

Synthesis of chiral bicyclo[3.3.1]nonane derivative as ionic liquid and using it for asymmetric Michael's addition reaction

Alicija Bilinska,

Albinas Žilinskas*

*Organic Chemistry Department,
Faculty of Chemistry,
Vilnius University,
Naugarduko 24,
LT-03225 Vilnius,
Lithuania*

In this study a chiral bicyclo[3.3.1]nonane derivative as an ionic liquid was synthesized starting from (+)-(1*S*,5*S*)-bicyclo[3.3.1]nonane-2,6-dione (**1a**). Resulting compound (+)-(1*S*,2*R*,5*S*,6*R*)-2,6-di{[(*N*-methylimidazol-3-ium-3-yl)acetyl]oxy}bicyclo[3.3.1]nonane di(tetrafluoroborate) (**4**) was used as a chiral catalyst for the asymmetric Michael's addition reaction of 1,3-diphenyl-2-propen-1-one (chalcone **5**) with diethyl malonate. In that case (+)-(S)-diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate (**7**) was obtained. Optical purity of purposive compound **7** was 57%, the enantiomeric excess calculated according to spectral data (¹H NMR) *ee* = 35%. This difference can be explained by the Horeau effect.

Key words: bicyclo[3.3.1]nonane, chiral ionic liquid, imidazolium cation, asymmetric Michael's addition reaction

Abbreviations: CIL – chiral ionic liquids, DCC – dicyclohexylcarbodiimide, DMAP – *N*-dimethylaminopyridine, Eu(TFC)₃ – Europium (III) tris[3-(trifluoromethylhydroxymethylene)-(+)–camphorate]

INTRODUCTION

Asymmetric induction is one of the widely developing areas of the organic chemistry [1]. It is based on the use of chiral substrates or reagents [2]. Chiral ionic liquids (CIL) are not well examined and the interest in them is gradually growing. Structurally, ionic liquids may include chiral fragments and for this reason they may induce the appropriate changes during reactions of polychiral compounds [3]. Accordingly, they are more often used in asymmetric synthesis [4]. Specific features of chiral ionic liquids allow enantioselective reactions [5]. During the asymmetric reaction ionic liquids can func-

tion as a chiral catalyst; the reaction is induced without any additional chiral supplements [6]. It has also been noticed that if an imidazole (heterocyclic base) fragment is induced into the structure of an ionic liquid, solubility and thermostability of the compound is being enlarged [7]. According to the data which has already been announced, we decided to synthesize an ionic liquid with a chiral centre and to use it in asymmetric synthesis.

RESULTS AND DISCUSSION

Bicyclo[3.3.1]nonane-2,6-dione **1** has been chosen as a parent compound (compound **1** has been synthesized according to [8] (Fig. 1)).

* Corresponding author. E-mail: albinas.zilinskas@chf.vu.lt

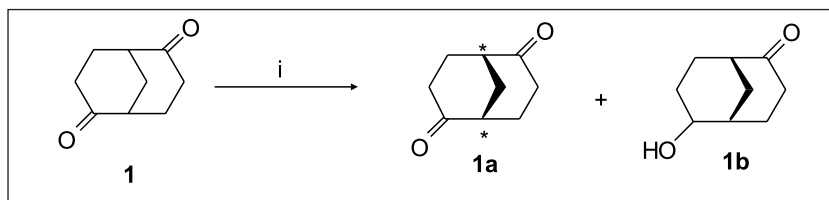


Fig. 1. Synthesis of (+)-(1*S*,5*S*)-bicyclo[3.3.1]nonane-2,6-dione (**1a**). Reagents and conditions; (i) D-glucose, baker's yeast, H₂O, +35 °C, 24 h

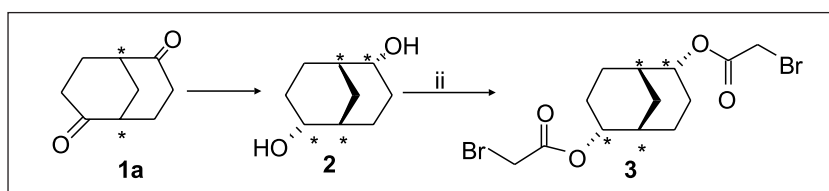


Fig. 2. Synthesis of (+)-(1*S*,2*R*,5*S*,6*R*)-2,6-di[(bromoacetyl)oxy]bicyclo[3.3.1]nonane (**3**). Reduction of diketone **1a** with NaBH₄ in abs. methanol. Reaction of (+)-(1*S*,2*R*,5*S*,6*R*)-bicyclo[3.3.1]nonane-2,6-diol (**2**) with monobromoacetic acid to form product **3**. Reagents and conditions; (ii) BrCH₂COOH, DCC, DMAP, 0 °C, 2 h

In this way we have obtained (+)-(1*S*,5*S*)-bicyclo[3.3.1]nonane-2,6-dione (**1a**) with a specific light polarization rotation angle $[\alpha]_D^{25} = +171^\circ$ (c 1.5, EtOH), (lit. data +176°).

The compound **1a** was used in other chiral ionic liquid synthesis stages [9] (Fig. 2).

We synthesized compound **3** according to the chosen CIL synthesis scheme. Firstly, we got diol **2** (determined $[\alpha]_D^{25} = +49^\circ$ (c 1.9, EtOH; lit. data. +55°)). The product was reacted with monobromoacetic acid (DCC/DMAP in dichloromethane). We got compound **3** ($[\alpha]_D^{25} = +19.6^\circ$) which was reacted with *N*-methylimidazole. After the ion exchange reaction we obtained (+)-(1*S*,2*R*,5*S*,6*R*)-2,6-di{[(*N*-methylimidazol-3-ium-

3-yl]acetyl}oxy}bicyclo[3.3.1]nonane di(tetrafluoroborate) (**4**) ($[\alpha]_D^{25} = +9.0^\circ$; c 2.0, in EtOH) (Fig. 3).

The ionic liquid **4** was used in further asymmetric synthesis.

There is an interesting case of the catalysis when asymmetric synthesis is being induced by simple chiral ionic liquids having two imidazolium cations. In literature this case is shown in the asymmetric Michael's addition reaction [10]. According to the literature sources, we have chosen the reaction which was being made with the use of the chiral catalyst of the similar structure and we got satisfactory exposures and enantiomeric excess (Fig. 4).

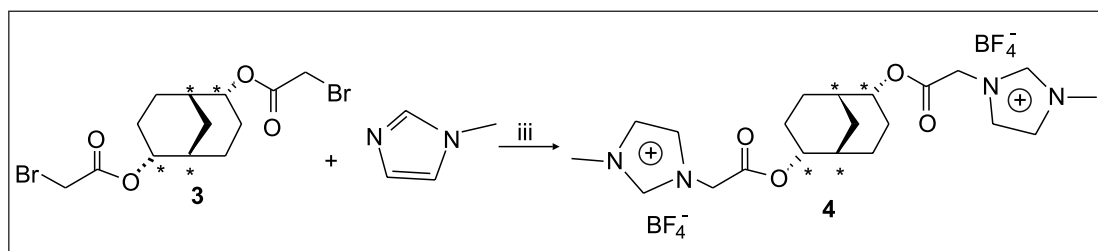


Fig. 3. Synthesis of (+)-(1*S*,2*R*,5*S*,6*R*)-2,6-di{[(*N*-methylimidazol-3-ium-3-yl)acetyl]oxy}bicyclo[3.3.1]nonane di(tetrafluoroborate) (**4**). Reaction of compound **3** with *N*-methyl-imidazole to form product **4**. Reagents and conditions; (iii) +150 °C, 12 hrs; then H₂O, KBF₄, rt, 1 h

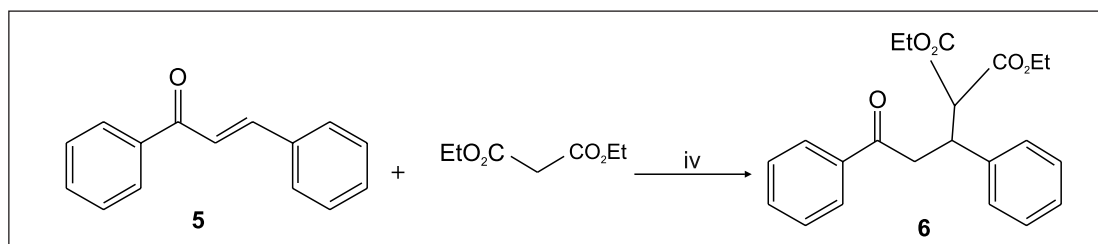


Fig. 4. Synthesis of diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate (**6**). Reaction of 1,3-diphenyl-2-propen-1-one (**5**) with diethyl malonate. Reagents and conditions; (iv) K₂CO₃, catalyst **4**, rt, 12 h

The reaction was made by stirring at room temperature a mixture of chalcone (1,3-diphenyl-2-propen-1-one) **5** with diethyl malonate and adding K_2CO_3 . After 12 hours we got product **6**. During this reaction a synthesized chiral catalyst **4** (amount – 15%) was being added. The thin-layer chromatography indicated the completed reaction and the resulting optical active diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate (**6**) was separated successfully from the catalyst using the flash chromatography with ethyl acetate. The structure was proved by the analysis of 1H -NMR, ^{13}C -NMR and IR spectrums [11]. Rotation angle measurements were done. $CHCl_3$ was chosen as a solvent (in order to compare with the data indicated in the references [12]). The indicated rotation angle showed the following results: $[\alpha]_D^{25} = +13^\circ$ (lit. data $+23^\circ$) and optical purity was about 57% according to the calculations by the rotation angle:

$$\text{Optical purity} = \left(\frac{\alpha_{\text{observed}}}{\alpha_{\text{pure enantiomer}}} \right) \times 100\% = \\ = (13/23) \times 100\% = 57\%.$$

After analysing the results and comparing them to those indicated in the references [12], we found out that *S*-configuration enantiomer **7** was in excess unambiguous (Fig. 5).

The ideal equivalence between the optical purity and enantiomeric excess (*ee*) does not always hold. It is known as the Horeau effect [13], i. e. the relationship between the mole based *ee* and the optical rotation based *ee* (optical purity) can be non-linear. It depends on different effects, for example, dimerization of chiral compounds, virtue of the forming *meso* diastereomer, which allows for removal of racemic material, etc.

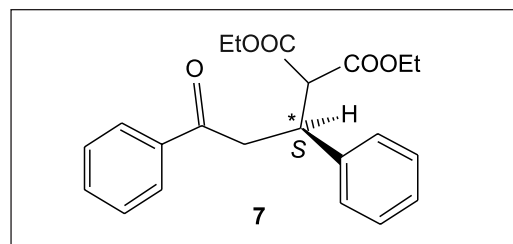


Fig. 5. (+)-(S)-diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate (**7**)

In that case we also calculated the enantiomeric excess according to 1H -NMR spectral analysis. Firstly, the spectrum of optical active compound **6** was written, then a small amount (about 15% mol) of chiral shift reagent $Eu(TFC)_3$ was added.

The very first test showed noticeable changes. The momentum can be seen which showed us interfering hydrogen atoms and helped to calculate the enantiomeric excess.

Below there are the parts of spectrums where the received spectral data can be compared. Fig. 6 shows the protons spectrum of compound **6** and Fig. 7 shows it after adding 15% mol of $Eu(TFC)_3$.

In Fig. 6 we see the signals of protons at the chiral centre together (3.65–3.75 ppm, multiplet). After addition of $Eu(TFC)_3$ those signals of *R* and *S* enantiomers are separated, i. e. the signal of *S* enantiomers' proton is at 3.98 ppm (quartet, $J = 7$ Hz), the signal of *R* enantiomers' proton is at 3.87 ppm (doublet, $J = 7$ Hz). Integrals of the signals give quantities of *R* and *S* enantiomers, i. e. the mole ratio is 1.31/0.63 (Fig. 7).

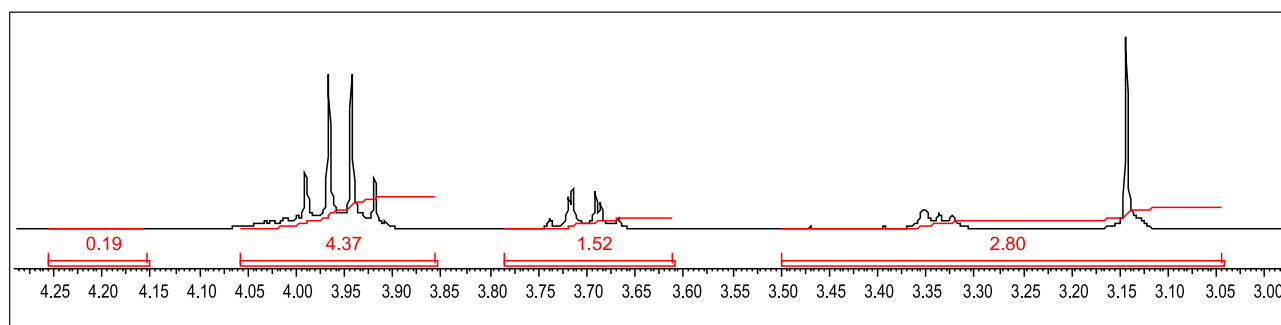


Fig. 6. Part of the ordinary 1H NMR spectrum of optical active diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate (**6**) in $CDCl_3$

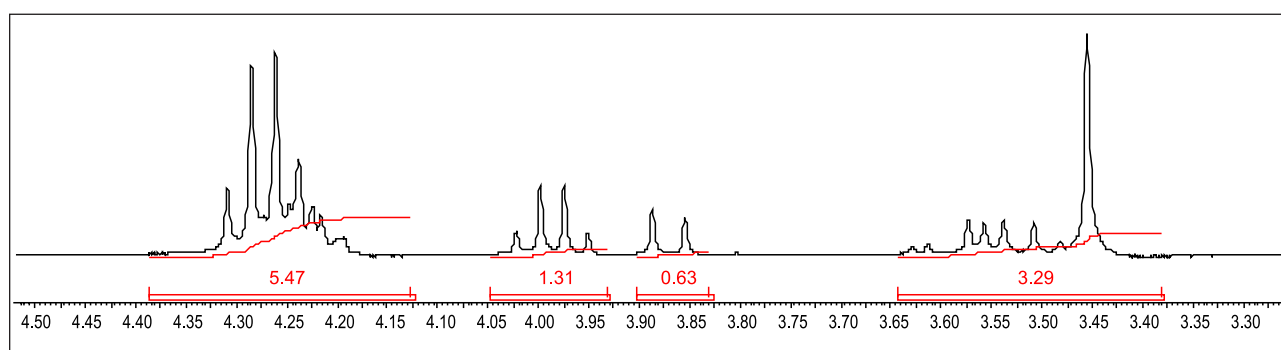


Fig. 7. Part of the 1H NMR spectrum of optical active diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate (**6**) after adding 15% mol of $Eu(TFC)_3$

Calculation of the enantiomeric excess was made according to the formula:

$$ee = [(R-S) / (R+S)] \times 100\% = \\ = [(1.31-0.63) / (1.31 + 0.65)] \times 100\% = 35\%.$$

It was proved that our catalyst 4 induced the given reaction, but *ee* was only 35%, so the Horeau effect has the evidence.

EXPERIMENTAL

Spectra ^1H and ^{13}C NMR were written with a Varian Unity Inova 300 MHz spectrometer by using residual solvent (CDCl_3) signals. Chemical shifts are given in the scale m. d. In descriptions of the spectra ^1H NMR the following abbreviations are used: s – singlet, d – doublet, dd – doublet duplicate, t – triplet and m – multiplet.

IR spectra were registered with a Perkin-Elmer Spectrum BX II spectrometer (nujol or KBr pellets). Melting points were determined with a Gallencamp melting apparatus in capillary tubes and are not corrected. Optical rotations were measured in a 10 cm cell on a polarimeter Polamat-A (Carl Zeiss) at 546 nm.

(+)-(1*S*,5*S*)-bicyclo[3.3.1]nonane-2,6-dione (1a)

82 g of D-glucose was dissolved in 450 ml of water in a 2.0 l round-bottomed flask, 35 g of baker's yeast were poured into the mixture, then 10 g (66 mmol) of bicyclo[3.3.1]nonane-2,6-dione (1) were added. The resulting mixture was heated and stirred at temperature $\sim +35^\circ\text{C}$ for 24 hours. The reaction mixture was filtered through the Celite filter which was washed with 100 ml of brine and diketone 1a was extracted from the final water solution with CHCl_3 (5 \times 50 ml). The solvent was evaporated and the product was purified by the flash chromatography (silicagel, EtOAc/petroleum ether = 1 : 2). Yield – 4.0 g (40% from starting racemic diketone 1). $[\alpha]_{\text{D}}^{25} = +171^\circ$ (c 1.5, EtOH); (lit. data $+176^\circ$), *ee* > 97%.

(+)-(1*S*,2*R*,5*S*,6*R*)-bicyclo[3.3.1]nonane-2,6-diol (2)

1.5 g (1 mmol) of diketone 1a were put into a round-bottomed flask (100 ml) and 50 ml abs. methanol were added. The mixture was stirred and cooled in an ice-bath till 0°C temperature and 1.0 g (3 mmol) NaBH_4 was added portions-wise. The reaction mixture was stirred for another one hour at 0°C . Methanol was evaporated and the product was extracted with EtOAc using a Soxhlet extraction apparatus. Finally, diol 2 was purified by the flash chromatography (silicagel, EtOAc). After evaporation of EtOAc 1.8 g of product was recovered (yield – 90%). Melting point 77°C (lit. data 78°C). $[\alpha]_{\text{D}}^{25} = +49^\circ$ (c 1.9, EtOH), (lit. data $+55^\circ$).

(+)-(1*S*,2*R*,5*S*,6*R*)-2,6-di[(bromoacetyl)oxy]bicyclo[3.3.1]nonane (3)

0.6 g (1 mmol) of diol 2 was put into a round-bottomed flask. The substance was dissolved in dry dichloromethane

(50 ml). The mixture was cooled off to 0°C . Then 0.75 g DCC, 0.375 g DMAP and 0.8 g (5 mmol) monobromoacetic acid were added to the mixture which was cooled and stirred for about 2 hours. The given mixture was filtered and the filter was washed with 10 ml of water and 10 ml of CH_2Cl_2 . The organic layer was separated and dried over the anhydrous Na_2SO_4 , then filtered and dichloromethane was evaporated. The rest part was crystallized from ethanol. The amount of the given product was 1.2 g (yield – 15%).

Melting point $82-84^\circ\text{C}$.

IR (KBr) cm^{-1} : 3428.5, 2928.5, 1706.13 (C=O), 1275.3.

^1H NMR (CDCl_3) ppm: 5.10 (m, 2H), 4.10 (m, 4H), 2.10 (t, 4H), 1.84 (m, 4H), 1.63 (m, 3H), 1.61 (m, 2H).

^{13}C NMR (CDCl_3) ppm: 166.9, 76.8, 41.4, 32.1, 30.5, 27.4, 23.4.

Elemental analysis ($\text{C}_{13}\text{H}_{16}\text{O}_4\text{Br}_2$) %: calculated: C – 39.22; H – 4.56; found: C – 37.22; H – 4.58. Compound 3: $[\alpha]_{\text{D}}^{25} = +19.6^\circ$ (c 1.8, EtOH).

(+)-(1*S*,2*R*,5*S*,6*R*)-2,6-di{[(*N*-methylimidazol-3-ium-3-yl)acetyl]oxy}bicyclo[3.3.1]nonane di(tetrafluoroborate) (4)

100 mg (0.5 mmol) of compound 3 and 168 mg (1 mmol) of *N*-methylimidazole were melted in a round-bottomed flask. The mixture was heated and stirred overnight at the constant temperature of 150°C . Then 50 mg of water were poured into the mixture, 50 mg of KBF_4 were added and everything was continued to stir for an hour. After the reaction, the water was reduced and a few ml of dichloromethane were poured into the mixture. After the residue melted, the product was filtered through the Celite filter and the filtrate was dried over the anhydrous Na_2SO_4 . The mixture was filtered, the solvent was evaporated and the residue was dried in vacuum at 80°C . The amount of the given product was 98.0 mg (yield – 72%).

Melting point $25-26^\circ\text{C}$.

^1H NMR (CDCl_3) ppm: 7.48 (s, 2H), 7.01 (s, 2H), 6.87 (s, 2H), 3.97 (m, 4H), 3.66 (s, 6H), 2.86 (m, 2H), 1.91 (m, 4H), 1.83 (m, 4H), 1.7 (m, 2H), 1.22 (m, 4H).

^{13}C NMR (CDCl_3) ppm: 160.8, 137.9, 129.1, 120.5, 47.2, 34.1, 33.6, 33.1, 25.6, 25.1, 24.9.

IR (KBr) cm^{-1} : 1706 (C=O), 1275 (C-O).

Elemental analysis ($\text{C}_{21}\text{H}_{30}\text{O}_4\text{N}_4 \cdot 2\text{BF}_4$) %: calculated: C – 43.78; H – 5.25; found: C – 43.39; H – 5.70. $[\alpha]_{\text{D}}^{25} = +9.0^\circ$ (c 2.0, EtOH).

(+)-(S)-diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate (7)

1 g (4 mmol) of 1,3-diphenyl-2-propen-1-one (chalcone) 5 was dissolved in 30 ml of toluene in a round-bottomed flask with the magnetic stirrer. 0.8 ml of diethyl malonate was poured into the mixture and 0.5 g of freshly heated K_2CO_3 was added. Everything was stirred at the room temperature for 15 minutes, and then 15% mol (0.35 g) of the catalyst (CIL) 4 were added. The mixture was stirred overnight. Then the given mixture was filtered, the solvent was reduced and

the product was purified by the flash chromatography (silicagel, EtOAc). Yield – 81%.

$[\alpha]_D^{25} = +13^\circ$ (c 2.1, EtOH), (lit. data $+23^\circ$); calc. optical purity 57%; calc. *ee* 35%.

CONCLUSIONS

1. A new chiral ionic liquid with two imidazolium cations – (+)-(1*S*,2*R*,5*S*,6*R*)-2,6-di[[*N*-methylimidazol-3-ium-3-yl)acetyl]oxy]bicyclo[3.3.1]nonane di(tetrafluoroborate) was synthesized starting from (+)-(1*S*,5*S*)-bicyclo-[3.3.1]nonane-2,6-dione.

2. A small amount (15% mol) of the chiral ionic liquid induced the asymmetric Michael's addition reaction of 1,3-diphenyl-2-propen-1-one with diethyl malonate.

3. The resulting adduct – diethyl-2-(3-oxo-1,3-diphenylpropyl)malonate showed a satisfactory optical activity. The optical purity of the (+)-(S)-enantiomer was 57% according to the calculations by the rotation angle and the enantiomeric excess calculated based on the ¹H-NMR spectral analysis was 35%. This inadequacy depends, doubtless, on the so-called Horeau effect.

Received 4 May 2012

Accepted 21 May 2012

References

1. S. Bertelsen, K. A. Jorgensen, *Chem. Soc. Rev.*, **38**, 2178 (2009).
2. Y. Q. Fu, Z. C. Li, L. N. Ding, J. C. Tao, S. H. Zhang, M. S. Tang, *Tetrahedron: Asymmetry*, **17**, 3351 (2006).
3. Y. Nishikawa, M. Kitajima, H. Takayama, *Org. Lett.*, **10**, 1987 (2008).
4. E. D. Siyutkin, A. S. Kucherenko, S. G. Zlotin, *Tetrahedron*, **66**, 513 (2010).
5. J. Ding, V. Desikan, X. Han, T. L. Xiao, R. Ding, W. S. Jenks, D. W. Armstrong, *Org. Lett.*, **7**, 335 (2005).
6. C. Baudequin, D. Bregeon, J. Levillain, *Tetrahedron: Asymmetry*, **16**, 921 (2005).
7. J. Pernak, A. Czepukowicz, R. Pozniak, *Ind. Eng. Chem. Res.*, **40**, 2379 (2001).
8. R. Bishop, S. Choudhury, *J. Chem. Soc.*, 1159 (1982).
9. R. A. Matos, C. Kleber, Z. Andrade, *Tetrahedron Lett.*, **49**, 1652 (2008).
10. Z. M. Wan, Q. Wang, W. L. Bao, *Tetrahedron Lett.*, **46**, 4657 (2005).
11. J. A. Zalikowski, K. E. Gilbert, W. T. Borden, *J. Org. Chem.*, **45**, 347 (1980).
12. S. Z. Luo, L. X. Mi, H. Xu, L. Zhang, *Angew. Chem.*, **118**, 3165 (2006).
13. J. P. Vigneron, M. Dhaenes, A. Horeau, *Tetrahedron*, **29**, 1055 (1973); V. Rautenstrauch, *Bull. Soc. Chim. Fr.*, **131**, 515 (1994).

Alicija Bilinska, Albinas Žilinskas

CHIRALINIO JONINIO SKYSČIO – BICIKLO[3,3,1]NONANO DARINIO SINTEZĖ IR JO PANAUDOJIMAS ASIMETRINIO MICHAELIO PRIJUNGIMO REAKCIJOJE

Santrauka

Iš enantiomeriškai gryno (+)-(1*S*,5*S*)-biciklo[3,3,1]nonan-2,6-diono sintezuotas naujas chiralinis joninis skystis su dviem imidazolio kationais (+)-(1*S*,2*R*,5*S*,6*R*)-2,6-di[[*N*-metilimidazol-3-ium-3-il)acetil]oksi]biciklo[3,3,1]nonano di(tetrafluorboratas), kuris panaudotas induktoriumi asimetrinio Michaelio prijungimo reakcijoje tarp 1,3-difenil-2-propen-1-ono ir dietilmalonato. Gauta adukto – dietil-2-(3-okso-1,3-difenilpropil)malonato optinis grynumas, skaičiuojant pagal išmatuotą sukimo kampą, buvo lygus 57 %, o enantiomerinis perteklius pagal ¹H-BMR spektrinės analizės duomenis sudarė tik 35 %. Tokį neatitikimą galima paaiškinti vadinauoju Horeau efektu.