STUDIA UNIVERSITATIS BABEŞ-BOLYAI, CHEMIA, LIV, 4, 2009

SYNTHESIS AND STRUCTURAL ANALYSIS OF SOME NEW STERICALLY HINDERED DIENES

FLAVIA PIRON[a], ELENA BOGDAN[a], CRINA CISMAŞ[a], ANAMARIA TEREC[a], ION GROSU[a]

ABSTRACT. The good yields synthesis of some new tetrabromo and tetraiodo dienes obtained via the Hay homo coupling reaction of two polyethyleneoxy terminal alkynes and the structural investigations on these sterically hindered compounds are reported.

Keywords: dienes, axial chirality, atropenantiomers, coupling reactions, diynes

INTRODUCTION

Compounds with axial chirality are of high interest in the field of chiral catalysts and chiral discriminators. Many biphenyl and binaphtyl derivatives [1] are commercially available as single enantiomers.

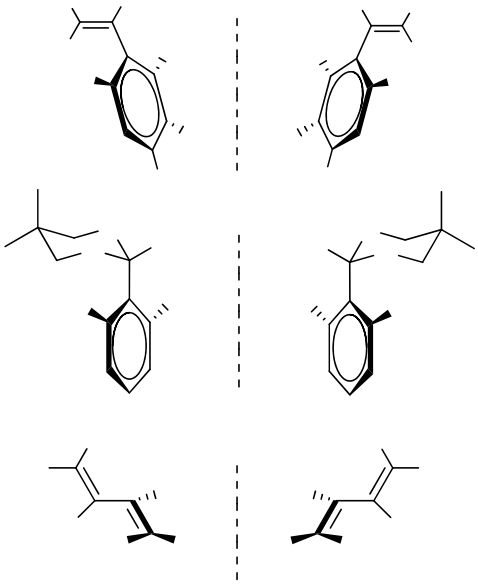
Besides the very well known atropenantiomeric compounds with biaryl units many other unexpected compounds (e.g. styrenes I [2], 2-aryl,2-methyl-1,3-dioxanes II [3], *EE*-tetrahalogeno-1,3-butadienes III [4,5]; Scheme 1) exhibit axial chirality and atropenantiomers.

The atropisomers of *EE*-1,3-butadienes are due to the hindrance of the rotation around the formal simple bond C^2-C^3. These compounds prefer the conformation with perpendicular arrangement of the double bonds, which insures the highest distance between the large substituents at positions 2 and 3 (**III**, Scheme 1). The racemization of the atropenantiomers (*aR*⇆*aS*) occurs by the rotation of the molecule around the C^2-C^3 bond, via either the *s-trans* isomer (*transoid*) or the *s-cis* structure (*cisoid*) of the 1,3-butadiene core. The barrier via the *transoid* conformation is considerably lower and the compounds prefer this itinerary for the racemisation reaction.

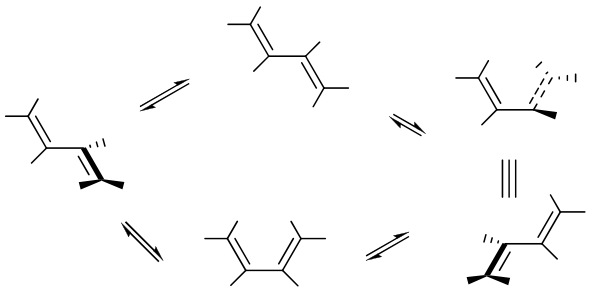
The values of the barriers of racemization depend of X and R groups (named internal substituents). The reported barriers were measured either by dynamic NMR [6], DHPLC [4] or using polarimetry measurements [7]. The R^1 groups (named external substituents) are not involved directly in the hindrance of the rotation around the C^2-C^3 bonds, but if they are large they increase the barrier of rotation by the *buttressing* effect. [8]

[a] *Universitatea Babeş-Bolyai, Facultatea de Chimie şi Inginerie Chimică, Str. Kogălniceanu, Nr. 1, RO-400084 Cluj-Napoca,Romania, igrosu@chem.ubbcluj.ro*

We considered of interest to develop the investigations in the field of chiral dienes and to obtain new compounds exhibiting a tetrahalogeno-1,3-butadiene core, to determine their structure and to estimate the hindrance of the rotation around the formal simple bond of the 1,3-butadiene unit.



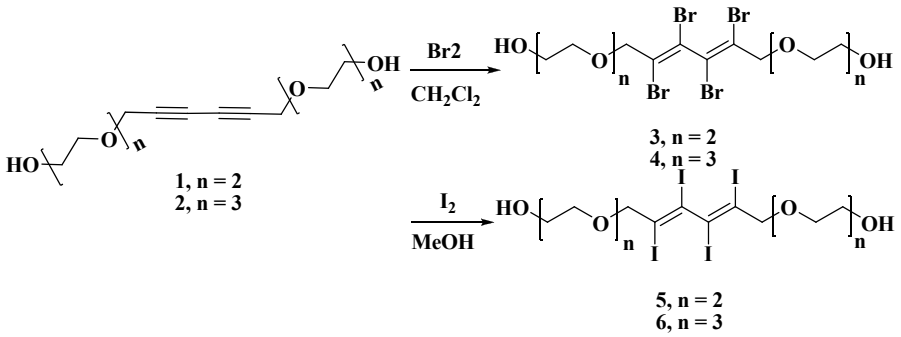
Scheme 1



Scheme 2

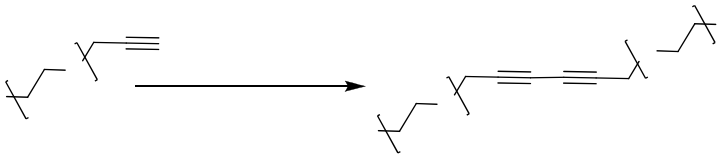
RESULTS AND DISCUSSION

New tetrahalogeno dienes (**3**-**6**) were synthesized by halogen addition reactions to the corresponding diynes (**1** and **2;** Scheme 3). The reactions underwent stereoselectively with the formation of the *EE* isomers.

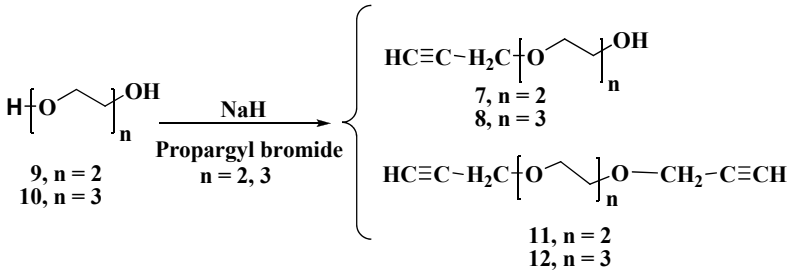


Scheme 3

Diynes **1** and **2** were synthesized by the coupling reaction of the monoalkyne alcohols **7** and **8** (Scheme 4) which were obtained by the reaction of the corresponding polyethyleneglycols (**9** and **10**) with propargyl bromide (Scheme 5). Even if compounds **7** and **8** are known [9] and their synthesis has been reported, they could be obtained in good yields only by adapting a procedure described in the literature for similar compounds [10].



Scheme 4



Scheme 5

The main product in the reaction of polyethyleneglycols with propargyl bromide is the monoalkyne, but the formation of dipropargyl derivatives **11** and **12** cannot be avoided. Diterminal diynes **11** and **12** were isolated but the yields in this case are poor. These diynes are interesting compounds and their good yields synthesis and structural investigations were reported in the literature [11].

Diyne **1** was reported by Wegner [12], but diyne 2 is a new compound.

The structural investigations on **3**-**6** were performed using NMR and LR ESI MS experiments.

The key signals in ^{1}H NMR spectra are those corresponding to the protons belonging to the CH_2 groups connected directly to the diene system (allylic positions). If the rotation of the 1,3-diene around the central simple bond is free the chirality of the system has no influence (an achiral average structure has to be considered) on the NMR signals and the ^{1}H NMR spectrum should show for the designed protons a singlet. If the rotation of the diene unit is hindered, the axial chirality of the molecule determines the diastereotopicity of the protons of the prochiral centers (CH_2 groups). In this situation the spectrum should exhibit two doublets (AB system) for the protons of the allyl CH_2 groups. The spectra for the investigated dienes (**3**-**6**) exhibit two doublets for the protons of the considered CH_2 groups (Figure 1, Table 1) proving the hindrance of the rotation in the diene unit.

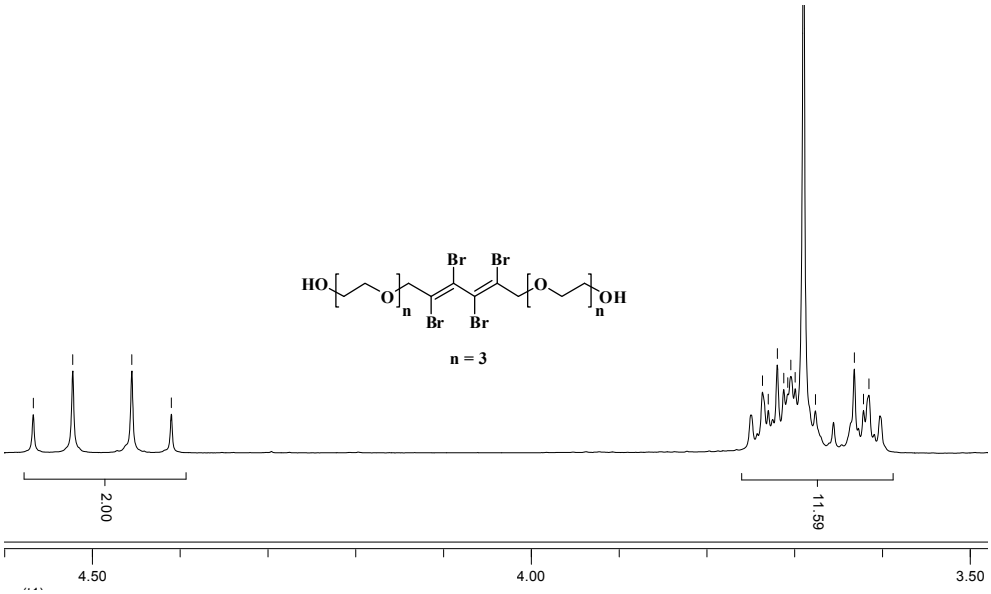


Figure 1. ^{1}H NMR spectrum ($CDCl_3$ rt,, fragment) of compound **4**

Table 1. Relevant NMR data for **3**-**6**

Compd.	δ (ppm)		Δδ (ppm)	*J* (Hz)
	-CX=CX-C*H*(H)-	-CX=CX-CH(*H*)-		
3	4.44	4.55	0.10	13.5
4	4.43	4.54	0.09	13.5
5	4.30	4.40	0.10	13.5
6	4.28	4.38	0.10	13.5

The spectrum of **4** run at *rt* (Figure 1) shows the two reference doublets at δ = 4.43; 4.53 ppm (J = 13.5 Hz), while the signals for the other protons of the CH_2 groups could not be assigned and they are all overlapped in the range 3.6-3.75 ppm. In the spectrum run at 60 °C no modification could be observed. This result is in agreement with the reported barriers for the racemization of other chiral tetrabromo $\Delta G^{\#}$ = 69.57±0.627 kJ/mol [5a] and tetraiodo $\Delta G^{\#}$ = 143 ± 1 kJ/mol [4] chiral dienes and reveals the high stability of the atropenantiomers of these compounds (the rotation in the diene unit is hindered at high temperatures, too).

CONCLUSIONS

Four new tetrahalogeno dienes with axial chirality were obtained in good yields and were investigated by NMR and ESI MS. The hindrance of the rotation in the diene unit and the high stability of the atropenantiomers of the compounds were also revealed. The high stability of the chiral unit located between two polyethylene glycol substituents recommend these compounds as useful building blocks for the obtaining of chiral host molecules.

EXPERIMENTAL SECTION

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. LR ESI MS were recorded on ion trap spectrometer in positive mode. Melting points are uncorrected. Thin layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel 60 F_{254} using UV and $KMnO_4$ visualization.

General procedure for the acetylenic coupling:

CuI (60 mmol) was added to a solution of alkynes **7** or **8** (3 mmol) in dry dichloromethane (200 mL) containing dry TMEDA (120 mmol). The reaction mixture was stirred for 1 hour under a stream of dry air. The mixture was then diluted with dichloromethane (100 ml) transferred into a separating funnel and washed with a solution of HCl 2M (2 x 30 ml) and then several times with water till the aqueous layer remains colourless. The organic layer was then separated, dried over Na_2SO_4 and evaporated. The final product was then purified by column chromatography (silica gel, diisopropylether/acetone 1/1).

3,6,13,16-tetraoxaoctadeca-8,10-diyne-1,18-diol (**1**) Colorless liquid, yield: 35% (300 mg); Calculated for $C_{14}H_{22}O_6$; C, 58.73; H, 7.74. Found: C, 58.89; H, 7.51. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.03 (2H, OH), 3.55-3.75 (m, 16H, 1-H, 2-H, 4-H, 5-H, 14-H, 15-H, 17-H, 18-H), 4.27 ppm (s, 4H, 7-H, 12-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 58.91 (7-C, 12-C), 61.70 (1-C, 18-C), 69.37, 70.13 (2-C, 4-C, 15-C, 17-C), 70.53 (9-C, 10-C), 72.47 (5-C, 14-C), 75.22 ppm (8-C, 11-C).

ESI-MS; m/z = 287.1 $[M+H]^+$, 309.1 $[M+Na]^+$.

3,6,9,16,19,22-hexaoxatetracosa-11,13-diyne-1,24-diol (**2**) Colorless liquid, yield: 33% (400 mg); Calculated for $C_{18}H_{30}O_8$; C, 57.74; H, 8.08. Found: C, 57.63; H, 8.28.^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.13 (2H, OH), 3.59-3.74 (m, 24H, 1-H, 2-H, 4-H, 5-H, 7-H, 8-H, 17-H, 18-H, 20-H, 21-H, 23-H, 24-H), 4.27 ppm (s, 4H, 10-H, 15-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 58.89 (10-C, 15-C), 61.69 (1-C, 24-C), 69.28, 70.24, 70.27, 70.60 (2-C, 4-C, 5-C, 7-C, 18-C, 20-C, 21-C, 23-C), 70.50 (12-C, 13-C), 72.51 (8-C, 17-C), 75.25 ppm (11-C, 14-C).
ESI-MS; m/z = 375.2 $[M+H]^+$, 397.2 $[M+Na]^+$.

General bromination procedure

To a solution of compounds **1** or **2** (0.26 mmol) in dichloromethane (20 ml), bromine (0.82 mmol, 130 mg solved in 1 ml dichloromethane) was added dropwise. The mixture was stirred at room temperature overnight, and at the end the organic phase was washed with a solution of sodium sulfite and then with water. After drying over sodium sulfate, the solvent was removed and the crude product was purified by column chromatography (silica gel, diisopropylether/acetone 1/1).

(8E,10E)-8,9,10,11-tetrabromo-3,6,13,16-tetraoxaoctadeca-8,10-diene-1,18-diol (**3**) Yellow liquid, yield: 47% (74 mg); Calculated for $C_{14}H_{22}Br_4O_6$; C, 27.75; H, 3.66; Br, 52.75. Found: C, 27.49; H, 3.78; Br, 52.91. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.88 (2H, OH), 3.61-3.76 (m, 16H, 1-H, 2-H, 4-H, 5-H, 14-H, 15-H, 17-H, 18-H), 4.44, (d, 2H, *J* = 13.5, 7-H, 12-H), 4.55 ppm (2d 2H, *J* = 13.5, 7'-H, 12'-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 61.79 (1-C, 18-C), 69.35, 70.18 (2-C, 4-C, 15-C, 17-C), 72.42 (5-C, 14-C), 73.06 (7-C, 12-C), 117.53 (8-C, 11-C), 124.79 ppm (9-C, 10-C).
ESI-MS; m/z (%) = 602.8 (21), 604.8 (79), 606.7 (100), 608.8 (66), 610.7 (16) $[M+H]^+$.

(11E,13E)-11,12,13,14-tetrabromo-3,6,9,16,19,22-hexaoxatetracosa-11,13-diene-1,24-diol (**4**) Yellow liquid, yield: 46% (85 mg); Calculated for $C_{18}H_{30}Br_4O_8$; C, 31.15; H, 4.36; Br, 46.05. Found: C, 31.44; H, 4.09; Br, 46.33. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.07 (2H, OH), 3.61-3.73 (m, 24H, 1-H, 2-H, 4-H, 5-H, 7-H, 8-H, 17-H, 18-H, 20-H, 21-H, 23-H, 24-H), 4.43, (d, 2H, *J* = 13.5, 10-H, 15-H), 4.54 ppm (d, 2H, *J* = 13.5, 10'-H, 15'-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ =61.75 (1-C, 24-C), 69.35, 70.29, 70.33, 70.67 (2-C, 4-C, 5-C, 7-C, 18-C, 20-C, 21-C, 23-C), 72.50 (8-C, 17-C), 73.09 (10-C, 15-C), 117.44 (11-C, 14-C), 124.85 (12-C, 13-C).
ESI-MS; m/z (%) = 690.9 (15), 692.9 (67), 694.9 (100), 696.8 (67), 698.8 (15) $[M+H]^+$.

General iodination procedure:

To a solution of compounds **1** or **2** (0.26 mmol) in methanol (10 ml), iodine (0.82 mmol) was added. The mixture was stirred at room temperature overnight, and at the end solvent was removed by low pressure evaporation.

Extraction was made with dichloromethane and was washed with water. After drying over sodium sulfate, the solvent was removed and the crude product was purified by column chromatography (silica gel, diisopropylether/ acetone 1/1).

(8E,10E)-8,9,10,11-tetraiodo-3,6,13,16-tetraoxaoctadeca-8,10-diene-1,18-diol (**5**) Red-brown liquid, yield: 40% (83 mg); Calculated for $C_{14}H_{22}I_4O_6$; C, 21.18; H, 2.79; I, 63.94. Found: C, 20.95; H, 2.93; I, 64.07. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.09 (2H, OH), 3.63-3.78 (m, 16H, 1-H, 2-H, 4-H, 5-H, 14-H, 15-H, 17-H, 18-H), 4.30, (d, 2H, *J* = 13.5, 7-H, 12-H), 4.40 ppm (d, 2H, *J* = 13.5, 7'-H, 12'-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 61.81 (1-C, 18-C), 69.27, 70.25 (2-C, 4-C, 15-C, 17-C), 72.40 (5-C, 14-C), 80.84 (7-C, 12-C), 97.08 (8-C, 11-C), 105.90 ppm (9-C, 10-C).

ESI-MS; m/z = 794.7 $[M+H]^+$, 816.7 $[M+Na]^+$.

(11E,13E)-11,12,13,14-tetraiodo-3,6,9,16,19,22-hexaoxatetracosa-11,13-diene-1,24-diol (**6**) Red-brown liquid, yield: 51% (120 mg); Calculated for $C_{18}H_{30}I_4O_8$; C, 24.51; H, 3.43; I, 57.55. Found: C, 24.44; H, 3.56; I, 57.74. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.86 (2H, OH), 3.61-3.74 (m, 24H, 1-H, 2-H, 4-H, 5-H, 7-H, 8-H, 17-H, 18-H, 20-H, 21-H, 23-H, 24-H), 4.28, (d, 2H, *J* = 13.5, 10-H, 15-H), 4.38 ppm (d, 2H, *J* = 13.5, 10'-H, 15'-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ =61.79 (1-C, 24-C), 69.30, 70.38, 70.73 (2-C, 4-C, 5-C, 7-C, 18-C, 20-C, 21-C, 23-C), 72.50 (8-C, 17-C), 80.87 (10-C, 15-C), 104.27 (11-C, 14-C), 106.02 (12-C, 13-C).

ESI-MS; m/z = 882.7 $[M+H]^+$, 903.7 $[M+Na]^+$.

ACKNOWLEDGMENTS

We acknowledge the financial support of this work by PNCDI II program (UEFISCSU; projects IDEAS 515, 570, 2358).

REFERENCES

1. a. Y. J. Zhang, H. Wei, W. B. Zhang, *Tetrahedron*, **2009**, *65*, 1281.; b. Y. Alpagut, B. Goldfuss, J. M. Neudoerfl, *Beilstein J. Org. Chem.*, **2008**, *4*, 25.; c. M. Kitamura, S. Shirakawa, Y. Arimura, X. Wang, K. Maruoka, *Chem. Asian. J.*, **2008**, *3*, 1702; d. Y. Sudo, D. Shirasaki, S. Harada, A. Nishida, *J. Am. Chem. Soc.*, **2008**, *130*, 12588.
2. Y.Q. Fang, M. Lautens, *Org. Lett.,* **2005**, *7*, 3549.
3. I. Grosu, G. Plé, S. Mager, E. Mesaros, A. Dulau, C. Gego, *Tetrahedron*, **1998**, *54*, 2905.
4. F. Piron, N. Vanthuyne, B. Joulin, J.-V. Naubron, C. Cismaş, A. Terec, R. A. Varga, C. Roussel, J. Roncali, I. Grosu, *J. Org. Chem.*, 2009, Doi: 10.1021/jo901762j

5. a. G. Köbrich, A. Mannschreck, R. A. Misra, G. Rissmann, M. Rösner, W. Zündorf, *Chem. Ber.,* **1972**, *105*, 3794; b. G. Köbrich, B. Kolb, A. Mannschreck, R. A. Misra, *Chem. Ber.*, **1973**, *106*, 1601; c. H. L. Elbe, G. Köbrich, *Chem. Ber.*, **1974**, *107*, 1654; d. M. Rösner, G. Köbrich, *Angew. Chem. Int. Ed.,* **1974**, *13*, 741; e. H. O. Bödecker, V. Jonas, B. Kolb, A. Mannschreck, G. Köbrich, *Chem. Ber.,* **1975**, *108*, 3497; f. M. Rösner, G. Köbrich, *Angew. Chem.* **1975**, *87*, 715.
6. a. A. J. P. Devaquet, R. E. Townshend, W. J. Hehre, *J. Am. Chem. Soc*., **1976**, *98*, 4068; b. S. M. Bachrach, M. Liu, *J. Am. Chem. Soc*., **1991**, *113*, 7929; c. M. E. Squillacote, F. Liang, *J. Org. Chem*., **2005**, *70*, 6564; d. A. E. Hansen, K. L. Bak, *J. Phys. Chem. A*, **2000**, *104*, 11362.
7. a. A. Mannschreck, M. Mintas, G. Becher, G. Stühler, *Angew. Chem*., **1980**, *92*, 490; b. G. Becher, A. Mannschreck, *Chem. Ber*., **1981**, *114*, 2365.
8. a. U. Berg, T. Liljefors, C. Roussel, J. Sandström, *Acc. Chem. Res*., **1985**, *18*, 80; b. R. Gallo, C. Roussel, U. Berg, *Adv. Heterocycl. Chem*., **1988**, *43*, 173.
9. a. b. G. Lu, S. Lam, K. Burgess, *Chem. Commun.*, **2006**, *15*, 1652.
10. S. Auricchio, S. Bruchner, L. Malpezzi, O. Vrajna de Pava, *J. Chem. Research (Miniprint)*, **1983**, 1201.
11. a. Z. J. Yao, H. P. Wu, Y. L. Yu, *J. Med. Chem.*, **2000**, *43*, 2484; b. M. M. McPhee, S. M. Kerwin, *Bioorg. Med. Chem.*, **2001**, *9*, 2809.
12. G.Wegner, *Makromolekulare Chemie* **1970**, *134*, 219.