 2025–2028. (d) Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* **2004**, *6*, 2583–2585. (e) Kenworthy, M. N.; McAllister, G. D.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 6661–6664. (f) Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* **2005**, *7*, 1275–1277. (g) Donohoe, T. J.; Chughtai, M. J.; Klauber, D. J.; Griffin, D.; Campbell, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 2514–2515. (h) Donohoe, T. J.; Bataille, C. J. R.; Gattrell, W.; Kloesges, J.; Rossignol, E. *Org. Lett.* **2007**, *9*, 1725–1728.

(25) (a) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188–196. (b) Baudin, J.-B.; Julia, M.; Rolando, C. *Tetrahedron Lett.* **1985**, *26*, 2333–2334. (c) Hwu, J. R. *J. Org. Chem.* **1983**, *48*, 4432–4433. (d) Chemla, F.; Julia, M.; Uguen, D. *Bull. Soc. Chim. Fr.* **1993**, *130*, 547–553. (e) Hoppe, D.; Tebben, P.; Reggelin, M.; Bolte, M. *Synthesis* **1997**, 183–189. (f) Fujishima, H.; Takeshita, H.; Toyota, M.; Ihara, M. *J. Org. Chem.* **2001**, *66*, 2394–2399.

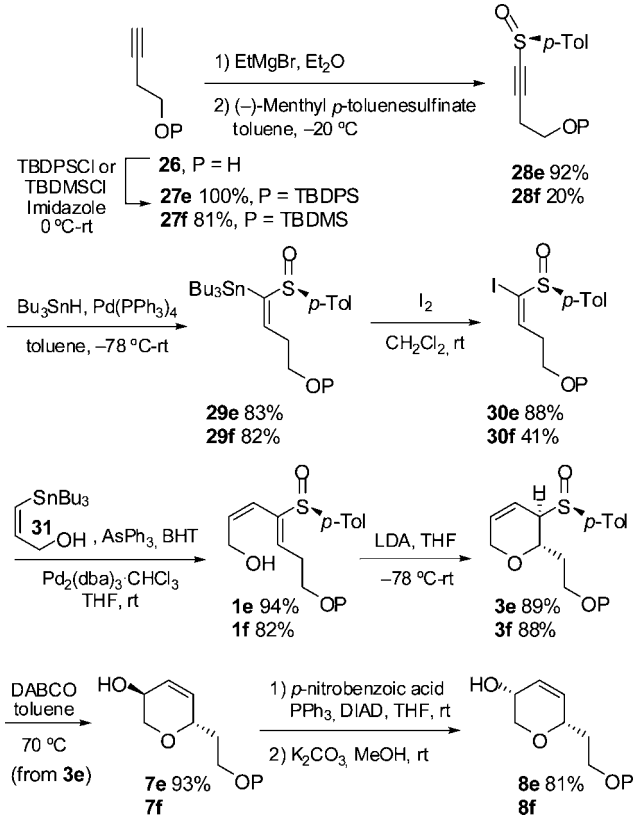
(26) Lwoff, N. MS thesis, Universidad Complutense de Madrid, September 2005.

(27) The tethered aminohydroxylation was carried out in small scale and it has been previously reported that under these conditions the yields vary unpredictably from 4 to 40%. See: Curtis, K. L.; Fawcett, J.; Handa, S. *Tetrahedron Lett.* **2005**, *46*, 5297–5300.

(28) Since the exploratory study with a TBDMS silyl ether was carried out at small scale, and the sequence was not completed, the intermediates could not be fully characterized.

(29) Merten, J.; Hennig, A.; Schwab, P.; Fröhlich, R.; Tokalov, S. V.; Gutzeit, H. O.; Metz, P. *Eur. J. Org. Chem.* **2006**, 1144–1161.

SCHEME 13. Synthesis of Alcohol 8e

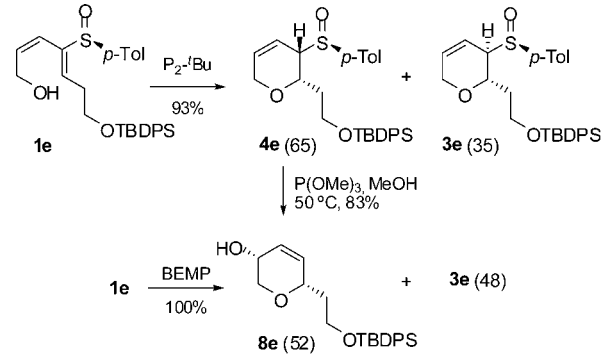


we started the synthesis from 3-butyn-1-ol **26** and after protection of the hydroxyl group as a TBDPS ether, alkynyl sulfoxide **28e** was formed by reaction with EtMgBr and (−)-menthyl *p*-toluenesulfinate in excellent yield.

Hydrostannylation of **28e** and tin−iodine exchange, led to vinyl iodide **30e** that underwent a Stille coupling with hydroxy vinyl stannane **31** to give sulfinyl diene **1e** in excellent yield. Base-promoted cyclization with LDA afforded sulfinyl dihydropyran **3e** as a single isomer. The sigmatropic rearrangement using $Na_2S\cdot 9H_2O$ surprisingly led to similar results to the TBDMS derivative (89% *cis*:*trans*, 94:6 deprotected derivatives **8g** and *ent*-**7g** as seen in Table 2, entry 4). We hypothesized that sulfenic acids formed in the sigmatropic rearrangement could be effecting cleavage of the silyl group, but addition of excess K_2CO_3 in the reaction media was not effective to avoid desilylation. Fortunately the optimized conditions for the [2,3]-sigmatropic rearrangement (DABCO, toluene) worked perfectly on allylic sulfoxide **3e** to produce allylic alcohol **7e** that was inverted by a Mitsunobu protocol to give 3,6-*cis* alcohol **8e**. It should be pointed out that, under different conditions, diene **1e** leads to allylic alcohol **8e** in one or two steps (Scheme 14). Reaction of **1e** with phosphazene P_2-^{t}Bu afforded the expected product **3e**, along with 2,3-*cis* sulfinyl dihydropyran **4e**[7] with moderate selectivity, which could be easily transformed into alcohol **8e** by sigmatropic rearrangement with $P(OMe)_3$. Cyclization of **1e** with BEMP, afforded **3e** and a considerable amount of **8e** obtaining the desired substrate in one step from the diene with moderate selectivity.

Treatment of alcohol **8e** with trichloroacetylisocyanate followed by aqueous K_2CO_3 as described above for the model substrate gave carbamate **23e** in excellent yield (98%) (Scheme 15). Carbamate **23e** was submitted to the original conditions for aminohydroxylation,[24a] to afford a disappointing 26% yield

SCHEME 14. Alternative Procedures To Obtain Alcohol 8e



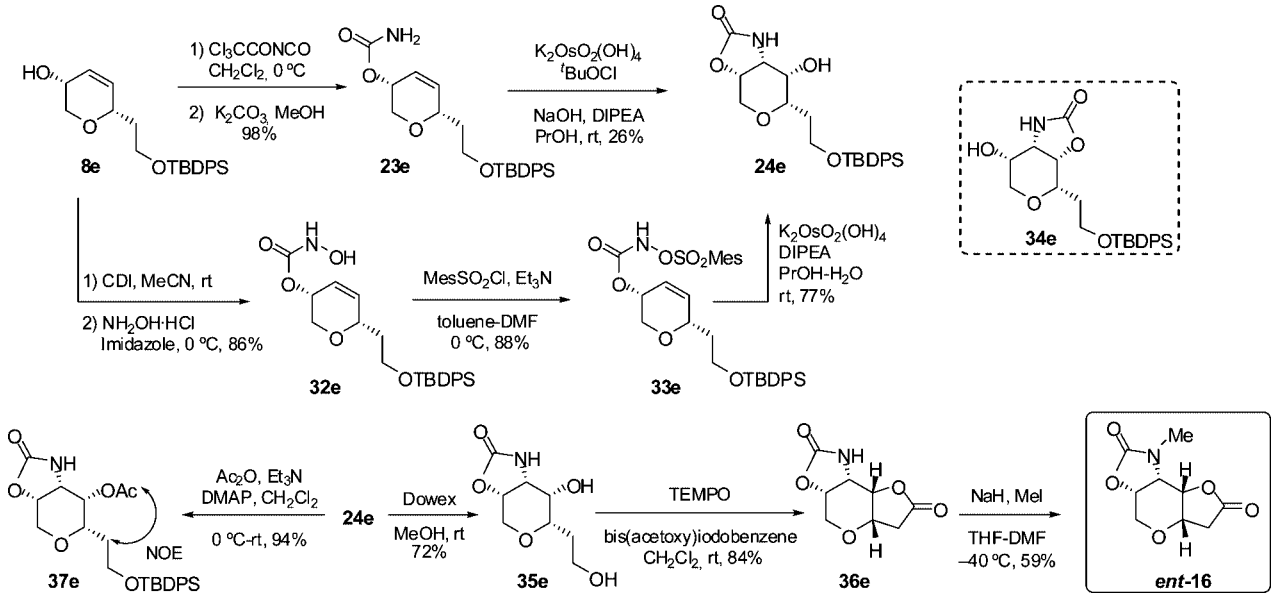
of oxazolidinone **24e**, along with 50% recovered starting material. In addition, **24e** was often produced along with variable amounts of a regioisomeric oxazolidinone **34e** that could be originated due to the presence of base in the reaction media; related isomerizations have been described by Chamberlin and Handa.[21k,27] This isomerization, along with the poor yield obtained for the aminohydroxylation, represented a major drawback for the success of the sequence.

At this time Donohoe reported a modification on the original conditions for the tethered aminohydroxylation that entailed the use of *N*-sulfonyloxy derivatives.[24g] This new protocol allowed for the reaction to proceed without chlorinating agent (*t*-BuOCl) or hydroxide base. Encouraged by this alternative we decided to examine the modified procedure for the aminohydroxylation and the required *N*-sulfonyloxy carbamate was readily prepared by sequential reaction of alcohol **8e** with carbonyldiimidazole and hydroxylamine to obtain **32e**, followed by sulfonylation to afford **33e** in good yield. We first studied the aminohydroxylation for the tosyloxy derivative, but the yields were low (25%) and the starting material was not recovered. In contrast, the mesitylsulfonyloxy derivative **33e** resulted more stable and gave higher yields in the key step. The tethered aminohydroxylation worked very well on this substrate leading to the expected oxazolidinone **24e** that contains the four contiguous *cis* stereocenters of the target. The regiochemistry of the product was confirmed by NOE measurements on acetate **37e**. Cleavage of the silyl ether of **24e** with Dowex (no reaction was observed with TBAF) afforded diol **35e** and selective oxidation of the primary alcohol to the acid with TEMPO with concurrent cyclization led to butyrolactone **36e**.[29] Finally an *N*-methylation, completed the synthesis of tricyclic structure *ent*-**16** that had identical data to that described in the literature, except for the sign and magnitude of the specific rotation (see Experimental Section).[21c,30]

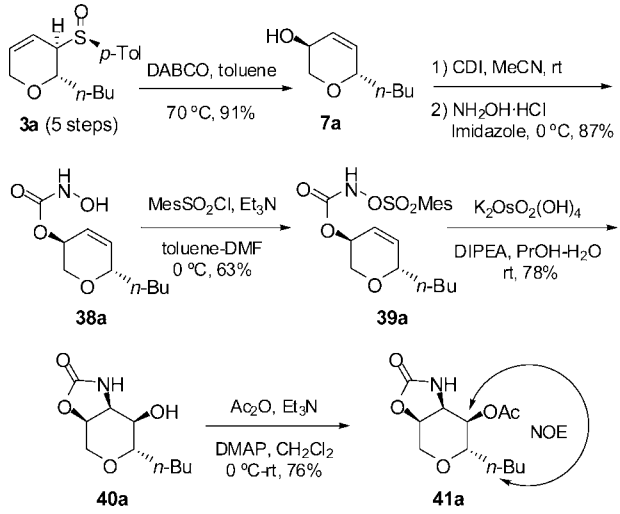
Since *trans* alcohol **7e** was readily accessible from sulfoxide **3e** in one step, we examined the application of this methodology to access an isomeric product with a *trans*-fused bicyclic structure like the core of deoxymalayamicin A. To test the aminohydroxylation reaction with the *trans* substituted substrate, we first explored the process for model substrate **7a** (Scheme 16). Hydroxycarbamate **38a** was prepared as described before, and after sulfonylation afforded the required *N*-sulfonyloxy precursor for the aminohydroxylation step. Under optimized conditions, oxazolidinone **40a** was obtained as a single product with good yield. The regiochemistry of the product was again confirmed by NOE interactions on acetate **41a**.

(30) Similar conditions to those previously used for the model substrate with MeI, BaO, and $Ba(OH)_2$ led to complex reaction mixtures, where only traces of the desired product could be identified.

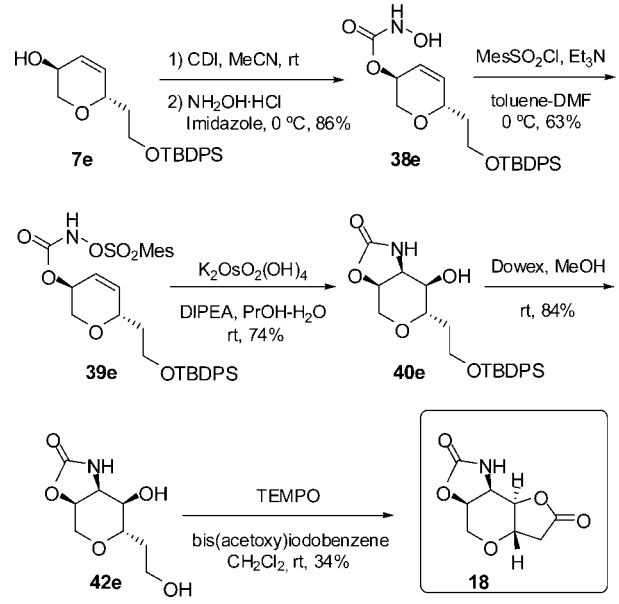
SCHEME 15. Synthesis of *ent*-16



SCHEME 16. Model Substrate for the Synthesis of 18



SCHEME 17. Synthesis of 18



Once we had secured that the aminohydroxylation was effective for the *trans* model substrate, we carried out the sequence from alcohol **7e** (Scheme 17). Reaction with carbonyldiimidazole and hydroxylamine led to **38e** that after sulfonylation with mesitylsulfonyl chloride afforded aminohydroxylation precursor **39e**. The aminohydroxylation of **39e** proceeded smoothly to give oxazolidinone **40e** as a single product. Cleavage of the silyl group with Dowex, and selective oxidation of the primary alcohol with TEMPO with concurrent cyclization as observed for the *cis* series, led to butyrolactone **18**. Unfortunately this intermediate had limited stability and led to ring opening degradation products upon standing for a few days in solution in $CDCl_3$.

In conclusion, we have studied the [2,3]-sigmatropic rearrangement of allylic sulfinyl dihydropyrans, under different conditions with various thiophilic agents. Under standard conditions [$P(OMe)_3$/MeOH], the products were obtained in low yields for the less reactive substrates; the yields were better using Et_2NH or $Na_2S \cdot 9H_2O$ in MeOH, but mixtures of diastereomers were obtained. Tertiary amines in toluene and slightly higher temperatures afforded the desired allylic alcohols stereoselectively and in moderate to excellent yields. We have applied these conditions to the formal synthesis of *ent*-dysiherbaine from commercially available 3-butyn-1-ol and from a common intermediate of this route, a new approach to the core of deoxymalayamicin A was explored. Thus, related structures ***ent*-16** and *trans*-fused isomer **18** were prepared from a common precursor using a [2,3]-sigmatropic rearrangement and a tethered aminohydroxylation as key steps.

Experimental Section

(+)-(S_s)-*tert*-Butyldiphenyl[4-(*p*-tolylsulfinyl)-but-3-ynyloxy]-silane (28e). From alkyne **27e** (558 mg, 1.81 mmol, 2.2 equiv), Mg turnings (40 mg, 1.65 mmol, 2 equiv), EtBr (0.14 mL, 1.81 mmol, 2.2 equiv) and (−)-menthyl *p*-toluenesulfinate (242 mg, 0.823 mmol, 1 equiv), according to the general procedure described in the Supporting Information (22 h) alkynyl sulfoxide **28e** was obtained. Purification by chromatography (5−30% EtOAc-hexane) afforded **28e** (340 mg, 0.761 mmol, 92%) as a colorless oil. R_f

0.22 (20% EtOAc-hexane). $[\alpha]^{20}_D$ +30.4 (c = 1.30). ^{1}H NMR (300 MHz) δ 1.01 (s, 9 H,), 2.39 (s, 3 H), 2.65 (t, 2 H, J = 6.6 Hz), 3.77 (t, 2 H, J = 6.6 Hz), 7.28 (d, 2 H, J = 8.3 Hz), 7.32−7.44 (m, 6 H), 7.61 (d, 2 H, J = 8.0 Hz), 7.61 (d, 2 H, J = 7.6 Hz), 7.66 (d, 2 H, J = 8.2 Hz). ^{13}C NMR (75 MHz) δ 19.1, 21.4, 23.8, 26.6 (3 C), 61.0, 79.1, 102.9, 125.0 (2 C), 127.7 (4 C), 129.7 (2 C), 130.1 (2 C), 133.0, 135.4 (5 C), 140.9, 142.1. IR (film): 3069, 3045, 2955, 2931, 2878, 2854, 2185, 1590, 1472, 1428, 1113, 1061, 810, 737, 703 cm^{-1}. MS (ES): 893 [2M + 1]$^+$, 447 [M + 1]$^+$, 469 [M + Na]$^+$, 369 [M − Ph]$^+$ (100%).

(−)-(*S*,*E*)-*tert*-Butyldiphenyl[4-(*p*-tolylsulfinyl)-4-(tributylstannyl)-but-3-enyloxy]silane (29e). From alkynyl sulfoxide **28e** (884 mg, 1.98 mmol), Bu_3SnH (0.6 mL, 2.2 mmol, 1.1 equiv) and $Pd(Ph_3P)_4$ (46 mg, 0.04 mmol, 0.02 equiv), according to the general procedure described in the Supporting Information (15 h) a 90:10 mixture of stannanes **29e** and **29e′** was obtained. Purification by chromatography (2−20% EtOAc-hexane) afforded **29e** (1.22 g, 1.65 mmol, 83%) and **29e′** (127 mg, 0.172 mmol, 9%) as colorless oils.

Data for 29e: R_f 0.26 (10% EtOAc-hexane). $[\alpha]^{20}_D$ −38.9 (c = 0.84). ^{1}H NMR (300 MHz) δ 0.80−1.01 (m, 15 H), 1.05 (s, 9 H), 1.13−1.52 (m, 12 H), 2.35 (s, 3 H), 2.66 (m, 1 H), 2.90 (m, 1 H), 3.78 (t, 2 H, J = 6.1 Hz), 6.38 (dd, 1 H, J = 7.6, 6.3 Hz), 7.18 (d, 2 H, J = 8.1 Hz), 7.34−7.44 (m, 8 H), 7.65 (d, 4 H, J = 7.6 Hz). ^{13}C NMR (75 MHz) δ 11.3 (3 C), 13.6 (3 C), 19.2, 21.2, 26.8 (3 C), 27.2 (3 C), 28.7 (3 C), 35.8, 62.7, 124.4, 127.7 (2 C), 129.5 (3 C), 129.7 (4 C), 133.4, 133.5, 135.5 (4 C), 139.9, 142.3, 145.6, 157.8. IR (film): 3069, 3045, 2956, 2928, 2857, 1587, 1488, 1463, 1428, 1378, 1112, 1039, 942, 822, 805, 736, 702 cm^{-1}. MS (ES): 761 [M + Na]$^+$, 681 [M − ^{t}Bu]$^+$ (100%).

Data for (−)-(*R*,*E*)-*tert*-Butyldiphenyl[4-(*p*-tolylsulfinyl)-3-(tributylstannyl)but-3-enyloxy]silane, 29e′: R_f 0.10 (10% EtOAc-hexane). $[\alpha]^{20}_D$ −63.3 (c = 1.40). ^{1}H NMR (300 MHz) δ 0.80 (m, 15 H), 1.06 (s, 9 H), 1.11−1.38 (m, 12 H), 2.35 (s, 3 H), 3.04 (m, 2 H), 3.60 (td, 1 H, J = 9.5, 6.2 Hz), 3.73 (td, 1 H, J = 9.5, 6.2 Hz), 6.18 (s, 1 H), 7.18 (d, 2 H, J = 8.3 Hz), 7.34−7.44 (m, 8 H), 7.64−7.70 (m, 4 H). ^{13}C NMR (75 MHz) δ 10.1 (3 C), 13.5 (3 C), 19.2, 21.3, 26.8 (3 C), 27.1 (2 C), 28.6 (3 C), 28.8, 39.0, 63.3, 124.2, 127.7 (4 C), 129.7 (2 C), 129.8 (2 C), 133.5, 135.5 (3 C), 135.6 (3 C), 140.6, 141.9, 145.5, 155.8. IR (film): 3069, 3045, 2957, 2929, 2857, 1590, 1492, 1464, 1428, 1378, 1111, 1081, 1043, 822, 808, 739, 702 cm^{-1}. MS (ES): 761 [M + Na]$^+$ (100%).

(−)-(*S*,*E*)-*tert*-Butyl[4-iodo-4-(*p*-tolylsulfinyl)but-3-enyloxy]diphenylsilane (30e). From stannane **29e** (1.22 g, 1.65 mmol) and iodine (502 mg, 1.98 mmol, 1.2 equiv), according to the general procedure described in the Supporting Information (1 h 30 min) iodide **30e** was obtained. Purification by chromatography (5−20% EtOAc-hexane) afforded **30e** (814 mg, 1.42 mmol, 86%) as a colorless oil. R_f 0.38 (30% EtOAc-hexane). $[\alpha]^{20}_D$ −51.0 (c = 0.67). ^{1}H NMR (300 MHz) δ 1.07 (s, 9 H), 2.36 (s, 3 H), 2.92 (m, 2 H), 3.82 (t, 2 H, J = 6.2 Hz), 6.93 (t, 1 H, J = 7.7 Hz), 7.19 (d, 2 H, J = 8.1 Hz), 7.36−7.46 (m, 8 H), 7.63−7−67 (m, 4 H). ^{13}C NMR (75 MHz) δ 19.0, 21.3, 26.7 (3 C), 36.4, 62.1, 115.8, 124.2 (2 C), 127.7 (4 C), 129.6 (2 C), 129.7, 132.9, 133.0, 135.3 (5 C), 139.6, 141.4, 148.7. IR (film): 3069, 3045, 2955, 2930, 2858, 1590, 1491, 1472, 1428, 1390, 1111, 1089, 942, 819, 810, 703 cm^{-1}. MS (ES): 1171 [2M + Na]$^+$, 597 [M + Na]$^+$ (100%), 497 [M − Ph]$^+$. Anal. calcd for $C_{27}H_{31}IO_2SSi$: C, 56.44; H, 5.44; I, 22.09; S, 5.58. Found: C, 56.36; H, 5.58; I, 21.96; S, 5.56.

(−)-(*S*)-2-(*Z*)-4-(*Z*)-7-(*tert*-Butyldiphenylsilyloxy)-4-(*p*-tolylsulfinyl)hepta-2,4-dien-1-ol (1e). From iodide **30e** (801 mg, 1.39 mmol), stannane **31** (1.2 equiv, 828 mg of 70:30 mixture **31** and **31′**, 1.67 mmol **31**), BHT (306 mg, 1.39 mmol), Ph_3As (85 mg, 0.278 mmol) and $Pd_2(dba)_3\cdot CHCl_3$ (72 mg, 0.07 mmol), according to the general procedure described in the Supporting Information (21 h), diene **1e** was obtained as a single isomer. Purification by chromatography (15−50% EtOAc-hexane) afforded **1e** (662 mg, 1.31 mmol, 94%) as a colorless oil. R_f 0.17 (50% EtOAc-hexane). $[\alpha]^{20}_D$ −34.8 (c = 0.71). ^{1}H NMR (300 MHz) δ 1.06 (s, 9 H), 2.36 (s, 3 H), 2.57 (dd, 1 H, J = 8.5, 4.7 Hz), 2.92 (ap q, 2 H, J = 6.8 Hz), 3.82 (m, 3 H), 4.01 (m, 1 H), 5.57 (d, 1 H, J = 11.3 Hz), 5.99−6.10 (m, 2 H), 7.18 (d, 2 H, J = 7.9 Hz), 7.30−7.45 (m, 8 H), 7.63−7.67 (m, 4 H). ^{13}C NMR (75 MHz) δ 19.2, 21.3, 26.8 (3 C), 32.1, 58.1, 63.0, 121.4, 124.3, 127.8 (3 C), 129.7 (3 C), 129.8 (3 C), 133.3 (2 C), 135.5 (4 C), 137.9, 138.2, 138.3, 141.0, 142.3. IR (film): 3401, 3069, 3045, 2955, 2931, 2858, 1590, 1471, 1428, 1390, 1112, 1039, 809, 753, 703 cm^{-1}. MS (ES): 1031 [2M + Na]$^+$, 527 [M + Na]$^+$ (100%), 505 [M + 1]$^+$. Anal. calcd for $C_{30}H_{36}O_3SSi$: C, 71.39; H, 7.19; S, 6.35. Found: C, 71.43; H, 7.13; S, 6.39.

(−)-(2*S*,3*R*,*R*$_S$)-*tert*-Butyldiphenyl-{2-[3-(*p*-tolylsulfinyl)-3,6-dihydro-2*H*-pyran-2-yl]-ethoxy}silane (3e), and (2*S*,3*S*,*R*$_S$)-*tert*-Butyldiphenyl-{2-[3-(*p*-tolylsulfinyl)-3,6-dihydro-2*H*-pyran-2-yl]-ethoxy}silane (4e). From dienyl sulfoxide **1e** (37 mg, 0.073 mmol) and P_2-^{t}Bu (40 μL, 0.08 mmol, 1.1 equiv) according to the general procedure D described in the Supporting Information (3 min), a 65:35 mixture of dihydropyrans **4e** and **3e** was obtained. Purification by chromatography (0−10% Et_2O−CH_2Cl_2) afforded **3e** (15 mg, 0.030 mmol, 41%) and **4e** (19 mg, 0.038 mmol, 52%) as colorless oils. Allylic sulfoxide **4e** was unstable; rapid sigmatropic rearrangement occurred to produce alcohol **8e**, and this prevented the complete characterization of the sulfoxide.

Data for 3e: R_f 0.16 (30% EtOAc-hexane). $[\alpha]^{20}_D$ −109.9 (c = 0.95). ^{1}H NMR (300 MHz) δ 1.03 (s, 9 H), 1.93 (q, 2 H, J = 6.6 Hz), 2.31 (s, 3 H), 3.27 (ap t, 1 H, J = 1.0 Hz), 3.77 (dd, 1 H, J = 10.0, 5.4 Hz), 3.84 (dt, 1 H, J = 10.4, 7.0 Hz), 3.95 (ap d, 2 H, J = 2.2 Hz), 4.35 (m, 1 H), 5.30 (ddd, 1 H, J = 10.5, 4.6, 2.4 Hz), 5.90 (ap d, 1 H, J = 10.3 Hz), 7.23 (d, 2 H, J = 8.3 Hz), 7.32−7.44 (m, 6 H), 7.51 (d, 2 H, J = 8.1 Hz), 7.63−7.67 (m, 4 H). ^{13}C NMR (75 MHz) δ 19.2, 21.5, 26.8 (3 C), 34.3, 61.5, 65.4 (2 C), 67.6, 116.6, 125.5 (2 C), 127.7 (4 C), 129.6 (4 C), 132.2, 133.5, 133.6, 135.6 (4 C), 138.3, 142.0. IR (film) 3069, 3047, 2955, 2930, 2859, 1590, 1493, 1472, 1428, 1390, 1261, 1186, 1112, 1084, 1047, 940, 812, 738, 703 cm^{-1}. MS (ES): 1031 [2M + Na]$^+$, 527 [M + Na]$^+$ (100%), 505 [M + 1]$^+$.

Partial Data for 4e: R_f 0.33 (20% EtOAc-CH_2Cl_2). ^{1}H NMR (300 MHz) δ 1.04 (s, 9 H), 2.09−2.20 (m, 1 H), 2.33−2.42 (m, 1 H), 2.39 (s, 3 H), 2.95 (dt, 1 H, J = 5.6, 2.8 Hz), 3.86 (quint, 1 H, J = 5.1 Hz), 3.98 (ddd, 1 H, J = 10.2, 8.5, 4.6 Hz), 4.13 (dm, 1 H, J = 17.3 Hz), 4.19 (m, 1 H), 4.34 (dm, 1 H, J = 17.3 Hz), 5.33 (m, 1 H), 6.23 (ddd, 1 H, J = 11.9, 2.8, 1.5 Hz), 7.27−7.35 (m, 3 H), 7.36−7.42 (m, 7 H), 7.63−7.68 (m, 4 H). ^{13}C NMR (75 MHz) δ 19.2, 21.3, 26.9 (3 C), 36.0, 60.0, 64.1, 66.2, 71.5, 115.7, 124.1 (2 C), 127.7 (3 C), 129.6 (2 C), 129.7 (3 C), 133.6, 133.8, 135.0, 135.5 (4 C), 139.5, 140.8. MS (ES): 1031 [2M + Na]$^+$, 527 [M + Na]$^+$ (100%), 505 [M + 1]$^+$.

(+)-(3*S*,6*S*)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-3,6-dihydro-2*H*-pyran-3-ol (7e). From sulfoxide **3e** (114 mg, 0.226 mmol) and DABCO (30 mg, 0.271 mmol, 2 equiv), according to the general procedure H described in the Supporting Information (17 h) alcohol **7e** was obtained. Purification by chromatography (0−15% EtOAc-CH_2Cl_2) afforded **7e** (80 mg, 0.209 mmol, 93%) as a colorless oil. R_f 0.25 (15% EtOAc-CH_2Cl_2). $[\alpha]^{20}_D$ +35.8 (c = 1.20). ^{1}H NMR (300 MHz) δ 1.03 (s, 9 H), 1.64 (d, 1 H, J = 8.3 Hz), 1.74 (ap q, 2 H, J = 6.0 Hz), 3.41 (dd, 1 H, J = 11.2, 6.3 Hz), 3.73 (quint, 1 H, J = 5.6 Hz), 3.82 (dt, 1 H, J = 10.4, 7.0 Hz), 3.95 (dd, 1 H, J = 11.3, 4.5 Hz), 4.11 (br s, 1 H), 4.31 (tm, 1 H, J = 7.5 Hz), 5.79 (ddd, 1 H, J = 11.2, 1.9, 1.0 Hz), 5.85 (dt, 1 H, J = 10.3, 2.2 Hz), 7.33−7.44 (m, 6 H), 7.61−7.68 (m, 4 H). ^{13}C NMR (100 MHz), HSQC δ 19.2 (^{t}Bu), 26.8 (3 C, ^{t}Bu), 36.6 ($\underline{CH_2}CH_2OTBDPS$), 60.1 ($\underline{CH_2}OTBDPS$), 62.9 (C-6), 68.1 (C-2), 70.4 (C-3), 127.6 (4 C), 127.7 (C-5), 129.6, 132.9, 133.7 (C-4), 133.8, 135.5 (3 C), 135.6 (2 C). IR (film): 3383, 3068, 3045, 2955, 2930, 2855, 1471, 1428, 1184, 1112, 1086, 823, 734, 702 cm^{-1}. MS (ES): 405 [M + Na]$^+$ (100%), 383 [M + 1]$^+$. Anal. calcd for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.90. Found: C, 72.26; H, 8.02.

(−)-(3*R*,6*S*)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-3,6-dihydro-2*H*-pyran-3-ol (8e). From sulfoxide **4e** (19 mg, 0.038 mmol) and $P(OMe)_3$ (45 μL, 0.54 mmol, 10 equiv), according to the general procedure A described in the Supporting Information (4 h) alcohol

8e was obtained. Purification by chromatography (0−15% EtOAc-CH_2Cl_2) afforded **8e** (12 mg, 0.031 mmol, 83%) as a colorless oil.

From alcohol **7e** (364 mg, 0.951 mmol), PPh_3 (748 mg, 2.85 mmol, 3 equiv), *p*-nitrobenzoic acid (476 mg, 2.85 mmol, 3 equiv), and DIAD (0.55 mL, 2.85 mmol, 3 equiv), according to the general Mitsunobu procedure B described in the Supporting Information (1 h 30 min), ester **8e′** was obtained. Purification by chromatography (5−20% EtOAc-hexane) afforded impure **8e′** (640 mg, 0.951 mmol, 100%) as a yellow oil. From impure ester **8e′** and K_2CO_3 (263 mg, 1.90 mmol) according to the general procedure (1 h 30 min), alcohol **8e** was obtained. Purification by chromatography (0−10% EtOAc-CH_2Cl_2) afforded **8e** (293 mg, 0.766 mmol, 81%) as a colorless oil. R_f 0.37 (20% EtOAc-CH_2Cl_2). $[\alpha]^{20}_D$ −39.8 (c = 1.07). ^{1}H NMR (300 MHz) δ 1.04 (s, 9 H), 1.70−1.86 (m, 2 H), 2.33 (d, 1 H, J = 2.0 Hz), 3.64 (dd, 1 H, J = 12.0, 2.2 Hz), 3.78 (ap q, 1 H, J = 5.4 Hz), 3.85 (m, 2 H, H-6), 3.92 (dt, 1 H, J = 12.0, 1.3 Hz), 4.21 (ap td, 1 H, J = 7.3, 1.7 Hz), 5.85 (dd, 1 H, J = 10.1, 1.3 Hz), 5.95 (ddt, 1 H, J = 10.0, 4.9, 1.7 Hz), 7.33−7.44 (m, 6 H), 7.66 (m, 4 H). ^{13}C NMR (75 MHz) δ 19.2, 26.8 (3 C), 37.9, 60.0, 62.6, 70.7, 71.4, 126.4, 127.6 (4 C), 129.6 (2 C), 133.8, 133.9, 134.5, 135.6 (4 C). IR (film): 3391, 3069, 3045, 3009, 2955, 2930, 2854, 1471, 1428, 1259, 1112, 1090, 1028, 822, 804, 758, 702 cm^{-1}. MS (ES): 405 [M + Na]$^+$ (100%).

(−)-(3*R*,6*S*)-6-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-3,6-dihydro-2*H*-pyran-3-yl carbamate (23e). From alcohol **8e** (25 mg, 0.065 mmol), trichloroacetyl isocyanate (10 μL, 0.078 mmol, 1.2 equiv), and K_2CO_3 (aq) (0.1 mL, 0.195 mmol, 3 equiv), according to general procedure K described in the Supporting Information (5 h 30 min), carbamate **23e** was obtained. Purification by chromatography (5−20% EtOAc-CH_2Cl_2) afforded **23e** (27 mg, 0.063 mmol, 98%) as a white solid. R_f 0.32 (20% EtOAc-CH_2Cl_2). mp 103−105 °C. $[\alpha]^{20}_D$ −64.3 (c = 1.02). ^{1}H NMR (300 MHz), COSY δ 1.03 (s, 9 H, ^{t}Bu), 1.80 (q, 2 H, J = 5.4 Hz, $\underline{CH_2}CH_2OTBDPS$), 3.70 (dd, 1 H, J = 13.1, 2.5 Hz, H-2), 3.78 (ap dd, 1 H, J = 10.3, 5.3 Hz, $\underline{CH_2}OTBDPS$), 3.87 (dt, 1 H, J = 10.5, 6.7 Hz, $\underline{CH_2}OTBDPS$), 4.03 (d, 1 H, J = 13.0 Hz, H-2), 4.22 (m, 1 H, H-6), 4.64 (br s, 2 H, NH_2), 4.91 (m, 1 H, H-3), 5.91 (dm, 1 H, J = 10.4 Hz, H-4), 5.99 (d, 1 H, J = 10.4 Hz, H-5), 7.33−7.43 (m, 6 H, Ar−H), 7.64 (m, 4 H, Ar−H). ^{13}C NMR (75 MHz) δ 19.2, 26.8 (3 C), 37.7, 59.9, 65.3, 68.1, 70.9, 122.2, 127.6 (3 C), 129.6, 133.7, 133.8, 135.5 (3 C), 135.6 (3 C), 136.7, 156.3 (C═O). IR (KBr): 3463, 3385, 3350, 3069, 2955, 2931, 2857, 1716, 1590, 1428, 1387, 1308, 1112, 1036, 823, 757, 702 cm^{-1}. MS (ES): 448 [M + Na]$^+$ (100%). Anal. calcd for $C_{24}H_{31}SiNO_4$: C, 67.73; H, 7.34; N, 3.29. Found: C, 67.81; H, 7.18, N, 3.41.

(−)-(3*R*,6*S*)-6-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-3,6-dihydro-2*H*-pyran-3-yl hydroxycarbamate (32e). From alcohol **8e** (56 mg, 0.146 mmol), *N*,*N*′-carbonyldiimidazole (71 mg, 0.438 mmol, 3 equiv), imidazole (40 mg, 0.584 mmol, 4 equiv) and hydroxylamine hydrochloride (51 mg, 0.73 mmol, 5 equiv), according to general procedure L described in the Supporting Information (17 h), hydroxy carbamate **32e** was obtained. Purification by chromatography (0−20% EtOAc-CH_2Cl_2) afforded **32e** (55 mg, 0.125 mmol, 86%) as a colorless oil. R_f 0.18 (15% EtOAc-CH_2Cl_2). $[\alpha]^{20}_D$ −47.9 (c = 0.39). ^{1}H NMR (300 MHz), COSY δ 1.03 (s, 9 H, ^{t}Bu), 1.76 (m, 3 H, $\underline{CH_2}CH_2OTBDPS$, OH), 3.70 (dd, 1 H, J = 13.0, 2.3 Hz, H-2), 3.76 (dd, 1 H, J = 10.4, 5.2 Hz, $\underline{CH_2}OTBDPS$), 3.85 (dt, 1 H, J = 10.3, 6.7 Hz, $\underline{CH_2}OTBDPS$), 4.03 (d, 1 H, J = 13.2 Hz, H-2), 4.23 (m, 1 H, H-6), 4.97 (m, 1 H, H-3), 5.89 (dd, 1 H, J = 10.2, 4.7 Hz, H-4), 6.00 (d, 1 H, J = 10.4 Hz, H-5), 6.79 (br s 1 H, NH), 7.30−7.43 (m, 6 H, Ar−H), 7.64 (m, 4 H, Ar−H). ^{13}C NMR (75 MHz) δ 19.2, 26.8 (3 C), 37.6, 59.8, 66.5, 67.8, 71.0, 121.6, 127.6 (4 C), 129.6 (2 C), 133.7, 133.8, 135.6 (4 C), 137.2, 158.7. IR (film): 3306, 3069, 3045, 2955, 2931, 2854, 1723, 1471, 1428, 1262, 1112, 1028, 822, 801, 739, 702 cm^{-1}. MS (ES): 464 [M + Na]$^+$ (100%). Anal. calcd for $C_{24}H_{31}SiNO_5$: C, 65.28; H, 7.08; N, 3.17. Found: C, 65.44; H, 7.18, N, 3.31.

(−)-(3*R*,6*S*)-6-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-3,6-dihydro-2*H*-pyran-3-yl mesitylsulfonyloxycarbamate (33e). From hydroxy carbamate **32e** (94 mg, 0.213 mmol), mesitylsulfonyl chloride (47 mg, 0.213 mmol) and Et_3N (89 μL, 0.639 mmol, 3 equiv), according to the general procedure described in the Supporting Information (30 min) **33e** was obtained. Purification by chromatography (5−20% EtOAc−hexane) afforded **33e** (117 mg, 0.188 mmol, 88%) as a colorless oil. R_f 0.23 (20% EtOAc-hexane). $[\alpha]^{20}_D$ −41.9 (c = 0.98). ^{1}H NMR (300 MHz) δ 1.03 (s, 9 H), 1.77 (m, 2 H), 2.28 (s, 3 H), 2.64 (s, 6 H), 3.59 (dd, 1 H, J = 13.2, 2.7 Hz), 3.72−3.89 (m, 3 H), 4.18 (m, 1 H), 4.81 (d, 1 H, J = 2.2 Hz), 5.71 (dd, 1 H, J = 10.2, 5.0 Hz), 5.98 (d, 1 H, J = 10.3 Hz), 6.94 (s, 2 H), 7.33−7.41 (m, 6 H), 7.64 (m, 4 H), 7.83 (d, 1 H, J = 3.7 Hz). ^{13}C NMR (75 MHz) δ 19.2, 21.1, 22.9 (2 C), 26.8 (3 C), 37.5, 59.8, 67.2, 67.6, 70.8, 120.9, 127.6 (5 C), 128.2, 129.6 (2 C), 131.7, 133.6, 133.7, 135.5 (5 C), 137.7, 142.0, 144.4, 155.1. IR (film): 3220, 3065, 3047, 2931, 2884, 2857, 1769, 1603, 1472, 1428, 1373, 1232, 1193, 1180, 1111, 1028, 824, 740, 704 cm^{-1}. MS (ES): 646 [M + Na]$^+$ (100%).

(−)-(3a*R*,6*S*,7*S*,7a*R*)-6-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-7-hydroxytetrahydro-1*H*-pyrano[4,3-*d*]oxazol-2(6*H*)-one (24e). From carbamate **23e** (30 mg, 0.070 mmol), NaOH (0.8 mL, 0.08 M, 0.063 mmol, 0.9 equiv), ^{t}BuOCl (8 mg, 0.070 mmol, 1 equiv), ^{i}Pr$_2$NEt (5 μL, 0.004 mmol, 0.05 equiv) and $K_2OsO_2(OH)_4$ (2 mg, 0.006 mmol, 0.08 equiv) according to general procedure M described in the Supporting Information (25 h), **24e** was obtained. Purification by chromatography (0−50% EtOAc-CH_2Cl_2) afforded **24e** (8 mg, 0.018 mmol, 26%) as a colorless oil and **34e** (8 mg, 0.018 mmol, 26%) as a white solid, along with recovered starting material (14 mg, 0.033 mmol, 48%).

From carbamate **33e** (110 mg, 0.176 mmol), ^{i}Pr$_2$NEt (5 μL, 0.009 mmol, 0.05 equiv) and $K_2OsO_2(OH)_4$ (4 mg, 0.011 mmol, 0.06 equiv) according to general procedure L described in the Supporting Information (4 h), **24e** was obtained. Purification by chromatography (0−50% EtOAc-CH_2Cl_2) afforded **24e** (60 mg, 0.136 mmol, 77%) as a colorless oil.

Data for 24e: R_f 0.21 (50% EtOAc-CH_2Cl_2). $[\alpha]^{20}_D$ −8.7 (c = 0.85). ^{1}H NMR (300 MHz), COSY δ 1.02 (s, 9 H, ^{t}Bu), 1.73 (m, 1 H, $\underline{CH_2}CH_2OTBDPS$), 1.91 (m, 1 H, $\underline{CH_2}CH_2OTBDPS$), 3.22 (d, 1 H, J = 8.7 Hz, OH), 3.45 (dd, 1 H, J = 8.6, 4.4 Hz, H-6), 3.55−3.66 (m, 3 H, H-4, H-7, H-7a), 3.72, (q, 1 H, J = 5.0 Hz, $\underline{CH_2}OTBDPS$), 3.80 (m, 1 H, $\underline{CH_2}OTBDPS$), 4.27 (d, 1 H, J = 14.3 Hz, H-4), 4.39 (dd, 1 H, J = 6.1, 2.3 Hz, H-3a), 6.30 (br s, 1 H, NH), 7.32−7.42 (m, 6 H, Ar−H), 7.59−7.63 (m, 4 H, Ar−H). NOESY-2D $\underline{CH_2}CH_2OTBDPS$/OH. ^{13}C NMR (75 MHz), HSQC, DEPT δ 19.2 (^{t}Bu), 26.9 (3 C, ^{t}Bu), 34.2 ($\underline{CH_2}CH_2OTBDPS$), 54.2 (C-7), 59.7 ($\underline{CH_2}OTBDPS$), 66.6 (C-4), 66.9 (C-7a), 73.5 (C-3a, C-6), 127.7 (4 C), 129.7 (2 C), 133.6, 135.5 (5 C), 161.7 (C-2). IR ($CHCl_3$): 3414, 3068, 3045, 2955, 2930, 2857, 1749, 1630, 1428, 1390, 1213, 1112, 1089, 1014, 953, 824, 703 cm^{-1}. MS (ES): 464 [M + Na]$^+$ (100%). Anal. calcd for $C_{24}H_{31}NO_5Si$: C, 65.28; H, 7.08; N, 3.17. Found: C, 65.42; H, 7.24; N, 3.05.

Data for (+)-(3a*S*,4*S*,7*R*,7a*S*)-4-(2-(*tert*-Butyldiphenylsilyloxy)-ethyl)-7-hydroxytetrahydro-1*H*-pyrano[4,3-*d*]oxazol-2(6*H*)-one, 34e: R_f 0.10 (50% EtOAc-CH_2Cl_2). mp 155−157 °C. $[\alpha]^{20}_D$ +27.7 (c = 0.61). ^{1}H NMR (300 MHz), COSY δ 1.03 (s, 9 H, ^{t}Bu), 1.90 (ddt, 1 H, J = 13.7, 9.1, 4.7 Hz, $\underline{CH_2}CH_2OTBDPS$), 2.01 (ddd, 1 H, J = 13.1, 9.2, 4.5 Hz, $\underline{CH_2}CH_2OTBDPS$), 2.79 (d, 1 H, J = 9.3 Hz, OH), 3.36 (d, 1 H, J = 12.5 Hz, H-6), 3.63−3.85 (m, 4 H, H-7, H-4, H-7a, $\underline{CH_2}OTBDPS$), 3.89 (dd, 1 H, J = 10.4, 4.3 Hz, $\underline{CH_2}OTBDPS$), 3.99 (dd, 1 H, J = 12.2, 2.4 Hz, H-6), 4.30 (dd, 1 H, J = 6.0, 2.1 Hz, H-3a), 5.77 (br s, 1 H, NH), 7.24−7.44 (m, 6 H, Ar−H), 7.61−7.65 (m, 4 H, Ar−H). ^{13}C NMR (75 MHz) δ 19.2, 26.9 (3 C), 33.9, 53.8, 59.5, 64.8, 68.8, 72.6, 75.7, 127.7 (4 C), 129.7 (2 C), 133.6, 135.5 (4 C), 161.1. IR ($CHCl_3$): 3367, 2955, 2925, 2854, 1717, 1646, 1447, 1428, 1248, 1093, 834 cm^{-1}. MS (ES): 464 [M + Na]$^+$ (100%).

(−)-(3a*R*,6*S*,7*S*,7a*R*)-7-Hydroxy-6-(2-hydroxyethyl)tetrahydro-1*H*-pyrano[4,3-*d*]oxazol-2(6*H*)-one (35e). From oxazolone **24e** (100 mg, 0.226 mmol) and DOWEX (113 mg, 0.5 g/mmol) according to the general procedure described in the Supporting Information

(3 days), alcohol **35e** was obtained. Purification by chromatography (0−30% MeOH-CH_2Cl_2) afforded **35e** (33 mg, 0.162 mmol, 72%) as a white solid. R_f 0.28 (20% MeOH-CH_2Cl_2). mp 144−146 °C. $[\alpha]^{20}_D$ −15.0 (c = 0.16 acetone). ^{1}H NMR (500 MHz, CD_3OD), COSY δ 1.61 (dtd, 1 H, J = 14.2, 7.1, 4.4 Hz, $\underline{CH_2}CH_2OH$), 1.87 (ddt, 1 H, J = 14.3, 8.9, 5.4 Hz, $\underline{CH_2}CH_2OH$), 3.36 (ddd, 1 H, J = 8.9, 4.3, 0.7 Hz, H-6), 3.49 (d, 1 H, J = 4.6 Hz, H-7), 3.59 (dd, 2 H, J = 7.1, 5.4 Hz, $\underline{CH_2}OH$), 3.70 (dd, 1 H, J = 14.2, 2.9 Hz, H-4), 3.72 (dd, 1 H, J = 6.4, 4.7 Hz, H-7a), 4.18 (d, 1 H, J = 14.2 Hz, H-4), 4.36 (dd, 1 H, J = 6.6, 2.7 Hz, H-3a), 4.50 (s, 3 H, NH, 2 OH). ^{13}C NMR (75 MHz, CD_3OD) δ 35.6, 55.0, 59.3, 67.4, 67.6, 74.9, 75.4, 163.9. IR (CCl_4): 3402, 2960, 2927, 2854, 1739, 1656, 1583, 1550, 1442, 1257, 1239, 1214, 1154, 1093, 1048, 973 cm^{-1}. MS (ES): 226 [M + Na]$^+$ (100%), 204 [M + 1]$^+$. Anal. calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.37; H, 6.53; N, 7.02.

(−)-(3a*R*,5a*S*,8a*S*,8b*S*)-Hexahydro-2*H*-furo[2′,3′:5,6]pyrano[4,3-*d*]-[1,3]oxazole-2,7(1*H*)-dione (36e). From alcohol **35e** (11 mg, 0.054 mmol), TEMPO (4 mg, 0.022 mmol, 0.4 equiv) and bis(acetoxy)-iodobenzene (71 mg, 0.216 mmol, 4 equiv) according to the general procedure described in the Supporting Information (22 h), **36e** was obtained. Purification by chromatography (0−20% MeOH-CH_2Cl_2) afforded **36e** (9 mg, 0.045 mmol, 84%) as a white solid. R_f 0.34 (20% MeOH-CH_2Cl_2). mp 177−179 °C. $[\alpha]^{20}_D$ −70.1 (c = 0.71 acetone). ^{1}H NMR (300 MHz, CD_3OD), COSY δ 2.48 (dd, 1 H, J = 17.6, 2.4 Hz, H-6), 2.85 (dd, 1 H, J = 17.6, 5.6 Hz, H-6), 3.64 (dd, 1 H, J = 14.0, 2.1 Hz, H-4), 4.02 (dd, 1 H, J = 13.9, 1.2 Hz, H-4), 4.18 (dd, 1 H, J = 7.7, 5.8 Hz, H-8b), 4.32 (ddd, 1 H, J = 6.0, 3.7, 2.3 Hz, H-5a), 4.51 (dd, 1 H, J = 5.8, 3.8 Hz, H-8a), 4.53 (ddd, 1 H, J = 8.2, 2.1, 1.3 Hz, H-3a). ^{13}C NMR (125 MHz), HSQC δ 38.2 (C-6), 50.5 (C-8b), 65.7 (C-4), 73.5 (C-5a), 73.6 (C-3a), 76.4 (C-8a), 162.4 (C-2), 176.6 (C-7). IR (KBr): 3444, 3313, 2926, 1789, 1752, 1725, 1634, 1384, 1231, 1166, 1131, 1094, 1061, 1032, 964, 915 cm^{-1}. MS (ES): 254 [M + Na + MeOH]$^+$ (100%), 232 [M + 1 + MeOH]$^+$, 222 [M + Na]$^+$, 200 [M + 1]$^+$.

(−)-(3a*R*,5a*S*,8a*S*,8b*S*)-1-Methylhexahydro-2*H*-furo[2′,3′:5,6]pyr-ano[4,3-*d*][1,3]oxazole-2,7(1*H*)-dione (*ent*-16). To a cold suspension (−40 °C) of NaH (2 mg, 0.080 mmol, 1 equiv) in THF-DMF (1:1) (0.8 mL, 10 mL/mmol substrate) MeI was added (10 μL, 0.16 mmol, 2 equiv) and the solution was stirred for 5 min. A solution of substrate **36e** (16 mg, 0.080 mmol, 1 equiv) in THF−DMF (1:1) (0.4 mL, 5 mL/mmol substrate) was added and the reaction was stirred at −40 °C for 5 h and then warmed to rt. When no more evolution was observed (TLC) the reaction was quenched with saturated NH_4Cl (4 mL/mmol) solution and H_2O (4 mL/mmol), and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 4 mL/mmol). The combined organic layers were washed with brine (3 mL/mmol), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography (0−10% MeOH-CH_2Cl_2) afforded *ent*-**16** (10 mg, 0.047 mmol, 59%) as a white solid that was recrystallized from CH_2Cl_2-Et_2O along with recovered starting material (3 mg, 0.015 mmol, 19%). R_f 0.39 (10% MeOH-CH_2Cl_2). mp 185−186 °C. $[\alpha]^{20}_D$ −91.8 (c = 0.40 MeOH). (Lit. for **16** +39.3 (c = 0.41 MeOH). ^{1}H NMR (300 MHz), COSY δ 2.69 (dd, 1 H, J = 17.8, 1.9 Hz, H-6), 2.79 (dd, 1 H, J = 17.8, 4.9 Hz, H-6), 2.97 (s, 3 H, Me), 3.71 (dd, 1 H, J = 13.9, 2.9 Hz, H-4), 3.97 (dd, 1 H, J = 7.5, 5.5 Hz, H-8b), 4.17 (dd, 1 H, J = 13.9, 2.2 Hz, H-4), 4.33 (ddd, 1 H, J = 5.0, 3.3, 1.7 Hz, H-5a), 4.46 (dt, 1 H, J = 7.5, 2.7 Hz, H-3a), 4.58 (dd, 1 H, J = 5.4, 3.2 Hz, H-8a). ^{13}C NMR (100 MHz, D_2O) δ 30.3, 38.7, 54.2, 64.3, 71.4, 73.6, 76.0, 161.7, 179.1. IR (KBr): 2941, 1791, 1754, 1439, 1228, 1170, 1115, 1032, 913 cm^{-1}. MS (ES): 268 [M + Na + MeOH]$^+$ (100%), 236 [M + Na]$^+$, 214 [M + 1]$^+$. Anal. calcd for $C_9H_{11}NO_5$: C, 50.70; H, 5.20; N, 6.57. Found: C, 50.82; H, 5.34; N, 6.61.

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Supporting Information Available: Experimental details and spectral data (^{1}H NMR and ^{13}C NMR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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