SYNTHESES OF D-CHIRO-3-INOSE AND (+)-D-CHIRO INOSITOL

Inventors: Tomas Hudlicky; Martin Mandel, both of Blacksburg, Va.

Filed: Mar. 22, 1995

ABSTRACT
There are described novel biocatalytic and chemical processes for the synthesis of various oxygenated compounds. Particularly, there are described processes for the synthesis of a useful synthon 12 made by reacting a protected diol (acetonide) with permanganate under appropriate conditions. Such synthon is useful of the synthesis of various pharmaceutically important compounds such as D-chiro-inositol and D-chiro-3-inosose. Also, there are disclosed novel compounds, including specifically the synthon 12 and compounds derived therefrom.

1 Claim, No Drawings
SYNTHESSES OF D-CHIRO-3-INOSE AND (+)-D-CHIRO INOSITOL

This is a continuation of application Ser. No. 07/974,057 filed Nov. 10, 1992, now abandoned, which is a continuation in part of U.S. application Ser. No. 07/956,522, filed Oct. 5, 1992, (now abandoned).

FIELD OF THE INVENTION

This invention relates to biocatalytic methods for the synthesis of various oxygenated compounds, such methods comprising enantiomerically selective functionalization of arene cis-diol starting materials to potentially all of the nine known inositols, shown below. More particularly this invention relates to the synthesis of specific compounds including but not limited to D-chiro-3-inosose 10, and D-chiro-inositol 6, shown below, and also relates to the necessary methods of synthesis for at least three other inositols, neo-, muco-, and allo-inositol.


BACKGROUND OF THE INVENTION

The expression of arene cis-diols was originally discovered and described by Gibson twenty-three years ago (Gibson, D. T. et al. Biochemistry 1970, 9, 1626). Since that time, use of such arene cis-diols in enantiocontrolled synthesis of oxygenated compounds has gained increasing acceptance by those skilled in the art. Many examples of applications to total synthesis of carbohydrates, cyclitols, and oxygenated alkaloids can be found in the literature, however much of the work done within this area has been with the more tradi-
functional approach of attaining optically pure compounds from the carbohydrate chiral pool. (Hanessian, S. in Total Synthesis of Natural Products: The Chiron Approach, 1983, Pergamon Press (Oxford)). Furthermore, none of the work done with these arene cis-diols teaches or suggests the synthesis of the oxygenated compounds which are the subject of the present invention.

In the present invention, unlike in the previous attempts to utilize these arene cis-diols, emphasis has been placed on the application of precise symmetry-based planning to further functionalization of arene cis-diols in enantiomeric fashion. This approach has previously been successfully applied for the synthesis of cyclitols and sugars. See for example, commonly owned patent applications PCT/US. Ser. No. 91/02594 (WO91/16290) and PCT/US. Ser. No. 91/01040 (WO91/12257), the disclosure of which is incorporated herein by reference.


While the therapeutic potential of D-chiro-inositol 6 is immense, its availability is limited. It is currently available from various sources which are not economically feasible for bulk supply of the drug to the pharmaceutical industry. For example, D-chiro-inositol 6 can be obtained as the demethylolation product from (+)-Pinitol. (+)-Pinitol can be made from chlorobenzene via a six step synthetic process as previously described in commonly owned application PCT/US. Ser. No. 91/02594 incorporated herein. In addition (+)-Pinitol can be obtained by the extraction of wood dust. (Anderson, A. B. Ind. and Eng. Chem. 1953, 593). The compound 6 may also be obtained by either cleavage of the natural antibiotic kasugamycin (Umezawa, H.; Okami, Y.; Hashimoto, T.; Suhara, Y.; Hamada, M. Takeuchi, T. J. Antibiotics (Tokyo)1965, Ser. A, 18, 101), or by a possible enzymatic inversion of C-3 of the readily available myo-inositol 8. (Umezawa, H.; Okami, Y.; Hashimoto, T.; Suhara, Y.; Hamada, M. Takeuchi, T. J. Antibiotics (Tokyo)1965, Ser. A, 18, 101.7. Umezawa, H.; Okami, Y.; Hashimoto, T.; Suhara, Y.; Hamada, M. Takeuchi, T. J. Antibiotics (Tokyo)1965, Ser. A, 18, 101.).

While these methods for synthesis of D-chiro-inositol 6 have been described they are not optimal for either clinical or bulk supply of the drug candidate.

Specifically, the known methods of synthesis are not amenable to scaleup or are too lengthy. One of the methods involves extraction of pinitol from wood dust (Anderson, A. B. Ind. and Eng. Chem. 1953, 593) and its chemical conversion to D-chiro-inositol. This procedure, applied to ton-scale would use large volumes of solvents and large quantities of other chemicals and would be either impractical or costly or both. The preparation of D-chiroinositol from the antibiotic kasugamycin (Umezawa, H.; Okami, Y.; Hashimoto, T.; Suhara, Y.; Hamada, M. Takeuchi, T. J. Antibiotics (Tokyo)1965, Ser. A, 18, 101) also suffers from drawbacks because, on a large scale, about half of the acquired mass of product would be committed to waste (the undesired amino sugar portion of kasugamycin), not to mention the expense with the development of the large scale fermentation process for this antibiotic. The inversion of one center in the available and inexpensive myo-inositol can in principle be accomplished enzymatically (Umezawa, H.; Okami, Y.; Hashimoto, T.; Suhara, Y.; Hamada, M. Takeuchi, T. J. Antibiotics (Tokyo)1965, Ser. A, 18, 101.7. Umezawa, H.; Okami, Y.; Hashimoto, T.; Suhara, Y.; Hamada, M. Takeuchi, T. J. Antibiotics (Tokyo)1965, Ser. A, 18, 101), however no further details on the commercial feasibility of this process have surfaced since 1965.

Based on the shortcomings of the above processes, there is a need for a biocatalytic approach to compound 6 that is an improvement over the above described processes. Such an approach should be environmentally benign as well as amenable to multi-kilogram scale. The currently disclosed process shown in Scheme 1, below is exceedingly brief and efficient in that it provides the epoxydiol 12 in one pot procedure without the necessity of isolation of protected derivative 11. This is an extremely advantageous transformation because it creates four chiral centers in a medium containing water, acetone, magnesium sulfate and manganese dioxide (a naturally occurring mineral), thus making this transformation more efficient and environmentally sound from the point of waste removal.

**Scheme 1.**

Synthesis of D-chiro-Inositol and chiro-3-inosose

```
```

X = Cl, Br, Ph, CH₃, CN
Methods for the synthesis of an epoxydiol 14, which is useful as a synthon, have previously been described (Hudlicky, T.; Price, J. D; Rulin F.; Tsunoda, T. J. Am. Chem. Soc 1990, 112, 9439). This synthon, which was previously used in the preparation of pinitols, as shown in Scheme 2 below, is now prepared by the controlled oxidation of 11 with potassium permanganate (KMnO₄) and a subsequent dehalogenation to 14 rather than previous methods described by Hudlicky et al., and is useful in the synthesis of various other compounds as shown in Scheme 1.

**Scheme 1.** Synthesis of D-chiro-inositol and chiro-3-inosose

![Synthesis of D-chiro-inositol and chiro-3-inosose](image)

(i) KMnO₄/MeSO₄/H₂O; acetone; (ii) For X: Br; Cl: Al₂O₃/H₂O; (iii) For X=Br, Cl: TTMSS/AIBN; (iv) Amberlyst 15/H₂O.

**Scheme 2.** Enantiodivergent Synthesis of Pinitols

![Enantiodivergent Synthesis of Pinitols](image)

(i) Pp39D; (ii) DMP/H⁺; (iii) OsO₄; (iv) m-CPBA; (v) LiAlH₄ or Bu₃SnH/AIBN; (vi) MeOH/H⁺

**SUMMARY OF THE INVENTION:**

Following the biocatalytic production of arene cis-diols, there are described chemical processes for the synthesis of various oxygenated compounds such as those represented by compounds 6,10–28 herein. Further, there are described methods for the synthesis of a substituted epoxydiol 12 useful as a synthon. This synthon 12, prepared by the controlled oxidation of 11 with potassium permanganate (KMnO₄), is useful in the synthesis of various other compounds. The synthesis of the unusual epoxydiol 12 is accomplished as illustrated in Scheme 1.

There are described, chemical processes for the synthesis of various oxygenated compounds such as those represented in Scheme 3 below. Specifically, there are described processes for the preparation of an epoxydiol or an acceptable salt thereof having the formula:

![Reacting an acetonide of the formula](image)

wherein X is as defined above; with permanganate in an appropriate solvent at a temperature from about -78° C. to about 40° C. and at a pH of from about 4–8. Preferably, X is Cl, Br, methyl, phenyl or CN.

There is also described a process for the preparation of D-chiro-inositol 6 or a pharmaceutically acceptable salt thereof, comprising reducing the epoxydiol 12 (X=Cl, Br) with a reducing agent to yield compound 14 and then hydrolyzing epoxydiol 14 with a hydrolyzing agent includ-
ing but not limited to water, an alkaline catalyst, an acidic catalyst, Al₂O₃ or a basic or acidic ion exchange resin.

Also described is a process for the direct hydrolysis of the epoxydiol 12 (X=Cl, Br) to the rare D-chiro-3-inosose 10 using but not limited to water, an alkaline catalyst, acidic catalyst, basic or acidic ion exchange resin, and then reduction of inosose 10 with a reducing agent.

Additional embodiments of the present invention are related to the synthesis of various oxygenated compounds using the epoxydiol (12) described above as a synthone and as illustrated in schemes 1 and 3 herein.

DETAILED DESCRIPTION OF THE INVENTION:

As used in the present invention “suitable or appropriate solvents” include but are not limited to water, water miscible solvents such as dialkylketones with 2—4 carbon atoms, lower alcohols with 1—3 carbon atoms, cyclic ethers and with 2—6 carbon atoms or mixtures thereof.

As used herein “reducing agent” includes but is not limited to a transitionmetal reagent, a hydride reagent or lower alcohols with 1—3 carbon atoms, cyclic ethers such as tetrahydrofuran (THF) or dioxane and mixtures thereof. Preferred solvents are mixtures of water and acetone or water and an alcohol.

As used in this invention, an appropriate temperature range for the synthesis of compound 12 is from about −78° C. to +40° C., preferably from about −15° C. to about +10° C. It is further understood that depending on the pH range of the reaction mixture, the stability of the desired compound may be affected. Therefore, in a preferred embodiment of the present invention, and particularly a preferred method for the synthesis of compound 12 the pH of the reaction should be maintained between about 4—8.

Any known method for controlling pH can be used, for example a buffering agent or system can be used to maintain such pH range, or one could saturate the reaction mixture with CO₂ or buffer the reaction mixture using some organic or inorganic weak acid such as acetic or boric acid, or by using a buffer working in the region of pH from about 4—8, such as phosphate buffer, acetate buffer, tetraborate buffer or borate buffer. In a preferred process for synthesizing compound 12, magnesium sulfate (MgSO₄) is used to maintain the pH between about 4—8. If the reaction mixture is allowed to go above about pH 8, the desired product 12 will be made, although it may be subject to rapid decomposition.

As demonstrated in scheme 1, the exposure of acetonide 11 to 2 eq of aqueous KMnO₄/MgSO₄ at −10° to 5° C. gave an 8:1 mixture of diols 12 and 13 in 60% yield, while higher temperature and lower concentration of the reagent afforded the expected diol 13 as a major product. The formation of 12 is both unexpected and unusual based on: a) the precedents in the literature regarding the oxidation of simple dienes with permanganate [See: Leo, D. G. in The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium, Open Court Publishing Company, (La Salle), 1980]. Two examples of formation of epoxydiols in low yields from permanganate oxidation of conjugated dienes not containing halogen have been reported: von Rudloff, E. Tetrahedron Lett. 1966, 993; and Sable, H. Z.; Anderson, T.; Tolbert, B.; Posternak, T. Helv. Chim. Acta 1963, 46, 1157]; b) the known instability of α-haloepoxides, [See: Carless, H. A. J.; Oak, O. Z. J. Chem. Soc. Chem. Commun., 1991, 61; Ganey, M. V.; Padykula, R. E.; and Berchtold, G. A. J. Org. Chem. 1989, 54, 2787]; and c) the unavailability of data concerning direct and controlled oxidation of 1-chloro-1,3-dienes with KMnO₄ or OSO₄.
As shown in scheme 3 above, the synthon 12 can be used to make several oxygenated compounds. Although applicants have illustrated and/or exemplified a finite number of compounds which can be made using the synthon 12, as a starting material, it is understood that those skilled in the art could readily prepare additional compounds. For example, see scheme 4 below which shows the synthesis of inositols 3, 4 and 5 from the synthon 12. These additional compounds are contemplated by the present invention.

Scheme 4.
Synthesis of Inositols: D-chiro-inositol 6, neo-inositol 5, musco-inositol 4 and allo-inositol 3 from the haloepoxide 12a.

Depending on the desired product, compound 12 can be reacted with a reducing agent such as a hydride reagent or trialkyltinhydride or tris(trimethylsilyl)silane. This reaction, if necessary as understood by those skilled in the art, may be carried out under conditions of radical initiation such as UV light and/or in the presence of an appropriate radical initiator such as AIBN or dibenzoyl peroxide or a radical initiator of a similar nature. Following reduction of the epoxide 12 as described above, the epoxide 14 can be opened and deprotected using pure water, an acid catalyzed hydrolysis with mineral acid (HCl), an organic acid (p-toluenesulfonic acid) or an acid ion exchange resin including but not limited to Amberlyst 15, Amberlyst IR 118, Amberlite CG-50, Dowex 50X8-100, or an alkaline catalyzed hydrolysis with weak bases such as a salt of organic acid, preferably sodium benzoate, sodium acetate or sodium citrate, or an alkaline ion exchange resin included but not limited to Amberlyst A 21 or organic bases including but not limited to aliphatic amines such as triethylamine or diisopropylamine. Reaction temperatures range from about -10° C. to about 110° C., and preferably from

5,563,281
These results constitute remarkably short and effective synthesis of D-chiro-inositol 6: five chemical steps, all but two performed in aqueous media, with a potential of further shortening of this sequence to four steps upon optimization of the reactions involved. For example, it is contemplated that the number of steps in this synthesis may be reduced. It is clear that an attractive industrial preparation of 6 will ensue as a result of such an optimization, as will other applications to the synthesis of functionalized cyclitols.
15

J=10.2 Hz, 1H), 2.38 (bd, J=12.1 Hz, 1H), 1.49 (s, 3H), 1.39 (s, 3H); 13C NMR (CDCl3) δ 110.5 (C), 77.2 (C), 74.2 (CH), 71.6 (CH), 67.9 (CH), 66.5 (CH), 63.7 (CH), 27.1 (CH2), 25.1 (CH3); and

16

For (15,3R,4R,5R,6S)-8,8-dimethyl-3-hydroxy-4,5-oxa-2-oxo-7,9-dioxacyclo[7.3.0]dodecane

A solution of 12a (112 mg, 0.398 mmol), tri-n-butyltin hydride (76.3 mg, 0.220 mmol) and AlBN (25 mg, 0.152 mmol) in toluene (2 ml) was heated for 4 h under argon to 105 °C. Flash chromatography (10% deact. silica gel, CHCl3; MeOH, 95:5) of the under reduced pressure evaporated reaction mixture yielded 37.1 mg (42%) of 14, and 16.2 mg (13%) of 22. For (15,3R,4R,5R,6S)-chloro-4,5-dihydroxy-8,8-dimethyl-2-oxo-7,9-dioxacyclo[7.3.0]dodecane (14): M. P.: 105°–108 °C; [α]20=+110.5° (c 1, CHCl3). IR (KBr) ν 3045, 2995, 1755, 1440, 1405, 1263, 1235, 1110, 1073 cm⁻¹; 1H NMR (CDCl3) δ 5.13 (dd, J=5.8, 1.4 Hz, 1H), 4.86 (dd, J=5.8, 1.4 Hz, 1H), 4.22 (dd, J=3.9, 1.5 Hz, 1H), 3.99 (dd, J=3.9, 1.4 Hz, 1H), 3.31 (bd, J=5.8 Hz, 1H), 1.60 (s, 3H), 1.39 (s, 3H).

For (12a,4R,5R,6S)-2-Chloro-2,3-oxa-6,6,11,11-tetramethyl-3,7,10,12-tetraoxatricyclo[7.3.0.04'8]dodecane (19). A solution of 12a (52.1 mg, 0.220 mmol) in a mixture of THF (1 ml) and MeOH (0.5 ml) was refluxed under argon for 1.5 h. Washing of the silicagel with EtOAc and evaporation of the extract under the reduced pressure furnished 110 mg (98%) of the crude product. Flash chromatography (10% deact. silica gel, CHCl3; MeOH, 95:5) furnished 77 mg (49%) of 21. For (15,3R,4R,5R,6S)-3,4-dihydroxy-8,8-dimethyl-2-oxo-7,9-dioxacyclo[7.3.0]dodecane (43.0) nonane (21): IR (KBr) ν 3450, 3060, 2970, 1750, 1155, 1100 cm⁻¹; 1H NMR (CDCl3) δ 4.45 (dd, J=6.3, 3.6 Hz, 1H), 4.49 (bd, 6.5 Hz, 1H), 4.29 (m, 1H), 4.17 (m, 1H), 2.81 (dd, J=15.0, 8.2, 1.0 Hz, 1H), 2.67 (dd, 15.0, 5.3 Hz, 1H), 2.51 (dd, J=3.3 Hz, 1H), 2.22 (bd, 6.4 Hz, 1H), 1.44 (s, 3H), 1.41 (s, 3H); 13C NMR (CDCl3) δ 206.7 (C), 110.5 (C), 78.2 (CH2), 77.0 (CH), 70.8 (CH), 68.1 (CH), 42.6 (CH3), 26.7 (CH2), 25.1 (CH3); MS (Cl) m/z (rel. intensity) 203 (M+, 20), 185 (20), 159 (15), 145 (30), 127 (100); Anal. calc. for C8H18O7C: C, 53.46; H, 6.98; Found: C, 53.25; H, 6.93. B) Analogous treatment of 12a (420 mg, 1.78 mmol) with solution of SmI2 (0.1M in THF, 18.0 ml, 1.95 mmol) added over the period of 2 min yielded after chromatography (10% deact. silica gel, CHCl3; MeOH, 95:5) 77 mg (22%) of 21 and a complex mixture of products (190 mg). Chromatography (10% deact. silica gel, EtOAc:hexane: 1:1) of this mixture furnished 110 mg (31%) of 21. For (15,3R,4R,5R,6S)-8,8-dimethyl-3-hydroxy-4,4-oxa-2-oxo-7,9-dioxacyclo[7.3.0]dodecane (nonane (23): [α]20=+84.8° (c 1.6, CHCl3); IR (KBr) ν 3590, 3060, 2970, 1760, 1405, 1240, 1185, 1100 cm⁻¹; 1H NMR (CDCl3) δ 4.75 (bd, J=9.1, 1.1 Hz, 1H), 4.53 (dd, J=9.1, 6.6 Hz, 1H), 4.10 (dd, 6.5, 4.3 Hz, 1H), 3.70 (d, J=6.6 Hz, 1H), 2.75 (m, 1H), 1.49 (s, 3H), 1.37 (s, 3H); 13C NMR (CDCl3) δ 201.1 (C), 109.8 (C), 78.0 (CH), 76.0 (CH), 71.5 (CH), 58.6 (CH), 54.9 (CH), 26.3 (CH3), 23.9 (CH3); MS (Cl) m/z (rel. intensity) 201 (M+, 100), 185 (20), 145 (15), 125 (15). A mixture of 12a (141 mg, 0.596 mmol), Zn powder (100 mg) and MeOH (5 ml) was refluxed under argon for 1.5 h. The solid was filtered off and washed with EtOAc. After the addition of Na2CO3 (0.5 ml of saturated solution) and water, the filtrate was evaporated with EtOAc. Evaporation and drying of the extract under the reduced pressure furnished 110 mg of crude product. Flash chromatography (10% deact. silica gel, CHCl3; MeOH, 95:5) furnished 77 mg (56%) of 24, 27 mg (21%) of 25 and 8 mg (6%) of starting material...
17 12a. For (1S,3R,4S,5R,6S)-4,5-dihydroxy-8,8-dimethyl-3-methoxy-2-oxo-7,9-dioxabicyclo[4.3.0]nonane (24): IR (CHCl₃) ν 3437, 2929, 2936, 1742, 1384, 1266, 1158, 1078 cm⁻¹; ¹H NMR (CDCl₃) δ 5.80 (dd, J=5.4, 1.2 Hz, 1H), 4.79 (dd, J=5.5, 5.0, 3.0 Hz, 1H), 4.59 (d, J=5.5, 1.2 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H); ¹³C NMR (CDCl₃) δ 188.4 (C), 151.9 (C), 115.5 (CH), 111.2 (C), 80.0 (CH), 76.6 (CH), 65.0 (CH), 158.9 (CH), 136.2 (CH); MS (Cl) m/z (rel. intensity) 201 (M⁺, 100), 183 (63), 174 (25), 157 (70), 143 (90), 125 (100); Anal. calcd. for C₁₀H₁₄O₂: C, 51.72; H, 6.94; Found: C, 51.64; H, 6.98.

18 D-chiro-inositol (6) A mixture of 14 (16.2 mg, 0.080 mmol), ion exchange resin Amberlyst 15 (100 mg) and water (1.5 ml) was heated for 3.5 h to 80°C. Filtering off the resin, washing with water and evaporation of the filtrate under reduced pressure yielded 12 mg of crystalline product containing 70% of 6 (based on ¹H NMR). B) A mixture of 14 (9.7 g, 44.05 mmol), sodium benzoate (30 mg, 0.21 mmol) and water (150 ml) was refluxed in darkness, under argon for 83 h. The reaction mixture was evaporated, dissolved in a mixture of water and methanol and the mixture was filtered with charcoal. The obtained colorless solution was evaporated to dryness. Recrystallization from the mixture of water and ethanol furnished 6.13 g (77%) of pure 6, identical with the natural product. C) The mixture of 10 (97 mg, 0.545 mmol), NaBH₄ (50 mg, 1.32 mmol) and acetone (5 ml) was stirred at room temperature for 2 h. Then diluted HCl (1:1; 0.2 ml) was added. After an additional 1 h of stirring the reaction mixture was evaporated to dryness to give 180 mg of the product containing 15 of 6 (¹H NMR, GC).

D-Chiro-3-inosito (10). A mixture of 12a (93.7 mg, 0.396 mmol), Al₂O₃ (activated, basic, Brockmann I, 150 mg) and 2 ml of water was heated while stirring for 0.5 h to 80°C. After filtering off the Al₂O₃, washing it and evaporation of the filtrate under reduced pressure, 72 mg (84%) of 10 was obtained. IR (KBr) ν 3346, 3006, 1735, 1576, 1420, 1312, 1078, 1005 cm⁻¹; ¹H NMR (D₂O) δ 4.40 (dd, J=3.4, 1.3 Hz, 1H), 4.16 (dd, J=9.7, 1.3 Hz, 1H), 3.94 (dd, J=4.1, 3.0 Hz, 1H), 3.84 (dd, J=4.1, 3.2 Hz, 1H), 3.59 (dd, J=9.7, 3.1 Hz, 1H); ¹³C NMR (D₂O) δ 208.0 (C), 75.7 (CH), 74.1 (CH), 73.6 (CH), 73.3 (CH), 71.1 (CH).

Neo-inositol (5). A mixture of epoxide 14 (0.69 g, 3.41 mmol), Amberlyst IR-118 (1.5 g) and water (10 ml) was stirred when heated to about 100°C for 30 min. The solid was filtered off, the solution was filtered with charcoal and evaporated to give 0.54 g (87%) of the mixture containing 70% of 6 and 25% of 5. Recrystallization of this product from aqueous ethanol furnished 96 mg of 5.

Muco-inositol (4). A mixture of epoxide 14 (0.58 g, 2.86 mmol), Amberlyst 15 (0.66 g) and water (20 ml) was stirred at room temperature for 24 h. The solid was filtered off, the solution was filtered with charcoal and evaporated to give 0.43 g (83%) of colorless product containing >90% of 4. Recrystallization of this product from aqueous ethanol furnished 4 (0.34 g) of >95% purity.

Alle-inositol (3). A mixture of inosose 10 (1.51 g, 6.45 mmol), Raney nickel (0.5 g) and methanol (15 ml) was hydrogenated at 60 psi for 24 h. The reaction mixture was then diluted with water, filtered with charcoal and evaporated to dryness to furnish 0.91 g (78%) of the crude yellow product containing >90% of 3.

Recrystallization of this product (0.626 g) from aqueous ethanol gave 0.24 g of 3.

What is claimed is:

1. A compound of the formula:

```
O
H
```

in its protected or unprotected form; wherein X is Cl or Br.

* * * * *