Résumé

Les deux composés (±)-(1,3,2,4)-1,2,3-tri-O-acétyl-4-bromo-5-cyclohexène-1,2,3-triols 7 et 8 ont été synthétisés par réaction du HBr sur le composé tétracetate conduritol-B selon les données de la littérature [1]. Les produits obtenus sont séparés, pour la première fois, purifiés et caractérisés. La réaction de ces derniers par le triphényle phosphine dans le THF anhydre conduit aux amines (±)-(1, 3/2, 4)-4-amino-5-cyclohexène-1,2,3-triol 6 et (±)-(1,3,2,4)-1,2,3-tri-O-Acétyle-4-amino-5-cyclohexène-1,2,3-triol 8. Ce dernier est obtenu par un auto-réarrangement interne du composé; le transfert du groupement acétyl de l’atome d’oxygène vers l’atome d’azote conduit au produit (±)-(1,3,2,4)-4-amino-5-cyclohexène-1,2,3-triol 8. L’acétylation du composé 11 à l’aide de l’acide acétique anhydride conduit à la formation de (±)-(1, 3, 2, 4)-1,2,3-tri-O-acétyl-4-acetamido-5-cyclohexène-1,2,3-triols 12 qui donne par oxydation le (±)-1-Acétamido-2,3-anhydro-4,5,6-tri-O-acétyl-1-deoxy-myo-inositol 13.

Mots clés: Azide-conduritol-B; Deoxy-myo-Inositol; Synthèse; O-N acyle migration; 1H-NMR.

Abstract

(±)-(1,3,2,4) - and (±)-(1,3,4,2) -1, 2, 3-tri-O-acetylated-4-bromo-5-cyclohexene-1,2,3-triols 7 and 8 have been prepared by treating conduritol-B-tetraacetate 1 with HBr according to literature [1], and isolated in pure state and characterised. Treatment of these bromides with tri-n-butylammonium azide yielded the corresponding amines 6 and 8 respectively. Reducing these amines with triphenyl phosphine in dry THF gave the corresponding 1H-NMR. 

Keywords: Azido-conduritol-B; Deoxy-myo-Inositol; Synthesis; O-N acyl migration; 1H-NMR.

Most of the conduritols and their derivatives act as inhibitors of D-glycosidases and almost all of the synthetic and inhibition works have done on stereoisomers and/or racemic mixtures [1→4], only few enantiomeric controlled and pure stereoselective syntheses have been reported [5].

The stereocontrolled synthesis, the separation of pure isomers and the determination of exact configuration of each isomer are of great importance to the biological work.

The following work describes the synthesis of (±)-1-acetamido-2, 3-anhydro-1, 5, 6-tri-O-acetylated-1-deoxy-myo-inositol 13 based on purely separated and characterised (±)-(1, 3, 4, 2)-1, 2, 3-tri-O-acetyl-4-bromo-5-cyclohexene-1, 2, 3-triols 8 and (±)-(1, 3, 2, 4)-1, 2, 3-tri-O-acetyl-4-azido-5-cyclohexene-1, 2, 3-triols 7 (see scheme 1).

RESULTS AND DISCUSSION

The reaction of conduritol-B-tetraacetate 1 with hydrobromic/acetic acids mixture has received a lot of attention but the results reported were...
rather contradictory concerning the percentages of yield of the monobromo conduritols resulted by this method (see ref., 1a and 2 particularly).

The treatment of conduritol-B-tetraacetate \( I \) with mixtures of HBr/HOAc of different concentrations 20% and 30% has shown that 68% of \( I \) has been converted into a mixture of dibromo-diacetates \( 2 \), monobromo-triacetates \( 3 \) (3.5%) and \( 4 \) (42.5%) which was separated by column chromatography. The high percentage of inversion of configuration at C4 (45%) in reaction of \( I \) with hydrobromic acid in
acetic acid is probably due to SN2 reaction and some SN1 reaction enhanced with the adjacent double bond and acetoxy group at C3.

The $^1$H NMR spectrum [see table 1] of the monobromide of Rf 0.28 showed a signal ddd at $\delta$ 4.66 ppm for H-4 with coupling constant $J_{3,4}$ of magnitude 8.25 Hz and $J_{4,5}$ of 3.5 Hz which indicates that H-4 and H-3 are pseudo diaxially disposed and therefore structure 3 was assigned to it. While the H-4 signal of the less mobile monobromide of Rf 0.20 appeared as dd at $\delta$ 4.86 ppm with a coupling constant $J_{3,4}$ = 4.5 Hz which indicated that C-4 must have the inverted configuration which is consistent with structure 4 [1]. The acetates groups of compounds 2-4 appeared as three singlets between 2.01—2.15 ppm.

Having ($\pm$)-(1,3, 4/2)-1, 2, 3-tri-O-acetyl-4-bromo-5-cyclohexene-1, 2, 3-triol 4 of Rf 0.20 being separated in pure state it was treated with freshly prepared tetra-n-butyl ammonium azide in methylene chloride at room temperature [6]. The result was a single product as indicated by TLC, Rf 0.19. $^1$H NMR spectrum of this azide [see table 1] has shown a signal at $\delta$ 4.18 ppm as ddd with coupling constant $J_{3,4}$ of the magnitude 7.5 Hz and $J_{4,5}$ = 2.5 Hz. This suggests that C4 has been inverted in configuration during the reaction and H-4 and H-3 are now diaxially oriented as in structure 7. Similarly when the ($\pm$)– (1,3/2,4)-1, 2, 3-tri-O-acetyl-4-bromo-5-cyclohexene-1,2,3-triol 3 was treated with tetra-n-butylamminum azide it gave the azide 5 which undergone an inversion in configuration.

Scheme 1: Synthesis pathway of 13 from conduritol-B-tetraacetate 1.
Table 1: 

<table>
<thead>
<tr>
<th>Compound</th>
<th>H-1</th>
<th>H-2</th>
<th>H-3</th>
<th>H-4</th>
<th>H-5</th>
<th>H-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Rf 0.39</td>
<td>5.59 (dd)</td>
<td>5.34 (dd)</td>
<td>overlapped</td>
<td>5.59 (dd)</td>
<td>5.59 overlapped</td>
<td>5.59 overlapped</td>
</tr>
<tr>
<td>3 Rf 0.28</td>
<td></td>
<td>5.63 (m)</td>
<td>overlapped</td>
<td>5.19 (dd)</td>
<td>5.48 (dd)</td>
<td>4.66 (dd)</td>
</tr>
<tr>
<td>3.5 %</td>
<td></td>
<td></td>
<td>with H-5</td>
<td>J1,2=8 Hz</td>
<td>J2,3=10.5 Hz</td>
<td>J4,5=2.25 Hz</td>
</tr>
<tr>
<td>4 Rf 0.20</td>
<td>5.627 (m)</td>
<td>overlapped</td>
<td>5.122 (dd)</td>
<td>4.935 (dd)</td>
<td>4.86 (dd)</td>
<td>6.033 (dd)</td>
</tr>
<tr>
<td>42.5 %</td>
<td></td>
<td></td>
<td></td>
<td>J2,3=4.5 Hz</td>
<td>J2,3=4.5 Hz</td>
<td>J4,5=7.5 Hz</td>
</tr>
<tr>
<td>5 Rf 0.24</td>
<td>5.48 (m)</td>
<td>overlapped</td>
<td>5.112 (dd)</td>
<td>4.35 (t)</td>
<td>5.79 (m)</td>
<td>5.862 (dd)</td>
</tr>
<tr>
<td>7 Rf 0.19</td>
<td>5.56 (ddd)</td>
<td>5.26 (m)</td>
<td>overlapped</td>
<td>4.18 (ddd)</td>
<td>5.75 (m)</td>
<td>5.862 (dd)</td>
</tr>
<tr>
<td></td>
<td>J1,2=7.5 Hz</td>
<td></td>
<td></td>
<td>J2,3=7.5 Hz</td>
<td>J4,5=2.5 Hz</td>
<td>J4,5=10.5 Hz</td>
</tr>
</tbody>
</table>

ADIL A. OTHMAN, ODAH M. AL-ZAMELY

EXPERIMENTAL

TLC was carried out on DC-Alufolian Kiesel- gel 60, Art.5553 produced by Merk. 1H NMR spectra were recorded (internal Me4Si) in CDCl3 at 300 MHz unless stated otherwise. Melting points were recorded by Büch; 510 melting point apparatus and they are uncorrected.

REACTION OF (±)-CONDURITOL-B-TETRAACETATE 1 WITH HYDROBROMIC ACID:

(±)-Conduritol-B-tetraacetate 1 (200 mg, 0.6 mmole) was dissolved in hydrobromic acid /acetic acid 30 % (1.5 ml,10 mmole) and the reaction mixture was set aside in dark at room temperature for 18 hours. Proceeding of reaction was followed by TLC eluted with CCl4/MeOH 9:1, (detected by alkaline potassium permanganate). Four spots were developed during the time of reaction of Rf: 0.64; 0.59; 0.54 and 0.42. Toluene (1ml) was added followed by gradual addition of solid NaHCO3 to the reaction mixture aided with magnetic stirring until evolution of gases seized. Saturated solution of NaHCO3 was then added dropwise with continuous stirring to neutrality. Two layers were separated and the toluene layer was then washed with brine, then dried on anhydrous MgSO4, filtered off to give clear yellow filtrate. The filtrate was evaporated to dryness on a warm water bath (50°) to give a brown syrup (162 mg, 81 %).

SEPARATION OF (±)-1,4- DIBROMO-2, 3-DI-O-ACETYL -CONDURITOLS 2 ; (±)-(1,3,2,4)-1,2,3-TRI-O-ACETYL-4-ACETOXY-CYCLOHEXENE-1,2,3-TRIOL 3 and (±)-(1,3,4,2)-1,2,3-TRI-O-ACETYL-4-ACETOXY-CYCLOHEXENE-1,2,3-TRIOL 4:

The crude reaction mixture of bromoconduritols 2,3 and 4 (0.85 g) was adsorbed into column of silica gel of the kind (TLC 10-40 µm) (302 g) packing and elution were done by aid of pumping air from above the column and connecting the column from below to a moderate vacuum. Column was eluted with n-hexane/ EtOAc 3:7. small fractions were collected (1ml every minute). Six groups of fractions were collected based on Rf values:

Fraction one of Rf 0.39 for (±)-1,4Dibromo-2, 3-di-O-acetyl-Conduritols 2 : (117 mg, 11.8 %) as colorless crystalline, m.p. 170-175°C recrystallized from methanol-hexane to give colorless crystals m.p., 170-173 °C, δmax at C4 (J3,4=4.5 Hz) similar to 4, J3,4=4.5 Hz.

Reduction of the azide 5 with triphenylphosphine [6] gave the amine 6. IR spectrum showed a broad band at 3450 cm⁻¹ attributed to free and bonded N-H and an absorption at 1740 cm⁻¹ for the acetate groups. NMR spectrum showed three single signals at 8 2.02 ; 2.1; 2.05 ppm for 3×OCOCH3. Reduction of the azide 7 with triphenylphosphine in a similar manner, TLC has shown the diminishing of azide spot Rf 0.19 but giving rise to a single spot of Rf 0.5 which did not respond to ninhydrine spray. Diminishing of azide spot Rf 0.19 but giving rise to a single spot of Rf 0.5 which did not respond to ninhydrine spray. Diminishing of azide spot Rf 0.19 but giving rise to a single spot of Rf 0.5 which did not respond to ninhydrine spray.

IR showed weak and broad bands absorptions at region 4000-3500 cm⁻¹ for free and bonded OH and NH and medium absorptions at 1730 and 1680 cm⁻¹ for CO and CON stretches respectively. These observations suggest that the product 8 might have converted to 9 by spontaneous O-N acetyl migration [7]. To avoid such migration, the acetate groups of the azide 7 have been removed by alkaline hydrolysis to give rise to the azide 10 free of acetates. The latter was reduced with triphenylphosphine to give the corresponding amine 11. Acetylation of 11 with acetic anhydride gave tri-O-acetyl-4-acetamido conduritol-B 12.

Epoxidation of the : (±)-(1,3,4/2)-1,2,3 - tri-O - acetyl - 4 - acetamido - 5 - cyclohexene - 1,2,3 - triol 12 with metalchloroperbenzoic acid [8,9] gave a single product. IR spectrum showed the following characteristic bands at γ max 1725cm⁻¹ for acetate groups; 1670cm⁻¹ for acetamido group and 850cm⁻¹ for the epoxide [10]. 1H NMR spectrum showed one singlet signal at 1.8 ppm integrated for 3H attributed to CH3 of acetamido group and three single signals integrated for 9H at δ 2.20; 2.25; 2.27 ppm for three acetate groups and a triplet at 3.2 ppm for one proton attributed to H2 based on J2,1 and J2,3 = 4.3 Hz and at 3.65 ppm as multiplet for one proton attributed to H3. This suggested that the direction of epoxidation was taken place almost entirely cis to the acetamido group.
1740 cm$^{-1}$ (Ac), $^1$H NMR (see table1). (Found: C, 34.54 %; H, 3.57 %. Calculated for C$_{10}$H$_{12}$O$_4$: C, 34.74 %; H, 3.40 %). 

Fraction two of Rf 0.39 and 0.28 attributed to a mixture of compounds 2 + 3 (3.4 mg, ~ 3.4 %) as a brownish syrup, $\gamma$max 1740 cm$^{-1}$.

Fraction three of Rf 0.28 attributed to (±) –(1,3, 4/2)-1, 2, 3-tri-O-acetyl-4-bromo-5-cyclohexene-1, 2, 3-triol 3 (34.7 mg, 3.5 %) as colorless crystalline product m.p. 65-68°C. IR has shown a relatively strong absorption at $\gamma$max 1740 cm$^{-1}$. $^1$H NMR (see table1). (Found: C, 42.83 %; H, 4.45 %. Calc. for C$_{12}$H$_{15}$O$_6$: C, 43.01 %; H, 4.51 %).

Fraction four of Rf 0.28 and 0.2 attributed to the mixture of compounds 3 and 4 (65.7 mg, 6.65 %) as a brownish solid recrystallised from n-hexane to give colorless crystalline (53.2 mg, 6.5 %) mp 76-81°C. IR, max 1740 cm$^{-1}$. 1H NMR (see table1). (Found: C, 43.51 %; H, 4.69 %. Calc. for C$_{12}$H$_{15}$O$_6$: C, 43.01 %; H, 4.51 %).

Fraction five of Rf 0.2 attributed to (±) –(1,3, 4/2)-1, 2, 3-tri-O-acetyl-4-bromo-5-cyclohexene-1, 2, 3-triol 4 (420 mg, 42.5 %) as colorless crystalline m.p.120-123°C, recrystallised from methanol/n-hexane to give colorless crystalline solid m.p., 120°C. IR has shown an absorption at $\gamma$max 1740 cm$^{-1}$ (Ac) in a similar intensity as for 3. $^1$HNMR (see table1). (Found: C, 42.82 %; H, 4.51 %. Calc. for C$_{12}$H$_{15}$O$_6$: C, 43.01 %; H, 4.51 %).

Fraction six of Rf 0.13 for starting conduritol-B-tetraacetate 1 (200 mg, 23 %) colorless crystalline solid m.p. 95,5°C IR, $\gamma$max 1740 cm$^{-1}$ (Ac) very strong.

(±)-(1,3,2,4)-1,2,3-TRI-O-ACETYL-4-AZIDO-5-CYCLOHEXENE-1, 2, 3-TRIOL 7:

Compound 4 (60 mg, 0.2 mmole) was added to a solution of freshly prepared tetra-n-butylammonium azide (1.23 g, 4.5 mmole) in methylene chloride (1 ml) and set aside at room temperature until TLC (eluted with n-hexane/EtOAc 3:7) showed the development of new spot of Rf 0.24 at the expense of disappearing of 4. Water (10 ml) was added and the mixture was extracted with ether (20 ml). The ethereal layer was dried over anhydrous MgSO$_4$, filtered and evaporated to dryness to yield white crystalline solid (47 mg) of a mixture of (±) –(1,3, 4/2)-tri-O-acetyl-4-amino-5-cyclohexene-1, 2, 3-triol 6 and some Ph$_3$P. The mixture was separated by column chromatography packed with silica gel (10-40µm for TLC) in the ratio of 1:350 (reaction mixture : silica gel) eluted with benzene/Methanol 7:3 using moderate pressure to aid flow of solution. Ph$_3$P was collected as a white crystalline (14.6 mg) and (±) –(1,3, 4/2)-tri-O-acetyl-4-amino-5-cyclohexene-1, 2, 3-triol 6 as white crystalline (13 mg; 65 %) m.p. 76-79°C. IR spectrum showed the following characteristic bands at 3450 cm$^{-1}$ (broad) for (free and bonded NH$_2$), 1740 cm$^{-1}$ for (OAc).

$^1$HNMR (90 MHz) spectrum showed: 2.02; 2.05; 2.15 ppm, 3s(3µmol), 5.22 ppm, 4s(4µmol). 

(±)-(1,3,4/2)-1,2,3-TRI-O-ACETYL-4-AMINO-5-CYCLOHEXENE-1, 2, 3-TRIOL 6:

The azide 5 (20 mg, 0.07 mmole) was dissolved into dry THF (2 ml), Ph$_3$P (60 mg, 0.23 mmole) was added and the reaction mixture was allowed to stand at room temperature. The progress of the reaction was monitored by TLC and IR. Each sample of TLC was spotted on two plates, both were eluted with toluene/methanol 7:3, one plate was detected as normal with alkaline potassium permanganate to show the diminishing of the spot of Rf 0.19 responsible for the starting azide 5. The second plate was detected with ninhydrin spray to show the development of the amine 6 as a pink spot of Rf 0.22. The reaction can be also followed by IR spectroscopy by means of taking one drop sample directly from the reaction mixture and spotting it on a NaCl disc. IR spectra showed the growing absorption band at 1660 cm$^{-1}$ for N$_3$P of the complex formation while the band at 2100 cm$^{-1}$ for N$_3$ was diminishing. When all azide 5 was consumed, water (2 drops) was added and the reaction mixture was heated on a warm water bath at 50°C for 12 hours to break down the reaction complex. Water (5 ml) was added and the mixture was extracted several times with ether. The etheral extracts were combined and dried over anhydrous MgSO$_4$, then filtered and evaporated to dryness to yield white crystalline solid (47 mg) of a mixture of (±) –(1,3, 4/2)-tri-O-acetyl-4-amino-5-cyclohexene-1, 2, 3-triol 6 and some Ph$_3$P. The mixture was separated by column chromatography packed with silica gel (10-40µm for TLC) in the ratio of 1:350 (reaction mixture : silica gel) eluted with benzene/Methanol 7:3 using moderate pressure to aid flow of solution. Ph$_3$P was collected as a white crystalline (14.6 mg) and (±) –(1,3, 4/2)-tri-O-acetyl-4-amino-5-cyclohexene-1, 2, 3-triol 6 as white crystalline (13 mg; 65 %) m.p. 76-79°C. IR spectrum showed the following characteristic bands at 3450 cm$^{-1}$ (broad) for (free and bonded NH$_2$), 1740 cm$^{-1}$ for (OAc).

$^1$HNMR (90 MHz) spectrum showed: 2.02; 2.05; 2.15 ppm, 3s(3µmol), 5.22 ppm, 4s(4µmol).

(±)-(1,3,4/2)-1,2,3-TRI-O-ACETYL-4-AZIDO-5-CYCLOHEXENE-1, 2, 3-TRIOL 8 and (±) –(1,3, 4/2)-1,2-DI-O-ACETAMIDO-5-CYCLOHEXENE-1, 2, 3-TRIOL 9:

The azide 7 (20mg, 0.07 mmole) was treated with Ph$_3$P as above. Separation achieved by column chromatography to give a white crystalline material (12mg) m.p. 136-140°C, attributed to (±) –(1,3,2,4)-1, 2, 3-tri-O-acetyl-4-amino-5-cyclohexene-1, 2, 3-triol 8 and (±) –(1,3, 4/2)-1, 2, -di-O-acetyl-4-acetamido-5-cyclohexene-1, 2, 3-triol 9 which did not react towards ninhydrin spray.

IR spectrum has shown a weak broad absorption at 4000-3500 cm$^{-1}$ (free and bonded OH and NH); 1730 cm$^{-1}$ (OAc) and 1680 cm$^{-1}$ (N-Ac).

---

* Caution: Several cases of explosions had occurred during evaporation to dryness under vacuum on a warm water bath.
(±)-(1,3,2,4)-4-AMINO-5-CYCLOHEXENE-1,2-3-TRIOIL 10:  
The azide 7 (64mg, 0.22 mmole) was dissolved in methanol (3 ml). Two drops of methanolic solution of sodium methoxide were added and the reaction mixture allowed to stand in dark at room temperature for 12 hours. TLC eluted with n-butanol/H2O/HOAc 4:1:1 showed the development of one spot Rf 0.41. Few drops of diluted acetic acid in methanol were added until neutralization. The mixture was evaporated to dryness to give white crystalline solid. THF (5 ml) was added to dissolve the organic material and filtered off. The filtrate dried over anhydrous MgSO4, filtered and evaporated to dryness under vacuum. Chloroform (2 ml) were added. The reaction mixture was heated on a warm water bath at 50 °C for 48 hours. The proceeding of the reaction was monitored by TLC and IR as described earlier in preparation of 11.

Water (10 drops) was added and the reaction mixture allowed to stand at room temperature, m.p. 133-135 °C. IR spectrum showed bands at 1725 cm -1 (C=O-acetate) and at 1670 cm -1 (C=O-amide). 1H NMR (90MHz), 3.2 t(1H,H2,J 2,1= 4.3 Hz, J 2,3= 4.3 Hz), 3.65 m (H-6). (Found: C, 41.93 %; H,5.35 %.; N, 24.66 %.

Calc. for C3H6N3O3: C, 49.66 %; H, 7.59 %, N, 19.65 %.

Notes: 
1: (±)(1,3,2,4)-4-AMINO-5-CYCLOHEXENE-1,2-3-TRIOIL 8:  
The azide 7 (64mg, 0.22 mmole) was dissolved in anhydrous THF; Ph3P (600 mg, 2.3 mmole) was added and stirred for 5 min. The reaction mixture was filtered off, and the solvent evaporated under vacuum to give a syrup. The mixture was dissolved in anhydrous acetic anhydride (9ml), anhydrous pyridine (2drops) and anhydrous THF; Ph3P (600 mg, 2.3 mmole) was added and the mixture was allowed to stand at room temperature. The reaction mixture allowed to stand in dark at room temperature for 12 hours. Aqueous saturated solution of NaHCO3 (25 ml) was added, the mixture was heated under reflux in darkness for two hours. Aqueous saturated solution of Na2S2O3.5H2O, then washed again with NaHCO3 followed with water. The organic layer was washed with an aqueous saturated solution of Na2SO3.H2O, then washed again with NaHCO3 followed with water. The organic layer dried over anhydrous MgSO4, filtered and evaporated to dryness to give semi solid which extracted with ether; The ether extract showed one spot on TLC eluted with toluene/McOH 7:3, Rf 0.35 which was detected by molybdate-phosphoric acid. The ether extract dried over anhydrous MgSO4, filtered and evaporated to dryness to give semi solid (±) –1-acetamido-2,3-anhydro-4,5,6-tri-O-acetyl-1-deoxy-myoo-inositol 13 (12 mg),crystallized by standing at room temperature, m.p. 148-154 °C. IR γmax 1725 cm-1 (OAc), 1670 cm-1 (N-Ac) and 850 cm-1 (epoxide). 1H NMR (90MHz), 3.2 t(1H,H2,J 2,1= 4.3 Hz, J 2,3= 4.3 Hz),3.65 m (1H,H3),2.20, 2.25, 2.27 3s(3xO-COCH3); 1.8s (N-COCH3). Anal. Found: C, 50.83%; H, 5.55 %; N, 4.46 %.

Calc. for C14H19NO8: C, 51.06 %; H, 5.77 %, N, 4.26 %.

REFERENCES


88