Heteroatom Chemistry
Volume 16, Number 7, 2005

Synthesis of 2-Phosphinoxidomethyl- and 2-Phosphonomethyl Glutaric Acid Derivatives

Kálmán Harsányi,[1*] György Domány,[1] István Greiner,[1] Henrietta Forintos,[2] and György Keglevich[2]

[1]*Gedeon Richter Ltd., 1475 Budapest, Hungary*

[2]*Department of Organic Chemical Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary*

Received 6 April 2005; revised 26 April 2005

ABSTRACT: *Michael addition of the corresponding anions derived from diphenylphosphine oxide, dialkylphosphites, and a cyclic phosphite to α-methylene-glutaric esters (***1***) afforded the title compounds (***2–6***). Double debenzylation of 2-phosphono glutaric esters* **4b** *and* **5a** *by catalytic hydrogenation under the appropriate conditions gave the corresponding diacides* **8** *and* **9***, respectively.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:562–565, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20142

INTRODUCTION

2-Phosphonomethyl-1,5-pentane diacid (2-PMPA) is known to be an efficient drug in decreasing the risk of stroke [1,2]. The beneficial result is based on the inhibition of the *N*-acetylated-α-linked acidic dipeptidase (NAALADase) enzyme. Jackson and coworkers studied the effect of structural modifications, such as the variation of the chain length, the modification of the phosphonic moiety to a phosphinic function, and the replacement of the phosphorus atom by other heteroatoms [3]. It was a challenge for us to synthesize glutaric acids and esters with a variety of $Y_2P(O)CH_2$-substituents (where Y is phenyl, alkoxy, or H) in position 2 that have potentially of NAALADase inhibition effect.

α-Methylene-glutaric esters (**1a** and **1b**) were reacted with diphenylphosphine oxide and dialkylphosphites in Michael addition. The >P(O)H reagents were converted to the more reactive $>P(O)^-$ anions by reaction with trimethylaluminum as described in earlier cases [4–6]. The reaction products were 2-diphenylphosphinoxidomethyl- and 2-dialkylphosphonomethyl-glutaric esters **2**, **3a–5a** **3b**, and **4b** that were obtained in 48–65% yield after column chromatography (Scheme 1), and were characterized by ^{31}P, ^{13}C, and ^1H NMR, as well as mass spectroscopy.

The method was then extended to the addition of a cyclic phosphite, 1,3,2-dioxaphosphinane 2-oxide at the end of the electron-poor double bond of **1a** and **1b** to afford 2-phosphonomethyl derivatives **6a** and **6b**, respectively (Scheme 1). Those were obtained in ~46% yield and were characterized by ^{31}P, ^{13}C, and ^1H NMR as well as mass spectroscopy.

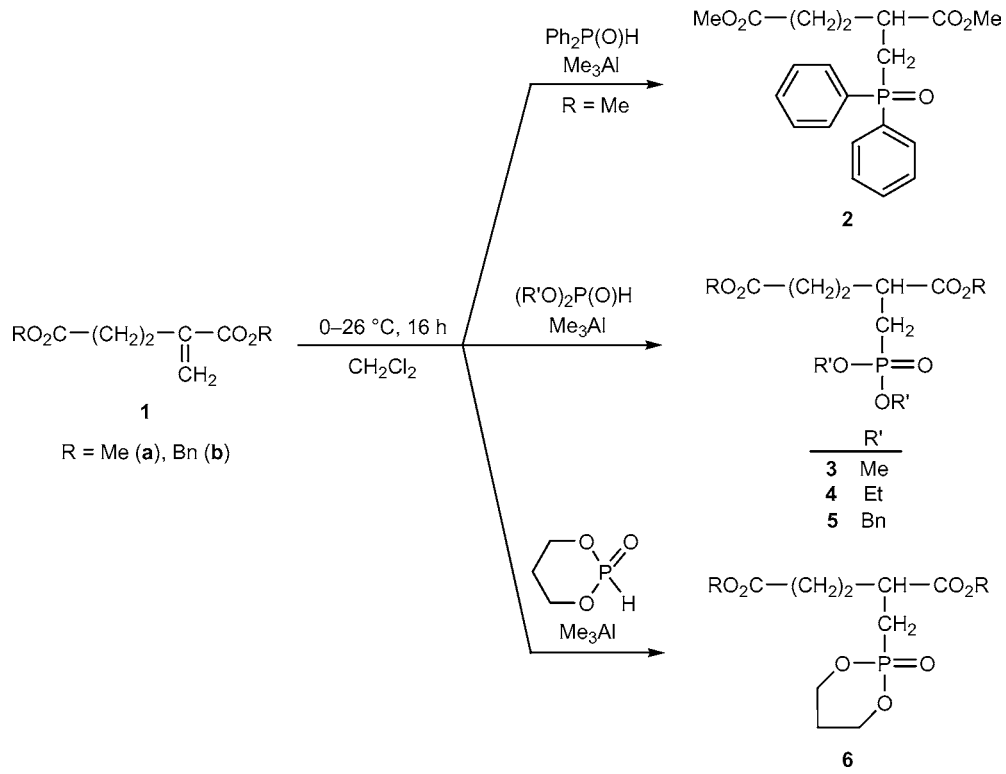
The double debenzylation of bis(carboxylic ester) **4b** was attempted at 26°C and 1 bar in methanol. Surprisingly, monomethylester **7** was obtained from the reaction mixture in a reasonable yield (65%) (Scheme 2).

Under the conditions of the reaction, the 2-substituted glutaric acid formed may undergo monoesterification with the methanol used as solvent; a direct alcoholysis by the action of methanol seems to be less probable. Obviously, the acidic product

Dedicated to Professor Dr. András Lipták (University of Debrecen) on the occasion of his 70th birthday.

*Professor Harsányi passed away while the paper was in press.

Correspondence to: György Keglevich; e-mail: keglevich@mail.bme.hu.

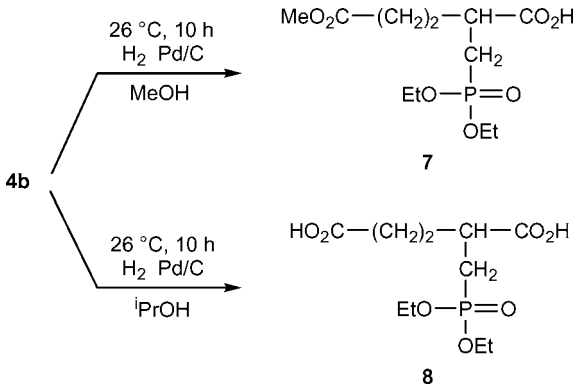


SCHEME 1

formed by debenzylation may catalyze the esterification. Presumably, the carboxyl group located far from the phosphonomethyl group was converted to an ester function due to its enhanced reactivity.

Using a less reactive alcohol, such as isopropanol as the solvent of the catalytic debenzylation, the expected phosphonomethyl-glutaric acid (**8**) was obtained in a neat reaction and in 51% yield after chromatography (Scheme 2).

2-Diethylphosphono-glutaric acid **8** was characterized by ^{31}P and ^{13}C NMR, as well as mass spectroscopy.



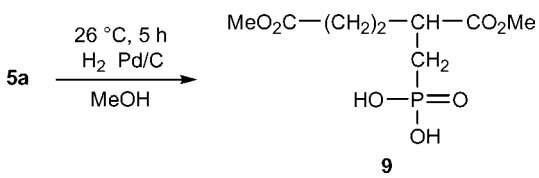
SCHEME 2

Double debenzylation of phosphonic ester **5a** by catalytic hydrogenation at ambient temperature and atmospheric pressure was successful in methanol even after a shorter reaction time and led to phosphonic acid **9** that was characterized only by ^{31}P NMR and MS due to its very poor solubility (Scheme 3).

To summarize our results, Michael addition of a variety >P(O)H species to the double bond of α-methylene glutaric esters led to the corresponding 2->P(O)CH_2-glutaric derivatives. Double debenzylation at the two carboxylic ester or phosphonic diester moieties afforded the corresponding diacids. Biological investigation of the above compounds will be published under separate cover.

EXPERIMENTAL

The ^{31}P, ^{13}C, and ^{1}H NMR spectra were obtained on a Bruker DRX-500 spectrometer operating at 202.4,



SCHEME 3

125.7, and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. The couplings are given in Hz. Mass spectrometry was performed on a ZAB-2SEQ instrument. The starting α-methylene-glutaric esters **1a** and **1b** were prepared by the dimerization of the corresponding acrylates in the presence of hexamethylphosphorous triamide as described earlier [1].

1,3,2-Dioxaphosphinane 2-oxide was prepared by a known procedure [7].

*General Procedure for the Synthesis of Phosphonomethyl- and Phosphinoxidomethyl-Glutaric Acid Esters (**2, 3a–6a, 3b, 4b, 6b**)*

A solution of 5.8 mmol of dialkylphosphite or diphenylphosphine oxide in 15 mL of dry dichloromethane was treated with 2.9 mL (5.8 mmol) of 2 M trimethylaluminum in hexane at 0°C. After a 20 min stirring, 5.8 mmol of α-methylene-glutaric ester (**1a** or **1b**) in 5 mL of dichloromethane was added dropwise. The mixture was stirred at room temperature for 16 h then treated with 5.6 mL of hydrochloric acid in 50 mL of water. The organic phase was separated, dried (Na_2SO_4), and evaporated. Purification by column chromatography (silica gel, 3% methanol in chloroform) afforded the title compounds.

*2-(Diphenylphosphinoxidomethyl)-Glutaric Acid Dimethyl Ester (**2**)*

Yield: 59%; ^{31}P NMR ($CDCl_3$) δ 29.3; ^{13}C NMR ($CDCl_3$) δ 28.5 ($J_{PC} = 9.7$, C_3), 30.8 (C_4), 31.4 ($J_{PC} = 70.7$, C_6), 37.9 ($J_{PC} = 2.1$, C_2), 51.1 (MeO), 51.4 (MeO), 172.2 (C_5), 173.9 ($J_{PC} = 6.2$, C_1); ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 3H, MeO), 3.61 (s, 3H, MeO); FAB-MS, 375 $(M + H)^+$; $(M + H)^+_{found} = 375.1351$, $C_{20}H_{24}O_5P$ requires 375.1361.

*2-(Dimethylphosphonomethyl)-Glutaric Acid Dimethyl Ester (**3a**)*

Yield: 48%; ^{31}P NMR ($CDCl_3$) δ 31.4; ^{13}C NMR ($CDCl_3$) δ 26.5 ($J_{PC} = 142.5$, C_6), 27.9 ($J_{PC} = 12.6$, C_3), 30.8 (C_4), 38.7 ($J_{PC} = 3.6$, C_2), 51.3 (MeO), 51.6 (MeO), 52.0 (d, $J = 6.9$, MeO), 52.1 (d, $J = 7.0$, MeO), 172.4 (C_5), 173.9 ($J_{PC} = 8.4$, C_1); ^{1}H NMR ($CDCl_3$) δ 3,67 (s, 3H, MeO), 3.71 (s, 3H, MeO), 3.72 (d, $J = 10.9$ Hz, 3H, MeO), 3.73 (d, $J = 10.9$ Hz, 3H, MeO); FAB-MS, 283 $(M+H)^+$; $(M+H)^+_{found} = 283.0946$, $C_{10}H_{20}O_7P$ requires 283.0947.

*2-(Dimethylphosphonomethyl)-Glutaric Acid Dibenzyl Ester (**3b**)*

Yield: 53%; ^{31}P NMR ($CDCl_3$)δ 30.1; ^{13}C NMR ($CDCl_3$) δ 27.9 ($J_{PC} = 142.2$, C_6), 28.1 ($J_{PC} = 13.6$, C_3), 30.8 (C_4), 38.8 (C_2), 51.3 (MeO), 51.6 (MeO), 67.1 ($J_{PC} = 6.0$, CH_2OP), 172.4 (C_5), 173.9 ($J_{PC} = 7.3$, C_1);^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3H, MeO), 3.65 (s, 3H, MeO); FAB-MS, 435 $(M + H)^+$; $(M + H)^+_{found} = 435.1530$, $C_{22}H_{28}O_7P$ requires 435.1573.

*2-(Diethylphosphonomethyl)-Glutaric Acid Dimethyl Ester (**4a**)*

Yield: 65%; ^{31}P NMR ($CDCl_3$) δ 28.7; ^{13}C NMR ($CDCl_3$) δ 16.0 (CH_3CH_2), 27.5 ($J_{PC} = 133.1$, C_6), 28.1 (C_3), 30.9 (C_4), 38.9 (C_2), 51.3 (MeO), 51.6 (MeO), 61.5 (CH_3CH_2), 172.5 (C_5), 174.1 ($J_{PC} = 6.3$, C_1); ^{1}H NMR ($CDCl_3$)δ 1.28 (dt, $^3J_{HH} = 7.1$, $^4J_{PH} = 3.6$, 6H, CH_3CH_2), 3.64 (s, 3H, MeO), 3.68 (s, 3H, MeO), 4.02–4.10 (m, 4H, CH_3CH_2), FAB-MS, 311 $(M + H)^+$; $(M + H)^+_{found} = 311.1236$, $C_{12}H_{24}O_7P$ requires 311.1260.

*2-(Diethylphosphonomethyl)-Glutaric Acid Dibenzyl Ester (**4b**)*

Yield: 48%; ^{31}P NMR ($CDCl_3$) δ 28.9; ^{13}C NMR ($CDCl_3$) δ 16.1 (CH_3CH_2), 27.5 ($J_{PC} = 142.3$, C_6), 28.1 ($J_{PC} = 12.2$, C_3), 31.0 (C_4), 39.0 (C_2), 61.5 ($J = 7.2$, CH_3CH_2), 61.5 ($J = 8.0$, CH_3CH_2), 66.0 (CH_2Ph), 66.4 (CH_2Ph), 171.9 (C_5), 173.4 ($J_{PC} = 8.3$, C_1); ^{1}H NMR ($CDCl_3$) δ 1.28 (dt, $^3J_{HH} = 12.6$, $^4J_{PH} = 5.8$, 6H, CH_2CH_3), 4.02–4.08 (m, 4H, CH_2CH_3) 5.08 (s, 2H, CH_2Ph) 5.12 (s, 2H, CH_2Ph); FAB-MS, 463 $(M + H)^+$; $(M + H)^+_{found} = 463.1840$, $C_{24}H_{32}O_7P$ requires 463.1886.

*2-(Dibenzylphosphonomethyl)-Glutaric Acid Dimethyl Ester (**5a**)*

Yield: 53%; ^{31}P NMR ($CDCl_3$) δ 30.1; ^{13}C NMR ($CDCl_3$) δ 27.9 ($J_{PC} = 142.2$, C_6), 28.1 ($J_{PC} = 13.6$, C_3), 30.8 (C_4), 38.8 (C_2), 51.3 (MeO), 51.6 (MeO), 67.1 ($J_{PC} = 6.0$, CH_2OP), 172.4 (C_5), 173.9 ($J_{PC} = 7.3$, C_1); ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3H, MeO), 3.65 (s, 3H, MeO); FAB-MS, 435 $(M + H)^+$; $(M + H)^+_{found} = 435.1530$, $C_{22}H_{28}O_7P$ requires 435.1573.

*2-(2′-Oxo-[1′,3′,2′]dioxaphosphinan-2′-ylmethyl)-Glutaric Acid Dimethyl Ester (**6a**)*

Yield: 50%; ^{31}P NMR ($CDCl_3$) δ 24.7; ^{13}C NMR ($CDCl_3$) δ 25.9 ($J_{PC} = 7.5$, C_8), 26.0 ($J_{PC} = 137.6$, C_6), 27.8 ($J_{PC} = 13.0$, C_3), 30.7 (C_4), 38.5 ($J_{PC} = 3.5$, C_2), 51.2 (MeO), 51.6 (MeO), 66.1 ($J_{PC} = 8.8$, C_7), 66.1 ($J_{PC} =$

9.4, C_7), 172.3 (C_5), 173.8 ($J_{PC} = 8.3$, C_1); ^{1}H NMR ($CDCl_3$) δ 3.67 (s, 3H, MeO), 3.71 (s, 3H, MeO); FAB-MS, 295 $(M + H)^+$; $(M + H)^+_{found} = 295.0945$, $C_{11}H_{20}O_7P$ requires 295.0947.

*2-(2′-Oxo-[1′,3′,2′]dioxaphosphinan-2′-ylmethyl)-Glutaric Acid Dibenzyl Ester (**6b**)*

Yield: 43%; ^{31}P NMR ($CDCl_3$) δ 25.2; ^{13}C NMR ($CDCl_3$) δ 26.0 ($J_{PC} = 7.4$, C_3), 26.3 ($J_{PC} = 138.7$, C_6), 28.1 ($J_{PC} = 13.3$, C_8), 31.0 (C_4), 38.8 ($J_{PC} = 3.4$, C_2), 65.9 ($J_{PC} = 6.2$, C_7), 66.0 (CH_2Ph), 66.5 (CH_2Ph), 171.8 (C_5), 173.3 ($J_{PC} = 8.1$, C_1); FAB-MS, 447 $(M + H)^+$; $(M + H)^+_{found} = 447.1561$, $C_{23}H_{28}O_7P$ requires 447.1573.

*Debenzylation of 2-(Diethylphosphonomethyl)-Glutaric Acid Dibenzyl Ester **4b**; 2-(Diethylphosphonomethyl)-Glutaric Acid (**8**)*

To the mixture of 2.3 g (5.0 mmol) of **4b** in 20 mL of isopropanol was added 0.20 g of 10% palladium on carbon (Selcat) and the suspension was then hydrogenated at 26°C and atmospheric pressure until two equivalents of hydrogen were absorbed. The mixture was filtered and the solvent evaporated. Purification of the crude product so obtained by column chromatography (silica gel, 20% methanol in chloroform) afforded 0.72 g (51%) of the diacid derivative **8**; ^{31}P NMR ($CDCl_3$) δ 29.6; ^{13}C NMR ($CDCl_3$) δ 16.5 ($J_{PC} = 6.0$, CH_3CH_2), 27.6 ($J_{PC} = 147.4$, C_6), 28.2 ($J_{PC} = 16.6$, C_3), 31.4 (C_4), 39.2 ($J_{PC} = 2.8$, C_2), 62.6 ($J_{PC} = 6.8$, CH_3CH_2), 177.1 (C_5), 177.8 ($J_{PC} = 8.6$, C_1); FAB-MS, 283 $(M + H)^+$; $(M + H)^+_{found} = 283.0939$, $C_{10}H_{20}O_7P$ requires 283.0947.

Catalytic hydrogenation carried out under the same conditions, but in methanol led to monomethyl ester **7**. Yield 65%; ^{31}P NMR ($CDCl_3$) δ 29.9; FAB-MS, $(M + H)^+_{found} = 297.1080$, $C_{11}H_{22}O_7P$ requires 297.1103.

Catalytic hydrogenation of dibenzyl phosphonate **5a** under similar conditions (in methanol, after a reaction time of 5 h) gave **9** in 95% yield; ^{31}P NMR ($CDCl_3$) δ 27.1; FAB-MS, 255 $(M + H)^+$; $(M + H)^+_{found} = 255.0620$ $C_8H_{16}O_7P$ requires 255.0634.

AKNOWLEDGMENTS

Gy.K is grateful to Dr Zsuzsa Jászay and Professor Dr. Imre Petneházy (Department of Organic Chemical Technology, Budapest University of Technology and Economics) for carrying out the debenzylations.

REFERENCES

[1] Jackson, P. F.; Cole, D. C.; Slusher, B. S.; Stetz, S. L.; Ross, L. E.; Donzanti, B. A.; Trainor, D. A. J Med Chem 1996, 39, 619.
[2] Slusher, B. S.; Vornov, J. J.; Thomas, A. G.; Hurn, P. D.; Harukuni, I.; Bhardwai, A.; Traystman, R. J.; Robinson, M. B.; Britton, P.; May Lu, X-C.; Tortella, F. C.; Wozniak, K. M.; Yudkoff, M.; Potter, B. M.; Jackson, P. F. Nature Medicine 1999, 5, 1396.
[3] Jackson, P. F.; Slusher, B. S. Curr Med Chem 2001, 8, 949.
[4] Green, K. Tetrahedron Lett 1989, 30, 4807.
[5] Keglevich, Gy.; Sipos, M.; Imre, T.; Ludányi, K.; Szieberth, D.; Tőke L. Tetrahedron Lett 2002, 43, 8515.
[6] Keglevich, Gy.; Sipos, M.; Szieberth, D.; Nyulászi, L.; Imre, T.; Ludányi, K.; Tőke, L. Tetrahedron 2004, 6619.
[7] Shakirov, I. H.; Safiullin, A. R.; Shagidullin, R. R.; Polozov, A. M. Izv Akad Nauk Ser Him 1992, 12, 2725.