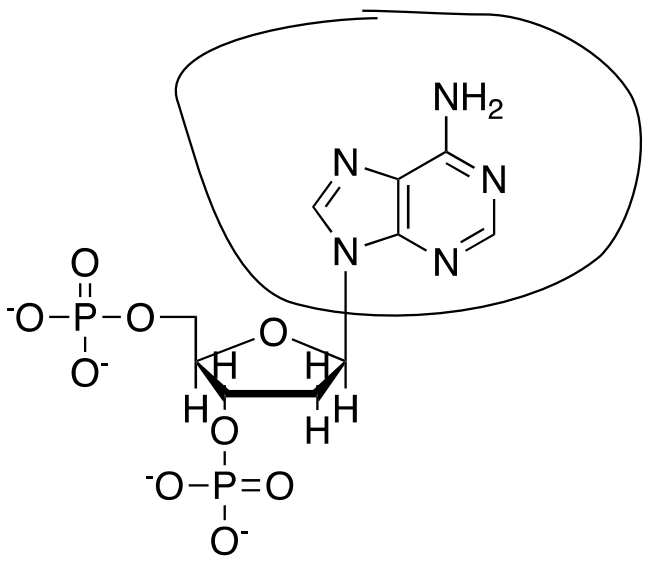
KEEMIA PEEGELDUSED ELUS JA ELU PEEGELDUSED KEEMIAS

NUKLEOSIIDID JA KEROGEEN

Pühendatud Akadeemik Prof. Margus Loppile

Tallinnas 11.09.2019

NUKLEOSIIDID



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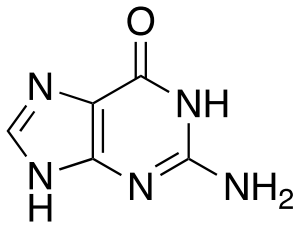

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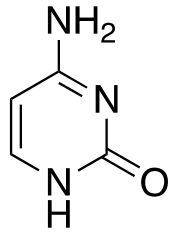

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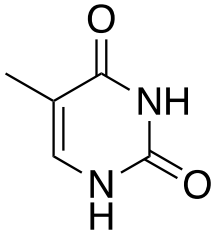

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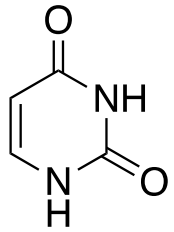


Uratsiil

NUKLEOSIIDIDE ANALOOGID, MIKS?

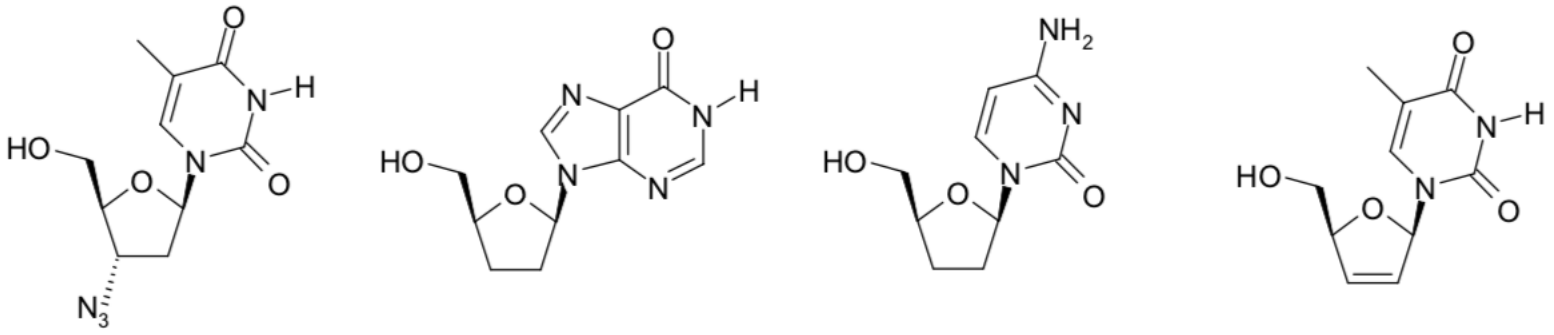


Figure 4. The structures of the nucleoside analogues acting as anti-HIV drugs

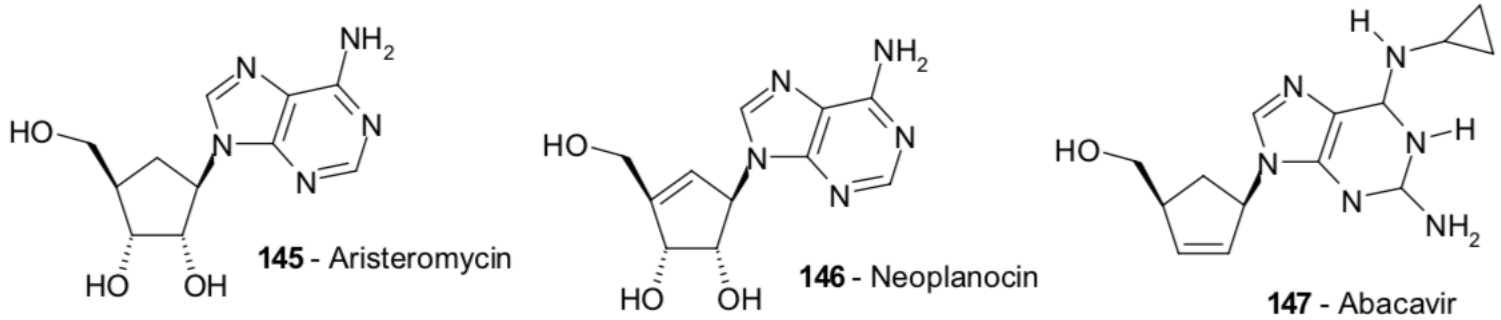
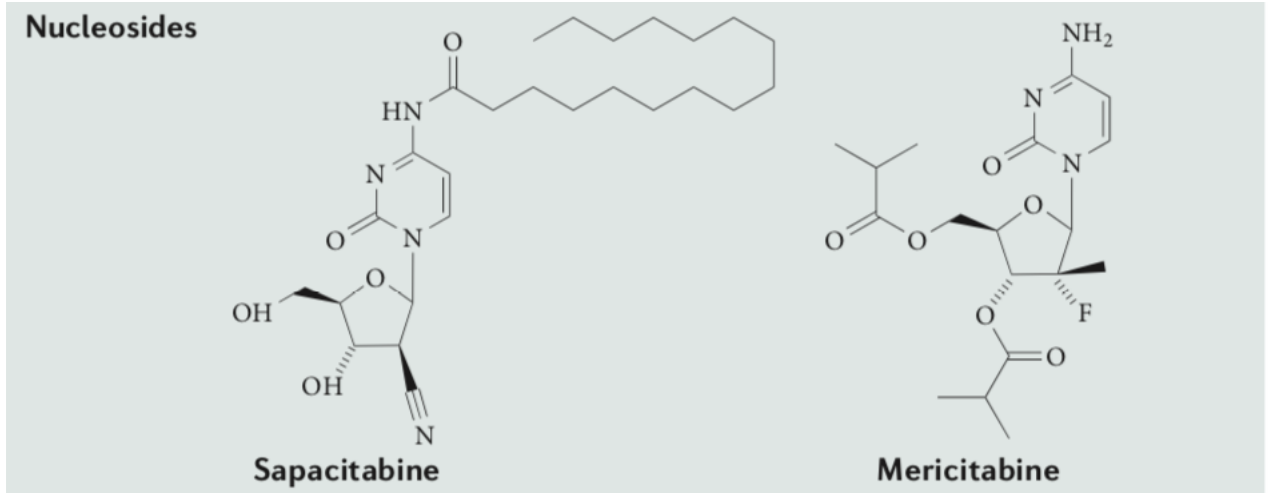


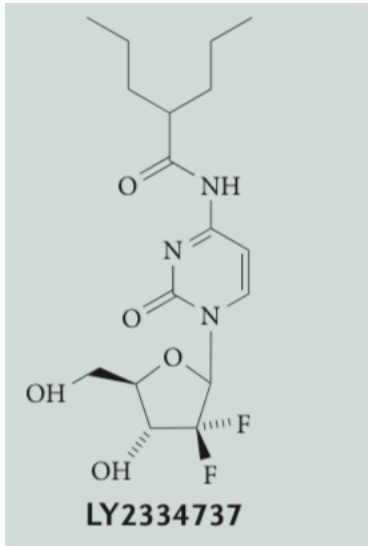
Figure 8. The structures of carbocyclic nucleosides

Jõgi, 2008

NUKLEOSIIDIDE ANALOOGID 21. SAJANDIL

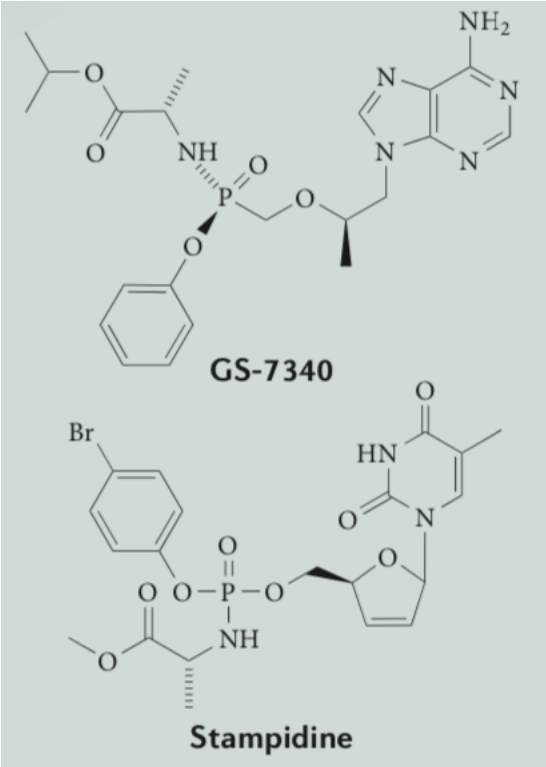


CNDAC (sapacitabine)	Phase III development in cancer
Mericitabine	Phase II for development chronic hepatitis C virus
LY2334737	Phase I development in cancer

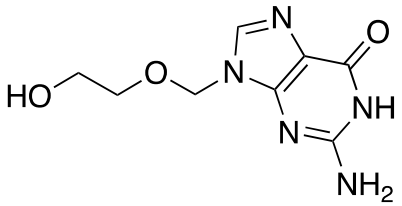


Jordheim 2013

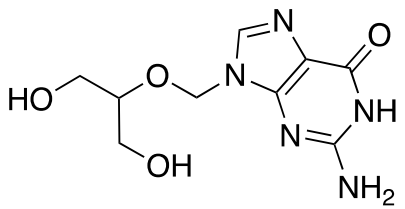
NUKLEOSIIDID 21. SAJANDIL



GS-7340	Phase I/II development for HIV and hepatitis B virus
Stampidine	Phase I development for HIV



Acyclovir (Zovirax)
Herpes simplex



Ganciclovir (Cytovene)
CMV

Jordheim 2013

Perigaud 1992

NUKLEOSIIDIDE ANALOOGID

Asymmetric Synthesis of 2-Aryl-5-oxotetrahydrofuran-2-carboxylic Acids

Artur Jõgi,[a] Anne Paju,[a] Tõnis Pehk,[b] Tiiu Kailas,[a] Aleksander-Mati Müürisepp,[a] Tõnis Kanger,[a] Margus Lopp*[a]

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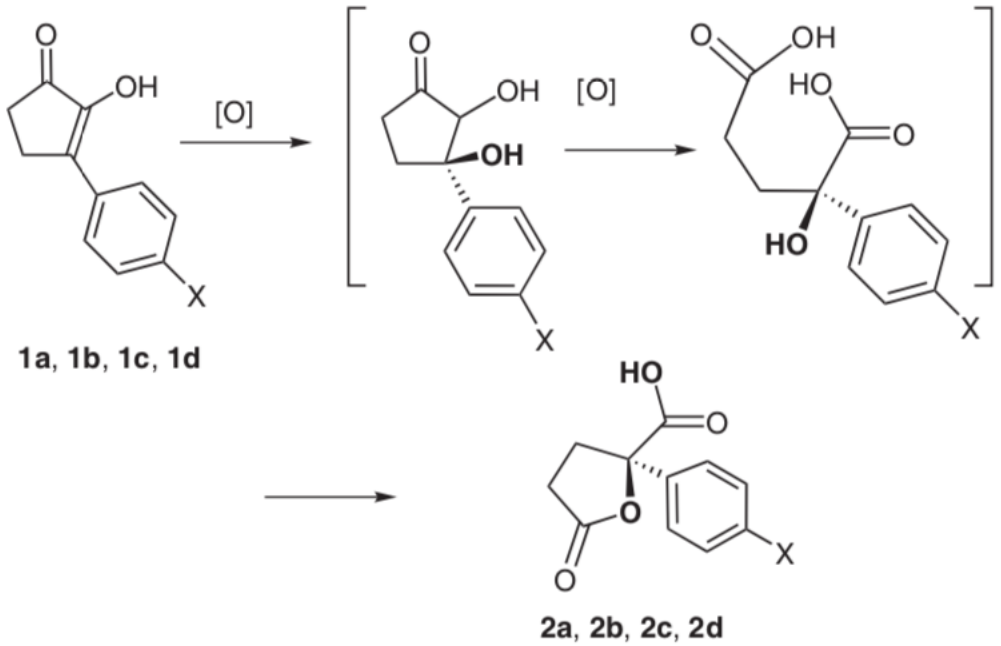
Received 7 April 2006; revised 1 June 2006

TAL TECH

NUKLEOSIIDIDE ANALOOGID



[O] = Ti(O*i*-Pr)$_4$/(+)-diethyl tartrate/*t*-BuOOH

a, X = H; **b**, X = F; **c**, X = *i*-Pr; **d**, X = OMe

Scheme 1 Synthesis of 2-aryl-5-oxotetrahydrofuran-2-carboxylic acids **2a–d** from achiral 3-aryl-2-hydroxycyclopent-2-en-1-ones **1a–d** by asymmetric oxidation.

TAL TECH

NUKLEOSIIDIDE ANALOOGID

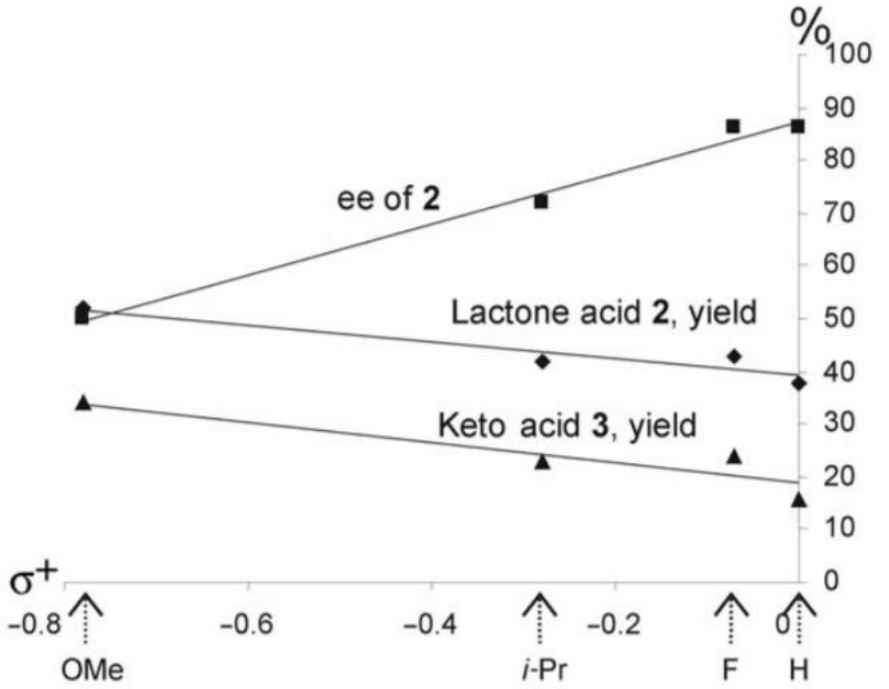


Figure 1 Correlation of yields of γ-lactone acids **2a–d**, keto acids **3a–d** and enantiopurity of **2a–d** with s^+ constants of the *para* substituents.[8]

TAL TECH

Asymmetric synthesis of 4′-*C*-benzyl-2′,3′-dideoxynucleoside analogues from 3-benzyl-2-hydroxy-2-cyclopenten-1-one

Artur Jõgi,[a] Marit Ilves,[a] Anne Paju,[a] Tõnis Pehk,[b] Tiiu Kailas,[a,c] Aleksander-Mati Müürisepp[a,c] and Margus Lopp[a,*]

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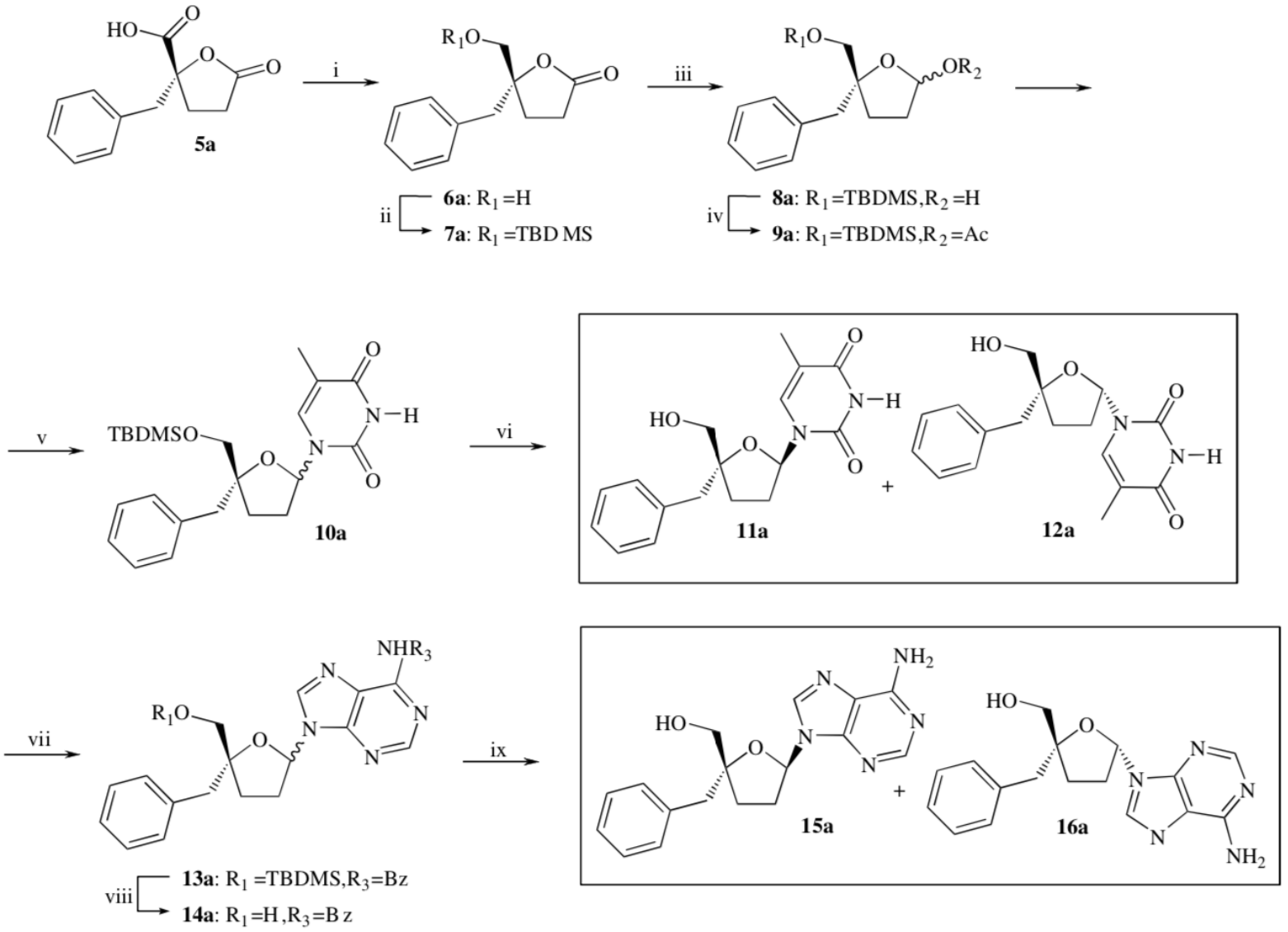
[b]*National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, 12618 Tallinn, Estonia*
[c]*Competence Centre for Cancer Research, Akadeemia tee 15, 12618 Tallinn, Estonia*

Received 14 January 2008; accepted 24 January 2008
Available online 4 March 2008

TAL TECH

NUKLEOSIIDIDE ANALOOGID



Scheme 3. Synthesis of 4′-benzyl substituted nucleoside analogues. Reagents: (i) $BH_3{\cdot}SMe_2$/THF; (ii) TBDMSCl, imidazole/CH_2Cl_2; (iii) DIBAH/toluene, (iv) $Ac_2O/Et_3N/CH_2Cl_2$; (v) Thymine, BSA, TMSOTf/CH_3CN; (vi) TBAF/THF; (vii) N^6-benzoyladenine, BSA, TMSOTf/CH_3CN; (viii) TBAF/ THF; (ix) NH_3/ MeOH.

NUKLEOSIIDIDE ANALOOGID

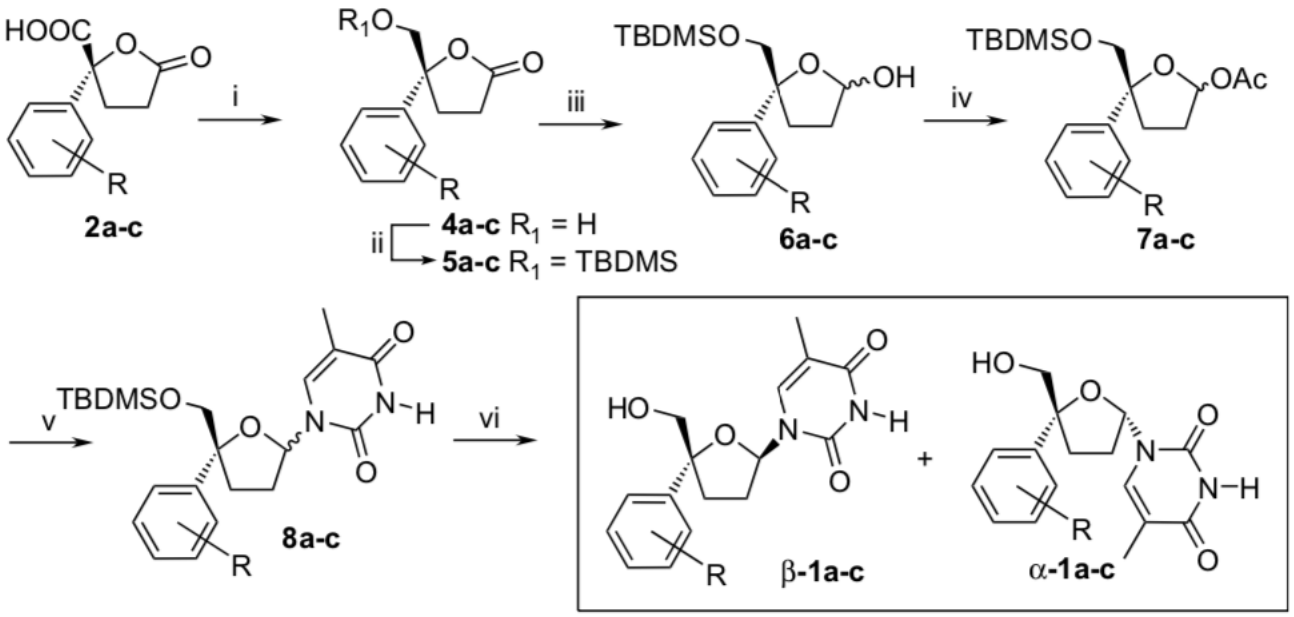
Synthesis of 4′-aryl-2′,3′-dideoxynucleoside analogues

Artur Jõgi [a], Anne Paju [a], Tõnis Pehk [b], Tiiu Kailas [a], Aleksander-Mati Müürisepp [a], Margus Lopp [a,*]

[a] *Department of Chemistry, Faculty of Science, Tallinn University of Technology, Ehitajate tee 5, 19086 Tallinn, Estonia*
[b] *National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, 12618 Tallinn, Estonia*

TAL TECH

NUKLEOSIIDIDE ANALOOGID



Scheme 2. Synthesis of 4′-aryl-2′,3′-dideoxynucleoside analogues **1**. Reagents: (i) $BH_3 \cdot SMe_2$/THF, (ii) TBDMSCl, imidazole/CH_2Cl_2, (iii) DIBAH/toluene, (iv) $Ac_2O/Et_3N/CH_2Cl_2$, (v) thymine, BSA, TMSOTf/CH_3CN, (vi) TBAF/THF.

Table 1
Synthesis of 4′-aryl-2′,3′-dideoxynucleoside analogues

Entry	Substrate	Substituent R	Yield % (ratio 2*R*/2*S*)						
			2 [ee%]	**4**	**5**	**6**	**7**	**8**	**β-1+α-1**
1	a	Ph	38 [86][5]	86	100	92 (3.8:1.0)	90 (3.8:1.0)	87 (1.0:1.0)	100
2	b	*p*-F-Ph	43 [86][5]	84	93	93 (4.0:1.0)[a]	81 (3.1:1.0)	100 (1.0:1.1)	78
3	c	*o*-BnO-Ph	57 [81]	44	78	88 (2.6:1.0)	67 (1.7:1.0)	91 (1.3:1.0)	100

[a] In the initial solution of **6b** the ratio of 2*R*/2*S*=1.0:1.3, after 12 h the ratio changed to 4.0:1.0.

TAL TECH

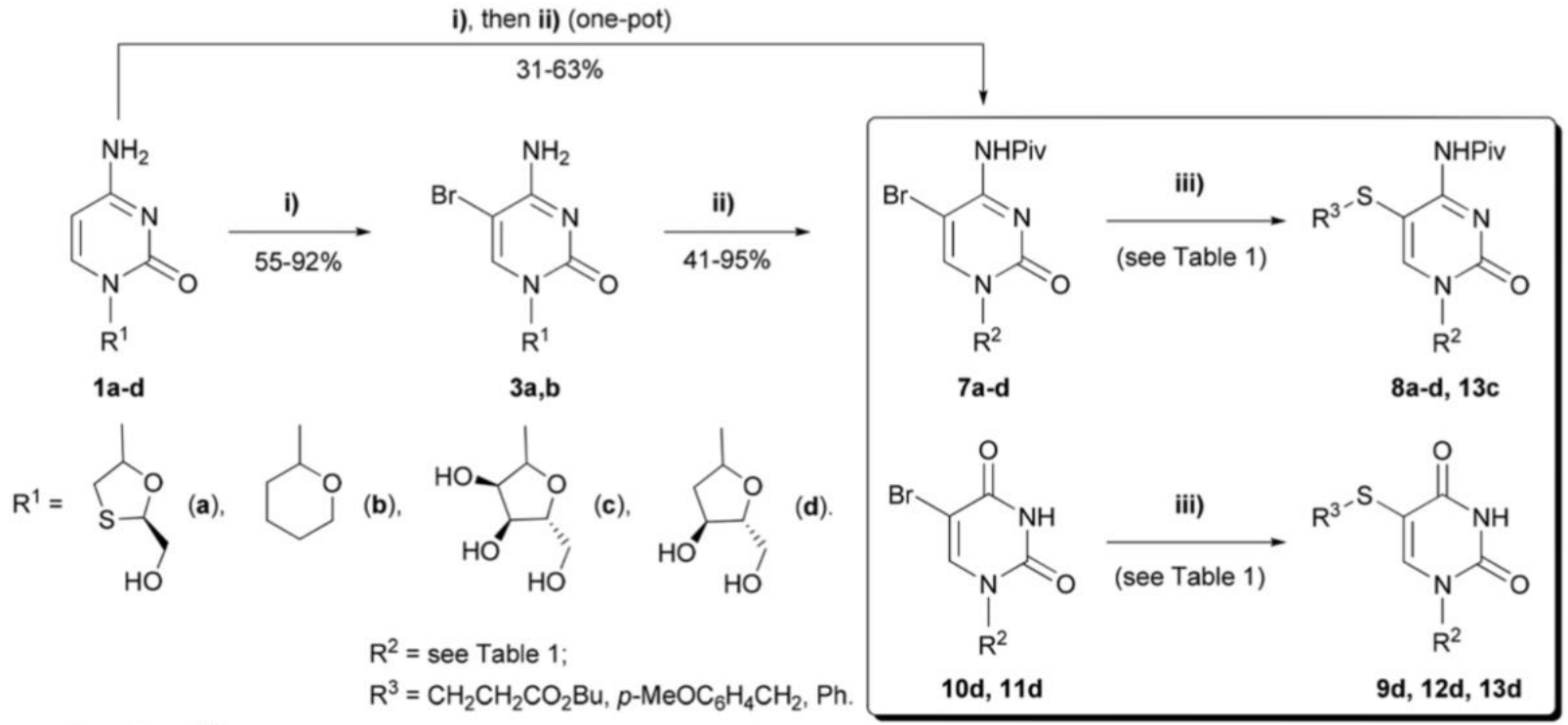
NUKLEOSIIDIDE ANALOOGID

A general approach to the synthesis of 5-*S*-functionalized pyrimidine nucleosides and their analogues†

Dzmitry G. Kananovich,[a] Alli Reino,[a] Kaja Ilmarinen,[a] Marko Rõõmusoks,[a] Mati Karelson[b] and Margus Lopp*[a]

TAL TECH

NUKLEOSIIDIDE ANALOOGID



Scheme 4 Synthesis of *S*-functionalized cytosine and uracil derivatives.

NUKLEOSIIDIDE ANALOOGID

Synthesis of Novel Acyclic Nucleoside Analogues with Anti-Retroviral Activity

A. Paju [a] , M. Päri [a] , A. Selyutina [b] , E. Žusinaite [b] , A. Merits [b] , T. Pehk [c] , K. Siirde [d] , A.-M. Müürisepp [a] , T. Kailas [a] & M. Lopp [a]

[a] Department of Chemistry , Tallinn University of Technology , Tallinn, Estonia

[b] Institute of Technology , Tartu University , Tartu, Estonia

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Published online: 11 Aug 2010.

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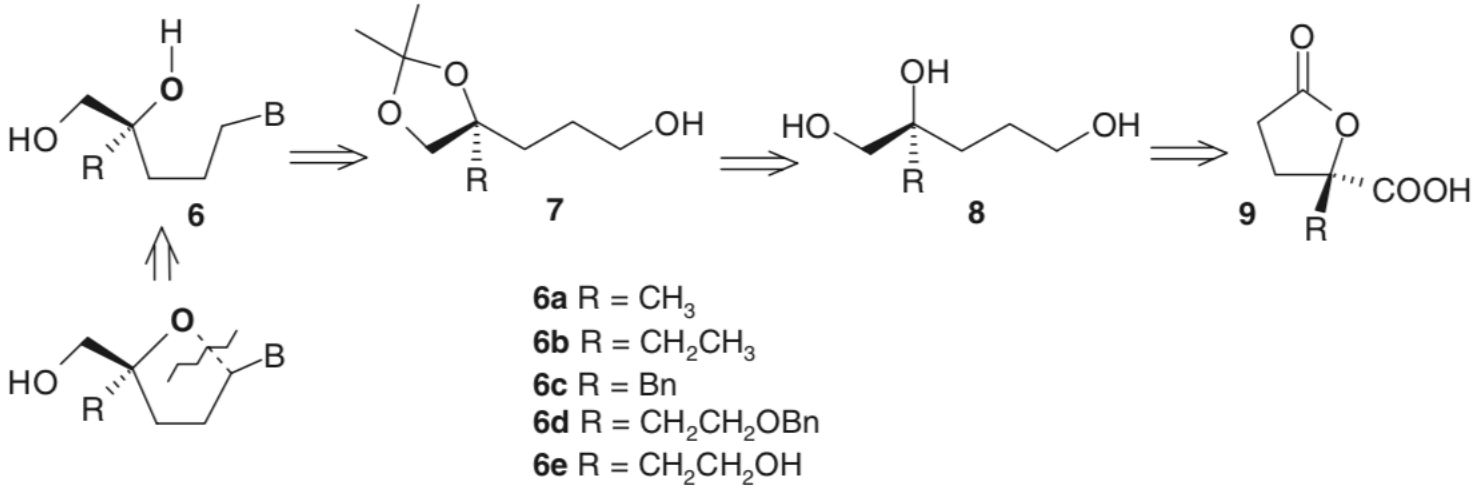
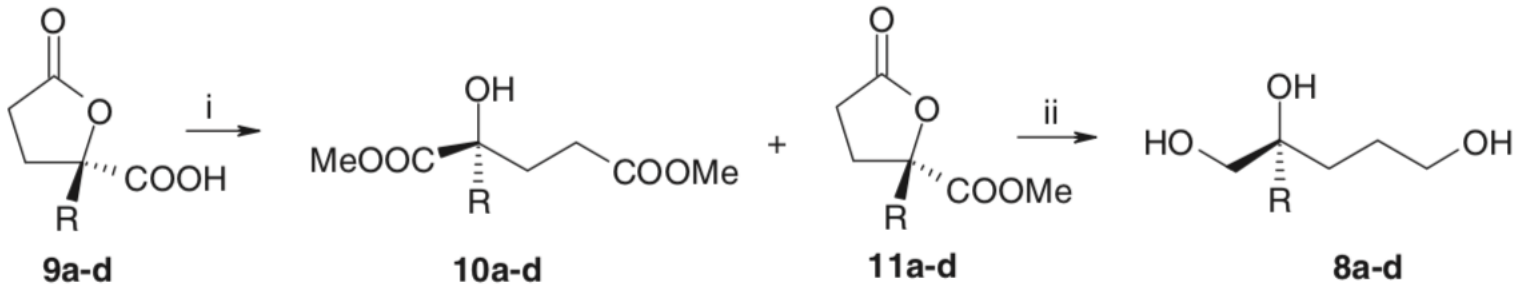
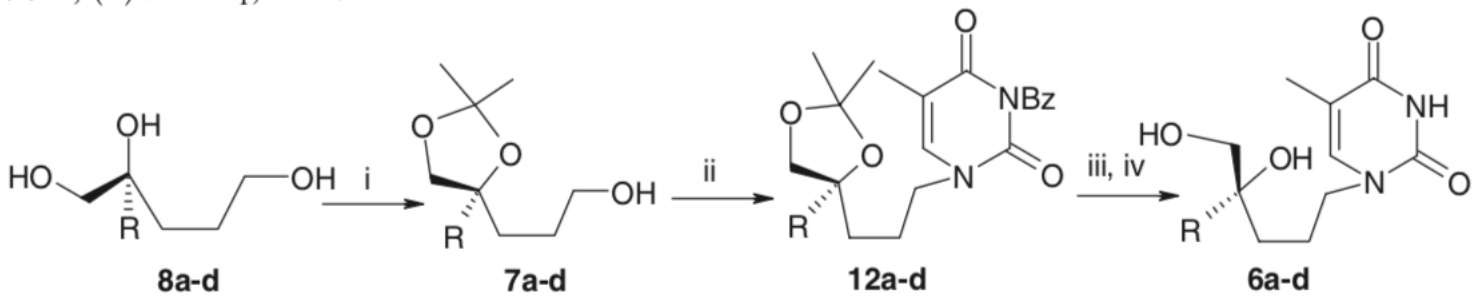
NUKLEOSIIDIDE ANALOOGID



SCHEME 1 Retrosynthetic route to acyclic 4′-alkyl-2′,3′-dideoxynucleoside analogues **6** from 2-alkyl-substituted 2-hydroxyglutaric acid-γ-lactones **9**.



SCHEME 2 Synthesis of triols **8**. Reagents: (i) HCl/MeOH; (ii) $LiAlH_4$, THF.



SCHEME 3 Synthesis of acyclic nucleoside analogues **6a–d**. Reagents: (i) Acetone, p-TsOH; (ii) N^3-Bz-thymine, PPh_3, DEAD THF; (iii) NH_3/MeOH, (iv) HCl/MeOH/H_2O.

TAL TECH

POLE TSÜTOTOKSILISED

TABLE 1 Results of the analysis of cytotoxic properties of compounds

No.	Compounds **6**	Cell viability	
		MCF-7*	HeLa**
1	**a**	119	97
2	**b**	119	104
3	**c**	129	110
4	**d**	102	108
5	**e**	117	103
6	**DMSO (control)**	100	100

*The number of viable cells in negative control samples (treated with DMSO alone) was taken as 100%. Cell viability is presented as a ratio (in percentage) of number of viable cells in experimental (treated with tested compound) to that in DMSO treated control cells.

**The $OD_{540\ nm}$ of DMSO-treated control cells was taken as 100%. Cell viability is presented as a ratio (in percentage) of the $OD_{540\ nm}$ of cells treated with the tested compounds to the $OD_{540\ nm}$ of DMSO-treated cells.

TAL TECH

AKTIIVSED RETROVIIRUSTE VASTU

TABLE 2 Inhibition of activity of HIV reverse transcription by acyclic nucleosides and control substances (colony formation assay)

		Anti-retroviral viral activity	
No.	Compounds **6**	Number of colonies	Efficiency of colony formation (%)
	DMSO (control)	75	100
1	**a**	45	60
2	**b**	36	48
3	**c**	39	52
4	**d**	34	45
5	**e**	47	63
6	**Lam**	7	9
7	**AZT**	2	3

TAL TECH

NUKLEOSIIDIDE ANAALOOGID

SYNTHESIS AND BIOLOGICAL ACTIVITY OF BIMORPHOLINE AND ITS CARBANUCLEOSIDE

Kerti Ausmees,[1] Anastasia Selyutina,[3] Kristel Kütt,[1] Kristin Lippur,[1] Tõnis Pehk,[2] Margus Lopp,[1] Eva Žusinaite,[3,4] Andres Merits,[3] and Tõnis Kanger[1]

[1]Department of Chemistry, Tallinn University of Technology, Tallinn, Estonia
[2]National Institute of Chemical Physics and Biophysics, Tallinn, Estonia
[3]Institute of Technology, University of Tartu, Tartu, Estonia
[4]Baltic Technology Development, Tallinn, Estonia

TAL TECH

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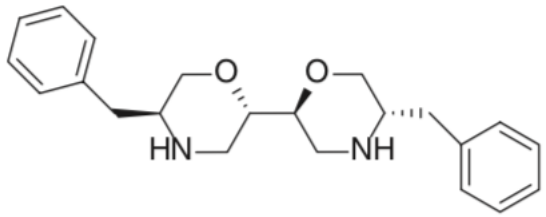

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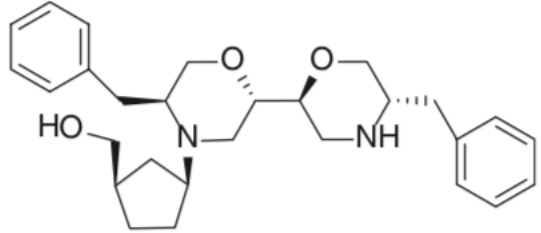


3

TABLE 1 Results of the analysis of cytotoxic properties of the compounds

Compound concentration	6 hours	24 hours	48 hours	72 hours
1, 50 μM	1.01	0.79	0.75	0.78
1, 10 μM	1.04	0.91	0.83	0.76
1, 1 μM	1.00	0.97	0.97	0.95
3, 50 μM	0.50	0.14	0.04	< 0.01
3, 10 μM	0.95	0.77	0.71	0.59
3, 1 μM	0.95	0.90	0.83	0.74

Note: Normalized cell indexes (values are normalized to the time point of the compound administration) are shown. Cell viability is presented as a ratio of the Normalized cell index of cells treated with the tested compounds to the Normalized cell index of the cells treated with relevant concentrations of DMSO (taken as 1).

TABLE 2 Results of the analysis of cytotoxic action of compound **1** to the Huh-7 Lunet cells, with or without HCV replicon.

Compound concentration	Huh7-Lunet 24 hours	Huh-Luc/neo-ET 24 hours	Huh7-Lunet 48 hours	Huh-Luc/neo-ET 48 hours
1, 50 μM	0.78	0.79	0.62	0.61
1, 10 μM	0.83	0.94	0.62	0.87
1, 1 μM	1.04	1.01	0.86	1.01

Note: Cell viability is presented as a ratio of the normalized cell index of cells treated with the tested compound to the normalized cell index of the cells treated with relevant concentrations of DMSO (taken as 1 for each concentration).

TAL TECH

TALLINNA TEHNIKAÜLIKOOL

Ehitajate tee 5, 19086 Tallinn, Tel 620 2002 (E-R 8.30–17.00)

taltech.ee

KEROGEEN

TAL TECH

VALITUD PÕLEVKIVIDE OMADUSED

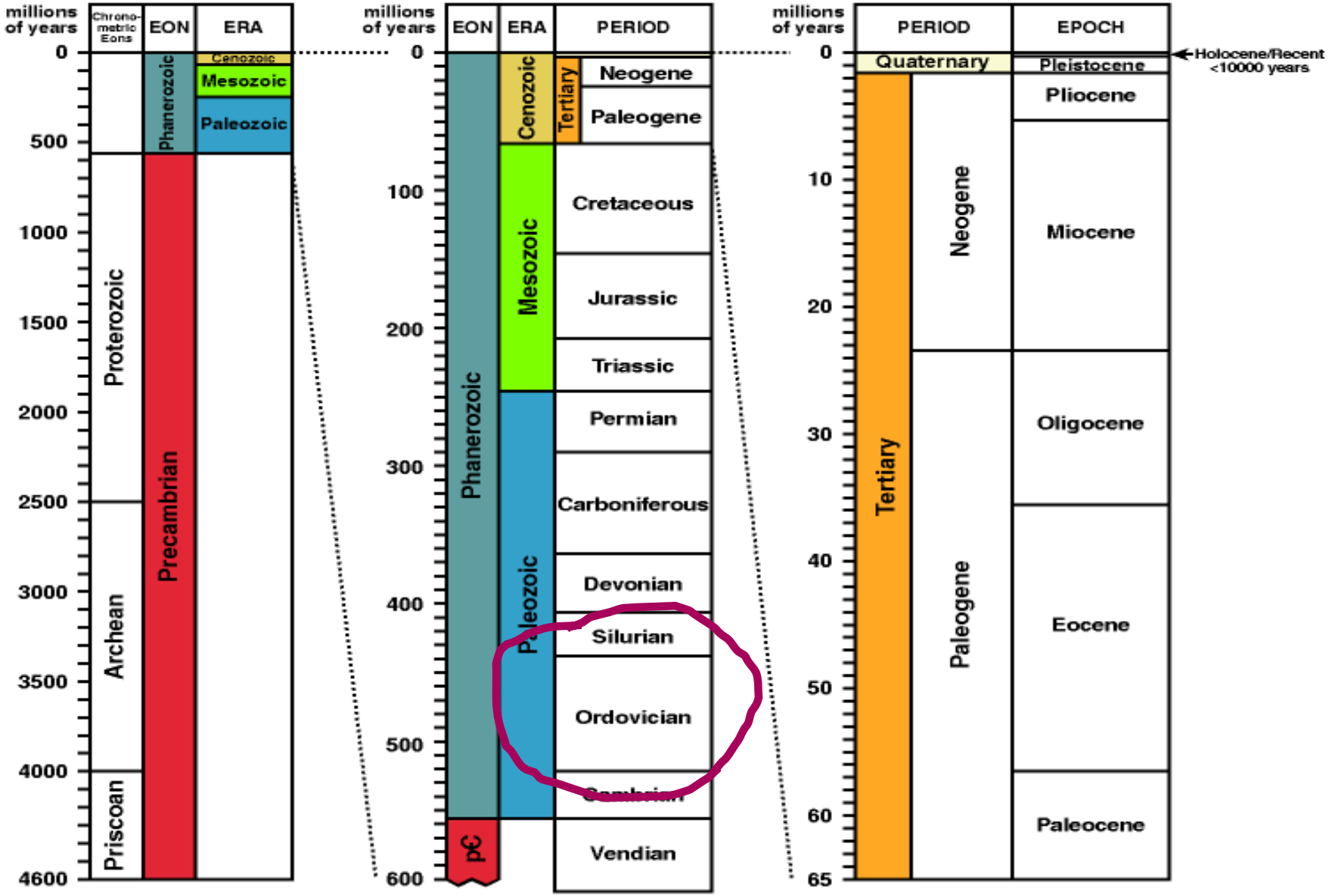
Country	Location	Age	Oil shale	Kerogen (atomic ratio)		Retorting			Shale oil		
			Organic carbon, %	H/C	O/C	Oil yield, %	Conversion ratio[1], %	Density (15°C)	H/C (atomic)	N, %	S, %
Australia	Glen Davis	Permian	40	1.6	0.03	31	66	0.89	1.7	0.5	0.6
Australia	Tasmania	Permian	81	1.5	0.09	75.0	78				
Brazil	Irati	Permian		1.2	0.05	7.4		0.94	1.6	0.8	1.0–1.7
Brazil	Tremembé-Taubaté	Permian	13–16.5	1.6		6.8–11.5	45–59	0.92	1.7	1.1	0.7
Canada	Nova Scotia	Permian	8–26	1.2		3.6–19.0	40–60	0.88			
China	Fushun	Tertiary	7.9			3	33	0.92	1.5		
Estonia	Estonia Deposit	Ordovician	77	1.4–1.5	0.16–0.20	22	66	0.97	1.4	0.1	1.1
France	Autun, St. Hilarie	Permian	8–22	1.4–1.5	0.03	5–10	45–55	0.89–0.93	1.6	0.6–0.9	0.5–0.6
France	Crevenay, Severac	Toarcian	5–10	1.3	0.08–0.10	4–5	60	0.91–0.95	1.4–1.5	0.5–1.0	3.0–3.5
S. Africa	Ermelo	Permian	44–52	1.35		18–35	34–60	0.93	1.6		0.6
Spain	Puertollano	Permian	26	1.4		18	57	0.90		0.7	0.4
Sweden	Kvarntorp	Lower Paleozic	19			6	26	0.98	1.3	0.7	1.7
UK	Scotland		12	1.5	0.05	8	56	0.88		0.8	0.4
USA	Alaska	Jurassic	25–55	1.6	0.10	0.4–0.5	28–57	0.80			
USA	Colorado	Eocene	11–16	1.55	0.05–0.10	9–13	70	0.90–0.94	1.65	1.8–2.1	0.6–0.8

[1] Conversion to oil based on organic carbon

TAL TECH

Oil Shale, 2006, Vol. 23, No. 3, pp. 211–227.

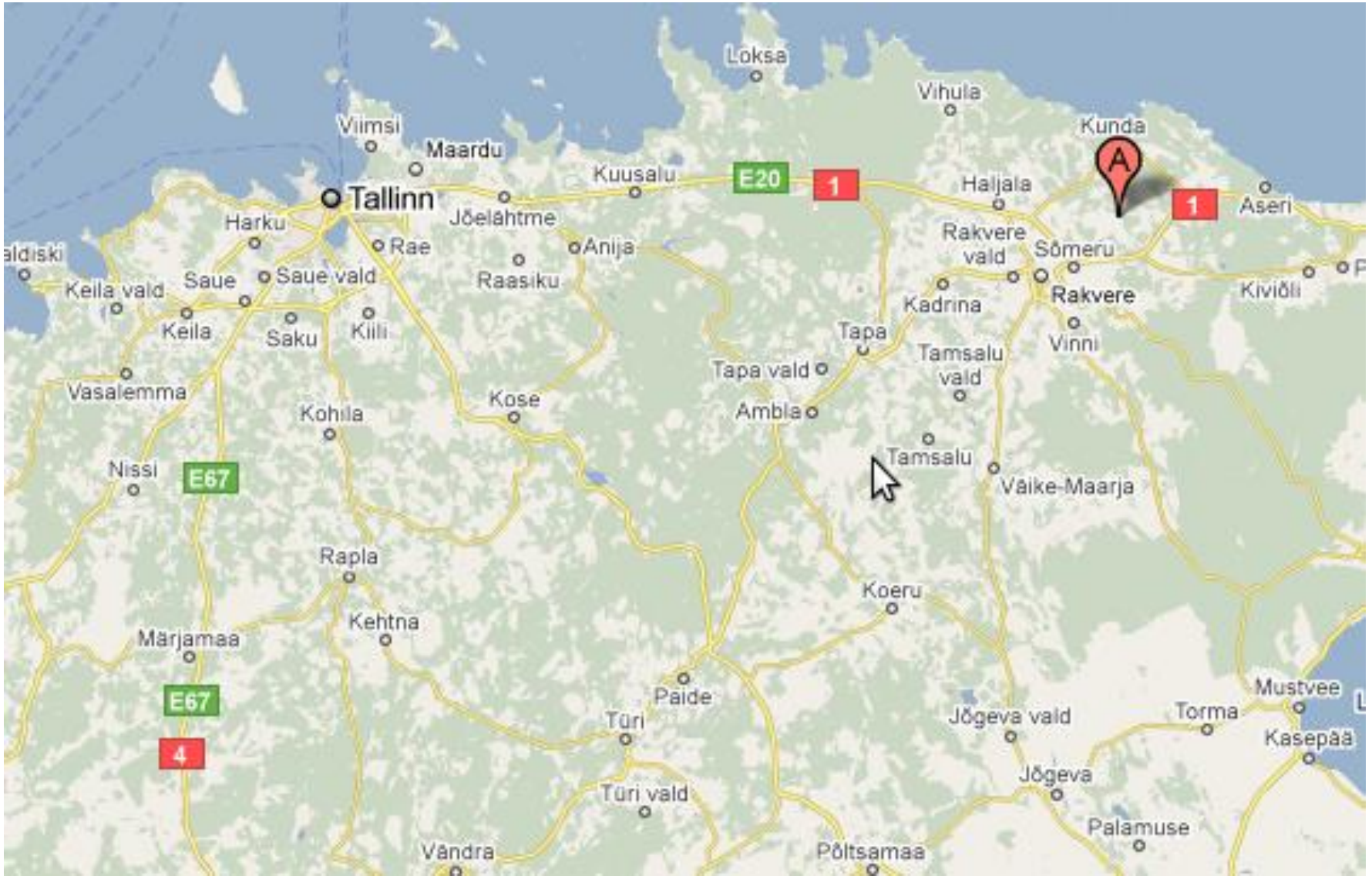
KUKERSIIDI MOODUSTUMINE



http://www.indiana.edu/~geol105b/images/gaia_chapter_6/time_scale.gif

PÕLEVKIVI EESTIS

Kohala mõis (Ungern-Sternberg)
Esimesed teated 18. saj.
St. Pererburgi Vabamajanduse Selts 1789
Samal ajal ka esimesed keemilise katsed – Johann Gottlieb Georg
19. saj. keskpaik stratigraafilised uuringud Haljalast Kohtlani
1879 nimetati Kukruse kihistuks
20. saj. Algusest Kukersiit (Mihhail Zalesski)
Õlitootmine:
20. saj. esimene kolmandik: Kohtla-Järve
Täna: Narva, Kohtla-Järve ja Kiviõli



E. Tammiksaar, Akadeemia 2013, 25 (1), 15-49.

KUS LEIDUB PÕLEVKIVI?

A. Aaloe, H. Bauert, A. Soesoo, “Kukersite oil shale” MTÜ GEOGuide Baltoscandia, Tallinn, 2007.

PÕLEVKIVI KUI KEEMIATÖÖSTUSE RESSURSS

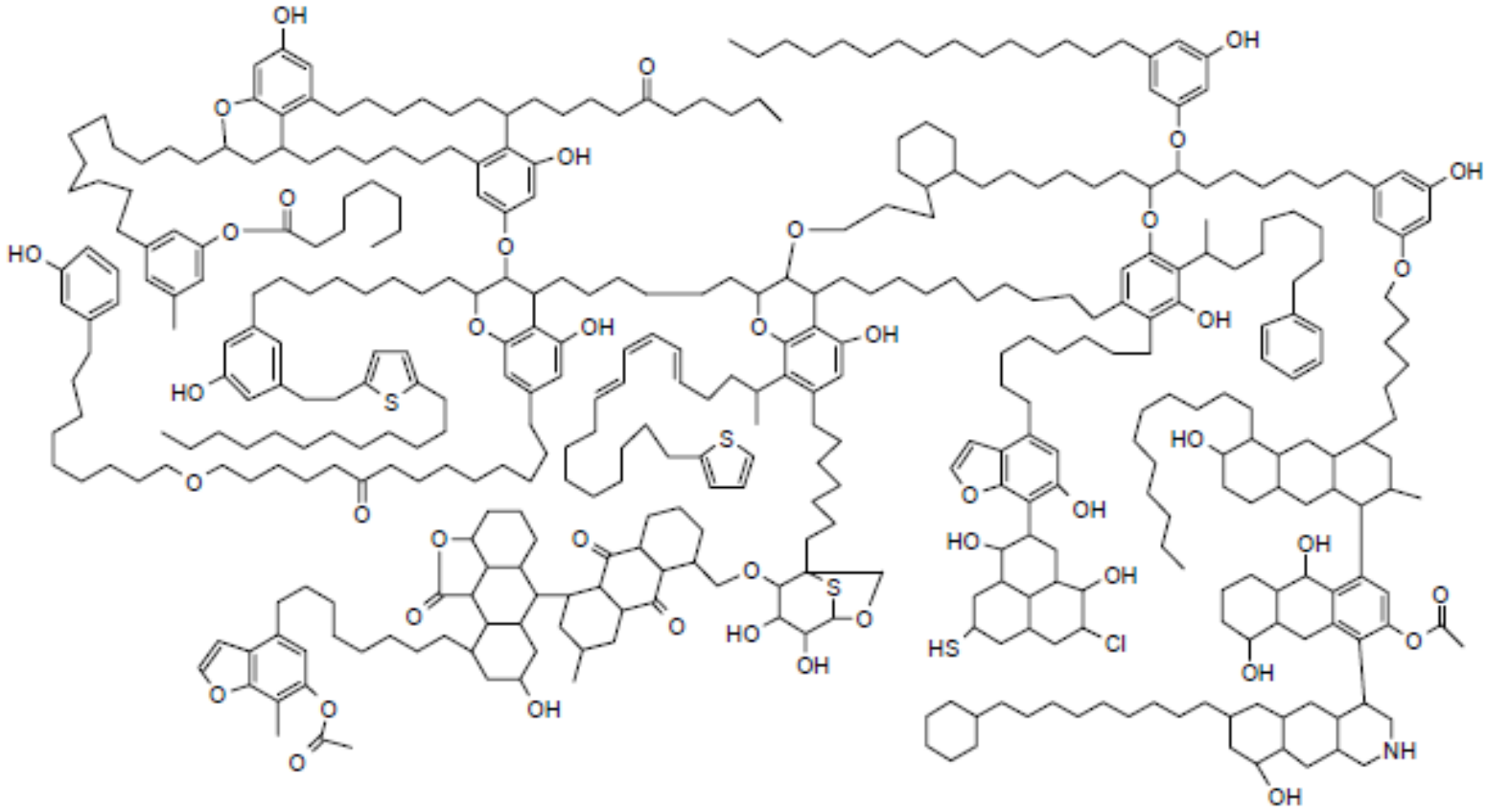
1.6 mlrd tonni põlevkivi Eestis

Ligikaudu 0,6 mlrd tonni kerogeeni

0,4-0,5 mlrd tonni dihappeid

Üleilmne põlevkivivarude hinnang u 400 mlrd tonni

KEROGEENI STRUKTUUR



Ü. Lille (Oil Shale, 2003, Vol. 20, No. 3, pp. 253-263.)

MIDA SAAB TEHA KEROGEENIST?

Hape	Süsinike arv
Merevaikhape	4
Glutaarhape	5
Adipiinhape	6
Pimeliinhape	7
Suberiinhape	8
Aselaiinhape	9
Sebatsiinhape	10

Polümeerid

- Ploüamiidid (Funktsionaalsed materjalid)
- Polüestrid
- Polüuretaanid

Estrid

- Alifaatsed
- Aromaatsed
- Kasutusel lubrikantidena

Soolad

- Metallid
- Amiinid
- Kasutusel korrosioonitõrjes

TAL TECH

KUIDAS?

Oksüdatsioon $KMnO_4$

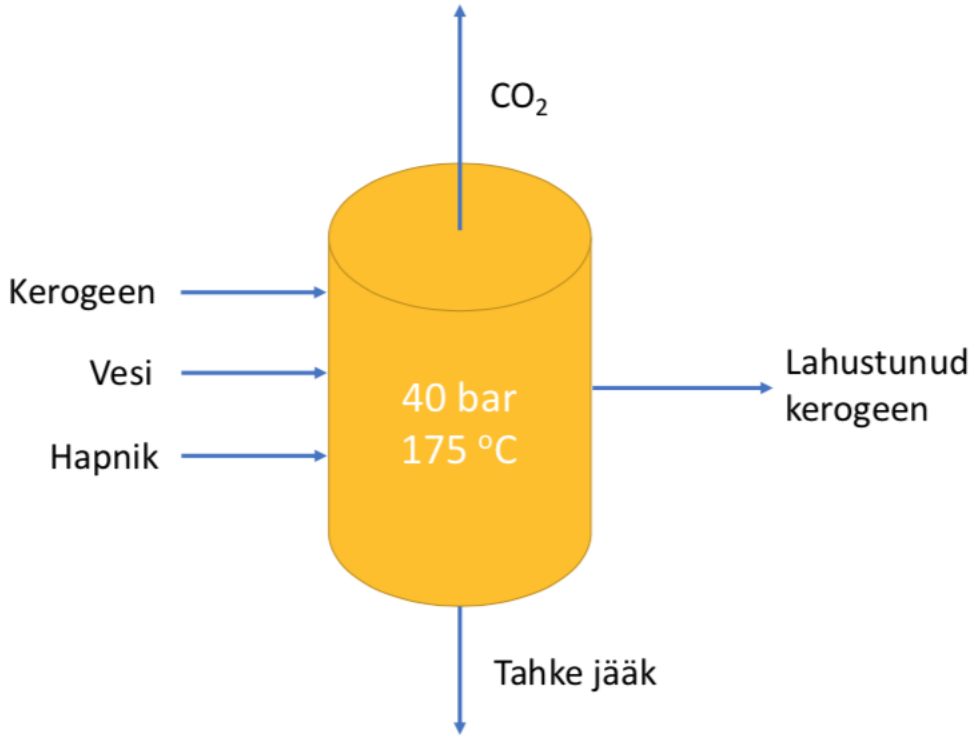
- Fomina, A. And Pobul, L. 1953
- Dihapped 10% saagisega
- @ 100C 74% moodustub peamiselt CO_2
- @ 50C 47% dihappeidcids
- Reaktsiooniaeg 20-28 h
- Permanganaadi ja kerogeeni massisuhe 4:1

Hiljem HNO_3 (Degtereva and Fomina, SU115343A1 1958)

- Kõrgemad saagised (kuni 63%)
- Lühem reaktsiooniaeg (4-8h)
- Lisati õhku rõhu all
- 70% hape

TAL TECH

OKSÜDATSIOON HAPNIKUGA



KEROGEENI OKSÜ DATIIVNE LAHUSTAMINE VEES

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b) Johan Gadolini nim. keemiatehnika keskus, Åbo Akademi Ü likool, Biskopsgatan 8, FI-20500, Turu, Soome

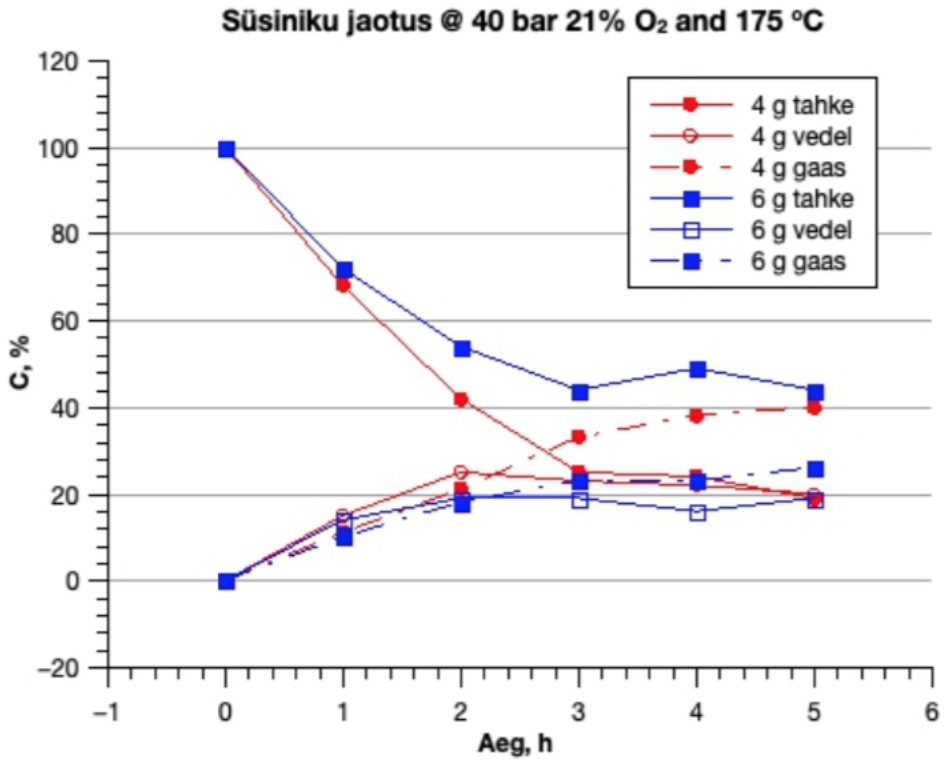
KEROGEENI OKSÜDATSIOON

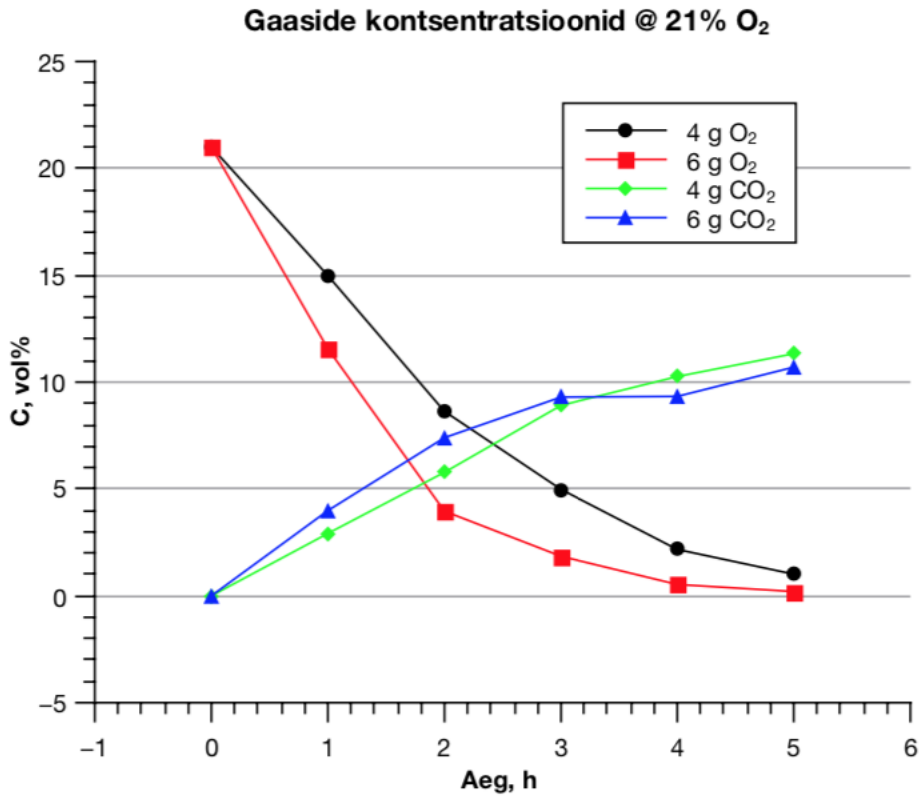
Kerogeeni kontsentratsioon 20 ja 30 g/l

Hapniku kontsentratsioon gaasifaasis 21% v 50%

T=175C

P=40 bar





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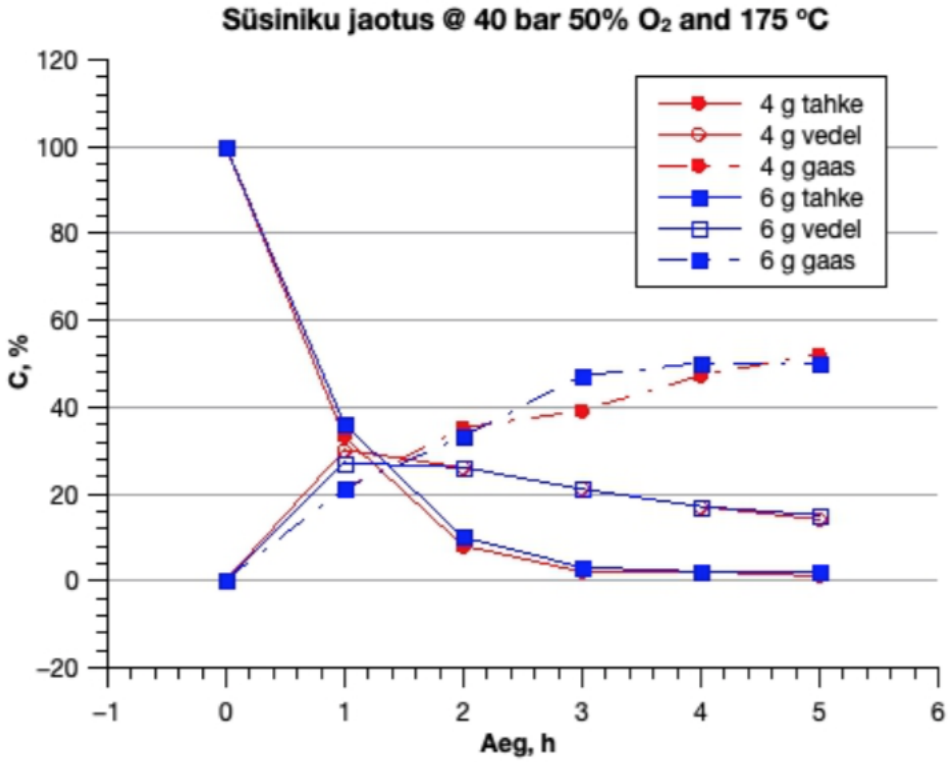

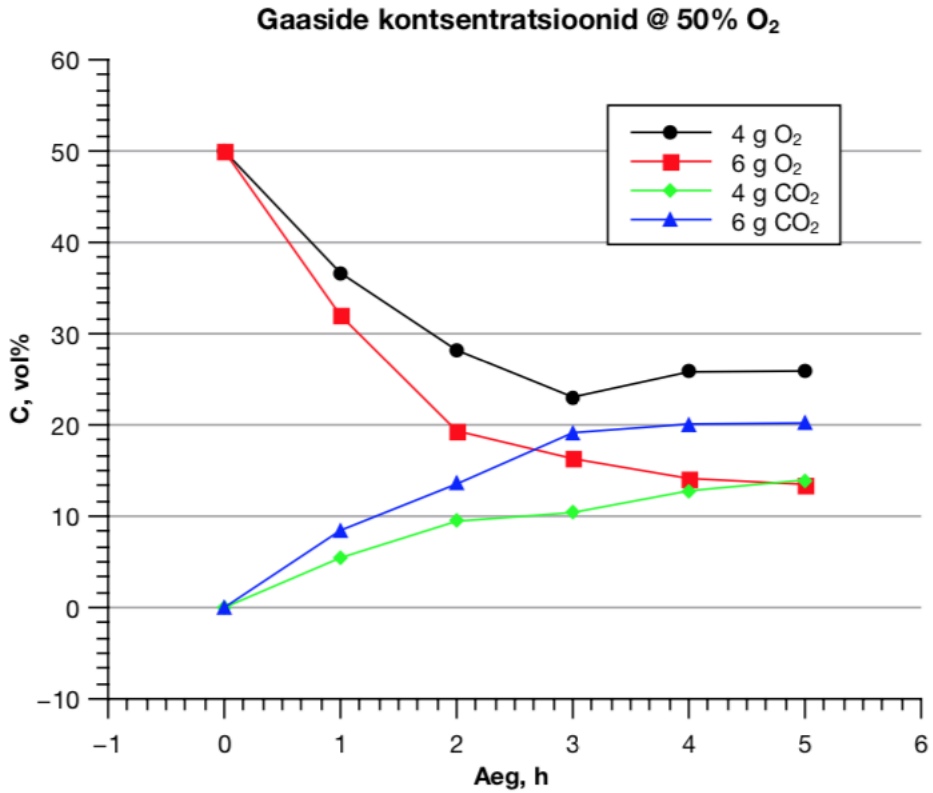

Maksimaalne lahustunud süsiniku hulk jääb vahemikku 25-30% 1h juures, kui hapniku lähtekontsentratsioon gaasifaasis on 50%.
Antud juhul süsiniku lahustumise kiirus ei sõltunud K-70 lähtehulgast.

DIHAPETE STABIILSUS

Reactivity of Aliphatic Dicarboxylic Acids in Wet Air Oxidation Conditions

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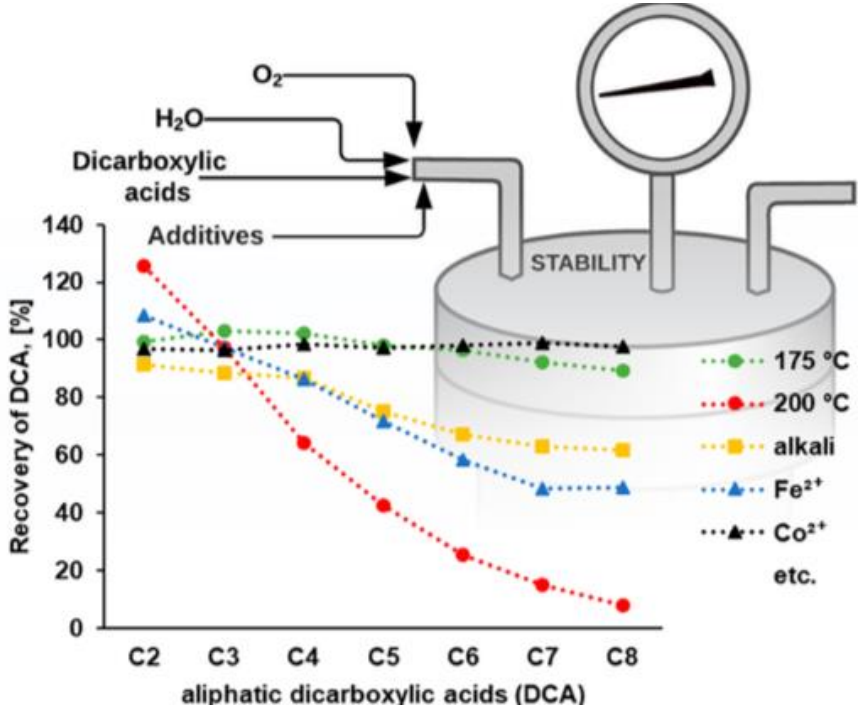


DIHAPETE STABIILSUS

Table 1. Recovery (%) of DCAs after Oxidation in Subcritical Conditions[a]

O_2, [%]	pH	succinic acid, [%]	glutaric acid, [%]	adipic acid, [%]	pimelic acid, [%]	suberic acid, [%]	azelaic acid, [%]	sebacic acid, [%]	sum, [%]
21	5	100	103	103	102	100	99	101	100
50	4	99	103	102	98	96	92	89	97
100	4	86	99	102	101	101	99	101	98
50	2[b]	85	96	99	98	98	96	98	96

[a]Reaction conditions: 40 bar of O_2/N_2 mixture; 175 °C; 3 h; [DCA] = 1g/L. [b]10 vol % solution of acetic acid.

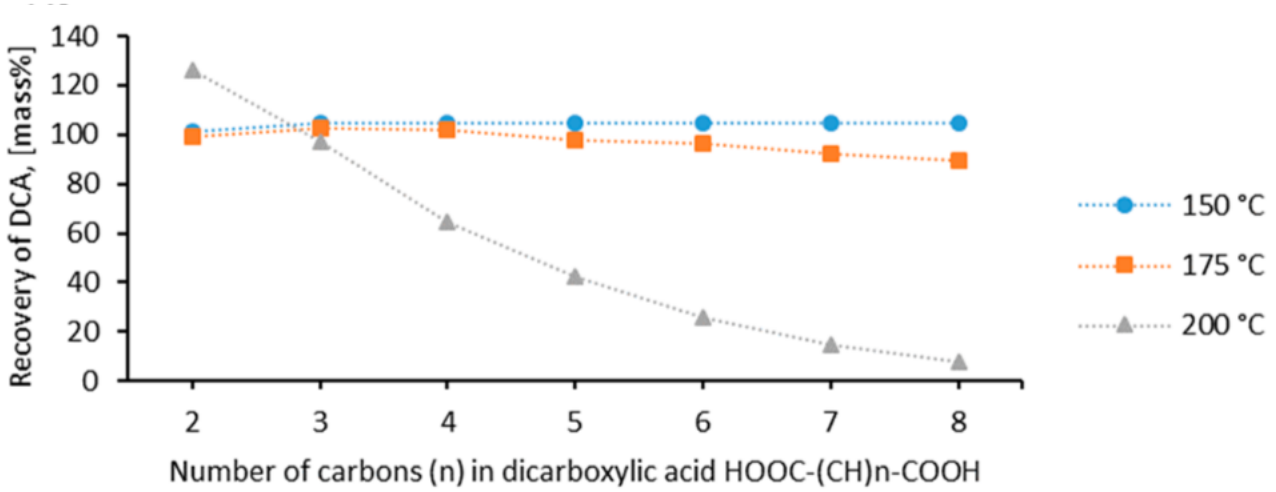


Figure 1. Recovery of DCAs at various temperatures. (Conditions: 40 bar of 50/50 O_2/N_2 mixture; 3 h; [DCA] = 1g/L.)

TAL TECH

DIHAPETE STABIILSUS - ALUSED

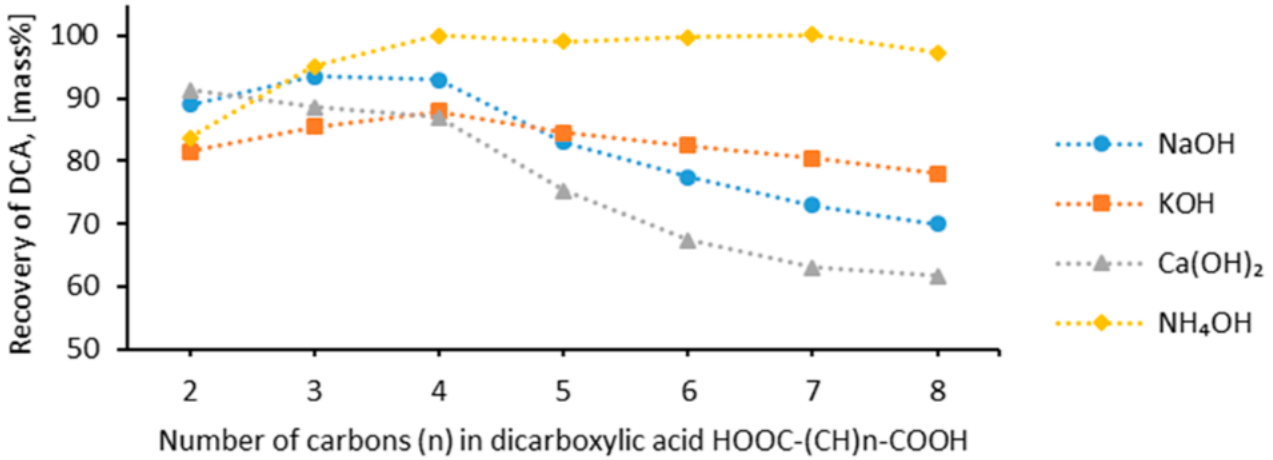


Figure 3. Stability of DCAs in alkali. (Conditions: [DCA] = 1 g/L; 2.2 equiv of alkali per mol of DCA; 40 bar of 50/50 O_2/N_2 mixture; 175 °C; 3 h.)

TAL TECH

DIHAPETE STABIILSUS - ALUSED

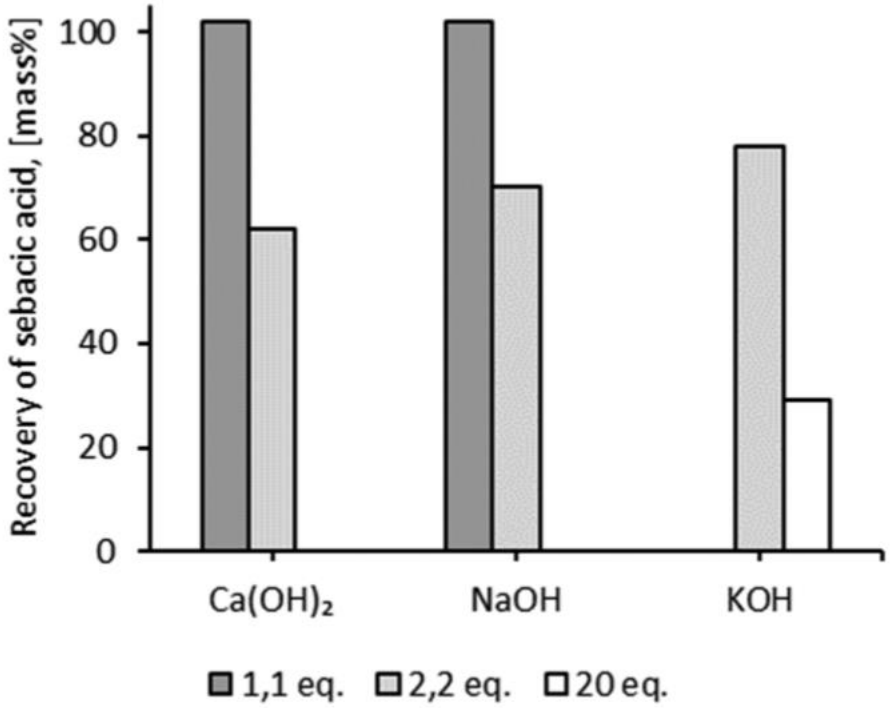
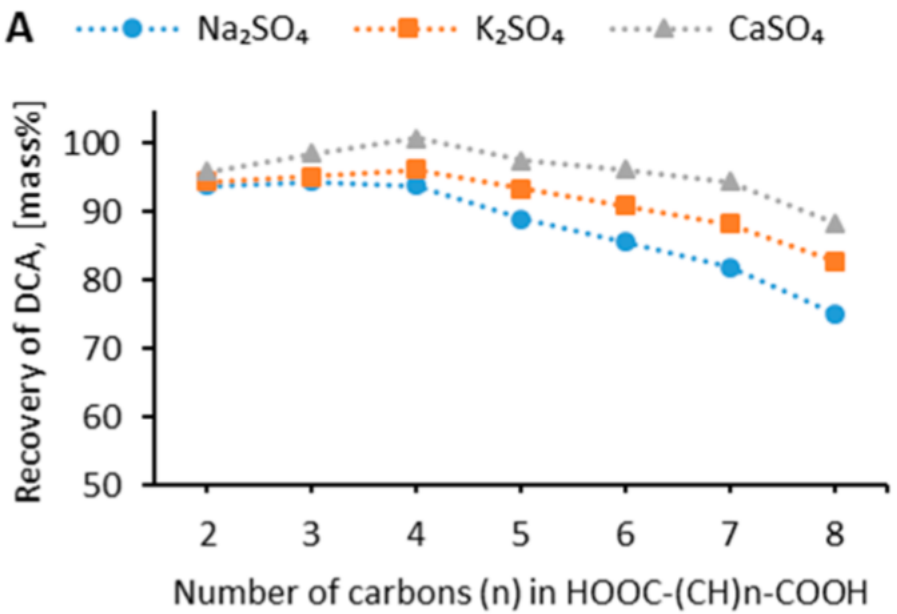
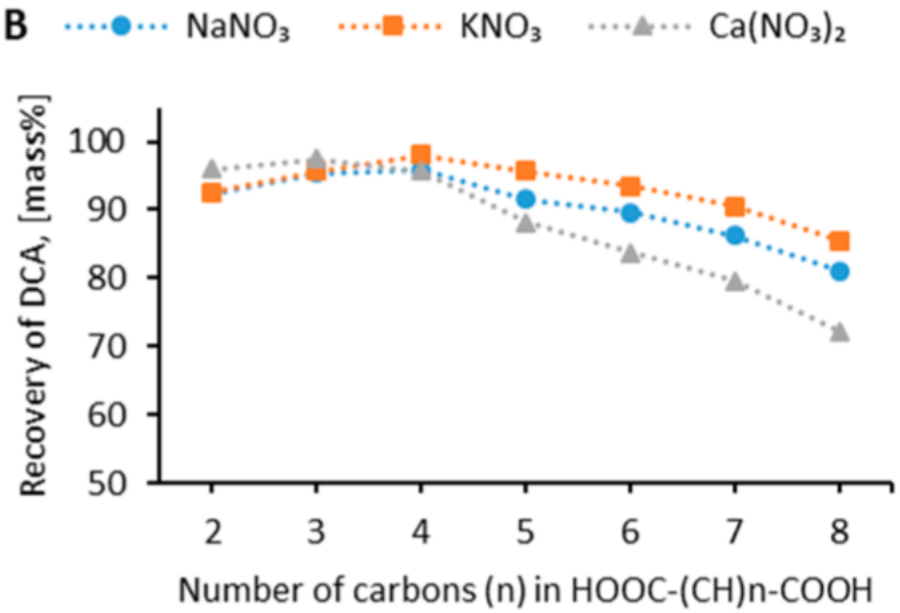


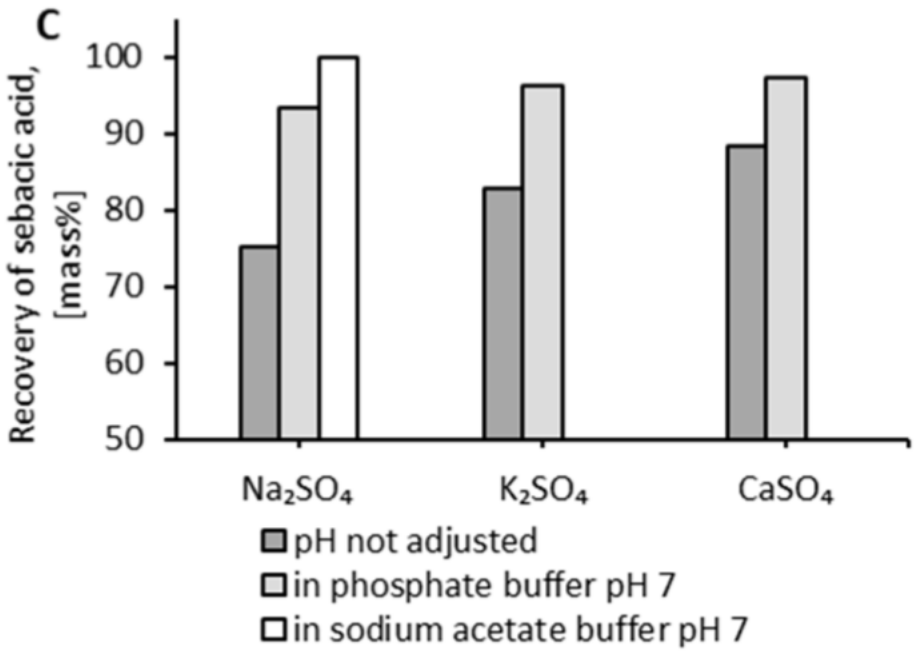
Figure 4. Stability of dicarboxylic acids in various alkali solutions with different concentrations. (Conditions: 40 bar of 50/50 O_2/N_2 mixture; 175 °C; 3 h; [DCA] = 1g/L.)

TAL TECH

SOOLADE MÕJU







TAL TECH

DIHAPETE STABIILSUS – pH MÕJU

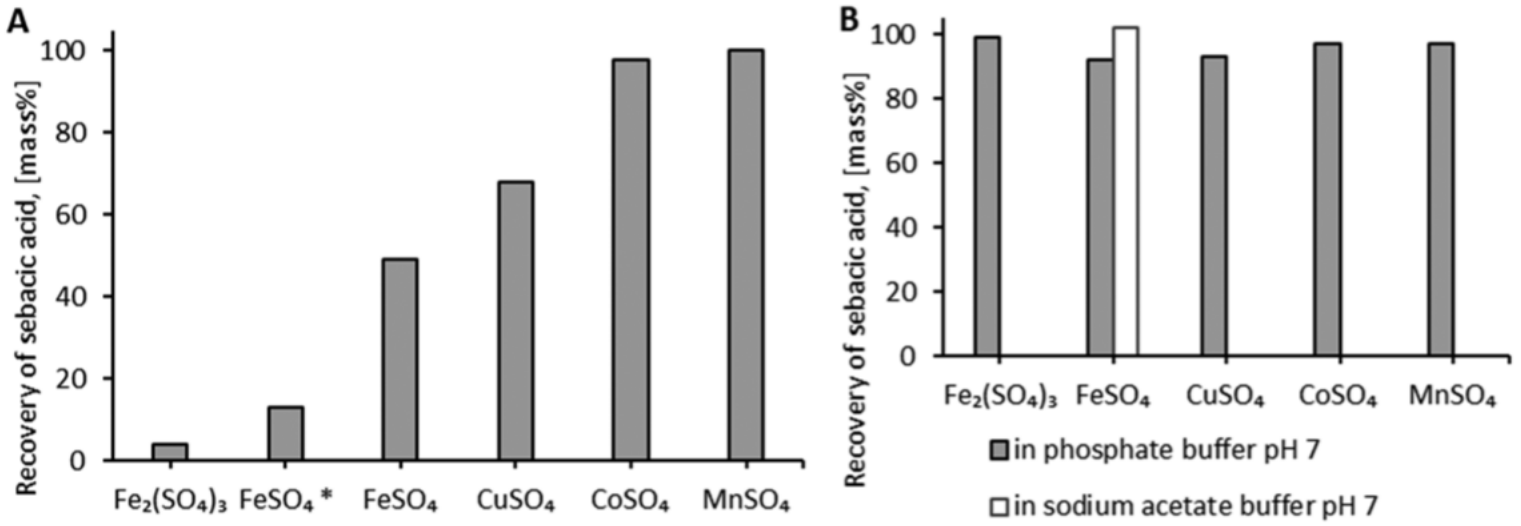
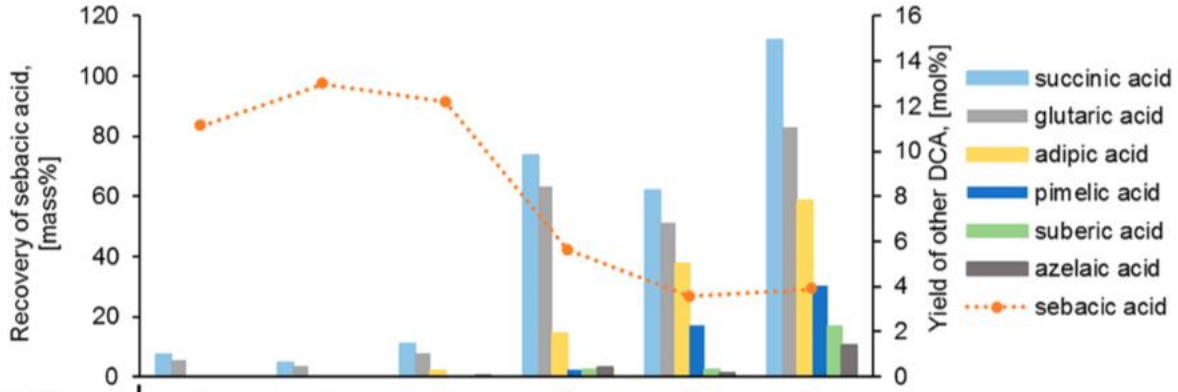


Figure 7. Stability of sebacic acid with different metal-salts. (A) pH not adjusted; (B) pH adjusted with buffer. (Conditions: 40 bar of 50/50 O_2/N_2 mixture; 175 °C; 3 h; [DCA] = 1g/L; metal salts 20 mol %; *40 mol %.)

TAL TECH

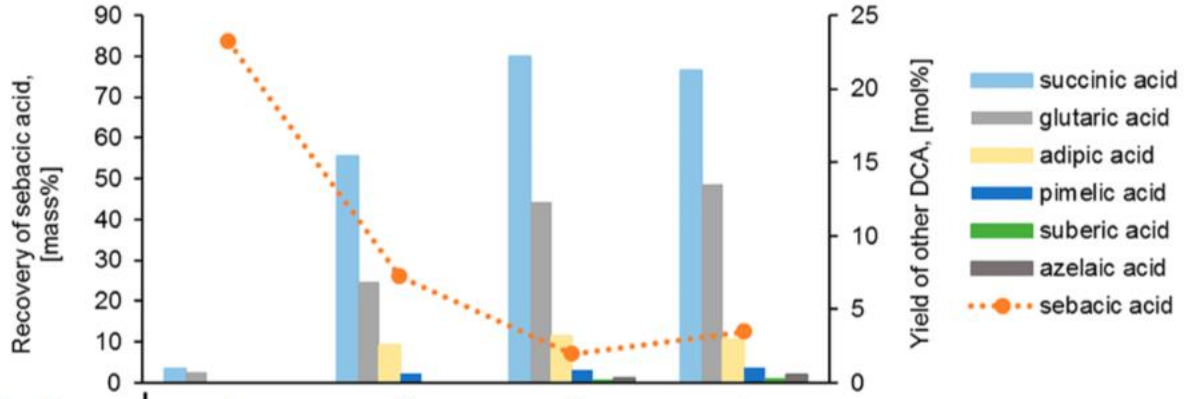
DIHAPETE STABIILSUS - KAASOKSÜDANDID



Exp. No.	1	2	3	4	5	6
Co-oxidant			Malonic acid	Malonic acid	Malonic acid	
Additive		10% CH_3COOH	10% CH_3COOH		0,1 M KOH	0,1 M KOH
Recovery of sebacic acid,	83	97	91	42	27	29
Yield of other DCA, [mol%]	1	<1	2	21	22	41
Recovery of org. C as DCA, [mass%]	84	98	93	52	38	51

TAL TECH

DIHAPETE STABIILSUS - KAASOKSÜDANDID



Exp. No	1	2	3	4
Co-oxidant		5-Me-resorcinol	5-Me-resorcinol	2-Me-resorcinol
Additive		10% CH_3COOH		
Recovery of sebacic acid,	83	26	7	13
Yield of other DCA, [mol%]	1	25	39	40
Recovery of org. C as DCA, [mass%]	84	37	25	31

TAL TECH

DIHAPETE STABIILSUS - JÄRELDUSED

Reaktsiooni kiirendavad

- Alused
- Rauasoolad
- Kaasoksüdeerijad

Stabiliseerivad

- Kaltsiumi soolad
- Puhverdatud keskkond

Reaktiivsus korreleerub soolade lahustuvusega

TAL TECH

LÕPPSÕNAD