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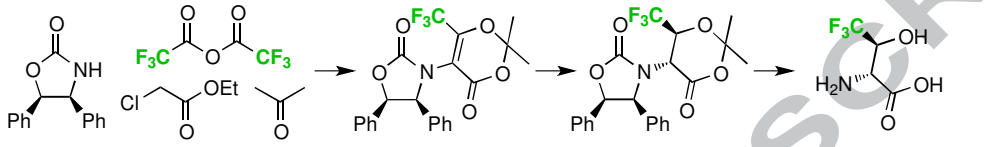

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A practical synthesis of enantiopure 4,4,4-trifluoro-*allo*-threonine from an easily available fluorinated building block

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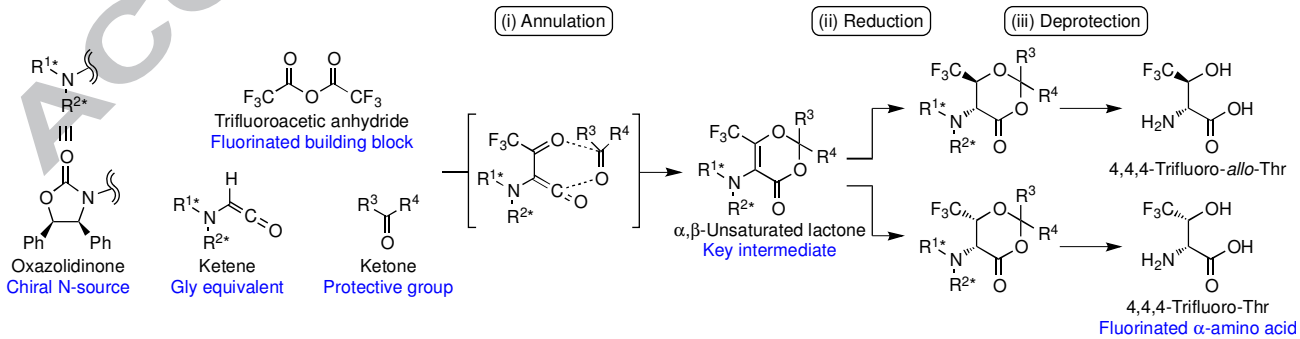
ABSTRACT

A practical method to prepare enantiopure 4,4,4-trifluoro-*allo*-threonine was developed by using an easily available fluorinated building block and a chiral auxiliary as starting materials. Trifluoroacetic anhydride was annulated with a ketene, derived from a glycine equivalent bearing a chiral oxazolidinone [(4*S*,5*R*)-4,5-diphenyloxazolidin-2-one], and acetone to afford a trifluoromethylated α,β-unsaturated lactone. The asymmetric hydride reduction of the α,β-unsaturated lactone proceeded with excellent stereoselectivity to give the corresponding (2*R*,3*S*)-4-oxapentan-5-olide derivative exclusively (diastereopurity, 99%). From the reduced product thus obtained, protecting groups were readily removed by acid treatment and subsequent catalytic hydrogenolysis to afford enantiopure (2*R*,3*S*)-4,4,4-trifluoro-*allo*-threonine in an excellent yield (7 steps, 51% overall yield).

Fluorinated analogues of proteinogenic α-amino acids have attracted considerable attention from various fields, such as pharmacology, agrochemistry, and peptide engineering.[1] Among fluorinated α-amino acids reported hitherto, most extensively studied are δ- and γ-fluorinated ones, owing to their chemical stability, tolerance toward racemization, and properly reactive amino group.[2] In particular, fluorinated analogues of threonine [(2*S*,3*S*)- and (2*R*,3*R*)-4,4,4-trifluorothreonines; L- and D-isomers] and its *allo*-forms [(2*S*,3*R*)- and (2*R*,3*S*)-4,4,4-trifluoro-*allo*-threonines; L- and D-isomers] are of interest. They possess a modifiable hydroxyl group in their side chain and are useful as precursors of various fluorinated chiral compounds, including other fluorinated α-amino acids. In addition, because of the electron-withdrawing nature of the trifluoromethyl group,[3] the hydrogen-bond donating ability of the hydroxyl group is highly enhanced, thereby bringing significant effects on the conformation of oligo-peptides when these fluorinated amino acids are incorporated in peptide sequences.[4] Also as a synthetic challenge, the stereocontrolled preparation of these amino acids is worthwhile, because the introduction of multiple functionalities (amino, carboxyl, hydroxyl, and trifluoromethyl groups) is required in a stereocontrolled manner at two stereogenic centers.

So far, several groups have developed methods to prepare



Scheme 1. Strategy for the asymmetric synthesis of 4,4,4-trifluoro-*allo*-threonine and 4,4,4-trifluorothreonine using trifluoroacetic anhydride as a fluorinated building block.

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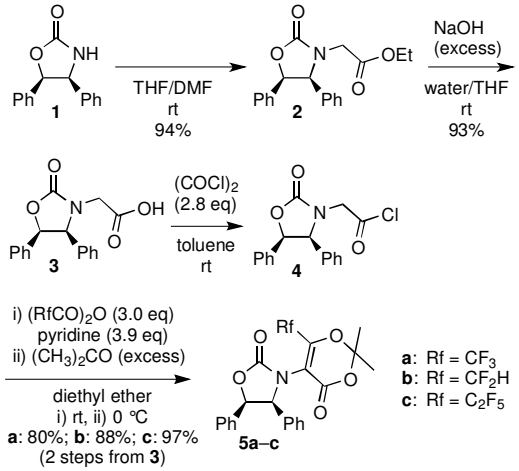
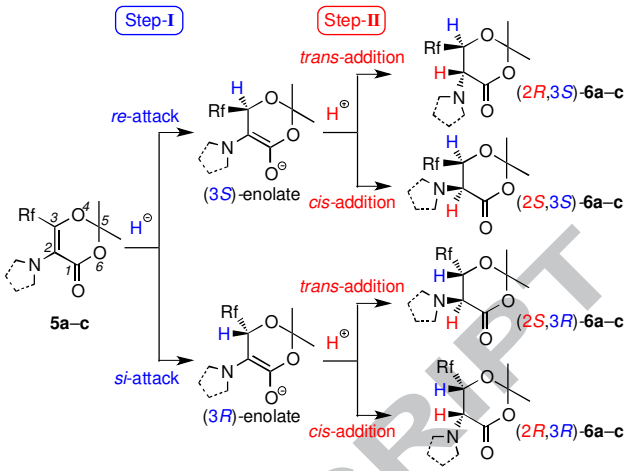


Scheme 2. Synthesis of the key intermediates **5a–c**.



Scheme 3. Hydride addition to the key intermediates **5a–c** (Step-I) and protonation of the resultant enolates (Step-II).

nonracemic 4,4,4-trifluoro-*allo*-threonine, which can be classified into the following three categories: (i) The enantioseparation of 4,4,4-trifluoro-3-hydroxybutanoic acid, the introduction of an amine-equivalent functional group, and the transformation of the functional group.[5] (ii) The cross-coupling of a bromoalkene and trifluoromethyl iodide, the asymmetric dihydroxylation of the trifluoromethylated alkene, and the transformation of the functional group.[6] (iii) The asymmetric aldol addition of a glycine equivalent with trifluoroacetaldehyde and subsequent deprotection.[7] However, these methods often have problems in accessibility and handling of fluorinated building blocks, stereocontrol, and lengthy synthetic steps. Therefore, it remains a challenge to develop more practical methods for the preparation of enantiopure 4,4,4-trifluoro-*allo*-threonine.

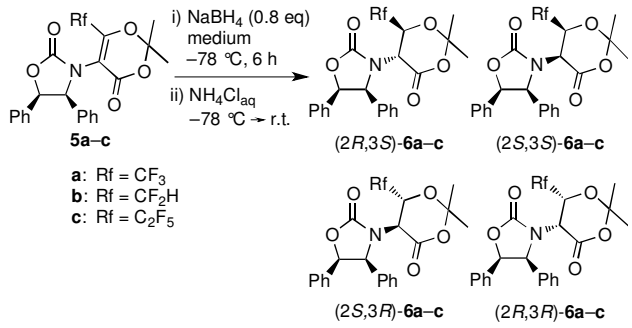
For this aim, we focused on a three-component annulation involving trifluoroacetic anhydride to form a trifluoromethylated cyclic ester, reported by Zard *et al.*[8,9] Trifluoroacetic anhydride (boiling point of 40 °C, ~US$300/500 g, half lethal dose of 100 mg kg^{-1}) is one of the most ideal fluorinated building blocks in terms of cost, safety, and handling. In this reaction, a ketene and trifluoroacetic anhydride generate a reactive trifluoroacetylketene (and/or its synthetic alternatives), which readily undergoes the [4 + 2] cycloaddition with a ketone to afford an α,β-unsaturated lactone substituted with a trifluoromethyl group (Scheme 1, i). By using this powerful one-pot reaction, a six-membered ring bearing multiple functionalities, including trifluoromethyl, ester, and enol ether units, can be constructed from easily available materials.[8,9]

In the present study, we envisioned that, if a glycine equivalent having a chiral N-substituent is used as the source of a ketene (Scheme 1, left), the resultant α,β-unsaturated lactone might serve as a key intermediate for the stereoselective synthesis of 4,4,4-trifluoro-threonine and/or 4,4,4-trifluoro-*allo*-threonine, through the asymmetric reduction of its α,β-unsaturated carbonyl unit (Scheme 1, ii) and subsequent deprotection (Scheme 1, iii). As a nitrogen source having a chiral substituent, we chose an enantiopure oxazolidinone [(4*S*,5*R*)-4,5-diphenyloxazolidin-2-one (**1**); Scheme 1, left].[10] Owing to its rigid five-membered-ring structure bearing sterically demanding two phenyl groups, this oxazolidinone serves as a promising chiral auxiliary in asymmetric synthesis.[11] In addition, the proper location of benzylic nitrogen and oxygen in this chiral auxiliary enables the efficient cleavage of the chiral N-protecting units under mild conditions. Based on this synthetic strategy, here we report a highly practical synthesis of enantiopure 4,4,4-trifluoro-*allo*-threonine from an easily available fluorinated building block.

The key intermediate **5a**, the trifluoromethylated α,β-unsaturated lactone bearing the oxazolidinone chiral auxiliary, was prepared as shown in Scheme 2. Firstly, the chiral oxazolidinone **1** was converted into the ester **2** having a glycine skeleton by treating with sodium hydride and ethyl bromoacetate. Through alkali-mediated hydrolysis and subsequent chlorination using oxalyl chloride, the ester **2** was converted into the corresponding acyl chloride **4**. In a manner similar to the procedure reported by Zard *et al.*,[9b] the annulation of trifluoroacetic anhydride, acetone, and the ketene *in situ* generated from **4** proceeded smoothly to afford the key intermediate **5a**. Interestingly, **5a** exhibited notable signal broadening in ^{1}H and ^{19}F NMR measurements (in $CDCl_3$ at 25 °C; Supplementary Figure S1). As discussed later, this signal broadening is most likely due to the restricted rotation around the C–N bond that connects sterically demanding five-membered (oxazolidinone) and six-membered (α,β-unsaturated lactone) rings in **5a**. In order to confirm the generality of this reaction, difluoroacetic anhydride and pentafluoropropionic anhydride were used in place of trifluoroacetic anhydride, and the corresponding fluorinated α,β-unsaturated lactones **5b** and **5c**, bearing difluoromethyl and pentafluoroethyl groups, respectively, were obtained in excellent yields (88% for **5b** and 97% for **5c**). Worth noting is that the key intermediates **5a–c**, characterized with multiple functionalities and a well-defined chiral structure, could be efficiently prepared from commercially available materials (4 steps, >70% overall yield).

With the key intermediates **5a–c** in hand, we carried out the asymmetric hydride reduction of their α,β-unsaturated carbonyl unit by using $NaBH_4$ as a hydride source. The reduction involves the following two consecutive asymmetric transformations (Scheme 3). Step-I: the addition of a hydride to the α,β-unsaturated carbonyl unit. Step-II: the protonation of the resulting enolate. Because two stereogenic centers are generated through these steps, four stereoisomers are possible [(2*R*,3*S*), (2*S*,3*R*), (2*R*,3*R*), and (2*S*,3*S*)] for the resultant saturated lactone **6a–c**. Quite interestingly, when the hydride reduction of **5a** was performed in methanol, followed by the treatment with aqueous ammonium chloride, the reaction smoothly proceeded with excellent diastereo- and enantioselectivities to exclusively yield one of the *trans* isomers [(2*R*,3*S*)-**6a**: Table 1, entry 1; 99% ratio]. Although a trace amount of the other *trans* isomer was

Table 1. Asymmetric hydride reduction of **5a–c**.



entry	substrate (Rf)	medium	diastereomer ratio[a] (2*R*,3*S*)	(2*S*,3*R*)	(2*S*,3*S*)	(2*R*,3*R*)	yield[b] (2*R*,3*S*)
1	**5a** (CF_3)	MeOH	99	1	n.d.	n.d.	82%
2	**5a** (CF_3)	EtOH	94	6	n.d.	n.d.	77%
3	**5a** (CF_3)	^{i}PrOH	71	29	n.d.	n.d.	55%
4	**5b** (CF_2H)	MeOH/THF[c]	99	1	n.d.	n.d.	92%
5	**5c** (C_2F_5)	MeOH	97	3	n.d.	n.d.	84%

a) Determined by ^{19}F NMR. b) Isolated yield. c) MeOH/THF = 1:4, v/v. Absolute MeOH could not dissolve **5b** sufficiently at –78 °C.

formed [(2*S*,3*R*)-**6a**; 1% ratio], these stereoisomers could be easily separated by silica gel column chromatography. The stereochemistry of these isomers was unambiguously determined by X-ray crystallography of the isomer (2*S*,3*R*)-**6a** itself or a derivative of (2*R*,3*S*)-**6a** (Supplementary Figures S7 and S8).[12,13] In the present hydride reduction, the choice of reaction medium brought a crucial effect on the ratio of the *trans* isomers [(2*R*,3*S*)-**6a**:(2*S*,3*R*)-**6a** = 71:29–99:1, entries 1–3]. Irrespective of the reaction medium used, the reaction mixtures always exhibited, in ^{19}F NMR measurement, only two signals for the reduced species that were attributable to the *trans* isomers [(2*R*,3*S*)- and (2*S*,3*R*)-**6a**] (Supplementary Figure S2). Therefore, we concluded that the *cis* isomers [(2*R*,3*R*)- and (2*S*,3*S*)-**6a**] were not generated at a detectable level in the present reaction. Under the conditions optimized for **5a**, the hydride reduction of the other fluorinated α,β-unsaturated lactones (**5b** and **5c**) proceeded in good yield with excellent stereoselectivity (entries 4 and 5),[14] suggesting the general utility of the present stereocontrolled reaction.

To elucidate this excellent stereoselectivity, reaction courses of the elementary steps (Scheme 3, Step-I and Step-II) were considered by using **5a** as the representative. Step-I is an irreversible and kinetically controlled reaction. As suggested by the ^{1}H and ^{19}F NMR signal broadening (Supplementary Figure S1), the molecular motion of **5a** is highly restricted, most likely in terms of the rotation around the C–N bond, due to the steric congestion of the directly connected five-membered (oxazolidinone) and six-membered (α,β-unsaturated lactone) rings. Therefore, two kinds of conformers (*syn* and *anti*) are supposed for **5a**, where *syn* and *anti* represent the relative orientation between the phenyl groups in the oxazolidinone unit and the trifluoromethyl group in the α,β-unsaturated lactones unit. Based on the molecular modeling study (MM2 and B3LYP/6-31G*), the *syn* conformer is more stable by 1.6 kcal mol^{-1} than the *anti* conformer (Figure 1a and Supplementary Figure S3). In the *syn*-conformer, the *si*-face of the α,β-unsaturated lactone is shielded by one of the phenyl groups of the oxazolidinone unit, while the *re*-face is exposed for an nucleophilic attack (Figure 1a). Therefore, the hydride addition is considered to proceed preferentially at the *re*-face to afford the

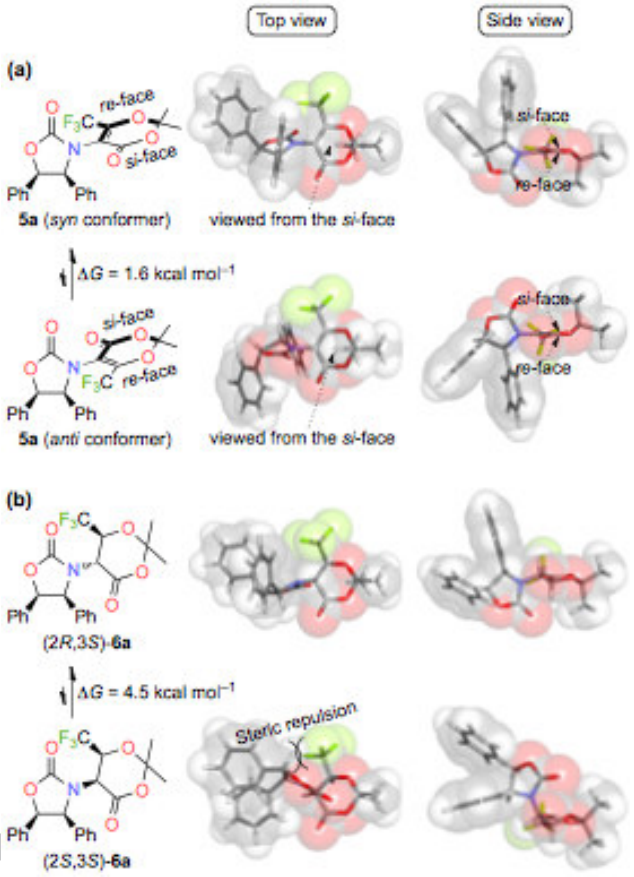
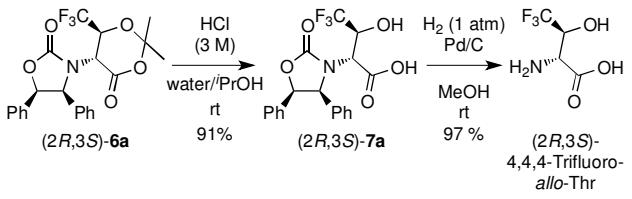


Figure 1. Optimized structures (B3LYP/6-31G*) of (a) the *syn*- and *anti*-conformers of **5a** (see Supplementary Figure S3 for details) and (b) (2*R*,3*S*)- and (2*S*,3*S*)-**6a** viewed from top (left) and side (right) of the six-membered ring.

(3*S*)-enolate (Scheme 3), which is in good agreement with the stereochemistry at the C(3) position of the major product [(2*R*,3*S*)-**6a**]. This mechanism can also explain the marked solvent effect on the stereoselectivity (Table 1), taking into account of the bulkiness of the hydride source. When the reduction was performed in reactive alcohols such as methanol (entry 1), the original hydride source $NaBH_4$ was likely to be converted into bulkier $NaB(OR)_nH_{4-n}$ (n = 1–3), leading to higher stereoselectivity. Contrary to this, when a less reactive alcohol such as 2-propanol was used as a reaction medium (entry 3), the conversion of the hydride source would be rather slow, so that less-bulky $NaBH_4$ served as the main hydride source to result in lower stereoselectivity.[15]

Supposing that Step-I carried out in methanol exclusively afford the (3*S*)-enolate from **5a**, possible products, obtained by the following protonation (Step-II), are (2*R*,3*S*)- and (2*S*,3*S*)-**6a** (Scheme 3). Concerning its stereocontrol mechanism, we found that the elimination and addition of the proton at the C(2) position are reversible, as proved by the quick H/D exchange of this proton in deuterated methanol at 25 °C (Supplementary Figure S4). This is most likely because the acidity of the proton at the C(2) position was highly enhanced by the electron-withdrawing nature of the carbonyl and trifluoromethyl groups, together with the effect of the constrained cyclic structure of the lactone unit. Therefore, the stereochemistry of Step-II was controlled in a thermodynamic manner. According to a molecular modeling study (MM2 and B3LYP/6-31G*), (2*R*,3*S*)-**6a** is much more stable than (2*S*,3*S*)-**6a** (ΔG = 4.5 kcal mol^{-1}). In



Scheme 4. Deprotection of (2*R*,3*S*)-**6a** to form (2*R*,3*S*)-4,4,4-trifluoro-*allo*-threonine.

the six-membered ring of the (2*S*,3*S*)-isomer, the oxazolidinone and trifluoromethyl substituents are arranged near to each other (Figure 1b, lower) to cause a sterically congested and unstable structure, compared with the (2*R*,3*S*)-isomer. This stability order is in good agreement with that of the *trans* and *cis* isomers of general cyclic compounds. The calculated ΔG value of 4.5 kcal mol^{-1} corresponds to the isomer ratio of 99.95:0.05 and can elucidate the observed high stereoselectivity in Step-II.

As we envisioned, two-stage deprotection of (2*R*,3*S*)-**6a** proceeded smoothly without losing diastereopurity to afford (2*R*,3*S*)-4,4,4-trifluoro-*allo*-threonine (Scheme 4). In the first stage, the acetal moiety of (2*R*,3*S*)-**6a** was removed by acid treatment to give (2*R*,3*S*)-**7a** in 91% yield. Because the ^{1}H and ^{19}F NMR spectra of the product showed one set of signals, we concluded that the stereochemistry at the C(2) and C(3) positions of the product was preserved through the acid treatment (Supplementary Figure S5). Otherwise, the product must be a mixture of multiple diastereoisomers, owing to the presence of chiral oxazolidinone unit, and would give multiple sets of NMR signals. Although the stereochemical stability at the C(2) position of (2*R*,3*S*)-**7a** was quite unlike to the above-described nature of its precursor (2*R*,3*S*)-**6a**, of which the C(2) proton can exchange with solvent protons at ambient conditions (Supplementary Figure S4), this is most likely because the scission of the cyclic structure in (2*R*,3*S*)-**6a** released the structural constraint and reduced the acidity of the C(2) proton.

In the next stage, the oxazolidinone unit of (2*R*,3*S*)-**7a** was cleaved by catalytic hydrogenolysis to give the target (2*R*,3*S*)-4,4,4-trifluoro-*allo*-threonine in 97% yield (Scheme 4). The ^{1}H and ^{19}F NMR spectra of the product again showed one set of signals, thereby excluding the formation of the diastereoisomers (Supplementary Figure S6). Furthermore, the specific rotation of the product ($[\alpha]_D^{26}$ = 11.6 deg cm^2 g^{-1}, (*c* 0.4, H_2O)) is in good agreement with those reported,[6] indicating that the stereochemistry at the C(2) and C(3) positions of the product was preserved through the hydrogenolysis.

In conclusion, we developed a highly practical and efficient method to prepare enantiopure (2*R*,3*S*)-4,4,4-trifluoro-*allo*-threonine (7 steps, 51% overall yield), using an easily available fluorinated building block and a chiral auxiliary. Trifluoroacetic anhydride is one of the most ideal fluorinated building blocks, in terms of cost, safety, and handling. Because all reactions proceeded in high yields without using expensive/toxic materials and special facilities/techniques, the present method is advantageous for large-scale synthesis. Moreover, this method is certainly applicable for the preparation of (2*S*,3*R*)-4,4,4-trifluoro-*allo*-threonine, because both enantiomers of the starting material, *erythro*-2-amino-1,2-diphenylethanol, for the chiral auxiliary are commercially available. Considering the possibility of further asymmetric transformation of the key intermediates **5a**–**c**, such as the 1,4-addition to the α,β-unsaturated carbonyl unit using various nucleophiles, the present method would lead to the large-scale stereocontrolled preparation of other fluorinated α-amino acids.

Acknowledgments

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/–designated by journal--.

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12. The minor isomer [(2*S*,3*R*)-**6a**] afforded large single crystals, which allowed for the determination of its stereochemistry by X-ray crystallography. On the other hand, the major isomer [(2*R*,3*S*)-**6a**] was of low crystallinity. Therefore, (2*R*,3*S*)-**6a** was converted into a more crystalline derivative [(2*R*,3*S*)-**8a**; see Supplementary Data], and its stereochemistry was determined by X-ray crystallography.
13. CCDC-1012850 [(2*R*,3*S*)-**8a**] and CCDC-1012851 [(2*S*,3*R*)-**6a**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
14. Through the hydride reduction of **5b** and **5c**, two kinds of products were exclusively obtained at ratios of 99:1 and 97:3. Judging from the ^{1}H NMR coupling constants between C(2)H and C(3)H in their lactone unit (~10 Hz), these products are deduced to be the *trans* isomers. Considering the analogy to **5a**, the major and

minor products were tentatively assigned to be the (2*R*,3*S*)- and (2*S*,3*R*)-isomers, respectively.

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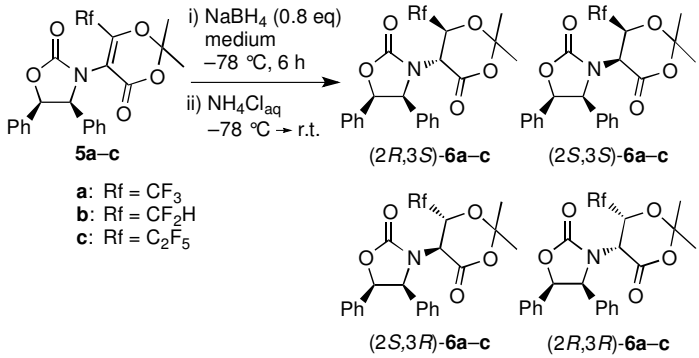
Table 1. Asymmetric hydride reduction of **5a–c**.



Entry	Substrates (Rf)	Medium	Diastereomer ratio (%)[a]				Yield (%)[b]
			(2*R*,3*S*)	(2*S*,3*R*)	(2*S*,3*S*)	(2*R*,3*R*)	(2*R*,3*S*)
1	**5a** (CF_3)	MeOH	99	1	n.d.	n.d.	82
2	**5a** (CF_3)	EtOH	94	6	n.d.	n.d.	77
3	**5a** (CF_3)	^{i}PrOH	71	29	n.d.	n.d.	55
4	**5b** (CF_2H)	MeOH/THF[c]	99	1	n.d.	n.d.	92
5	**5c** (C_2F_5)	MeOH	97	3	n.d.	n.d.	84

[a]Determined by ^{19}F NMR. [b]Isolated yield. [c]MeOH/THF = 1:4, v/v. Absolute MeOH could not dissolve **5b** sufficiently at –78 °C.