A Total Stereoselective Synthesis of *myo-*, *allo*, *neo-*, and *epi*-Inositols[1]

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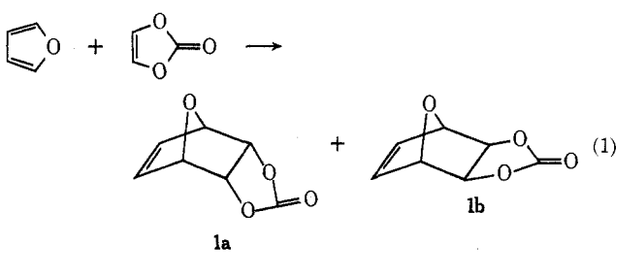
A total stereoselective synthesis of 1,4-anhydroinositols and *myo-*, *allo-*, *neo-*, and *epi*-inositols was effected. The adducts, *exo-* and *endo*-oxabicyclo[2.2.1]-hept-5-ene carbonate, were epoxidized and upon alkaline hydrolysis yielded 1,4-anhydro-D-*allo-* and *-cis*-inositols, respectively. Upon additional mild acidic hydrolysis, the above mentioned inositols were obtained. Methods of preparations and identification were considered.

The inositols are well-known natural products.[2-4] Althouth numerous attempts to synthesize them were made in the past,[5-12] none of them were stereoselective. This approach was applied by Criege[13] and by Sarel and Kowarski.[14,15] Their method was to build a well-structured, sterically built, six-membered ring and introduce the missing hydroxyl groups in a well-defined steric position. This paper will describe a total stereoselective synthesis of 1,4 anhydroinositols and inositols. The plan of work is outlined. Vinylene carbonate[16] was condensed *via* Diels–Alder addition with furan and the *endo-* and *exo*-oxabicyclo[2.2.1]-hept-5-ene-2,3-diol carbonate adducts were obtained (eq 1, **1a**, **1b**).



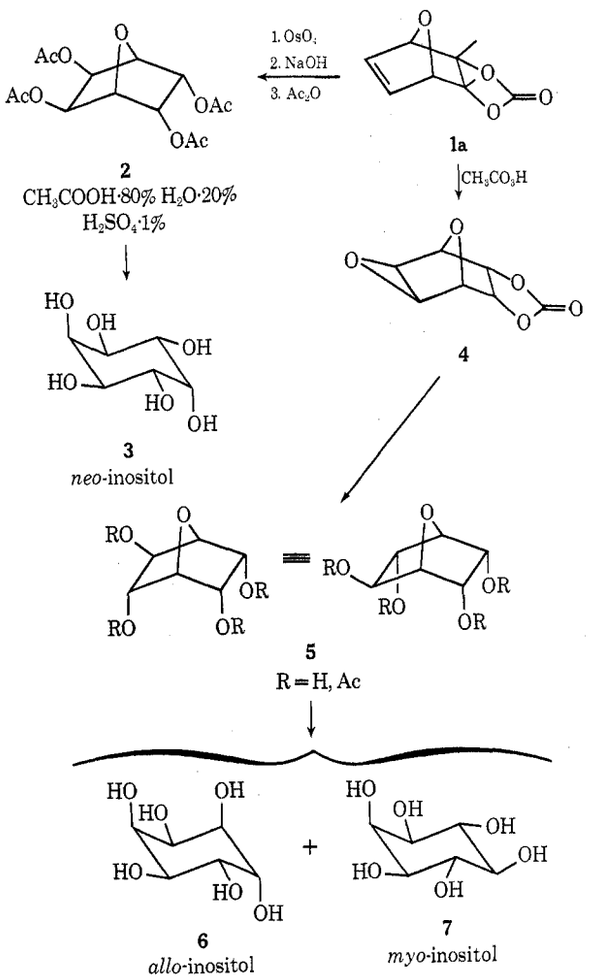
(1)

1a **1b**

Trans hydroxylation of the olefinic center in endo adduct **1a** was effected *via* epoxide **4**, which was prepared with peracetic acid. (See Scheme I.) After alkaline hydrolysis of **4**, the D-1,4-anhydroinositol was obtained and isolated as the tetraacetate (**5**). Hydrolysis of this substance with acetic acid and minute amounts of sulfuric acid resulted in *myo-* (**7**) and *allo*-inositol (**6**).

Cis hydroxylation of endo adduct **1b** was effected with osmium tetroxide to give 1,4-anhydro-*allo*-inositol, which was isolated as tetraacetate **2**. Treatment with $HOAc–H_2SO_4$ as described above gave *neo*-inositol (**3**).

SCHEME I



Similar transformation was carried out with the exo adduct **1b**. (See Scheme II.) Epoxidation with peracetic acid gave peroxide **8**. Acid hydrolysis of this substance, or of the derived 1,4-anhydrotetrol, gave *allo-* (**6**) and *myo*-inositol (**7**). Cis hydroxylation as described for the endo adduct and subsequent acid treatment afforded *epi*-inositol, characterized as the hexaacetate (**11**).

Experimental Section

Monochloroethylene Carbonate.[16]—A stream of chlorine was passed through 250 g (2.8 mol) of freshly distilled ethylene carbonate at 63–70° in the presence of a Mazda lamp of 500 W. After 12 hr, vacuum rectification yielded pure monochloroethylene carbonate, bp 106–107° (10–11 mm), $n^{25}D$ 1.4530.

Anal. Calcd for $C_3H_3O_3Cl$: C, 29.4; H, 2.5; Cl, 29.0. Found: C, 29.6; H, 2.5; Cl, 29.2.

Vinylene Carbonate.[16]—Triethylamine (25.3 g) in 50 ml of ether was added to 30.0 g (0.24 mol) of monochloroethylene

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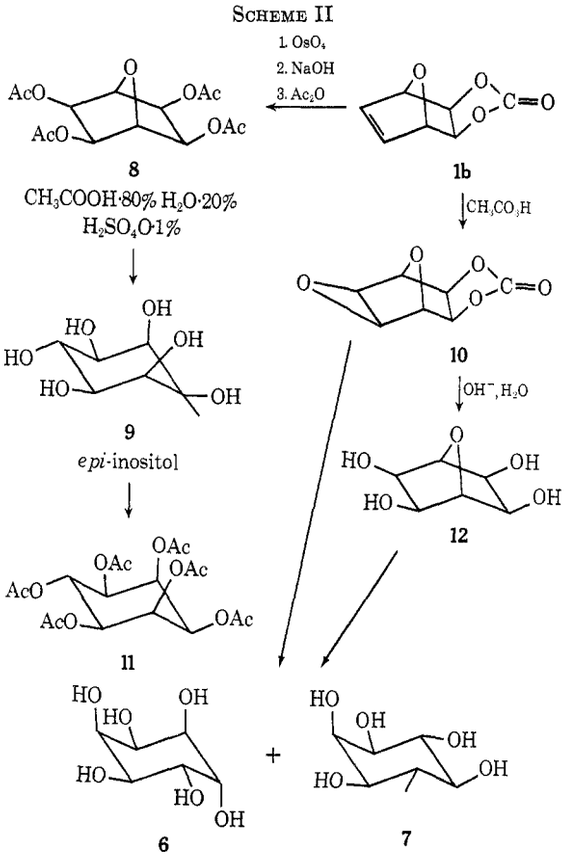
SCHEME II



carbonate in 100 ml of dry ether at reflux temperature dropwise over a 7-hr period. Following refluxing and stirring overnight, the solids were removed and distillation yielded 12.4 g (59%) of colorless liquid, bp 76–79° (37 mm). Further rectification produced pure vinylene carbonate, bp 73–74° (32 mm), n^{25}D 1.149.

Anal. Calcd for $C_3H_2O_3$: C, 41.9; H, 2.3. Found: C, 42.1; H, 2.4.

***exo*- and *endo*-Oxabicyclo[2.2.1]hept-5-ene-2,3-diol Carbonates (1a,b).**—The method followed in preparing the adduct was Newman's procedure.[17a] Vinylene carbonate (25.0 g, 0.29 mol) and 4.0 g of furan were sealed into an ampoule of 100 ml volume having a wall thickness of 3 mm. The ampoule was maintained in Dry Ice while the ingredients were mixed together. The sealed ampoule was then placed in a dry heat oven at a temperature of 120° and kept there for 12 hr. Unaffected vinylene carbonate was distilled and reused for further reaction. The residue was distilled at a temperature of 155° (2 mm). Upon distillation, a crystalline product having a melting point range of 95–150° was obtained. According to Newman,[17b] this crystalline white powder was a mixture of endo and exo adducts. These adducts, upon column chromatography separation,[17a] yielded 700 mg of the endo isomer, mp 144–148°, and 150 mg of the exo isomer, mp 137–139°. The total yield of the two isomers was 21% (based on furan).

Anal. Calcd for $C_7H_6O_4$: C, 54.6; H, 3.9. Found (137° isomer): C, 54.5; H, 4.1; (149° isomer) C, 54.6; H, 4.1.

***endo*-Epoxyoxabicyclo[2.2.1]hept-5-ene-2,3-diol Carbonate (4).**—To 1.5 g (9.7 mmol) of the adduct 1a were added 15 ml of glacial acetic acid, 5 ml of H_2O_2 (30%, v/v), and 0.02 ml of concentrated sulfuric acid. The mixture was kept at 40° in a dry heat oven for a period of 48 hr. The oxidized product was filtered off, and the precipitate was boiled in 20 ml of chloroform and rinsed with chloroform, yielding 1.19 g (79%). When 4 was heated, it sublimed into needles which later melted at 205–210°, ir max 1800, 1287, 915, 865 cm^{-1}.

Anal. Calcd for $C_7H_6O_5$: C, 49.4; H, 3.5. Found: C, 49.7; H, 3.6.

***exo*-5,6-Epoxybicyclo[2.2.1]heptane-2,3-diol Carbonate (10).**—Acetic acid (5 ml), 1.5 ml of hydrogen peroxide (30%, v/v), and 0.45 ml of concentrated sulfuric acid were added to 300 mg (0.02 mol) of the exo adduct, 1b. This solution was maintained at 40° during 48 hr. It was cooled for 24 hr and the precipitate yielding 30 mg (13%) was filtered and washed with chloroform. The filtrate was dried, mp 188–190°, ir max 1800, 1274, 940, 935 cm^{-1}.

1,4-Anhydro-D-inositol (5) and Its Acetate.—An aqueous solution of 2 *N* sodium hydroxide (10 ml) was added to 1.0 g (5.9 mmol) of 4 dissolved in 3 ml of ethanol. This mixture was heated over a water bath for 4 hr. After the hydrolysis was complete, the solution was neutralized with 2 *N* sulfuric acid. The water was evaporated, and the residue was dried at 60–80°.

The hydrolyzed product was isolated as the tetraacetate in the following way. The crude residue of 1,4-anhydroinositol was acetylated by adding 50 ml of acetic anhydride. The mixture was warmed slightly for 24 hr in an oven and maintained for 24 hr. After completion of the reaction, the acetic anhydride was removed *in vacuo*, and the waxy residue had mp 155–160°, yielding 60 mg (60%), ir max 1750, 1250, 840 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_9$: C, 50.9; H, 5.4. Found: C, 50.4; H, 5.8.

***myo*- and *allo*-Inositol (7, 6).**—A solution (52 ml) consisting of 80% (v/v) acetic acid, 20% (v/v) water, and 1% (v/v) sulfuric acid was added to 700 mg (4.1 mmol) of 5,6-epoxybicyclo[2.2.1]-heptane-2,3-diol (4, 10). This mixture was heated for 48 hr over a water bath. The hydrolyzed products were tested for the presence of inositols by a Scherer[18] test, which was positive. The paper chromatography[19,20] revealed spots at the same location as authentic samples of the inositols, R_f 0.185 for *myo*-inositol and 0.30 for *allo*-inositol.

The separation of the inositols was effected by using a cellulose column.[7] The separated inositols were collected, and the desired fraction was converted into hexaacetates[7] by adding 10 ml of acetic anhydride and 4–5 drops of concentrated sulfuric acid for 48 hr. A white precipitate was formed which, when mixed with cold ice, yielded a white, crystalline precipitate. The crystals obtained from toluene had mp 215–216°. The yield was 100 mg (14.2%) of *myo*-inositol, ir max 1250, 750, 863, 887, 760, 960 cm^{-1}.

1,4-Anhydro-*allo*-inositol (2).—Cis hydroxylation of the adducts was effected with osmium tetroxide;[13] then 1.2 g (7.8 mmol) of *endo*-oxabicyclo[2.2.1]heptene-2,3-diol carbonate was dissolved in 30 ml of freshly distilled ethyl acetate. To it, 1.54 ml of dry pyridine and 2 g of osmium tetroxide, dissolved in 4 ml of ethyl acetate, were added. Upon addition of osmium tetroxide, a black precipitate was formed. After remaining at room temperature for 24 hr, the black precipitate weighed 4.159 g. This precipitate was refluxed for 7 hr with 14 g of sodium sulfite, and the black precipitate of $Na_4[OS(SO_3)_3]\cdot 6H_2O$ was filtered off. This solution was then concentrated to a small volume, and the pH was adjusted to 9 by adding 20 ml of sodium hydroxide. This solution was left at 20° for 1 hr. After neutralization with sulfuric acid, it was evaporated.

Acetate of 1,4-Anhydro-*allo*-inositol (2).—Acetic anhydride (50 ml) was added to the previously obtained residue. The solution was boiled for 24 hr. After the reaction, the acetic anhydride was removed by distillation and the remaining brown liquid was washed off with cold water. The residue was recrystallized from benzene, which produced a crystalline product, mp 128°, yield 100 mg (8.3%), ir max 1750, 830 cm^{-1}.

Anal. Calcd for $C_{14}O_9H_{18}$: C, 50.9; H, 5.4. Found: C, 51.6; H, 5.3.

***neo*-Inositol (3).**—A solution (5 ml) composed of 80% (v/v) acetic acid, 20% water, and 1% (v/v) sulfuric acid was added to 10 mg (0.8 mmol) of 1,4-anhydro-*allo*-inositol. The solution was warmed over a water bath for 60 hr, and then tested for Scherer reaction,[18] which was positive. The paper chromatography[19,20] revealed the presence of *neo*-inositol according to its R_f 0.19.[20]

(17) (a) M. S. Newman, *ibid.*, **77**, 3789 (1955). (b) The fine structure of stereoisomeric forms endo and exo was not established by Newman.[17a] Additional support was given to Newman's rationale when the authors measured the dipole moments of the adducts. The dipole moments measurements were performed through the use of the Heterodyne method [A. Weisberger, "Physical Methods in Organic Chemistry," Vol. I, Part II, Interscience, New York, N. Y., 1900, p 1617]. The dipole moments found were the following: for exo adduct of mp 139° the μ = 5.6 D and for endo adduct of mp 149° μ = 3.6 D. These results are in agreement with Newman's conception of the fine structure of the two adducts.

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Tetraacetate of *exo*-Oxabicyclo[2.2.1]hept-5-ene-2,3-diol (8).—Oxabicyclo[2.2.1]-hept-5-ene-2,3-diol carbonate (**1b**) (600 mg, 3.8 mmol) was dissolved in 15 ml of the ethyl acetate and 0.77 ml of dry pyridine; 1 g of osmium tetroxide dissolved in 2 ml of ethyl acetate was added. This mixture was sealed and left for 24 hr at room temperature. The solution was filtered, and a dry, black precipitate weighing 1.4 g was collected; 60 g of sodium sulfite (Na_2SO_3), previously dissolved in 300 ml of water, and 300 ml of ethyl alcohol were added to the black precipitate. The mixture was boiled for 7 hr, producing a new, black precipitate, $Na_4[OS(SO_3)_3]\cdot 6H_2O$. This solution was concentrated, and its volume was reduced to 50 ml. Sodium hydroxide solution (5 ml), 5% (w/v) was added. This mixture was maintained at room temperature for 1 hr. Once again it was neutralized with acid, then concentrated to dryness, and dried at 60–80° for 4 hr.

Acetylation of the Anhydro *cis*-Inositol 8.—Acetic anhydride (50 ml) was added to the dry residue previously obtained. This mixture was warmed for 24 hr in an electric bath. Then the aceetic anhydride was removed *in vacuo*, and the residue resembled needles, mp 188–190°, yield 40 mg (6.6%), ir max 1750, 1250, 840, 820 cm^{-1}.

***epi*-Inositol (9,11).**—A solution (5 ml) consisting of 80% (v/v) acetic acid, 20% (v/v) water, and 1% (v/v) sulfuric acid was added to 10 mg (0.061 mmol) of hydroxylated material **8**. The mixture was warmed over a water bath for 14 hr, then tested by paper chromatography.[19,20] One spot was revealed which corresponded to *epi*-inositol, R_f 0.20.[20] Also the Scherer reaction[18] was positive. The dry residue was acetylated by adding 5 ml of acetic anhydride and a few drops of concentrated sulfuric acid. This mixture was left at 40° for 24 hr and poured into cold water, and then yielded crystals of **11**. Further purification from toluene yielded crystals, mp 186–190°.[7]

Registry No.—**1a**, 32384-16-0; **1b**, 32384-17-1; **2** tetraacetate, 36912-06-8; **4**, 36912-07-9; **5** (R = Ac), 36912-08-0; **6**, 643-10-7; **7**, 87-89-8; **8** tetraacetate, 36912-10-4; **10**, 36912-11-5; **11**, 20108-71-8; monochloroethylene carbonate, 3967-54-2; vinylene carbonate, 872-36-6.

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Sterol Metabolism. XX. Cholesterol 7β-Hydroperoxide[1]

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3β-Hydroxycholest-5-ene 7β-hydroperoxide was isolated along with 6β-hydroperoxycholest-4-en-3-one from autoxidation of crystalline cholesterol. Epimerization of 3β-hydroxycholest-5-ene 7α-hydroperoxide also provided the 7β-hydroperoxide in low conversion yield. The structure of 3β-hydroxycholest-5-ene 7β-hydroperoxide was established by sodium borohydride reduction to cholest-5-ene-3β,7β-diol and by spectral means. The 7β-hydroperoxide decomposed thermally to cholest-5-ene-3β,7β-diol and 3β-hydroxycholest-5-en-7-one, thereby accounting for the ubiquitous presence of cholest-5-ene-3β,7β-diol in cholesterol autoxidation products. An alternate pathway of derivation of cholest-5-ene-3β,7β-diol *via* epimerization of cholest-5-ene-3β,7α-diol was also demonstrated. Autoxidation of cholesterol 3β-acetate afforded the acetate derivatives of the cholesterol 7β-, 20α-, and 25-hydroperoxides.

The autoxidation of cholesterol (**1a**) under a variety of conditions leads to formation of the well-known epimeric cholest-5-ene-3β,7-diols (**3b**, **4b**), 3β-hydroxycholest-5-en-7-one (**5a**), cholesta-3,5-dien-7-one, cholest-5-ene-3β,25-diol, and 5α-cholestane-3β,5,6β-triol. Chromatographic evidence[2] and isolation work[3] have established that autoxidation proceeds *via* initial hydroperoxide fomation followed by thermal decomposition to give the better known stable autoxidation products mentioned. The numerous stable autoxidation products of cholesterol oxidized in the side-chain are satisfactorily accounted in this manner, arising *via* initial formation of the cholesterol 20α-, 24-, 25-, and 26-hydroperoxides.[3] The well-known B-ring autoxidation products **3b**, **5a**, and cholesta-3,5-dien-7-one are likewise properly accounted for *via* reduction and dehydration processes acting on the Δ⁵-7α-hydroperoxide **3a**, formed by stereospecific rearrangement[4] of the Δ⁶-5α-hydroperoxide **2a** formed by initial attack of oxygen on cholesterol.[5]

Such direct pathways do not account for the ubiquitous presence in autoxidized cholesterol of the 3β,7β-diol **4b** in substantial amounts along with the 3β,7α-diol **3b**. As established in the present study, the 7β-alcohol **4b** may be derived by two pathways, one proceeding *via* the previously unrecognized epimerization of the 7α-alcohol **3b**, the other *via* similar epimerization of the 7α-hydroperoxide **3a** to give the previously undescribed 7β-hydroperoxide **4a** whose thermal decomposition provides the 7β-alcohol **4b** and the 7-ketone **5a**.

In continued examination of cholesterol autoxidation products[3] we isolated for the first time from crystalline cholesterol samples heated in air 6β-hydroperoxy-

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