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NMR Determination of the Absolute Configuration of Cyclic Chiral Alkenes

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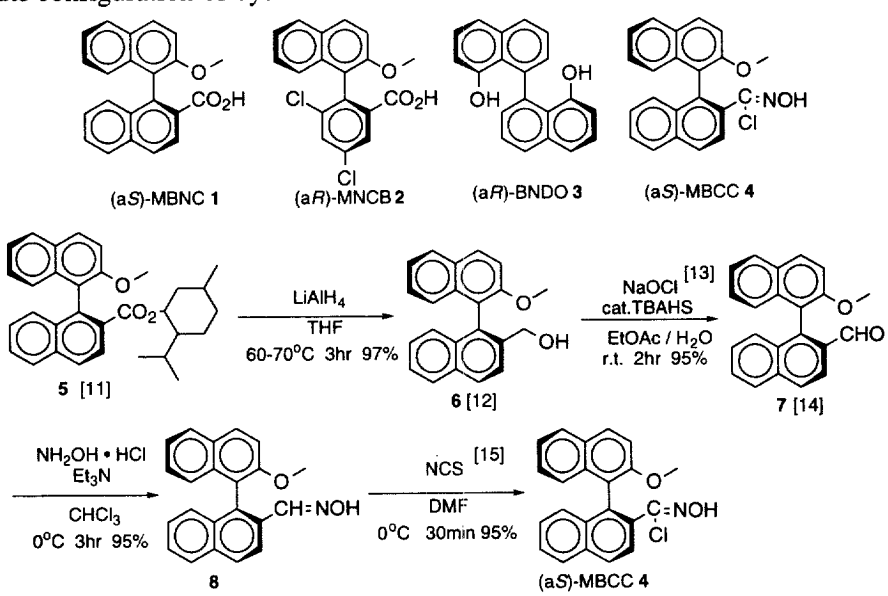
Abstract : By the use of a new axially chiral reagent, 2'-methoxy-1,1'-binaphthalene-2-carbohydroximoyl chloride (MBCC), chiral cyclic alkenes were stereoselectively derivatized into 4,5-dihydroisoxazoles. NOEs were observed between the protons of the reagent moiety and those of the alkene moiety in cycloadducts. The absolute configuration of the original alkenes was unambiguously determined by the NOE correlation.

In recent years, many reagents have been developed for chiral recognition of organic compounds by NMR [1~6]. Our group and others have reported that the axially chiral reagents (**1~3**) are applicable to chiral alcohols, amines, and carboxylic acids for the same purpose [7~10]. However, to our knowledge, there is no useful chiral derivatizing reagent for chiral alkenes. In this paper we report a new method using an axially chiral reagent, 2'-methoxy-1,1'-binaphthalen-2-carbohydroximoyl chloride (MBCC **4**), for determination of the absolute configuration of cyclic chiral alkenes.



Scheme 1.

This reagent **4**[1] was prepared as shown in Scheme 1. We expected that the nitrile oxide (**9**),

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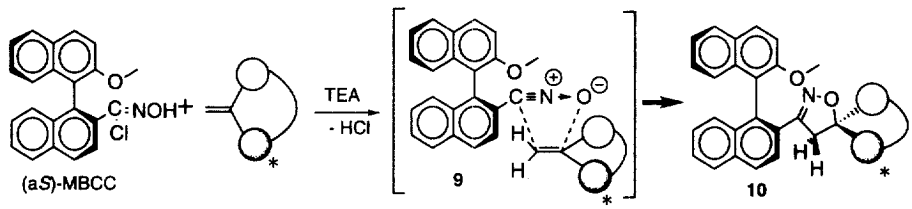
generated from MBCC (**4**) by elimination of HCl with triethylamine, could stereoselectively add to alkenes from the less bulky site of their double bonds to afford 4,5-dihydroisoxazoles (Scheme 2).



Scheme 2.

Two stable conformers (**1A** and **1B** in Fig. 1) can be estimated for the cycloadduct **10** in solution. In each conformer, the C=N bond conjugates the attached naphthalene ring and they lie in the same plane. When the MBCC derivative **10** is in the conformer **1A**, due to the diamagnetic effect of the naphthalene ring, the signals for the protons of the alkene moiety should appear upfield relative to those of the original alkene, and Hb should be shielded by the naphthalene ring in comparison with Ha. NOEs will be observed between the methoxy protons of the reagent moiety and Ha, and between 8'-H and Hb. From this NOE correlation, Ha and Hb can be assigned. Consequently, NOEs among Ha,Hb and the alkene moiety reveal the relative configuration of the alkene moiety in **10**. Thus, the relative configuration of **10** can be determined nonempirically. Since the absolute configuration of the reagent is known, that of the alkene can be determined. On the other hand, in the conformer **1B**, little or no shielding effect by the naphthalene ring may be observed on the alkene moiety. In this case, NOEs will be observed between 3-H of the reagent moiety and Ha, Hb.

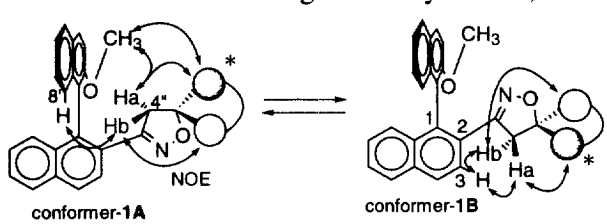


Figure 1.

To substantiate these hypotheses, we prepared the 4,5-dihydroisoxazole derivatives (**12**, **13**)[2] from (-)-β-pinene (**11**) and (a*S*), (a*R*)-MBCC (**4**), and analyzed them by NMR in $CDCl_3$. It was evident that the individual proton signal of the alkene moieties of **12** and **13** appears in upper field than the corresponding one of the original alkene **11** (Table 1). NOEs were observed between the methoxy protons and Hb, 9-CH_3 of the (-)-β-pinene moiety , between 8'-H and Ha, between Ha and 3β-H, and between Hb and 1-H in **12** (Fig. 2). On the contrary, NOEs were observed between the methoxy protons and Ha, 8-CH_3, between 8'-H and Hb, between Ha and 3β-H, and between Hb and 1-H in **13**. Therefor, the absolute configuration of chiral alkene **11** can be determined by using its derivative from one

enantiomer of MBCC. On the chemical shift differences of the protons of the (-)-β-pinene moieties in **12** and **13** [Δδ=**12**(a*S*)-**13**(a*R*), Fig. 3], the values for the protons on the right side of the plane containing the 4,5- dihydroisoxazole ring are positive. Those for the protons the left side of the plane are negative.

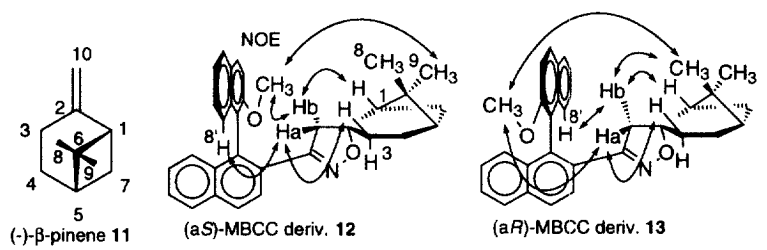


Figure 2. (-)-β-Pinene and its MBCC derivatives.
NOE correlations are shown by arrows.

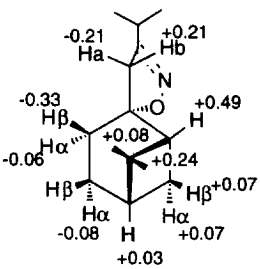


Figure 3.
Δδ=**12**(a*S*)-**13**(a*R*)

Table 1. : ^{1}H-NMR Data of (-)-β-pinene (**11**), its (a*S*)-MBCC adduct (**12**) and (a*R*)-MBCC adduct (**13**)

	1	3	4	5	7	8	9	10
11	2.45 (dd)	α:2.52 (m) β:2.24 (ddd)	1.78- 1.88 (m)	1.97 (m)	α:1.42 (m) β:2.31 (d)	0.71 (m)	1.23 (m)	4.61 (br s) 4.55 (br s)
12	1.62 (dd)	α:1.47 (ddd) β:1.24 (ddd)	α:1.69 (m) β:2.02 (m)	1.75 (m)	α:1.42 (m) β:2.06 (d)	0.22 (s)	1.06 (s)	a:1.91 (d) b:2.15 (d)
13	1.13 (d)	α:1.53 (ddd) β:1.57 (ddd)	α:1.77 (ddd) β:2.15 (ddd)	1.72 (m)	α:1.35 (ddd) β:1.93 (ddd)	0.14 (s)	0.82 (s)	a:2.15 (d) b:1.91 (d)

The result suggests that the absolute configuration of this alkene can be determined from the difference in chemical shift between the (a*S*)- and (a*R*)-MBCC adducts, which is based on the same principle as that of the Mosher method [16].

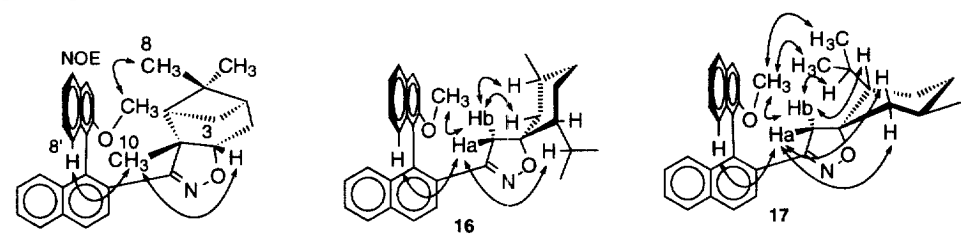


Figure 4. Other MBCC derivatives.
NOE correlation is shown by arrows.

Subsequently, (-)-α-pinene was reacted with (a*S*)-MBCC to give **14**[2]. An exo-methylene compound (**15**) was prepared[3] by reaction of trimethylsilylmethylmagnesium chloride [17] with (-)-menthone. **15** was also reacted with (a*S*)-MBCC to give **16** and **17** (**16**:**17**=2:1). The NOE correlations revealed their relative configuration as shown in Fig. **4**. The absolute configuration of the alkene moieties in **14**, **16** and **17** corresponded with that of original

cyclic chiral alkenes (Fig. 4).

In summary, we have developed a new method for determination of the absolute configurations of chiral cyclic alkenes by use of an axially chiral reagent, MBCC (**4**). Further application of this reagent to other types of alkenes is under study.

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1 Spectral data : (a*R*)-2'-methoxy-1,1'-binaphthyl-carbohydroximoyl chloride
yellow oil
$[a]^{24}_{D}$ -29.0° (*c* 2.0×10^{-4}, CH_2Cl_2)
^{1}H-NMR δ (500MHz, $CDCl_3$) : 3.67 ($OC\underline{H}_3$, 3H, s), 7.24 (NO<u>H</u>, 1H, s), and Hs-Ar, 1H each; 6.87 (d, *J*=8.6), 7.24 (ddd, *J*=1.2, 6.9, 6.9), 7.32 (ddd, *J*=1.2, 6.9, 6.9), 7.33 (d, *J*=8.9), 7.34 (ddd, *J*=1.2, 6.9, 6.9), 7.47 (d, *J*=9.1), 7.54 (ddd, *J*=1.2, 6.9, 6.9), 7.66 (d,*J*=8.6), 7.89 (d, *J*=8.1), 7.93 (1H, d, *J*=8.1), 7.96 (1H, d, *J*=8.6), 8.04 (d, *J*=8.9).
^{13}C-NMR δ (270MHz, $CDCl_3$) : 56.5($\underline{C}H_3$), 96.1(<u>C</u>=N), and Cs-Ar; 113.2, 119.1, 123.9, 124.3, 126.7, 127.1, 127.4, 127.5, 127.7, 127.8, 127.9, 128.3, 128.7, 128.9, 131.1, 132.7, 133.4, 133.9, 140.5, 154.8.
EI-MS *m/z* (rel. int. %) : 326 (M^+-HCl+1, 26), 325 (M^+-HCl, 100), 309 (M^+-OCH_3, 100), 268 (14), 85 (20), 84 (12).
FD-MS *m/z* (rel. int. %) : 325 (M^+-HCl, 100).
Store this reagent in a freezer. MBCC gradually dimerizes to form a furoxan at room temperature.

2 To a chloroform (1ml) solution of **1 1** (50.0mg, 304μmol) was added **4** (110mg, 367μmol) and triethylamine (56.0μl, 402μmol). The reaction mixture was stirred at room temperature for 6hr and directly applied to column chromatography (SiO_2, 20% EtOAc/hexane) to afford the product **1 2** (94.0mg, 67%). Similarly, **1 3** was prepared in 69% yield.
1 4 was prepared in 79% yield by stirring a mixture of (-)-α-pinene (26.7mg, 196μmol), **4** (121mg, 334μmol) and triethylamine (50.0μl, 358μmol) in $CHCl_3$ (1ml) at room temperature for 3 days, followed by usual work up.

3 To a Et_2O (30ml) solution of (-)-menthone (0.97g, 6.3mmol) was added 15.3ml of 1.0 *M* trimethylsilylmethylmagnesium chloride in Et_2O. The reaction mixture was stirred at room temperature for 8hr. The residue was purified by chromatography on silica gel with hexane as eluent to give the product **1 5** (141.2mg, 15% yield).
EI-MS *m/z* (rel. int. %) : 152 (M^+, 22), 137 (12), 110 (70), 109 (100), 108 (15), 96 (20), 95 (77), 93 (12), 82 (18), 81 (46), 79 (13), 73 (13), 69 (11), 68 (19), 67 (66), 55 (24), 43 (16), 41 (27), 39 (10).