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Rapid Acyl Migration Between Pyrogallyl 1,2- and 1,3-Dipivaloates

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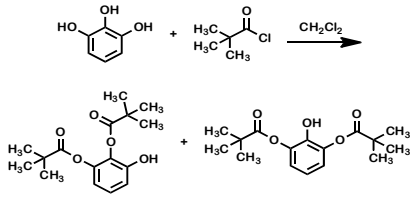
Pyrogallol and its derivatives are biologically active compounds, and pyrogallol also forms the basis of an increasingly important tetrameric supramolecular scaffold. Pyrogallol[4]arenes are tetrameric macrocycles that form from 1,2,3-trihydroxybenzene and aldehydes under acidic conditions. Pyrogallol was treated with two equivalents of pivaloyl chloride to form pyrogallyl dipivaloate. A mixture of regioisomers was invariably obtained and a rapid equilibrium was observed between the 1,2- and 1,3-diesters in polar solvents. A pure sample of solid pyrogallyl 1,2-dipivaloate was isolated and its crystal structure was obtained. The pure compound was shown to rearrange to mixtures similar to those isolated initially.

Keywords: Pyrogallol, Pyrogallol[4]arene, Pivalic acid, Protecting group, Acyl migration, Solvent effect.

The biological activity of pyrogallol has been known for decades. For example, the analgesic effect of pyrogallol was reported by Gardella *et al.* in 1970 [1]. Pyrogallols have also been implicated in both base substitution and frame shift mutations [2]. Apoptosis-inducing [3] and anti-proliferative activities [4] have also been documented. The study of pyrogallol biological activity is expanding and remains vital [5]. In recent years, pyrogallolarenes, the condensation products of pyrogallol and aldehydes, have taken their place as prominent and versatile macrocycles in the area of supramolecular chemistry [6]. The versatility of pyrogallol[4]arenes parallels earlier macrocycles [7], but their ability to form capsules has distinguished them from many of their predecessors [8].

Our own work with pyrogallol[4]arenes has focused mainly on derivatives having alkyl chains that show either amphiphilic properties [9] or that form pores in bilayer membranes [10]. In an extension of this work, we wished to prepare 5-bromopyrogallol for further derivatization. Owing to the three adjacent hydroxyl groups on benzene, the 4- and 6-positions, rather than the 5-position, are activated for electrophilic substitution. Numerous methods are available for the protection of hydroxyl groups, both aliphatic and aromatic [11]. These include ethers, silyl ethers, esters, carbonates, carbamates, phosphinates, and sulfinates. The protection of adjacent hydroxyls can also be accomplished by using either cyclic acetals or ketals, or carbonate or boronate esters.

We considered forming the 1,3-dibenzhydryl diether of pyrogallol. The advantages of this approach were expected to be ease both of formation and removal, and the bulk of the protecting group. Owing to the latter, we anticipated that ether formation on the 1,3-positions would be favored over the 2-position. This approach was not pursued because of the potential for brominating the additional four aromatic rings rather than pyrogallol itself. Instead, we focused on the bulky aliphatic ester pivaloate (trimethyl-acetate), which we anticipated would form a 1,3-diester and be readily removable [12]. We could find no pivaloate esters of pyrogallol reported in the literature, but Van Duuren *et al.* showed in 1967 that treatment of pyrogallol with less bulky lauroyl chloride gave various esters and even a ketone, presumably by an uncatalyzed Friedel-Crafts reaction [13].



We anticipated that treatment of pyrogallol with less than stoichiometric pivaloyl chloride would result in the formation of pyrogallyl 1,3-dipivaloate. It was expected that this pyrogallol diester would brominate in the 5-position and facilitate further modification. We report here that the attempted protection of the 1,3-hydroxyl groups of pyrogallol gave a mixture of 1,2- and 1,3-dipivaloates and that the diesters exist in solution in a solvent-dependent equilibrium.

The reaction of two equivalents of pivaloyl chloride with pyrogallol was conducted in CH_2Cl_2 at ambient temperature for 24 h. A mixture was obtained that was separated by silica gel column chromatography. The major fraction was a mixture of 1,2- and 1,3-pyrogallyl dipivaloates, as shown in Scheme 1. The composition of the mixture was determined both by ^{1}H NMR spectroscopy and by HPLC. The NMR spectrum of the mixture, determined in CD_2Cl_2, showed the presence of both regioisomers, in a ratio of 2:3 for the 1,2- and 1,3-diesters.

It was anticipated that the steric bulk of pivalic acid would afford predominantly the 1,3-diester of pyrogallol rather than the more congested 1,2-isomer. The 2:3 mixture that was obtained contained more of the vicinal product than expected, but the 1,3-isomer did predominate. In order to further characterize the product mixture, it was subjected to HPLC analysis. The results are shown in Figure 1.

Panel a of Figure 1 shows the initial scan of the mixture obtained from column chromatography (see above). The two regioisomers were observed with baseline separation at retention times of 4.3 and 6.7 min. We have assigned the less abundant isomer as the 1,2-regioisomer (retention time of 4.3 min) based on polarity and ^{1}H NMR spectral data. We note that the 2-hydroxyl in the 1,3-diester

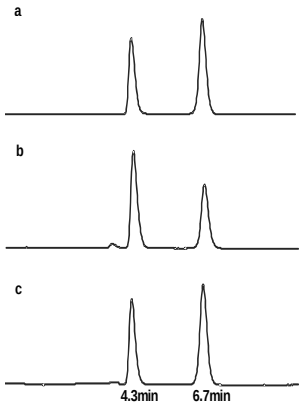


Figure 1: HPLC of a dipivaloylpyrogallol mixture eluted with 1:1 *n*-hexane EtOAc (v/v) on a Shodex 5Sil 4E reversed phase column. Elution times are in minutes. Panel a: Initial separation. Panel b: reinjection of the 4.3 min peak. Panel c: reinjection of the 6.7 min peak.

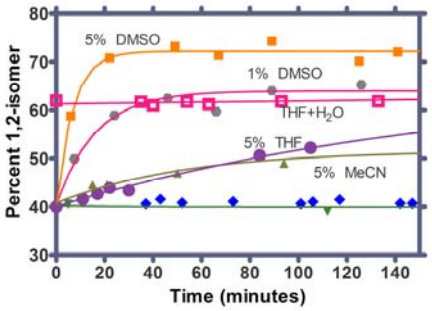
will be more protected than in the 1,2-isomer and the former should, therefore, be less polar and retained better on a reverse-phase column.

The peak observed at 4.3 min was collected and immediately re-injected. The trace obtained is shown in panel b of Figure 1. Conversely, the peak collected at 6.7 min (assigned as the 1,3-isomer) was re-injected with the result shown in panel c. The collection and re-injection of each sample was conducted at room temperature as rapidly as possible (total time <5 min). Figure 1 is representative of three replicates conducted for the data shown in each panel.

The HPLC data clearly suggested that the 1,2- and 1,3-dipivaloate esters are in rapid equilibrium. The material isolated initially and the re-injection data suggest that in the 1:1 (v/v) EtOAc/*n*-hexane solvent system, the equilibrium between the 1,2- and 1,3-isomers was established quickly. Of course, contact with the HPLC column may affect the results. In any event, if the dipivaloates were as labile as seemed to be the case, we assumed that the equilibrium would be solvent dependent. We used samples of the mixture obtained from the initial column chromatography for this study (see below).

The 2:3 mixture (1,2-:1,3-) isolated as a solid by column chromatography (silica gel, 10% MeOH/CH_2Cl_2 v/v) was dissolved in various deuterated solvents or solvent mixtures (RT) and the isomer ratios were observed by ^{1}H-NMR integration for 24 h. The mixed sample was used because its composition was known from NMR and it was chemically pure by normal criteria. Dideuteriodichloromethane (CD_2Cl_2) was chosen as the "base solvent" because the isomer composition did not change in it. This is apparent in the graph of Figure 2, inverted triangles. A similar result was observed when a mixture of 5% toluene-d_8 in CD_2Cl_2 was used as solvent. The effect of 5% $CDCl_3$ in CD_2Cl_2 was insignificantly different from either dichloromethane or toluene (data not shown).

The ^{1}H NMR spectrum in CD_2Cl_2 showed that the mixture of 1,2- and 1,3-dipivaloates was 2:3. The mixture proved to be stable almost indefinitely in CD_2Cl_2 (see below). The data shown in Figure 2 confirm this stability during an observation period of >4 h. However, in more polar solvent mixtures, the isomer ratio changed rapidly to new compositions. The rearrangement was followed by NMR for 250-1500 min in 5% $CDCl_3$ in CD_2Cl_2, CD_2Cl_2, 5% toluene-d_8 in CD_2Cl_2, 5% CD_3CN in CD_2Cl_2, 5% THF-d_8 in CD_2Cl_2, 5%THF-d_8 + 5% D_2O in CD_2Cl_2, 1% CD_3SOCD_3 in CD_2Cl_2, and 5% CD_3SOCD_3 in CD_2Cl_2 (all v/v). Generally, but not invariably, in solvents of lower polarity, the 1,3-dipivaloate dominated. In solvents of higher polarity, the 1,2-isomer was favored. Indeed, in 5% DMSO in CD_2Cl_2, the most polar solvent studied, the ratio of 1,2-:1,3-dipivaloate increased to ~7:3.



The solid state structure and Gaussian 03 calculations (not shown) reveal a structure in which the carbonyl groups lie on opposite sides of the arene. This minimizes congestion; the *t*-butyl groups are not crowded, even in the 1,2-isomer. The lack of contact is apparent in the right

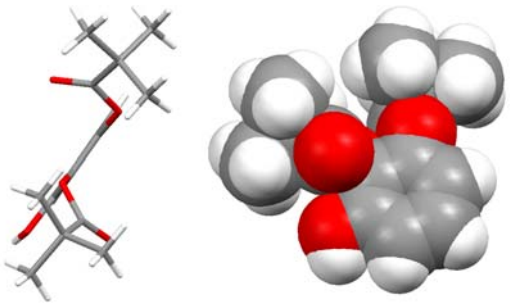
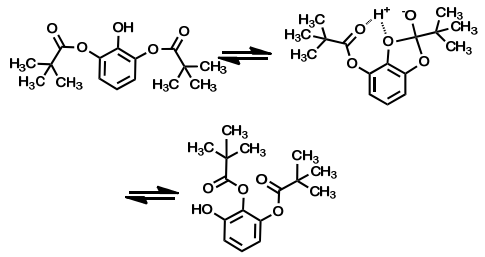


Figure 3 Solid state structure of pyrogallyl 1,2-dipivaloate. Left, stick structure viewed from above. Right, space filling model of the side view.

panel of Figure 3. Of course, the compound would exhibit conformational dynamics in the solution phase, enabling the acyl migration documented above.

The single crystal structure determination indicated that pyrogallyl 1,2-dipivalate crystallized in the orthorhombic system with *P*na2$_1$ space group and cell parameters *a*=18.7183(9), *b*=9.2715(4), *c*=9.2414(5) and *V* = 1603.81(14) Å^3 (Table 1).

Although we are unaware of any literature concerning acylated pyrogallols other than that reported by van Duuren *et al.* in 1967 [13], there are three reports of acyl migration in carbohydrates. Li *et al*. analyzed acyl migration in glycerol esters [14]. Migrations of acyl groups on sugars has been reported recently by Kröger and Theim [15] and by Roslund *et al*. [16]. Li *et al.* [14] conducted a systematic investigation of solvent effects in acyl migrations of both 1,2-diglyceride and 2-monoglycerides. Included in their studies were alkanes, haloalkanes, ethers, ketones, and alcohols embodying a total of 14 solvents. They found that "[g]enerally, the rates within each group decreased with increasing value of the solvent polarity parameters. However, it was not always the case between different groups of solvent, which indicated that the acyl migration rate was not only influenced by solvent polarity but also influenced by the structure of solvents."



Scheme 2

The studies reported by Kröger and Theim were directed to methods of glycosylation and did not systematically explore physical organic principles with respect to acyl migration [15]. In contrast, Roslund *et al.* used NMR spectroscopic methods to assess the effect of pH on the migration of acetyl, pivaloyl, and benzoyl protective groups in a series of β-D-galactopyranoses [16]. The influence of solvent polarity was not addressed in this study. The migration of pivaloyl groups at pD = 8 was found to be "very slow in comparison to that of the smaller acetyl group." The migration rate of pivaloyl was also found to be slower than for benzoyl. The authors suggested that the "larger ester group used migrated slower, possibly due to blocking of the nucleophilic attack of the neighboring hydroxyl group on the ester carbonyl."

Irrespective of acyl group size, solvent polarity, solvent structure, or acidity, the migration of acyl groups must occur through a bridging mechanism of the type shown in Scheme 2.

A crystal that was identical under 40x magnification to that used for the solid state structure determination was examined by ^{1}H NMR spectroscopy in CD_2Cl_2. The spectrum showed only the 1,2-isomer and the spectrum was unchanged during more than 48 h of observation. However, addition of CD_3SOCD_3 (~5%) to the sample led to rapid (<20 min) equilibration to a 3:1 mixture of 1,2-:1,3-isomers. This experiment, conducted on a small scale confirmed the results shown in Figure 1 and validated the use of the mixture obtained by column chromatography.

Attempts to deprotect the 1,3-positions of pyrogallol resulted in mixtures of regioisomers that could be isolated and separated, but which rapidly re-equilibrated in solution. Generally, increasing solvent polarity correlated to increasing pivaloyl migration rates, as previously observed for acyl migrations in sugars. The correlation with polarity was not monotonic, however, as others have noted an effect of solvent structure. We conclude that selective acylation in general and pivaloylation in particular of pyrogallol is and will prove to be problematic.

Experimental

General: All reagents, unless otherwise stated, were purchased from Sigma Aldrich, were the highest grade commercially available, and were used without further purification. Deuterated solvents were obtained from Cambridge Isotope Laboratories, Inc. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in CD_2Cl_2, and chemical shifts (δ) are reported in ppm.

Acylation procedure: Pyrogallol (1.26 g, 0.01 mol) was dissolved in CH_2Cl_2 (5 mL, dried over CaH_2) in a flask fitted with a reflux condenser, stirbar, and N_2 flow. Pivaloyl chloride (2.4 g, 0.02 mol) was dissolved in dry CH_2Cl_2 (3 mL) and the solution was added dropwise to the pyrogallol solution (HCl evolution). Stirring was continued for 15 min after the addition. The mixture was poured onto ice (~5 g) and H_2O (~5 mL). The products were extracted with CH_2Cl_2 (~10 mL, 2x), washed with 5% aq. $NaHCO_3$ (~10 mL, 2x), and then brine (10 mL, 2x). The organic solution was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to afford a yellow oil (2.5 g). TLC showed the presence of three products, possibly mono-, di- and triacylated pyrogallols. These components were separated by HPLC and characterized by NMR spectroscopy and mass spectrometry (observed MW 294).

Pyrogallyl 1,2-dipivaloate

^{1}H NMR: 1.32 (9H, s, 3 x CH_3), 1.36 (9H, s, 3 x CH_3), 6.69-6.72 (1H, d, *J*=4.5 Hz, Ar-H), 6.85-6.88 (1H, d, *J* = 4.5Hz, Ar-H), 7.10-7.16 (1H, t, *J* = 4.5 Hz, Ar-H).

Pyrogallyl 1,3-dipivaloate

^{1}H NMR: 1.37 (18H, s, 3 x CH_3), 6.94-6.96 (3H, m, Ar-H).

HPLC studies: HPLC experiments were conducted on an XperChrom Model 1400 HPLC equipped with a UV-vis detector (λ = 271 nm) using a Shodex 5SIL 10E normal/reverse phase column. Experiments were performed at least in duplicate, the flow rate was 1 mL/min, and traces were recorded using Peak Simple v. 2.08 software. Samples were dissolved in *n*-hexane/EtOAc (1:1, v/v), and the eluent was also *n*-hexane/EtOAc (1:1, v/v).

Single crystal X-ray analysis: A crystal with approximate dimensions 0.14 x 0.14 x 0.25 mm^3 was mounted on a Mitgen cryoloop in a random orientation. Preliminary examination and data collection were performed using a Bruker Kappa Apex II Charge Coupled Device (CCD) Detector single crystal X-Ray diffractometer equipped with an Oxford Cryostream LT device. All data were collected using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) from a fine focus sealed tube X-Ray source. Preliminary unit cell constants were determined with a set of 36 narrow frame scans. Intensity data set consisted of combinations of φ and ω scan frames with scan width of 0.5º and counting time of 10 secs/frame at a crystal to detector distance of 3.5 cm. The collected frames were integrated using an orientation matrix determined from the narrow frame scans.

Crystal data and structure refinement for pyrogallyl 1,2-dipivaloate

Compound	Pyrogallyl 1,2-dipivaloate	
Empirical formula	$C_{16}H_{22}O_5$	
Formula weight	294.34	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*P*na2$_1$	
Unit cell dimensions	*a* = 18.7183(9) Å	α= 90°
	b = 9.2715(4) Å	β= 90°
	c = 9.2414(5) Å	γ= 90°
Volume	1603.81(14) Å^3	
Z (molecules/cell)	4	
Density (calculated)	1.219 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(0 0 0)	632	
Crystal size	0.25 x 0.14 x 0.14 mm^3	
Θ range for data collection	2.18 to 30.79°	
Index ranges	-26≤h≤26, -13≤k≤13, -13≤l≤13	
Reflections collected	79143	
Independent reflections	4989 [R_{int} = 0.0321]	
Completeness toΘ = 25.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9874 and 0.9782	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4989 / 11 / 206	
Goodness-of-fit on F^2	1.03	
Final R indices [$I > 2\sigma$ (I)]	R_1 = 0.0292, wR_2 = 0.0768	
R indices (all data)	R_1 = 0.0317, wR_2 = 0.0787	
Absolute structure parameter	-0.1(5)	
Largest diff. peak and hole	0.286 and -0.209 e.Å^{-3}	

Apex II and SAINT software packages [17] were used for data collection and data integration. Analysis of the integrated data did not show any decay. Final cell constants were determined by global refinement of xyz centroids of 9618 reflections above 20 σ(I) (4.903° < 2θ < 61.14°) from the complete data set. Collected data were corrected for systematic errors using SADABS based on the Laue symmetry using equivalent reflections.

Crystal data and intensity data collection parameters are listed in Table 1. Structure solution and refinement were carried out using the SHELXTL- PLUS software package [18]. The structure was solved by direct methods and refined successfully in the orthorhombic space group, $Pna2_1$. Full matrix least-squares refinement was carried out by minimizing $\sum w(F_o^2-F_c^2)^2$. The non-hydrogen atoms were refined anisotropically to convergence. All hydrogen atoms were treated using an appropriate riding model (AFIX m3). Two of the 3 methyl groups were disordered. The disorder was resolved with partial occupancy methyl groups in the ratio of 83:17%. The final residual values and structure refinement parameters are listed in Table 1.

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References

[1] Gardella JL, Izquierdo JA. (**1970**) The analgesic action of catecholamines and of pyrogallol. *European Journal of Pharmacology*, ***10***, 87-90.
[2] Ben-Gurion R. (**1979**) Mutagenic and colicine-inducing activity of two antioxidants: pyrogallol and purpurogallin. *Mutation Research*, ***68***, 201-205.
[3] Saeki K, Hayakawa S, Isemura M, Miyase T. (**2000**) Importance of a pyrogallol-type structure in catechin compounds for apoptosis-inducing activity. *Phytochemistry*, ***53***, 391-394.
[4] Khan MT, Lampronti I, Martello D, Bianchi N, Jabbar S, Choudhuri MS, Datta BK, Gambari R. (**2002**) Identification of pyrogallol as an antiproliferative compound present in extracts from the medicinal plant *Emblica officinalis*: effects on *in vitro* cell growth of human tumor cell lines. *International Journal of Oncology*, ***21***, 187-192.
[5] (a) Han YH, Kim, SH, Kim SZ, Park WH. (**2008**) Caspase inhibitor decreases apoptosis in pyrogallol-treated lung cancer Calu-6 cells via the prevention of GSH depletion. *International Journal of Oncology*, ***33***, 1099-1105; (b) Han YH, Kim SZ, Kim SH, Park WH. (**2008**) Pyrogallol inhibits the growth of human lung cancer Calu-6 cells via arresting the cell cycle arrest. *Toxicology In Vitro*, ***22***, 1605-1609; (c) Han YH, Kim SZ, Kim SH, Park WH. (**2008**) Pyrogallol as a glutathione depletor induces apoptosis in HeLa cells. *International Journal of Molecular Medicine*, ***21***, 721-730; (d) Han YH, Kim SZ, Kim SH, Park WH. (**2008**) Apoptosis in pyrogallol-treated Calu-6 cells is correlated with the changes of intracellular GSH levels rather than ROS levels. *Lung Cancer*, ***59***, 301-314; (e) Han YH, Kim SZ, Kim SH, Park WH. (**2008**) Pyrogallol inhibits the growth of lung cancer Calu-6 cells via caspase-dependent apoptosis. *Chemico-Biological Interactions*, ***177***, 107-114; (f) Kim SW, Han YW, Lee ST, Jeong HJ, Kim SH, Kim IH, Lee SO, Kim, DG, Kim SZ, Park WH. (**2008**) A superoxide anion generator, pyrogallol, inhibits the growth of HeLa cells via cell cycle arrest and apoptosis. *Molecular Carcinogenesis*, ***47***, 114-125; (g) Mitsuhashi S, Saito A, Nakajima N, Shima H, Ubukata M. (**2008**) Pyrogallol structure in polyphenols is involved in apoptosis-induction on HEK293T and K562 cells. *Molecules*, ***13***, 2998-3006; (h) Han YH, Kim SH, Kim SZ, Park WH. (**2009**) Pyrogallol inhibits the growth of human pulmonary adenocarcinoma A549 cells by arresting cell cycle and triggering apoptosis. *Journal of Biochemical and Molecular Toxicology*, ***23***, 36-42.
[6] Steed JW, Atwood JL. (**2009**) *Supramolecular Chemistry*, 2nd Ed., John Wiley & Sons, Ltd., Chichester.
[7] (a) Gutsche CD. (**2008**) *Calixarenes: An Introduction (Monographs in Supramolecular Chemistry)*. Royal Society of Chemistry, 2nd Ed., Cambridge, UK, 248 pp; (b) Sliwa W, Kozlowski C. (**2009**) *Calixarenes and Resorcinarenes: Synthesis, Properties, and Applications*. Wiley-VCH Verlag GmbH & Co., Weinheim, 316 pp.
[8] (a) Atwood JL, Barbour LJ, Jerga A. (**2001**) Hydrogen-bonded molecular capsules are stable in polar media. *Chemical Communications*, 2376-2377; (b) Atwood JL, Szumna A. (**2002**) Hydrogen bonds seal single-molecule capsules. *Journal of the American Chemical Society*, ***124***, 10646-10647; (c) Atwood JL, Barbour LJ, Jerga A. (**2002**) Organization of the interior of molecular capsules by hydrogen bonding. *Proceedings of the National Academy of Science U. S. A.*, ***99***, 4837-4841.
[9] (a) Kulikov OV, Rath NP, Zhou D, Carasel IA, Gokel GW. (**2009**) Guest molecule entrapment by both capsule and hydrocarbon sidechains in self-assembled pyrogallol[4]arenes. *New Journal of Chemistry*, ***33***, 1563-1569; (b) Kulikov OV, Li R, Gokel GW. (**2009**) A synthetic ion channel derived from a metallogallarene capsule that functions in phospholipid bilayers. *Angewandte Chemie International Edition in English*, ***48***, 375-377; (c) Kulikov OV, Daschbach MM, Yamnitz CR, Rath N, Gokel GW. (**2009**) Self-assembled, cogged hexameric nanotubes formed from pyrogallol[4]arenes with a unique branched side chain, *Chemical Communications*, 7497-7499.
[10] (a) Li R, Kulikov OV, Gokel GW. (**2009**) Pyrogallarene-based ion-conducting pores that show reversible conductance properties. *Chemical Communications*, 6092-4; (b) Negin S, Daschbach MM, Kulikov OV, Rath N, Gokel GW. (**2011**) Pore formation in phospholipid bilayers by branched-chain pyrogallol[4]arenes. *Journal of the American Chemical Society*, ***133***, 3234-3237.
[11] Wuts PGM, Greene TW. (**2007**) *Protective Groups in Organic Synthesis*, 4th Ed. John Wiley & Sons, New York, 1082 pp.
[12] Yamada S. (**1992**) Selective pivaloylation of hydroxyl groups by 3-pivaloyl-1,3-thiazolidine-2-thione under neutral conditions. *Tetrahedron Letters*, ***33***, 2171-2174.
[13] van Duuren BL, Conklin M, Lavers GC, Segal A. (**1967**) Synthesis of laurate esters of pyrogallol and related phenols. *Journal of the Chemical Society C*, 588-590.
[14] Li W, Du W, Li Q, Li R.-w, Liu D. (**2010**) Dependence on the properties of organic solvent: Study on acyl migration kinetics of partial glycerides. *Bioresource Technology*, ***101***, 5737-5742.
[15] Kroger L, Thiem J. (**2007**) Synthesis and evaluation of glycosyl donors with novel leaving groups for transglycosylations employing *beta*-galactosidase from bovine testes. *Carbohydrate Research*, ***342***, 467-481.
[16] Roslund MU, Aitio O, Warna J, Maaheimo H, Murzin DY, Leino R. (**2008**) Acyl group migration and cleavage in selectively protected *beta*-D-galactopyranosides as studied by NMR spectroscopy and kinetic calculations. *Journal of the American Chemical Society*, ***130***, 8769-8772.
[17] Bruker Analytical X-Ray, Madison, WI, 2010
[18] Sheldrick GM. (**2008**) A short history of SHELX. *Acta Crystallographica Part A*, ***A64***, 112-122.