A Highly Diastereoselective Synthesis of (1*R*)-(+)-Camphor-Based Chiral Allenes and Their Asymmetric Hydroboration−Oxidation Reactions†

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Synthesis of camphor derived chiral allenes and their hydroboration−oxidation reactions are described. Reaction of (1*R*)-(+)-camphor with alkynyllithium followed by the reduction of the resulted propargyl alcohol derivatives using AlH_3 furnished chiral allenes **2a**−**g** in excellent yields with high diastereoselectivity. Reduction of the propargyl alcohols with aluminum hydride proceeded through selective intermolecular *anti*-addition of hydride ion. The stereochemistry of the chiral allenes **2** was assigned based on lanthanide shift studies and chemical correlations. Diastereoselectivity was observed in the hydroboration−oxidation of **2** which produced a mixture of (*E*,*R*) and (*E*,*S*) stereoisomers in a ratio of 6:1 to 18:1.

Introduction

Chiral allenes gained significant importance as versatile intermediates for asymmetric synthesis via the axial to centered chirality transfer.[1] Recently chiral allenes are explored as potential chiral synthons in the synthesis of bioactive molecules and natural products.[1n,s,2] The S_N2' addition of nucleophiles to suitably derivatized, optically active propargyl derivatives is one of the most widely used routes for the asymmetric synthesis of chiral allenes.[1e,3,4] In conjunction with our program to develop a general, simple and efficient means of synthesizing chiral allenes for further usage in organic synthesis, we report herein a substrate-controlled asymmetric synthesis of camphor-derived chiral allenes and the stereochemical course of their hydroboration−oxidation reactions.

Results and Discussion

Most of the reported synthetic procedures for the chiral allenes made use of enantiomerically enriched chiral compounds either as substrates[5] or as reagents.[6] We have envisaged the synthesis of chiral allenes through chiral propargyl alcohols. Reaction of (1*R*)-(+)-camphor and lithium acetylides in THF gave the corresponding chiral alcohols **1a**−**g** with >95% diastereoselectivity (Table 1) as judged from their ^{1}H NMR spectra. The major product presumably arose from the *endo* addition of the alkynyllithium to the carbonyl group as the *exo* face in hindered by C_8 protons.[7] Earlier, Mattay[8] and co-workers have reported two approaches for the preparation of allenic compounds from optically pure propargyl derivatives, but inseparable mixtures of allenic products were obtained in these reactions. We found that reduction of propargyl alcohols **1** with AlH_3[1c] afforded the corresponding optically active allenes **2** stereospecifically except in the case of propargyl alcohol **1g** (R = CH_2CH_2OH) which gave a chromatographically inseparable mixture of diastereomers **2g** and **3g** in a 5:1 ratio (66% de).

The stereochemistry of allenes **2** was determined by means of lanthanide shift studies[9] employing Eu(fod)$_3$ as

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Table 1. Yields of Propargyl Alcohols 1, Allenes (2 and 3), and Allylic Alcohols 4/5

R	alcohol **1** yield (%)	allenes (**2**+**3**) yield (%)	ratio (**2**:**3**) (% de)	allylic alcohol (**4**+**5**) yield (%)	ratio (**4**:**5**) (% de)
a: CH_3	92	84	>50:1 (>95)	66	6:1 (72)
b: C_2H_5	89	85	>50:1 (>95)		
c: C_3H_7	80	88	>50:1 (>95)	80	15:1 (88)
d: C_4H_9	83	90	>50:1 (>95)	82	15:1 (88)
e: C_5H_{11}	83	86	>50:1 (>95)	77	18:1 (89)
f: CH_2OBn	76	51	>50:1 (>95)		
g: CH_2CH_2OH	65	43	5:1 (66%)		
h: CH_2CH_2OBn	72	87	>50:1 (>95)	71	15:1 (88)

[a] Proportions of EA/hexanes used as eluent in the purification of products by column chromatography: **1a**, **1b** (1:30); **1c**, **1d**, **1e** (1:15); **1f** (1:8); **1g**, **1h** (1:2); **2a**, **2b**, **2c**, **2d**, **2e** (0:100); **2f**, **2h** (1:30); **2g** and **3g** (1:10); **4a** and **5a, 4h** and **5h** (1:4); **4c** and **5c, 4d** and **5d**, **4e** and **5e** (1:6).

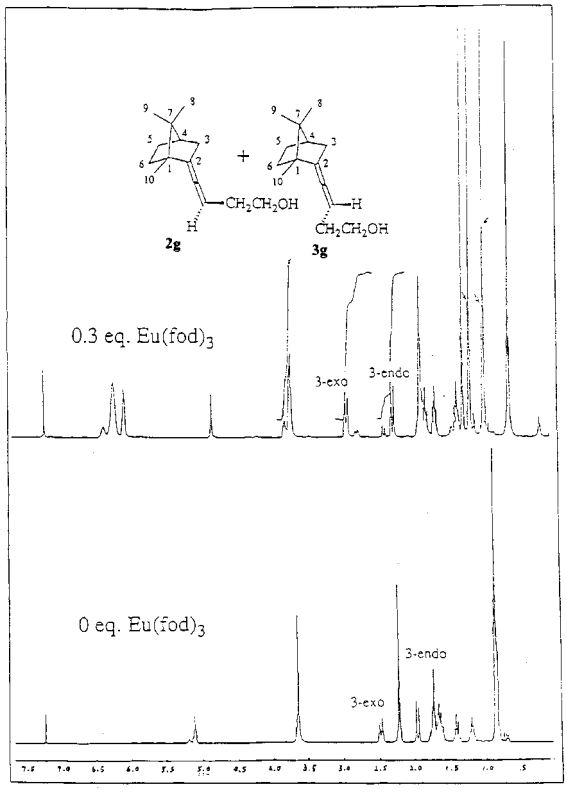

Figure 1. ^{1}H NMR spectra of the mixture **2g**/**3g** (5:1) in the presence and absence of Eu(fod)$_3$.

the shift reagent and by chemical correlations. Diastereomeric mixture of **2g** and **3g** was used for such purpose. In the ^{1}H NMR spectrum of the mixture, almost all the signals of **2g** and **3g** except those of allenic protons have similar chemical shift values and overlap with each other. When Eu(fod)$_3$ was added to a solution of this mixture in $CDCl_3$, significant shifts were observed in the signal positions and the resolution increased with the amount of the europium complex. The upper and lower ^{1}H NMR spectra in the Figure 1 correspond to the mixture of allenes **2g** and **3g** in the presence and absence of the shift reagent, respectively. Apparently in the upper spectrum, peaks of the two diastereomers could be resolved completely in the presence of 0.3 molar amount of Eu(fod)$_3$. Further, signals corresponding to the 3-*exo* and 3-*endo* protons of **2g** are discernible in the spectrum.

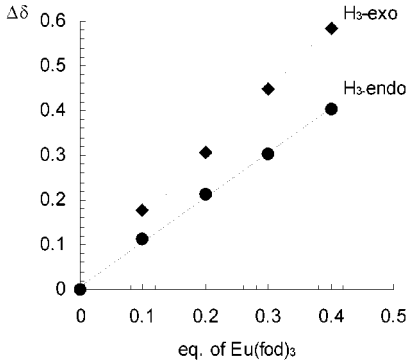

Figure 2. The Δδ of 3-exo and 3-endo protons of **2g** vs the equivalents of Eu(fod)$_3$.

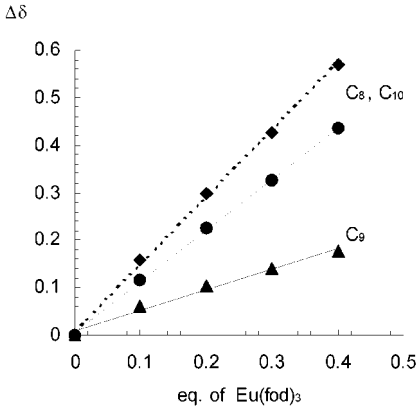

Figure 3. The Δδ of C8, C9, and C10 protons of **2g** vs the equivalents of Eu(fod)$_3$.

Figure 2 shows the variation of chemical shifts of 3-*exo* and 3-*endo* protons with the amount of shift reagent. Shift in the signal position of 3-*exo* proton with the increase in the concentration of shift reagent is more significant when compared to that of 3-*endo* proton, indicating that the former proton is spatially closer to the hydroxyl group. In other words, the CH_2CH_2OH group and the 3-*exo* proton of the major product **2g** must be *syn* to each other. The C_8 and C_{10} protons being spatially closer to the hydroxyl group, a similar shift in their signal positions should be observed when the shift reagent is used. Plots on the variation of chemical shift values of C_8, C_9, and C_{10} protons with the concentration of the shift reagent are shown in Figure 3. As expected, the chemical shifts of C_8 and C_{10} protons were shifted substantially upon the addition of shift reagent. This further corroborates the stereochemical assignment of **2g**. Stereochemistry of the minor diastereomer **3g** was established in a similar manner from Figure 4 in which plots on the variation of chemical shift positions of 3-*exo* and 3-*endo* protons of **3g** with the concentration of the shift reagent are shown. Relatively larger shift in the signal position of 3-*endo* proton when compared to that of 3-*exo* proton strongly suggests the proximity of 3-*endo* proton and hydroxyl group. Obviously CH_2CH_2OH group and 3-*exo* proton in **3g** must be anti to each other. This postulation was confirmed by Figure 5 in which plots on the change in the chemical shift of three methyl groups of **3g** with the concentration of shift reagent are shown. As expected, only the signal position of C_{10} protons was shifted substantially upon the addition of shift reagent.

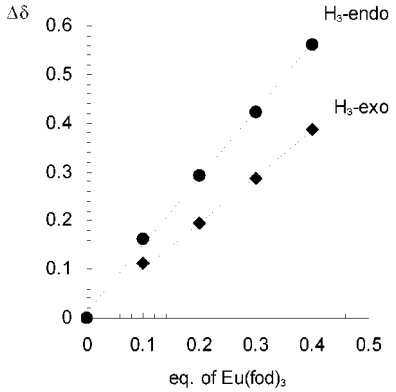

Figure 4. The Δδ of 3-exo and 3-endo protons of **3g** vs the equivalents of $Eu(fod)_3$.

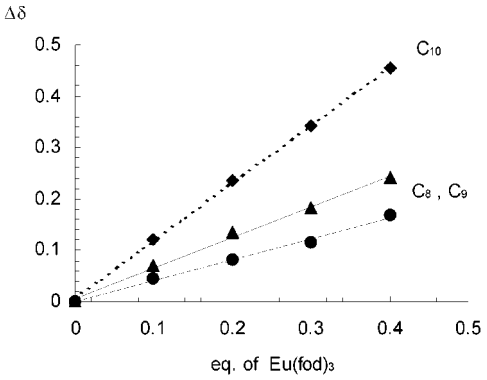

Figure 5. The Δδ of C8, C9, and C10 protons of **3g** vs the equivalents of $Eu(fod)_3$.

Chemical correlation was done to assign the stereochemistry of other chiral allenes. Treatment of the mixture of **2g** and **3g** with $MsCl/Et_3N$ followed by $LiAlH_4$ reduction produced a mixture of two diastereomers. The ^1H NMR spectrum of the major compound was identical with that of allene **2b**, indicating that the ethyl group of **2b** is *syn* to the C_{10} protons. Since allenes **2a**, **2b**, **2c**, **2d**, and **2e** with an alkyl substituent have close structural similarity, logically they should have the same stereochemistry in the allene moiety. Mixture of **2g** and **3g** was benzylated with benzyl bromide to give a major product whose ^1H NMR spectrum was identical with that of **2h**, indicating that CH_2CH_2OBn group is *syn* to the C_{10} protons in **2h**. Allenes **2h** and **2f** have similar ethereal functionality and are expected to have the same stereochemistry.

Propargyl alcohols **1a**−**h** undergo reductive elimination through an *anti* mode (Scheme 1) contrary to the observation of Claesson and co-workers[1c] who reported the *syn* mode of reaction of AlH_3 with propargyl alcohols. The reason for this discrepancy is presumably due to the steric effect of the C_8 protons that prevents the alignment of propargyl ate complex for an intramolecular *syn*-hydride delivery. Thus, preparation of chiral allenes **2** could be achieved with high diastereoselectivity when there is no second hydroxyl group in the intermediate propargyl alcohols.

Earlier Brown and co-workers have studied the hydroboration reactions of allenes and demonstrated that 9-BBN is one of the most useful hydroboration reagents exhibiting a high degree of regio- and stereospecificity and is remarkably sensitive to the structure of allenes.[10]

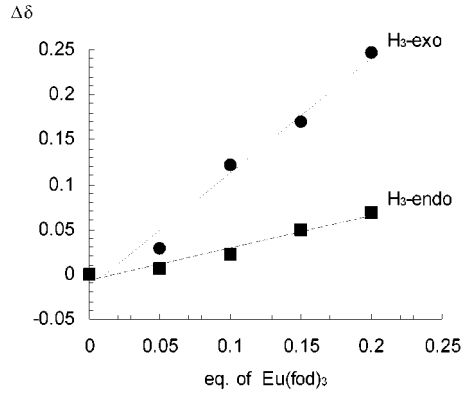

Figure 6. The Δδ of 3-exo and 3-endo protons of **12d** vs the equivalents of $Eu(fod)_3$.

To test the scope and limitation of diastereoselectivity on the camphor-based chiral allenes **2**, we have conducted the hydroboration−oxidation reactions with them. When the less-substituted double bond of the allene reacts with 9-BBN, the facial selectivity would depend on the steric bulk of the substituents of the other double bond. As the *re* face of the less-substituted double bond is blocked by the bridgehead methyl group, 9-BBN is expected to approach selectively from the *si* face (Scheme 2). Treatment of allenes **2** with 9-BBN in THF at room temperature followed by oxidative workup with basic hydrogen peroxide produced a mixture of allylic alcohols **4** and **5** with good diastereoselectivity (Table 1). Chiral alcohol **4** was the major product and selectivity varied from 6:1 to 18:1 depending on the substituent. The stereochemistry of the trisubstituted double bond of compound **4** was established by NOE studies. For example, irradiation of the bridgehead methyl signal of **4d** produced 12.7% peak enhancement in the olefinic proton signal. On the other hand, irradiation of the methine signal of the carbinol produced peak enhancement for both *exo* and *endo* C_3 protons. These observations suggested that the olefinic proton is spatially closer to the bridgehead methyl group as expected for *E*-isomer **4d**. Allyl alcohol **5d** was characterized as the *E*-isomer by a similar NOE experiment. To confirm that compounds **4** and **5** are $C_{2'}$ diastereomers, **4d** was oxidized with PCC to enone **6** and then reduced with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$.[11] Two products were obtained in a ratio of 1 to 1.7 and their spectral data was identical with that of compounds **4d** and **5d**, respectively. The formation of the major product **4** in the hydroboration−oxidation of allene **2** can be explained by two different reaction pathways. First, the addition of 9-BBN to the *si* face of allene **2** produces allyborane **9** as an intermediate, and its subsequent oxidation gives allyl alcohol **4**. Alternatively, 9-BBN may add to the *re* face of allene **2** to produce allyborane **7** which suffers from an $A^{1,3}$-strain. Allylborane rearrangement of allylborane **7**[12] from the less-hindered face to borane **8**, followed by its $C_{1'}-C_2$ bond rotation and subsequent repetition of allylborane rearrangement results in allylborane **9**. However, allylborane rearrangement was ruled out from the temperature variation ^1H NMR experiments. ^1H NMR spectra

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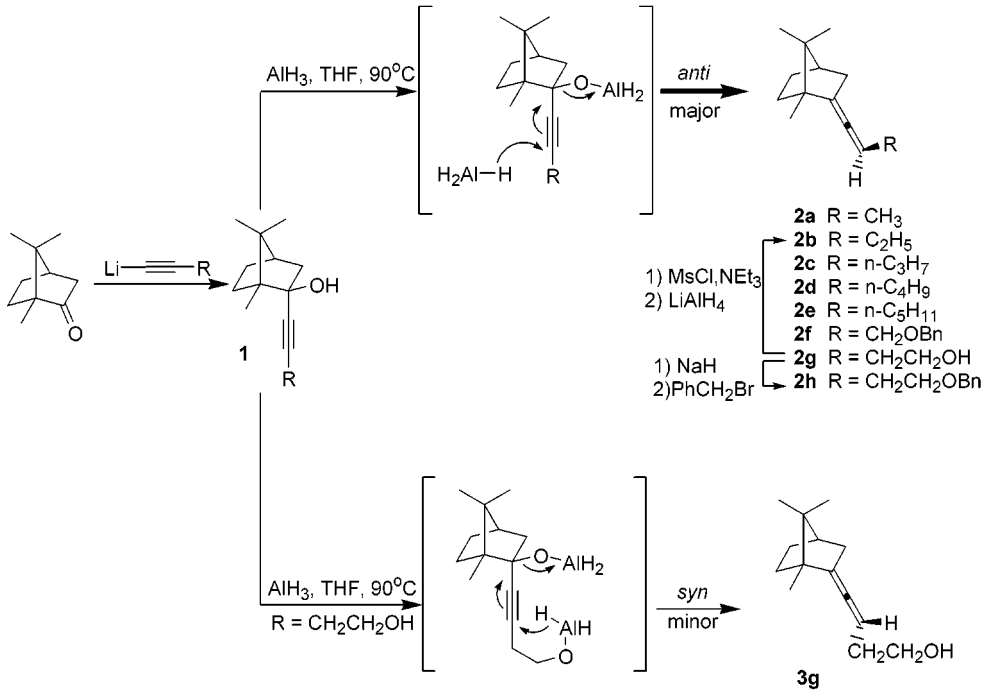
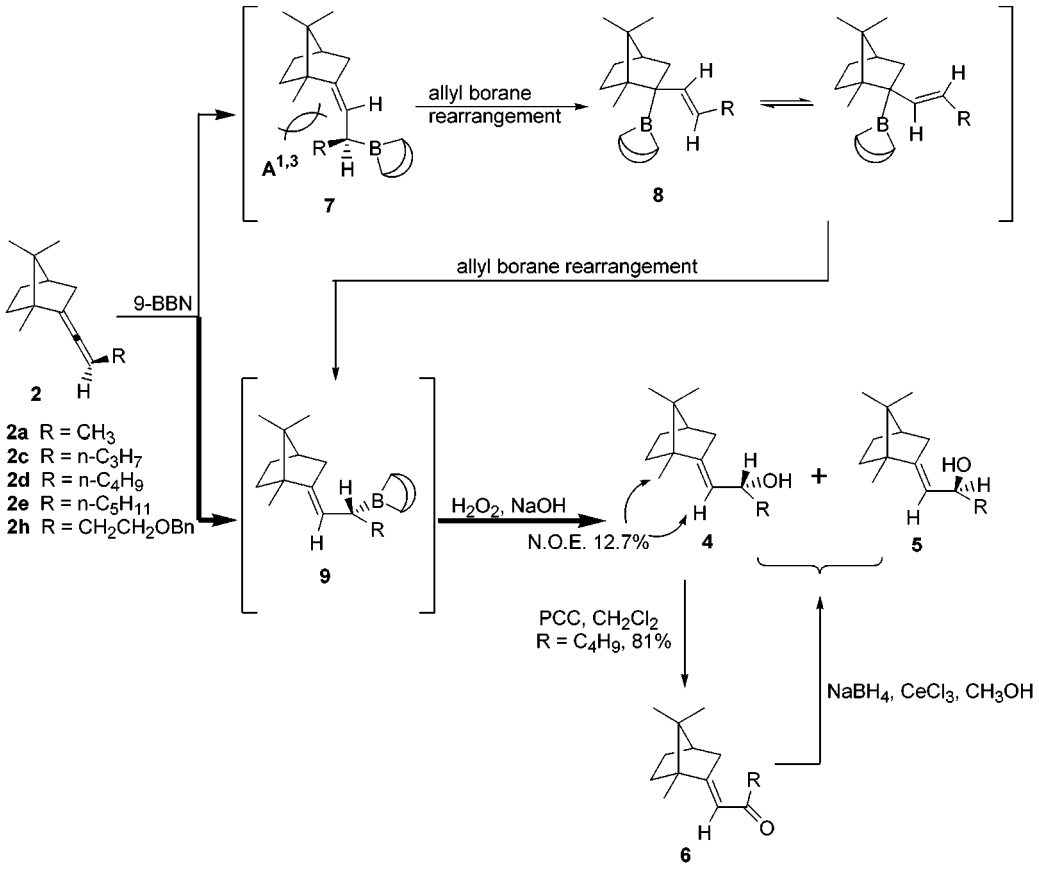
Scheme 1



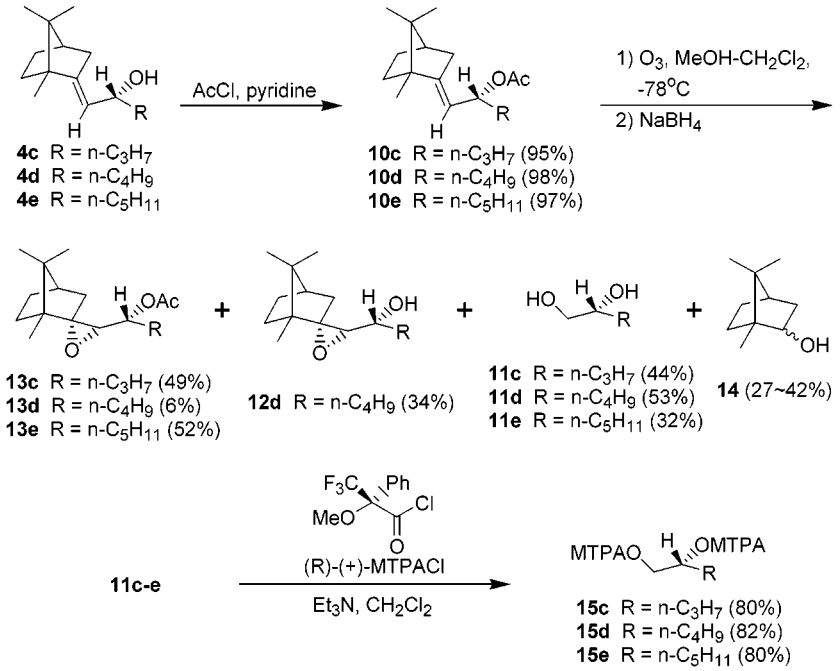
Scheme 2



were recorded for a sample containing allene **2** and 9-BBN over a range of temperature from −60 °C to room temperature. The spectral data obtained from all these experiments was identical, indicating that rearrangement did not take place. Apparently, the reaction may be proceeding with the addition of 9-BBN to **2** through the *si* face. On the other hand, formation of the minor product **5** is unusual and could not be rationalized at this moment. It might have resulted from the epimerisation of either allyl alcohol **4** or allylborane **9** during the course of the reaction, though such phenomena were not reported earlier.

The absolute configuration at the carbinol carbon of compounds **4c**−**e** was established by a two steps conver-

Scheme 3



sion of **4** to the corresponding (*R*)-1,2-hexanediol **11**[13] (Scheme 3). Acetylation of **4d** with acetyl chloride in the presence of pyridine provided allyl acetate **10d**. Ozonolysis of **10d** followed by reductive workup by stirring with $NaBH_4$ for 2 h at room temperature yielded a mixture of (*R*)-1,2-hexanediol **11d**, epoxides **12d** and **13d**, and borneol **14** in 53%, 34%, 6%, and 42% yields, respectively. Diol **11d** was characterized by its ^1H and ^{13}C NMR spectra. Optical rotation of **11d**, $[\alpha]^{32}_D$ +19.2 (*c* 1.65, EtOH) was similar to the reported value of *R* isomer (lit. $[\alpha]^{22}_D$ +15.2 (*c* 13.14, EtOH))[13] indicating its *R* configuration. Optical purity of **11d** was further confirmed from the comparison of ^{19}F spectra (Figure 7) of its bis-α-methoxy-α-trifluoromethyl-α-phenyl acetate[14] and the corresponding derivative of its racemic mixture. Mosher esters from racemic diol showed two ^{19}F resonances, where as, the Mosher ester **15d** prepared from **11d** has exhibited only one ^{19}F resonance confirming that compounds **11d** and **15d** are >95% ee. The stereochemistry of **12d** was established by NOE experiment. Irradiation of carbinol proton signal produced larger peak enhancement for *exo* proton (3.9%) when compared to that of *endo* proton (1.7%), indicating the configurational proximity of *exo* and carbinol protons. This was further corroborated by the lanthanide shift studies. The variation of chemical shift of 3-*exo* and 3-*endo* protons with the amount of $Eu(fod)_3$ was shown in Figure 6. The shift for 3-*exo* proton is more prominent confirming its proximity to hydroxyl group. This experimental data suggests that epoxide oxygen of **12d** is in the α face. Stereochemistry of epoxide **13d** was demonstrated to be identical with that of **12d** from the conversion of **13d** into **12d** by saponification. Acetylation of allyl alcohols **4c** and **4e** under similar experimental conditions afforded corresponding allyl acetates **10c** and **10e**. By reducing the reaction temperature and time during reductive workup with $NaBH_4$ after ozonolysis, **10c** and **10e** furnished a mixture of only three compounds **11**, **13**, and **14**, presumably due to the prevention of ester hydrolysis of **13** under the relatively mild reaction conditions. Diols **11c** and **11e** were converted into the corresponding Mosher esters **15c** and **15e**, respectively, in >95% ee, vide ^{19}F NMR.

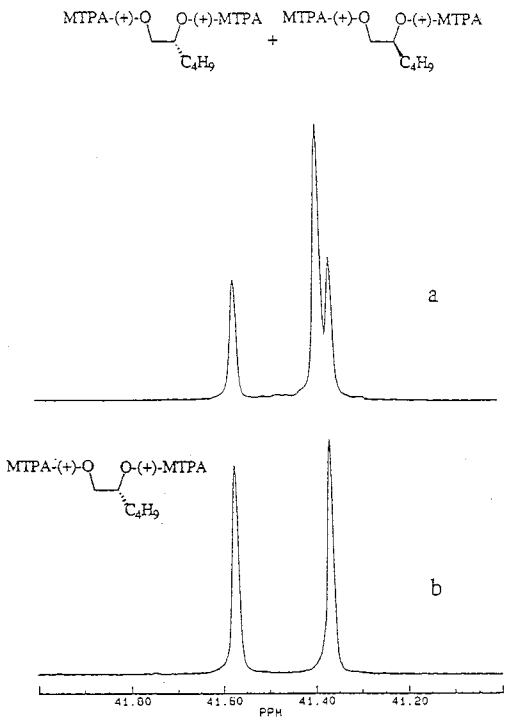


Figure 7. (a) ^{19}F NMR spectrum of (±)-1,2-hexanediol bis-Mosher ester. (b) ^{19}F NMR spectrum of (+)-1,2-hexanediol bis-Mosher ester **15d**.

In summary, a general and highly stereoselective procedure is developed for the synthesis of camphor-based chiral allenes. Hydroboration−oxidation reactions of these chiral allenes proceeded with moderate to high diastereoselectivity.

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Supporting Information Available: Spectroscopic and experimental procedures for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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