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RESEARCH ARTICLE

Enantiodivergent cyclization by inversion of the reactivity in ambiphilic molecules

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Dedicated to Professor Julius Rebek, Jr. on occasion of his 75th birthday

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Abstract: Inverting the reactivity of the functional groups in ambiphilic molecules provides a new synthetic strategy to carry out late-stage enantiodivergence. Both enantiomers of the final compound can be obtained from a common chiral precursor. As a proof of concept, the synthesis of substituted five- and six-membered oxacycles is described. The key step is the cyclization of an ambiphilic linear precursor bearing a propargylic alcohol and an epoxide linked through an alkyl chain. Through a slight modification of these linear precursors and employing different reaction conditions, these functional groups can inverse their chemical reactivity, producing one enantiomer or another of the final product. This enantiodivergent cyclization involves three stereogenic centers that can undergo fully controlled retention or inversion of their configuration depending on the cyclization pathway that is activated. The cyclization provides late-stage enantiodivergence, enabling the synthesis of either enantiomers of the oxacycles from a common chiral substrate with total transfer of the enantiomeric purity.

Introduction

Continued demand for both enantiomers of a given compound by pharmaceutical and chemical companies has prompted the development of a large number of enantiodivergent processes, starting from achiral substrates.[1] This approach usually requires the use of both enantiomers or pseudo-enantiomers of a chiral reagent, or ligand/catalyst.[2] However a serious drawback of this approach is the fact that many natural chiral sources are accessible in only one absolute configuration. There are some examples where by varying the external stimuli it is possible to obtain both enantiomers of a compound using a single enantiomer of a chiral reagent or ligand/catalyst.[3] Another interesting alternative to obtain both enantiomers is the enantiodivergent strategy that starts from chiral substrates. In this regard, two main approaches can be considered: one that sequentially modifies the functional groups, without altering the stereochemistry of the chiral elements present in the starting substrate (Figure 1A),[4] and the other that implies changes in the stereochemistry, which can be define as an enantiodivergent reaction.[5] In both cases, only one enantiomer of the starting material is required, and the use of chiral reagents or catalysts is optional.[6] Herein we define an enantiodivergent reaction as any reaction which generates both enantiomers of the final product starting from the same (or two very similar) enantiomeric substrate(s), just by changing the catalyst, reagent, or reaction conditions. There are very few examples of such enantiodivergent reactions, and usually they occur with a single element of symmetry such as a stereogenic center or an axis of chirality (Figure 1B).[5] Therefore, a great challenge for synthetic organic chemists is to find enantiodivergent reactions where a greater number of

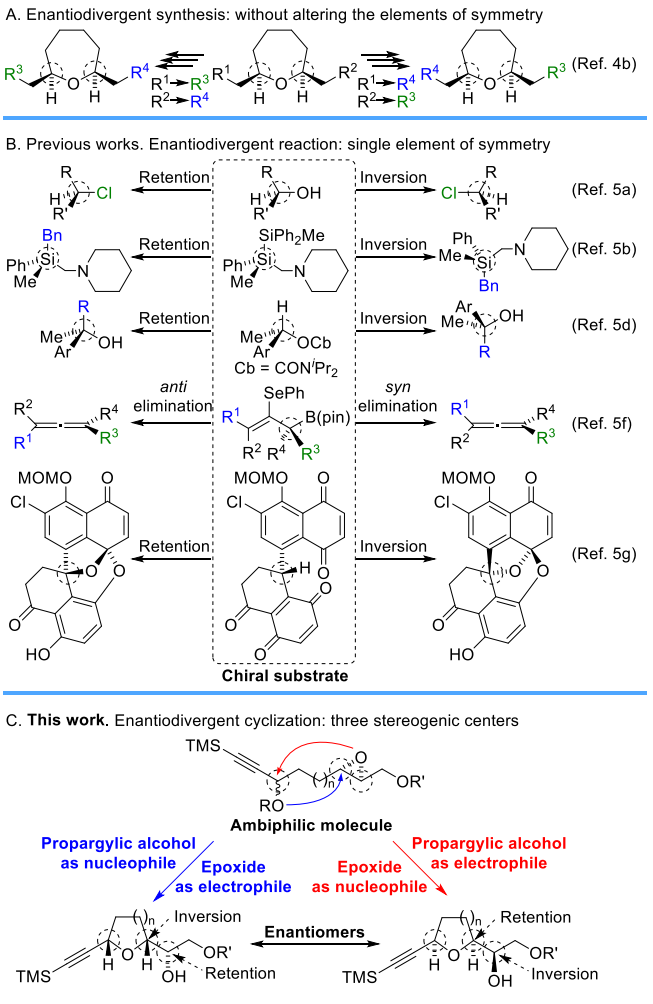

Figure 1. Examples of an enantiodivergent synthesis (A) and previous works for enantiodivergent reactions (B), and our strategy for the enantiodivergent cyclization by inversion of the reactivity in ambiphilic molecules (C).

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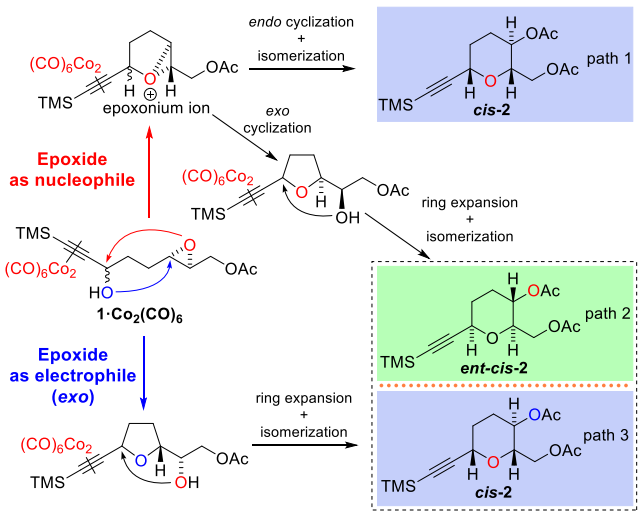
stereogenic centers are involved. The advantage of such an approach is that it would allow both enantiomers to be obtained in a more advanced stage in the synthesis of a desired compound. We thought that this could be achieved through an ambiphilic molecule (a molecule bearing electrophilic and nucleophilic sites) where the reactivities of the functional groups could be inverted depending on the reaction conditions. As a proof of concept, we focus on the synthesis of cyclic ethers. We figured that an epoxide and a propargylic alcohol placed in suitable positions of a linear precursor constitute adequate functional groups to carry out this aim. In this way, one could act as nucleophile and the other as an electrophile or vice versa, providing an enantiodivergent route to obtain both enantiomers of the final cyclic ether (Figure 1C). In order to achieve this goal, it is essential that both cyclization mechanisms occur in an orthogonal manner, since otherwise it would result in partial or total racemization of the final product.

To the best of our knowledge, herein we present the first example of an enantiodivergence process achieved by inversion of the reactivity in ambiphilic molecules, as well as the first report embracing more than one stereogenic center. This concept was exemplified by the synthesis of substituted five- and six-membered oxacycles through an enantiodivergent cyclization step, where all the stereogenic centers of the starting material are involved in the process.

To develop this idea, the epoxide is required to act as nucleophile (to attack the propargylic position, Figure 1C). Although this being a non-trivial problem, we could fortunately resort to our previously developed strategy for the synthesis of polysubstituted oxanes and oxepanes. In those studies, we were able to perform this transformation with a high degree of stereocontrol using a Nicholas reaction, based on the intramolecular nucleophilic attack of an epoxide to a carbocation generated by acid treatment of hexacarbonyl dicobalt complexes of propargylic alcohols.[7,8] Thus, a more thorough analysis of this Nicholas reaction with the cobalt complex of epoxide **1** allowed us to disclose three possible routes to the cyclization products (Scheme 1). Two of these routes have an epoxonium ion as a common intermediate,[9] which can evolve through an *endo* pathway followed by isomerization of the propargylic position to give the tetrahydropyran ***cis*-2** (path 1). However, if this intermediate goes through an *exo* pathway, a tetrahydrofuran is produced that could undergo ring expansion and isomerization to give the tetrahydropyran ***ent-cis*-2**, *i.e.* the enantiomer of the ***cis*-2** (path 2). The third route is the nucleophilic attack of the propargylic alcohol on the epoxide through an *exo* pathway giving a tetrahydrofuran that could undergo ring expansion and isomerization to provide the tetrahydropyran ***cis*-2** (path 3).[10] In order to achieve an enantiodivergent event in the cyclization, it is necessary that the reaction takes place *via* path 2 or *via* path 3 exclusively in an orthogonal fashion. To limit the number of possible routes in the cyclization step, we thought about protecting the propargylic alcohol of **1** as an acetate, this would prevent it from acting as a nucleophile. In this way, we would ensure that only the Nicholas reaction occurs, where the epoxide would act exclusively as a nucleophile. If the reaction took place exclusively following path 2, we would obtain the tetrahydropyran ***ent-cis*-2**. On the other hand, it would be necessary to find the appropriate conditions for the nucleophilic attack of propargylic alcohol on the epoxide following path 3 that would lead to the enantiomeric tetrahydropyran ***cis*-2** (Scheme 1).



Scheme 1. Possible routes in the Nicholas reaction for the formation of trisubstituted tetrahydropyrans. Ac = acetyl. TMS = trimethylsilyl.

Results and Discussion

We began the study with the preparation of linear precursors, in which an epoxy-alcohol and a propargylic alcohol were linked through an alkyl chain with two different lengths.[11] The linear precursor **1** was prepared from the 2,3-epoxide alcohol **3**, which was obtained by a Katsuki-Sharpless asymmetric epoxidation of the suitable allylic alcohol using the (*R*,*R*)-(+)-diisopropyl tartrate.[12] The enantiomeric excess of epoxy-alcohol **3** was determined by chiral HPLC using *p*-nitrobenzoate derivative **4** (Scheme 2).[13] The next step was to use precursor **1** in the cyclization step, and after several attempts we found that the *exo*-cyclization of **1** through the nucleophilic attack of propargylic alcohol on the epoxide was achieved quantitatively using catalytic amounts of zinc chloride in dichloromethane at room temperature. This results in an equimolecular mixture of the tetrahydrofurans ***cis*-5** and ***trans*-5**. This mixture could be easily separated after carrying out an acetylation of the secondary alcohols to afford the diacetylated tetrahydrofurans ***cis*-6** and ***trans*-6**. In order to determine the enantiomeric purity of these compounds, the benzoates ***cis*-7** and ***trans*-7** were prepared,[13] and it was found that the enantiomeric purity of the epoxide **3** is maintained during the cyclization process. On the other hand, to study the Nicholas reaction, diacetate **8** was prepared from compound **1**, which was then transformed into the corresponding hexacarbonyl dicobalt complex. Fortunately, the reaction could be stopped at the tetrahydrofurans ***ent-cis*-5** and ***ent-trans*-5** using montmorillonite K-10 as mild acidic conditions (*vide infra*).[14] These compounds were obtained in an approximately equimolar ratio and their subsequent acetylation of the secondary alcohols allowed us to reach the diacetates ***ent-cis*-6** and ***ent-trans*-6** that were easily separated.[15] Analysis of the specific rotation values revealed that the latter are enantiomers of the diacetates ***cis*-6** and ***trans*-6**, respectively. Additionally, chiral HPLC analysis of the benzoates ***ent-cis*-7** and ***ent-trans*-7** confirms that the reaction proceeded with total transfer of the enantiomeric purity from epoxide **3** (Scheme 2).[13] This clearly indicates that the Nicholas reaction proceeds through the epoxonium ion and subsequent *exo*-

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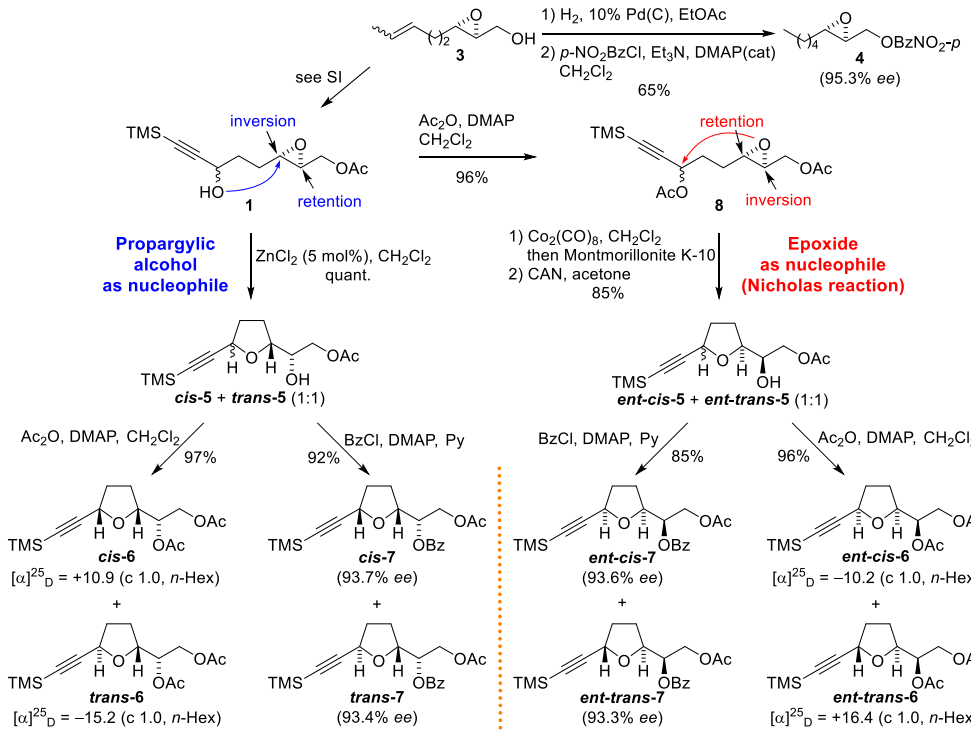
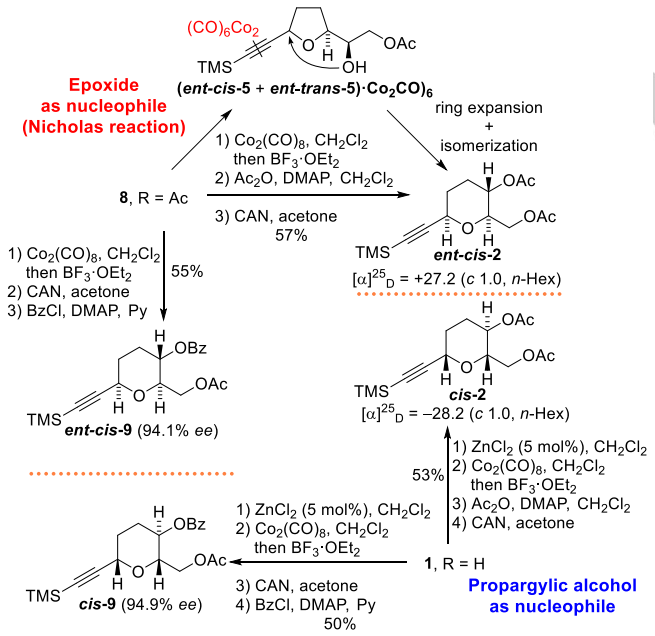


Scheme 2. Enantiodivergent synthesis of disubstituted tetrahydrofurans. The enantiomeric excess (*ee*) was determined by chiral HPLC, Chiralpak IC-3. Ac = acetyl. Bz = benzoyl. CAN = ceric ammonium nitrate. DMAP = 4-dimethylaminopyridine. TMS = trimethylsilyl.

cyclization following path 2 (Scheme 1). It should be noted that the enantiodivergent event lies exclusively in the cyclization step, whereas all of the subsequent transformation (decomplexation, acetylation, benzoylation, etc.) are carried out to reach the final compounds that allow direct comparison.



Scheme 3. Enantiodivergent synthesis of trisubstituted tetrahydropyrans. The enantiomeric excess (*ee*) was determined by chiral HPLC, Chiralpak IC-3. Ac = acetyl. Bz = benzoyl. CAN = ceric ammonium nitrate. DMAP = 4-dimethylaminopyridine. TMS = trimethylsilyl.

However, when the Nicholas reaction was carried out with the linear precursor **8** using $BF_3{\cdot}OEt_2$ as a Lewis acid, the trisubstituted tetrahydropyran ***ent-cis*-2** was obtained directly after acetylation (Scheme 3).[16] Taking into account the stereochemical outcome of the reaction, this compound derives from the ring expansion undergone by the cobalt complexes of the tetrahydrofurans ***ent-cis*-5** and ***ent-trans*-5** due to the attack of the exocyclic secondary alcohol to the stabilized propargylic carbocation and subsequent isomerization of the *trans*- to the *cis*-isomer following path 2 in Scheme 1.[17] The driving force for the isomerization process is the greater thermodynamic stability of the cobalt complex of the *cis*-isomer compared to that of the *trans*-isomer.[18] This result was also confirmed by treatment of the hexacarbonyl dicobalt complexes of the tetrahydrofurans ***ent-cis*-5** and ***ent-trans*-5** with $BF_3{\cdot}OEt_2$, which yielded the tetrahydropyran ***ent-cis*-2** after acetylation and decomplexation. Similarly, by performing the same sequence of reactions on the hexacarbonyl dicobalt complexes of the tetrahydrofurans ***cis*-5** and ***trans*-5**, the tetrahydropyran ***cis*-2** was obtained after acetylation and decomplexation. Again, the specific rotation value confirmed ***cis*-2** being the enantiomer of ***ent-cis*-2**. In addition, the chiral HPLC analysis of the benzoate derivatives ***cis*-9** and ***ent-cis*-9** demonstrated that the enantiomeric purity of epoxide **3** is maintained throughout both cyclization processes: the nucleophilic attack of the propargylic alcohol on the epoxide and the Nicholas reaction, where the propargylic carbocation is the electrophile and the epoxide is the nucleophile (Scheme 3).[13]

Trying to extend the concept, the next step was to use a precursor with an additional carbon atom in the alkyl chain that links the epoxide and the propargylic alcohol. In this way, the disubstituted

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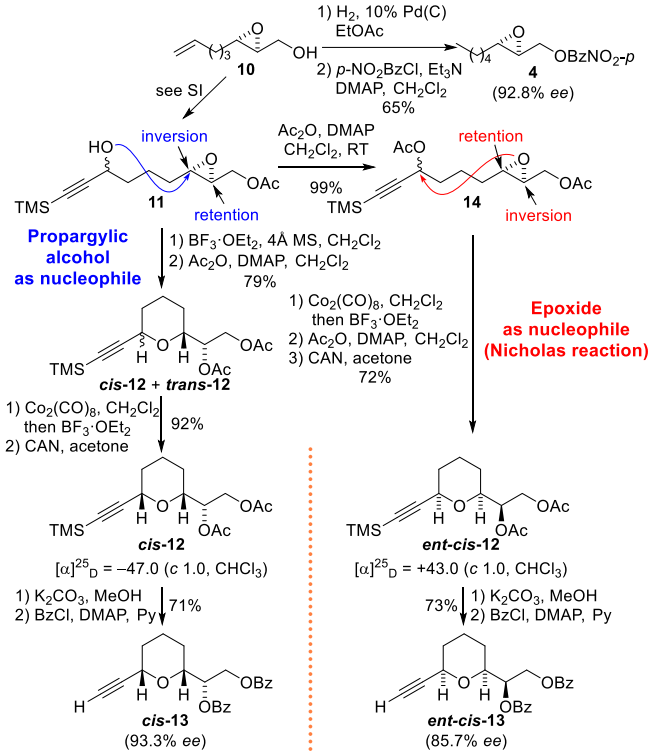
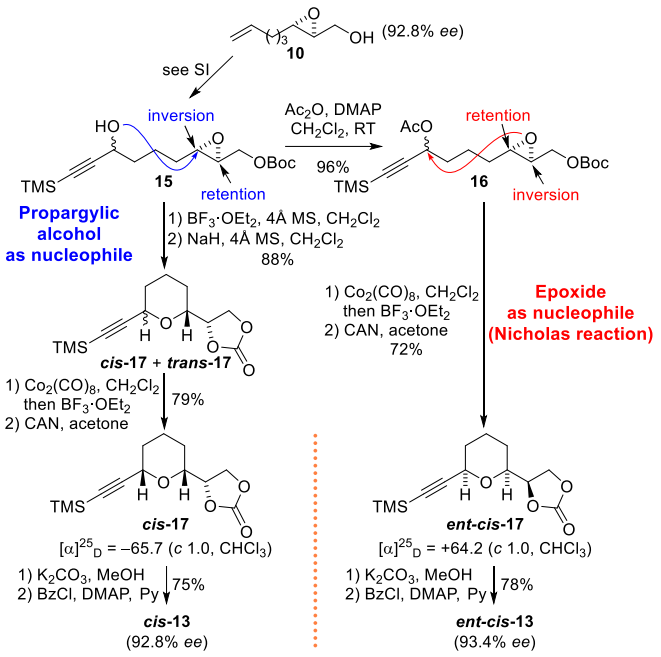


Scheme 4. Enantiodivergent synthesis of disubstituted tetrahydropyrans. The enantiomeric excess (*ee*) was determined by chiral HPLC, Chiralpak IC-3. Ac = acetyl. Bz = benzoyl. CAN = ceric ammonium nitrate. DMAP = 4-dimethylaminopyridine. TMS = trimethylsilyl.



Scheme 5. Enantiodivergent synthesis of disubstituted tetrahydropyrans. The enantiomeric excess (*ee*) was determined by chiral HPLC, Chiralpak IC-3. Ac = acetyl. Boc = *tert*-butoxycarbonyl. Bz = benzoyl. CAN = ceric ammonium nitrate. DMAP = 4-dimethylaminopyridine. MS = molecular sieves. TMS = trimethylsilyl.

tetrahydropyran could be obtained directly. The linear precursor **11** was prepared from the 2,3-epoxide alcohol **10**. In this case the (*R*,*R*)-(+)-diethyl tartrate was used as a chiral auxiliary in the Katsuki-Sharpless asymmetric epoxidation.[12] The enantiomeric excess of epoxide alcohol **10** was determined by chiral HPLC using the *p*-nitrobenzoate derivative **4** (Scheme 4).[13] After several attempts, we found that $BF_3{\cdot}OEt_2$ at low temperature is able to activate the epoxide of precursor **11** and produce the attack of the propargylic alcohol to give an equimolecular mixture of the tetrahydropyrans ***cis*-12** and ***trans*-12** after acetylation.[16] In the next stage, we pondered to perform an isomerization to the *cis*-compound via alkyne-hexacarbonyl dicobalt complexes under acidic conditions, considering that the complex of this stereoisomer is thermodynamically more stable.[18] While the relatively mild acid montmorillonite K-10 failed, complete isomerization to the tetrahydropyran ***cis*-12** was observed using $BF_3{\cdot}OEt_2$. The preparation of the dibenzoate ***cis*-13** derivative allowed us to confirm that the enantiomeric purity of the starting epoxide **10** was maintained during the cyclization process (Scheme 4).[13] To avoid competition between the two cyclization mechanisms, that would result in a loss of the enantiomeric purity of the final product, we decided again to protect the propargylic alcohol of **11** as an acetate, ensuring that only the Nicholas reaction will take place. Thus, starting from linear precursor **14** and following a sequence of cobalt complex formation, cyclization, acetylation and decomplexation, we were able to obtain the tetrahydropyran ***ent-cis*-12** in good yields. To determine whether the cyclization or the isomerization of the obtained tetrahydropyrans controls the final stereochemistry of this process, a Nicholas cyclization of linear precursor **14** was carried out using montmorillonite K-10 as an acid. After acetylation and decomplexation, a mixture of tetrahydropyrans ***ent-cis*-12** and ***ent-trans*-12**, in a ratio of 3.6:1.0, was obtained. Considering that montmorillonite K-10 was unable to isomerize neither the hexacarbonyl dicobalt complex of the tetrahydropyran ***trans*-12** nor the hexacarbonyl dicobalt complex of the monoacetate of the *trans*-tetrahydropyran[19] (the cyclization product of **11** with $BF_3{\cdot}OEt_2$) it is clear that the stereochemical course is dictated by the isomerization using $BF_3{\cdot}OEt_2$ and not by the cyclization. It is necessary to point out that the specific rotation value of ***ent-cis*-12** and the chiral HPLC analysis of the benzoate derivative ***ent-cis*-13** showed a slight loss of enantiomeric purity with respect to that of the starting epoxide **10**. Such loss of enantiomeric purity may be consistent with the fact that the cyclization reaction does not exclusively occur *via* Nicholas pathway (epoxide as nucleophile), as it is possible that 3.5% of **14** react through the epoxide acting as an electrophile. We have two possible explanations for this fact: first, moisture in the reaction triggers a Nicholas reaction occurs with water to generate the propargylic alcohol, which acts as a nucleophile in the cyclization. However, this possibility was ruled out because when the reaction was performed in the presence of 4Å MS, a similar loss of enantiomeric purity was observed. Second, the acetate in the primary alcohol is not fully capable of driving the Nicholas reaction. In this case, the $BF_3{\cdot}OEt_2$, instead of coordinating to the propargylic acetate to form a stabilized carbocation, activates the epoxide and as a result the oxygen in the acetate of the propargylic alcohol acts as a nucleophile generating the small amount of the undesired enantiomer.

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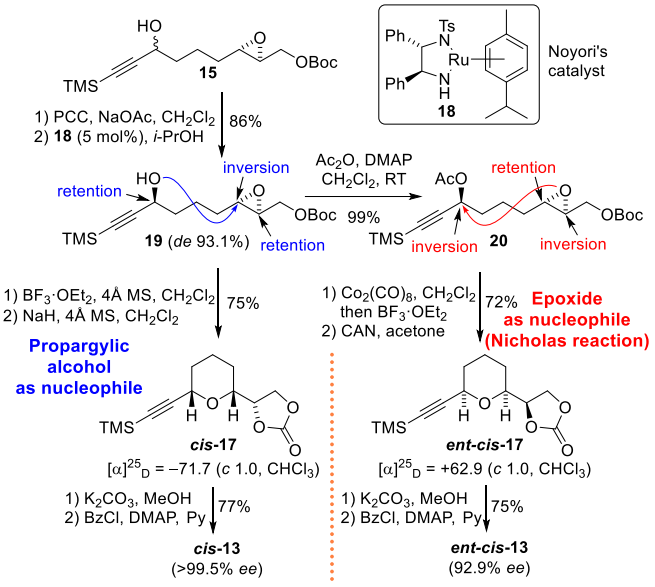

Scheme 5. Enantiodivergent synthesis of disubstituted tetrahydropyrans. The enantiomeric excess (*ee*) was determined by chiral HPLC, Chiralpak IC-3. Ac = acetyl. Boc = *tert*-butoxycarbonyl. Bz = benzoyl. CAN = ceric ammonium nitrate. DMAP = 4-dimethylaminopyridine. MS = molecular sieves. TMS = trimethylsilyl. Ts = tosyl.

In order to solve this problem, the influence of the protecting group in the primary alcohol on the stereochemical course of the cyclization step was studied by changing the acetate group to a Boc group. The introduction of the Boc protecting group is known to generate a terminating nucleophile for acid-promoted cascades.[20] In this case, when the Nicholas reaction was performed with linear precursor **16**, with the propargylic alcohol as acetate and the primary alcohol as Boc, the cyclic carbonate ***ent-cis*-17** was obtained exclusively (Scheme 5). Gratifyingly, after transformation of ***ent-cis*-17** to the dibenzoate ***ent-cis*-13** we found that the enantiomeric purity of epoxide **10** was completely transferred.[13] On the other hand, when compound **15** was treated with $BF_3{\cdot}OEt_2$ at low temperature, the *cis*- and *trans*-tetrahydropyrans were obtained with the primary alcohol protected as *tert*-butyl carbonate, which were transformed into the cyclic carbonates ***cis*-17** and ***trans*-17** with sodium hydride. Following the isomerization protocol of the *trans*-tetrahydropyran to the *cis*-tetrahydropyran described above, the cyclic carbonate ***cis*-17** was obtained in good yields. Again, the transformation of the compound ***cis*-17** to the dibenzoate ***cis*-13** confirms that the cyclization takes place with a complete transfer of the enantiomeric purity of epoxide **10**.[13] With these results, it can be stated that we developed an enantiodivergent cyclization for the synthesis of disubstituted tetrahydropyrans, where all three stereogenic centers are involved in the process.

Finally, to prove that the reactivity inversion of the functional groups occurs only in the cyclization step (without the need of subsequent isomerization), we turned our attention towards linear precursor **19** where all three stereocenters are well-defined. Compound **19** was obtained from the oxidation of the propargylic alcohol of compound **15** to the corresponding acetylenic ketone, and its subsequent asymmetric reduction through an asymmetric transfer hydrogenation carried out with Noyori's catalyst **18**.[21] Considering the proton NMR spectrum of the benzoate of propargylic alcohol **19**, as well as its chromatogram in chiral HPLC, we can affirm that the reduction occurred with an enantiomeric excess >99%. Therefore, compound **19** is a mixture of diastereoisomers in the epoxide with a diastereomeric excess (*de*) of 93.1%, which corresponds to the enantiomeric excess that derives from the asymmetric epoxidation of compound **10** (Scheme 6).[11]

Cyclization of compound **19** with $BF_3{\cdot}OEt_2$ at low temperature generated mostly *cis*-tetrahydropyran with the primary alcohol as *tert*-butyl carbonate, which was converted to cyclic carbonate ***cis*-17** by treatment with sodium hydride. The enantiomeric excess of this compound was determined through its dibenzoate derivative ***cis*-13**, giving >99.5%.[13] This is because the other diastereoisomer of **19** (<4%) provided the *trans*-isomer in the cyclization stage, which was probably lost in the purification process. On the other hand, the Nicholas reaction carried out on linear precursor **20** leads to the opposite enantiomer of the ***cis*-17**, that is, the cyclic carbonate ***ent-cis*-17**. The dibenzoate derivative ***ent-cis*-13** confirmed that the enantiomeric purity from epoxide **10** is conserved throughout the cyclization, indicating that the process runs exclusively through the Nicholas reaction where the epoxide acts as a nucleophile.[13]

Conclusion

In summary, we have introduced the concept of enantiodivergence by inverting the reactivity of specific functional groups in ambiphilic precursors. This strategy opens a new approach for the synthesis of either enantiomer of a given compound from a common chiral substrate. Using linear precursors that possess a propargylic alcohol and an epoxide linked through an alkyl chain, we have developed an enantiodivergent cyclization step, leading to both enantiomers of substituted oxacycles. In this way, depending on the reaction conditions, in one case the epoxide acts as an electrophile and the propargylic alcohol as a nucleophile, and in the other case the opposite occurs, the epoxide acts as a nucleophile and the propargylic alcohol as an electrophile. Therefore, all three stereogenic centers present in the substrate participate in the processes, undergoing fully controlled retention or inversion of their configuration, depending on the reaction conditions used. It is noteworthy that the enantiomeric purity of the linear precursor is completely transferred to the final products throughout both cyclization pathways. The herein developed method allows enantiodivergence to be carried out at a late stage of the synthesis of a desired compound, holding great potential to dramatically decrease the synthetic effort when both enantiomers of a target compound are required.

Supporting Information. Material and general methods; detailed experimental procedures and spectral data; copies of ^{1}H, ^{13}C and 2D NMR spectra; chiral HPLC analysis.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: enantiodivergent reactions • ambiphilic molecules • cyclic ethers • epoxides • Nicholas reaction

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[7] F. R. P. Crisóstomo, T. Martín, V. S. Martín, *Org. Lett*. **2004**, *6*, 565-568.

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[10] It is well-known that the cyclization reactions involving opening of epoxides favored 5-*exo-tet* over 6-*endo-tet* processes, generating mostly tetrahydrofurans. J. E. Baldwin, *J. Chem. Soc*., *Chem. Commun*. **1976**, 734-736.

[11] See the Supporting Information for further details.

[12] Reference 2a and T. Kasutki, V. S. Martín, *Organic Reactions*, *Vol. 48* (Ed.: L. A. Paquette), Wiley, New York, **1996**, pp. 1-299.

[13] The benzoate or *p*-nitrobenzoate derivatives were prepared exclusively with the purpose to determine the enantiomeric excess using a UV detector coupled to chiral HPLC.

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[15] To determine if the stereochemical control in the formation of the equimolecular mixture comes from the cyclization or isomerization reaction of the propargylic position, the ***ent-trans*-6·$Co_2(CO)_6$** was treated with montmorillonite K-10, and after 5 hours (same time used to complete the cyclization reaction of **8**) and subsequent decomplexation, a mixture of the compound ***ent-trans*-6** and ***ent-cis*-6** was obtained in proportions 1.3:1.0, respectively. This result indicates that the stereochemical course of this process is controlled mainly by the isomerization reaction and not by the cyclization.

[16] The acetylation step is carried out to facilitate structural determination.

[17] Ring contraction from oxepanes to tetrahydropyrans has been observed with epoxides as trapping agents in the transposition of allylic alcohols with catalytic amounts of Re_2O_7. See reference [9d].

[18] In the *trans* isomer, the bulkiest substituent, the hexacarbonyl dicobalt complex, is placed in the equatorial position and the other substituents are located in the axial positions, generating three 1,3-diaxial interactions. However, in the *cis* isomer, all substituents are placed at equatorial positions and, therefore, the *cis* complex is more stable than the *trans*, analogously to what happens in disubstituted tetrahydropyrans. a) S. Tanaka, T. Tsukiyama, M. Isobe, *Tetrahedron Letters* **1993**, *34*, 5757-5760; b) S. Tanaka, M. Isobe, *Tetrahedron* **1994**, *50*, 5633-5644.

[19] The final product of the Nicholas cyclization of **14** (before acetylation and decomplexation) is the hexacarbonyl dicobalt complex of tetrahydropyran monoacetate, and therefore we need to assure that this complex does not isomerize with montmorillonite K-10. This could be done using its enantiomer coming from the cyclization of **11** with $BF_3{\cdot}OEt_2$, in this way an equimolecular mixture of the tetrahydropyrans *cis* and *trans* monoacetates is obtained. The hexacarbonyl dicobalt complexes in this mixture were treated with montmorillonite K-10 for four days and only a slight change in the *cis:trans* ratio was observed.

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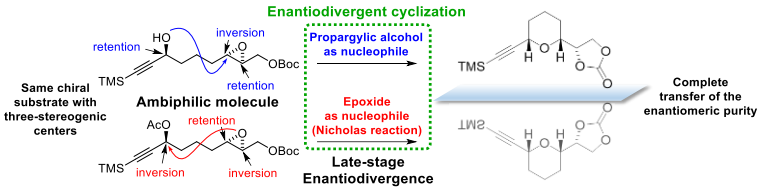
RESEARCH ARTICLE

Entry for the Table of Contents



Two for one: Inverting the reactivity of the functional groups in ambiphilic molecules provides a new way to carry out late-stage enantiodivergence. Thus, starting from a common chiral substrate both enantiomers of the final product can be obtained. This concept was exemplified by the synthesis of substituted five- and six-membered oxacycles.