Journal of the Iranian Chemical Society
https://doi.org/10.1007/s13738-019-01810-3

ORIGINAL PAPER

A novel and stereoselective synthesis of 2-bromo-6-chloro-5-methylcyclohex-4-ene-1,3-diyl diacetate: conduritol-A derivative

Latif Kelebekli[1] · **Dilek Kaplan**[1]

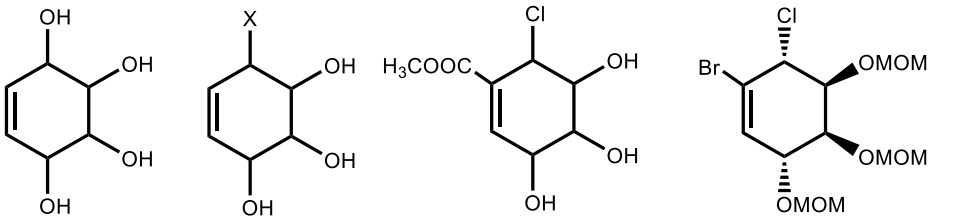
Received: 22 June 2018 / Accepted: 11 November 2019

Abstract
The stereoselective synthesis of 2-bromo-6-chloro-5-methylcyclohex-4-ene-1,3-diyl diacetate, methyl-substituted dihaloconduritol-A is reported. Bromination of 2-methylbenzo-1,4-quinone followed by the reduction in the carbonyl groups with $NaBH_4$ to give a dioldibromo compound. The diol was converted to diacetates by acetylation with Ac_2O-pyridine. Reaction of methyl-dioldibromodiacetate with LiOH gave stereoselectively the monoepoxide compound. Controlled reaction of the epoxide with AcCl in methylene chloride furnished the desired new dihaloconduritol-A derivative which was characterized by spectroscopic methods. All the synthesized compounds were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, COSY (2D-NMR), and HRMS analyses.

Keywords Dihalogen cyclitol · Dihaloconduritol · Cyclitol · Dihaloconduritol-A derivative

Introduction

Conduritols and carbasugars are a class of polyhydroxylated cyclohexanoids that have continued to attract the attention of chemists and biologists due to their involvement in various biological processes [1]. Conduritols which are precursors for the synthesis of cyclitols and their derivatives have interesting biological activities. Their biological activities, particularly glycosidase inhibition, have extensively been evaluated [2]. Bromoconduritol (6-bromo-3,4,5-trihydroxycyclohex-1-ene) is an active-site-directed irreversible inhibitor of glucosidases [3, 4]. Notably, bromoconduritol has been known as an inhibitor of glucosidase II, which plays pivotal roles in glycoprotein processing and folding in the endoplasmic reticulum [5]. In connection with the conduritols, haloconduritols (with halo-substituents such as –Br, –Cl, and –F), particularly mono- and dihaloconduritols have also gained increasing importance over the last decade [6–11]. All of them have been carried out using an acid or Lewis acid-catalyzed reactions (HX, H_2SO_4, BX_3, Li_2CuCl_4, etc.).



Conduritol **Haloconduritol X= Cl, Br, F** **Pericosine** **Haloconduritol derivative**

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13738-019-01810-3) contains supplementary material, which is available to authorized users.

✉ Latif Kelebekli
lkelebekli@odu.edu.tr

[1] Department of Chemistry, Faculty of Science and Arts, Ordu University, 52200 Ordu, Turkey

Published online: 06 December 2019

On the other hand, pericosines are a class of highly oxygenated cyclohexenoid natural products and have been targets of many synthetic studies. C7-cyclitols, such as gabosines (gabosine A, N, and H) [12–14] with a methyl substituent and pericosines (pericosine A, D, and E) [15–18] with chloride group which include a cyclohexenoid moiety, represent an important category of highly oxygenated natural products and may be classified as pseudo- or carbasugars. Conduritols A–F are useful intermediates in organic synthesis. In connection with the conduritols, haloconduritols and double bond-substituted conduritols (such as methy-, phenyl-, bromo-substituted conduritols) have also gained importance in the last decade [19–23]. For instance, bromoconduritols are interesting molecules in AIDS research because they are active-site-directed covalent inhibitors of α-glucosidases [22]. Moreover, since these compounds show structural similarities to carbohydrates, they exhibit interesting biological activities such as antibiotic, anticancer, and DNA binding properties [24–26].

There is considerable interest in the stereocontrolled synthesis of these compounds as they have proved to be useful intermediates for the preparation of cyclitols. Recently, we have reported the stereospecific synthesis of some polyhydroxylated compounds [27–30]. Consequently, based on these results, we aimed to synthesize a dihaloconduritol derivative. Herein, we report the synthesis of a dihaloconduritol derivative including a methyl substituent having the conduritol-A construction.

Results and discussion

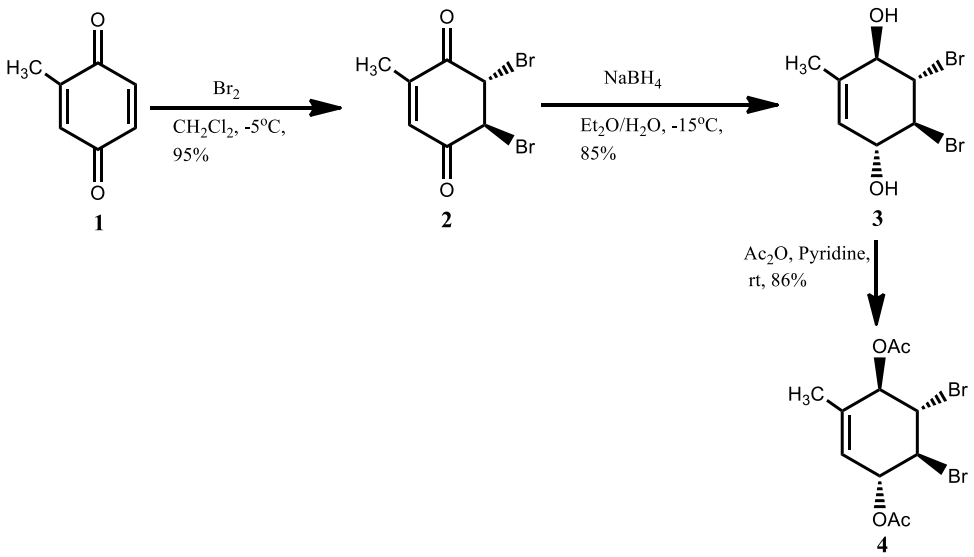
Methyl-substituted *para*-benzoquinone **1** was brominated at low temperature to give only the *trans*-dibromo compound **2** in high yield. The required allylic *trans*-diol **3** for synthesis of the target compound was obtained as the sole product by stereoselective reduction in the carbonyl groups with the $NaBH_4$ in ether [19]. The stereochemical course of the reduction was mainly determined as the *trans* configuration to bromide groups. After successful isolation and characterization of the result of reduction, the acetylation of **3** with Ac_2O/pyridine system at room temperature gave dibromodiacetoxy compound **4** [19, 20] as a sole product in 86% yield. Thus, stereochemistry of compound **4** was protected such as in **3** as conduritol B (Scheme 1).

Epoxide **5** was regioselectively prepared from dibromide **4** by treatment with lithium hydroxide as a base [19, 20]. Although epoxide **5** was known, the observed regio- and stereoselectivity for this reaction was remarkable. Thus, we focused on the detailed spectroscopic studies to provide the best approach by checking related structure. In the ^{1}H-NMR spectrum of **5**, the irradiation of H-4 at 5.62 ppm (CH=C) resulted in the signal of H-6 at 3.36 ppm changing from a double doublet to a doublet (J = 4.0 Hz). Upon irradiation of H-3 at 4.49–4.43 ppm, both the signal of H-2 at 4.02 ppm and the signal of –OH proton at 2.47 ppm changed from a double doublet to a broad singlet and from a doublet to a singlet, respectively. When H-6 at 3.36 ppm was irradiated, both the signal of H-4 at 5.62 ppm and the signal of H-1 at 3.74 ppm changed from a double doublet to a triplet (J = 1.6 Hz) and from a double doublet to a singlet, respectively. These results clearly indicate that H-6 with H-1 and the H-4 with H-3 are the neighboring protons with each other.

Additionally, for this interesting epoxide formation, geometry optimization calculations (DFT) were carried out on the epoxide **5** without any simplification using the ORCA program package with the RI-BP86 [31]. The epoxide **5** is 5.60 kcal/mol more stable than epoxide in other allylic position, which was not obtained.

The products of the ring opening of epoxides by various carbon, nitrogen, oxygen, halogen, and sulfur-containing

Scheme 1 Synthesis of compound **4**



nucleophiles are versatile intermediates in the synthesis of various biologically active compounds [32]. The chlorohydrins are very important intermediates in the production of epoxides and chlorohydrin esters and in the preparation of many natural products [33–35]. As well as halohydrin derivatives, a convenient pathway to halohydrin esters from epoxides is the direct reaction with acyl halides. The halohydrin-ester synthesis from acyl halides and epoxides has been versatilely investigated. Previous reports have described the acylative cleavage of cyclic ethers using metal-reagent systems in conjunction with acid chlorides [33–39].

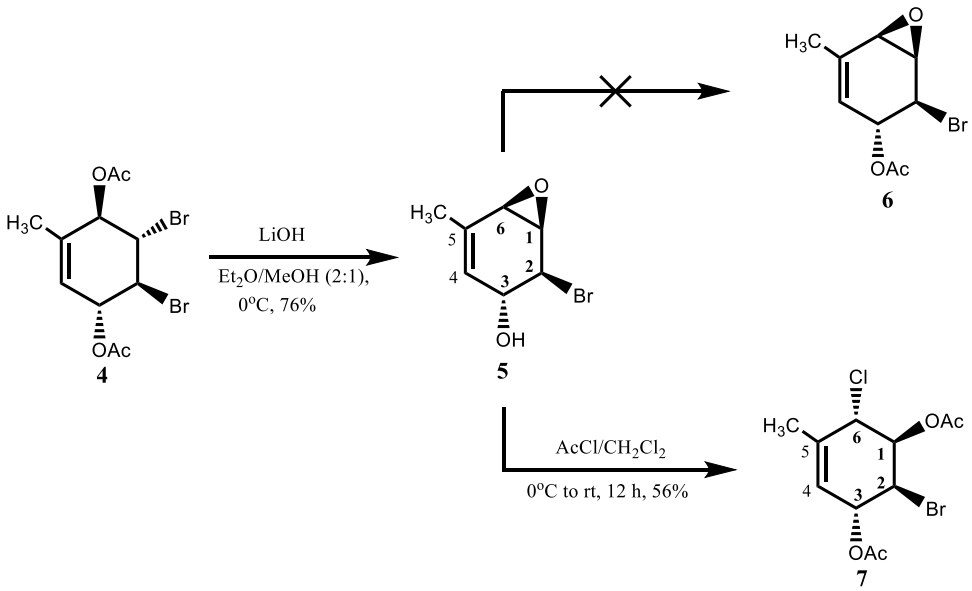
We firstly aimed the acetylation of hydroxyl group in the molecule. However, after the treatment with CH_3COCl in methylene chloride at room temperature for acetylation of –OH, the expected acetoxy compound **6** was not obtained as deduced from the ^{1}H-NMR data. Contrary to expectation, regio- and stereoselective ring opening of epoxide **5** with CH_3COCl resulted in (±)-(1RS,2SR,3RS,6SR)-2-bromo-6-chloro-5-methylcyclohex-4-ene-1,3-diyl diacetate **7** which possess a conduritol-A-type configuration as the only reaction product (Scheme 2). All analytical methods showed the formation of a single isomer with high selectivity. Especially, the NMR spectral studies showed the formation of two acetate groups. Additionally, the most conspicuous features in the ^{13}C-NMR spectrum of **7** are only the resonances of the two carbonyl groups. These results clearly indicate that epoxide ring has been opened under these conditions. The observed regio- and stereoselectivity for this reaction was remarkable since stereochemistry is transformed into conduritol-A-type configuration in the compound **7** from conduritol-B-type configuration in the compound **4**. The exact configuration of compound **7** was determined on the basis of the ^{1}H-NMR and ^{13}C-NMR spectra in conjunction with 2D-NMR (COSY) experiments. The ^{1}H-NMR and ^{13}C-NMR spectra reveal the formation of only one isomer. The eleven-line ^{13}C-NMR spectrum is in agreement with structure **7** having the asymmetry element.

In the ^{1}H-NMR spectrum of **7**, the irradiation of H-3 at 5.58 ppm resulted in the signal of H-2 at 4.49 ppm changing from a double doublet to a broad singlet. When H-2 at 4.49 ppm was irradiated, H-3 showed a singlet and H-1 also showed a doublet (J = 3.6 Hz) but H-6 remained unchanged. These results clearly indicate that H-2 with H-1 and H-3 are the neighboring protons with each other. Upon irradiation of H-1 at 5.39 ppm, both the signal of H-2 at 4.49 ppm and the signal of H-6 at 4.34 ppm changed from a double doublet to a doublet (J = 7.6 Hz) and from a doublet to a singlet, respectively. When H-6 at 4.34 ppm was irradiated, H-1 showed a broad singlet but for H-2 no change was observed. These results clearly indicate that connectivity of **7** is as shown (Scheme 2).

Notably, analysis of the COSY (2D-NMR) spectrum shows that the H-6 (–C<u>H</u>Cl) at 4.34 ppm is coupled to H-1 at 5.39 ppm. The proton for H-2 (–C<u>H</u>Br) at 4.49 ppm is coupled to the H-3 at 5.58 ppm as well as the H-1 at 6.39 ppm. The proton for H-3 (–C<u>H</u>OAc) at 5.58 ppm is coupled to the H-2 at 4.49 ppm and H-4 at 5.49–5.52 ppm. The proton for H-1 (–C<u>H</u>OAc) at 5.39 ppm is coupled to the H-2 at 4.49 ppm and H-6 at 4.34 ppm (Fig. 1). These results also clearly illustrate that these protons are the neighboring protons with each other.

We suggest the following mechanism for the formation of stereospecific synthesis of methyl-substituted dihaloconduritol-A **7** from epoxide **5** (Scheme 3). At first, compound **5** is acetylated under CH_3COCl in methylene chloride. One mole of HCl comes out under these reaction conditions. The formed HCl during the reaction leads to contribute the stereoselective epoxide ring opening as a subtle difference. That

Scheme 2 Synthesis of compound **7**



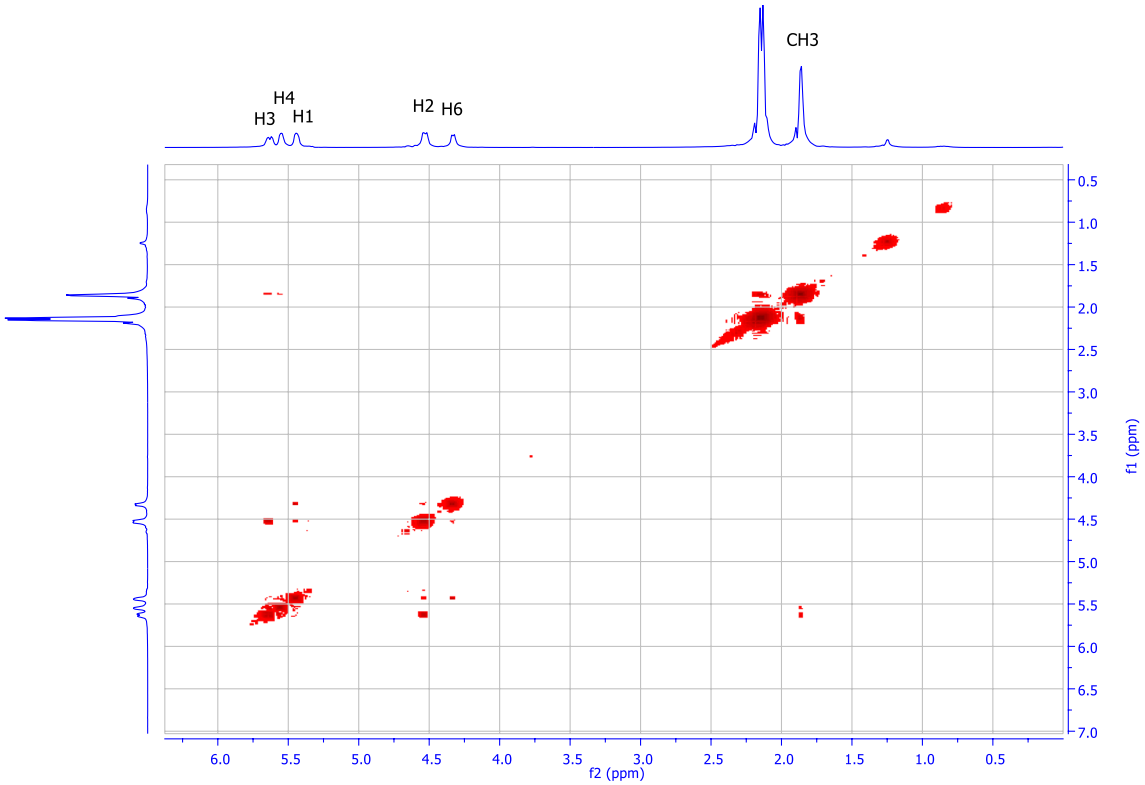


Fig. 1 The COSY spectrum for compound **7** in $CDCl_3$ at room temperature (400 MHz)

is, it can be easily understood here that the opening of the epoxide ring is catalyzed by acid (HCl). The formed cyclic oxonium ion **9** undergoes ring opening through attack by chloride ion, most likely at the allylic C-atom to produce compound **10**. In the final step, compound **7** can be obtained by the acetylation of –OH group. Thus, the observed *cis*-relation of the Br-atom and –OAc C(1) in compound **7** can be explained by this mechanism.

Conclusion

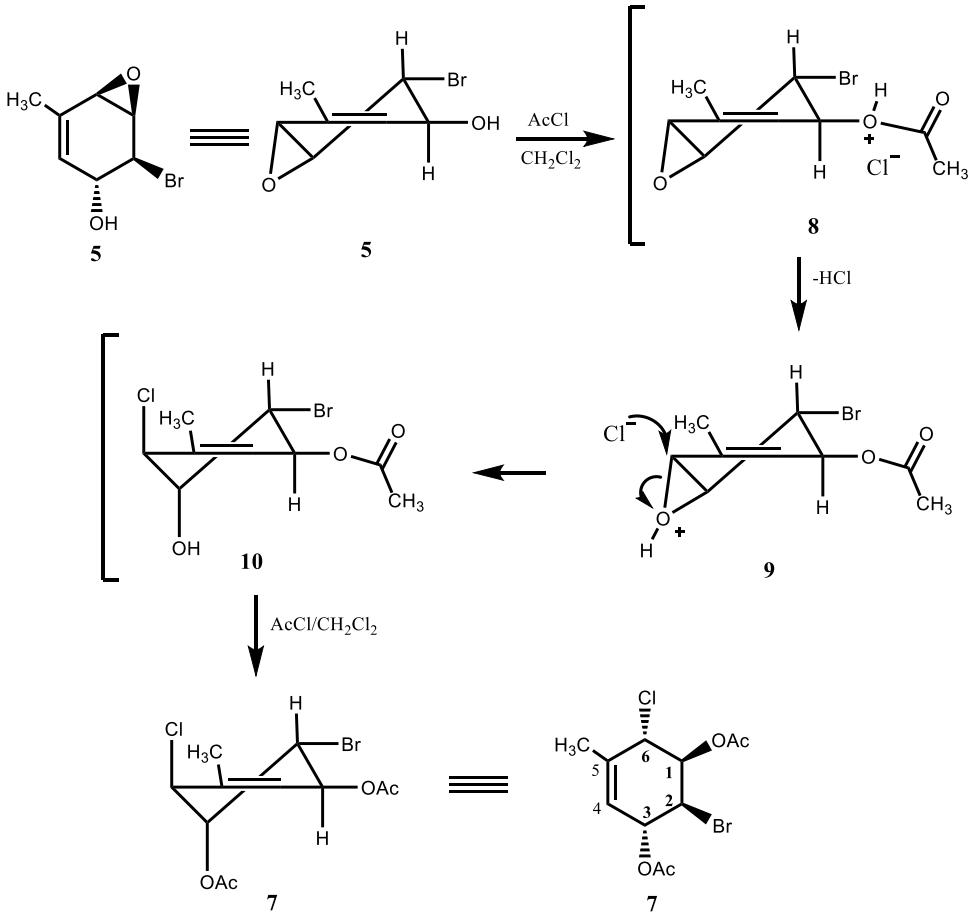
In conclusion, we have reported stereospecific synthesis of novel methyl-substituted dihaloconduritol (including Br- and Cl atoms) via an allylic epoxide starting from 2-methylbenzo-1,4-quinone. We underline that AcCl can serve to forming halocyclitols without any catalyst. All the synthesized compounds were thoroughly characterized by IR, ^{1}H-NMR, ^{13}C-NMR, COSY (2D-NMR), HRMS, melting point, etc. With continuous research of novel halogened conduritols, new approaches to this type of products can be anticipated to appear in the future and be applied extensively in practical synthesis. This compound has potential to be used as a precursor for the synthesis of metoxy-, azido-, and aminocyclitol derivatives.

Experimental section

Melting points were determined on a capillary melting apparatus (Electrothermal) and are uncorrected. IR spectra were obtained from KBr (solution in 0.1 mm cells) or film with a Shimadzu spectrophotometer. The ^{1}H NMR, ^{13}C NMR, and 2D NMR (COSY) spectra were recorded on 400 (100)-MHz Varian spectrometer and are reported in δ units with $SiMe_4$ as internal standard. TLC was performed on E. Merck silica gel 60 F_{254} plate (0.2 mm). All column chromatography was performed on silica gel (60 mesh, Merck). HRMS were recorded by LC–MS TOF electrospray ionization technique (6230, Agilent).

(±)-(1RS,2SR,3RS,6RS)-2-bromo-5-methyl-7-oxabicyclo[4.1.0]hept-4-en-3-ol (5) A solution of dibromodiacetoxy **4** (4.20 g, 11.30 mmol) in 80 mL diethyl ether and 60 mL MeOH is cooled to 0 °C, and then 0.61 g (24.41 mmol) anhydrous LiOH to stirring solution under N_2 atmosphere is added. The reaction mixture is stirred for 2 h at this temperature. The reaction mixture was monitored by TLC, and after the reaction is completed, H_2O (100 mL) to the residue was added, and the reaction mixture was quenched by the addition of water. Then, Et_2O (100 mL) was added, the layers were separated, and the aqueous layer

Scheme 3 Mechanism of formation of compound **7**



extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure to afford (±)-(1RS,2SR,3RS,6RS)-2-Bromo-5-methyl-7-oxabicyclo[4.1.0]hept-4-en-3-ol **5** (1.76 g, 76%). The product **5** was recrystallized from AcOEt/hexane as colorless crystals, mp 128–130 °C; ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ 5.62 (dd, 1H, J = 3.8, 1.8 Hz, HC=C), 4.49–4.43 (m, 1H, –CHO), 4.02 (dd, 1H, J = 8.4, 1.2 Hz, –CHBr), 3.74 (dd, 1H, J = 4.0, 0.8 Hz, –CHO), 3.36 (dd, 1H, J = 4.0, 2.4 Hz, –CHO), 2.47 (d, 1H, J = 4.3 Hz, –OH), 1.96 (dd, 3H, J = 2.6, 1.7 Hz, –CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$, ppm): δ 132.2 (C=C), 127.5 (C=C), 70.9 (C–O), 56.0 (C–Br), 55.6 (C–O), 55.5 (C–O), 21.1 (–CH_3); IR (KBr, cm^{-1}): 3318, 3252, 3024, 2978, 2916, 1663, 1450, 1381, 1339, 1273, 1234, 1180, 1185, 1034, 1011, 944, 899, 800, 822, 756, 656, 611; HRMS: m/z calculated for $C_7H_9BrKO_2$ $[M+K]^+$ (Br^{79}), 242.9418; found: 243.0123 and $C_7H_9BrKO_2$ $[M+K]^+$ (Br^{81}), 244.9397; found: 245.0002.

(±)-(1RS,2SR,3RS,6SR)-2-bromo-6-chloro-5-methylcyclohex-4-ene-1,3-diyl diacetate (7) To a solution of epoxide **5**, (0.85 g, 4.14 mmol) in CH_2Cl_2 (15 mL) was added AcCl (8 mL) and the resulting solution was stirred overnight at room temperature. The excess of unreacted AcCl and solvent was evaporated (60 °C, 20 mmHg). The residue was dissolved in CH_2Cl_2. Further purification was carried out by short column chromatography on silica gel. Evaporation of solvent gave (1R,2S,3R,6S)-2-bromo-6-chloro-5-methylcyclohex-4-ene-1,3-diyl diacetate **7** as colorless oil (0.66 g, 56%); ^{1}H-NMR (400 MHz $CDCl_3$, ppm): δ 5.58 (br d, 1H, J = 7.6 Hz, H_3), 5.49–5.52 (m, 1H, H_4), 5.39 (dd, 1H, J = 3.6, 2.4 Hz, H_1), 4.49 (dd, 1H, J = 7.6, 2.4 Hz, H_2), 4.34 (d, 1H, J = 3.6 Hz, H_6), 2.11 (s, 3H, –OAc), 2.09 (s, 3H, –OAc), 1.82 (s, 3H, –CH_3); ^{13}C-NMR (100 MHz $CDCl_3$, ppm): δ 170.1 (C=O), 169.7 (C=O), 135.3 (C quaternary), 123.6 (C=C), 74.8 (–O–C), 71.7 (–O–C), 57.3 (–C–Br), 46.2 (–C–Cl), 20.9 (–CH_3), 20.7 (–CH_3), 20.6 (–CH_3); IR (KBr, cm^{-1}): 2359, 2324, 1746, 1373, 1223, 1085, 1035, 862, 788; HRMS: m/z calculated for $C_{11}H_{14}BrClNaO_4$

$[M+Na]^+$ (Br^{79}, Cl^{35}), 346.9656; found: 346.9692 and $C_{11}H_{14}BrClNaO_4$ $[M+Na]^+$ (Br^{81}, Cl^{35} or Br^{79}, Cl^{37}), 348.9636; found: 348.9670.

References

1. M.P. Thomas, S.J. Mills, B.V.L. Potter, Angew. Chem. Int. Ed. **55**, 1614 (2016)
2. O. Arjona, A.M. Gomez, J.C. Lopez, Chem. Rev. **107**, 1919 (2007)
3. M. Salvucci, Arch. Insect Biochem. Physiol. **45**, 117 (2000)
4. G. Legler, Methods Enzymol. **46**, 368 (1979)
5. Y. Takeda, K. Totani, I. Matsuo, Y. Ito, Bioorg. Med. Chem. Lett. **20**, 5357 (2010)
6. Z.X. Guo, A.H. Haines, R.J.K. Taylor. Synlett 607 (1993)
7. Z.X. Guo, A.H. Haines, S.M. Pyke, S.G. Pyke, R.J.K. Taylor, Carbohydr. Res. **264**, 147 (1994)
8. A.H. Haines, A.S.H. King, J.R. Knight, V.A. Nguyen, Tetrahedron Lett. **39**, 4393 (1998)
9. T. Hudlicky, H. Luna, H.F. Olivo, C. Andersen, T. Nugent, J.D. Price, J. Chem. Soc. Perkin Trans. **1**, 2907 (1991)
10. A. Baran, C. Kazaz, H. Seçen, Y. Sutbeyaz, Tetrahedron **59**, 3643 (2003)
11. A. Baran, C. Kazaz, H. Seçen, Tetrahedron **60**, 861 (2004)
12. P. Bayón, M. Figueredo, Chem. Rev. **113**, 4680 (2013)
13. D.H. Mac, S. Chandrasekhar, R. Grée. Eur. J. Org. Chem. **2012**, 5881 (2012)
14. D. Chanti Babu, Ch. Bhujanga Rao, K. Venkatesham, J. Jon Paul Selvam, Y. Venkateswarlu, Carbohydr. Res. **388**, 130 (2014)
15. Y. Usami, K. Mizuki, J. Nat. Prod. **74**, 877 (2011)
16. D.R. Boyd, N.D. Sharma, C.A. Acaru, J.F. Malone, C.R. O'Dowd, C.C. Allen, P.J. Stevenson, Org. Lett. **12**, 2206 (2010)
17. Y. Usami, H. Ichikawa, M. Arimoto, Int. J. Mol. Sci. **9**, 401 (2008)
18. Y. Usami, K. Mizuki, H. Ichikawa, M. Arimoto, Tetrahedron Asymmetry **19**, 1461 (2008)
19. T. Leermann, O. Block, M.A.L. Podeschwa, U. Pfüller, H.J. Altenbach, Org. Biomol. Chem. **8**, 3965 (2010)
20. L. Kelebekli, D. Kaplan, Tetrahedron **73**, 8 (2017)
21. S. Cantekin, R. Çalışkan, E. Sahin, M. Balci, Helv. Chim. Acta **90**, 2227 (2007)
22. S. Cantekin, A. Baran, R. Çalışkan, M. Balci, Carbohydr. Res. **344**, 426 (2009)
23. M. Matveenko, A.C. Willis, M.G. Banwell, Aust. J. Chem. **62**, 64 (2009)
24. C.F.M. Huntley, D.S. Hamilton, D.J. Creighton, B. Ganem, Org. Lett. **2**, 3143 (2000)
25. Y.Q. Tang, C. Maul, R. Höfs, I. Sattler, S. Grabley, X.Z. Feng, A. Zeek, R. Thiericke. Eur. J. Org. Chem. 149 (2000)
26. A. Maier, C. Maul, M. Zerlin, R. Grabley, R. Thiericke, J. Antibiot. **52**, 952 (1999)
27. L. Kelebekli, N. Balcı, E. Sahin, Tetrahedron **70**, 5175 (2014)
28. L. Kelebekli, Synth. Commun. **43**, 2998 (2013)
29. L. Kelebekli, J. Chem. Res. **11**, 626 (2007)
30. L. Kelebekli, K. Aksu, E. Sahin, Tetrahedron Lett. **59**, 1258 (2018)
31. F. Neese, *ORCA, An Ab Initio, DFT, and Semienpirical Electronic Structure Package, Version 2.7.0* (Universitat Boon, Boon, 2010)
32. M. Fallah-Mehrjardi, A.R. Kiasat, K. Niknam, J. Iran. Chem. Soc. **15**, 2033 (2018)
33. K. Nakano, S. Kodama, Y. Permana, K. Nozaki, Chem. Commun. 6970 (2009)
34. F.M. Moghaddam, H. Saeidian, Z. Mirjafary, M.J. Javan, M.M. Farimani, M. Seirafi, Heteroat. Chem. **20**, 157 (2009)
35. N. Azizi, B. Mirmashhori, M.R. Saidi, Catal. Commun. **8**, 2198 (2007)
36. G. Aghapour, R. Hatefipour, Synt. Commun. **43**, 1030 (2013)
37. F.A. Luzzio, R.A. Bobb, Tetrahedron **55**, 1851 (1999)
38. Y. Taniguchi, S. Tanaka, T. Kiamura, Y. Fujiwara, Tetrahedron Lett. **39**, 4559 (1998)
39. L. Kelebekli, B. Anil, S. Goksu, E. Sahin, J. Iran. Chem. Soc. **15**, 1969 (2018)