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GRAPHICAL ABSTRACT

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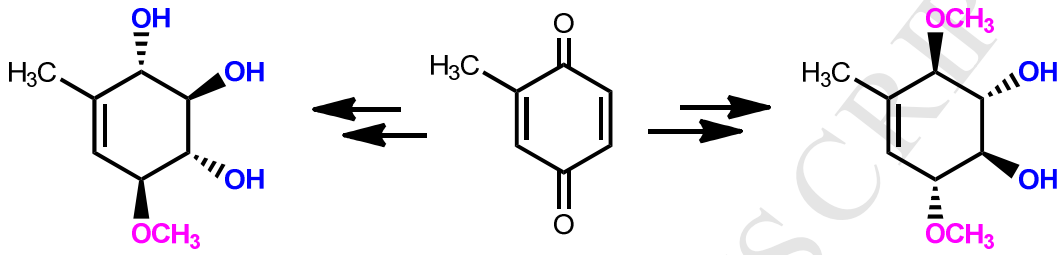

Stereospecific synthesis of novel methyl-substituted mono- and di-methoxy conduritols

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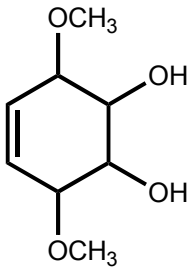
Abstract

Methyl-monomethoxy conduritol-B and methyl-dimethoxy conduritol-B were synthesized starting from 2-methylbenzo-1,4-quinone. Bromination of 2-methylbenzo-1,4-quinone was followed by the reduction of the carbonyl groups with $NaBH_4$ to give a dioldibromo compound. Methyl-dimethoxy conduritol-B was synthesized from the reaction of the dioldibromo compound with CH_3ONa, followed by acetylation with Ac_2O-pyridine to obtain methyl-dimethoxy diacetate. On the other hand, acetylation of the methyl-dioldibromo compound followed by reaction with LiOH gave a monoepoxide compound stereoselectively. The reaction of the epoxide with H^+/Ac_2O afforded the monobromo triacetate. Controlled reaction of monobromo-triacetate with CH_3ONa in MeOH furnished the desired new methyl-monomethoxy conduritol-B. The structures of all synthesized compounds were characterized by spectroscopic methods.

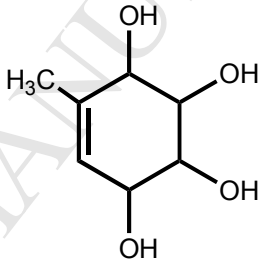
Keywords: *Conduritol, Methyl-methoxy conduritol-B, Methyl-conduritol*

1. Introduction

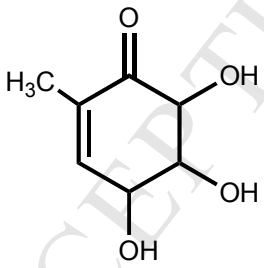
Cyclitols, their derivatives and analogs have continued to attract the attention of chemists and biologists due to their involvement in various biological processes.[1] Conduritols and their epoxide derivatives possess interesting biological properties, epoxyconduritols and aminoconduritols act as inhibitors of glycosidases.[2] Recently, dimethoxy conduritols have been synthesized from some natural compounds.[3-5] Among these compounds, (+)-1,4-dimethoxy conduritol-B and –F were enantioselectively synthesized starting from D-sorbitol.[4] In connection with the conduritols, vinylic-substituted conduritols (with -CH_3, -Ph, and halo-substituents) have also gained importance over the last decade.[6-11]



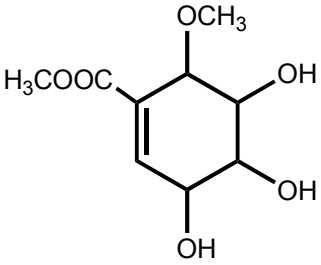
1,4-Dimethoxy conduritol



Methyl-substituted conduritol



Gabosine



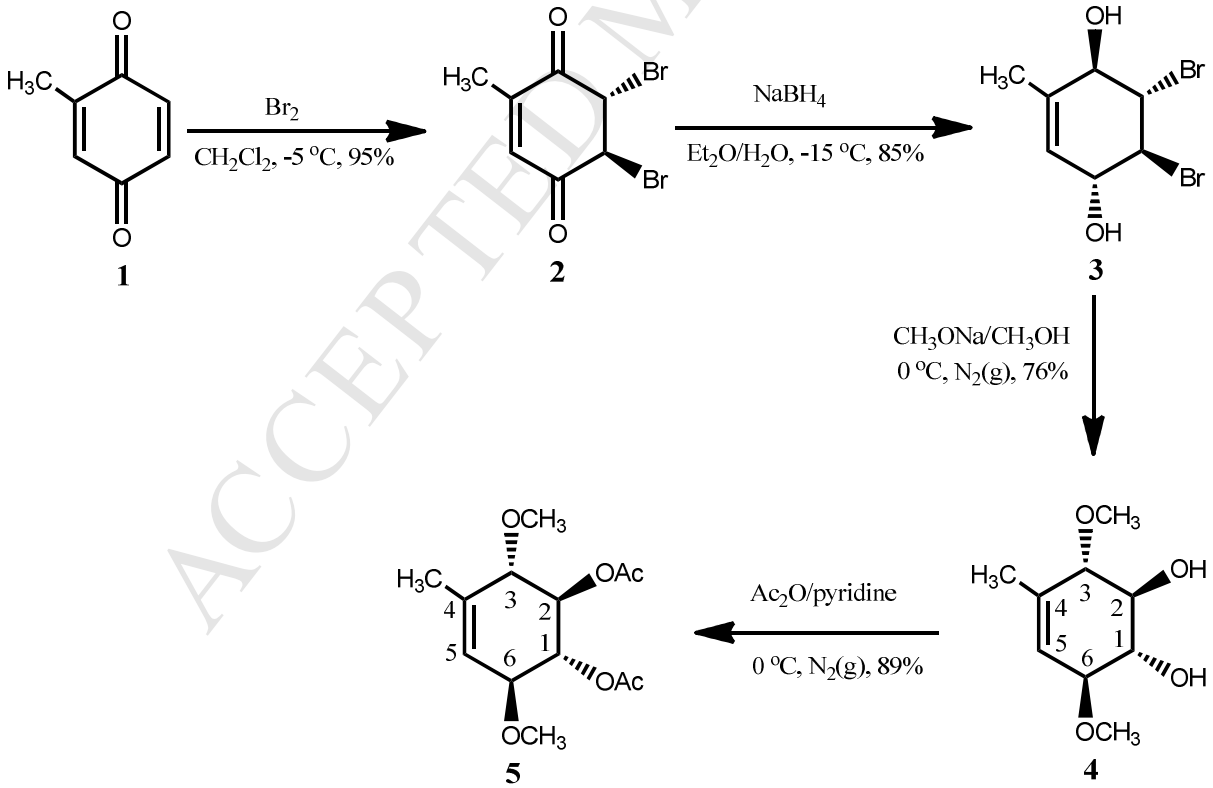
Pericosine

C7-cyclitols, such as gabosines[12] with a methyl substituent (gabosine A, N, and H) and pericosines[13] with a methoxy group (pericosine B and C) which include a cyclohexenoid moity, represent an important category of highly oxygenated natural products and may be classified as pseudo- or carbasugars. Since these compounds show structural similarities to carbohydrates, they exhibit interesting biological activities because of their antibiotic, anticancer, and DNA binding properties.[14] Among these base-sensitive ketocarbasugars, gabosine features a trihydroxylated cyclohexanone or cyclohexenone core with a methyl or

hydroxymethyl substituent.[12a] The preparation of cyclitols and their analogues are challenging due to the dense stereochemistry of the hydroxylated carbon centers. Recently, we have reported the stereospecific synthesis of some polyhydroxylated compounds.[15] Consequently, based on these results, we aimed to synthesize polyoxygenated cyclohexenes (cyclitols or carbasugars). Herein, we report the synthesis of two new mono- and dimethoxy conduritol-B analogues including methyl substituent.

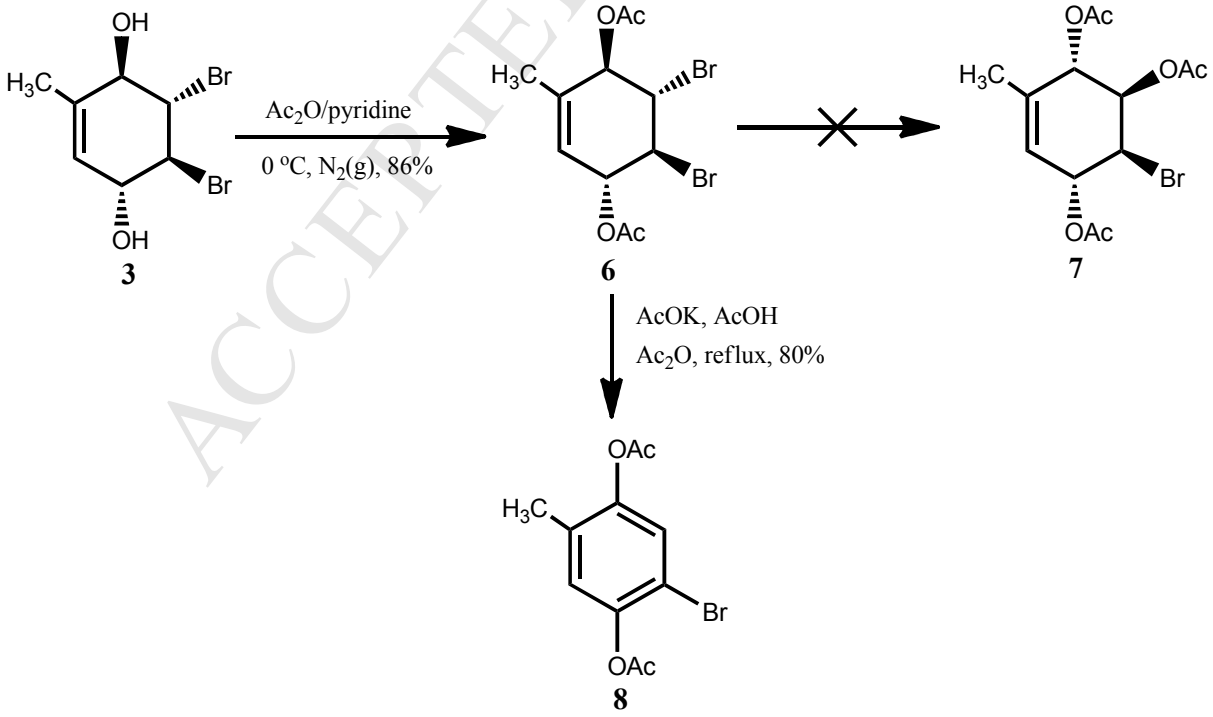
2. Results and discussion

Methyl-substituted *para*-benzoquinone **1** was brominated at low temperature to give only the *trans*-dibromo compound **2** in high yield. The allylic *trans*-diol **3** is a key intermediate for the synthesis of target compounds which are methyl-monomethoxy conduritol and methyl-dimethoxy conduritol. The required allylic *trans*-diol **3** was obtained as the sole product by stereoselective reduction of the carbonyl groups with $NaBH_4$ in ether.[6] The stereochemical course of the reduction was mainly determined as the *trans* configuration to bromide groups.



Scheme 1. Dimethoxy conduritol-B **4**

Treatment of dibromodiol **3** with a metallic sodium-methanol system (MeONa/MeOH)[16] under N_2(g) leads to a stereocontrolled transformation to conduritol-B derivative **4** in 76% yield (Scheme 1). The structure of **4** was unambiguously deduced from its ^{1}H and ^{13}C NMR spectra in $CDCl_3$. Compound **4** showed the presence of two –OCH_3 groups at 3.37 and 3.32 ppm in ^{1}H NMR spectrum. Furthermore, the ^{13}C NMR spectrum of **4** consisted of nine carbon resonances. In the ^{13}C NMR spectrum of **4**, in particular, two olefinic and methoxy carbons (-OCH_3) were observed at 135.8, 124.1, 58.3 and 57.1 ppm, respectively. Thus, by arranging from a conduritol-B derivative having full *trans*-structure to a different methyl-substituted conduritol-B derivative including two methoxy function, all substituents are in a mutual *trans*-arrangement (Scheme 1). The formation depends on nucleophilic ring opening from the allylic position of the *trans*-diepoxide which occurred as an intermediate product.[16] For further structural proof, diol **4** was converted into the corresponding diacetate **5**. After purification, **5** was obtained in 89% yield as the only isomer detected by NMR spectroscopy. The coupling constant between H-1 and H-2 in **5** are measured as J = 11.0 Hz because they are in *trans* configuration. The ^{13}C NMR spectrum of **5** consisted of thirteen carbon resonances. The carboxyl carbons were particularly observed at 170.2 and 170.1 ppm (C=O). These results also clearly show that compound **5** has a methyl-substituted conduritol-B diacetate structure protected stereochemistry in **4**.



Scheme 2. Reaction of **6** under basic conditions

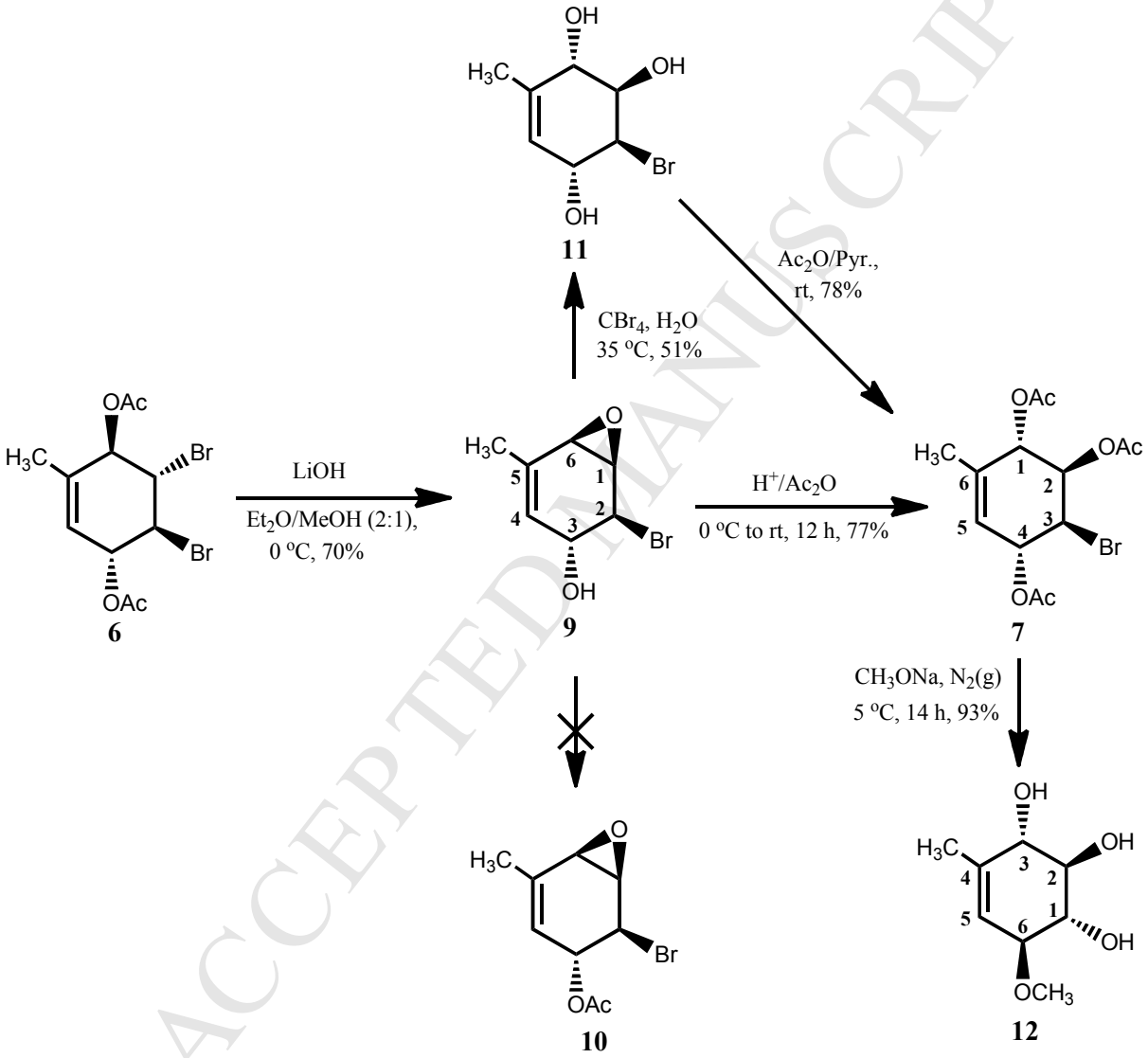
After successful isolation and characterization of the methyl-dimethoxy conduritol-B **4**, we turned our attention to the synthesis of its monomethoxy derivative. For this purpose, the acetylation of **3** with Ac_2O/pyridine system gave compound **6** as a sole product in 86% yield. We firstly aimed for the synthesis of compound **7** *via* a short way known in literature.[6] When compound **6** was treated with AcOK and Ac_2O in AcOH in order to substitute the Br-atom by an AcO group, contrary to our expectations, acetylation of **6** resulted in the formation of 2-bromo-5-methyl-1,4-phenylene diacetate **8**[17] having an aromatic structure in 80% yield (Scheme 2). In the literature, only the melting point (mp) of aromatic compound **8** has been reported until now.

The structure of **8** was assigned on the basis of ^{1}H and ^{13}C NMR spectra. Compound **8** showed the presence of two -OAc and a -CH_3 as well as a signal belonging to two aromatic protons in the ^{1}H NMR spectrum. Furthermore, the ^{13}C NMR spectrum of **8** consisted of eleven carbon resonances. In the ^{13}C NMR spectrum of compound **8**, the carbonyl and aromatic carbons were observed at 168.7 and 168.6 ppm (C=O) and 147.2, 145.8, 131.1, 126.5, 125.4 and 112.9 ppm (arom.) as well as the three methyl signals at 20.8, 20.7 and 16.1 ppm. respectively. These results also clearly show that compound **8** has an aromatic structure.

Epoxide **9** was regioselectively prepared from dibromide **6** by treatment with lithium hydroxide (Scheme 3).[6] The observed regio- and stereoselectivity for this reaction was remarkable since the stereochemistry is transformed into a conduritol-A type-configuration. The position of the epoxide-ring protons were determined by means of a COSY experiment. In the ^{1}H NMR spectrum of **9**, irradiation of H-4 at 5.62 ppm (CH=C), the signal of H-6 at 3.36 ppm turned from a double doublet to a doublet (J = 4.0 Hz). The irradiation of H-6 at 3.36 ppm, the signal of H-4 at 5.62 ppm turned from a double doublet to a triplet (J = 1.6 Hz) and the signal of H-1 at 3.74 also turned from a double doublet to a doublet to a singlet. These results clearly indicate that H-6 with H-1 and H-4 with H-3 are the neighboring protons with each other.

For the synthesis of our target compound, **7** is a key compound because of a conduritol-A type-configuration in the structure that may be stereoselectively prepared from epoxide **9**. However, treatment with CH_3COCl in methylene chloride at room temperature for the acetylation of the -OH group in **9**, it did not afford the expected acetoxy compound **10** as deduced from the ^{1}H NMR data. In order to overcome this potential challenge, we explored alternative acetylation methods. Treatment of the epoxide in hand with Ac_2O in a catalytic amount of H_2SO_4 at 0 ^{o}C (then at room temperature) for 12 h afforded the bromotriacetate **7** in

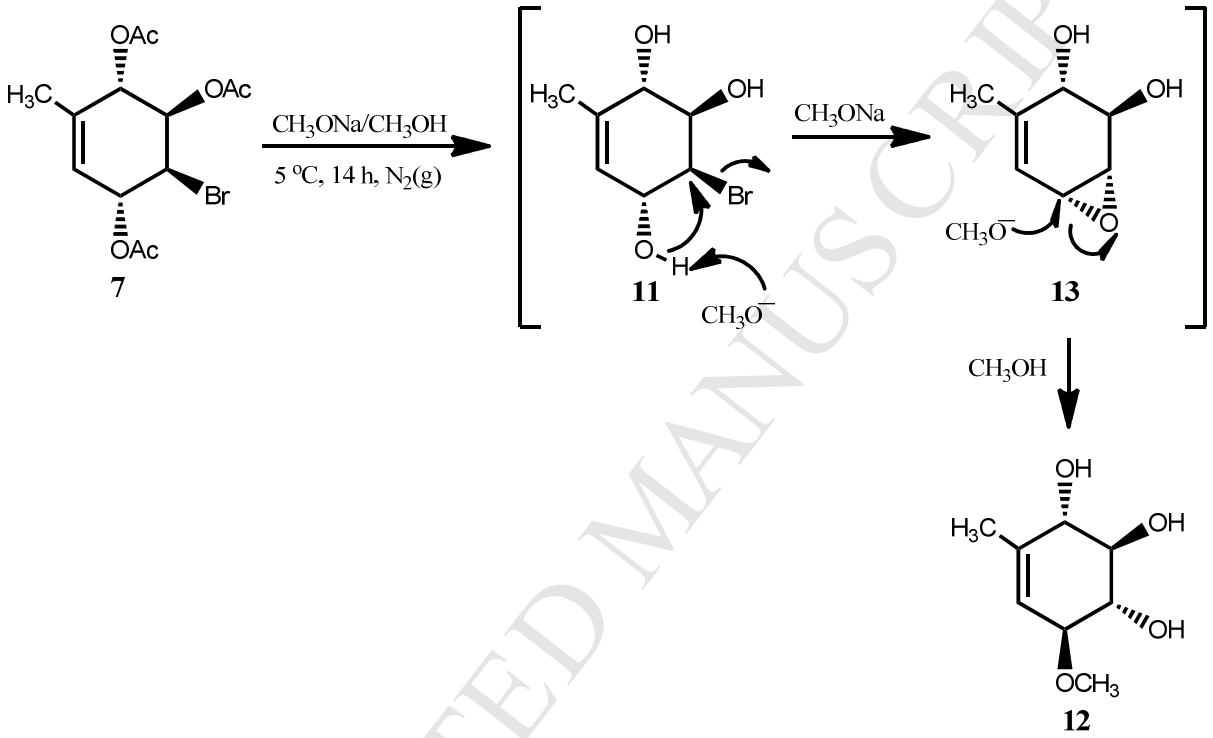
77% yield. The structure of **7** was elucidated on the basis of ^{1}H and ^{13}C NMR data. We assume that the epoxide first undergoes a ring-opening followed by acetylation to give the bromotriacetate **7**. Since the ring-opening takes place at the allylic position under acidic conditions, the configuration of the free hydroxyl group will be preserved. Additionally, to test the potential of this approach, bromotriacetate **7** was obtained in two steps from epoxide **9** following a reported procedure in the literature.[6]



Scheme 3. Monomethoxy conduritol-B **12**

After we obtained the dimethoxy conduritol-B **4** successfully, we tried to synthesize monomethoxy conduritol-B **12** using the same procedure as described above. For this purpose, treatment of bromotriacetate **7** with a metallic sodium-methanol system (MeONa/MeOH) under N_2(g) atmosphere led to a stereocontrolled transformation to a new

conduritol-B derivative **12** in 93% yield (Scheme 3). Thus, methyl-monomethoxy conduritol-B **12** was stereoselectively synthesized in high yield. The structure of **12** was unambiguously deduced from its ^{1}H and ^{13}C NMR spectra in $CDCl_3$. Compound **12** showed the presence of only one -OCH_3 at 3.46 ppm in particular in ^{1}H NMR spectra. Furthermore, the ^{13}C NMR spectrum of **12** consisted of eight carbon resonances owing to asymmetry in the molecule. In the ^{13}C NMR spectrum of **12**, in particular, two olefinic and one methoxy carbon (-OCH_3) signals were observed at 137.2, 121.2 and 56.8 ppm, respectively.



Scheme 4. Mechanism of formation of monomethoxy conduritol-B **12**

We suggest the following mechanism for the stereospecific synthesis of **12** from **7** (Scheme 4). At first, compound **7** is deacetylated under Zemplén conditions[18] (NaOMe in MeOH). Reaction of the **11** under the above-mentioned mildly basic conditions resulted in the formation of an epoxide intermediate **13**. The formed diol epoxide **13** undergoes a regioselective ring-opening from the allylic position through attack by methoxide ion to produce the monomethoxy derivative **12** as described above. Thus, in the final step, transformation from a conduritol-A to a conduritol-B type-configuration is provided.

3. Conclusion

In conclusion, we have reported a stereospecific synthesis of novel methyl-substituted mono- and di-methoxy conduritols starting from commercially available 2-methylbenzo-1,4-quinone. For the stereoselective reduction of the keto function in **2**, employing sodium borohydride in ethanol gave the allyl dioldibromo compound. The reactions of allylic *trans*-diol and epoxide compounds with CH_3ONa/MeOH resulted in the related methoxy-conduritols, respectively. We assume that these types of compound may have important biological activities and may be used as a precursor for the synthesis of other cyclitol derivatives such as conduritol and inositol.

4. Experimental section

4.1. General

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 and ^{13}C NMR spectra were recorded on 400 (100) MHz Bruker spectrometer (Avance III) 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).

4.2. (±)-(*1R*,4R*,5S*,6S**)-5,6-Dibromo-2-methylcyclohex-2-ene-1,4-diol (3):

Prepared according to the procedure described in the literature.[6] (19 g, 85%) (recrystallized from AcOEt/hexane), mp 111-112 ^{o}C; ^{1}H-NMR (400 MHz, CD_3OD) δ 5.48 (dd, 1H, J = 1.7, 3.3 Hz, -CH=C), 4.20-4.39 (m, 2H, -OH), 4.06-4.18 (m, 2H, -CHBr), 1.79-1.81 (m, 3H, -CH_3); ^{13}C-NMR (100 MHz, CD_3OD) δ 137.4 (C=C), 125.9 (C=C), 75.4 (C-O), 72.7 (C-O), 60.3 (C-Br), 60.2 (C-Br), 17.9 (-CH_3); IR (KBr, cm^{-1}): 3390, 3352, 2974, 2908, 1678, 1400, 1284, 1161, 1060, 1041, 991, 956, 840, 694, 547.

4.3. (±)-(*1S*,2S*,3S*,6S**)-3,6-Dimethoxy-4-methylcyclohex-4-ene-1,2-diol (4):

In a 250 mL round-bottomed flask fitted with a stirring bar at 0 ^{o}C, sodium metal (*ca.* 2.6 g, 113.0 mmol) was added to dry methanol (100 mL) and the resulting suspension was stirred until all the sodium had disappeared and hydrogen liberation ceased. Dibromo-1,4-diol **3** (1.9

g, 6.64 mmol) was added slowly and the mixture was stirred under N_2 for 1 h at 0 ^oC and stirring was continued for 24 h at room temperature to provide complete conversion. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with AcOEt (3 × 300 mL). The organic extracts were combined, dried (Na_2SO_4), and the solvent removed *in vacuo* to give 3,6-dimethoxy-4-methylcyclohex-4-ene-1,2-diol **4** as colorless crystals (0.96 g, 76%); mp 159-161 ^oC (recrystallized from CH_2Cl_2/Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.37 (d, 1H, *J* = 1.3 Hz, -CH=C), 5.01 (d, 1H, *J* = 4.8 Hz, -COH), 4.96 (d, 1H, *J* = 4.8 Hz, -COH), 3.58-3.56 (m, 1H, -CHOC), 3.26-3.20 (m, 1H, CHOC), 3.37 (s, 3H, -OCH_3), 3.32 (s, 1H, -OCH_3), 3.36 (s, 1H, -OH), 2.51-2.50 (m, 3H, -OH), 1.65 (s, 3H, -CH_3); ^{13}C-NMR (100 MHz, CD_3OD) δ 135.8 (C=C), 124.1 (C=C), 83.8 (C-OCH_3), 81.2 (C-OCH_3), 74.8 (C-O), 74.5 (C-O), 58.3 (-OCH_3), 57.1 (-OCH_3), 19.1 (CH_3); IR (KBr, cm^{-1}): 3390, 3352, 2974, 2908, 1678, 1400, 1284, 1161, 1060, 1041, 991, 956, 840, 694, 547; HRMS: m/z calculated for $C_9H_{16}NaO_4$ $[M+Na]^+$, 211.0941; found: 211.0970.

4.4. (±)-(*1R*,2R*,3S*,6S)-3,6-Dimethoxy-4-methylcyclohex-4-ene-1,2-diyl diacetate (5):**

3,6-Dimethoxy-4-methylcyclohex-4-ene-1,2-diol **4** (5.6 g, 29.75 mmol) was dissolved in pyridine (12 mL). To the magnetically stirred solution was added Ac_2O (13 mL) and stirred at room temperature for 12 h. The mixture was poured into ice-water (30 mL) and 4 M HCl solution (20 mL) was added and the mixture extracted with ether (3×100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (100 mL) and water (50 mL) and then dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel by using AcOEt/hexane (3:2) to give 3,6-dimethoxy-4-methylcyclohex-4-ene-1,2-diyl diacetate **5** (7.2 g, 89%); Compound **5** was recrystallized from CH_2Cl_2/hexane to give colorless crystals, mp 66-68 ^oC; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.50-5.46 (m, 1H, -CH=C), 5.22 (dd, 1H, A part of AB system, *J* = 7.8, 11.0 Hz, -CHOAc), 5.11 (dd, 1H, B part of AB system, *J* = 7.8, 11.0 Hz, -CHOAc), 4.02-3.92 (m, 2H, -CH-O), 3.31 (s, 3H, -OCH_3), 3.30 (s, 3H, -OCH_3), 2.03 (s, 3H, -OAc), 2.02 (s, 3H, -OAc), 1.74 (s, 3H, -CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.2 (C=O), 170.1 (C=O), 136.2 (C=C), 123.8 (C=C), 80.9 (C-O), 78.2 (C-O), 72.3 (C-O), 71.9 (C-O), 56.9 (-OCH_3), 56.4 (-OCH_3), 29.7 (-CH_3), 20.9 (-CH_3), 18.6 (-CH_3); IR (KBr, cm^{-1}): 2951, 1748, 1435, 1366, 1238, 1215, 1096, 1033, 957, 880, 736, 698, 651, 601, 571; HRMS: m/z calculated for $C_{13}H_{20}NaO_6$ $[M+Na]^+$, 295.1152; found: 295.1211.

4.5. (±)-(*1R*,4R*,5S*,6S)-5,6-Dibromo-2-methylcyclohex-2-ene-1,4-diyl diacetate (6):**

5,6-Dibromo-2-methylcyclohex-2-ene-1,4-diol **3** (10.0 g, 34.97 mmol) was dissolved in pyridine (13 mL). To the magnetically stirred solution was added Ac_2O (13 mL) and stirred at room temperature for 12 h. The mixture was poured into ice-water (30 mL) and 4 M HCl solution (20 mL) was added and the mixture extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (100 mL) and water (50 mL) and then dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel by using EtOAc/hexane (4:1) to give 5,6-dibromo-2-methylcyclohex-2-ene-1,4-diyl diacetate **6** (11.15 g, 86%); Compound **6** was recrystallized from EtOH as colorless crystals, mp 94-96 ^oC (Lit.[19] enantipure (-)-**6**, mp:102-103 ^oC); ^1H-NMR (400 MHz, $CDCl_3$): δ 5.84-5.79 (m, 1H, H_4), 5.70-5.64 (m, 1H, H_1), 5.53-5.49 (m, 1H, H_3), 4.32-4.24 (m, 2H, -CHBr), 2.19 (s, 3H, $-COCH_3$), 2.14 (s, 3H, $-COCH_3$), 1.67 (s, 3H, $-CH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.0 (C=O), 169.9 (C=O), 136.2 (C=C), 123.8 (C=C), 74.8 (C-O), 73.6 (C-O), 53.4 (C-Br), 52.6 (C-Br), 20.9 ($-CH_3$), 20.7 ($-CH_3$), 18.8 ($-CH_3$); IR (KBr, cm^{-1}): 2978, 1724, 1435, 1369, 1228, 1169, 1123, 1088, 1053, 1022, 995, 910, 883, 772, 702;

4.6. 2-Bromo-5-methyl-1,4-phenylene diacetate (8):

A vigorously stirred mixture of **6** (1.0 g, 2.70 mmol) in AcOH (15 mL), Ac_2O (3 mL), and anhydrous AcOK (1.55 g, 15.8 mmol) was heated at reflux for 3 days under N_2. The solvent was evaporated, MeOH (10 mL) and H_2O (5 mL) to the residue were added, and the mixture was stirred for 10 min. The mixture was extracted with Et_2O (3×50 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (50 mL) and water (50 mL) and then dried over Na_2SO_4 and concentrated *in vacuo*. The product **8** was recrystallized from EtOH (0.62 g, 80%) as colorless crystals, mp 123-125 ^oC (lit:[17] 125.0-125.4 ^oC); ^1H-NMR (400 MHz, $CDCl_3$): δ 7.31 (br s, 1H, H_3 or H_6), 7.03 (br s, 1H, H_3 or H_6), 2.36 (s, 3H, -OAc), 2.33 (s, 3H, -OAc), 2.16 (s, 3H, $-CH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.7 (C=O), 168.6 (C=O), 147.2 (arom-quaternary), 145.8 (arom-quaternary), 131.1 (arom-CH_3), 126.5 (arom.), 125.4 (arom.), 112.9 (arom-Br), 20.8 ($-CH_3$), 20.7 ($-CH_3$), 16.1 ($-CH_3$); IR (KBr, cm^{-1}): 2939, 1744, 1485, 2369, 1204, 1142, 1007, 918, 867, 810, 652, 586; HRMS: m/z calculated for $C_{13}H_{20}O_6$ $[M+H]^+$, 286.9914; found: 286.9882.

4.7. (±)-(*1R*,2S*,3R*,6R)-2-Bromo-5-methyl-7-oxabicyclo[4.1.0]hept-4-en-3-ol (9):**

A solution of **6** 11.15 g (30.13 mmol) in 200 mL diethyl ether and MeOH (100 mL) was cooled to 0 ^{o}C and then 1.67 g (69.75 mmol) anhydrous LiOH was added to stirring solution under N_2 atmosphere. The reaction mixture was stirred for 2 h at this temperature. After the reaction mixture was monitored by TLC, H_2O (250 mL) was added to the reaction mixture. The phases were separated and the aqueous phase was extracted with diethyl ether (3×200 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated to epoxide **9** (4.30 g, 70%). The product **9** was recrystallized from AcOEt/hexane as colorless crystals, mp 128-130 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.62 (dd, 1H, *J* = 1.8, 3.8 Hz, CH=C), 4.49-4.43 (m, 1H, -CHO-), 4.02 (dd, 1H, *J* = 1.2, 8.4 Hz, -CHBr), 3.74 (dd, 1H, *J* = 0.8, 4.0 Hz, -CHO-), 3.36 (dd, 1H, *J* = 2.4, 4.0 Hz, -CHO-), 2.47 (d, 1H, *J* = 4.3 Hz, -OH), 1.96 (dd, 1H, *J* = 1.7, 2.6 Hz, -CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): 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 $C_7H_9KO_2$ $[M+K]^+$, 242.9418; found: 243.0123.

4.8. (±)-(*1S*,2R*,3S*,4R)-3-Bromo-6-methylcyclohex-5-ene-1,2,4-triyl triacetate (7):**

To a stirred solution of epoxide **9** (1.4 g, 6.83 mmol) in Ac_2O (10 mL) was added dropwise H_2SO_4 (four drops) and stirred for 12 h at 0^{o}C. The solution was neutralized with $NaHCO_3$ and extracted with AcOEt (3 × 300 mL). The organic extracts were combined, dried (Na_2SO_4), and the solvent removed *in vacuo*. The crude material was purified by column chromatography on silica gel by using AcOEt/hexane (3:7) to give 3-bromo-6-methylcyclohex-5-ene-1,2,4-triyl triacetate **7** (1.74 g, 77%). Compound **7** was recrystallized from AcOEt/hexane as colorless crystals, mp 86-88 ^{o}C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.65-5.62 (m, 1H, CH=C), 5.55 (dd, 2H, *J* = 2.8, 6.0 Hz, -CHOAc), 5.30 (dd, 1H, *J* = 2.8, 6.0 Hz, -CHOAc), 4.36 (dd, 1H, *J* = 2.8, 5.6 Hz, -CHBr-), 2.14 (s, 3H, -$COCH_3$), 2.13 (s, 6H, -$COCH_3$), 1.74 (s, 3H, -CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170 (C=O), 169.9 (C=O),169.8 (C=O), 136.3 (C=C), 122,6 (C=C), 71.4 (C-O), 71.1(C-O), 70.8 (C-O), 47.7 (C-Br), 20.9 (-CH_3), 20.8 (-CH_3), 20.7 (-CH_3), 19.4 (-CH_3); IR (KBr, cm^{-1}): 2322, 1736, 1520, 1435, 1369, 1219, 1157, 1096, 1022, 976, 910, 860, 775, 663, 509, 451;

4.9. (±)-(*1S*,2R*,3S*,4R)-3-Bromo-6-methylcyclohex-5-ene-1,2,4-triol (11):**

4.14 g (20.19 mmol) **9** was are suspended in 40 mL H_2O, 0.72 g (2.17 mmol) CBr_4 was added and the suspension was heated to 35 ^{o}C under N_2 for 14 h. The aqueous layer was extracted with AcOEt (3×50 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated to give bromotriol **11** (2.3 g, 51%). The product **11** was recrystallized from EtOH as colorless crystals, mp 132 ^{o}C; ^{1}H-NMR (400 MHz, CD_3OD): δ 5.55 (dd, 1H, *J* = 1.6, 4.0 Hz, CH=C), 4.26 (dt, 1H, *J* = 2.2, 8.4 Hz, H_4), 4.01 (dd, 1H, *J* = 1.2, 8.4 Hz, H_1), 3.72 (dd, 1H, *J* = 0.8, 4.0 Hz, H_2), 3.39 (dd, 1H, *J* = 2.4, 4.0 Hz, H_3), 1.96 (dd, 3H, *J* = 1.6, 2.6 Hz, -CH_3); ^{13}C-NMR (100 MHz, CD_3OD): δ 132.1 (C=C), 128.6 (C=C), 70.3 (C-O), 55.7 (C-O), 55.2 (C-O), 54.6 (C-Br), 19.6 (-CH_3); IR (KBr, cm^{-1}): 3317, 3240, 1450, 1338, 1273, 1234, 1180, 1010, 948, 898, 860, 821, 756, 655, 601, 547; HRMS: m/z calculated for $C_{13}H_{20}NaO_6$ $[M+Na]^+$, 244.9784; found: 244.9766.

4.10. Synthesis of 7 from 11:

Bromotriol **11** (1.2 g, 5.38 mmol) was dissolved in pyridine (10 mL). To the magnetically stirred solution Ac_2O (10 mL) was added and stirred at room temperature for 12 h. The mixture was poured into ice-water (30 mL) and was added 4 M HCl solution (50 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with saturated solution $NaHCO_3$ (100 mL) and water (40 mL) and then dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel by using EtOAc/hexane (15:85) to give triacetate **7** (1.46 g, 78 %);

4.11. (±)-(*1S*,2R*,3S*,6S)-6-Methoxy-4-methylcyclohex-4-ene-1,2,3-triol (12):**

In a 250 mL round-bottomed flask fitted with a stirring bar at 0 ^{o}C, sodium metal (*ca.* 0.74 g, 32.18 mmol) was added to dry methanol (100 mL) and the resulting suspension was stirred until all the sodium has disappeared and hydrogen liberation ceased. Compound **7** (2.5 g, 7.15 mmol) was added slowly and the mixture which was stirred in N_2 atmosphere for 1 h at 0 ^{o}C and stirring was continued for 24 h at +5 ^{o}C to provide complete conversion. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3 ×

300 mL). The organic extracts were combined, dried (Na_2SO_4), and the solvent removed *in vacuo*. The crude material was purified by column chromatography on silica gel using AcOEt/MeOH (1:0.1) to give 6-methoxy-4-methylcyclohex-4-ene-1,2,3-triol **12** as a colorless crystals (1.16 g, 93%); mp 63-65 ^oC (recrystallized from EtOH); ^1H-NMR (400 MHz, $CDCl_3$) δ 5.4-5.42 (m, 1H, CH=C), 5.15-5.09 (m, 1H, -CHO-), 4.66-5.61 (m, 1H, -CHO-), 4.45-4.44 (m, 1H, -CHO-), 4.05 (s, 1H, -OH), 3.82 (s, 1H, -OH), 3.65-3.56 (m, 1H, -CHOMe), 3.46 (s, 3H, $-OCH_3$), 2.71 (s, 1H, -OH), 1.79 (s, 3H, $-CH_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.2 (C=C), 121.2 (C=C), 81.2 (C-O), 75.9 (C-O), 74.2 (C-O), 73.9 (C-O), 56.8 ($-OCH_3$), 18.7 ($-CH_3$); IR (KBr, cm^{-1}): 3316, 2974, 2903, 2877, 1454, 1371, 1321, 1283, 1194, 1088, 1051, 995, 966, 891, 825, 611, 521; HRMS: m/z calculated for $C_8H_{14}NaO_4$ $[M+Na]^+$, 197.0785; found: 197.0874.

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References

1. (a) Duchek, J.; Adams, D. R.; Hudlicky, T. *Chem. Rev*. **2011**, *111*, 4223-4258; (b) Arjona, O.; Gomez, A. M.; Lopez, J. C.; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919-2036.
2. Ridley, C. M.; Thur, K. E.; Shanahan, J.; Thillaiappan, N. B.; Shen, A.; Uhl, K.; Walden, C. M.; Rahim, A. A.; Waddington, S. N.; Platt, F. M.; van der Spoel, A. C. *J. Biol. Chem.* **2013**, *288*, 26052-26066.
3. Cere, V.; Minzoni, M.; Pollicino, S.; Ricci, A.; Gasparrini, F.; Ciogli, A.; D'Acquarica, I. *J. Comb. Chem.* **2006,** *8*, 74-78.
4. Cere, V.; Mantovani, G.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron* **2000**, *56*, 1225-1231.
5. Lee, W. W.; Chang, S. *Tetrahedron: Asymmetry* **1999**, *10*, 4473-4475.
6. Leermann, T.; Block, O.; Podeschwa, M. A. L.; Pfüller, U.; Altenbach, H. J. *Org. Biomol. Chem*. **2010**, *8*, 3965-3974.
7. Cantekin, S.; Çalışkan, R.; Şahin, E.; Balci, M. *Helv. Chim. Acta.* **2007**, *90*, 2227-2235.
8. Cantekin, S.; Baran, A.; Çalışkan, R.; Balci, M. *Carbohydr. Res*. **2009**, *344*, 426-431.

9. Boyd, D. R.; Sharma, N. D.; Llamas, N. M.; O'Dowd. C. R.; Allen. C. C. R. *Org. Biomol. Chem.* **2007**, *5*, 2267-2273.
10. Boyd, D. R.; Sharma, N. D.; Llamas, N. M.; O'Dowd. C. R.; Allen. C. C. R. *Org. Biomol. Chem.* **2006**, *4*, 2208-2217.
11. Bellomo, A.; Bertucci, A.; Stefani, H.; Vazquez, A.; Gonzalez, D. *Tetrahedron: Asymmetry* **2009**, *20*, 2673-2676.
12. (a) Babu, D. C.; Rao, Ch. B.; Venkatesham, K.; Selvam, J. J. P.; Venkateswarlu, Y. *Carbohydr. Res.* **2014**, *388*, 130-137; (b) Bayón, P.; Figueredo, M. *Chem. Rev.* **2013**, *113*, 4680-4707; (c) Mondal, S.; Prathap, A.; Sureshan, K. M.; *J. Org. Chem.* **2013**, *78*, 7690-7700; (d) Mac, D. H.; Chandrasekhar, S.; Grée, R. *Eur. J. Org. Chem.* **2012**, 5881-5895; (e) Shing, T. K. M.; Chen, W. L. Ng. Y. *Synlett* **2011**, *9*, 1318-1320; (f) Prasad, K. R.; Kumar, S. M. *Synlett* **2011**, *11*, 1602-1604; (g) Kumar, V.; Das, P.; Ghosal, P.; Shaw, A. K. *Tetrahedron* **2011**, *67*, 4539-4546; (h) Shing, T. K. M.; So, K. H.; Kwok. W. S. *Org. Lett.* **2009**, *11*, 5070-5073; (i) Shing, T. K. M.; Cheng, H. M. *J. Org. Chem.* **2007**, *72*, 6610-6613; (i) Alibes, R.; Bayon, P.; de March, P.; Figueredo, M.; Font, J.; Marjanet, G. *Org. Lett.* **2006**, *8*, 1617-1620.
13. (a) Reddy, Y. S.; Kadigachalam, P.; Basak, R. K.; Pal, A. P. J.; Vankar, Y. D. *Tetrahedron Lett.* **2012**, *53*, 132-136; (b) MuniRaju, Ch.; Rao, J. P.; Rao, B. V. *Tetrahedron: Asymmetry* **2012**, *23*, 86-93; (c) Boyd, D. R.; Sharma, N. D.; Acaru, C. A.; Malone, J. F.; O'Dowd, C. R.; Allen, C. C. R.; Stevenson, P. J. *Org. Lett.* **2010**, *12*, 2206-2209; (d) Donohoe, T. J.; Blades, K.; Helliwell, M.; Waring, M. J. *Tetrahedron Lett.* **1998**, *39*, 8755-8758.
14. (a) Huntley, C. F. M.; Hamilton, D. S.; Creighton, D. J.; Ganem, B. *Org. Lett.* **2000**, *2*, 3143-3144; (b) Tang, Y. Q.; Maul, C.; Höfs, R.; Sattler, I.; Grabley, S.; Feng, X. Z.; Zeek, A.; Thiericke, R. *Eur. J. Org. Chem.* **2000**, 149-153; (c) Bach, G.; Breiding, M. S.; Grabley, S.; Hammann, P.; Hütter, K.; Thiericke, R.; Uhr, H.; Wink, J.; Zeeck, A. *Liebig. Ann. Chem.* **1993**, 241-250; (d) Maier, A.; Maul, C.; Zerlin, M.; Grabley, R.; Thiericke, R. *J. Antibiot.* **1999**, *52*, 952-959.
15. (a) Kelebekli, L.; Balcı, N.; Şahin, E. *Tetrahedron* **2014**, *70*, 5175-5181; (b) Kelebekli, L. *Synth. Commun.* **2013**, *43*, 2998-3009; (c) Oztaskin, N.; Kelebekli, L.; Göksu, S.; Anil, B.; Şahin, E. *J. Chem. Res.* **2009**, 231-233; (d) Balcı, N.; Kelebekli, L.; Göksu, S.; Anil, B.; Şahin, E. *J. Chem. Res.* **2009**, 248-251; (e) Kelebekli, L.; Kara, Y.; Balci, M. *Carbohydr. Res.* **2005**, *340*, 1940-1948; (f) Balcı, N.; Anil, B.; Kelebekli, L.; Şahin, E.; Göksu, S. *Synth. Commun.* **2013**, *43*, 3054-3063.

16. Kelebekli, L. *J. Chem. Res*. **2007**, *11*, 626-628.
17. Inonue, S.; Saito, K.; Kato, K.; Nozaki, S.; Sato, K. *J. Chem. Soc., Perkin Trans 1*, **1974**, *18*, 2097-2101.
18. (a) Ren, B.; Wang, M.; Liu, J.; Ge, J.; Zhanga, X.; Dong, H. *Green Chem*. **2015**, *17*, 1390-1394; (b) Zemplen, G. *Ber. Deutsch. Chem. Ges*. **1926**, *59*, 1254-1266.
19. Gu, J.; Heeg, M. J.; Johnson, C. R. *Tetrahedron Lett.* **2001**, *42*, 1213-1215.

GRAPHICAL ABSTRACT

Stereospecific synthesis of novel methyl-substituted mono- and di-methoxy conduritols

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