Journal of Molecular Catalysis A: Chemical 397 (2015) 48–55

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Heterogeneous catalysis for transformation of biomass derived compounds beyond fuels: Synthesis of monoterpenoid dioxinols with analgesic activity

Alexandra Torozova[a], Päivi Mäki-Arvela[a], Atte Aho[a], Narendra Kumar[a], Annika Smeds[a], Markus Peurla[b], Rainer Sjöholm[a], Ivo Heinmaa[c], Dina V. Korchagina[d], Konstantin P. Volcho[d,e], Nariman F. Salakhutdinov[d,e], Dmitry Yu. Murzin[a,*]

[a] *Process Chemistry Centre, Åbo Akademi University, 20500 Turku/Åbo, Finland*
[b] *University of Turku, Turku, Finland*
[c] *Institute of Chemical Physics and Biophysics, Tallinn, Estonia*
[d] *N.N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Russian Academy of Sciences, Novosibirsk 630090, Russia*
[e] *Novosibirsk State University, Novosibirsk 630090, Russia*

ARTICLE INFO

Article history:
Received 3 September 2014
Received in revised form 21 October 2014
Accepted 24 October 2014
Available online 1 November 2014

Keywords:
Zeolite
Addition
Terpenoid
Dioxinol

ABSTRACT

Catalytic synthesis of a dioxinol compound, (2*S*,4a*R*,8*R*,8a*R*)-4,4,7-trimethyl-2-phenyl-4a,5,8,8a-tetrahydro-4*H*-benzo[d][1,3]dioxin-8-ol, exhibiting analgesic activity was demonstrated over Fe-modified beta zeolite. During interactions between cis-verbenol oxide and benzaldehyde, two main reactions occurred. In the first reaction, namely isomerization of verbenol oxide both cyclopentenic hydroxyketone, oxetane as well as a cyclohexyl compound, (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol were formed. In the second parallel reaction the target compound was generated. The highest yield of the target compound was achieved in the reaction between verbenol oxide and benzaldehyde at their molar ratio of 1:133 with the bifunctional iron modified Fe-H-Beta-150 catalyst at 70 °C giving a much higher yield than reported earlier in the literature, being 46 mol-% at complete conversion of verbenol oxide.

1. Introduction

New biologically active substances are synthesized from a variety of compounds isolated from natural sources or from side products of softwood industry [1], for example from α-pinene and verbenone found in coniferous trees [2]. α-Pinene belongs to the largest group of natural compounds, terpenes. Oxidation or rearrangement leads to formation of terpenoids, such as verbenone. α-Pinene can be easily obtained by fractional distillation of commercial natural terpenes, in which it is a major constituent [3]. The process for obtaining verbenone from α-pinene in the presence of biocatalysts (e.g. liquid cultures of *Saccharomyces cerevisiae*, or *Rauwolfia Sellowii* or *Psychotria Brachyceras* cells) leads to 80% yield during transformation in 5–10 days [4]. Catalytic oxidation of α-pinene in the presence of Co(II) and Cu(II) polyphtalocyanines exhibits the yield of 70% of the aimed product at 70 °C and 4 days of the reaction time [5]. Further epoxidation with hydrogen peroxide in the presence of NaOH and reduction using $LiAlH_4$ allow to synthesize cis-verbenol oxide [6], a starting monoterpenoid for synthesis of chiral compounds with various types of framework [7].

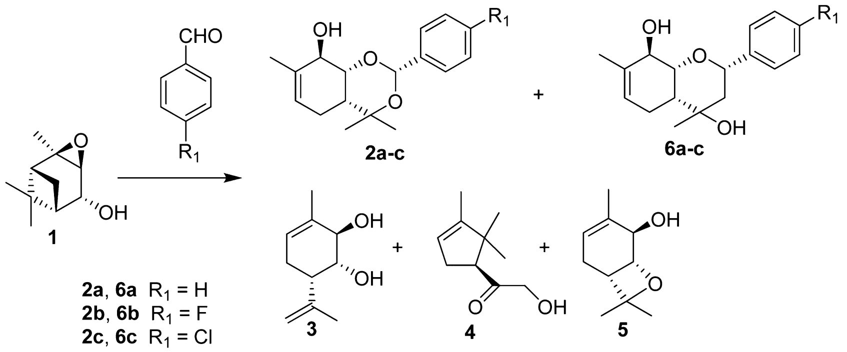
For example, verbenol oxide **1** may be isomerized [8] or react with aromatic aldehydes [9] to form compounds with anti-Parkinsonian [10] or analgesic activity [9,11] of new structural types, respectively. It should be noted that traditional analgesic and anti-inflammatory agents, such as opiates, steroids, and non-steroidal anti-inflammatory drugs all have serious side effects, and the development of highly effective, low-toxic analgesics thus remains a challenge in pharmacology and medicinal chemistry [12].

Compounds with benzodioxin framework which possess promising analgesic activity were synthesized early by the reaction between cis-verbenol oxide **1** and aromatic aldehydes in the presence of an excess of montmorillonite clay (mass ratio between clay and aldehyde was 5.7 [13] or 5 [9]). The reactions were carried out in dichloromethane at room temperature using an equimolar ratio of aldehyde and verbenol oxide. The isolated yields of the desired dioxinols **2** exhibiting benzodioxin framework, separated

---

[*] Corresponding author. Tel.: +358 2215 4985.
E-mail address: dmurzin@abo.fi (D.Yu. Murzin).

http://dx.doi.org/10.1016/j.molcata.2014.10.023
1381-1169/



Scheme 1. Products of reaction of verbenol oxide **1** with aldehydes (compounds **2** and **6**), and isomerization products **3**–**5**.

by column chromatography, and formed using either fluorobenzaldehyde or chlorobenzaldehyde as a reactant were 10% and 29%, respectively, based on aldehyde consumption with complete conversion of terpenoid [9] (Scheme 1). A moderate yield of the target products can be explained by a number of competitive reactions including isomerization of verbenol oxide to diol **3** with cyclohexene framework, hydroxyketone **4** with cyclopentyl skeleton and oxetane **5**, as well as formation of heterocyclic compounds of type **6** with chromene framework (Scheme 1) [9]. Furthermore, the exact nature of the catalyst is not known and the role of iron oxide present in montmorillonite clay K10 remained unclear [14].

Due to importance of the target compound, low selectivity towards it and a very limited amount of experimental data available only for one type of clay [9,13], there is a need to investigate the reaction between verbenol oxide and benzaldehyde for synthesis of compounds with promising biological activity. The aim of this work was to find for the first time an effective catalyst for synthesis of dioxinols starting from verbenol oxide and benzaldehyde. The main parameters were the reaction conditions and a type of heterogeneous catalysts, namely proton and bifunctional, metal modified zeolites. H-Beta-300 catalyst was selected due to its high selectivity towards isomerization of verbenol oxide to diol [8]. H-Beta zeolite was also used earlier in transformations of monoterpenoids [15], although the first attempts to use this type of catalyst in the reaction of verbenol oxide with aldehydes (in CH_2Cl_2 at room temperature) were unsuccessful [6].

2. Experimental

2.1. Catalyst synthesis and characterization methods

NH_4-Beta-25 ($SiO_2/Al_2O_3 = 25$), NH_4-Beta-150 ($SiO_2/Al_2O_3 = 150$) and NH_4-Beta-300 ($SiO_2/Al_2O_3 = 300$) zeolites were purchased from Zeolyst International. The ammonium forms of these zeolites were transformed to proton forms using step calcination procedure at 500 °C for 4 h. 5 wt% Fe-H-Beta-150 zeolite catalyst was prepared using an aqueous solution of ferric nitrate. H-Beta-150 zeolite and the aqueous solution of ferric nitrate was subjected to ultrasound irradiation for 4 h. Thereafter a round bottom flask containing the above mentioned solution was rotated in a rotavapor for 24 h followed by evaporation of water, drying of Fe-H-Beta-150 zeolite catalyst at 100 °C and calcination in a muffle oven [16].

Nitrogen physisorption measurements were performed using Sorptomatic 1900. The sample preparation was carried out by outgassing at 150 °C for 3 hours. Specific surface area (m^2/g) and micropore volume (cm^3/g) were calculated with Dubinin's method.

The morphology of some catalysts was studied with scanning and transmission electron microscopy. Zeiss Leo Gemini 1530 microscope was equipped with SE (secondary electron) and BSE (backscattered electron) detectors. The equipment for TEM was JEM 1400 plus with acceleration voltage of 120 kV and resolution of 0.98 nm using Quemsa II MPix bottom mounted digital camera.

The phase purity and structure of zeolites were investigated by XRD using X'Pert Pro MPD instrument using monochromated CuKα radiation at 40 kV/50 mA. The collimation of X-ray beam was performed with a fixed 0.25° divergence slit with a fixed 20 mm mask. The measurements were performed in a range of 1.15° - 90° with a scanning speed of 0.04°/2 s. The diffractograms were analyzed by Philips High Score and Maud programmes [17] and the crystal structures were confirmed with those presented in IZA web site [18].

The acidity of the catalysts was determined with ATI Mattson FTIR of adsorbed pyridine (Sigma–Aldrich, ≥99.5%, a.r.) as a probe molecule. Infrared transmission spectra were recorded on the thin pressed tablets with mass about 10–20 mg. The pretreatment of the pellets was made at temperature of 450 °C for 1 hour at 7 Pa before the measurement. At first pyridine was adsorbed for 30 min at temperature of 100 °C. To get the distribution of weak, medium and strong Brønsted and Lewis acid sites desorption of pyridine was made at the range of temperatures: 250 °C, 350 °C and 450 °C.

Brønsted and Lewis acid site concentrations were calculated by the integration of the infrared bands at 1545 cm^{-1} (1.67 cm/mmol as a molar absorption coefficient) and at 1455 cm^{-1} (2.22 cm/mmol as a molar absorption coefficient), respectively. The molar extinction coefficients were taken from the work of Emeis [19].

MAS-NMR of the proton forms of Beta zeolites was performed. Single pulse excitation spectra were obtained with Bruker AVANCE-III-800 spectrometer in 18.8 T magnetic field, where ^{27}Al resonance frequency was 208.4 MHz, Bruker MAS probe for 3.2 mm outer diameter zirconia rotors was used. The spinning speed of the samples was 22.0 kHz in all experiments. To keep quantitative intensities 10° short excitation pulses at RF field strength 50 kHz and 0.1 s relaxation delay between the accumulations were used. Intensity was normalized dividing the absolute intensity with the mass of the sample and with the number of scans. The spectra were referenced to the resonance frequency of $KAl(SiO_4)_2 \times 12H_2O$.

^{29}Si MAS-NMR spectra of the H-Beta samples were recorded with Bruker AVANCE-II-360 spectrometer at 8.5 T magnetic field (^{29}Si resonance at 71.45 MHz) using home built MAS probe for 10 mm outer diameter zirconia rotors. The spinning speed of the samples was 5 kHz, 90° excitation pulse was 7 μs, relaxation delay between the pulses was 100 s. About 800 scans were accumulated for each spectrum. The intensities were normalized by dividing the absolute intensity with the sample weight and with the number of scans.

2.2. Experimental set-up for evaluation of catalytic activity

The reactor set-up for the reaction between verbenol oxide and aldehydes at atmospheric pressure consisted of a four necked glass flask (total volume 250 ml) for feeding the catalyst, the solvent, the reactant and cooling with a condenser. Kinetic experiments were performed under argon atmosphere using the stirring speed of 390 rpm in order to minimize the impact of external mass transfer. Furthermore, the catalyst particle size below 90 μm was used to eliminate potential influence of internal diffusion as made in the previous publications [20,21]. A motor coupled with a stirrer was used. The constant heating was organized with an electric oven and controlled with a thermocouple. Samples were taken during the experiments and analyzed with gas chromatograph and mass spectrometer. In some cases, where an excess of benzaldehyde was used in order to shift the reaction towards formation of dioxinols, toluene was used for making the initial solution of verbenol oxide. This procedure guaranteed that the desired amount of verbenol oxide was transferred into the reactor, which contained the pre-dried catalyst. The reaction was commenced by addition of verbenol oxide solution to benzaldehyde, injecting it into the reactor and starting stirring. In the reproducibility tests in the catalytic transformations of terpene oxides with zeolite catalysts the experimental error was below 2%.

2.3. Chemicals

Verbenol oxide was synthesized in Novosibirsk Institute of Organic Chemistry. The purity of verbenol oxide was determined by NMR being 87.5%. The impurities are mainly oligomeric compounds which usually do not influence the reactivity of verbenol epoxide. The following chemicals and solvents were used: benzaldehyde (Fluka analytical, ≥99.0), fluorobenzaldehyde (Sigma–Aldrich, 98%), tetrahydrofuran (Sigma–Aldrich, anhydrous, ≥99.9%, inhibitor-free), toluene (J.T. Baker, p.a.), ethyl acetate (Sigma–Aldrich, 99.8%, anhydrous) and pentadecane (Sigma–Aldrich, ≥99) as an internal standard.

3. Analytical methods

The samples were analyzed by a gas chromatography using the column HP-5.5% Phenyl Methyl Siloxane (Agilent 1909J-413, length 30 m, internal diameter 320 μm, film thickness 0.25 μm), which has the maximum allowed temperature of 325 °C. The GC programme used featured injection at 120 °C, where the temperature was held for 1 minute, followed by a ramp of 2 °C/min until 280 °C, where it was maintained for 3 min.

For the identification of the reaction mixture composition a mass spectrometer–gas chromatograph was used. The column was HP-5 (Agilent Technologies, length 25 m, internal diameter 0.2 mm, film thickness 0.11 μm). The GC oven temperature started from 80 °C, which was held for 1 min, followed by a ramp of 8 °C/min until 320 °C (held for 6 min). For the reaction between verbenol oxide **1** and benzaldehydes, pentadecane was used as an internal standard. The standard solution contained 1.675 mg/ml pentadecane in toluene. The samples with the internal standard for determining response factors were prepared by mixing a known amount of it, verbenol oxide and two products of the target reaction. The reaction products, (2*S*,4a*R*,8*R*,8a*R*)-4,4,7-trimethyl-2-phenyl-4a,5,8,8a-tetrahydro-4*H*-benzo[*d*][1,3]dioxin-8-ol (Peak 6 in the chromatogram), **2a** and (2*S*,4*S*,4a*R*,8*R*,8a*R*)-4,7-dimethyl-2-phenyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol, **6a** (Scheme 1) were obtained as synthesized standards for GC analysis from Novosibirsk Institute of Organic Chemistry.

Isomerization product (1*R*,5*R*,6*R*)-4,8,8-trimethyl-7-oxabicyclo[4.2.0]oct-3-en-5-ol **5** was identified by comparison of MS-spectrum with corresponding data for the pure compound obtained in Novosibirsk Institute of Organic Chemistry. The compound was not previously described in the literature. NMR spectra were recorded using Bruker DRX-500 apparatus. ^{1}H NMR spectrum (500.13 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.17 (s, Me(10)), 1.42 (s, Me (11)); 1.83 (m, all $J \leq 2.5$ Hz, Me(9)); 2.04 (br. dd, $J(2e,2a) = 17.6$, $J(2e,3) = 6.3$, H_e-C(2)), 2.19 (dddq, $J(2a,2e) = 17.6$, $J(2a,1) = 7.8$, $J(2a,3) = 2.7$, $J(2a,9) = 2.5$, H_a-C(2)); 2.71 (ddd, $J(1,2a) = 7.8$, $J(1,6) = 7.7$, $J(1,2e) = 1.5$, H-C(1)); 3.88 (d, $J(5,6) = 2.5$, H-C(5)), 4.81 (dd, $J(6,1) = 7.7$, $J(6,5) = 2.5$, H-C(6)); 5.74 (dm, $J(3,2e) = 6.3$, other $J \leq 2.7$ Hz, H-C(3)). ^{13}C NMR spectrum (125.76 MHz, $CDCl_3$), δ, ppm ($^{1}J_{C,H}$, Hz): 38.06 (d, C(1), 143.7), 21.90 (t, C(2), 127.5); 123.96 (d, C(3), 155.7); 134.87 (s, C(4)); 69.90 (d, C(5), 143.7), 77.15 (d, C(6), 151.70); 83.64 (s, C(8)); 22.01 (q, C(9), 125.6); 23.68 (q, C(10), 126.5); 30.43 (q, C(11), 125.2). Optical rotation was measured using polAAr 3005 spectrometer: $[\alpha]_D{}^{33} = -16.7$ (c 0.6692, EtOH). HR–MS (DFS Thermo Scientific spectrometer in a full scan mode, 15–500 *m*/*z*, 70 eV electron impact ionization): 168.1145 (M^+, $C_{10}H_{16}O$; calc. 168.1146) (Scheme 1, compound **5**).

Table 1
Specific surface areas of catalysts determined by nitrogen adsorption.

Catalyst	Specific surface area (m^2/g)
H-Beta-25	807
H-Beta-150	664
H-Beta-300	805
5 wt% Fe-H-Beta-150	686

4. Results and discussion

4.1. Catalyst characterization results

The specific surface areas for H-Beta-25 and H-Beta-300 were relatively close to each other (Table 1). It should be noted that the value of specific surface area for 5 wt% Fe-Beta-150 is higher than for proton form H-Beta-150. The increase of the surface area of Fe-H-Beta-150 zeolite catalyst may be attributed to the formation of micropores during calcination after iron modification.

SEM analysis was used to investigate the morphology of some zeolite catalysts. A typical Beta-zeolite crystal morphology is depicted in Figs. 1a and 2a illustrating that this type of zeolites has round shaped crystals.

The structure of zeolites can be shown clearly by transmission electron microscopy (Figs. 1b and 2b). The crystallite sizes of 5 wt% Fe-H-Beta-150 are in the range of 2.7–15.1 nm. The diffractograms (not depicted here) showed clearly the presence of H-Beta zeolite structure with its specific peaks at 2Θ values at 22.4° and 7.6° [22].

The acidity of Beta-zeolites increases as expected with increasing alumina content in the row: H-Beta-25 > H-Beta-150 » H-Beta-300 (Table 2). After Fe modification the amount of Lewis acid sites in Fe-H-Beta-150 increased 2.7 fold compared to the Lewis acid site concentration present in the parent material. The acidities of H-Beta-25, H-Beta-150 and H-Beta-300 were also determined by ^{27}Al MAS-NMR showing that total intensity in the spectra of H-Beta-25 and H-Beta-150 is almost the same, and in the case of

Table 2
Brønsted and Lewis acidity of the catalysts determined by pyridine adsorption/desorption.

Catalyst	Brønsted acidity (μmol/g)			Lewis acidity (μmol/g)		
	250 °C	350 °C	450 °C	250 °C	350 °C	450 °C
	W + M + S	M + S	S	W + M + S	M + S	S
H-Beta-25	219	187	125	82	43	25
H-Beta-150	176	161	72	43	23	10
H-Beta-300	54	49	23	28	9	4
Fe-H-Beta-150 [27]	72	14	3	123	60	15

Table 3
Catalyst testing results.[a]

Entry	System	T (°C)	Catalyst mass (mg)	Solvent, (ml)	Dielectric constant, ε	VO/ aldehyde molar ratio	Conversion after 120 min (%)	Selectivity to target product (%)	Selectivity to diol (%)	Selectivity to ketone, (%)	Selectivity to oxetane (%)	Selectivity to unknown products (%)	
												1[b]	2[c]
1	H-Beta-300 m(VO) = 0.300 g m(FBA) = 0.227 g	25	75	THF 100	7.58	1/1	25	0	42	0	22	36	0
2	H-Beta-25 m(VO) = 0.300 g m(FBA) = 0.227 g	40	150	THF 100	7.58	1/1	66	<1	40	30	13	17	0
3	H-Beta-25 m(VO) = 0.307 g m(FBA) = 0.233 g	60	150	THF 50	7.58	1/1	74	<1	27	18	33	15	7
4	H-Beta-25 m(VO) = 0.303 g m(FBA) = 0.456 g	70	150	EA 50	6.02	1/2	100	1	21	0	53	25	0
5	H-Beta-25 m(VO) = 0.303 g m(FBA) = 1.141 g	70	300	T 50	2.38	1/5	100	13	0	1	47	30	9
6	5 wt% Fe-Beta-150 m(VO) = 0.308 g m(BA) = 0.9582 g	70	300	T 50	2.38	1/5	100	9	10	4	41	33	3
7	5 wt% Fe-Beta-150 m(VO) = 0.303 g m(FBA) = 1.148 g	70	300	T 50	2.38	1/5	100	10	24	5	45	4	12

[a] Solvents are referred with the following abbreviation: THF, tetrahydrofuran; EA, ethylacetate; T, toluene; DMA, *N*,*N*-dimethylacetamide; selectivities are given at the conversion level achieved after 120 min of reaction time.
[b] Products of isomerization.
[c] Products of reaction between VO and aldehyde.

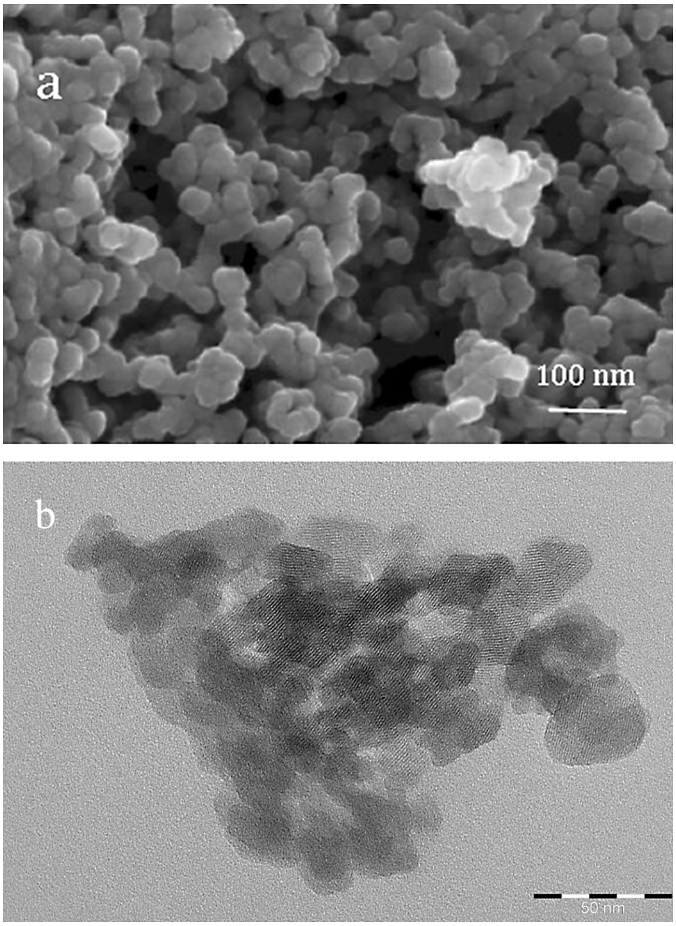


Fig. 1. (a) SEM and (b) TEM image of H-Beta-25.

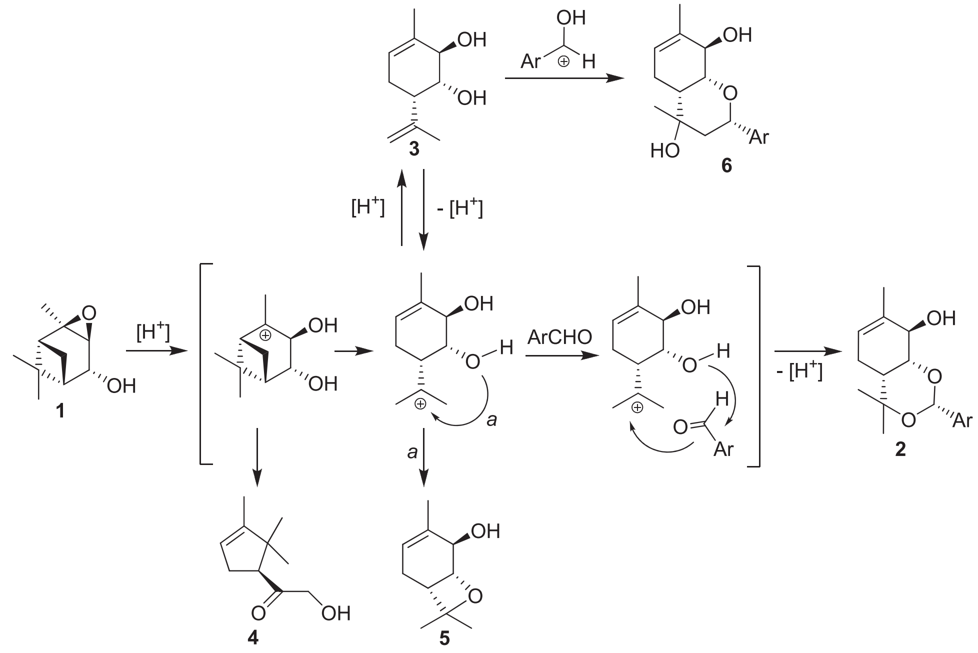
H-Beta-300 it is four times lower. The amounts of aluminium in tetrahedral and octahedral framework correlate well with acidity values measured by pyridine adsorption/desorption (compare Tables 2 and 3). The relative amounts of different Al species were measured by MAS Al NMR. The peak around 60 ppm (Al IV(a) and Al IV(b)) is responsible for framework aluminium in tetrahedral sites (Brønsted acids) and the peak around 0 ppm (Al VI(a) and Al VI(b)) corresponds to framework aluminium in specific octahedral sites (Lewis acids) [20,23,24]. The ratio between the Al species corresponding to the amount of Brønsted acid sites for H-Beta-300: H-Beta-150: H-Beta-25 was 1:12:12 indicating that H-Beta-300 catalyst exhibited much less Brønsted acid sites. The broad line between 58 ppm and 0 ppm was assigned as Al(V). Furthermore, the corresponding ratio of Lewis acid sites for H-Beta-300:H-Beta-150:H-Beta-25 was 1:8:8. It can be seen that the peak intensity is more around the tetrahedral forms; most of the Al atoms are present in the Brønsted acid sites for all the studied H-Beta catalysts.

Deconvolution of MAS-NMR spectra for ^{29}Si of H-Beta zeolites showed that the nine different Si(4Si) lattice sites of environment of siloxane bridges have chemical shifts around 111 and 115 ppm. The lines at −103 ppm and −108 ppm can be assigned to the sites Si(3Si,1OH) and Si(3Si,1Al) respectively [24]. The broad line belongs to amorphous silica.

4.2. *Catalytic results for synthesis of dioxinols*

4.2.1. *Preliminary experiments*

The reactions between verbenol oxide (VO) and two aldehydes, namely benzaldehyde (BA) and 4-fluorobenzaldehyde (FBA) were investigated. Preliminary screening of suitable reaction conditions and catalysts was performed at different temperatures in the range of 25–70 °C using different solvents, such as toluene, tetrahydrofuran and ethyl acetate (Table 3). In addition to reaction temperature and solvent, also the initial concentration of VO, as



Scheme 2. A possible mechanism of formation of target (**2**) and side products from verbenol oxide (**1**): hydroxyketone (**4**), oxetane (**5**) and another addition product (**6**).

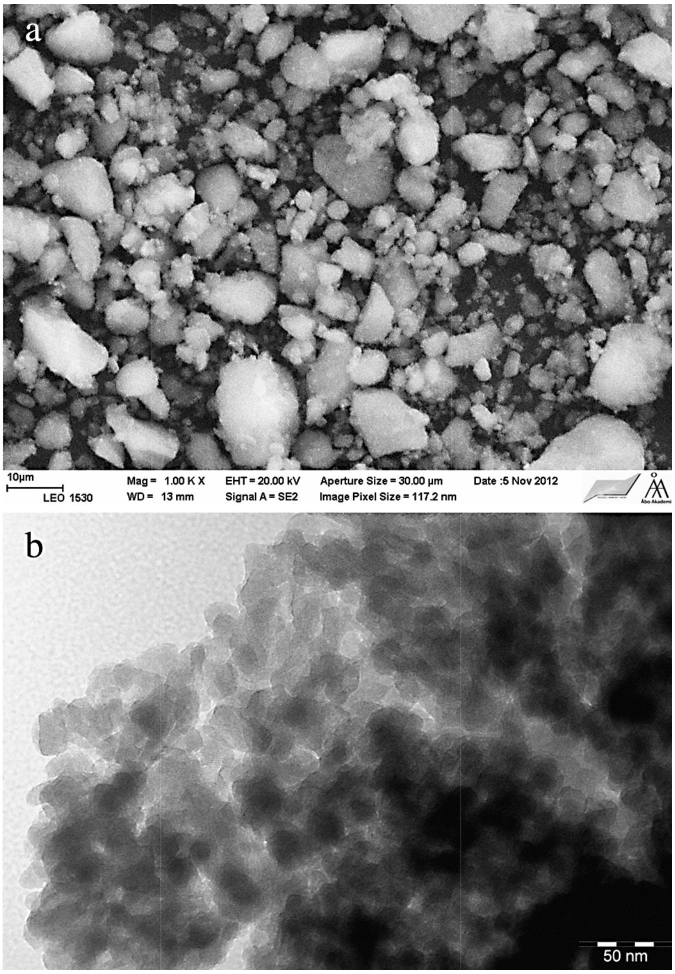


Fig. 2. (a) SEM and (b) TEM images of 5 wt% Fe-H-Beta-150.

well as the ratio between VO and aldehyde were varied. The following catalysts were studied in the reactions of verbenol oxide with benzaldehydes: H-Beta-300, H-Beta-25 and 5 wt% Fe-H-Beta-150.

First the addition reaction was investigated at low temperatures with a mildly acidic H-Beta-300 as a catalyst (Table 3, entry 1). In this case only isomerization products diol **3**, cyclopentenic hydroxyketone **4**, and oxetane **5** were formed, also formation of bicyclic compound is possible. This was determined in isomerization experiments, although the corresponding peak is not visible in GC spectra. It should, however, be pointed out here, that initially an equimolar ratio of VO and FBA was used. Thus several changes in the reaction conditions were made in the experiments 2–5 (Table 3), such as elevation of temperature, catalyst amount in experiment 5, higher initial reactant concentration and larger excess of FBA in experiments 4 and 5 and introduction of solvents with different polarity. An increase in conversion and selectivity to the target product was observed, when changing the solvent to toluene with a low dielectric constant and with increasing the molar ratio between aldehyde and VO at the same time. The highest selectivity to the target compound **2** was 13% at complete VO conversion, although the main products were still cyclopentene product, hydroxy ketone **4** and oxetane **5**, formed via the isomerization reaction (Table 3, entry 5). It should also be pointed out that only traces of compound **6** (in Scheme 1) were found in the reaction mixture.

Fe-modified H-Beta-150 zeolite catalyst was studied in the reaction of VO with BA (Table 3, entry 6) or with FBA (Table 3, entry 7). In these cases the ratio of aldehyde to verbenol oxide of 5:1 was used. Both these experiments resulted in 9–10% selectivity to the target compound in toluene at 70 °C indicating that the effect of fluorine is minor. The main products in both cases were a result of VO isomerization. From the mechanistic point of view these results showed that in both cases with H-Beta-25 and 5 wt% Fe-H-Beta-150 catalysts the formation of the target compound from diol, which is the product of isomerization, took place. For example in the former case the initial ratio between diol **3** and the target product was 7, however, after 120 min the diol vanished from the reaction mixture. An analogous trend was visible with 5 wt% Fe-H-Beta-150. The possibility of formation of compound of types **2** and **6** from diol **3** was demonstrated early when the reaction of terpenoid **3** with

Table 4
Selectivities to different products at 100% of VO conversion and in parenthesis after 120 min in the reaction between VO and BA over H-Beta-150 and 5 wt% Fe-H-Beta-150. Compound notations are in Figs. 5 and 6.

Catalyst	Selectivity (%)				
	Target product (**2a**)	Side product (compound **6a**)	Diol (**3**)	Pentyl (**4**)	Unknown addition products
H-Beta-150	49 (40)	4 (4)	8 (4)	14 (2)	18 (34)
5 wt% Fe-H-Beta-150	35 (46)	4 (8)	20 (12)	15 (6)	18 (11)

3,4,5-trimethoxybenzaldehyde in the presence of montmorillonite clay was studied [7].

A hypothetical mechanism of the formation of all products from verbenol oxide **1** is shown in Scheme 2. It involves the protonation and cleavage of the epoxide ring, then the cation can be converted into compound **4** with cyclopentene framework or be subjected to the skeletal rearrangement into the cation with a *para*-menthane framework which may either transform into diol **3** or react with an aldehyde molecule acting as a nucleophile, to give the target compound **2** [7]. Compound **6** may be formed by the reaction of diol **3** with the protonated aldehyde [7]. Obviously initially formed diol **3** may also be protonated in the presence of an acid catalyst and then gives either bicyclic monoterpenoid **5** as a product of intramolecular heterocyclization or compound **2** as a result of an interaction with the aldehyde (Scheme 2).

The performed preliminary experiments gave some hints about the reaction conditions and catalysts, which could be investigated in more detail. Although 13% selectivity to the target compound was achieved over H-Beta-25 (Table 3, entry 5), no diol was found in the reaction mixture after 120 min in that case. Since it was shown that diol could react further to the target compound and the second best result was achieved with Fe-H-Beta-150 in toluene at 70 °C using a five-fold excess of aldehyde compared to VO, it was decided to investigate specifically the effect of the metal with Beta-150 catalyst by applying a large excess of benzaldehyde.

4.2.2. Catalytic results with the selected catalysts, H-Beta-150 and Fe-H-Beta-150

Experiments with a large excess of benzaldehyde corresponding to the molar ratio of VO:BA 1:133 were carried out with H-Beta-150 and 5 wt% Fe-H-Beta-150 catalysts in a solvent mixture consisting of benzaldehyde (40 ml) and toluene (10 ml). The kinetics of the reaction with both of these catalysts is depicted in Fig. 3a and b. When comparing these results, it can be stated that there were large differences both in the reaction rates and in the product distribution.

The reaction was initially very rapid, since already in the beginning of the reaction only 13% and 27% verbenol oxide remained unreacted with H-Beta-150 and 5 wt% Fe-H-Beta-150, respectively. This result indicated, however, that the reaction rate was higher with the parent H-Beta-150 even if the Brønsted acid site concentrations of these two catalysts are comparative (Table 2).

Selectivity to different products at 100% of VO conversion and after 120 min of reaction time achieved either with H-Beta-150 or 5 wt% Fe-H-Beta-150 is shown in Table 4. Selectivity to addition products decreased with increasing reaction time in the case of H-Beta-150, whereas the opposite is valid for 5 wt% Fe-H-Beta-150. High initial reaction rates for formation of the isomerization products, diol **3**, hydroxyl ketone **4** and oxetane **5** as well as the target product **2a** in the beginning of the reaction over Fe-H-Beta-150 are visible from Fig. 3. After 5 min the formation of the target product **2a** from diol **3** takes place and then linearly increases until the completion of the reaction in the case of Fe-H-Beta-150.

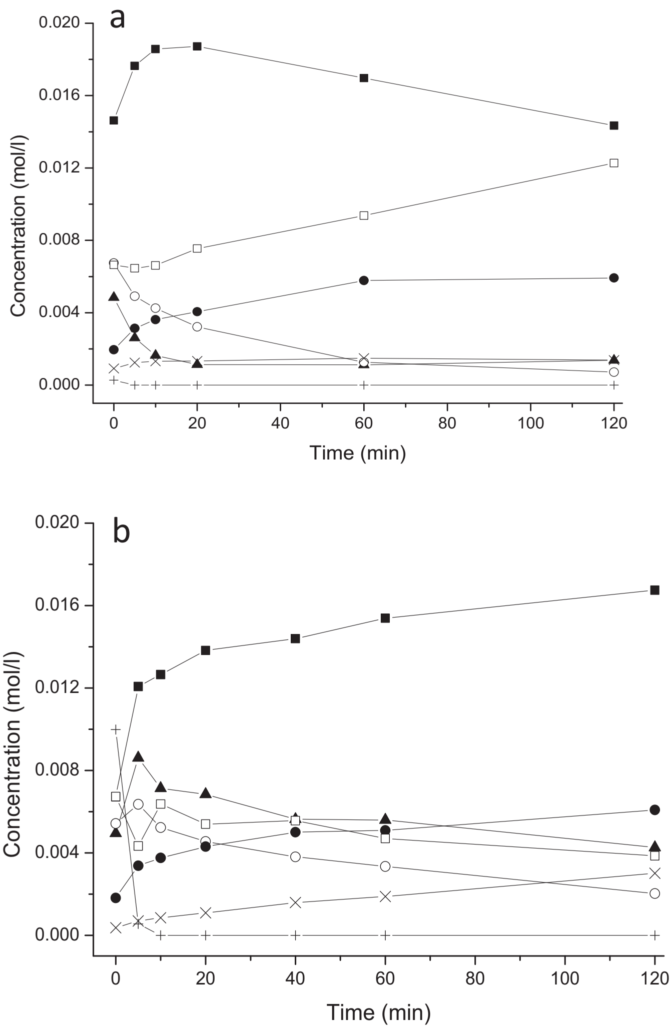


Fig. 3. Kinetics of VO reaction with BA over (a) H-Beta-150 and (b) 5 wt% Fe-H-Beta-150 at 70 °C, C_0(VO) = 0.037 mol/l, 10 ml of toluene and 40 ml of BA, mass of the catalyst 300 mg, particle size <90 μm. Symbols: (+) verbenol oxide (**1**), (■) target product (**2**), (▲) diol (**3**), (●) α-hydroxy ketone (**4**), (o) oxetane (**5**), (×) compound **6** and (□) unknown addition compounds. Numbers of the compounds are shown in Scheme 1.

After prolonged reaction time, 120 min, the reaction was more selective to the known products, i.e. target product **2a**, compound **6a**, diol **3**, hydroxyl ketone **4** and and oxetane 5 over Fe-H-Beta-150 compared to the results achieved with a parent H-Beta-150. When comparing the chromatograms of both of these reaction mixtures with H-Beta-150 and 5 wt% Fe-H-Beta-150 (Fig. 4), it can be seen that an unknown compound **8** was formed with retention time 7.35 min. This compound is located in the chromatogram between the target product **2a** (RT = 7.02 min) and compound **6a** (RT = 7.6, the structure is given in Scheme 1) and has a boiling point close to the target and side products. The amount of unknown products increased during the reaction in the case of H-Beta-150. A more detailed investigation of the chromatogram showed, however, that when calculating the area percentage of the peaks in H-Beta-150 and in 5 wt% Fe-H-Beta-150 chromatograms, it was found that the area of the known compounds, target compound **2a**, compound **6a**, and the isomerization products, diol **3** and cyclopentene product **4** and oxetane **5**, were for H-Beta-150 and for 5 wt% Fe-H-Beta-150, 68% and 89% from the total peak area, respectively. In the case of Fe-H-Beta-150, the product mixture contained very many small, unknown peaks eluting in the range of both isomerization as well as addition products (Fig. 4). This result can be explained by the

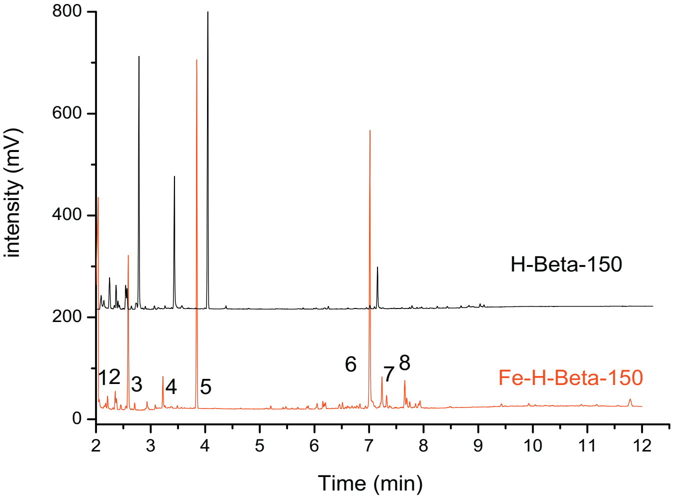


Fig. 4. Chromatogram of the reaction mixtures made in between verbenol oxide and benzaldehyde at 70 °C using 40 ml BA and 10 ml toluene as a solvent over H-Beta-150 and 5 wt% Fe-H-Beta-150 with the initial VO concentration of 0.037 mol/l. Notation: 1: oxetane **5**, 2: unknown, 3: 1-(2,2,3-trimethylcyclopent-3-enyl)-2-hydroxy-ethanone (hydroxy ketone with cyclopentane framework) (**4**), 4: diol (**3**), 5: pentadecane (std), 6: target compound **2**, (2*S*,4a*R*,8*R*,8a*R*)-4,4,7-trimethyl-2-phenyl-4a,5,8,8a-tetrahydro-4*H*-benzo[d][1,3]dioxin-8-ol, 7: unknown compound **8**, 8: compound **6**. The shift for H-Beta-150 chromatogram is $\Delta x = 0.2$ min, $\Delta y = 200$ mV. Numbers of the compounds are shown in Scheme 1.

fact, that H-Beta-150 has less Lewis acid sites than 5 wt% Fe-H-Beta-150 and thus the reaction over the former catalyst is much more selective.

Kinetic results also confirmed that in the case of 5 wt% Fe-Beta-150 diol **3** reacts further to the target compound **2a**. In addition, compound **6a** was formed to a minor extent from diol **3**. The ratio between the formation rates for **6a** and the target product **2a** is not linear (Fig. 5) and increased also 1.3 fold already after 5 min reaction time in comparison to the initial ratio. It is interesting to note that the reactions of diol **3** with aldehydes in the presence of montmorillonite clay in all cases preferably lead to compounds of type **6** with chromene framework, but not to benzodioxines **2** [7,25,26].

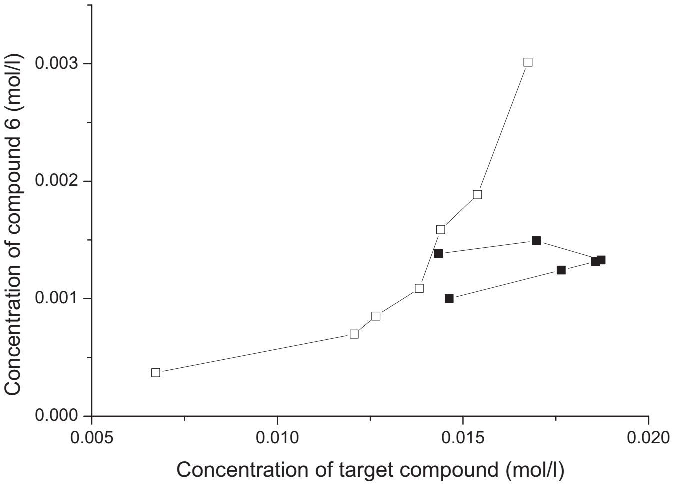


Fig. 5. Concentration of target product 2 versus compound **6** in the reaction between verbenol oxide and BA with (■) H-Beta-150 and (□) 5 wt% Fe-H-Beta-150 at 70 °C in 10 ml toluene and 40 ml BA with 300 mg catalyst with particle size < 90 μm.

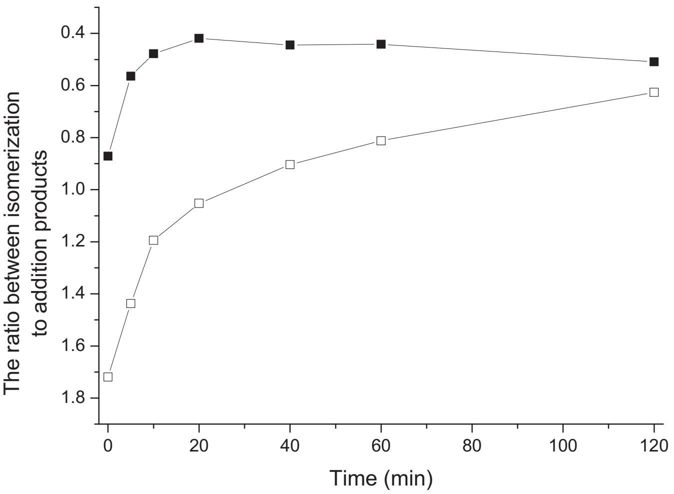


Fig. 6. The ratio between the known isomerization products to the known addition products in the reaction between verbenol oxide and BA with (■) H-Beta-150 and (□) 5 wt% Fe-H-Beta-150 at 70 °C in 10 ml toluene and 40 ml BA with 300 mg catalyst with particle size <90 μm.

On the other hand, in the absence of iron in H-Beta-150 the concentration of compound **6a** was not increasing with increasing reaction time. The effect of iron was additionally elucidated by calculating the ratio between the sum of the concentrations of the known isomerization products and the sum of the known addition products (Fig. 6). This result showed also clearly the beneficial effect of Lewis acid sites for the production of the addition products **2a** and **6a**. The ratio between the initial rates for the formation of VO, target product and the other diol isomer is 1.15:1:0.06 on Fe-H-Beta-150 showing that VO isomerization occurs most rapidly followed by the reaction between diol **3** and benzaldehyde. On the other hand the formation of compound **6** occurs after prolonged reaction times, especially on more Lewis acidic catalyst (Fig. 5).

5. Conclusions

Monoterpenoid derived dioxinols with analgesic activity were synthesized by a reaction between verbenol oxide and benzaldehyde or 4-flourobenzaldehyde over heterogeneous catalysts. Zeolite H-Beta with three different SiO_2/Al_2O_3 ratio, namely 25, 150 and 300 as well as a bifunctional Fe-H-Beta-150 were used. The catalysts were characterized by nitrogen adsorption, XRD, TEM, SEM, EDXA, pyridine desorption and MAS-NMR for ^{27}Al and ^{29}Si.

The concentration of acid sites of three zeolites with decreasing SiO_2/Al_2O_3 ratio increased as expected according to pyridine desorption. These results agreed well with the results obtained with ^{27}Al MAS-NMR. The Brønsted acidity of Fe-Beta-150 was about the same as for H-Beta-150, whereas Lewis acidity of the iron modified catalyst was increased after introduction of Fe.

The synthesis of (2*S*,4a*R*,8*R*,8a*R*)-4,4,7-trimethyl-2-phenyl-4a,5,8,8a-tetrahydro-4*H*-benzo[d][1,3]dioxin-8-ol has earlier been demonstrated in the presence of a large excess of montmorillonite clay. In this work the reaction between verbenol oxide with benzaldehyde or 4-flourobenzaldehyde was demonstrated in a temperature range of 25–70 °C in the presence of zeolite Beta or bifunctional iron modified Beta. At low temperature using 1:1 molar ratio of reactants only isomerization of verbenol oxide to hydroxyketone, oxetane and (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol occurred, whereas already at 70 °C 13% of the target compound was formed at complete conversion of verbenol oxide over H-Beta-25 in toluene in the reaction between verbenol oxide and 4-fluorobenzaldehyde using 1–5 ratio of the reactants. The main products were, however, verbenol oxide isomerization products.

In addition to H-Beta-25, also Fe-H-Beta-150 was a promising catalyst for the desired reaction. Under the above mentioned reaction conditions, 10% of the target compound was formed. The preliminary experiments also revealed that the diol, formed in the isomerization reaction, can further react to the addition products.

A comparative study using H-Beta-150 and 5 wt% Fe-H-Beta-150 as catalysts at 70 °C in the mixture of benzaldehyde and toluene with the verbenol oxide to benzaldehyde ratio of 1: 133 showed that H-Beta-150 was more active than Fe-H-Beta-150 although the Brønsted acid site concentrations of these catalysts were about the same. On the other hand, a higher amount of Lewis acid sites was present in Fe-H-Beta-150. Higher selectivity to the target compound was achieved with Fe-H-Beta-150, whereas over H-Beta-150 the target compound reacted further to several minor products. After prolonged reaction time the third product of an addition reaction was formed over Fe-H-Beta-150. These results also showed clearly that the addition reaction instead of isomerization was catalyzed more intensively compared to isomerization in the presence of Fe-H-Beta-150 than with H-Beta-150.

Based on the kinetic analysis for Fe-H-Beta-150 a reaction network was proposed for formation of (2*S*,4a*R*,8*R*,8a*R*)-4,4,7-trimethyl-2-phenyl-4a,5,8,8a-tetrahydro-4*H*-benzo[d][1,3]dioxin-8-ol. Three parallel routes occurred, out of which the two major ones were isomerization and the reaction between verbenol oxide and benzaldehyde. In the third minor reaction, of the addition character, (2*S*,4*S*,4a*R*,8*R*,8a*R*)-4,7-dimethyl-2-phenyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol was formed. The diol from isomerization reacted also further to the addition products, since the kinetic results showed that the selectivity to them increased with increasing conversion of verbenol oxide.

These results demonstrated that the catalytic synthesis of the target compound can be rather efficiently achieved over functional iron modified Beta zeolite at 70 °C in toluene. Further studies are, however, needed in order to optimize the reaction conditions and the catalyst properties.

Acknowledgement

This work is part of the activities of Åbo Akademi University Process Chemistry Centre (ÅA-PCC).

References

[1] D.J. Newman, J. Med. Chem. 51 (2008) 2589.
[2] V.V. Costa, K.A. da Silva Rocha, L.F. de Sousa, P.A. Robles-Dutenhefner, E.V. Gusevskaya, J. Mol. Catal. A: Chem. 345 (2011) 69–74.
[3] M. Gscheidmeier, H. Fleig, Ullmann's Encyclopedia of Industrial Chemistry, vol. 37, 6th ed., Wiley-VCH, Weinheim, 2003, pp. 561–575.
[4] A.G. Fett-Neto, A.T. Henriques, A.M. Alexio, R.P. Limberger, Patent BR 2002005431 (2004).
[5] T.I. Zvereva, O.S. Kykovinets, V.G. Kasradze, M.I. Abdullin, F.Z. Galin, Bashk Chem J. 13 (2006) 58–59.
[6] I.V. Il'ina, K.P. Volcho, D.V. Korchagina, V.A. Barkhash, N.F. Salakhutdinov, Helv. Chim. Acta 90 (2007) 353–368.
[7] I.V. Il'ina, K.P. Volcho, O.S. Mikhalchenko, D.V. Korchagina, N.F. Salakhutdinov, Helv. Chim. Acta 94 (2011) 502–513.
[8] M. Stekrova, N. Kumar, P. Mäki-Arvela, A. Aho, K.P. Volcho, N.F. Salakhutdinov, D. Yu Murzin, React. Kinet. Mech. Catal. 110 (2013) 449–458.
[9] S. Yu Kurbakova, I.V. Il'ina, A. Pavlova, D. Korchagina, O. Yarovaya, T. Tolstikova, K.P. Volcho, N.F. Salakhutdinov, Med. Chem. Res. 23 (2014) 1709–1717.
[10] O.V. Ardashov, A.V. Pavlova, I.V. Il'ina, E.A. Morozova, D.V. Korchagina, E.V. Karpova, K.P. Volcho, T.G. Tolstikova, N.F. Salakhutdinov, J. Med. Chem. 54 (2011) 3866–3874.
[11] O. Mikhalchenko, I. Il'ina, A. Pavlova, E. Morozova, D. Korchagina, T. Tolstikova, E. Pokushalov, K. Volcho, N. Salakhutdinov, Med. Chem. Res. 22 (2013) 3026–3034.
[12] I. Melnikova, Nat. Rev. 9 (2010) 589.
[13] I.V. Il'ina, D.V. Korchagina, K.P. Volcho, N.F. Salakhutdinov, Russ. J. Org. Chem. 46 (2010) 1002–1005.
[14] P. Rangel-Rivera, G. Rangel-Porras, H. Pfeiffer-Perea, E. Lima-Munoz, J. Therm. Anal. Calorim. 115 (2010) 1359–1369.
[15] N.F. Salakhutdinov, K.P. Volcho, I.V. Il'ina, D.V. Korchagina, L.E. Tatarova, V.A. Barkhash, Tetrahedron 54 (1998) 15619–15642.
[16] N. Kumar, P. Mäki-Arvela, S. Faten Diaz, A. Aho, Y. Demidova, J. Linden, A. Shepidchenko, M. Tenhu, J. Salonen, P. Laukkanen, A. Lashkul, J. Dahl, I. Sinev, A.-R. Leino, K. Kordas, T. Salmi, D. Yu Murzin, Top. Catal. 56 (2013) 696–713.
[17] MAUD Program. http://www.ing.unitm.it∼maud/cited (accessed 19.8.14).
[18] International Zeolite Association. http://www.iza-online.org (accessed 20.8.14).
[19] C.A. Emeis, J. Catal. 141 (1993) 374–375.
[20] M. Stekrova, N. Kumar, A. Aho, I. Sinev, W. Grünert, J. Dahl, J. Roine, S.S. Arzumanov, P. Mäki-Arvela, D. Yu Murzin, Appl. Catal. A: Gen. 470 (2014) 162–176.
[21] M. Stekrova, N. Kumar, P. Mäki-Arvela, O.V. Ardashov, K.P. Volcho, N.F. Salakhtdinov, D. Yu Murzin, Materials 6 (2013) 2103–2118.
[22] W. Guo, C. Xiong, L. Huang, Q. Li, J. Mater. Chem. 11 (2001) 1886–1890.
[23] P.P. Pescarmona, K.P.F. Janssen, C. Strobants, B. Molle, J.S. Paul, P.A. Jacobs, B.F. Sels, Top. Catal. 53 (2010) 77–85.
[24] J.A. van Bokhoven, D.C. Koningsberger, P. Kunkeler, H. van Bekkum, A.P.M. Kentgens, J. Am. Chem. Soc. 122 (2000) 12842–12847.
[25] O.V. Ardashov, I.V. Il'ina, D.V. Korchagina, K.P. Volcho, N.F. Salakhutdinov, Mend. Commun. 17 (2007) 303–305.
[26] I. Il'ina, O. Mikhalchenko, A. Pavlova, D. Korchagina, T. Tolstikova, K. Volcho, N. Salakhutdinov, E. Pokushalov, Med. Chem. Res. 23 (2014) 5063–5073.
[27] M. Stekrova, N. Kumar, S.F. Diaz, P. Mäki-Arvela, D.Y. Murzin, Catal. Today (2013), http://dx.doi.org/10.1016/Cattod.2013.12.004 (in press).