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A Novel Synthesis of 3-*O*-Allyl-4, 5, 6-tri-*O*-benzyl-1-*O*-(*p*-methoxybenzyl)-D-*myo*-inositol

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Abstract: Highly efficient synthesis of the entitled compound was achieved from a readily available *myo*-inositol derivative. The key step involved a desymmetrization with (+)-camphor dimethyl ketal to give two diastereomers. The two diastereomers could be used to synthesize the same compound by changing the orders to introduce the protective groups.

Keyword: Inositol, (+)-camphor dimethyl ketal, desymmetrization.

Inositol phospholipid metabolism was involved in a wide variety of cellular processes. Investigation of these processes demanded a large number of various substrates, substrates analogues and inhibitors of enzymes[1].

The 2-hydroxy of the *myo*-inositol ring was essential in the PI-PLC catalyzing hydrolysis of phosphatidylinositol. Phosphatidylinositol analogues lacking the freely axial 2-hydroxy were not hydrolyzed by several PI-PLCs[2]. They might be enormous leading compounds as PI-PLC inhibitors[3].

The chemical modulation of the phospholipids depending on phosphatidylinositol 3-kinase (PI 3-K) signal cascade might offer a basis for the selective control of cancer cell growth while minimizing effects on normal cells[4]. In pursuit of this particular strategy to develop novel anticancer drug, it was needed to synthesize a number of phosphatidylinositol analogues embodying modification to the 3-position of the *myo*-inositol ring as PI 3-K inhibitor's candidates[5]. Besides, it was necessary to modify the 2-hydroxy to prevent the degradation occurred through PI-PLC[6].

This needed to differentiate the three hydroxyes at 1, 2 and 3 positions of the inositol ring and distinguish them from the other three hydroxyes at 4, 5 and 6 positions in order to synthesize the compounds mentioned above. Therefore, it was very valuable to synthesize the inositol intermediates with the common structure of **1** for subsequently selective modification. We selected 3-*O*-allyl-4, 5, 6-tri-*O*-benzyl-1-*O*-(*p*-methoxybenzyl)-D-*myo*- inositol **2** as our aimed compound to synthesize.

The published method for the preparation of **2** is chemoenzymatic method *via* cyclohexylidene ketal[7]. We now described a novel procedure to prepare compound **2** in high yield, which avoided the arduous procedure (**Scheme 1**).

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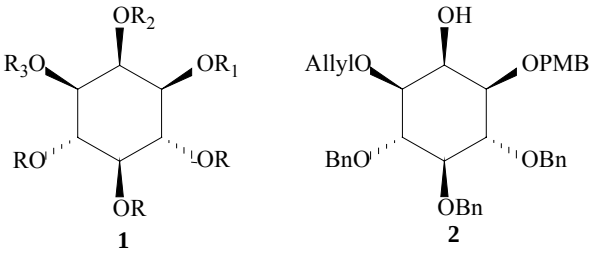
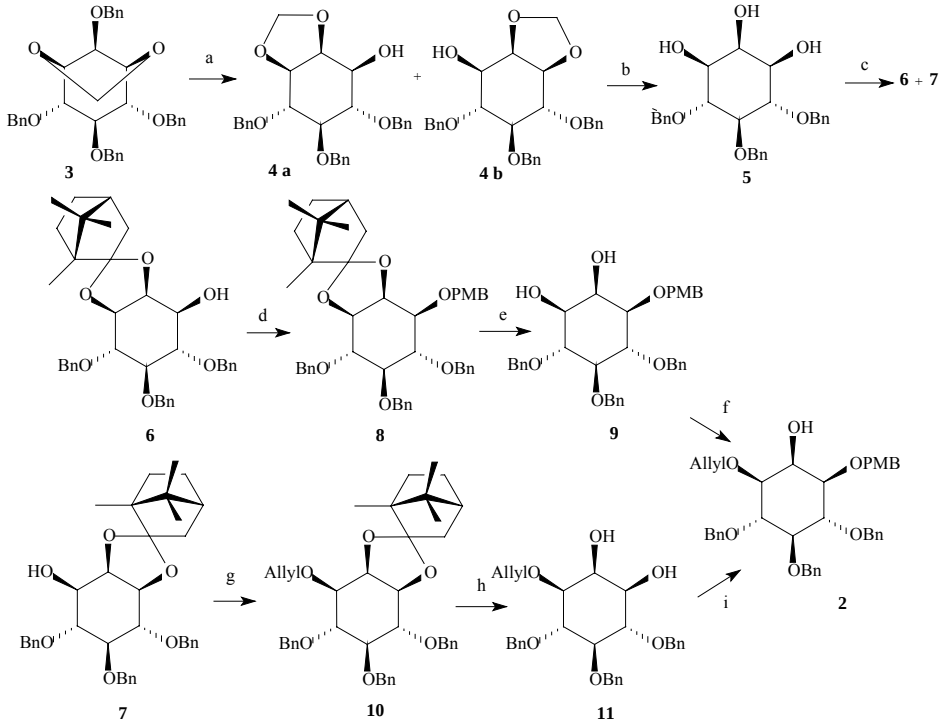


Scheme 1 The preparation of **2**



Reagents and conditions: (a) $TiCl_4$, CH_2Cl_2, -78℃, 1 h (85%); (b) HBr (48%), CH_3OH, r.t., 36 h (95%); (c) (+)-camphor dimethyl ketal, *p*-TsOH.H_2O, CH_2Cl_2, reflux, 100 min (75%; 35 for **6** and 40% for **7**); (d) PMBCl, NaH, DMF, r.t., 24 h (90%); (e) AcCl, CH_2Cl_2-CH_3OH(2:1), r.t., 5 h (79%); (f) *n*-Bu_2SnO, toluene, reflux, 6 h; AllylBr , CsF, DMF, r.t., 24 h (90%); (g) AllylBr, NaH, DMF, r.t., 24 h (90%); (h) AcCl, CH_2Cl_2-CH_3OH(2:1), r.t., 5 h (79%); (i) *n*-Bu_2SnO, toluene, reflux, 16 h: PMBCl, CsF, DMF, r.t., 24 h (90%)

The common starting material **3** could be prepared easily from *myo*-inositol in large scale[8-10]. **3** could react with titanium(Ⅳ)chloride to give **4a** and **4b** as a mixture[10]. We found the routine could be used in large scale[11]. Hydrolysis of **4a** and **4b** with hydrochloric acid and methanol under reflux for long time，the product **5** was very complicated and in low yield (38%)[10]. We used hydrobromic acid instead of hydrochloric acid at room temperature to give **5** in high yield (95%) with large scale[11].

Then compound **5** was simultaneously protected and resolved with (+)-camphor

dimethyl ketal[12] by *p*-toluenesulfonic acid catalyzing exchange *via* cyclic ketal[13]. The camphor fragment served as not only a protective group but also a chiral auxiliary. This provided a convenient access to desymmetrize compound **5** to give the ketals **6** and **7** which could be separated by flash chromatography on the silica gel in good overall yield [R_f=0.25 (**6**) and 0.42 (**7**), *n*-hexane/chloroform (2: 3)][14]. Careful chromatographic and spectral analysis revealed that **6** and **7** were single stereoisomer, respectively[15].

The configuration of **6** and **7** were assigned *via* chemical correlation as following: **6** and **7** were transformed into the corresponding tetrabenzyl etheric camphor ketal respectively, then cleaved with 80% acetic acid to give 1,4,5,6-tetra-*O*-benzyl-D-*myo*-inositol and 3,4,5,6-tetra-*O*-benzyl-D-*myo*-inositol, respectively. Comparing their rotation, melt points and ^{1}H-NMR with literature confirmed the integrity of **6** and **7**[16].

The orientations (*exo*/*endo* geometry relative to O-1 of the *myo*-inositol moiety) of the (+)-camphor residues in **6** and **7** were determined by Rosey ^{1}H-NMR spectroscopy of the corresponding tetrabenzyl etheric camphor ketal. The correlations between the signal from Me-10 in the camphor moiety and the signal for hydrogenes of the *myo*-inositol ring are definitive to decide the orientations. No positive correlation between the signals Me-10 and H-2 was observed in the both spectrum, although the existence of the correlation is essential to determine that the orientation of **6** is 1D-2-*O*-*endo*-3-*O*-*exo* and the orientation of **7** is 1D-1-*O*-*endo*-2-*O*-*exo*. On the contrary, it was very obvious that the signal Me-10 was correlated with the signal H-4 in the derivative of **6**. This indicated that the orientation of **6** was 1D-2-*O*-*exo*-3-*O*-*endo*. Similarly, obvious correlation was observed between the signal Me-10 and the signal H-6 of the derivative of **7**. This testified that the orientation of **7** was 1D-1-*O*-*exo*-2-*O*-*endo*. So the orientation of **6** was assigned as 1D-2-*O*-*exo*-3-*O*-*endo* and the orientation of **7** was assigned as 1D-1-*O*-*exo*-2-*O*-*endo* accordingly[13,17,18].

The two (+)-camphor ketal diastereomers **6** and **7** could be used to synthesize the same compound **2** by changing the order to introduce the protective *p*-methoxybenzyl group and allyl group (**Scheme 1**). Treating **6** with sodium hydride and *p*-methoxybenzyl chloride gave ether **8**. Subsequent cleavage of the camphor ketal of **8** afforded the 2, 3-diol **9**. Then chemoselective D-3-*O*-allylation of **9** was affected *via* stannane acetal generated *in situ* with azeotropic removal of water, followed by allylation in the presence of cesium fluoride to afford the aimed compound **2**. Due to the steric hindrance at the axial 2-hydroxy, the allylation proceeded with extremely high regioselectivity, exclusively at 3-hydroxy[7].

Another diastereomer **7** was first allylated on the D-3-hydroxy to give allylic ether **10**, followed by cleavage of the camphor ketal. The resulting **11** was protected selectively at 1-hydroxy with the aid of cesium fluoride *via* its cyclic dibutylstannylene derivative to give the desired **2** according to the method as described above.

In conclusion, we developed a novel and practical access to a versatile precursor **2** from which many chiral phosphatidyl-D-*myo*-inositols, D-*myo*-inositol polyphosphates and their derivatives and analogs could be synthesized. The effect and the yield of the desymmetrization were enhanced *via* changing the order to introduce the protective groups.

References and Notes

1. B. V. L. Potter, D. Lampe, *Angew. Chem. Int. Ed.,* **1995**, *34*(18), 1933.
2. K. S. Bruzik, M. D. Tsai, *Bioorg. Med. Chem.*, **1994**, *2*(1), 49.
3. L. O. Essen, O. Perisic, R. Cheung, *et al*., *Nature,* **1996**, *380*(6575), 595.
4. C. Berrie, *Expert. Opin. Investig. Drugs*, **2001**, *10*(6), 1085.
5. H. Y. Sun, G. B. Reddy, C. George, *et al*., *Tetrahedron Lett*., **2002**, *43*(15), 2835.
6. R. J. Hondal, Z. Zhao, A. V. Kravchuk, *et al.*, *Biochemistry,* **1998**, *37*(13), 4568.
7. D. S. Wang, C. S. Chen, *J. Org. Chem.,* **1996**, *61*(17), 5905.
8. S. J. Angyal, *Carbohydr. Res*., **2000**, *325*, 313.
9. D. C. Billington, R. Baker, J. J. Kulagowski, *et al*., *J. Chem. Soc., Perkin Trans.1,* **1989**, (8), 1423.
10. H. Gilbert, A. B. Holmes, M. J. Pestchanker, *et al.*, *Carbohydr. Res*., **1992**, *234*, 117.
11. Typical procedure: To a solution of acetal **3** (18.89 g, 34.2 mmol) in anhydrous CH_2Cl_2 (350 mL) at -78℃ under Ar was added fresh redistilled $TiCl_4$ (7.0 mL, 63.8 mmol). The mixture was stirred at -78℃ for 1 hour and H_2O (68 mL) was added. The mixture was allowed to warm to room temperature and poured into 2 mol/L HCl (1 L). Extractive workup with CH_2Cl_2 and concentration gave crude **4** as yellow oil (19.8 g). Then 48% HBr (100 mL) and methanol (250 mL) were added. The solution was stirred at room temperature for 40 hour. TLC (*n*-hexane / EtOAc = 3/2, R_f = 0.39) show the starting material had disappeared. The solution was neutralised with solid Na_2CO_3, filtered and concentrated. The residue was extracted with EtOAc and concentrated. Recrystallization with ethanol gave **5** as white solid (10.31 g). The mother liquid was concentrated. Flash-column chromatography (EtOAc, R_f=0.45) of the residue gave **5** 2.50 g. The yield is 83.1%.
12. K. B. Wiberg, W. C. Cunningham, *J. Org. Chem*., **1990**, *55*(2), 679.
13. K. S. Bruzik, G. M. Salamonczyk, *Carbohydr. Res.,* **1989**, *195*, 67.
14. Typical procedure: To a solution of the triol **5** (19.4 g, 43.1 mmol) in dry CH_2Cl_2 (750 mL) was added the (+)-camphor dimethyl ketal (24 mL, 25 g, 126 mmol) and *p*-TsOH.H_2O (284 mg, 1.7 mmol) under Ar. The solution was refluxed for 1.5 hour under Ar, then cooled to room temperature. The reaction was quenched by the addition of Et_3N (10 mL) and stirred for 0.5 hour. The solvent was removed *in vacuo*. Flash chromatography eluting with $CHCl_3$ / *n*-hexane (1:1) gave **6** (8.74 g, 34.7%) and **7** (10.1 g, 39.8%) as colorless oil.
15. Spectral data for **6**: $[\alpha]_D^{20}$ +15.8 (c 3.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz):δ ppm 7.26- 7.38 (m, 15H), 4.61-4.89 (m, 6H), 4.22-4.25 (m, 2H), 4.06-4.07 (m, 1H), 4.02 (dd, 1H, J= 9.2Hz, 9.2Hz), 3.83 (t, 1H, J=5.9Hz), 3.56 (dd, 1H, J=9.2 Hz, 9.4Hz), 2.48 (d, 1H, J=2.9Hz), 2.04-2.08 (m, 1H), 1.90-1.95 (m, 1H), 1.73-1.80 (m, 2H), 1.42-1.48 (m, 2H), 1.18-1.26 (m, 1H), 1.06 (s, 3H), 0.87 (s, 3H), 0.86 (s, 3H); ^{13}C-NMR ($CDCl_3$,, 125 MHz): δ ppm 138.7, 138.5, 138.0 (aromatic *C*), 128.4, 128.3, 127.9, 127.8, 127.5, 127.4 (aromatic *CH*), 117.5 (C2 of camphor ketal), 82.3, 82.2, 76.7, 76.1, 74.4, 69.2 (*CH* inositol), 74.0, 73.9, 73.6 (Ph*C*H_2), 51.5, 47.9 (*C*-1,7), 45.1(*C*H-4), 43.9 (*C*H_2-3), 29.9, 26.9 (*C*H_2-5,6), 20.5, 20.2, (CH_3-10, 9), 9.9 (CH_3- 8). HREIMS calcd. for $C_{37}H_{44}O_6$ (M+) 584.3138; found 584.3134.

    Spectral data for **7**: $[\alpha]_D^{20}$ -15.4 (c 3.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz):δ ppm 7.26-7.40 (m, 15H), 4.62-4.91 (m, 6H), 4.37 (dd, J=7.3Hz, 7.2 Hz, 1H), 4.08 (t, J=7.2 Hz, 2H), 3.94 (dd, J=9.1Hz, 9.1Hz, 1H), 3.81 (t, J=5.9Hz, 1H), 3.56 (dd, J=9.2 Hz, 9.1Hz, 1H), 2.47 (s, 1H), 1.96-2.05 (m, 2H), 1.71-1.79 (m,2H), 1.38-1.49 (m, 2H), 1.21-1.27 (m, 1H), 1.01 (s, 3H), 0.87 (s, 3H), 0.85 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ ppm 138.8, 138.5, 138.0 (aromatic *C*), 128.4, 128.3, 127.9, 127.8, 127.5, 127.4 (aromatic *C*H), 117.7 (C2 of camphor ketal), 82.4, 82.2, 81.1, 77.9, 72.8, 69.1 (*C*H inositol), 74.0, 73.4, 73.3 (Ph*C*H_2), 51.3, 48.1 (*C*-1,7), 45.0 (*C*H-4), 43.9 (*C*H_2-3), 29.8, 26.9 (*C*H_2-5, 6), 20.4, 20.2 (CH_3-10, 9), 10.6 (CH_3-8). HREIMS calcd. for $C_{37}H_{44}O_6$ (M^+) 584.3138; found 584.3138.
16. 1,4,5,6-Tetra-O-benzyl-D-*myo*-inositol: $[\alpha]_D^{20}$ +25.3 (c 0.5, $CHCl_3$), mp 140-1℃ [reference 13: $[\alpha]_D^{20}$ +24 (c 2.7, $CHCl_3$), mp 141-3℃]; 3,4,5,6-tetra-O-benzyl-D-*myo*-inositol: $[\alpha]_D^{20}$ -26 (c 0.2, $CHCl_3$), mp 142-3℃ [reference 13: $[\alpha]_D^{20}$ -25 (c 2.7,$CHCl_3$), mp 140-2℃].
17. K. M. Pictrusiewicz, G. M. Salamonczyk, K. S. Bruzik, *Tetrohedron,* **1992**, *48*(26), 5523.
18. K. S. Bruzik, M. D. Tsai, *J. Am. Chem. Soc*., **1992**, *114*(16), 6361.

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