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A FACILE SYNTHESIS OF PENTADEUTERATED DOMIODOL (2-IODOMETHYL-4-HYDROXYMETHYL-1,3-DIOXOLANE) FROM GLYCEROL-1,1,2,3,3-d_5

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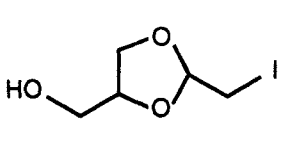
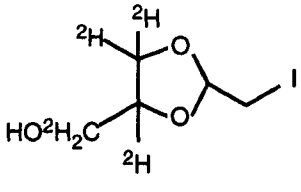
Summary The acid catalyzed reaction of glycerol-d_5 with bromoacetaldehyde dimethyl acetal affords the corresponding 2-bromomethyl-4-hydroxymethyl-1,3-dioxolane, which was treated with lithium iodide in 2-butanone to afford the pentadeuterated domiodol **1** in high isotopic purity.

Key Words Domiodol, mucolytic drug, deuterium, synthesis

For ongoing projects to study the absorption, distribution, and excretion of the mucolytic drug domiodol (2-iodomethyl-4-hydroxymethyl-1,3-dioxolane, **1**)[1] by gas chromatography-mass spectrometry, we needed a sample of the deuterated iododerivative **2**.



1



2

Glycerol-d_5 with 99% isotopic purity was commercially available (MSD Isotopes, Germany) and the synthesis of the deuterated iodo compound **2** had to be modelled on this starting labelled material. The method reported on the preparation of domiodol **1** heating at high temperatures a mixture of glycerol and iodine could not be used, since a mixture of about twenty iodinated compounds was formed.[2] A more convenient synthesis of unlabelled domiodol **1** started from 1-benzyl glycerol **3**, which reacted with bromoacetaldehyde dimethyl acetal to afford bromoderivative **4a**, in turn

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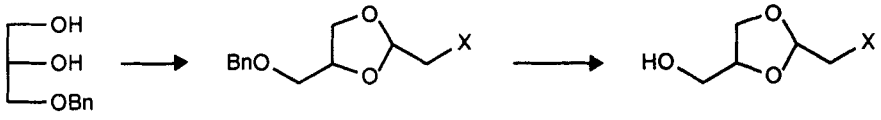
converted into the iododerivative **4b** by displacement of the bromine with iodine.[3] Hydrogenolysis of the benzyl group of compound **4b** afforded the required domiodol **1.** A similar procedure was followed for the synthesis of ^{14}C-domiodol **1**, except that the formation of the dioxolane ring containing the iodine atom was realized by ketalization of 1-benzyl glycerol **3** with the relatively uncommon 2-iodoacetaldehyde to afford directly the derivative **4b**, which was later transformed into ^{14}C-domiodol **1**.[4]

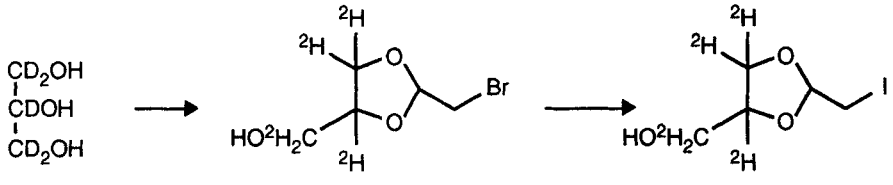


3 4 5

a. X = Br a. X = Br

b. X = I b. X = I

For the preparation of domiodol-d_5 **2** we could rely on the above syntheses which started from 1-benzyl glycerol **3.** This compound, however, could not be prepared directly from glycerol[5] and an alternative synthesis could start from glycerol acetonide that, however, is not easily prepared pure in small scale starting from glycerol itself.[6] Furthermore, the direct condensation of glycerol with bromoacetaldehyde dimethylacetal has been described to afford a mixture of 5 and 6 member rings, the main product being 2-bromomethyl-1-hydroxymethyl-1,3-dioxolane **5**.[7] Starting from this report, we have realized a simple procedure for the preparation of domiodol-d_5 **2** from glycerol-d_5.



6 2

The reaction with excess bromoacetaldehyde diethyl acetal in the presence of p-toluenesulfonic acid without addition of solvent afforded the crude pentadeuterated 2-bromomethyl-4-hydroxymethyl-1,3-dioxolane **6** which was purified from the acid catalyst and then reacted with lithium iodide in 2-butanone. The final iodinated material was purified by column chromatography

on neutral alumina, affording the required domiodol-d_5 **2** (30% yield). Starting from 99% deuterated glycerol, the sample of domiodol-d_5 **2** contained the labeling at >98% isotopic purity and could be therefore used as internal standard for a GC-MS analysis of the drug from plasma and other material, using the selected-ion recording technique.

Experimental Section

All the solvents and reagents were from Fluka (Switzerland), except glycerol-d_5 (99% isotopic purity) that was purchased from MSD Isotopes (Germany). Analytical TLC were performed on silica gel Merck 60 F254 plates and distillations for analytical purposes were carried on a glass tube oven Büchi GKR-50. The 60 MHz ^{1}H-NMR spectra of sample solutions in $CDCl_3$ were recorded on a Varian EM 60 spectrometer using $SiMe_4$ as internal standard. GLC-MS were registered on a Finnigan 4021 mass spectrometer (electron impact mode) equipped with a SPB-1 fused silica column (30 m X 0.32 mm i.d., 0.20 μm thickness; Supelco, Bellofonte, USA).

***Domiodol-d_5* 2.** - To a solution of gycerol-d_5 (0.5 g, 5.1 mmol) in bromoacetaldehyde dimethyl acetal as solvent and reactant (2.1 mL, 13.5 mmol), p-toluenesulfonic acid (0.005 g) was added and the solution kept at 70 °C under stirring (1 h). TLC monitoring of the reaction (toluene/ethyl acetate, 8:2) showed the formation of three products and at the end of the reaction diethyl ether (4 mL) was added and the organic phase washed with an aqueous solution of sodium hydrogen carbonate and then water to completely remove the acid catalyst. The solution was dried on anhydrous sodium sulfate and evaporated at reduced pressure to leave a final crude mixture (1.3 g) which was used as for the next step without any purification. Thus, to a solution of the above mixture in 2-butanone (10 mL), lithium iodide (1.08 g, 8 mmol) was added and the solution kept at 90 °C for 3 days. By this time the conversion of the bromoderivatives was complete, as judged by GLC analysis and a 10% aqueous solution of sodium thiosulfate was added. The solvent 2-butanone was removed at reduced pressure and from the concentrated solution the products were extracted with dichloromethane (3 x 5 mL). The organic solution was dried on sodium sulfate and evaporated at reduced pressure. The crude mixture of products (1.5 g) was purified by column chromatography on neutral alumina (III grade activity) and the elution with hexane/ethyl acetate, 1:1 afforded the deuterated domiodol **2** (0.37 g, 30%). The chemico-physical characteristics were in full agreement with the data reported in Ref. 3. ^{1}H-NMR, δ 2.40 - 2.70 (m, 1 H, exchangeable), 3.30 (d, 2 H, CH_2I), 4.70 (t, 1 H, O-*CH*-O); MS, m/z 248 (M^+ for d_5), 243 (M^+ for unlabelled, <1% of 248). The trimethylsilyl derivative [prepared *in situ* with bis(trimethylsilyl)trifluoroacetamide (BSTFA) in pyridine] of the *unlabelled* **1**

showed the following fragmentations: m/z 315 (M^+-1), 301 (M^+-CH_3), 271 [M^+- $(CH_3)_3$], 243 [M^+-$Si(CH_3)_3$], 213 [M^+ - $CH_2OSi(CH_3)_3$], 175 [M^+ - CH_2J]. For the silyl derivative of the deuterated domiodol **2** : m/z 320 (M^+-1), 306 (M^+-CH_3), 216 [M^+ - $CD_2OSi(CH_3)_3$], 194 [M^+ - J], 180 [M^+ - CH_2J].

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References and Notes

1. (a) Finiguerra, M.; Conti, P.; Figura, I.; Legnani, W.; Morandini, G. C. *Curr. Ther. Res.* **1982**, *31*, 895. (b) Bandera, M.; Fioretti, M.; Legnani, W. *Curr. Ther. Res.* **1982**, *32*, 312. (c) Casali, L.; Rampulla, C.; Rossi, A. *Int. J. Clin. Pharm. Ther. Tox.* **1982**, *20*, 554.
2. Hoffnagle, G. F.; Osol, A. *J. Am. Pharm. Ass.* **1958**, *47*, 303.
3. Cantarelli, G.; Carissimi, M.; Gentili, P.; Ravenna, F. *Il Farmaco* **1979**, *34*, 393.
4. Ohtsuki, T.; Takaichi, M.; Jin, Y.; Yokoshima, T,; Kato, R.*Il Farmaco* **1984**, *39*, 291.
5. A few attempts to prepare 1-benzyl glycerol **3** from glycerol on millimolar scale afforded a mixture of products of difficult purification. For a review on the synthesis of glycerides, see: Mattson, F. H.; Volpenhein, R. A. *J. Lipid Res.* **1962**, *3*, 281.
6. Howe, R. J.; Malkin, T. *J. Chem. Soc. (C)* **1951**, 2663.
7. Baggett, N.; Duxbury, J. M.; Foster, A. B.; Webber, J. M. *J. Chem. Soc. (C)* **1966**, 208.