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The Synthesis and Formation of Complexes between Derivatives of Chiral Aza-18-Crown-6 Ethers and Chiral Primary Organic Ammonium Salts

MEHMET KARAKAPLAN, YILMAZ TURGUT*, TARIK ARAL and HALIL HOŞGÖREN
Department of Chemistry, University of Dicle, 21280, Diyarbakır, Turkey

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Abstract

Chiral mono aza-18-crown-6 derivatives have been prepared in optically active form and high yield from amino alcohols via a cyclization reaction with tetraethylene glycol ditosylate.The enantiomeric recognition by these chiral aza-crown ethers between chiral primary ammonium perchlorate salts has been characterized by UV–Vis at 25 °C in chloroform.

Introduction

Host-guest chiral recognition is important in a variety of physical, chemical and biological process including sensing, purification and resolution of enantiomers, asymmetric catalysis reactions and single enantiomeric forms of amino acids and sugars.[1] Therefore, the design, synthesis, and use of molecules capable of enantiomeric recognition of other molecules are of great interest to workers in these fields. Chiral crown ethers have been extensively developed to provide enhanced structural recognition of alkyl ammonium cations and particularly a number of investigations of enantioselectivity in complexation of chiral alkyl ammonium salts by chiral crown ethers have been reported.[2] Among the numerous types of host molecules studied, chiral-18-crown-6 derivatives have been recognized as the most successful for chiral discrimination and molecular design of new chiral 18-crown-6 and their analog toward chiral primary amine compounds. The recognition of aza-crown ethers [3, 4] and their polycyclic derivatives [5] could for strongly bound and well defined complexes with primary alkyl ammonium salts lead us to investigate chiral aza-18-crown-6 derivatives.

Several aza-crown ethers have been synthesized from amino acid [6] and their enantiomeric recognition properties studied. [2, 7]

The present contribution provides synthesis of new chiral aza-18-crown-6 derivatives ((*R*)-**4**, (*S*)-**5** and (*S*)-**6**) from (*R*)-2-amino-1-butanol, (L)-valinol and (L)-leucinol, respectively. The host-guest interactions of these chiral ligands between chiral primary ammonium salts were characterized. K_a, and $-\Delta G_o$ values for these host-guest interactions are reported in order to investigate the effect of substituent on the stereogenic center and cavity size of these macrocycles.

Results and discussion

In the present study, chiral aza-18-crown-6 ether derivatives (*R*)-**4**, (*S*)-**5**, and (*S*)-**6** were synthesized from precursor (*R*)-1, (*S*)-2, and (*S*)-3 as shown in Scheme 1. Chiral precursors (*R*)-1, (*S*)-2 and (*S*)-3 were synthesized from (*R*)-2-amino-1-butanol, (L)-valinol and (L)-leucinol respectively, by benzylation then followed by ring opening of ethylene oxide as previously reported method [8–10]. Ring closure reaction of (*R*)-1, (*S*)-2, and (*S*)-3) with tetraethlene glycol ditosylate under high dilution conditions gave (*R*)-**4**, (*S*)-**5**, and (*S*)-**6** in high yield. $NaClO_4 \cdot H_2O$(*Caution*! the perchlorate salts must be handled with care as they are potential explosives) was added to macrocyclics in order to obtain the products as a solid (for easier isolation). Then, these macrocycles were recovered as their complex forms by column chromatography on silica jel using triethyl amine / ethylacetate / petroleum ether: 3/17/80 as eluent gave yellow oils in 64%, 56% and 61% yield, respectively. The structures of proposed for these chiral macrocycles are consistent with data obtained from ^{1}H NMR, ^{13}C NMR, IR spectra and elemental analyses. However, (*R*)- and (*S*)- enantiomers of 1-phenylethylammonium percholorate (AM1) and 1-(α-naphtylethyl)ammonium

* Author for correspondence. E-mail: yturgut@dicle.edu.tr

percholorate (AM2) were prepared from 1-phenylethylamine and 1-(α-naphtylethyl)amine by treating with percholoric acid respectively. In our previous studies, [9, 10] we have shown that on the factors governing enantiomeric recognition of chiral organic ammonium salt by chiral aza-15-crown-5 ethers formed complexes of appreciable stability with primary ammonium cations and displayed good chiral recognition toward enantiomers of these guests. Now, we turned to the synthesis of the chiral aza-18-crown-6 ((*R*)-**4**, (*S*)-**5**, and (*S*)-**6**) ethers and their enantiomeric recognition of chiral organic ammonium salts with effect of the substituent at the stereogenic center and cavity size of these macrocycles.

Molecular recognition

The main purpose of synthesizing these receptors is to study their molecular recognition for guest molecules. The molecular recognition can be characterized by various spectroscopic methods, such as ultraviolet visible (UV–vis), NMR, fluorescence and infrared (IR), which are powerful tools used for the examination of the recognition ability of new chiral macro cycles [1, 11, 12].

UV–vis spectroscopy is a convenient and widely used method for the study of binding phenomena [13]. When the receptor (or substrate) absorbs light at different wavelengths in free and complexed states, the differences in the UV–vis spectra may suffice for the estimation of molecular recognition thermodynamics. In UV spectroscopic titration experiments, the addition of varying concentration of guest molecules results in a gradual increase or decrease of characteristic absorptions of the host molecules. The complexation of ammonium cations (G) with chiral aza-crown ether type molecular (H) is expressed by Eq. (1):

$$\mathrm{H} + \mathrm{G} \overset{K}{\rightleftharpoons} \mathrm{H.G} \qquad (1)$$

under the conditions employed, herein, chiral organic ammonium perchlorate salts were selected as the guest molecules. The association constants of the supramolecular systems formed were calculated according to the modified Benesi-Hildebrand equation, Eq. (2), [14] where $[H]_o$ and $[G]_o$ refer to the total concentration of crown ether and organic ammonium salt respectively, $\Delta\varepsilon$ is the change in molar extinction coefficient between the free and complexed crown ether and ΔA denotes the absorption changes of crown ether on the addition of organic ammonium salts.

$$[H]_o[G]_o/\Delta A = 1/K_a\Delta\varepsilon + [G]_o/\Delta\varepsilon \qquad (2)$$

for all guest molecules examined, plots of calculated $[H]_o[G]_o/\Delta A$ values as a function of $[G]_o$ values give a linear relationship and supporting the 1:1 complex formation. The typical UV–vis spectral changes upon the addition of (*S*)-AM1 salt to (*S*)-**5** are shown in Figure 1 while typical plots are shown for the complexation of (*S*)-**5** with (*S*)-AM1 salt in Figure 2.

The binding constant, K_a, of the complexes of the crown ether (*R*)-**4**, (*S*)-**5** and (*S*)-**6** with organic ammonium salts were determined by the Benesi–Hildebrand equation on the basis of the UV–visible spectrum of the complexes in $CHCl_3$ collected at 25 ± 1 °C. Binding constants (K_a) and the Gibbs free energy changes, ($-\Delta G_o$) of these hosts with guest molecules obtained from usual curve fitting analyses ($R > 0.9875$) of observed absorbance changes are summarized in Table 1, along with enantioselectivity K_R/K_S or $\Delta\Delta G_o$ calculated from $-\Delta G_o$ for the complexation of (*R*/*S*)-organic ammonium salts by these hosts.

The determination of *K* values for chiral host-guest interactions provides information about the capability of the chiral hosts to recognize enantiomers of the chiral guest under given sets of conditions. The correlation of the degree of recognition with the structural features of

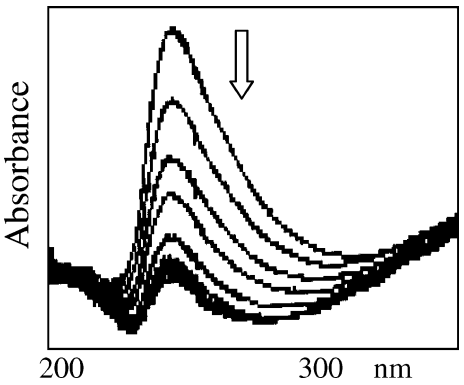
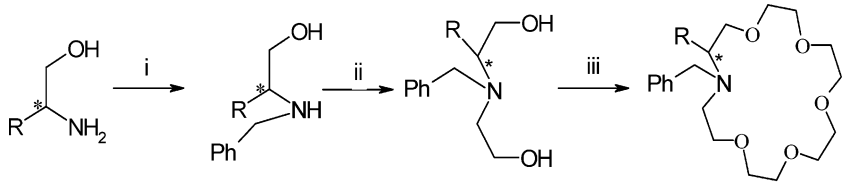


Figure 1. UV–vis spectra of (*S*)-**5** (4.0×10^{-4} mol dm^{-3}) in the presence of (*S*)-AM1 (1.0×10^{-4}–1.4×10^{-3} mol dm^{-3})



R= Ethyl (*R*)-**1** (*R*)-**4**
R= Isopropyl (*S*)-**2** (*S*)-**5**
R= Isobutyl (*S*)-**3** (*S*)-**6**

Scheme 1. Reagent and Conditions, (i): BnCl, K_2CO_3, 110 °C, 24 h., (ii): Ethylene oxide, −20 °C, 24 h, (iii): NaH/THF then tetraethlene glycol ditosylate, reflux, 50 h.

Table 1. Binding constants (K), the Gibbs free energy changes ($-\Delta G_o$), enantioselectivities K_R/K_S or $-\Delta\Delta G_o$ calculated from $-\Delta G_o$ for the including complexation of R/S guest with the chiral hosts in $CHCl_3$ at 25°C

Host	Guest[a]	K (dm^3 mol^{-1})	K_R/K_S	$-\Delta G_o$(kJmol^{-1})	[b]$\Delta\Delta G_o$(kJmol^{-1})
(*R*)-**4**					
	(*R*)-AM1	$(3.8 \pm 0.045) \times 10^3$	0.52	20.30	−1.60
	(*S*)-AM1	$(7.0 \pm 0.045) \times 10^3$		21.90	
	(*R*)-AM2	$(2.5 \pm 0.060) \times 10^3$	0.94	19.40	−0.10
	(*S*)-AM2	$(2.7 \pm 0.033) \times 10^3$		19.50	
(*S*)-**5**					
	(*R*)-AM1	$(2.2 \pm 0.028) \times 10^3$	1.46	19.10	1.00
	(*S*)-AM1	$(1.5 \pm 0.062 \times 10^3$		18.10	
	(*R*)-AM2	$(1.5 \pm 0.045) \times 10^3$	0.60	18.10	−1.30
	(*S*)-AM2	$(2.5 \pm 0.035) \times 10^3$		19.40	
(*S*)-**6**					
	(*R*)-AM1	$(3.3 \pm 0.033) \times 10^4$	2.50	25.80	2.30
	(*S*)-AM1	$(1.3 \pm 0.033) \times 10^4$		23.50	
	(*R*)-AM2	$(1.0 \pm 0.035) \times 10^3$	0.93	17.20	−0.20
	(*S*)-AM2	$(1.1 \pm 0.013) \times 10^3$		17.40	

[a]AM1: α-phenylethylamine perchlorate salts.
AM2: α-(-1-naphthyl) ethylamine perchlorate salts.
[b]$\Delta\Delta G_o = -\Delta G_{o(R)} - \Delta G_{o(S)}$.

the host-guest complexes is essential in understanding the origin of the chiral recognition.

The choice of the 18-membered macrocyclic rings was based on the fact that 18-crown-6 generally forms more stable complexes than other crown ethers of different ring size with primary ammonium cations in solvents. It is well known that 18-crown-6 type ligands form stable complexes with ammonium and primary ammonium cations through a three point (tripod) hydrogen bond interaction.[15] The examples of chiral recognition involving chiral 18-crown-6 ligand and chiral organic ammonium cations have been shown by Izatt and others.[16, 17]

In order to examine the binding constants and enantiomer selective complexation of (*R*)-**4**, (*S*)-**5**, and (*S*)-**6** aza-crown ethers with *R* and *S* enantiomers of AM1 and AM2 salts were selected as guests. The binding constants and enantiomer selectivities of these hosts are summarized in Table 1 which is the ratio of binding constants (K_R/K_S). As it can be seen from Table 1, the binding constants of (*R*)-**4**, (*S*)-**5**, and (*S*)-**6** (1.01×10^3-3.33×10^4) are high as those recently reported data for aza-15-crown-5 ether derivatives [9, 10]. These results indicate that chiral mono aza-18-crown-6 derivatives form stable complexes towards these primary ammonium cations but have a less enantiomeric selectivity than those aza-15-crown-5 ether derivatives. We have also shown that (*R*)-**4**, (*S*)-**5**, and (*S*)-**6** aza-crowns displayed a good chiral recognition toward enantiomers of these guests. The stability constants of (*R*)-**4** with the (*R*) and (*S*) enantiomers of AM1 were found to be 3.80×10^3 and 7.00×10^3,respectively, the (*S*) form, 1.91 times more stable than the (*R*) form of AM1 ($K_R/K_S = 0.52$ or $K_S/K_R = 1.91$). However, (*R*)-**4** showed poor enantiomeric recognition towards AM1 cation, but in favour of the (*S*) instead of the (*R*) form. In the case of (*S*)-**5**, the binding constants of *R* and *S* of AM1 cations were found to be 2.20×10^3 and 1.50×10^3 ($K_R/K_S = 1.46$) respectively. On the other hand, enantiomer selectivity of (*S*)-**5** toward AM2 cation found to be somewhat lower ($K_R/K_S = 0.6$). It has been reported that better enantiomer selectivity were found for AM1 ($K_R/K_S = 3.2$) and AM2 ($K_S/K_R = 3.1$) guest with those reported aza-15-crown-5 ether derivatives which also have isopropyl substituent on stereogenic center.[9] On the other hand, (*S*)-**6** exhibit the highest binding

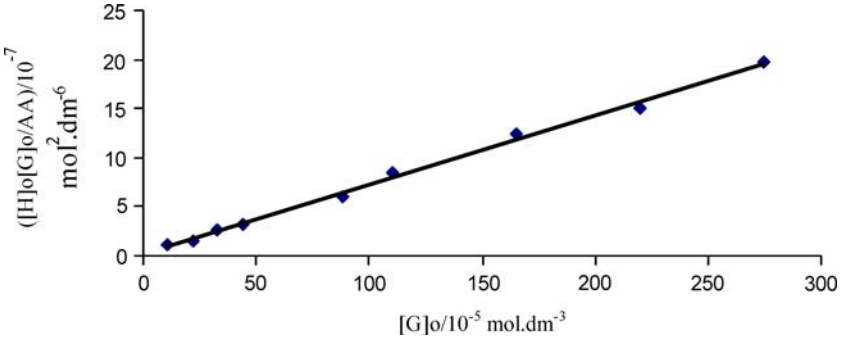


Figure 2. Typical plot of $[H]_o[G]_o/\Delta A$ versus $[G]_o$ for the host-guest complexation of (*S*)-**5** and (*S*)-AM1 in $CHCl_3$.

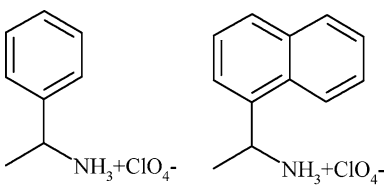
constant and the best enantiomeric selectivity ability toward AM1 isomers that the (*R*)- form of AM1 is 2.50 times more stable than formed with the (*S*)- form. In contrast to the case of AM1, (*S*)-**6** exhibit very poorly enantiomeric selectivity towards AM2 cation ($K_R/K_S = 0.93$). The better selectivity have been found toward AM1 ($K_R/K_S = 4.76$) and AM2 ($K_R/K_S = 1.33$) with that aza-15-crown-5 ether derivative which have also isobutyl substituent. [10] Among the tree ligands, the best enantiomeric selectivity is (*S*)- > (*R*)-AM1 for (*R*)-**4** ($K_S/K_R = 1.91$) (*R*)- > (*S*)-AM1 for (*S*)-**5** ($K_R/K_S = 1.46$) and (*R*)- > (*S*)-AM1 for (*S*-6) ($K_R/K_S = 2.50$). The observed enantiomer discrimination is assumed to be due to a steric repulsion between the substituent may be on the guest and the chiral barrier on the host.

In conclusion, it has been demonstrated that the substituent on the chiral center has a very important effect on the chiral recognition. These results show that the cavity size, steric effect or repulsion and structural (rigidity or flexibility) of host, hydrogen binding, cation–π interaction between host and guest may be the most important factors for the enantioselective recognition of ammonium cations. Since one of the origins for enantiomeric recognition was expected to be the steric repulsion between the substituents at the stereogenic centers and the alkyl group of the ammonium cations [18], it is expected that the extent of enantiomeric recognition could be improved upon due to bulkiness of the substituent at the stereogenic center [1].

Experimental

Materials and methods

All chemicals were reagent grade unless otherwise specified. *R*/*S* α-phenyl ethylamine and [α-(1-naphthyl) ethyl] amine were purchased from Fluka chemical company. Silica gel 60 (Merck, 0.040–0.063 mm) and silica gel / TLC- cards (F254) were used for flash column chromatography and TLC. Melting points were determined by a Gallenkamp Model apparatus with open capillaries. Infrared Spectra were recorded on a Mattson 1000 FTIR model spectrometer. Elemental analyses were performed with a Carlo-Erba 1108 model apparatus. Optical rotations were taken on a Perkin Elmer 341 model polarimeter. ^1H (400 MHz) and ^{13}C (100 MHz) nmr spectra were recorded on a Bruker DPX-400 High Performance Digital FT-NMR Spectrometer.



(*R*-,*S*-)-AM1 (*R*-,*S*-)-AM2

Scheme 2. α-Phenylethylamine (AM1) and α-(-1-naphthyl) ethylamine percholorate (AM2) salts used as the guest.

UV–vis.

The abilities of crown ethers to coordinate to chiral organic ammonium salts were investigated using UV spectroscopic titration.[19] The UV–vis spectra were measured at 25 ± 1 °C with a thermostated cell compartment by Shimadzu 160 uv spectrometer. The same concentrations of guest solution were added to the sample cell and reference cell. The maximum wavelength is 242.8 nm for hosts in $CHCl_3$.The concentrations of the host are 4.0×10^{-4} mol dm^{-3} with the increasing concentration of the added guest.

Job plot

The stoichiometry of the complex between 4, 5, 6 and amine salts were determined by continuous variation plot (Job plot) according to method described in literature. [20] (Figure 3)

Synthesis

Tetraethylene glycol di(p-toluenesulfonate)
p-Toluenesulfonyl chloride (10.47 g, 55.00 mmol) in small portions was added to tetraethylene glycol (4.45 g, 25.0 mmol) in 30 mL of distilled pyridine at −10 °C. The mixture was kept overnight at 4 °C. Then, the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was extracted with 6 N HCl at 0 °C. The combined organic layers were washed with water (2 × 25 mL) and saturated $NaHCO_3$ solution and dried with $CaCl_2$ and the solvent was evaporated. Purification by flash column chromatography (eluent: 2% ethanol/ CH_2Cl_2) yielded 10.59 g (84%) of tetra (ethylene glycol) di(*p*-toluenesulfonate).

(R)-2-Ethyl-N-benzyl-4, 7, 10, 13, 16-pentaoxa-1-azacyclooctadecane (R)-4
To a suspension of NaH (0.887 g, 29.5 mmol, % 80 in mineral oil)in 150 mL dry THF at 0 °C was added a solution of diol (*R*)-1 (1.46 g, 6.55 mmol) in 250 mL of

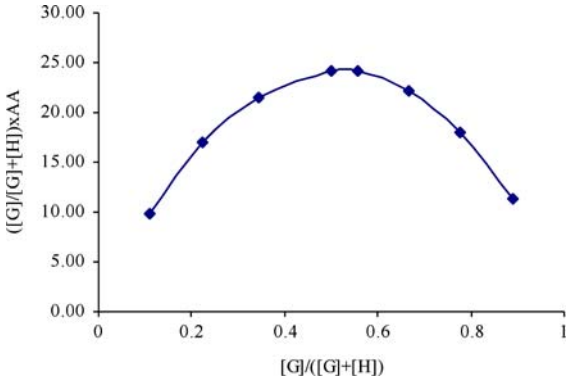


Figure 3. Job plots for (*S*)-AM1 and 5

THF. The reaction mixture was refluxed for 2 h. After cooling to 0 °C, a solution of tetraethlene glycol ditosylate (3.29 g, 6.55 mmol) in 250 mL of THF slowly added. The suspension was refluxed for 50 h. The solvent was evaporated and 150 mL of water were added to the residue. The mixture was extracted with CH_2Cl_2 (3×150 mL). The combined organic layers were washed with 100 mL water again, dried with anhydrous Na_2SO_4 and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel (eluent: triethylamine/ ethyl acetate/ petroleum ether 60–80 = 3/17/80) to give 1.6 g (64%) of an oil;$[\alpha]_D^{20}$ +11 (*c* 1, $CHCl_3$), ir: *v* 3095, 3063, 3031, 1503, 1458, 1355, 1297, 1252, 1124, 990, 951, 939, 707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, $J = 7.4$ Hz, 3H), 1.39–1.51 (m, 2H), 2.76–2.84 (m, 1H), 2.94–2.97 (m, 2H), 3.45–3.77 (m, 22H) 7.22–7.32 (m, 5H) ; ^{13}C NMR ($CDCl_3$) δ 11.89, 21.84, 23.24, 50.37, 55.19, 61.50, 70.28, 70.57, 70.63, 70.67, 70.70, 70.84, 70.92, 70.96, 72.32, 126.50, 128.02, 128.50, 128.73. *Anal*. Calc. for $C_{21}H_{35}NO_5$: C, 66.48; H, 9.54; N, 3.42, Found: C, 66.50; H, 9.50; N, 3.58.

(S)-2-Isopropyl-N-benzyl-4, 7, 10, 13, 16-pentaoxa-1-azacyclooctadecane (S)-5

This compound was prepared as described for (*R*)-**4** by using NaH (1.34 g, 40.3 mmol), (*S*)-2 (2.12 g, 9.96 mmol) and ditosylate (5.00 g, 9.96 mmol). The crude product was isolated by flash column chromatography on silica gel (eluent: triethylamine/ ethyl acetate/ petroleum ether 60-80 = 3/17/80), as an oil 1.98 g (56%); $[\alpha]_D^{20}$ -27.0 (c 1, $CHCl_3$), ir: *v* 3089, 3063, 3031, 1503, 1471, 1452, 1291, 1252, 1124, 990, 951, 855, 732, 701 cm^{-1}; ^1H NMR ($CDCl_3$) (0.90 (d, $J = 6.6$ Hz, 3H), 1.02 (d, $J = 6.6$ Hz, 3H), 1.83–1.87 (m, 1H), 2.18–2.48 (m, 1H), 2.92–2.96 (m, 2H), 3.47–3.76 (m, 22H), 7.21–7.37 (m, 5H) ; ^{13}C NMR ($CDCl_3$) (19.20, 20.18, 29.32, 50.15, 55.38, 60.45, 67.00, 68.77, 69.19, 70.69, 70.85, 71.35, 71.65, 72.80, 72.98, 73.20, 125.92, 127.53, 128.95, 140.50. *Anal*. Calc. for $C_{22}H_{37}NO_5$: C, 66.84; H, 9.36; N, 3.54, Found: C, 66.75; H, 9.40; N, 3.50.

(S)-2-Isobutyl-N-benzyl-4, 7, 10, 13, 16-pentaoxa-1-azacyclooctadecane (S)-6

This compound was prepared as described for (*R*)-**4** by using NaH (1.30 g, 44.8 mmol), (*S*)-3 (2.13 g, 8.98 mmol) and ditosylate (4.51 g, 8.98 mmol). The crude product was isolated by flash column chromatography on silica gel (eluent: triethylamine/ ethyl acetate/ petroleum ether 60–80 = 3/17/80), as an oil 2.5 g (61%); $[\alpha]_D^{20}$ -13.0 (*c* 1, $CHCl_3$), ir: *v* 3089, 3069, 3030, 1602, 1497, 1457, 1358, 1298, 1252, 1183, 1034, 1011, 955 cm^{-1}; ^1H NMR ($CDCl_3$) (0.88 (dd, $J = 6.5$ Hz, 6H), 1.11–1.16 (m, 1H), 1.38–1.45 (m, 1H), 1.78–1.81 (m, 1H), 2.77–2.79 (m, 1H), 2.96–3.03 (m, 2H), 3.43–3.79 (m, 22H), 7.18–7.37 (m, 5H) ; ^{13}C NMR ($CDCl_3$) (21.90, 22.55, 23.60, 31.80, 39.40, 50.25, 54.25, 56.95, 57.23, 70.70, 70.95, 71.00, 71.25, 71.38, 71.50, 72.40, 73.15, 126.98, 128.15, 128.92, 141.48.

Anal. Calc. for $C_{23}H_{39}NO_5$: C, 67.48; H, 9.54; N, 3.42, Found: C, 67.75; H, 9.40; N, 3.50.

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