A Short and Efficient Route from *myo*- to *neo*-Inositol

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Abstract: An efficient route from *myo*- to *neo*-inositol is described. The key steps of the sequence are oxidation of the hydroxy group at C-5 to the corresponding ketone, followed by a highly (dr = 7.8:1) stereoselective reduction. The route includes nine steps with an overall yield of 51% and is therefore superior to all hitherto reported methods for the preparation of *neo*-inositol.

Key words: inositols, cyclitols, carbocycles, stereoselective synthesis, regioselectivity

Inositol is the collective term for a substance class formed by the nine stereoisomeric hexahydroxy cyclohexanes whose structures are summarized in Figure 1.

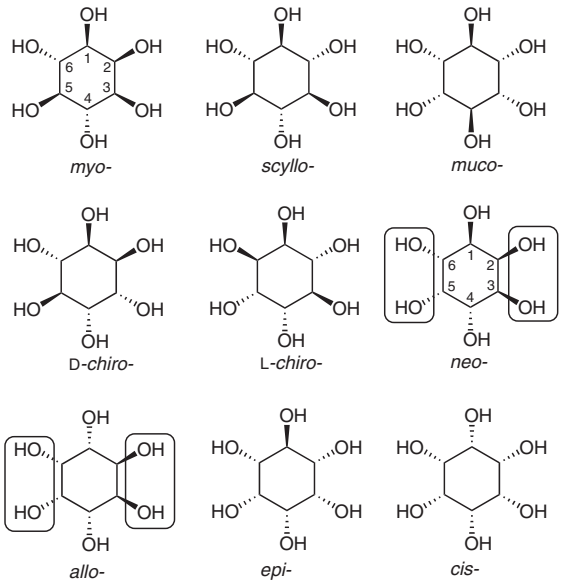

Figure 1 Structure of the nine inositols

Some phosphorylated derivatives of inositols, especially of *myo*-inositol, play an important role in signal transduction[1] and other cellular processes.[2] Besides the biological significance the inositols are very interesting building blocks for the synthesis of natural products,[3] catalysts,[4] metal-complexing agents,[5] gelators,[6] and supramolecular assemblies.[7] On the other hand, only four of the nine inositols occur in nature and only *myo*-inositol is commercially available for an acceptable price.

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In connection with our investigations concerning the development of molecular rods with oligospiroketal (OSK) backbone[8] we were interested in a building block, which could replace the hitherto used pentaerythritol but is furnished with two additional substituents for solubility enhancement. Inositols should fulfill these demands. Bearing in mind that ketals of *vic*-dihydroxycyclohexanes are only smoothly formed if the two hydroxy groups are in *cis* arrangement and that the two pairs of these *cis*-diol moieties at opposing sides of the cyclohexane ring should be positioned *trans* to each other to avoid a kink in the OSK rod backbone, only *allo*- and *neo*-inositol are considered for our purpose (see boxes in Figure 1). Since the two remaining hydroxy groups should not lower the symmetry of the OSK rods, *neo*-inositol is the only suitable isomer for our approach (Figure 2).

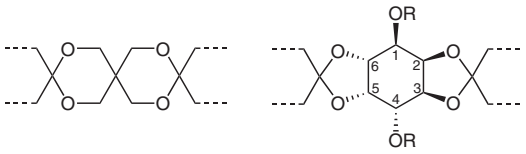


Figure 2 OSK rods with pentaerythritol (left) and *neo*-inositol (right) tetrol unit

It should be noted that *neo*-inositol differs from *myo*-inositol only by the relative configuration in 5-position. Only two routes are known, which explicitly attend to the total synthesis of *neo*-inositol.

The method by Potter et al.[9] starts from *myo*-inositol. After protection of four hydroxy groups in 1,3,4,6-position as BDA derivatives using butane-2,3-dione a selective monosulfonylation of one of the remaining hydroxy groups in 5-position with triflic anhydride is reported. The key step of this method is a subsequent S_N2 substitution of the triflate moiety giving the *neo*-inositol substitution pattern. Unfortunately, we could not reproduce the sulfonylation step. Even after numerous optimization attempts we always obtained a mixture of mono- and disulfonylated product. Instead of the reported 17% overall yield (5 steps) we obtained at best 5% of the desired product.

The second total synthesis of *neo*-inositol by Hudlicky et al.[10] uses enantiomerically pure 3-bromocyclohexa-3,5-diene-1,2-diol, the enzymatic preparation of which from bromobenzene was previously reported.[11] Besides the difficulties to scale up this first step (a run in a 2800 ml flask gave only 160 mg product) the following steps require some reagents, which are not commercially

available (1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione, DBH), highly toxic (Bu_3SnH, OsO_4) or expensive (OsO_4). The reported overall yield amounts to 19%.

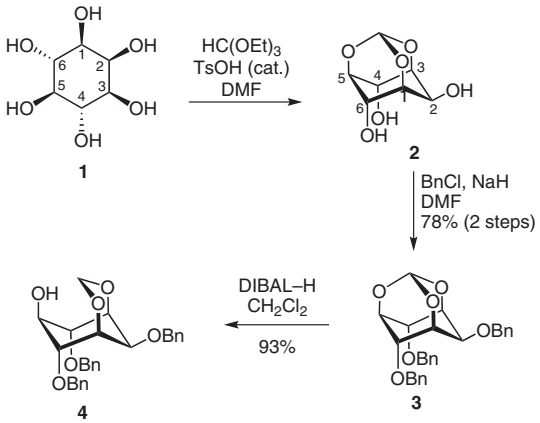
Chung and Kwon[12] reported a route to a tetraprotected *neo*-inositol derivative starting from a hexaprotected *myo*-inositol.[13] The two key steps to switch from *myo*- to *neo*-stereochemistry are an elimination of a *trans*-1,2-diol with I_2, Ph_3P and imidazole, and a *cis*-dihydroxylation of the resulting cyclohexene (a conduritol C derivative) using OsO_4 and NMO. The overall yield to the *neo*-inositol derivative came to 13% or 10%, respectively, assuming that two subsequent deprotection steps proceed with >90% yield.

Conduritols are also the key intermediates in the interesting work by Altenbach and co-workers.[14] Unlike the route by Chung and Kwon conduritols E with a different stereochemical pattern were prepared and therefore a *trans*-dihydroxylation (carried out by a epoxidation/epoxide ring-opening sequence) is necessary, circumventing the OsO_4-catalyzed dihydroxylation. The overall yield of the eight-step sequence amounts to approximately 20%.

Furthermore, *neo*-inositol or derivatives were mentioned in some other publications but by a critical review none of these methods was considered an efficient access to the target compound.[15–21]

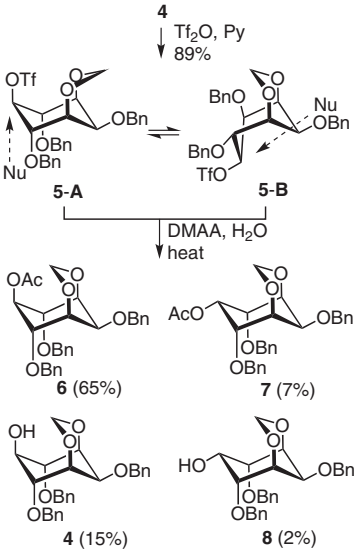
In the face of this unsatisfactory situation we decided to develop a new short and efficient route to *neo*-inositol.

Commencing with *myo*-inositol (**1**) we prepared the ortho ester **2** according to literature.[22] Unlike the previously reported methods[23] we succeeded in directly converting **2** without further purification into the completely protected *myo*-inositol **3** by alkylation with benzyl chloride. The subsequent reductive ring opening of the ortho ester moiety liberated the axial hydroxy group in 5-position and provided the five-fold protected *myo*-inositol **4** in excellent yield (Scheme 1).[24]



Scheme 1 Optimized preparation of **4**

At this point an epimerization at C-5 suggests itself to switch from *myo* to *neo* configuration. For this purpose **4** was converted into the triflate **5**, which was treated with a mixture of dimethylacetamide–water.[9] Surprisingly we obtained the acetate **6** with *myo*-configuration as main product together with only minor amounts of the desired *neo*-acetate **7** and epimeric alcohols **4** and **8** (Scheme 2). This outcome could be explained by steric hindrance of the preferred S_N2-trajectory both in conformer **5-A** and **5-B** (see dashed arrows in Scheme 2).



Scheme 2 Preparation of triflate **5** and treatment with DMAA–H_2O

Interestingly, both acetates **6** and **7** and alcohols **4** and **8** were formed at the same ratio (10:1). This suggests that the formation of these four products passes through the same reactive intermediate. We assume an S_N1-like mechanism with stabilization of the intermediate carbocation at C-5 by the neighboring two benzyloxy groups at C-4 and C-6. Several attempts to convert **4** into the 4-nitrobenzoate of **8** by a Mitsunobu reaction[25] with DEAD, Ph_3P and 4-nitrobenzoic acid gave only a complex product mixture beside unconverted reactant. Finally, we succeeded with an oxidation–reduction sequence. To this end **4** was oxidized to ketone **9**[28] with Dess–Martin periodinane (DMP)[26] and was, without further purification,[27] subjected to numerous reduction conditions. The results are summarized in Table 1. The best ratio between **8**[29] and **4** was obtained with sodium borohydride in refluxing methanol (entry 4) but this ratio decreased with increasing amounts of **9** used in the reaction (entries 5 and 6). The best compromise is to start the reaction at room temperature and let the temperature increase to 40 °C by reaction heat (entry 3). Interestingly, lower reaction temperatures (entry 1) or ethanol as solvent (entry 7) gave poorer product ratios. Other reduction agents such as $LiAlH_4$ (entry 9), borane (entries 10 and 11), aluminum triisopropylate (Meerwein–Ponndorf reduction, entry 12) or DIBAL-H (entry 13) also consistently resulted in lower selectivity.

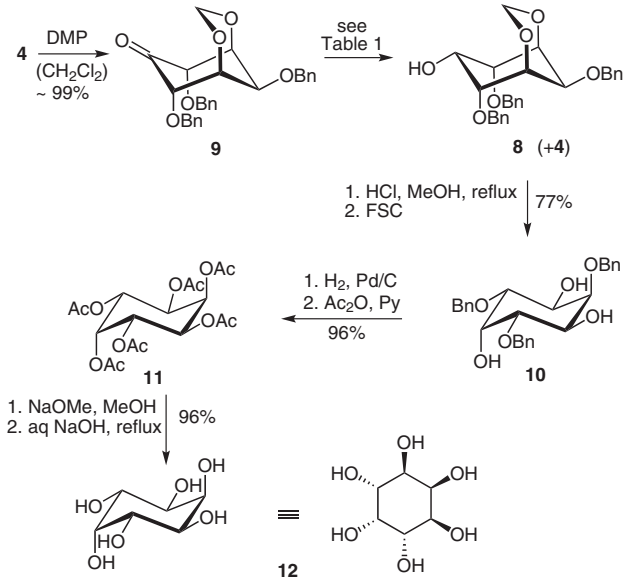
To obtain a pure *neo*-configured derivative, the product mixture (**8** + **4**) was first partly deprotected by treatment with HCl in refluxing methanol followed by separation with flash column chromatography ($CHCl_3$–EtOAc) giving **10**[30] with an overall yield of 76% based on **4**.

Table 1 Reduction of Ketone **9**

Entry	Reagent	Solvent	Temp	n[a]	dr[b]	Yield (%)
1	$NaBH_4$	MeOH	0 °C	0.3	5.4:1	97
2	$NaBH_4$	MeOH	r.t.	0.5	6.5:1	93
3	$NaBH_4$	MeOH	r.t.[c]	43.1	7.8:1	98
4	$NaBH_4$	MeOH	reflux	0.7	9.5:1	94
5	$NaBH_4$	MeOH	reflux	19.0	7.6:1	83
6	$NaBH_4$	MeOH	reflux	45.0	6.5:1	46
7	$NaBH_4$	EtOH	reflux	0.7	7.1:1	76
8	$NaBH_4$[d]	MeOH	r.t.	0.7	1.2:1	89
9	$LiAlH_4$	Et_2O	r.t.	0.3	4.8:1	–[e]
10	BH_3·THF	THF	0 °C	0.7	4.4:1	27
11	BH_3·THF	THF	r.t.	0.7	1.7:1	21
12	Al(O*i*-Pr)$_3$	*i*-PrOH	reflux	0.3	4.3:1	97
13	DIBAL-H	CH_2Cl_2	0 °C	0.5	1:1.3	95

[a] Amount of **9** in mmol.
[b] Ratio **8** (*neo*)/**4** (*myo*) determined via ^{1}H NMR.
[c] The temperature increased to 40 °C during reaction.
[d] $CeCl_3$ (1 equiv) was added.
[e] A third unidentified product was also detected.

The three benzyl groups could be quantitatively removed by catalytic hydrogenation (H_2, Pd/C). Unfortunately, it turned out to be difficult to remove traces of charcoal due to the scarce solubility of *neo*-inositol. Therefore, we converted the crude product into the hexaacetate **11**, which could easily be purified by recrystallization. In the final step the six acetyl groups were removed by saponification[14] giving the desired *neo*-inositol **12** with nearly quantitative yield (Scheme 3).



Scheme 3 Preparation of *neo*-inositol **12**

In summary, we developed a short and efficient route from *myo*-inositol (**1**) to *neo*-inositol (**12**), which is clearly superior to all hitherto described methods. The overall yield of the nine-step sequence amounts to 51%. Furthermore, three intermediate products were used in the next reaction step without purification (**2**, **8**, **9**).

Acknowledgment

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(27) Ketone **9** was obtained as an oil, which was partly decomposed upon flash column chromatography on silica gel.
(28) Alcohol **4** (20.18 g, 43.63 mmol) was dissolved in anhyd CH_2Cl_2 (500 mL) and Dess–Martin periodinane (20.59 g, 48.55 mmol, 1.1 equiv) was added. The resulting mixture was stirred at r.t. until complete conversion of **4** was monitored by TLC. The organic layer was washed several times with an aq solution of $Na_2S_2O_3$/$NaHCO_3$, dried, and evaporated. Ketone **9** was obtained as an oil (19.85 g, 43.10 mmol, 99%) and can be used without further purification; R_f = 0.7 (hexanes–EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.95–3.97 (m, 2 H), 4.51 (d, ^2J = 11.6 Hz, 2 H), 4.52–4.54 (m, 2 H), 4.64 (d, ^2J = 4.8 Hz, 1 H), 4.67 (d, ^2J = 11.6 Hz, 2 H), 4.73 (s, 2 H), 4.76 (t, ^3J = 1.3 Hz, 1 H), 5.52 (d, ^3J = 4.8 Hz, 1 H), 7.24–7.41 (m, 15 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 69.8 (CH), 71.1 (CH_2), 72.2 (CH), 72.3 (CH_2), 81.6 (CH), 85.5 (CH_2), 127.8 (CH), 127.9 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 136.8 (C), 137.3 (C), 202.7 (C). HRMS: *m/z* $[M + H]^+$ calcd for $C_{28}H_{28}O_6$ + H: 461.1964; found: 461.1986.
(29) Ketone **9** (19.84 g, 43.08 mmol) was dissolved in anhyd MeOH (800 mL) and $NaBH_4$ (1.98 g, 52.39 mmol, 1.2 equiv) was added. The reaction mixture was stirred about 20 min until gas and heat evolution ceased. This mixture was directly used in the next step. To obtain spectroscopic data a small sample (2 mL) was taken from the mixture, and the solvent was evaporated. The resulting residue was treated with 0.1 M aq HCl solution and extracted thrice with Et_2O. The combined organic layers were dried and evaporated giving a pale yellow oil (49 mg, 0.10 mmol, 98%) with a ratio of **8** (*neo*) to **4** (*myo*) of 7.8:1 (determined by ^{1}H NMR); R_f (**8**) = 0.46 (hexanes–EtOAc, 2:1); R_f (**4**) = 0.44 (hexanes–EtOAc, 2:1). ^{1}H NMR (**8**): δ = 2.74 (br s, 1 H), 3.91–3.96 (m, 2 H), 4.30–4.32 (m, 1 H), 4.34–4.37 (m, 2 H), 4.43–4.47 (m, 1 H), 4.52 (s, 2 H), 4.59 (d, ^2J = 11.9 Hz, 2 H), 4.63 (d, ^2J = 4.5 Hz, 1 H), 4.67 (d, ^2J = 11.9 Hz, 2 H), 5.52 (d, ^2J = 4.5 Hz, 1 H), 7.25–7.39 (m, 15 H). ^{1}H NMR (**4**): matches with literature.[24]
(30) The reaction mixture of the previous step, containing **8** + **4**, was treated with concd HCl (60 mL) and refluxed for 3 h. The solvents were evaporated, and the resulting residue was treated with H_2O and extracted thrice with CH_2Cl_2. The combined organic layers were dried, evaporated, and the resulting residue purified by flash chromatography (silica, $CHCl_3 \rightarrow CHCl_3$–EtOAc, 1:2) giving **10** as colorless crystals (14.96 g, 33.21 mmol, 77%); mp 97–98 °C; R_f = 0.26 ($CHCl_3$–EtOAc, 1:2).