Direct Determination of the Enantiomeric Purity of Chiral Trisubstituted Allenes by Using Permethylated Cyclodextrin as a Chiral Solvating Agent

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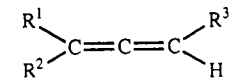
The heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TRIMEB) has been successfully used as convenient chiral solvating agent to determine the enantiomeric composition of chiral trisubstituted allenes by ^{1}H NMR spectroscopy: the analysis of the effect of the molar ratio TRIMEB/allene, temperature, and nature of the solvent allowed us to optimize the experimental conditions to enhance the separation between the signals of the two enantiomers of each allene.

Introduction

In spite of the widespread interest in the study of chiral allenes,[1] no general methods for the determination of their enantiomeric purities are available. When their enantiomeric excesses are correlated to that of chiral precursors or reaction products, one must be concerned about the stereospecificity of the reactions involved.[2] In some cases, their enantioseparation has been achieved by chiral liquid[3] or gas chromatography.[4,5] NMR methods,[6] although very attractive, were used only in limited cases: chiral silver shift reagents[7] or transition-metal complexes[8] have been employed as chiral auxiliaries to convert the enantiomers of allenes, respectively, into diastereoisomeric solvates or stable diastereoisomers, the composition of which can be determined by ^{1}H NMR spectroscopy. The formation of diastereoisomeric platinum(II)–allene complexes[9] and the detection of their ^{195}Pt NMR resonances allowed us to determine the enantiomeric purity of some alkyl trisubstituted allenes.

In the present paper, we report that heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TRIMEB), a commercially available derivatized cyclodextrin, can be successfully used as chiral solvating agent (CSA) for the NMR determination of the enantiomeric purity of trisubstituted allenes $R^1R^2C{=}C{=}CHR^3$ **a–f** (Chart 1). An accurate analysis of the experimental conditions (molar ratio allene/TRIMEB, temperature, and solvent) which should be used in order to optimize the enantioseparations has been also carried out.

Chart 1



allene	R^1	R^2	R^3
a	*t*-Bu	Me	Br
b	Et	Me	Br
c	Pr	Me	Br
d	*t*-Bu	Me	Ph
e	Et	Me	Ph
f	*t*-Bu	Me	*t*-Bu

t-Bu = *t*-butyl, Et = ethyl, Me = methyl, Ph = phenyl, Pr = propyl

Results and Discussion

Racemic 3,3-dialkyl-1-bromoallenes **a–c** have been obtained, according to a described procedure,[2] by reaction of the appropriate propargylic methanesulfonate with a suspension of $LiCu_2Br_3$ in THF (Scheme 1). Treatment of compounds **a** and **b** with phenyl- or *tert*-butylmagnesium chloride in the presence of catalytic amounts of anhydrous CuBr (5%) afforded the trisubstituted allenes **d–f** in high yields (Scheme 1).[10]

The ^{1}H NMR spectra of TRIMEB, allenes **a–f**, and the mixtures TRIMEB/allene have been recorded at 300 MHz in CD_3OD as solvent.

The proton spectrum of the permethylated cyclodextrin at room temperature is completely included in the restricted region between 3.0 and 4.0 ppm, with the exclusion of the sharp doublet centered at 5.14 ppm. The free allene **a** shows a well-recognizable singlet at 1.09 ppm, due to the absorption of the *tert*-butyl group, and a doublet (J = 2.2 Hz) centered at 1.82 ppm, corresponding to the resonance of the methyl group; in the low-field spectral

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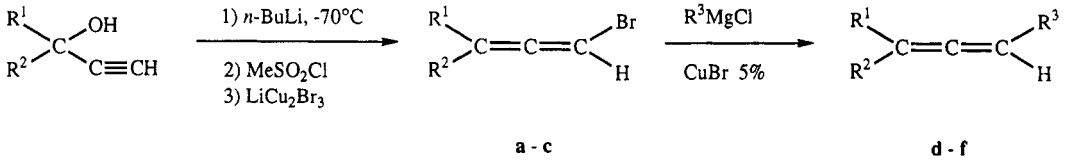
Scheme 1



region, only the quartet centered at 6.01 ppm is present, arising from the proton directly bound to the allene moiety. Similar to **a**, the other allenes **b–f** show resonances between 0.9 and 2.2 ppm, due to the alkyl protons R^1 and R^2 (and R^3 for **f**) (Chart 1), and a well-resolved signal, near 6.0 ppm for **b–e** and near 5.0 ppm for **f**, which is due to the allene proton. In the case of allenes **d** and **e**, absorptions between 7.0 and 7.7 ppm are observed, arising from the aromatic protons of the phenyl ring. Therefore, the absorptions of the allenes and cyclodextrin fall in distinct spectral regions and any reciprocal interference is not observed in the spectra.

By comparing the spectra of the racemic allenes **a–f** in the free state and in the presence of the cyclodextrin, it has been observed that TRIMEB produced duplication of almost all signals of allenes. As an example, the well-resolved quartet of the allene proton of free **a** (6.01 ppm at 25 °C in CD_3OD, Figure 1a) duplicates into two partially superimposed quartets centered at 6.04 and 6.03 ppm (Figure 1b, $\Delta\delta$ = 3.9 Hz), in the presence of equimolar amounts of TRIMEB. These two absorptions correspond in position to those obtained starting from each enantiomer of the allene, respectively, at same molar ratio allene/TRIMEB, total concentration, and temperature (Figure 1c,d). Therefore, the splitting observed is due to the fact that TRIMEB induces nonequivalence in the proton nuclei of the two enantiomers of the allenes, thus allowing its use as a chiral solvating agent for the determination of their enantiomeric purities.

In all cases examined the extent of the unequivalence, i.e., the difference of the proton chemical shifts of the two enantiomers in the presence of TRIMEB, can be made larger by increasing the molar ratio TRIMEB/allene, and data relative to the allene proton of **a–f** are summarized in Table 1. As shown in Figure 2 for the allene proton of **a**, the unequivalence increases from 3.9 Hz (Figure 2a) in the equimolar solution to 7.0 Hz (Figure 2b) by adding a further equivalent of TRIMEB and to 10.9 Hz (Figure 2c) in the presence of 3 equiv of the cyclodextrin, giving rise to two completely separated signals.

The use of CD_3OD as solvent also allowed us to affect the unequivalence by temperature variations (Table 1): the absorptions of the allene proton of **a** in the two enantiomers are separated by 11.9 Hz at −20 °C (Figure 3a) and by 18.1 Hz at −40 °C (Figure 3b). The possibility of increasing the unequivalence by decreasing the temperature instead of increasing the molar ratio CSA/allene represents an advantage under two aspects: the measurement requires a minor amount of TRIMEB, thus becoming less expensive, and better results are obtained, taking into account that the unequivalence is very sensitive to temperature variations.

On the basis of the above results it can be concluded that, at least for the allenes investigated, the complete separation of the two allene absorptions can be achieved both by varying the molar ratio and by lowering the temperature, and hence, the enantiomeric composition

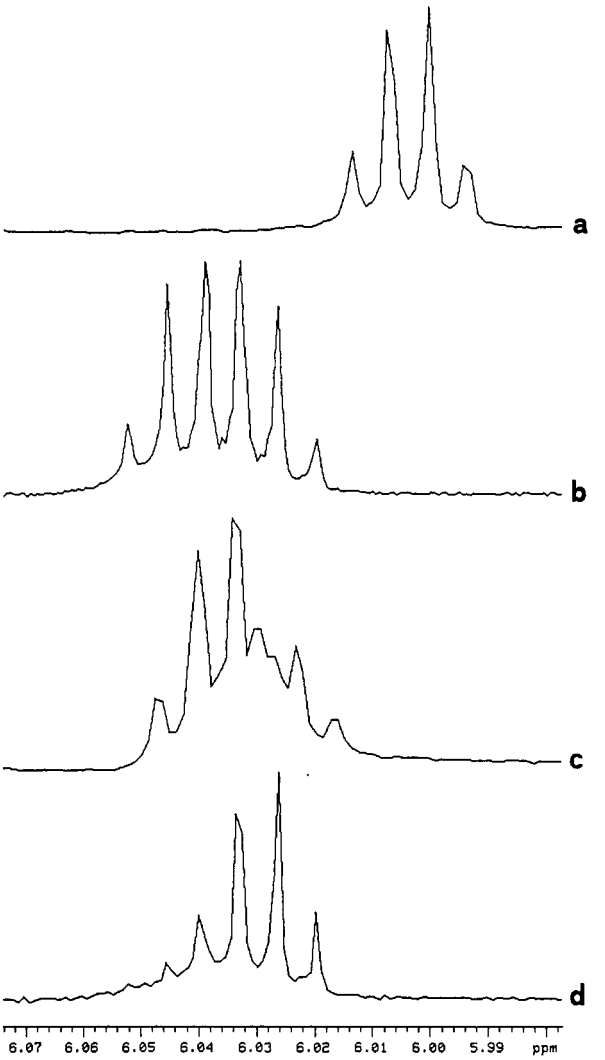


Figure 1. ^1H NMR spectra (300 MHz, CD_3OD, ppm referred to TMS as external standard, 25 °C) of (a) free compound **a** (40 mM), (b) equimolar mixture of (*R*,*S*)-**a**/TRIMEB, (c) equimolar mixture formed starting from a sample of **a** enriched in the (+)-(*S*)-enantiomer, and (d) equimolar mixture formed starting from a sample of enantiomerically pure (−)-(*R*)-**a**.

can be accurately determined by comparing the areas of the two absorptions by integration.

It is worthy of note that the greatest unequivalences have been obtained for the allene proton; however, the other absorptions of the allenes also show splitting in the presence of TRIMEB, and even if the extent of the unequivalences is lower with respect to those obtained for the allene proton, in the case of simple signals, such as the singlet produced by the *tert*-butyl groups of the allenes **a**, **d** and **f**, the enantiomeric composition can be simply evaluated by comparing the intensities of the signals (taking into account that their line widths are almost equal, ≈1.2 Hz) (Figure 4).

In order to investigate the effect of the nature of the solvent on the magnitude of the unequivalence, we

Table 1. Unequivalence ($\Delta\delta$,[a] 300 MHz, CD_3OD) Induced in the Allene Proton of Trisubstituted Allenes (40 mM) in the Presence of TRIMEB, as a Function of the Temperature and of the Molar Ratio Allene/TRIMEB

	25 °C		−40 °C
allene	molar ratio 1:1	molar ratio 1:2	molar ratio 1:1
a	3.9	7.0	18.1
b	1.8	2.0	7.4
c	1.1	4.2	5.9
d	3.3	7.0	23.4
e	2.9	3.3	11.7
f	0.5	2.9	4.9

[a] $\Delta\delta$ = difference of the proton chemical shifts (Hz) of the two enantiomers in the presence of TRIMEB.

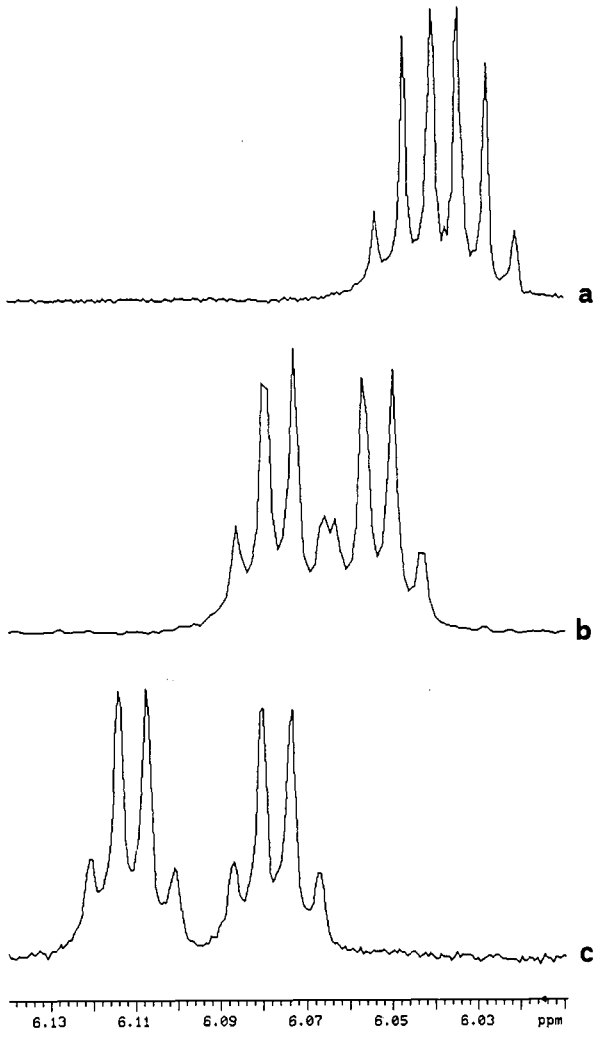


Figure 2. ^1H NMR spectra (300 MHz, CD_3OD, ppm referred to TMS as external standard, 25 °C) of (a) equimolar mixture of (*R,S*)-**a**/TRIMEB, (b) 1:2 mixture of (*R,S*)-**a**/TRIMEB, and (c) 1:3 mixture of (*R,S*)-**a**/TRIMEB.

compared the ^1H NMR spectra of the equimolar mixture TRIMEB/**a** in CD_3OD, DMSO-d_6, and acetone-d_6. Comparable unequivalences of the allene proton were obtained in the two solvents CD_3OD and DMSO-d_6 (3.9 Hz and 3.7 Hz, respectively), whereas a poor separation was obtained in acetone-d_6 (1.9 Hz). In any case, CD_3OD should be considered the best choice; indeed, only this solvent affords the opportunity to perform low-temperature measurements, which are not possible in DMSO-d_6, and hence to increase the unequivalence by mantaining unchanged the molar ratio CSA/allene.

The effectiveness of TRIMEB as chiral solvating agent has been also compared to that of two other derivatized cyclodextrins, heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (DIMEB) and triacetyl-β-cyclodextrin (TRIAC), both commercially available, by measuring the unequivalences originated in the protons of the allene **a** in the equimolar mixtures allene/cyclodextrin at the same temperature and overall concentration. In the case of the DIMEB/**a** mixture, in CD_3OD as solvent, only splitting of the allene proton was observed, but the unequivalence (1.8 Hz) was lower with respect to that originated by TRIMEB (3.9 Hz). In addition, DIMEB was less soluble in CD_3OD relative to TRIMEB, and hence, it was difficult to enhance the unequivalence by adding further equivalents of the cyclodextrin. As TRIAC was almost insoluble in CD_3OD, the ^1H NMR spectrum of the TRIAC/**a** mixture was recorded in DMSO-d_6; however, any enantioseparation was not observed. Furthermore, in this solvent low-temperature measurements were precluded.

In conclusion, the use of TRIMEB as chiral solvating agent for the determination of the enantiomeric purities of chiral allenes is undoubtedly of general applicability, at least in the case of trisubstituted allenes; indeed, by

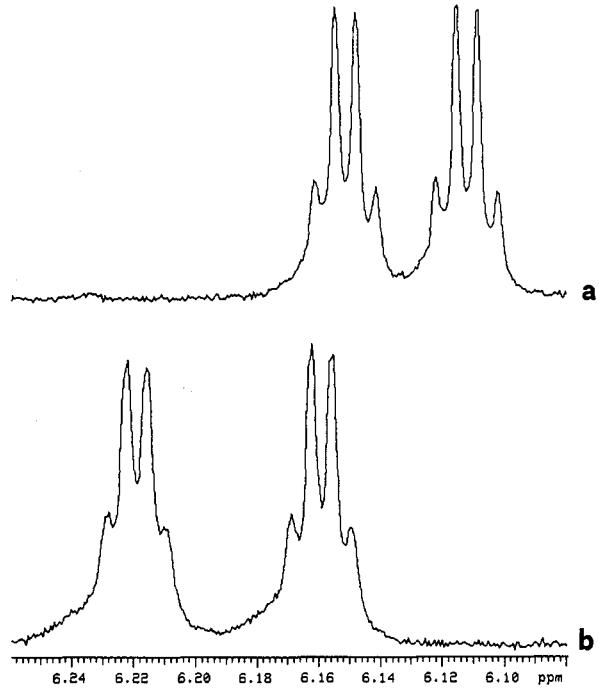


Figure 3. ^1H NMR spectra (300 MHz, CD_3OD, ppm referred to TMS as external standard) of the equimolar mixture (*R,S*)-**a**/TRIMEB, recorded at (a) −20 °C and (b) −40 °C.

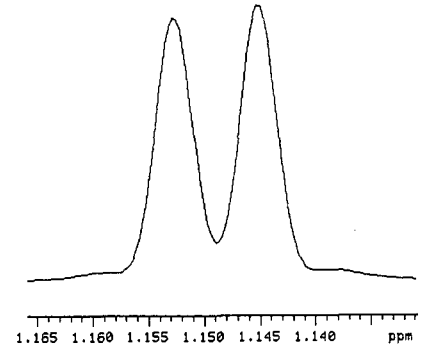


Figure 4. ^1H NMR spectrum (300 MHz, CD_3OD, ppm referred to TMS as external standard, 0 °C) of the equimolar mixture (*R,S*)-**d**/TRIMEB.

this method, the enantioseparation of alkyl-, aryl-, and bromoallenes has been successfully achieved. This is a very important goal for all researchers interested to the chemistry of chiral allenes, taking into account that the other NMR methods, previously reported, for the determination of the enantiomeric purity of allenes have very restricted applications.[7-9]

Experimental Section

General Methods. The ^1H NMR measurements were performed on a Varian VXR-300 spectrometer operating at 300 MHz in CD_3OD as solvent; the temperature was controlled (accuracy ± 0.1 °C) by the Varian control unit. ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer at 50.3 MHz in $CDCl_3$. Mass spectra were determined on a VG-Analytical 7070 GC-MS instrument (EI; 70 eV). All reactions were carried out under an inert atmosphere of dry argon.

Materials. Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TRIMEB) was obtained from Sigma. THF was distilled from $LiAlH_4$ prior to use. Grignard reagents were prepared in THF and standardized by titration methods. *n*-Butyllithium was purchased from Fluka A. G. Co., Buchs, as a 1.6 M solution in hexane. Commercial (Fluka) lithium bromide and cuprous bromide were used without purification. Tertiary propargylic carbinols were prepared according to the procedure of Papa and co-workers.[11]

General Procedure. Bromoallenes a–c. To a stirred solution of the appropriate propargylic carbinol (60 mmol) in THF (150 mL) were successively added, at −70 °C, 60 mmol of butyllithium in hexane (38 mL) and 65 mmol of methanesulfonyl chloride. After 5 min at −70 °C a suspension of $LiCu_2Br_3$ (from 78 mmol of LiBr and 156 mmol of CuBr in 270 mL of anhydrous THF) was added, and the mixture was allowed to warm to room temperature within 30 min. The reaction mixture was quenched with saturated ammonium chloride solution, and the organic materials were extracted with ether. The combined extracts were washed with additional aqueous ammonium chloride and water, dried (Na_2SO_4), and concentrated in vacuo (15–20 mmHg). The pure bromoallene was obtained by fractional distillation as a colorless liquid.

1-Bromo-3,4,4-trimethyl-1,2-pentadiene (**a**):[2a,d] 90% yield; bp 68 °C (17 mmHg); mass spectrum *m/e* 188 for ^{79}Br (M^+); ^1H NMR δ 1.09 (9H), 1.82 (3H), 6.01 (1H); ^{13}C NMR δ 14.6, 20.5, 34.0, 71.5, 120.1, 198.8.

According to the above procedure, samples of (+)-(*S*)- and (−)-(*R*)-1-bromo-3,4,4-trimethyl-1,2-pentadiene (**a**) were obtained starting from (−)-(*R*)- (31% ee) and (+)-(*S*)-3,4,4-trimethyl-1-pentyn-3-ol (95% ee), respectively.[2a,b]

1-Bromo-3-methyl-1,2-pentadiene (**b**):[2a] 80% yield; bp 42–43 °C (17 mmHg); mass spectrum *m/e* 160 for ^{79}Br (M^+); ^1H NMR δ 1.04 (3H), 1.82 (3H), 2.11 (2H), 6.04 (1H); ^{13}C NMR δ 11.5, 18.7, 26.9, 71.7, 113.4, 199.3.

1-Bromo-3-methyl-1,2-hexadiene (**c**):[2c] 85% yield; bp 78 °C (17 mmHg); mass spectrum *m/e* 174 for ^{79}Br (M^+); ^1H NMR δ 0.94 (3H), 1.50 (2H), 1.81 (3H), 2.08 (2H), 6.01 (1H); ^{13}C NMR δ 13.5, 18.8, 20.2, 35.8, 71.1, 112.2, 199.2.

Trisubstituted Allenes d–f. To a stirred suspension of CuBr (0.7 mmol) in dry THF (40 mL) were added the appropriate bromoallene (14.5 mmol) and, at −70 °C, a THF solution of phenyl- or *tert*-butylmagnesium chloride (29 mmol). After being stirred for 3–5 min at −70 °C, the mixture was allowed to warm to room temperature and stirring was continued for 2 h. The mixture was then treated with saturated ammonium chloride solution, and the organic materials were extracted with diethyl ether. After the usual workup, fractional distillation (Fischer–Spaltrohr MMS 202 column) yielded pure products **d–f**.

1-Phenyl-3,4,4-trimethyl-1,2-pentadiene (**d**):[12] 90% yield; bp 98 °C (20 mmHg); mass spectrum *m/e* 186 (M^+, 27), 57 (100); ^1H NMR δ 1.13 (9H), 1.81 (3H), 6.05 (1H), 7.04–7.68 (5H); ^{13}C NMR δ 14.7, 29.1, 34.2, 94.1, 112.6, 126.2, 126.3, 128.5, 136.3, 201.8.

1-Phenyl-3-methyl-1,2-pentadiene (**e**):[12] 95% yield; bp 62–63 °C (0.8 mmHg); mass spectrum *m/e* 158 (M^+, 69), 143 (100); ^1H NMR δ 1.05 (3H), 1.81 (3H), 2.09 (2H), 6.08 (1H), 7.05–7.30 (5H); ^{13}C NMR δ 12.3, 18.7, 27.2, 94.5, 105.4, 126.3, 126.5, 128.4, 136.1, 202.3.

2,2,3,6,6-Pentamethyl-3,4-heptadiene (**f**):[10] 82% yield; bp 62–63 °C (17 mmHg); mass spectrum *m/e* 166 (M^+, 10), 57 (100); ^1H NMR δ 1.00 (9H), 1.04 (9H), 1.67 (3H), 4.98 (1H); ^{13}C NMR δ 15.4, 29.2, 30.3, 32.0, 33.2, 102.3, 109.7, 197.3.

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