The Free Internet Journal
for Organic Chemistry

Paper

Archive for
Organic Chemistry

Arkivoc **2020**, part vi, 105-113

The synthesis and characterization of *N*-tosyl halodihydroconduramines from corresponding mono-epoxy derivative

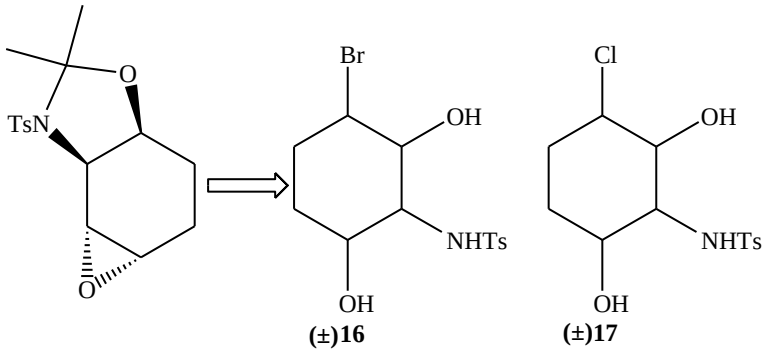
Namudar İzzet Kurbanoğlu,*[a] Arif Baran,[b] and Sümeyye Çöl[b]

[a] *Department of Science Education, Faculty of Education, Sakarya University, 54300, Hendek/ Sakarya, Turkey*
[b] *Department of Chemistry, Faculty of Art and Sciences, Sakarya University, 54100, Esentepe/ Sakarya, Turkey*
Email: kurbanoglu@sakarya.edu.tr

Received 10-17-2019 **Accepted** 04-02-2020 **Published on line** 04-30-2020

Abstract

Cyclitols and their halogen derivatives are important compounds in organic chemistry, and thus their synthesis with high efficiency has gained importance. In this study, BX_3-assisted (X=Br or Cl) ring-opening reactions of the mono-epoxide **15** of [(*3aR(S),7aS(R)*)]-2,2-dimethyl-3-tosyl-2,3,3a,6,7,7a-hexahydrobenzo[*d*]oxazole (**12**) have been investigated. In BX_3-assisted (BBr_3 or BCl_3) ring-opening processes, this epoxide reacts exclusively via nucleophilic attack at carbon 3a-C of the substrate and such regioselectivity has been exploited in the synthesis of the *N*-tosyl bromo- and *N*-tosyl chloro-dihydroconduramines. The structures of the products were established by chemical correlation studies.



Keywords: Cyclitols, dihydroconduramines, halodihydroconduramines, mono-epoxide

Introduction

Cyclitols (**1**–**5**) are cyclic compounds containing at least three hydroxyl groups in their structures attached to different carbons atoms.[1-6] Cyclitols are grouped according to the number of hydroxyl groups attached to the cyclohexane ring as dihydroconduritols (**2**),[7-9] conduritols (**3**),[2,10-12] quercitols (**4**),[13-15] and inositols (**5**)[16,17] (Figure 1).

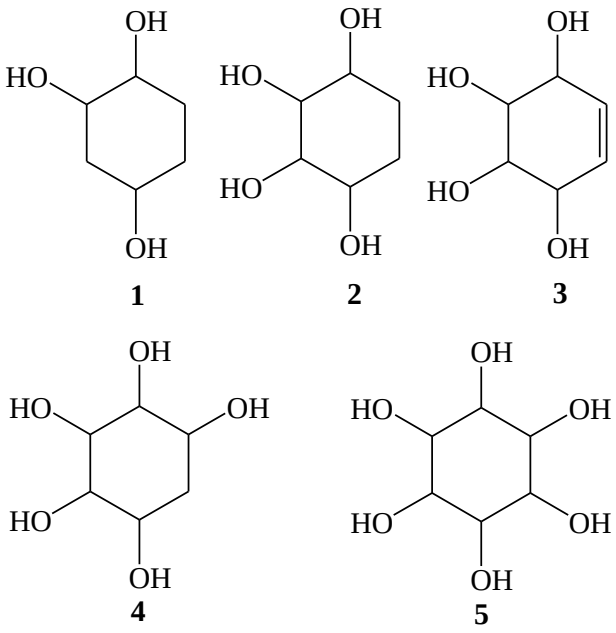


Figure 1. Various types of cyclitols.

Cyclitols have multiple structural isomers (**1** and **2**) and stereoisomers (**1**–**5**).[1-17] However, there are also derivatives of these compound groups (**6**-**9**) containing halo (X: F, Cl, Br, I) and amino (-NH_2) groups (Figure 2).

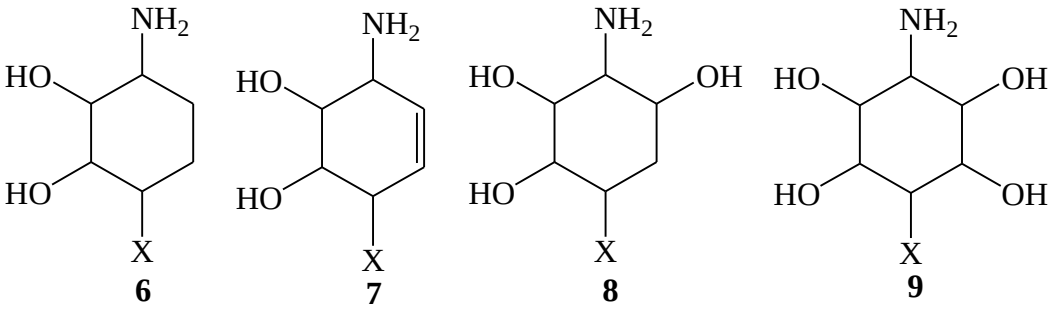


Figure 2. Halogen and amino derivatives of cyclitols.

Cyclitols (1-5) and their derivatives (6-9) are important compounds in organic chemistry. The halogen derivatives of the cyclitols can be synthetic intermediates of biological products, and thus their synthesis with high efficiency has been gained importance.[2-6]

 ©**AUTHOR(S)**

Owing to their functionalities, mono-epoxides and derivatives (**13**–**15**) have been used as starting materials in the preparation of cyclitols and related molecules.[18-21] The initial phases of chemical synthesis often involve the preparation and nucleophilic or acid-catalyzed ring-opening of the mono-epoxides (**13**–**15**) of compounds such as **10**–**12**[22-24] (Figure 3).

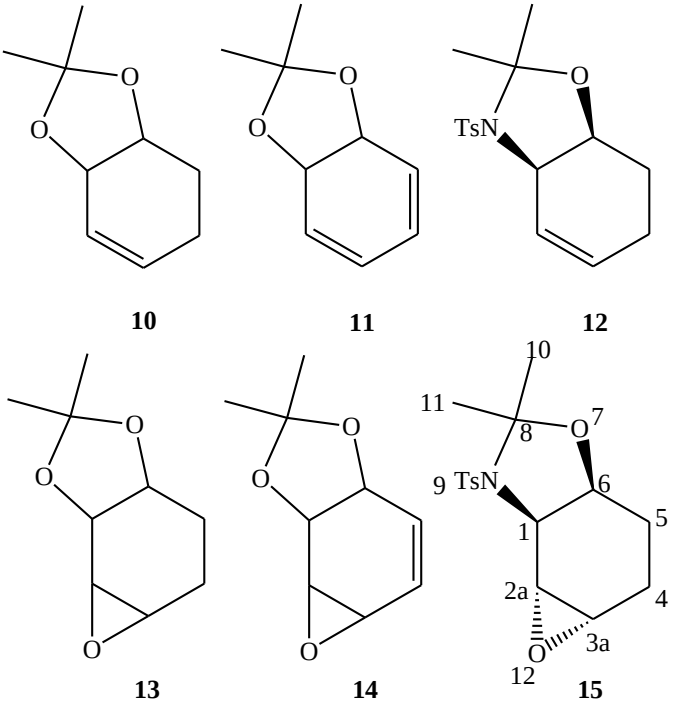
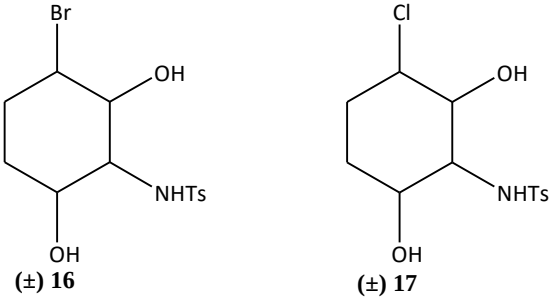


Figure 3

However, there is some variation in the regiochemical outcomes of such ring-opening reactions. As part of a continuing series of studies on the applications of [(*3aR(S),7aS(R)*)]-2,2-dimethyl-3-tosyl-2,3,3a,6,7,7a-hexahydrobenzo[*d*]oxazole (**12**) in chemical synthesis, we examined the regio- and stereo-chemical outcomes of reactions involving BX_3-assisted (X= Br or Cl) ring opening of the mono-epoxide form **15** of compound **12** and realized the synthesis of the *N*-tosyl bromo- (**16**) and *N*-tosyl chloro-dihydroconduramines (**17**).

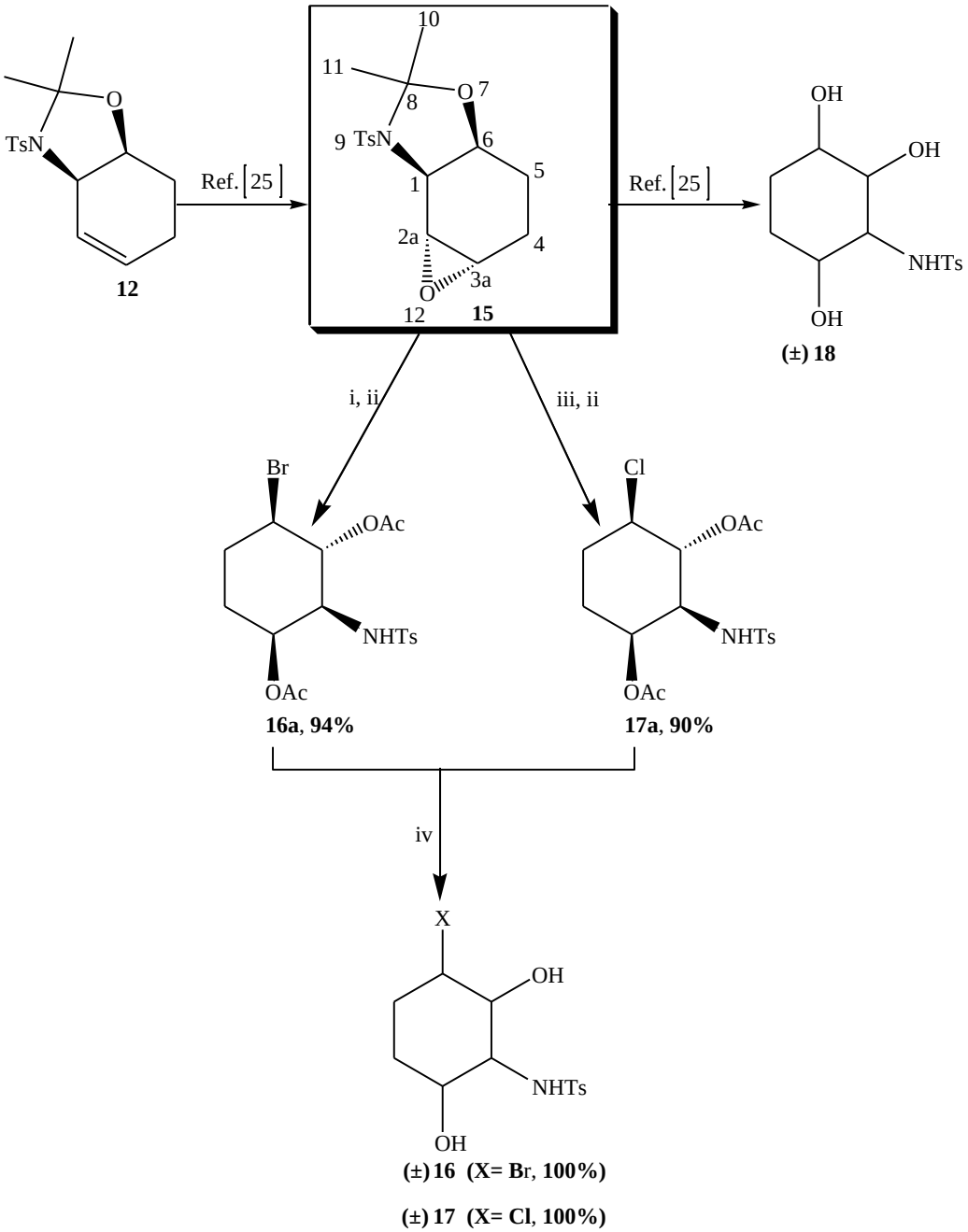


Results and Discussion

First, to synthesize the mono-epoxide **15**, the starting material [(*3aR(S),7aS(R)*)]-2,2-dimethyl-3-tosyl-2,3,3a,6,7,7a-hexahydrobenzo[*d*]oxazole (**12**) was prepared from the photooxygenation reaction of 1,3-

 ©**AUTHOR(S)**

cyclohexadiene as reported in the literature.[25-28] In the epoxidation of oxazolidine **12**, the bicyclic ring is *cis*-fused and the methyl groups of the oxazolidine **12** that point above the plane of the olefin may also force the electrophile to approach from the anti direction.[25,29] Such a directing effect may rationalize the stereochemical outcome of the epoxidation of oxazolidine **12**, which provides **15** as a single isomer. In our previous study, we reported the first acid-mediated epoxide ring opening and subsequent acetonide removal of **15**, which furnished **18** as a single isomer (Scheme 1).[25] In the literature, the Boron tribromide and boron trichloride have been successfully used to cleave ethers since years.[30] For instance, Vogel[31] et al. and Baran[32] et al. showed stereospecific cleavage of the etheric bond using BBr_3.



Scheme 1. (i) BBr_3, CH_2Cl_2, -50 °C, then $NaHCO_3$ and H_2O; (ii) AcCl, CH_2Cl_2, rt., 10 h, 100%; (iii) BCl_3, CH_2Cl_2, 0 °C, then $NaHCO_3$ and H_2O; (iv) MeOH, HCl, 0 °C.

 ©**AUTHOR(S)**

Since the aim of this research was the synthesis of the *N*-tosyl bromo- and *N*-tosyl chloro dihydroconduramines (**16** and **17**) from the BX_3-assisted (X= Br or Cl) ring opening reaction of the mono-epoxide **15**, we followed the same strategy for the synthesis of **16** and **17**. The synthesis steps for halodihydroconduramines **16** and **17** are summarized in Scheme 1. In the current study, BX_3-assisted (X= Br or Cl) ring-opening reactions of the mono-epoxide **15** were carried out at various temperatures and durations. First, we attempted the BBr_3-assisted ring-opening reaction of the mono-epoxide **15**. We treated mono-epoxide **15** with BBr_3 in methylene chloride and then stirred the reaction mixture at -50 °C for 45 minutes. After quenching the reaction with water and chromatographic separation, the reaction mixture was converted into acetate by treatment with AcCl in methylene chloride. In addition, we treated mono-epoxide **15** with BCl_3 in methylene chloride and then stirred the reaction mixture at 0 °C for 70 minutes. After quenching the reaction with water, the reaction mixture was converted into acetate by the treatment with AcCl in methylene chloride. The ^{1}H and ^{13}C NMR results showed that **16a** and **17a** were the main products of the first and second reactions, respectively. In these reactions, the steric and conformational effects of the bicyclic ring system influenced the stereoselectivity of the epoxide opening reaction. Thus, there appears to be no exception, so far, to the rule that BX_3-assisted (X= Br or Cl) ring opening of the mono-epoxide **15** predominantly involves attack at carbon 3a-C. The main products of the first and second reactions were separated chromatographically. Acid-catalyzed hydrolysis of the acetyl groups in **16a** and **17a** provided the *N*-tosyl bromo- and *N*-tosyl chloro dihydroconduramines (**16** and **17**) as single isomers. The *N*-tosyl bromo- and *N*-tosyl chloro- dihydroconduramines (**16** and **17**) were characterized by 2D spectroscopy, namely COSY, NOESY as well as by the ^{1}H and ^{13}C NMR spectra data.

Conclusions

We have reported the synthesis of a new *N*-[(*1S(R),2R(S),3R(S),6S(R)*)-3-bromo-2,6-dihydroxycyclohexyl]-4-methylbenzenesulfonamide (**16**) and *N*-[(*1S(R),2R(S),3R(S),6S(R)*)-3-chloro-2,6-dihydroxycyclohexyl]-4-methylbenzenesulfonamide (**17**) that can be used for various biological studies.

Experimental Section

General. Solvents were purified and dried by the standard procedures before use. Melting points were recorded on a Gallenkamp Hot Stageapparatus. The ^{1}H and ^{13}C NMR spectra were recorded on a 300 (75) MHz Varian spectrometer. Infrared spectra were obtained from Shimatzu Fourier Transform Infrared Spectrophotometer (IR Prestige-21, 200VCE). Column chromatography was performed on silica gel 60 (70-230 mesh). Thin layer chromatography was carried out on Merck 0.2 mm silica gel, 60 F_{254} analytical aluminum plates. Elemental analyses were carried out on a Leco-932 model CHNS analyzer.

Synthesis of the [(*3aR(S),7aS(R)*)]-2,2-dimethyl-3-tosyl-2,3,3a,6,7,7a-hexahydrobenzo[*d*]oxazole (12) and the mono-epoxide 15. These compounds were synthesized from the photooxygenation reaction of 1,3-cyclohexadiene as reported in the literature.[25-28]

 ©**AUTHOR(S)**

***N*-[(*1S(R),2R(S),3R(S),6S(R)*)-3-bromo-2,6-dihydroxycyclohexyl]-4-methylbenzenesulfonamide (16).** Under nitrogen atmosphere, to a stirred solution of the mono-epoxide **15** (0.2 g, 0.62 mmol) in 15 mL of CH_2Cl_2 was added dropwise a solution of BBr_3 (0.1 mL, 1.24 mmol) in 20 mL of CH_2Cl_2 at -50 ^oC over 10 min. After addition was completed, the mixture was stirred at -50 ^oC for 45 min and then at room temperature for 1 h under air atmosphere. To the reaction mixture was added solution (5 mL, saturated) of $NaHCO_3$ and H_2O (0.5 mL). The organic phase was separated. The aqueous phase was additionally extracted with CH_2Cl_2 (3x15 mL). The combined organic phases were dried over Na_2SO_4. Evaporation of the solvent gave the crude product mixture (colorless oil). To a solution of the product mixture in 20 mL of CH_2Cl_2 was added acetyl chloride (0.32 g, 4.1 mmol). The resulting mixture was stirred for 10 h. Removal of the solvent and excess acetyl chloride under reduced pressure (30 ^oC, 25 mm Hg) gave the diacetate crude product (**16a**, colorless oil, quantitative), which was crystallized from CH_2Cl_2-hexane, 3:7, to give (**16a**) as a brown solid (0.18 g, 94%), mp 108-110 ^oC. ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (A part of AB system, d, 2H, *J* 7.9 Hz, aromatic), 7.3 (B part of AB system, d, 2H, J_{AB} 7.6 Hz, aromatic), 7.3 (d, 1H, -NH), 5.16 (m, 1H), 5.01 (m, 1H), 3.83 (m, 1H), 3.44 (m, 1H), 2.42 (s, 3H), 2.15 (m, 1H), 2.11 (s, 3H), 2.02 (m, 1H), 1.83 (s, 3H), 1.6 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.30, 169.95, 143.89, 138.39, 130.03, 127.01, 74.05, 72.32, 57.90, 49.41, 30.01, 28.48, 21.75, 21.29, 20.76. IR (ART) 2776, 1724, 1597, 1483, 1454, 1373, 1323, 1260, 1232, 1152, 1059, 953, 816, 546 $cm.^{-1}$

A stirred solution of **16a** (0.18 g, 0.40 mmol) in 20 mL of methanol was cooled to 0 ^oC. At the given temperature, HCl gas was passed through the solution over 15 min. The reaction flask was closed with a stopper and stirred at room temperature for 10 h. Removal of the solvent, methyl acetate and HCl under reduced pressure (30 ^oC, 25 mm Hg) gave the crude product, which was recrystallized from MeOH-hexane, 4:1, to give *N*-tosyl bromo-dihydroconduramine **16** as a white solid (0.14 g, quantitative), mp 210-211 ^oC. ^1H NMR (300 MHz, CD_3OD) δ 7.61 (A part of AB system, d, 2H, *J* 8.5 Hz, aromatic), 7.15 (B part of AB system, d, 2H, J_{AB} 7.9 Hz, aromatic), 4. 00 (s, 2H, 2xOH), 3.80 (d, 1H, -NH), 3.78 (m, 1H), 3.55 (m, 2H), 2.78 (d, 1H, *J* 9.2 Hz), 2.26 (s, 3H), 2.04 (m, 1H), 1.92 (m, 1H), 1.62 (m, 1H), 1.28 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 143.69, 137.27, 129.71, 127.14, 72.89, 68.08, 61.23, 55.45, 31.03, 29.84, 21.44. IR (ART) 3427, 3198, 2929, 1599, 1464, 1441, 1355, 1297, 1140, 1108, 1087, 810, 571, 457 $cm.^{-1}$ Anal. calcd for $C_{13}H_{18}BrNO_4S$ (364.26): C, 42.87; H, 4.98; N, 3.85; S, 8.80. Found: C, 42.68; H, 5.01; N, 3.87; S, 8.71.

***N*-[(*1S(R),2R(S),3R(S),6S(R)*)-3-chloro-2,6-dihydroxycyclohexyl]-4-methylbenzenesulfonamide (17).** Under nitrogen atmosphere, to a stirred solution of the mono-epoxide **15** (0.2 g, 0.62 mmol) in 15 mL of CH_2Cl_2 was added dropwise 0.1 mL (1.24 mmol) BCl_3 at 0 ^oC. After addition was completed, the mixture was stirred at 0 ^oC for 70 min and then, to the reaction mixture was added solution (5 mL, saturated) of $NaHCO_3$ and H_2O (0.5 mL). The organic phase was separated. The aqueous phase was additionally extracted with CH_2Cl_2 (3x15 mL). The combined organic phases were dried over Na_2SO_4. Evaporation of the solvent gave the crude product mixture (colorless oil). To a solution of the product mixture in 20 mL of CH_2Cl_2 was added acetyl chloride (0.32 g, 4.1 mmol). The resulting mixture was stirred for 12 h. Removal of the solvent and excess acetyl chloride under reduced pressure (30 ^oC, 25 mm Hg) gave the diacetate crude product (**17a**, colorless oil, quantitative), which was crystallized from CH_2Cl_2-hexane, 4:6, to give (**17a**) as a white solid (0.15 g, 90%), mp 186-188 ^oC. ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (A part of AB system, d, 2H, *J* 8.4 Hz, aromatic), 7.27 (B part of AB system, d, 2H, J_{AB} 8.0 Hz, aromatic), 7.25 (d, 1H, -NH), 5.18-4.98 (m, 2H), 3.82 (m,1H), 3.5 (m, 1H), 2.42 (s, 3H, $-CH_3$), 2.22 (s, 3H, -OAc), 2.02 (m, 1H, $-CH_2-$), 1.83 (s, 3H, -OAc), 1.82 (m, 1H, $-CH_2-$), 1.62 (m, 2H, $-CH_2-$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.35, 169.93, 143.85, 138.42, 130.03, 127.02, 74.03, 72.15, 58.84, 57.73, 29.19, 27.25, 21.73, 21.26,

 ©**AUTHOR(S)**

20.72. IR (ART) 3259, 2962, 1726, 1598, 1555, 1455, 1375, 1334, 1322, 1224, 1186, 1159, 1092, 1049, 1020, 915, 813, 663, 572 cm.$^{-1}$

A stirred solution of **17a** (0.15 g, 0.37 mmol) in 20 mL of methanol was cooled to 0 ^{o}C. At the given temperature, HCl gas was passed through the solution over 15 min. The reaction flask was closed with a stopper and stirred at room temperature for 11 h. Removal of the solvent, methyl acetate and HCl under reduced pressure (30 ^{o}C, 25 mm Hg) gave the crude product, which was recrystallized from MeOH-hexane, 8:2, to give *N*-tosyl chloro-dihydroconduramine **17** as a white solid (0.12 g, quantitative), mp 226-228 ^{o}C. ^{1}H NMR (300 MHz, CD_3OD) δ 7.66 (A part of AB system, d, 2H, *J* 8.0 Hz, aromatic), 7.20 (B part of AB system, d, 2H, J_{AB} 7.9 Hz, aromatic), 3.85 (d, 1H, -NH), 3.83 (s, 2H, -OH), 3.57-3.37 (m, 3H), 2.82 (d, 1H, *J* 7.8 Hz), 2.41 (s, 3H, $-CH_3$), 1.81 (dd, 2H, *J* 14.7, 3.7 Hz), 1.75 (m, 1H), 1.32 (t, 1H, *J* 14.9 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 143.66, 137.31, 129.67, 127.08, 72.82, 67.98, 63.16, 61.16, 29.78, 28.86, 21.36. IR (ART) 3417, 3194, 2922, 2534, 1599, 1442, 1296, 1138, 1091, 955, 811, 518 cm.$^{-1}$ Anal. calcd for $C_{13}H_{18}ClNO_4S$ (319.8): C, 48.82; H, 5.67; N, 4.38; S, 10.03. Found: C, 48.84; H, 5.68; N, 4.29; S, 10.12.

Acknowledgements

The authors greatly acknowledge the Scientific and Technical Research Council of Turkey (TUBITAK) for financial support (Project No: 106T374).

References

1. Posternak, T. *The phosphoric esters of the cyclitols. The cyclitols*; Holden-Day: San Fransisco, CA, 1965(semposium).
2. Balci, M.; Sütbeyaz, Y.; Seçen, H. *Tetrahedron* **1990**, 46, 3715. https://doi.org/10.1016/S0040-4020(01)90509-5
3. Hudlicky, T.; Cebulak, M., *Cyclitols and Their Derivative. A Handbook of Physical, Spectral and Synthetic Data;* VCH Weinheim: New York, Cambridge, **1993**. https://doi.org/10.1002/pauz.19940230116
4. Hudlicky, T.; Entwistle, D.A.; Pitzer, K.K.; Thorpe, A. J., *Chem. Rev.* **1996**, 96, 1195. https://doi.org/10.1021/cr9403300
5. Gültekin, M.S.; Çelik, M.; Balci, M. *Curr. Org. Chem.* **2004**, 8, 1159. https://doi.org/10.2174/1385272043370069
6. Kurbanoğlu, N.I.; Celik, M.; Kilic, H.; Alp, C.; Ertan, S.; Balci, M. *Tetrahedron* **2010**, 66, 3485. https://doi.org/10.1016/j.tet.2010.03.028
7. Pandey, G.; Tiwari, N. K.; Puranik, G. V. *Org. Lett.* **2008**, 10, 3611. https://doi.org/10.1021/ol801381t
8. Hudlicky, T.; Olivio, F. H. *Tetrahedron Lett.* **1991**, 32, 6077. https://doi.org/10.1016/0040-4039(91)80757-W
9. Hesegawa, A.; Nishimura, D.; Kurokawa, T.; Nakajima, M. *Agric. and Biol. Chem.* **1972**, 36, 1773. https://doi.org/10.1271/bbb1961.36.1773
10. Kübler, K. *Arch. Pharm. (Weinheim).* **1908**, 246, 620.

 ©**AUTHOR(S)**

https://hdl.handle.net/10803/116082
11. Dangschat, G.; Fisher, H. O. L. *Naturwissenschaften* **1939**, 27, 756. https://doi.org/10.1002/cber.19320650621
12. Dangschat, G.; Fischer, H. O. L.; MacDonald, D. L. *Carbohydr. Res.* **1987**, 164, 343. https://doi.org/10.1016/0008-6215(87)80140-4
13. McCasland, G. E.; Naumann, M. O.; Durham, L. J. *J. Org. Chem.* **1968**, 33, 4220. https://doi.org/10.1021/jo01275a043
14. Salamci, E.; Secen, H.; Sutbeyaz, Y.; Balci, M. *J. Org. Chem.* **1997**, 3263, 2453. https://doi.org/10.1021/jo962092+
15. Aydın, G.; Savran, T.; Aktaş, F.; Baran, A.; Balci, M. *Org. Biomol. Chem.* **2013**, 11, 1511. https://doi.org/10.1039/C3OB26909D
16. Kılbaş, B.; Balci, M. *Tetrahedron* **2011**, 67, 2355. https://doi.org/10.1016/j.tet.2011.01.012
17. Baran, A.; Balci, M. *J. Org. Chem.* **2009**, 74, 88. https://doi.org/10.1021/jo801344f
18. Carless, H. A. J. *Tetrahedron*: *Asymmetry*, **1992**, 3, 795. https://doi.org/10.1016/S0957-4166(00)82174-6
19. Hudlicky, T.; Thorpe, A. J. *Chem. Commun.*, **1996**, 1993. https://doi.org/10.1039/CC9960001993
20. Banwell, M. G.; Haddad, N.; Hudlicky, T.; Nugent, T. C.; Mackay, M. F.; Richards, S. L. *J. Chem. Soc., Perkin Trans.* **1997**, 1, 1779. https://doi.org/10.1039/A700733G
21. Baran, A.; Kazaz, C.; Seçen, H. *Tetrahedron,* **2004**, 60, 861. https://doi.org/10.1016/j.tet.2003.11.054
22. Hudlicky, T.; Price, J. D.; Rulin F.; Tsunoda, T. *J. Am. Chem. Soc*., **1990**, 112, 9439. https://doi.org/10.1021/ja00181a081
23. Hudlicky, T.; Rouden, J.; Luna, H.; Allen, S. *J. Am. Chem. Soc*., **1994**, 116, 5099. https://doi.org/10.1021/ja00091a011
24. Koreeda, M.; Gapalaswamy, R. *J. Am. Chem. Soc.,* **1995**, 117, 10595. https://doi.org/10.1021/ja00147a031
25. Kurbanoglu, N.I.; Besoluk, S.; Zengin, M. *ARKIVOC*, **2010**, X, 77. https://doi.org/10.3998/ark.5550190.0011.a07
26. Balci, M. *Chem. Rev*. **1981**, 81, 91. https://doi.org/10.1021/cr00041a005
27. Kurbanoğlu, N.İ. *J. Iran Chem. Soc*., **2017**, 14, 95. https://doi.org/10.1007/s1373
28. Trost, B. M.; van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992,** 114, 9327. https://doi.org/10.1021/ja00050a013
29. Angelaud, A.; Babot, O.; Charvat, T.; Landais, Y. *J. Org. Chem.* **1999**, 64, 9613. https://doi.org/10.1021/jo991225z
30. Bhatt, M. V.; Kulkarni, S. U. *Synthesis,* **1983**, 249. https://doi.org/10.1055/s-1983-30301
31. Jotterand, N.; Vogel, P.; Schenk, K. *Helv. Chim. Acta*, **1999**, 82, 821.

 ©**AUTHOR(S)**

https://doi.org/10.1002/(SICI)1522-2675(19990609)82:6<821::AID-HLCA821>3.0.CO;2-K
32. Baran, A.; Kazaz, C.; Seçen, H.; Sütbeyaz, Y. *Tetrehedron* **2003**, 59, 3643. https://doi.org/10.1016/S0040-4020(03)00510-6

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/)