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for the Preparation
of Organic Compounds

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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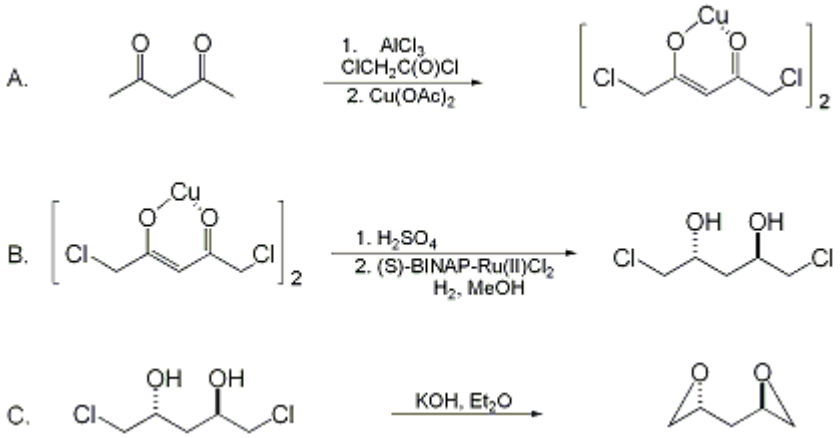
PREPARATION OF (R,R)-1,2:4,5-DIEPOXYPENTANE

[D-threo-Pentitol, 1,2:4,5-dianhydro-3-deoxy-]



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Checked by Gavin F. Painter and Andrew B. Holmes.
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1. Procedure

Caution! Part A of this procedure must be carried out in a well-ventilated hood and the apparatus must be equipped with a hydrogen chloride (HCl) trap to avoid exposure to HCl gas.

Caution! The 1,2:4,5-diepoxypentanes are bisalkylating agents and have been identified as mutagens.[2] They should be considered carcinogenic and handled with care.

A. Bis(1,5-dichloro-2,4-pentanedione)copper(II) complex .[3] A dry, 1-L, three-necked, round-bottomed flask is equipped with a 250-mL addition funnel, reflux condenser, rubber septum with nitrogen inlet, and a magnetic stirrer bar. The reflux condenser is equipped with a line to an HCl trap (Note 1) and the apparatus is maintained under a positive flow of nitrogen. The flask is charged with aluminum chloride (65.0 g, 0.487 mol) followed by the addition of nitrobenzene (82 mL) (*Caution! Evolution of HCl gas*) via the addition funnel. 1,2-Dichloroethane (96 mL) (Note 2) is added via the addition funnel and the mixture is stirred until all solids dissolve (ca. 15 min). The resulting olive green solution is placed in an ice bath, and the funnel is charged with 2,4-pentanedione (50.0 mL, 0.487 mol) (Note 3). The 2,4-pentanedione is added to the solution dropwise over 15 min (*Caution! Evolution of HCl gas*), and the funnel is charged with chloroacetyl chloride (85.0 mL, 1.07 mol) (Note 4). The chloroacetyl chloride is added to the solution dropwise over 15 min, followed by removal of the ice bath. The dark green solution is allowed to warm for 30 min. The reflux condenser is replaced with a thermometer and the addition funnel is replaced with a jacketed short path distillation head connected to a vacuum adapter. The vacuum adapter on the distillation head is connected to the HCl trap and the flask is immersed in an electrically heated oil bath equipped with a magnetic stirrer and external thermometer (Note 5). The reaction is slowly heated over 2 hr to 60°C (Note 6) when acetyl chloride begins to distill (collected at 39°C). The solution temperature is maintained between 60°C and 70°C for the course of the distillation (Note 7). When the distillate temperature falls below 35°C the oil bath is removed, and the solution is cooled to room temperature with an ice bath. The solution is poured into a 2-L Erlenmeyer flask containing 1 L of ice, concentrated hydrochloric acid (80 mL), and a magnetic stirrer bar. The reaction flask is rinsed with 1 N HCl (3 × 50 mL), and the washings are added to the Erlenmeyer flask. The rust colored reaction mixture is stirred vigorously for 17 hr and the phases are separated. The aqueous phase is extracted with diethyl ether (2 × 150 mL) and the organic layers are

combined. The organic layers are added to 1 L of a saturated copper(II) acetate solution in a 2-L Erlenmeyer flask, and the resulting green-brown suspension is stirred vigorously with a magnetic stirrer for 3 hr. The solution is filtered through a Buchner funnel, and the green solid is washed with diethyl ether (3 × 100 mL). The solid is triturated with 125 mL of diethyl ether , refiltered, and washed with diethyl ether (5 × 75 mL) to give 55.6-56.4 g of product as a green-gray powder (57-58% based on 2,4-pentanedione) (Note 8).

B. (2R,4R)-1,5-Dichloro-2,4-pentanediol . Catalyst preparation: A 100-mL Schlenk flask is equipped with a magnetic stirrer bar, rubber septum, and an argon vacuum line. The flask is flame-dried under vacuum and cooled under oxygen-free dry argon (twice), and it is then charged with 1,5-cyclooctadieneruthenium(II) chloride ($RuCl_2$, COD) (79.2 mg, 0.283 mmol) (Note 9) and [(S)-BINAP, 212 mg, 0.340 mmol] (Note 10). The flask and its contents are purged by evacuation and flushed with argon (twice). Triethylamine (Et_3N, 470 µL, 3.37 mmol) (Note 11) is added via syringe followed by toluene (20 mL) via cannula. The solution is heated at reflux for 16 hr under argon, then allowed to cool to room temperature. The resulting orange solution is concentrated by stirring while the flask is held at a vacuum of ca. 1 mm and the toluene and excess triethylamine are condensed in a liquid nitrogen trap to give crude $[RuCl_2$-(S)-BINAP$]_2$-Et_3N catalyst as an orange solid.

1,5-Dichloro-2,4-pentanedione . A 1-L, round-bottomed flask is charged with bis(1,5-dichloro-2,4-pentanedione)copper(II) complex (22.0 g, 55.1 mmol) followed by diethyl ether (200 mL) and 10% sulfuric acid (200 mL). The reaction is stirred vigorously until all the solid dissolves (ca. 45 min). The organic layer is separated and the aqueous phase is extracted with ether (2 × 200 mL). The combined ether layers are washed with brine (2 × 300 mL) and dried (Na_2SO_4). The drying agent is removed by filtration, and the ether phase is concentrated under reduced pressure. The resulting crude material (ca. 20 g) is hydrogenated without further purification (Note 12).

The crude dione (ca. 20 g) is dissolved in dry methanol (MeOH, 40 mL) (Note 13), and the solution is degassed with a stream of dry oxygen-free argon. This solution is transferred via cannula into the flask containing the freshly prepared $[RuCl_2$-(S)-BINAP)]-Et_3N catalyst under argon. The resulting suspension is stirred and heated with a hair dryer to dissolve the catalyst. The resulting solution is transferred via cannula under argon pressure into a flame-dried, 250-mL Schlenk flask sealed with a septum and vented with a syringe needle. The septum is replaced with a high-vacuum stopcock (Note 14) and the Schlenk flask is transferred to a nitrogen glove box where the contents are transferred to a 250-mL pressure reaction vessel equipped with a magnetic stirring bar. The vessel is sealed (Note 15). The pressure vessel is then transferred from the glove box to an electrical heating jacket preheated to 70°C and the vessel is pressurized to 1250 psi with hydrogen gas in an explosion proof fume hood. The vessel is heated until the internal temperature is 65°C, and the contents are stirred with a magnetic stirrer at that temperature for 12-14 hr (Note 16). The vessel is cooled to room temperature and cautiously vented to discharge excess hydrogen gas. The reaction mixture is concentrated under reduced pressure and filtered through a plug of silica gel that is washed with 1:1 ethyl acetate/hexanes (ca. 300 mL). Solvent is removed on a rotary evaporator and the crude product is crystallized from a mixture of hexane:dichloromethane (2:3, v/v), and the solid is collected by suction filtration and rinsed with a mixture of hexane:CH_2Cl_2 (2:3, v/v). The off-white solid is recrystallized from hexane:CH_2Cl_2 (2:3, v/v), to give three crops of crystals (Note 17). The combined yield of the white crystalline product is 7.66 g (40%) (Note 18).

C. (2R,4R)-1,2:4,5-Diepoxypentane . A 1-L, round-bottomed flask with a magnetic stirrer bar is charged with (2R,4R)-1,5-dichloro-2,4-pentanediol (6.00 g, 34.7 mmol) and diethyl ether (270 mL), and the solution is cooled to 0°C. Freshly powdered potassium hydroxide (KOH, 18.5 g, 330 mmol) is added and the solution is stirred for 3 hr at 25°C (Note 19). The reaction mixture is filtered through a plug of magnesium sulfate ($MgSO_4$), and the ether is removed under reduced pressure from an ice bath to give 3.20 g (92%) of the product as a colorless oil (Note 20). The optical purity of the product is >97% ee (Note 21).

2. Notes

1. The reflux condenser is fitted with an outlet that is connected with Tygon tubing to a Drechsel bottle and then an inverted funnel in a crystallizing dish filled with water which serves as the HCl trap (the

submitters used Lab Glass #LG-8605).
2. 1,2-Dichloroethane, 99%, was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
3. 2,4-Pentanedione, 99+%, was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
4. Chloroacetyl chloride, 98%, was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
5. The submitters heated the flask with a heating mantle and wrapped the exposed part of the flask in glass wool. This serves as an insulator to allow the subsequent distillation to proceed at lower temperatures.
6. Care must be taken not to heat the reaction mixture above 70°C.
7. The distillation typically requires 8-10 hr. Note that there is a slow nitrogen stream running *through* the apparatus when set up as described. The checkers found that the acetyl chloride only condensed when the nitrogen flow was decreased or stopped.
8. The submitters obtained 58.6 g (60%) of a gray powder.
9. 1,5-Cyclooctadieneruthenium(II) chloride, 95%, was purchased from Aldrich Chemical Compay, Inc. , and used without further purification.
10. (S)-(−)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, 99% was purchased from Aldrich Chemical Company, Inc. , and used without further purification.
11. Triethylamine was distilled from calcium hydride and stored over KOH under argon. Toluene was distilled from and stored over sodium under argon.
12. The crude dione could be purified at this stage by Kugelrohr distillation (oven temp. 80°C at 1 mm) to give the 1,5-dichloro-2,4-pentanedione as a clear, colorless oil. The enol:keto ratio is ca. 5.7:1. The physical properties are as follows: ^{1}H NMR (250 MHz, $CDCl_3$) (enol) δ: 4.07 (s, 4 H), 6.14 (bs, 1 H), the acidic OH was not recorded; ^{13}C NMR (62.5 MHz, $CDCl_3$) (enol) δ: 44.1, 96.8, 187.3 ; ^{1}H NMR (250 MHz, $CDCl_3$) (keto) δ: 3.95 (bs, 2 H), 4.16 (s, 4 H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) (keto) δ: 48.3, 50.5, 196.2 .
13. The checkers used MeOH that had been freshly distilled from sodium methoxide (NaOMe) that was stored over 3 Å molecular sieves under argon. The submitters used Fisher ACS certified methanol without purification.
14. A J. Young high vacuum stopcock was purchased from Aldrich Chemical Compay, Inc.
15. A Bergof 250-mL autoclave with PTFE seal was used. The submitters did not use a glove box. They used a Parr #4751, 125-mL pressure vessel that was assembled with a glass liner and a magnetic stirring bar, but without the top fitting. They then purged the vessel with a stream of Ar, and then the reaction mixture was added from the Schlenk flask via cannula through the top opening of the pressure vessel. The valve block assembly was attached, and hydrogenation was begun. The reaction vessel was wrapped in heating tape or placed in a heating mantle and pressurized to 1250 psi with H_2 gas in an explosion proof fume hood.
16. Temperature control is important for the success of the reaction. The internal temperature should be monitored, and the temperature should be held around 65°C. The submitters found that when the autoclave (Parr #4751) is heated with heating tape and the internal temperature cannot be monitored, an externally measured temperature of ca. 100°C is appropriate. Too high a temperature leads to cyclization of the diol to give 2-chloromethyl-4-hydroxytetrahydrofuran.
17. The second crop of crystals was obtained by concentrating the supernatant from the first crystallization under reduced pressure, then redissolving in a minimum hexane:CH_2Cl_2 (2:3, v/v). The third crop was obtained in a similar manner.
18. The submitters obtained 7.40 g (39%). The physical properties are as follows: mp 85-86°C; $[\alpha]_D^{24}$ +21.1 ($CHCl_3$, *c* 1.125); IR (KBr) cm^{-1}: 3364, 2959, 2890, 1435, 1402, 1340, 1294, 1103, 1072, 1052, 910, 710 ; ^{1}H NMR (250 MHz, acetone-d_6) δ: 1.70 (dd, 2 H, J = 6.9, 5.4), 3.50-3.65 (m, 4 H), 4.02-4.12 (m, 2 H), 4.22 (d, 2 H, J = 5.6) ; ^{13}C NMR (62.5 MHz, acetone-d_6, APT) δ: 38.7, 50.8, 68.0 . Anal. Calcd. for $C_5H_{10}Cl_2O_2$: C, 34.71; H, 5.83. Found C, 34.7; H, 5.8. The optical purity of the 1,5-dichloro-2,4-pentanediol can be assayed by its Mosher ester analysis. The checkers prepared the bis-Mosher ester from the (R,R)-diol with (R)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride acid chloride as follows: A flame-dried flask, under argon, is charged with (2R,4R)-1,5-dichloro-2,4-pentanediol (10 mg, 0.058 mmol) and 4-dimethylaminopyridine (DMAP) (ca. 1 mg). The flask is evacuated, then repressurized with argon. Following the addition of dry Et_3N (55 μL, 0.39 mmol)s (Note 11) and dry

CH_2Cl_2 (3 mL) (dried over calcium hydride and stored over 4Å molecular sieves), (R)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Aldrich Chemical Company, Inc.) (50 mg, 0.20 mmol) is added, and the reaction mixture is stirred at 25°C under argon for 24 hr, at which time silica TLC (silica gel, 50% EtOAc/hexane) indicated that no diol remained. The reaction mixture is concentrated under reduced pressure and filtered through a plug of silica (CH_2Cl_2) to give the bis Mosher ester (25 mg, 0.041 mmol, 71%); $[\alpha]_D^{22}$ +50.0 ($CHCl_3$, *c* 0.30); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.20 (dd, 2 H, J = 7.3, 5.7 (central CH_2)), 3.53 (bs, 6 H, OMe), 3.57 (dd, 2 H, J = 12.1, 4.0), 3.69 (dd, 2 H, J = 12.0, 4.9), 5.13-5.21 (m, 2 H), 7.41-7.45 (m, 6 H), 7.50-7.55 (m, 4 H) ; ^{19}F NMR (235 MHz, $CDCl_3$) δ: −69.6 ; FAB-MS m/z 627.0785 ($[M+Na]^+$, calcd. for $C_{25}H_{24}Cl_2F_6O_6Na$ 627.0752), 605 (5), $[M]^+$, 535 (5), 472 (3), 371 (5), 189 (100) . The diastereomeric bis Mosher ester derived from the (S,S)-diol and (R)-acid chloride displays the central CH_2 as a doublet of doublets (J = 7.5, 5.5) at δ 2.07.

19. The KOH is ground with a mortar and pestle in a fume hood, and the ether is used as supplied. The submitters noted that when very dry KOH and ether were used, the reaction did not proceed to completion. They then effected the reaction with 50% aqueous KOH solution instead of powdered KOH, followed by a standard aqueous workup.

20. The submitters obtained 4.50 g (45.0 mmol, 90%) from 8.65 g (50 mmol) of diol. A sample purified by Kugelrohr distillation (bp 65°C at 28 Torr) gave the following spectral data: $[\alpha]_D^{24}$ +57.6 ($CHCl_3$, *c* 2.24); IR (neat) cm^{-1}: 3055, 2997, 2924, 1421, 1256, 980, 938, 912, 844, 792, 747 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.72 (t, 2 H, J = 5.7), 2.51 (dd, 2 H, J = 4.9, 2.6), 2.73 (dd, 2 H, J = 4.9, 4.1), 3.03-3.09 (m, 2 H) ; ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ: 36.2, 46.9, 49.5 . Anal. Calcd. for $C_5H_8O_2$; C, 59.98; H, 8.05. Found C, 60.0; H, 8.2.

21. The enantiomeric purity of the (R,R)-1,2:4,5-diepoxypentane was measured as 96% by comparing the sample with (S,S)-1,2:4,5-diepoxypentane using GC analysis on a B-PH (beta-cyclodextrin, permethylated hydroxypropyl) GC column. The submitters prepared both (S,S)- and (R,R)-enantiomers with enantiomeric excess >97% using the enantiomeric BINAP-Ru(II)Cl_2 catalysts. The enantiomeric purity of their 1,2:4,5-diepoxypentane was assayed by GC analysis using a B-PH (β-cyclodextrin, permethylated hydroxypropyl) column (20 m × 0.25 mm × 0.25μ); split ratio = 100:1; column flow 1.0 mL/min.; 50°C - 5 min; 3°C/min until 150°C. Retention times: (R,R)-12.55 min; (S,S)-12.75 min.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The (R,R)-1,2:4,5-diepoxypentane was first prepared in optically pure form by Ley using a multistep route from D-(+)-ribonic acid γ-lactone .[4] Ley used this diepoxide as a linchpin to assemble the spiroacetal segments of (+)-milbemycin β_1 [5] [4] and avermectin B_{1a}.[6] [7] The route described here[8] is based on the enantioselective hydrogenation of 1,5-dichloro-2,4-pentanedione [3] using Ru(BINAP)Cl_2 catalyst.[9] [10] [11] Both the (R,R)- and the (S,S)-1,2:4,5-diepoxypentane can be prepared by this route using the appropriate BINAP catalyst. The C_2 symmetric diepoxypentanes are very useful synthons for anti-1,3-diols[8] and have been key precursors in the synthesis of roflamycoin and its isomer.[12] [13] They also have been used to prepare optically pure A-ring intermediates for the synthesis of vitamin-D_3 analogs.[14]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R,R)-1,2:4,5-Diepoxypentane:
D-threo-Pentitol, 1,2:4,5-dianhydro-3-deoxy- (12)- (109905-51-3)

Bis(1,5-dichloro-2,4-pentanedione) copper(II) complex:
Copper, bis(1,5-dichloro-2,4-pentanedionato-O,O')- (12); (135943-96-3)

Aluminum chloride (8,9); (7446-70-0)

Nitrobenzene: *HIGHLY TOXIC*:
Benzene, nitro- (8,9); (98-95-3)

2,4-Pentanedione (8,9); (123-54-6)

Chloroacetyl chloride:
Acetyl chloride, chloro- (8,9); (79-04-9)

(2R,4R)-1,5-Dichloro-2,4-pentanediol:
2,4-Pentanediol, 1,5-dichloro-, [R-(R,R)]- (12); (136030-28-9)

1,5-Cyclooctadieneruthenium(II) chloride:
Ruthenium, dichloro[(1,2,5,6-η)-1,5-cyclooctadiene]- (9); (50982-12-2)

Triethylamine (8);
Ethanamine, N,N-diethyl- (9); (121-44-8)

(S)-(−)-BINAP:
(S)-(−)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl:
Phosphine, [1,1'-binaphthalene]-2,2'-diylbis(diphenyl-, (S)- (10); (76189-56-5)

Ruthenium chloride-(S)-BINAP-triethylamine:
Ruthenium, bis[[1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine]-P,P']di-μ-chlorodichloro(N,N-diethylethanamine)di- (12); (114717-51-0)

1,5-Dichloro-2,4-pentanedione:
2,4-Pentanedione, 1,5-dichloro- (9); (40630-12-4)

Hydrogen (8,9); (1333-74-0)

Potassium hydroxide (8,9); (1310-58-3)