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# Desymmetrization of 4,6-diprotected *myo*-inositol†

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**The asymmetric desymmetrization of 4,6-diprotected *myo*-inositol derivatives was achieved by using a bifunctional, readily available nucleophilic catalyst. The orthogonally protected products were obtained in 80–99% yield with 90–99% ee. Such structures serve as potential enantiopure building blocks for the synthesis of *myo*-inositol phosphates.**

Phosphatidyl inositol phosphates are biologically ubiquitous molecules, which serve as building blocks in membranes and take part in cell signalling and regulation events.[1–4] Naturally occurring inositol phosphates display various substitution patterns (higher degree of phosphorylation of inositol at C1 to C6), which are constantly modified in biological processes by enzymes, such as kinases and phosphatases, during signalling.[2–4] In depth structure–activity relationship studies are dramatically limited since inositol concentrations in biological systems are at the detectable limit and do not allow for isolation. The full synthetic access to this material is laborious since tedious protecting group transformation and separation of diastereomers are required.[5–12] Only recently the first solid phase supported synthesis of *myo*-inositol phosphates[13] has been described, but the access to suitable enantiopure, orthogonally protected inositol precursors in synthetically useful amounts is limited. An efficient process for the organocatalytic asymmetric desymmetrization[14] of *myo*-inositol (**1**) was developed by Miller.[15–22] A key requirement for the highly enantioselective phosphorylation is the protection of carbinol C2 in **2** (Chart 1) and the application of a tetrapeptide as a nucleophilic catalyst.[20,23–25] This methodology is an elegant entry to a variety of 3-phosphorylated *myo*-inositol derivatives.

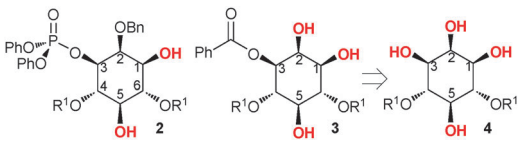


**Chart 1** Protected *myo*-inositol derivatives.

However, other substitution patterns[22] require alternative common intermediates. A suitable candidate for such a task is the 3-benzoylated, orthogonally protected *myo*-inositol derivative **3**. Here the carbinols C1, C2 and C5 can be selectively addressed. This intermediate might be obtained by asymmetric desymmetrization of the readily accessible precursor *meso*-**4** by enantioselective acylation[26,27] in the presence of a nucleophilic catalyst. In this report we present the enantioselective desymmetrization of 4,6-protected *myo*-inositol derivatives in excellent yields, which are highly valuable phosphorylation precursors and building blocks for the synthesis of enantiopure *myo*-inositol phosphates.

The readily available phosphinit catalyst **5** (see Table 1) has been successfully applied in the asymmetric desymmetrization of *meso* 1,2-diols with benzoic acid chloride (**6**) providing the products in high yield with high enantioselectivity.[28] We anticipated that the asymmetric acylation of **4a** would occur selectively on the C1 or C3-carbinol[29,30] since cooperative substrate activation/recognition by the nucleophilic and the Brønsted-basic site was assumed earlier.[28] We initiated our investigation with the synthesis of the three derivatives **4a–c** according to a three step synthesis from commercially available starting materials. *Myo*-inositol (**1**) was converted into the *ortho*-ester **7**[31] and selectively protected on carbinol C4 and C6 in only one step (**7** → **8**, Scheme 1).[32,33] Subsequent cleavage of the *ortho*-ester liberated the precursors **4a–c** for the desymmetrization step in excellent yields (90–99%).

Next we turned our attention to the desymmetrization of **4a**. Indeed, when **5** (30 mol%) was subjected to the reaction of **4a** with benzoic acid chloride (**6**) in the presence of $iPr_2NEt$ as a base at 0 °C in $CH_2Cl_2$ the benzoylation product **3a** was obtained in 70% yield with an enantiomeric excess of 60% (Table 1, entry 1).

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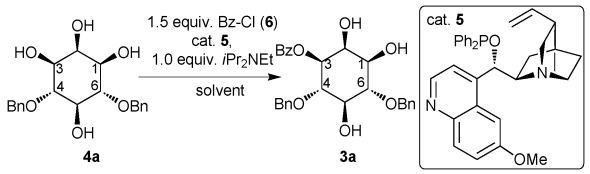
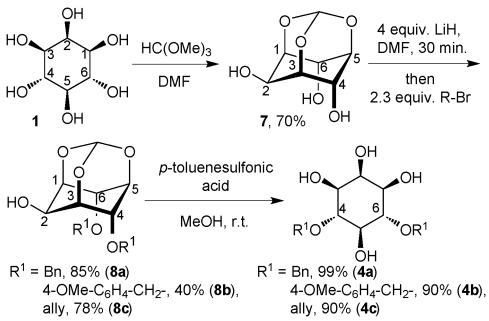
† Electronic supplementary information (ESI) available: Synthetic procedures and analytical data; X-ray crystal structure data for **9** CCDC 938831, **4a** 938829, **4c** 938830. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc43663b

**Table 1** Desymmetrization of **4a**[a]




| Entry | Solvent | Temp. [°C] | Cat. loading [mol%] | Time [h] | Yield[b] [%] | Enantiomeric excess[c] [%] |
|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 0 | 30 | 5 | 70 | 60 |
| 2 | $CHCl_3$ | 0 | 30 | 5 | 75 | 80 |
| 3 | Toluene | 0 | 30 | 5 | 40 | 87 |
| 4 | DMF | 0 | 30 | 5 | 0 | — |
| 5 | Acetonitrile | 0 | 30 | 5 | 88 | 81 |
| 6 | Propionitrile | 0 | 30 | 5 | 72 | 87 |
| 7 | Propionitrile | −78 | 30 | 24 | 94 | 99 |
| 8 | Propionitrile | −78 | 20 | 24 | 99 | 99 |
| 9 | Propionitrile | −78 | 10 | 24 | 74 | 97 |
| 10 | Propionitrile | −78 | 2 | 24 | 26 | 96 |
| 11[d] | Propionitrile | −78 | 20 | 48 | 72 | 99 |
| 12[d] | Propionitrile | −78 | 10 | 48 | 65 | 97 |

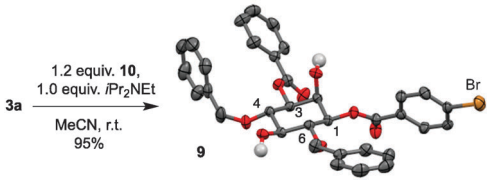
[a] Reactions were performed on a 0.1 mmol scale of **4a**. [b] Yield after purification by column chromatography. [c] Enantiomeric excess determined by HPLC with a chiral stationary phase (Chiralpak OD). [d] The reaction was performed on a 1.38 mmol scale.



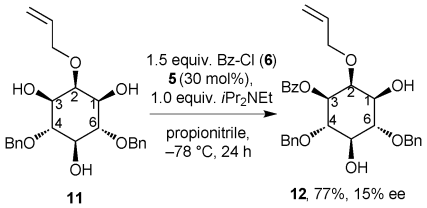

**Scheme 1** Synthesis of 4,6-diprotected *myo*-inositols **4a–c**.

Chloroform, toluene and acetonitrile proved to be viable solvents for the reaction (entries 2–5), but the best balance between the yield and the enantiomeric excess was achieved with propionitrile as a solvent (entry 6). The efficiency of the reaction was significantly improved when performed at −78 °C for 24 h. The product was obtained in high yield (94%) with an excellent enantiomeric excess of 99% (entry 7). The catalyst loading was reduced to 20 mol% without loss of reactivity or enantioselectivity (entry 8). A successive decrease in the catalyst loading from 20 mol% to 2 mol% resulted in a significant decrease in chemical yield without loss of enantioselectivity (entries 9 and 10). The synthetic practicability of this methodology was demonstrated by the desymmetrization of 0.50 g (1.38 mmol) **4a** with two different catalyst loadings (entries 11 and 12). In both cases the enantiopure product **3a** was obtained with excellent enantiomeric excess (99% ee (20 mol%) and 97% ee (10 mol%)) with only marginally differing yields (72% and 65% yield).

For the determination of the absolute configuration enantiopure **3a** was converted to **9** by reaction with 4-bromobenzoic acid chloride (**10**). The absolute configuration of **9** was established using X-ray crystal structure analysis (Scheme 2).‡




**Scheme 2** Derivatization of **3a** for determination of the absolute configuration; X-ray crystal structure of **9** (selected hydrogen atoms were omitted for clarity).

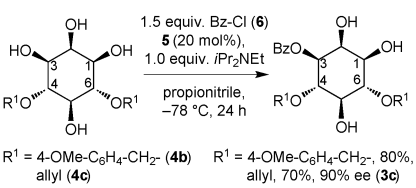



**Scheme 3** Benzoylation of 2-allylated *myo*-inositol derivative **11**.

The second benzoylation was found at carbinol C1. Consequently the first catalyzed asymmetric esterification was achieved at carbinol C3, which led to the enantioselective formation of (1*R*, 2*S*, 3*S*, 4*S*, 5*R*, 6*S*)-3-*o*-benzoyl-4,6-di-*o*-benzyl-*myo*-inositol (**3a**).

From a mechanistic view, the lack of reactivity in the strongly polar solvent DMF suggests that ion-pairing and hydrogen-bonding is important for the product-formation and enantioselectivity (Table 1, entry 4). This hypothesis is supported by the observation of the diminished enantioselectivity when carbinol C2 was protected. The reaction of 2-allylated *myo*-inositol **11** with benzoyl chloride (**6**) under identical reaction conditions provided only a somewhat enantioenriched product **12** (15% ee) with slightly diminished yield (Scheme 3). This demonstrates that the interaction of the quinuclidine-fragment in the benzoylated catalyst at the phosphorous with the OH-group of C2 is essential for high enantioselectivity.

Finally we investigated the scope of the methodology. Protecting groups other than benzyl offer a highly flexible approach to enantiopure *myo*-inositol derivatives. Therefore we subjected 4,6-bis-(4-methoxy-benzyl) and 4,6-allyl substituted *myo*-inositol derivatives **4b** and **4c** to asymmetric benzoylation (Scheme 4). The chiral products **3b** and **3c** were produced in high yield with excellent enantioselectivity (90–99% ee) under identical reaction conditions to those for **3a**. This renders the presented approach as a reliable tool for the synthesis of orthogonally 3,4,6-protected enantiopure *myo*-inositol derivatives which serve as highly valuable starting materials for the synthesis of biologically active compounds.




**Scheme 4** Desymmetrization of 4-methoxy-benzyl- and allyl-protected *myo*-inositol derivatives.

We have demonstrated the highly enantioselective desymmetrization of 4,6-diprotected *myo*-inositol derivatives by acylation. The nucleophilic catalyst (one step) as well as the starting materials (three steps) are readily accessible from commercially available starting materials. The chiral products were obtained in high yield with excellent enantiomeric excess providing access to orthogonally protected enantiopure starting materials for the synthesis of biologically active *myo*-inositol phosphates.

## Notes and references

‡ X-ray crystal structure analysis **9**: formula $C_{34}H_{31}BrO_8 \times 2H_2O$, $M$ = 683.53, colourless crystal, 0.28 × 0.23 × 0.23 mm, $a$ = 11.9744(2), $b$ = 8.0367(2), $c$ = 17.1372(3) Å, $\beta$ = 108.858(1)°, $V$ = 1560.67(2) Å$^3$, $\rho_{calc}$ = 1.455 g cm$^{-3}$, $\mu$ = 1.376 mm$^{-1}$, empirical absorption correction ($0.699 \leq T \leq 0.742$), $Z$ = 2, monoclinic, space group $P2_1$ (no. 4), $\lambda$ = 0.71073 Å, $T$ = 223(2) K, $\omega$ and $\varphi$ scans, 8893 reflections collected ($\pm h$, $\pm k$, $\pm l$), [$(\sin\theta)/\lambda$] = 0.67 Å$^{-1}$, 4744 independent ($R_{int}$ = 0.021) and 4550 observed reflections [$I > 2\sigma(I)$], 439 refined parameters, $R$ = 0.031, w$R^2$ = 0.070, max. (min.) residual electron density 0.17(−0.21) e Å$^{-3}$, hydrogen atom at O51 was refined freely; the hydrogen atoms from the water molecule (O71, O72 and O72A) were refined freely, but with O–H distance restraints (SADI) and with a fixed $U$-value. The Flack parameter was refined to −0.014(8); data sets were collected using a Nonius KappaCCD diffractometer. Programs used: data collection, COLLECT (Nonius B.V., 1998); data reduction Denzo-SMN (Z. Otwinowski, W. Minor, *Methods Enzymol.* 1997, **276**, 307–326); absorption correction, Denzo (Z. Otwinowski, D. Borek, W. Majewski, W. Minor, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 2003, **59**, 228–234); structure solution SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 1990, **46**, 467–473); structure refinement SHELXL-97 (G. M. Sheldrick, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 2008, **64**, 112–122) and graphics, XP (BrukerAXS, 2000). $R$-values are given for observed reflections, and w$R^2$ values are given for all reflections.

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