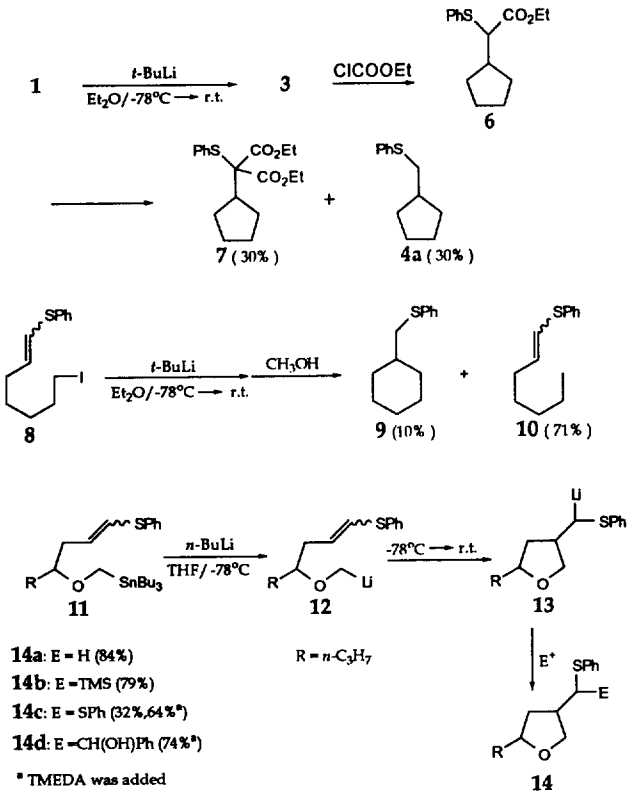

Scheme 2.

perature to afford **13**. **13** was further reacted with several electrophiles to afford **14** as shown in Scheme II. The addition of TMEDA was beneficial to improve the isolated yields of cyclized products. The stereochemistry of the substituents has not been determined, although 1,3-*cis* isomer was reported to be normally a major product.[9c]

Finally, a vinyl sulfide *vs.* an unactivated alkene competition as an internal electrophile has been studied. Treatment of **15** with *t*-butyllithium (2.2 equiv) in diethyl ether at −78 ℃ for 0.5 h followed by the addition of TMEDA (2.0 equiv) at −78℃ and warming to room temperature afforded the cyclized product **16** (74%) along with the direct protonated product **17** (20%) after trapping with methanol. When the reaction was carried out in tetrahydrofuran under the similar conditions, a mixture of **16** (53%) and **17** (40%) was isolated.

The results obtained in this study clearly demonstrate that a vinyl sulfide group is a much better electrophilic acceptor than an unactivated alkene and allows us to functionalize the cyclized products by the reaction with various electrophiles.

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10. (i) Mg, n-C_3H_7CHO, THF (53%). (ii) Ac_2O, pyridine (88%). (iii) PhSH, BF_3-Et_2O, CH_2Cl_2 (88%). (iv) MCPBA, CH_2Cl_2 (77%). (v) $(MeO)_3P$, DME (80%). (vi) NaOH, aq MeOH (92%). (vii) KH, Bu_3SnCH_2I, THF (47%).

The Complete ^1H NMR Study of Bicyclo[3.1.1] heptane Derivative for its Conformation

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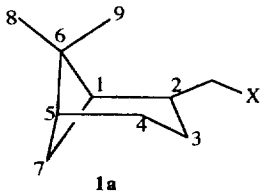
In all the aspects of high-resolution NMR study, resonance assignment is one of the key that unlocks all of the information present in the spectrum. Therefore, the importance of correct assignment can never be overstated. For simple spectra with only a few widely dispersed resonances, assignment is more often than not a trivial exercise, but for narrow chemical shift ranges and extended spin systems, it can be a very severe problem and make even the structure determi-

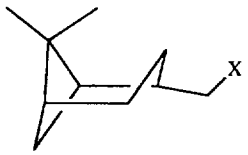
nation of small molecule a worthwhile challenge.

The structure of bicyclic [3.1.1] system is one of the great interest system because of the complexity of spin system and role they play in the stereochemical relationship between dihedral angle and coupling constants.[1] However, this system particularly presents several troublesome spectroscopic problems. The most obvious of these is the problem of spectral overlap which is severe even at 500 MHz NMR. On the other hand, the strong coupling between the spins not only makes the first order spectral analysis invalid but also leads to spreading of NOE enhancements between the protons involved.[2] Another major problem will be the flexibility of three carbon bridge, which means that averaging can occur over different conformations. This could lead to particularly misleading results where the NOE is concerned. Therefore, ^{1}H NMR studies have been used for the highly substituted derivatives under the influence of the chemical shift reagent with partial assignment of coupling constants[3] and many ^{13}C NMR studies have been used as a mean of determining the conformations of bicyclic [3.1.1] derivatives.[4]

It is generally known that bicyclo [3.1.1] heptane derivatives have the two extreme conformations, the bridged boat (**1a**) and the bridged chair (**1b**), depending on the substituent.[4] Thus, the severe interaction between the C-9 atom and C-3 atom in bridged boat conformation is relieved by the favourable quasi-equatorial position of C-2 or C-3 substituent. Therefore, it is clear that the conformation depends mainly on the substituent group, which always tends to take an equatorial position. On the basis of this idea, the ^{13}C chemical shift difference between the carbon 6 and 7 was used to differentiate these two qualitative conformations.[4]



1a



1b

In the course of our study on the revised ^{13}C chemical shift of bicyclic [3.1.1] heptane derivatives (We reported that many carbon assignment was wrong),[5] we became interested in the analysis of proton NMR because the proposed conformation not only be established quantitatively by the use of exact coupling constants between protons involved but also can give additional coupling constants of the dihedral angles larger than about 120°. Although there is a series of Karplus equations for specific types of compounds to date because of the uncertainty in applying the Karplus equation to compounds far from the standard model systems, there is only a few experimental data for dihedral angles larger than about 120°.[6] As a consequence, the predictions of conformation by using the vicinal coupling in the dihedral angles larger than about 120° are not reliable.

In this communication, we present a complete proton analysis of *trans*-myrtanol as one of representative bicyclic [3.1.1] derivatives by the combined use of various 1D-, 2D-NMR techniques, and spectral simulation by NUMARIT program.[7]

Spectra were recorded at 297 K in $CDCl_3$ solution by using Bruker AMX-500 spectrometer operating at 500.13 MHz for proton and 125.76 MHz for carbon. In 1D-spectrum, the accurate determination of chemical shifts and coupling constants was impossible to estimate owing to the complication due to the spectral overlap, the presence of second-order effects, and unresolved long range coupling constants. However, in the benzene and acetone solvents the proton 1 was isolated from the overlapped region, which is responsible for the protons, 4*s*,[8] 5, and 1, which were severely overlapped in $CDCl_3$. Therefore, these spectra served only to determine the coupling constants of the limited protons in order to have an independent confirmation of the correctness of the corresponding values obtained from the $CDCl_3$ solvent. The employed 2D-NMR techniques were COSY and CH-correlation using the pulse sequences provided by Bruker.[9] NOE difference spectra were used to distinguish the 7*a* and 7*s* protons upon saturation of the signal of methyl protons 8. Homodecoupling experiments were also useful to get the partial coupling constants between protons. In 1D-NOESY spectrum obtained by Gausian shape pulse[10] exciting the signal of methyl protons 9 clearly differentiated the proton 4*a* and 4*s*. The protons 1, 4*a*, 4*s*, and 5 were also determined by selective slice spectrum obtained from 2D-CH correlation spectrum with the previously published 2D-INADEQUATE result.[5] With all of these results, spectrum was simulated by means of the nine-spins version of the program NUMARIT, which runs on Bruker X-32 computer. The coupling spin system, which consists of 11 spins, is still too large to be handled by current simulation software. Therefore, the substituted methylene protons were excluded in simulation. However, the final analysis of the spectrum could be done because the other protons, 1, 3*a*, and 3*s*, could give the coupling constants with the proton 2. The experimental and simulated spectra are shown in Figure 1. As can be seen, even at 500 MHz the proton spectrum is heavily overlapped and distorted due to second-order effects. Nevertheless, the agreement between experimental and simulated spectrum is excellent. The chemical shifts and coupling constants are given in Table 1. Although the digital resolution of experimental spectrum was 0.06 Hz, the measurement of exact coupling constants and chemical shifts was difficult owing to the unresolved long range coupling and the presence of second-order effects. Therefore, the final reported coupling constants and chemical shifts were modified by the simulation. All the final assignment in chemical shifts of syn and anti protons, which belong to equatorial or axial protons of cyclohexane depending on position, is generally valid for the relationships, $\delta H_a < \delta H_e$. However, the chemical shift of 4*a*, which is equivalent to equatorial proton, resonates at higher field than that of axial proton 4*s*. This anomaly of chemical shift is very unusual in terms of several reports stating that similar bicyclic systems agree with the general rule observed in six membered rings.[1] It was already noted that application of the Karplus equation to the vicinal coupling constants between protons on a tortuous small cyclobutane ring in bicyclic system gives poor agreement.[3] However, it was shown that the coupling constants between the protons on the rather flexible plane consisting of three carbon bridge in this bicyclic system are applicable for dihedral angle by using Karplus equation.[11] In our case, the experimental vicinal coupling constants are not in good agreement with the calculated coupling constants obtained by MM2 calculations[12] and Karplus equation modified by cyclohexane system,[6,13] as shown

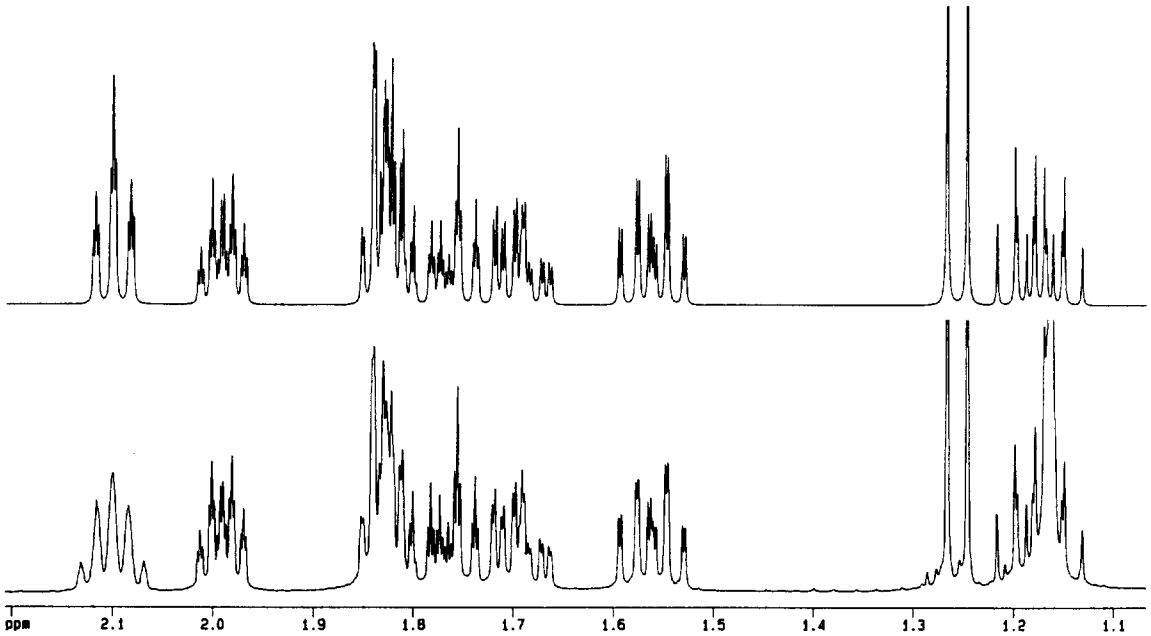


Figure 1. Lower trace: 500.13 MHz ^{1}H NMR spectrum of *t*-myrtanol in $CDCl_3$. Upper trace: Computer simulation of the experimental spectrum. The peak at 1.167 ppm arising from 8 methyl group was not simulated. The multiplet peaks of proton 2 at 2.1 ppm do not have coupling with the AB protons of 10 and 10′ (see text).

Table 1. Experimental ^{1}H chemical shifts (δ, ppm) and ^{1}H-^{1}H coupling constants (Hz) of *t*-myrtanol in $CDCl_3$ solution and calculated coupling constants obtained from MM2 calculation and Karplus equation.[6,13]

Proton	δ	Protons	$J_{exp.}(J_{cal.})^a$	Protons	$J_{exp.}(J_{cal.})^a$
1	1.839	1-2	1.2 (1.4)	4*a*-5	4.5 (2.1)
2	2.100	1-5	5.5	4*s*-5	1.5 (1.0)
3*a*	1.175	1-7*s*	5.8 (4.7)	4*s*-7*s*	1.3
3*s*	1.562	2-3*a*	8.9 (5.3)	4*s*-4*s*	−13.5
4*a*	1.693	2-3*s*	8.6 (4.7)	5-7*s*	5.8 (4.6)
4*s*	1.766	2-7*s*	1.5	7*a*-7*s*	−10.1
5	1.819	2-10	6.5	10-10′	−10.4
7*a*	1.256	2-10′	7.5		
7*s*	1.990	3*a*-4*a*	10.2 (5.5)		
8	1.167	3*a*-4*s*	8.9 (4.5)		
9	0.801	3*a*-3*s*	−14.6		
10	3.365	3*s*-4*a*	1.3 (2.0)		
10′	3.337	3*s*-4*s*	9.0 (5.3)		

[a] Coupling constants corresponding to MM2 steric energy of 45.71 Kcal.

in the Table 1. These results demonstrate that the spectroscopic inferences made for the bicyclic compounds in the previous studies should be reinvestigated.

In summary, this study has shown that the combined use of high-field (500 MHz) NMR with modern pulse techniques and simulation program (NUMARIT) can analyze the bicyclic system completely without any chemical shift reagent. However, the conformation predicted by MM2 calculations did not agree with the conformation calculated from NMR coupling constants and Karplus equation. A full report on the NMR data and discussions of other related derivatives will be published in the future.

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New Synthetic Receptors Containing Two Binding Sites for the Recognition of Amino Esters

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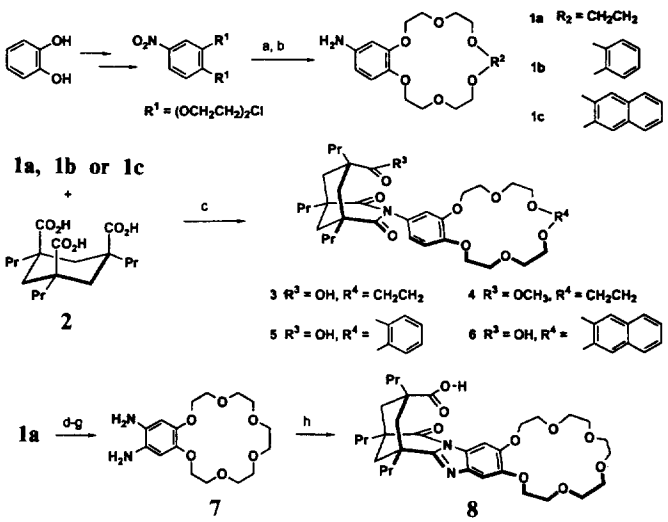
The design and synthesis of a molecule which can imitate a function of biological systems are of great interest in bioorganic chemistry.[1] Selective recognition of the reaction partner through weak non-covalent interactions is crucial to success of a synthetic molecule as an enzyme model. Several artificial receptors have been reported for the recognition of amino acids or their derivatives.[2]

Herein, we report new receptors for amino esters through multiple hydrogen bonds. New receptors are highly rigid and consist of two recognition sites, crown ether and carboxylic acid. The crown ether part is designed for the binding ammonium group,[3] and the carboxylic acid part for binding ester group of amino ester hydrochlorides. Two binding sites are completely separated from each other and thus their conformations are not affected by each other. This is a great advantage of our receptors because the contribution of each part to the binding phenomena can be evaluated by systematic manipulation.

New receptors, **3-6**, were prepared by heating of a well-ground mixture of triacid[4] **2** and amino-benzocrown ethers **1a-c**, among which **1b** and **1c** were prepared from catechol following literature procedures.[5] More rigid amidine receptor **8** was also prepared from triacid **2** and diamino-benzocrown ether **7**, which was synthesized from **1a** as described in Scheme 1.

All of the receptors and their complexes studied are highly soluble in a variety of organic solvents. Three amino esters, Phe-OMe, Tyr-OMe, and Trp-OMe hydrochloride are chosen for binding studies because they are relatively insoluble in CH_2Cl_2 so that extractions into CH_2Cl_2 layer occur mostly by complexation. The binding affinities have been determined by solid-liquid and liquid-liquid extractions. In the solid-liquid extraction experiments,[4] the amount extracted was measured by GC using triethyleneglycol benzyl methyl ether as an internal standard after amino esters extracted were transformed to the corresponding trifluoroacetyl derivatives. The results of solid-liquid extractions are summarized on Table 1.



Scheme 1. (a) catechol, or 2,3-dihydroxylnaphthalene/Cs_2CO_3/DMF, 100℃, 24 h. (b) H_2/Pd-C, 3 h. (c) 180℃/1.5 h, 35-45% isolated yield for three steps (a-c). (d) Ac_2O/CH_2Cl_2-1 M Na_2CO_3 aq. (e) NH_4NO_3-$(CF_3CO)_2O/CHCl_3$. (f) K_2CO_3/MeOH. (g) H_2/Pd-C, 2 days. (h) **2**, 180℃, 1.5 h, 11% isolated yield from **1a**.

Table 1. Solid-Liquid Extractions of Amino Ester Hydrochlorides into CH_2Cl_2 at 23± 1℃.[a]

Receptor	Molar equivalents[b]		
	Phe-OMe	Tyr-OMe	Trp-OMe
blank	0.31	nd[c]	nd[c]
dibenzo-18-C-6	0.41	<0.05	<0.05
3	2.2	0.49	0.73
4	2.2	0.18	0.21
5	2.1	0.37	0.53
6	2.2	0.30	0.43
8	2.0	0.39	0.34

[a] In all cases, 0.5 mL of 15 mM receptor and 10 mg of L-amino ester hydrochloride were used for extraction experiments. [b] All are the average values of two or three extractions and errors are within 10%. [c] not detected.

Solubility depends on the relative strength of solute-solute, solute-solvent, and solute-receptor interactions. As shown in Table 1, Phe-OMe hyrochloride is appreciably soluble in CH_2Cl_2 without any receptor, and thus weak solute-receptor interaction is enough to extract it. Two equivalents of Phe-OMe hydrochloride are roughly extracted by all of our synthetic receptors.

Extraction experiments for Tyr-OMe and Trp-OMe hydrochlorides demonstrate an importance of the basicity of an oxygen in the strength of hydrogen bonds. As an example, monobenzo receptor **3**, having four dialkyl and two alkyl aryl oxygens, is more effective on extractions of Tyr-OMe and Trp-OMe hydrochlorides than both dibenzo receptor **5** and