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# Regio- and stereo-chemical ring-opening reactions of the 2,3-epoxy alcohol derivative with nucleophiles: Explanation of the structures and C-2 selectivity supported by theoretical computations

Özlem Gündoğdu[a], Abdurrahman Atalay[b], Neslihan Çelebioğlu[c], Barış Anıl[c], Ertan Şahin[c], Gülşah Şanlı-Mohamed[d], Uğur Bozkaya[b], Yunus Kara[c,*]

[a] Vocational School of Kaman, Ahi Evran University, Kırşehir 40100, Turkey
[b] Department of Chemistry, Faculty of Sciences, Hacettepe University, Ankara 06800, Turkey
[c] Department of Chemistry, Faculty of Sciences, Atatürk University, Erzurum 25240, Turkey
[d] Department of Chemistry, Faculty of Sciences, İzmir Institute of Technology, İzmir 35430, Turkey

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ABSTRACT

The ring-opening reactions of (1a*S*,2*S*,6b*R*)-5-ethyl-2-hydroxyhexahydro-4*H*-oxireno[2,3-e]isoindole-4,6(5*H*)-dione were investigated under very mild and nonchelated conditions. C-2 selective ring-opening products were obtained with nucleophilic additions such as $Cl^-$, $Br^-$ and $N_3^-$. The exact configuration of (3a*S*,4*R*,5*R*,6*S*,7a*S*)-5-chloro-2-ethyl-4,6-dihydroxyhexahydro-1*H*-isoindole-1,3(2*H*)-dione was determined by X-Ray diffraction analysis which was obtained from the reaction of epoxy alcohol with HCl . On the other hand, theoretical computations were carried out to explain the regioselectivity in the ring opening reaction of epoxy alcohols. The results showed that the ring-opening reaction of both epoxy alcohols proceeds in a kinetically controlled manner and regioselectivity occurs depending on the transition state.


## 1. Introduction

2,3-Epoxy alcohols contain three reactive sites for nucleophilic substitution due to their unique functional combinations. Because of these properties, they play an important role as starting materials in the preparation of various building blocks of some biological active natural products such as carbohydrates, nucleosides, or related products. The ring-opening reaction of epoxy alcohols **1** is very interesting and synthetically useful for the synthesis of polyfunctionalized molecules [1–5]. Katsuki-Sharpless synthesized a series of epoxy alcohols starting from allyl alcohol derivatives in 1980 [6]. After Sharpless's pioneering work, epoxy alcohols have been extensively used for the synthesis of biologically important compounds by several research groups [7–10]. The importance of ring-opening reactions is due to the regioselective addition of the nucleophile (Scheme 1).

Nucleophilic substitution of epoxy alcohols at the C-2 or C-3 positions is not as straightforward because the ring-opening reactions are not always regioselective. The structural properties of the epoxides and reaction conditions of epoxides are decisive in influencing the regioselectivity of the ring opening. The structural features of the epoxides indicate that, in addition to steric effects, electronic effects may play an important role in epoxide ring-opening reactions [11]. On the other hand, C-3 selective ring opening reactions with nucleophiles such as O, N, and halides have been effectively carried out in organic synthesis *via* a metal chelate catalyst [12–15].

In contrast, the C-2 selective ring-opening reaction of 2,3-epoxy alcohol is known to be extremely limited. Despite its synthetic utility, there are only a few examples of C-2 selective substitution reaction. In these reactions, it has been reported that steric or electronic factors are determinative in influencing the regioselectivity [11].

Very recently, Lidskog et al. investigated the asymmetric ring opening of epoxides catalyzed by metal-salen complexes and obtained enantioselective ring opening products [16]. Hubbell and Coates studied the nucleophilic transformations of Lewis acid-activated disubstituted epoxides with catalyst-controlled regioselectivity [17]. Moschona et al. investigated the catalytic asymmetric synthesis of epoxide intermediates and their subsequent ring-opening reactions with various nucleophiles for the synthesis of approved medicines and drug candidates [18].

* Corresponding author.
*E-mail address:* yukara@atauni.edu.tr (Y. Kara).

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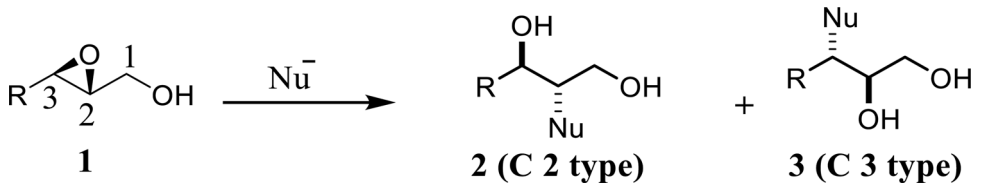
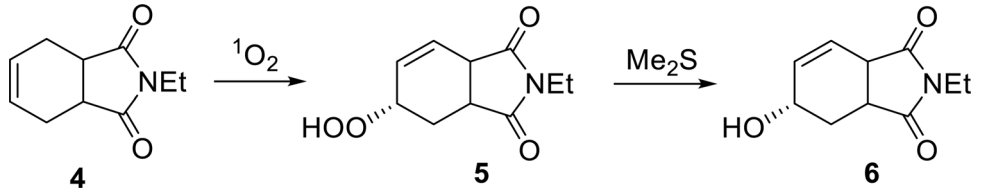
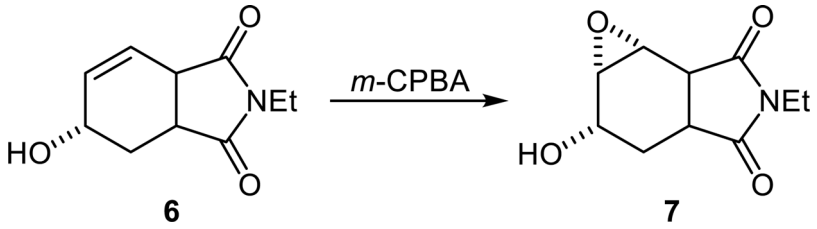


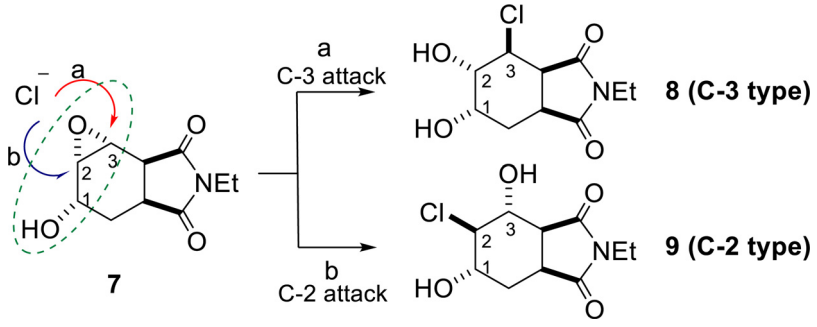

**Scheme 1.** The ring opening reaction of epoxy alcohol and formation of C-2 and C-3 isomers.



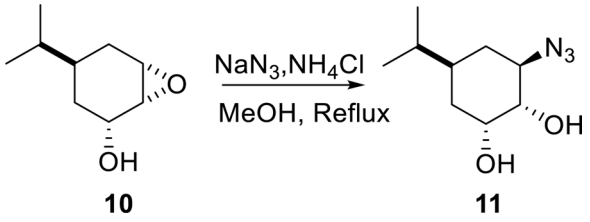

**Scheme 2.** Synthesis of isoindole derivative **6** containing allyl alcohol unit.




**Scheme 3.** Synthesis of epoxy alcohol **7**.




**Scheme 4.** The ring opening reaction of epoxy alcohol and structure of C-2 and C-3 type isomers.




**Scheme 5.** The ring opening reaction of epoxy alcohol **10** with azide and formation of C-3 type isomer **11**.

In our previous studies, we reported the synthesis of some disubstituted isoindole-1,3-dione derivatives via the ring-opening reaction of cyclic ethers. We also determined that they have potential cytotoxic effects on some cancer cells [19–21]. Based on these studies, we decided to synthesize trisubstituted cyclohexane isoindole-1,3-dione with the same skeleton structure as an alternative to previous isoindole derivatives, and to investigate its biological activities. For this purpose, we focused on the synthesis of new isoindole-1,3-dione analogs by various manipulation of 2,3-epoxy alcohols. In this paper, we report the regio- and stereospecific synthesis of trisubstituted cyclohexane isoindole-1,3-dione **9, 12** and **13** *via* the C-2 regioselective ring-opening of 2,3-epoxy alcohols with nucleophiles. We explained the regioselectivity observed in epoxide ring opening reactions via theoretical calculations.

## 2. Result and discussion

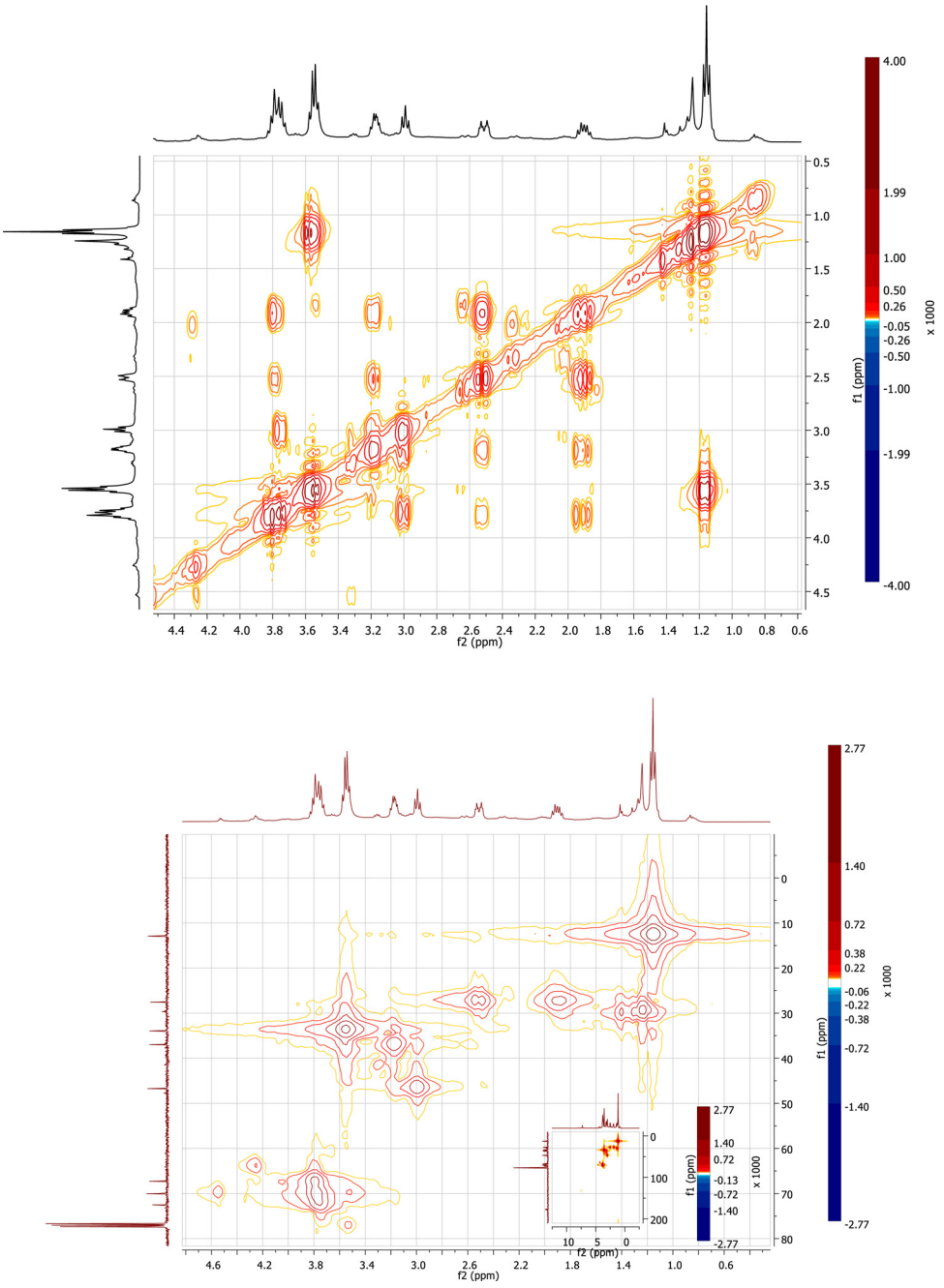
Our starting material was 2-ethyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (**4**) which has been synthesized in our previous studies [22]. We synthesized allyl alcohol **6** from hydroperoxides, obtained by ene reaction of singlet oxygen with bicyclic imide **4** (Scheme 2).

Singlet oxygen produced in the reaction medium significantly affects both the yield of hydroperoxide and the reaction time. Therefore, it is important to optimize the reaction conditions in order to increase the concentration of singlet oxygen in the reaction medium. For this purpose, we used a different light source than that used in previous studies to generate singlet oxygen. For instance, we used a 400-watt LED lamp (white light) instead of a 500-watt projection lamp for singlet oxygen generation. The results showed that the reaction is completed in a shorter time. In addition, the overheating problem of the lamp used in the reactions was prevented and it became possible to use a larger amount of

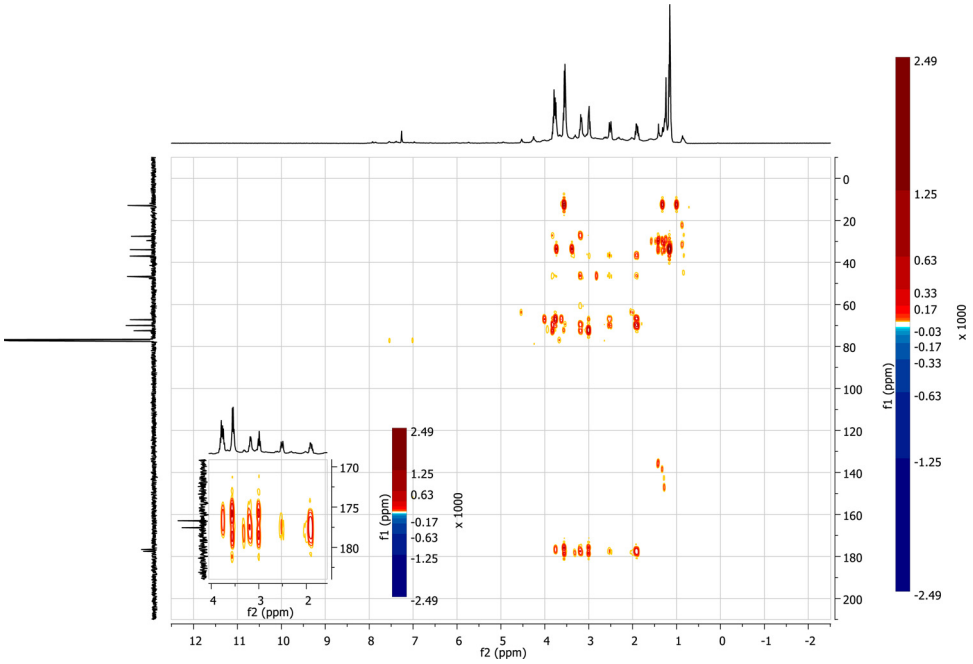
reagent. Thus, bicyclic imide **4** was subjected to ene reaction of singlet oxygen to give peroxide. The peroxide functionality of compound **5** was then converted to compound **6** containing allyl alcohol unit with dimethyl sulfide. Subsequently, compound **6** was reacted with *m*-chloroperbenzoic acid (*m*-CPBA) to give *syn*-epoxy alcohol **7** in high yield (Scheme 3). In previous studies [21,23], we used per acid at 60% concentration for the epoxidation and the reaction was completed in a long time. In this study, we used peracid at 77-79% concentration for epoxidation, and the reaction took place in a shorter time and with a good yield.

Thus, a noticeable improvement in both hydroperoxide and epoxy alcohol synthesis was achieved through the simple processes applied. After the epoxy alcohol **7** was synthesized, its regio- and stereo-controlled ring-opening reactions were investigated for the synthesis of trisubstituted isoindole-1,3-dione derivatives. For the chlorosubstituted derivative, the epoxy alcohol **7** was subjected to a ring-opening reaction with HCl in MeOH. As seen, in 2,3-epoxy alcohol **7** the steric and electronic environments at C-2 and C-3 are essentially asymmetrical, therefore C-2 and C-3 type isomers can form in this reaction (Scheme 4). Although two regioisomers were expected, only one isomer was obtained according to the $^{1}$H-NMR and $^{13}$C NMR spectrum of the crude product.

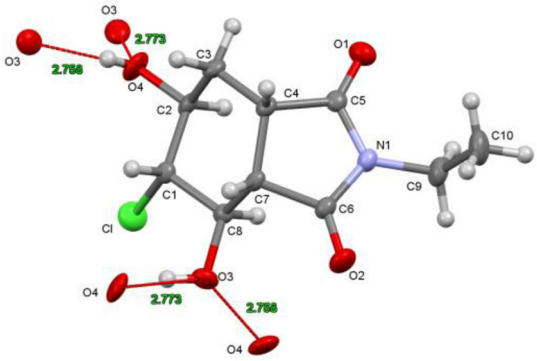
It was no surprise to us that a single isomer was formed in this reaction because regioselectivities on the opening reaction of asymmetric epoxy alcohols have been reported in the literature. For instance, Gravel et al. [24] reported that C-3 type isomer **11** is formed from the ring opening reaction of epoxy alcohol **10** with azide ($N_3^-$) (Scheme 5). According to these results, we thought that C-3 type isomer **8** would have formed from the epoxy alcohol **7**. However, we could not definitively determine the isomer **8**




**Scheme 6.** **a)** COSY NMR spectrum **b)** HMQC NMR spectrum **c)** HMBC NMR spectrum of **9**.




**Scheme 6.** Continued



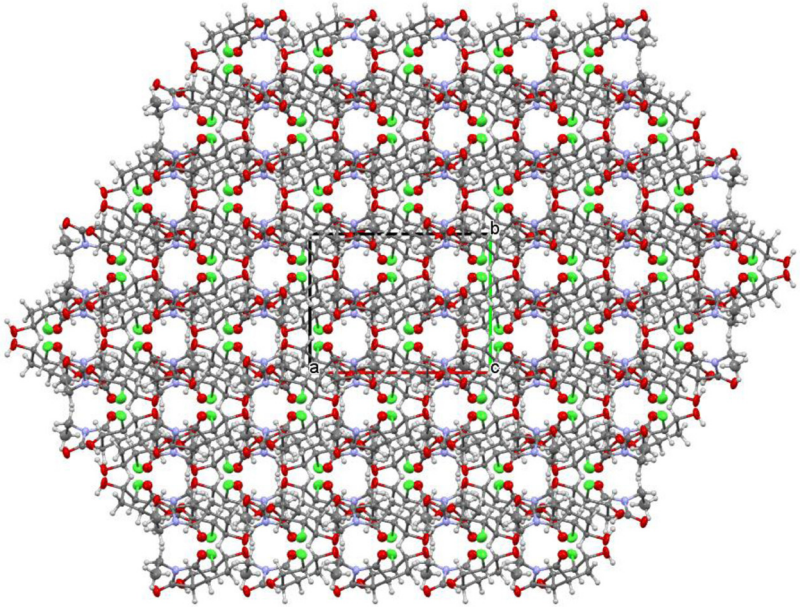
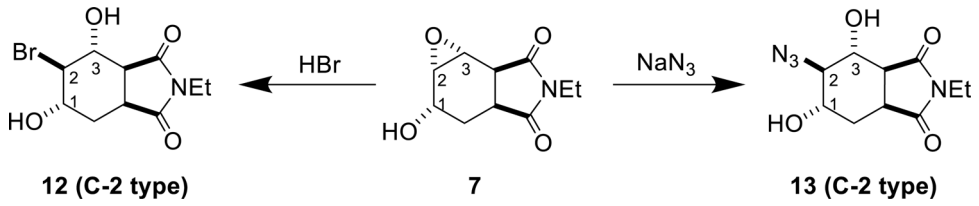




**Fig. 1.** (Up) X-ray structure of the molecule **9**. Thermal ellipsoids are drawn at the 40% probability level. Dashed red lines indicate O-H···O interactions. (Down) Stacking motif with the unit cell viewed down along the *c*-axis.




**Scheme 7.** The ring opening reaction of epoxy alcohol **7** with azide ($N_3^-$) and Bromide ($Br^-$).

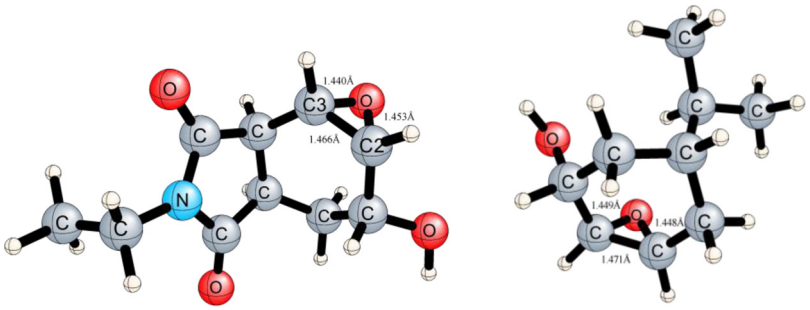



**Fig. 2.** The optimized geometries of epoxy alcohol **7** and **10**.

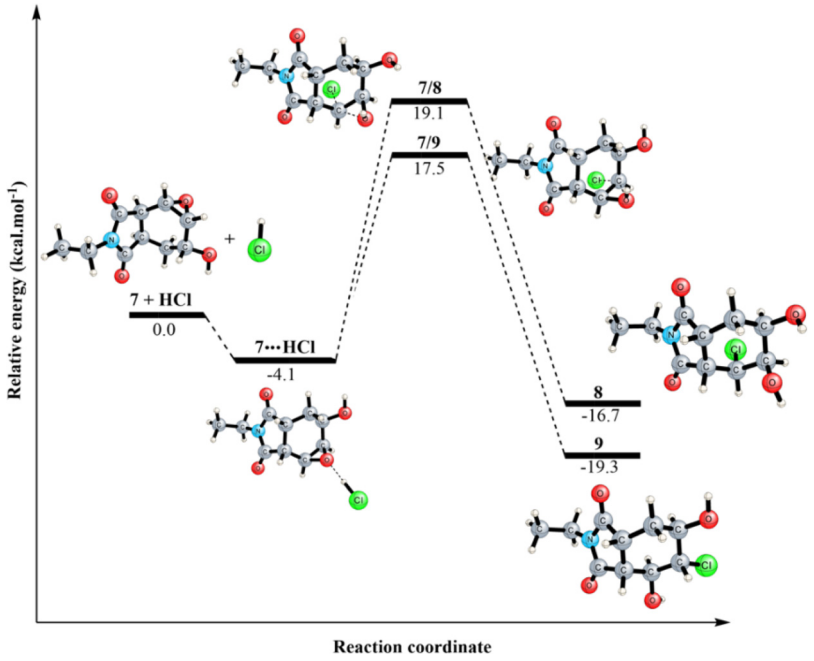



**Fig. 3.** The potential energy profile for the reaction between epoxy alcohol **7** and HCl.

formed in the reaction mixture by $^1$H and $^{13}$C NMR data. Especially, in the $^1$H NMR spectrum of ring opening product, the chemical shift values of the protons of both isomers are very close to each other and their signals overlap substantially. In addition, it is too difficult to differentiate each one from the other here, since the signal groups of CH(Cl) or CH(OH) resonate at the same region in $^1$H NMR.

Thus, we decided to use 2D NMR techniques and carry out additional studies to determine the isomer formed. Firstly, the resonance signals of the two protons (-*CH*-O and -C*H*-Cl) bound to neighboring carbon atoms had to be determined in the recorded $^1$H NMR spectrum of the isomer. After determining the signals of these protons and their carbons, $^1$H NMR decoupling experiments would be used to identify which of these protons is close to the bridgehead proton. Thus, the isomer's structure would be easily characterized.

When the $^1$H NMR spectrum of the formed isomer is examined, the resonance signals of two neighboring protons (-*CH*-O and -*CH*-Cl) spread between the range of 3.85 to 3.67. A complex system is formed because the signals of these protons are very close to each other. For this reason, it is necessary to determine which proton belongs to each signal in this region. We used simulated $^1$H NMR spectra of chlorodiols **8** and **9** to determine which protons the signal groups belong to. The $^1$H NMR spectra of both possible isomers (C-2 type and C-3 type) obtained by simulation were compared with the recorded experimental NMR spectra. As a result of this comparison, we saw that the virtual NMR spectrum of the C-2 type of the isomer **9** was agreement with the recorded NMR spectrum

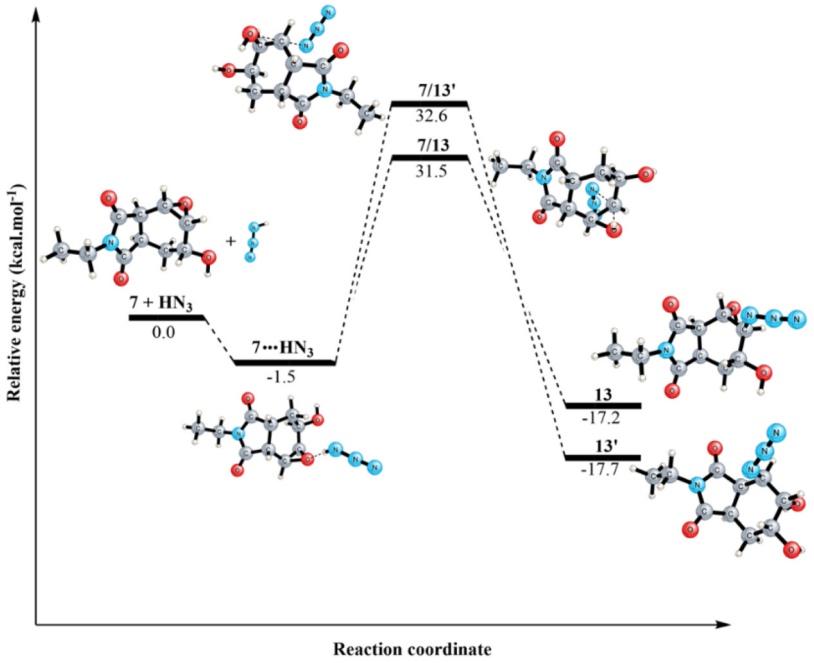



**Fig. 4.** The potential energy profile for the reaction between epoxy alcohol **7** and $HN_3$.

of the synthesized compound **9**. Thus, it was assigned which protons the signals belong to in the $^1$H NMR spectrum. Then, Correlation Spectroscopy (COSY), Heteronuclear Multiple Bond Correlation (HMBC) Heteronuclear Multiple Quantum Correlation (HMQC) experiments were used to determine the structure of chlorodiol **9** (Scheme 6). We assigned the proton-proton coupling and proton-carbon correlations using the COSY and HMQC spectrum of chlorodiol **9**. Double resonance experiments clearly indicated that the -C*H*-Cl proton was located between the carbon atoms bearing hydroxy groups. In addition, the recorded HMBC spectrum of the isomer shows the correlation of the carbonyl carbon in the imide ring with the CH-O proton in the cyclohexane ring over three bonds ($^3J_{CH}$). The correlation observed over three bonds ($^3J_{CH}$) is only agreement with the C-2 type product **9** structure. If the C-3 type product **8** were to be obtained, the carbonyl carbon would be expected to correlate with the CH-Cl proton. These results support the formation of the C-2 type product **9**. Finally, the structure of isomer **9** was further confirmed by single-crystal analysis and found to have an interesting crystal structure (Fig. 1).

The exact conformation of the 5-chloro-2-ethyl-4,6-dihydroxyhexahydro-1*H*-isoindole-1,3(2*H*)-dione (**9**) was confirmed by X-ray diffraction analysis (Fig. 1). Compound **9** crystallizes in the orthorhombic space group Pbca with one molecule in the asymmetric unit. Cyclohexane unit has chair conformation, C-C (cyclohexane) distances are in the range of 1.517(6)-1.538(6) Å, all have the single bond character. C1-Cl bond distance is 1.800(3) Å. The structure contains five asymmetric carbon atoms and stereogenic centers are as follows; C1(R), C2(S), C4(S), C7(S), C8(R). In the solid state, compound **9** is stabilized via strong intermolecular O-H···O hydrogen bonds [D···A=2.753(4)-2.773(4) Å] which leads to the formation of the polymeric structure. Along with that C-H···Cl [3.491(4)- 3.847(4)Å] halogen interactions have a contribution to the formation of a stable structure. Three of the four cis-hydrogens of the cyclohexane ring form C-H···Cl bonds with the neighboring chlorine molecule. The other *cis*-hydrogen forms a dimeric structure by making mutual C4-H···O1 (3.311 Å) bonds with the ketone oxygen of the molecule in a different neighborhood. Cylindrical nanotubes with a diameter of about 10 Å appear to be formed along the c-axis in the crystal lattice, as shown in Fig. 1.

After determining the structure of C-2 type product **9**, we performed epoxide ring-opening reactions of epoxy alcohol **7** with HBr and $NaN_3$ (Scheme 7). It was determined from the recorded $^1$H NMR spectrum of the crude products that a single isomer was formed in both reactions. The structure of the ring-opening products formed in both reactions was determined using spectroscopic methods. As in the HCl reaction, C-2 type products were obtained from the ring-opening reaction with HBr and $NaN_3$.

The different regioselectivity of compounds **7** and **10** with similar epoxy alcohol units led us to carry out additional studies, as shown in Schemes 4 and 5. In this context, we decided to make theoretical calculations to explain the different regioselectivities of similar epoxy alcohol units independent of other functional groups in the compounds **7** and **10**. We performed theoretical computations to better understand the regioselectivity in ring opening of epoxy alcohols **7** and **10** with nucleophiles such as $Cl^-$ and $N_3^-$ (Fig. 2).

For this purpose, geometry optimizations for all stationary point structures were carried out using B3LYP [25] functional with Pople's polarized triple-$\zeta$ split valence basis set with diffuse functions, 6-311++G(d,p) [26]. Harmonic vibrational frequency computations were performed to characterize each stationary structure. Note that for the TS between A and B, we use the notation A/B throughout the article. The geometry optimizations of all considered structures were performed in the presence of methanol as solvent using a solvation model based on density (SMD) [27]. All computations were carried out with the Gaussian 09 software [28]. All relative energies are given in the form of the ZPVE-corrected energies.

The reaction barriers for the plausible pathways, *a* (C-2 attack) and *b* (C-3 attack) (Scheme 3), in the attacking of $Cl^-$ to epoxy alcohol **7** are 19.1 and 17.5 kcal.mol$^{-1}$ for **7/8** and **7/9**, respectively, indicating that pathway *a* is kinetically more favorable (Fig. 3). On the other hand, in the case of using $N_3^-$ nucleophile, the reaction barriers for the possible pathways are 31.5 and 32.6 kcal.mol$^{-1}$ for **7/13** and **7/13'**, respectively, which indicate that the C-2 attack

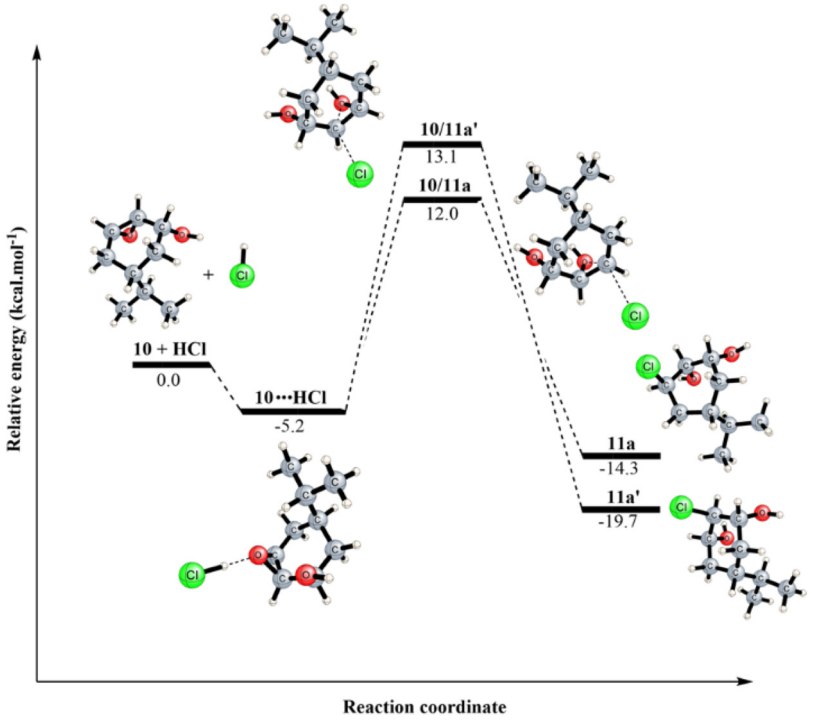



**Fig. 5.** The potential energy profile for the reaction between epoxy alcohol **10** and HCl.

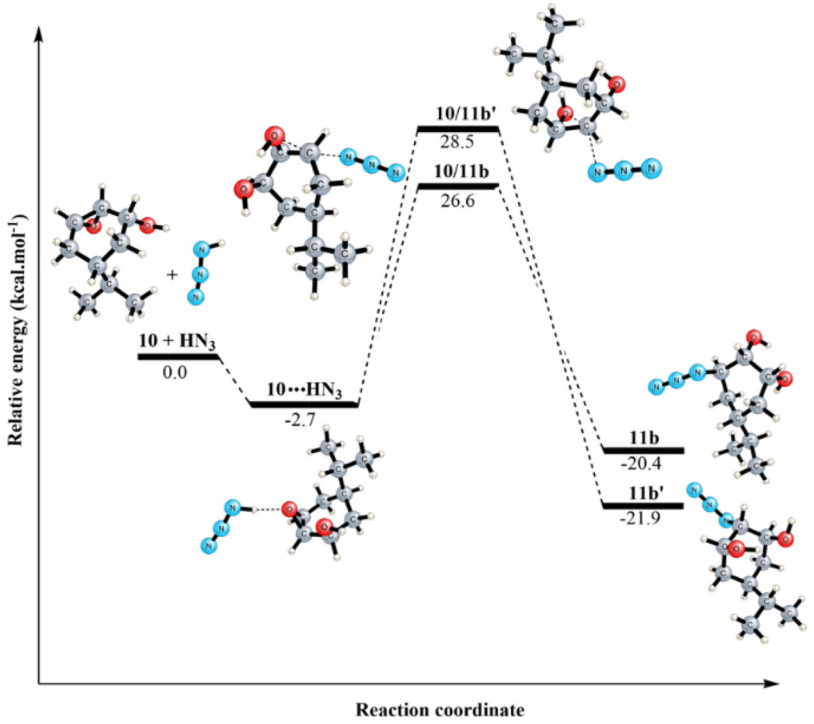



**Fig. 6.** The potential energy profile for the reaction between epoxy alcohol **10** and $HN_3$.

with lower reaction barrier is kinetically more favorable pathway (Fig. 4). These results are in agreement with experimental observations.

We performed theoretical computations for nucleophile attack on similar alcohols, to compare our results with the previous study of Gravel et al. [15] According to computational results, for the attack of $Cl^-$ to epoxy alcohol **10**, the reaction barriers for **10/11a** and **10/11a'** are 12.0 and 13.1 kcal.mol$^{-1}$, respectively (Fig. 5). For the attacking of $N_3^-$ to related epoxy alcohol the reaction barriers are 26.6 and 28.5 kcal.mol$^{-1}$ for **10/11b** and **10/11b'**, respectively (Fig. 6). This indicates that the C-3 regioselectivity is kinetically more favorable in the nucleophile attack on epoxy alcohol **10**.

## 3. Conclusion

In conclusion, we have reported an efficient synthesis of new derivatives of isoindole-1,3-dione with functional groups at the 1,2,3-position of the cyclohexane ring. This method has the potential to be widely used in the synthesis of trisubstituted isoindole-1,3-dion synthesis. We have also realized the C-2 selective substitution reactions of epoxy alcohols with nucleophiles having extremely high selectivity under mild condition in trisubstituted isoindole-1,3-dione. On the other hand, it is known that the reactivity and regioselectivity of the epoxide ring-opening reaction depend on structural features of the epoxides, the pH of the reaction medium, the catalysts used, chelated and nonchelated process. Using a different approach, we have explained the different regioselectivity of both epoxy alcohols **7** and **10** by theoretical computations. It was determined that the regioselectivity was dependent on the transition state and the reactions proceeded in a kinetically controlled manner.

## 4. Experimental

Column chromatography: Silica gel 60 (70-230 mesh) and Analytical thin layer chromatography (TLC): Silica gel 60 F254. All of the reagents used in the experiments are commercially available unless otherwise specified, and all solvents were distilled before use. $^1$H and $^{13}$C NMR spectra were recorded on Varian 400 and Bruker 400 spectrometers. Elemental analysis was performed on a Leco CHNS-932 instrument. Melting point was measured with Gallenkamp melting point devices. X-Ray: Rigaku R-AXIS RAPID IP diffractometer. HR-MS: electron spray technique (M+/M-) from the soln. in MeOH (Waters LCT Premier TM XE UPLC/MS TOF (Manchester, UK)). All the computations were performed using the Gaussian 09 program package. The energies of all the structures are on the B3LYP/6-311G++ (d, p) level.

Bicyclic imide **4** was synthesized as described in literature [21–22]. By using the same method, we were able to obtain allyl alcohol **7**.

### *4.1. anti-2-Ethyl-5-hydroperoxy-3a,4,5,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (5)*

The synthesis was carried out following a modified literature procedure [22]. Tetraphenyl porphyrin (20 mg) was added to a stirred solution of imide **4** (3 g, 16.74 mmol) in $CH_2Cl_2$ (150 mL). The mixture was irradiated with a 400-watt LED lamp while oxygen was passed through the solution and the mixture was stirred at room temperature. After 18 h the solvent was then evaporated at 30°C under reduced pressure. The major product **5** was separated using fractional crystallization in $CH_2Cl_2$–petroleum ether. Colorless crystals; mp 101–102°C. Yield: 94% $^1$H NMR (400 MHz, $CDCl_3$): 8.3 (s, 1H, OOH), 6.1 (m, 2H, 2xCH), 4.46 (m, 1H, CH), 3.53 (q, $J$ = 7 Hz, 2H, $CH_2$), 3.46 (dm, $J$ = 8 Hz, A part of AB system, 1H, CH), 3.23 (q, $J$ = 8 Hz, B part of AB system, 1H, CH), 2.18 (t, $J$ = 6 Hz, 2H, $CH_2$), 1.14 (t, $J$ = 7 Hz, 3H, $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): 178.7, 176.2, 129.1, 126.2, 75.5, 41.3, 36.3, 34.0, 25.5, 13.1. Elemental Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.92; H, 6.38; N, 6.61.

### *4.2. (3aS,5S,7aR)-2-ethyl-5-hydroxy-3a,4,5,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (6)*

A solution of peroxide **5** (3 g, 14.20 mmol) in $CH_2Cl_2$ (25 mL) was added to magnetically stirred slurry of $Me_2S$ (1.76 g, 28.40 mmol) in $CH_2Cl_2$ (25 mL) at room temperature. After the addition was complete (~ at 10 min), the mixture was stirred for six hours. The solvent was then removed by rotary evaporation. Onto the the residue was added solution of $NH_4Cl$ (30 mL) and extracted with $CH_2Cl_2$ (3 × 30 mL). The extracts were dried ($Na_2SO_4$) and the solution was concentrated. The crude product was purified by filtration through column chromatography (EtOAc–petroleum ether) providing **7** (96% yields) as colorless crystals; mp 93–94°C. $^1$H NMR (400 MHz, $CDCl_3$): 6.00 (dtd, $J$ = 10.1, 2.2, 0.7 Hz, A part of AB system, 1H, CH), 5.85 (ddd, $J$ = 10.1, 4.2, 1.8 Hz, B part of AB system, 1H, CH), 4.11 (m, 1H, OH), 3.49 (q, $J$ = 7.3 Hz, 2H, $CH_2$), 3.44 (tt, $J$ = 6.4, 1.8 Hz, 1H, CH), 3.18 (dt, $J$ = 5.5, 1.1 Hz, 1H, CH), 2.43 (dtd, A part of AB system $J$ = 13, 4.9, 0.7 Hz, 1H, CH), 1.73 (ddd, B part of AB system $J$ = 13, 9.2, 6.2 Hz, 1H, CH), 1.09 (t, $J$ = 7.3 Hz, 3H, $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): 178.8, 176.8, 135.2, 122.9, 62.6, 41.1, 37.0, 34.0, 30.2, 13.1. Elemental Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.53; H, 6.78; N, 7.15.

### *4.3. (1aS,2S,6bR)-5-ethyl-2-hydroxyhexahydro-4H-oxireno[2,3-e]isoindole-4,6(5H)-dione (7)*

A solution of allyl alcohol **6** (1.0 g, 5.12 mmol) in $CH_2Cl_2$ (25 mL) was added 77–79% *m*-CPBA (1.49 g, 6.66 mmol) at 0°C. The reaction was allowed to slowly warm to room temperature for 6 hours of stirring. After this period, the reaction mixture were evaporated under reduced pressure. The resulting residue was purified by column chromatography with EtOAc– petroleum ether (40:60) providing **7** (85% yield) as a colorless soil. mp 94–97°C. $^1$H NMR ($CDCl_3$): 3.94 (m, 1H, CH), 3.57 (q, $J$ = 7.3 Hz, 2H, $CH_2$), 3.56 (d, $J$ = 1.8 Hz, 1H, CH), 3.34–3.32 (m, 2H, 2xCH), 2.95 (ddd, $J$ = 8.6, 6.2, 2.4, 1H, CH), 2.33 (ddd, $J$ = 13.0, 2.2, 1.8 Hz, 1H, CH), 2.02 (brs, 1H, OH), 1.90 (ddd, $J$ = 13.0, 11.3, 6.2 Hz, 1H, CH), 1.16 (t, $J$ = 7.3 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): 178.2, 175.5, 64.9, 56.1, 54.8, 38.5, 38.6, 34.5, 25.5, 13.3.

### *4.4. (3aS,4R,5R,6S,7aS)-5-chloro-2-ethyl-4,6-dihydroxyhexahydro-1H-isoindole-1,3(2H)-dione (9)*

A solution of epoxy alcohol **7** (500 mg, 2.37 mmol) in MeOH (25 mL) was added HCl (37%, 3.55 mmol) and strirred for three hours at 0°C. The reaction solvent was removed by rotary evaporation. The crude product was purified by crystallization in $CH_2Cl_2$–petroleum ether providing **9** (92% yields) as a colorless crystals; mp 167-168 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.85 – 3.70 (m, 3H, 3xCH), 3.55 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 3.10 – 3.20 (m, 1H, CH), 2.90-2.80 (quasi t, 1H, CH), 2.50 (quasi dt, $J$ = 14.0, 4.5 Hz, 1H, CH), 1.90 (quasi ddd, $J$ = 14.0, 9.3, 7.4 Hz, 1H, CH), 1.10 (t, $J$ = 7.2 Hz, 3H, $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 177.56, 176.70, 72.53, 70.03, 67.29, 46.74, 36.89, 33.92, 27.56 12.90. HRMS: (ESI), m/z: $[M+H]^+$ Calcd for $C_{10}H_{14}ClNO_4$ 248.0611; found 248.0670.

### *4.5. (3aS,4S,5S,6S,7aS)-5-bromo-2-ethyl-4,6-dihydroxyhexahydro-1H-isoindole-1,3(2H)-dione (12)*

A solution of epoxy alcohol **7** (500 mg, 2.37 mmol) in MeOH (25 mL) was added HBr (47%, 3.55 mmol) and strirred for three hours in 0°C. The solvent was removed by rotary evaporator. The crude product was purified by crystallization in $CH_2Cl_2$– petroleum ether providing **12** (90% yields) as a colorless crystals; mp 141-142. $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 3.96 – 3.87 (m, 2H, 2CH), 3.84 (ddd, $J$ = 9.0, 7.0, 4.3 Hz, 1H, CH), 3.47 (q, $J$ = 7.1 Hz, 2H, $CH_2$), 3.33 (dt, $J$ = 7.8, 4.8 Hz, 1H, CH), 3.01 (dd, $J$ = 11.2, 5.2 Hz, 1H,CH), 2.38 (dt, $J$ = 13.9, 4.5 Hz, 1H, CH), 1.91 (ddd, $J$ = 14.0, 9.0, 7.4 Hz, 1H, CH), 1.10 (t, $J$ = 7.2 Hz, 3H, $CH_3$). $^{13}$C NMR (100 MHz, Acetone-$d_6$) $\delta$ 178.67, 176.94, 73.79, 71.49, 63.56, 48.11, 42.58, 38.41, 33.95, 13.06. Elemental Anal. Calcd. for $C_{10}H_{14}BrNO_4$: C, 41.12, H, 4.83, N, 4.79; Found: C, 40.88, H, 4.84. N,4,93

*4.6. (3aS,4R,5R,6S,7aS)-5-azido-2-ethyl-4,6-dihydroxyhexahydro-1H-isoindole-1,3(2H)-dione (13)*

A solution of epoxy alcohol **7** (458 mg, 5.52 mmol) in EtOH/$H_2O$ (15:10 mL) were added $NH_4Cl$ (232 mg, 4.34 mmol), $NaN_3$ (846 mg, 13.01 mmol) and strirred for five hours at 80°C. The reaction was monitored by TLC. After this period, the solvent was removed by rotary evaporation. The reaction mixture was extracted with $NH_4Cl$ (30 mL) and $CH_2Cl_2$ (3 × 30 mL). The resulting residue was then purified by crystallization in $CH_2Cl_2$–petroleum ether providing **13** (45% yield) as a colorles crystals. mp 168-169 °C $^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 4.71 (d, $J$ = 4.5 Hz, 1H, OH), 4.45 (d, $J$ = 3.8 Hz, 1H, OH), 3.40 (td, $J$ = 8.7, 3.5 Hz, 1H, CH), 3.31 (m, 2H, 2xCH), 3.21 – 3.11 (m, 3H, 3xCH), 2.82 (t, $J$ = 8.5 Hz, 1H, CH), 2.23 (dt, $J$ = 13.9, 4.2 Hz, 1H, CH), 1.68 (ddd, $J$ = 14.0, 9.9, 7.4 Hz, 1H, CH), 0.94 (t, $J$ = 7.2 Hz, 3H, $CH_3$). $^{13}$C NMR (100 MHz, Acetone-$d_6$) $\delta$ 178.39, 177.39, 72.58, 72.12, 69.18, 48.17, 38.77, 33.85, 13.05. HRMS (ESI), m/z: $[(M+H)-(N_2)]^+$ Calcd for $C_{10}H_{14}N_2O_4$ 227.0954; found 227.1019.

*4.7. X-Ray*

For the crystal structure determination, single-crystal of the compound **9** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). Graphite-monochromated Mo-K$\alpha$ radiation ($\lambda$ = 0.71073 Å) and oscillation scans technique with $\Delta$w = 5° for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with F2 > 2$\sigma$(F2). Integration of the intensities, correction for Lorentz and polarization effects and cell refinement were performed using CrystalClear (Rigaku/MSC Inc., 2005) software. The structures were solved by direct methods using SHELXS-97 [29] which allowed for the location of most of the heaviest atoms, with the remaining non-hydrogen atoms being located from different Fourier maps calculated from successive full-matrix least squares refinement cycles on F2 using SHELXL-97. All non-hydrogen atoms were refined using anisotropic displacement parameters. Hydrogens attached to carbons were located at their geometric positions using appropriate HFIX instructions in SHELXL. The final difference Fourier maps showed no peaks of chemical significance. Crystal data for **9**: $C_{10}H_{14}NO_4Cl$, crystal system, space group: orthohombic, Pbca; (no:61); unit cell dimensions: a =11.9545(8), b = 9.1937(6), c = 19.9133(9) Å, $\alpha$= 90, $\beta$ = 90, $\gamma$ = 90°; volume; 2188.6(3) Å3, Z=8; calculated density: 1.503 g/cm3; absorption coefficient: 0.348 mm-1; F(000): 1040; $\theta$-range for data collection 2.4-28.3°; refinement method: full matrix least-square on F2; data/parameters: 2704/148; goodness-of-fit on F2: 1.257; final R-indices [I > 2$\sigma$(I)]: R1 = 0.090, wR2 = 0.193; largest diff. peak and hole: 0.464 and -0.432 e Å-3. CCDC-2090073 number contains the supplementary crystallographic data for this structure (12). These data are provided free of charge via the joint CCDC/FIZ Karlsruhe deposition service www.ccdc.cam.ac.uk/structures

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Özlem Gündoğdu:** Investigation, Writing – original draft. **Abdurrahman Atalay:** Software, Investigation. **Neslihan Çelebioğlu:** Investigation. **Barış Anıl:** Software, Formal analysis. **Ertan Şahin:** Software, Formal analysis. **Gülşah Şanlı-Mohamed:** Writing – original draft, Visualization. **Uğur Bozkaya:** Software, Formal analysis. **Yunus Kara:** Conceptualization, Methodology, Writing – original draft.

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