4th International Electronic Conference on Medicinal Chemistry
1-30 November 2018
chaired by Dr. Jean Jacques Vanden Eynde
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Z-Stereoselective Catalytic Synthesis of Natural Acids, Lembehynes, and Acetogenins - Modern Preparations for Medicine

Vladimir A. D'yakonov [1,*], Lilya U. Dzhemileva [1], Alexey A. Makarov [1], Regina A. Tuktarova [1], Svetlana R. Ishmukhametova [1], Evgenii N. Andreev [1], and Usein M. Dzhemilev [1]

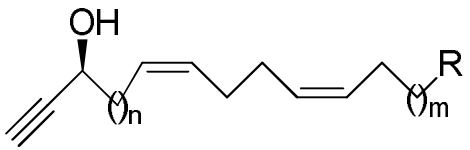
[1] Institute of Petrochemistry and Catalysis, Russian Academy of Sciences, 141 Prospekt Oktyabrya, Ufa 450075, Russian Federation

* Corresponding author: DyakonovVA@gmail.com

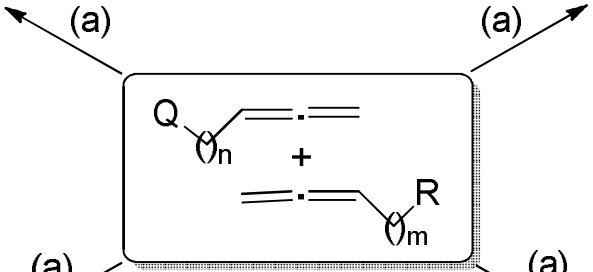
Institute of Petrochemistry and Catalysis, Russian Academy of Sciences

Z-Stereoselective Catalytic Synthesis of Natural Acids, Lembehynes, and Acetogenins - Modern Preparations for Medicine

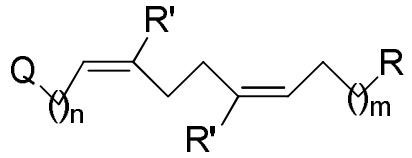
Graphical Abstract



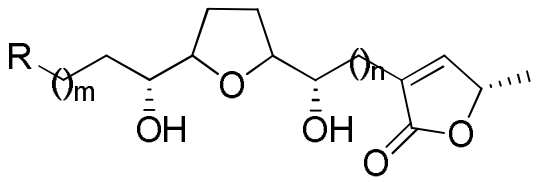
Lembehynes
(antitumor and neritogenic activity)



(a) EtMgBr, [Ti], Mg
R = alkyl, aryl, cyclo
Q = OR, NR_2, SiR_3

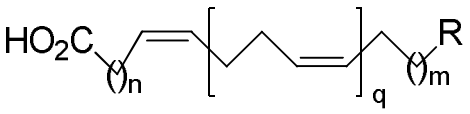


Substituted 1*Z*,5*Z*-dienes
(fragrant substances, pheromones, isoprenoids)



Acetogenins

(antitumor, antiviral and antibacterial activity)



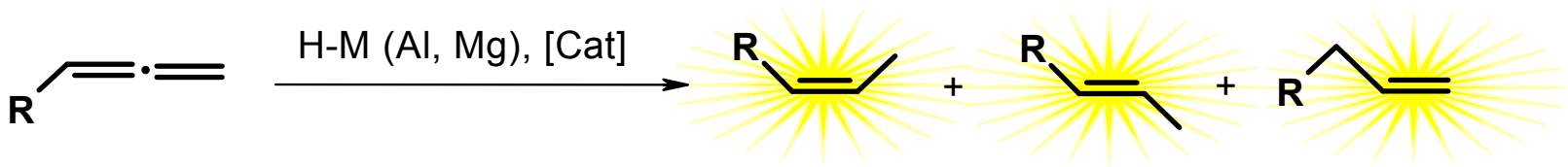
Di-, tri- and polyenic acids

(antitumor, antiviral and antibacterial activity)

Abstract:
The report discusses the latest achievements of the authors in developing original methods for stereoselective synthesis of natural acetogenins, higher bis-methylene-separated di- and trienoic acids, lembehynes that are of exceptional interest as low-toxic target antitumor drugs, as well as compounds with neritogenic activity for treating neurodegenerative diseases.
The synthetic approaches to the above listed natural compounds are based on the use at the key stage of the synthesis, of new organometallic reactions, such as Ti-catalyzed homo- and cross-cyclomagnesiation of 1,2-dienes, involving available Grignard reagents.
The studies of the synthesized compounds for their antitumor and antibacterial activities *in vitro* were performed with the use of unique equipment in "Centre for Molecular Design and Biological Screening of Candidate Substances for the Pharmaceutical Industry" at the Institute of Petrochemistry and Catalysis of RAS using modern methods such as flow cytofluorometry, fluorescence microscopy and Western blotting.
For compounds that showed the greatest activity, in vivo tests were performed for linear mice with grafted malignant Lewis carcinoma.
Key words: Natural acetogenins; Higher bis-methylene-separated(interrupted) di- and trienoic acids; Lembehynes; Antitumor drugs; Neritogenic activity.

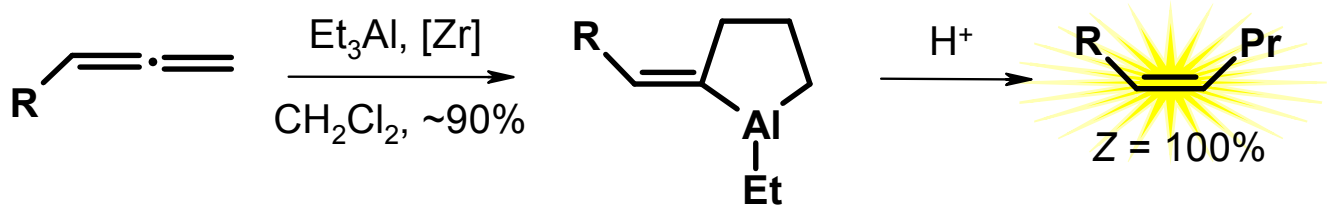
1,2-DIENES IN STEREOSELECTIVE SYNTHESIS OF ALKENES

Hydrometalation of 1,2-dienes



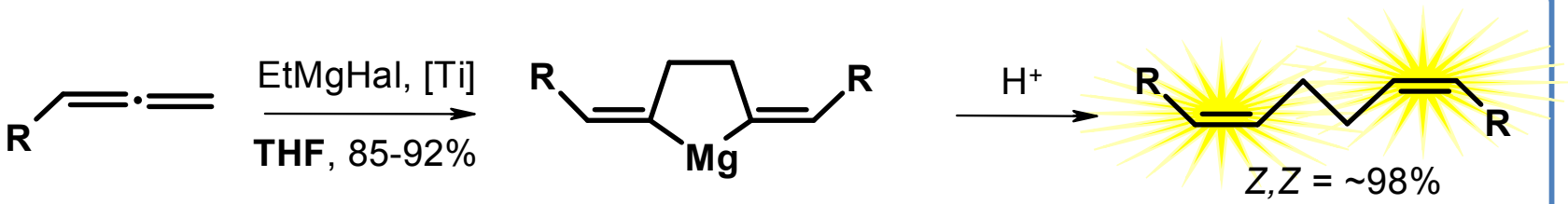
S. Nagahara et el. Bull. Chem. Soc. Jpn., 1993, 66, 3783.

Cycloalumination of 1,2-dienes



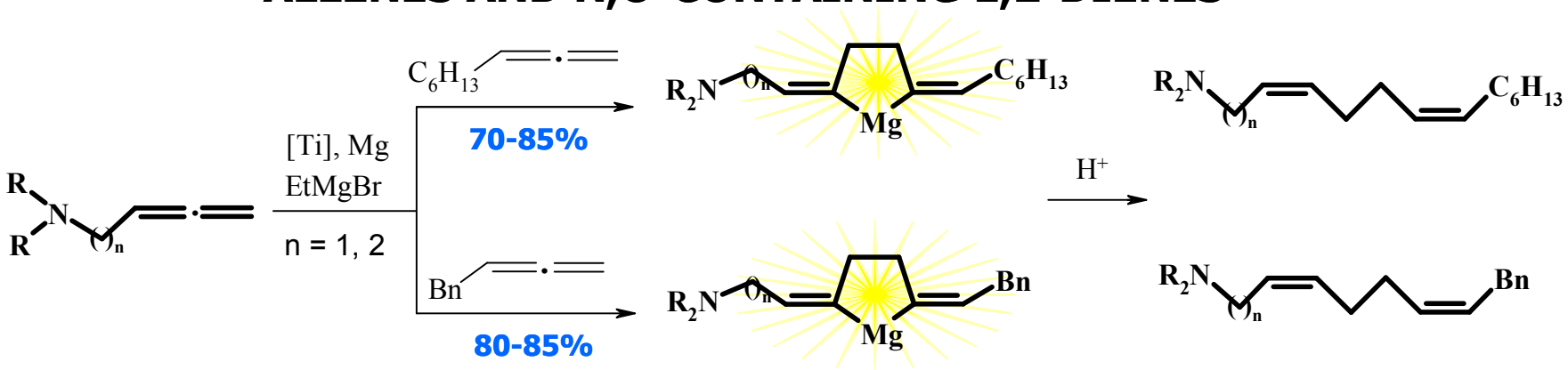
U.M. Dzhemilev et al. Russ. Chem. Bull. 2002, 51, 2255.

Cyclomagnesiation of 1,2-dienes



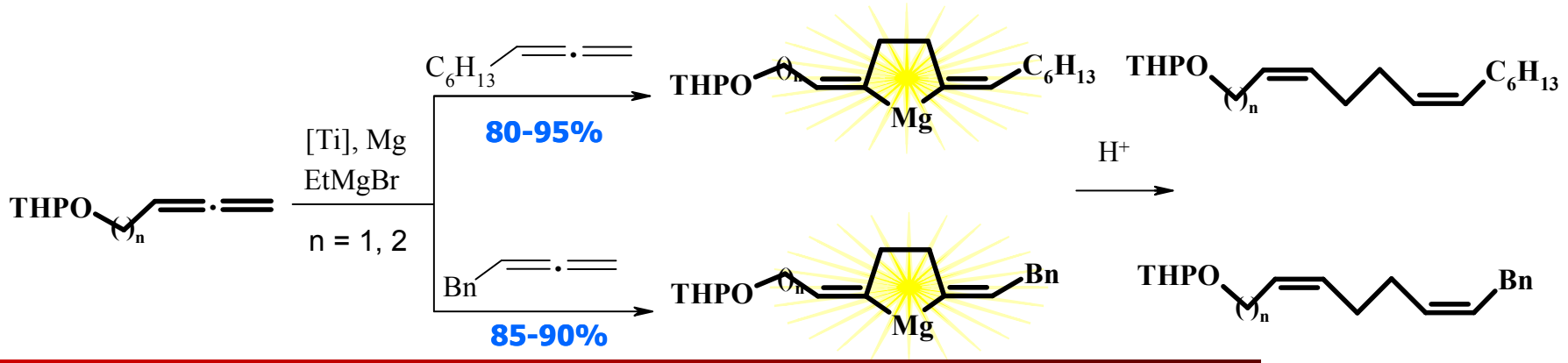
U.M. Dzhemilev et al. Tetrahedron., 2004, 60, 1287.

INTERMOLECULAR CYCLOMAGNESIATION OF ALKYL(ARYL) ALLENES AND N,O-CONTAINING 1,2-DIENES



[Ti] = Cp_2TiCl_2; R = Et, i-Pr, -$(CH_2)_5$-, -C_2H_4-O-C_2H_4-.

N-containing 1,2-diene:cyclo-1,2-diene:EtMgBr:Mg:[Ti]= 10:12:26:20:1; Et_2O, 6 h, r. t.

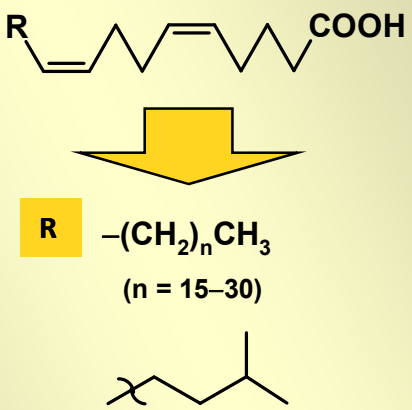


O-containing 1,2-diene:cyclo-1,2-diene:EtMgBr:Mg:[Ti]= 10:11:24:20:0.5; Et_2O, 6 h, r. t.

V.A. D'yakonov, A.A. Makarov, E.Kh. Makarova, U.M. Dzhemilev, *Tetrahedron.*– 2013, V. 69, P. 8516-8526

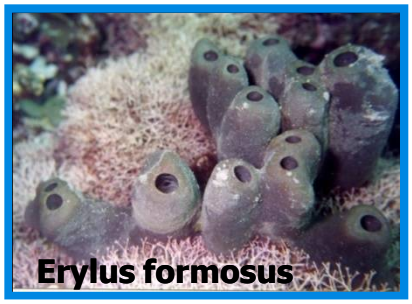
NATURAL SOURCES OF 5*Z*,9*Z*-DIENOIC ACIDS

Natural 5*Z*,9*Z*-dienoic acids



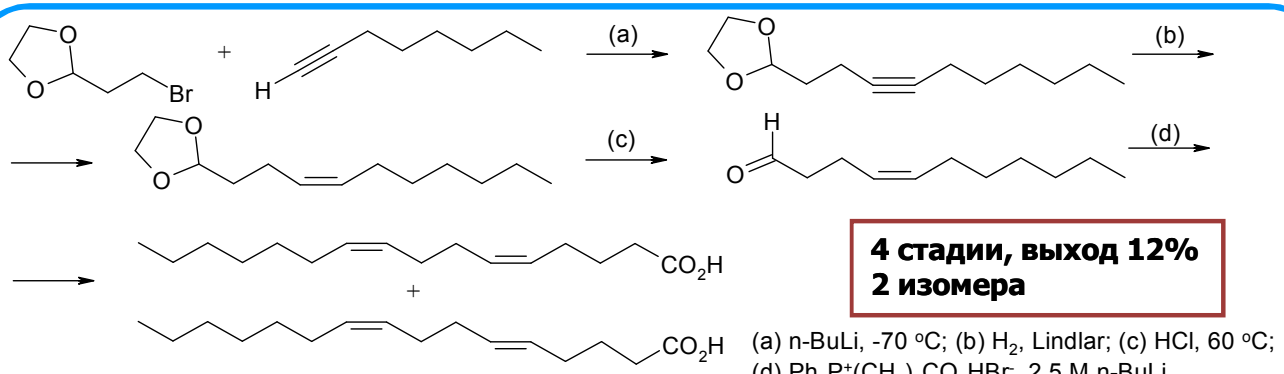
Isolated from the marine sponges (Aplysina fistularis, Axinella verrucosa) and seeds (Pinus tabulaeformis)

Carballeira N.M., et al. J. Nat. Prod., 2002, 64, 1715



Efficient inhibitors of topoisomerases I and II; simultaneously exhibit antitumor, antiviral, antiparasitic and antibacterial activities

KNOWN METHODS FOR THE SYNTHESIS OF 5*Z*,9*Z*-DIENOIC ACIDS

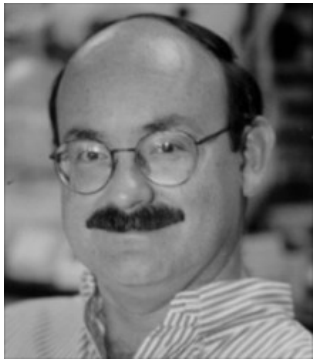


4 стадии, выход 12%
2 изомера

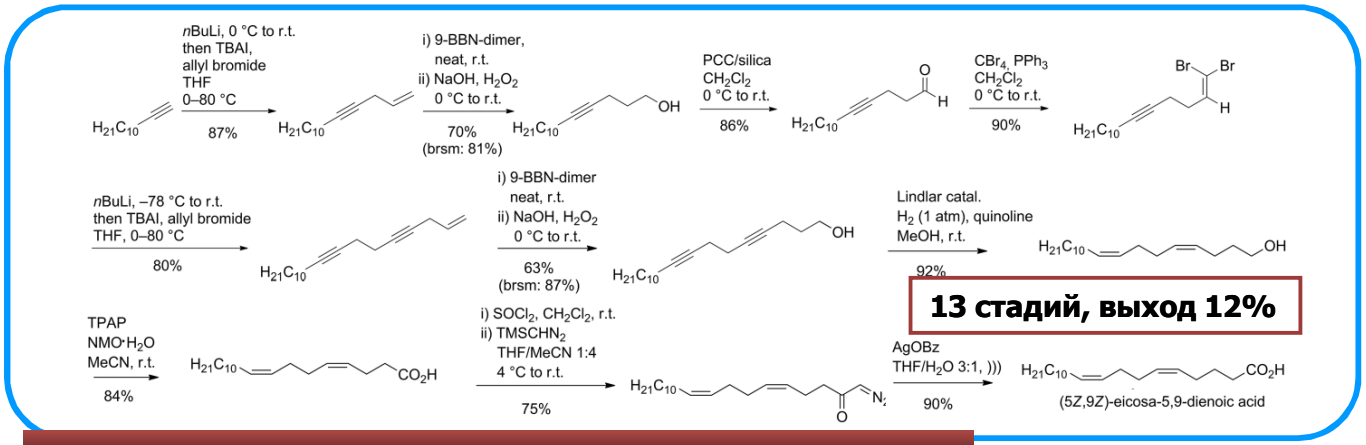
(a) n-BuLi, -70 °C; (b) H_2, Lindlar; (c) HCl, 60 °C;
(d) $Ph_3P^+(CH_2)_4CO_2HBr^-$, 2.5 M n-BuLi.

N.M. Carballeira, A. Emiliano, A. Guzman. Chem. Phys. Lipids, 100, (1999), 33-40

N.M. Carballeira, J.E. Betancourt, E.A. Orellano, F.A. Gonzalez. J. Nat. Prod, 65, (2002), 1715-1718



Prof. Nestor Carballeira
University of Puerto Rico



13 стадий, выход 12%

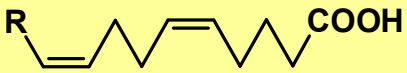
J. Adrian , C. B. W. Stark, Eur. J. Org. Chem, 27, (2016), 4607-4610

Prof. Christian B. W. Stark
Universität Hamburg

EFFICIENT SYNTHESIS OF 5*Z*,9*Z*-DIENOIC ACIDS

Known

Natural 5*Z*,9*Z*-dienoic acids



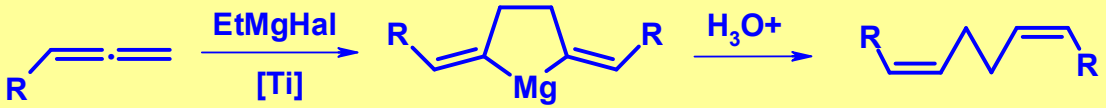
$R = -(CH_2)_nCH_3$

(n = 15–30)

Isolated from the marine sponges (Aplysina fistularis, Axinella verrucosa) and seeds (Pinus tabulaeformis)

Carballeira N.M., et al. J. Nat. Prod., 2002, 64, 1715

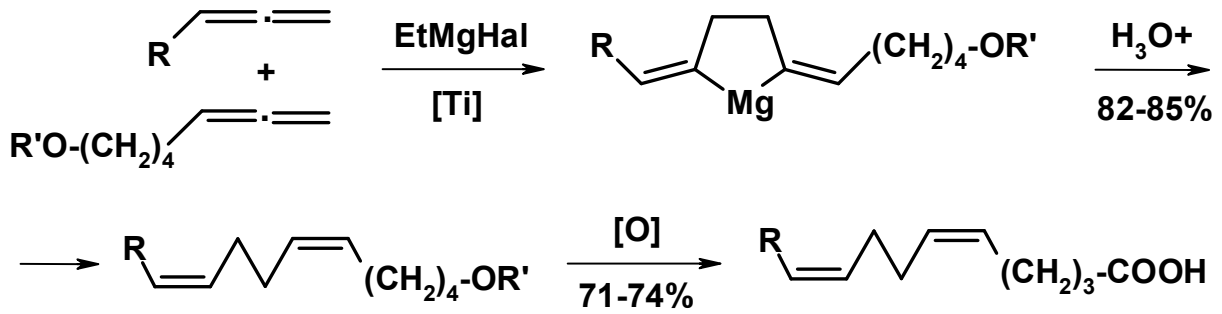
The cyclomagnesiation reaction of allenes to give 2,5-dialkylidenemagnesacyclopentanes



Dzhemilev U.M., et al. Tetrahedron, 2004, 60, 1287
D'yakonov V.A., et al. Tetrahedron, 2008, 64, 10188

NEW METHOD :

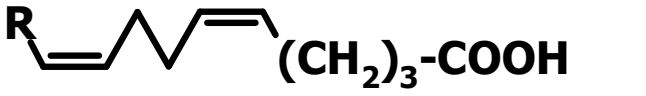
Stereoselective synthesis of practically important 5*Z*,9*Z*-dienoic acids is based on the new reaction.



Russ.Chem.Bull., 2012, 61(1),158; Russ.J. Org.Chem., 2012, 48(3), 349; Tetrahedron, 2013, 69, 8516; Chem.Commun., 2013, 49, 8401.

IN VITRO STUDY ON TOPOISOMERASE I INHIBITORY ACTIVITY OF THE SYNTHESIZED 5*Z*,9*Z*-DIENOIC ACIDS

V. A. D'yakonov, A. A. Makarov, L. U. Dzhemileva, E. H. Makarova, U. M. Dzhemilev, *Chem. Commun.*, 2013, 49, 8401



R	Активность
C_8H_{17}	>10 μM
$C_{10}H_{21}$	>0.1 μM
$C_{11}H_{23}$	>2 μM
$C_{12}H_{25}$	>1 μM

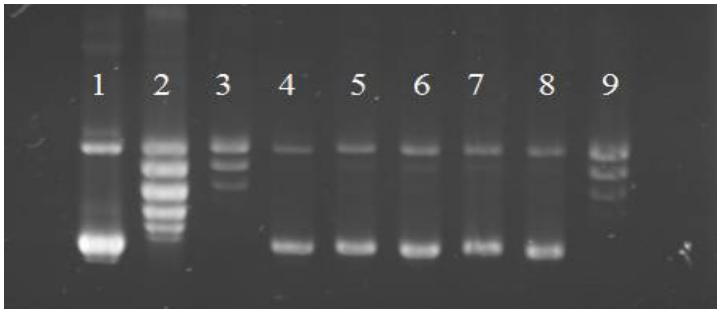
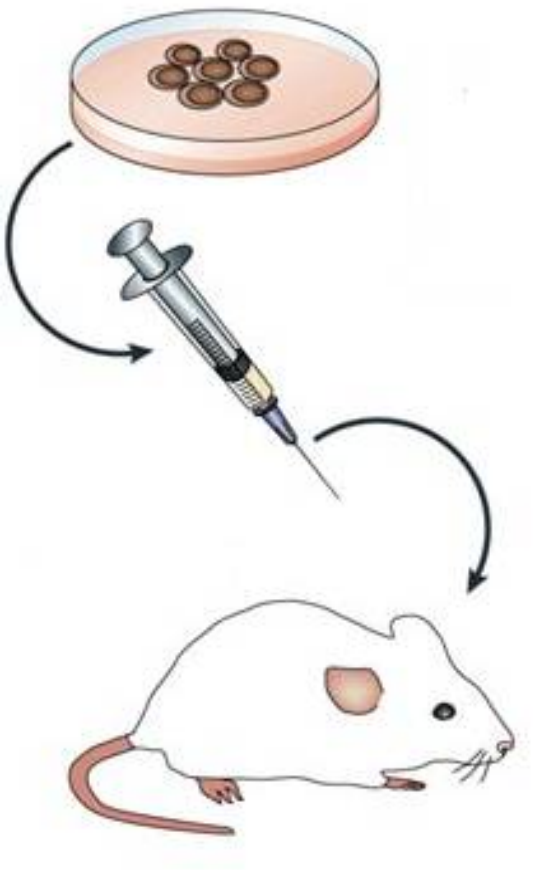
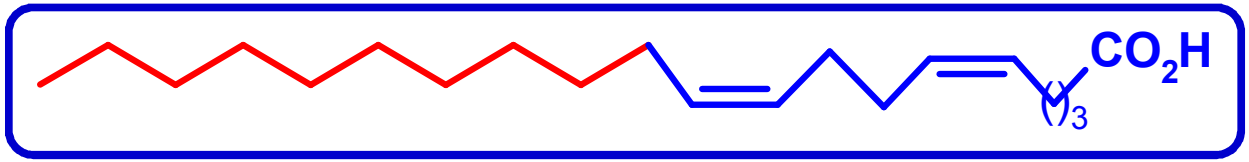


Fig. Electrophoregram of the products of relaxation of supercoiled plasmid DNA in vitro induced by topoisomerase I (Topogen, USA) in the presence of (5Z,9Z)-5,9-eicosadienoic acid. 1. Supercoiled plasmid DNA (pHOT1). 2. Relaxed DNA form (visualization of the set of topoisomers). 3. Negative control with DMSO (concentration 3%). 4. Relaxation reaction of plasmid DNA in the presence of camptothecin (10 μM). 5–9. Effect of different concentrations of (5Z,9Z)-5,9-eicosadienoic acid on the relaxation of plasmid DNA (5 – 0.75, 6 – 0.5, 7 – 0.25, 8 – 0.1, 9 – 0.01 μM).

EICOSA-5*Z*,9*Z*-DIENOIC ACID





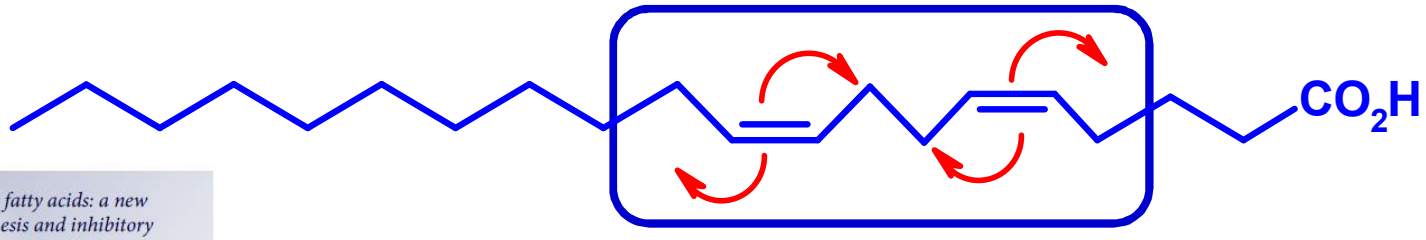
As a tumor model, malignant Lewis lung carcinoma (LLC) was taken, growing as a solid node, metastasizing hematogenically into the lungs, Which is not subjected to spontaneous regression. In the experiments, 53 female C57Bl / 6j mice with an average body weight of 20 g, were used.

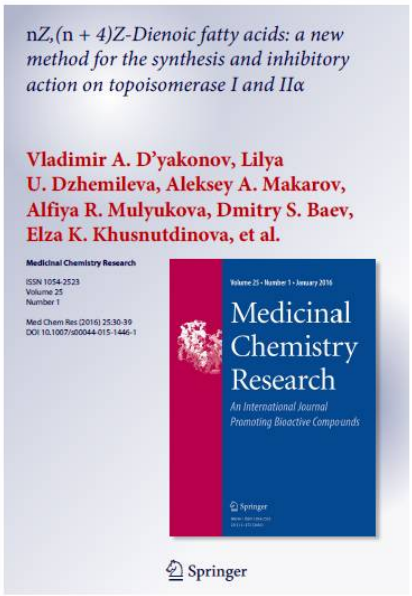
1) Analysis of survival rates revealed a significant increase in the lifespan of mice under the influence of agent B-1 at a dose of 30 mg / kg relative to the control group and mice in the administration of paclitaxel.

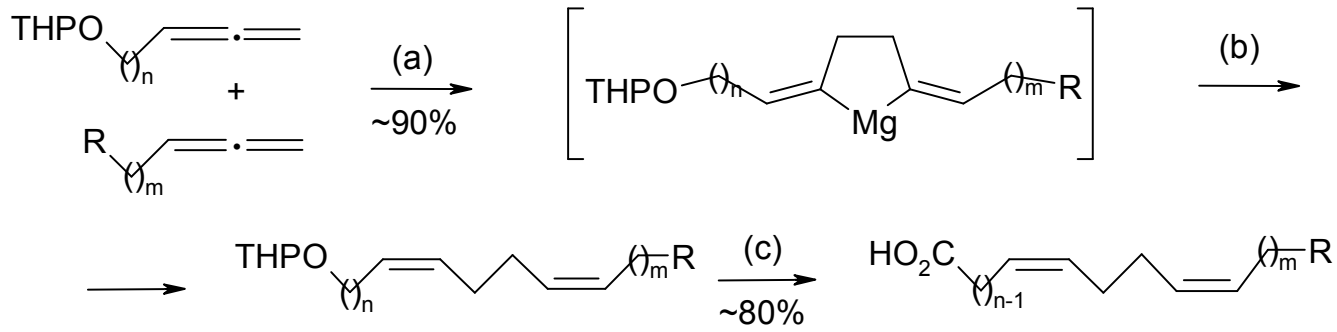
2) With intraperitoneal administration during the period of progressive growth of LLC, the agent B-1 effectively retards the growth of the primary node by inhibiting tumor cell division.

Conclusion: The conducted studies reveal, that agent B-1 possesses antitumor properties. They are manifested, when introduced into mice intraperitoneally during tumor progression. The tolerability of the agent B-1 in animals upon course administration of up to 100 mg / kg is good.

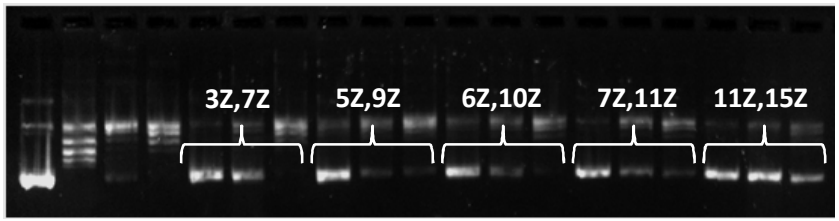
EFFECT OF THE POSITION OF THE 1*Z*,5*Z*-DIENE GROUP ON THE INHIBITORY ACTIVITY OF hTOPI AND hTOPII

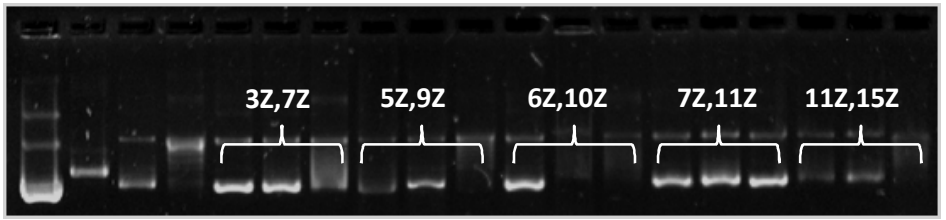






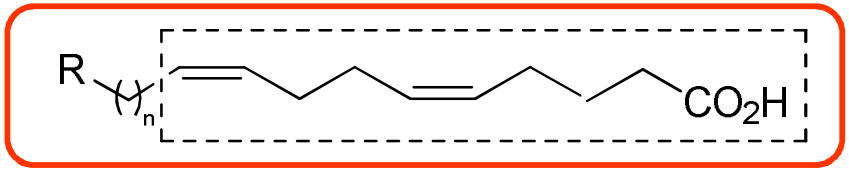
(a): EtMgBr, Mg, [Ti]; (b): H_3O^+; (c) Jones oxidation. [Ti] = Cp_2TiCl_2
(R = Me) n = 2: m = 11; n = 4: m = 5, 9, 11, 13, 17;
n = 5: m = 8; n = 6: m = 7; n = 10: m = 3, 11.

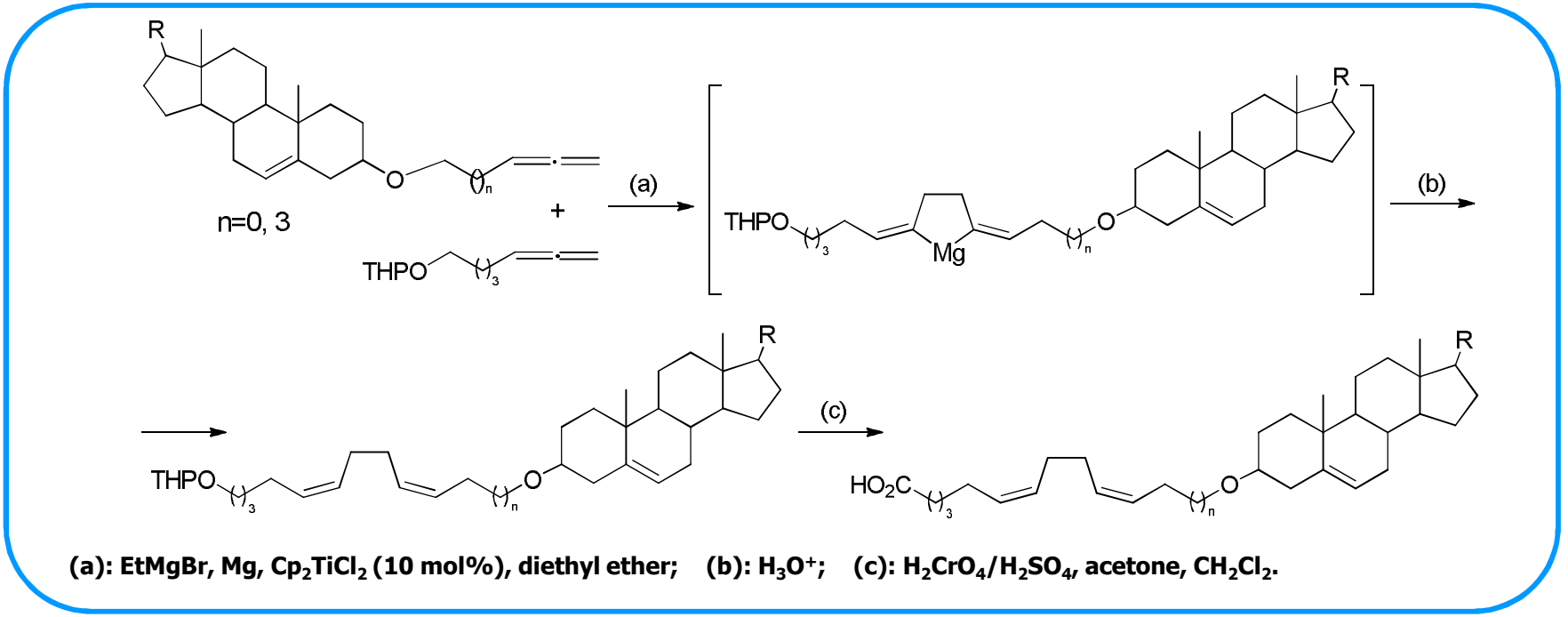




V.A. D'yakonov, et al. Med. Chem. Res., 2016, 25(1), 30-39
V.A. D'yakonov, et al. Bioorg. and Med. Chem. Lett., 2015, 25(11), 2405–2408

SYNTHESIS OF STEROID 5*Z*,9*Z*-DIENOIC ACIDS



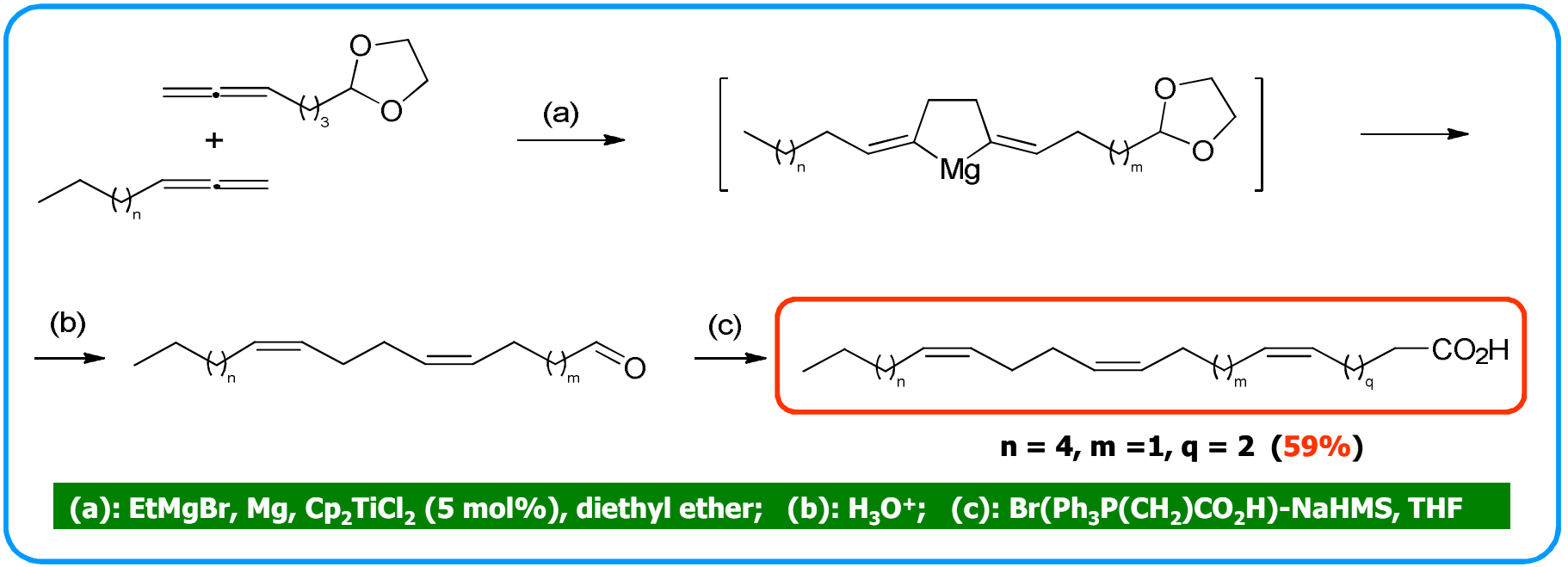


(a): EtMgBr, Mg, Cp_2TiCl_2 (10 mol%), diethyl ether; (b): H_3O^+; (c): H_2CrO_4/H_2SO_4, acetone, CH_2Cl_2.

V.A. D´yakonov, L.U. Dzhemileva, A.A. Makarov, A.R. Mulyukova, R.A. Tuktarova, I.I. Islamov, U.M. Dzhemilev. Russ. Chem. Bull., 2015, 64(9), 2135-2140.

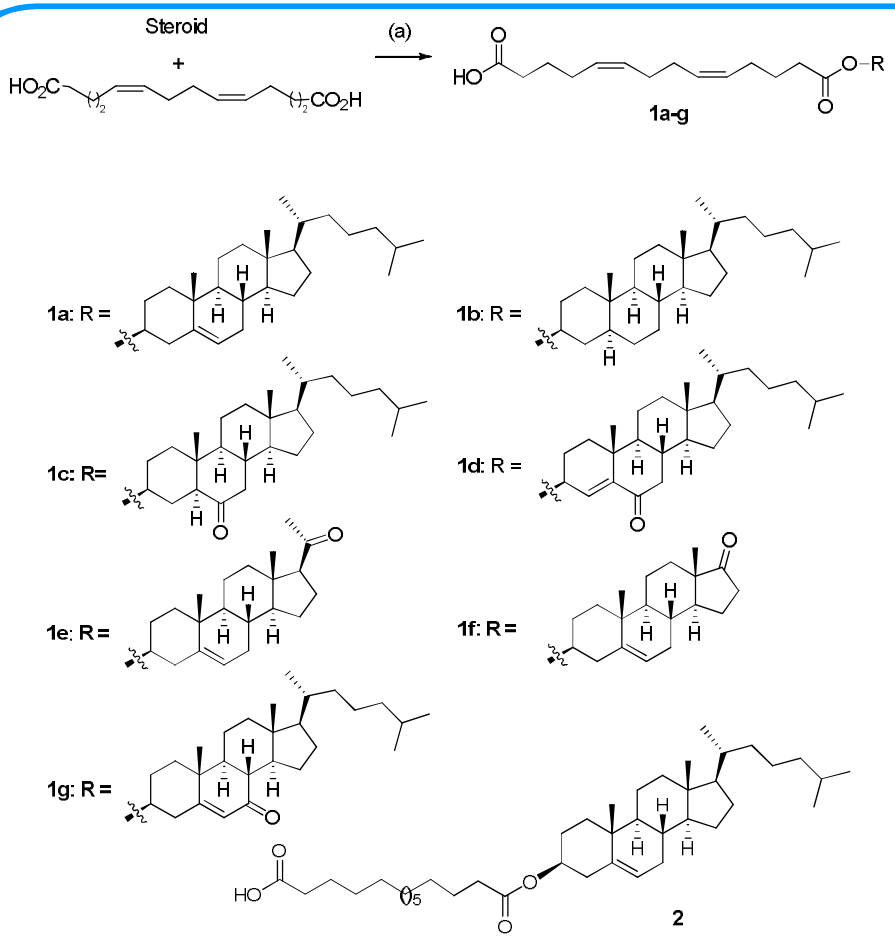
FIRST SYNTHESIS OF 5*Z*,9*Z*,13*Z*-EICOSATRIENOIC ACID

Haliclona cinerea



V. A. D'yakonov, A. A. Makarov, A. R. Salimova, E. N. Andreev, U. M. Dzhemilev, *Mendeleev Communications*, 2017, *27*, 234-236

SYNTHESIS AND IN VITRO STUDY OF CYTOTOXIC ACTIVITY OF STEROID 5*Z*,9*Z*-DIENOIC ACIDS



Comp.	IC_{50} (μM) HEK 293	IC_{50} (μM) Jurkat	IC_{50} (μM) K562	IC_{50} (μM) Normal Lympho-cytes	IC_{50} (μM) Fibro-blasts	Top I Inhib. (μM)
1a	0.13 ±0.02	0.10 ±0.01	0.25 ±0.03	0.45 ±0.06	0.67 ±0.04	0.02
1b	1.4 ±0.09	0.8 ±0.008	0.28 ±0.001	0.50 ±0.003	0.54 ±0.01	0.04
1c	0.16 ±0.013	0.40 ±0.01	0.28 ±0.016	0.34 ±0.011	0.55 ±0.01	0.02
1d	0.19 ±0.016	0.13 ±0.04	0.25 ±0.01	0.28 ±0.06	0.21 ±0.06	0.06
1e	0.11 ±0.010	0.18 ±0.001	0.19 ±0.014	4.24 ±0.013	8.28 ±0.016	0.02
1f	2.6 ±0.09	3.5 ±0.1	3.8 ±0.12	6.6 ±0.10	8.0 ±0.15	0.06
1g	0.12 ±0.07	0.26 ±0.05	0.71 ±0.09	1.8 ±0.16	2.0 ±0.10	0.02
2	22.0 ±1.3	21.5 ±1.2	14.4 ±1.2	18.18 ±0.8	62.4 ±1.2	>500
Choles-tane	125.17 ±0.9	133.6 ±2.3	145.4 ±1.6	182.9 ±1.3	145.1 ±1.6	>100
Pregne-nolone	78.2 ±0.5	59.6 ±0.2	183.9 ±1.1	143.2 ±1.2	130.1 ±3.7	>100
Andro-sterone	88.2 ±1.7	70.6 ±2.1	135.9 ±2.1	128.2 ±1.2	100.3 ±1.4	>100
Campto-thecin	25.17 ±0.9	45.4 ±1.6	33.6 ±2.3	60.9 ±1.6	82.9 ±1.3	0.38
Etopo-side	19.45 ±0.8	48.6 ±2.5	34.7 ±1.5	74.5 ±1.8	68.5 ±1.4	>100

V.A. D'yakonov, L.U. Dzhemileva, R.A. Tuktarova, A.A. Makarov, I.I. Islamov, A.R. Mulyukova, U.M. Dzhemilev. *Steroids*, 2015, *102*, 110-117 ; V.A. D'yakonov, R. A. Tuktarova, L.U. Dzhemileva, M.M. Yunusbaeva, I.R. Ramazanov, U.M. Dzhemilev. *Anti-Cancer Agents in Medicinal Chemistry*, 2017, 17, 1126-1135.

4th International Electronic Conference on Medicinal Chemistry
1-30 November 2018
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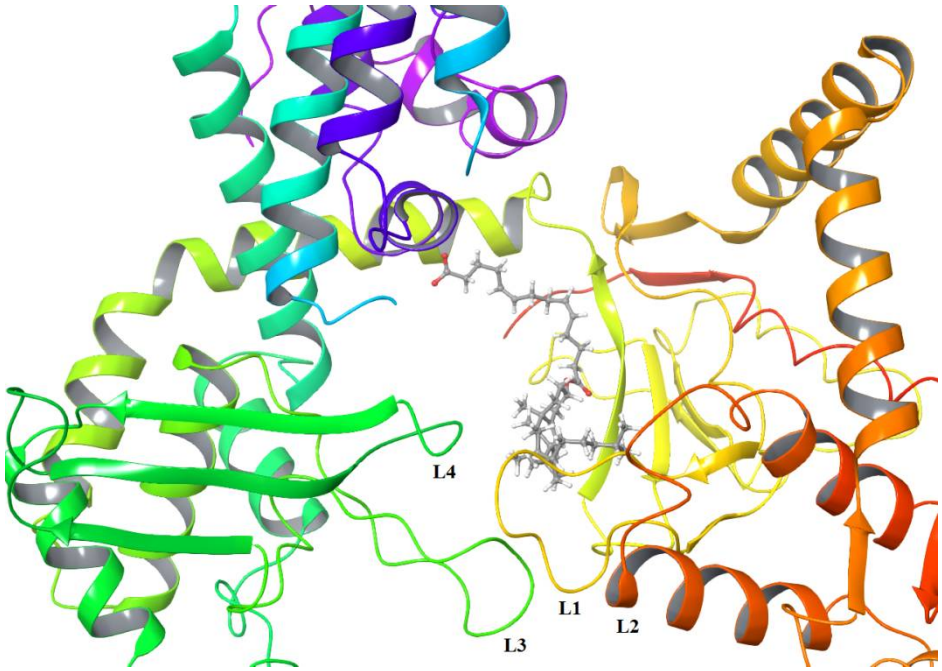
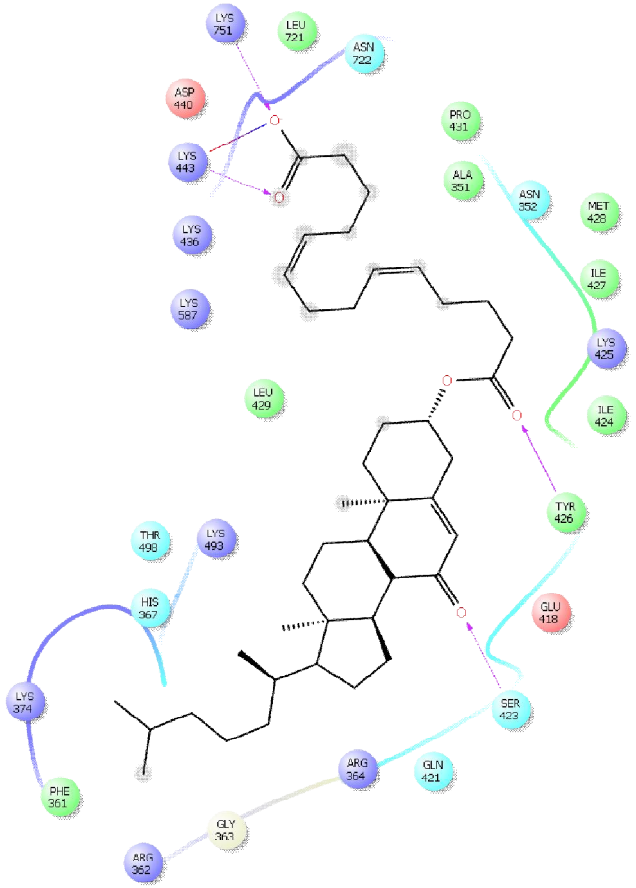
MECHANISM OF TOPOISOMERASE I INHIBITION IN THE PRESENCE OF STEROID 5*Z*,9*Z*-DIENOIC ACIDS





V.A. D'yakonov, R.A. Tuktarova, L.U. Dzhemileva, M.M. Yunusbaeva, I.R. Ramazanov, U.M. Dzhemilev. Novel Hybrid Molecules on the Basis of Steroids and (5Z,9Z)-Tetradeca-5,9-dienoic Acid: Synthesis, Anti-Cancer Studies and Human Topoisomerase I Inhibitory Activity. *Anti-Cancer Agents in Medicinal Chemistry*, 2017, 17, 1126-1135.

4th International Electronic Conference on Medicinal Chemistry
1-30 November 2018

sponsors: MDPI pharmaceuticals

Prof. Christian B. W. Stark

Organic LETTERS

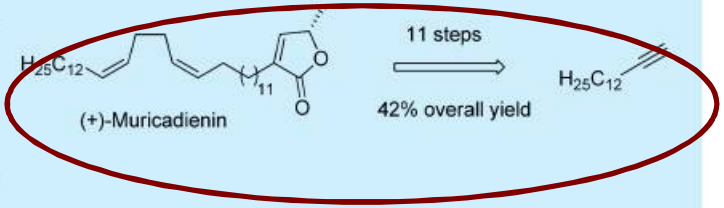
Total Synthesis of Muricadienin, the Putative Key Precursor in the Solamin Biosynthesis

Juliane Adrian and Christian B. W. Stark*

Fachbereich Chemie, Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King Platz 6, 20146 Hamburg, Germany

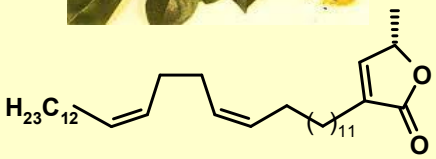
Supporting Information

ABSTRACT: The first total synthesis of muricadienin, the unsaturated putative precursor in the biosynthesis of *trans*- and *cis*-solamin is described. Key steps in the synthesis are a chemoselective hydroboration, a *Z*-selective Wittig reaction, and a Fries rearrangement for introducing the terminal α-substituted butenolide. Thus, muricadienin can be synthesized in 11 steps from commercially available starting materials in 42% overall yield.



Org. Lett., 2014, 16 (22), pp 5886–5889

ORIGINAL METHOD FOR THE SYNTHSIS OF MURICADIENIN AND ITS ANALOGS – THE FOUNDATION FOR THE DEVELOPMENT MODERN ANTIBACTERIAL, ANTIVIRAL AND ANTITUMOR DRUGS

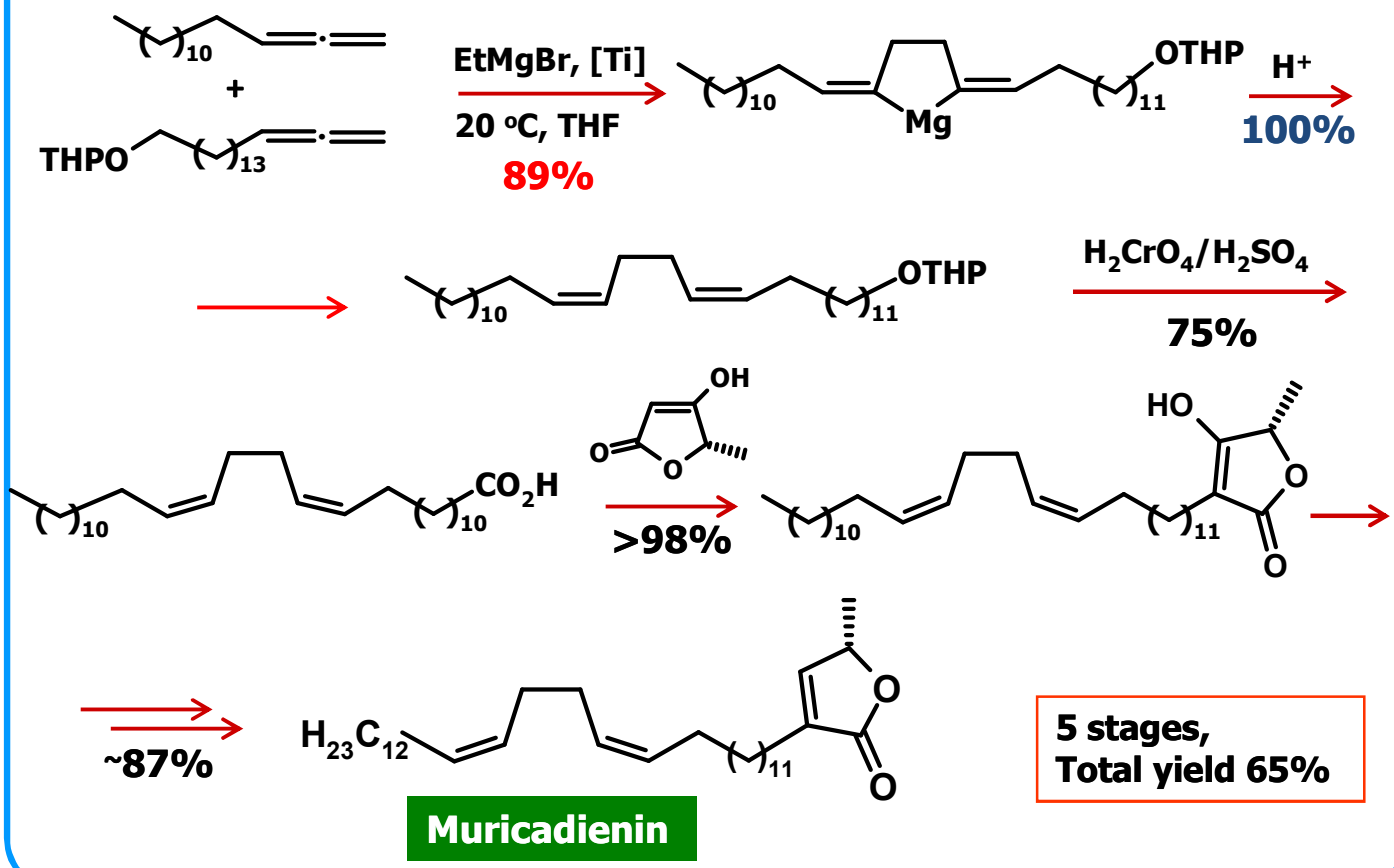


Muricadienin

Isolated from the roots of the plant *Annona muricata*

Can be synthesized in 11 stages in 42% yield

Org. Lett., 2014, 16 (22), pp 5886–5889



Usein M. Dzhemilev; Vladimir A. D'yakonov; Regina A. Tuktarova; Lilya U. Dzhemileva; Svetlana R. Ishmukhametova; Milyausha M. Yunusbaeva; Armin de Meijere; *J. Nat. Prod.* August 17, 2016 (Article) pp 2039–2044

BRAIN DISEASES - THE EPIDEMIC OF THE XXI CENTURY

Prevalence of socially significant diseases:

- Neurological / Mental
- Cardiovascular
- Oncological

PROGNOSES

Disease	2009	2040
	million people	
Parkinson's Disease	16	32
Alzheimer's Disease	25	75

In the world: 2013 - 44.5 million, 2030 - 75.5 million; 2050 - 135.5 million people

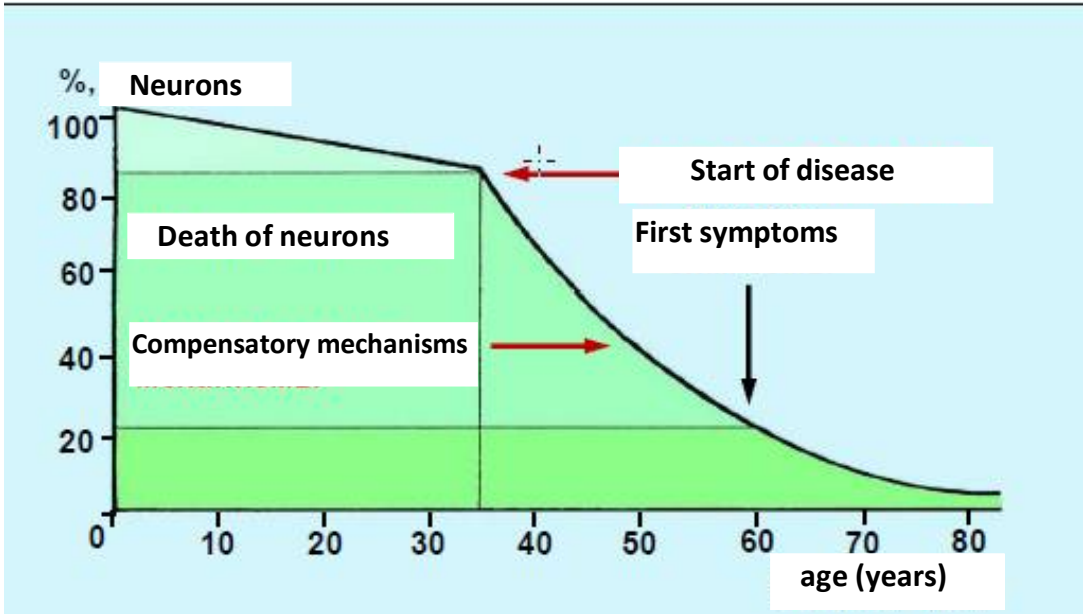
DEMENTIA

Russia: 1.4 - 1.8 million people

Extract from G8 Science Ministers and Presidents of Science Academies protocol (London UK, 12 June 2013)

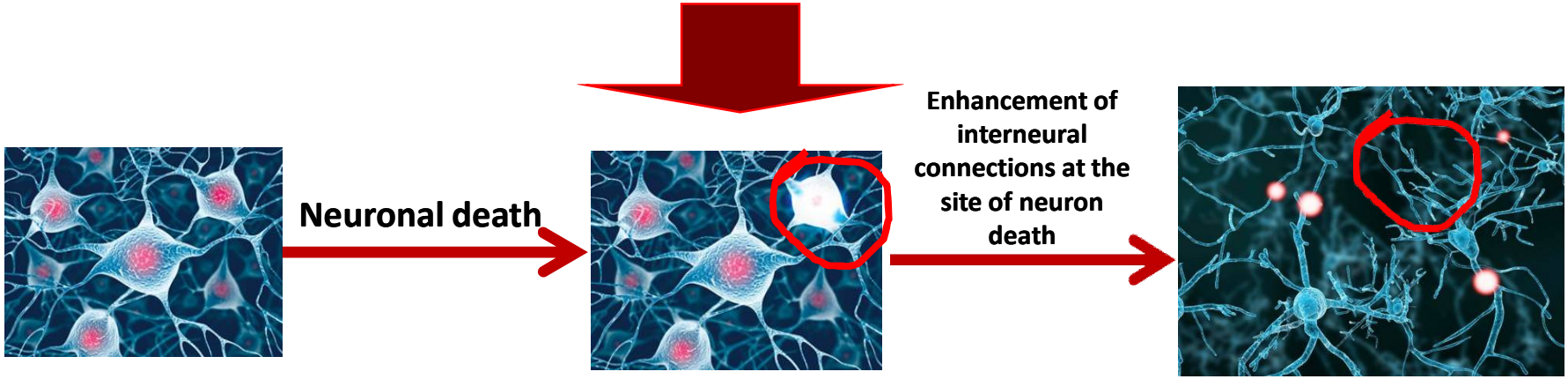
«...Cooperation in the field of neurodegenerative diseases is considered as an example of global challenges involving the creation of a global research infrastructure, which is confirmed by increased funding for this in the US and Canada, as well as by organizing relevant research centers in Paris and Bonn.»

CURRENT CONCEPTS OF PATHOGENESIS, DIAGNOSIS, AND TREATMENT OF NEURODEGENERATIVE DISEASES



Nonspecific neuronal cell death mechanisms

- ✓Increased secretion of growth factors
- ✓Activation of antioxidant systems



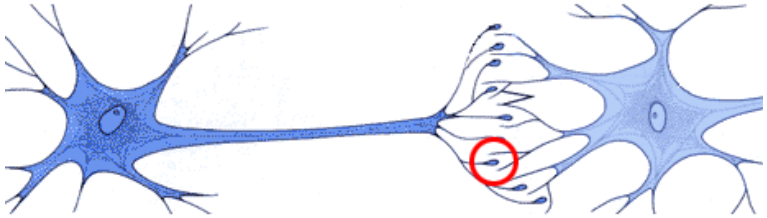
BASIC CONCEPT IN THE TREATMENT OF NEURODEGENERATIVE DISEASES (NDD)

Most NDD causes changes in the chemical communication system in the neural tissue

Oxidative stress

because of the mitochondria destruction

Apoptosis of neurons and microglia



Neurotrophic factors as neuroprotectors upon neurodegenerative diseases

Neurotrophic (growth) factors (BDNF, GDNF, NGF, FGF, etc.)

Problem with addressable delivery!

Drugs

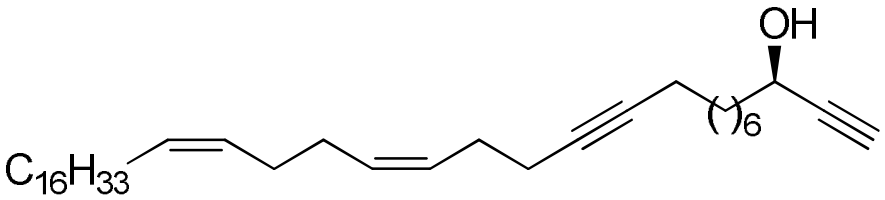
SEMAX *(Met-Glu-His-Phe-Pro-Gly_Pro)*

SELANK *(Thr-Lys-Pro-Arg-Pro-Gly-Pro)*

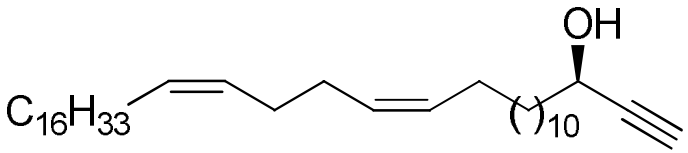
EXPENSIVE! And not always effective! Quickly destroyed!

LEMBEHYNES - EFFICIENT NEURITOGENIC COMPOUNDS

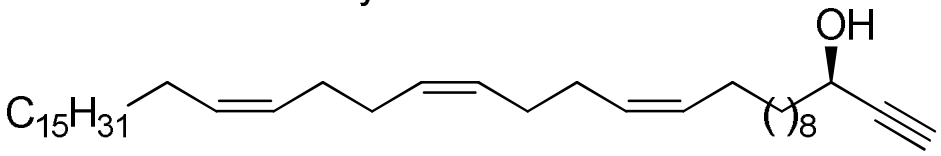
Prof. Motomasa Kobayashi
Osaka University



Lembehyne A



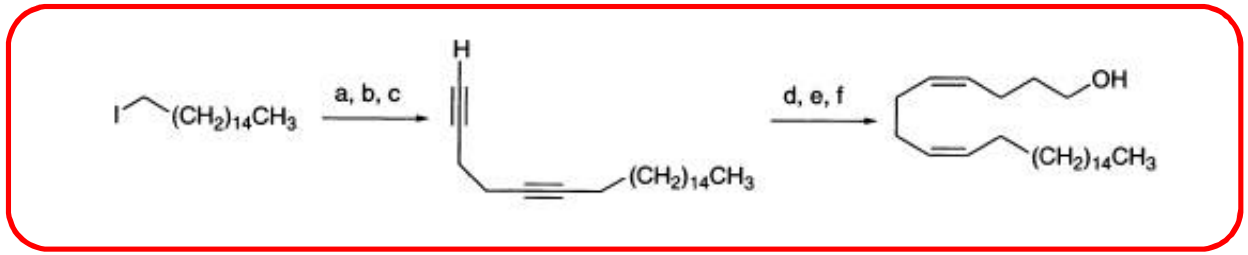
Lembehyne B

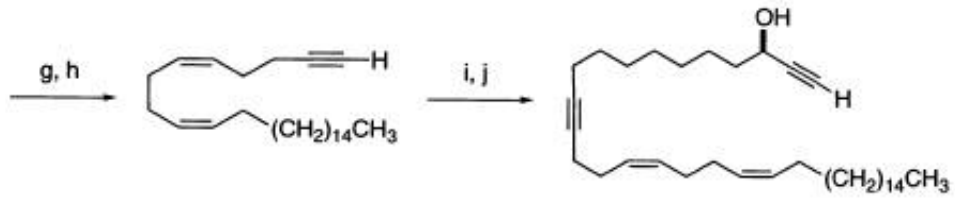


Lembehyne C

Haliclona sp.

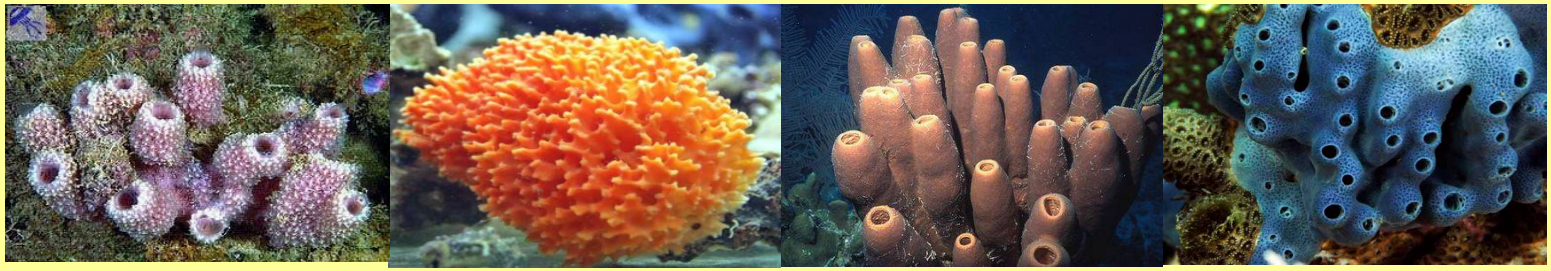
TOTAL SYNTHESIS OF LEMBEHYNE A



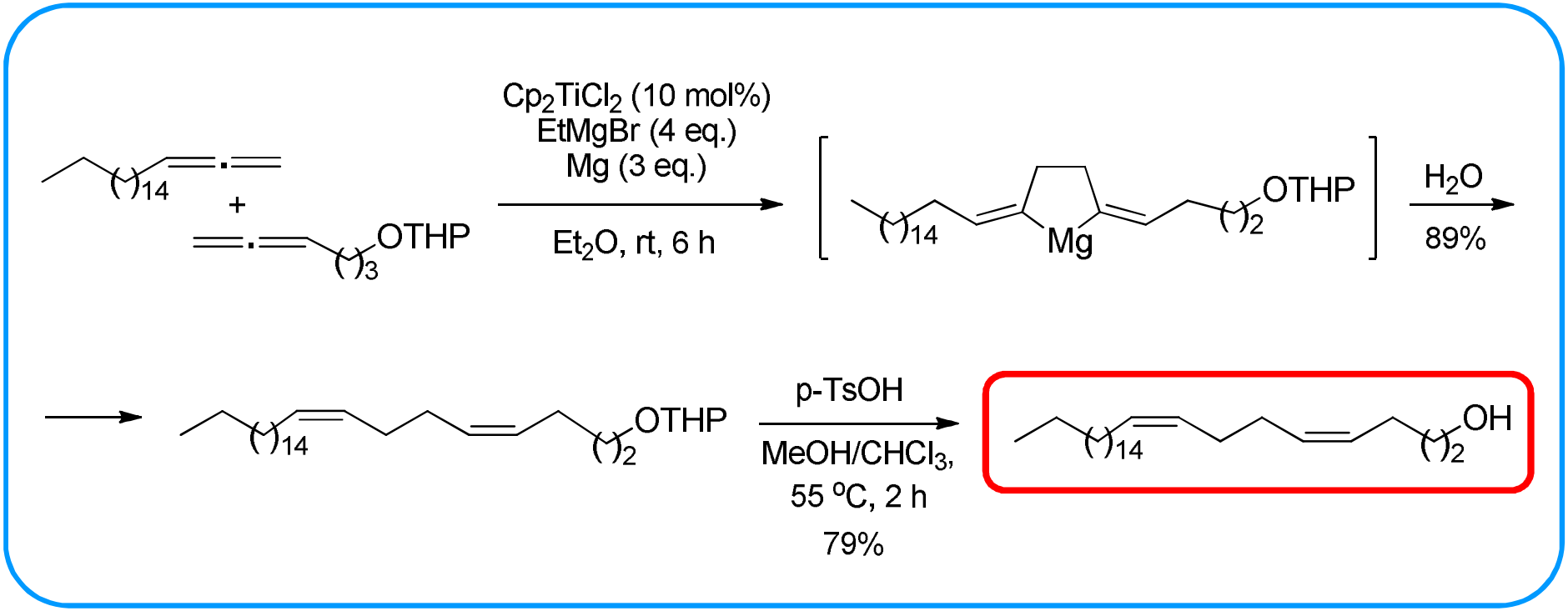


lembehyne A

Scheme. Reagents and conditions: (a) $HC{\equiv}CCH_2CH_2CH_2OH$, ^{n}BuLi, THF, HMPA, −78 to 10°C, 80%; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 85%; (c) $CH_3COCN_2PO(OMe)_2$, K_2CO_3, MeOH, rt, 84%; (d) $ICH_2CH_2CH_2OTBS$, ^{n}BuLi, THF, HMPA, −40°C to rt, 75%; (e) H_2, $Pd/BaSO_4$, quinoline, EtOH, rt; (f) TBAF, THF, rt, 89% two steps; (g) Dess–Martin periodinane, CH_2Cl_2, rt, 84%; (h) $CH_3COCN_2PO(OMe)_2$, K_2CO_3, MeOH, rt, 72%; (i) **6**, ^{n}BuLi, THF, HMPA, −40 to 0°C, 68%; (j) TBAF, THF, rt, 75%.



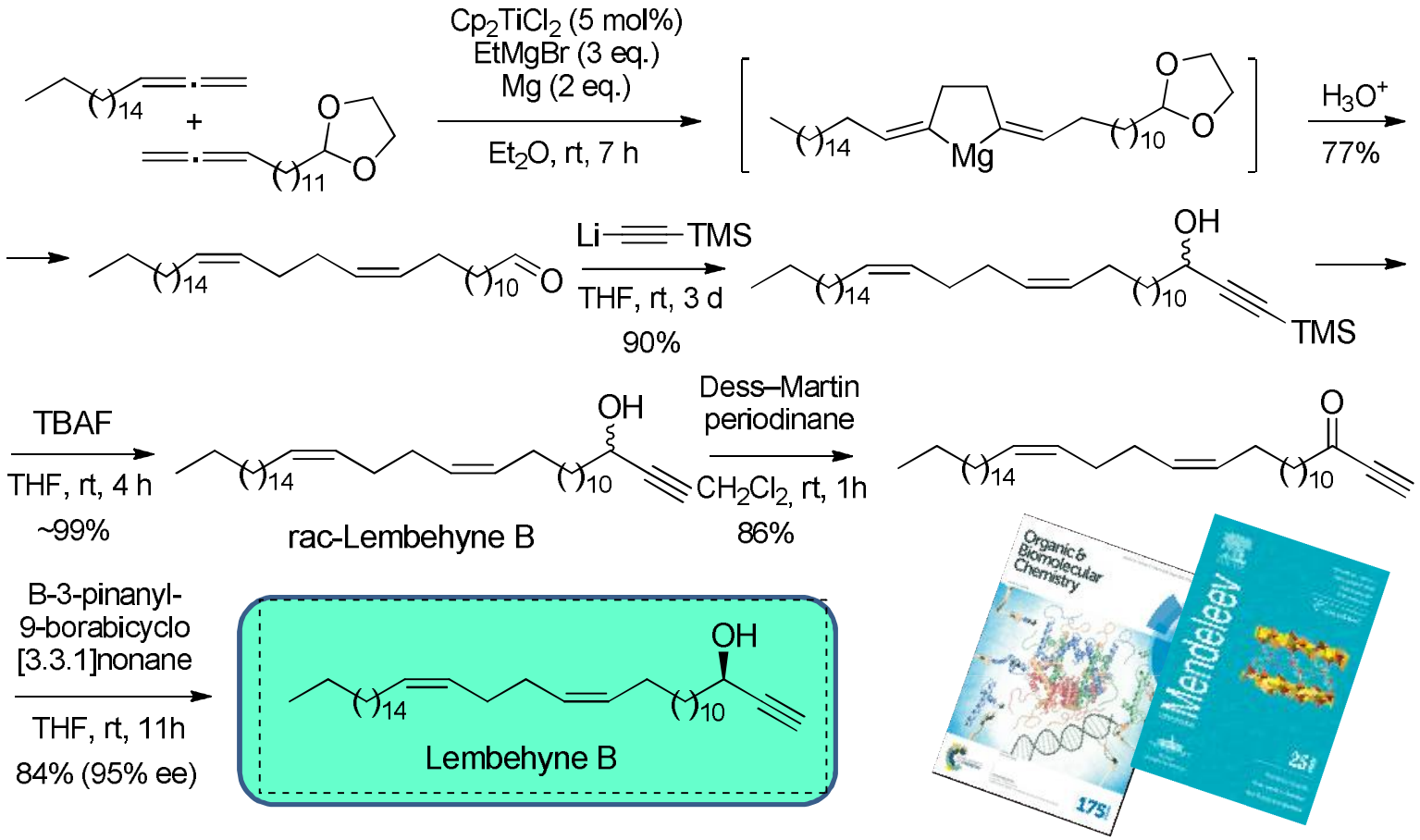
PREPARATION OF THE KEY MONOMER IN THE SYNTHESIS OF LEMBEHYNE A



V.A. D'yakonov, L.U. Dzhemileva, A.A. Makarov, E.N. Andreev, U.M. Dzhemilev, Russ. J. Org. Chem., 2016, V. 52(12), 1844–1846;

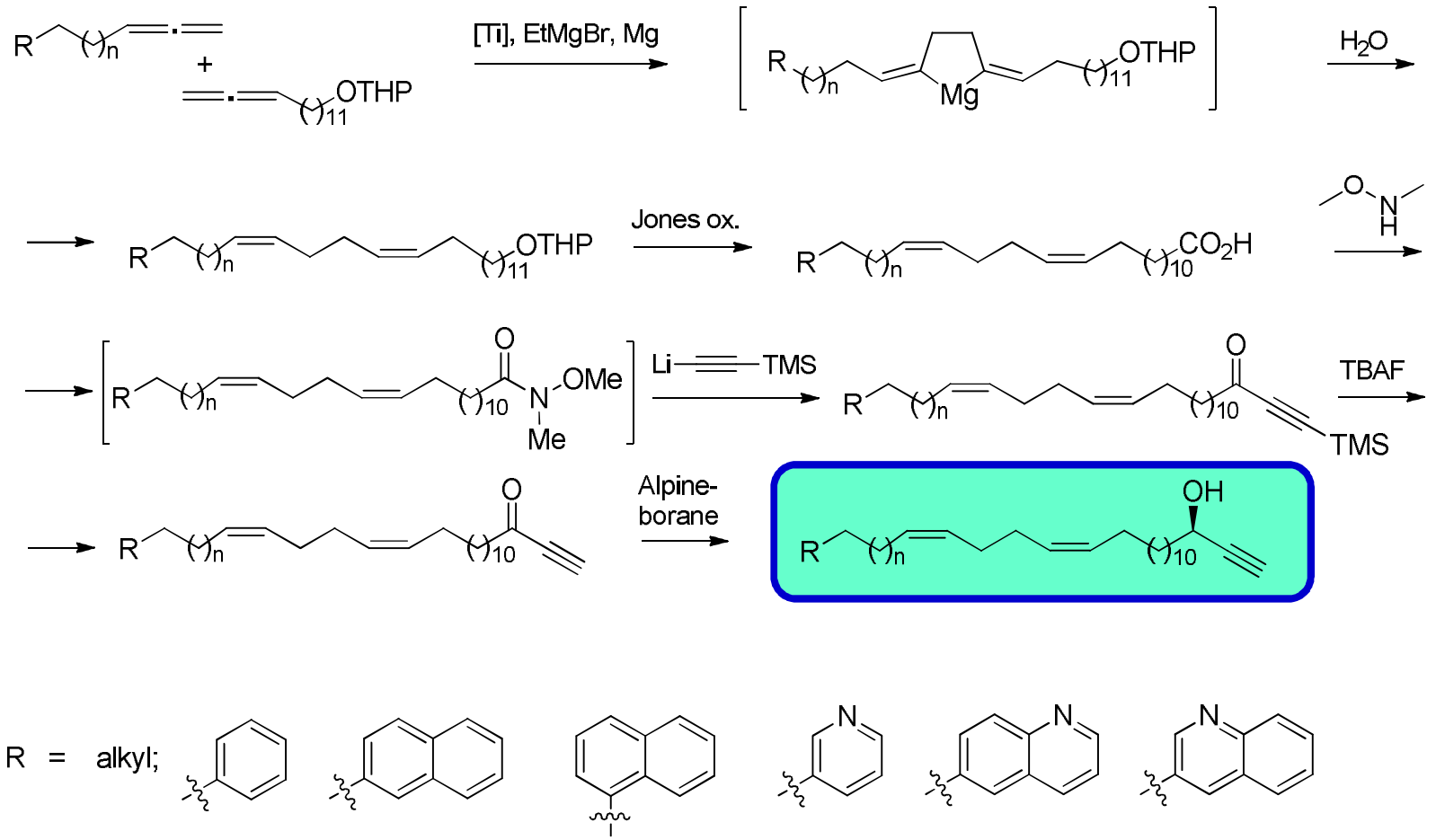
V.A. D'yakonov, A.A. Makarov, L.U. Dzhemileva, E.N. Andreev, U.M. Dzhemilev. Total Synthesis of Neuritogenic Alkynes: Lembehyne B and Key Intermediate of Lembehyne A. *ChemistrySelect*, 2017, *2,* 1211.

CROSS-CYCLOMAGNESIATION FOR THE SYNTHESIS OF NEIRITOGENIC ALKYNE – LEMBEHYNE B

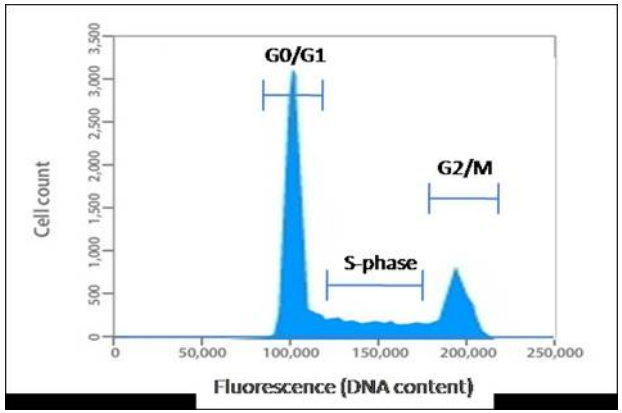


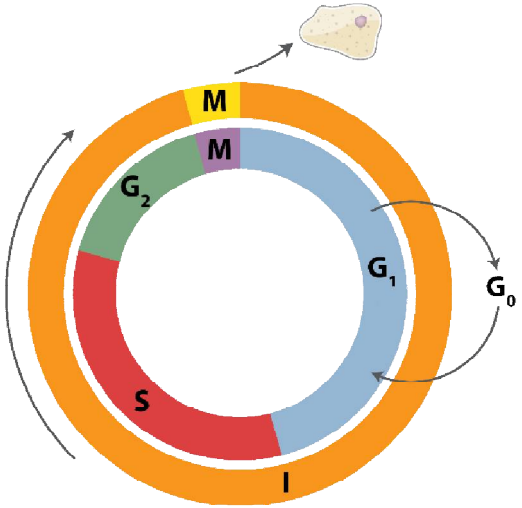
V. A. D'yakonov, A. A. Makarov, L. U. Dzhemileva, E. N. Andreev, U. M. Dzhemilev, Mendeleev Communications, 2017, 27, 122-124; L.U. Dzhemileva, V.A. D'yakonov, A.A. Makarov, E.N. Andreev, M.M. Yunusbaeva, U.M. Dzhemilev, *Org. Biomol. Chem.* 2017, *15*, 470.

PREPARATION OF NATURAL LEMBEHYNE B AND ITS SYNTHETIC ANALOGS INVOLVING THE WEINREB AMID

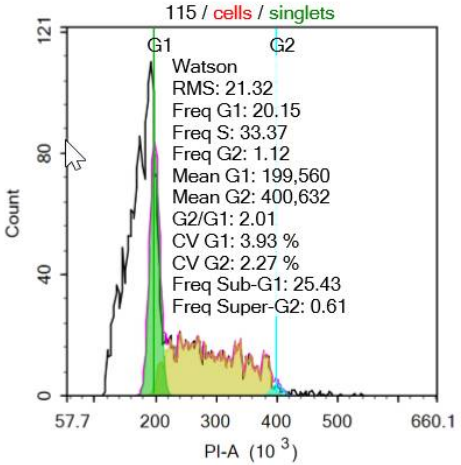


IN VITRO ANALYSIS OF CELL CYCLE OF LEMBEHYNE B ON THE LEUKEMIA CELL LINES AND NEUROBLASTOMA CELLS

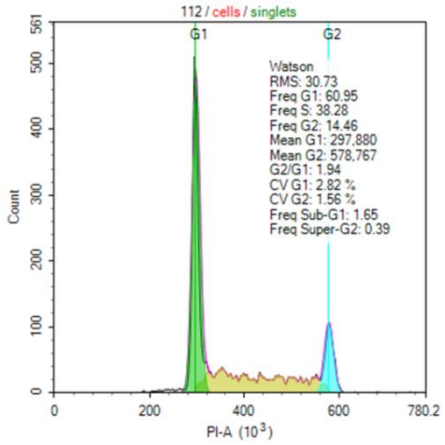




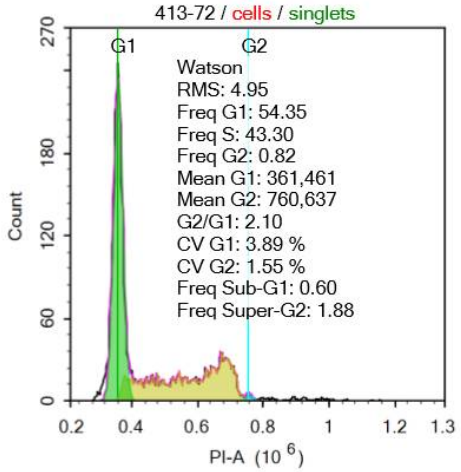
Cell cycle progression in Jurkat cells



The cell cycle in Jurkat cells without treatment with Lembehyne B

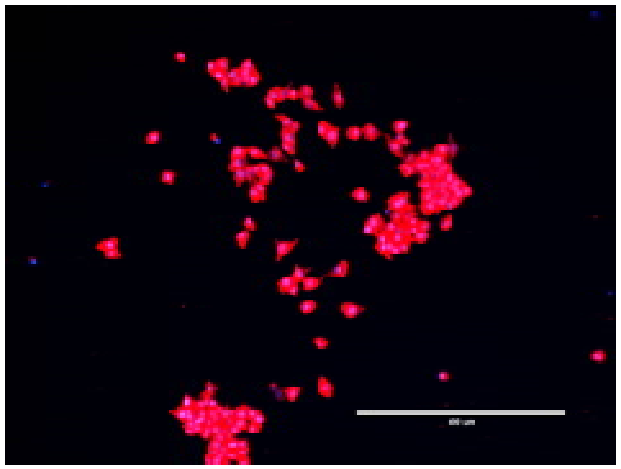


Cell cycle progression in Neuro2A cells

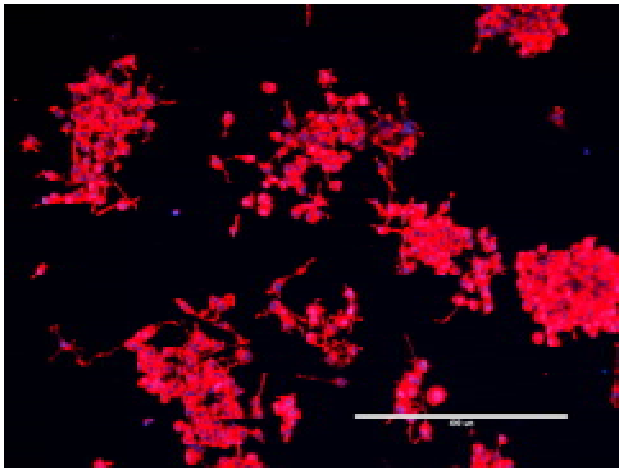


STUDY OF NEURITOGENIC ACTIVITY OF LEMBEHYNE ON NEURO2A CELLS

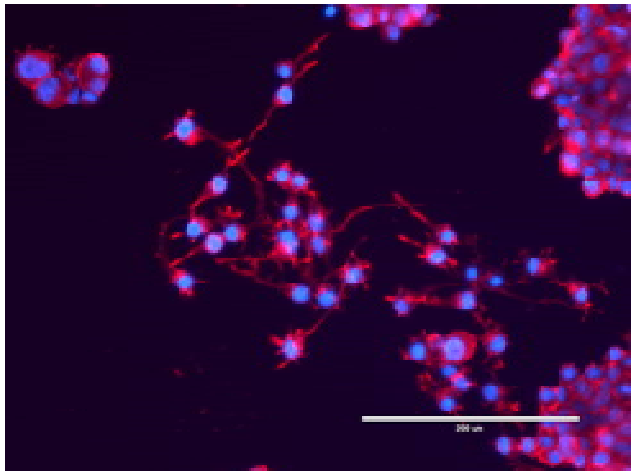
Control – after incubation for 72 h



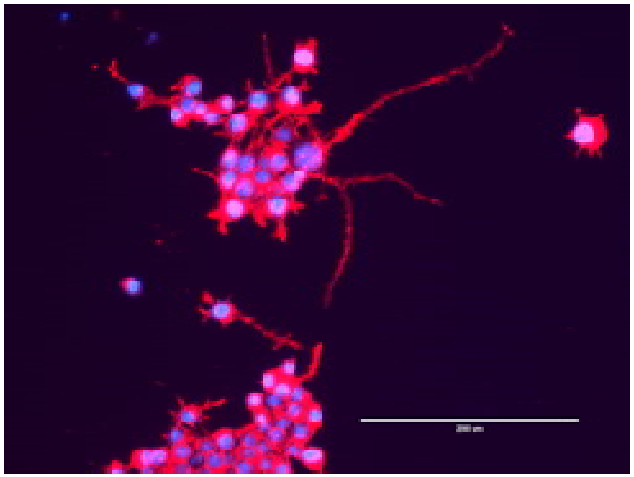
Incubation for 24 h



For 48 h



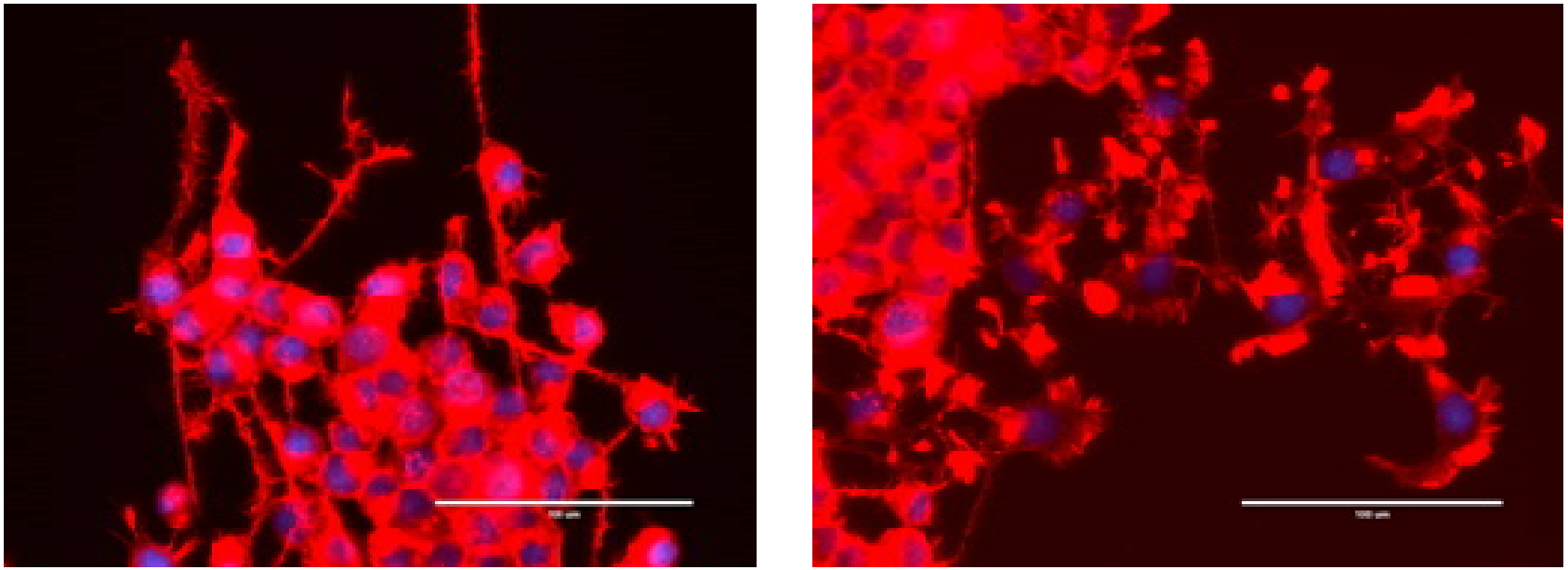
For 72 h



STUDY OF NEURITOGENIC ACTIVITY OF LEMBEHYNE B ON NEURO2A CELLS IN COMPARISON WITH NERVE GROWTH FACTOR

Lembehynes

NGF



Differentiation of Neuro2A cells during incubation for 48-72 hours with the addition to the cultivation medium only of lembehyne B (left) and only of NGF (nerve growth factor) (right). Staining with DAPI and ActinRedTM 555 ReadyProbesTM Reagent (InvitrogenTM).

Conclusions

Reactions of catalytic homo- and cross-cyclomagnesiation of aliphatic and functionally substituted allenes using available Grignard reagents are efficient tools for the design and stereoselective synthesis of natural functionally substituted bis-methylene-separated Z-dienes, fatty acids, acetogenins and lembehynes, exhibiting a broad spectrum of biological activities.

Acknowledgments

This work was financially supported by the Russian Science Fundation(Grants 14-13-00263, 16-13-10172, 18-73-10030), Russian Foundation for Basic Research (Grants16-03-00543, 17-43-020502, 18-29-09068) and Grant of the RF President for the support of leading scientific schools(NS-5240.2018.3).

RUSSIAN FOUNDATION FOR BASIC RESEARCH

RSF Russian Science Foundation

Transparency - Competence - Result