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(*R*)-(+)-[VCD(+)945]-4-Ethyl-4-methyloctane, the simplest chiral saturated hydrocarbon with a quaternary stereogenic center

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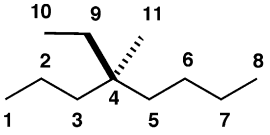
Abstract—Enantiopure (*R*)-(+)-[VCD(+)945]-4-ethyl-4-methyloctane, the simplest chiral saturated hydrocarbon with a quaternary stereogenic center, was synthesized by the use of MαNP acid method, and its absolute configuration was first unambiguously determined by the ^{1}H NMR anisotropy, X-ray crystallography, and VCD methods.

Compound, 4-ethyl-4-methyloctane **1**, is the simplest chiral saturated hydrocarbon with a quaternary stereogenic center, to which four different unbranched alkyl groups, that is, methyl, ethyl, propyl, and butyl groups, are bonded (Scheme 1). Hydrocarbon **1** is one of the compounds with cryptochirality,[1] because of its extremely small optical rotation.

In 1980, Wynberg and a co-worker first reported the synthesis of both enantiomers (−)-**1** of 95% ee and (+)-**1** of 85% ee, which showed small specific rotations, $[\alpha]_{578}$ −0.198 and $[\alpha]_{578}$ +0.185 (neat), respectively (Scheme 2).[2] It was thus difficult to synthesize enantiopure hydrocarbon **1**. In addition, the absolute configuration of **1** had remained undetermined. In 1988, Lardicci and co-workers reported the synthesis and absolute configurational assignment of (+)-**1**,[3] where chiral acetylene *tert*-alcohol **3** was converted to hydrocarbon (+)-**1** via bromo-allene **5** (Scheme 2). Namely, the chirality of *tert*-alcohol was transferred to the allene chirality and then to the chirality of a quaternary stereogenic center.



(*R*)-(+)-[VCD(+)945]-**1**

enantiopure (*R*)-(+)-**1**,
$[\alpha]_D^{25}$ +0.19 (σ 0.02, neat, ρ 0.7565);
$[\alpha]_{365}^{23}$ +0.70 (σ 0.01, neat, ρ 0.7565)

Scheme 1. Absolute configuration of 4-ethyl-4-methyloctane **1**: this study.

Such a chirality transfer, however, is not ideal for the absolute configurational assignment. In addition, although the absolute configuration of acetylene *tert*-alcohol **3** was determined by applying the CD exciton chirality method[4] to its benzoate **4**, the observed CD ($\Delta\varepsilon$ +0.8)[3] is too small to make a clear assignment. Therefore, it is a challenging problem to synthesize enantiopure hydrocarbon **1** with cryptochirality and to determine its absolute configuration in an unambiguous way.[5] We communicate here the synthesis of enantiopure (+)-**1**, the first absolute configurational assignment by ^{1}H NMR anisotropy and X-ray crystallography, and the characterization by VCD (vibrational circular dichroism).[6] As will be discussed below, the ^{13}C NMR

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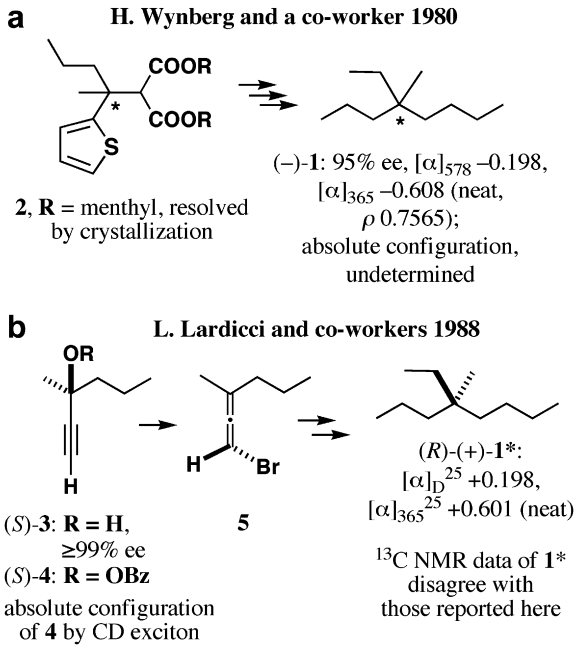
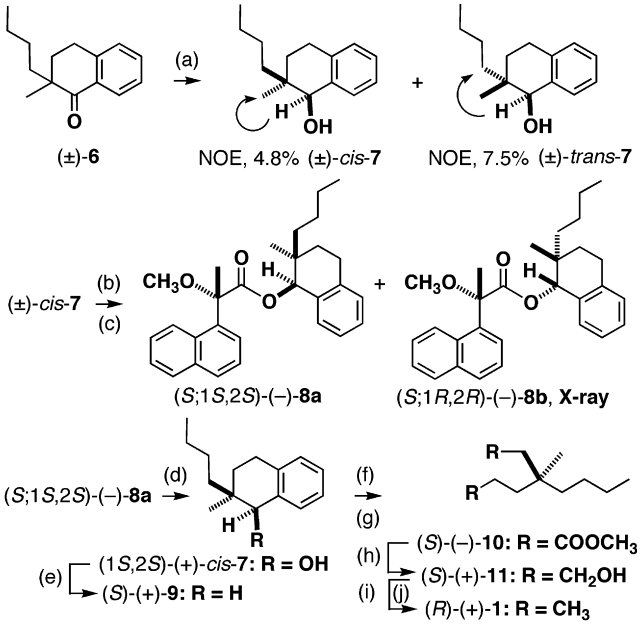


Scheme 2. Syntheses of chiral hydrocarbon **1** previously reported.



Scheme 3. Preparation of enantiopure 4-ethyl-4-methyloctane (*R*)-(+)-[VCD(+)945]-**1**. (a) $LiAlH_4$/THF, *cis*-**7**, 69%, *trans*-**7**, 31%. (b) (*S*)-(+)-MαNP acid, DCC, DMAP, CSA/CH_2Cl_2, reflux. (c) HPLC (silica gel, hexane/EtOAc 15:1): **8a**, 50%; **8b**, 45%. (d) NaOMe/MeOH, 84%. (e) $NaBH_4$, $AlCl_3$/THF, reflux, 89%. (f) $RuCl_3$, HIO_4/CCl_4, CH_3CN, water. (g) CH_3I, K_2CO_3/DMF, 52% for two steps. (h) $LiAlH_4$/THF, 95%, (i) CBr_4, PPh_3/CH_2Cl_2. (j) $NaBH_4$/HMPA, 77% for two steps.

data of (+)-**1** reported by Lardicci and co-workers disagree with ours, indicating that their final product is not hydrocarbon **1**.

Recently we have developed the MαNP ester method[7] using chiral 2-methoxy-2-(1-naphthyl)propionic (MαNP) acid, which is very powerful for enantioresolution of alcohols and simultaneous determination of their absolute configurations by ^{1}H NMR anisotropy, and has been successfully applied to various alcohols. We adopted the strategy of the MαNP ester method as shown in Scheme 3. Tetralone was converted to 2-butyl-2-methyltetralone **6**, which was reduced with $LiAlH_4$ yielding *cis*-alcohol **7** (69%) and *trans*-alcohol **7** (31%). The relative configuration of *cis*-**7** was determined by NOE (4.8%) between the 2-methyl group and 1-methine proton. The configuration of *trans*-**7** was similarly determined as shown in Scheme 3. The major alcohol (±)-*cis*-**7** was esterified with (*S*)-(+)-MαNP acid giving diastereomeric esters, which were easily separated by HPLC on silica gel (hexane/EtOAc 15:1; $t_1 = 24.7$ min, $t_2 = 35.0$ min; $\alpha = 1.81$; $R_s = 5.97$) affording the first-eluted ester (–)-**8a** {50%, $[\alpha]_D^{25}$ –87.7 (*c* 1.09, $CHCl_3$)} and the second-eluted ester (–)-**8b** {45%, $[\alpha]_D^{25}$ –7.7 (*c* 1.02, $CHCl_3$)}. It should be noted that MαNP esters **8a**/**8b** were effectively separable with a large separation factor $\alpha = 1.81$.

To determine the absolute configurations, the ^{1}H NMR signals of both esters **8a** and **8b** were fully assigned by ^{13}C NMR, HMQC, and HMBC spectra. From the chemical shift data, $\Delta\delta$ values {$=\delta$ (**8b**) – δ(**8a**)} reflecting the anisotropy effects were calculated as shown in Figure 1; the protons showing positive $\Delta\delta$ values were placed at the right side, while the protons showing negative $\Delta\delta$ values at the left side. From the projection illustrated in Figure 1, the absolute configuration of

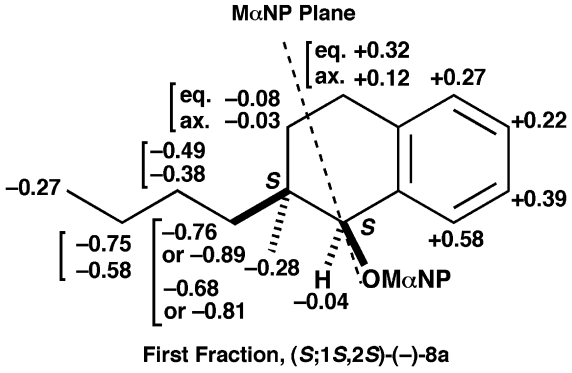


Figure 1. Absolute configuration of (–)-**8a** as determined by ^{1}H NMR anisotropy method.

the first-eluted ester (–)-**8a** was determined to be (*S*;1*S*,2*S*). The absolute configuration of the second-eluted ester (–)-**8b** was naturally assigned as (*S*;1*R*,2*R*).

The relative and absolute configurations of MαNP ester (–)-**8b** were established by X-ray crystallography as follows; single crystals were obtained by recrystallization from hexane/EtOAc. As shown in the X-ray stereoview in Figure 2, the absolute configuration of the alcohol part was clearly determined to be (1*R*,2*R*) by reference to the *S* absolute configuration of the MαNP acid part. The cis-configuration determined by NOE was also confirmed. The X-ray crystallographic data of (–)-**8b** was published together with those of other various MαNP esters for reporting the crystalline state conformations of MαNP esters.[8]

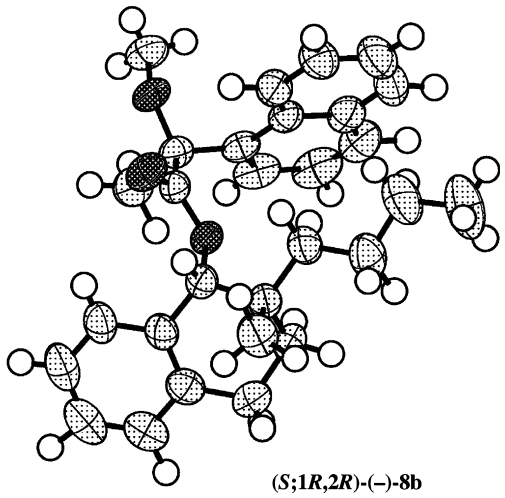


Figure 2. X-ray stereoview of (*S*;1*R*,2*R*)-(−)-**8b**, taken from Ref. 8.

The first-eluted MαNP ester (−)-**8a** was subjected to solvolysis with $NaOCH_3$ yielding enantiopure alcohol (1*S*,2*S*)-(+)-*cis*-**7**, $[\alpha]_D^{28}$ +10.8 (*c* 1.26, $CHCl_3$) which was then reduced with $NaBH_4$ and $AlCl_3$ giving tetrahydronaphthalene derivative (*S*)-(+)-**9**, $[\alpha]_D^{29}$ +1.5 (*σ* 0.03, *c* 1.00, $CHCl_3$) (Scheme 3). To convert the benzene ring to the diester moiety, compound (*S*)-(+)-**9** was oxidized with $RuCl_3$ and HIO_4 affording a dicarboxylic acid, which was esterified with CH_3I and K_2CO_3 yielding diester (*S*)-(−)-**10**, $[\alpha]_D^{24}$ −2.4 (*σ* 0.04, *c* 1.00, $CHCl_3$). Diester (*S*)-(−)-**10** was reduced with $LiAlH_4$ to diol (*S*)-(+)-**11**, $[\alpha]_D^{25}$ +0.54 (*σ* 0.02, *c* 1.53, $CHCl_3$), which was subjected to bromination with CBr_4 and PPh_3 followed by reduction of the dibromide with $NaBH_4$ in HMPA. This furnished the target hydrocarbon, 4-ethyl-4-methyloctane (*R*)-(+)-**1**, $[\alpha]_D^{25}$ +0.19 (*σ* 0.02, neat, *ρ* 0.7565) and $[\alpha]_{365}^{23}$ +0.70 (*σ* 0.01, neat, *ρ* 0.7565), where *σ* is the standard deviation of the observed [α] value, and density *ρ* was taken from the literature.[2] The observed $[\alpha]_{365}$ value agrees well with the absolute value reported by Wynberg and a co-worker: (−)-**1**, 95% ee, $[\alpha]_{365}$ − 0.608 (neat, *ρ* 0.7565), although they have not determined the absolute configuration of (−)-**1**.[2]

During these synthetic studies of hydrocarbon **1**, we found that our results conflicted with those reported by Lardicci and co-workers, as follows.[3] As a preliminary study, we first synthesized racemic hydrocarbon (±)-**1** in the same way as shown in Scheme 3; the ^1H and ^{13}C NMR data of (±)-**1** naturally agree with those of (+)-**1**. However, we found that the ^{13}C NMR data of (±)-**1** and (+)-**1** disagree with those reported by Lardicci and co-workers[3] as shown in Table 1. Unfortunately, no ^{13}C NMR data of (−)-**1** were reported by Wynberg and a co-worker.[2]

Such disagreement of ^{13}C NMR data prompted us to check the structure of **1** again by various NMR methods including ^1H, ^{13}C, HMBC, HSQC, and HSQC-TOCSY, among which HSQC-TOCSY was very powerful for the assignment of carbon and proton signals. For example, the ^1H triplet signal at *δ* 0.89 ppm corresponding to one of the terminal methyl groups showed four cross peaks

Table 1. ^{13}C NMR data of 4-ethyl-4-methyloctane **1** in $CDCl_3$

This work, 100 MHz	Calcd by the Lindeman–Adams method[9]	Lardicci and co-workers, 50 MHz[3]
7.9 (10-C)	7.9 (10-C)	6.3
14.2 (8-C)	13.9 (8-C)	7.2
15.1 (1-C)	14.8 (1-C)	8.9
16.6 (2-C)	17.5 (2-C)	16.0
23.7 (7-C)	23.2 (7-C)	16.7
24.5 (11-C)	24.8 (11-C)	18.0
25.7 (6-C)	27.3 (6-C)	23.8
31.5 (9-C)	31.9 (9-C)	27.1
34.8 (4-C)	36.3 (4-C)	31.0
38.6 (5-C)	38.7 (5-C)	33.9
41.5 (3-C)	41.4 (3-C)	41.3

in the HSQC-TOCSY spectra, which were measured using the mixing time at 12, 25, and 80 ms. The results indicate that this terminal methyl group is that of a butyl group; the 8-C and 8-H_3 signals could be thus assigned. From the time dependence of the cross peak intensity, the connectivity of 8-C, 7-C, 6-C, and 5-C was clearly determined together with their chemical shift data; see Supplementary data. From the cross peaks in the HSQC, the methylene protons, 7-H_2, 6-H_2, and 5-H_2, were also assigned.

On the other hand, the triplet signal at *δ* 0.87 ppm showed three cross peaks in the HSQC-TOCSY spectra, indicating that this methyl group is contained in a propyl group; the 1-C and 1-H_3 signals could be assigned. From the time dependence of the cross peak intensity, the connectivity of 1-C, 2-C, and 3-C was similarly determined together with their chemical shift data. From the HSQC, the methylene protons, 2-H_2 and 3-H_2, were also assigned.

In a similar way, the ^{13}C and ^1H signals of an ethyl group were assigned. The triplet signal at *δ* 0.755 ppm showed two cross peaks in the HSQC-TOCSY spectra, indicating the presence of an ethyl group; the 10-C, 9-C, 10-H_3, and 9-H_2 signals were thus determined. The singlet signal at 0.762 ppm showing one cross peak in the HSQC-TOCSY spectra was naturally assigned as the methyl group at the position 4. The ^{13}C signal at *δ* 34.8 ppm showed no cross peak in the HSQC-TOCSY spectra, and hence it was assigned to the quaternary carbon, 4-C. In consequence, all ^1H and ^{13}C signals were fully assigned as listed in Table 1 and Supplementary data, establishing the structure of 4-ethyl-4-methyloctane **1**. The ^{13}C NMR of compound **1** was calculated by the empirical Lindeman–Adams method;[9] the calculated chemical shift data and carbon assignments agree well with those observed (Table 1). On the other hand, the ^{13}C NMR data reported by Lardicci and co-workers[3] clearly disagree with the data observed here, indicating that their final product is not 4-ethyl-4-methyloctane **1**.

Hydrocarbon **1** has no functional groups, and therefore, in general, it is difficult to discriminate between enantiomers, although the specific rotation at 365 nm, $[\alpha]_{365}$, is

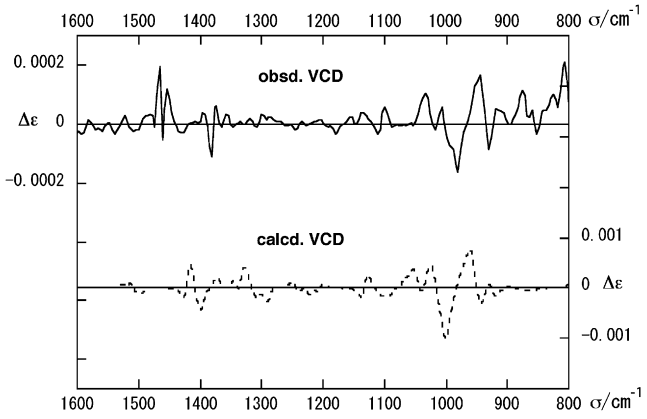


Figure 3. Obsd. and calcd. VCD spectra of (*R*)-(+)-**1**: obsd., neat, BaF_2 cell; calcd. using the B3PW91/6-31G(d,p) basis set.

useful in this case. As another chiroptical method for discriminating between enantiomers, we have adopted the vibrational circular dichroism,[6] VCD, that is, CD spectrum in the IR region, which is applicable to non-chromophoric compounds. The VCD spectrum of 4-ethyl-4-methyloctane (*R*)-(+)-**1** was measured neat using a cell of BaF_2, $l = 46$ μm, measurement time = 3 h. As shown in Figure 3, compound (*R*)-(+)-**1** showed a positive Cotton effect at 945 cm^{-1}. Therefore, hydrocarbon **1** is characterized as (*R*)-[VCD(+)945], which indicates that the enantiomer showing a positive VCD band at 945 cm^{-1} has an *R* absolute configuration. The VCD spectrum of (*R*)-4-ethyl-4-methyloctane **1** was calculated by the ab initio MO method using B3PW91/6-31G(d,p) basis set; the calculated VCD curve agrees well with the observed one, especially at 1100–900 cm^{-1} (Fig. 3). The absolute configuration of (+)-4-ethyl-4-methyloctane **1** was thus determined also by VCD, and the results are consistent with those obtained by X-ray crystallography and ^1H NMR anisotropy.

In conclusion, we have succeeded in the synthesis of enantiopure (*R*)-(+)-[VCD(+)945]-4-ethyl-4-methyloctane **1**, the simplest chiral saturated hydrocarbon with a quaternary stereogenic center, and the first determination of its absolute configuration by X-ray, ^1H NMR anisotropy, and VCD methods. The methodology discussed here is generally applicable to various chiral compounds with a quaternary stereogenic center, and the extension to other chiral systems is in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.079.

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