Pergamon

Tetrahedron Letters 40 (1999) 8491–8493

TETRAHEDRON LETTERS

Bisphosphonate prodrugs: a new synthetic strategy to tetraacyloxymethyl esters of methylenebisphosphonates

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Received 19 July 1999; accepted 22 September 1999

Abstract

A concise and simple method to prepare $Cl_2C[P(O)(OCH_2O_2CCMe_3)_2]_2$ starting from $H_2C[P(O)(OMe)_2]_2$ with high selectivity and reasonable yield is developed.

Keywords: bisphosphonates; transesterification; protecting groups; biologically active compounds.

Methylenebisphosphonates (MBP) are commonly used to inhibit mineralization of soft tissues as well as bone formation and resorption disorders.[1] Clodronate, Cl_2MBP, is one of the best documented MBP derivatives but like other MBP tetraacids, its bioavailability is low due to its very polar and ionic structure.[2] Masking one or more ionizable groups of clodronate to form prodrug derivatives, which should release the active drug in the body after absorption by enzymatic and/or chemical hydrolysis, could increase the lipophilicity of the molecule and thus increase its bioavailability.[3,4]

Several less polar tetraalkyl,[5] partial ester derivatives[6] and amide ester derivatives[7] of Cl_2MBP have been prepared, but these compounds are poor prodrugs since simple alkyl/aryl esters are hydrolytically stable[8] and amides release Cl_2MBP via chemical hydrolysis.[9] Recently, we have reported a novel unexpected stable anhydride prodrug of Cl_2MBP, $Cl_2C[P(O)(O^-)(OCOR)]_2$, which is bioreversible in human serum. Unfortunately, only two of the four anion groups can be masked using this approach.[10]

Acyloxymethyl esters are more labile than simple esters[11] and these derivatives, especially pivaloyloxymethyl esters (POM), have been used as prodrugs of phosphonates in several cases,[12] but a proper synthesis of the corresponding MBP derivatives is unclear. In this paper, a convenient and simple method starting the synthesis from the H_2MBP methyl ester **1** via H_2MBP POM ester **2** to tetrapivaloyloxymethyl ester of Cl_2MBP (**3**) is described.

Typically H_2MBP tetraesters are prepared from $H_2C[P(O)(OH)_2]_2$ using a large excess of tri-*n*-alkyl orthoformate[13] as the alkylating agent, or from $H_2C[P(O)Cl_2]_2$ and the appropriate alcohol,[14] but in this case these methods are useless since the corresponding starting acyloxymethyl compounds are not stable. The third method to the target tetraesters is reported in a patent, starting from tetraacid **4** and

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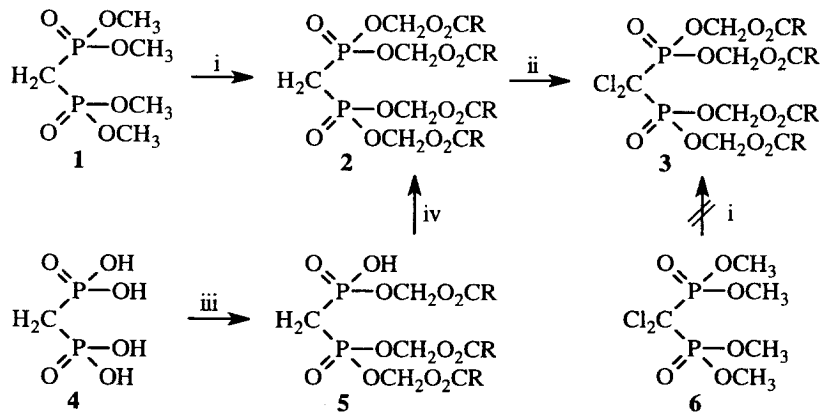
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01799-2

$Me_3CCO_2CH_2Cl$ with a hindered amine as base.[15] In our hands, this method led to corresponding triesters **5**. However, when this triester **5** was converted into a silver salt, tetraester[16] **2** was obtained in poor yield.

Our solution to prepare **2** is transesterification, which is quite common with carbon esters but rather seldomly used with phosphorus esters. Quantitative conversion into **2** was observed when **1** was treated with excess of $Me_3CCO_2CH_2Cl$ using NaI as a co-reagent. Starting the synthesis from higher H_2MBP esters, e.g. ethyl or 2-propyl derivatives, a complex mixture was obtained and only a partial conversion to target ester **2** was achieved. This method is also practical with other activated halogen compounds, since for example reaction of **1** with benzyl chloride under the same conditions leads to the corresponding $H_2C[P(O)(OBn)_2]_2$ derivative in good yield.

The target halogenated clodronate POM ester **3** was achived following the known procedure[5] with neutralized NaOCl solution at 20°C. Trials to prepare **3** directly from corresponding Cl_2MBP methyl ester **6** were not successful (Scheme 1).



Scheme 1. (i) NaI, $Me_3CCO_2CH_2Cl$, MeCN, refl., 12 h; (ii) $NaHCO_3$, NaOCl, 20°C, 30 min; (iii) Pr^i_2NEt, $Me_3CCO_2CH_2Cl$, DMF, 80°C, 8 h; (iv) $AgNO_3$, $Me_3CCO_2CH_2Cl$

Tetra(pivaloyloxymethyl) methylenebisphosphonate (**2**): tetramethyl methylenebisphosphonate **1** (3.0 g, 13 mmol), NaI (7.7 g, 52 mmol), chloromethyl pivalate (10.0 g, 66 mmol) and acetonitrile (10 ml) were mixed and refluxed overnight. After adding ether (100 ml) the mixture was washed with water (2×20 ml), dried and evaporated. The solid residue was washed with cold hexane and dried in vacuo to give 5.84 g (71%) of **2** as a pale yellow solid. NMR ($CDCl_3$): δ_H 5.73 (8H, m), 2.72 t (2H, $^2J_{HP}$=21.7 Hz), 1.24 (36H, bs); δ_C 176.66 s, 82.00 t,[17] 38.67 s, 26.96 t+t ($^1J_{CP}$=137.6 Hz), 26.90 q; δ_P 18.74.

Tetra(pivaloyloxymethyl) (dichloromethylene)bisphosphonate (**3**): prepared by the known method[5] from **2** to give **3** with 66% yield. NMR ($CDCl_3$): δ_H 5.82 (8H, m), 1.25 (36H, s); δ_C 176.53 s, 83.68 t,[17] 69.88 t ($^1J_{CP}$=160.1 Hz), 38.75 s, 26.82 q; δ_P 6.75. Anal. calcd for $C_{25}H_{44}O_{14}P_2Cl_2$: C, 42.81; H, 6.32. Found: C, 42.38; H, 6.24.

Acknowledgements

We would like to thank Dr. Sirpa Peräniemi (University of Joensuu) for elemental analyses and Mrs Maritta Salminkoski for technical assistance.

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