Pergamon

Tetrahedron Letters, Vol. 36, No. 40, pp. 7239-7242, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01494-2

Synthesis of Optically Active (+)-D-3,4,5-tri *O*-Phenylcarbamoyl *Myo*-Inositol from Phytic Acid.

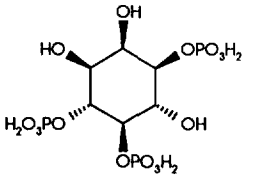
Corinne Blum[+], Susanne Karlsson,[#] Gilbert Schlewer[+*], Bernard Spiess[+], and Nicola Rehnberg[#]

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

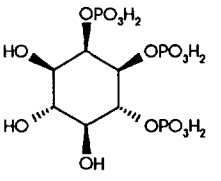
[#]Perstorp Pharma S-284 80 Perstorp Sweden.

Abstract: Baker's yeast phosphatases induced regioselective hydrolysis on phytic acid leading to D-*myo*-inositol 1,2,6-tris(phosphate) which was transformed in optically active (+)-D-3,4,5-tri-*O*-phenylcarbamoyl-*myo*-inositol.

Myo-inositol derivatives, and particularly *myo*-inositol phosphates are now well recognized for their biological properties.[1-8] The second messenger properties of D-*myo*-inositol 1,4,5-tris(phosphate) **1** have been demonstrated in 1984[1] and (+)-D-*myo*-inositol 1,2,6-tris(phosphate) **2** a regioisomer of the former possesses anti-inflammatory properties.[5-8]



1



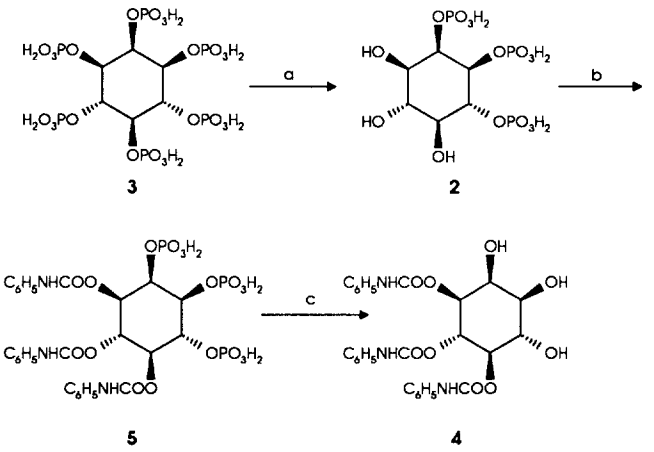
2

As biological receptors usually recognize selectively one of the possible enantiomers, the structure-activity relationships require the synthesis of optically active products.

In the particular field of inositol phosphates, optically active compounds have been obtained by resolution of racemates through the formation of diastereomeric derivatives[9-11] or by stereocontrolled synthesis starting from chiral material such as quebrachitol[12] or quinic acid[13] Enzymatic reactions were also used in some synthetic schemes to obtain optically active intermediates.[14]

Phytic acid **3** is an abundant compound usually derived from corn steep liquor, wheat bran, rice bran, etc and is marketed as a calcium or calcium/magnesium salt. This polyphosphorylated *myo*-inositol could be a starting material of choice to prepare new inositol derivatives. Unfortunately this material is a *meso* compound.

We want to report here, how we have used phytic acid for the preparation of optically active (+)-D-3,4,5-tri-*O*-phenylcarbamoyl *myo*-inositol **4.** This compound could be a lead compound for the preparation of new optically active inositol phosphate derivatives and related compounds.



Scheme: a: baker's yeast, b: phenylisocyanate, CH_2Cl_2, iPr_2NEt, RT 48h;
c: HCO_2H,HCO_2Na, pH 4.2, H_2O, 30h, 100 °C, Overall yield 48%.

The originality of the synthesis was based of the use of baker's yeast.[15] This yeast contains phosphatases which selectively hydrolysed the phosphates in positions 3, 4 and, 5 of phytic acid leading to optically active D-*myo*-inositol-1,2,6-tris(phosphate) **2**[15]($[\alpha]_D^{25}$ = -19.5°(C 1.1, H_2O)) also named α-trinositol[16] (Scheme).

This seems to be the first example of using phosphatases to yield an optically active derivative starting from a *meso* compound.

Compound **2** is interesting as such and possesses biological properties,[5-8] but is also an interesting chiral intermediate. The three free hydroxyl groups were then protected as phenyl carbamate by means of phenylisocyanate giving compound **5** in good yield ($[\alpha]_D^{25}$ = -8.5 (C 0.4, H_2O))[17]. Treatment of the tris(phosphate) with a formate buffer (pH 4.2) hydrolysed the three phosphates keeping the carbamates unchanged and led to the expected totally dephosphorylated (+)-D-3,4,5-tri-*O*-phenylcarbamoyl *myo*-inositol **4** ($[\alpha]_D^{25}$ = +34.4 (C 0.018, THF))[18].

More work is in progress to use this optically active material in the *myo*-inositol field by means of the classical protection and deprotection pathways.

References and notes.

1. Berridge, M.J.; Irvine, R.F. *Nature* **1984**, *312*, 315-321.
2. Downes, C.P.; MacPhee, C.H. *Eur. J. Biochem.* **1990**,*193*, 1-18.
3. Shamsuddin, A.M.; Sakamoto, ; *Cancer Chemoprevention*, **1992**, 285-308
4. Baxter, M.A.; *Trends Endocrinol. Metab.* **1991**, *2*, 187-190.,
5. Siren, M.; Linne, L.; Persson, L. in *Inositol phosphates and derivatives* Reitz, A.B. ed. ACS Symposium Series 463, **1991**, 103-110
6. Claxson, A.; Morris, C.; Blake, D.; Sirén, M.; Halliwell, B.; Gustafsson, T.; Löfkvist, B.; Bergelin, I. *Agents Actions*, **1990**, *29*, 68-70.
7. Wahlestedt, C.; Reis, D.J.; Yoo, H.; Adamsson, M.; Andersson, D.; Edvinsson, L. *Neurosci. Lett.* **1992**, *143*, 123-126.
8. Lund, T.; Reed, R.K. *J. Trauma.* **1994**, *36*, 761.
9. Ozaki, S.; Watanabe, Y.; Ogasawara, T. Kondo, J.; Shiotani, N.; Nishii, H.; Matsuki, T. *Tetrahedron Lett.* **1986**, *27*, 3157-3160.
10. Vacca, J.P.; de Solms, S.J.; Huff, J.R. *J. Amer. Chem. Soc.*, **1987**, *109*, 3478-3479.
11. Stepanov, A.E.; Runova, O.B.; Schlewer, G.; Spiess, B.; Shvets, V.I. *Tetrahedron Lett.* **1989**, *30*, 5125-5128.
12. Kozikowski, A.P.; Ognyanov, V.I.; Fauq, A.H.; Nahorski, S.R.; Wilcox, R.A. *J. Amer. Chem. Soc.* **1993**, *115*, 4429-4434.
13. Falck, J.R.; Yadagiri, P. *J. Amer. Chem. Soc.* **1989**, i, 5851-5852.
14. Ling, L.; Ozaki, S. *Carbohydr. Res.* **1994**, i, 49-58.
15. Sirén, M. *EPO* 179440.

16. Sodium phytate (0.7 g) was dissolved in 600 ml sodium acetate buffer (pH 4.6). Baker's yeast (50 g) was added and the mixture was stirred for 7 h at 45°C. Enzymatic reaction was quenched by adding ammonia till pH 12. After centrifugation the supernatant was collected and passed through an ion exchange column (Dowex 1 chlorine form) eluted with a linear gradient of hydrochloric acid (0-0.7N HCl). Fractions containing the expected product were neutralized to pH 7.0 with an aqueous solution of NaOH. An equivalent volume of ethanol was added and the volume was reduced by evaporation. The sodium salt was centrifuged recrystallized (water - ethanol) and dried in vacuum. Enantiomeric excess higher than 98%. ^{1}H-NMR (300 MHz, D_2O): 4.49 (*broad d*, J = 8.5, 1H, H_2), 4.08 (*q*, J = 9.0, 1H, H_6), 3.88 (*broad t*, J = 9.0, 1H, H_1), 3.60 (*t*, J = 9.8, 1H, H_4), 3.31 (*dd*, J = 10.0, J = 2.2, 1H, H_3), 3.28 (*t*, J = 9.1, 1H, H_5). ^{13}C-NMR (75 MHz, D_2O): 79.6 (*t*, J = 5.9, C_6), 77.8 (*d*, J = 5.2, C_2), 77.5 (*s*, C_5), 76.6 (*q*, J = 4.8, C_1), 75.5 (*s*, C_4), 74.1 (*s*,C_3); the assignment used two dimentional H-C correlation. ^{31}P-NMR (D_2O): 0.0 (P_2), 0.8 (P_1, P_6); the assignment is based on two dimentional H-P correlation.
17. ^{1}H-NMR (D_2O): 7.6-7.0 (*m*, 15H, $(C_6H_5)_3$), 5.45 (*t*, J = 7.9, 1H, H_4), 5.23 (*dd*, J = 8.0, J = 1.4, 1H, H_3), 5.17 (*t*, J = 8.1, 1H, H_5), 4.90 (*d*, J = 1.2, 1H, H_2), 4.68 (*q*, J = 7.3, 1H, H_6), 4.35 (*t*, J = 7.3, 1H, H_1).
18. ^{1}H-NMR (DMSO-d_6): 9.75 (*s*, 1H, N*H*), 9.60 (*s*, 2H, N*H*), 7.6-6.9 (*m*, 15H, $(C_6H_5)_3$), 5.45 (*t*, J = 10.1, 1H, H_4), 4.86 (*t*, J = 9.6, 1H, H_5), 4.82 (*dd*, J = 10.5, J = 2.4, 1H, H_3), 4.02 (*t*, J = 2.0, 1H, H_2), 3.75 (*t*, J = 9.7, 1H, H_6), 3.46 (*dd*, J = 9.4, J = 2.1, 1H, H_1).

(*Received in France* 12 *June* 1995; *accepted* 4 *August* 1995)