Enantioselective Synthesis of Acyclic Stereotriads Featuring Fluorinated Tetrasubstituted Stereocenters

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Enantioselective Synthesis of Acyclic Stereotriads Featuring Fluorinated Tetrasubstituted Stereocenters

Na Shao[+],[a] Xueyang Liu[+],[a] Valérie Monnier,[b] Laurence Charles,[c] Jean Rodriguez,[a] Cyril Bressy,*[a] and Adrien Quintard*[a]

Abstract: Elaboration of enantioenriched complex acyclic stereotriads represents a challenge for modern synthesis even more when fluorinated tetrasubstituted stereocenters are targeted. We have been able to develop a simple strategy in a sequence of two unprecedented steps combining a diastereoselective aldol-Tishchenko reaction and an enantioselective organocatalyzed kinetic resolution. The aldol-Tishchenko reaction directly generates a large panel of acyclic 1,3-diols possessing a fluorinated tetrasubstituted stereocenter by condensation of fluorinated ketones with aldehydes under very mild basic conditions. The *anti* 1,3-diols featuring three contiguous stereogenic centers are generated with excellent diastereocontrol (typically >99:1 *dr*). Depending upon the precursors both diastereomers of stereotriads are accessible through this flexible reaction. Furthermore, from the obtained racemic scaffolds, development of an organocatalyzed kinetic resolution enabled to generate the desired enantioenriched stereotriads with excellent selectivity (typically er >95:5).

Introduction

Given the urgency at moving out of the plane in drug development, the stereoselective construction of complex acyclic architectures featuring multiple contiguous stereogenic centers represents a golden goal for synthetic chemists.[1] However, the discovery of efficient methods is hampered by the difficulty at selectively assembling simple available building blocks into correctly arranged complex scaffolds. While enzymes are able to accommodate their machinery for this purpose, in contrast, Nature only produces a handful of fluorinated building blocks.[2] Consequently, considering the impact of fluorine insertion on key parameters such as acidity of adjacent functions, stability, bioavailability or conformation, medicinal chemists must rely on man-made synthetic methods for its introduction in bioactive scaffolds.[3] While the control over fluorinated trisubstituted stereocenters is now established, the stereoselective elaboration of complex sterically crowded fluorinated tetrasubstituted stereocenters is by far more challenging.[4] Given the structure of fluorinated tetrasubstituted stereocenters-containing drugs often featuring complex stereo-settings and vicinal alcohols functions (Figure 1),[5] the identification of enantioselective routes enabling the rapid simultaneous generation of a monofluorinated[6] tetrasubstituted stereocenter with adjacent stereocenters would be highly desirable. Most notably, 1,3-diols stereotriads are crucial fragments of natural polyketide drugs and natural products (Figure 2a).[7] Their impressive bioactive profiles render pivotal the discovery of new strategies for the elaboration of modified versions possessing enhanced properties. Recent studies indicated that secondary fluorohydrins could dramatically modify 1,3-diols biological properties.[8] As a result, modification of classical polyketide triads by incorporation of fluorinated tetrasubstituted stereocenter should add highly useful scaffolds to medicinal chemist's toolbox (Figure 2a).

However, while different solutions exist for fluorinated trisubstituted stereocenter introduction,[9] a synthetic route to

[a] N. Shao,[+] X. Liu,[+] Dr. J. Rodriguez, Dr. C. Bressy, Dr. A. Quintard
Aix Marseille Univ, CNRS, Centrale Marseille, iSm2
Marseille (France)
E-mail: cyril.bressy@univ-amu.fr
adrien.quintard@univ-amu.fr
Homepage: https://ism2.univ-amu.fr/fr/stereo/stereo

[b] Dr. V. Monnier
Aix Marseille Univ, CNRS, Centrale Marseille, FSCM
Marseille (France)

[c] Dr. L. Charles
Aix Marseille Univ, CNRS, ICR
Marseille (France)

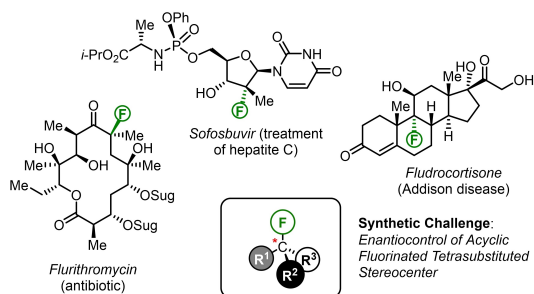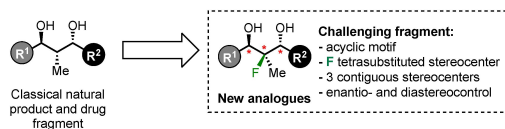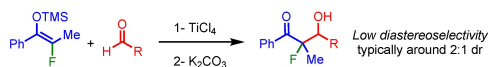[+] These authors contributed equally to this work.

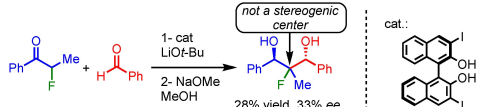**Figure 1.** Examples of drugs bearing a fluorinated tetrasubstituted stereocenter.

2a. Acyclic stereotriads featuring a fluorinated tetrasubstituted stereocenter

Classical natural product and drug fragment

New analogues

Challenging fragment:
- acyclic motif
- F tetrasubstituted stereocenter
- 3 contiguous stereocenters
- enantio- and diastereocontrol

2b. Previous Mukaiyama-Aldol reaction

1- TiCl₄
2- K₂CO₃

Low diastereoselectivity typically around 2:1 dr

2c. Previous Aldol-Tishchenko reaction (only one acyclic fluorinated example)

not a stereogenic center

1- cat LiOt-Bu
2- NaOMe MeOH

cat.:

28% yield, 33% ee

2d. Our strategy: Aldol-Tishchenko reaction/DoCKR sequence

Diastereocontrol:
Aldol-Tishchenko reaction

(+/−)

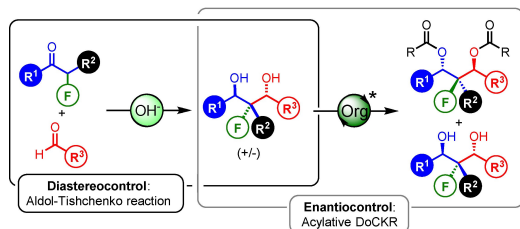Enantiocontrol:
Acylative DoCKR

Figure 2. The fluorinated stereotriad challenge.

more challenging acyclic polyketides featuring a stereogenic fluorinated tetrasubstituted carbon is unknown.[10] This is due to the difficulty at assembling all the diol elements while concomitantly controlling the three contiguous stereocenters. While trapping of fluorinated enolates with various electrophiles such as imines or π-allyl intermediates has recently been developed,[4] efficient aldolization methods are inexistent for this type of system.[11] The challenge lies in the control of the enolate geometry and orientation during the aldolization. Alternative diastereoselective control of this stereocenter by Mukaiyama-type aldolization of preformed silyl enol ethers also only provided modest results (Figure 2b).[12]

The aldol-Tishchenko reaction is an excellent solution to rapidly create diastereoselectively 1,3-diols. However, enantioselective versions are limited and the control of acyclic fluorinated tetrasubstituted stereocenter remains unaddressed.[13] Kotani and Nakajima have shown that the diastereo- and enantioselective Tishchenko reaction could be efficiently applied to fluorinated cyclic ketones. However, the single acyclic symmetrical 1,3-diol lacking the key fluorinated stereogenic center prepared in this study from α-fluorinated propiophenone, was obtained in low yield and stereoselectivity (28%, 33% ee) (Figure 2c). Bypassing these issues, we disclose a strategy to build rapidly and with good diastereo- and enantio-control these key fluorinated polyketides. Our approach is based on a sequence involving two unprece-

dented steps. A diastereoselective aldol-Tishchenko cascade occurring under mild conditions builds the racemic stereotriad while a subsequent Double organocatalyzed Kinetic Resolution (DoCKR) generates the final diol featuring the fluorinated tetrasubstituted stereocenter with excellent enantioselectivity (Figure 2d). The reaction is modular and provides access to two sets of diastereomeric 1,3-anti-diols with equal efficiency.

Results and Discussion

Development of the aldol-Tishchenko reaction

In order to develop the desired sequence, at first, we examined the reactivity of fluorinated ketones **1**[10f–h] with aldehydes **2** under basic conditions (Scheme 1). Gratifyingly, a simple protocol involving KOH in the presence of 20 mol% of TBAI, in toluene at room temperature promoted the formation of the expected diols in excellent yields (typically >80%). Applying TBAI slightly improves yields (see Supporting Information), which might be attributed to an increase in the solubility of the basic salts in the reaction media. This cascade is occurring with high level of diastereocontrol for the three new contiguous stereocenters (16 examples at 99:1 dr). The reaction is general using a broad range of ketones and aldehydes. In detail, starting from aromatic ketone **1a**, all benzaldehyde derivatives **2a**–**l** tested were well tolerated. Various electron-withdrawing as well as electron-donating substituents at *meta*- and *para*- positions provided the stereotriads **3**–**9** with more than 78% yield and 99:1 dr. Ortho-substitution revealed more challenging and diols **10** and **11** were isolated with a lower but still synthetically interesting 10:1 dr. Furan and thiophene could also be efficiently inserted in diols **12**–**13** with good yield and once again perfect diastereocontrol. Finally, symmetrical diol **14** could also be prepared with the same efficiency. Use of other aromatic ketones also proved satisfactory. Of outmost importance, exchanging substituents between ketone and aldehyde unlocked the access to the two diastereomeric *anti*-diols **7** and **15**, both with 99:1 dr, demonstrating the flexibility of the method. Finally, replacing the ketone methyl substituent by an ethyl or benzyl chain did not modify the excellent selectivity and both sterically congested diols **16** and **17** could be isolated in 99:1 dr. Under those conditions, a limitation was reached when using an α,β-unsaturated aldehyde, providing only trace amount of **18**.

Most interestingly, in the context of the preparation of drug-like scaffolds, aliphatic aldehydes and ketones were also particularly well tolerated. Starting from aromatic ketones **1a** and **1b**, different branched aliphatic chains could be efficiently incorporated in compounds **19**–**22** with diastereoselectivities above 13:1. Interestingly, starting from enantiopure citronellal, the pre-existing stereocenter partially controlled the diastereoselectivity over the three new stereocenters, generating enantiopure *anti*-diol **23** in 1.8:1 dr. Aliphatic ketones also reacted well in the process generating diols **24** and **25** in 71 and 91% yield, respectively and >99:1 dr. Once again, it is
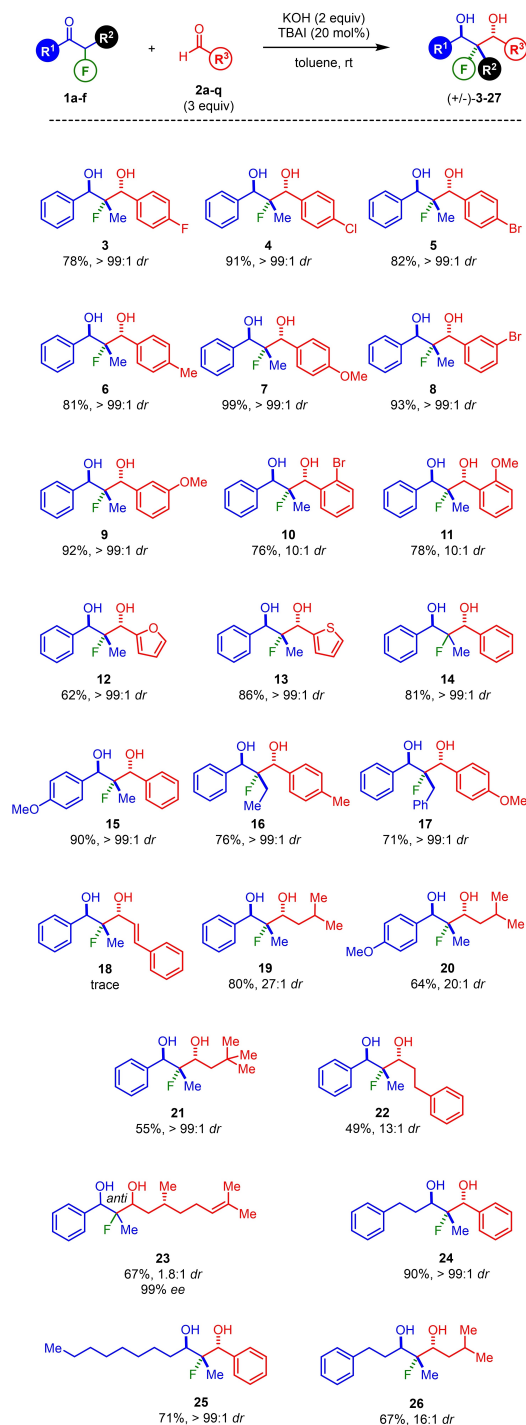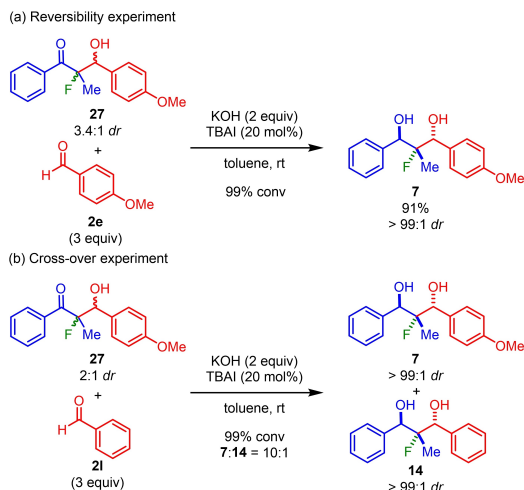
Scheme 1. Scope of the aldol-Tishchenko reaction.

remarkable that exchanging donors and acceptors in this transformation enabled to access **22** and **24**, two diastereomeric fluorinated *anti*-diols. Finally, compound **26** featuring aliphatic substituents on both sides of the diol was formed in 67% yield and still excellent 16:1 *dr*.

Of importance, when using aliphatic ketones, functionalization occurs exclusively at the more hindered fluorinated center. This could be explained by the higher acidity of the proton at the fluorinated center, favoring the regioselective deprotonation under the mild conditions used. Alternatively, the selectivity could also arise during the irreversible reduction of the generated aldol product (see below).

With such wide scope, mechanistic experiments were then performed in order to shed light on the origin of the high diastereocontrol (Scheme 2). For this purpose, aldol adduct **27** was prepared in 3.4:1 *dr* through Mukaiyama-type aldolization.[11] Subjecting this adduct to the conditions of the aldol-Tishchenko reaction in the presence of aldehyde **2e**, the two diastereomers converged to the formation of diol **7** generated with >99:1 *dr* (Scheme 2a). This suggests a dynamic process from the intermediate aldol adduct further confirmed by the following cross-over experiments.[9–13] Mixing **27** in the presence of benzaldehyde **2l**, a mixture of diols **7** and **14** could be observed confirming the reversibility of the C–C bond formation.

From these experiments, the proposed mechanism of the aldol-Tishchenko is depicted in Scheme 3. The KOH/TBAI combination induces the generation of the aldol adduct probably with moderate diastereocontrol. From this aldol adduct, only one diastereomer reacts in the irreversible hydride transfer. The preferential chair-like transition state where all substituents are perfectly arranged in an equatorial position while the carbonyl and the fluorine are in *anti* as in classical Cornforth-Evans transition states, minimize dipole-dipole interactions generating the stereotriad in excellent

**Scheme 2.** Mechanistic study on the aldol-Tishchenko reaction.
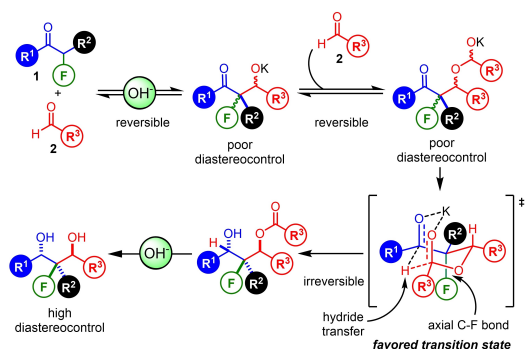
Scheme 3. Mechanism of the aldol-Tishchenko reaction.

diastereocontrol.[14] The reversibility of the aldolization enables to convert the other diastereomer of the aldol adduct to the single observed stereotriad. In contrast to other type of aldolization where the control over the geometry of the enolate is crucial, here the last step of hydride transfer dictates the overall stereochemistry of the stereotriad. Finally, under the basic conditions, the generated ester is readily cleaved so that only the diol is observed at the end of the reaction.

Kinetic resolution of the aldol-Tishchenko diols

With a convenient access to diastereomerically pure racemic fluorinated stereotriads, we next attempted to develop a kinetic resolution (KR) in order to obtain the desired enantioenriched scaffolds. Organocatalyzed acylation of alcohols is one of the most developed method for the kinetic resolution of secondary alcohols[15] and has notably been applied with success to simple 1,3-*anti*-diols.[16] However, implementing such a strategy to the obtained fluorinated diols presented substantial challenges. First of all, enantioselective acylation of α-fluorohydrins has been poorly studied and the rare examples were based on fluorinated monosubstituted or CF$_2$ groups without any chirality on the fluorinated center.[17] Only few studies were reported on the enantiocontrol of compounds bearing a fluorinated tetrasubstituted stereocenter by acylative KR using enzyme.[17e–g] However, these studies indicated a dramatic impact of the fluorination over the selectivity of the KR. As a result, in the present scenario, given its central position, the stereogenic fluorinated center would have a strong and opposite impact on both *syn-* and *anti-* adjacent alcohols, strongly imparting the selectivity of the overall process. Consequently, we were eager to know if the chiral catalyst could effectively recognize the desired enantiomer while bypassing the steric congestion around the reactive sites.

Chiral isothioureas are organocatalysts of choice for enantioselective acylation,[18] and we choose HyperBTM[19] given the previous results obtained on diols using this catalytic structure (Scheme 4).[16,17] As diols offer the possibil-
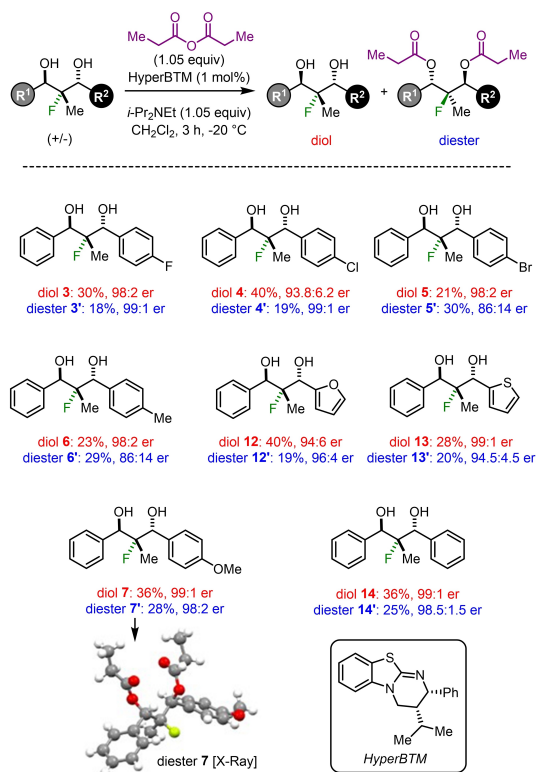
Scheme 4. DoCKR of fluorinated stereotriads.

ity of a double acylation, the amount of anhydride was adjusted to perform a double catalytic KR (DoCKR). Gratifyingly, despite the challenge at controlling three stereogenic centers, the sterically demanding fluorinated polyketides did undergo the expected DoCKR with high selectivity. We performed the KR on 8 examples of benzylic alcohols affording both recovered diols and diesters in yields varying from 21 to 40% and 18 to 30%, respectively. For most examples, both diols and diesters are obtained in *er* typically above 95:5. As a consequence of this DoCKR process, complex fluorinated stereotriads featuring three contiguous stereogenic centers can be prepared with excellent enantiocontrol. The relative and absolute configuration could be confirmed on diester **7′** through single crystal X-Ray analysis.[20] This indicates that in these diols, the enantiocontrol by the catalyst is governed through π-interactions between the aromatic substituent and the catalyst.[21] The formation of the diesters and diols with excellent enantiocontrol is accompanied by the formation of a sacrificial amount of mono-esters (typically around 25%). For example, in the case of starting diol **7**, the monoester, which is acylated as a mixture at both alcohols positions, is obtained in a low 56.4:43.6 er (see Supporting Information for details). This confirms the amplification of enantioselectivity observed

through the two successive acylation events. However, as compared to the selectivity observed for other type of diols,[16,17a] the *er* on these monoesters is relatively low, indicating a competition in the recognition by the catalyst with the aromatic ring and the fluorine.[17a]

In order to push further the limits of the system, we performed the single KR on diastereomeric diols **22** and **24** possessing an aliphatic chain on one side (Scheme 5a–b). Using 0.53 equivalent of anhydride, acylation chemoselectively occurred on the benzylic alcohol. While diol **22**, possessing the same stereochemical arrangement as **24** provided a s value of 19 in the KR, diastereomer **24** gave an excellent s value of 86, with a diol and monoester isolated in 93.8:6.2 and 96.7:3.3 er respectively. This clearly demonstrates the importance of the stereochemistry of the fluorinated tetrasubstituted center over the selectivity in these KR processes. Using more sterically

demanding aliphatic alcohol as in **19**, the selectivity decreased and the compounds were isolated in reduced enantiocontrol. Finally, aliphatic diol **26** lacks of reactivity and only provided modest conversion under the standard conditions.

With these highly enantioenriched diols in hands, we took the opportunity to remove the hydroxyl groups by a double deoxygenation (Scheme 6). Under standard conditions,[22] enantioenriched diol **7** (> 99:1 er) was converted in 63% yield into compound **28** bearing a single fluorinated stereogenic center with three alkyl groups without loss of the stereochemical information (> 99:1 er).

Conclusion

To conclude, acyclic *anti* diols featuring a fluorinated tetrasubstituted stereocenter could represent crucial bioactive molecule fragments not accessible through conventional methods. Through this study, we have been able to develop a simple, flexible, and straightforward route to these complex stereotriads in a two-step sequence. The process involves an unprecedented aldol-Tishchenko reaction between acyclic fluorinated ketones and aldehydes. This reaction generates the expected racemic diols in most cases with perfect diastereoselectivity. Additionally, with aliphatic α-fluoroketones, a complete regioselectivity of the aldol-Tishchenko reaction was observed due to the higher acidity of the enolizable position bearing the fluorine atom. Of importance, exchanging ketone donors and aldehyde acceptors unlocks the access to diastereomeric pairs of *anti*-1,3-diols with equal efficiency. Mechanistic investigation revealed that the diastereocontrol was arising from an excellent selectivity during the irreversible final hydride transfer.

Subsequent simple or double organocatalyzed kinetic resolution (DoCKR) through enantioselective acylation enables to generate the enantioenriched scaffolds with enantiomeric ratios typically above 95:5. The crucial role of the fluorinated tetrasubstituted stereocenter stereochemistry over the selectivity of the organocatalyzed process was also demonstrated. As a result, this strategy enables to control the three contiguous stereocenters and notably the challenging fluorinated tetrasubstituted stereocenter through a two-step process. Moreover, we demonstrated with a single additional step that such optically active fluorinated diols can be transformed in chiral building block bearing only a fluorinated tetrasubstituted center as stereogenic element. Overall, it opens broad perspective for the introduction of such motif in drug but also for the design of other synthetic routes towards complex motifs featuring several stereogenic centers or challenging fluorinated tetrasubstituted stereocenters.
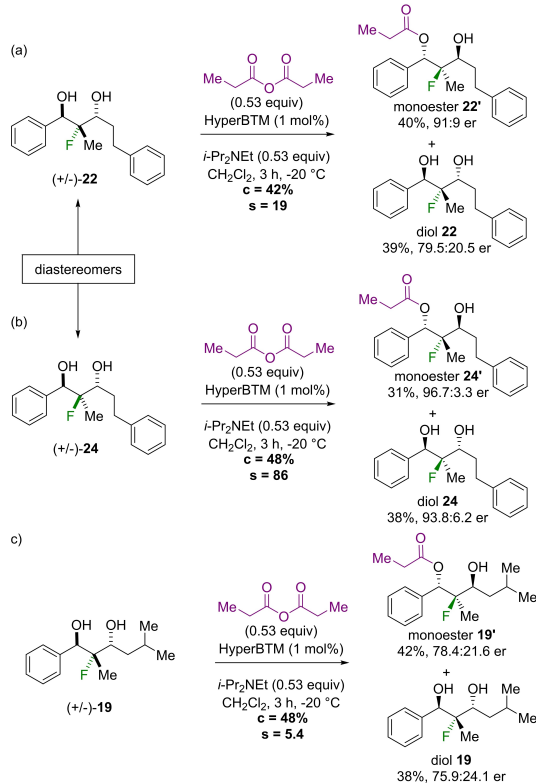
Scheme 5. KR of aliphatic alcohols and importance of the diastereomers.
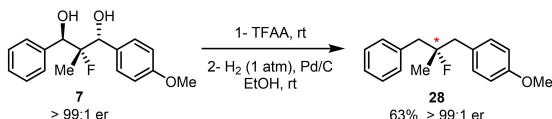
Scheme 6. Deoxygenation of diol **7**.

Conflict of Interest

The authors declare no conflict of interest.

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