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

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ABSTRACT



The new macrocycle 9 (>70% yield from hydroxythiol 10) was treated with several nucleophilic reagents (RMgX, RLi, and LiAlH₄) affording carbinols $12a_{-j}$ ($80_{-96\%}$ yield, >99:1 dr). Oxidative hydrolysis of $12a_{,c,e}$, followed by LiAlH₄ 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 re-

search 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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 ^{(1) (}a) Eliel, E. L.; Koskimies, J. K.; Lohri, B. J. Am. Chem. Soc. 1978, 100, 1614. (b) Eliel, E. L.; Frazee, W. J. J. Org. Chem. 1979, 44, 3598. (c) Eliel, E. L.; Lynch, J. E. Tetrahedron Lett. 1981, 22, 2855. (d) Eliel, E. L.; Soai, K. Tetrahedron Lett. 1981, 22, 2859. (e) Eliel, E. L.; Morris-Natschke, S. J. Am. Chem. Soc. 1984, 106, 2937.

⁽²⁾ Solladié-Cavallo, A.; Balaz, M.; Salisova, M.; Suteu, C.; Nafie, L. A.; Cao, X.; Freedman, T. B. *Tetrahedron: Asymmetry* **2001**, *12*, 2605.

⁽³⁾ Chacón-García, L.; Lagunas-Rivera, S.; Pérez-Estrada, S.; Vargas-Díaz, M. E.; Joseph-Nathan, P.; Tamariz, J.; Zepeda, L. G. *Tetrahedron Lett.* **2004**, *45*, 2141.

⁽⁴⁾ Martínez-Ramos, F.; Vargas-Díaz, M. E.; Chacón-García, L.; Tamariz, J.; Joseph-Nathan, P.; Zepeda, L. G. *Tetrahedron: Asymmetry* **2001**, *12*, 3095.

⁽⁵⁾ Vargas-Díaz, M. E.; Chacón-García, L.; Velázquez, P.; Tamariz, J.;
Joseph-Nathan, P.; Zepeda, L. G. *Tetrahedron: Asymmetry* 2003, *14*, 3225.
(6) (a) Vargas-Díaz, M. E. M. Sc. dissertation, Escuela Nacional de Ciencias Biológicas-IPN, Mexico City, 2002. (b) Solladié-Cavallo, A.; Balaz, M.; Salisova, M. *Eur. J. Org. Chem.* 2003, 337.



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 LiAlH₄. 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 Et₂O·BF₃ (Scheme 1) gave 11a,



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.



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 LiAlH₄, 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.

⁽⁷⁾ Vargas-Díaz, M. E.; Lagunas-Rivera, S.; Joseph-Nathan, P.; Tamariz, J.; Zepeda, L. G. *Tetrahedron Lett.* **2005**, *46*, 3297.



entry	nucleonhile	Nu	product	yield (%)a	dr 12/13 ^{b}
	nucleophile	nu	product	(70)	ur 12/10
1	MeMgBr	${ m Me}$	12a	95	>99:1
2	EtMgBr	\mathbf{Et}/\mathbf{H}^d	12b/12j	$30/70^{c}$	>99:1
3	BnMgCl	Bn	12c	98	>99:1
4	i-PrMgBr	<i>i</i> -Pr/H	12d/12j	$20/80^{c}$	>99:1
5	$CH_2 = CHMgBr$	$CH_2 = CH$	12e	98	>99:1
6	CH2=C(Me)CH2MgBr	$CH_2 = C(Me)CH_2$	12f	98	>99:1
7	$ m CH_3CCMgBr$	$CH_{3}CC$	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	<i>n</i> -Bu	12i	98	>99:1
12	${ m LiAlH_4}$	Н	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.	¹ 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 LiAlH₄, 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 Et₃N and DMAP in CH₂Cl₂ (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 LiAlH₄ addition to **9** or when it is obtained as a byproduct (Table 1, entries 2, 4, and 10) because the ¹H 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.

An additional question is whether a chelated transition state (TS) could participate in the mechanistic model. First, it is well-known that a Cram chelated⁸ 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,Sacetal), 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 CH₂-18 (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 CH₂-18 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 LiAlH₄ 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).



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 precursor¹² 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 LiAlH₄. 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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⁽⁸⁾ Cram, D. J.; Kopecky, K. R. J. Am. Chem. Soc. 1959, 81, 2748.
(9) MMFF94 calculations were performed using the Spartan 04, v. 1.0.1

software package for Windows (Wavefunction Inc., Irvine, CA, 2004).

⁽¹⁰⁾ Fujisawa, T.; Watai, T.; Sugiyama, T.; Ukaji, Y. Chem. Lett. 1989, 2045-2048 and references cited therein.

⁽¹¹⁾ Colombo, L.; Di Giacomo, M.; Brusotti, G.; Milano, E. Tetrahedron Lett. **1995**, *36*, 2863.

⁽¹²⁾ Kraatz, U. Ger. Patent DE 3703082 AI 19880811, 1988.