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Synthesis and stereoselective evaluation of a (1*R*)-(−)-myrtenal-derived pseudo C_2-symmetric dodecaheterocycle as a potential heterofunctional chiral auxiliary

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ABSTRACT

The synthesis and diastereoselective performance of the pseudo C_2-symmetric dodecaheterocycle **3** in nucleophilic and electrophilic reactions are reported. Compound **3** proved to be a highly diastereoselective template to generate a pair of enantiomeric moieties within its structure in a programmed manner. Hence, this study describes the synthesis of a novel potential heterobifunctional chiral auxiliary.

Introduction

The use of chiral auxiliaries in asymmetric synthesis is still one of the most reliable and effective methods for the preparation of a wide range of enantiopure compounds [1,2]. In the early 1990's, there were reports on the preparation and study of homobifunctional C_2-symmetric chiral auxiliaries [3–12]. The two reactive sites in such compounds allow for two diastereoselective reactions producing two new stereogenic centers with the same configuration [10]. Homobifunctional C_2-symmetric chiral auxiliaries have been reported to take part in various reactions (e.g. alkylation, aldol, Michael, and Diels-Alder) in which they show exceptional diastereoselectivity. Our group has reported that the addition of nucleophiles to the benzoyl group of the (1*R*)-(−)-myrtenal-derived chiral auxiliary **1** proceeded with high diastereoselectivity [13]. Likewise, we previously reported the efficient synthesis of chiral auxiliary **2**, where the reaction of its bis-sulfoxide anion with benzaldehyde proceeded with a high degree of stereochemical control [14] (See Fig. 1).

Considering these precedents, the aim of the present study was to design a structure with two reaction sites that can give rise to two distinct groups of opposite stereochemistry, allowing for the programmed delivery of two compounds with opposite chirality, as a potential heterobifunctional chiral auxiliary. Herein, we report the synthesis and stereoselective study of the new pseudo C_2-symmetric dodecaheterocycle **3** with two reactive sites, a nucleophilic bis-sulfoxide methylene active group [15–22] and an electrophilic benzoyl group [23–28]. These sites react in a programmed manner with electrophiles and nucleophiles, respectively, exhibiting modest to excellent stereochemical control to afford adducts of type **4**, which in turn are suitable for the controlled release of chiral tertiary alcohols of opposite configuration (Fig. 2b).

Results and discussion

The synthesis of **3** was accomplished in three steps, starting from the (1*R*)-(−)-myrtenal derived diol **5** [13]. Oxidation of diol **5** with $NaIO_4$ afforded mono-sulfoxide **6** in 85% yield. The dodecaheterocycle **7** was obtained by transacetalization of monosulfoxide **6** with 2,2-diethoxyacetophenone using ZnI_2 and $BF_3{\cdot}OEt_2$ as catalysts. Compound **7** was obtained as a mixture of diastereoisomers

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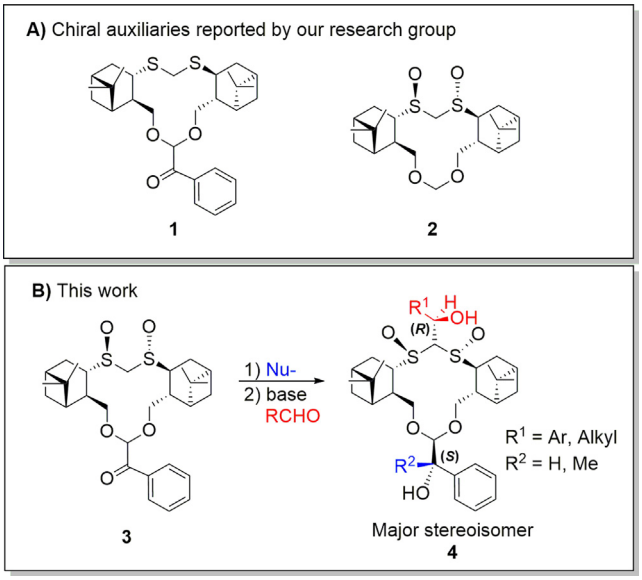


Figure 1. A) Chiral auxiliaries reported by our research group. B) Diastereoselective reaction of the new pseudo C_2-symmetric dodecaheterocycle **3** with nucleophiles and electrophiles.

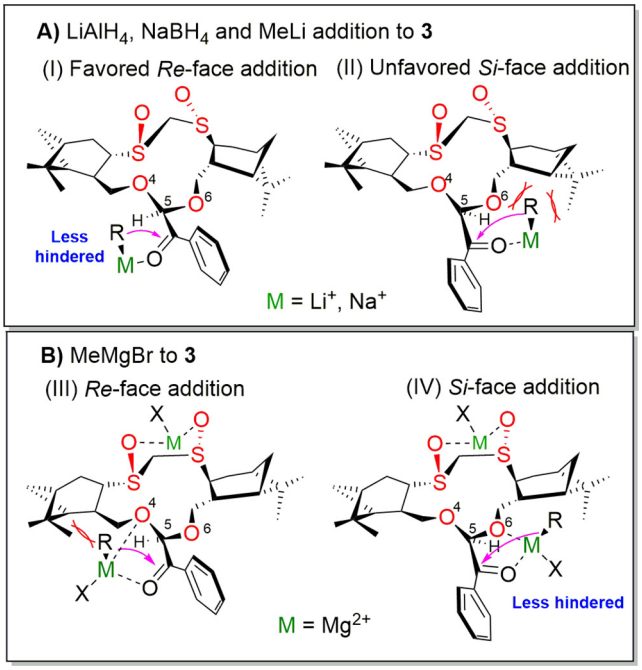
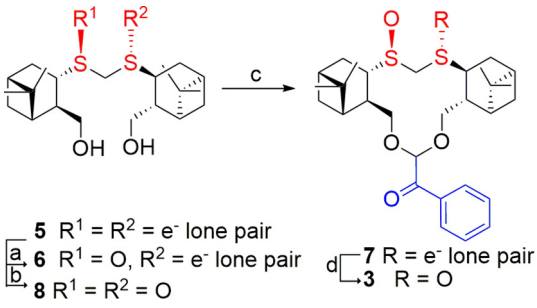


Figure 2. Hypothetical chelated model illustrating A) the diastereoselective addition of $LiAlH_4$, $NaBH_4$ and MeLi, and B) MeMgBr to **3.**

(*dr* = 64:36). Single crystal X-ray diffraction analysis revealed that the benzoyl and sulfoxide groups are *trans* in the major isomer **7a** (Fig. S7). Further oxidation of the diastereoisomeric mixture of **7** with $NaIO_4$ gave the pseudo C_2-symmetric dodecaheterocycle **3** in excellent yield (96%) as a single stereoisomer. Alternatively, the synthesis of **3** was attempted *via* the condensation of bis-sulfoxide **8** with 2,2-diethoxyacetophenone, but this procedure resulted in poor yield (9%) (Scheme 1). The structural elucidation of **3** was carried out by ^1H, ^{13}C and two-dimensional NMR experiments and the *trans* configuration of the sulfoxide groups was assigned by single crystal X-ray diffraction of selected derivatives (see below).

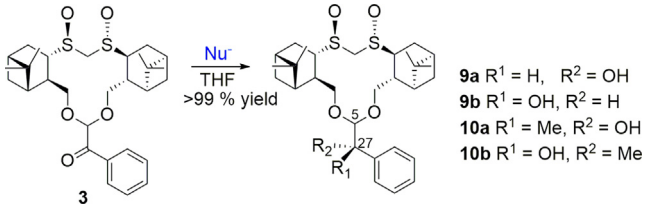


Scheme 1. Synthesis of pseudo C_2-symmetric compound **3**. Reagents and conditions: a) $NaIO_4$ (1.5 equiv.), EtOH, H_2O, 60 °C, 5 h, 85%; b) $NaIO_4$ (3.0 equiv.), EtOH, H_2O, 60 °C, 10 h, 92%; c) 2,2-diethoxyacetophenone, ZnI_2 (10 mol%), $BF_3{\cdot}OEt_2$ (20 mol%), chlorobenzene, 60 °C, 15 h, 70%; d) $NaIO_4$ (1.5 equiv.), EtOH, H_2O, 60 °C, 5 h, 96%.

With the synthesis of **3** completed, its diastereoselectivity was evaluated in successive nucleophilic and electrophilic reactions. Considering that **3** may generate up to six diastereoisomers, we decided to simplify the reaction process into two steps: nucleophilic addition to the benzoyl group followed by reaction of the bis-sulfoxide anion with electrophiles. Accordingly, **3** was reacted with various nucleophilic reagents, producing carbinols **9**–**10** (Scheme 2). Table 1 shows the diastereoselectivity and absolute configuration of the newly formed chiral center C27 of the major adducts.

Compared to the more coordinative magnesium Grignard reagent (MeMgBr), the least coordinative reagents ($LiAlH_4$, $NaBH_4$ and MeLi) afforded higher diastereoselectivity and the same *S* configuration at C27 of the major diastereoisomer. MeMgBr afforded a major diastereoisomer with the opposite configuration (*R*), as revealed by the ^1H NMR spectrum of the crude product (Fig. S17). The *R* configuration at C27 of the minor adduct **9b** was assigned based on single crystal X-ray diffraction data (Fig. S16). Hence, because of the C_2-symmetry, the *S* configuration at C27 of the major adduct **9a** could be inferred**.** The *S* configuration of **10a** was determined by chemical correlation to the known diol (+)-(*S*)-**11** [24]. Thus, after the HCl-catalyzed hydrolysis of a diastereomeric mixture of **10a**/**10b** (*dr* = 88:12), $NaBH_4$ reduction of the resulting mixture gave diol **11** in 53% yield and a specific rotation of $[\alpha]_D^{25}$ = +2.8 (*c* 0.32, EtOH), having the same sign as (+)-(*S*)-**11**$[\alpha]_D^{25}$ = + 5.7 (*c* 0.45, EtOH, >98% *ee*) [24]. Hence, the *S* configuration at the new chiral center C27 of the major adduct **10a** was deduced (Scheme 3).

To rationalize the observed diastereoselectivity, a mechanistic model was proposed in which the main factor for the diastereoselective addition of $LiAlH_4$, $NaBH_4$ and MeLi is assumed to be steric effects of one of the oxygens (O6) of the acetal group and one of the geminal methyl groups of the pinane system, favoring the *Re*-face addition (Fig. 2A) [23]. Furthermore, the poor diastereoselectivity generated by the Grignard reagent was attributed to the greater coordination capacity of magnesium, showing that the addition occurred on both pro-chiral faces in almost the same ratio as a



Scheme 2. Diastereoselective addition of nucleophiles to **3**.

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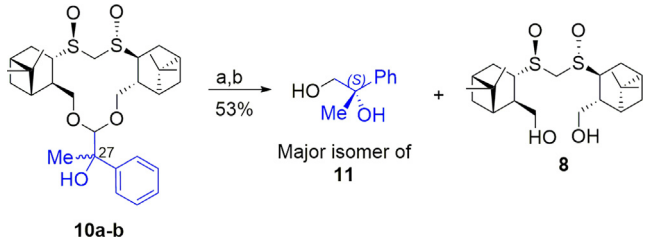
Table 1
Diastereoselectivity for nucleophilic addition to 3.

Entry	Reagent	Nu^-	Major adduct	**a**/**b** (*dr*)[a]	Abs. conf. at C27 major isomer
1	$LiAlH_4$	H^-	**9a**	90:10	*S*
2	$NaBH_4$	H^-	**9a**	88:12	*S*
3	MeLi	Me^-	**10a**	84:16	*S*
4	MeMgBr	Me^-	**10b**	39:61	*R*

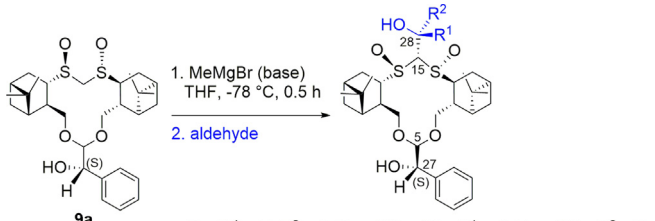
[a] Diastereomeric ratios were calculated by integration of the ^{1}H NMR signals for the H5 position in the crude reaction mixture.



Scheme 3. Acid hydrolysis of adduct **10a-b** (by the addition of MeLi) and reduction of the resulting aldehydes. Reagents and conditions: a) HCl (40% v/v), MeCN, 60 °C, 10 h; b) $NaBH_4$, MeOH, 0 °C, 2 h.

result of the almost equal chelation of magnesium to either oxygen of the acetal group [29,30]. The inversion of diastereoselectivity is probably caused by chelation of the magnesium atom to the sulfoxide groups, forming a six-membered ring, which would induce the geminal methyl groups of the pinane system to adopt such a conformation to allow stronger chelation to the carbonyl functionality along with one oxygen (O6) of an acetal group during the nucleophilic addition (Fig. 2B). This suggests that such addition took place *via* the *Si*-face, which would likely be the less hindered one.

Then, the diastereoselectivity of the reaction of the bis-sulfoxide anion of **3** with aldehydes was evaluated. Due to the ease of preparation, adduct **9a** was used in this reaction. Formation of the bis-sulfoxide anion of **9a** was attempted with different bases. For example, NaHDMS failed to form the bis-sulfoxide anion, whereas NaH, *n*-BuLi, *sec*-BuLi, *tert*-BuLi and MeLi formed the anion but the adduct easily dehydrated. In contrast, methylmagnesium bromide was able to form the bis-sulfoxide anion and reacted with the aldehydes without further dehydration of the adducts. Following this procedure, the bis-sulfoxide anion of **9a** was reacted with various aromatic aldehydes and butyraldehyde, producing adducts **12**–**17** (Scheme 4).



12a, R^1 = H, R^2 = C_6H_4-*p*-NO_2 **12b**, R^1 = C_6H_4-*p*-NO_2, R^2 = H
13a, R^1 = H, R^2 = C_6H_4-*p*-CN **13b**, R^1 = C_6H_4-*p*-CN, R^2 = H
14a, R^1 = H, R^2 = C_6H_4-*p*-F **14b**, R^1 = C_6H_4-*p*-F, R^2 = H
15a, R^1 = H, R^2 = -$(CH_2)_2CH_3$ **15b**, R^1 = -$(CH_2)_2CH_3$, R^2 = H
16a, R^1 = H, R^2 = C_6H_4-*p*-OMe **16b**, R^1 = C_6H_4-*p*-OMe, R^2 = H
17a, R^1 = H, R^2 = C_6H_5 **17b**, R^1 = C_6H_5, R^2 = H

Scheme 4. Electrophilic addition to **9a** (the derivative of **3**).

Reactions conducted at -78 °C afforded slightly higher diastereoselectivity but lower yields compared to those at 0 °C (Table 2). Of the four possible stereoisomers, two adducts with *cis* and two with *trans* relative configuration at C5 and C15 carbinol groups, only those with relative *trans* configuration were observed (Fig. 3 and S23). At the new stereogenic center C28, the major adduct has an *R* configuration and the minor adduct an *S* configuration. In adducts **12a**, **13a**, **14a** and **17a**, the relative *trans* configuration and absolute *R* configuration at C28 were established by single crystal X-ray diffraction (Fig. S26, S29, S32 and S45, respectively). ROESY NMR experiments served the same purpose for **15a** and **16a** (Fig. S35 for **15a** and S41 for **16a**). The *S* configuration at C28 of adduct **15b** was assigned based on the correlation between H28 and H13 and between H29 and H17 observed in the ROESY experiment (Fig. S38). For the minor adducts, the relative *trans* configuration at the C5 and C15 carbinol groups was determined by ROESY NMR experiments recorded on **15b** (Fig. S38). Hence, the resulting correlations of H15 with H13, H17, and H7 provided evidence of the intra-annular position of H15. The reason that the *cis* isomers were not formed is probably due to an unfavorable abstraction of the proton which would lead to these stereoisomers. Considering the diastereomeric ratios shown in Table 2 (*dr* = 75:25 to 90:10), the electrophilic addition seems to not be influenced by the C_6H_4-*para*-substituents of the aldehyde.

To rationalize the formation of both adducts, a model of a chair-like reactive conformation is proposed (Fig. 4), maintaining a close structural analogy with the X-ray perspective view of the chiral center C28 of adduct **12a** (Fig. 3). In the hypothetical model which would explain the observed diastereoselectivity, the metal coordinates the oxygen of one sulfoxide group, and the incoming aldehyde approaches the anion from the *Si*-face in such a way that the most voluminous Ar or alkyl groups occupy the least hindered *pseudo*-axial position (Fig. 4A). In contrast, when the aldehyde approaches *via* the *Re*-face in the same model, the Ar or alkyl

Table 2
Electrophilic addition of various aldehydes to **9a** (the directed derivative of **3**).

Entry	Electrophile	Major adduct	Yield (%)		*dr* (*R*:*S*) of C28[a]		Abs. conf. at C28 major isomer
			0 °C	-78 °C	0 °C	-78 °C	
1	4-Nitrobenzaldehyde	**12a**	>99	45	68 : 32	76 : 24	*R*
2	4-Formylbenzonitrile	**13a**	>99	50	72 : 28	75 : 25	*R*
3	4-Fluorobenzaldehyde	**14a**	92	58	75 : 25	80 : 20	*R*
4	Butyraldehyde	**15a**	72	56	74 : 26	78 : 22	*R*
5	*p*-Anisaldehyde	**16a**	70	64	74 : 26	79 : 21	*R*
6	Benzaldehyde	**17a**	34	30	84 : 16	90 : 10	*R*

[a] Diastereomeric ratio established by integration of the ^{1}H NMR signals for the H5 position in the crude reaction mixture.

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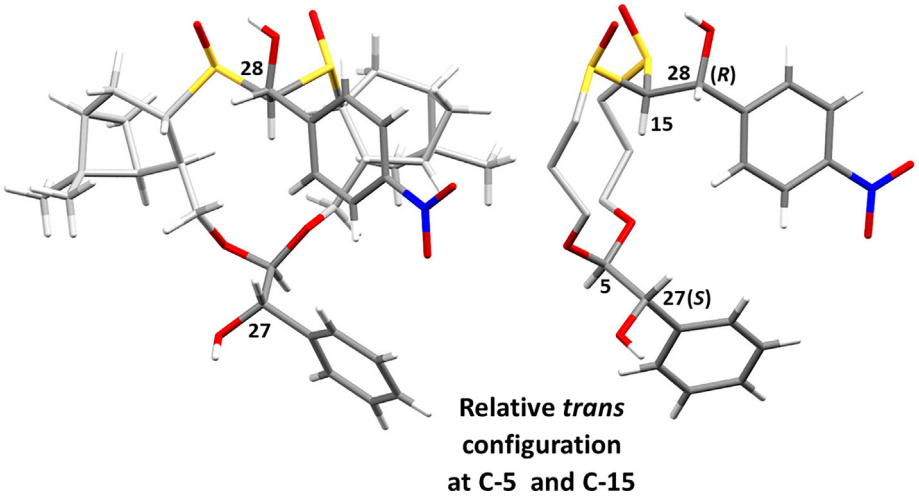


Figure 3. A) Single crystal X-ray image of adduct **12a** and B) fragment of **12a**, portraying the absolute and relative configurations of both carbinols.

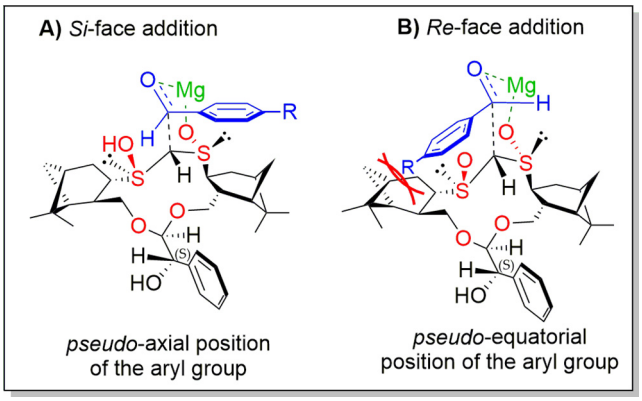
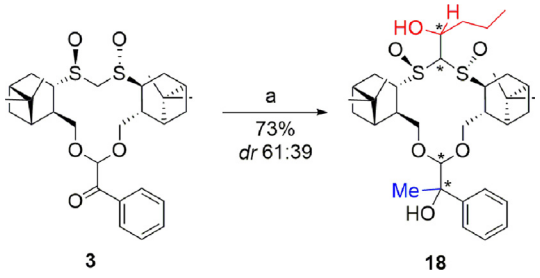


Figure 4. A) Hypothetical chelated model illustrating the highly preferred *Si*-face addition of aromatic aldehydes, and B) the chelated model for *Re*-face addition that would explain the absolute *S* configuration of the minor adducts.

groups occupy the *pseudo*-equatorial position, generating steric interactions with one of the pinane systems (Fig. 4B).

Taking all this information into account, along with the fact that methylmagnesium bromide acts as the base and nucleophile, an increase in its stoichiometry was expected to allow the nucleophilic and electrophilic reactions to be carried out in a one-pot, two-step procedure as a simple method to generate four chiral centers. Consequently, **3** was reacted with three equivalents of methylmagnesium bromide at -78 °C and after full consumption of the substrate, butyraldehyde was added. A mixture of two diastereoisomers **18a** and **18b** was isolated in a *dr* of 61:39 and 73% yield (Scheme 5).

These results are significant because **3** could be a potential chiral auxiliary producing both enantiomers of α-hydroxy carbonyl compounds (for example **17a**); or different optically pure compounds (e.g. adducts **12a-16a**). Furthermore, the acetal and bis-sulfoxide functionalities would allow for the selective release of each enantiomer. Previously, our group reported chemoselective hydrolysis of the acetal and 1,3-dithiane groups to release enantiomerically pure α-hydroxyaldehydes from similar chiral auxiliaries [13,24]. In addition, procedures for cleaving the bis-sulfoxide group have been reported [31–34]. One of these involves reduction of the sulfoxide group to the corresponding 1,3-dithiane, which is then hydrolyzed to provide the enantiomerically pure carbonyl compounds.



Scheme 5. Nucleophilic and electrophilic reactions using the one-pot, two-step procedure. Reagents and conditions: (a) MeMgBr, dry THF, -78 °C, 2 h. (ii) butyraldehyde, r.t., 8 h.

Conclusion

In summary, we have synthesized a pseudo C_2-symmetric dodecaheterocycle **3** bearing a benzoyl group and an active bis-sulfoxide-methylene group. The former reacts diastereoselectively with nucleophile reagents, while the latter with electrophiles. The addition of $LiAlH_4$, $NaBH_4$, and MeLi to the benzoyl group of **3** furnished adducts with an *S* configuration at the new stereogenic center (C27), indicating that the addition took place preferentially from the *Re*-face. In contrast, the addition of MeMgBr proceeded with reverse stereoselectivity. The reaction of the bis-sulfoxide anion of adduct **9a** with benzaldehydes and butyraldehyde occurred with good diastereoselectivity (*dr* = 75:25–90:10) approaching from the *Si*-face to yield the *R* configuration. The successive treatment of **3** with MeMgBr and butyraldehyde generated **18** as two adducts with a *dr* of 61:39 using a one-pot, two-step procedure. These findings emphasize the potential of the **3** as a heterobifunctional C_2-symmetric chiral auxiliary to produce a pair of enantiomers in a programmed manner and with significant diastereoselectivity. Further research is currently underway to establish the factors controlling and improving the diastereoselectivity.

Conflicts of interest

There are no conflicts to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2018.11.012.

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