Russian Journal of Organic Chemistry, Vol. 38, No. 6, 2002, pp. 895–899. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 6, 2002, pp. 937–941.

Synthesis and Enantiomeric Selectivity of Chiral Crown Ethers

N. G. Luk'yanenko, A. V. Lobach, O. N. Leus, and N. Yu. Titova

Bogatskii Physico-chemical Institute, National Academy of Sciences of Ukraine, Odessa, 65080 Ukraine

Received December 6, 2001

Abstract–Condensation of (4*S*,5*S*)-4,5-dihydroxymethyl-2-substituted dioxolanes with polyethylene glycols ditosylates yielded new chiral crown ethers. By potentiometry the enantioselectivity of complexing between the compounds obtained and L- and D-valine methyl ester hydrochlorides was evaluated.

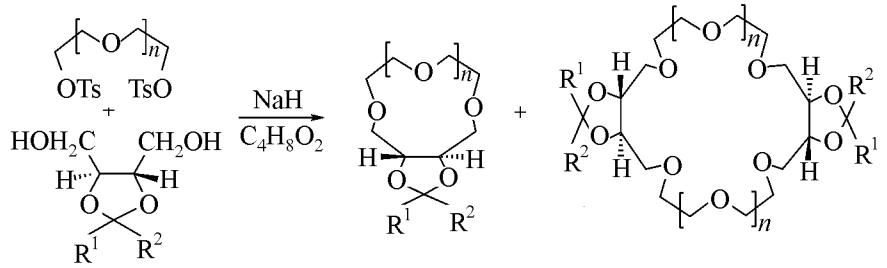
The supramolecular chemistry involves as a part the synthesis of chiral receptors and investigation of their properties [1]. Their capability to enantioselective recognition of chiral "guests" provides new ways for creating catalysts of asymmetric reactions, enantioselective sensors, "switches", and other molecular gadgets, and also for simulation of fundamental biological processes based on noncovalent interactions [1–4]. Among the synthetic chiral receptors the most common are crown ethers that are able to form complexes enantioselectively with chiral amines and derivatives of amino acids [4, 5]. One of the most accessible and convenient precursor of chiral crown ethers and podandes is the natural L-tartaric acid. Its derivatives were used in the synthesis of quite a number of various crown ethers. However in most cases the syntheses are multistage and afford the target products in low yield [6–13].

We formerly prepared certain chiral crown ethers and demonstrated that they were capable of enantioselective binding of amino acids esters [14, 15]. In extension of these studies we report here on the synthesis of new chiral crown ethers on the basis of L-tartaric acid derivatives and on evaluation of enantioselectivity of their complexing with L-and D-valine methyl ester hydrochlorides chosen as model compounds.

Diethyl L-tartrate (**I**) served as initial synthon in preparation of chiral crown ethers and podandes. By reaction with pinacolone or benzaldehyde compound **I** was transformed into corresponding dioxolanes **II** and **III**. The choice of pinacolidene and benzylidene protection of the hydroxy groups in ether (**I**) was due to their high stability and to facility of isolation of intermediate and final products. Reduction of dioxolane **II, III** with lithium aluminum hydride resulted in diols **IV** and **V**.

The condensation of diols **IV, V** with polyethylene glycols ditosilates in the presence of sodium hydride furnished previously unknown crown ethers **VI–XVII** that were products of common reaction of ditosylates with glycols along [1 + 1] and [2 + 2] scheme.

The isolation and purification of compounds **VI–XVII** was carried out by column chromatography on neutral alumina. All compounds were colorless oily substances. Their composition and structure were



IV, V **VI–XI** **XII–XVII**

IV, VI–VIII, XII–XIV, R^1 = Me, R^2 = *t*-Bu; **V, IX–XI, XV–XVII**, R^1 = H, R^2 = Ph; **VI, IX, XII, XV**, *n* = 2; **VII, X, XIII, XVI,** *n* = 3; **VIII, XI, XIV, XVII,** *n* = 4.

1070-4280/01/3806-895$27.00 © 2002 MAIK "Nauka/Interperiodica"

Table 1. Yields, specific rotation, ^{1}H NMR spectra, and elemental analyses of compounds **II**–**XVII**

Compd. no.	Yield %	$[\alpha]_D^{20}$, deg, $CHCl_3$ (*c*, %)	^{1}H NMR spectrum ($CDCl_3$), δ, ppm	Found, %		Formula	Calculated, %	
				C	H		C	H
II	90	–38.0 (5.0)	0.98 s (9H, *t*-Bu), 1.25–1.36 m (9H, CH_3), 4.17–4.27 m (4H, OCH_2), 4.46 q, (2H, OCH)	58.29	8.34	$C_{14}H_{24}O_6$	58.32	8.39
III	87	–49.2 (5.0)	1.28–1.39 m (6H, CH_3), 4.19–4.31 m (4H, OCH_2), 4.80 q, (2H, OCH), 6.05 s (1H), 7.34–7.56 (5H, Ph)	61.28	6.10	$C_{15}H_{18}O_6$	61.22	6.16
IV	79	6.8[a] (5.0)	0.98 s (9H, *t*-Bu), 1.30 s (3H, CH_3), 2.16 br.s. (2H, OH), 3.82–3.94 m (4H, OCH_2), 4.02–4.16 m (2H, OCH)	58.86	9.91	$C_{10}H_{20}O_4$	58.80	9.87
V	72	–10.0[a] (2.0)	2.10 br.s. (2H, OH), 3.72–3.92 m (4H, $C\underline{H}_2OH$), 4.10–4.22 m, (2H, OCH), 5.98 s (1H), 7.38–7.52 m (5H, Ph)	62.79	6.67	$C_{11}H_{14}O_4$	62.85	6.71
VI	32	6.4 (1.0)	0.98 s (9H, *t*-Bu), 1.30 s (3H, CH_3), 3.50–3.62 m (16H, OCH_2), 3.93–4.14 m (2H, OCH)	60.40	9.47	$C_{16}H_{30}O_6$	60.36	9.50
VII	67	12.8 (5.0)	0.98 s (9H, *t*-Bu), 1.30 s (3H, CH_3), 3.50–3.62 m (20H, OCH_2), 3.88–3.96 m (2H, OCH)	59.60	9.42	$C_{18}H_{34}O_7$	59.65	9.45
VIII	75	7.1 (1.0)	0.98 s (9H, *t*-Bu), 1.30 s (3H, CH_3), 3.50–3.62 m (24H, OCH_2), 3.81–3.90 m, (2H, OCH)	59.14	9.37	$C_{20}H_{38}O_8$	59.09	9.42
IX	28	–12.5 (1.0)	3.54–3.64 m (16H, OCH_2), 3.98–4.05 m (2H, OCH), 5.98 s (1H), 7.38–7.52 m (5H, Ph)	62.98	7.49	$C_{17}H_{24}O_6$	62.95	7.46
X	70	–13.8 (1.0)	3.54–3.64 m (20H, OCH_2), 3.91–3.99 m (2H, OCH), 5.98 s (1H), 7.38–7.52 m (5H, Ph)	61.87	7.70	$C_{19}H_{28}O_7$	61.91	7.66
XI	72	–12.9 (1.0)	3.54–3.64 m (24H, OCH_2), 3.87–3.96 m, (2H, OCH), 5.98 s (1H), 7.38–7.52 m (5H, Ph)	61.20	7.86	$C_{21}H_{32}O_8$	61.15	7.82
XII	60	–8.2 (1.0)	0.98 s (18H, *t*-Bu), 1.30 s (6H, CH_3), 3.52–3.62 m (32H, OCH_2), 3.90–4.02 m (4H, OCH)	60.41	9.47	$C_{32}H_{60}O_{12}$	60.36	9.50
XIII	19	–10.2 (1.0)	0.98 s (18H, *t*-Bu), 1.30 s (6H, CH_3), 3.52–3.62 m (40H, OCH_2), 3.84–3.96 m, (4H, OCH)	59.70	9.41	$C_{36}H_{68}O_{14}$	59.65	9.45
XIV	12	–9.3 (1.0)	0.98 s (18H, *t*-Bu), 1.30 s (6H, CH_3), 3.52–3.62 m (48H, OCH_2), 3.79–3.90 m, (4H, OCH)	59.14	9.39	$C_{40}H_{76}O_{16}$	59.09	9.42
XV	55	18.4 (1.0)	3.54–3.64 m (32H, OCH_2), 3.94–4.00 m (4H, OCH), 5.98 s (2H), 7.38–7.52 m (10H, Ph)	63.00	7.51	$C_{34}H_{48}O_{12}$	62.95	7.46
XVI	16	21.2 (1.0)	3.54–3.64 m (40H, OCH_2), 3.87–3.94 m (4H, OCH), 5.98 s (2H), 7.38–7.52 m (10H, Ph)	61.99	7.71	$C_{38}H_{56}O_{14}$	61.94	7.66
XVII	10	19.3 (1.0)	3.54–3.64 m (48H, OCH_2), 3.82–3.89 m (4H, OCH), 5.98 s (2H), 7.38–7.52 m (10H, Ph)	61.22	7.78	$C_{42}H_{64}O_{16}$	61.15	7.82

[a] Recorded in CH_3OH.

confirmed by elemental analyses, ^{1}H NMR and mass spectroscopy.

The characteristic feature of ^{1}H NMR spectra of crown ethers **VI–XVII** is the presence of multiplets from protons of polyether OCH_2 groups and of OCH protons at asymmetric centers. Also all the signals of the proton groups in keeping with the assumed structure are observed (Table 1). In the mass spectra of all compounds studied appear the peaks of the respective molecular ions.

The enantioselectivity in the complexing of crown ethers **VI–XVII** with L-and D-valine methyl ester hydrochlorides was evaluated by potentiometric enantioselectivity factors $1K_{LD}$ [16, 17].

In Table 2 are listed the values of K_{LD} averaged over 5–7 measurements characterizing the preferable complexing of crown ethers with one of the substrate enantiomers. At K_{LD} = 1 enantioselectivity of complexing is lacking; the values of K_{LD} more or less than 1 indicate the preference for L- or D-isomer of valine methyl ester respectively.

The highest selectivity in the series of crown ethers under study was exhibited by compounds **VIII, XI**, and **XV**. A characteristic feature of this series consists in inversion of enantioselectivity among the similar crown ethers **VI–VIII, IX–XI, XII–XIV**, and **XV–XVII** with growing size of the ring. This fact is presumably due to the difference in the structure and stoichiometry of the arising complexes. The results obtained show that the search for highly enantioselective crown ethers among compounds containing fragments of L-tartaric acid derivatives is a promising task.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometer Bruker AM-250 (250 MHz) in $CDCl_3$, internal reference HMDS. Molecular weights were measured on mass spectrometers Varian MAT-112 and MKh 1321 with direct injection of sample into the ion source, ionizing electrons energy 70 eV. The values $[\alpha]_D^{20}$ were measured on polarimeter Perkin-Elmer 241 MC from solutions in chloroform.

GLC was carried out on chromatograph Chrom-5 equipped with flame-ionization detector, glass column 1200×3 mm, stationary phase 5% SE-30 on Inerton AW-DMCS (0.100–0.125 mm). TLC was performed on glass plates with a fixed layer of neutral alumina (L 5/40), eluent chloroform–benzene–methanol–2-propanol, 8 : 3 : 0.3 : 0.3, development in iodine vapor.

Table 2. Enantioselectivity factors of crown ethers **VI**–**XVII**

Compd. no.	K_{LD}	Compd. no.	K_{LD}
VI	0.84	**XII**	0.77
VII	1.22	**XIII**	0.92
VIII	1.38	**XIV**	1.22
IX	0.79	**XV**	0.68
X	1.25	**XVI**	1.12
XI	1.45	**XVII**	1.28

The preparative liquid chromatography was carried out using glass columns packed with neutral alumina (L 40/250), eluent chloroform–benzene–methanol–2-propanol, 8 : 3 : 0.3 : 0.3.

(4*R*,5*R*)-2-*tert*-Butyl-4,5-diethoxycarbonyl-2-methyldioxolane (II) and (4*R*,5*R*)-4,5-diethoxycarbonyl-2-phenyldioxolane (III). A solution of diethyl L-tartrate (200 g, 0.97 mol), freshly distilled pinacolone (150 g, 1.5 mol) or benzaldehyde (159 g, 1.5 mol) and *p*-toluenesulfonic acid (2.6 g, 0.015 mol) in benzene (600 ml) was boiled in a flask equipped with a Dean–Stark trap till the end of water liberation. The reaction mixture was washed with water (2 × 200 ml), with saturated water solution of sodium carbonate (2 × 200 ml), and again with water (2 × 200 ml). After drying with Na_2SO_4 benzene and pinacolone excess were distilled off on a rotary evaporator, and the residue was distilled in a vacuum. Compound **II**, bp 130–131°C (2 mm Hg); compound **III**, bp 162–163 °C (2 mm Hg), colorless crystals, mp 43–44°C (from ethanol).

(4*S*,5*S*)-2-*tert*-Butyl-4,5-dihydroxymethyl-2-methyldioxolane (IV) and (4*S*,5*S*)-4,5-dihydroxymethyl-2-phenyldioxolane (V). To a dispersion of lithium aluminum hydride (13.7 g, 0.36 mol) in anhydrous THF (300 ml) cooled with ice under argon atmosphere at vigorous stirring was slowly added dropwise a solution of dioxolane **II** (86.4 g, 0.3 mol) or dioxolane **III** (88.2 g, 0.3 mol) in anhydrous THF (130 ml). The mixture was stirred for 8 h and left overnight. Then to the cooled by ice reaction mixture was added at stirring ice water till the end of vigorous reaction. The precipitate of aluminum hydroxide was filtered off, washed with THF (3 × 100 ml), the filtrate was dried on Na_2SO_4. THF was distilled off on a rotary evaporator, and diols **IV** and **V** were distilled in a vacuum. Compound **IV**, bp 142–143°C (2 mm Hg), colorless crystals, mp 83–84°C (from hexane). Compound **V**, bp 168–169°C (2 mm Hg), colorless crystals, mp 71–72°C (from hexane).

(3a*S*,15a*S*)-2-(*tert*-Butyl)-2-methyldecahydro-[1,3]dioxolo[4,5-*l*][1,4,7,10]tetraoxacyclotetradecane (VI), (3a*S*,18a*S*)-2-(*tert*-butyl)-2-methyldodecahydro[1,3]dioxolo[4,5-*o*][1,4,7,10,13]pentaoxacycloheptadecane (VII), (3a*S*,21a*S*)-2-(*tert*-butyl)-2-methyltetradeca-hydro[1,3]dioxolo[4,5-*r*]-[1,4,7,10,13,16]hexaoxacycloeicosane (VIII), (3a*S*,15a*S*)-2-phenyldecahydro[1,3]dioxolo[4,5-*l*]-[1,4,7,10]tetraoxacyclotetradecane (IX), (3a*S*,18a*S*)-2-phenyldecahydro[1,3]dioxolo[4,5-*o*][1,4,7,10,13]-pentaoxacycloheptadecane (X), (3a*S*,21a*S*)-2-phenyldecahydro[1,3]dioxolo[4,5-*r*][1,4,7,10,13,16]-hezaoxacycloeicosane (XI), (3a*S*, 15a*S*,18aS,30aS)-2,17-di(*tert*-butyl)-2,17-dimethyleicosahydrodi[1,3]-dioxolo-4,5-*l*: 4,5-*z*][1,4,7,10,15,18,21,24]octaoxa-cyclooctacosane (XII), (3a*S*,18a*S*,21a*S*,36a*S*)-2,20-di(*tert*-butyl)-2,20-dimethyltetracosahydrodi[1,3]dioxolo[4,5-*o*:4,5-*f*′][1,4,7,10,13,18,21,24,27,30]decaoxacyclotetratriacontine (XIII), (3a*S*,21a*S*,24a*S*,-42a*S*)-2,23-di(*tert*-butyl)2,23-dimethyloctacosahydrodi[1,3]dioxolo[4,5-r:4,5-l1][1,4,7,10,13,16,21,-24,27,30,33,36]dodecaozacyclotetracontine (XIV), (3a*S*,15a*S*, 18a*S*,30a*S*)-2,17-diphenyleieicosahydrodi[1,3]dioxolo[4,5-*l*:4,5-*z*][1,4,7,10,15,18,21,24]-octaoxacyclooctacosane (XV), (3a*S*,18a*S*,21a*S*,36a*S*)-2,20-diphenyltetracosahydrodi[1,3]dioxolo[4,5-*o*:4,5-*f*′][1,4,7,10,13,18,21,24,27,30]decaoxacyclotetratriacontine (XVI) and (3a*S*, 21a*S*,24a*S*,42a*S*)-2,23-diphenylocta©›`hydrodi[1,3]dioxolo[4,5-*r*:4,5-*l*′][1,4,7,10,13,16,21,24,27,30,33,36]dodecaoxacyclotetracontine (XVII). To a suspension of sodium hydride (7.2 g, 0.3 mmol) in anhydrous dioxane (400 ml) at stirring under argon atmosphere was added dropwise a solution of diol **IV** (6.12 g, 0.03 mol) or **V** (6.3 g, 0.03 mol) in anhydrous dioxane (50 ml). The mixture was stirred at 50–60°C for 1 h, and then was added dropwise a solution of ditosylate of tri- (16,03 g, 0,035 mol), tetra- (17.57 g, 0.035 mol), or pentaethylene glycol [18] (19.11 g, 0.035 mol) in anhydrous dioxane (500 ml). The reaction mixture was stirred for 16 h at 90–100°C, cooled, and poured into ice water (200 ml). Reaction products were extracted into chloroform (5 × 100 ml). The combined extracts were died on Na_2SO_4, the solvent was evaporated on a rotary evaporator, the residue was subjected to column chromatography on neutral alumina.

Estimation of crown ethers **VI–XVII** enantioselectivity was performed by measuring the membrane potential of a cell [Ag, AgCl/internal solution// membrane//measured solution/Ag, AgCl] by the method of biionic potentials in 0.01 M solutions of L- and D-valine methyl ester hydrochlorides. The internal solution consisted of 0.01M solution of L,D-valine methyl ester hydrochloride, the membrane was 1% solution of the appropriate ligand in chloroform. The membrane was separated from the measured solution with a cellophane film 20μm thick. EmF was measured on digital pH-meter Radelkis OP-208/1 at 20±1°C. The slope of the calibration curves for all compounds studied was 50±9 mV per decade in the concentration range 10^{-4}–10^{-1} mol l^{-1}. The values K_{LD} were calculated by equation (1) [17].

$$\log K_{LD} = (E_L - E_D)/S = \Delta E_{LD}/S, \quad (1)$$

where E_L and E_D are electrode potentials at equal concentrations of L- and D-valine methyl ester hydrochlorides, S is the slope of the calibration curve.

REFERENCES

1. Len, Zh.-M., *Supramolekulyarnaya khimiya* (Supramolecular Chemistry), Novosibirsk.: Nauka, 1998.
2. Stoddart, J.F., *Progress in Macrocyclic Chemistry*, Izatt, R.M. and Christensen, J.J., Eds., New York: Willey, 1981, vol. 2, pp. 173–245.
3. Khiraoka, M., *Kraun-soedineniya* (Crown-Compounds), Moscow: Mir, 1986.
4. Potvin, P.G. and Lehn, J.-M., *Synthesis of Macro-Cycles: The Design of Selective Complexing Agents–Progress in Macrocyclic Chemistry*, Izatt, R.M., and Christensen, J.J., New York: Willey, 1987, vol. 3, pp. 167–239.
5. Zhang, X.X., Bradshaw, J.S., and Izatt, R.M., *Chem. Rev.*, 1997, vol. 97, pp. 3313–3362.
6. Baxter, S.L. and Bradshaw, J.S., *J. Heterocyclic Chem.*, 1981, vol. 18, no. 2, pp. 233–245.
7. Sutherland, J.O., *Heterocycles*, 1984, vol. 21, no. 1, pp. 235–248.
8. Chadwick, D.J., Cliffe, J.A., Sutherland, J.O., and Newton, R.F., *J. Chem. Soc., Perkin Trans. I*, 1984, no. 8, pp. 1707–1717.
9. Fyles, T.M., James, T.D., Pryhitka, A., and Zojaji, M., *J. Org. Chem.*, 1993, vol. 58, no. 26, pp. 7456–7468.
10. MacFarland, D.K. and Landis, C.R., *Organometallics*, 1996, vol. 15, no. 2, pp. 483–485.
11. Cross, J.J. and Fyles, T.M., *J. Org. Chem.*, 1997, vol. 62, no. 18, pp. 6226–6230.
12. Zeng, B. and Fyles, T.M., *J. Org. Chem.*, 1998, vol. 63, no. 23, pp. 8337–8345.
13. Wenzel, T.J. and Thurston, J.E., *J. Org. Chem.*,

2000, vol. 65, no. 5, pp. 1243–1248.
14. Luk'yanenko, N.G., Lobach, A.V., Lyamtseva, L.N., Nazarova, N.Yu., and Karpenko, L.P., *Zh. Org. Khim.*, 1988, vol. 24, no. 2, pp. 324–331.
15. Luk'yanenko, N.G., Lobach, A.V., Nazarova, N.Yu., Karpenko, L.P., and Lyamtseva, L.N., *Khim. Geterotsikl. Soed.*, 1988, no. 5, pp. 687–691.
16. Luk'yanenko, N.G., Bogatskii, A.V., Basok, S.S., Ostrovskaya, L.K., Nazarova, N.Yu., and Karpenko, L.P., *Zh. Org. Khim.*, 1984, vol. 20, no. 7, pp. 1580–1587.
17. Thoma, A.P., Viviani-Nauer, A., Schellenberg, K.H., Bedecovich, D., Pretch, E., Preiog, V., and Simon, W., *Helv. Chim. Acta*, 1979, vol. 62, pp. 2303–2316.
18. Lobach, A.V., Basok, S.S., Pastushok, V.N., Shcherbakov, S.V., and Ostrovskaya, L.K., *Reaktivy i osobo chistye veshchestva* (Chemicals and Reagents and Super High Purity Compounds), Moscow: NIITEKhIM, 1983, no. 3, pp. 41–43.