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# Structural Features of Diacyldodecaheterocycles with Pseudo-$C_2$-Symmetry: Promising Stereoinductors for Divergent Synthesis of Chiral Alcohols

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Cite This: *ACS Omega* 2023, 8, 20611−20620

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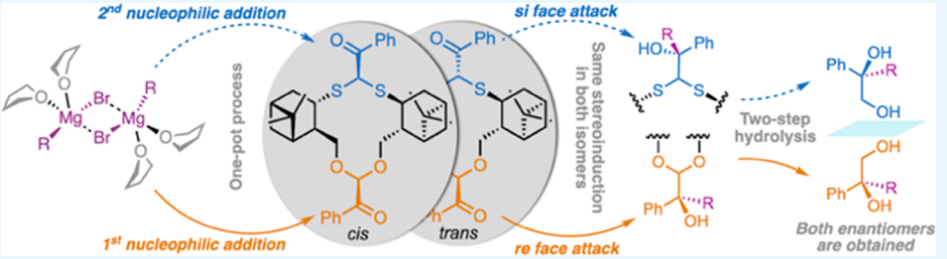



**ABSTRACT:** Pseudo-$C_2$-symmetric dodecaheterocyclic structures, which possess two acyl/aroyl groups disposed on either a cis- or trans-relative configuration, were prepared from the naturally occurring (−)-(1*R*)-myrtenal. Addition of Grignard reagents (RMgX) to the diastereoisomeric mixture of these compounds unexpectedly showed that nucleophilic additions to the two prochiral carbonyl centers gave the same stereochemical result in both cis/trans diastereoisomers, making unnecessary the separation of this mixture. Noticeably, both carbonyl groups showed different reactivity because one of them is attached to an acetalic carbon and the other to a thioacetalic carbon. Furthermore, addition of RMgX to the carbonyl attached to the former carbon takes place through the *re* face, while addition to the second one proceeds through the *si* face, thus affording the corresponding carbinols in a highly diastereoselective process. This structural feature allowed the sequential hydrolysis of both carbinols, yielding separately (*R*)- and (*S*)-1,2-diols after reduction with $NaBH_4$. The mechanism of the asymmetric Grignard addition was explained by density functional theory calculations. This approach contributes to the development of the divergent synthesis of structurally and/or configurationally different chiral molecules.

## INTRODUCTION

The discovery and evaluation of new drugs rely on screening different structures and configurations of molecules.[1] The assessment of diverse configurations is more relevant in structure−activity relationships based on a specific spatial arrangement.[2] There are different ways to build stereocenters. The chiral pool approach uses an enantiopure molecule readily available as a starting material that is transformed in a linear pathway. However, the simultaneous generation of both enantiomers of a target molecule requires a de novo approach to the chemical synthesis of the asymmetric carbon. Switchable divergent asymmetric synthesis, mainly applied in organocatalysis,[3] describes the preparation of two or more different types of chiral products with diverse chemo-, regio-, or diastereoselectivity from an identical set of starting materials under tunable conditions. The appropriate modification of the catalytic system by combining different catalysts or enantiomeric ligands has allowed the stereodivergent synthesis of molecules containing multiple stereocenters.[4] Another way to access all stereoisomers is through dynamic kinetic resolution using the same set of chiral catalysts.[5] Stereodivergence in chiral auxiliaries is not common and has been accomplished using different reaction conditions[6] or by altering the sequence in which they are used,[7] often successfully changing the stereochemical course of the asymmetric induction. To the best of our knowledge, no stoichiometric chiral scaffolds capable of independently exerting asymmetric double induction to generate stereocenters with opposite configuration, under the same reaction conditions in a single synthesis protocol, have been reported.

We reported previously the synthesis of functionalized macrocyclic scaffolds **1**−**4** from the monoterpene (−)-(1*R*)-myrtenal and their application to generate carbinols with

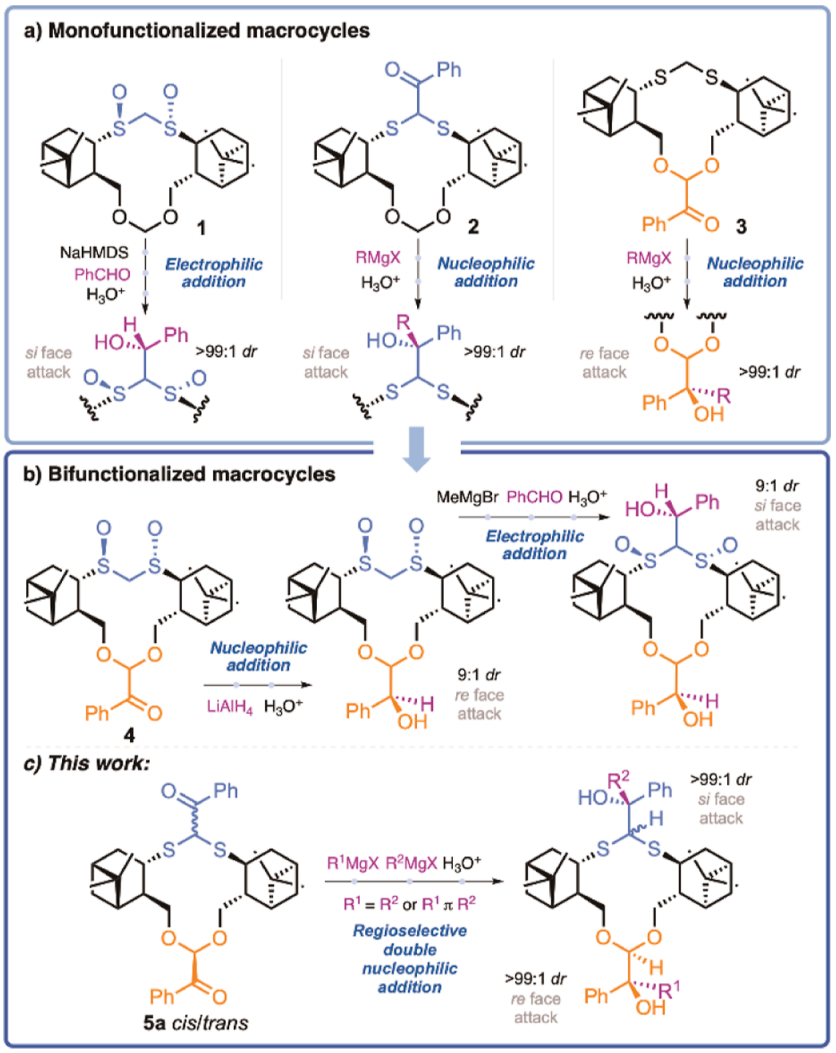
**Received:** February 20, 2023
**Accepted:** April 24, 2023
**Published:** May 3, 2023





https://doi.org/10.1021/acsomega.3c01161
*ACS Omega* 2023, 8, 20611−20620

Scheme 1. (−)-(1*R*)-Myrtenal-Derived (a) Monofunctional and (b,c) Bifunctional Dodecaheterocycles Reported by Our Research Group for the Preparation of Chiral Tertiary Alcohols




complete diastereoselective control (Scheme 1a).[8] It can be observed that bis-sulfoxide **1** possesses $C_2$-symmetry, while dodecaheterocycles **2**−**4** have pseudo-$C_2$-symmetry due to the presence of the benzoyl group at the thioacetalic or acetalic carbons. Highly diastereoselective electrophilic and nucleophilic additions to the anion of 1,3-bis-sulfoxide **1**[8a] and to acylmacrocycles **2** and **3** were achieved.[8b,c] Subsequent hydrolysis of the corresponding thioacetal or acetal groups, followed by the reduction of the $\alpha$-hydroxycarbonyl intermediates with $NaBH_4$, afforded the corresponding 1,2-diols, which are valuable chiral building blocks,[9] in excellent enantiopurity. In order to fully exploit the structural pseudo-$C_2$-symmetry attributes of this dodecaheterocyclic scaffold and, at the same time, to reduce the effective molecular mass, functionalization of acetal and thioacetal moieties in the same dodecaheterocyclic skeleton was devised. As a proof of concept, we reported the synthesis of macrocycle **4** by incorporating the different reactive sites of macrocycles **1** and **3** in the same framework (heterobifunctionality) and its evaluation in a two-step protocol involving a nucleophilic addition to the benzoyl group followed by an electrophilic addition to the corresponding 1,3-bis-sulfoxide anion (Scheme 1b).[8d] It should be noted that the diastereofacial selectivity of the reactions on prochiral substrates with **1** and **3** is opposite, giving carbinols with the shown stereochemistry at the acetal and thioacetal moieties. Thus, the extrapolation of individual asymmetric inductions of monofunctional macrocycles **1**−**3** to a bifunctional macrocycle allows for the enantiodivergent synthesis of chiral alcohols by using the same stereoinductor scaffold. Accordingly, we postulate that performing a double asymmetric reaction as two independent processes can be carried out in a one-pot process by using a macrocyclic scaffold bearing two equal reactive sites (homobifunctionality).

In this paper, we present the synthesis of new (−)-(1*R*)-myrtenal-derived dodecaheterocycles **5** bearing two prochiral carbonyl groups (Scheme 1c), which can serve as structural prototypes to achieve a fully controlled stereodivergent synthesis of chiral tertiary carbinols. We also consider it appropriate to analyze the addition of Grignard reagents theoretically by density functional theory (DFT), to gain a deeper understanding of the reactivity of these novel macrocycles with interesting and unusual structural features.

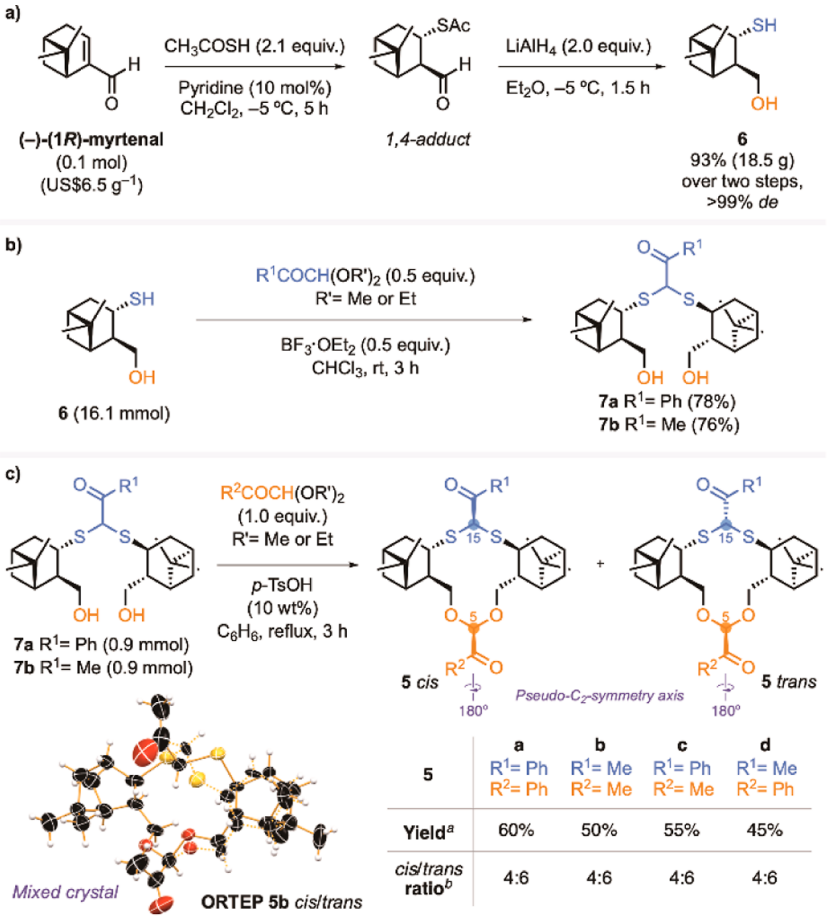
## RESULTS AND DISCUSSION

Our research group developed a robust, diastereoselective, and expedient synthesis of hydroxythiol **6** by a two-step process



https://doi.org/10.1021/acsomega.3c01161
ACS Omega 2023, 8, 20611−20620

**Scheme 2. Synthesis of Cis/Trans Diacylmacrocycles 5a−d by (a) Multigram Scale Synthesis of Hydroxythiol 6 Followed by (b,c) Two Sequential Transacetalization Reactions**[a]




| 5 | a R1= Ph R2= Ph | b R1= Me R2= Me | c R1= Ph R2= Me | d R1= Me R2= Ph |
|---|---|---|---|---|
| Yield[a] | 60% | 50% | 55% | 45% |
| cis/trans ratio[b] | 4:6 | 4:6 | 4:6 | 4:6 |

[a]Yield of the mixture after column chromatography. [b]Ratio of **5a−d** cis/**5a−d** trans, determined by $^1$H NMR.

from commercially available (−)-(1*R*)-myrtenal in high yield and on a multigram scale (Scheme 2a).[8e] The formation of diacyldodecaheteroycles by incorporation of thioacetal and acetal groups was performed by two transacetalizations catalyzed by $BF_3{\cdot}OEt_2$ and *p*-TsOH, respectively (Scheme 2b,c). It is noteworthy that the 12-membered ring formation occurs with low formation of linear oligomers and without the need for extreme dilution; also, the diastereomeric ratio of the cis/trans isomers was always the same, regardless of the substitution of the acyl moiety. As can be seen, the two-step macrocyclization protocol with different $\alpha$-ketoacetals allows us to prepare all possible combinations of bifunctionalized macrocycles **5** with the same or different acyl groups; therefore, a broad structural scope can be achieved from this stage.

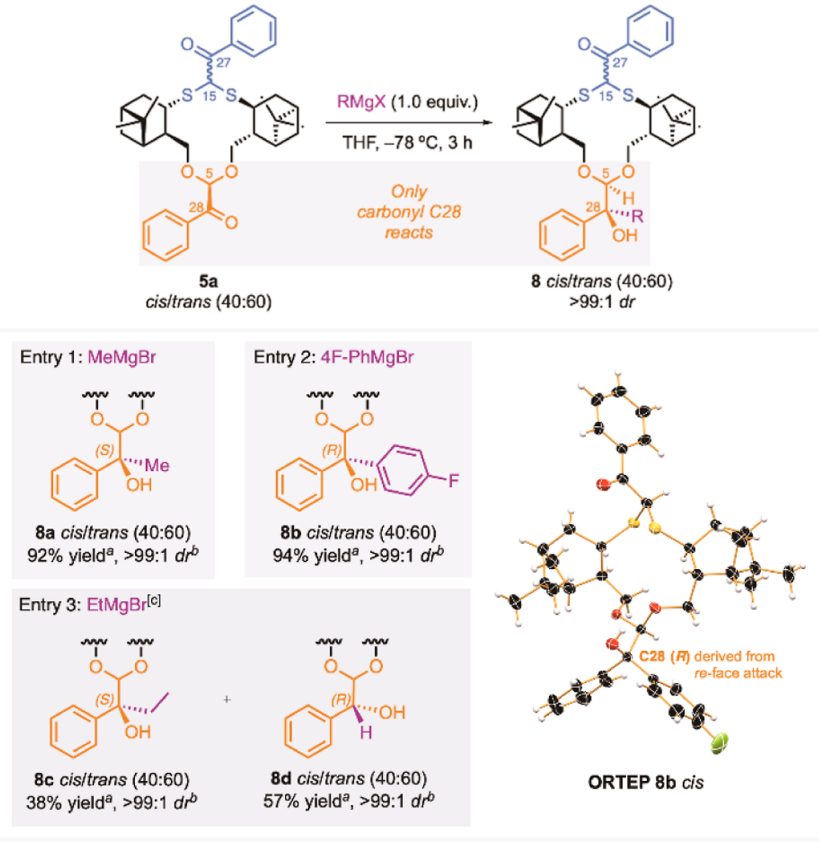
The orientation of one acyl group with respect to the other around the dodecaheterocycle determines the relative cis/trans configuration. The stereochemical designators cis-$\beta,\beta$ and cis-$\alpha,\alpha$ are equivalent representations of the same structure by rotation of a pseudo-$C_2$-symmetry axis passing through the acetalic (C5) and thioacetalic (C15) carbons (Scheme 2c); the same applies for the trans-$\beta,\alpha$ and trans-$\alpha,\beta$ representations. Unfortunately, separation of the cis/trans mixtures of **5a−d** by column chromatography was unsuccessful and could only be achieved for the cis/trans mixture of **5a** using analytical high-performance liquid chromatography (HPLC). From the cis/trans mixture of diacetylmacrocycle **5b**, a single crystal was obtained. Surprisingly, its X-ray diffraction analysis revealed that the crystal lattice was formed by both diastereoisomers (mixed crystal) in a 4:6 ratio, with **5b** trans being the major isomer.[10] Notably, both diastereomeric crystalline structures show great conformational similarity, mainly in both carbonyl groups, despite the opposite relative orientation at the thioacetalic carbon (C15) (Scheme 2c, ORTEP **5b** cis/trans).

Thus, it was interesting to investigate whether this conformational arrangement persists in solution. The nuclear Overhauser effect (NOE) enhancements observed by selective irradiation of each H15 singlet peak in the $^1$H NMR spectrum of the cis/trans mixture of **5b** correlated very well with the relative C15 configuration observed in the crystal structures (Supporting Information, Figure S9). In addition, selective H15 irradiations of the minor and major isomers allowed us to assign the relative cis and trans configurations, respectively.

To explore the reactivity and stereochemical outcome of the pseudo-$C_2$-symmetric diacyldodecaheterocycles **5** in the addition of Grignard reagents, the reaction was carried out with the cis/trans mixture of **5a** as a model substrate. Initially, the treatment of **5a** with 1.0 equiv of MeMgBr at −78 °C in tetrahydrofuran (THF) afforded two products that kept the same diastereomeric ratio (40:60) as the starting cis/trans mixture. The corresponding $^1$H NMR spectrum revealed that nucleophilic addition occurred with high regioselectivity at


https://doi.org/10.1021/acsomega.3c01161
ACS Omega 2023, 8, 20611−20620

**Table 1. Regioselective Nucleophilic Additions to Dibenzoylmacrocycle 5a Cis/Trans (40:60)**




[a]Calculated after column chromatography as a cis/trans mixture. [b]Diastereoisomeric ratio obtained by $^1$H NMR integration of H5 signals in the crude reaction mixture. [c]EtMgBr leads to ethyl and hydride addition, the latter formed by $\beta$-elimination and added with opposite diastereofacial selectivity.

carbonyl C28 attached to the acetalic carbon (C5), while carbonyl C27 remained unchanged, giving carbinol **8a** cis/trans in high diastereoselectivity at C28 (>99:1 *dr*) (Table 1, entry 1). The highly regio- and diastereoselective nucleophilic additions to the carbonyl (C28) were also observed when 4F-PhMgBr and EtMgBr were used (Table 1, entries 2 and 3). It must be mentioned that addition of EtMgBr yielded carbinol **8c** cis/trans in low yield (38%) because a competing reduction by hydride at C28 took place, by $\beta$-hydrogen atom elimination from EtMgBr.[11,12] It can be concluded that the diastereofacial selectivity of these nucleophilic additions favors attack onto the *re* face of C28, as was inferred from X-ray diffraction analysis of a single crystal obtained from **8b** cis (Table 1, ORTEP **8b** cis[10]). However, the hydride transfer from EtMgBr takes places through the *si*-face at C28 (Table 1, entry 3) as was demonstrated by correlation with the absolute configuration of C28 observed in ORTEP **9c** trans[10] (Table 2).

In this sense, treatment of **5a** cis/trans (40:60) with an excess (2.0–5.0 equiv) of the Grignard reagent afforded the double-addition products **9** cis/trans with high diastereoselectivity (Table 2). The addition of 3.0 equiv of MeMgBr gave **9a** cis/trans (40:60) in 95% yield (Table 2, entry 1) without the formation of configurational diastereoisomers despite the formation of the two stereocenters. We only observe the initial cis/trans ratio. On the other hand, the addition of 3.0 equiv of EtMgBr afforded four products, which were identified as **9b** cis, **9c** cis, **9c** trans, and **9d** trans (Table 2, entry 2) after separation by column chromatography and NMR characterization. An interesting behavior was observed in this reaction: (a) double addition of ethyl only occurred in **5a** cis; (b) reduction occurs mainly at carbonyl C28, while ethyl addition occurs mainly at carbonyl C27; and (c) double hydride addition only takes place on **5a** trans.

In turn, bulky Grignard reagents such as BnMgCl and 4F-PhMgBr showed low preference for giving double-addition products despite using 5.0 and 4.0 equiv, respectively (Table 2, entries 3 and 4), affording only diadducts **9e** cis and **9f** cis in low yields. In order to demonstrate the potential of a programed protocol for the synthesis of structurally different chiral alcohols, the sequential addition of two different Grignard reagents to the cis/trans (40:60) mixture of **5a** in a one-pot process was carried out. Thus, regioselective addition of 1.0 equiv of 4F-PhMgBr to C28, followed by the addition of 1.0 equiv of $CH_2{=}C(CH_3)MgBr$ to C27, after complete consumption of starting material **5a**, gave the double-addition product **9g** cis/trans in 92% yield with high diastereoselectivity (Table 2, entry 5). Diastereofacial selectivity of the nucleophilic additions for the *si* face at C27 was determined by the absolute configuration of C27 observed in ORTEP **9c** trans[10] (Table 2). The relative cis/trans configuration assigned to the double-addition products **9** was established by NOE experiments (Supporting Information).

It is well known that acetal groups are prone to hydrolysis in the presence of protic acids, while thioacetal groups are not.[13] Therefore, it was possible to perform a two-step hydrolysis of the double-addition products **9a** cis/trans and **9b** cis to


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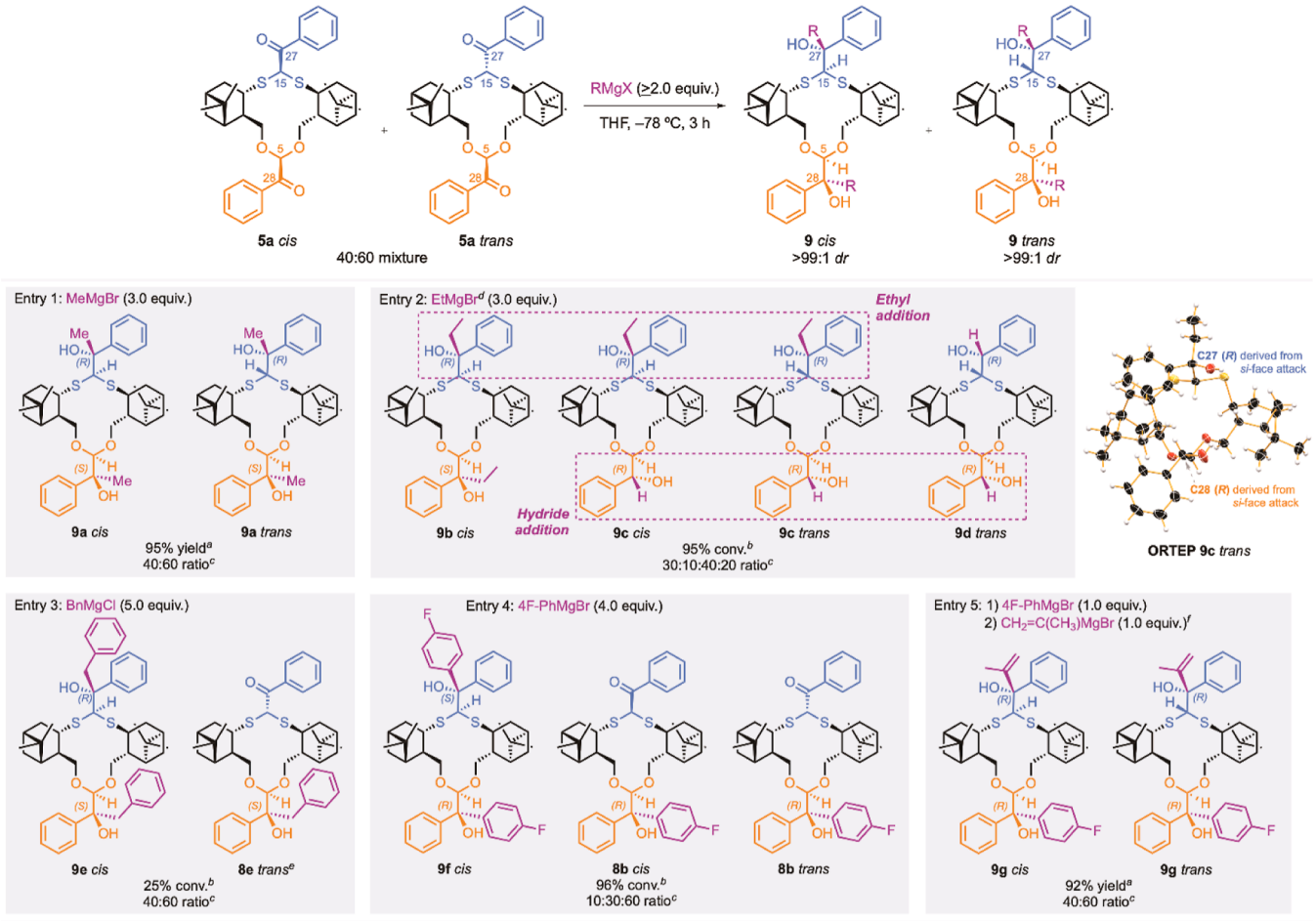
**Table 2. Double Nucleophilic Additions on Dibenzoylmacrocycle 5a Cis/Trans (40:60)**




[a]Calculated after column chromatography. The yield represents a cis/trans mixture of products. [b]The conversion is equal to the sum of the yield of each product. [c]Ratio of products measured by $^1$H NMR of the crude reaction mixture. [d]EtMgBr leads to ethyl and hydride addition, the latter formed by $\beta$-elimination and added with the opposite diastereofacial selectivity on C28. [e]The second equivalent of RMgX was added after complete consumption of the starting material.

sequentially release each carbinol, to obtain separately both enantiomers with high optical purity (Scheme 3). Thus, acetalic hydrolysis of **9a** with catalytic *p*-TsOH at 54 °C in MeCN/$CH_2Cl_2$/$H_2O$ led to bis-pinanediol **10a** along with $\alpha$-hydroxyaldehyde **11a**. In situ treatment of **11a** with $NaBH_4$ yielded 1,2-diol **12a**. Acetalic hydrolysis of the cis/trans (40:60) mixture of **9a** gave only one diastereoisomer of bis-pinanediol **10a** (>99:1 *dr*) and the enantioenriched diol (*S*)-**12a**[14a] (94:6 *er*).[15] This result simultaneously showed that carbinols C27 and C28 have the same absolute configuration in both cis/trans isomers of **9a**. This means that nucleophilic additions occur with the same facial stereoselectivity in both **5a** cis/trans isomers, thus concluding that separation of this mixture is not necessary. Similarly, acetalic hydrolysis of **9b** cis gave the bis-pinanediol **10b** (99:1 *dr*) and the enantioenriched diol (*S*)-**12b**[14b] (92:8 *er*).[15] Thioacetalic hydrolysis of bis-pinanediols **10**, following the oxidative procedure reported by Corey and Erickson[16] with $AgNO_3$ and N-chlorosuccinimide (NCS), gave dimer **13** and $\alpha$-hydroxyaldehydes **11**, which were treated in situ with $NaBH_4$ giving 1,2-diols **12** and hydroxythiol **6** in excellent yield. Thioacetalic hydrolysis of bis-pinanediols **10a** and **10b** delivered the enantioenriched diols (*R*)-**12a**[14a] (99:1 *er*) and (*R*)-**12b**[14a] (99:1 *er*), respectively. Accordingly, the opposite diastereofacial selectivity observed in the nucleophilic addition to the carbonyls attached to thioacetalic and acetalic carbons of the monofunctional macrocycles **2** and **3**, respectively, is still conserved; thus, each carbonyl group in **5a** cis/trans performs an independent asymmetric induction in a single reaction step.

In order to gain mechanistic insights into the addition of Grignard reagents to this new pseudo-$C_2$-symmetric bifunctional assembly, the energy profiles for the reaction of MeMgBr on **5a** cis/trans were obtained from DFT calculations (Supporting Information, Figures S59−S62), which were based on the recently published mechanistic model of the Grignard reaction proposed by Cascella and co-workers.[17a] Diastereomeric transition states shown in Figure 1 were calculated through a reaction with a MeMgBr tetrasolvated dinuclear complex (**MDC**), one of the most abundant and reactive species in the Schlenk equilibrium for nucleophilic addition.[17b] We chose dimethyl ether ($Me_2O$) as the explicit solvent to reduce the computational cost of the actual reaction system, which takes place in THF. Initially, the regioselective approach of **MDC** to **5a** cis was calculated considering the substitution of one of the $Me_2O$ molecules coordinated to Mg1 with carbonyl O28, which is favored by 10.7 kcal/mol over the substitution with carbonyl O27 (Figure S58). Substitution of the second $Me_2O$ molecule in Mg1 by coordination with the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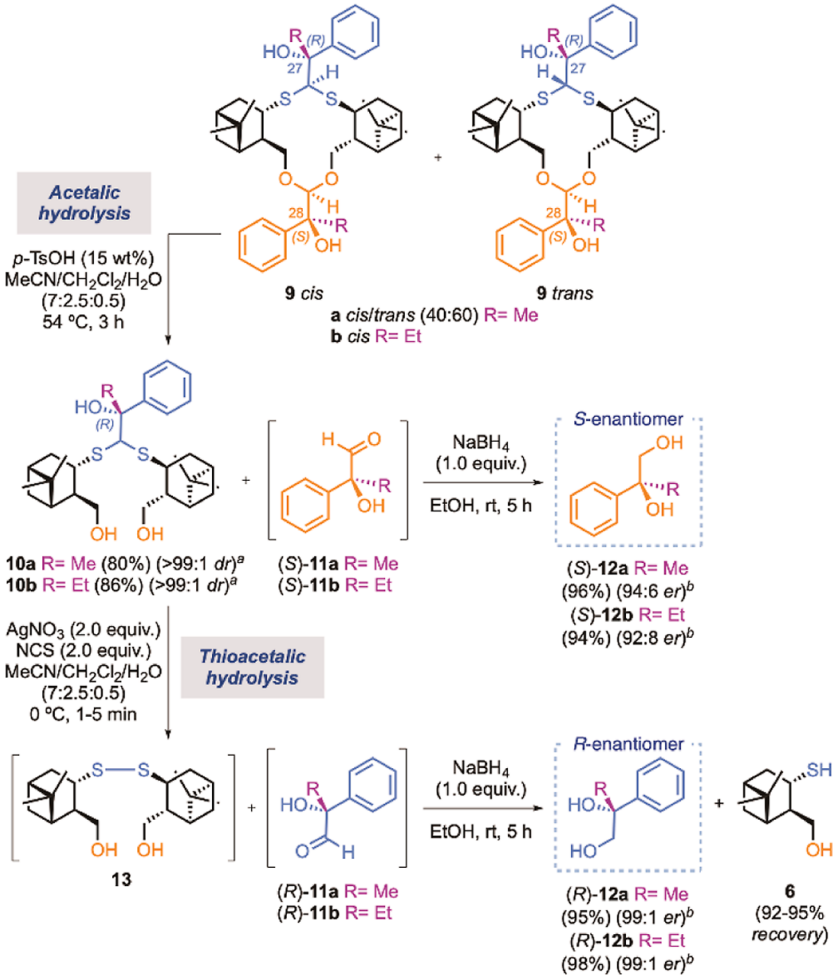
Scheme 3. Two-step Hydrolysis of Double-Addition Products 9a Cis/Trans (40:60) and 9b Cis[a]




[a]*dr* obtained by $^1$H NMR of the crude reaction mixture. [b]Determined by HPLC analysis on a chiral stationary phase.

less sterically hindered O6 of the acetal moiety leads to a chelated Cram complex. The nucleophilic attack onto the *re* face of C28 in **TS1**$_{re}$ and **TS2**$_{re}$ occurs after the entry of O28 into the coordination sphere of Mg2, with a $\Delta\Delta G‡$ = 6.6−7.9 kcal/mol for the approach to the *si* face (Figure 1a). Similarly, nucleophilic addition to carbonyl C27 with a second **MDC** complex was modeled from the optimized geometries of the magnesium alcoholates at C28. In this case, a monocoordinated complex formed by substitution of one $Me_2O$ coordinated to Mg1 with carbonyl O27, and its subsequent coordination to Mg2, leads to **TS3**$_{si}$ and **TS4**$_{si}$ (Figure 1b), which explain the facial diastereoselectivity for the *si* face of C27. The similar energy barriers calculated for **TS1**$_{re}$ and **TS2**$_{re}$ justify the same stereochemical outcome of the addition to C28 in both cis/trans isomers. Although the same energy preference for the *si* face of C27 in **TS3**$_{si}$ and **TS4**$_{si}$ was calculated, the energy barrier is higher in the trans isomer, which is consistent with the lower reactivity shown by **5a** trans in the double addition reaction. Mechanistic studies of the Grignard reaction support the fact that nucleophilic addition to the carbonyl group involves a dimeric form of RMgX, while the side reduction by hydride transfer occurs under its monomeric form.[11,18] Our initially calculated transition states with the monomeric complex formed between MeMgBr and carbonyl C28 of **5a** cis (Figures S56 and S57) do not explain the observed facial diastereoselectivity during nucleophilic additions but could be the pathway explaining the opposite facial diastereoselectivity observed in C28 during reduction by hydride transfer from EtMgBr (Tables 1 and 2, entries 3 and 2, respectively).

## CONCLUSIONS

In summary, the present study reveals key structural features of diacyldodecaheterocycles **5** derived from (−)-(1*R*)-myrtenal, which allow them to be used as efficient chiral auxiliaries for the diastereoselective divergent synthesis of chiral alcohols. The construction of this pseudo-$C_2$-symmetric macrocyclic structures from simple starting materials (hydroxythiol **6** and α-ketoacetals) bearing two carbonyl groups with different chemical environments leads to stereodivergent Grignard additions to each one, yielding chiral alcohols with different configurations in a single reaction step. The observed R-group-dependent regioselectivity of the Grignard reagent is a consequence of the fact that carbonyl C28 is attached to an acetalic carbon and carbonyl C27 to a thioacetalic carbon, both present on the same macrocyclic scaffold. In this regard, the first nucleophilic addition occurs exclusively at carbonyl C28 and the second at C27. Furthermore, the later addition can be performed with a different nucleophile from the one added to C28, under a one-pot procedure. Thus, enantiomeric pairs of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ACS Omega 2023, 8, 20611−20620

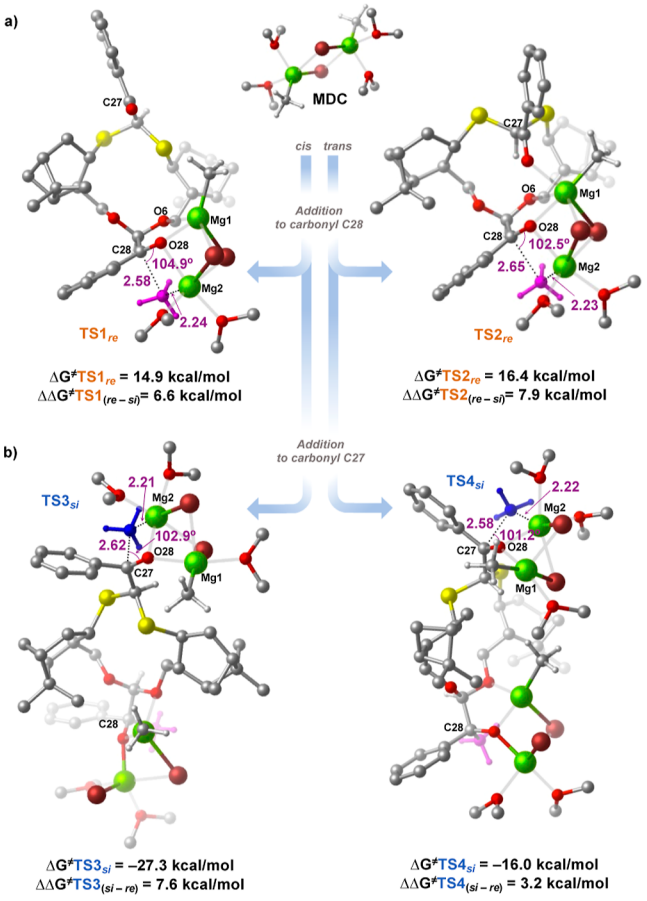


**Figure 1.** Lowest-energy diastereomeric transition state structures for the sequential addition of the Grignard reagent by a dinuclear complex of MeMgBr (**MDC**) to (a) carbonyl C28 and (b) carbonyl C27 of **5a** cis/trans. Calculations were performed at the M06-2X/6-311G(d,p)//M06-2X/6-31G(d) level of theory. The color codes are magenta for $Me^-$ added to C28 and blue for $Me^-$ added to C27; the other atoms are colored according to standard color codes. Some hydrogen atoms are omitted for clarity.

chiral 1,2-diols (or chiral 1,2-diols structurally different) can be obtained in high optical purity after sequential hydrolysis of double-addition products **9**, followed by the reduction of the intermediate hydroxyaldehydes **11** with $NaBH_4$. To the best of our knowledge, this is the first example describing a unique methodology that allows obtaining both enantiomers of an alcohol in which chirality is introduced in the same synthetic step. Experimental conformational information and DFT calculations support the same observed highly diastereoselective reaction outcome in both cis/trans isomers of dibenzoylmacrocycles **5**, making their separation unnecessary. Work is currently underway in our laboratory to expand the structural diversity of these pseudo-$C_2$-symmetric chiral auxiliaries using different carbonyl groups and a larger assortment of nucleophilic reagents.

## EXPERIMENTAL SECTION

**General Information.** Optical rotations were measured at 589 nm using a 1 dm cell on a JASCO P-2000 polarimeter. Infrared spectra were recorded on a PerkinElmer Spectrum 2000 spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were obtained on a Varian NMR System spectrometer at 500 and 125 MHz, respectively. Chemical shifts ($\delta$) are reported in parts per million (ppm) relative to internal tetramethylsilane ($Me_4Si$, $\delta$ 0.0) for $^1H$ NMR and $CDCl_3$ ($\delta$ 77.0) for $^{13}C$ NMR. Coupling constants ($J$) are reported in Hertz. Peak assignments of the $^1H$ and $^{13}C$ NMR spectra were confirmed by using 2D NMR experiments (DQCOSY, zTOCSY, ROESYAD, gHSQCAD, and gHMBCAD). High-resolution mass spectrometry-electrospray ionization (HRMS-EI) was determined on a JEOL GCmate spectrometer at 70 eV, or HRMS-ESI on a Bruker microOTOF-Q II time-of-flight LC/MS spectrometer, as specified. The X-ray crystallographic structure for **5b** cis/trans, **8b** cis, and **9c** trans was obtained on an Oxford XcaliburS diffractometer using MoK$\alpha$ radiation ($\lambda$ = 0.7073 AÅ). Thin layer chromatograms were obtained on precoated thin layer chromatography sheets of silica gel 60 $F_{254}$ (E. Merck). Flash chromatography was carried out using silica gel (Merck 230−400 mesh). HPLC was performed on an Agilent Technology 1260 Infinity with a ZORBAX SB-CN column eluting AcOEt/hexane at room temperature, unless otherwise stated, and monitored by a diode array detector, and chiral HPLC was performed with a Chiralpak AD-H column eluting hexane/*i*-PrOH. All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware, unless the reaction procedure states otherwise. Benzene used in the synthesis of macrocycles **5a−d** cis/trans and THF used in the nucleophilic additions were distilled from sodium−benzophenone immediately prior to use. Grignard reagents were purchased commercially and titrated by a colorimetric titration using an indicator of salicylaldehyde phenylhydrazone;[19] all other reagents were used without further purification. Racemic samples of **12a** and **12b** for the standard of chiral HPLC chromatograms were prepared from addition of Grignard reagents MeMgBr or EtMgBr, respectively, to commercially available 2-hydroxyacetophenone in anhydrous THF, at room temperature.

**Preparation of Ketones 7a and 7b.** The synthesis of ketone **7a** has been reported.[8b] Ketone **7b** was synthesized according to the procedure reported.[8b]

**Preparation of Diacylmacrocycles 5a−d Cis/Trans.** To a well-stirred solution of ketone **7a** or **7b** (1 equiv) and *p*-TsOH (10 mol %) in anhydrous benzene at 50 °C, 2,2-dietoxyacetophenone or pyruvic aldehyde dimethyl acetal (0.5 equiv) was added and allowed to reach a temperature of 70−72 °C and was stirred for 3 h. The reaction mixture was poured into a cold saturated solution of $NaHCO_3$, extracted with dichloromethane (DCM), washed with a saturated solution of $NaHCO_3$ (2 × 50 mL), dried over anhydrous $Na_2SO_4$, and concentrated to dryness to give the corresponding mixture of diacylmacrocycles **5a−d** cis/trans. Column chromatography separation was unsuccessful due to very similar $R_f$ of diastereoisomers in the mixture, and therefore, specific rotations are not reported. The spectroscopy data of diastereoisomers **5a−d** cis/trans obtained from the spectra of the corresponding mixture are described.

**General Procedure for Addition of Grignard Reagents to Dibenzoylmacrocycles 5a Cis/Trans.** To a solution of dibenzoylmacrocycles **5a** cis/trans (40:60 *dr*) (1 equiv) in anhydrous THF, at −78 °C, the Grignard reagent was added under a nitrogen atmosphere. After stirring for 3 h, the reaction mixture was quenched at the same temperature with THF. The reaction mixture was allowed to warm to room temperature, after which the THF was eliminated by evaporation, and the remaining emulsion was extracted with DCM. The organic layer was washed with water, dried over


https://doi.org/10.1021/acsomega.3c01161
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anhydrous $Na_2SO_4$, and evaporated to dryness to give the corresponding mixture of carbinols. Column chromatography separation was unsuccessful due to very similar $R_f$ of diastereoisomers in the mixture, and therefore, specific rotations are not reported, unless the purification procedure states otherwise.

**General Procedure for the Acetalic Hydrolysis of Double-Addition Products 9a Cis/Trans and 9b Cis and Successive Reduction to Obtain 1,2-Diols (*S*)-12a and (*S*)-12b.** A solution of **9a** cis/trans (40:60 *dr*) or **9b** cis (>99:1 *dr*) (1 equiv) in 15 mL of $CH_3CN/CH_2Cl_2/H_2O$ (7:2.5:0.5) was treated with *p*-TsOH (15 mol %) at 54 °C. After stirring for 3 h, the reaction mixture was allowed to cool to room temperature, and then, $NaBH_4$ (1 equiv) in ethanol was added, and stirring was continued for 5 h after which the mixture was extracted with DCM, and the organic layer was dried over anhydrous $Na_2SO_4$ and evaporated to dryness. The yellowish oil residue, whose $^1H$ NMR spectrum showed the presence of two compounds, was flash-chromatographed using a mixture of hexane/EtOAc (70:30) as the eluent, giving the corresponding bis-pinanediols **10** and 1,2-diols **12**.

**General Procedure for the Thioacetalic Hydrolysis of Bis-Pinanediols 10a and 10b and Successive Reduction to Obtain 1,2-Diols (*R*)-12a and (*R*)-12b.** A solution of **10a** (99:1 *dr*) or **10b** (99:1 *dr*) (1 equiv) in 15 mL of $CH_3CN/CH_2Cl_2/H_2O$ (7:2.5:0.5) was treated with NCS (2 equiv) and $AgNO_3$ (2 equiv) at 0−4 °C for 1−5 min. The work-up was carried out by successive addition of solutions of NaCl, $Na_2SO_3$, and $Na_2CO_3$ (1 mL each); the white precipitate was filtered, and the filtrate was treated with $NaBH_4$ (1.0 equiv) in ethanol and stirred at room temperature for 5 h, followed by addition of 10 mL of hot water. The stirring continued for 20 min, and the mixture was extracted with DCM. The organic layer was dried with anhydrous $Na_2SO_4$ and concentrated to dryness, and the yellowish oily residue was flash-chromatographed using a mixture of hexane/EtOAc (70:30) as the eluent, giving hydroxythiols **6** and the corresponding 1,2-diols **12**.

**Computational Modeling of the Grignard Reaction of MeMgBr with 5a Cis/Trans.** Geometry optimizations and vibrational frequency calculations were performed using *Gaussian 16* software, Revision A.03[20] at the M06-2X/6-31G(d)[21] level of theory in the gas phase. The nature of all stationary points was confirmed by the number of imaginary frequencies. All minima have zero imaginary frequency, and all transition states have only one imaginary frequency. Single-point energy calculations on the optimized geometries were carried out using the same functional (M06-2X) and the Pople's triple-split 6-311G(d,p)[22] basis set. Thermal corrections were calculated from the unscaled vibrational frequencies at the M06-2X/6-31G(d) level on the optimized geometries. The gas-phase Gibbs free energies for all species were obtained at 298.15 K and 1 atm at optimized structures. Explicit solvent molecules were added to solvate the Mg atoms in the dimeric form of MeMgBr (**MDC**), according to the model proposed by Cascella.[17a] The interaction of the **MDC** with carbonyl groups at **5a** cis and **5a** trans was built by replacing one (non-chelate approach) or two (chelate approach) explicit $Me_2O$ molecules coordinated to Mg with a carbonyl oxygen. The initial conformation of **5a** cis and **5a** trans was taken from the X-ray diffraction structures, while the geometries of reactants, products, and transition states were modeled from geometric data reported in a recent study for the Grignard reaction with the dimeric form of MeMgCl and acetaldehyde.[17a]

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c01161.

Experimental procedures; X-ray crystallographic information; $^1H$, $^{13}C$, and NOE NMR spectra of products; HPLC chromatograms; calculated energy profiles; and DFT-optimized geometries (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This research received financial support through grants from SIP-IPN (20160607, 20170808, and 20180092) and CONACyT (239906). G.G.F.B. is grateful for the scholarships awarded by CONACyT (599198) and BEIFI-IPN. The authors thank the personnel at the Centro de Nanociencias y Micro y Nanotecnologías (CNMN-IPN) and the Central de Instrumentación de Espectroscopía (ENCB-IPN) for the acquisition of mass, IR, and HPLC spectra. We are also thankful to UNAM-DGTIC-252 for the allotment of computer time. G.G.F.B. and L.G.Z. are grateful to Dr. Luis D. Miranda (UNAM) for giving laboratory time and space to consolidate this paper.



https://doi.org/10.1021/acsomega.3c01161
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