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Synthesis of a New (1*R*)-(−)-Myrtenal-Derived Dioxadithiadodecacycle and Its Use as an Efficient Chiral Auxiliary

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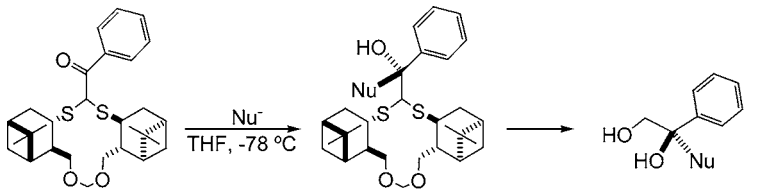
ABSTRACT



9 **12a-j** Nu = Me, Et, Bn, *i*-Pr, H_2C=CH, H_2C=CH(CH_3), H_3CCC, PhCC, *n*-Bu, H. **16a,c,e** Nu = Me, Bn, $CH=CH_2$

The new macrocycle 9 (>70% yield from hydroxythiol 10) was treated with several nucleophilic reagents (RMgX, RLi, and $LiAlH_4$) affording carbinols 12a–j (80–96% yield, >99:1 dr). Oxidative hydrolysis of 12a,c,e, followed by $LiAlH_4$ reduction of the resulting mixture, gave 16a,c,e in >95% ee,16c being a key precursor for the preparation of fungicide 17. The absolute configuration of 9 and 12j (Nu = H) was established by single-crystal X-ray diffraction analyses and chemical correlation.

After the pioneering work of Eliel concerning the use of chiral 2-acyl-1,3-oxathianes **1**−**4** as chiral auxiliaries,[1] structural analogues **5**−**8**[2−5] were developed by other research groups. From them, compounds **3**, **4**, and **6**−**8** are synthesized from natural products (Figure 1). The main application of these compounds in asymmetric synthesis has been focused on the diastereoselective addition of several nucleophilic reagents to the prostereogenic C=O group, wherein RMgX ∼ K and L-selectride > RLi > DIBAL ∼ LAH is the most common diastereoselectivity trend.[1−5]

After the synthesis of macrocycle **8a** was described,[6] we decided to explore the chiral auxiliary proficiency of this new structural arrangement. Thus, preparation of bissulfoxide

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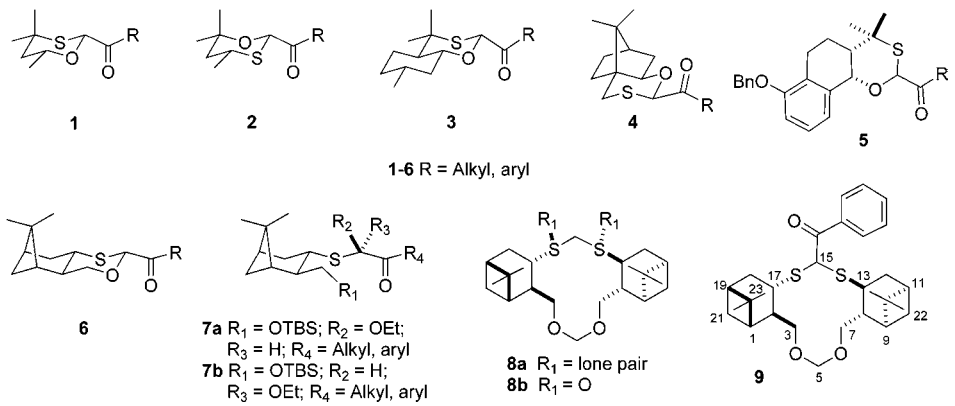
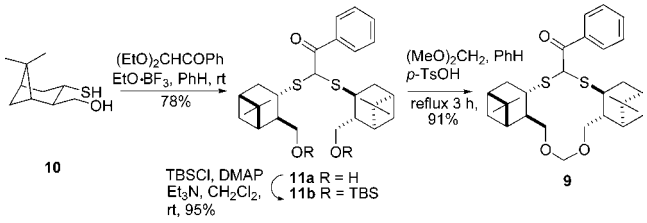


Figure 1. Acyloxathiane derivatives used in asymmetric synthesis (**1**−**5**) and pinane-based chiral auxiliaries **6**−**9**.

8b was the first derivative recently described,[7] which was successfully used as an efficient chiral acyl donor (Figure 1). In connection with that work, we now report the efficient synthesis of benzoyl derivative **9** and its assessment as a chiral auxiliary by performing nucleophilic addition of Grignard reagents, lithium alkylides, and $LiAlH_4$. The results revealed that all nucleophilic additions were highly diastereoselective (>99:1 dr) irrespective of the kind of nucleophile used, representing a new diastereoselectivity order not previously shown by chiral auxiliaries **1**−**7**.

Thus, treatment of **10**[4] with 0.5 equiv of 2,2-diethoxyacetophenone catalyzed with $Et_2O{\cdot}BF_3$ (Scheme 1) gave **11a**,

Scheme 1



which reacted with $CH_2(OMe)_2$ and *p*-TsOH to give **9** (91%). X-ray analysis of **9** provided the structure shown in Figure 2, which evidenced that the thioacetalic carbon atom is a pseudostereogenic center, generating only one diastereoisomer. Conversely, chiral auxiliaries **1**−**7** lack a pseudostereogenic center.

All carbinols **12a**−**j** (Table 1) were obtained from **9** in a highly diastereoselective manner irrespective of the reagent used. This is the first report in which nucleophilic additions performed on a carbonylic prostereogenic center at the α position of *O*,*O*-, *S*,*O*-, or *S*,*S*-acetals, by employing either of the above nucleophiles, proceed in >99:1 diastereomeric ratios (dr) in a chiral auxiliary based protocol.

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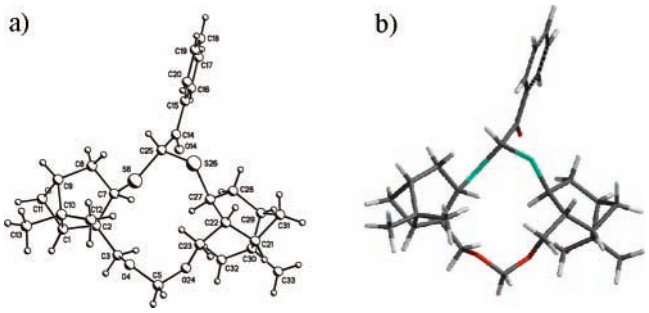


Figure 2. X-ray structure (a) and MMFF major conformer (b) of macrocycle **9**.

Initial evidence for the stereochemical route followed from the X-ray structure of **12j** (Figure 3), which shows the *R* configuration for the new chiral center, denoting that the diastereofacial attack of the hydride proceeded through the *si* face of the carbonyl group. Interestingly, the addition of EtMgBr and *i*-PrMgBr led predominantly to the same carbinol **12j** obtained by addition of $LiAlH_4$, confirming the approach of the reagents from the same face of the carbonyl group. The addition of EtLi also gave carbinol **12j** in a smaller ratio. In these three cases, the availability of protons

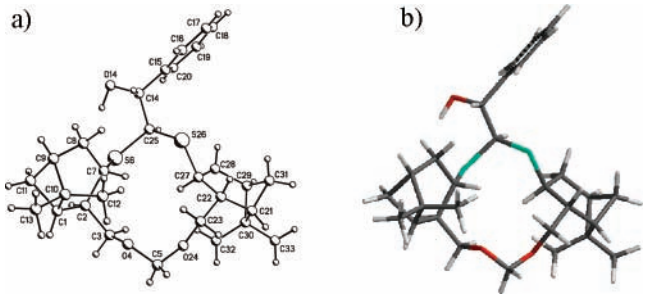
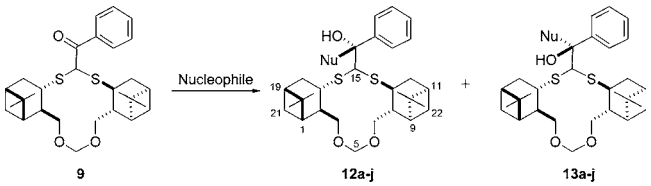


Figure 3. X-ray structure (a) and MMFF major conformer (b) of macrocycle **12j**.

Table 1. Diastereoselective Nucleophilic Additions to Dodecacycle **9**



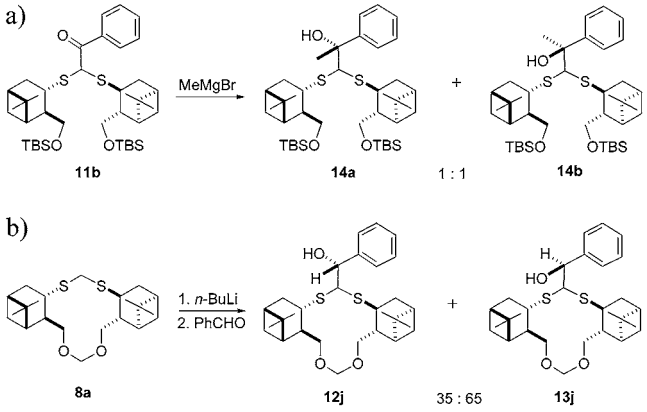
entry	nucleophile	Nu	product	yield (%)[a]	dr **12/13**[b]
1	MeMgBr	Me	**12a**	95	>99:1
2	EtMgBr	Et/H[d]	**12b/12j**	30/70[c]	>99:1
3	BnMgCl	Bn	**12c**	98	>99:1
4	*i*-PrMgBr	*i*-Pr/H	**12d/12j**	20/80[c]	>99:1
5	CH_2=CHMgBr	CH_2=CH	**12e**	98	>99:1
6	CH_2=C(Me)CH_2MgBr	CH_2=C(Me)CH_2	**12f**	98	>99:1
7	CH_3CCMgBr	CH_3CC	**12g**	95	>99:1
8	PhCCMgBr	PhCC	**12h**	98	>99:1
9	MeLi	Me	**12a**	95	>99:1
10	EtLi	Et/H[d]	**12b/12j**	65/35[c]	>99:1
11	*n*-BuLi	*n*-Bu	**12i**	98	>99:1
12	$LiAlH_4$	H	**12j**	95	>99:1

[a] All reactions were carried out in THF at −78 °C. [b] Diastereoisomeric ratio (dr) as measured by ^{1}H NMR. [c] In >94% yield of the mixture. [d] The fact that EtMgBr favors reduction while EtLi favors addition is under consideration in our laboratory.

at the β position of the alkyl chain allows the hydride transfer into the carbonyl group, thus affording adduct **12j** as a byproduct. Furthermore, addition of both MeMgBr and MeLi also gave carbinol **12a**, whereas ethylide transfer from EtMgBr and EtLi yielded carbinol **12b**. These results strongly support a common diastereofacial selectivity by Grignard reagents, RLi and $LiAlH_4$, all of them preferring the *si* face of the prostereogenic center.

In search of a reasonable mechanistic proposal to explain the highly preferred *si* diastereofacial approach of the nucleophiles, we performed the nucleophilic addition on noncyclic benzoylthioacetal **11b**, prepared (95%) by protecting the hydroxyl groups of **11a** with TBSCl in the presence of Et_3N and DMAP in CH_2Cl_2 (Scheme 1). The addition of MeMgBr to **11b**, under the same reaction conditions as those used for **9**, gave an equimolecular mixture of the two possible adducts **14a** and **14b** in almost quantitative yield (Scheme 2a). This result shows the requirement of a cyclic structure like **9** to achieve the highly diastereoselective nucleophilic additions. Complementarily, the corresponding anion of macroheterocycle **8a** was reacted with benzaldehyde in THF to afford a 35:65 mixture of carbinols **12j** and **13j** (Scheme 2b). Here, the requirement of a prostereogenic center forming part of the molecule was evidenced. Furthermore, this result supports the sole presence of diastereoisomer **12j** after $LiAlH_4$ addition to **9** or when it is obtained as a byproduct (Table 1, entries 2, 4, and 10) because the ^{1}H NMR signals of H-15 for both diastereoisomers **12j** and **13j** are easily distinguishable (**12j**, δ H-15 4.44 ppm; **13j**, δ H-15 5.01 ppm) and can be integrated accurately.

Scheme 2



An additional question is whether a chelated transition state (TS) could participate in the mechanistic model. First, it is well-known that a Cram chelated[8] TS is the most accepted model for the observed diastereoselectivity when chiral auxiliaries **1**−**7** are used.[1−5] However, in these systems, an oxygen atom is present at the α position of the prostereogenic carbonyl group (they are *S*,*O*-acetals), being in principle that both parts are the ideal mutual complement to form the rigid Cram chelated TS by coordination with the metal. This situation explains the above-mentioned diastereoselective order of nucleophiles used, which match the coordinating ability of the metal present in each nucleophilic reagent. Conversely, it is worth noting that **9** does not possess any oxygen atom α to the prostereogenic center (it is an *S*,*S*-acetal), and therefore a Cram chelated-type TS, similar to that formed with chiral auxiliaries **1**−**7**, would not be significant. Although a chelated TS such as that depicted in

Figure 4a is not fully discarded, its participation would also be questioned because it requires a large conformational change to attain the coordinated arrangement **15**.

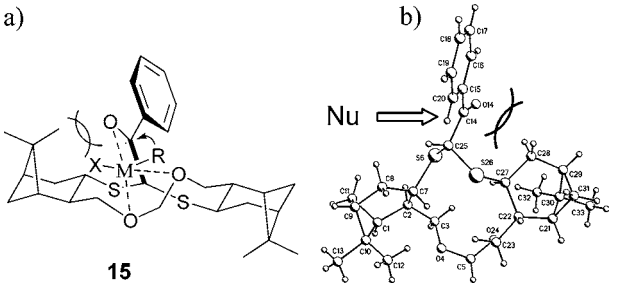
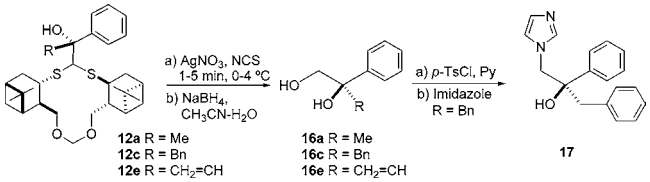


Figure 4. (a) Hypothetic chelated TS illustrating how the bridging *gem*-dimethyl moiety would block the nucleophilic addition through the *re* face. (b) Perspective of the X-ray diagram of **9** showing the preferred attack by nucleophiles, in which methylene C28 (C-12 in Figure 1) clearly blocks the *re* face of the carbonyl group.

According to the above arguments, a mechanistic model that comprises steric effects as the main driving force to explain the observed diastereoselectivity would be expected. Analysis of the X-ray structure of **9**, viewed in another perspective in Figure 4b, shows the close proximity of CH_2-18 (C-28 in the X-ray structure) and the prostereogenic carbonyl group, precluding the nucleophilic attack from the *re* face (Figure 4b). It is worth noticing that there is practically no conformational change of the macrocyclic ring on going from **9** to **12j** (Figures 2 and 3). A very similar minimum energy conformation for both compounds was found by calculation (MMFF94, Spartan 04)[9] (Figures 2 and 3), suggesting that a significant conformational change of the macrocyclic ring is not taking place at the TS, and therefore the CH_2-18 group could always preclude addition of the nucleophile from the *re* face.

The stereofacial preference of the nucleophilic addition to **9** was also confirmed by chemical correlation. Thus, oxidative hydrolysis of **12a**, followed by $LiAlH_4$ reduction of the resulting mixture, gave diol **16a** in 71% yield ($[\alpha]^{24} = -5.7$ ($c = 0.5$, EtOH); lit.[10] $[\alpha]^{24} = -5.8$ ($c = 0.17$, EtOH)), having the *R* absolute configuration (Scheme 3).

Scheme 3



Also, diol **16e** was obtained from **12e** in 80% yield ($[\alpha]^{24} = +35.5$ ($c = 0.2$, EtOH); lit.[11] $[\alpha]^{24} = +41.2$ ($c = 1.2$, EtOH)). From these representative chemical correlations, and from the X-ray structure of **12j**, it is assumed that all remaining carbinols possess the same absolute configuration.

Of particular interest is the preparation of diol **16c**, a key precursor[12] for the synthesis of fungicide **17** (Scheme 3). This goal was achieved by applying the same oxidative hydrolysis−reduction protocol to carbinol **12c**, which allowed access to the precursor **16c** in 78% yield ($[\alpha]^{25} = +59.5$ ($c = 0.25$, EtOH)), this being the first time that diol **16c** was prepared in its optically pure form. The synthesis of **17** was completed as shown in Scheme 3.[12]

In conclusion, the synthesis of **9** was achieved in two steps and 70% overall yield from **10**. The highly diastereoselective nucleophilic additions performed on **9** with several kinds of nucleophiles overcome the limitation of chiral auxiliaries **1**−**7** when they are reacted with less chelating and less diastereoselective nucleophiles, such as lithium alkylides and $LiAlH_4$. The highly diastereofacial discrimination shown by **9** seems important in asymmetric synthesis to prepare chiral targets in high optical purity, as proven for the highly diastereoselective synthesis of carbinol **16c**, a precursor of fungicide **17**.

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Supporting Information Available: All experimental procedures and spectroscopic data for new compounds and crystallographic data for compounds **9** (CCDC 627539) and **12j** (CCDC 627540). This material is available free of charge via the Internet at http://pubs.acs.org.

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