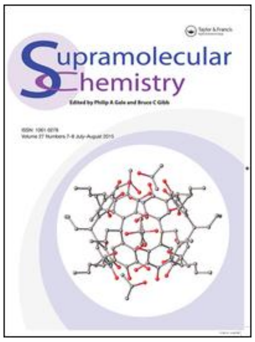

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ARTICLE

A reactive and environmentally friendly protocol for expeditious synthesis of various resorcinarenes using zinc hydrogen sulfate

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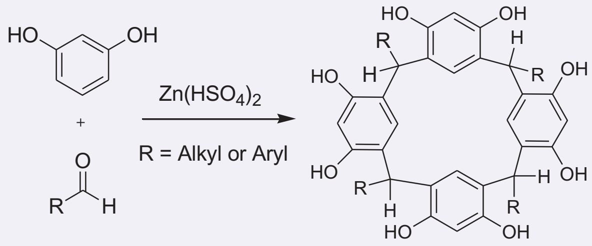
ABSTRACT

In this work, for the first time, metal hydrogen phosphates and sulfates have been studied as effective solid acid catalysts for the condensation of resorcinol with aromatic and aliphatic aldehydes to give tetrameric cyclic products, resorcinarenes, which have major roles in biological and industrial activities. This catalyst has several advantages, it is non-toxic, thermally and mechanically stable, inexpensive and highly resistant against organic solvents. It increases the reaction rate about six fold and makes this method an attractive alternative to the existing methods for resorcinarene formation. Interestingly, the present catalyst exhibited a high turnover number (TON) and turnover frequency (TOF) which were even comparable with that of HCl.



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KEYWORDS
Resorcinarene; metal hydrogen sulfates and phosphates; solid acid; zinc hydrogen sulfate; stereoisomer

1. Introduction

Calixarenes are a class of macrocycles formed by condensation of phenols with various aldehydes. Calix[4] resorcinarene macrocycles are one of the calixarene compounds comprising four phenolic moieties joined in cyclic array at the *meta*-positions by methylene bridges (1). The possibility of modifying these compounds either via nucleophilic aromatic substitutions on the aromatic ring or the phenol hydroxyl groups or the lower rim increases their potential for forming multifunctional compounds. These macrocycles are the subject for increasing interest in the field of host-guest chemistry, liquid crystals, sensors, surfactants, catalyst, etc (2–9). Hence, a practical method for the preparation of such compounds is of great interest in synthetic organic chemistry.

Although a variety of strategies have been reported in this area (10–15), most of these methods suffer from the absence of green chemistry, and have been associated with several shortcomings such as the use of toxic, expensive and unrecyclable catalysts such as $Yb(OTf)_3$, $Bi(CF_3SO_3)_3 \cdot 4H_2O$ and *p*-TsOH, multiple steps, long reaction times (2–4 days), low product yields, difficult workup procedures and the use of large quantities of concentrated HCl. Therefore, it is still a great challenge to find simple and fast ways to synthesise these compounds according to principles of green chemistry using mild reaction conditions in short reaction times.

Solid inorganic acidic salts play a prominent role in organic synthesis under heterogeneous conditions. In view of green chemistry, the substitution of harmful liquid acids by reusable solid acids as catalysts in organic synthesis is the most promising approach (16–18). These factors, coupled with the normal advantages of solid acids (e.g. low toxicity, high stability towards humidity, recyclability and air stability) make the compounds attractive materials to organic and industrial chemists.

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Supplemental data for this article can be accessed here.

In continuation of our new interest in the application of calix[4]resorcinarene and its 3D-network porous polymer for the preparation of biologically important molecules (19–24) in this work, for the first time, we report the application of new inexpensive solid acids as an eco-efficient and environmentally friendly catalyst for the synthesis of resorcinarene derivatives.

2. Experimental

2.1. General

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. Monitoring of the reactions was accomplished by TLC. IR spectra were obtained on a Bomen MB:102 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz, respectively, in DMSO. MS spectra were measured on a Finnigan MAT TSQ 70 mass spectrometer.

2.2. Synthesis of metal hydrogen phosphates and sulfates

All metal hydrogen phosphates and sulfates were synthesised from the corresponding anhydrous metal chlorides and the appropriate amount of concentrated sulfuric acid or phosphoric acid by the method previously described (25).

2.3. Typical procedure for the condensation of aliphatic aldehydes with resorcinol catalysed by $Zn(HSO_4)_2$

To a solution of 1.10 g (10^{-2} mol) of resorcinol in 20 ml of 95% ethanol, 10 mol% $Zn(HSO_4)_2$ was added under nitrogen at room temperature. To this stirred mixture, 10^{-2} mol of the relevant aldehyde was added dropwise over a period of 30 min. After the addition was complete, the reaction was cooled in a water bath to control the exotherm (15 min.). Then, the reaction mixture was heated at reflux (80°C). The reaction was monitored by TLC using a 20:80 mixture of ether: *n*-hexane as an eluent, after completion of the reaction, the catalyst was then separated by vacuum filtration. The water (50 ml) was added to the filtrate to precipitate the product, which was then recrystallised from ethanol/water (50:50) to give the pure product (82–98% yields).

This general procedure is exemplified by the synthesis of resorcinarene A: 1.1 g resorcinol was dissolved in 20 ml ethanol and 0.1 g $Zn(HSO_4)_2$ was added under nitrogen. Then, 0.44 g acetaldehyde was added over a period of 30 min. After the addition was completed, the reaction was cooled about 15 min. Then, the reaction was reflux for 65 min. After TLC indicated that the reaction had gone to completion, the catalyst was separated by vacuum filtration. Fifty-millilitre water was added to filtrate to precipitate resorcinarene A and recrystallised from ethanol/water (50:50) to give pure product (82.7% yield).

2.4. Typical procedure for the condensation of aromatic aldehydes with resorcinol catalysed by $Zn(HSO_4)_2$

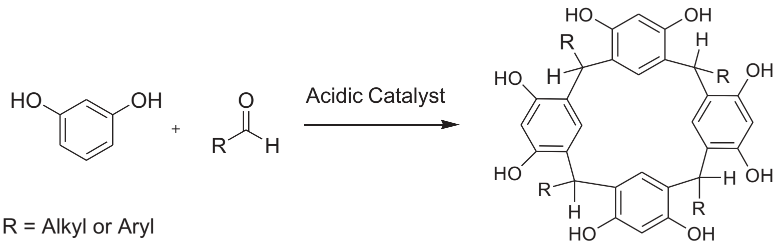
To a solution of 1.1 g (10^{-2} mol) of resorcinol and 10^{-2} mol of substituted benzaldehyde in 30 ml of 95% ethanol was added 10 mol% of $Zn(HSO_4)_2$. The resulting heterogeneous mixture was heated at 80°C under nitrogen. The reaction was monitored by TLC using a 20:80 mixture of ether: *n*-hexane as an eluent, after completion of the reaction, catalyst and precipitated C_{4v} isomer was separated by vacuum filtration. The solid residue was triturated with water (50 ml) at ambient temperature to remove the catalyst from C_{4v} isomer (25–40% yields). Then, water was added to the filtrate to precipitate the C_{2h} isomer. The C_{2h} isomer was filtered and washed several times with water (30 ml) and recrystallised from hot ethanol (5–10 ml) and then cooled slowly to ambient temperature (30–60% yields).

This general procedure is exemplified by the synthesis of resorcinarene D: 1.1 g resorcinol was dissolved in 30 ml ethanol and 0.1 g $Zn(HSO_4)_2$ was added under nitrogen. Then, 2.05 g benzaldehyde was added over a period of 30 min. The reaction was reflux for 20 min. After TLC indicated that the reaction had gone to completion, the catalyst and precipitated C_{4v} isomer was separated by vacuum filtration. The residue triturated with 50 ml water at ambient temperature to remove the catalyst from C_{4v} isomer.Then, water (20 ml) was added to the filtrate to precipitate the C_{2h} isomer. The C_{2h} isomer was filtered and washed several times with 30 ml water and recrystallised from 5 ml hot ethanol and then cooled slowly to ambient temperature (57.6% for both C_{4v} and C_{2h} isomer).

3. Results and discussion

Resorcinarene derivatives are prepared by the acid-catalysed cyclocondensation of resorcinol with various aliphatic or aromatic aldehydes (Scheme 1).

Preliminary tests were carried out to survey the requisite reaction conditions and establish the modifications required for this methodology. The reaction of



Scheme 1. Synthesis of resorcinarene derivatives from resorcinol by acidic catalyst.

acetaldehyde and resorcinol for the synthesis of calix[4] resorcinarene was chosen as the model reaction to identify and optimise the reaction conditions.

Metal hydrogen sulfates and phosphates were easily prepared from the corresponding anhydrous metal chlorides and sulfuric or phosphoric acid, respectively (25). The reactions are very clean and did not require a work-up procedure because HCl evolves as a by-product from the reaction vessel immediately.

Therefore, we have tabulated the model reaction in the presence of a catalytic amount of solid acids such as metal hydrogen sulfates including $Al(HSO_4)_3$, $Mg(HSO_4)_2$, $Zn(HSO_4)_2$, $Fe(HSO_4)_3$, and metal dihydrogen phosphates including $Al(H_2PO_4)_3$, $Mg(H_2PO_4)_2$, $Zn(H_2PO_4)_2$ (Table 1).

Table 1. Synthesis of C-methyl calix[4]resorcinarene catalysed by various solid acids.

Entry	Solid acid	Time
1	$Al(HSO_4)_3$	15 h
2	$Al(H_2PO_4)_3$	15 h
3	$Mg(HSO_4)_2$	80 min
4	$Mg(H_2PO_4)_2$	140 min
5	$Zn(HSO_4)_2$	65 min
6	$Zn(H_2PO_4)_2$	15 h
7	$Fe(HSO_4)_3$	120 min

As shown in Table 1, the corresponding calix[4]resorcinarene was synthesised successfully in the presence of $Zn(HSO_4)_2$ with high yield at 65 min, while this reaction was done in the presence of HCl as the common catalyst in a 4 days period (26).

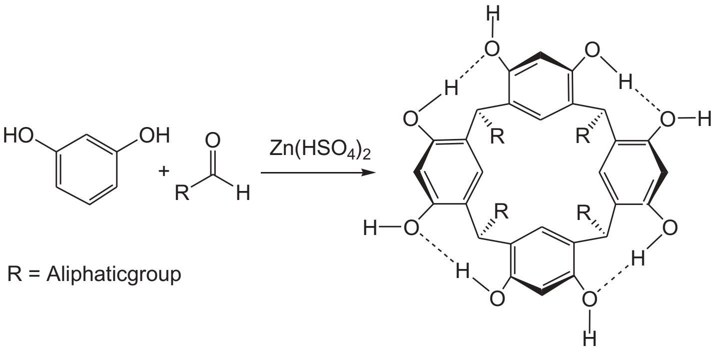
$Mg(HSO_4)_2$ also catalysed this condensation but with longer reaction times. In the presence of other catalysts unidentified products were observed.

The structure of product was settled from their physical and spectroscopic (IR, ^1H NMR, ^{13}C NMR and Mass) data (see ESI).

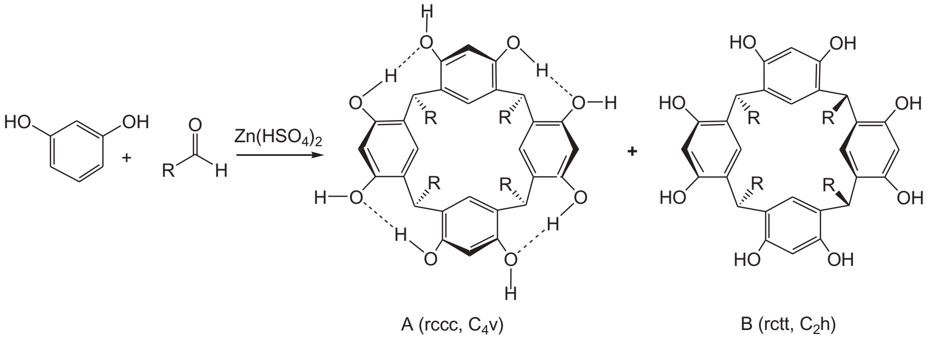
Encouraged by this observation, further experiments were designed to optimise this reaction in the presence of $Zn(HSO_4)_2$. The best results were obtained when 10 mol% of catalyst in ethanol as solvent were used.

To further examine the efficacy of this synthetic opportunity, the process is illustrated with various aliphatic aldehydes in the presence of $Zn(HSO_4)_2$ as catalyst (Table 2). In these reactions, only the C_{4v} isomers (thermodynamically isomer) were isolated with high selectivity.

Table 2. The reaction of resorcinol with various aliphatic aldehydes using $Zn(HSO_4)_2$ under optimised conditions.



Entry	R	Time (min)	Yield (%)	m.p. °C
1	CH_3	65	82.7	> 360
3	$CH_3(CH_2)_3$	50	87.6	345
4	$CH_3(CH_2)_4$	40	98	330



Scheme 2. The diastereomers A (rccc, C_4v) and B (rctt, C_2h).

As can be observed in Table 2, the reaction of other aliphatic aldehydes with resorcinol was successful too in short reaction times and high yields compared with conventional methods.

In order to further expand the scope of this catalytic system, resorcinol was treated with aromatic aldehydes. In the presence of aromatic aldehydes a mixture of diastereomers A (rccc) and B (rctt) was observed which is in agreement with the authentic samples (Scheme 2). Due to the different solubility of two stereoisomers ($C_{4v,}$ C_{2h}) in ethanol and water, separation of the two stereoisomers was accomplished by simple crystallisation. Since the relative ratio of the A/B dependent on the reaction times, we reported the total yields of reactions (Table 3).

Pleasingly, in all cases the desired products obtained in good yields. Since the vibration of rccc and rctt isomers was different, their behaviour in IR spectra was different too. Due to hydrogen bonds between phenolic groups, the OH peak is wider in the rccc isomer than in rctt isomer (ESM section). All products identified by comparing their physical and spectral data with those of authentic samples (10–15).

It is noteworthy that the formation of various resorcinarenes by the present method are of considerable interest, since this is the first attempt at the synthesis of these privileged compounds in the presence of $Zn(HSO_4)_2$ as an effective solid acid catalyst.

In order to show the merit of the catalyst, Table 4 compares the results obtained from commercially available HCl with the results in the presence of $Zn(HSO_4)_2$ as a catalyst under optimised conditions (Table 4).

Table 3. The reaction of resorcinol with various aromatic aldehydes using $Zn(HSO_4)_2$ under optimised conditions.

Entry	R	Time (min)	Yield (%): A/B	m.p. °C
1	C_6H_5	20	57.6: 40.2/17.4	285–330
2	4-BrC_6H_4	35	97.7: 52/45.7	> 360
3	4-ClC_6H_4	60	92.5: 52.5/40	> 360
4	4-$CH_3OC_6H_4$	155	98: 56.3/41.7	> 360

Table 4. The comparison of the catalytic performance of $Zn(HSO_4)_2$ with commercially available HCl as a catalyst.

Entry	R	Time in $Zn(HSO_4)_2$	Time in HCl	Yield (%) in $Zn(HSO_4)_2$	Yield (%) in HCl
1	CH_3	65 min	4 days	82.7	60
2	$CH_3(CH_2)_3$	50 min	6 days	87.6	89
3	$CH_3(CH_2)_4$	40 min	6 days	98	77
4	C_6H_5	20 min	4 days	57.6*	64*
5	4-BrC_6H_4	35 min	5 days	97.7*	84*
6	4-ClC_6H_4	60 min	5 days	92.5*	88*
7	4-$CH_3OC_6H_4$	155 min	6 days	98*	93*

* Total yields including C_{4v} and C_{2h} isomers.

The results in Table 4 show a greater superiority of $Zn(HSO_4)_2$ to HCl. It can be seen that the $Zn(HSO_4)_2$ exhibited a significantly higher turnover (TON) number and turnover frequency (TOF) than those reported for HCl systems. Based on these results, we believe that $Zn(HSO_4)_2$ is a suitable catalyst for synthesis of valuable resorcinarenes in laboratory and industrial applications.

4. Conclusions

In summary, the superiority of using $Zn(HSO_4)_2$ over other methods includes a very rapid reaction with effective and readily available catalyst. Further, our method can be applied to a wide range of substrates and results in good yield and short reaction times. Overall, the present protocol offers more efficient and particularly economically advantageous process towards the synthesis of valuable resorcinarenes, which serves a useful synthetic alternative for large-scale conversions.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

(1) Weinelt, F.; Schneider, H.J., Host-Guest Chemistry. 27. Mechanisms of Macrocycle Genesis. The Condensation of Resorcinol with Aldehydes. *J. Org. Che.*. **1991**, *56*, 5527–5535. DOI: 10.1021/jo00019a011.

(2) Dalcanale, E.; Du Vosel, A.; Levelut, A.-M.; Malthere, J., Columnar Mesomorphic Properties of New Macrocyclic Mesogens. *Liq. Cryst*. **1991**, *10*, 185–198. DOI: 10.1080/02678299108036424.

(3) Cometti, G.; Dalcanale, E.; Du Vosel, A.; Levelut, A.M. New bowl-shaped columnar liquid crystals. *J. Chem. Soc., Chem. Commun*. **1990**, 163–165. DOI: 10.1039/C39900000163.

(4) Misra, T.K.; Liu, C.-Y., Synthesis, Isolation, and Redispersion of Resorcinarene-Capped Anatase TiO2 Nanoparticles in Nonaqueous Solvents. *J. Colloid Interface Sci*. **2007**, *310*, 178–183. DOI: 10.1016/j.jcis.2007.01.094.

(5) Ehrler, S.; Pieles, U.; Wirth-Heler, A.; Shahgaldian, P. Surface modification of resorcinarene based self-assembled solid lipid nanoparticles for drug targeting. *Chem.Commun*. **2007**, 2605–2607. DOI: 10.1039/B703106H.

(6) Arora, V.; Chawla, H.M.; Singh, S.P. Calixarenes as sensor materials for recognition and separation of metal ions. *Arkivoc*. (*ii*), **2007**, 2457, 172–200. DOI: 5550190.0008.205.

(7) Shirakawa, S.; Shimizu, S. Dehydrative amination of alcohols in water using a water-soluble calix[4]resorcinarene sulfonic acid. *Synlett*. **2008**, *10*, 1539–1542. DOI: 10.1055/s-2008-1078416.

(8) Vovk, A.I.; Shivanyuk, A.M.; Bugas, R.V.; Muzychka, O.V.; Melnyk, A.K., Antioxidant and Antiradical Activities of Resorcinarene Tetranitroxides. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 1314–1317. DOI: 10.1016/j.bmcl.2009.01.070.

(9) Deska, M.; Dondela, B.; Sliwa, W. Selected applications of calixarene derivatives. *Arkivoc*.(*vi*) **2015**, 8958, 393–416. DOI: 5550190.p008.958.

(10) Cometti, G.; Dalcanale, E.; DuVosel, A.; Levelut, A.M., A New, Conformationally Mobile Macrocyclic Core for Bowl-Shaped Columnar Liquid Crystals. *Liq. Cryst*. **1992**, *11*, 93–100. DOI: 10.1080/02678299208028973.

(11) Moore, D.; Watson, G.W.; Gunnlaugsson, T.; Matthews, S. E., Selective Formation of the Rctt Chair Stereoisomers of octa-O-alkyl Resorcin[4]Arenes Using Brønsted Acid Catalysis. *New J. Chem*. **2008**, *32*, 994–1002. DOI: 10.1039/b714735j.

(12) Gerkensmeier, T.; Mattay, J.; Näther, C., A New Type of Calixarene: Octahydroxypyridine[4]Arenes. *Chem. Eur. J.* **2001**, *7*, 465–474. DOI: 10.1002/(ISSN)1521-3765.

(13) Burilov, A.R.; Knyazeva, I.R.; Pudovik, M.A.; Syakaev, V.V.; Sh, L.; Baier, K.; Khabikher, I.; Konovalov, V.D., New Phosphorus-Containing Analog of Calix[4] Resorcinarene Based on 2,6-Dihydroxypyridine. *Russ. Chem. Bull. Int. Ed*. **2007**, *56*, 364–366. DOI: 10.1007/s11172-007-0060-x.

(14) Parac-Vogt, T.N.; Binnemans, K., Lanthanide(III) Nosylates as New Nitration Catalysts. *Tetrahedron Lett*. **2004**, *45* 3137–3139. DOI: 10.1016/j.tetlet.2004.02.084.

(15) Hedidi, M.; Hamidi, S.M.; Mazari, T.; Boutemeur, B.; Rabia, C.; Chemat, F.; Hamidi, M., Microwave-Assisted Synthesis of Calix[4]Resorcinarenes. *Tetrahedron*. **2006**, *62*, 5652–5655. DOI: 10.1016/j.tet.2006.03.095.

(16) Nikname, N.; Zolfigol, M.A.; Sadabadi, T.; Nejati, A., Preparation of Indolylmethanes Catalyzed by Metal Hydrogen Sulfates. *J. Iran. Chem. Soc.*. **2006**, *3*, 318–321. DOI: 10.1007/BF03245953.

(17) Kiasat, A.R.; Mouradzadegun, A.; Elahi, S.; Fallah-Mehrjardi, M., Al(HSO4)3/silica Gel as a Novel Catalytic System for the Ring Opening of Epoxides with Thiocyanate Anion under Solvent-Free Conditions. *Chin. Chem. Lett*. **2010**, *21*, 146–150. DOI: 10.1016/j.cclet.2009.10.030.

(18) Ramachandran, K.; Sivakumar, P.; Susanya, T.; Renganathan, S. Production of biodiesel from mixed waste vegetable oil using an aluminium hydrogen sulphate as a heterogeneous acid catalyst. *Bioresour. Technol*.. **2011**, *102*, 7289–7293. DOI: 10.1016/j.biortech.2011.04.100.

(19) Mouradzadegun, A.; Elahi, S.; Abadast, F., Synthesis of a 3d-Network Polymer Supported Bronsted Acid Ionic Liquid Based on Calix[4]Resorcinarene via Two Post-Functionalization Steps: A Highly Efficient and Recyclable Acid Catalyst for the Preparation of Symmetrical Bisamides. *RSC Adv*. **2014**, *4* 31239–31248. DOI: 10.1039/C4RA03463E.

(20) Mouradzadegun, A.; Elahi, S.; Abadast, F., One-Pot Synthesis of Tweezer-Like Calix[4]Resorcinarene Decorated with Pendant Heterocyclic Moieties: An Efficient and Recyclable Heterogeneous PTC for the Preparation of Azidohydrins in Water. *Catal. Lett*. **2014**, *144*, 1636–1641. DOI: 10.1007/s10562-014-1300-y.

(21) Mouradzadegun, A.; Abadast, F.; Elahi, S., Tetraphenolate C-Methylcalix[4]Resorcinarene as a New Heterogeneous Phase Transfer Catalyst for Ring-Opening of Triaryl Substituted Pyrylium Salts in Aqueous Biphasic Medium. *Monatsh. Chem*. **2014**, *145*, 1663–1667. DOI: 10.1007/s00706-014-1235-4.

(22) Mouradzadegun, A.; Elahi, S.; Abadast, F., Synthesis of A Functionalized Polymer Based on A Calix[4] Resorcinarene via Covalently Anchored Cationic Moieties: A Reactive Solid Support for Ring Transformation and Expansion of Thiopyrylium Salts. *Synthesis*. **2015**, *47*, 630–640. DOI: 10.1055/s-00000084.

(23) Mouradzadegun, A.; Kiasat, A.R.; Kazemian Fard, P. 3D-network porous polymer based on calix[4]resorcinarenes as an efficient phase transfer catalyst in regioselective conversion of epoxides to azidohydrins. *Catal. Chem*. **2012**, *29*, 1–5. DOI: 10.1016/j.catcom.2012.09.006.

(24) Mouradzadegun, A.; Elahi, S.; Abadast, F.; Motamedi, H., A Straightforward Route for Covalently Anchored Pyridinium Salt onto Upper Rim of C-Methylcalix[4] Resorcinarene with Selective Antibacterial Activity against Gram-Positive Bacteria. *Res. Chem. Intermed*. **2016**, *42*, 1583–1591. DOI: 10.1007/s11164-015-2104-4.

(25) Mirjalili, B.F.; Zolfigol, M.A.; Bamoniri, A., Al(HSO4)3 as an Efficient Catalyst for Acetalization of Carbonyl Compounds under Heterogeneous or Solvent -Free Conditions. *J. Braz. Chem. Soc*. **2005**, *16*, 877–880. DOI: 10.1590/S0103-50532005000500031.

(26) Tunstad, L.M.; Tucker, J.A.; Dalcanale, E.; Weiser, J.; Bryant, J.A.; Sherman, J.C.; Helgeson, R.C.; Knobler, C.B.; Cram, D.J., Host-Guest Complexation. 48. Octol Building Blocks for Cavitands and Carcerands. *J.Org. Chem*. **1989**, *54*, 1305–1312. DOI: 10.1021/jo00267a015.