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Stereospecific Synthesis of *cis*/*trans*-dicarbamates

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Abstract

The efficient synthesis of a new class of allylic *cis/trans-dicarbamates* are described. Allylic diols as key intermediates of the targeted compounds were prepared in a facile way, starting from *p*-benzoquinone. Reaction of allylic diol compounds with *p*-TsNCO resulted in the formation of *cis*/*trans*-dicarbamate groups. The structure of *cis*/*trans*-dicarbamates were determined by ^{1}H-NMR, ^{13}C-NMR, FT-IR and elemental analysis techniques.

Keywords: stereospecific, *bis*-carbamates, *trans*-carbamate, *cis*-carbamate

cis/trans-dikarbamatların Stereospesifik Sentezi

Öz

Yeni bir allilik *cis*/*trans*-dikarbamat sınıfının verimli sentezi açıklanmaktadır. Hedeflenen bileşiklerin anahtar ara maddeleri olarak allilik dioller, *p*-benzokinon'dan başlayarak kolay bir şekilde hazırlandı. Allilik diol bileşiklerinin *p*-TsNCO ile reaksiyonu *cis*/*trans*-dikarbamat gruplarının oluşumuyla sonuçlandı. *cis*/*trans*-Dikarbamatların yapısı ^{1}H-NMR, ^{13}C-NMR, FT-IR ve elemental analiz teknikleriyle aydınlatıldı.

Anahtar Kelimeler: stereospesifik, *bis*-karbamatlar, *trans*-karbamat, *cis*-karbamat

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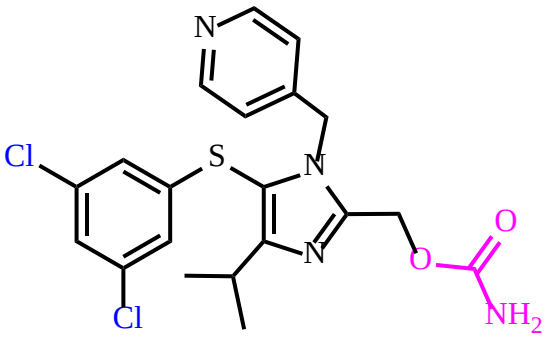
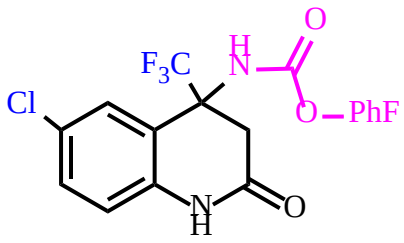
Introduction

Carbamate-bearing molecules play a vital role in modern drug discovery and medicinal chemistry (Ghosh & Brindisi, 2015). Most carbamates in medicinal chemistry are drugs or drug candidates marketed in preclinical or clinical trials (Vacondio et al., 2010). Structurally, carbamate functional groups are directly related to amide ester hybrid functions and show good chemical and proteolytic stabilities as standard. Organic carbamates and isothiocyanates have an outstanding property in organic synthesis and peptide chemistry as optimum protecting groups for amines and amino acids in general (Ghosh & Brindisi, 2015; Gupte et al., 2001; Matošević & Bosak, 2020; Yakan, 2020). Additionally, many of the oxazolidinone-containing cyclic carbamate compounds constitute a new class of synthetic antibiotics with potent activity against a wide range of drug-resistant Gram-positive bacteria (Prasher et al., 2023).

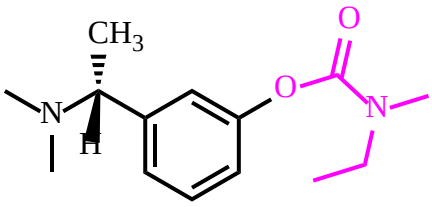
In particular, allylic carbamates have attracted great attention due to their important roles in various fields (Ghrairi et al., 2022; Kelebekli et al. 2012). In fact, it is claimed to belong to the structural or functional part of many approved drugs (Matošević et al., 2020; Dal Corso et al., 2020) and prodrugs (Mattarei et al., 2015) used in the treatment of various diseases such as Alzheimer's disease (Košak et al., 2020), cancer (Huxley et al., 2020), hepatitis C, etc. (Krzywik et al., 2021), HIV infection (Chander et al., 2016), anxiety and epilepsy (Löscher et al., 2021).



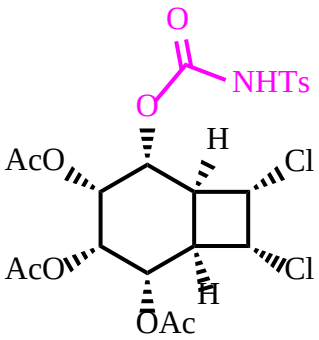
Capravirine 1: anti-HIV



Carbamate 2: Antidiabetic



Rivastigmine 3: Anti-alzheimer



Monocarbamat 4

Figure 1. Selected Compounds Containing Carbamates

The carbamate-yielding reaction of alcohols with isocyanates has been studied by many researchers. On the other hand, isocyanates such as 4-methyl-benzenesulfonyl isocyanate (*p*-TsNCO) and phenyl isocyanate (PhNCO) are frequently used in the preparation of aminocyclitols and are also widely used in the preservation of alcohols (Huang & Yan, 2017; Kelebekli, 2020; Seo & Chung, 2017; Trost & Kalnmals, 2020). In addition, some drugs containing halogen atoms as well as carbamate function are widely reported in the literature (Scattolin et al., 2019), such as capravirine **1** (Li et al., 2012), 1-benzoxazin-4-yl]methyl-(4-fluorophenyl)carbamate **2** (Mizutani et al., 2009) that is antibacterial drug,

Rivastigmine **3** for Alzheimer's disease (Franz et al., 2018), monocarbamate **4** (Kelebekli, 2022) (Figure 1).

Regio- and/or stereoselective reactions are very important in synthetic organic chemistry and therefore vary depending on the type of reagent. For this reason, carbamates attract the attention of pharmacologists as well as chemists.

On the other hand, the development of new methods based on carbamate synthesis will lead to different research in the field of organic synthesis. We considered allylic diol groups for the formation of *cis*/*trans*-carbamates. As a result, we planned to investigate the importance of dicarbamate functional groups due to the effectiveness of pharmaceutical drugs.

Material and Method

Experimental

A capillary melting apparatus (Electrothermal) was used for determination of melting points and are the results are presented without correction. IR spectra were obtained from KBr (solution in 0.1 mm cells) or film with a Shimadzu spectrophotometer. The ^{1}H-NMR, ^{13}C-NMR spectra were recorded on 400 (100) MHz Bruker spectrometer (Avance III) and are reported in δ units with $SiMe_4$ as internal standard. TLC was performed on E. Merck Silica Gel 60 F_{254} plate (0.2 mm). Flash-column chromatography was performed on Merck silica gel (60 mesh). All organic extracts were dried with $MgSO_4$, filtered, and concentrated on a rotary evaporator. The distilled solvents in all synthesis were used. Elemental analyses were carried out on a Carlo Erba 1108 model CHNS-O analyzer.

(1RS,4SR,4aRS,5SR,8RS,8aSR)-/(1RS,4SR,4aRS,5SR,8SR,8aSR)-1,4,4a,5,8,8a-Hexahydro-1,4-ethanonaphthalene-5,8-diol (9)

The title compound was prepared in 90% yield as described in the literature (Ishii et al, 2015; Kelebekli, 2013).

(1RS,4SR,4aRS,5SR,8RS,8aSR)-1,4,4a,5,8,8a-Hexahydro-1,4-ethanonaphthalene-5,8-diyl bis(tosylcarbamate) (10) and (1RS,4SR,4aRS,5SR,8SR,8aSR)-1,4,4a,5,8,8a-Hexahydro-1,4-ethanonaphthalene-5,8-diyl bis(tosylcarbamate) (11)

To a stirred solution of tricyclic *cis/trans*-diol **9** (1.00 g, 5.21 mmol) in anhydrous THF (15 mL) under nitrogen at room temperature was added *p*-toluenesulfonyl isocyanate (*p*-TsNCO) (2.13 g, 10.80 mmol, 1.64 mL) dropwise *via* a syringe. The reaction mixture was stirred at room temperature to give crude *bis*-dicarbamates for 12 h. After removal of the solvent under reduced pressure (50 ^{o}C, 20 mmHg), the reaction mixture was chromatographed on silica gel (60 g) by eluting with 25% ethyl acetate/hexane to afford (1RS,4SR,4aRS,5SR,8RS,8aSR)-1,4,4a,5,8,8a-hexahydro-1,4-ethanonaphthalene-5,8-diyl bis(tosylcarbamate) **10** (2.32 g, 76%) and (1RS,4SR,4aRS,5SR,8SR,8aSR)-1,4,4a,5,8,8a-hexahydro-1,4-ethanonaphthalene-5,8-diyl bis(tosylcarbamate) **11** (0.46 g, 15%).

cis-dicarbamate **10:** White crystals, mp 130-131 ^{o}C (from EtOAc/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.59 (br s, 2H, -NH), 7.88 (d, A part of AA'BB' system, *J* = 8.4 Hz, 4H, aromatic), 7.30 (d, B part of AA'BB' system, *J* = 8.4 Hz, 4H, aromatic), 5.90 (t, *J* = 4.0 Hz, 2H, -CH=CH, H6 and H7), 5.75 (d, *J* = 1.2 Hz, 2H, -CH=CH, H2 and H3), 5.17 (br s, 2H, CH-O), 2.45 (br s, 2H, bridgehead-CH, H4a and H8a), 2.41 (s, 6H, arom-CH_3), 2.31 (br s, 2H, bridgehead-CH, H1 and H4), 1.39 (d, 2H, A part of AB system, *J* = 7.2 Hz, geminal effect-CH_2CH_2), 1.11 (d, 2H, B part of AB system, *J* = 7.2 Hz, geminal effect-CH_2CH_2);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 150.7 (×2, C=O, -CO-NHTs), 145.2 (×2, arom-ipso), 135.8 (×2, arom-ipso), 132.5 (×2, C=C), 130.5 (×2, C=C), 129.9 (×4, aromatic), 128.4 (×4, aromatic), 70.6 (×2, C-O), 41.0 (×2, bridgehead-CH, C4a and C8a), 31.3 (×2, bridgehead-CH, C1 and C4), 26.0 (-CH_2CH_2), 21.9 (×2, tosyl-CH_3); IR ($CHCl_3$, cm^{-1}): 3246, 3052, 2947, 2908, 1744, 1598, 1448, 1348, 1227, 1162, 1090, 892, 871,

758, 738, 664, 548; Anal. Calcd for $C_{28}H_{30}N2O_8S_2$: C, 57.32; H, 5.15; N, 4.78; S, 10.93; Found: C, 56.75; H, 5.77; N, 4.48; S, 11.67 %.

trans-dicarbamate **11:** White crystals, mp 176-177 °C (from EtOAc/hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.02 (Br S, 2H, -NH), 7.92 (d, A part of AA'BB' system, *J* = 8.4 Hz, 4H, aromatic), 7.36 (d, B part of AA'BB' system, *J* = 8.4 Hz, 4H, aromatic), 6.53 (dd, *J* = 9.6, 6.4 Hz, 1H, H6), 6.22 (t, *J* = 7.2 Hz, 1H, H3), 6.10 (dd, *J* = 9.6, 6.4 Hz, 1H, H7), 5.84 (t, *J* = 7.2 Hz, 1H, H2), 5.43 (t, *J* = 6.0 Hz, 1H, H8, -CH-O), 4.42 (ddd, *J* =11.2, 6.0, 5.6 Hz, 1H, H5, -CH-O), 2.75 (d, *J* = 5.2 Hz, 1H, bridgehead-CH, H4), 2.50 (brd, *J* = 4.4 Hz, 1H, bridgehead-CH, H1), 2.45 (s, 6H, arom-CH_3), 2.23 (dd, *J* = 11.2, 5.2 Hz, 1H, bridgehead-CH, H8a), 2.10 (dd, *J* = 11.2, 4.8 Hz, 1H, bridgehead-CH, H4a), 1.51 (m, 2H, -CH_2), 1.26 (m, 2H, -CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 150.5 (×2, C=O, -CO-NHTs), 144.9 (×2, arom-ipso), 139.4 (×2, arom-ipso), 136.3 (×2, C=C), 133.6 (C=C), 131.7 (C=C), 129.7 (×4, aromatic), 128.5 (×4, aromatic), 69.6 (C-O), 65.2 (C-O), 44.3 (bridgehead-C, C4a or C8a), 43.8 (bridgehead-C, C4a or C8a), 33.0 (bridgehead-C, C1 or C4), 32.7 (bridgehead-C, C1 or C4), 26.4 (-CH_2), 26.0 (-CH_2), 21.8 (×2, tosyl-CH_3); IR ($CHCl_3$, cm^{-1}): 3046, 2939, 2868, 1745, 1597, 1464, 1350, 1223, 1210, 1160, 1088, 977, 879, 815, 728, 661, 560; Anal. Calcd for $C_{28}H_{30}N2O_8S_2$: C, 57.32; H, 5.15; N, 4.78; S, 10.93; Found: C, 56.81; H, 5.81; N, 4.42; S, 11.12 %.

Result and Discussion

This study started with the endoselective Diels–Alder cycloaddition of *p*-benzoquinone **5** and 1,3-cyclohexadiene **6**, and the required cycloaddition product **7** was obtained as a single product in 83% yield (Ishii et al., 2015; Kelebekli, 2013) (Figure 2). The structure of the synthesized diketone compound **7** was clearly deduced from their ^{1}H and ^{13}C-NMR spectra the structure of the obtained compound. Reduction reaction is a frequently used method in organic synthesis, and various reducing reagents are defined for the successful conduct of such reactions. $LiAlH_4$ and $NaBH_4$ are widely used among the strongest and mildest reducing agents developed for the reduction of functional groups in synthetic organic chemistry.

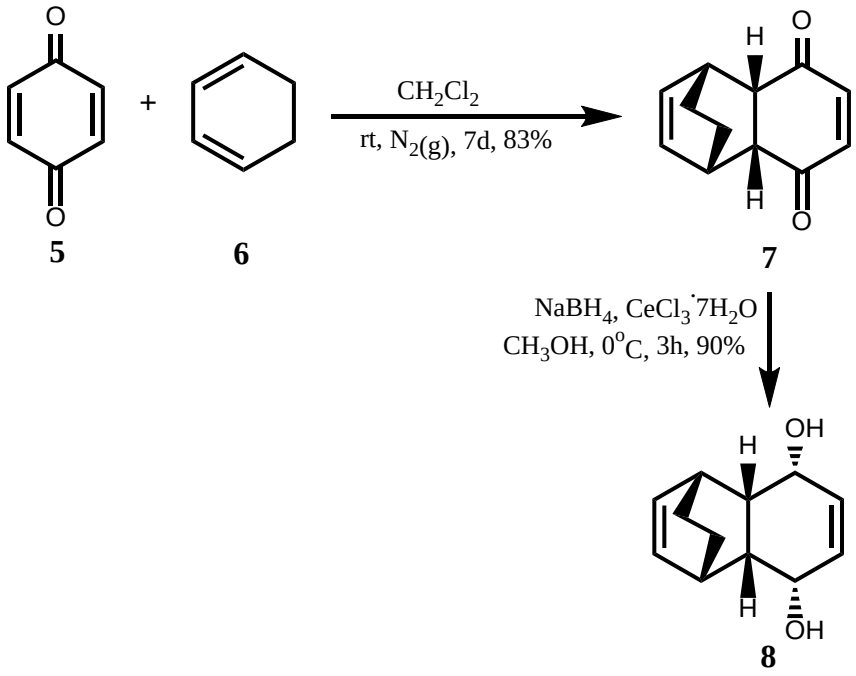


Figure 2. Synthesis of Compound **8**

There are many studies in the literature on the reduction of α,β-unsaturated ketone compounds. The carbonyl groups in these compounds and their derivatives are generally reduced with $NaBH_4$ and/or $NaBH_4$-$CeCl_3 \cdot 7H_2O$ (Kelebekli & Atlı, 2019; Luce, 1978; Marchand et al., 1986). Allylic *cis*-diols are a useful intermediate in organic syntheses.

Therefore, in our previous study, the Luche reduction on **7** ($NaBH_4$-$CeCl_3 \cdot 7H_2O$/MeOH) resulted in the addition of a hydride from the stereoselectively preferred convex face. As expected, *cis* reduction led to compound **8** (Kelebekli & Şahin, 2023) (Figure 2).

Therefore, reduction of α,β-unsaturated ketones functional groups with $NaBH_4$ in a polar solution in the presence of $CeCl_3 \cdot 7H_2O$ yields almost exclusively the allylic alcohol functional groups, sometimes stereoselectively.

In our subsequent study, the same procedure was used and it was observed that two products were formed as a result of the reduction of compound **7** and the protection of the diols formed with TsNCO. It is understood from this that the reduction product represents *cis*/*trans* diols products. Treatment of allylic *cis*/*trans*-diol **9** with 2 equivalents of 4-methyl-benzenesulfonyl isocyanate (*p*-TsNCO) in THF yielded *cis*-dicarbamate **10** and *trans*-dicarbamate **11** in high yield. It was observed that the reaction was completed in 12 hours. The resulting carbamates were purified by chromatography method and gave allylic *cis*-dicarbamate **10** and allylic *trans*-dicarbamate **11** products. The total yield after purification was determined to be 91% from *cis*/*trans*-1,4-diol **9** (Figure 3). Thus, in this study, the protection of *cis*/*trans*-diol with *p*-TsNCO was successfully achieved. The structures of *cis*-dicarbamate **10** and *trans*-dicarbamate **11** were established on the basis of ^{1}H-NMR, ^{13}C-NMR data and for further structural evidence IR and HRMS data were also used. To our knowledge so far, we have not encountered *trans* diol formation from the reduction of diketone **7**. Therefore, the formation of *trans* diol was an interesting approach in this system.

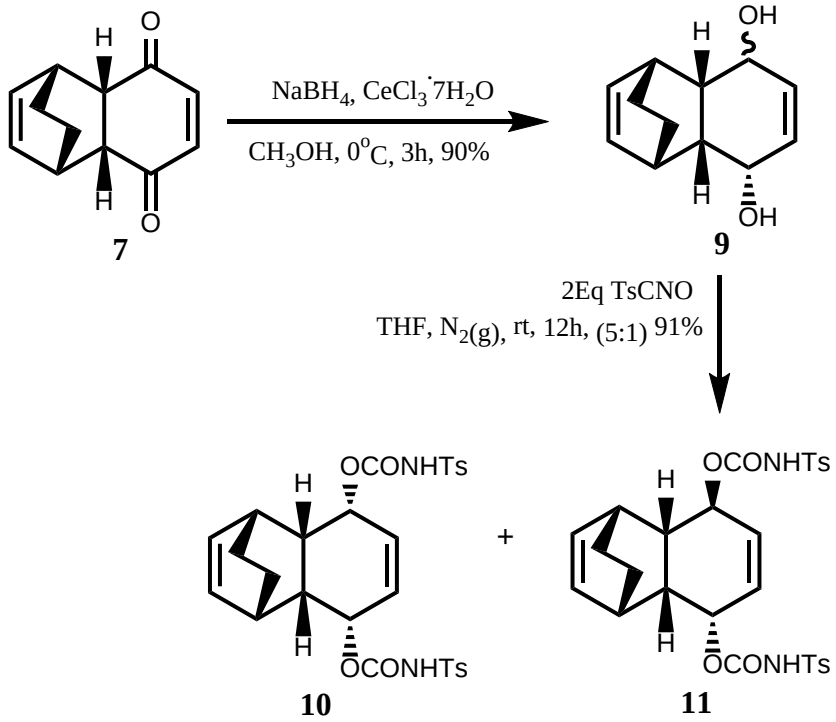


Figure 3. Synthesis of Allylic *cis*-/*trans*-dicarbamates **10** and **11**

The relative configuration of *cis*-dicarbamate **10** is clearly deduced from the evaluation of ^{1}H and ^{13}C-NMR spectra (Figure 4). On the other hand, the configuration of symmetric *cis*-dicarbamate **10** was elucidated spectroscopically. The protons that are most helpful in the configuration analysis of the symmetric structure are bridgehead H4a and H8a. The bridgehead H4a and H8a resonated at 2.45 ppm as a broad singlet. On the other hand, H6 and H7 resonated with H5 or H8 at 5.90 ppm ($J_{6,5}$ or $J_{7,8}$=4.0 Hz) as a triplet. Due to the allylic interaction, it is possible to see the same coupling constant for H6 (H7) bonded to the double bond carbon C6 (C7) at 5.90 ppm (J = 4.0 Hz). Likewise, the double bond protons H2 or H3 resonated at 5.75 ppm (J=1.2 Hz) as a doublet. Moreover, the bridgehead H1 and H4 resonated at 2.31 ppm as a broad singlet. As a result of these findings, it is obvious that there is a cis relationship between the configurations of the two carbamate groups (-OCONHTs) and that the molecule also has symmetry.

On the other hand, the 12-line ^{13}C-NMR spectrum clearly revealed the existence of a symmetric structure. In the ^{13}C-NMR spectrum of *cis*-dicarbamate **10**, the typical signals of the carbonyl carbon and carbon to which the tosyl group (-C-O) is attached of the *cis*-dicarbamates appeared at 150.2 ppm, at 70.6 ppm, respectively (Figure 4). In light of this information, these results fully support the proposed structure.

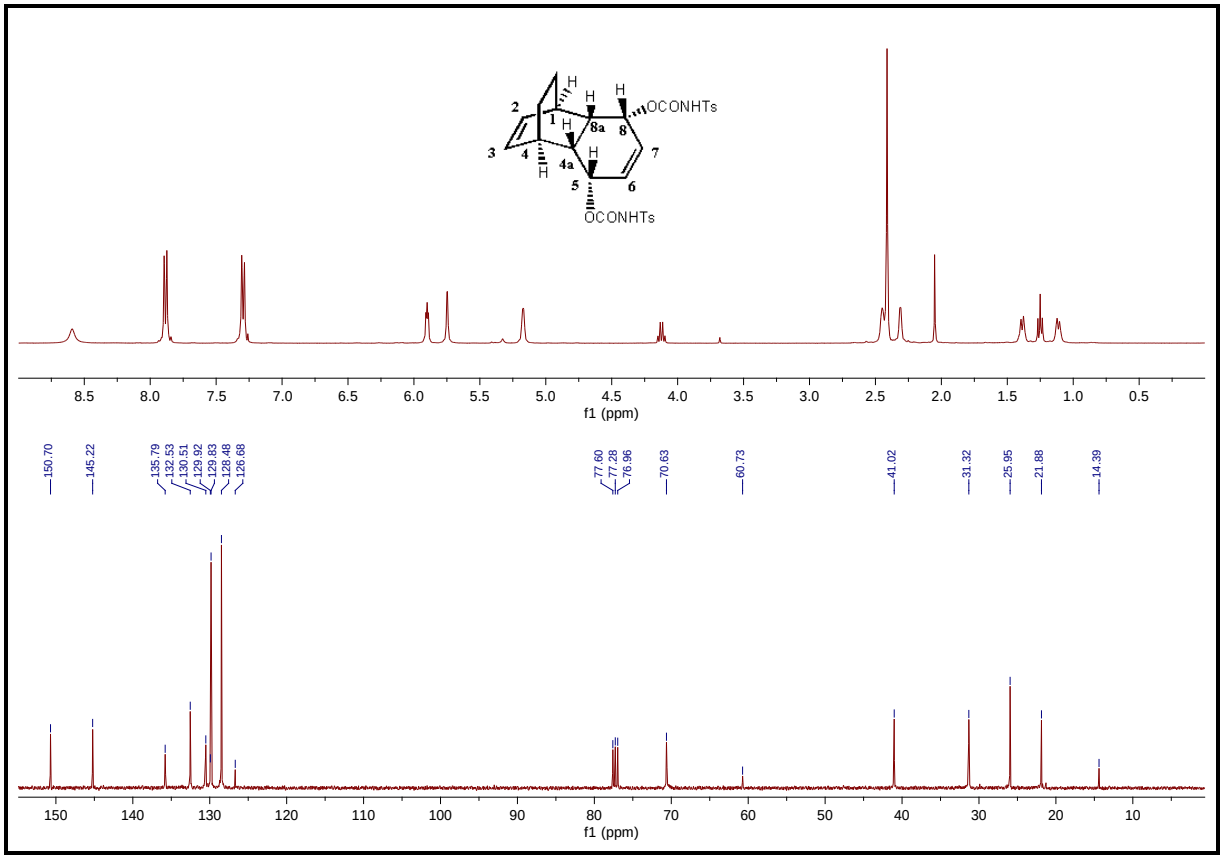


Figure 4. 400 Mhz ^{1}H-NMR and 100 Mhz ^{13}C-NMR Spectra of *cis*-Dicarbamate **10**

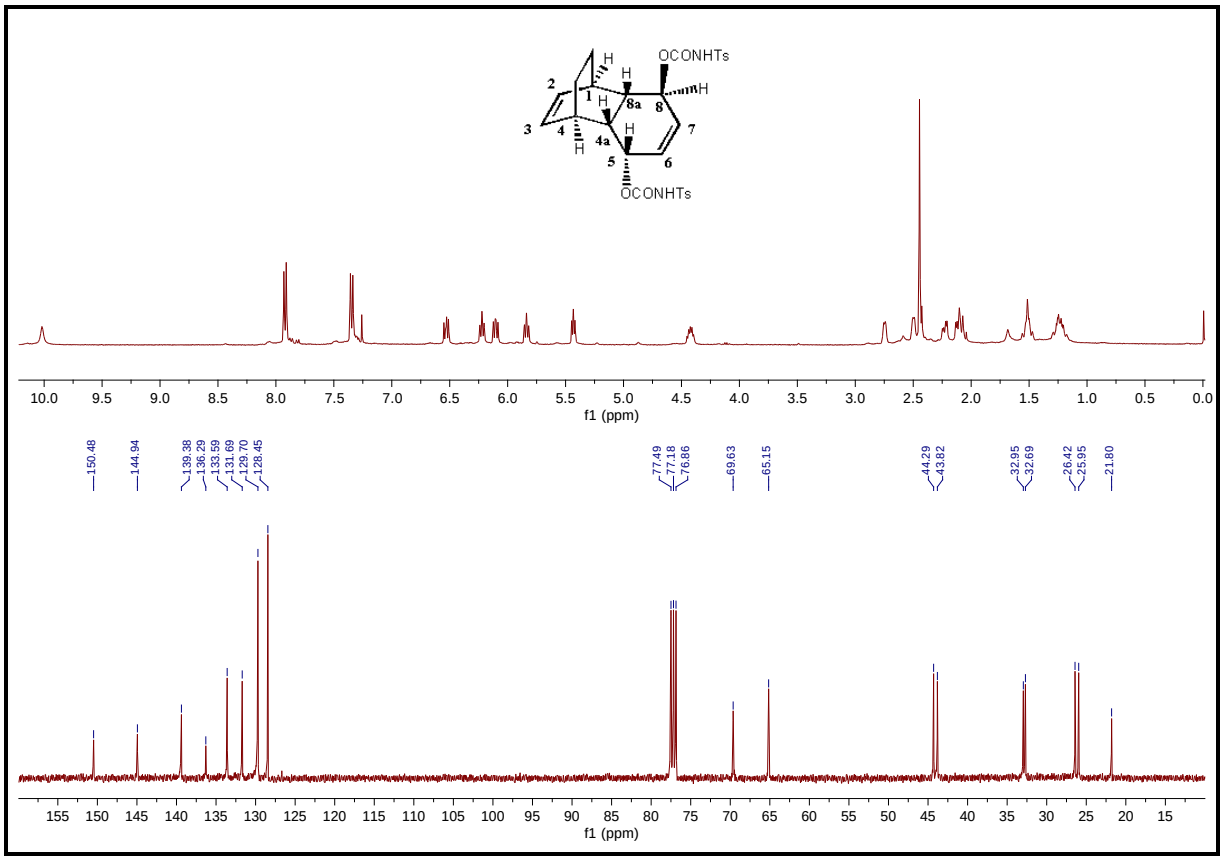


Figure 5. 400 MHz ^{1}H-NMR and 100 MHz ^{13}C-NMR Spectra of trans-dicarbamate **11**

The relative configuration of *trans*-dicarbamate **11** was unambiguously deduced from their ^{1}H and ^{13}C-NMR spectra (Figure 5). The ^{1}H-NMR spectrum of compound **11** provided important information about the structure of the molecule. The most important thing that distinguishes the configuration of compound **11** from the configuration of the symmetric compound **10** is based on the binding of protons in the *trans*-position attached to C5 and C8 in compound **11**. All protons in the compound resonated separately, which is clear evidence that this compound is not symmetrical. In particular, according to these data, it can be explained that there is a *trans* relationship between the two -OCONHTs and as a result, the molecule does not have symmetry. In particular, the ^{13}C-NMR spectrum provided more detailed information in elucidating this molecule. Thus, the 16-line ^{13}C-NMR spectrum clearly shows that the molecule has an asymmetric structure. In the ^{13}C-NMR spectrum of *trans*-dicarbamate **11**, the typical peak of the carbonyl carbon of the dicarbamates appeared at 150.2 ppm (in $CDCl_3$). In the ^{13}C-NMR spectrum of **11**, in particular, two aliphatic carbons (-CH-O) were observed at 69.6 and 65.2 ppm, respectively. On the other hand, two bridgehead carbons C4a and C8a were observed at 44.3 and 43.8 ppm, respectively. In light of this information, these results fully support the proposed *trans* structure.

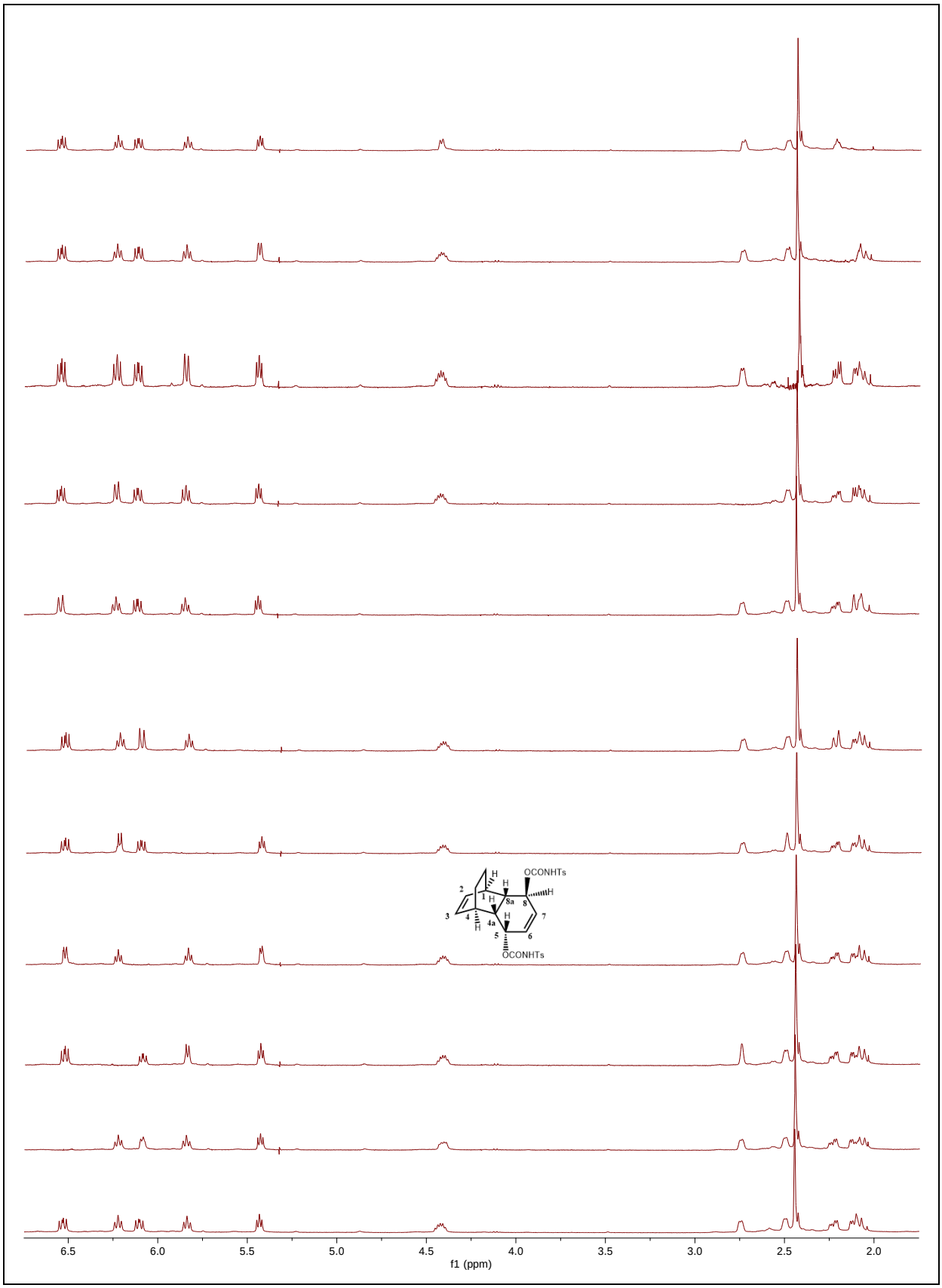
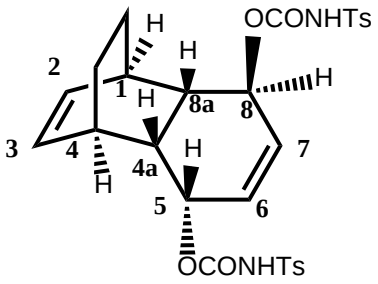


Figure 6. The ^{1}H-NMR Irradiation Spectrum of *trans*-dicarbamate **11** ($CDCl_3$, 400 MHz, ppm)



11

Figure 7. ^{1}H-NMR Spectrum of trans-carbamate **11**

In the ^{1}H-NMR spectrum of *trans*-carbamate **11** (Figure 6), when H-3 at 6.22 ppm was irradiated, the H-2 signal at 5.84 ppm caused the change from triplet to a doublet. At the same time, it is clearly seen that the bridgehead H-4 signal at 2.75 ppm changes from doublet to broad singlet. The irradiation of bridgehead H-4 at 2.75 ppm caused the signal of H-3 at 6.22 ppm changing from a triplet to a doublet and at the same time, the signal of H-4a at 2.75 ppm changing. Thus, it can be stated that it is clearly seen that H-3 with H-2 and H-4a with H-4 are protons adjacent to each other. Irradiation of H-5 at d 4.42 ppm (-CHO) caused the H-6 signal at 6.53 ppm to change from a doublet of doublets into clearly doublet. At the same time, the resonance signal of the bridgehead proton H-4a at 2.75 ppm clearly changes from a doublet of doublets into a broad doublet. Thus, it has vicinal bond with H-5, H-6 and bridgehead H-4a. Upon irradiation at the resonance signal of H-8 at 5.43 ppm, as the signal of H-7 at 6.53 ppm changing from a doublet of doublets into a doublet, at the same time the resonance signal of bridgehead H-8a at 3.35 ppm also changing from a doublet of doublets into clearly doublet. Thus, H-7 and H-8a with H-8 are the neighboring protons with each other. In irradiation of H-8a at 3.35 ppm resulted in the signal of H-8 at 5.43 ppm changing from a triplet to a doublet, in addition, it led to signal enhancement of the resonances at H-4a. These results show us that they also provide evidence that H-8 and H-4a are protons adjacent to H-8a. We thus easily described the relative stereochemistry of all protons in *trans*-carbamate **11** by taking into account the coupling constants.

Conclusion

In conclusion, a novel of *cis*/*trans*-dicarbamates has been synthesized reasonably in good yields. Since carbamates are intermediate products of oxazolidones, the synthesis of dicarbamates, especially those with a *trans* structure, will become more important in the future. It may also enable expansion of oxazolidinone synthesis for various purposes and provide an alternative possibility in this regard.

Ethics

There are no ethical issues related to the publication of this article.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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