Synthesis of α-Trinositol Analogues Derived from D-(-)-Quinic Acid as Affinity Probe Precursors

P. Guédat[a], N. Rehnberg[b], B. Spiess[a], G. Schlewer[a]*

[a]Laboratoire de Pharmacochimie Moléculaire UPR421 du CNRS Faculté de Pharmacie, 74, route du Rhin, 67401 Illkirch France

[b]Perstorp Pharma, Perstorp S-284 80, Sweden

*Fax 33 388 67 47 94 e. mail schlewer@pharma.u-strasbg.fr

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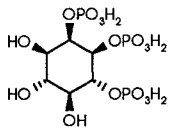
Abstract: D-(-)-Quinic acid was appropriately protected to permit the phosphorylation of the three vicinal hydroxyl groups. Final deprotection lead to tris(phosphates) possessing the same configuration as the parent α-trinositol and an arm suitable for the attachement of a photoactivable group.

α-Trinositol, (D-*myo*-inositol-1,2,6-tris(phosphate)) **1** possesses anti-inflammatory and analgesic properties.[1,2] This optically active compound is obtained in large quantities from phytic acid, a *meso* compound, by fermentation with baker's yeast.[3] The mechanisms of its biological actions remain unknown. However, they are different from those of *myo*-inositol 1,4,5-tris(phosphate), the well-known second messenger.[4] For this reason, it seemed to us useful to prepare affinity probes to label the α-trinositol binding sites. These binding sites seem to tolerate relatively large functional variations. Thus, structure-activity relationships around α-trinositol have shown that, to some extent, the introduction of an additional polar group was not detrimental to the activity. Recently, Prestwich has published the synthesis of *myo*-inositol 1,2,5,6-tetrakis(phosphate) substituted by a photoaffinity label at he phosphate in position 5.[5] Removal of unphosphorylated hydroxyl groups do not dramatically reduced the activities.[6] Changes of the relative orientations of the hydroxyl groups, led to *chiro* or *epi* inositol derivatives equipotent with α-trinositol (unpublished). Modifications of the α-trinositol backbone leading to carbohydrate and deoxy carbohydrates analogues;[6-9] isosteric changes on the phosphate moieties, gave products as active as the parent compound.[10,11] Taking these large tolerances into account, quinic acid derivatives could be molecules of choice to label the binding sites of α-trinositol.



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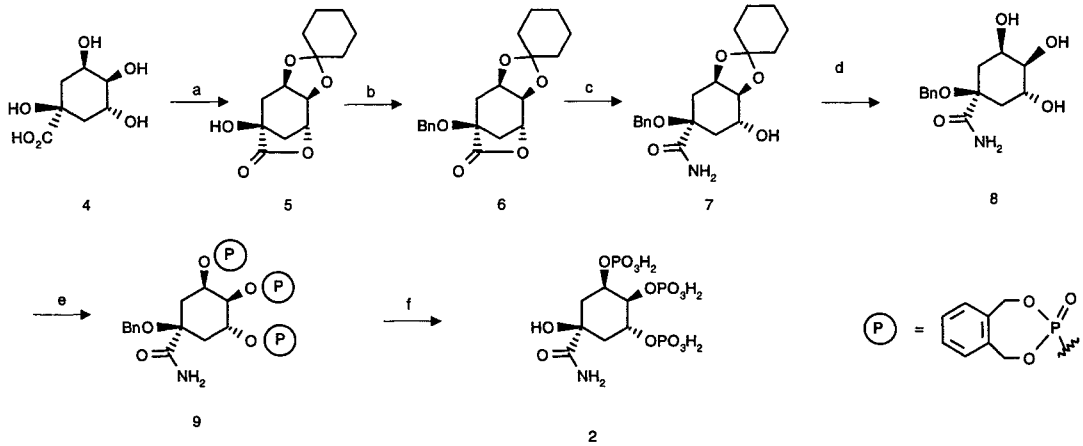
As part of this work we would like to report here the synthesis of D-1-carbamoyl-2,6-dideoxy-*epi*-inositol 3,4,5-tris(phosphate) **2** and D-quinic acid 3,4,5-tris(phosphate) **3**. The amide or acid group of these α-trinositol mimics are suitable for the attachement of the labelling moieties.

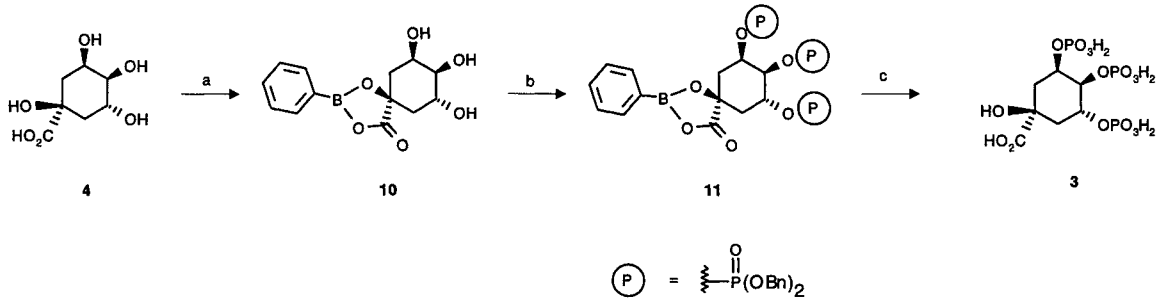
The synthesis of the carbamoyl derivative **2** is shown in Scheme 1.

Quinic acid **4**, which can be considered as 1-carboxy-2,6-dideoxy-*epi*-inositol, was first treated with cyclohexanone in the presence of orthophosphoric acid according to the procedure of Mercier *et al* [12] modified by Shing *et al.*[13] This led to compound **5** with the concomitant formation of a γ-butyrolactone and an acetal using the vicinal *cis* diol in position 3 and 4. The last hydroxyl group was then protected as benzyl ether giving the totally protected compound **6**.[14] Opening of the lactone by means of liquid ammonia formed the amide **7**,[15] and hydrolysis of the acetal protective group furnished the triol **8**. Compound **8** was phosphorylated in a two-step one-pot procedure using 3-(diethylamino)-2,4,3-benzodioxaphosphepane, in the presence of 1*H*-tetrazole, which gave an intermediate tris(phosphite), which was oxidized *in situ* into tris(phosphate) **9** by means of *m*CPBA.[16-18] The protected phosphate was totally deprotected by simple hydrogenolysis in the presence of palladium on charcoal to give the expected 1-carbamoyl-2,6-dideoxy-



*Scheme 1: Synthesis of 1-carbamoyl-2,6-dideoxy-*epi*-inositol 3,4,5-tris(phosphate)* **2**: a) cyclohexanone (3eq), H_3PO_4 cat, reflux, 45min, 87%, b) NaH (2eq), BnBr (1.5eq), DMF, RT, 15h, 58%, c) liquid NH_3, THF, reflux, 6h, then evaporation overnight, 93%, d) MeOH, HCl, 1N, reflux, 1h, 99%, e) 3-diethylamino-2,4,3-benzodioxaphosphepane, tetrazole, THF, -78°C, 1h, then RT, 6h, then *m*CPBA, CH_2Cl_2, -78°C, 15 min, then, RT, 1h, 62%, f) H_2, (5 atm), Pd/C (10%),CH_2Cl_2, MeOH, H_2O, RT, 20h, 95%.

Scheme 1



Scheme 2: Synthesis of quinic acid 3,4,5-tris(phosphate) 3. a) $C_6H_5B(OH)_2$ (1eq) , C_6H_6, reflux, 24h, mp 145°C,99%, b) NaH (6eq), tetrabenzyl pyrophosphate (5 eq), THF, 0°C, 1h; RT, 12h, 37%, c) H_2 (1 atm), Pd/C (10%), CH_2Cl_2, MeOH, H_2O, 16h

Scheme 2

epi-inositol 3,4,5-tris(phosphate) **2**. The final product was crystallized as its cyclohexylammonium salt.[19]

The preparation of the corresponding acid **3** is shown in Scheme 2. Quinic acid **4,** treated with phenylboronic acid,[20] gave the borate **10** in quantitative yield. Phosphorylation could not be accomplished using the phosphite approach due to the instability of the borate group in these conditions; thus, the tris(alkoxide) of **10** was reacted with tetrabenzyl pyrophosphate[21,22] leading to the protected compound **11**. Hydrogenolysis of **11** in the presence of palladium on charcoal furnished the quinic acid 3,4,5-tris(phosphate) **3**[23] which was purified by ion exchange chromatography.[24]

The compounds **2** and **3** possess the same tris(phosphate) configuration as the parent α-trinositol **1**. The amide and the acid function offer the possibility of introducing new substituents, particularly, they permit the introduction of photoactivatable groups which could be useful to characterize the binding site of α-trinositol.

References and Notes

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14. Compound **6**: mp: 136 °C.$[\alpha]_D^{22}$: +2.2±0.1 (c: 0.0198, $CHCl_3$). Analysis calculated for $C_{20}H_{24}O_5$: C 69.75, H 7.02; found: C 69.52, H 6.85. ^{1}H-NMR ($CDCl_3$): δ 7.45-7.20 (*m*, 5H, ($CH_2C_6H_5$); 4.73 (*dd*, J=4.7 Hz, J=2.6 Hz, 1H, H_4); 4.13 (*AB*, J_{AB}=11.0 Hz, Δδ=0.08, 2H, -$CH_2C_6H_5$); 4.55 (*dt*, J=7.3 Hz, J=3.3 Hz, 1H, H_5); 4.33 (*dd*, J=6.2 Hz, J=2.5 Hz, 1H, H_3); 2.6-2.4 (*m*, 3H); 2.28 (*dd*, J=15.0 Hz, J=3.3 Hz, 1H); 1.8-1.3 (*m*, 10H, C_6H_{10}).
15. Compound **7**: mp: 127 °C.$[\alpha]_D^{22}$: -29.6±0.1 (c: 0.0059, $CHCl_3$). Analysis calculated for $C_{20}H_{27}NO_5$: C 66.46, H 7.53, N 3.88; found: C 66.41, H 7.78, N 3.85. ^{1}H-NMR ($CDCl_3$): δ 7.5-7.2 (*m*, 5H, -$CH_2C_6H_5$); 6.67 and 5.68 (2 *broad s*, 2H, NH_2); 4.55 (*AB*, J_{AB}=11.0 Hz, Δδ=0.18, 2H, -$CH_2C_6H_5$); 4.5-4.4 (*m*, 1H, H_5); 4.2-4.0 (*m*, 2H, H_3, H_4); 3.79 (*d*, J=3.6 Hz, 1H, O*H*); 2.5-1.9 (*m*, 4H, H_{2a}, H_{2b}, H_{6a}, H_{6b}); 1.9-1.3 (*m*, 10H, C_6H_{10}).
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18. Compound **9**:$[\alpha]_D^{22}$: -34.7±0.5 (c: 0.018 $CHCl_3$). FAB$^+$: m/z 828 (MH^+, 100); 628 (37); 429 (11); 200 (34). ^{1}H-NMR ($CDCl_3$): δ 7.4-7.0 (*m*, 17H, -CH_2-C_6H_5 and (-CH_2-C_6H_4-CH_2-)$_3$); 6.63 and 5.72 (2*s*, 2H, -$CONH_2$); 5.6-4.5 (*m* , 17H, -CH_2-C_6H_5 (-CH_2-C_6H_4-CH_2-)$_3$ H_3,H_4,H_5); 3.0-2.9 (*m*, 1H); 2.7-2.6 (*m*, 1H); 2.4-2.3 (*m* , 2H). ^{31}P-NMR ($CDCl_3$): -0.62, -0.90, -1.64.
19. Compound **2** after ion exchange chromatography[24] : ES$^-$ (M^{6-} 425): m/z: 430 $(425+5H^+)^-$, 452 $(425+4H^++Na^+)^-$, 468 $(425+4H^++K^+)^-$, 474 $(425+3H^++2Na^+)^-$.
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